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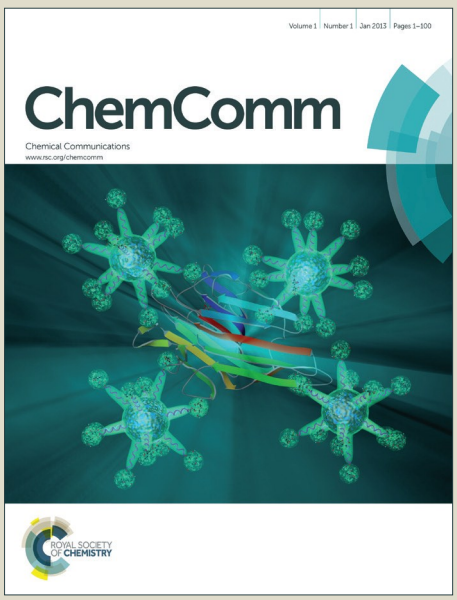

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Multicomponent ternary cocrystals of the sulfonamide group with pyridine-amides and lactams

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Receipt/Acceptance Data **[DO NOT ALTER/DELETE THIS TEXT]**
Publication data **[DO NOT ALTER/DELETE THIS TEXT]**
DOI: 10.1039/b000000x [DO NOT ALTER/DELETE THIS TEXT

SMBA was selected as a bifunctional sulfa drug to design ternary cocrystals with pyridine amides and lactam coformers. Supramolecular assembly of five ternary cocrystals of p-sulfonamide benzoic acid with nicotinamide and 2-pyridone is demonstrated and reproducible heterosynthons are identified for crystal engineering.

Crystal engineering[1] connects chemistry to crystallography and it serves as a rationale for the understanding of molecular solids. The design and assembly of three complementary functional groups during cocrystallization is extremely challenging because this process involves a subtle discrimination of selective hydrogen bonding among multiple recognition sites. Furthermore, several factors such as the shape or conformation of molecules, solubility match between the components, and the size of coformers[2] must be matched. The daunting task of assembling three different molecular components in the same crystal lattice has been approached by the simultaneous optimization of hydrogen bonds and intermolecular interactions, space filling or close packing, and chemical and geometrical factors in molecular recognition.[3] "Making a stoichiometric ternary cocrystal from three substances that are all solids under ambient conditions is far more difficult and demands a good knowledge of the interaction preferences".[4] Even as design strategies to make binary cocrystals are well studied,[5] ternary cocrystals are relatively less explored in comparison.[6] The reported systems deal with hydrogen bond preferences and their strengths,[6a] shape/size mimicry of coformer,[2] charge transfer interactions,[6f] and halogen bonds,[6g] among other factors to assemble ternary systems. Several of these studies target model compounds in which the functional groups are deliberately selected to maximize directed intermolecular interactions and minimize competition or cross-over pairing; the latter will result in unpredictable results or no ternary system. Secondly, the sulfonamide group, which is a cornerstone for sulfa drugs, has been studied for pharmaceutical binary cocrystals only recently,[7] and no example of a ternary system involving the sulfonamide group is reported. The second functional group in the sulfonamide molecule was selected as the carboxylic acid to provide p-sulfonamide benzoic acid (SMBA, chemical name 4-sulfomylbenzoic acid). Yet another motivation for selecting SMBA was that the SO_2NH_2 and COOH functional groups are present in a few well-known drugs, such as furosemide and bumetanide. Ternary cocrystals are important not only as a challenge in supramolecular assembly, but could also find application in pharmaceutical materials,[6e,i] e.g. two different drugs in a ternary cocrystal. The self-assembly of three different chemical components (A, B, C) residing in the same crystal lattice is one among multiple possibilities, and hence an entropic uphill: (1) any two of the three components may combine to give a binary system (AB, BC or AC); (2) the ternary product should be less soluble than the binary possibilities and/or the pure components; (3) the components must be congruent (similar solubility) in some solvents while non-congruent in others; (4) hydrogen bonding between A and B (or C) must be strong and specific, while that between B and C should be moderate. Even with the best of planning (enthalpy, hydrogen bonding maximized), the results can be unpredictable, e.g. the appearance of polymorphs, solvates and hydrates during crystallization. If the three components are ground[8] to avoid solubility issues and solvated by-products, then what will be the reactivity sequence? Will crystal nucleation follow a binary to ternary sequential two-step process or give the ternary cocrystal directly in a single step?

