Tautomerisation and Polymorphism in Molecular Complexes of Piroxicam with Mono-Substituted Benzoic Acids

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The supplementary information contains additional experimental data relating to the relative stabilities of the two tautomeric polymorphs of 2-fluorobenzoic acid and piroxicam and detailed structural descriptions of the nineteen molecular complexes.

Section S1. 2-Fluorobenzoic acid Tautomeric Polymorphs

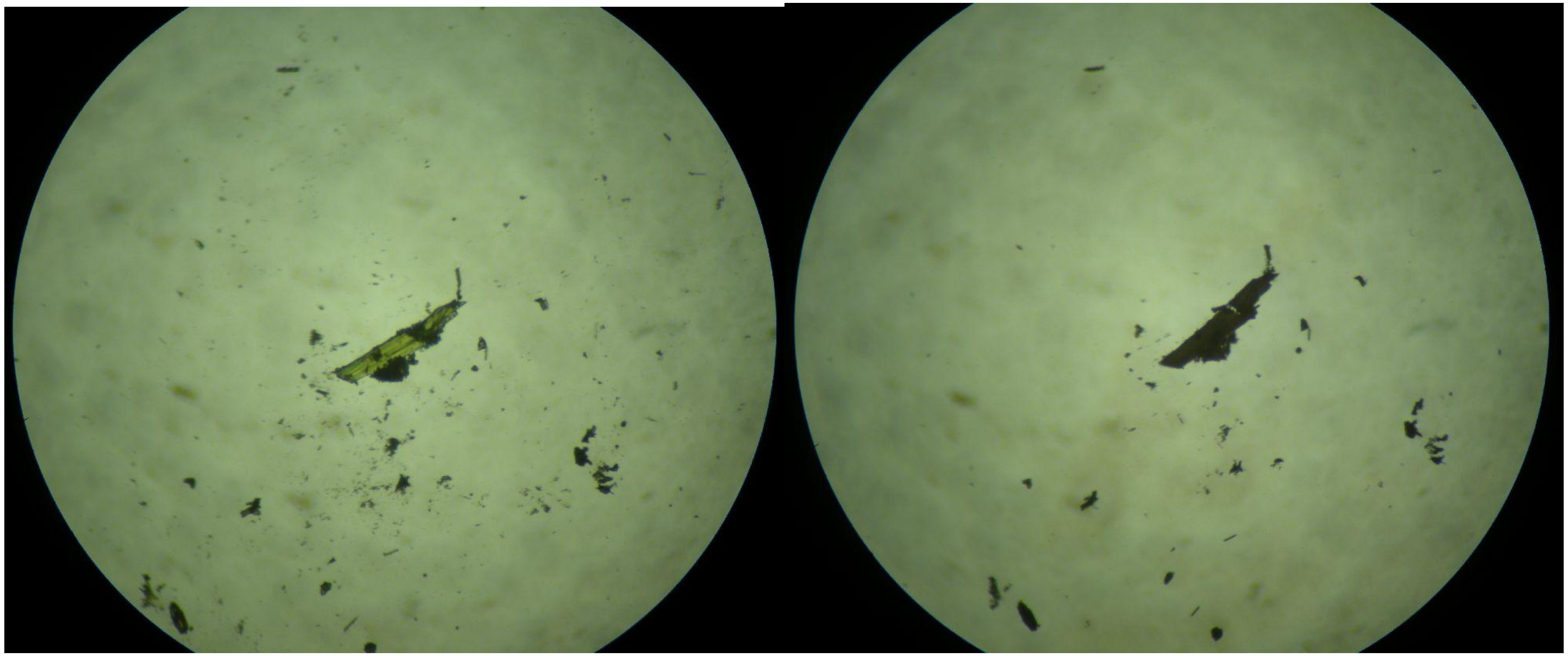

Figure S1. Hot stage microscopy showing the interconversion of the zwitterionic and non-ionised polymorphs of 2-fluorobenzoic acid and piroxicam after annealing of at 140 °C for 20 mins. Left, yellow/green crystal characteristic of a zwitterionic form of piroxicam prior to annealing and right, darkening of crystal corresponding to the phase change to the non-ionised form of piroxicam after annealing.

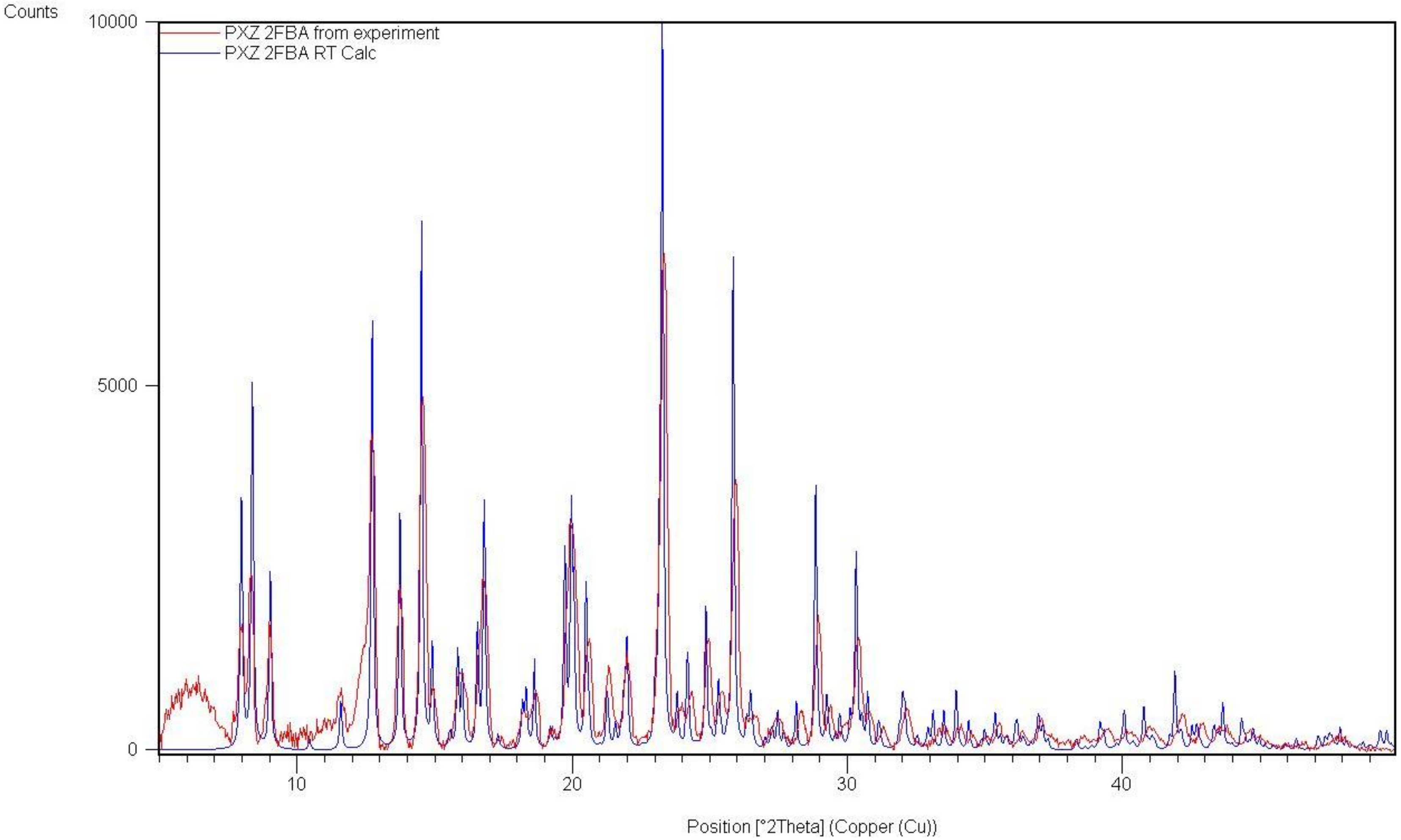

Figure S2. PXRD of the zwitterionic polymorph, PXZ : 2FBA complex prior to annealing measured at room temperature (red) showing a good match to the calculated PXRD pattern from the crystal structure of PXZ : 2FBA measured at 100K (blue).

