Formation of Pharmaceutical Salts and Cocrystals via Vapour-Assisted Tumbling (VAT) – A Solvent Efficient Process

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VAT – Supporting Information

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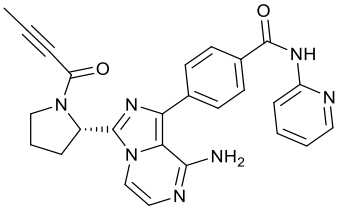
Experimental Summary

Expt	Coformer 1 (eq)	Coformer 2 (eq)	Mass Recovery / g	Mass Recovery %§	Time / hr	Residual MeOH /ppm	Ref
1	Acalabrutinib (2)	Urea (3)	5.42	91	24	600	[1]
2	Aripiprazole (1)	Catechol (1)	5.79	93	3 + 18 h age	3200	[2]
3	Aripiprazole (1)	Resorcinol (1)	3.70	99	4	3400	[2]
4	Caffeine (1)	Citric Acid (1)	9.45	95	42	1100	[3]
5	Carbamazepine (1)	Nicotinamide (1)	7.28	93	28	ND	[4]
6	Isonicotinamide (1)	Resorcinol (1)	7.70	96	18	ND	[5]
7	Nicotinamide (1)	Fumaric Acid (1)	9.29	95	72	ND	[6]
8	Carvedilol (2)	Oxalic Acid (1)	4.76	90	46	ND	[7]
9	Olanzapine (1)	Nicotinic Acid (1)	6.80	96	18	500	[8]
10	Olanzapine (1)	Oxalic Acid (1)	6.33	90	2.5 + 72 h age	16000	[9]

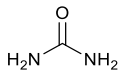
VAT Trials

Cocrystals

Acalabrutinib : Urea (1:1.5)



Acalabrutinib
Acl



Urea
Ura

VAT Mk.3:

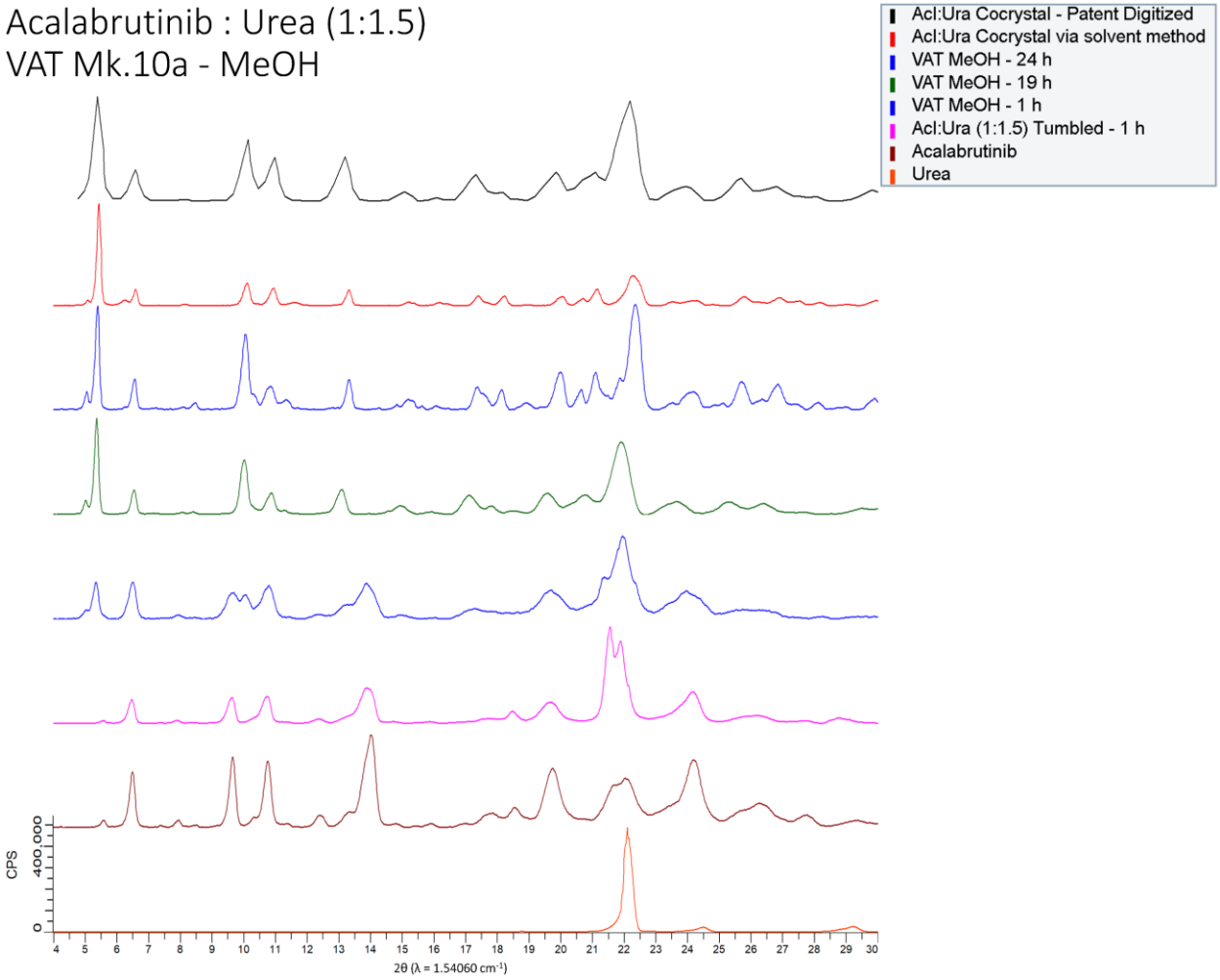
Acalabrutinib (10.00 g) was mixed with finely powdered urea (1.94 g, 1.5 eq) and added to a glass sample tumbler attached the VAT Mk.3 apparatus. The sample was then slowly tumbled at room temperature. Acetone, EtOH or MeOH vapour was introduced to the sample via bubbling though the solvent with N_2 carrier gas. After 18 hours of tumbling in an environment of EtOH vapour, the EtOH vapour source was removed, and the sample dried with tumbling using a flow of dry N_2. After one hour the sample was removed.

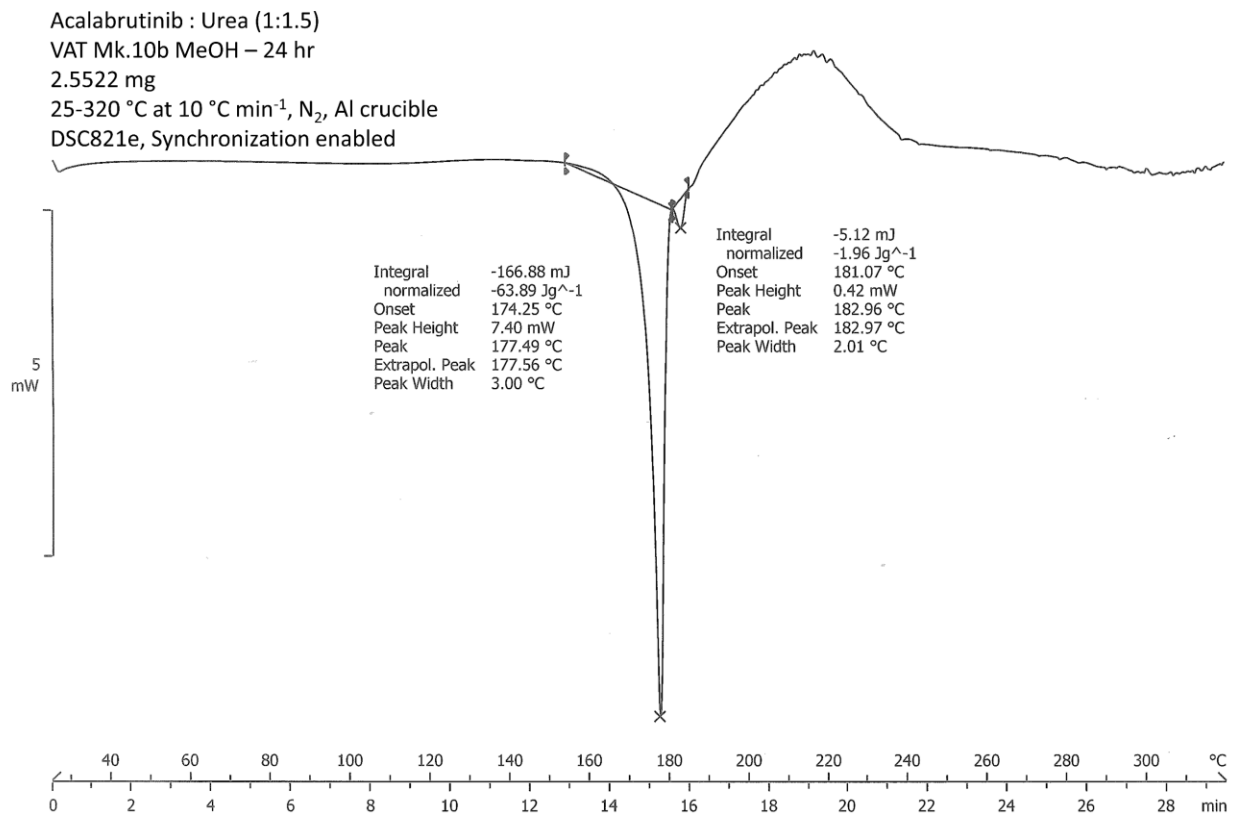
The Acl:Ura system was tested in VAT Mks: 1, 3, 8, 9, 9b, and 10a with repeatable results.

VAT Mk.10b:

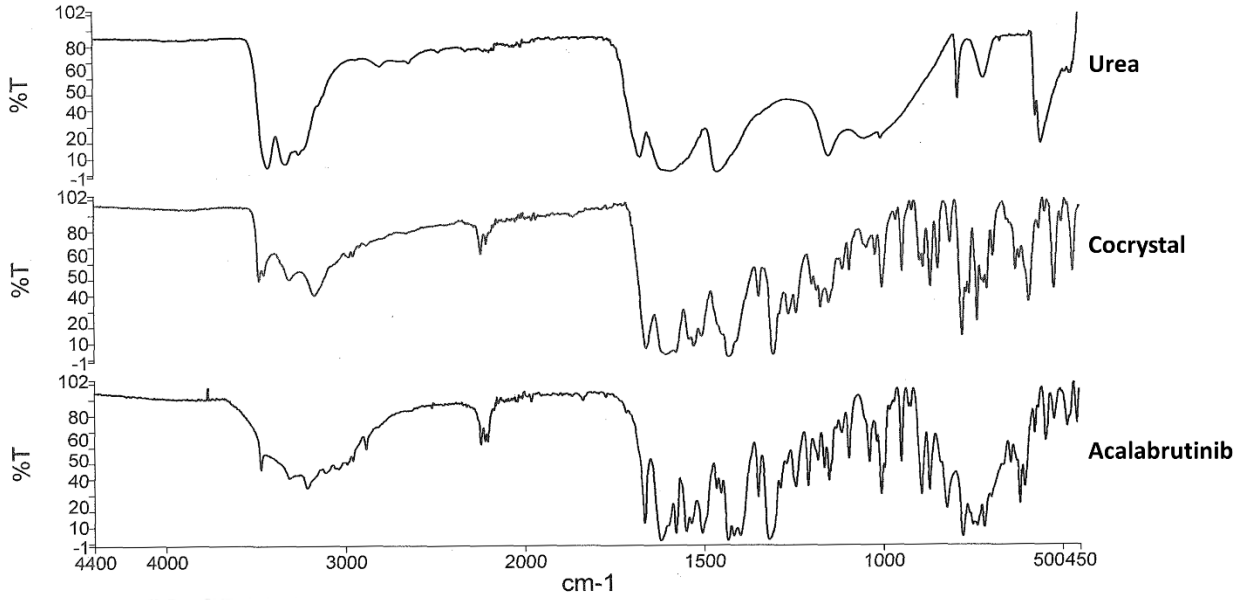
Acalabrutinib was ground in a mortar and pestle for 5 min. Urea was added to a stainless-steel milling jar with two stainless-steel balls and milled in a ball mill for 30 min at 25 Hz. Milled Acl (5.00 g, 10.74 mmol, 1 eq) and Ura (0.97 g, 16.11 mmol, 1.5 eq) were added to the sample tumbler of the VAT Mk.10b apparatus and tumbled in ambient conditions. After 1 hr a PXRD showed no conversion to the reported Acl:Ura (1.1.5) "APO-V" cocrystal.[10] A flow of N_2 bubbled through MeOH (~45 mL min^{-1}) was introduced to the tumbler. After tumbling in N_2/MeOH for 1 hr, a PXRD showed a significant conversion to the cocrystal, with weak peaks of the Acl starting material remaining. The solids were tumbled for a total of 24 hrs. A final PXRD showed good conversion to the cocrystal, with no peaks of the starting material. The solid was removed from the tumbler with a recovered mass = 5.42 g. A DSC showed the major endotherm at 174 °C with a minor endotherm at 181 °C followed by a decomposition.

Acalabrutinib : Urea (1:1.5)
VAT Mk.10a - MeOH

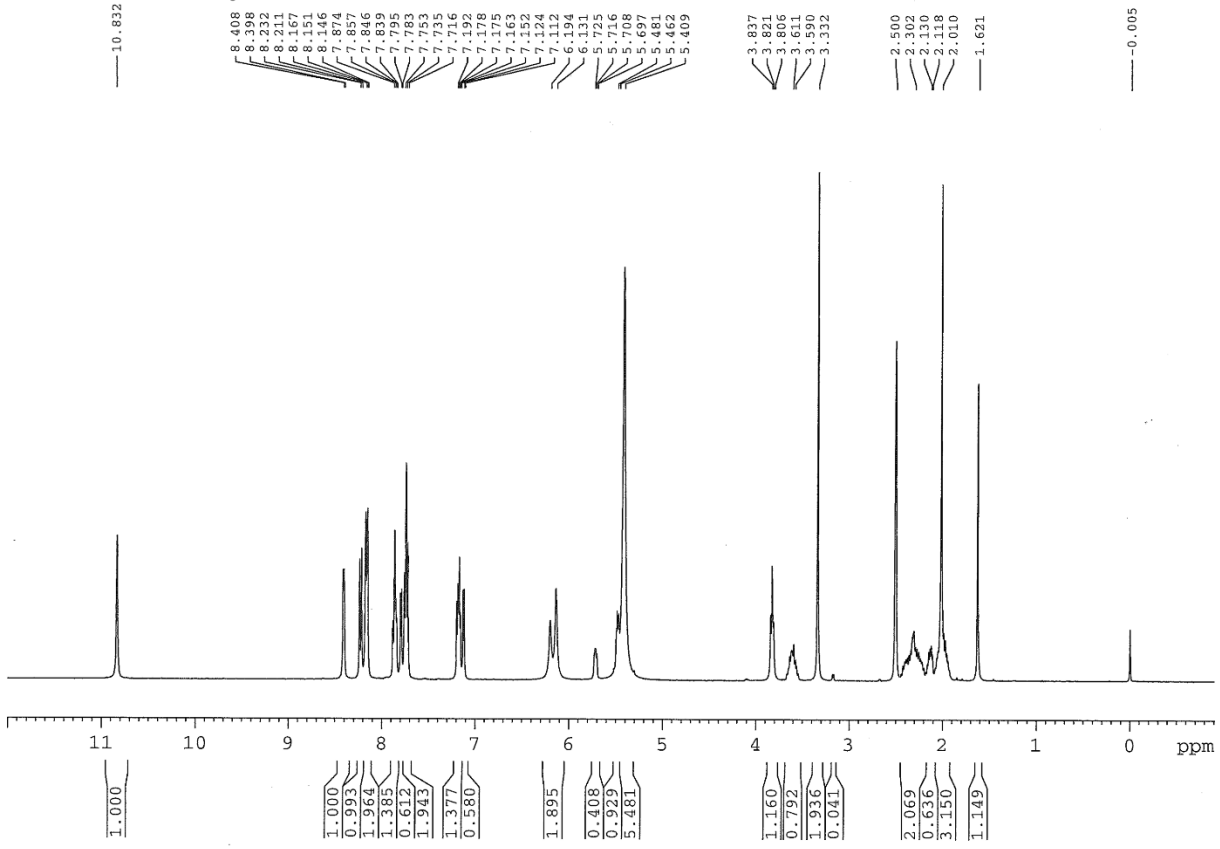




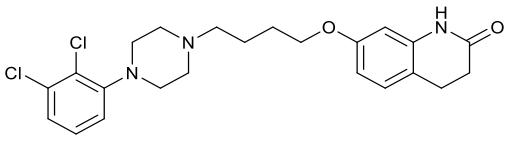
Acalabrutinib : Urea (1:1.5) – IR



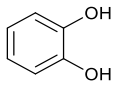
Acalabrutinib : Urea (1:1.5)
VAT Mk.10b - MeOH
^{1}H NMR – DMSO-d_6



Aripiprazole : Catechol (1:1)



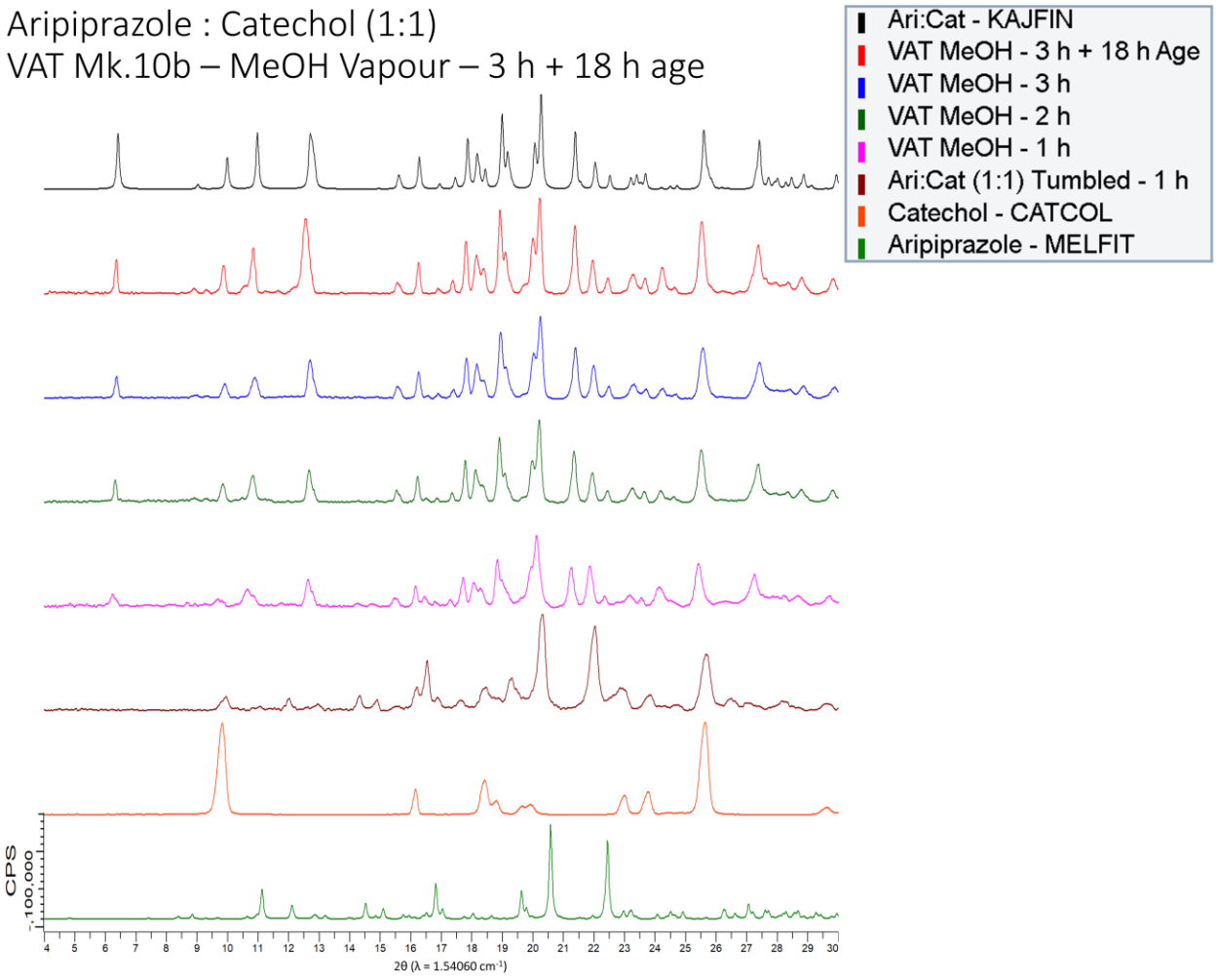
Aripiprazole
Ari



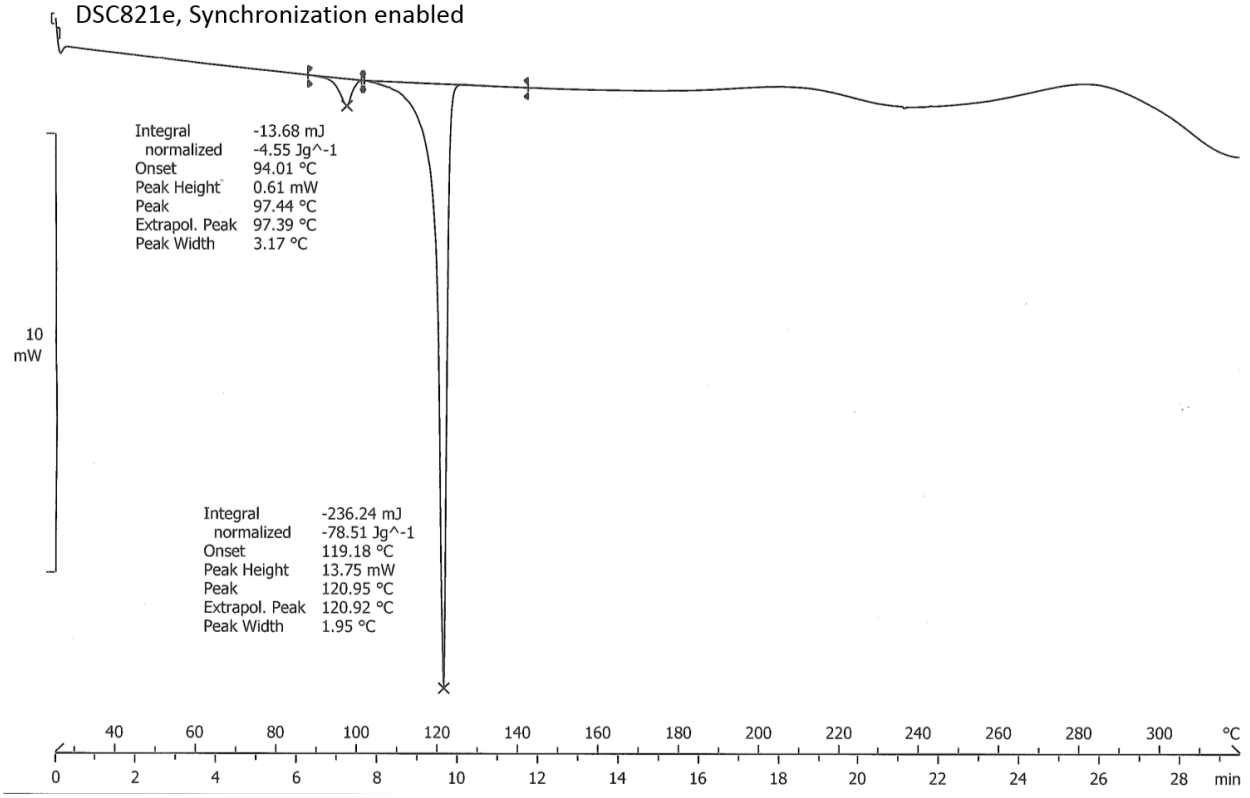
Catechol
Cat

Aripiprazole and catechol were milled separately in stainless steel grinding jars loaded with two 12 mm stainless steel balls for 30 min at 25 Hz. Ari (5.00 g, 11.15 mmol) and Cat (1.23 g, 11.15 mmol) were added to the sample tumbler of the VAT Mk.10b and tumbled for 1 hr in atmospheric conditions. A PXRD did not show any new peaks. The tumbling was resumed with a flow of N_2 bubbled through the MeOH reservoir (~77 mL min^{-1}). After 1 hr of tumbling in N_2/MeOH the solid had become very sticky and had "balled", One of the balls was broken up and a PXRD of the resulting powder showed a good conversion to the reported Ari:Cat (1:1) cocrystal (CSD: KAJFIN).[2] The balls of sticky solid were broken up as much as possible before

