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From Discovery to Scale-up: α-Lipoic Acid:Nicotinamide Co-crystals in a Continuous Oscillatory Baffled Crystalliser

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Co-crystal Formers

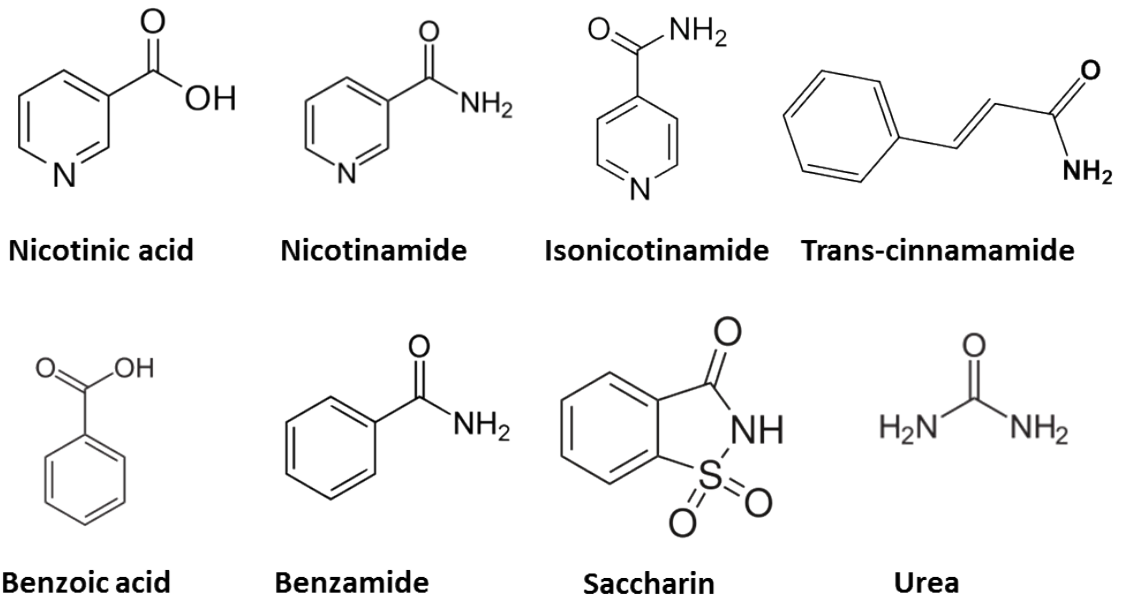

Fig. 1.Chemical structures of co-crystal former selected for co-crystallisation trials

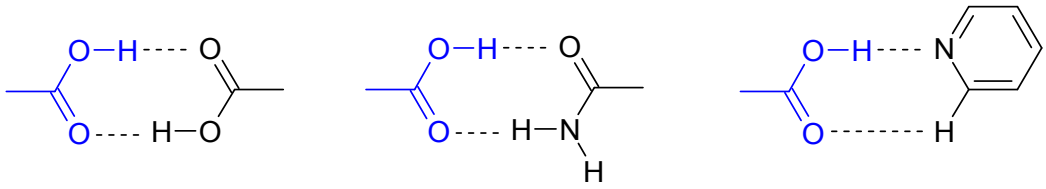

Fig. 2. Examples of potential H-bonded supramolecular synthons within carboxylic acid of ALA and various functional groups present in selected co-formers.

