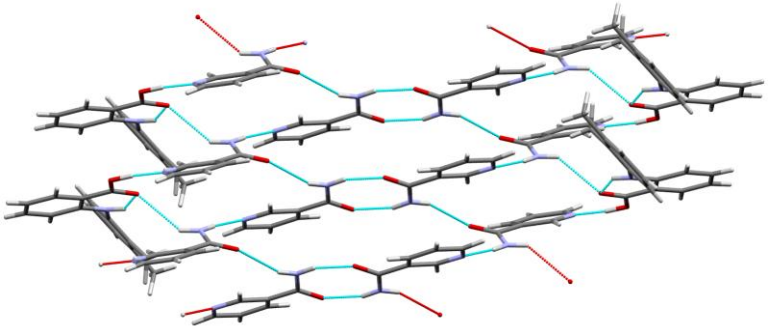
Cocrystals of fenamic acids with nicotinamide

*László Fábián,[†] Noel Hamill,[‡] Kevin S. Eccles,[†] Humphrey A. Moynihan,[†] Anita R. Maguire,[#] Linda McCausland,[‡] & Simon E. Lawrence.[†]**

[†]Department of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland, [‡]Almac Sciences, Seagoe Industrial Estate, Craigavon, UK. [#]Department of Chemistry and School of Pharmacy, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland.

Cocrystal formation between nicotinamide and five fenamic acid derivative drugs: flufenamic acid, niflumic acid, tolfenamic acid, mefenamic acid and meclofenamic acid was investigated using solution-based and solid-state preparation methods. It was anticipated that the well-known acid–aromatic nitrogen heterosynthon would provide sufficient driving force for cocrystallization. The experiments yielded cocrystals with four of the five acids. Although the structures of these molecules are similar, they showed marked differences in both the stability and the stoichiometry of the cocrystals. A detailed analysis of the structures and properties of both the starting materials and the cocrystals allows tentative explanation of these differences, but it also shows that even though all four cocrystals utilize one of the most predictable supramolecular synthons (COOH…N), their structures and properties remain elusive to design.



*Corresponding author: Simon E. Lawrence

Address: Department of Chemistry, ABCRF, University College Cork, Cork, Ireland

Email: s.lawrence@ucc.ie, Tel.: +353 21 490 3143, Fax: +353 21 427 4097

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[†]Department of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland, [‡]Almac Sciences, Seagoe Industrial Estate, Craigavon, UK. [#]Department of Chemistry and School of Pharmacy, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland.

AUTHOR EMAIL ADDRESS: s.lawrence@ucc.ie

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TITLE RUNNING HEAD: Cocrystals of fenamic acids with nicotinamide

ABSTRACT: Cocrystal formation between nicotinamide and five fenamic acid derivative drugs: flufenamic acid, niflumic acid, tolfenamic acid, mefenamic acid and meclofenamic acid was investigated using solution-based and solid-state preparation methods. It was anticipated that the well-known acid–aromatic nitrogen heterosynthon would provide sufficient driving force for cocrystallization. The experiments yielded cocrystals with four of the five acids. Although the structures of these molecules are similar, they showed marked differences in both the stability and the stoichiometry of the cocrystals. A detailed analysis of the structures and properties of both the starting materials and the cocrystals allows tentative explanation of these differences, but it also shows that even though all four cocrystals utilize one of the most predictable supramolecular synthons (COOH…N), their structures and properties remain elusive to design.

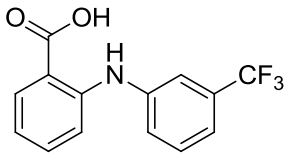
Introduction

Fenamic acids (Scheme 1) are an important class of non-steroidal anti-inflammatory drugs (NSAIDs) derived from *N*-phenylanthranilic acid, which have recently been shown to exhibit neuroprotective[1] and anti-tumor properties.[2] A common property of fenamic acids is their low aqueous solubility, which has been suggested to be a key factor in restricting their bioavailability.[3,4] Numerous formulation approaches have been employed historically to increase solubility (*e.g.*, use of polymers,[5] cyclodextrins,[6] layered hydroxides,[7] nanoparticulates,[8] salts[9] and amorphous materials[10]). Cocrystallization of active pharmaceutical ingredients (APIs) with water soluble guests is an emerging strategy to increase kinetic solubility and, thus, bioavailability.[11]