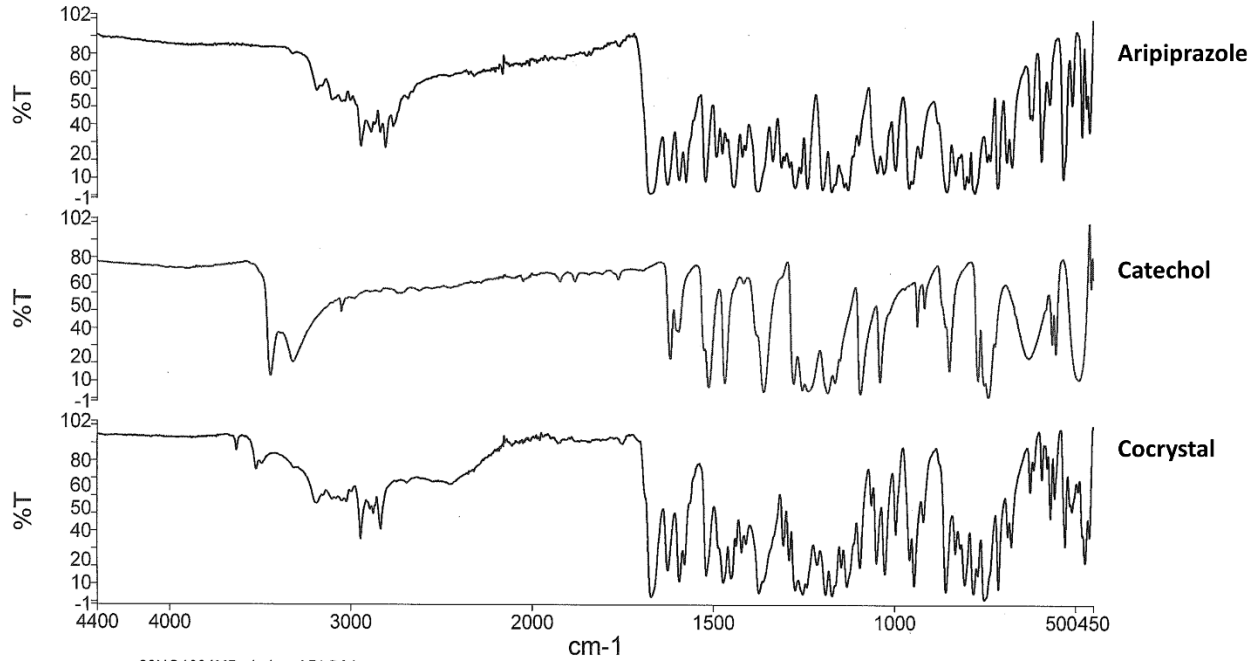
tumbling in N_2/MeOH resumed. After a further hour (2 hrs in total), the solid was observed to be no long sticky, with many small balls. The solid was gently broken up in a mortar and pestle before returning to the sample tumbler. The solid was then left enclosed inside the sample tumbler without tumbling, but with a low flow of N_2 (~45 mL min^{-1}) overnight (~18 hrs). A final PXRD showed a good conversion to the Ari:Cat (1:1) cocrystal, along with small peaks seemingly from excess catechol (CSD: CATCOL). Recovered weight = 5.79 g. A DSC showed a small endotherm at 94.0 °C followed by the main endothermic melting peak at 119.2 °C (Reported Ari:Cat M.P. = 121.2 °C) without any noticeable peak from Ari (reported M.P. = 139.0 °C).



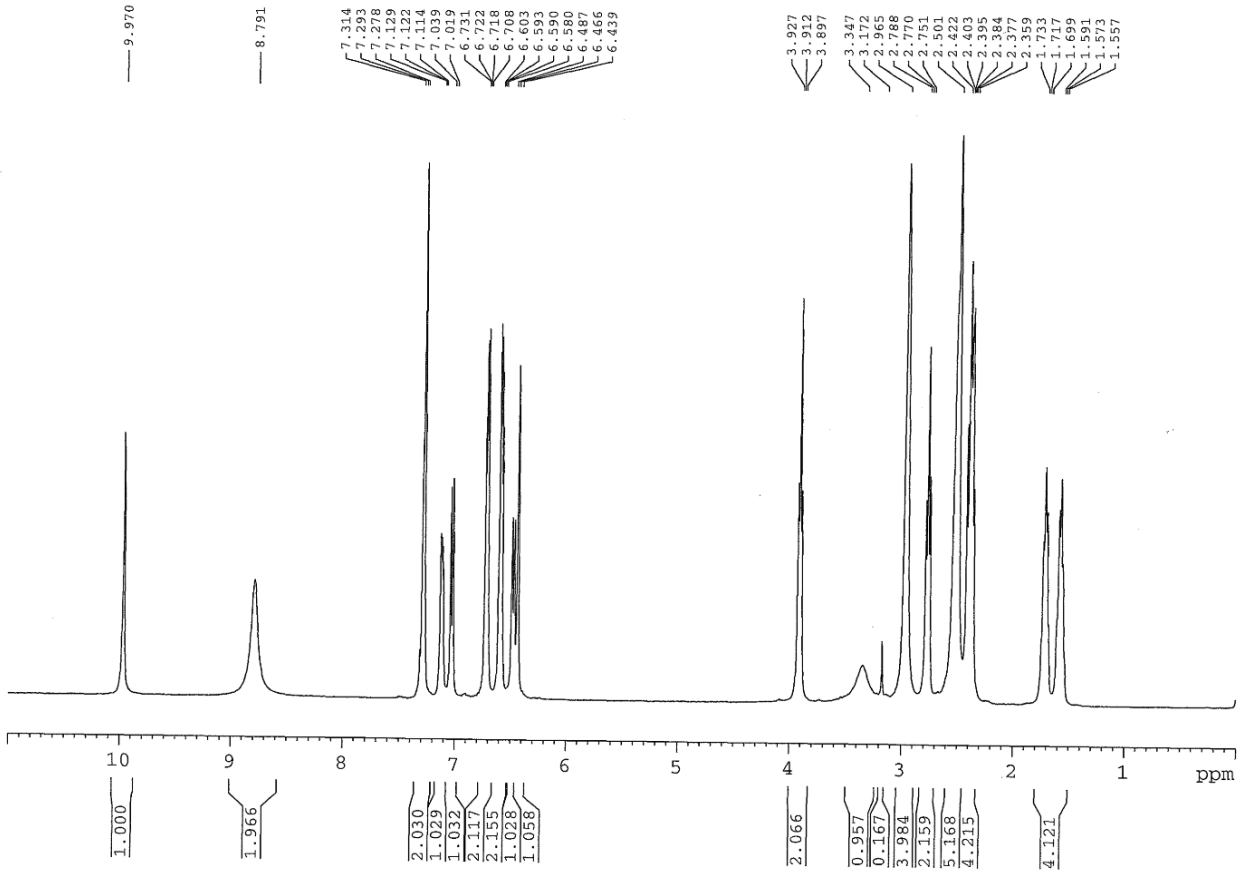
Aripiprazole : Catechol (1:1)
VAT Mk.10b MeOH – 3 hr + 19 hr age
3.0090 mg
25-320 °C at 10 °C min^{-1}, N_2, Al crucible
DSC821e, Synchronization enabled



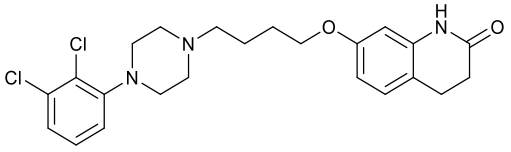
Aripiprazole : Catechol (1:1) - IR



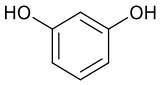
Aripiprazole : Catechol (1:1)
VAT Mk.10b - MeOH
^{1}H NMR – DMSO-d_6



Aripiprazole : Resorcinol (1:1)



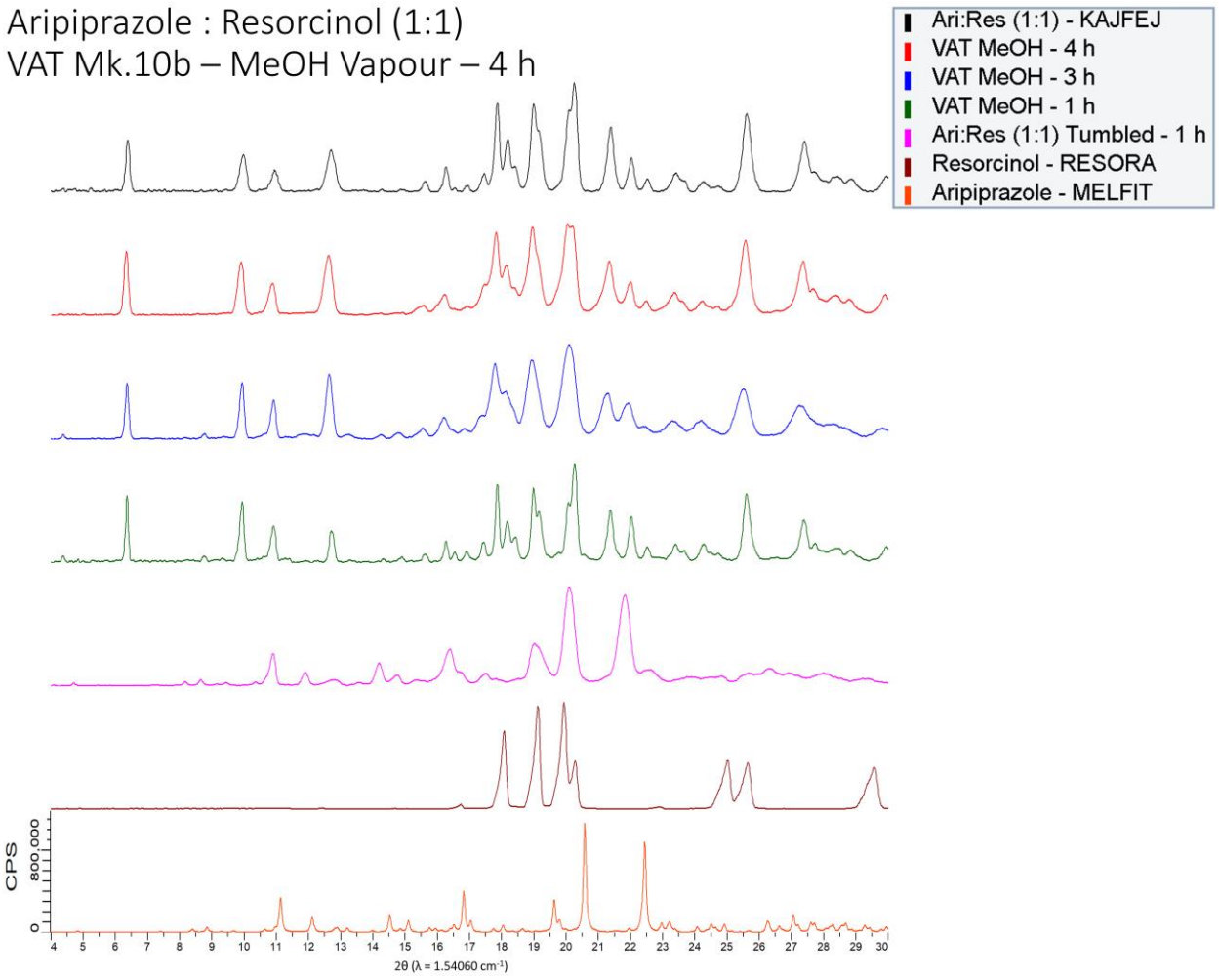
Aripiprazole
Ari



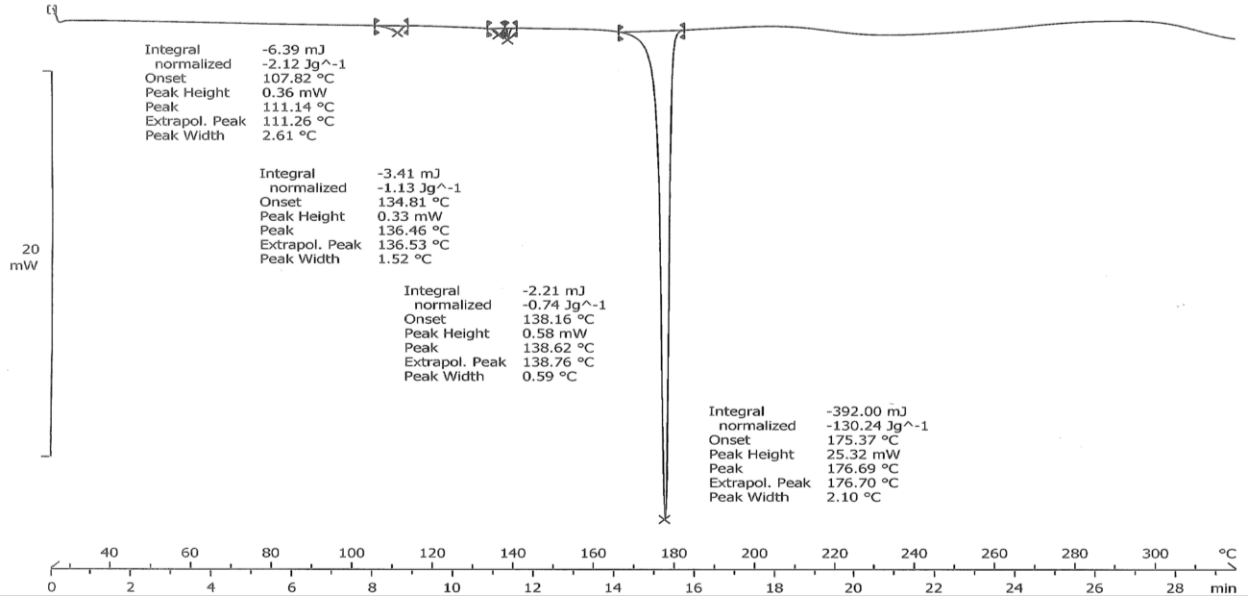
Resorcinol
Res

Aripiprazole (prepared in house) and resorcinol (Aldrich) were each ground separately using in stainless steel ball milling jars with two stainless steel balls each at 25 Hz for 5 min. Aripiprazole (3.00 g, 6.96 mmol, 1 eq) and resorcinol (0.74 g, 6.69 mmol, 1 eq) were added to the sample tumbler of the VAT Mk.10b apparatus and tumbled dry for 10 min. A PXRD showed no conversion. N_2 carrier gas was bubbled through MeOH at an approximate rate of ~77 mL min^{-1} though the apparatus with tumbling. After 1 hr, the initially fine free flowing powder had become hardened balls. The balls were crushed with a spatula and a PXRD

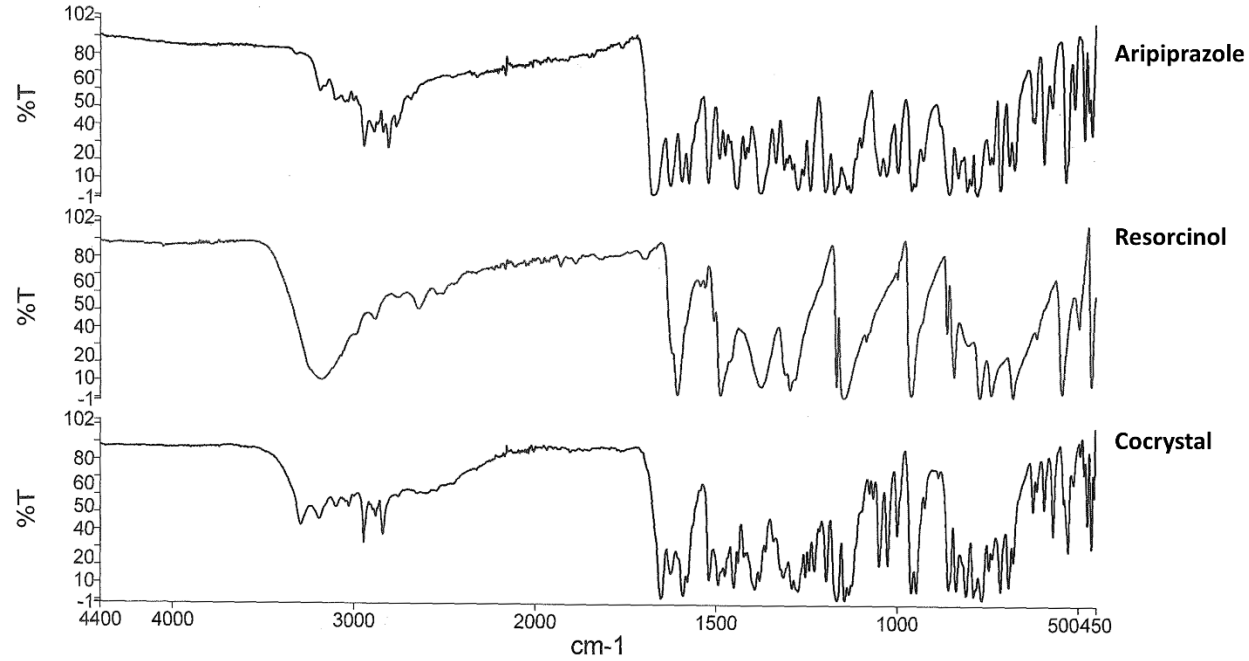
taken of the powders. The PXRD showed good new peaks with very weak peaks of ARI remaining. After a further 3 hr of tumbling in N_2/MeOH, a PXRD did not show any peaks from the ARI starting material. After a further 1 hr (4 hr in total), the solid balls were removed from the tumbler and crushed with a spatula. A PXRD did not show any peaks of Ari or Res and only peaks matching with the reported Ari:Res cocrystal (CCDC: KAJFEJ).[2] Recovered mass: 3.70 g. A DSC on the final material showed a small amount of resorcinol melting at 108 °C and two additional endotherms from polymorphs of aripiprazole occurred at 135 °C and 138 °C. The major melting endotherm was seen at 175 °C, consistent with the reported Ari:Res cocrystal at 175.6 °C.[2]



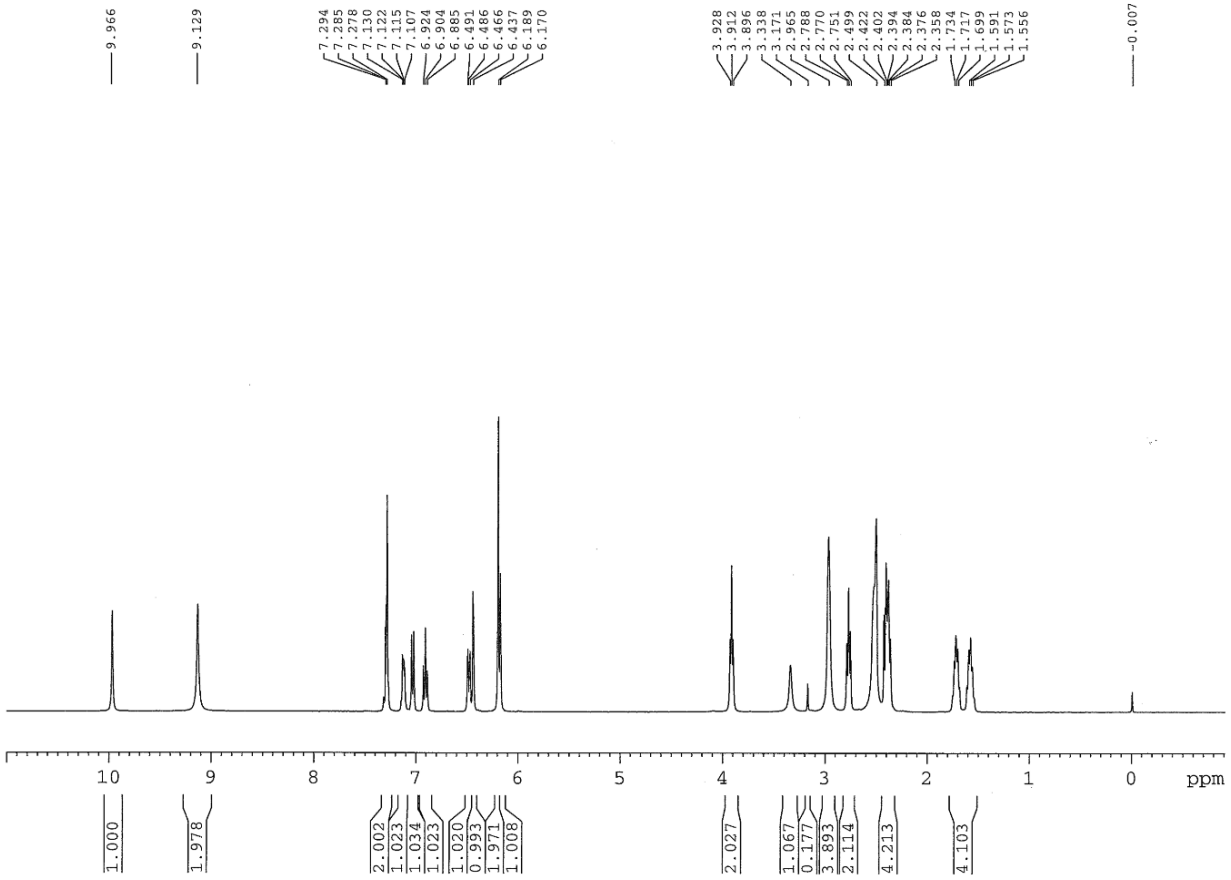
Aripiprazole : Resorcinol (1:1)
VAT Mk.10b MeOH – 4 h
3.0099 mg
25-320 °C at 10 °C min^{-1}, N_2, Al crucible
DSC821e, Synchronization enabled