There are about 70 X-ray crystal structures of ternary systems in the Cambridge Structural database (ver. 5.36, May 2105 upda Table S1 and Figure S1, ESI†). The most recent result on ternary cocrystals is by Desiraju,[6h] wherein they combined interaction mimicry, synthon modularity, as well as weak interactions or halogen bonding to assemble three complementary components in a single crystalline adduct. Aakeröy[6a-c] have reported ternary systems based on carboxylic acid-pyridine and acid-amide supramolecular synthons between isonicotinamide, pyridyl and benzimidazolyl base by introducing carboxylic acids of varying strengths (pK_a's) to preferentially bond with pyridine and amide functional groups of different basicity. Ternary cocrystals of the anti-TB drug isoniazid,[6e] 1,3,5-cyclohexane tricarboxylic acid,[6d] as well as 3,5-dinitrobenzoic acid[6f] are known. A graded variation in hydrogen bond strength and basicity, size and shape of the coformers, together with mechanochemistry and controlled crystallization conditions for ternary cocrystals of sulfonamides are reported in this paper. Surprisingly, there is relatively little cocrystal engineering reported for sulfonamides.[7]

Our strategy was to explore the synthesis of ternary cocrystals from primary sulfonamides and cyclic amides (lactams) via t heterosynthons observed in binary systems. SMBA has sulfonamide and carboxylic acid groups for hydrogen bonding with coformers, which were selected from among pyridine carboxamides (e.g. PAM, NAM, INA) and syn-amides or lactams (VLM, CPR, 2HP). The three component types are labelled as A, B and C (Figure 1). A library of binary cocrystals was analyzed to reveal the possible synthons, which will then provide a template to make the target ternary systems. Given the multiple pairing combinations for hydrogen bonding functional groups, it is difficult to predict the synthons when the starting compounds have multiple functional groups[9] (Figure 1). Our previous work[7b,c] suggests that sulfonamide–lactam synthon is predictive to assemble binary cocrystals (Figure 1b). Thus, all possible binary systems of SMBA (A) with B and C coformers were prepar d and their structures confirmed by single crystal X-ray diffracti n (see Figure S2-S4, Table S2, ESI†). Whereas the stoichiometry in a majority of the cases was 1:1, a few 1:2 cocrystals were also observed. The cocrystal products A–B and A–C yielded a single crystalline form in each case except SMBA–2HP which turned out to be trimorphic. An encouraging observation was that no B–C combination cocrystals were isolated under similar conditions and efforts (Figure 2). All the binary cocrystals were first prepared by solvent-drop or liquid-assisted grinding[8,10] in a

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† Electronic Supplementary Information (ESI) available: Experimental procedures, CCDC Nos. 1414163-1414177.

mortar pestle and the product was then recrystallized from the same solvent or solvent mixture to obtain diffraction quality single crystals (see Experimental Section in ESI†). Towards the final goal of ternary cocrystals, the three components (A+B, C) were ground and powder X-ray diffraction (PXRD) was recorded to confirm a new crystalline phase in each case. The microcrystalline powder was recrystallized from suitable solvents to obtain single crystals which afforded structure solution for five ternary cocrystals: SMBA–NAM–2HP, SMBA–INA–2HP, SMBA–NAM–MeHP, SMBA– NAM–OMeHP, SMBA–PAM–MeHP (Table S2, ESI†). A detailed structure description of binary cocrystals is provided in the ESI†.