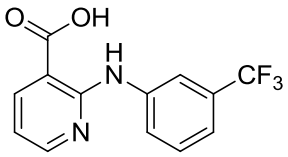
As carboxylic acids form strong hydrogen bonds with nitrogen atoms in heteroaromatic rings, this interaction has been widely utilized as a robust supramolecular heterosynthon (**I**, Scheme 2) in the design of cocrystals.[12,13] Exemplifying this strategy, nicotinamide has been used successfully as a pharmaceutically acceptable cocrystal former with carboxylic acids.[13] Previous evidence for the reliability of synthon **I** as a driving force for cocrystallisation[12d] suggests that it should be easy to obtain

fenamic acid/nicotinamide cocrystals. Owing to the possibility of complex formation in solution and to the higher solubility of nicotinamide, these cocrystals are expected to be more soluble in water than the parent acids.[13c] We were keen to establish whether these expectations were justified and whether any structure–property relationships can be identified in a series of related compounds and their cocrystals.

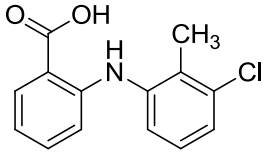
Scheme 1. Structural formulas of the fenamic acids and nicotinamide.



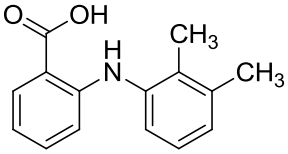
flufenamic acid (**1**)



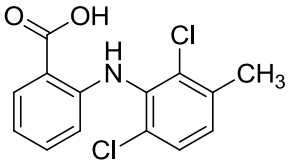
niflumic acid (**2**)



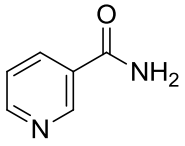
tolfenamic acid (**3**)



mefenamic acid (**4**)

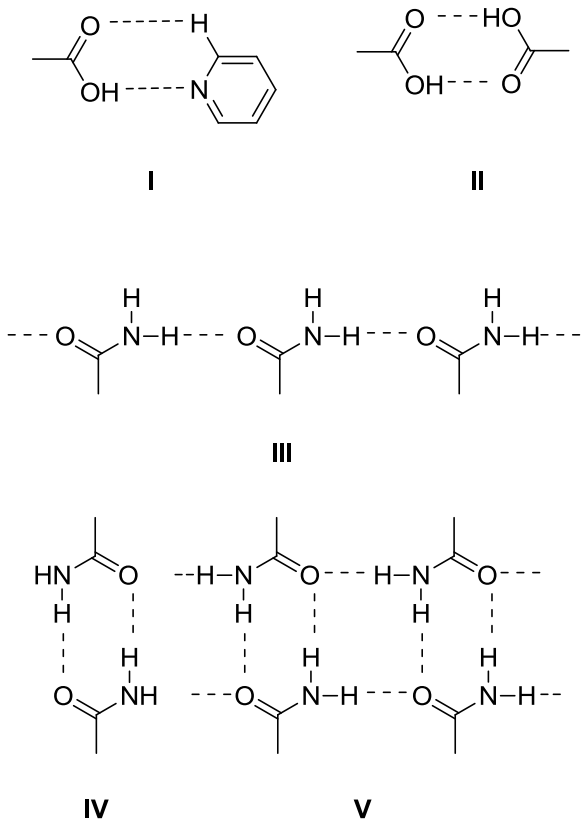


meclofenamic acid (**5**)



nicotinamide (**6**)

Scheme 2. Common supramolecular synthons and hydrogen bond motifs.



Our screening strategy involved three preparative methods: crystallization from solution (using the reaction crystallization method),[14] liquid-assisted grinding[15] and sonication[16] (see Experimental Section). The formation of a new phase was detected by powder X-ray diffraction (PXRD) and the resulting new materials were characterized by differential scanning calorimetry (DSC). The flufenamic acid/nicotinamide cocrystal (**1**·**6**) was easily obtained from solution, and gave crystals suitable for single crystal X-ray diffraction. Cocrystals of nicotinamide with niflumic acid (**2**·**6**), tolfenamic acid (**3**·**6**) and mefenamic acid (**4**·**6**) could only be prepared as polycrystalline powders, so their structures were determined from powder diffraction data. Meclofenamic acid and nicotinamide did not form a cocrystal in any of our experiments. The relative solubilities of the cocrystals and the starting materials were assessed by slurry experiments.