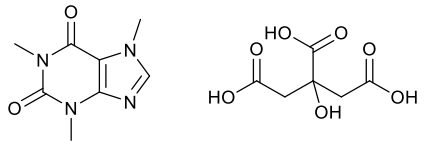
Aripiprazole : Resorcinol (1:1) - IR



Aripiprazole : Resorcinol (1:1)
VAT Mk.10b - MeOH
^{1}H NMR – DMSO-d_6



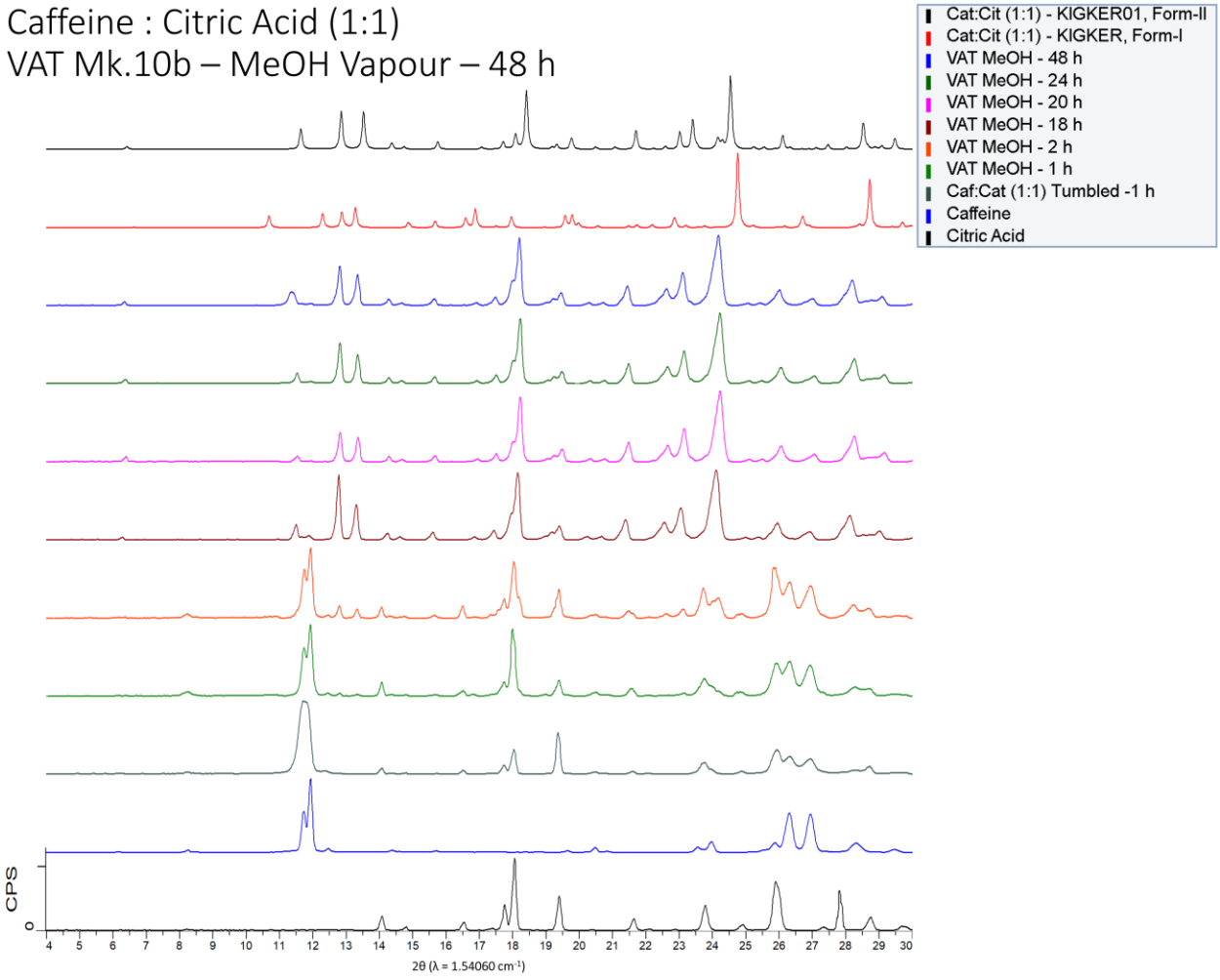
Caffeine : Citric Acid (1:1)

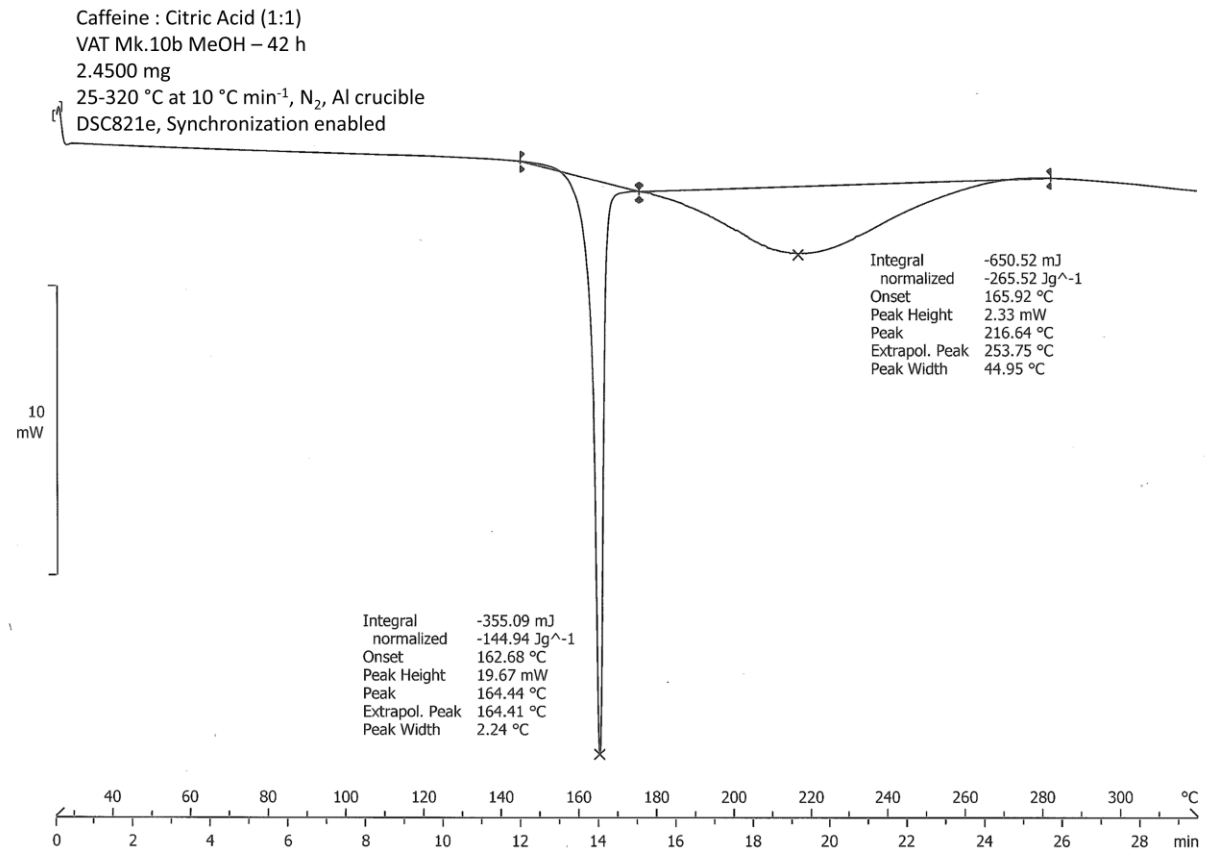


The starting materials of caffeine and citric acid were milled separately in batches in 15 mL stainless steel jars loaded with 2 × 7 mm stainless steel balls for 15 min at 25 Hz. This pre-milled starting material was used in subsequent VAT experiments.

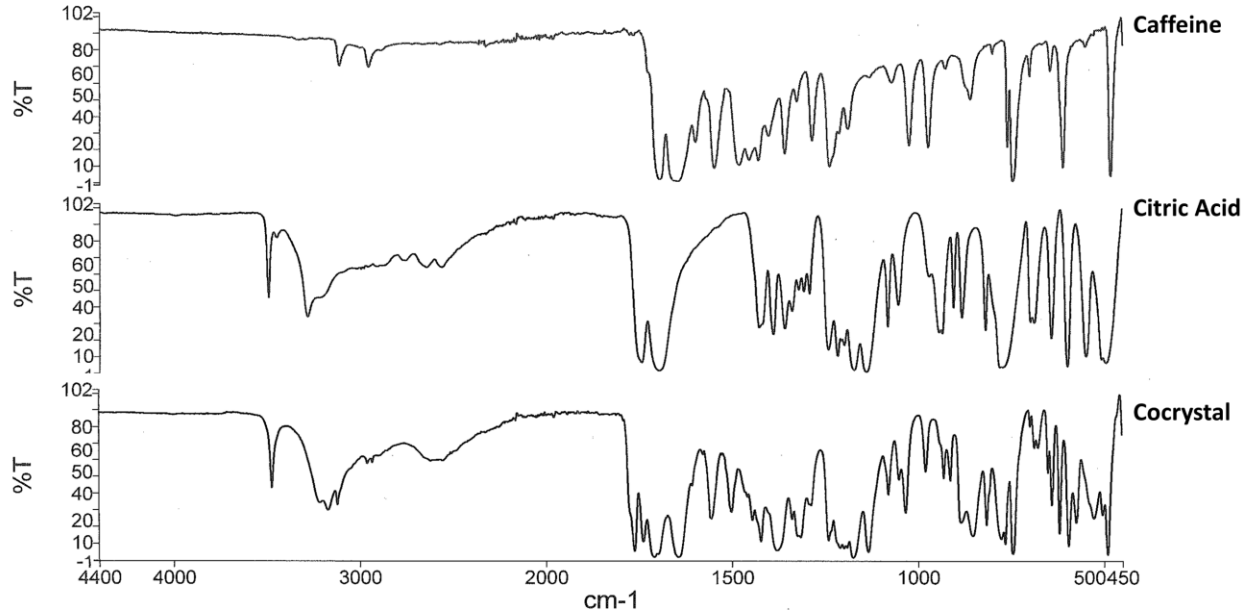
Caffeine (5.00 g, 25.75 mmol) and citric acid (4.95 g, 25.75 mmol) were added to the sample tumbler of VAT Mk.10b and tumbled at 9 rpm in a flow of dry N_2 for 1 h. A PXRD showed no conversion. The flow of

N_2 was bubbled through the MeOH reservoir at approximately ~45 mL min^{-1} and added to the sample tumbler. After 2 h of bubbling in N_2/MeOH, weak peaks of either the reported KIGKER (Form-I) and KIGKER01 (Form-II) polymorphs of the caffeine-citric acid (1:1) cocrystal were seen.[3,11] The intensity and resolution was too low to accurately decipher if one or the other polymorph had been made. After a total of 18 h, the PXRD showed the KIGKER01 (Form-II) cocrystal with miner peaks of the caffeine and citric acid. After a total of 42 h of tumbling in N_2/MeOH, the experiment was stopped, and the sample removed from the tumbler. Recovered mass: 9.45 g. A final PXRD showed a good conversion to the KIGKER01 (Form-II) cocrystal. A DSC showed a narrow endothermic melt at 162.68 °C and a very broad endotherm at 165.92 °C.

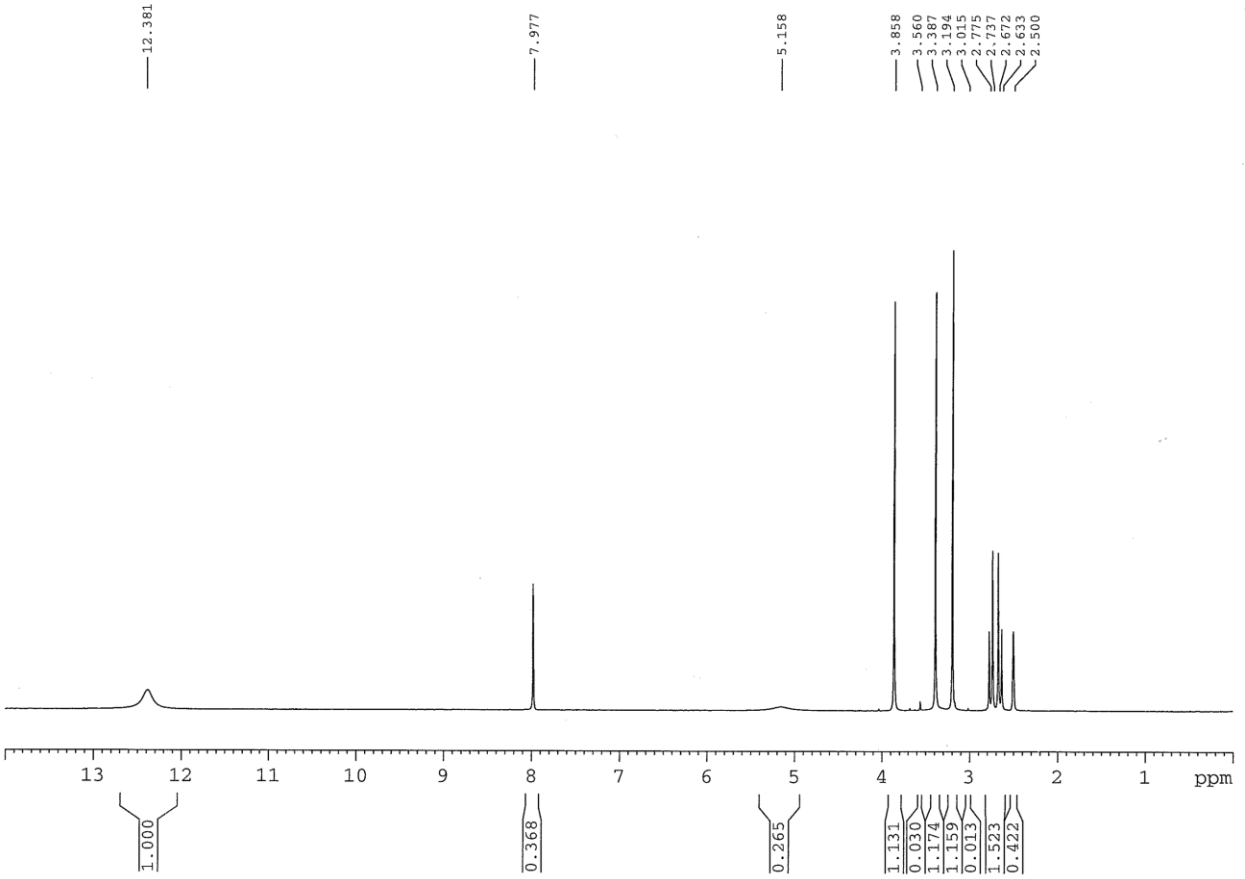




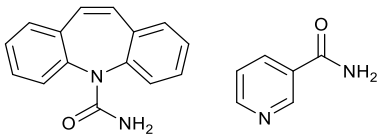
Caffeine : Citric Acid (1:1) - IR



Caffeine : Citric Acid (1:1)
VAT Mk.10b - MeOH
^{1}H NMR – DMSO-d_6



Carbamazepine : Nicotinamide (1:1)

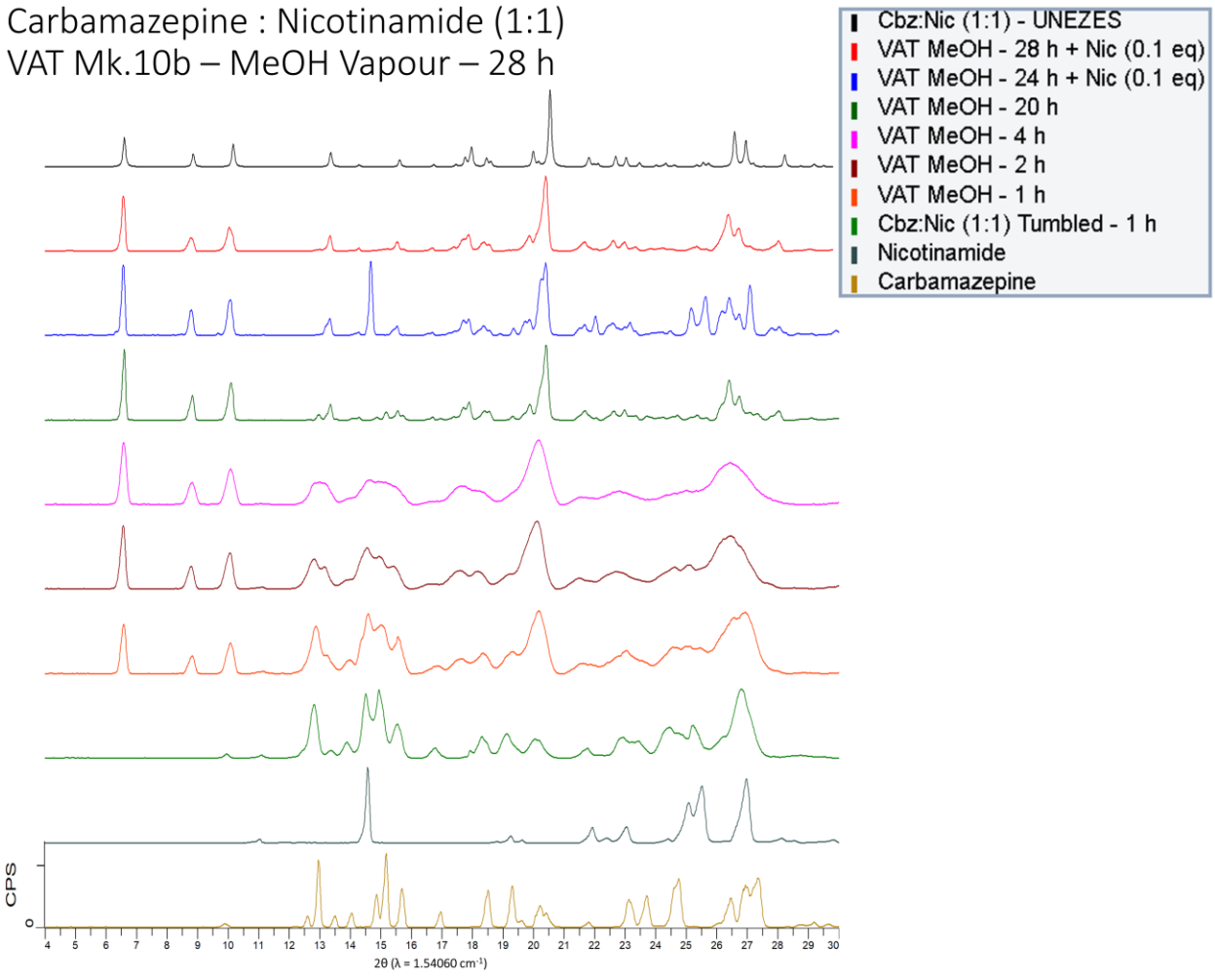


Carbamazepine
Cbz

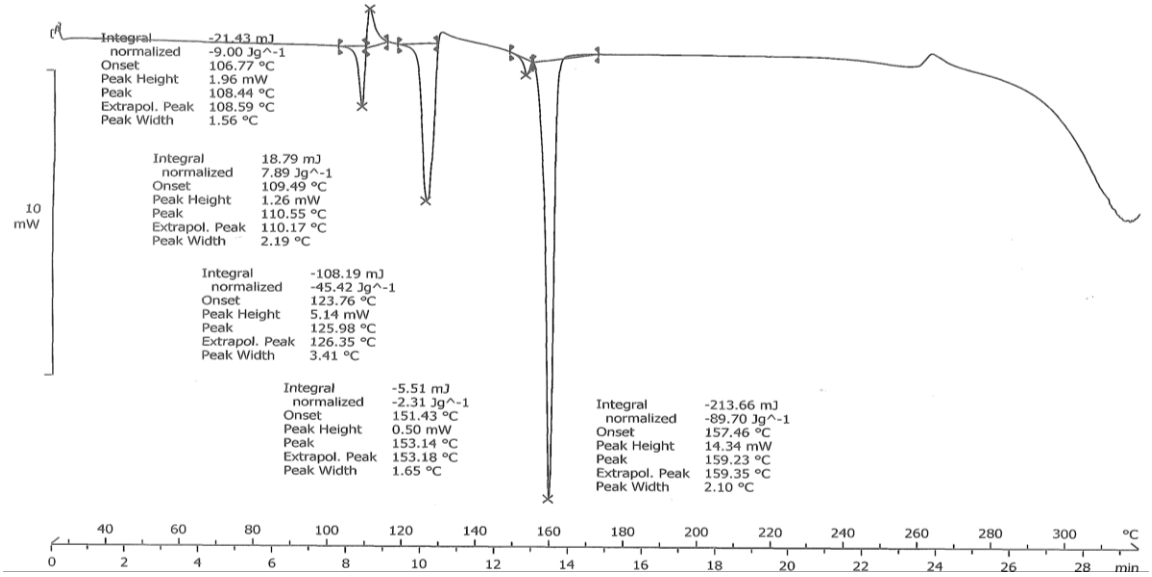
Nicotinamide
Nic

Carbamazepine (Cbz) and nicotinamide (Nic) were ball-milled separately in stainless steel milling jars with two stainless steel balls in each jar for 15 min at 25 Hz. The milled carbamazepine (5.00 g, 21.16 mmol, 1 eq) and nicotinamide (2.58 g, 21.16 mmol, 1 eq) were added to the sample tumbler of VAT Mk.10b and