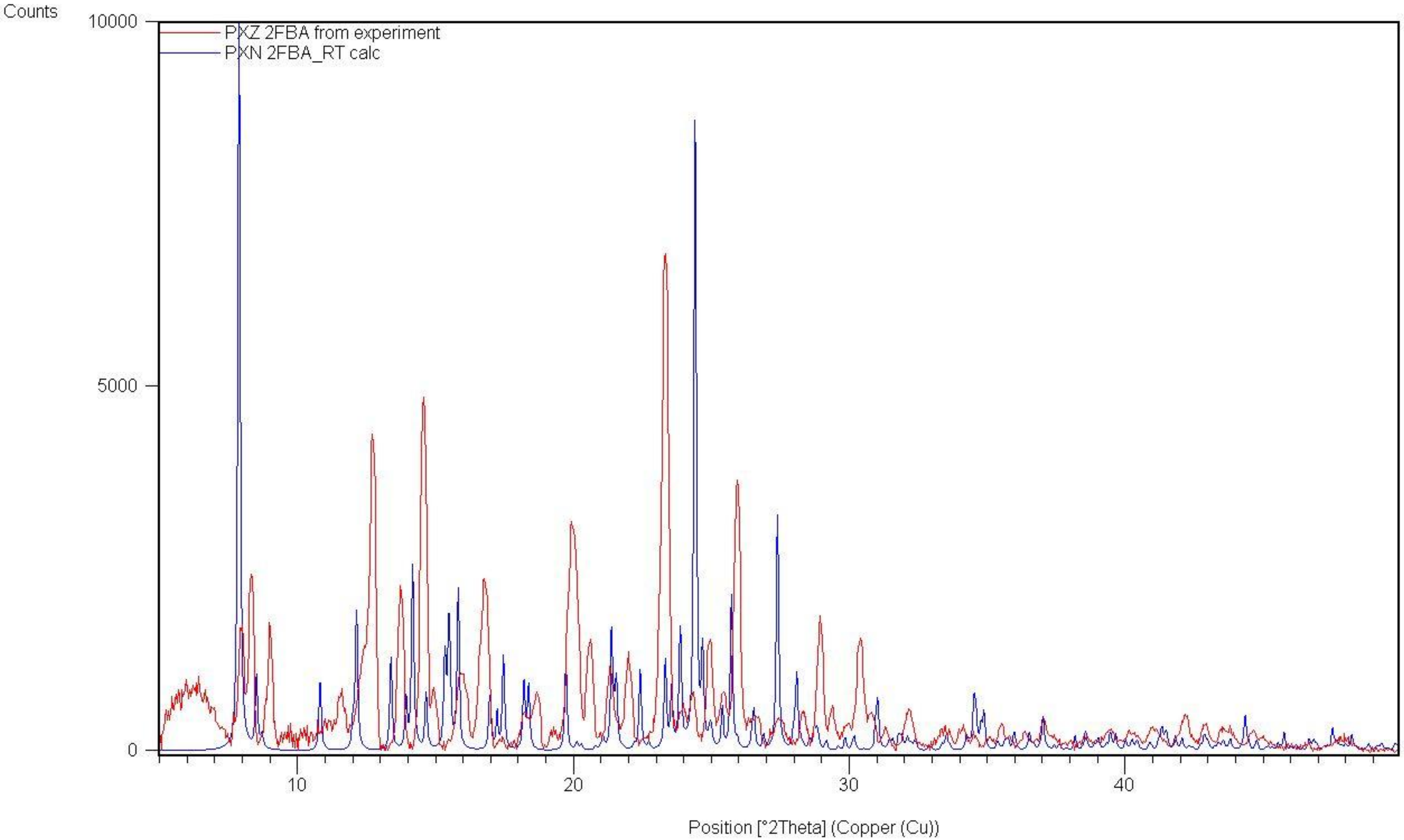

Figure S3. PXRD of the zwitterionic polymorph PXZ : 2FBA complex measured at room temperature prior to annealing (red) showing a poor match with the calculated PXRD from the crystal structure of the non-ionised polymorph, PXN : 2FBA (blue).

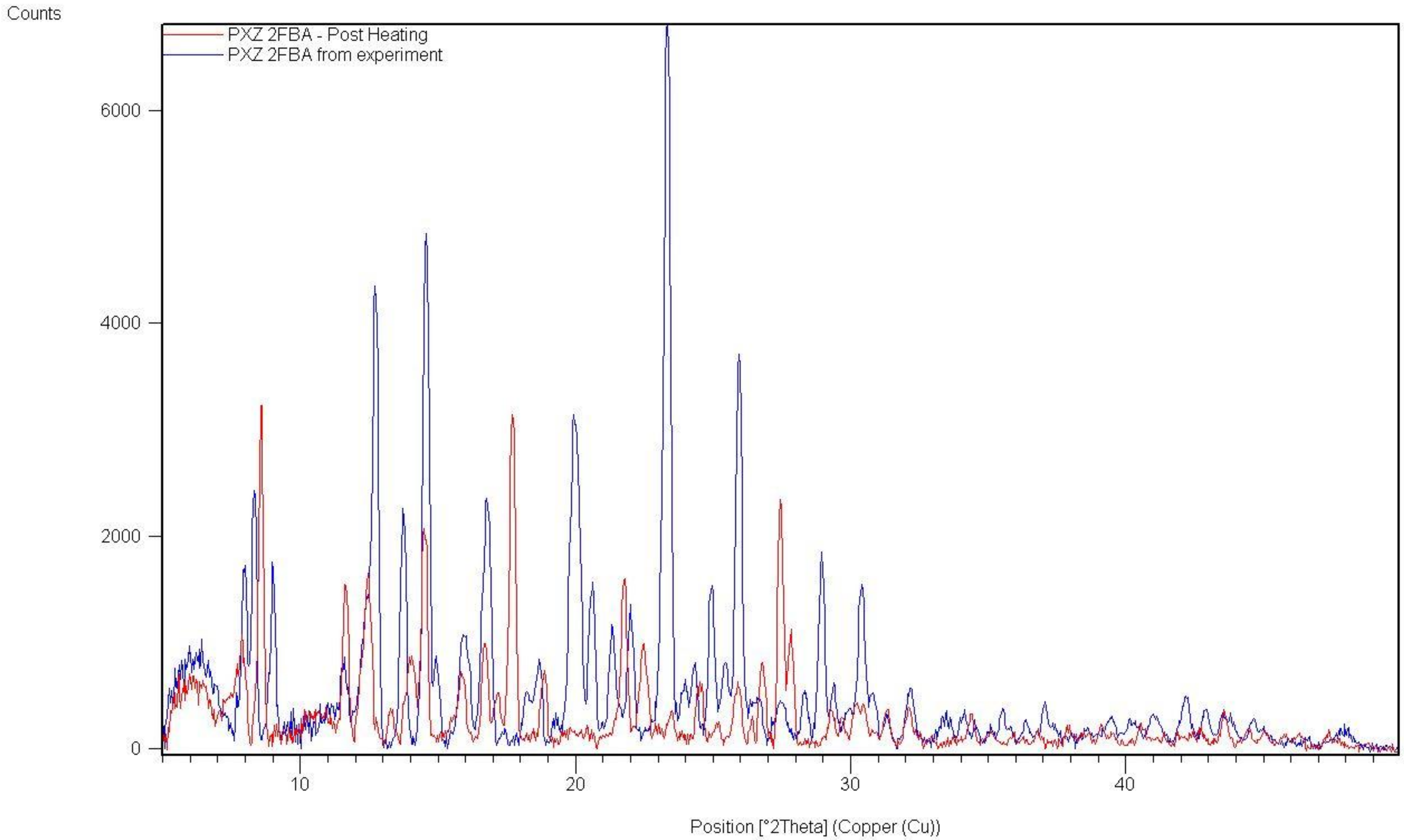

Figure S4. PXRD of PXZ : 2FBA sample after annealing at 140°C for 20 minutes (red), showing a distinct change when compared with the PXRD of the PXZ : 2FBA complex before annealing (blue).

