

Memo

12 Nov 2002

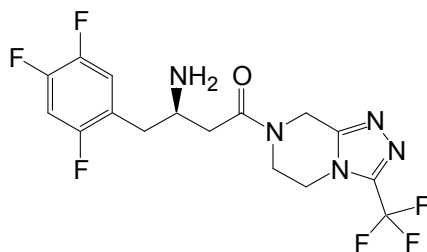
TO: K. Hansen, J. Armstrong, E. Grabowski, Y. Xiao
FROM: K. Somerville, V. Vydra, J. Chilenski
Cc: L. Crocker, D. Mathre, R. Sidler

SUBJECT: L-000224715 Phosphate Salt Polymorph Screen

Summary

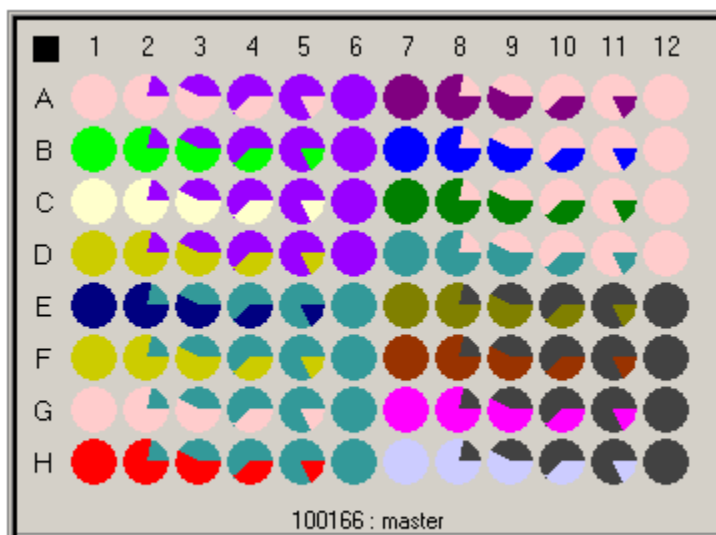
A polymorph screen of L-000224715 Phosphate salt was performed. Bulk compound was supplied as the crystalline phosphate salt. Very few crystalline solids were obtained from these experiments. Two notable forms identified were the hydrate evaporated from ethanol/water and the alcohol solvate precipitated from ethanol/ethylene glycol into butyl ether.

Design



Legend:

- L-000224715 Phosphate Salt
- WATER
- cyclohexane
- ETHANOL
- 1-propanol
- ACETONITRILE
- 1,4-dioxane
- nitromethane
- toluene
- perfluoroheptane
- Ethylene Glycol
- diisopropyl amine
- trifluorotoluene
- 1,2-dichloroethane
- 2-butanone
- 1,2-dimethoxyethane
- Trichloroethylene
- IPAc



Procedure

The substrate (L-000224715 Phosphate salt, K. Hansen) was dispensed as a powder (10mg +/-1 mg) using the Autodose Powdernium. After the substrate was dispensed to each of the wells, the 96-well plate was placed on the Cavro Liquid Handling Robot deck, with the wash solvent as methanol, for the solvent dispense (800 uL/well). The 96-well plate was mapped by quadrants.

The solvent mapping of the 96-well plate is as follows:

Quadrant 1: (upper left) 0-100% (v/v) Water by 20% increments

- Row A: Ethanol
- Row B: 1-Propanol
- Row C: Acetonitrile
- Row D: 1,4-Dioxane

Quadrant 2 (upper right) 0-100% (v/v) Ethanol by 20% increments

- Row A: Ethylene Glycol
- Row B: Diisopropyleamine
- Row C: Trifluorotoluene
- Row D: 1,2-Dichloroethane

Quadrant 3 (lower left) 0-100% (v/v) 1,2-Dichloroethane by 20% increments

- Row E: Nitromethane
- Row F: 1,4-Dioxane
- Row G: Toluene
- Row H: Perfluoroheptane