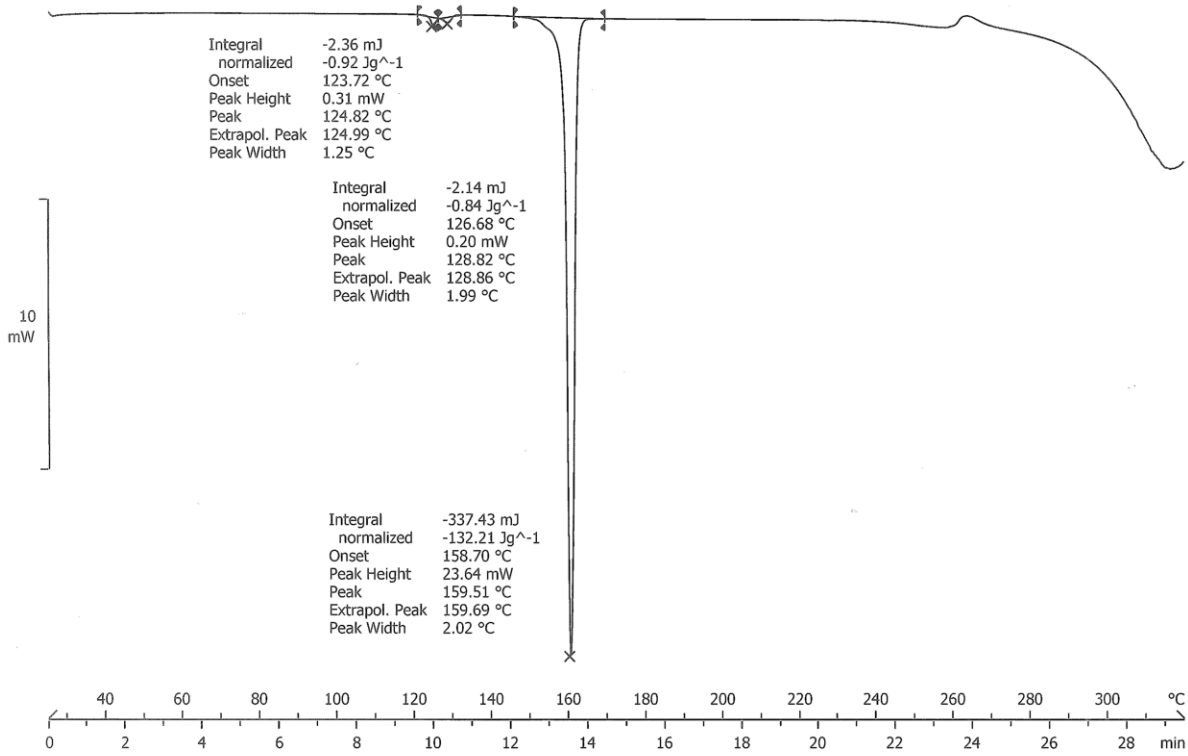
tumbled for 1 hr in atmospheric conditions. A PXRD was taken, that showed no new peaks other than carbamazepine (CBMZPN01)[12] and nicotinamide (NICOAM)[13]. Tumbling was started again with a flow of N_2 bubbled through MeOH at ~45 mL min^{-1} passing through the tumbler. After 1 hr, a PXRD showed strong new peaks corresponding to the reported Cbz:Nic (1:1) cocrystal (UNEZES)[4], along with peaks of both Cbz and Nic, however, the peaks were very broad.[4] After 20 hr of tumbling in N_2/MeOH, only slight peaks of Cbz could be seen in the majority of the Cbz:Nic, the peaks had also sharpened considerably. Nic (258 mg, 0.1 eq) was then added to the tumbler. After a further 4 hr of tumbling, no more Cbz peaks were observed in the PXRD. The powder was removed from the tumbler. Recovered mass: 7.28 g. A DSC of the final powder showed two small peaks at 123 °C and 127 °C which are close to the reported melting point of nicotinamide (129 °C). The major melting peak was found at 159 °C, consistent to the reported cocrystal.[4]



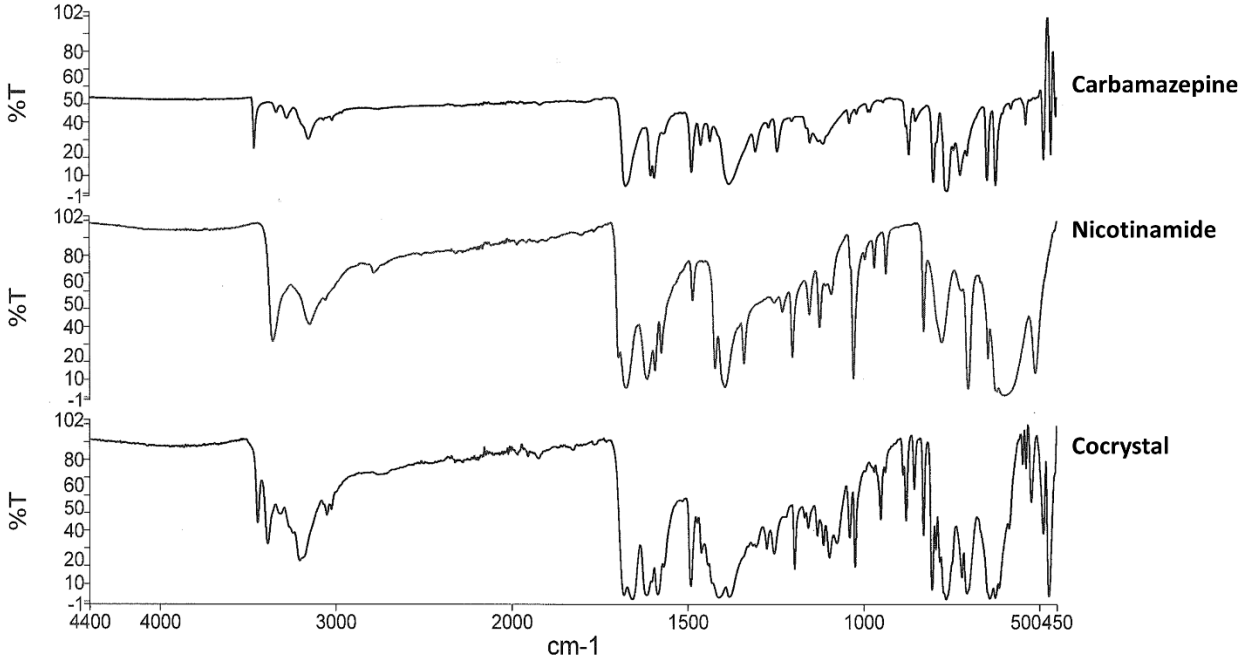
Carbamazepine : Nicotinamide (1:1)
Neat tumbling – 1 h
2.3819 mg
25-320 °C at 10 °C min^{-1}, N_2, Al crucible
DSC821e, Synchronization enabled



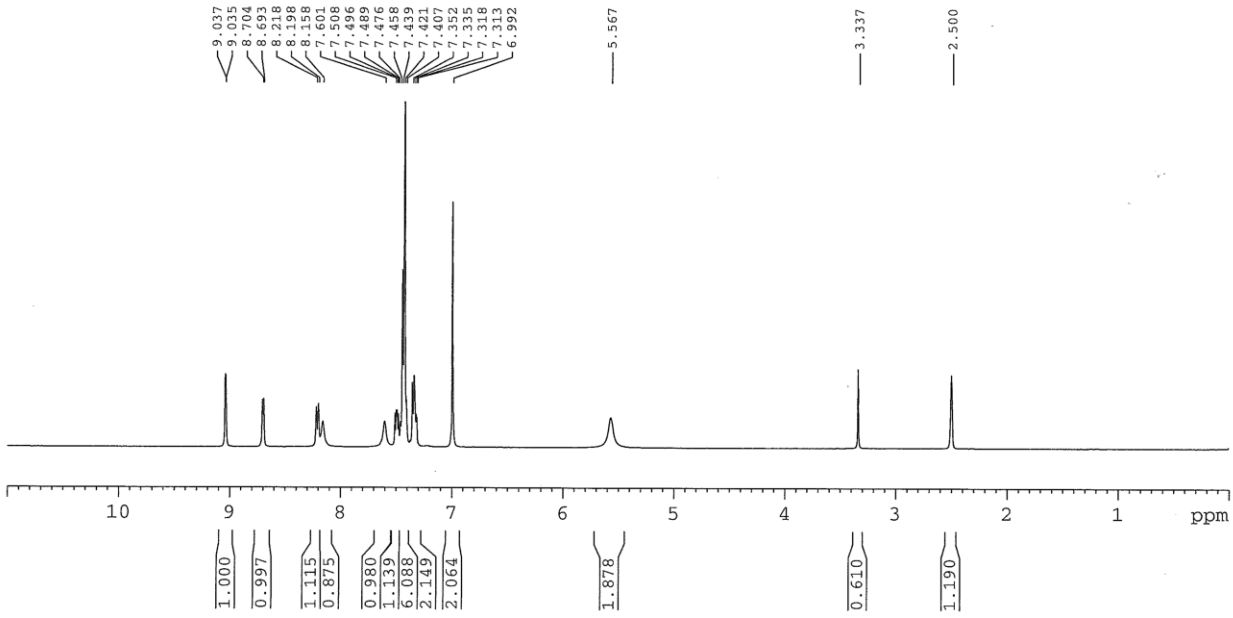
Carbamazepine : Nicotinamide (1:1)
VAT Mk.10b MeOH – 28 h
2.5522 mg
25-320 °C at 10 °C min^{-1}, N_2, Al crucible
DSC821e, Synchronization enabled



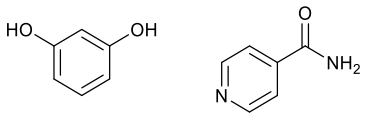
Carbamazepine : Nicotinamide (1:1) - IR



Carbamazepine : Nicotinamide (1:1)
VAT Mk.10b - MeOH
^{1}H NMR – DMSO-d_6



Isonicotinamide : Resorcinol (2:1)

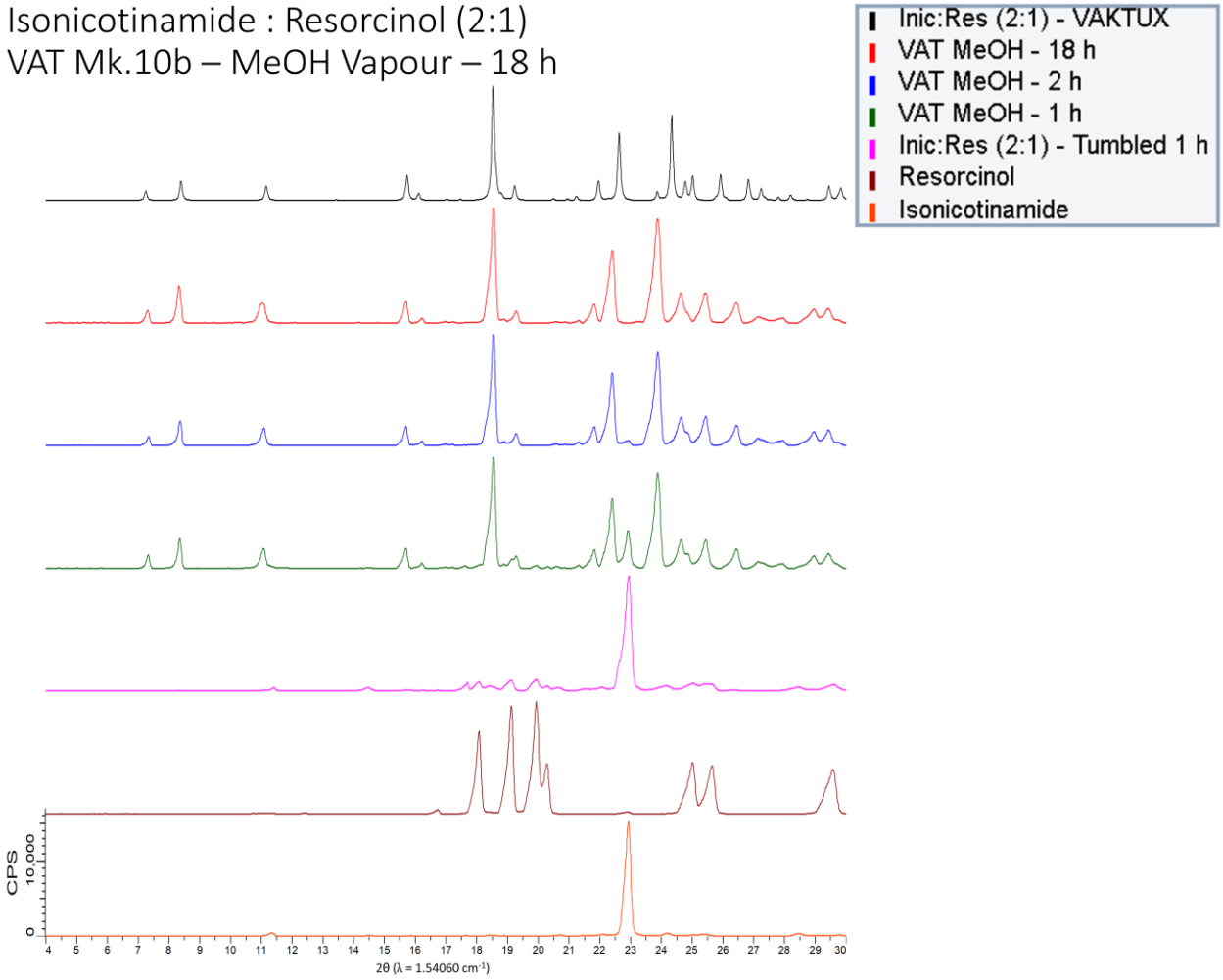


Resorcinol
Res

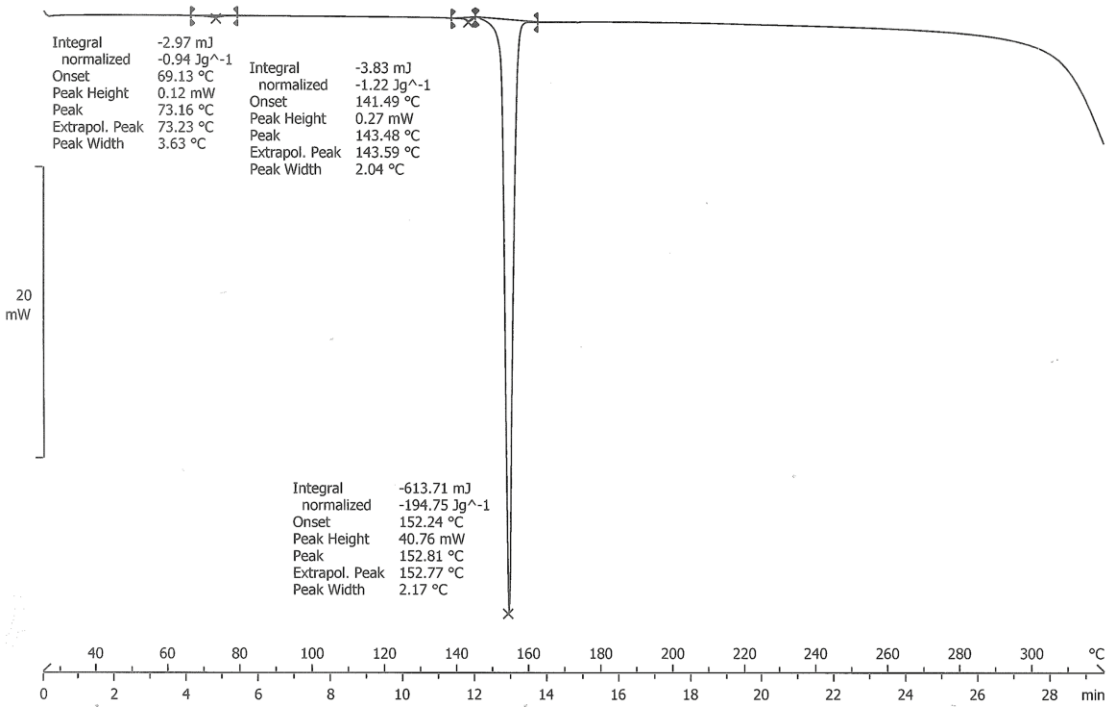
Isonicotinamide
Inic

Resorcinol (Res) and Isonicotinamide (Inic) were ball-milled separately in stainless steel milling jars with two stainless steel balls in each jar for 30 min at 25 Hz. The milled resorcinol (2.50 g, 22.71 mmol, 1 eq) and milled isonicotinamide (5.55 g, 45.41 mmol, 2 eq) were added to the sample tumbler of VAT Mk.10b. and tumbled without a flow of N_2 for 1 hr to mix. PXRD of the mixed powders taken showing no conversion to a cocrystal. Tumbling was started again with a flow of N_2 bubbled through MeOH at ~420 mL min^{-1} passing through the tumbler. After 1 hr of tumbling in vapour, a PXRD showed good conversion to the reported Res:Inic cocrystal (VAKTUX) with peaks from isonicotinamide and resorcinol (RESORA) remaining.[5] After further tumbling in N_2/MeOH overnight , a PXRD showed excellent conversion to the cocrystal without peaks from the coformers. The powder was removed from the tumbler, with 7.70 g of solid being recovered. A DSC of the final powder showed two very small peaks 69 °C and 141 °C. The largest melting point peak was found at 152 °C, a little lower than the reported MP of 155 °C.[5]

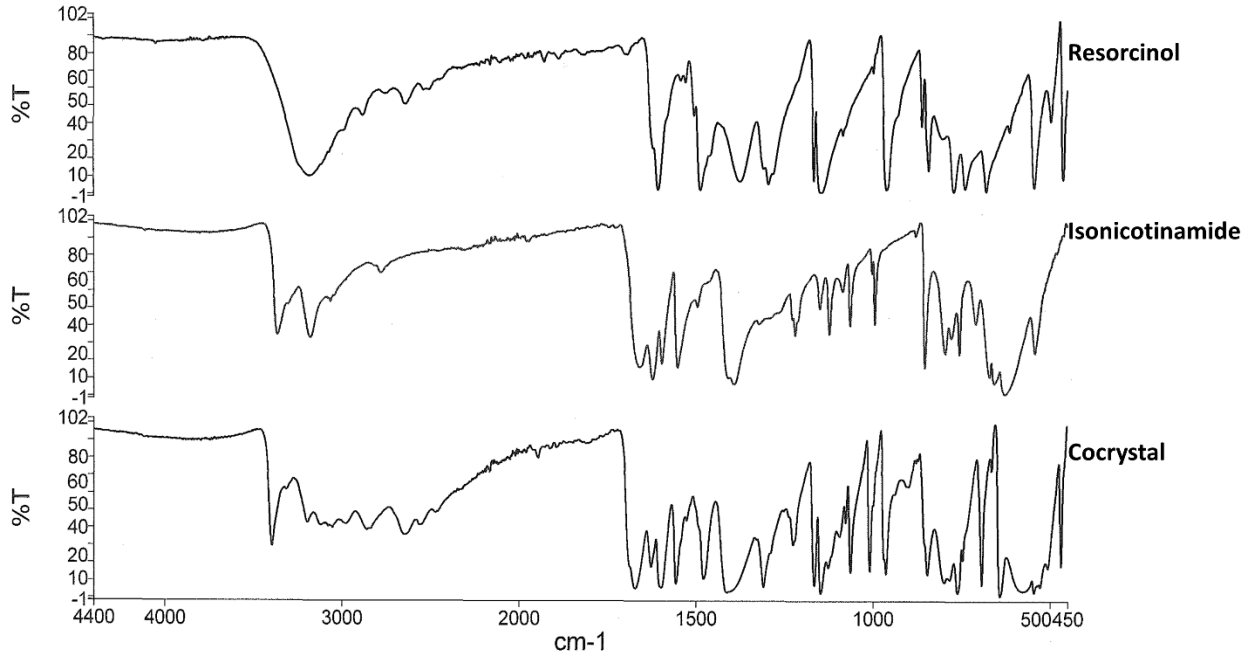
Isonicotinamide : Resorcinol (2:1)
VAT Mk.10b – MeOH Vapour – 18 h

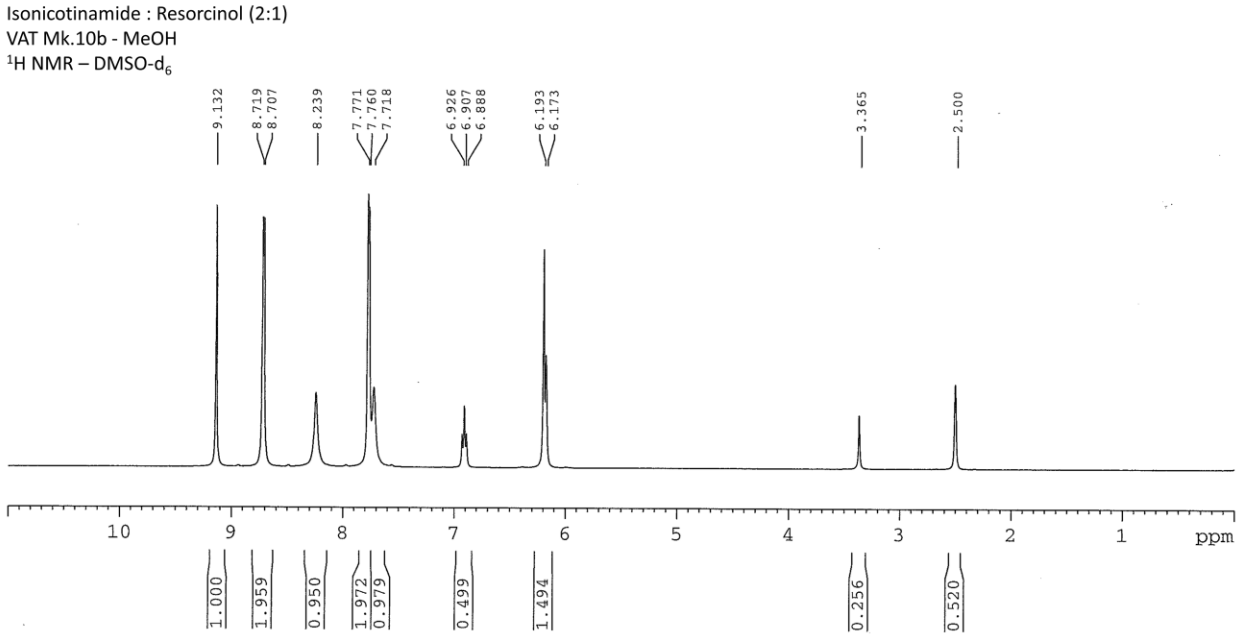


Isonicotinamide : Resorcinol (2:1)
VAT Mk.10a MeOH – 18 h
3.1512 mg
25-320 °C at 10 °C min^{-1}, N_2, Al crucible
DSC821e, Synchronization enabled

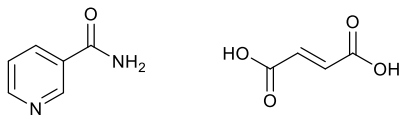


Isonicotinamide : Resorcinol (2:1) - IR





Nicotinamide : Fumaric Acid (1:1)

