Pharmaceutical Powder Diffraction: Structure Solution from PXRD

How reliable are our structures?




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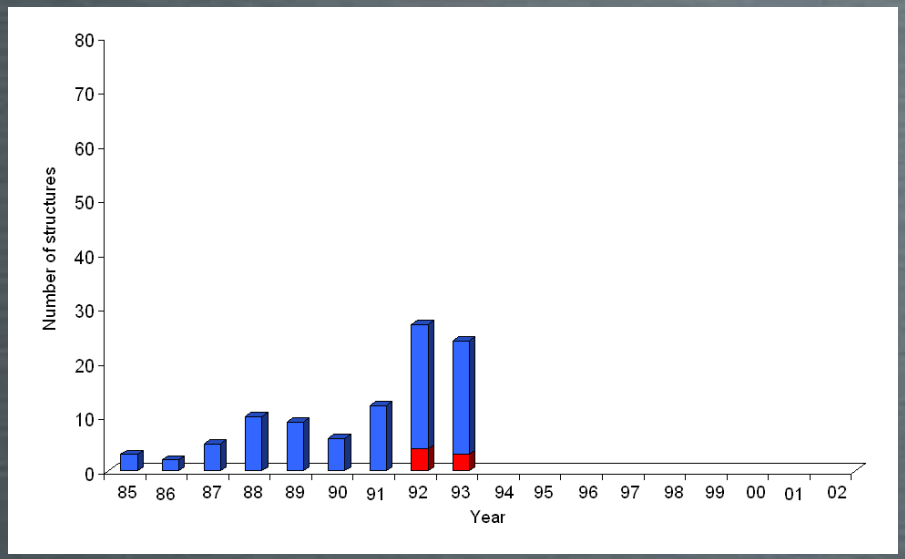
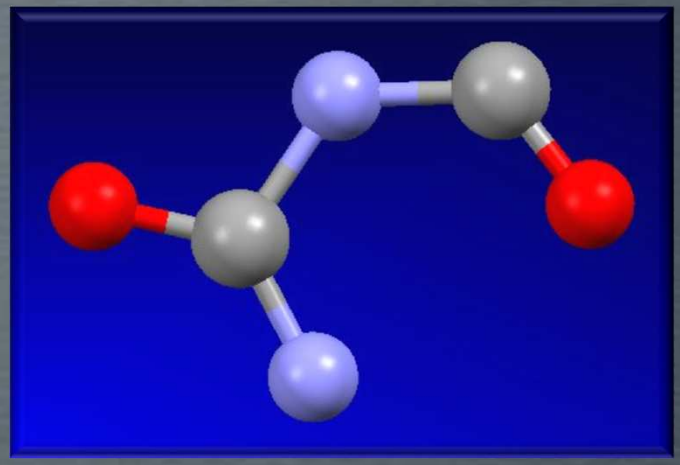
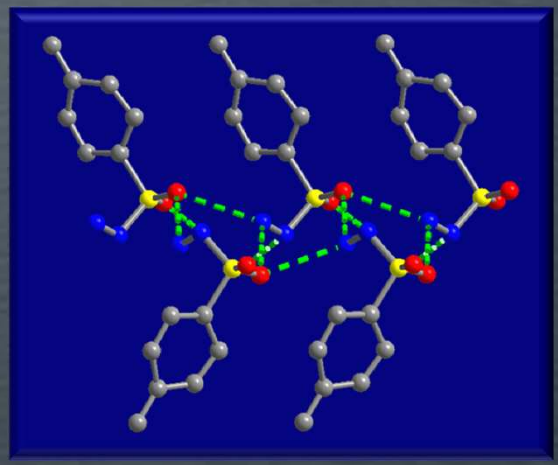
SDPD Molecular Materials 82-93





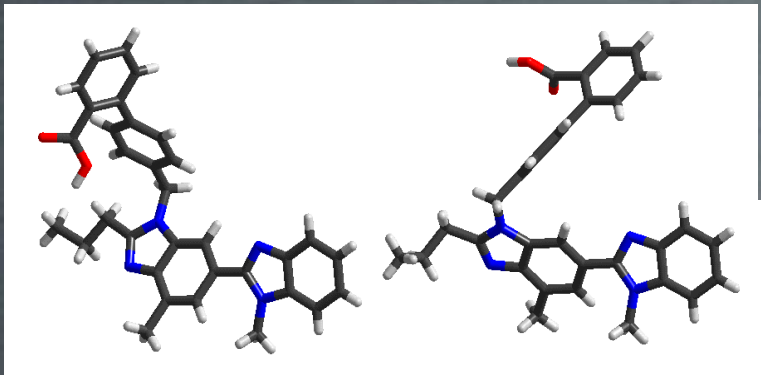
Lightfoot, Tremayne, Harris & Bruce., *Chem.Comm.* (1992), 1012

- Direct Methods:
  - SIR & SHELXS
  - Maximum Entropy: MICE
  - Patterson

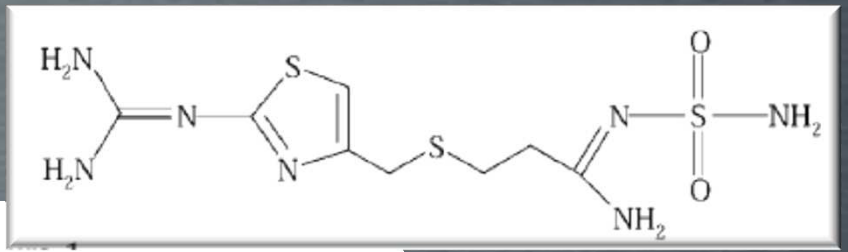


Lightfoot, Tremayne, Glidewell, Harris & Bruce., *J.Chem.Soc.PerkinTrans2.,* (1993), 1625

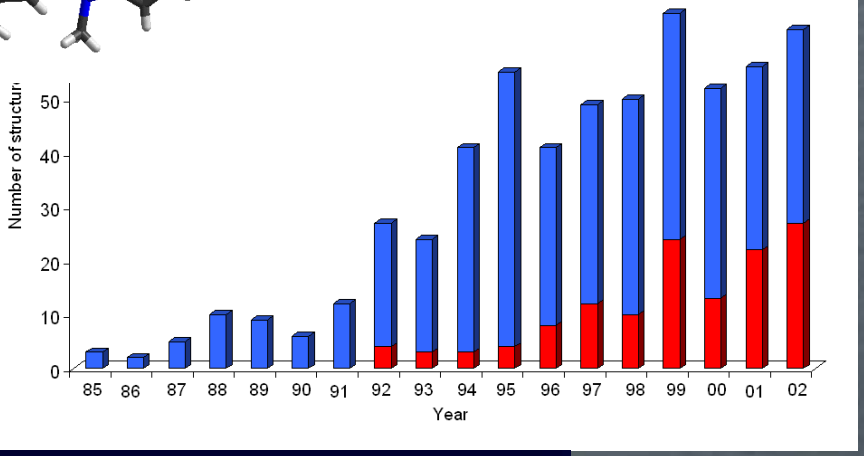
SDPD Molecular Materials 93-02

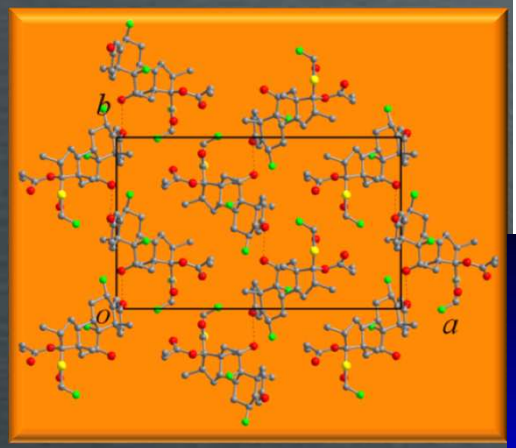


Dinnebier et al., *J.Pharm. Sci.* (2000), 89, 1465

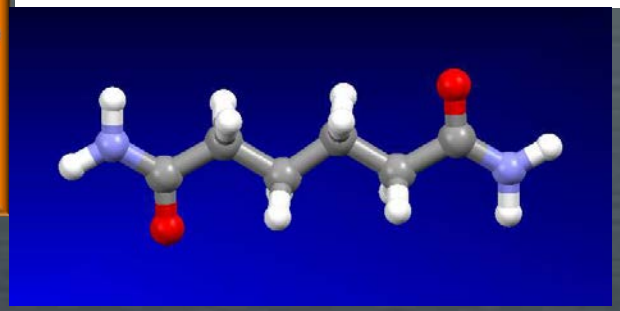


Shankland et al., *J.Appl.Cryst.* (2002), 35, 443

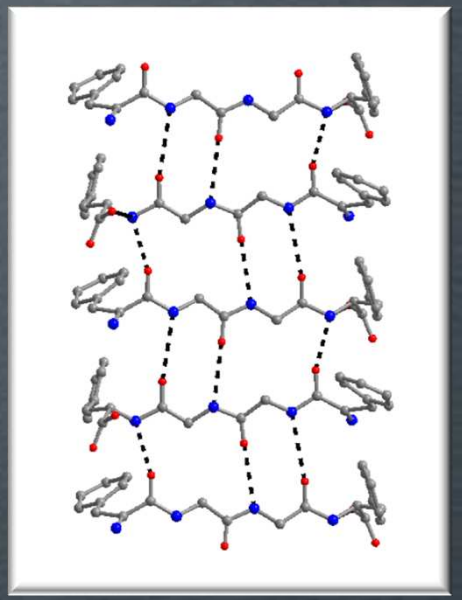




Kariuki et al., *Chem. Comm.,* (1999), 1677



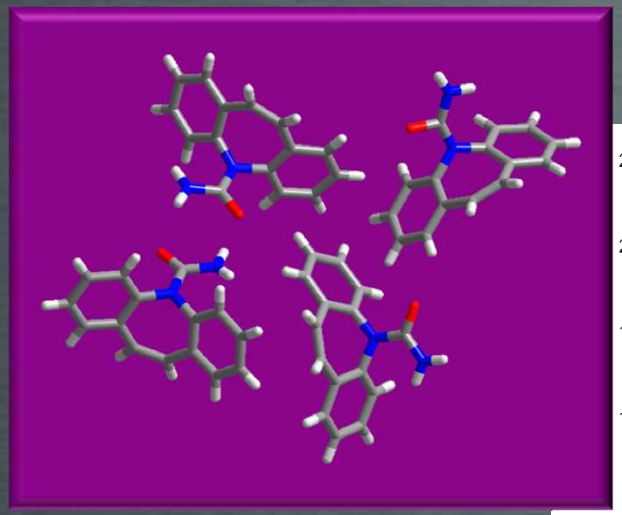
Seaton et al., *Chem Comm.,* (2002), 880



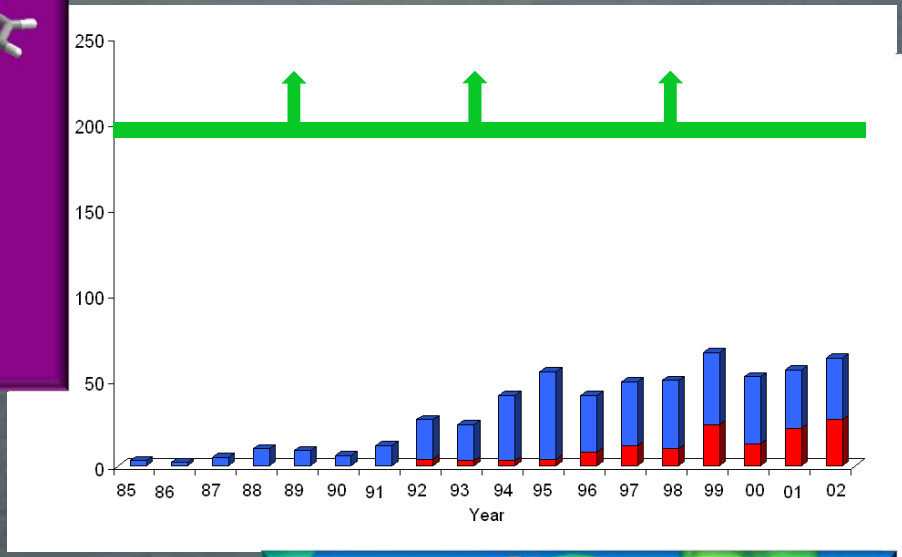
Tedesco et al., *Angew.Chem.* (2000), 39, 4488