Quadrant 4: (lower right) 0-100% (v/v) Cyclohexane by 20% increments

- Row E: 2-Butanone
- Row F: 1,2-Dimethoxyethane
- Row G: Trichloroethylene
- Row H: Isopropyl Acetate

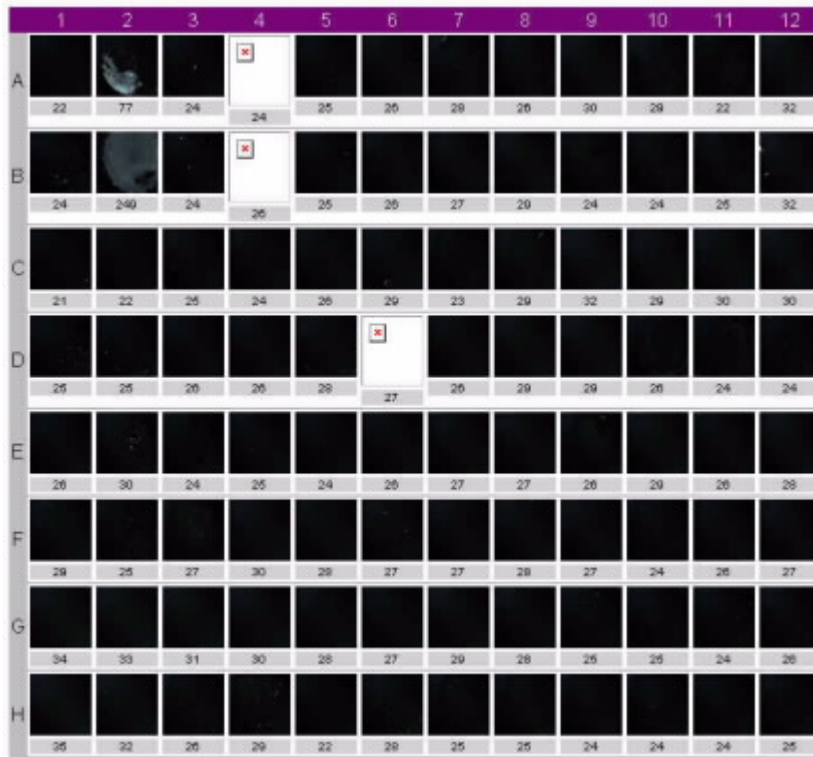
Once all the solvents were dispensed to each well, the 96-well plate was capped and placed on the crystallizer deck. The system was equilibrated at 65°C for 2 hours (during which anti-solvents were added to the precipitation plate), filtered hot at 65°C and daughtered to each of the three experiment plates (Evaporation 200uL, Precipitation 100uL and Cooling 200uL). The cooling plate was thermal cycled with a cubic cool down temperature gradient of 65-10 °C over 8 hours. The plate was equilibrated at 10 °C for 2 hours and then the supernatant was removed from the cooling and precipitation experiment plates. The following day, each experiment was wicked to dry the remaining solvent and the plates were removed for analysis.