XRPD Analysis

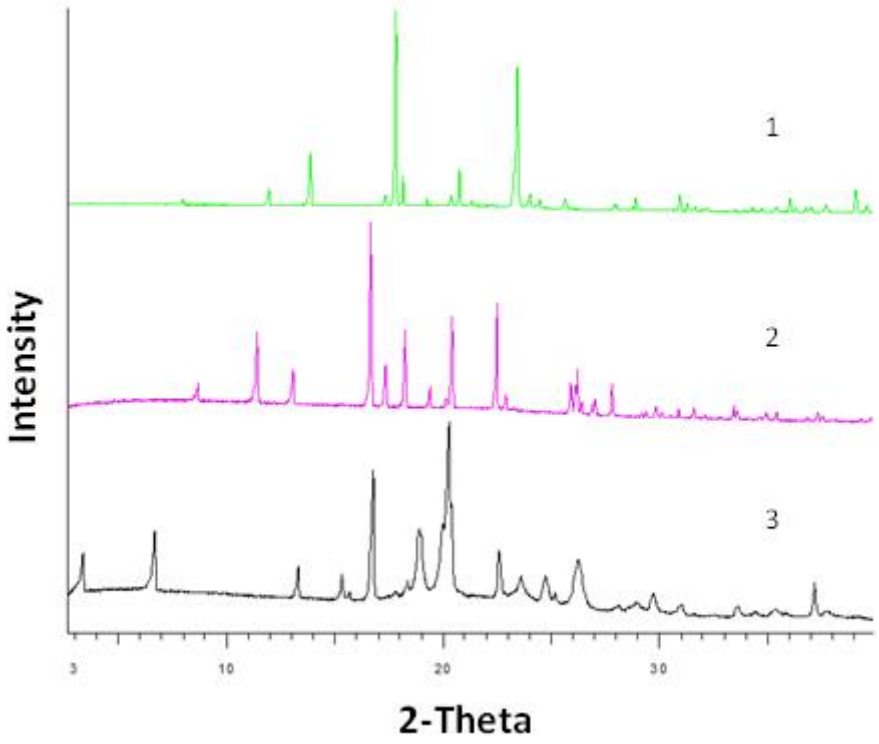

Fig. 3 XPRD patterns of co-crystals from OBC co-crystallisation trials (1. ALA; 2. NIC; 3. ALA:NIC co-crystals)