The crystal structure of ternary system SMBA–NAM–2HP (1:1:1) contains the robust acid–pyridine heterosynthon (A–B), which extends via the amide group of pyridine carboxamide–lactam synthon (B–C) to give an A–B–C array (Figure 3a). The B–C amide heterodimers are connected as the amide tape via N–H···O hydrogen bonds,[11] with the pyridine acceptor bonding to the acid donor of SMBA (in inversion related C–B–A unit). Another side of this quadruple forms the acid–pyridine heterosynthon with the COOH of SMBA. The left over sulfonamide groups of SMBA engages in a 1D catemer N–H···O chain along the *b*-axis (Figure S5a,b, ESI†). This ternary structure is related to the binary cocrystal SMBA–NAM (1:2, Figure S2a,b ESI†), in that the second NAM is replaced by an equivalent of 2HP in SMBA–NAM–2HP (1:1:1). The driving force for ternary formation is that the heterodimer between NAM and 2HP is favored over the NAM homodimer. The addition of a methyl group to the lactam coformer gave an analogous ternary cocrystal SMBA–NAM–MeHP (1:1:1), which also exhibits ABC type 1 units and amide-lactam tetramer (Figure 3b). In the ternary cocrystal with isonicotinamide, SMBA–INA–2HP (1:1:1), the strongest acid···pyridine heterosynthon (A–B) is present. The amide NH of INA is bonded to the dimer of 2HP via an auxiliary N–H··O hydrogen bond (Figure 3c) instead of a tetramer ring $R_4^2(8)$ motif[12] as in Figure 3a,b. In SMBA–PAM–MeHP (1:1:1), there is an *intra*molecular N–H···N hydrogen bond of PAM and the strong pyridine N acceptor is not available for *inter*molecular H bonding with SMBA. The COOH donor of SMBA is bonded to the amide dimer of MeHP via an O–H···O hydrogen bond (Figure 3d). The left over amide NH of PAM bonds with the sulfonyl acceptor of SMBA in a B–A–C type molecular array. SMBA and PAM are hydrogen bonded via sulfonamide, amide and carbonyl groups in a $R_4^4(26)$ ring motif[12] (Figure S5g, ESI†) involving two molecules, and the COOH donors bond with a dimer of MeHP to give the observed 1:1:1 stoichiometry. The fifth ternary structure SMBA–NAM–OMeHP (2:1:2) has multiple molecules of the same component in the crystallographic asymmetric unit. The carboxylic acid donor of two different SMBA molecules hydrogen bond to a NAM coformer via acid–pyridine and acid–amide synthons.[13] Symmetry-independent OMeHP molecules form a $R_2^2(8)$ amide dimer, which is connected to SMBA sulfonamide group via bifurcated N–H···O hydrogen bond (Figure 3e). In contrast to the previous structures, this ternary system has an extended molecular sequence A–B–A–C.

Whereas the assembly of two molecular components in the same crystal lattice is difficult and requires a heterosynthon engineering strategy,[5] bringing in a third component poses additional challenges, particularly when one is operating in the realm of strong hydrogen bonding functional groups, as are present in drugs. (1) Structural insulation, or modular control for a functional group such as SO_2NH_2 becomes increasingly difficult because its hydrogen bond synthons are somewhat mixed in pairing hierarchy,[7b,c] and (2) hydrogen bonding and halogen bonding/ π-stacking type approaches[6g,h] are inapplicable because the latter directing groups are absent here. The present strategy for sulfonamide ternary cocrystals builds up on the idea of simultaneously manipulating chemical recognition and geometric fit,[3,4] but with the added factor that hydrogen bond mimicry is also optimized for the third component. In practice, both B and C coformers have the amide group and are planar molecules/ aromatic core of 6 member ring size. Furthermore B and C should not be self-complementary (otherwise they will form a binary cocrystal as a side-product and interrupt further supramolecular assembly with the third component) but must exhibit strong recognition and bonding to A. Hence the observation that cocrystallization of B and C did not yield a binary complex, was an important result in our ternary design plan. Coformer planarity and geometric fit requirement of B and C were confirmed in experiments. NAM, PAM, INA (B molecules) and 2HP, MeHP, OMeHP (C molecules) gave ternary complexes with SMBA (A) but not valerolactam and caprolactam (VLM, CPR, see Figure 1a), because the latter are conformationally flexible, non-planar molecules and cannot interchange places with NAM (or equivalent PAM, INA) in the crystal lattice. The observation th the B-C hydrogen bonded array is present in a few ternary cocrystals even though no B-C binary complex could be isolat is ascribed to the fact that the $R_4^2(8)$ motif (Figure 3a,b) is a self-complementary amide heterodimer, and such discrete units would not be able to extend the structure. It is the donor groups in A which propagate the structure to the ternary cocrystals.