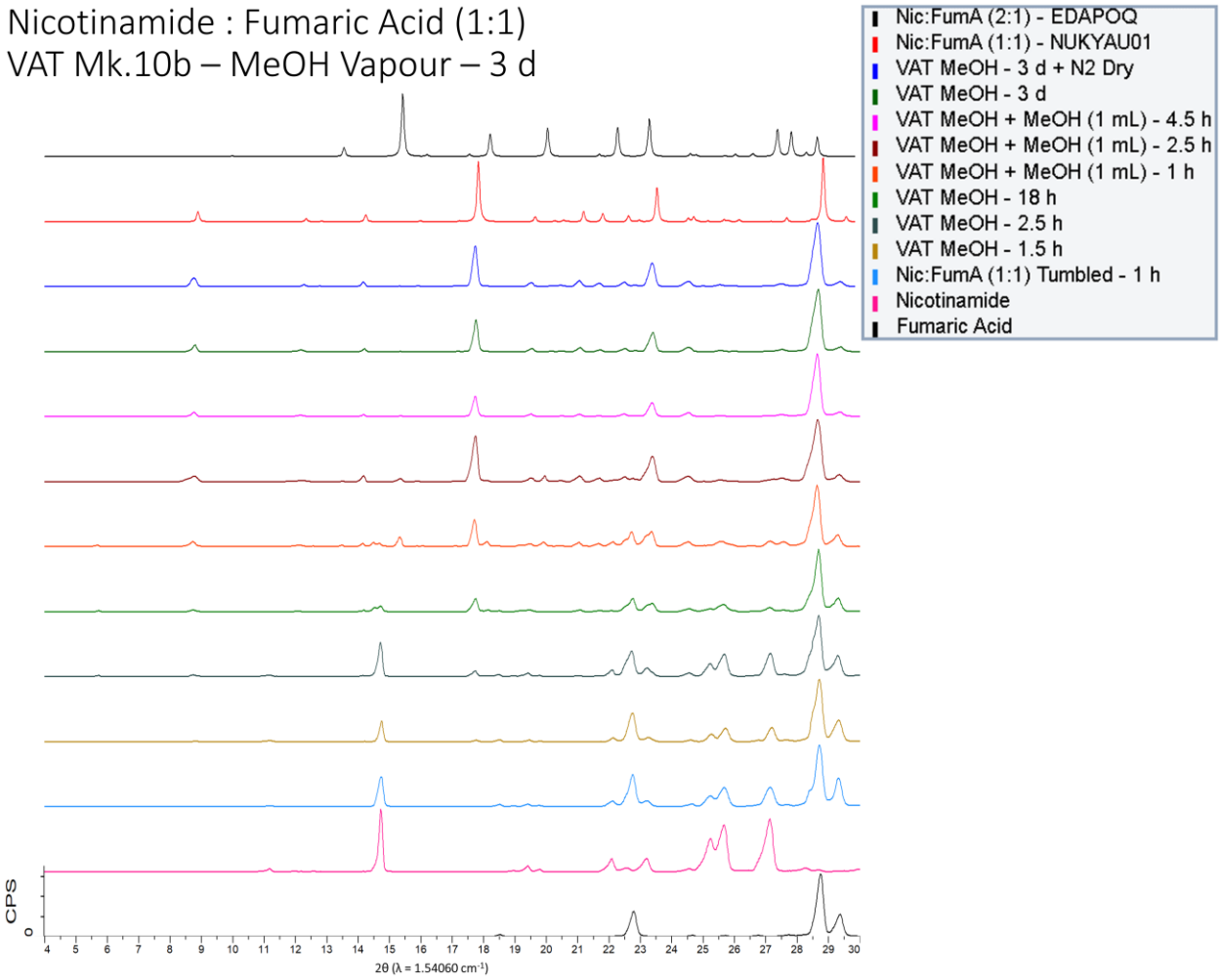


Nicotinamide
Nic

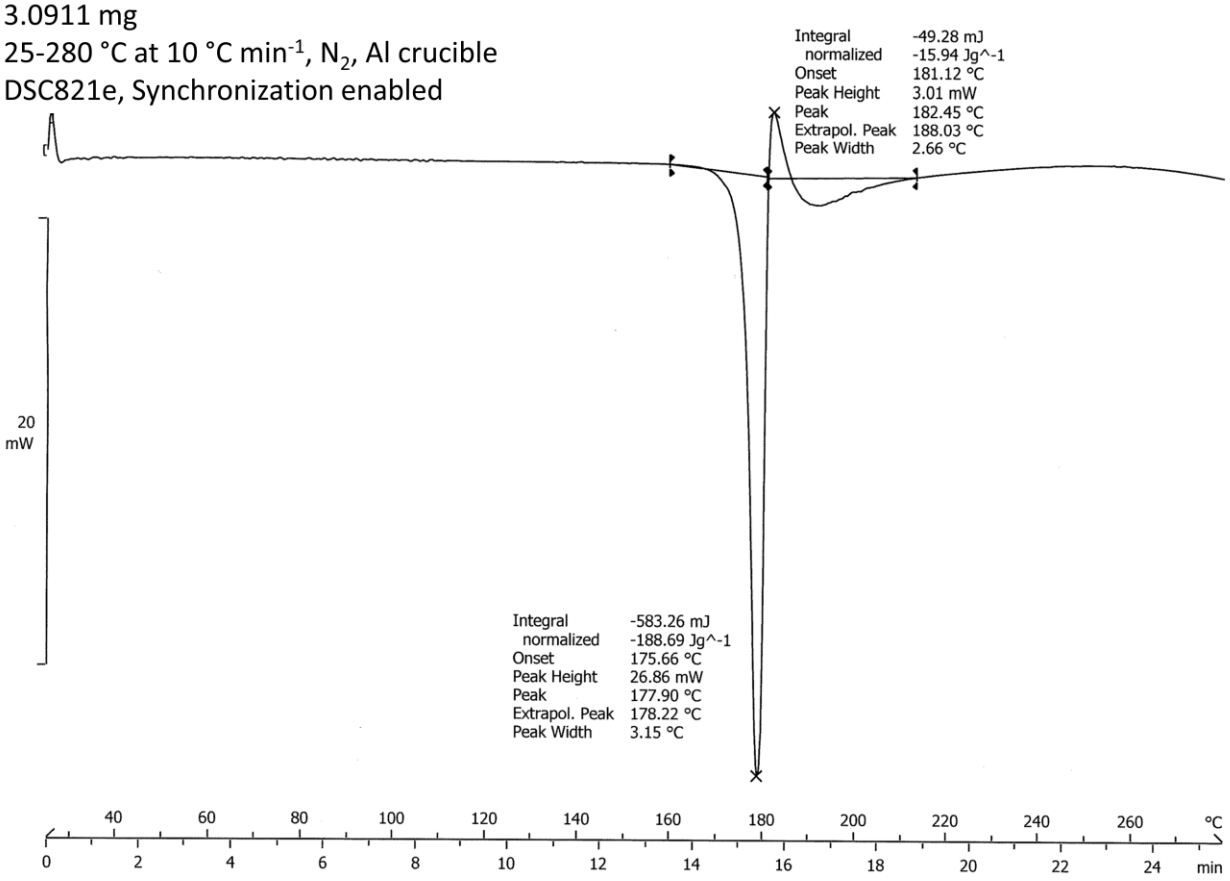
Fumaric Acid
FumA

Milled nicotinamide (5.00 g, 40.94 mmol) and fumaric aid (4.75 g, 40.94 mmol) were added to the sample tumbler of VAT Mk.10b. The powders were tumbled under a flow of dry N_2 (~77 mL min^{-1}) for 1 h. A PXRD did not show any conversion to either of the reported Nic:FumA (1:1) or Nic:FumA (2:1) cocrystals (CCDC: NUKYAU01 and EDAPOQ respectively.[6] The flow of N_2 was then bubbled through a reservoir containing MeOH (250 mL). The powders were tumbled in N_2/MeOH for 18 h with periodical PXRDs taken. After 18 h, MeOH (1 mL) was added directly to the sample tumbler and the powders tumbled in N_2/MeOH for 1 h. After 1 h this MeOH addition was repeated two more times after 2.5 h and 4.5 h. An aliquot (0.10 g) of the mixture was set aside. The powders were finally tumbled in N_2/MeOH for 2 more days before the solvent reservoir being bypassed and the powders tumbled in a dry N_2 flow. After 1 h, the powders were removed from the sample tumbler. Recovered mass: 9.29 g.

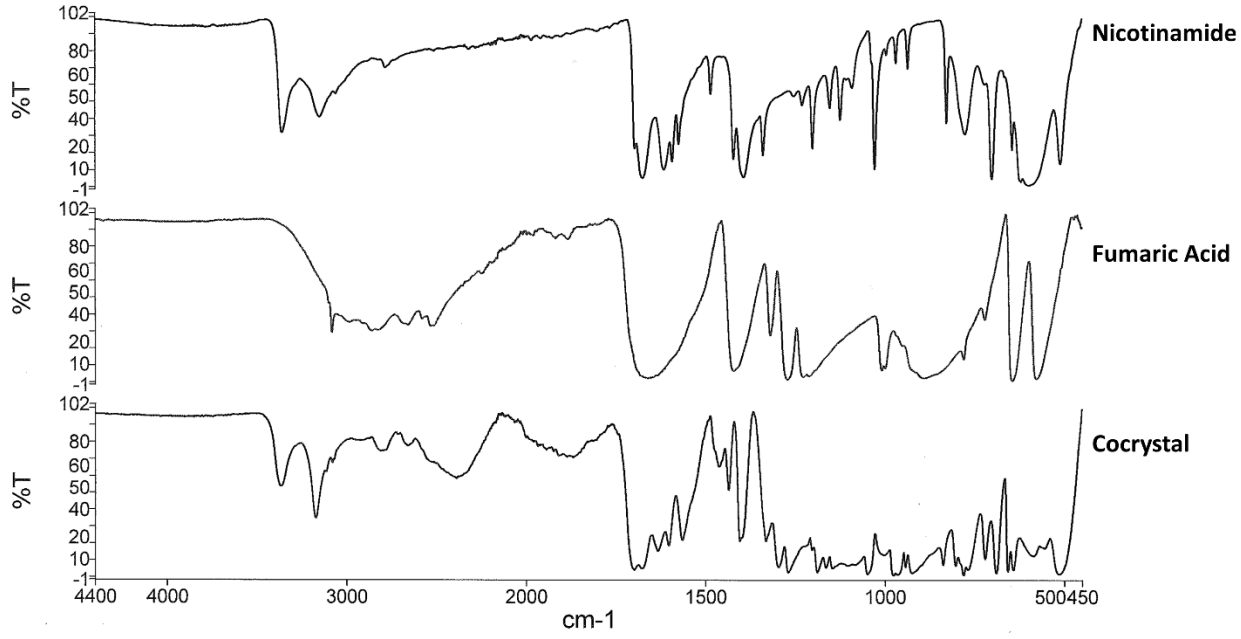
Nicotinamide : Fumaric Acid (1:1)
VAT Mk.10b – MeOH Vapour – 3 d



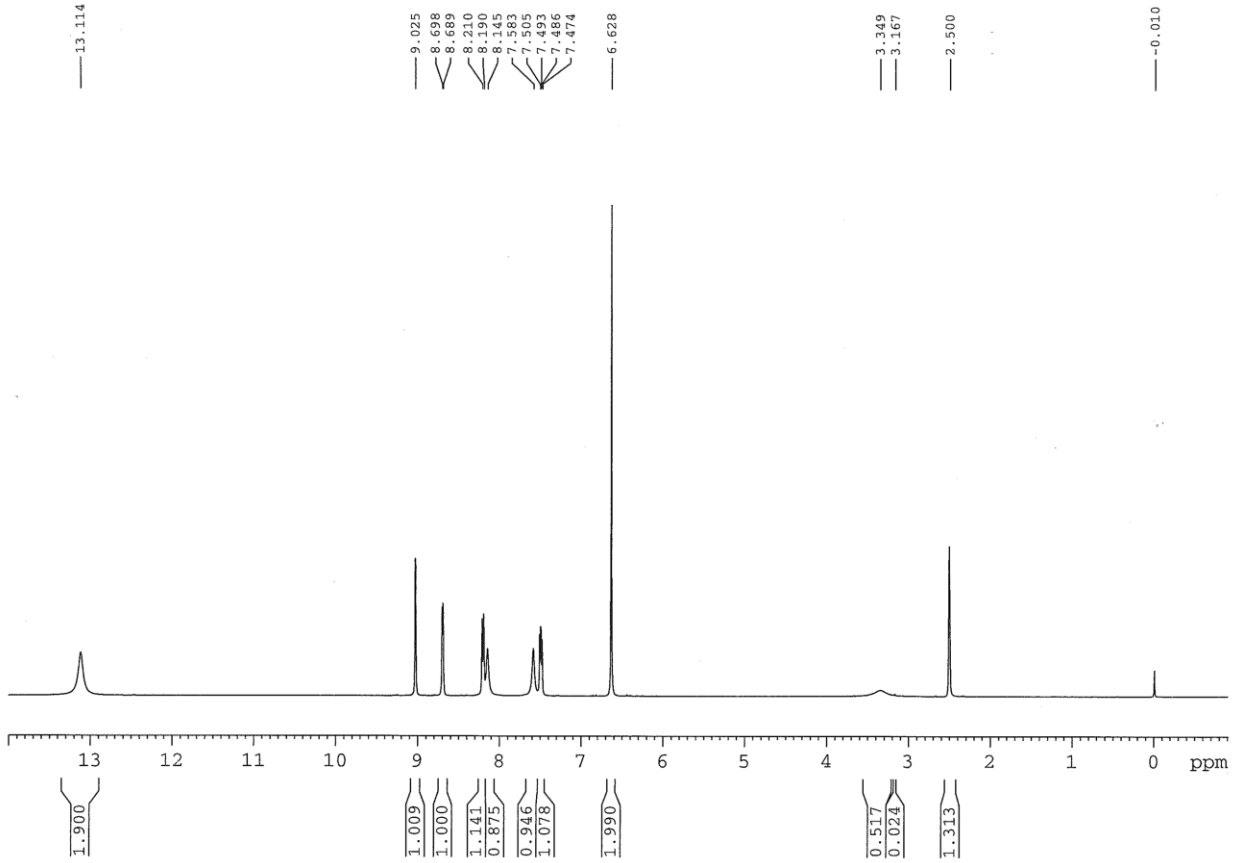
Nicotinamide : Fumaric Acid (1:1)
VAT Mk.10b MeOH
3.0911 mg
25-280 °C at 10 °C min^{-1}, N_2, Al crucible
DSC821e, Synchronization enabled



Nicotinamide : Fumaric Acid (1:1) - IR

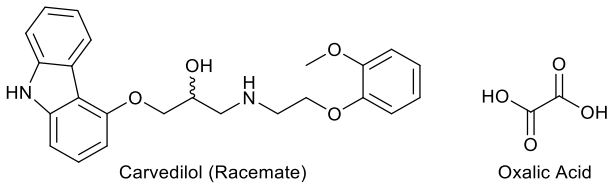


Nicotinamide : Fumaric Acid (1:1)
VAT Mk.10b - MeOH
^{1}H NMR – DMSO-d_6



Salts

Carvedilol : Oxalic Acid (2:1)



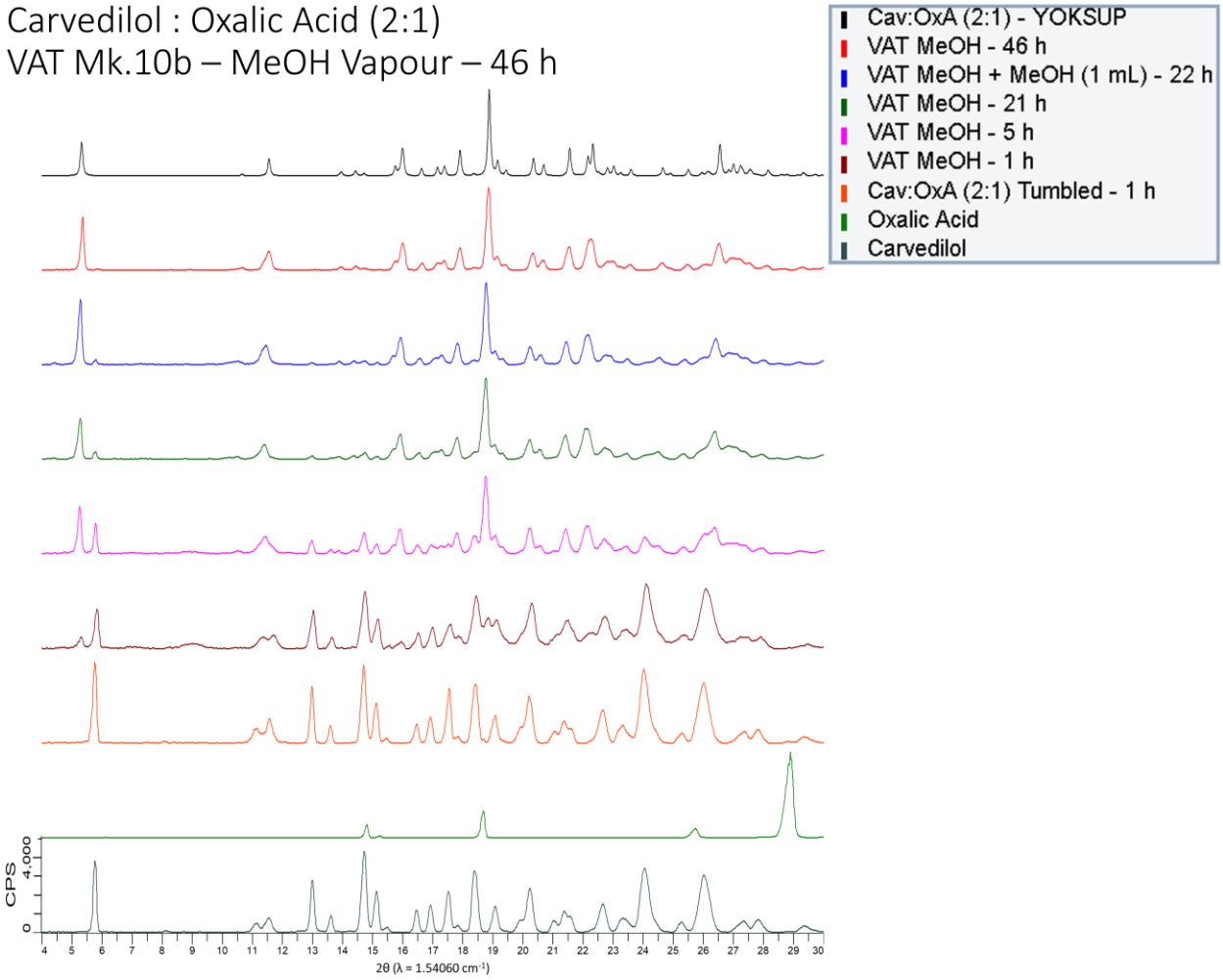
Carvedilol (Racemate)
Cav

Oxalic Acid
OxA

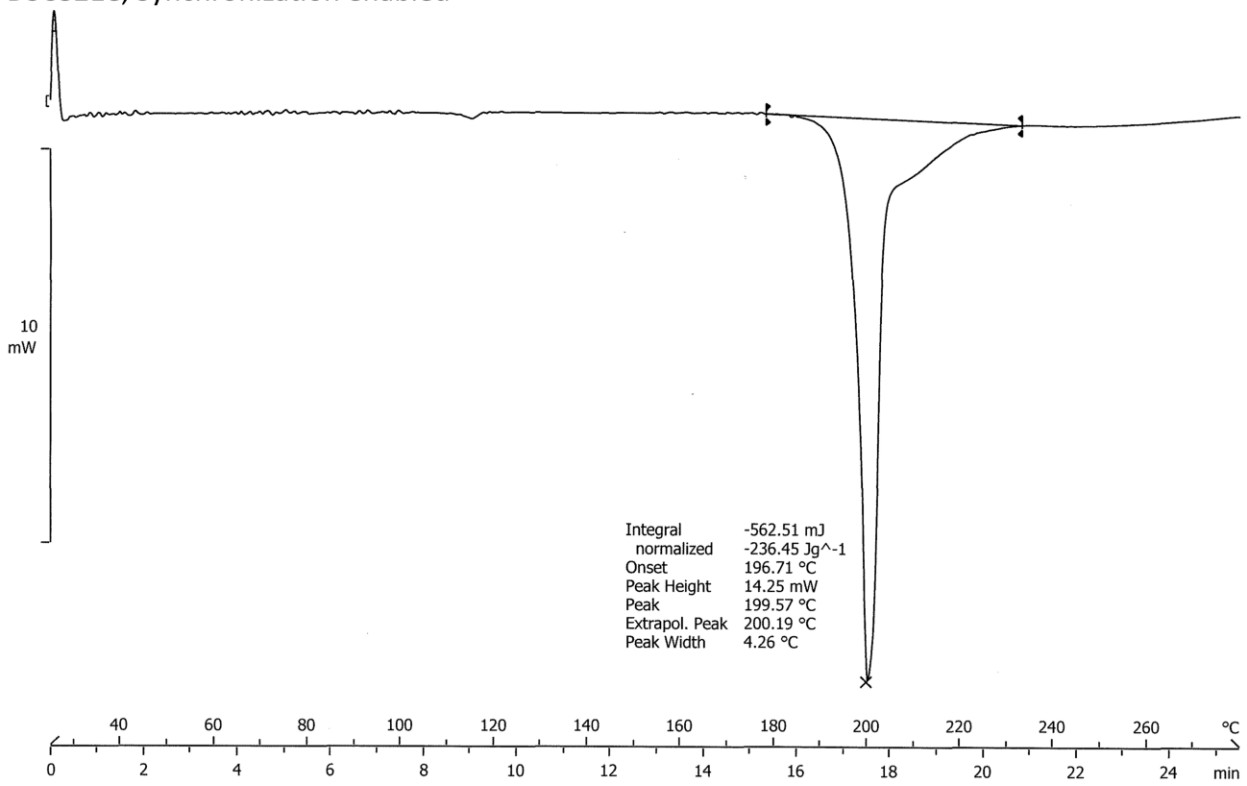
Carvedilol freebase (CCDC: GIVJUQ01) and oxalic acid dihydrate were milled separately in stainless steel grinding jars loaded with two stainless steel balls for 30 min at 25 Hz. The milled Cav (4.30 g, 10.58 mmol, 2 eq) and OxA (0.48 g, 5.29 mmol, 1 eq) were added to the sample tumbler of VAT Mk.10b and tumbled

in a flow of dry N_2 (~420 mL min^{-1}) for 1 hr. A PXRD showed no conversion to the reported salt (CCDC: YOKSUP).[7] A flow of N_2 (~420 mL min^{-1}) bubbled through the reservoir of MeOH (250 mL) was then passed through the sample tumbler. After 1 h the solids had become clumpy and slightly sticky. A PXRD showed new peaks of the Cav:OxA salt. In addition to this, unidentified peaks, notably at 2θ = 7.009 and 8.937 were seen. These new peaks were not seen to be associated with any reported forms on the CCDC. The flow of N_2/MeOH was lowered to ~77 mL min^{-1}. After a total of 5 h tumbling in N_2/MeOH a PXRD showed a drop in intensity for the freebase peak at 2θ = 5.782, and a large increase of the salt peak at 2θ = 5.256. The unknown peaks had decreased into the baseline. The solids were left to further tumble for a total of 21 h. MeOH (1 mL) was added directly to the powders via a syringe and tumbling in N_2/MeOH resumed. After a further 1 h, the solids were clumpy, but no longer sticky. The solids were left to tumbler overnight for a total of 46 h in N_2/MeOH. The final powders were free flowing without any clumps. A PXRD did not show either of the unknown peaks and a very slight freebase peak at 2θ = 5.856 with the rest of the peaks in good agreement with the YOKSUP salt. Recovered mass: 4.47 g. Remaining volume of MeOH: 230 mL.