Thermal Analysis

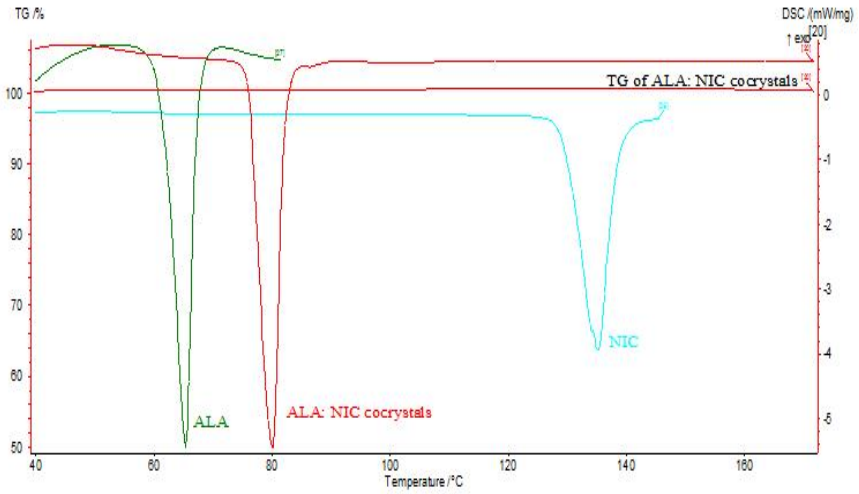

Fig. 4. DSC of ALA:NIC co-crystals

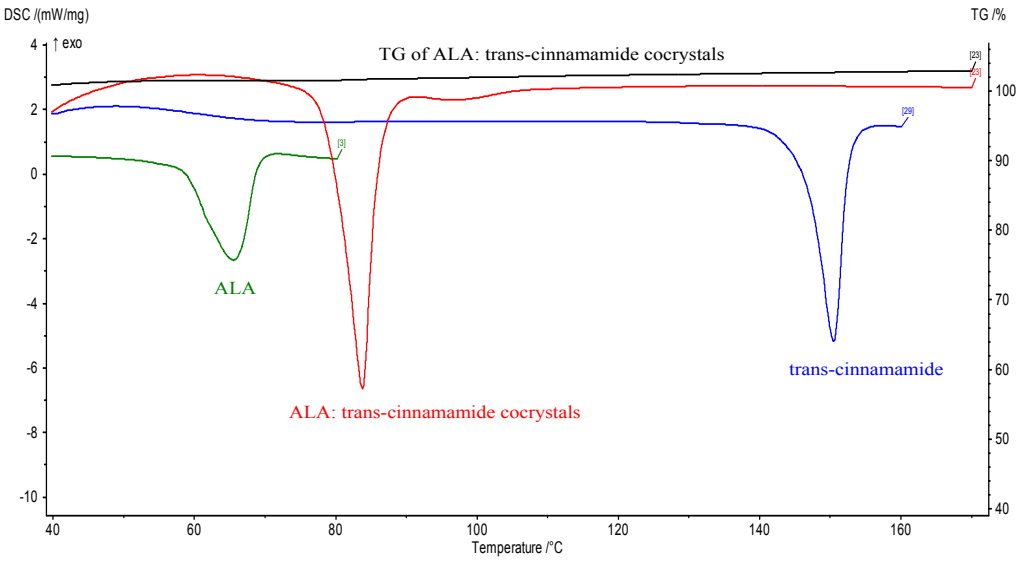

Fig. 5 DSC of ALA:trans-cinnamamide co-crystals.