Experimental Section

Chemicals. All solvents and chemicals (>99% purity) were available commercially and were used without further purification. Nicotinamide, mefenamic acid, niflumic acid, tolfenamic acid and meclofenamic acid were all confirmed as Form I by PXRD and DSC. Flufenamic acid was heated to 85 ˚C to generate pure Form I prior to use.

Solution crystallization of flufenamic acid/nicotinamide (1·6) and niflumic acid/nicotinamide (2·6) cocrystals. Nicotinamide (400 mg) was dissolved in ethanol (6 mL) and filtered through a 0.2 μm PTFE syringe filter into a suspension of the acid (1 eq) in ethanol (2 mL). For both acids, the individual components dissolved before thick precipitation of the cocrystal, which occurred within a few minutes. The mixtures were stirred for 3 hours prior to vacuum filtration and air-dried. Pure 1:1 cocrystals with flufenamic acid (**1·6**) and niflumic acids (**2·6**) were obtained as white and pale yellow crystalline solids, respectively. The crystals of **1·6** were suitable for single crystal diffraction experiments without recrystallization. All attempts to grow **2·6** single crystals gave needles that were too thin for single crystal X-ray analysis.

Liquid-assisted grinding. 100 mg of a 1:1 or 1:2 stoichiometric mixture of the solid fenamic acid and nicotinamide respectively was placed in the grinding jar of a Retsch MM400 ball mill and 25 μL of ethanol (or ethyl acetate for mefenamic acid) was added. The mixtures were ground for 30 min at 30 Hz frequency.

Liquid-assisted sonication. 50 mg of a 2:1, 1:1 or 1:2 mixture of the solid fenamic acid and nicotinamide was mixed in a 2 mL HPLC vial with enough solvent to give a wet paste. The paste was sonicated using a Cole Parmer 130 W sonic probe with 3 mm tip at a power setting of 70% for approximately 30-40 s.

Competitive slurry experiments. Cocrystals (50 mg of each) were stirred in 1 mL of water, with equimolar amounts of the relevant fenamic acid (~5.5 mg) and nicotinamide (~2.5 mg) for 48 hours at 20 ˚C. The solids were isolated by vacuum filtration and air-dried prior to analysis.

Differential scanning calorimetry. Thermal analysis was performed using a Perkin Elmer Jade Differential Scanning Calorimeter (DSC) system, which was calibrated for temperature and enthalpy using indium. Samples (3-5 mg) were crimped in non-hermetic aluminum pans and scanned from 30 to 300 °C at a heating rate of 10 °C/min under a continuously purged dry nitrogen atmosphere.

Single crystal diffraction. X-ray diffraction data were collected on a Bruker APEX II DUO diffractometer using graphite monochromatized Mo *K*α radiation (λ = 0.7107 Å). The crystal was cooled with an Oxford Cryosystems COBRA fitted with a N_2 generator. All calculations were performed using the *APEX2* software suite,[17,18] and the diagrams prepared using Mercury.[19] Suitable crystals of the flufenamic acid/nicotinamide cocrystal (**1·6**) were selected from the batch grown by solution crystallization.

Powder diffraction. Powder diffraction data for the screening experiments were collected on Panalytical Xpert Pro MPD (2θ = 3 – 40°, total scan time = 22 min, Cu *K*α radiation) and Stöe Stadi MP (2θ = 3 – 40°, scan time = 30 min, Cu *K*α_1 radiation) diffractometers. The diffraction patterns of the materials obtained in the screening experiments were compared to those of the starting materials. Cocrystal formation was inferred from the appearance of new peaks, while the presence of peaks from the starting materials was used to determine cocrystal stoichiometry in the grinding and sonication experiments. Peaks from all known polymorphs of the starting materials were considered in order to check for the possibility of a polymorphic transformation.