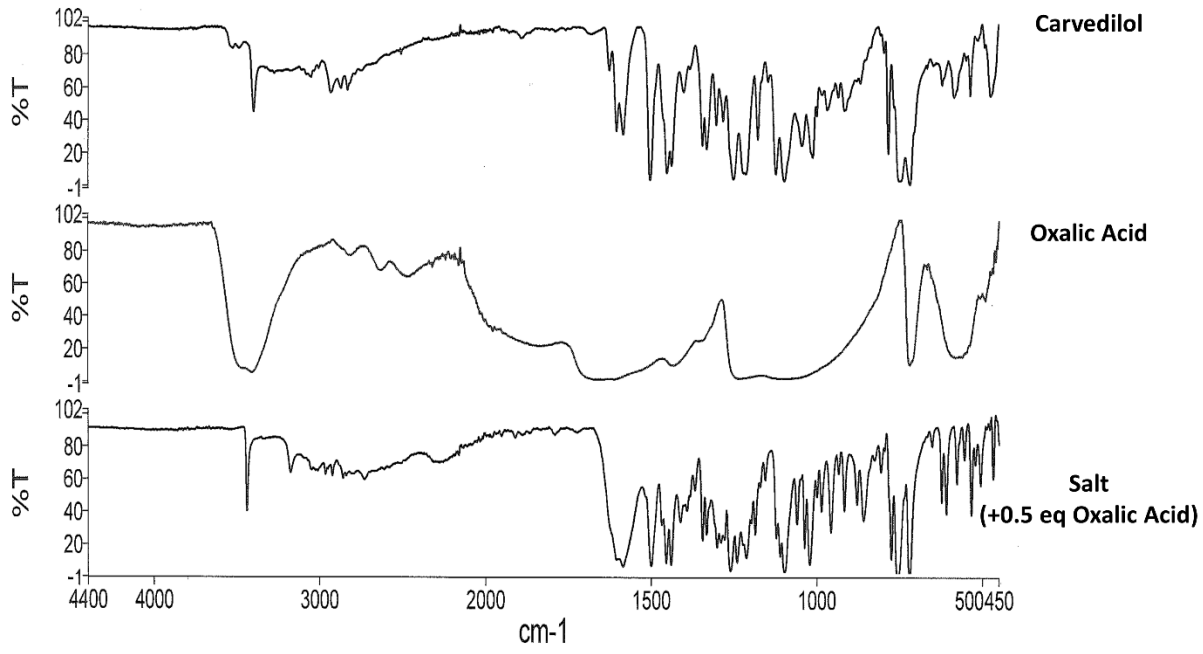
Carvedilol : Oxalic Acid (2:1)
VAT Mk.10b – MeOH Vapour – 46 h



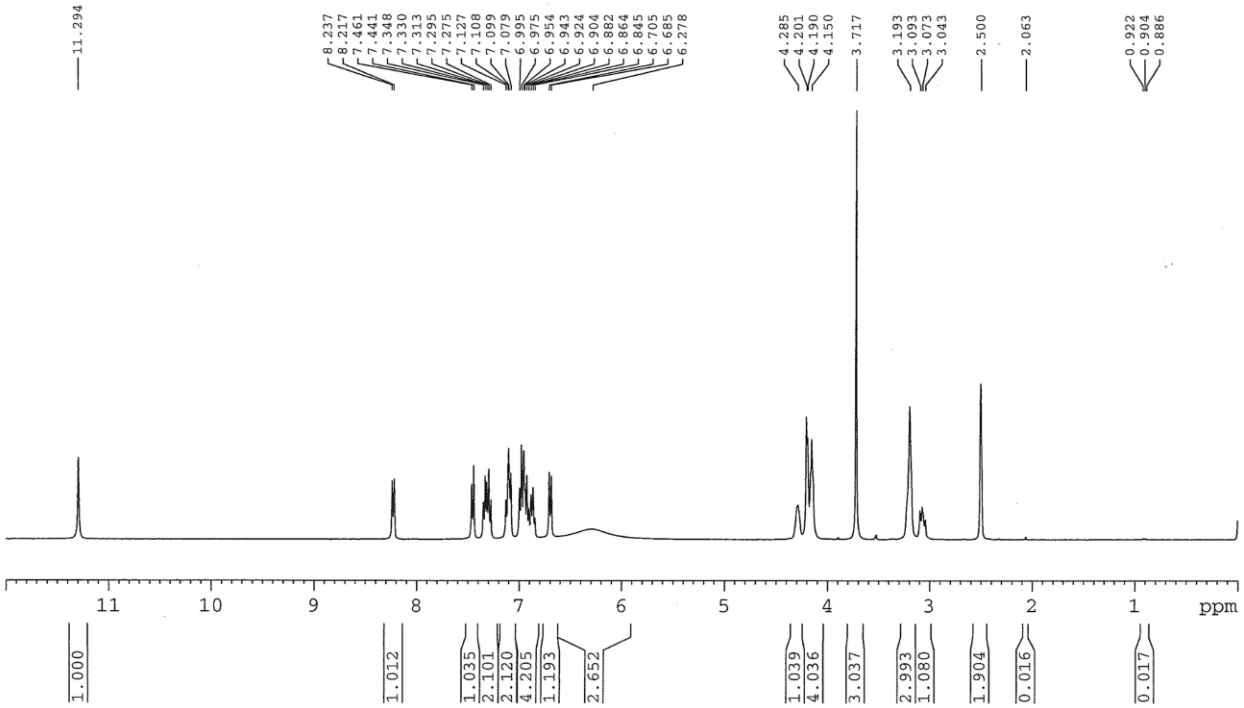
Carvedilol Oxalate
VAT Mk.10b VAT MeOH
2.3790 mg
25-280 °C at 10 °C min^{-1}, N_2, Al crucible
DSC821e, Synchronization enabled



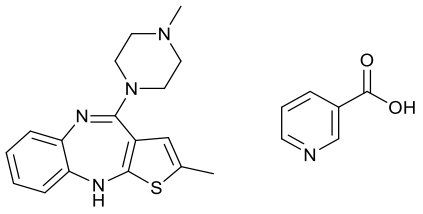
Carvedilol Oxalate (2:1) - IR



Carvedilol Oxalate
VAT Mk.10b - MeOH
^{1}H NMR – DMSO-d_6



Olanzapine Nicotinate (1:1) – VAT Mk.1

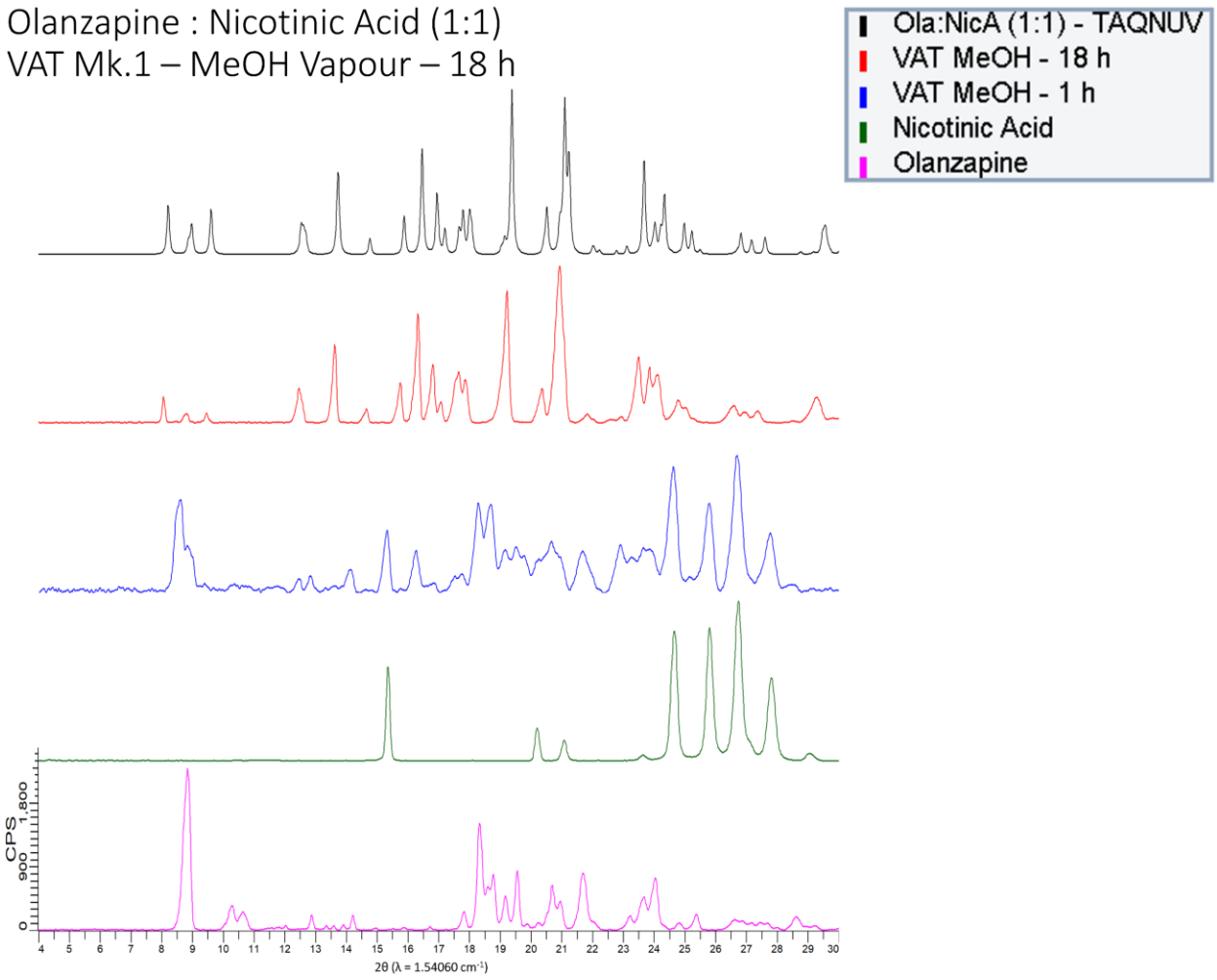


Olanzapine
Ola

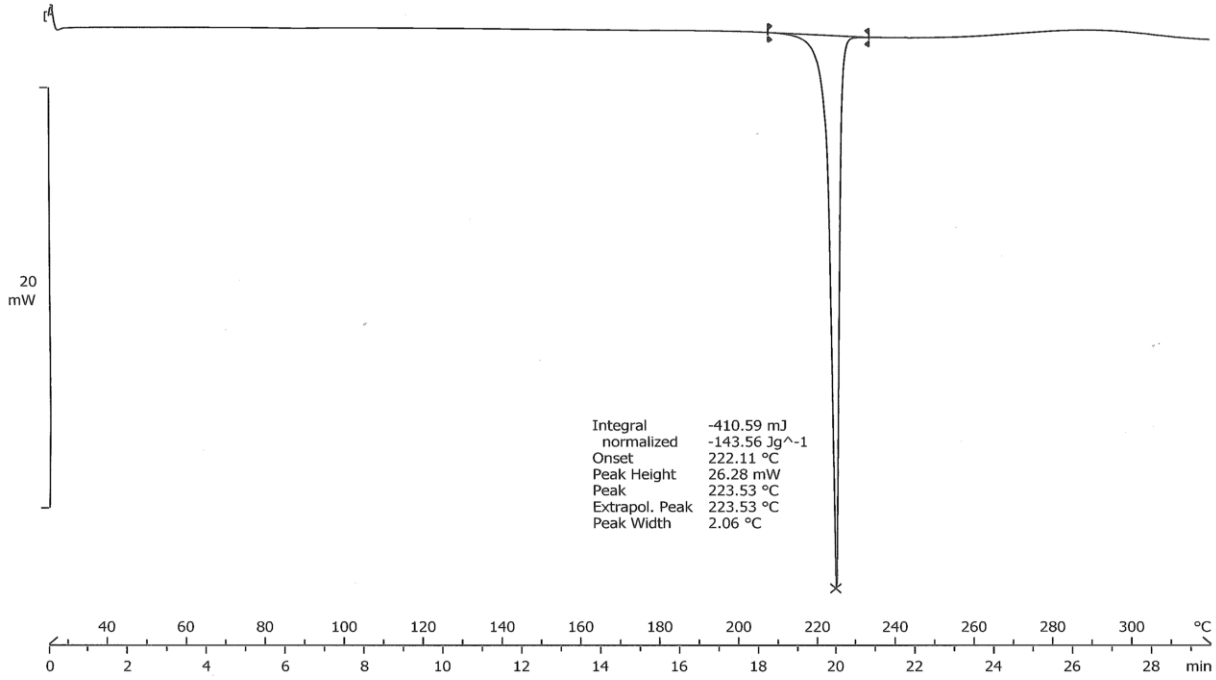
Nicotinic Acid
NicA

Olanzapine free base (1.00 g, 3.20 mmol, 1 eq) and nicotinic acid (0.34 g, 3.20 mmol, 1 eq) were added to a 100 mL RB flask along with a 1.5 cm stir bar. A rotovap trap was filled with MeOH and attached to a rotary evaporator (VAT Mk.1). The RB flask was then attached to the trap and the system placed under vacuum. The vacuum pump was stopped and the system allowed to equilibrate providing a MeOH vapour rich environment. The sample was then rotated for 1 hr. A PXRD after 1 hr showed no conversion to the salt. The MeOH environment was applied again, and the sample left to tumble overnight. Recovered mass:

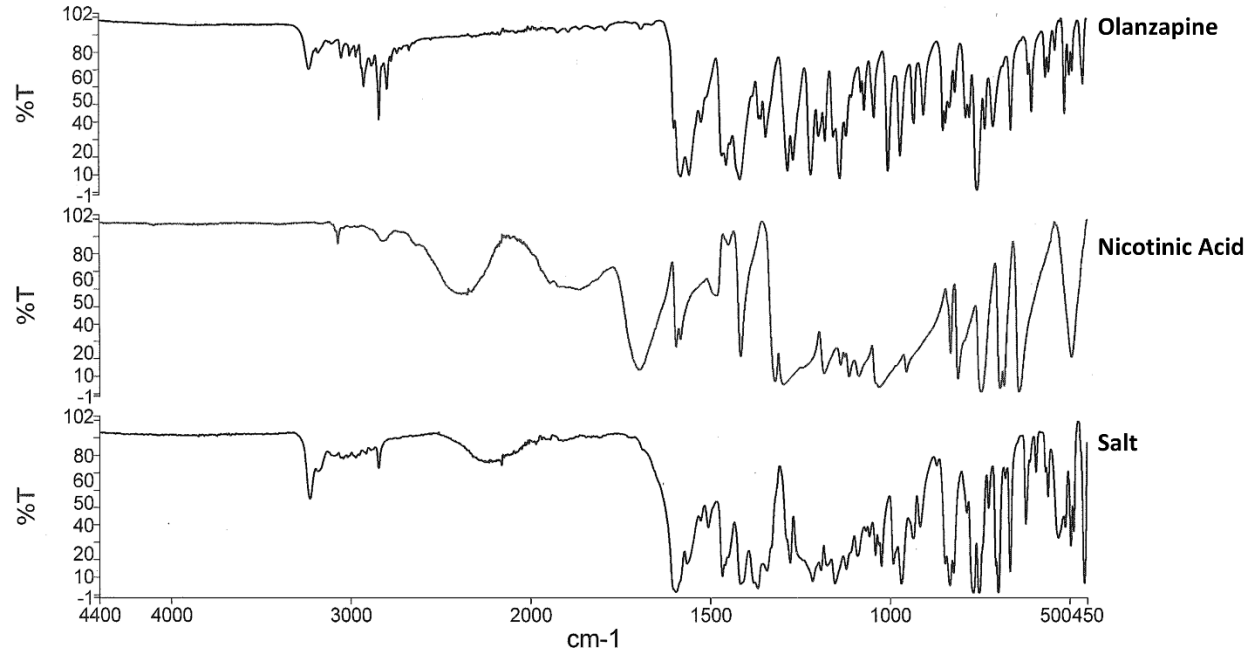
1.27 g. A PXRD showed excellent conversion to the reported olanzapine nicotinate (TAQNUV) without peaks of either olanzapine or nicotinic acid being seen.[8] A DSC showed a single melting even at 224 °C.

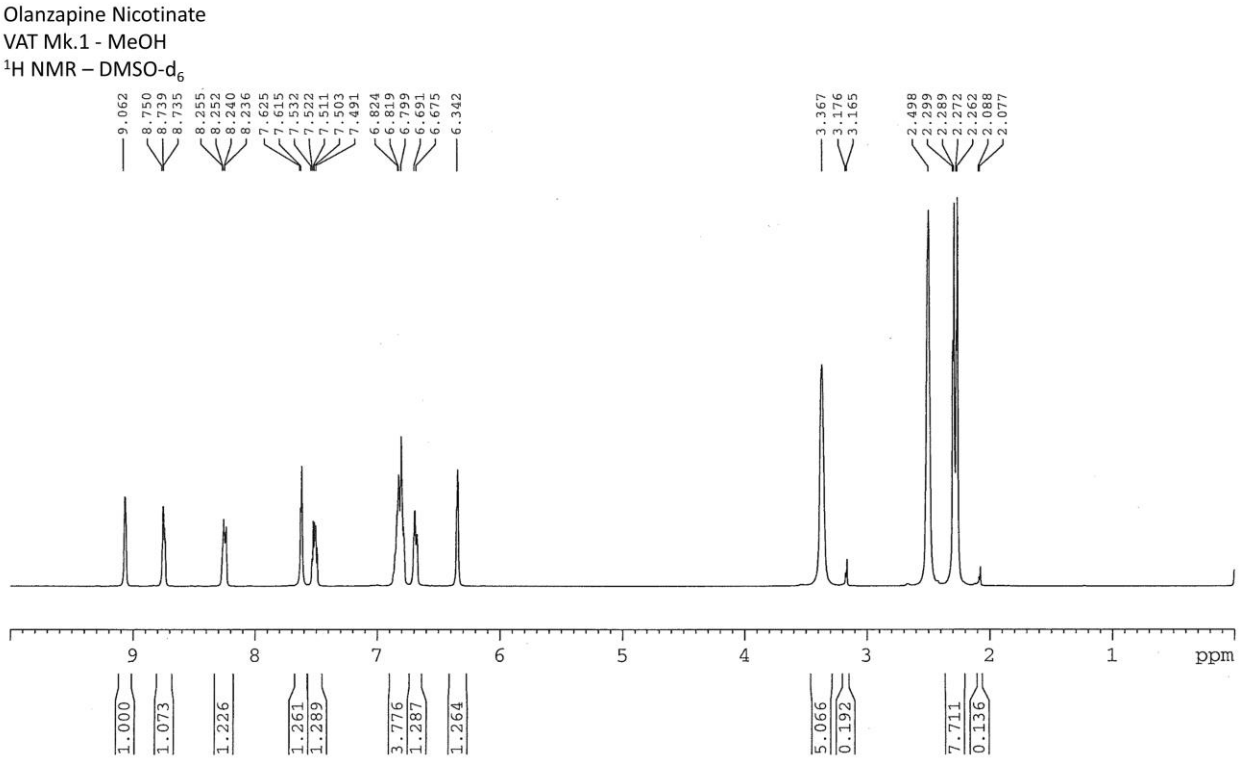


Olanzapine Nicotinate
VAT Mk.1 MeOH – 18 h
2.8600 mg
25-320 °C at 10 °C min^{-1}, N_2, Al crucible
DSC821e, Synchronization enabled

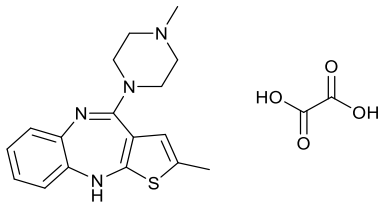


Olanzapine Nicotinate (1:1) - IR





Olanzapine Oxalate (1:1)

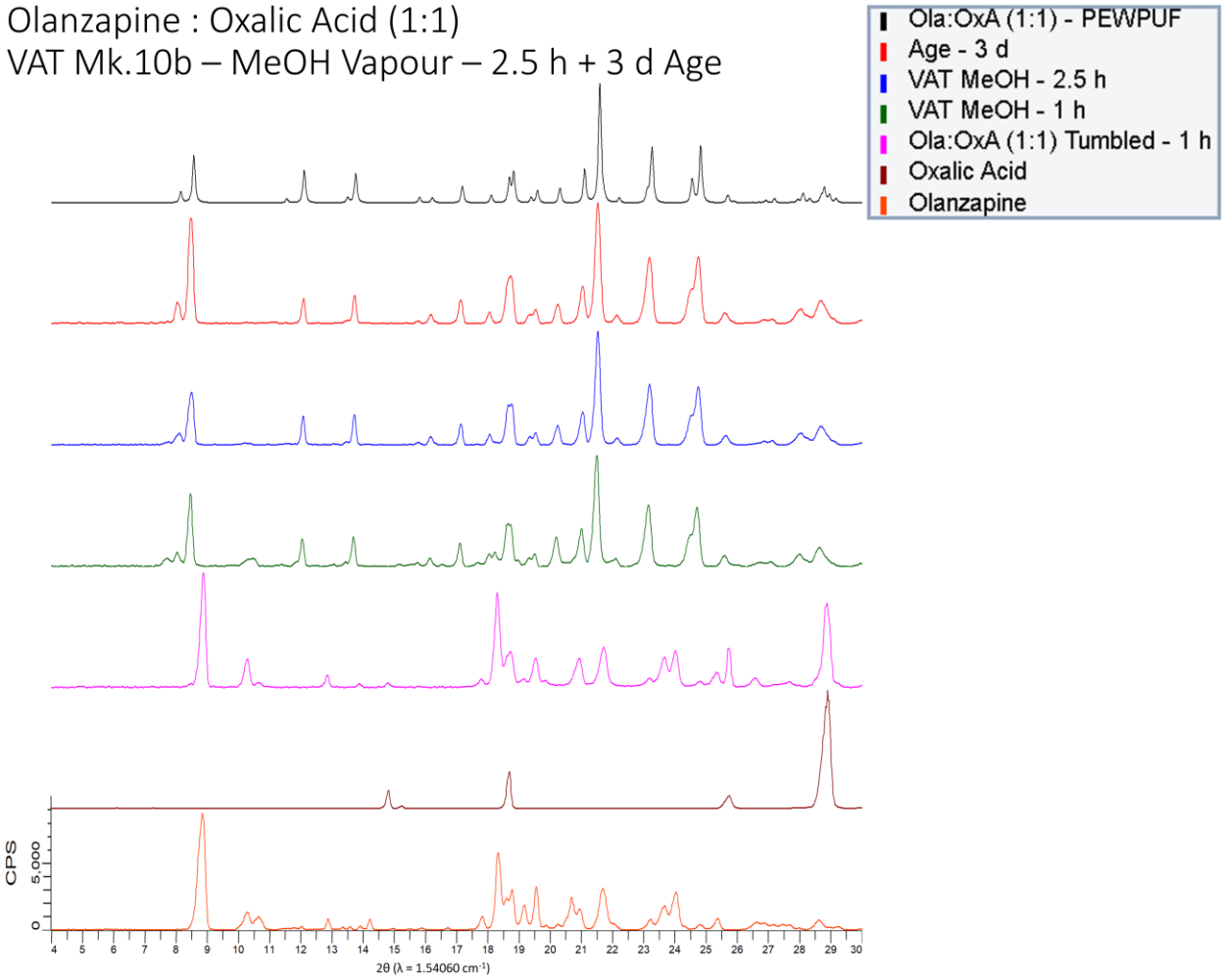


Olanzapine
Ola

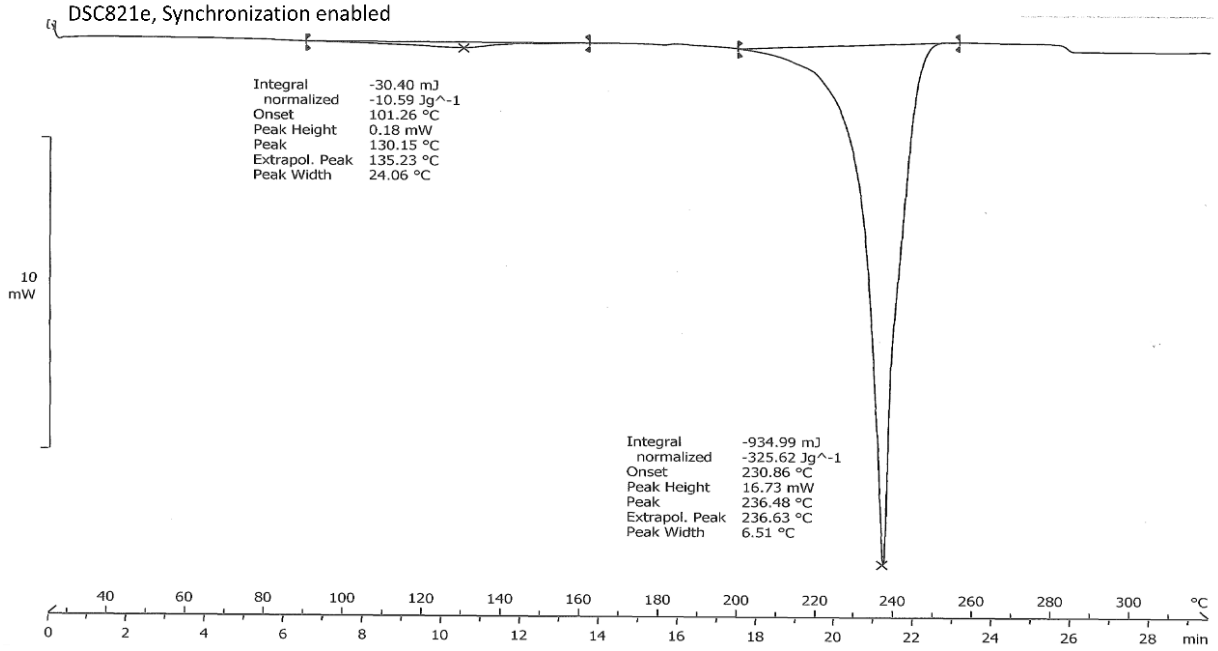
Oxalic Acid
OxA

Oxalic acid was added to a stainless steel milling jar along with two stainless-steel balls and milled in a ball mill for 15 min at 25 Hz. Olanzapine freebase (5.00 g, 16.00 mmol, 1 eq) and milled oxalic acid (1.44 g, 16.00 mmol, 1 eq) were added to the sample tumbler of the VAT Mk.10b and tumbled in ambient conditions. After 1 hr, a PXRD showed no conversion to the reported salt (CCDC: PEWPUF).[9] A flow of N_2 bubbled through MeOH (~420 mL min^{-1}) was introduced to the tumbler. After 1 hr on tumbling in N_2/MeOH a PXRD showed a rapid disappearance of the starting material peaks, and the growth of the reported salt. In addition, some additional peaks from an unidentified form were observed. Visually the sample went from a light yellow to a bright orange colour. The sample was tumbled in N_2/MeOH 2.5 hrs