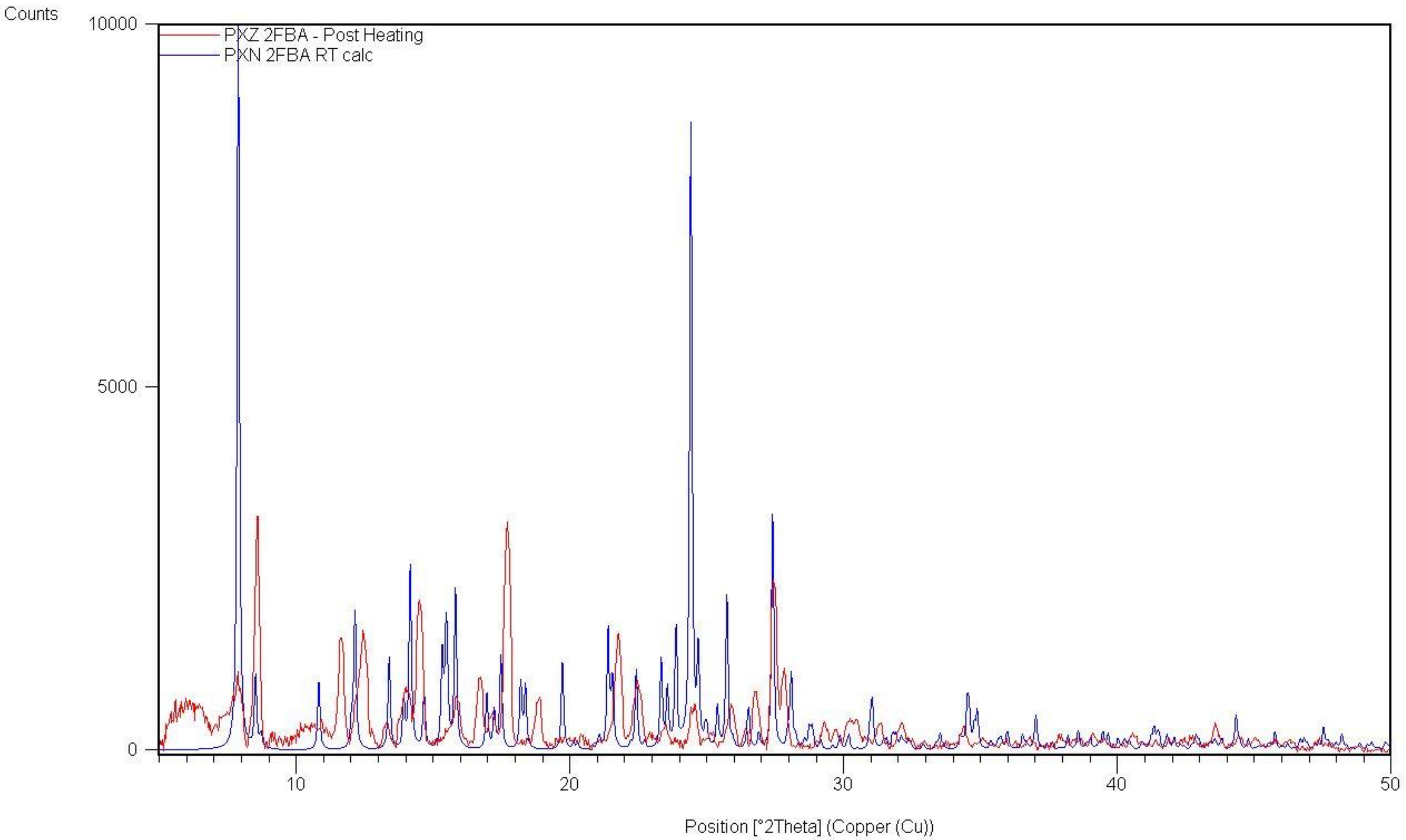

Figure S5. PXRD of PXZ : 2FBA sample post annealing (red, measured at room temperature) showing a closer match with the calculated PXRD pattern from the non-ionised polymorph PXN : 2FBA crystal structure (blue, measured at 100K). 100% conversion to the non-ionised polymorph is not achieved through annealing at 140°C for 20 mins; small quantities of the zwitterionic polymorph PXZ : 2FBA can still be identified.

Section S2. Crystal Structure Analysis

1. Piroxicam: 2-Fluorobenzoic Acid (Zwitterionic) (PXZ: 2FBA). The zwitterionic PXZ: 2FBA complex crystallises with one PXZ molecule and one 2FBA molecule in the asymmetric unit. It features a tetrameric building block with a BA-PXZ-PXZ-BA (BZZB) configuration (Figure 1a) with an inversion centre located in the middle of the PXZ dimer. The dimer is formed by charge-assisted, DHAA bifurcated intra- and intermolecular hydrogen bonds (HBs) between the protonated PXZ pyridinal NH and the amide carbonyl oxygens forming a $R_2^2(12)$ hydrogen bonded (H bonded) ring. The N···O distances of these interactions are 2.611(4)Å and 2.920(3)Å, respectively. The 2FBA molecule (Figure S6, top) is orientationally disordered over two positions. The relative occupancy of these two positions was refined to approximately 60:40; the major component has the fluorine atom located on the hydroxyl side of the ring. The carboxylic acid OH of the 2FBA molecule forms a charge assisted O-H···O$^-$ HB (O···O = 2.568(3)Å) to the deprotonated PXZ oxygen atom to form the tetramer. A weak HB is also formed between the carbonyl O and the aromatic CH of PXZ (C···O = 3.233(4)Å). π-π interactions involving the pyridine ring of PXZ hold tetramers above and below each other. These interactions are between the enolate oxygen and the benzene ring of the PXZ molecule below such that the molecules lie head to tail relative to one another. Further weak interactions involving the fluorine atoms are formed, with the sulfonyl oxygen interacting with the disordered fluorine atom of the 2FBA in the minor position of the disordered pair, as well as weak methyl C-H···F HBs when the fluorine is in the major position. The tetramers are arranged in stacks forming a herring bone structure as shown in Figure S6 (bottom), with weak CH···π interactions occurring between 2FBA molecules in neighbouring stacks.

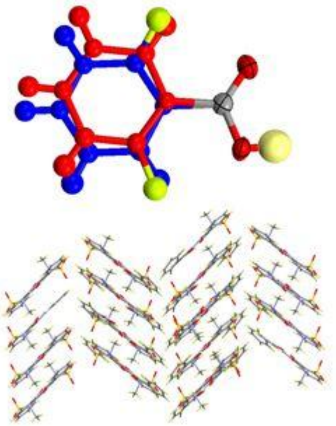

Fig. S6 Top: the two disordered positions of the 2-fluorobenzoic acid molecule in **1** with major position (60%) shown in red and minor position (40%) in blue. Bottom: Herringbone structure of **1**.

2. Piroxicam: 3-Fluorobenzoic Acid (Zwitterionic) (PXZ: 3FBA). The zwitterionic PXZ: 3FBA complex is isomorphous to the PXZ: 2FBA structure; the change in substituent position therefore has no significant affect on the crystal packing. It features the same BZZB tetrameric building block (as shown in Figure 1), but in this case, the 3FBA molecule is not disordered. The F atom lies solely on the hydroxyl side of the ring, and forms weaker aromatic C-H···F HBs (C···F = 3.171(7)Å, c.f. 2.948(5)Å in the 2FBA complex) with the methyl CH of a neighbouring PXZ molecule. The different position of the F atom and different C-H···F HBs result in slight changes in the packing. The N···O distances of the PXZ dimer interactions are 2.604(5)Å (intra) and 2.913(6)Å (inter).