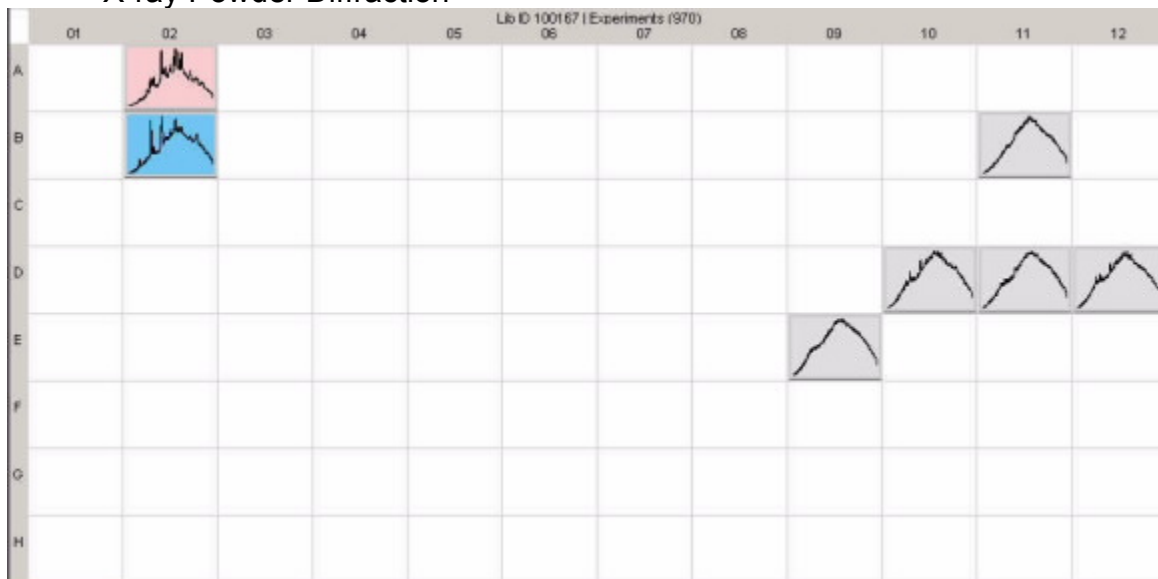
Results

The wells were inspected both visually and by polarized light microscopy for birefringence. Wells containing material were then scanned by XRPD.