Powder X-ray diffraction data for the structure determination of the 1:1 niflumic acid/nicotinamide cocrystal (**2·6**) were collected on a Stöe Stadi MP diffractometer, equipped with a linear position sensitive detector, in transmission mode (foils) using Cu *K*α_1 radiation (λ = 1.5406 Å) in the 2θ range 3 – 59° over a 10 h total scan time. Data collected for the 1:2 cocrystals with tolfenamic acid (**3·6**) and mefenamic acid (**4·6**) using the same experimental settings could not be indexed reliably. Therefore, synchrotron data for these materials were collected at the Swiss Light Source[20] (Paul Scherrer Institute, Villingen, Switzerland) using a wavelength of 1.0002 Å in the 2θ range 2 – 120°. Samples were

mounted in 0.5 mm capillaries and the patterns were acquired using the Mythen II detector[21] over a total exposure time of 40 and 60 s in 2 s runs for **3·6** and **4·6**, respectively. Consecutive runs showed no radiation damage. Synchrotron data in the 2θ = 2 – 60° range were used for Rietveld refinement.

The powder patterns were indexed and the structures solved using the program DASH.[22] Rietveld refinement was completed using the EXPGUI interface to GSAS.[23] Bond lengths and angles were restrained to values taken from the known crystal structures of the starting materials. A good fit for **3·6** and **4·6** could only be obtained by modeling the effects of anisotropic strain on the peak shapes.[24] Details of the refinement are given in Table 1 and in the Supporting Information.

Table 1. Crystallographic data.

Structure	**1·6**	**2·6**	**3·6**	**4·6**
Formula	$C_{20}H_{16}F_3N_3O_3$	$C_{19}H_{15}F_3N_4O_3$	$C_{26}H_{24}ClN_5O_4$	$C_{27}H_{27}N_5O_4$
Formula weight	403.36	404.35	505.96	485.54
Crystal system	monoclinic	monoclinic	triclinic	triclinic
Space group	$P2_1/c$	$P2_1/c$	P-1	P-1
a / Å	5.1054(14)	15.1502(5)	4.00638(2)	4.064104(14)
b / Å	15.961(4)	5.06025(6)	12.55456(6)	12.50989(5)
c / Å	22.119(6)	24.6743(5)	24.12612(13)	24.08865(10)
α / °	90	90	100.3237(3)	99.8930(4)
β / °	90.471(6)	112.1745(18)	90.4099(3)	90.7285(4)
γ / °	90	90	92.5309(4)	92.4340(4)
V / Å^3	1802.4(8)	1751.72(7)	1192.555(15)	1205.154(8)
Z	4	4	2	2
D_c / g cm^{-3}	1.486	1.533	1.409	1.338
λ / Å	0.7107	1.5406	1.0002	1.0002
T / K	100	293	295	295
2θ range / °	3.14–54.38	3.00–59.00	2–60	2–60

Data / parameters / restraints	4009 / 277 / 0	5599 / 156 / 174	15162 / 222 / 197	15388 / 240 / 206
R indices (all data)	$R_1 = 0.068$, $wR_2 = 0.125$	$R_p = 0.030$, $R_{wp} = 0.041$, $R_{exp} = 0.028$	$R_p = 0.008$, $R_{wp} = 0.011$, $R_{exp} = 0.004$	$R_p = 0.004$, $R_{wp} = 0.006$, $R_{exp} = 0.004$
Goodness of fit	$S = 1.017$	$\chi^2 = 2.504$	$\chi^2 = 6.613$	$\chi^2 = 2.574$
Largest diff. peak and hole / e Å^{-3}	0.38 / -0.31	0.19 / -0.18	0.44 / -0.52	0.33 / -0.33

Results and Discussion

Preparation of cocrystals. Despite the variation of methods and starting compositions used, only one cocrystal phase was identified for each acid, except for meclofenamic acid, **5**, which yielded none (Table 2). Liquid-assisted grinding produced pure samples of each cocrystal only when the initial acid/nicotinamide ratio corresponded with the stoichiometry of the cocrystal. Therefore, grinding experiments could be used to determine the correct stoichiometry of each cocrystal produced. Sonication is a much faster screening method than grinding and product composition can be controlled similarly to grinding when care is taken to ensure that neither of the components is dissolved preferentially and the sample remains homogenous. However, the mefenamic acid/nicotinamide cocrystal (**4**·**6**), which appeared to be the least stable of the four cocrystals in our experiments, could not be synthesized by sonication, only by grinding.