SIRPOW, EXPO, EAGER, OCTOPUS, FOX, DASH, POSSUM, TOPAS, PowderSolve, ESPOIR, PSSP, XLENS, Endeavour

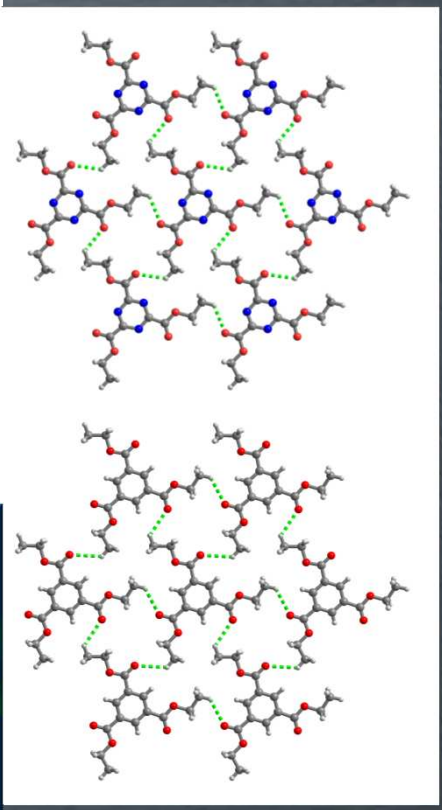
SDPD Molecular Materials 03-13

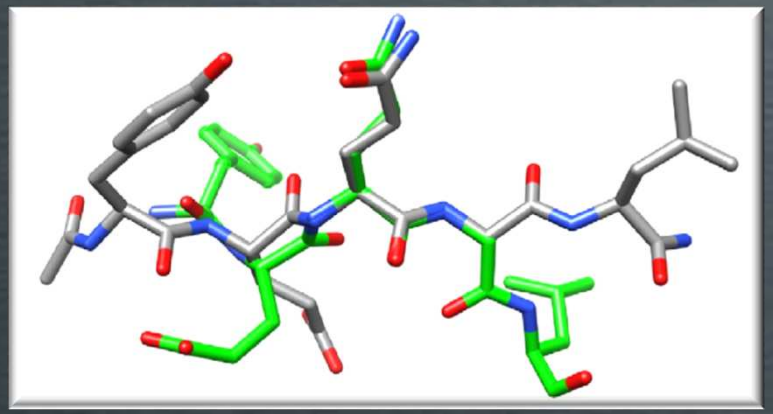


Fernandez et al., *J.Pharm.Sci.* (2007), 96, 1192

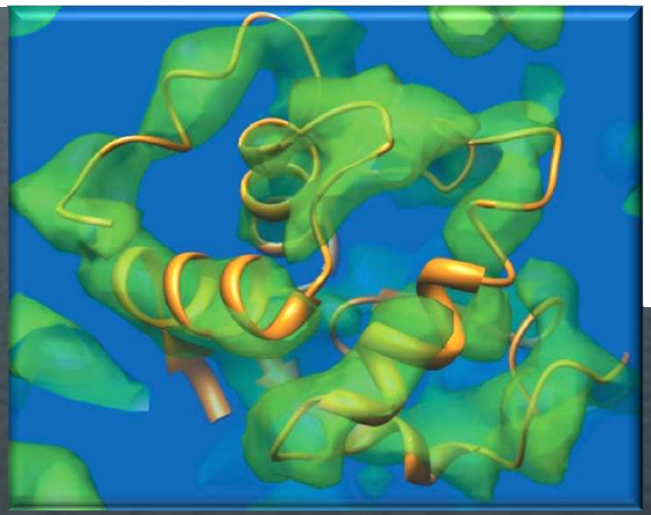


Chong et al., *Acta Cryst.*. (2006), B62, 864





Fujii et al., *J.Struct.Biol.*. (2011), 174, 461

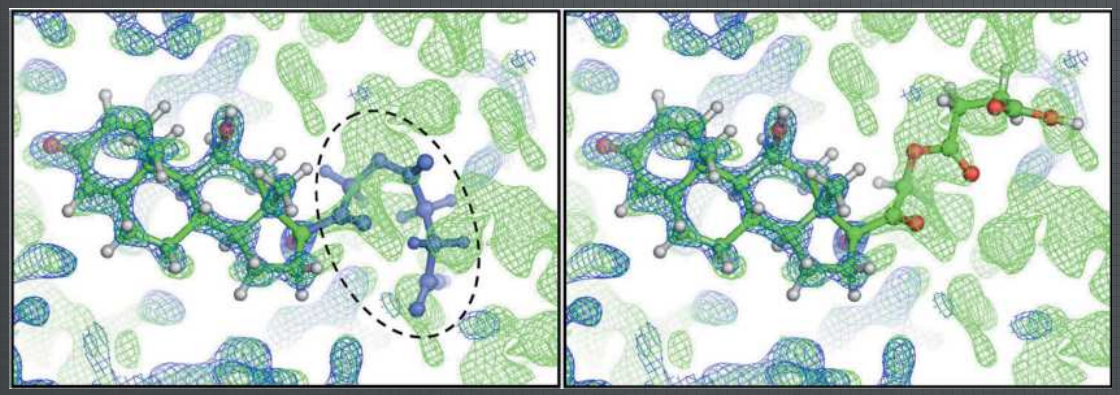


Basso et al., *Acta Cryst.*. (2010), D66, 756

Prednisolone succinate

- 2 molecules in asu; 65 non-H atoms; 25 dof
- Synchrotron data, d > 1.00Å

Genetic Algorithm & Rigid-body refinement : R_{wp}=8.2%



Omit MEM charge density model
R_{wp}=3.7%,
refined
R_{wp}=2.9%

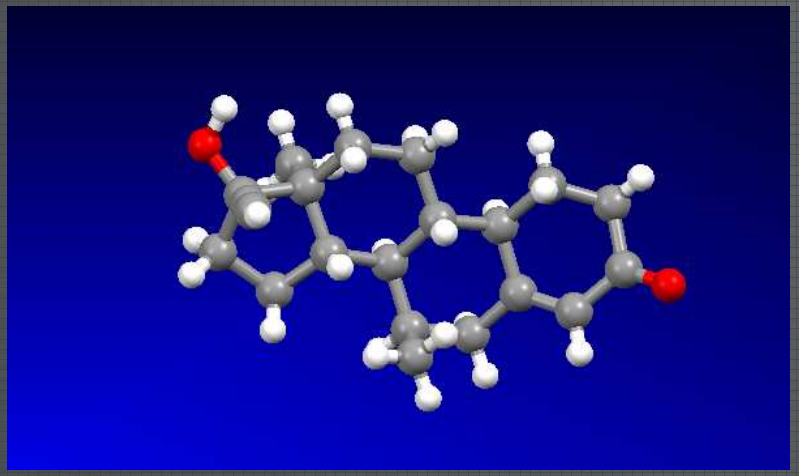
Dual data refinement with inner angle restraints, R_{wp}=1.3%

"accuracy of structure increased"…"using procedures"…"eliminating model bias during refinement"

Nishibori, Ogura, Aoyagi & Sakata, *J. Appl. Cryst.,* (2008), 41, 292

Isotibolone

Degradation impurity in dosage of tibolone API

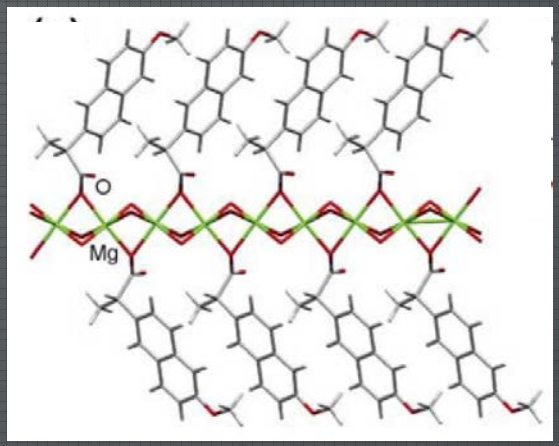


Genetic Algorithm
Laboratory data

Gomez, Antonia, Barros de Araujo, Ferreira & Paiva-Santos, *CrystEngComm.*, (2012), 14, 2826

Naproxen

Liquid assisted grinding (alcohol/water):
$Mg(nap)_2.H_2O$ - SXRD
$Mg(nap)_2.4H_2O$ - PXRD

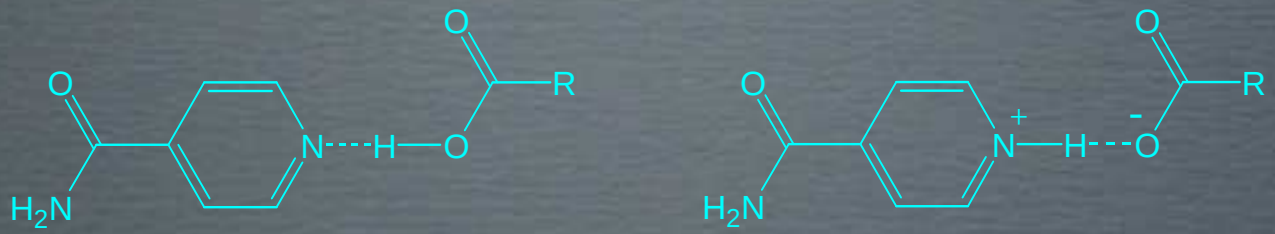


Simulated Annealing
Laboratory data

Friščić, Halasz, Strobridge, Dinniebier, Stein, Fabian & Curfs, *CrystEngComm.*, (2011), 13, 3125

Molecular Cocrystals (& Salts)

- Crystalline solids containing 2 or more building blocks (solids at rt) in stoichiometric amounts



- Materials that retain the chemical properties of components but display new physical properties

melting point *stability* *solubility*
bioavailability *dissolution* *morphology*

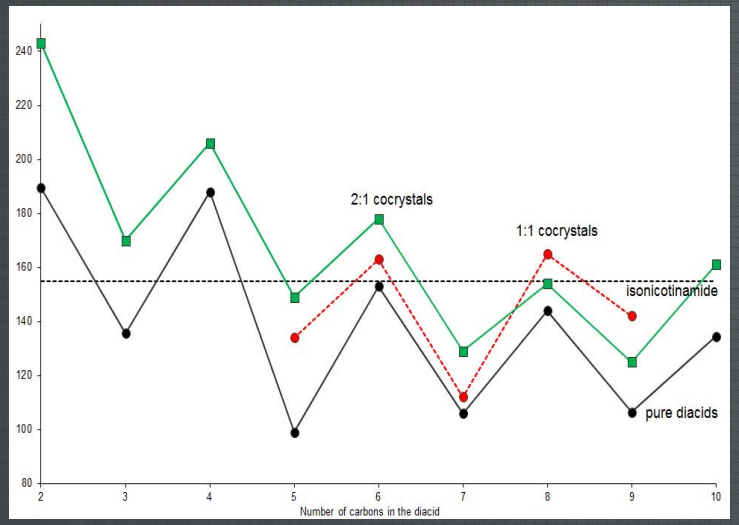
- Combination of API with 'GRAS' component