3. Piroxicam: 4-Fluorobenzoic Acid (Zwitterionic) (PXZ: 4FBA). The zwitterionic PXZ: 4FBA complex features the same BZZB tetrameric building block lying on an inversion centre as the other FBA complexes, but is not isomorphous to these, crystallising instead in space group P1 . The N-H···O HBs in the PXZ dimer have N···O distances of 2.6348(14)Å (intra) and 2.8518(14)Å (inter). The O-H···O HB between the PXZ molecule and the 4FBA molecule has an O···O distance of 2.5985(13)Å. Figure S7a shows how the tetramer differs from that of the other FBA complexes, with the 4FBA molecules lying much further out of plane of the PXZ molecules. The PXZ molecules interact via π···π interactions and lie head to tail almost directly above each other in the 2FBA and 3FBA complexes with the pyridine ring forming further π-interactions with the BA molecule. In the 4FBA complex, on the other hand, the PXZ molecules are more staggered relative to each other with significant π···π interactions between the benzene rings (Figure S7b). The π···π interactions assist in the arrangement of PXZ molecules into planar layers with the out of plane 4FBA molecules intersecting the layers diagonally (Figure S7c). The F atom also forms weak HBs between layers. These are formed with the aromatic CH of another 4FBA molecule as well as the methyl CH and pyridinal NH of PXZ molecules.

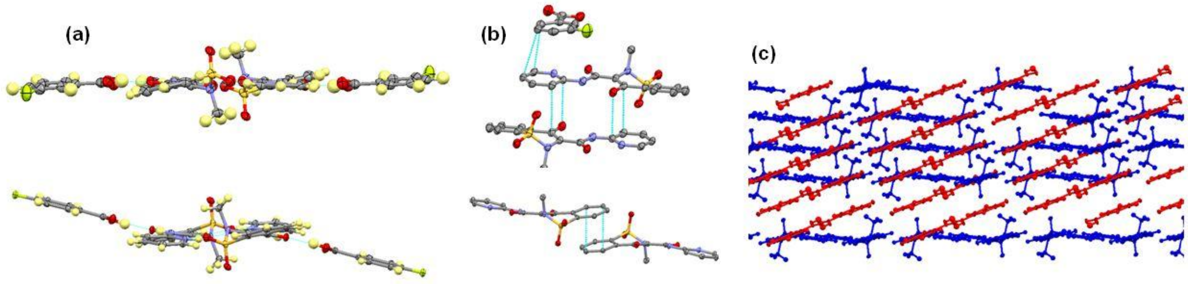

Fig. S7 (a) Top, planar tetramers in complex **2** (identical to **1**, not shown**)** and bottom, non-planar tetramers in **3.** (b) Top, relative arrangement of π-stacked molecules in **2** (identical to **1**, not shown) and bottom, **3** with H-atoms omitted for clarity. (c) Layered structure of **3**, PXZ in blue, 4FBA in red

4. Piroxicam: 2-Fluorobenzoic Acid (Non-Ionised) (PXN: 2FBA). The PXN molecules in this complex dimerise but due to different conformation adopted by non-ionised PXN molecules, the dimer formed is completely different to that seen in the zwitterionic PXZ complexes. The dimer (Figure 2a), is formed via two equivalent HBs between the hydroxyl groups and the sulfonyl oxygen atoms, with the two PXN molecules lying in different planes related by an inversion centre. The HB is bifurcated with the shorter distance between the OH and the amide carbonyl (O···O = 2.587(2)Å c.f. 2.961(2)Å). The 2FBA molecules HB to each PXN molecule in the dimer via N-H···O (N···O = 2.997(2)Å) and O-H···N (O···N = 2.676(2)Å) HBs to form an $R^2_2(8)$ H bonded ring, ,(also Figure 2a). This again forms into a tetrameric building block with a BA-PXN-PXN-BA (BNNB) configuration, in which the PXN-2FBA pair lie relatively coplanar to one another and the inverted pair are staggered relative to the first. The methyl groups, which lie out of the plane of the PXN molecule, also form weak HBs to the fluorine (C···F = 3.098(2)Å) and hydroxyl oxygen atoms of other 2FBA molecules (Figure S8). This creates a layered structure, with the methyl groups and sulfonyl oxygen atoms acting as bridges between layers.

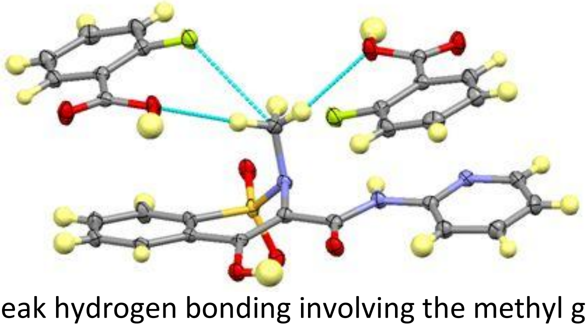

Fig. S8 Weak hydrogen bonding involving the methyl group in **4.**

5. Piroxicam: 3-Fluorobenzoic Acid (Non-Ionised) (PXN: 3FBA). As in the case of the zwitterionic complexes, this complex is isomorphous to PXN: 2FBA with the fluorine interactions changing from methyl C-H···F HBs to weaker aromatic C-H···F H bonds (C···F = 3.405(2)Å) as a consequence of the different position of the fluorine atom. The HB between PX molecules has an O···O distance of 2.931(2)Å and the intramolecular PX HB has an O···O distance of 2.591(2)Å. The $R^2_2(8)$ ring has an O···N distance of 2.676(2)Å and an N···O distance of 2.974(2)Å.

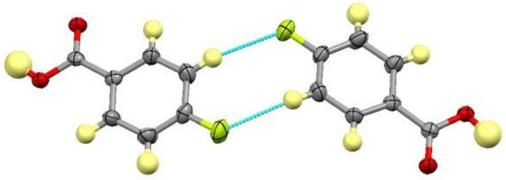

Fig. S9 4FBA dimers comprised of symmetry related C-H···F hydrogen bonds in **6.**

6. Piroxicam: 4-Fluorobenzoic Acid (Non-Ionised) (PXN: 4FBA). As is the case for the zwitterionic structures, the PXN: 4FBA complex is not isostructural to the 2- and 3-FBA complexes, crystallising in space group $P4_2/n$ as opposed to $P\bar{1}$. Once again, the primary building block is a BNNB tetrameric unit; however, the interactions between PXN molecules are very different in this case (Figure 2b). The 4FBA molecules HB to the PXN molecules in exactly the same way as the 2- and 3-FBA complexes by forming the $R^2_2(8)$ H bonded ring (N···O = 2.905(2)Å, O···N = 2.715(2)Å), but in this case the O-H···O HBs between PXN molecules are replaced by weaker C-H···O HBs between aromatic C-H groups and the hydroxyl oxygen atoms. These interactions have a C···O distance of 3.207(2)Å. 4FBA dimers are also formed by weak C-H···F HBs (Figure S9). PXN molecules above and below each other interact via further weak HBs to the sulfonyl oxygen atom from the methyl group and CH group of two other PXN molecules (Figure S10).