Solution crystallization is the most favorable means of obtaining pure cocrystals while facilitating scale up. As part of the screening methodology, the fenamic acids and nicotinamide were suspended or dissolved in an organic solvent in which the solubility of both components was roughly equal, as this is more likely to produce a congruently saturating system (Table S1, Supporting Information). This strategy has been reported to maximize the chance of cocrystal precipitation[25] and indeed, using ethanol as a solvent, was successful in the isolation of the 1:1 cocrystals **1**·**6** and **2**·**6**. However, the 1:2 cocrystals **3**·**6** and **4**·**6** were always observed with residual acid and/or nicotinamide present, even when

a wide variety of alternative solvents and 1-10 equivalents of nicotinamide were used. All attempts at washing or re-suspension of the cocrystals resulted in dissociation, sometimes leading to the formation of metastable fenamic acid polymorphs. This was not entirely unexpected, as the isolation of pure cocrystal phases can require detailed understanding of the ternary phase diagrams for the acid, nicotinamide and the solvent; especially when narrow regions of stability exist for the pure cocrystal phase.[26] This work is currently underway and will be reported in a forthcoming publication.

Table 2. Results of screening experiments as determined by PXRD.

Experiment	**1 + 6**	**2 + 6**	**3 + 6**	**4 + 6**
1:1 grinding	cocrystal	cocrystal	cocrystal + acid	cocrystal + acid
1:2[a] grinding	cocrystal + nicotinamide	cocrystal + nicotinamide	cocrystal	cocrystal (+ trace nicotinamide)
1:1 sonication	not tested[b]	not tested[b]	cocrystal + acid	acid + nicotinamide
1:2[a] sonication	not tested[b]	not tested[b]	cocrystal	acid + nicotinamide
2:1[a] sonication	not tested[b]	not tested[b]	cocrystal + acid	acid + nicotinamide
solution crystallization	cocrystal	cocrystal	cocrystal + nicotinamide	cocrystal + nicotinamide

[a]The ratio given is the acid : nicotinamide molar ratio in the solid mixture. [b]Cocrystals of these compounds were obtained by solution crystallization prior to screening using sonication.

Stability of the cocrystals. Competitive slurry experiments are used to assess the relative solubilities of various solid forms. If the solid added to the slurry is not the least soluble form, the slurry is not in equilibrium: the original solid will dissolve and the least soluble form will crystallize. Therefore, analysis of the suspended solid at various time points will show a gradual increase in the amount of the more stable form due to solution mediated phase transition.

After 48 hours slurrying of the cocrystals in water, powder diffraction analysis of the solid phases showed that the cocrystals **2·6** and **3·6** had converted to mixtures of the acid and nicotinamide, whereas the cocrystal **1·6** remained intact. These preliminary results suggest that the cocrystals **2·6**, **3·6** and **4·6** are more soluble in water than the free acid and, conversely, that the cocrystal **1·6** is less soluble than flufenamic acid, **1**. It is interesting to note the difference in the stability of the niflumic acid cocrystal (**2·6**) when suspended in water, as opposed to ethanol, from which it is easily prepared. This highlights the need for adequate ternary phase solid-liquid equilibrium data in organic solvents and water when considering the utility and scale up of cocrystals as therapeutic drug forms.

The melting points of the four cocrystals (Table 3) show much smaller variation that the melting points of the four acids (Table 4)[27,28] despite the two different stoichiometries. There is no correlation between the melting points of the acids and their respective cocrystals: the melting point of flufenamic acid/nicotinamide cocrystal, **1·6**, is higher than that of both the acid and the amide (401 K[29]), while the melting points of the other cocrystals are between those of the pure components. The high melting point of **1·6** relative to that of its components is consistent with the stability of this material in the solution experiments, as is the low melting point of the unstable mefenamic acid/nicotinamide cocrystal, **4·6**, more than 100 K below the melting point of the acid.

Table 3. Thermoanalytical data for the fenamic acid/nicotinamide cocrystals.

	1·6	**2·6**	**3·6**	**4·6**
T_m, K	410	413	426	~400[a]
ΔH_{fus} [kJ mol^{-1}]	57	48	98	~50[a]
ΔS_{fus} [J mol^{-1} K^{-1}]	139	117	229	~120[a]

[a]Only approximate values can be given as these samples contained nicotinamide, resulting in overlap of the melting peaks for the cocrystal and nicotinamide.