Evaporation (Library ID 100167)
Birefringence



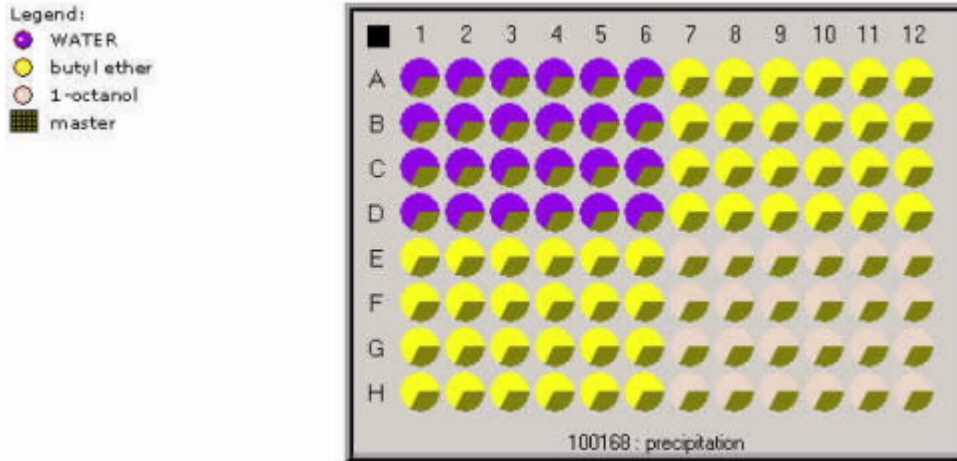
X-ray Powder Diffraction



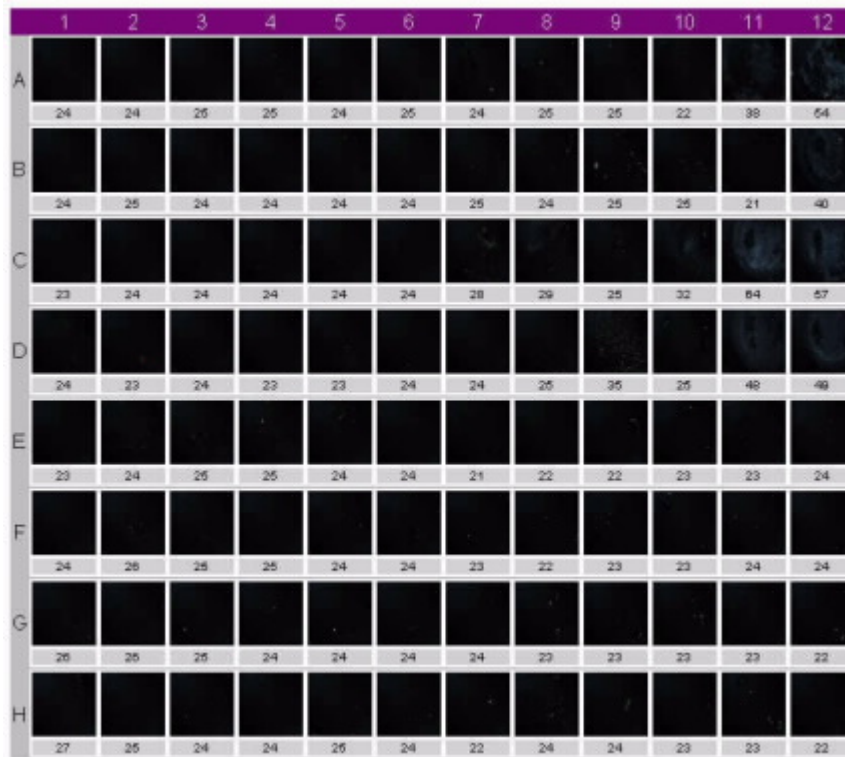
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Precipitation (Library ID 100168)

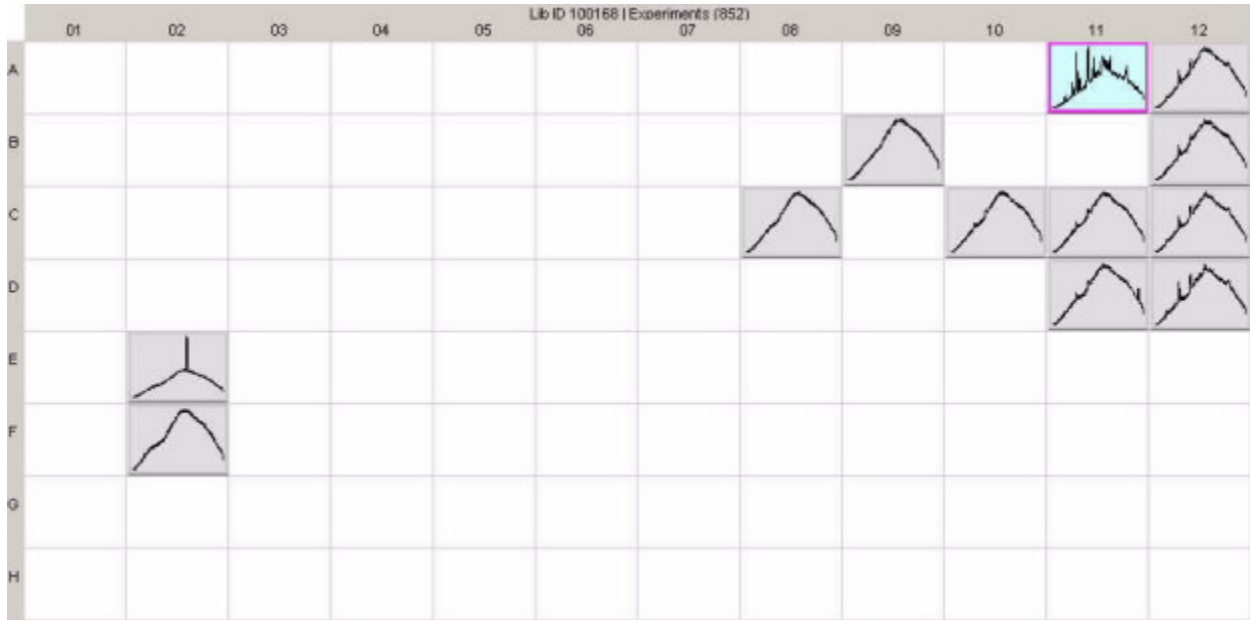
Anti-solvents for the precipitation plate were mapped as follows (200uL/well).



Birefringence



X-ray Powder Diffraction



Cooling (Library ID 100169) Birefringence



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