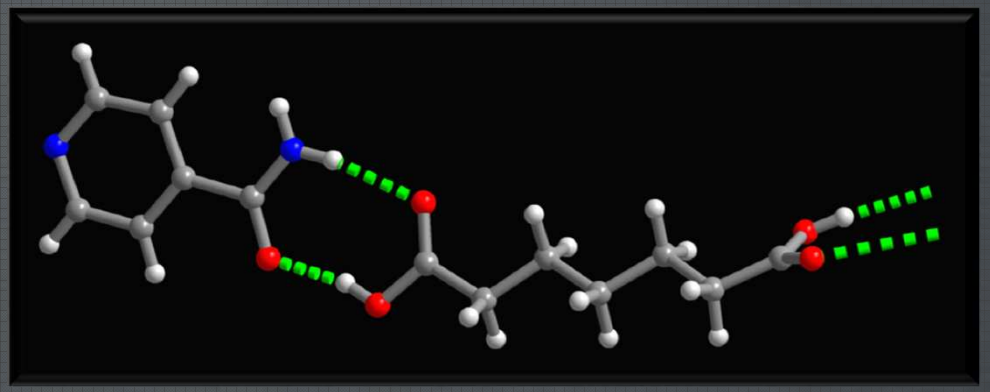
Schultheiss & Newman., *Cryst.Growth & Des.* (2009), 9, 2950

Aakeroy et al., *CrystEngComm.* (2005), 7, 439 Almarsson et al., *Chem.Comm.* (2004), 1889

… melting point …

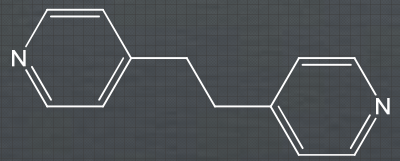
- Used to mimic physical property trends……



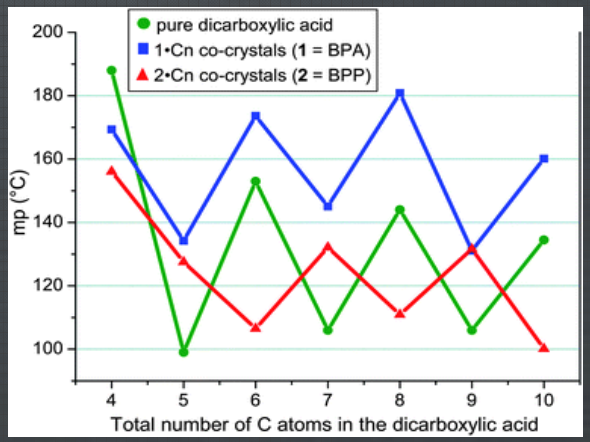


Thompson, Voguri, Male & Tremayne, *CrystEngComm,* (2011), 13, 4188

… or not! …

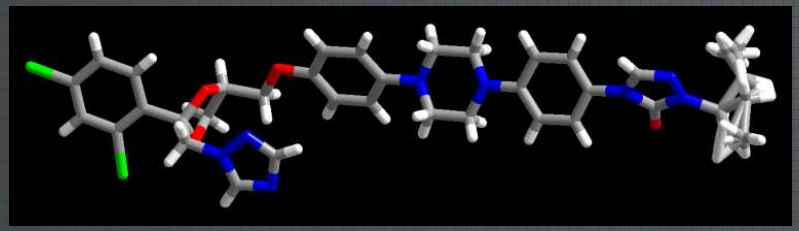


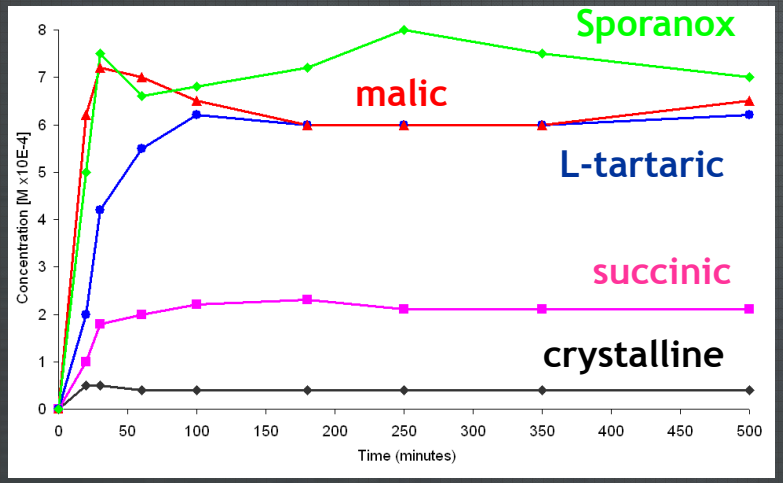
Braga et al., *CrystEngComm.* (2010), 12, 3534



… solubility …

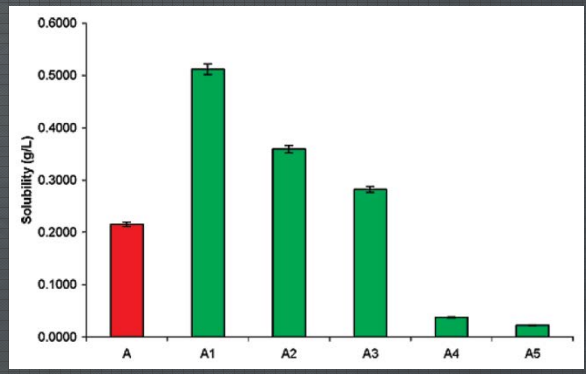
- Tuned to level of commercial material

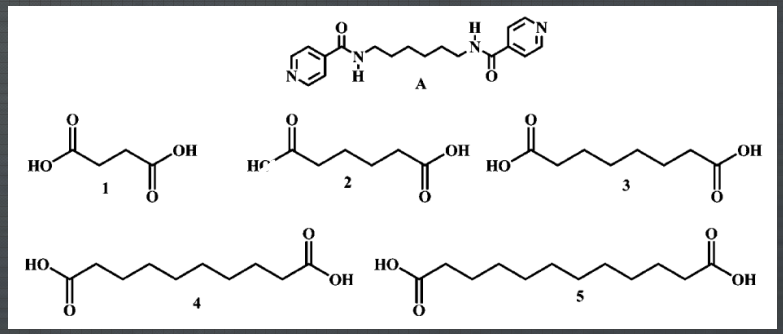




Remenar et al., *J.Am.Chem.Soc.,* (2003), 125, 8456

- Property rationalised by diacid solubility





Aakeroy, Forbes & Desper, *J.Am.Chem.Soc.,* (2009), 131, 17048

Why Powder Diffraction?

Products showing poor crystal growth resulting from:

solvent-mediated crystallisation or sonic slurry

Products from solid state synthesis:

liquid assisted or dry grinding

alternative stoichiometry
incompatable solubilities
solvent-free form
or atypical structural behaviour

Delori, Friscic & Jones., *CrystEngComm.* (2012), 14, 2350

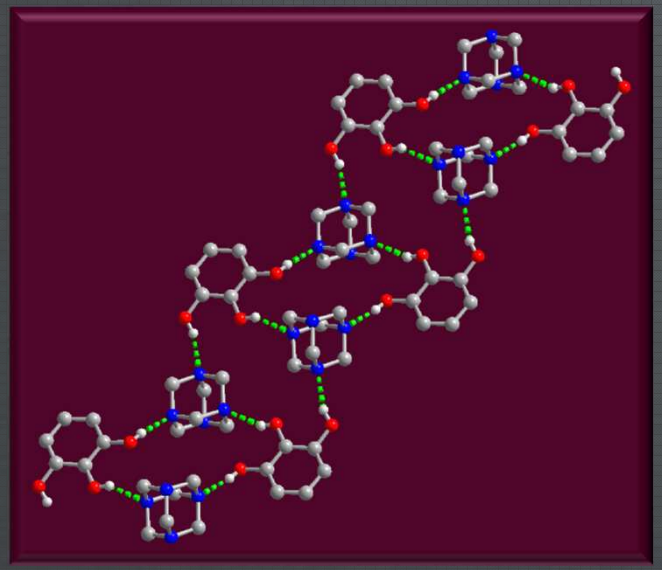
James et al., *Chem.Soc.Rev.* (2012), 41, 413

Shan, Toda & Jones., *Chem.Comm.* (2002), 2372; Friscic & Jones., *Faraday.Disc.* (2007), 136, 167

SDPD of Cocrystals

- Independent components in direct space; greater complexity wrt search surface & parameters

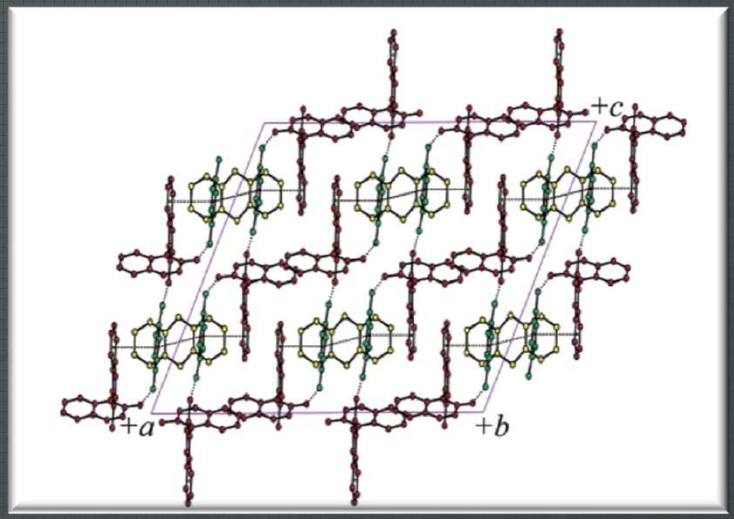
1,2,3-trihydroxybenzene: HMTA (1:1)



Monte Carlo
Laboratory data

Tremayne & Glidewell, *Chem.Comm.,* (2000), 2425

Benzoquinone: bis-naphthol: anthracene (2:2:1)

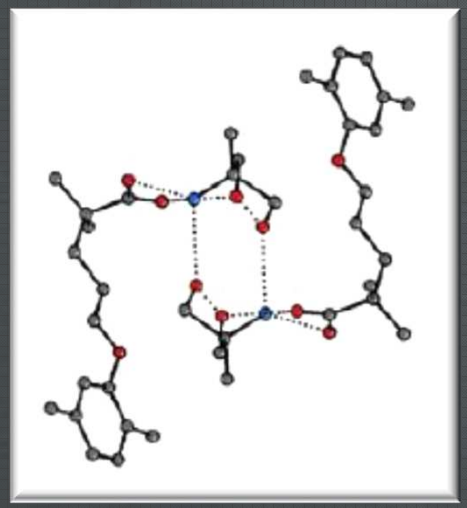


Dry grinding; Genetic Algorithm
Laboratory data

Cheung, Kitchin, Harris, Imai, Tajima & Kuroda, *J.Am.Chem.Soc.,* (2003), 125, 14658

SDPD of Cocrystals

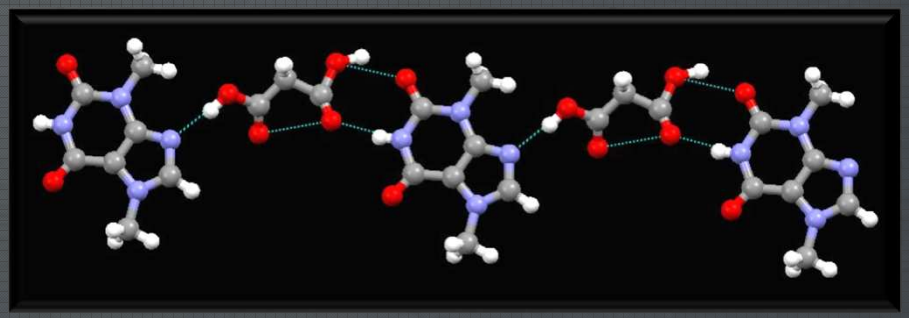
Gemfibrozil: hydroxybutylamine (1:1)



Genetic Algorithm
Laboratory data
Proton transfer

Cheung, David, Harris, Conway & Timmins, *J.Solid.State.Chem.,* (2007), 180, 1068

Theobromine: malonic acid (1:1)