Table 4. Thermodynamic characteristics of fenamic acids: fusion, sublimation (at 298 K), solubility in un-buffered water and ethanol at 25 °C, and proton dissociation data.

	1 *(form I)*	**2**	**3** *(form I)*	**4** *(form I)*	**5**
T_m, K	405.3[a]	478.5[a]	484.3[a]	503.5 (form II)[a,b]	531.5[c]
ΔH_{fus} [kJ mol^{-1}]	26.7[a]	36.5[a]	38.6[a]	38.7 (form II)[a,b]	37.1[c]
ΔH_{sub} [kJ mol^{-1}]	121.2[a]	130.2[a]	128.4[a]	136.2[a]	unknown
ΔG_{sub} [kJ mol^{-1}]	54.3[a]	61.3[a]	53.9[a]	59.2[a]	unknown
S_{water} [μmol L^{-1}]	45[d]	170[d]	2.3[e]	0.6[d]	0.5[f]
S_{EtOH} [mol L^{-1}]	0.88	0.19	0.17	0.14	0.04
pK_a	3.97[d]	4.44[d]	4.3[g]	4.22[h]	4.39[i]

[a]Data from ref. 27. [b]Form I transforms to form II at 450 K, so melting data is available only for form II. [c]Data from ref. 28. [d]Data from ref. 35. [e]Data from ref. 5. [f]Data from ref. 36. [g]Data from ref. 37. [h]Data from ref. 38. [i]Data from ref. 39.

It may be expected that lower melting compounds form cocrystals more readily than higher melting ones (at least within a family of similar compounds). The behavior of the five fenamic acids supports this expectation. The highest melting compound, meclofenamic acid (**5**), did not cocrystallize at all with nicotinamide. The second highest melting acid, mefenamic acid (**4**), gave unstable cocrystals, while the lowest melting of them, flufenamic acid (**1**), readily formed stable cocrystals. Solubility in ethanol follows the same trend, with the most soluble compound giving the most stable cocrystal and the least soluble one forming no cocrystals. Aqueous solubilities of the fenamic acids are much lower than those in ethanol (note the different units in Table 4), explaining why it was easier to produce cocrystals from alcohol than from aqueous solutions. Aqueous solubilities of the acids do not show a straightforward correlation with the stabilities of the corresponding cocrystals in the slurry experiments.

Similarly, sublimation data (Table 4) do not correlate with the observed stability of the cocrystals. Heats of sublimation are directly related to lattice energies, so a lack of correlation here suggests that

differences in cocrystal formation can not be explained relying solely on the energies of fenamic acid structures.

All known fenamic acid structures[30-34] show the same hydrogen-bond motif, even in their different forms. The amine donates an intramolecular bond to the carbonyl oxygen atom, while the carboxyl groups form centrosymmetric dimers (**II**, Scheme 2). The relative strength of the acids as hydrogen bond donors can be estimated from their pK_a values.[5,35-39] It is clear from Table 4 that differences in pK_a and thus differences in the hydrogen bonding ability of the acids do not explain the different outcomes of the screening experiments. The conformation of the fenamic acids shows a large variation in their crystal structures (Table 5), but the different conformations can not be linked directly to the different compositions and stabilities of the cocrystals. Therefore, knowledge of the fenamic acid structures provides no obvious explanation for their different behavior.

To summarize, the melting points of the acids and their solubilities in ethanol appear indicative of the ease of cocrystal formation, but none of the parameters investigated could be used to predict the different stoichiometries observed in these cocrystals.

Table 5. Conformation of fenamic acid molecules.