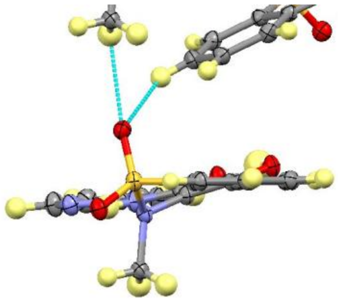

Fig. S10 Weak CH···O hydrogen bonds in **6.**

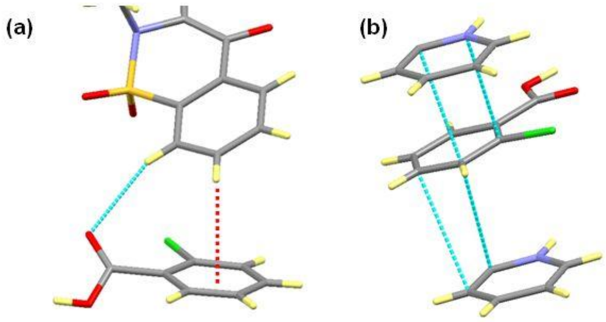

Fig. S11 Differing weak interactions formed by symmetry independent 2CLBA molecules in **7**. (a) CH···O hydrogen bond (blue dashed line) and CH···π interactions (red dashed) in twisted 2CLBA molecule. (b) π···π interactions in planar 2CLBA.

7. Piroxicam: 2-Chlorobenzoic Acid (Zwitterionic) (PXZ: 2CLBA). In this complex, PX is present as the zwitterionic tautomer, and the structure is built up from the BZZB unit (Figure 1). The structure consists of relatively flat layers, with the methyl and sulfonyl groups bridging between layers. Unlike the previously described zwitterionic complexes, the BZZB tetramer consists of two independent molecules of each of PXZ and 2CLBA. The BZZB units are linked within the layers by weak C-H···O=S HBs on both sides. One 2CLBA molecule has a twisted conformation, with the carboxylic group out of the plane of the benzene ring. Aromatic ring CH groups of the PXZ molecule above form a weak HB to the twisted carbonyl O as well as a weak CH···π interaction with the aromatic π cloud (Figure S11a). The other 2CLBA molecule, however, is more planar and forms π···π interactions with the pyridine rings of PXZ (Figure S11b). The bridging methyl groups and sulfonyl oxygen atoms interact via weak HBs (Fig S12) with the methyl group also forming weak interactions with the chlorine of the 2CLBA in the next layer.

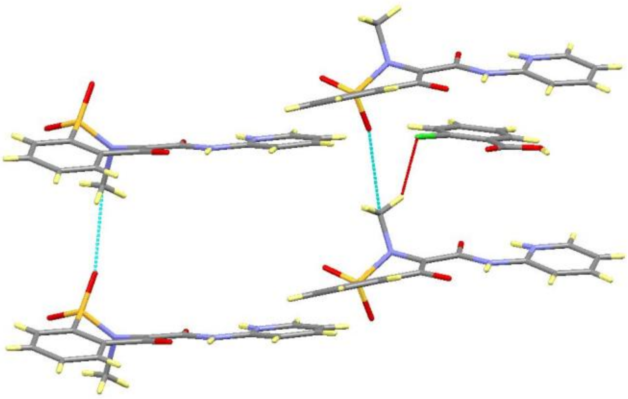

Fig. S12 Weak methyl CH···O hydrogen bonds (blue dashed lines) and methyl CH···Cl interactions (red dashed lines) bridging layers in **7.**

8. Piroxicam: 3-Chlorobenzoic Acid (Non-Ionised) (PXN: 3CLBA). In this complex, non-ionised PXN molecules dimerise, forming a new synthon, different to any of the non-ionised PXN: fluorobenzoic acid complexes reported above (Figure 2c). The dimers consist of bifurcated DHAA intra- and intermolecular O-H···O=C HBs with an inversion centre lying at the centre of the $R_2^2(6)$ H bonded ring formed. The intramolecular interaction is considerably shorter than the intermolecular interaction with an O···O distance of 2.579(2)Å, c.f. 2.982(2)Å for the intermolecular interaction. The 3CLBA molecule is linked to both sides of the dimer via the $R^2_2(8)$ H bonded ring also seen in the PXN: FBA complexes, with an N···O distance of 2.966(2)Å and an O···N distance of 2.648(2)Å (Figure 2c). This forms a new type of BNNB tetramer. Once again the structure consists of relatively planar layers with C-H···O weak HBs between the methyl group and sulfonyl oxygen bridging the layers as well as methyl interactions with the bromine. The tetramer building blocks are held together in the layers via weak HBs between the aromatic CH groups of the 3CLBA and the sulfonyl oxygen of PXN (Figure S13a). The other sulfonyl oxygen also forms weak C-H···O HBs to the aromatic CH groups of PXN molecules in the layers above and below (Figure S13b).

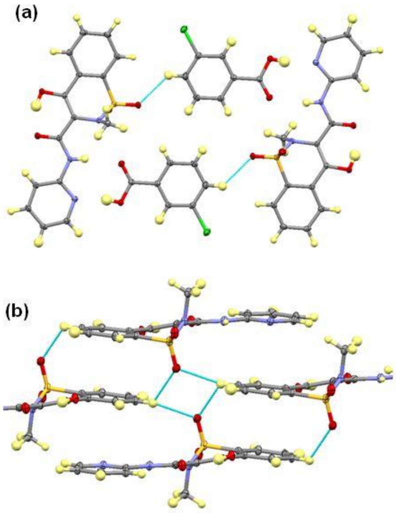

Fig. S13 (a) Weak CH···O hydrogen bonds within the layers of **8,** (b) weak CH···O hydrogen bonds between layers of **8.**

9. Piroxicam: 2-Bromobenzoic Acid (Zwitterionic) (PXZ: 2BRBA). The zwitterionic PXZ: 2BRBA complex again features the BZZB tetramer (Figure 1). The HBs in the tetramer are similar in strength to those in the FBA complexes with N···O distances of 2.660(3)Å (intramolecular) and 2.874(3)Å (intermolecular) and an O···O distance of 2.558(3)Å. The structure is layered (Figure S14a), with the BZZB units in the layers held together by bifurcated DDHHA C-H···O HBs between the aromatic CH groups of the 2BRBA and the sulfonyl O of PXZ similar to the 2CLBA complex (Figure S14b). PXZ molecules above and below each other are staggered, with the other sulfonyl bridging between layers, forming weak aromatic C-H···O=S HBs (Figure S14c). There are also significant short contacts between this sulfonyl oxygen and the bromine atom of the 2BRBA. The carboxylic acid group of 2BRBA twists out of the plane of the benzene ring, a consequence of the larger Br atom positioned adjacent to it. The PXZ methyl group also bridges between layers, forming a weak C-H···O HB to the hydroxyl O of the carboxylic group.

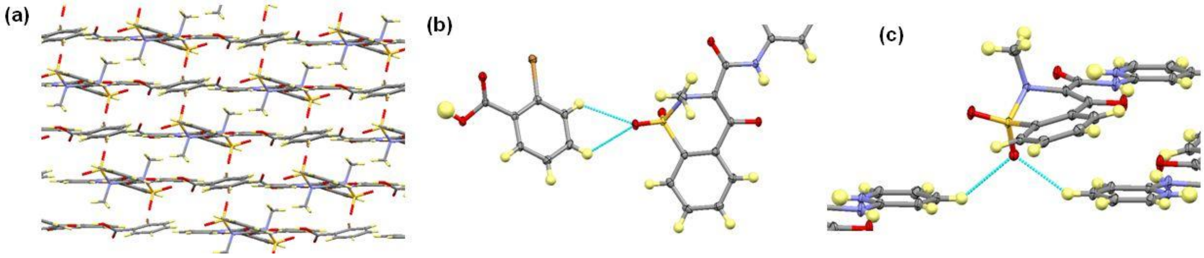

Fig. S14 Crystal structure of **9.** (a) Layered arrangement of molecules with sulfonyl O and methyl groups bridging layers, (b) CH···O hydrogen bonds between PX and 2BRBA, (c) weak CH···O interactions between pyridinal CH of PX and the bridging sulfonyl O.