Liquid assisted grinding
Simulated Annealing
Laboratory data

Karki, Fabián, Friščić & Jones, *Org.Lett.,* (2007), 9, 3133

SDPD of Cocrystals

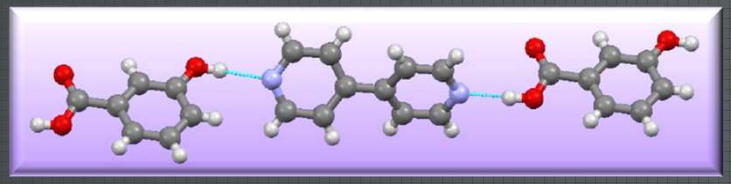
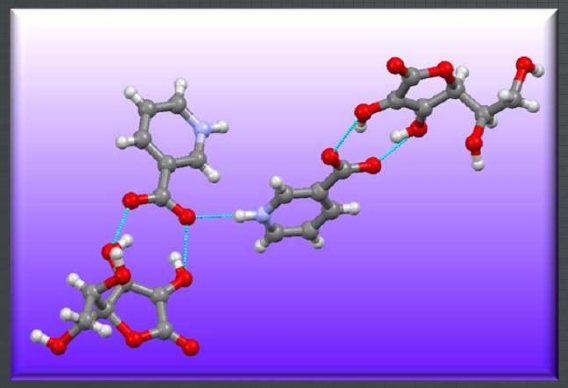


Table 1. Compounds

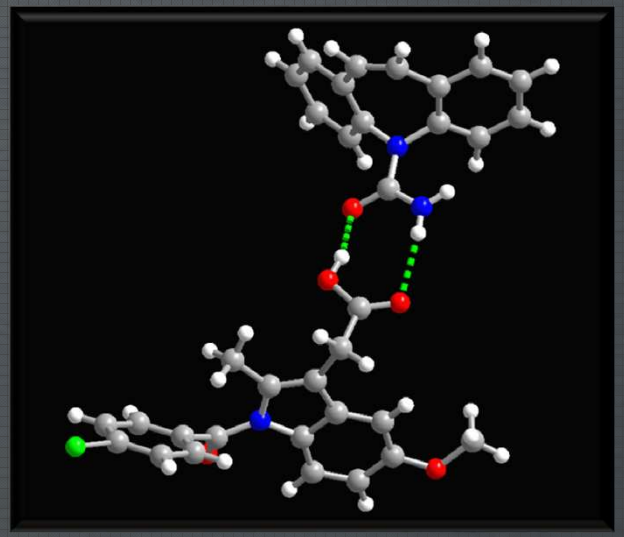
name
4-hydroxybenzoic acid and 4-phenylpyridine (1:1)
3-hydroxybenzoic acid and 4-phenylpyridine (1:2)
3-hydroxybenzoic acid and tetramethylpyrazine (2:3)
3-hydroxybenzoic acid and 4,4′-bipyridine (1:1)
3-hydroxybenzoic acid and 1,2-bis(4-pyridyl)ethane (1:1)
4-hydroxybenzoic acid and 1,2-bis(4-pyridyl)ethene (1:1)
3-hydroxybenzoic acid and *trans*-1,2-bis(4-pyridyl)ethene (1:1)
4-hydroxybenzoic acid and 1,2-bis(4-pyridine)ethane (2:1)
3-hydroxypyridine and isophthalic acid (1:1)
L-ascorbic acid and nicotinic acid (1:1)



Grinding
Synchrotron
Simulated Annealing

Lapidus, et al., *Cryst.Growth.Des.*, (2010), 10, 4630

Carbamazepine: indomethacin (1:1)

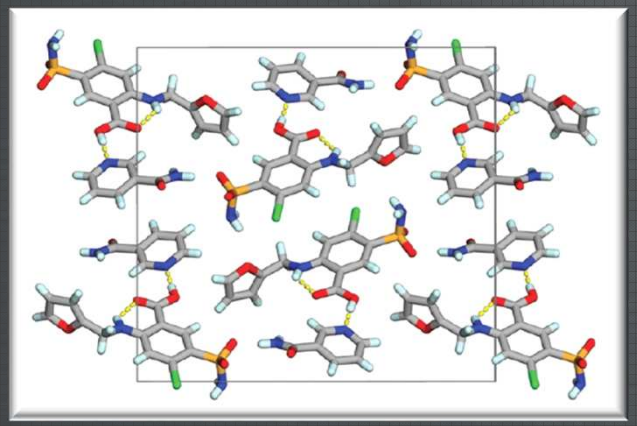


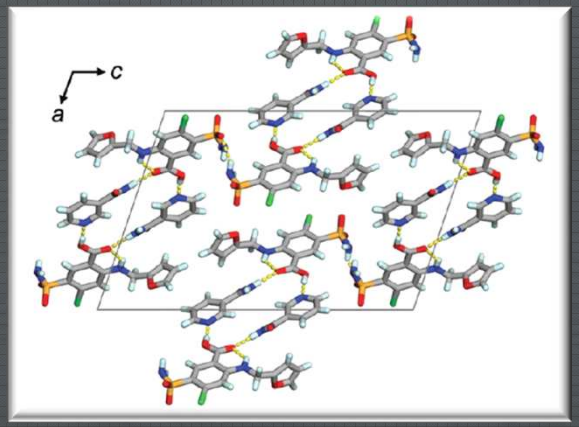
Dry grinding
Simulated Annealing
Laboratory data

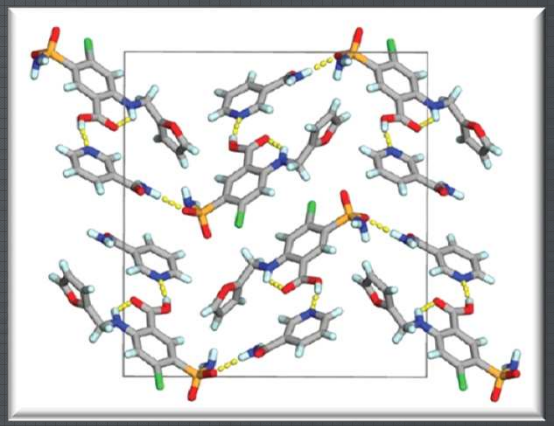
Majumder, Buckton, Rawlinson-Malone, Williams, Spillman, Shankland & Shankland, *CrystEngComm.*, (2011), 13, 6327

SDPD of Cocrystals

Furosemide:nicotinamide (1:1)

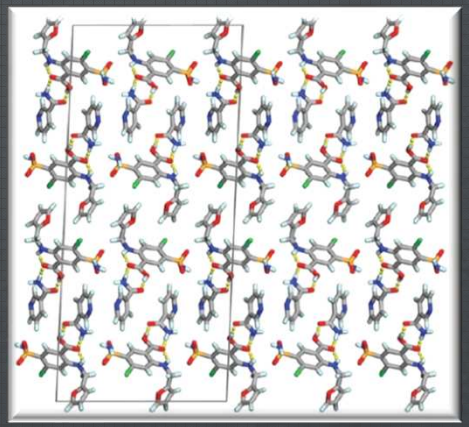


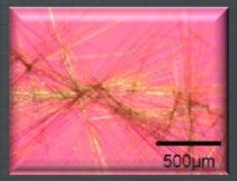


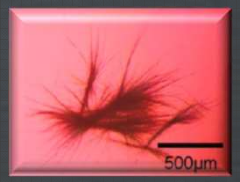


Four cocrystal polymorphs
Solvent crystallisation / drying
Parallel Tempering
Laboratory data

Cocrystal/salt from ΔpKa?

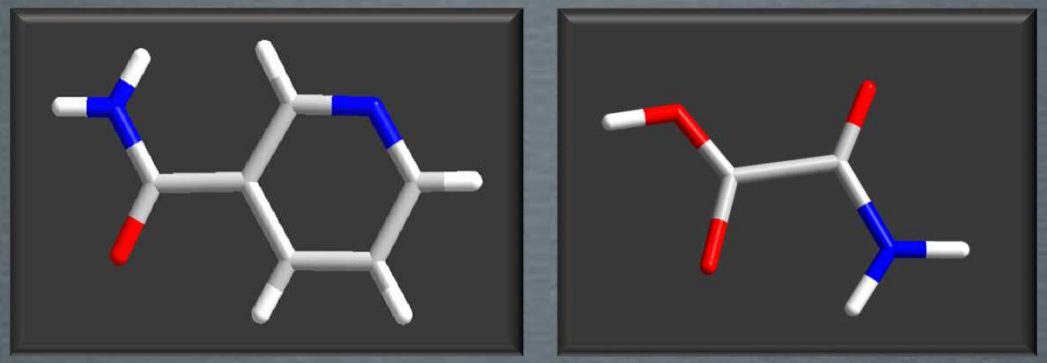






Ueto, Takata, Muroyama, Nedu, Sasaki, Tanida & Terada,
Cryst.Growth.Des., (2012), 12, 485

Nicotinamide : Oxamic Acid

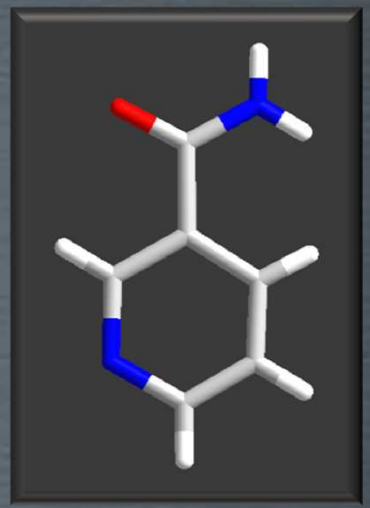


Crystallisation from MeOH, 1:1 ratio
Solid state IR – salt
GC & EA & NMR – 1:1 stoichiometry

Structure determination from lab PXRD (DE)
2 independent molecules, 14 parameters
210000 *Evaluations (1500 Generations),* R_{wp} *= 10.38%*