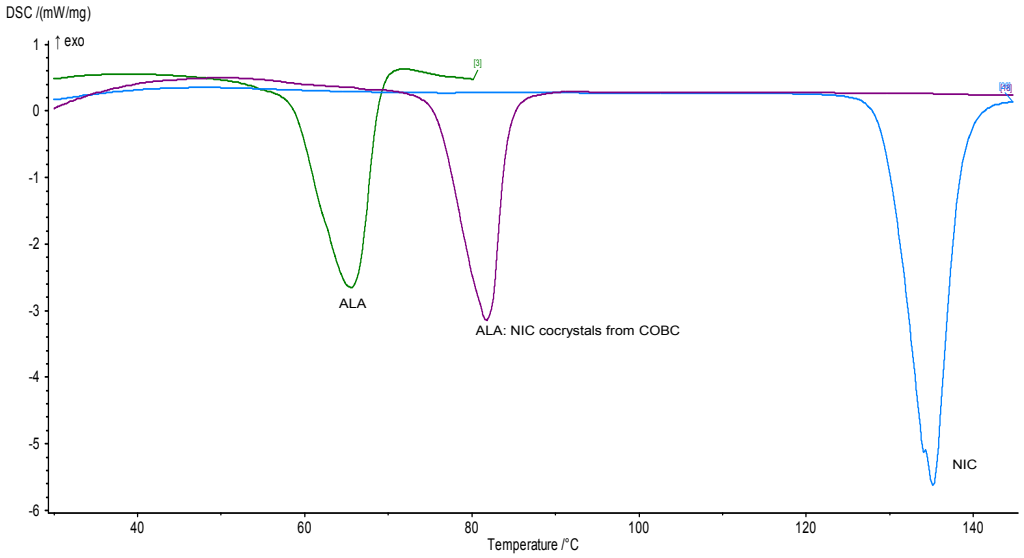

Fig. 6 DSC of co-crystals from OBC co-crystallisation trials

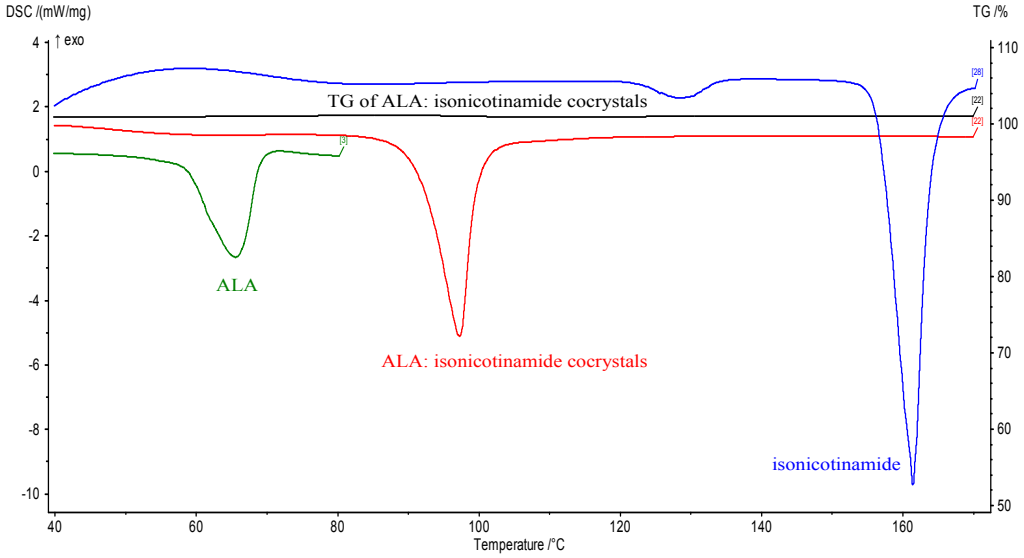

Fig. 7 DSC of ALA:ISN co-crystals.

XRPD and DSC data of ALS:ISN co-crystals samples obtained from various molar ratios of ALA and ISN (1:1, 1:2, 2:1 and 3:2) suggest that the stoichiometry of ALA:ISN co-crystals is 1:1. Preliminary assessment of samples of ALA:transcinnamide co-crystals also suggests 1:1 stoichiometry. Although further experiments would be required to confirm the structures including single crystals for both co-crystals.