10. Piroxicam: 3-Bromobenzoic Acid (Non-Ionised) (PXN: 3BRBA). PX in this complex is in the non-ionised tautomeric form PXN and the structure is isomorphous to that of the PXN: 3CLBA complex. The PXN dimer has intramolecular and intermolecular OH···O HBs with O···O distances of 2.578(3)Å and 2.992(2)Å, respectively. The $R^2_2(8)$ ring between the PXN and 3BRBA has NH···O HBs of 2.968(3)Å (N···O) and OH···N HBs of 2.660(3)Å (O···N) in length.

11. Piroxicam: 2-Hydroxybenzoic Acid (Zwitterionic) (PXZ: 2HBA). The PXZ: 2HBA complex contains zwitterionic PXZ molecules with the BZZB tetramer (Figure 1) again the structural unit. The PXZ dimer has inter- and intramolecular NH···O HBs with N···O distances of 2.929(3)Å and 2.655(3)Å, respectively. The OH···O PXZ HB with 2HBA has an O···O distance of 2.533(3)Å. The OH group of 2HBA does not form any intermolecular HBs with the only interaction being a moderately strong intramolecular HB with the carbonyl oxygen of the carboxylic acid group (O···O = 2.624(3)Å). The 2HBA molecule is twisted relative to the PXZ molecule and is involved in a number of weak HBs between aromatic CH groups and the sulfonyl oxygen atoms of two PXZ molecules and to the hydroxyl oxygen of a neighbouring 2HBA molecule (Fig S15a). PXZ molecules above and below each other are linked by further weak HBs between pyridinal CH groups and sulfonyl oxygen atoms (Figure S15b). This gives the PXZ dimers a step-like arrangement relative to each other (Figure S16a), with the twisted 2HBA molecules running diagonal to the plane (Figure S16b).

12. Piroxicam: 3-Hydroxybenzoic Acid Monohydrate (Zwitterionic) (PXZ: 3HBA.H_2O). The PXZ: 3HBA.H_2O complex features the BZZB tetramer (Figure 1b) with PXZ in the zwitterionic form. The PXZ dimer has intra- and intermolecular N-H···O HBs with N···O distances of 2.629(4)Å and 2.907(4)Å, respectively. The PXZ OH···O HB with 3HBA has an O···O distance of 2.587(4)Å. Two water molecules act as linkers between dimers, forming an $R_4^4(8)$ H bonded ring with two 3HBA molecules (Figure S17a). The water oxygen is acceptor to a HB from the hydroxyl OH of one 3HBA molecule (O···O = 2.708(4)Å) and donor to the hydroxyl oxygen of the other (O···O = 3.033(5)Å). The BZZB tetramers connected by this ring are almost co-planar with one another, forming layers. The water molecule forms another HB to the carboxylic carbonyl O (O···O = 2.812(5)Å) of the 3HBA molecules lying above/below (Figure S17b) which links the layers together. Further interactions between layers occur between PXZ molecules, with weak C-H···O HBs between the aromatic CH and sulfonyl O (Figure S17c) as well as π···π interactions between the pyridine ring and the delocalised enolate π-bond (also Figure S17c). The pyridine ring also forms π···π interactions with the benzene ring.

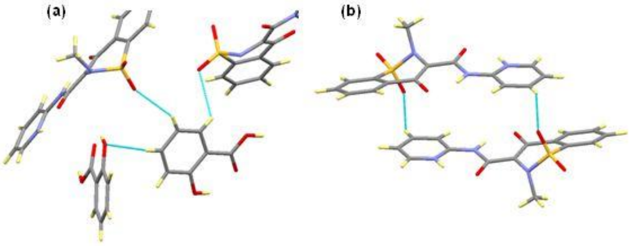

Fig. S15 (a) Weak CH···O hydrogen bonds involving 2HBA in **11,** (b) weak CH···O hydrogen bonds between PX molecules in **11.**

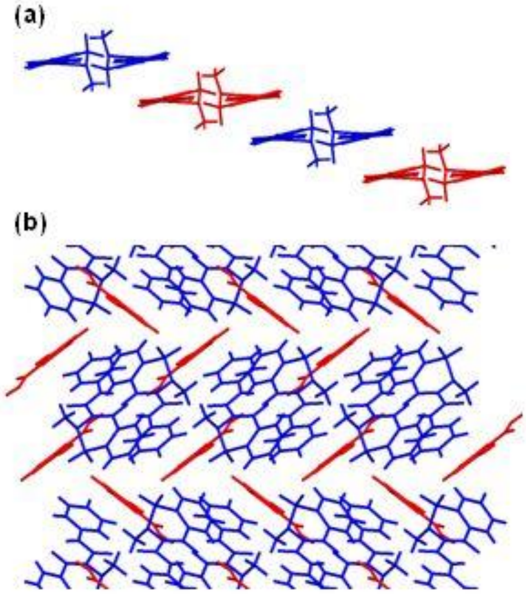

Fig. S16 Structure of **11** showing (a) the step-like arrangement of the PXZ dimers (alternate dimers shown in different colours) and (b) the 2HBA molecules (red) running diagonal to the plane of the PXZ molecules (blue).

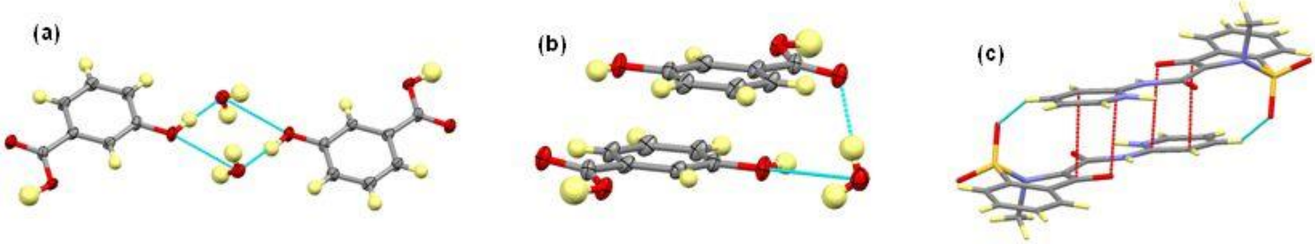

Fig. S17 Intermolecular interactions in **12.** (a) $R^{4}_{4}(8)$ rings, (b) hydrogen bonding between layers via water molecules, (c) π···π interactions between PXZ molecules (red dashed lines) and weak CH···O hydrogen bonds between the aromatic CH and sulfonyl O atoms.

13. Piroxicam: 2- Nitrobenzoic Acid (PXZ: 2NBA). The PXZ: 2NBA complex contains PX in the zwitterionic tautomer and thus forms a BZZB tetramer building block (Figure 1c). The NH···O HBs in the PXZ dimers have N···O distances of 2.643(2)Å (intramolecular) and 2.896(2)Å (intermolecular). The OH···O HB with the 2NBA molecule has an O···O distance of 2.584(2)Å. These tetrameric building blocks are linked by weak C-H···O HBs between the aromatic CH of the 2NBA molecule with the PXZ sulfonyl O and weak interactions of the aromatic CH of the PXZ pyridine ring with the nitro group O (Figure S18a). This helps link the tetramers into layers (Figure S18b), with a C-H···O HB between the methyl group and a sulfonyl oxygen atom bridging the layers. The layers are not planar due to twisting of the PXZ molecule and the non-planar nature of the 2NBA molecule, in which both the nitro- and carboxylic group of 2NBA are twisted due to steric effects. The twisting of the carboxylic acid group allows a HB to be formed between the protonated pyridinal N of the PXZ molecule above with the carbonyl O (Figure S18c). The twisted nitro group also forms a weak interaction with the methyl CH of the same PXZ molecule. A weak C-H···O HB is also formed between the bridging sulfonyl oxygen of PXZ and the aromatic CH of the 2NBA molecule below (Figure S18c).