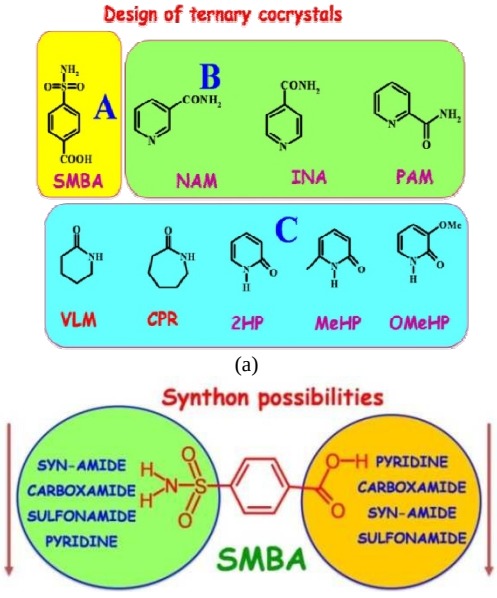
Desiraju extended the synthon concept to larger organized assemblies, referred to as Long-range Synthon Aufbau Module (LSAM).[14a] Whereas synthons provide excellent starting poin for crystal engineering[1] as one moves to more complex and larger hydrogen bonded architectures, the LSAM is a better model to understand structure evolution and build up from the molecules.[14b,c] The primary synthons which aggregate the 3 molecules A, B and C in the X-ray crystal structure (Figure 3) may be built up to the next level of the structure via amide N–H···O hydrogen bond dimer to give the LSAMs displayed schematically in Figure 4. Thus the SO_2NH_2 group of SMBA is responsible to hook-up and drag the third component into the supramolecular assembly while the COOH brings in the second partner. The amide groups of the coformers extend the ternary assembly to larger sub-structures via $R_4^2(8)$ and $R_2^2(8)$ mot (Figure 4). Another point that emerges from a comparison of the structures is the isostructurality between the binary cocrystal SMBA–NAM (1:2) and its ternary counterpart SMBA–NAM–2HP (1:1:1). The similar layer arrangement of the respective structures (Figure S6) highlights the hydrogen bond synthon and molecular geometry match necessary for ternary design. The dimers of symmetry independent NAM molecules (blue and green) are replaced by the geometric fit and similar amide hydrogen bonding 2HP molecules in the 2D layer of the ternary cocrystal, with the SMBA molecules (green) occupying similar positions in both the structures. Taken together, the LSAM classification and binary to ternary evolution suggest structural design and predictability for a functional group such as sulfonamide, which has defied a synthon analysis until recently.