IR spectroscopy

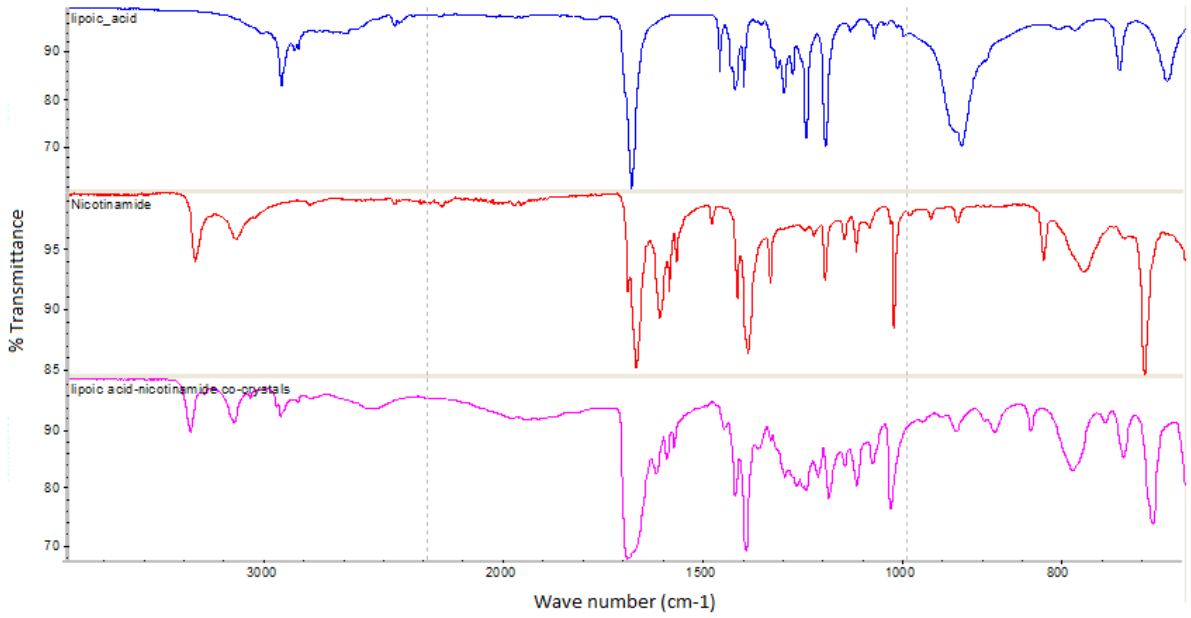

Fig. 8 FTIR spectra of ALA:NIC co-crystals and its components

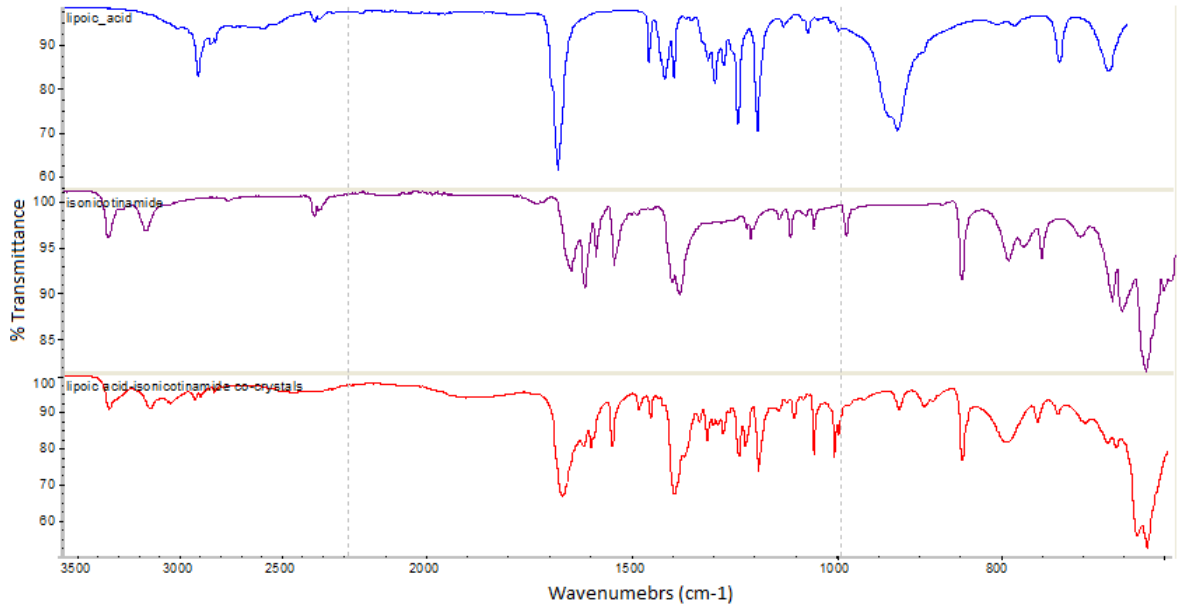

Fig. 9 FTIR spectra of ALA:ISN co-crystals and its components