Structure solution (DE) – rigid body →

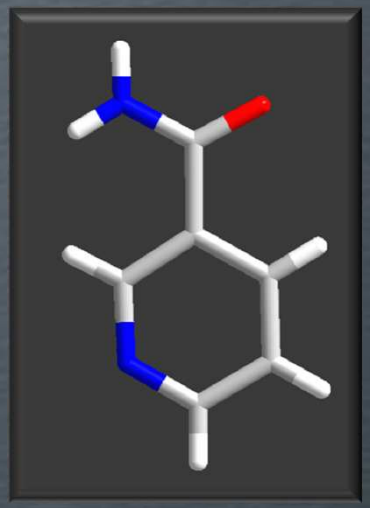
anti R_{wp}=10.38%



Restrained Rietveld refinement indicated 'flip' of amide group

Syn conformation as DE model – rigid body →

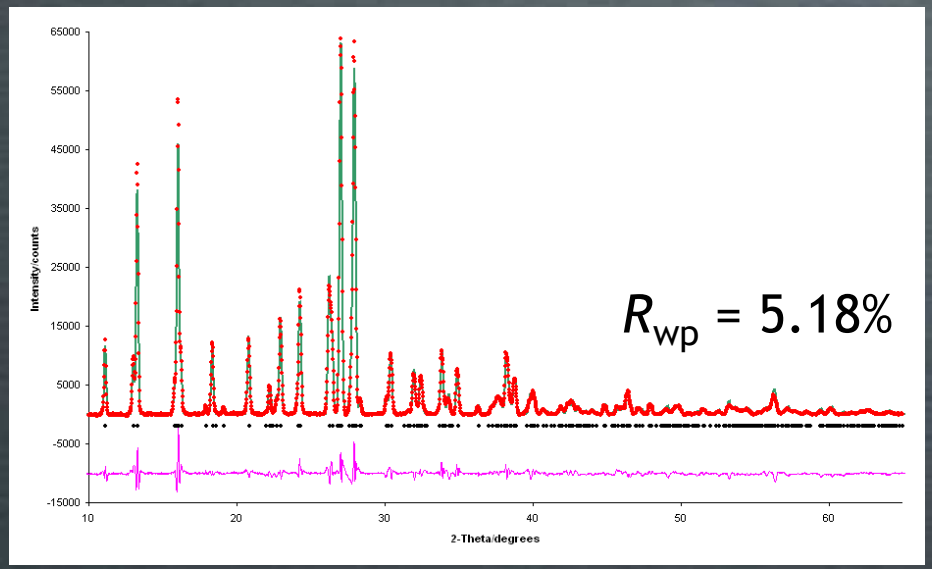
syn R_{wp}=11.21%

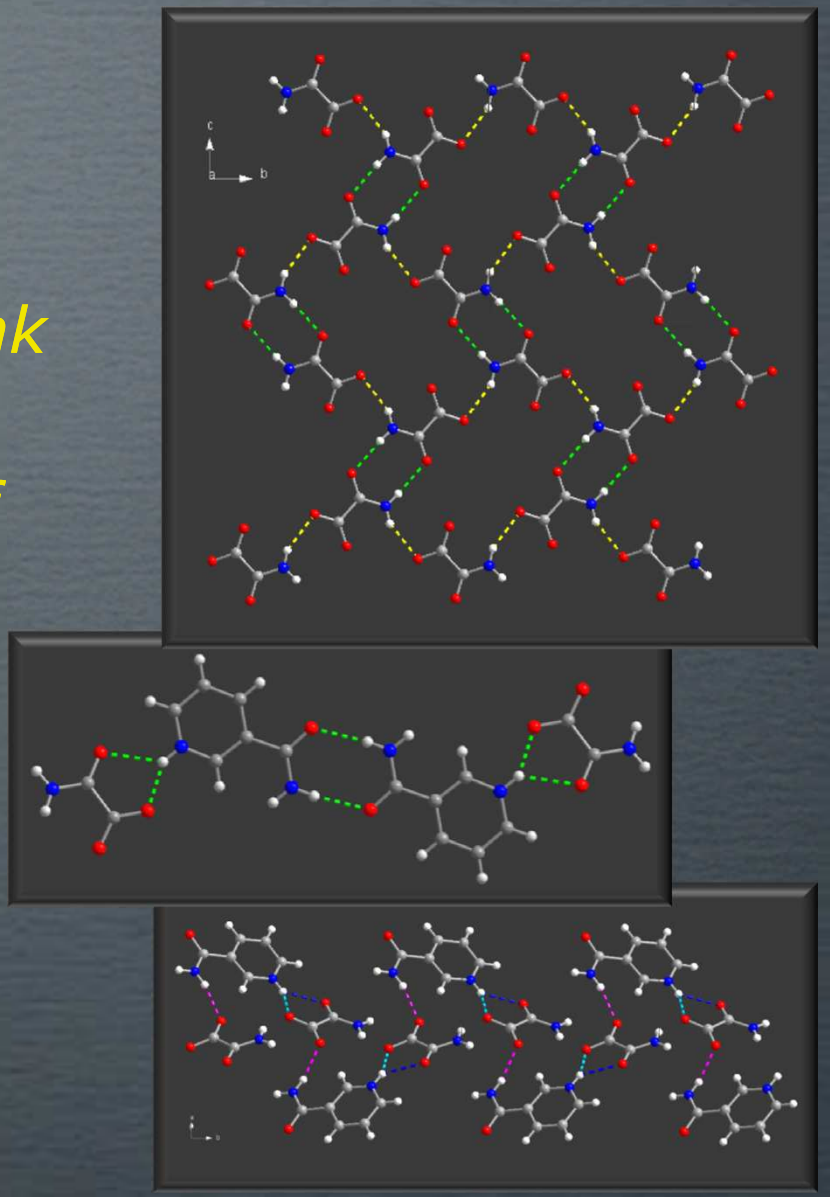


DE solution *correctly* located *solution minimum*, but amide group *incorrect* compared to final *refined relaxed* structure

Nicotinamide : Oxamate

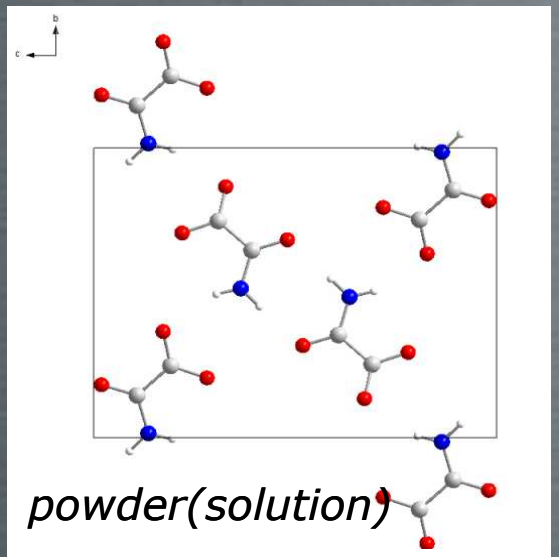
- Distinct layers of molecular components
- 1:1 salt form
- *Bifurcated hetero N(H)…O link*
- *Amide dimer*
- *Oxamate amide-amide motif*



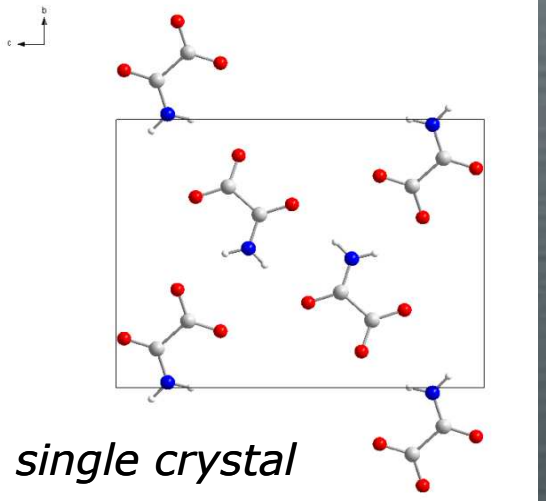


Nicotinamide : Oxamate

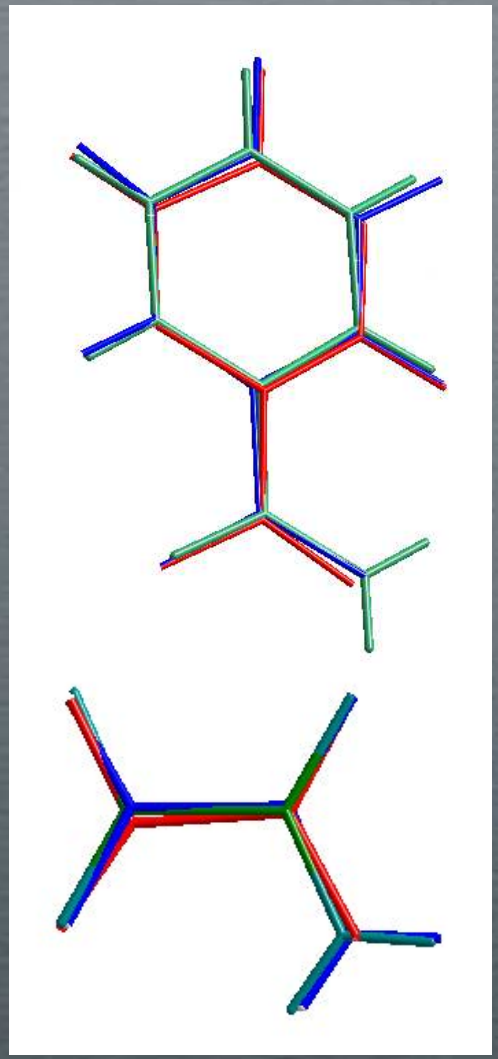
Structure & syn-conformation confirmed by single crystal

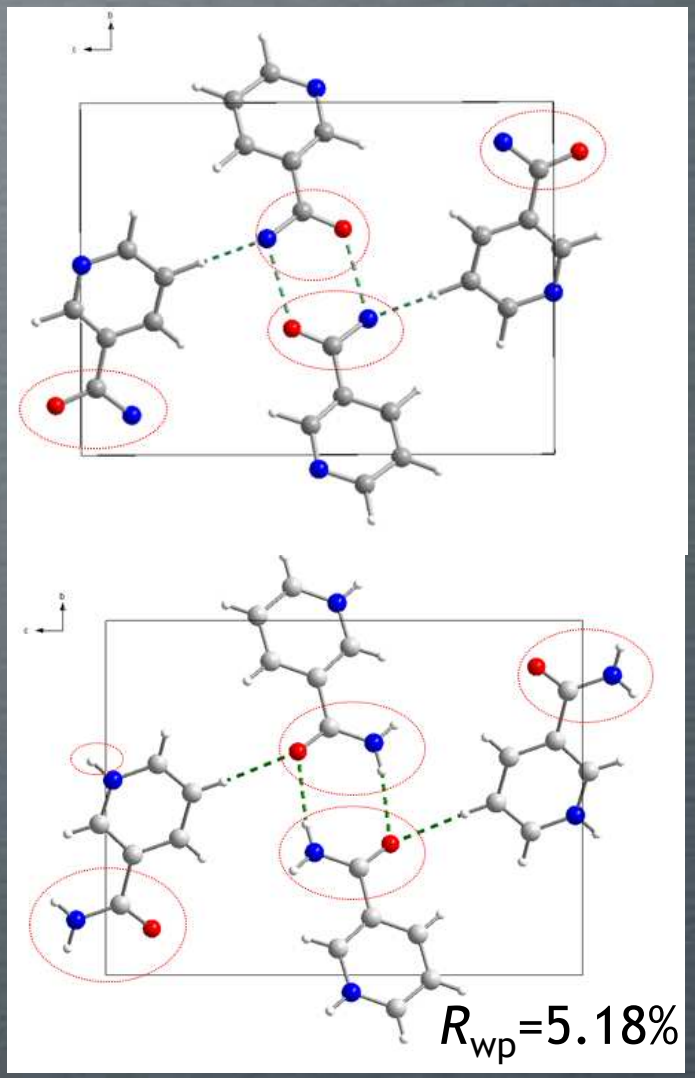


powder(solution)



single crystal





R_{wp}=5.18%

Nicotinamide with … Succinic Acid

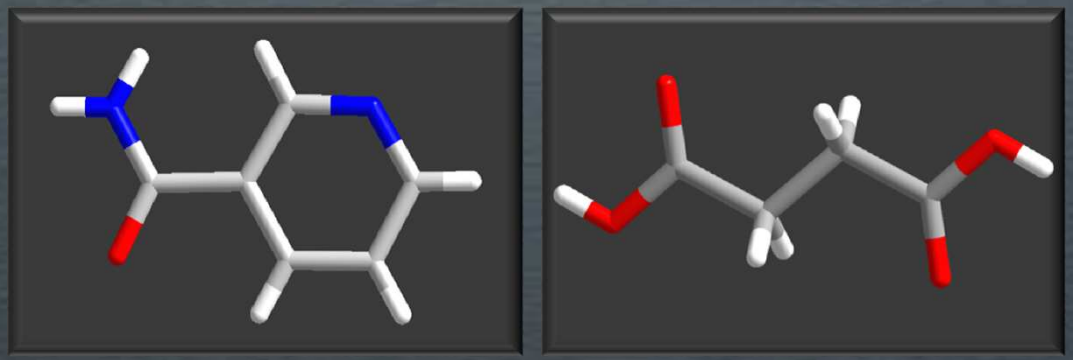
- Nicotinamide is a prolific coformer with dicarboxylic acids in stoichiometric variations

Karki, Friscic & Jones., *CrystEngComm,* (2009), 11, 470

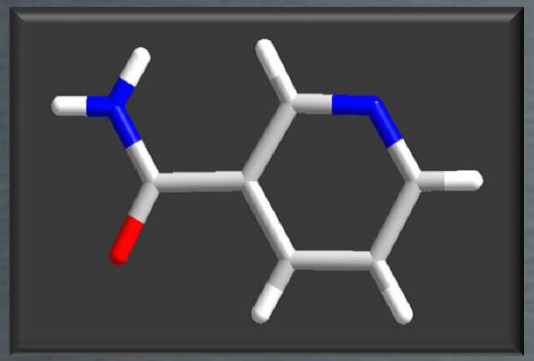
oxalic	malonic	succinic	glutaric	adipic	pimelic	suberic	azelaic	sebacic	fumaric
1:1			1:1	1:1	1:1	1:1	1:1	(1:1)	1:1
(2:1)	2:1	(2:1)		2:1	(2:1)	2:1		2:1	2:1