Lastly, we discuss the practical method of mechanochemical synthesis[8,10] to obtain ternary cocrystals. The purpose of our experiments was to examine the results depending on the order of mixing and grinding: (A+B)+C, (A+C)+B, (B+C)+A. First all possible binary systems were prepared by liquid assisted grinding[15] and then the third component was added. Numerous experiments and crystallizations performed by the stepwise addition of the components resulted in either the starting

materials or the binary systems. SMBA formed binary systems (AB) with pyridine carboxamides and further addition of synamides (C) gave the starting adduct (AB) during crystallization from EtOAc solution. The same result was obtained with SMBA and lactams (C) to give AC and then addition of pyridine carboxamides (B) gave no new compounds. This means that once the coformers are hydrogen bonded to SMBA, it is difficult to dissociate the stable adduct and insert a third component for enthalpic reasons. The other sequence, i.e. when B and C were first ground and then A was added, gave new binary adducts with stronger hydrogen bonding synthons, AB and AC. Finally when all the three components were ground together, the result was ternary cocrystals ABC which were recrystallized as single crystals for X-ray diffraction. Solution crystallization of the ground product (confirmed cocrystal by PXRD) was found to be practically suited for obtaining the single crystals, because the product seeds act as a template to promote crystal growth.

The present study shows that when structural control is lacking in strong hydrogen-bonded multicomponent systems, then introducing a similarity in size and shape of the molecules provides a greater degree of synthon reproducibility. Factors such as the solubility of a compound in a particular solvent, and geometry of the third component play a key role in the assembly of ternary cocrystals. The planar pyridones proved successful compared to the non-planar lactams (Figure 5). Even though there is interplay and competition of several functional groups in the multicomponent system, when geomteric factors are kept in control, the hydrogen bonding synthons are predictable and recurring for an otherwise less consistent sulfonamide group. The identification of LSAMs in the ternary structures shows that directed hydrogen bonding from COOH and SO_2NH_2 groups of SMBA to the pyridine amide and pyridone coformers has potential in ternary cocrystals of drugs, e.g. furosemide. The sulfonamide functional group exhibits potential congruency with other functional groups and the synthon possibilities from binary to ternary adducts of SMBA are reported together with their mechanochemistry for synthetic access to crystalline products.

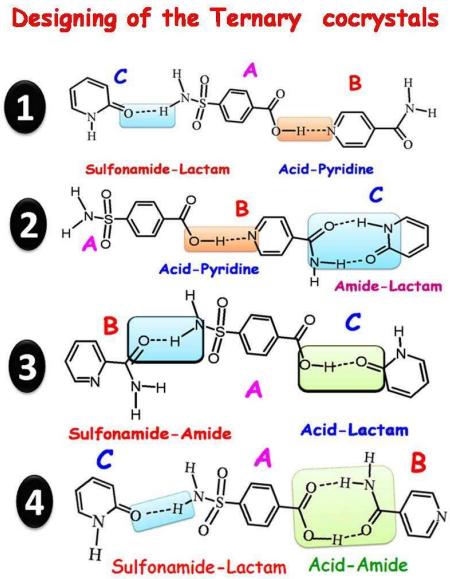
GB thank the UGC for fellowship. We thank DST-SERB Scheme on APIs (SR/S1/OC-37/2011) and JC Bose Fellowship (SR/S2/JCB-06/2009) for funding and University Grants Commission (UPE) and Department of Science & Technology (PURSE) for providing instrumentation facilities.



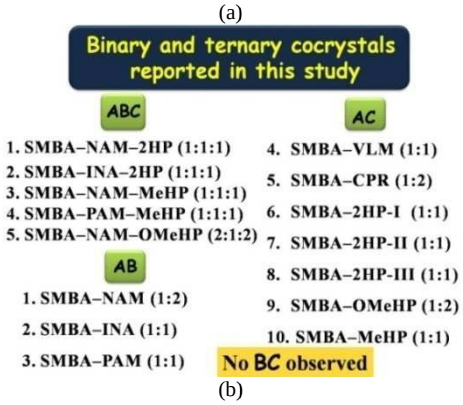
(a)

(b)

Figure 1 (a) Molecular structures of the starting materials used to obtain binary and ternary cocrystals. (b) p-Sulfonamide benzoic acid (SMBA), a model drug containing the SO_2NH_2 and another strong H-bonding group, COOH. The preference of the SO_2NH_2 and COOH functional groups to bond with complementary functional groups was derived from an analysis of the binary cocrystals. More to less preferred synthons are displayed from top to bottom.