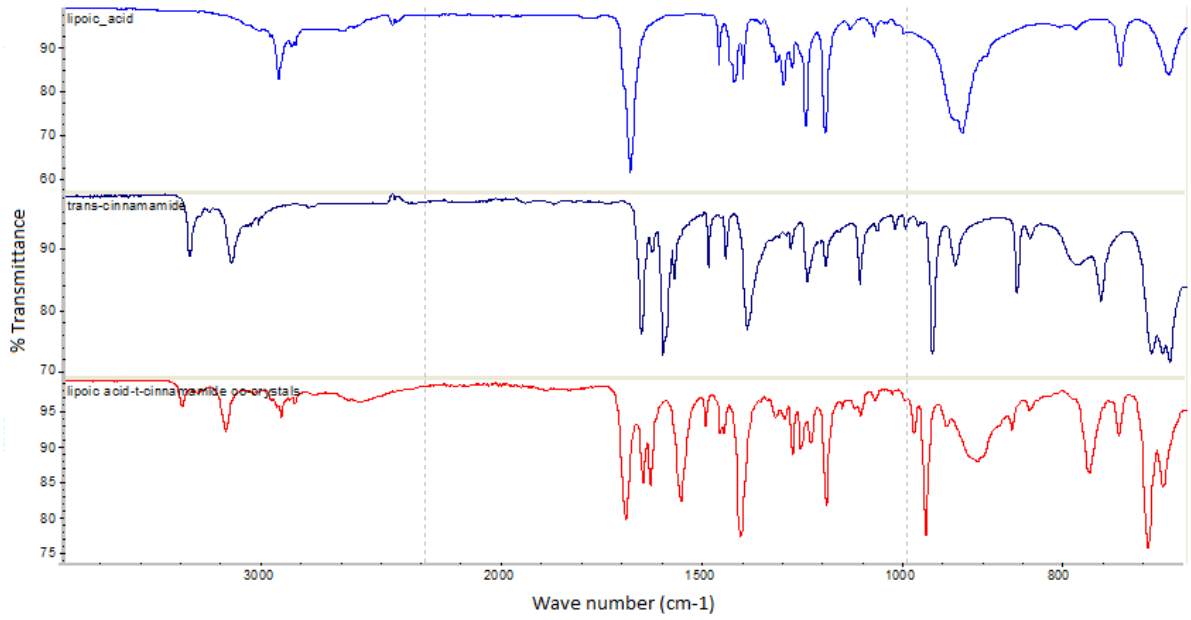

Fig. 10 FTIR spectra of ALA:trans-cinnamamide co-crystals and its components

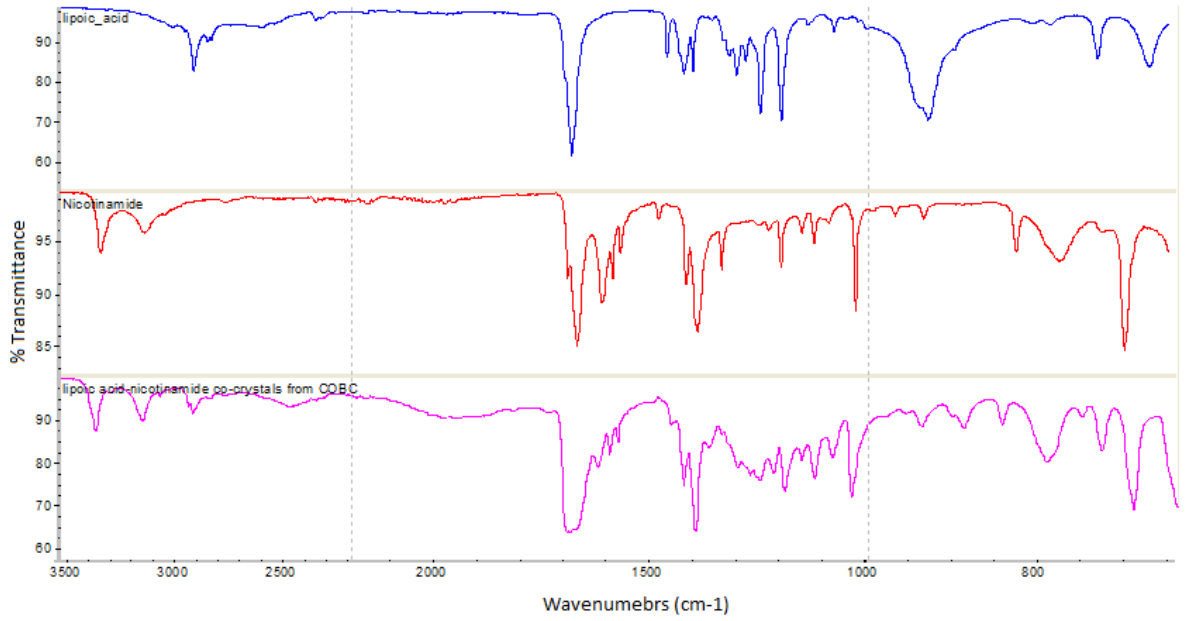

Fig. 11 FT-IR Spectra of ALA:NIC co-crystals obtained from three different COBC experiments.

