Towards Engineering the Polymorphs of Cocrystals

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Recently we reported the ability of the anti-malarial drug 11-azaartemisinin to form cocrystals with a variety of coformers. [1-3] For carboxylic acids roughly 50\% of systems studied allowed formation of cocrystals driven by a well-preserved lactam-acid synthon. In a series of arylsulfonyl derivatives of 11-azaartemisinin we further demonstrated that new polymorphs could be accessed via seeds of the molecular analogues in which the aryl group substituents were varied by single point 'atomic mutation' resulting in a different structure type. [4] We were interested to see whether a combination of these two approaches could allow extension of this route to afford polymorphs of molecular cocrystals. As a first step we have now prepared 15 substituted variations of the cocrystal between 11-azaartemisinin and salicylic acid (11-Aza:SalA) using substituted SalA compounds. In all cases to-date a molecular pair with retained synthon is present (Fig 1) and these form 2-fold screw stacks with similar geometry. In some cases (e.g. from 5-Br-SalA, 5-I-SalA) the products are clearly isostructural with the parent cocrystal, which has a monoclinic $P2_1$ polar structure with $Z' = 1$ and just have simple lattice expansion. Others might be deemed 'homostructural' with highly related packings, but with slippage of molecular layers so that the interactions and contacts between the 1D stacks are modified. (4-Br-SalA) Further variations include doubling of asymmetric unit to create two independent stacks, that have opposite 'polarity' whilst still being $P2_1$. (5-Cl-SalA). Polarity reversal is also possible by adopting an orthorhombic $P2_12_12_1$ arrangement, again with a 'doubled' cell. (Fig 2, 3,5-Cl-SalA). Quadrupled axis systems are also identified so that the chiral 1D stacks are rotated in either 41 or 43 screw manner. (e.g. 3-Me-SalA, 5-Me-SalA respectively) A total of seven structurally distinct ways of arranging the 1D stacks have been identified which might be deemed 'Quasi-polymorphs'. That is they each represent a possible packing of the basic 11-Aza:SalA molecular pair. We are now proceeding to see whether seeding using one form can induce another cocrystal to adopt the alternative arrangement and hence a true polymorph of the same cocrystal composition and will report our current findings. References 1. Nisar et al., Acta Cryst. (2017). A73, a268. 2. Nisar et al., CrystEngComm (2018). 20, 1205-1219. 3. Nisar et al., Acta Cryst. (2018). C74, 742-751. 4. Nisar et al., Acta Cryst. (2018). A74, a104.