Amide:Acid Stoichiometry

Athimoolan et al., *Acta Cryst.,* (2007), 63, o263 Orola & Veidis., *CrystEngComm,* (2009), 11, 415

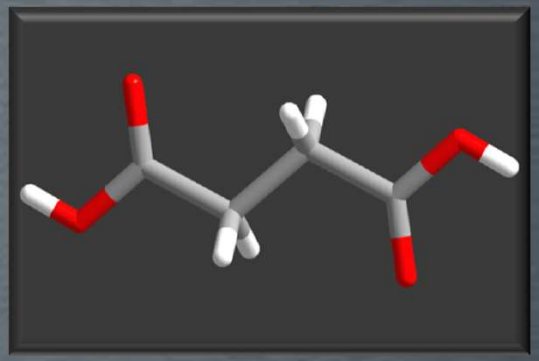


Nicotinamide : Succinic Acid 2:1

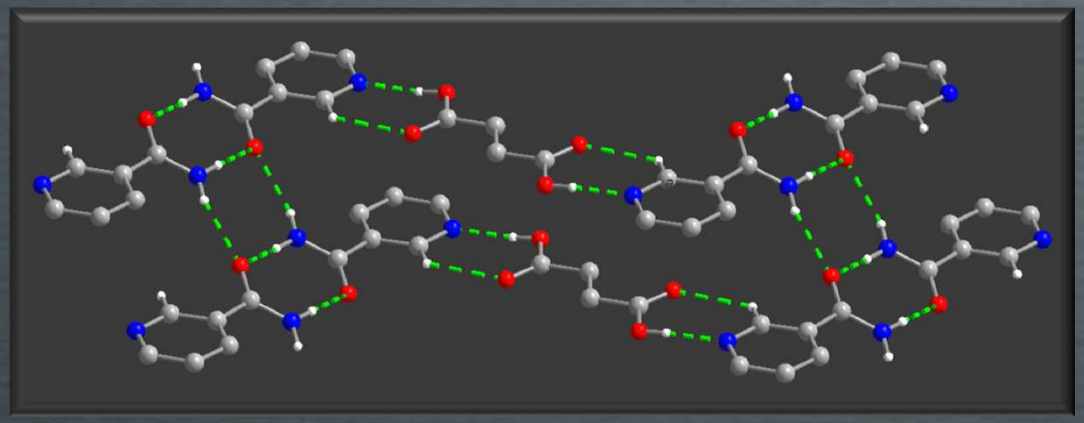


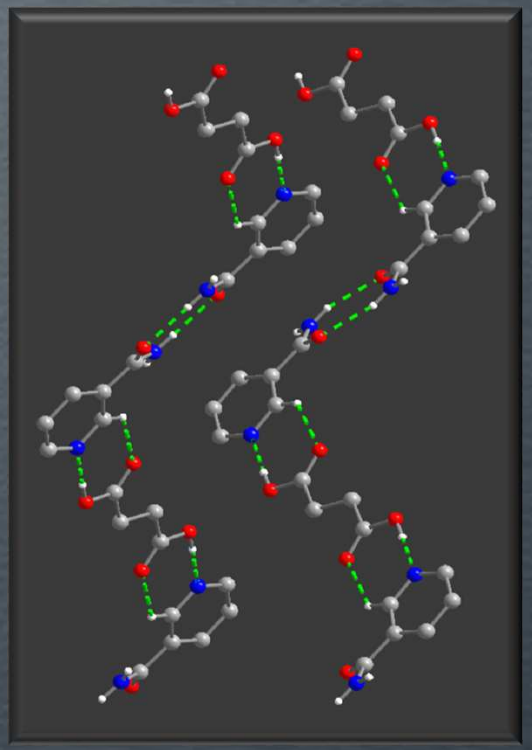
Crystallisation
from MeOH
1:1 ratio

2:1 cocrystal



(Single crystal determination)





- *Acid-pyridine & amide-amide motifs*
- *Anti & syn nicotinamide conformations*

Thompson, Voguri, Cowell, Male & Tremayne, *Acta Cryst,* (2010), C66, o421

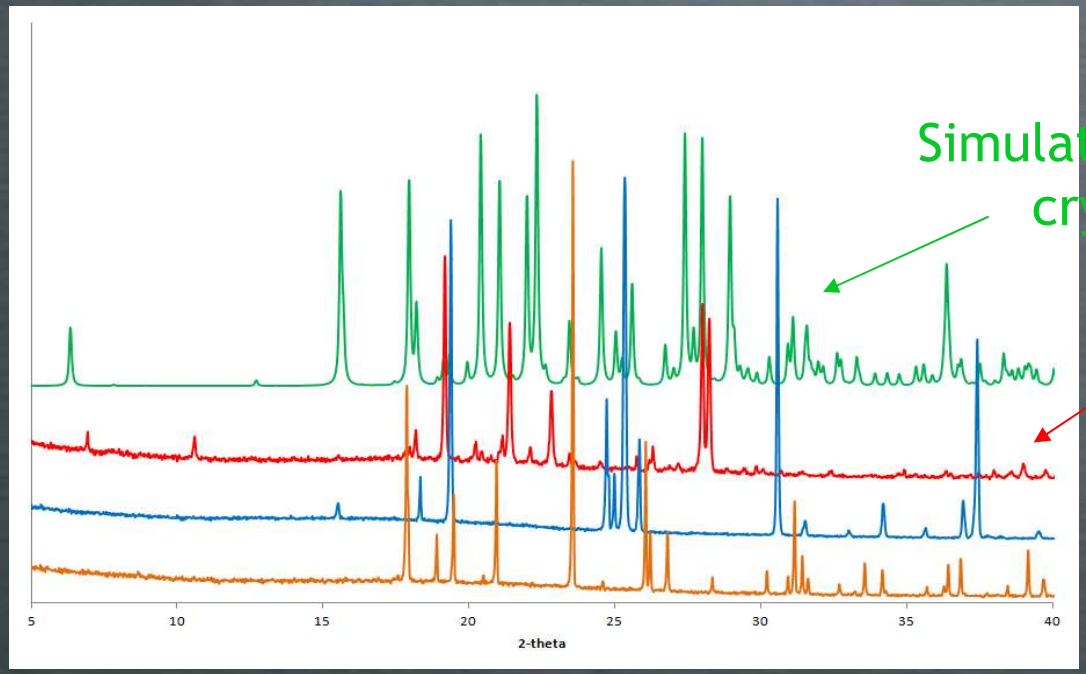
Nicotinamide : Succinic Acid 1:1

Crystallisation (MeOH), 1:1 ratio in 'controlled conditions'

Fine polycrystalline material

Solid state IR – inconclusive

GC & EA & NMR – 1:1 stoichiometry

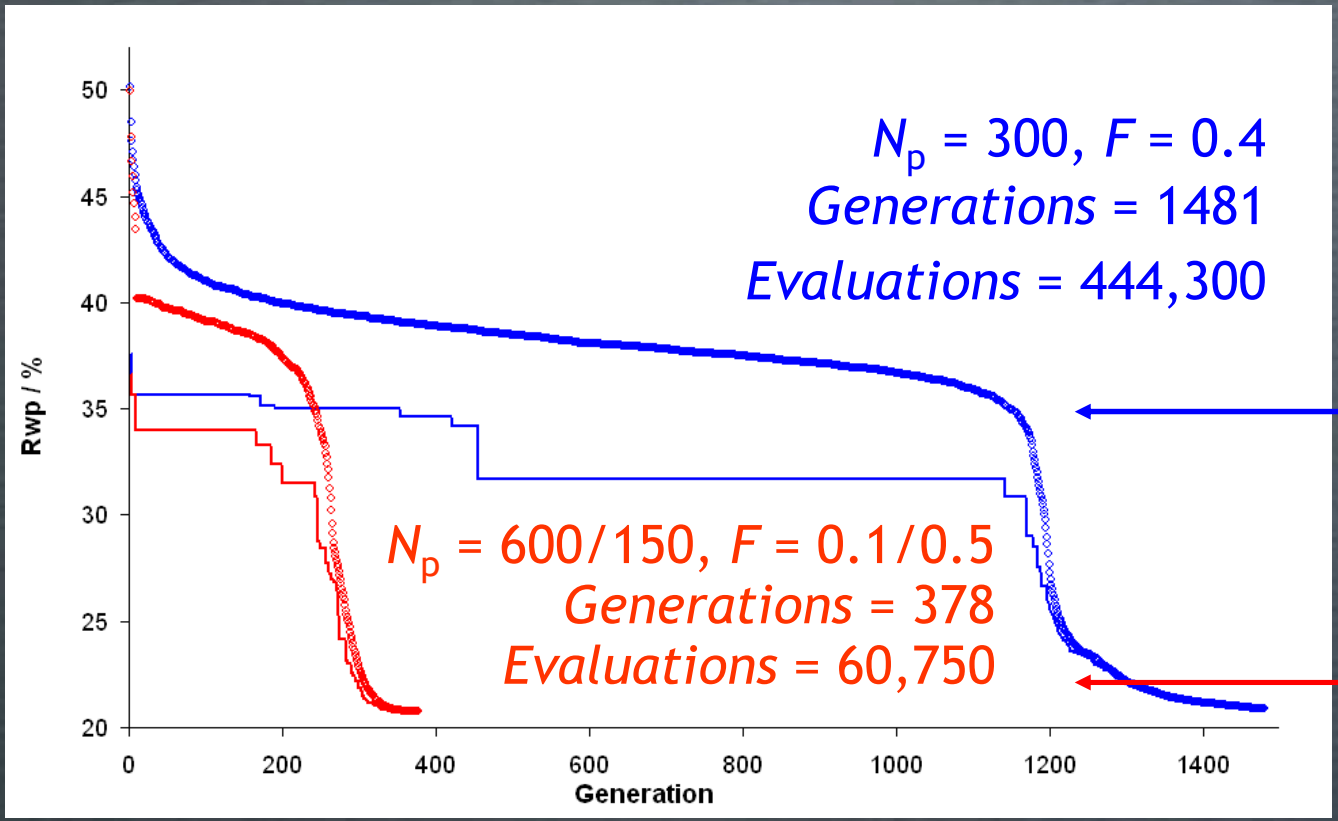


Structure determination from *PXRD (using DE)*

2 independent molecules, 16 parameters

More efficient optimisation……

- Evolutionary algorithms:
  - ⟶ population of trial structures
  - ⟶ mating, mutation & natural selection until global minimum is found