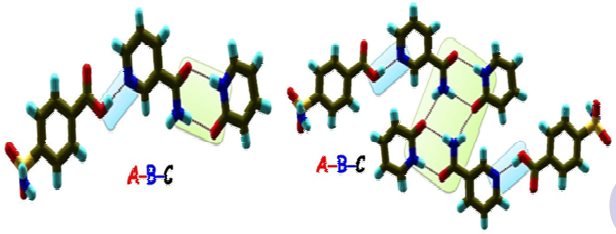


(a)

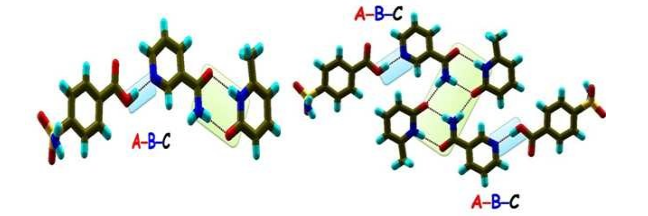


(b)

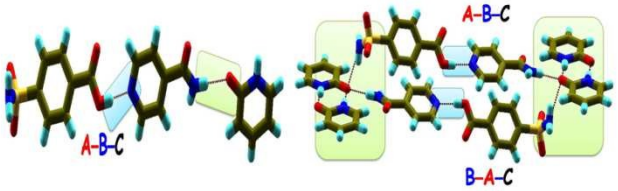
Figure 2 (a) Possible supramolecular synthons of the carboxylic acid and sulfonamide functional groups with other complementary hydrogen bonding groups. (b) Binary and ternary cocrystals reported in this study.



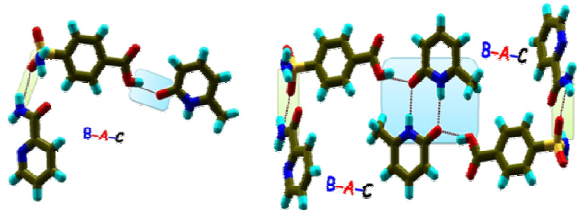
(a) SMBA–NAM–2HP (1:1:1)



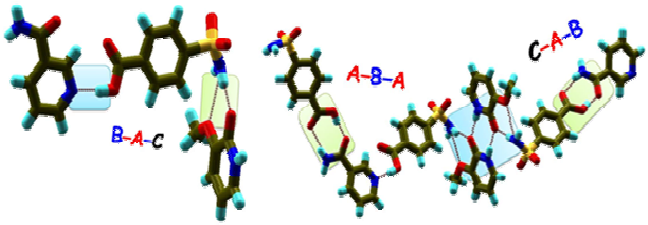
(b) SMBA–NAM–MeHP (1:1:1)



(c) SMBA–INA–2HP (1:1:1)

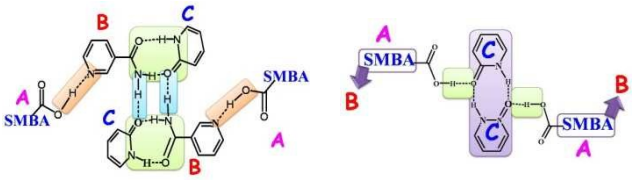


(d) SMBA–PAM–MeHP (1:1:1)



(e) SMBA–NAM–OMeHP (2:1:2)

Figure 3 (a) and (b) Hydrogen bonding in SMBA–NAM–2HP (1:1:1) and SMBA–NAM–MeHP (1:1:1) consists of amide-amide heterodimer and acid-pyridine synthons. (c) Large ring motifs of two SMBA, two INA and two 2HP via hydrogen bonds and ladder network in SMBA–INA–2HP (1:1:1). (d) Tetramer rings of two SMBA and two PAM are interlinked via MeHP dimers in SMBA–PAM–MeHP (1:1:1). (e) Acid-amide heterodimer and OMeHP homodimer in SMBA–NAM–OMeHP (2:1:2).