Solubility Analysis

Table 1. Approximate solubility of ALA and NIC in representative solvents

Solvent	Solubility of ALA (g/L)	Solubility of NIC (g/L)	Results from co-crystallisation trials
Alcohol (methanol, ethanol, isopropanol, cyclohexanol)	~ 960 (IPA)	~ 670 (ethanol)	General pure co-crystals
water	~ 2	~ 1000	ALA (mainly) + co-crystals
Ethyl acetate	~ 900	<1	No co-crystals. NIC only
Ether (diethyl ether, diisopropyl ether, methyl t-butylether)	~50	<1	No co-crystals. NIC only
Alkane (hexane, cyclohexane)	< 5	<1	No products formed
Toluene	~ 25	<1	NIC (mainly) + co-crystals
Acetone	> 600	~ 44	NIC (mainly) + co-crystals

HPLC Analysis

Table 2. Thermal Stability of ALA and co-crystals determined by HPLC

Crystals	Original ALA purity (%)	ALA purity after 30 minutes at 60 ºC	ALA purity after 30 minutes at 80 ºC
ALA	100	61.83	17.94
ALA:NIC co-crystals	100	99.73	99.58
ALA:isonicotinamide coccrystals			99.9
ALA:trans-cinnamamide coccrystals			97.31

Hydrogen-Bonding in ALA:NIC Co-crystal

Table 3. Hydrogen-bonding present in ALA:NIC co-crystal. Hydrogen bonds with H..A < r(A) + 2.000 Å and <DHA > 110 °.

D-H	A	d(D-H) (Å)	d(H..A) (Å)	<DHA (°)	d(D..A) (Å)
O6-H6	N5	0.840	1.769	171.82	2.603
N2-H1N	O8	0.834	2.065	175.08	2.897
N2-H2N	O5	0.848	2.308	175.59	3.155
N3-H3N	O4	0.850	2.247	169.12	3.086
N3-H4N	O7	0.853	2.048	171.62	2.894
N1-H5N	O2	0.851	2.168	172.22	3.013
N1-H6N	O9	0.852	2.034	177.03	2.885
O1-H1	N4	0.840	1.806	168.20	2.634
O3-H3A	N6	0.840	1.784	174.68	2.622

Pawley-type Refinement

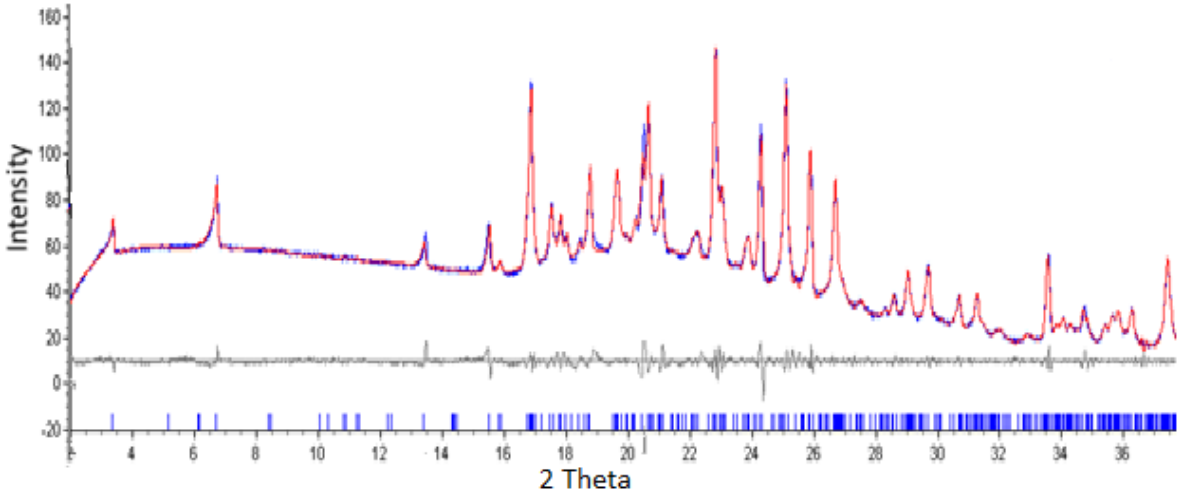

Fig. 12 Pawley-type refinement of lattice cell parameters of ALA:NIC structure obtained from SXD against the XRPD pattern of samples obtained from COBC experiments in the

range of 3-37° 2θ. Observed and calculated profiles are represented in blue and red colour respectively. The black curve represents the difference plot [(yobs - ycalc)/σ(yobs)].