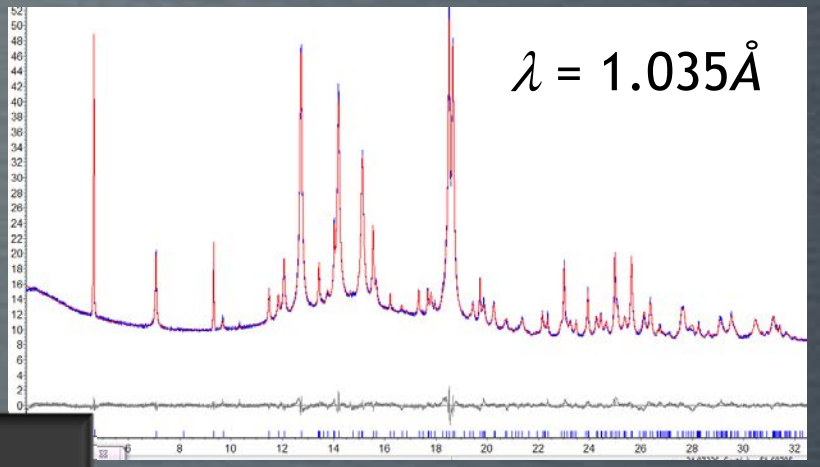


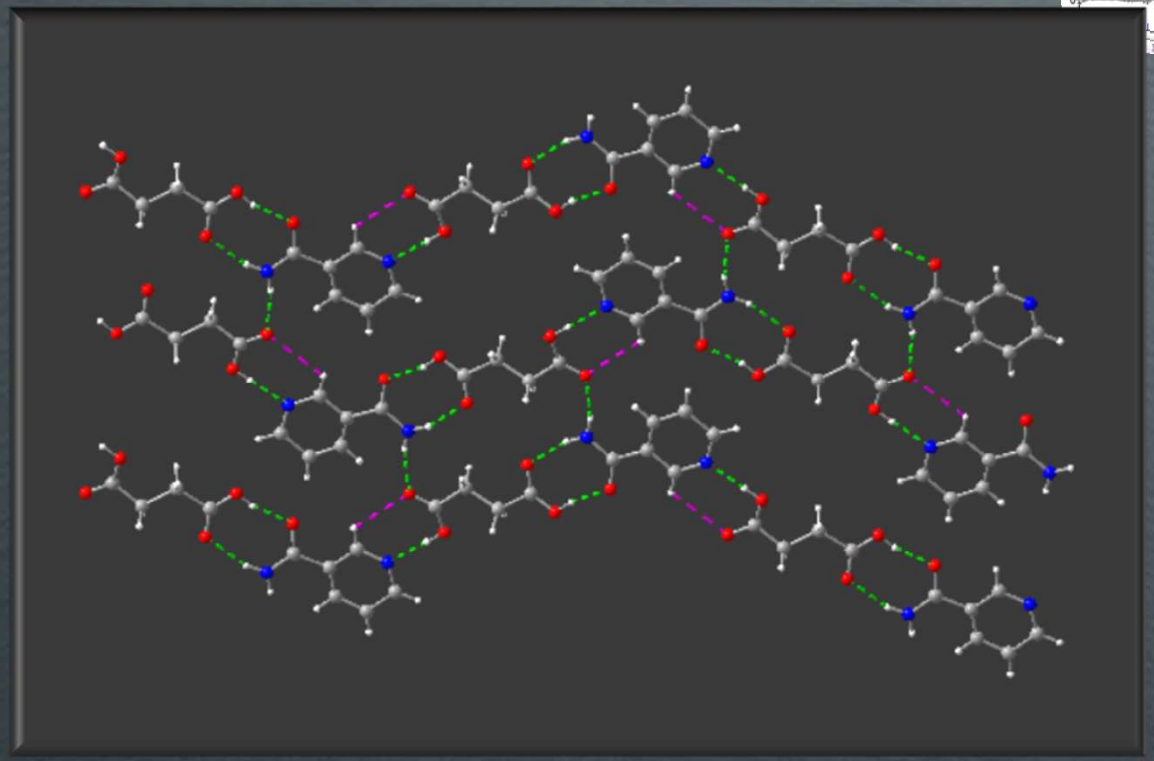
Traditional DE

Population-managed 'eugenic' DE

Nicotinamide : Succinic Acid 1:1

- Acid-pyridine & amide-acid motifs
- Distinctive supramolecular chain motif (1:1)

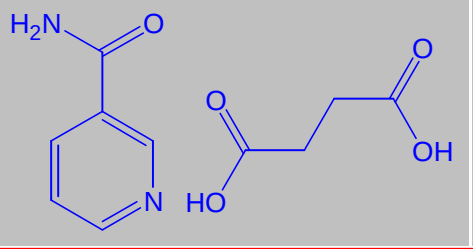
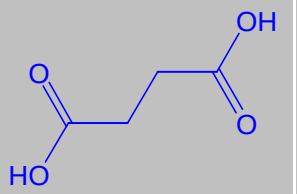
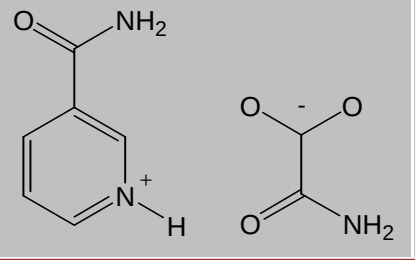
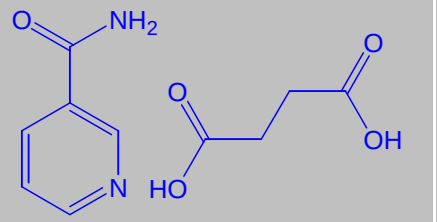
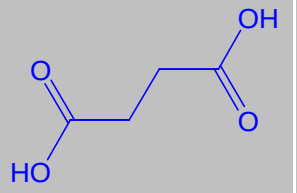
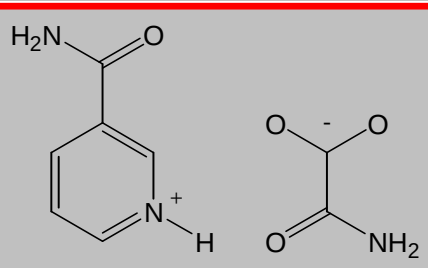
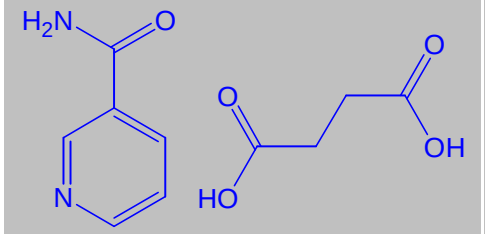
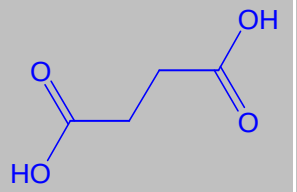
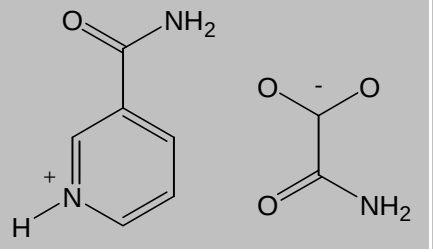
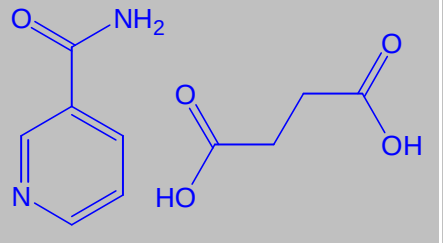
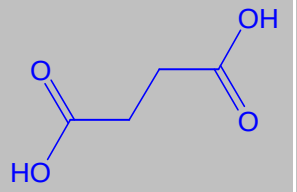
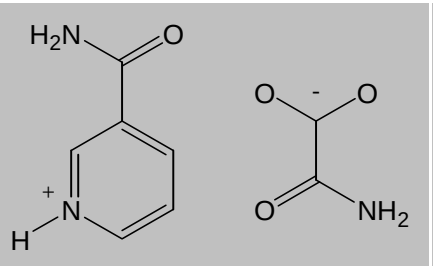




Anti nicotinamide & *Cis* succinic acid conformation?

Not in CSD
but isostructural with suberic & fumaric 1:1

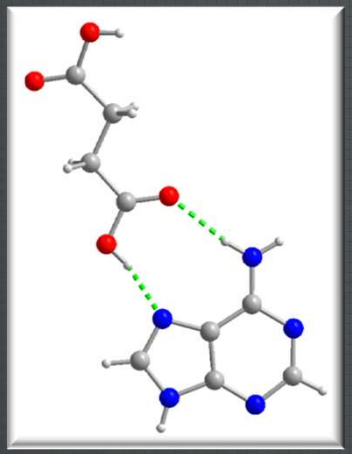
Is the Conformation Correct?

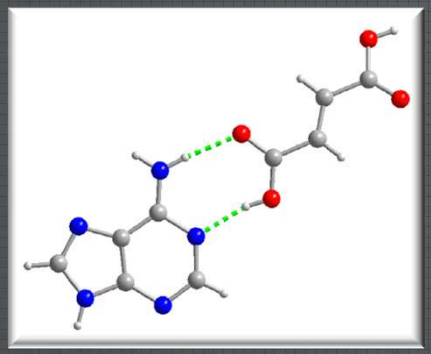
Conformation	R_{wp}(%)		R_{wp}(%)	Conformation	R_{wp}(%)
	**3.95** (4.37)		**4.14**		**5.65**
	4.77 (4.61)		4.80		6.04
	5.02 (4.63)		5.32		6.38
	5.63 (5.24)		5.76		6.79

Tautomer control: adenine adducts

- Adenine forms adducts with diacids with reduced melting point

9H cocrystals

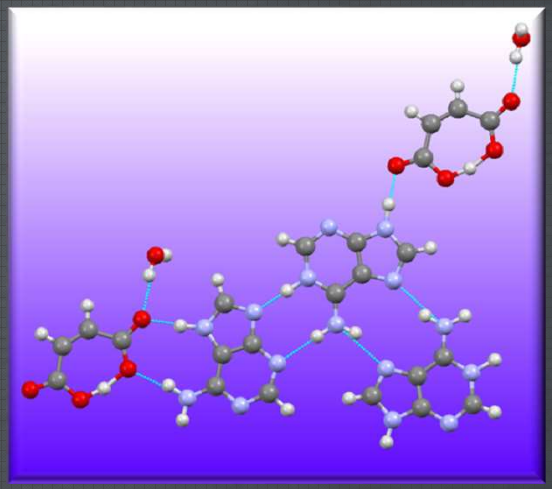




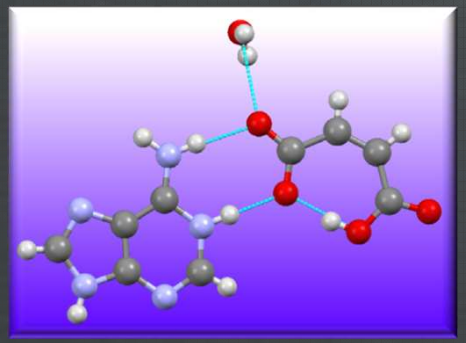
Thompson, Elias, Male & Tremayne, *Cryst.Growth & Des.,* (2013), 13, 1464