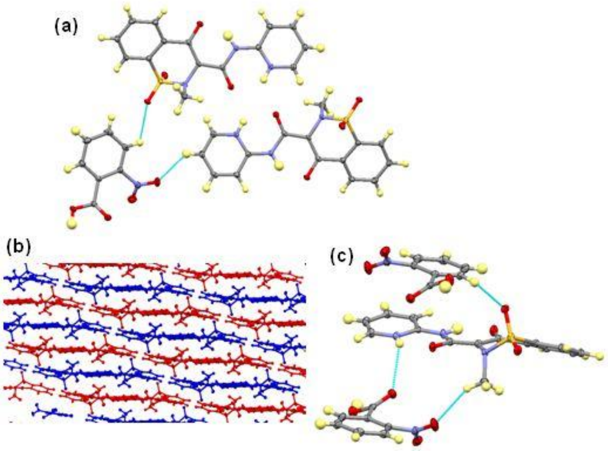

Fig. S18 Crystal Structure of **13.** (a) Weak interactions within layers, (b)layered arrangement of molecules, (c) weak interactions between layers

14. Piroxicam: 3-Nitrobenzoic Acid (Non-Ionised) (PXN: 3NBA). PX in this complex is in the non-ionised tautomeric form and the structure is isomorphous to the PXN: 3ClBA complex (**8**). The nitro group occupies the location occupied by the chlorine atom in **8**, forming weak HBs with the methyl group of the PXN molecule above as well as with the aromatic CH groups of the two neighbouring PXN molecules. The intra- and intermolecular OH···O HBs in the PXN dimer have O···O distances 2.573(2)Å and 3.011(2)Å, respectively. The $R^2_2(6)$ ring between the PXN and 3NBA has NH···O and OH···N HBs of 2.970(2)Å (N···O) and 2.618(2)Å (O···N) in length.

15. Piroxicam: 2-Methylbenzoic Acid (Non-Ionised) (PXN: 2MBA). The non-ionised PXN molecules dimerise through the S=O···H-O dimer (O···O = 2.938(1)Å) seen in the non-ionised PXN complexes with 2- and 3-FBA (Figure 2a). The 2MBA molecules are then H bonded to the PXN molecules through an $R^2_2(8)$ ring (Figure 2b) with NH···O and OH···N HBs of 3.187(1)Å (N···O) and 2.7001(8)Å (N···O) in length. The sulfonyl oxygen atom also forms HBs with the aromatic CH groups of two neighbouring PXN molecules (Figure S19a). The other sulfonyl oxygen atom forms weak HBs with the aromatic CH of the adjacent 2MBA molecule as well as with the methyl group of the 2MBA molecule that is H bonded to the same PXN molecule via the $R^2_2(8)$ ring (Figure S19b). There are also π···π interactions between these two 2MBA molecules (Figure S19b). The non-planar arrangement of the 2MBA molecules relative to the PXN molecules in the tetramer results in layers of approximately planar regions of PXN molecules intersected by 2MBA molecules running diagonal to the plane of the PXN molecules (Figure S19c).

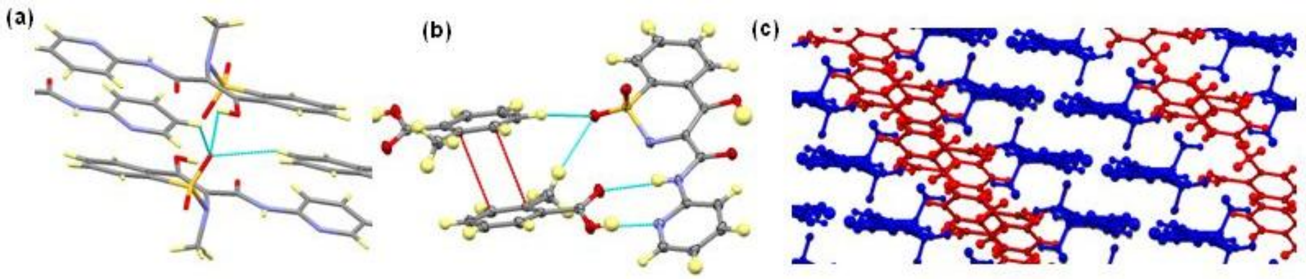

Fig. S19 Crystal structure of **15.** (a) Weak CH···O hydrogen bonds between sulfonyl O and CH of PXN molecules, (b) weak CH···O hydrogen bonds between sulfonyl O and 2MBA molecules (blue dashed lines) and π···π interactions between 2MBA molecules (red dashed lines), (c) 2MBA molecules (red) running diagonal to planes of PXN molecules (blue).

16. Piroxicam: 3-Methylbenzoic Acid (Zwitterionic) (PXZ: 3MBA). The structure consists of the zwitterionic PXZ: 3MBA BZZB tetramers (Figure 1). The PX dimers have N···O distances of 2.635(3)Å (intramolecular) and 2.865(3)Å (intermolecular). The carboxylic OH···O HB to PX has an O···O distance of 2.581(3)Å. The PXZ molecules are stacked upon each other through π···π interactions and aromatic C-H···O=S HBs (Figure S20a). Further π···π interactions occur between the PXZ molecules and the 3MBA molecules (Figure S20b) resulting in stacks of the tetramers. The stacks run alternately in different planes (Figure S20c). Interactions between stacks in different planes are relatively weak with C-H···O HBs as well as C-H···π interactions as shown in (Figure S20d).

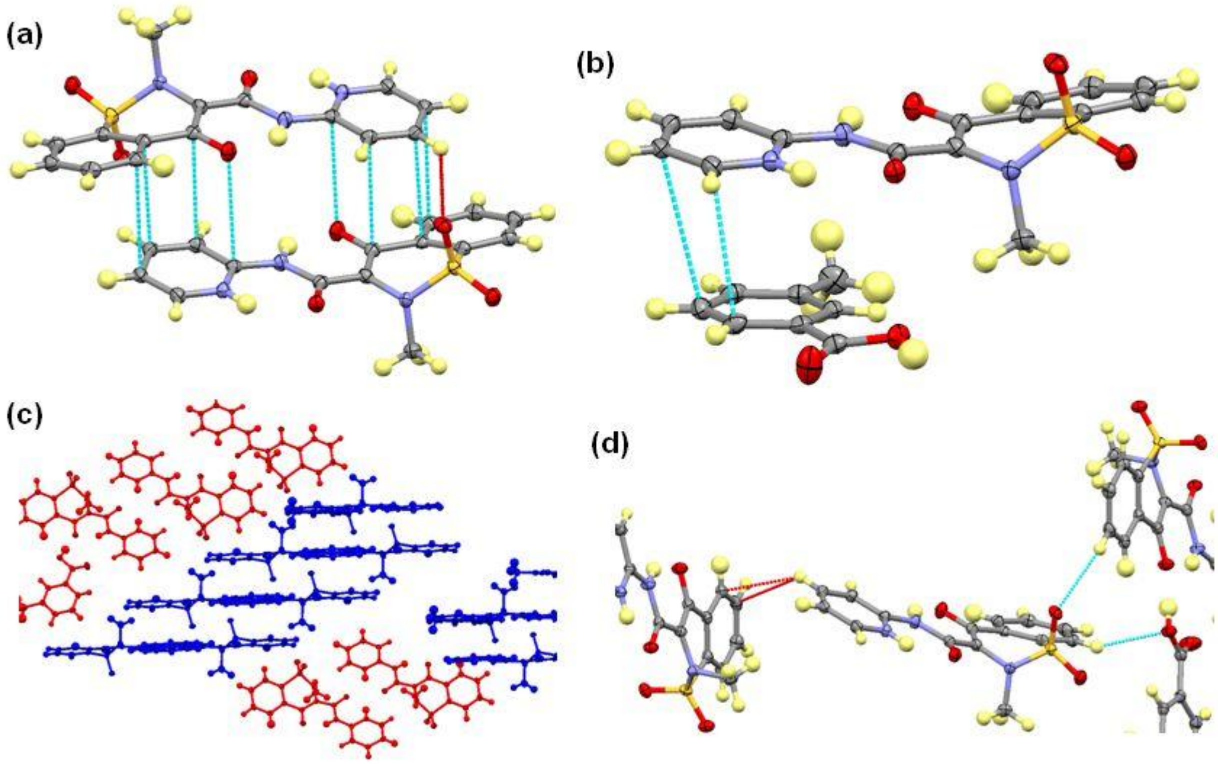

Fig. S20 Crystal Structure of **16.** (a) π···π interactions (blue dashed lines) and aromatic C-H···O=S hydrogen bonds (red dashed line) between PXZ molecules, (b) π···π interactions between PXZ and 3MBA molecules, (c) regions of stacks lying in different planes with 3MBA in red and PXZ in blue, and (d) weak interactions between molecules lying in different planes.