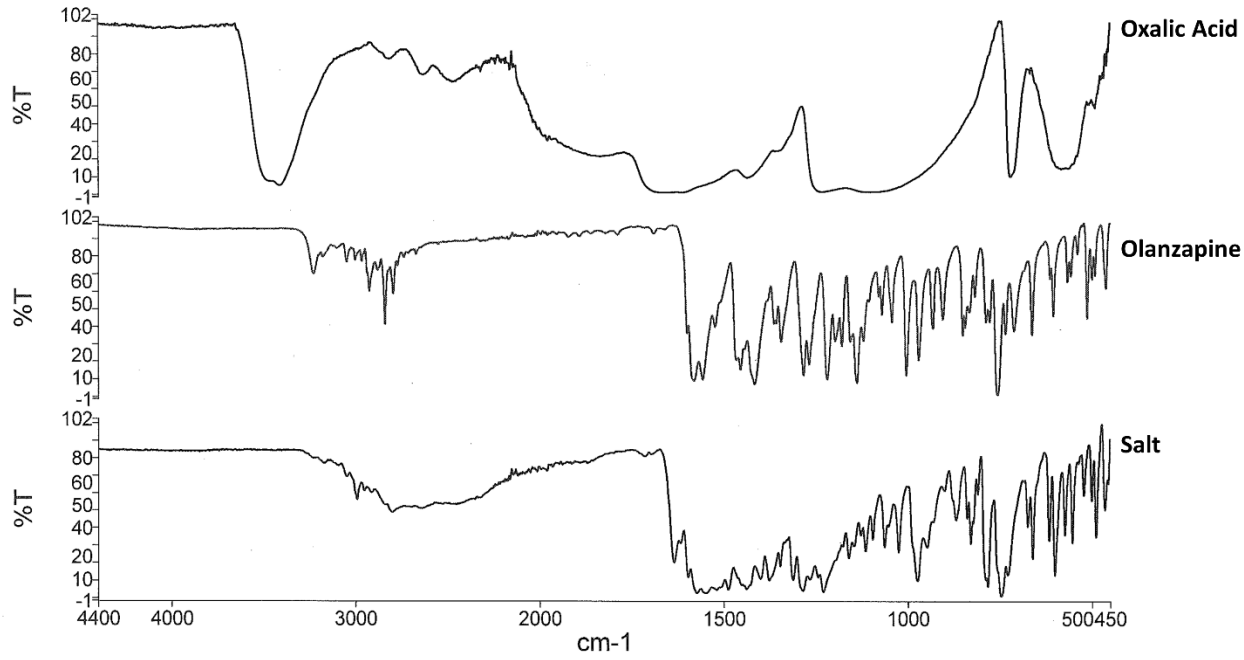
more before leaving to statically age in the tumbler for 3 days. After 3 days the PXRD matched the PEWPUF salt, with the peaks of the unknown form barely visible. The solids were removed from the tumbler with a recovered mass: 6.33 g. A DSC showed a broad major endotherm with an onset of 231 °C and a peak of 236 °C. The reported onset for PEWPUF being 252.43 °C.[9]



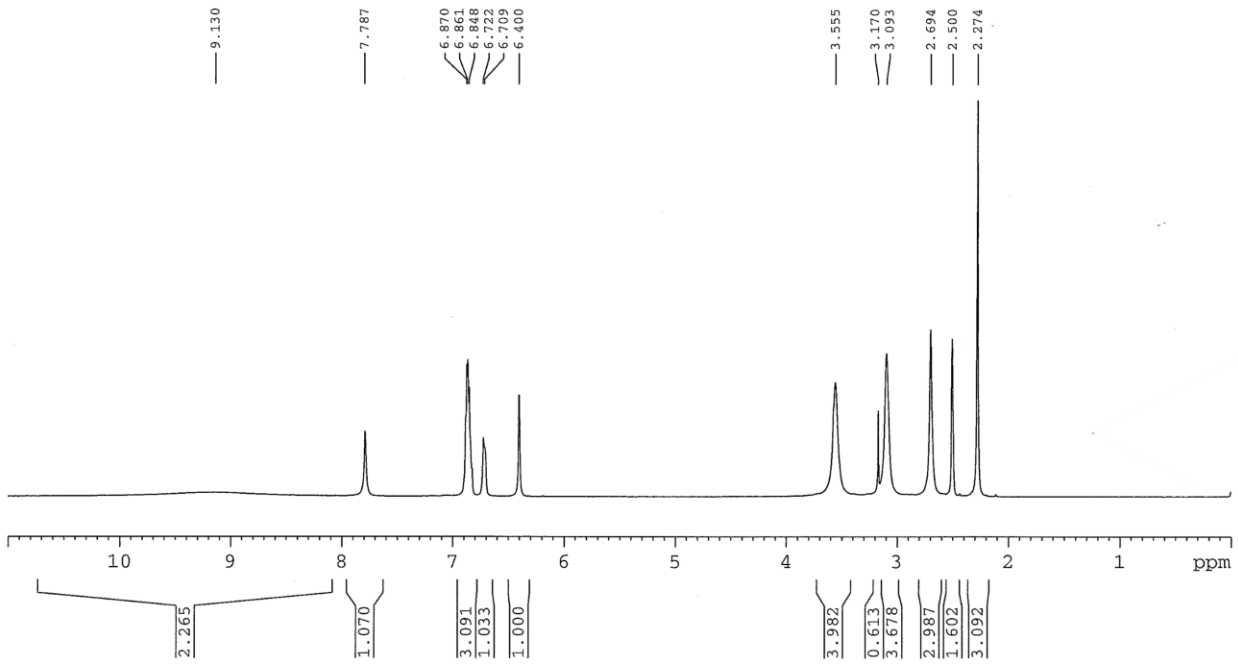
Olanzapine Oxalate (1:1)
VAT Mk.10b VAT MeOH 2.5 hrs + 3 day age
2.8714 mg
25-320 °C at 10 °C min^{-1}, N_2, Al crucible
DSC821e, Synchronization enabled



Olanzapine Oxalate (1:1) - IR

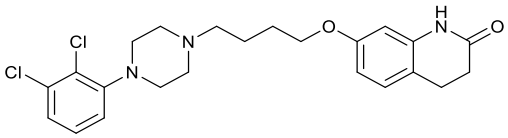


Olanzapine Oxalate
VAT Mk.10b - MeOH
^{1}H NMR – DMSO-d_6

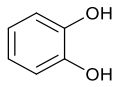


Control Example

Aripiprazole : Resorcinol (1:1) Control



Aripiprazole
Ari

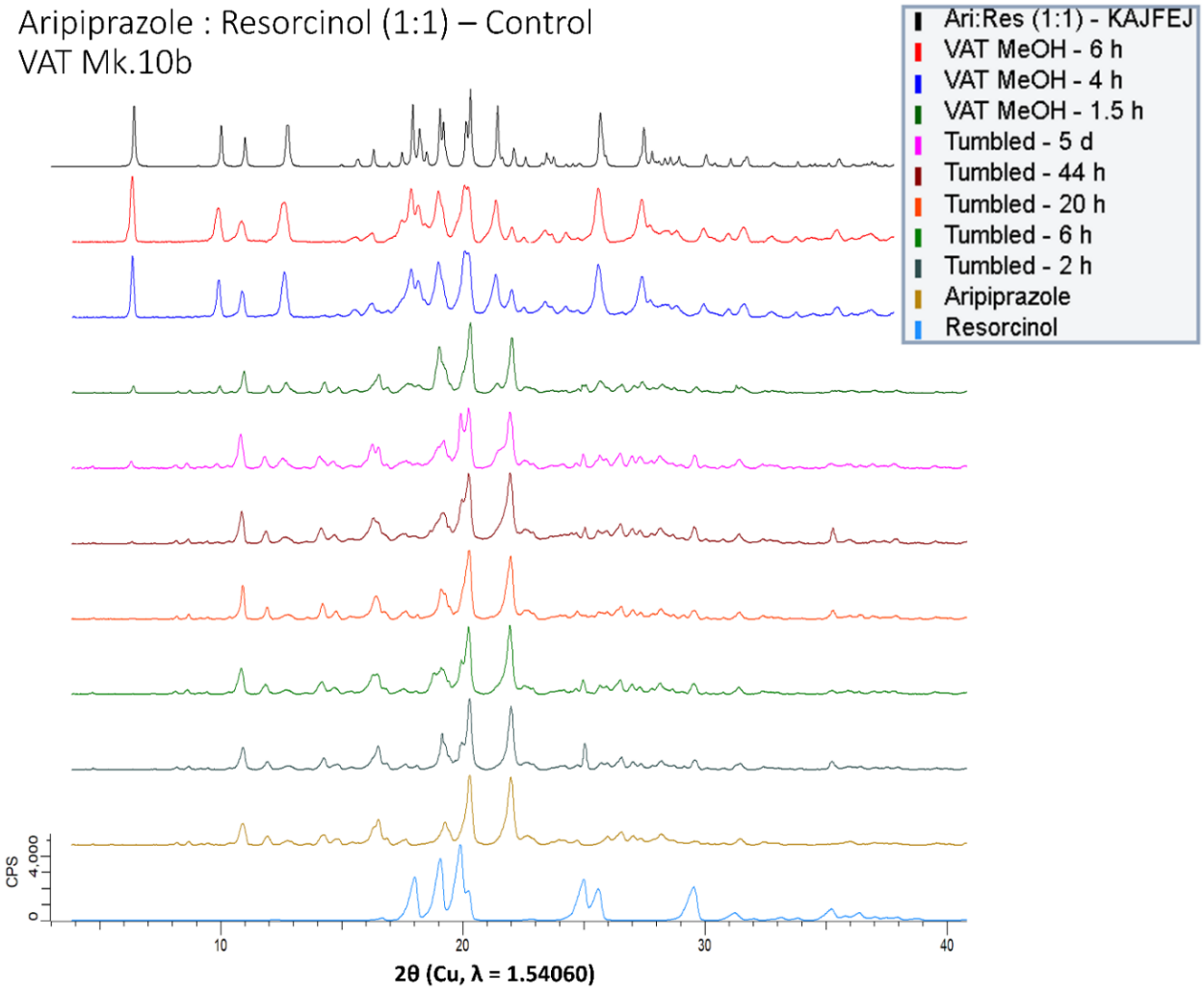


Catechol
Cat

Ari and Res were milled separately in stainless steel milling jars loaded with 2 × stainless steel balls. The milled Ari (5.00 g, 11.15 mmol) and Res (1.23 g, 11.15 mmol) were added to the sample tumbler of the VAT Mk.10b apparatus. The powders were tumbled under ambient conditions without a flow of N_2/solvent. Aliquots were periodically taken and PXRDs taken of the material. After 5 days of tumbling, only slight peaks of the Ari:Res cocrystal were seen (CCDC: KAJFEJ). An aliquot (1.01 g) was removed from the sample tumbler and set aside. After these 5 days, the solvent reservoir was filled with MeOH and connected to the VAT apparatus. A N_2 flow of 420 mL min^{-1} was introduced through the solvent reservoir and the sampled tumbler. After 4 h, the peaks of the Ari:Res cocrystal became much more prevalent. After

a total of 6 h of tumbling in N_2/MeOH, the sample was removed from the sample tumbler. Recovered mass: 5.10 g.

Other control experiments on other systems showed similar “catalytic” effects of the solvent vapour or no reaction at all without the presence of solvent vapours.

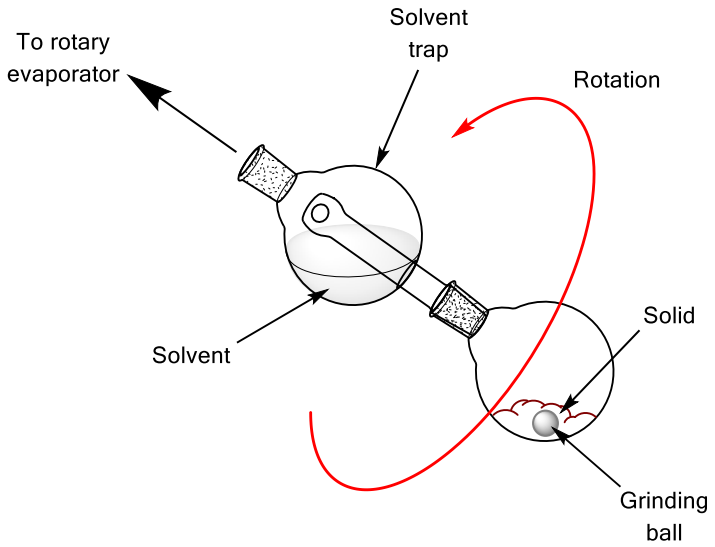


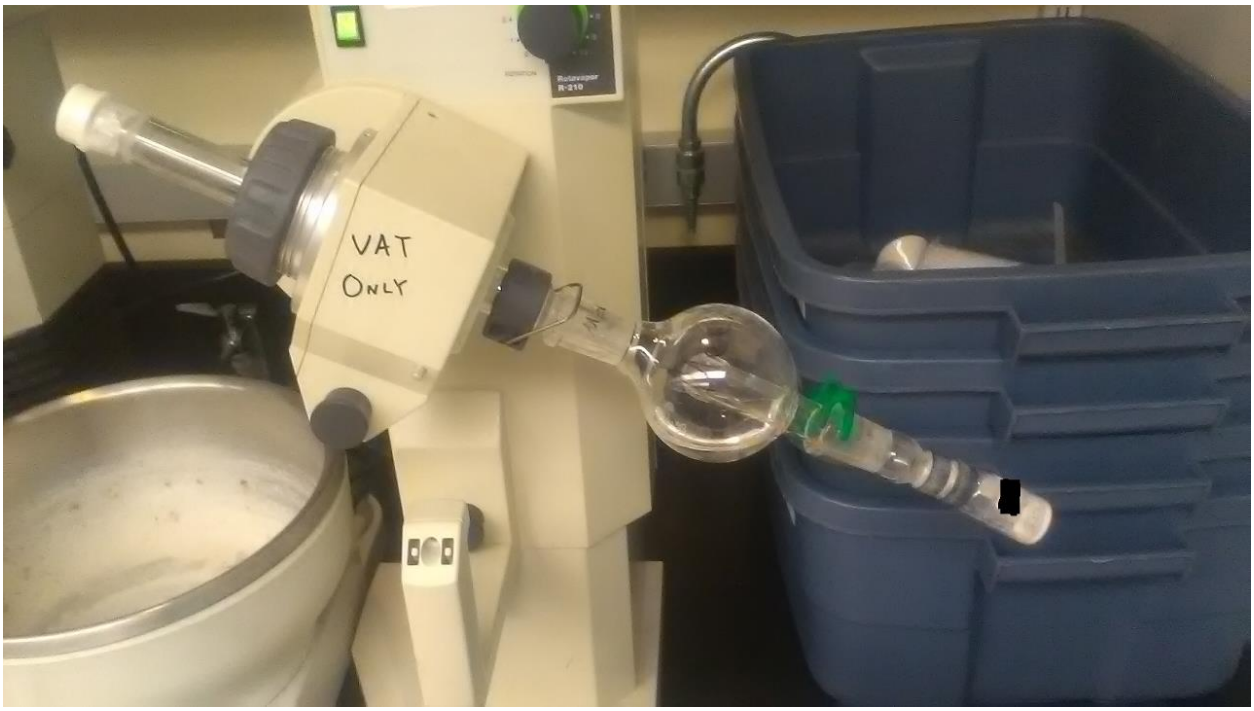
VAT Mk.# Schematics:

Many approaches to VAT were made with differing degrees of success. Shown here were the ones found to be the most effective or ones that are easily assembled in a standard chemistry lab. The analogues were all rotated at 9 rpm in all experiments to better mimic the full scale RCD standard operating procedures.

Mk.1 – Rotary Evaporator with Solvent Trap Reservoir (Back-Fill)

The first attempt at a cost-effective VAT apparatus and to explore the concept of vapour assisted solid-solid transformations. The apparatus can be assembled quickly and is common in almost all chemistry wet labs. The solids can be mixed first with rotation and an optional element of grinding can be provided by using a large heavy stir bar, ball bearings or any other suitable agitator. Using the vacuum pump, the apparatus can be evacuated until the solvent bubbles and then the apparatus closed. This allows the pressure to increase to that of the solvent pressure ensuring a saturated vapour environment. The usual solvent trap of the evaporator can be removed and instead a Suba-seal top and a needle inlet provided atmospheric control. In examples with limited amounts of reagents, then a 20 mL vial adaptor was used (picture below). If an in-line solvent trap is not available, then the standard solvent trap of the rotary evaporator can also be used.

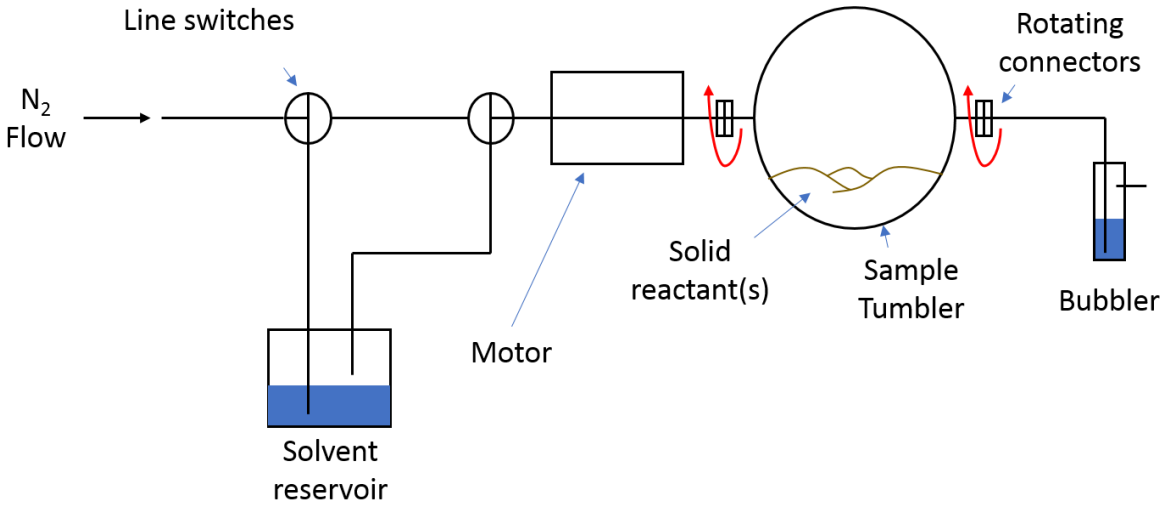


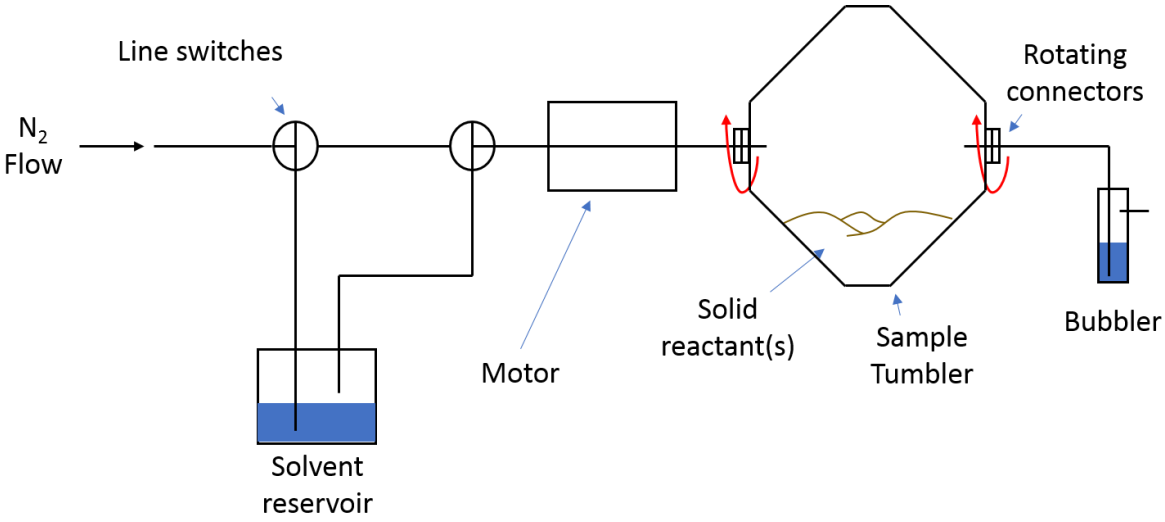

VAT
ONLY


250ML

Mk. 3 – Horizontal Rotary Evaporator (Flow-Through)

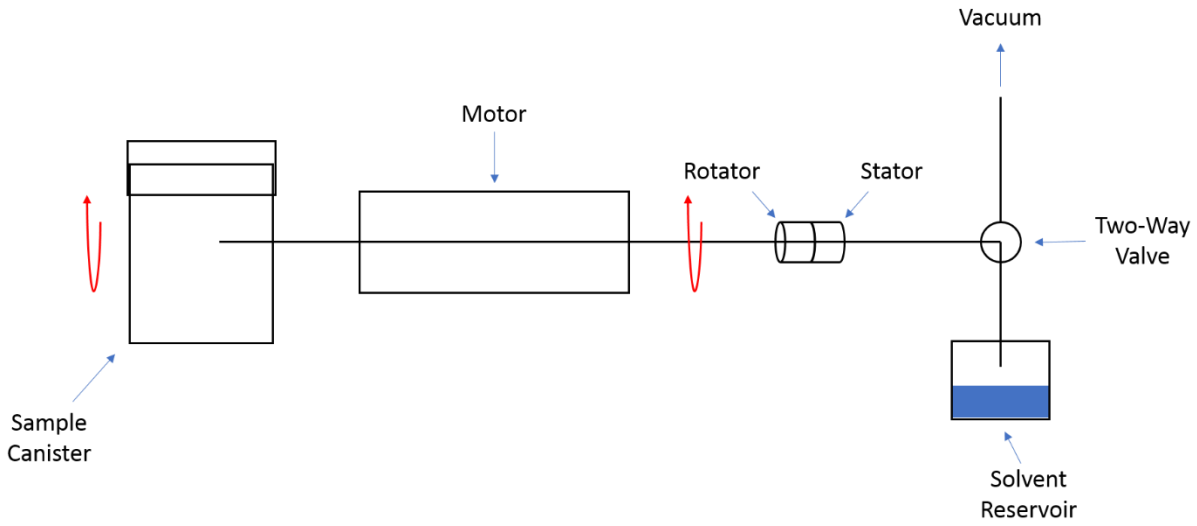
A repurposed rotary evaporator motor provided a controllable rotation and enabled the use of a flash column solvent reservoir as a sample tumbler. Majority of modification came from changing the size, shape and material of the sample tumbler.