1H,9H salt & 7H neutral

McHugh & Erxleben, *Cryst.Growth & Des.* (2011), 11, 5096

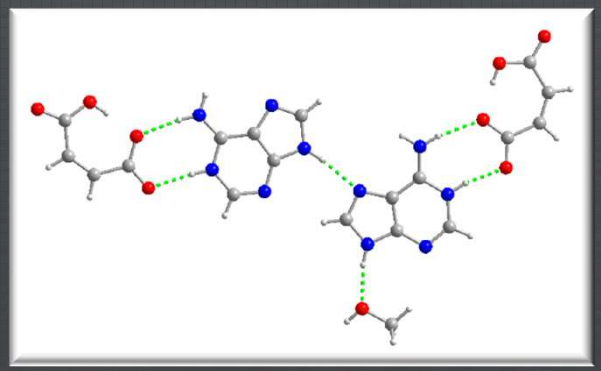


1H,9H salt

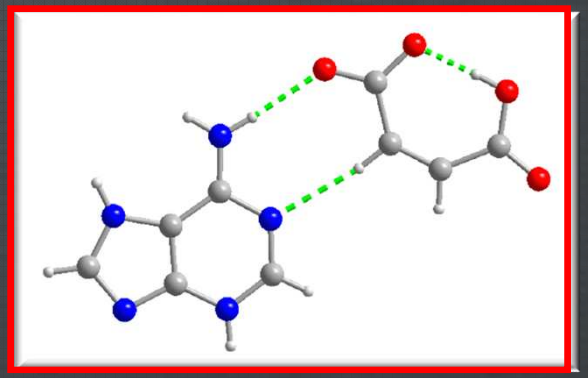


Sridhar & Ravikumar, *Acta Cryst.* (2007), C63, o415

1H,9H salt



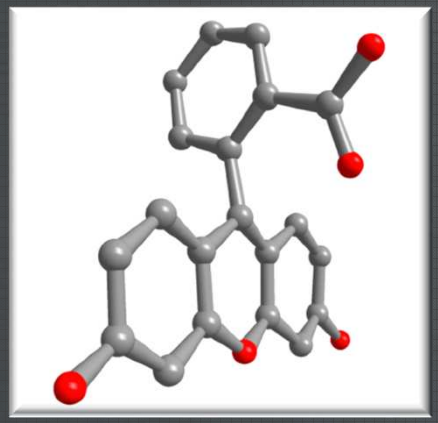
3H,7H salt

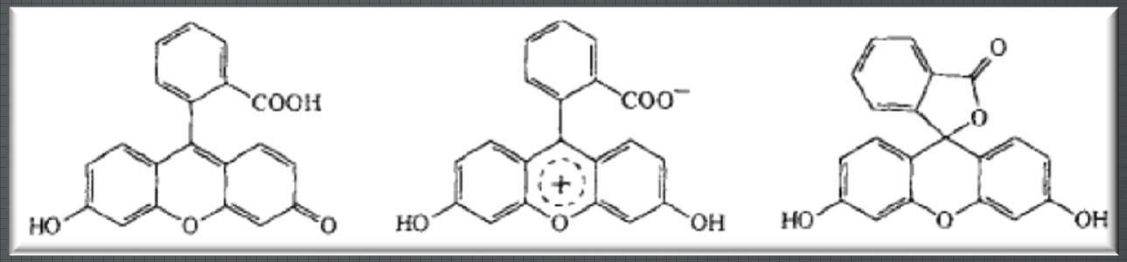


Thompson, Elias, Male & Tremayne, *CG&D,* (2013), 13, 1464

SDPD of Tautomers

Fluorescein





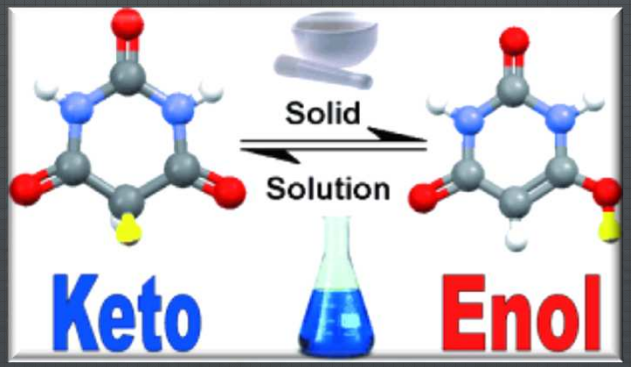
Monte Carlo
Synchrotron data

C-OH & C=O determined by restrained Rietveld

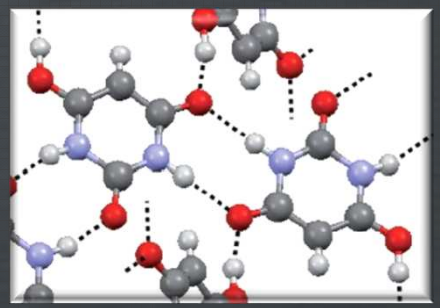
Tremayne, Kariuki & Harris, *Angew.Chem.Int.Ed.,* (1997), 36, 770

Barbituric Acid

Simulated Annealing
Lab/Synchrotron
data



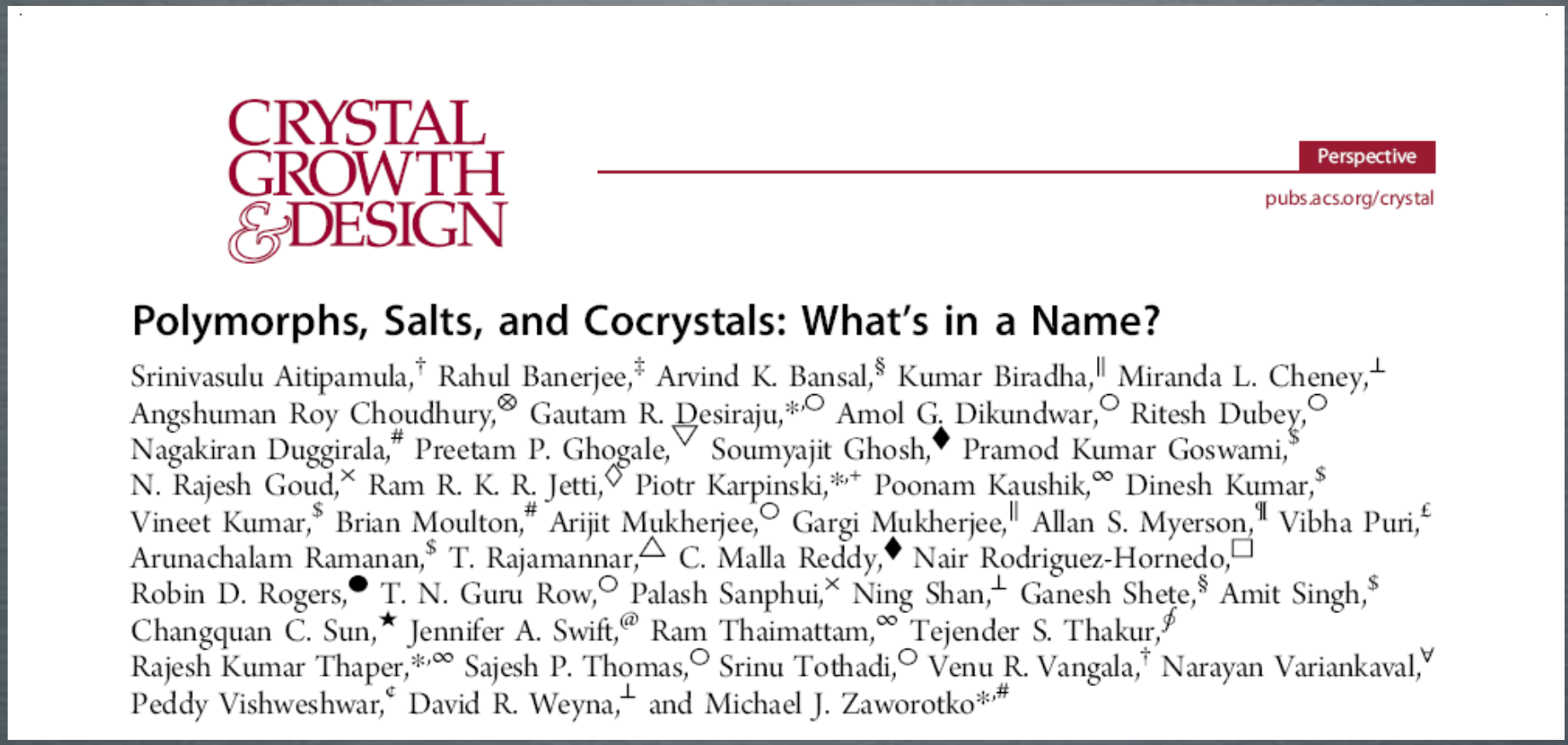
OCN framework revealed tautomer by Rietveld



New tautomeric polymorph stabilized by Hbonds:

M.U.Schmidt et al., *Angew.Chem.Int.Ed.,* (2011), 50, 7924

Is it a Cocrystal or a Salt?



CRYSTAL GROWTH & DESIGN

Perspective

pubs.acs.org/crystal

Polymorphs, Salts, and Cocrystals: What's in a Name?

Srinivasulu Aitipamula,[†] Rahul Banerjee,[‡] Arvind K. Bansal,[§] Kumar Biradha,[∥] Miranda L. Cheney,[⊥] Angshuman Roy Choudhury,[⊗] Gautam R. Desiraju,[*,○] Amol G. Dikundwar,[○] Ritesh Dubey,[○] Nagakiran Duggirala,[#] Preetam P. Ghogale,[▽] Soumyajit Ghosh,[♦] Pramod Kumar Goswami,[$] N. Rajesh Goud,[×] Ram R. K. R. Jetti,[◇] Piotr Karpinski,[*,+] Poonam Kaushik,[∞] Dinesh Kumar,[$] Vineet Kumar,[$] Brian Moulton,[#] Arijit Mukherjee,[○] Gargi Mukherjee,[∥] Allan S. Myerson,[¶] Vibha Puri,[£] Arunachalam Ramanan,[$] T. Rajamannar,[△] C. Malla Reddy,[♦] Nair Rodriguez-Hornedo,[□] Robin D. Rogers,[●] T. N. Guru Row,[○] Palash Sanphui,[×] Ning Shan,[⊥] Ganesh Shete,[§] Amit Singh,[$] Changquan C. Sun,[★] Jennifer A. Swift,[@] Ram Thaimattam,[∞] Tejender S. Thakur,[ϕ] Rajesh Kumar Thaper,[*,∞] Sajesh P. Thomas,[○] Srinu Tothadi,[○] Venu R. Vangala,[†] Narayan Variankaval,[∀] Peddy Vishweshwar,[ç] David R. Weyna,[⊥] and Michael J. Zaworotko[*,#]

Crystal Growth & Design, (2012), 12, 2147

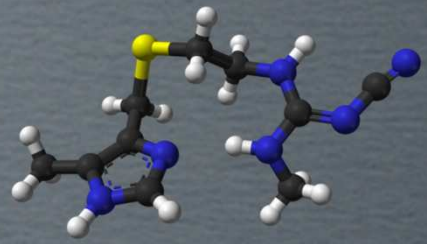
Cocrystal or Salt: Does it Really Matter?

Aakeroy, Fasulo & Desper, *Molecular Pharmaceutics*, (2007), 4, 317

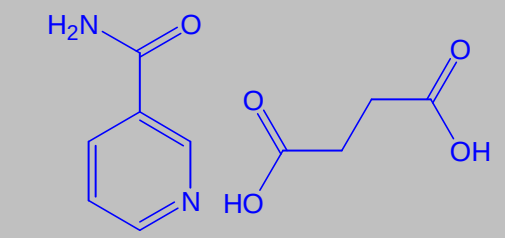
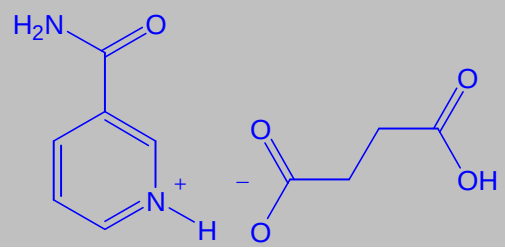
Is it a Cocrystal or a Salt?

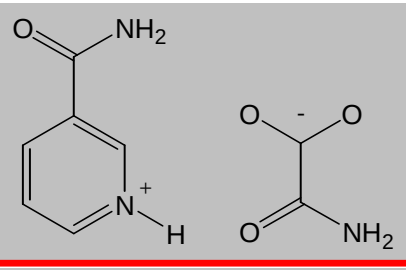
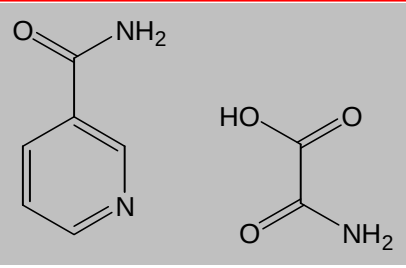
Can hydrogen atom positions be reliably determined from PXRD?

Cernik, Cheetham, Prout, Watkin, Wilkinson & Willis., *J.Appl.Cryst.*, (1991), 24, 222



Noritake *et al.*, *Appl.Phys.Lett.*, (2002), 81, 2008; J-P Soulie *et al.*, *J.Alloys Cmpds.*, (2002), 346, 200.

Conformation	R_{wp}(%)
	**3.95**
	4.04

Conformation	R_{wp}(%)
	**5.65**
	5.76

Conclusions …… and Acknowledgements

Adam Cowell
Duncan Bell
Raja Voguri
Laura Thompson
Benson Kariuki
Louise Male
Elizabeth Shotton

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