(a) (b)

Figure 4 The N–H···O dimers of $R_4^2(8)$ motif in Fig. 3a, 3b and $R_2^2(8)$ motif of Figure 3d make the LSAMs of these ternary cocrystals. (a) SMBA–NAM–2HP and SMBA–NAM–MeHP having the dimeric A–B–C units, and (b) SMBA–PAM–MeHP having the dimeric B–A–C units.

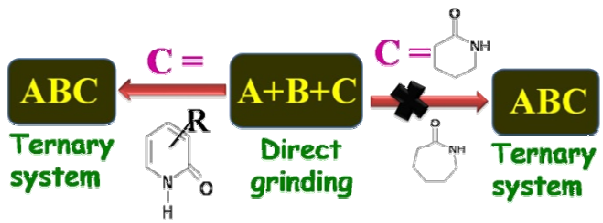


Figure 5 Schematic representation of the results when C is a lactam (no ternary product) or a 2HP derivative (ternary product).

References:

1 (a) G. R. Desiraju, *Crystal Engineering: The Design of Organic Solids*, Elsevier, Amsterdam, 1989; (b) G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2311–2327.

2 S. Tothadi, A. Mukherjee and G. R. Desiraju. *Chem. Commum.*, 2011, **47**, 12080–12082.

3 A. Mukherjee, S. Tothadi and G. R. Desiraju, *Acc. Chem. Res.*, 2014, **47**, 2514−2524.

4 R. Dubey and G. R. Desiraju, *Angew. Chem. Int. Ed.*, 2014, **53,** 13178–13182.

5 (a) E. Cheung, S. Kitchin, K. Harris, Y. Imai, N. Tajima and R. Kuroda, *J. Am. Chem. Soc.*, 2003, **125**, 14658–14659; (b) C. B. Aakeröy and D. Salmon, *CrystEngComm*, 2005, **7**, 439–448; (c) B. Bhogala, S. Basavoju and A. Nangia, *Cryst. Growth Des.*, 2005, **5**, 1683–1686; (d) T. Friščić, *Chem Soc. Rev.*, 2012, **41,** 3493–3510; (e) A. Delori, T. Friščić and W. Jones, *CrystEngComm*, 2012, **14**, 2350–2362; (f) B. Bhogala, S. Basavoju and A. Nangia, *CrystEngComm*, 2005, **7**, 551–562; (g) S. Palash, M. K. Mishra, U. Ramamurty and G. R. Desiraju. *Mol. Pharmaceutics*, 2015, **12**, 889–897; (h) S. L. Childs, L. J. Chyall , J. T. Dunlap, V. N. Smolenskaya, B. C. Stahly and G. P. Stahly, *J. Am. Chem. Soc.*, 2004, **126**, 13335–13342; (i) G. Bolla, P. Sanphui, A. Nangia, *Cryst. Growth Des.*, 2013, **13,** 1988–2003.

6 (a) C. B. Aakeröy, A. M. Beatty and B. A. Helfrich, *Angew. Chem. Int. Ed*. 2001, **40**, 3240–3242; (b) C. B. Aakeröy, J. Desper and J. Urbina, *Chem. Commum.*, 2005, 2820–2822; (c) C. B. Aakeröy, D. Salmon, *CrystEngComm*, 2005, **7,** 439–448; (d) B. Bhogala, S. Basavoju and A. Nangia, *Cryst. Growth Des.*, 2005, **5**, 1683–1686; (e) S. Aitipamula, A. B. H. Wong, P. S. Chow and B. H. Tan , *CrystEngComm*, 2013, **15**, 5877–5887; (f) C. Seaton, N. Blagden, T. Munshi and I. Scowen, *Chem. Eur. J.*, 2013, **19,** 10663–10671; (g) S. Tothadi and G. R. Desiraju, *Chem. Commum.*, 2013, **49**, 7791–7793; (h) S. Tothadi, P. Sanphui and G. R. Desiraju, *Cryst. Growth Des.*, 2014, **14**, 5293–5302; (i) R. Dubey and G. R. Desiraju, *IUCrJ*, 2015, **2**, 402–417.