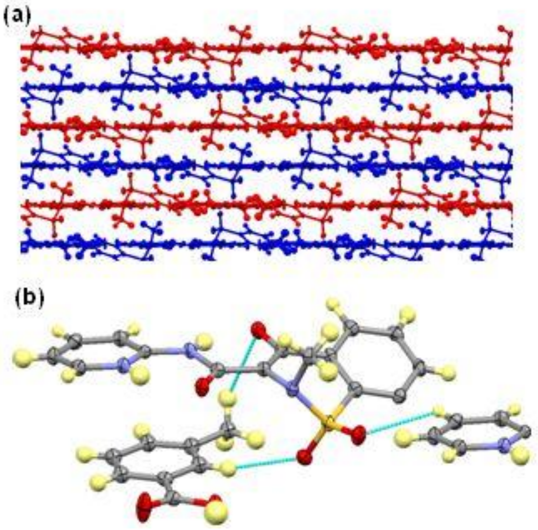

Fig. S21 (a) layered arrangement of **17,** (b) weak CH···O hydrogen bonds in **17.**

17. Piroxicam: 3-Methylbenzoic Acid Acetonitrile Solvate (Zwitterionic) (PXZ: 3MBA.ACN). The complex crystallises in a 2:1:1 ratio, with the PX molecules in the zwitterionic form. Although the BZZB tetramer (Figure 1) is present, the 3MBA and acetonitrile (ACN) molecules are disordered over two positions related by an inversion centre (Figure 8). This results in three possible tetramer configurations on a local-level when the disorder is removed; the first is the standard BZZB tetramer with two PXZ molecules sandwiched by two 3MBA molecules (BZZB); the second is the PXZ dimer flanked by two ACN molecules (ACN:Z:Z:ACN); the third is a combination of the two, an ACN:Z:Z:B. It is not possible to resolve the combination of these which contribute to the average disordered structure from this analysis. The PXZ dimer has typical N-H···O HB lengths of 2.625(3)Å (intramolecular) and 2.862(3)Å (intermolecular). The ACN molecule is H bonded to the PXZ molecule via C-H···O HBs between the methyl group and the PXZ enolate O atom (C···O = 3.1911(94)Å as well as C-H···N HBs between aromatic PXZ CH groups and the ACN N (C···N = 3.4431(66)Å) (Figure 8b). The OH···O HB between the PX and the 3MBA molecule (also Figure 8b) has an O···O distance of 2.597(7)Å. The disordered tetramers are once again arranged in layers with the methyl group and a sulfonyl oxygen pointing outward from the layers (Figure S21a). The sulfonyl oxygen atoms form weak C-H···O HBs with the aromatic CH groups of the neighbouring PXZ pyridine ring and the aromatic ring of the 3MBA molecule below (Figure S21b). The 3MBA molecule below also forms weak HBs to the PXZ enolate oxygen via the methyl group.

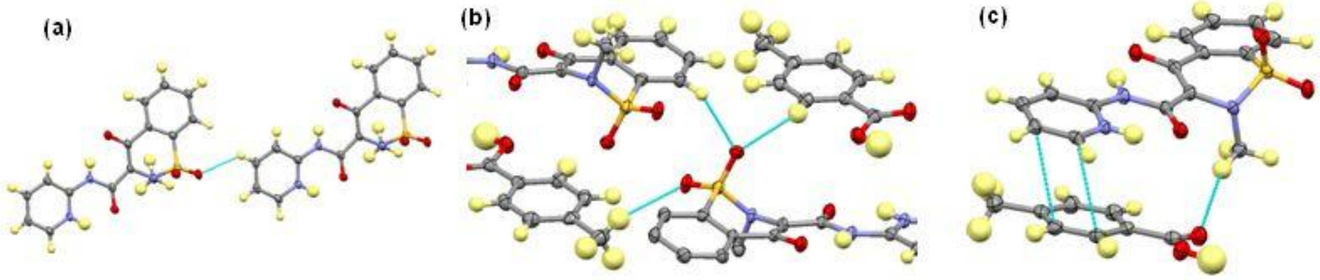

Fig. S22 Crystal Structure of **18.** (a) Weak hydrogen bonding between PXZ molecules of different tetramers in the same layer, (b) weak hydrogen bonding involving sulfonyl oxygen atoms, (c) weak interactions connecting layers.

18. Piroxicam: 4-Methylbenzoic Acid (Zwitterionic) (PXZ: 4MBA). The PX molecules are in the zwitterionic form with the BZZB tetramer again the H bonded building block (Figure 1d). The BZZB building unit differs from the others reported here, with the 4MBA molecule H bonding to the same deprotonated hydroxyl oxygen atom but the second HB in this case being made to the aromatic H atom of the benzene ring and not with the pyridinal CH of the PXZ molecule. The H bonded dimer between PXZ molecules, however, is the same. Weak aromatic C-H···O=S HBs link PXZ molecules together (Figure S22a) into layers. The sulfonyl oxygen atoms form further weak CH···O HBs with the aromatic CH groups of PXZ molecules in the layers above as well as the methyl CH groups of 4MBA molecules in the alternate layer (Figure 22b). Further weak HBs occur between the PXZ methyl group and the carbonyl oxygen of 4MBA accompanied by π···π interactions between the two molecules (Figure 22c). This again results in layers where the weak HBs involving the non-coplanar methyl groups and a sulfonyl oxygen connect the layers.

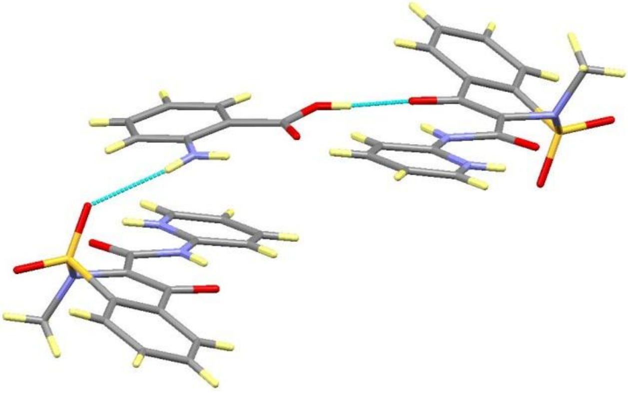

Fig. S23 NH···O hydrogen bond of the amino group and sulfonyl O in **19.**

19. Piroxicam: 2-Aminobenzoic Acid (Zwitterionic) (PXZ: 2ABA). In this complex, the PXZ molecules are in the zwitterionic form and despite the added competition for H bonding due to the amino group, the structure is isomorphous to **3** with the BZZB tetramer (Figure 1) remaining the main building block. The PX dimer has N···O distances of 2.651(3)Å (intramolecular) and 2.843(3)Å (intermolecular) and the OH···O HB between PXZ and 2ABA has an O···O distance of 2.594(2)Å. The 2ABA molecules lie diagonal to the plane of the PXZ dimer as in complex **3**, with the formation of a moderately strong hydrogen bond between the amino NH and the sulfonyl oxygen of the PXZ molecule below (N···O = 3.137(3)Å) (Figure S23). The other NH of the amino group forms an intramolecular H-bond with the carbonyl oxygen (N···O = 2.730(3)Å).