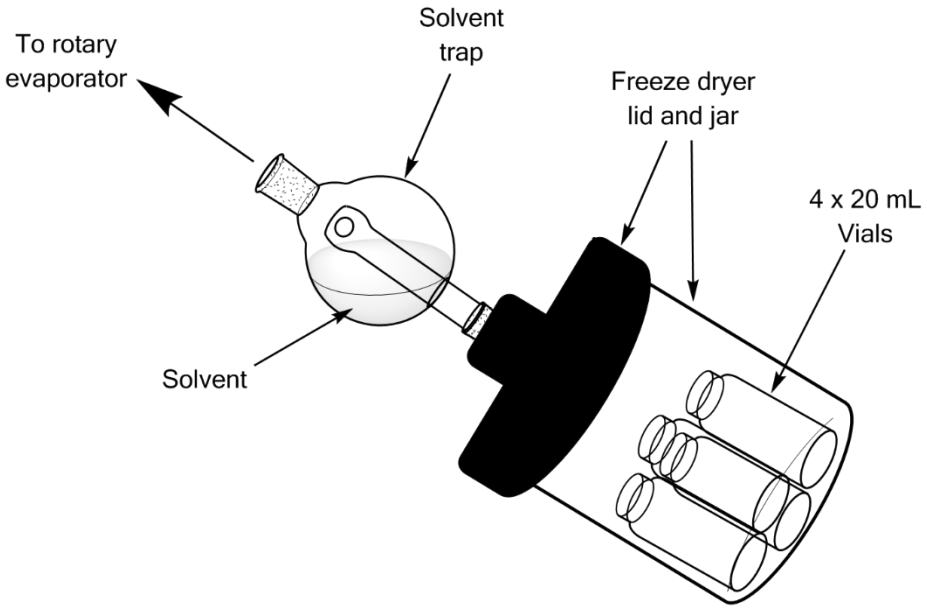
Mk.5 – Stainless-Steel Piping with Rotovap Motor (Back-fill)

To better simulate the industrial scale rotary cone, a stainless-steel VAT was constructed. Difficulties in ensuring a vacuum tight fit were apparent, along with preventing tumbling powders from sucking back into the piping.



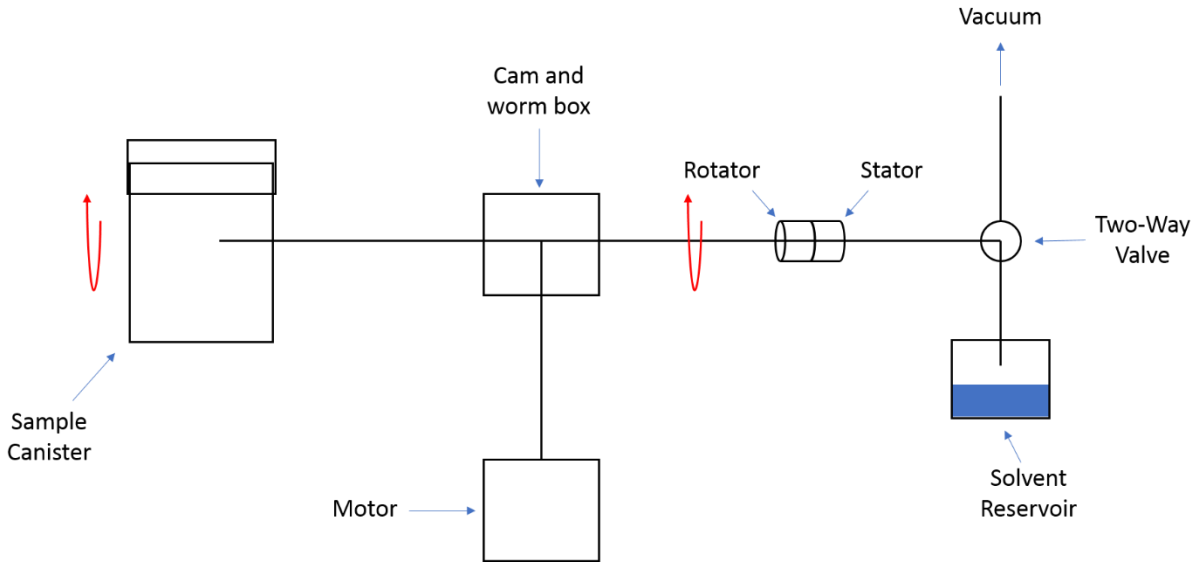
Mk.6 – High-Throughput VAT (Back-fill)

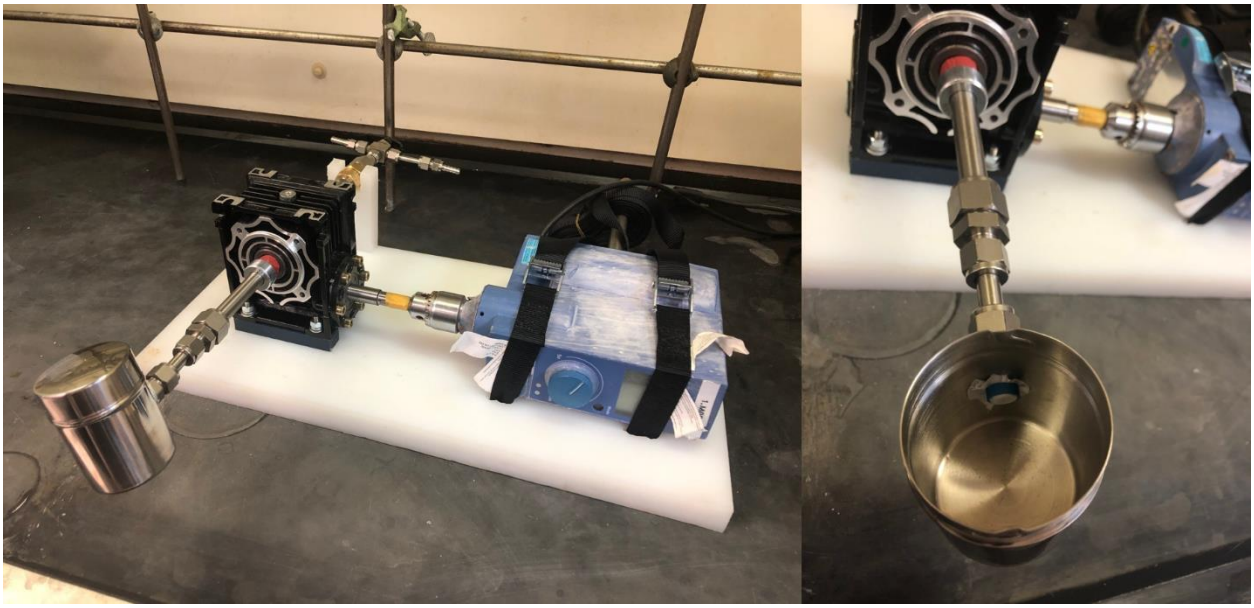
A modification to the Mk.1 VAT apparatus. The use of a rubber-sealed freeze-drying jar proved effective for using the same solvent vapour in four simultaneous VAT experiments in individual scintillation vials. This provided a degree of high-throughput screening (HTS) of small scale VAT solvent vapour conditions.



Mk.8 – Geared Overhead Geared Overhead Stirrer Motor, Stainless-Steel Construction, In-Line filter (Back-Fill)

Using a worm gearbox, the high speed and high torque of an overhear stirrer could be geared down to a more manageable speed, while keeping the desired torque. Initial experiments did not produce the desired results as the exposure to the solvent vapour appeared limited. The system was quickly converted to the Mk.10 systems

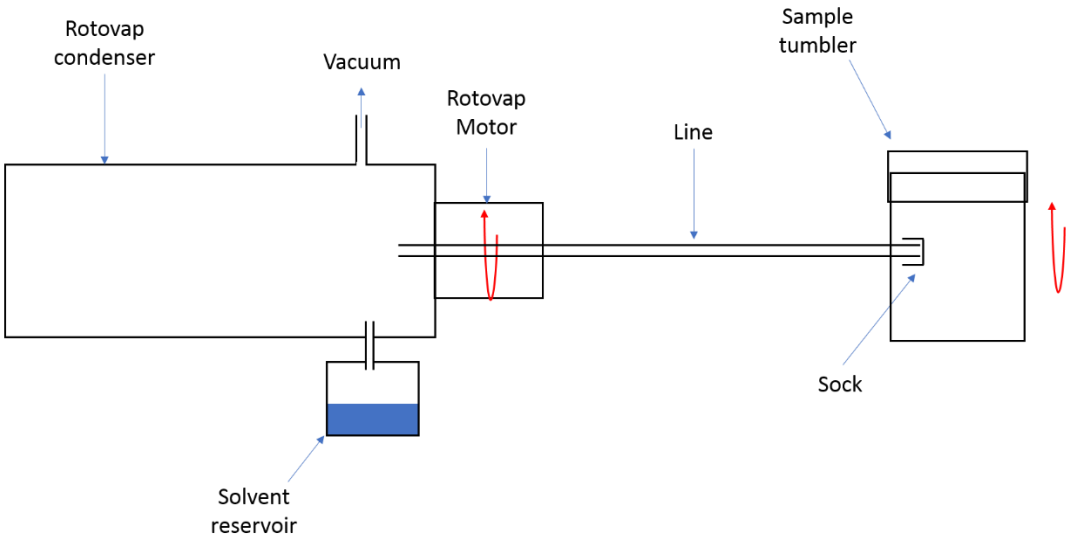




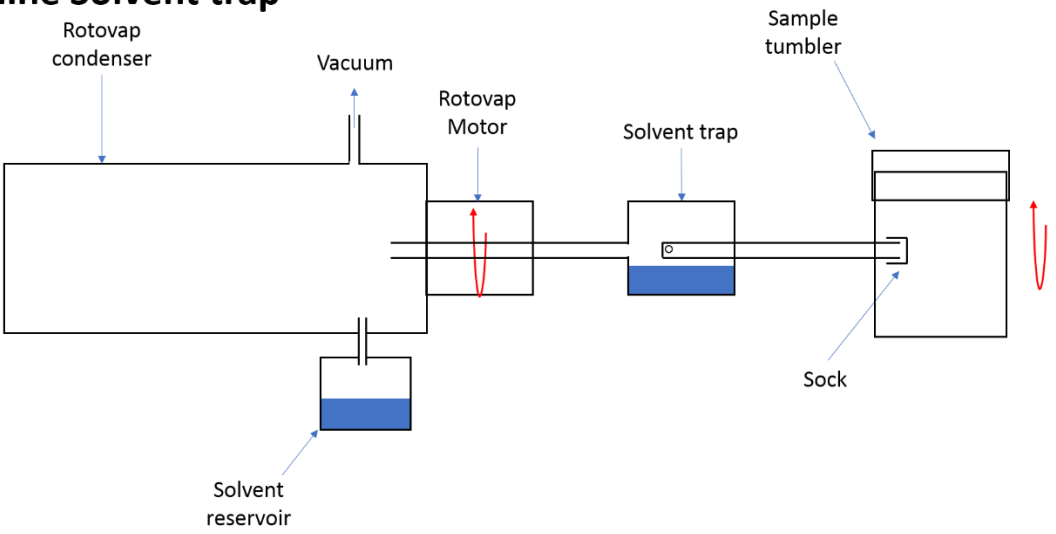
Mk.9a + Mk.9b – Rotary Evaporator, Stainless Steel Sample Tumbler (Back-Fill)

This design encompassed attaching the stainless steel sample tumbler with the glass condenser of a rotovap. This design was poorly executed and was rapidly disassembled after a few tests.

Mk.9a – Rotovap motor and enclosure – Stainless Steel Container



Mk.9b – Rotovap motor and enclosure – Stainless Steel Container + Inline Solvent trap

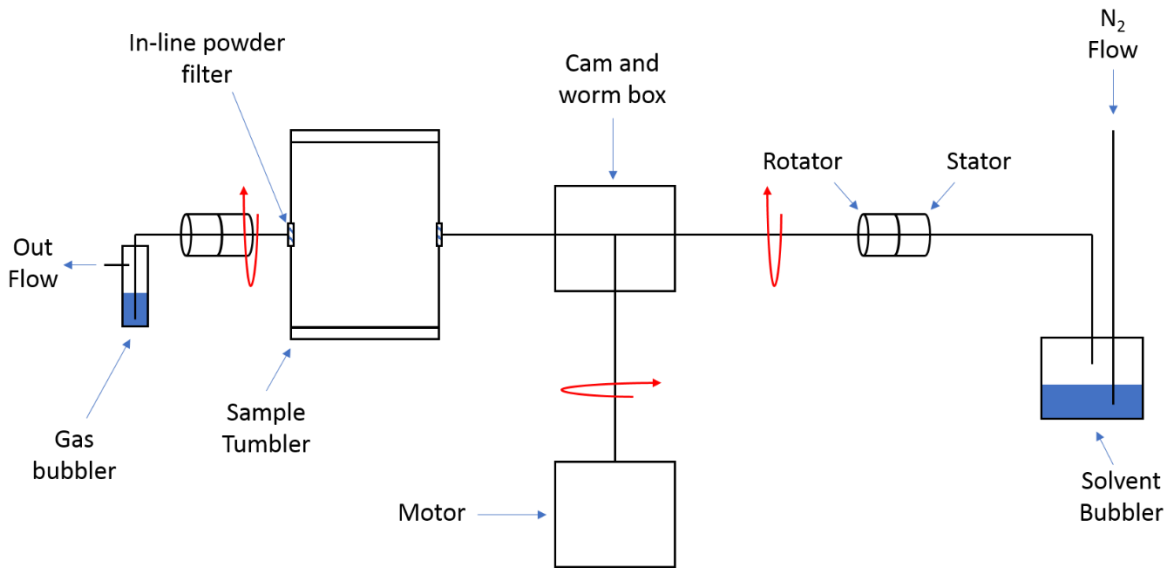


Mk.10a + Mk.10b – Geared Overhead Stirrer Motor, Stainless Steel Construction, In-Line filter (Flow-Through)

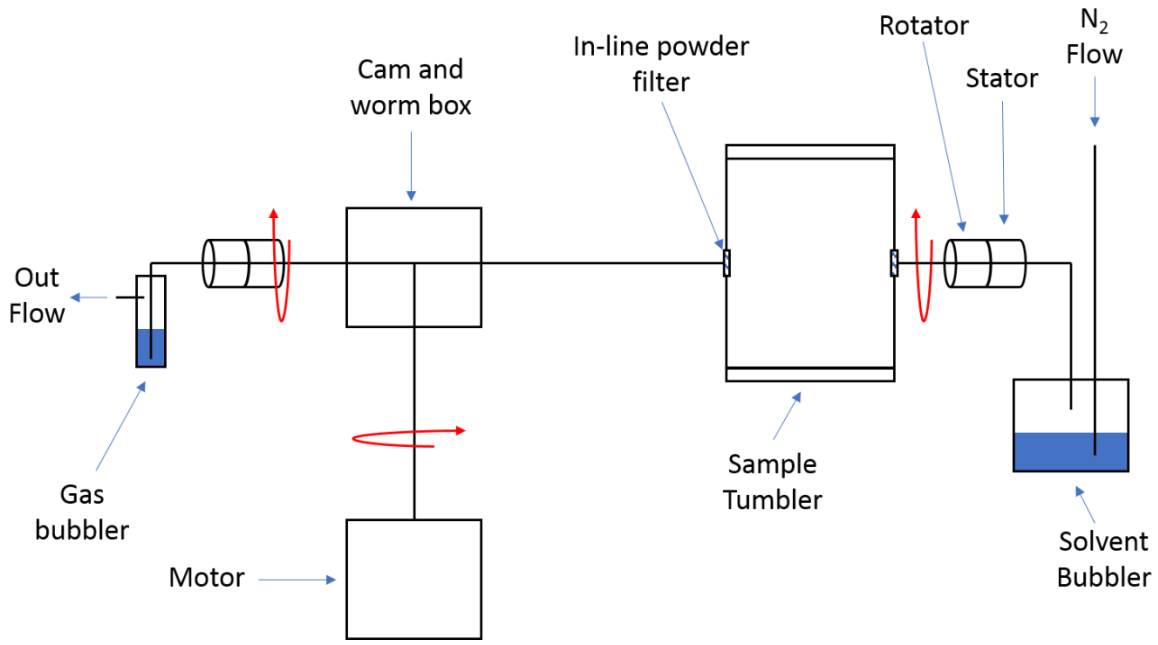
To date of publication, the most successful of the trialed systems. The apparatus is the closest in operation to an industrial rotary cone dryer. The solvent reservoir was placed in the orders; motor-tumbler (Mk.10a)

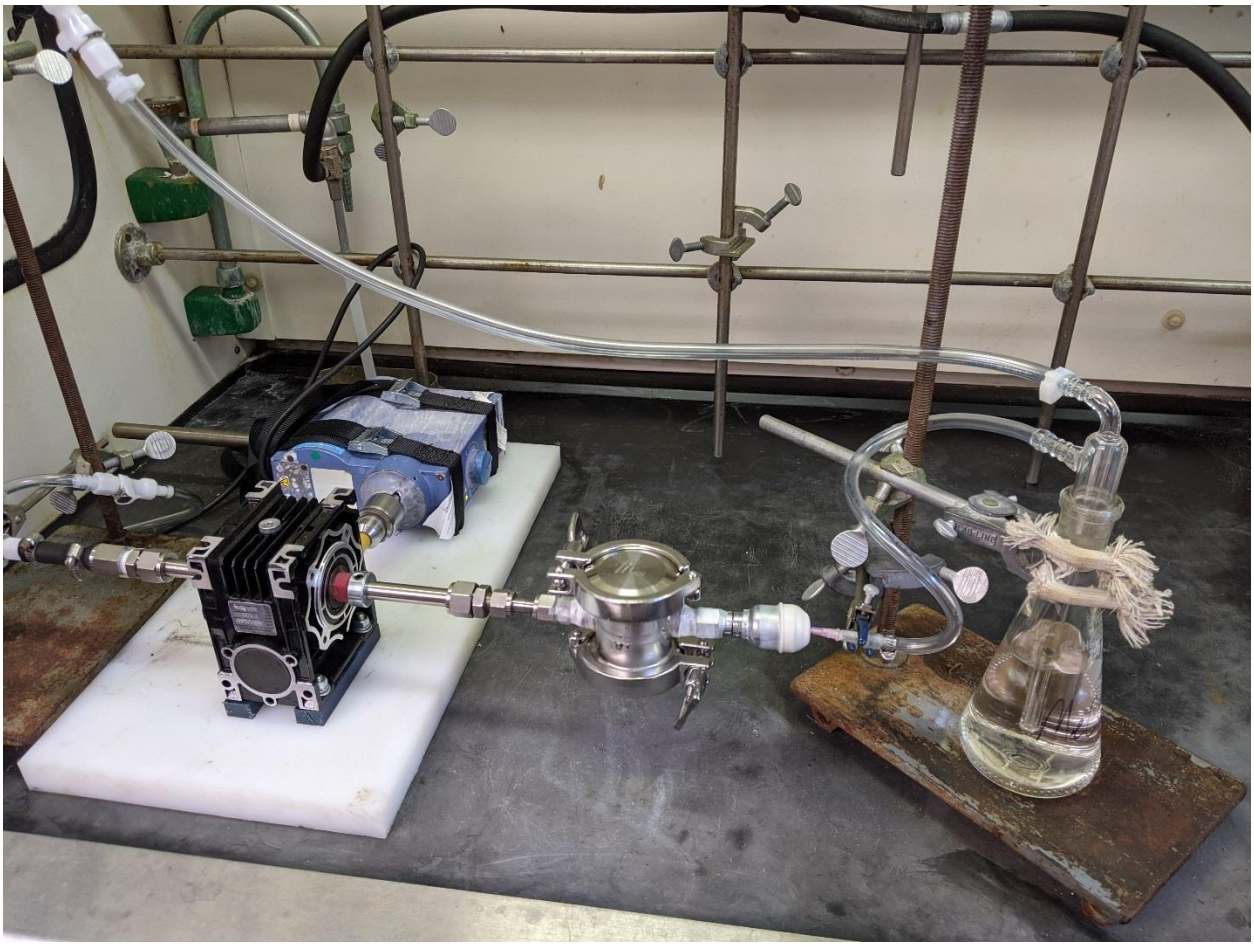
and tumbler-motor (Mk.10b), with the Mk.10b showing the best conversion rates. Presumably because the solvent reservoir is closer to the sample powders so vapour loss through condensation/leaks is minimized. The design also features a custom-made sample tumbler. The sample tumbler exhibits two in-line filter cloth powder filters that prevent any solids from escaping the tumbler. Also, the tumbler can be opened from both sides enabling easy sample addition/removal and cleaning. A gas sparger was later added to the N_2 inlet submersed in the solvent reservoir to increase carrier gas efficiency.

Mk.10a:



Mk.10b:


Out
Flow
Gas
bubbler
Cam and
worm box
Motor
In-line powder
filter
Sample
Tumbler
Rotator
Stator
N_2
Flow
Solvent
Bubbler



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