7 (a) M. R. Caira, *Mol. Pharmaceutics*, 2007, **4**, 310–316; (b) G. Bolla, S. Mittapalli and A. Nangia, *IUCRJ*, 2015, **2**, 389–401; (c) G. Bolla, S. Mittapalli and A. Nangia, *CrystEngComm*, 2014, **16**, 24–27.

8 N. Shan, F. Toda and W. Jones, *Chem. Commum.*, 2002, 2372–2373.

9 (a) B. Sarma, N. K. Nath, B. R. Bhogala and A. Nangia, *Cryst. Growth Des.*, 2009, **9,** 1546–1557; (b) C. B. Aakeröy, K. Epa, S. Forbes, N. Schultheiss and J. Desper, *Chem. Eur. J.*, 2013, **1**, 14998–15003.

10 (a) M. Rak, N. Saadé, T. Friščić and A. Moores, *Green Chem.*, 2013, **16**, 86–89; (b) D. Tan, V. Štrukil, C. Mottillo, T. Friščić, *Chem. Commum.*, 2014, **50**, 5248–5250; (c) I. Halasz, A. Puškarić, S. Kimber, P. Beldon, A. Belenguer, F. Adams, V. Honkimäki, R. Dinnebier, B. Patel, W. Jones, V. Štrukil and T. Friščić, *Angew. Chem. Int. Ed.*, 2013, **125**, 11752–11755; (d) A. V. Trask, W. D. S. Motherwell and W. Jones, *Chem. Commum.*, 2004, 890–981.

11 L. Yang, X. Tan, Z. Wang, X. Zhang, *Chem. Rev.*, 2015, **115**, 7196–7239.

12 (a) M. C. Etter and J. C. Macdonald, *Acta Crystallogr.*, 1990, **B46**, 256–262; (b) J. Bernstein, R. E. Davis, L. Shimoni and N. L. Chang, 1995, *Angew. Chem. Int. Ed. Engl.*, **34**, 1555–1573.

13 (a) T. R. Shattock, K. K. Arora, P. Vishweshwar and M. J. Zaworotko, *Cryst. Growth Des.*, 2008, **8**, 4533–4545; (b) T. L. Adalder, R. Sankolli and P. Dastidar, *Cryst. Growth Des.*, 2012, **12**, 2533–2542.

14 (a) P. Ganguly and Gautam R. Desiraju *CrystEngComm*, 2010, **12**, 817–833; (b) A. Mukherjee, K. Dixit, S. P. Sarma and G. R. Desiraju, *IUCrJ*, 2014, **1**, 228–239; (c) A. Mukherjee, S. Tothadi and G. R. Desiraju, *Acc. Chem. Res.*, 2014, **47**, 2514−2524.

15 (a) A. V. Trask, D. A. Haynes, W. D. S. Motherwell and W. Jones, *Chem. Commum.*, 2006, 51–53; (b) A. V. Trask, and W. Jones, *Top. Curr. Chem.*, 2005, **254**, 41–70; (c) T. Friscic, A. V. Trask, W.

400 Jones and W. D. S. Motherwell, *Angew. Chem. Int. Ed.*, 2006, **45**, 7546–7550.

Graphical abstract

Ternary cocrystals of the sulfonamide group with pyridine carboxamide and lactams are engineered using a combination of hydrogen bond mimicry and geometric fit of the coformers.