	1	**2**	**3**	**4**	**5**
Angle between the two aromatic rings in the fenamic acid crystals[30-34]	53° (form I) 43° (form III)	9°	73° (form I) 44° (form II) 54°, 55° (form III) 58°, 64°, 61° (IV) 79° (form V)	62°(form I) 68°(form II)[a]	81°
Angle between the two aromatic rings in the cocrystals	54.89(9)°	9.03(15)°	46.9(2)°	50.04(2) °	

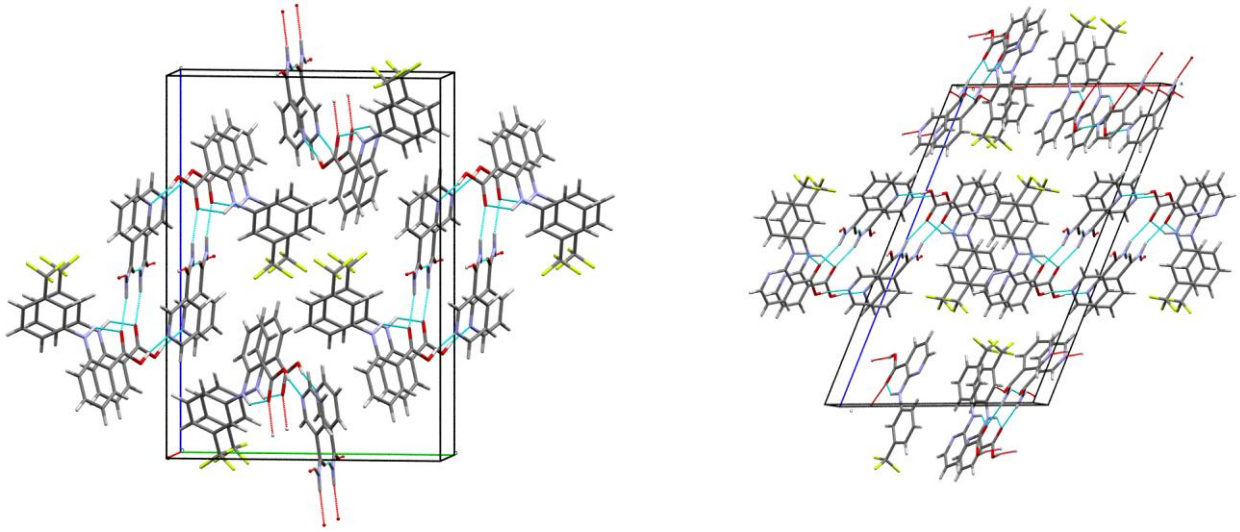
[a]Calculated using the torsion angles published in ref. 30(b).

Crystal structures. An intramolecular NH…O=C hydrogen bond keeps the anthranilic acid fragment planar in each of the fenamic acid crystal structures[30-34] and in the four cocrystals. The rotation of the other aromatic ring around the N–C bond differentiates the conformers in these structures (Table 5). In most structures the two aromatic planes enclose an angle of 40–80°, which avoids steric clashes between the *ortho* H atoms and substituents on the two benzene rings. Conversely, niflumic acid (**2**) assumes a nearly planar conformation in both the pure acid and in the cocrystal with nicotinamide. This unusual conformation is stabilized by an intramolecular CH…N interaction between the aromatic N atom and the *ortho* H atom on the other ring.

Despite the difference in the conformation of the acid molecules, both 1:1 cocrystals (**1·6** and **2·6**) show the same hydrogen bond motif (Figure 1). The expected acid–aromatic N heterosynthon is formed, providing the main driving force for cocrystallization. This interaction replaces amide–aromatic N hydrogen bonds in the nicotinamide[40] and the acid dimers in the flufenamic and niflumic acid structures.[30,31] Amide–amide hydrogen bonds form infinite chains (Scheme 2, **III**) in the cocrystal (perpendicular to the plane of the sheet in Figure 1), while the second amide H atom forms a hydrogen bond with the carbonyl O atom of the acid. This set of hydrogen bonds (acid–aromatic N, amide–amide and amide–acid) is common among the cocrystals of carboxylic acids with isonicotinamide,[12] although the amide–amide bonds typically form dimers (**IV**) rather than chains (**III**). Nicotinamide cocrystals, on the other hand, often show two amide–amide bonds and no amide–acid bond, thus combining the chain and dimer motifs to form a ladder pattern (**V**).[13]

In both 1:1 cocrystals, hydrogen-bonded rings are formed by two fenamic acid and two nicotinamide molecules (Figure 1). These four-molecule rings are linked into infinite tubes by the amide chain motif (**III**). The main difference between the two cocrystal structures is in the packing arrangement of the tubes, which is consistent with the different conformations of the flufenamic and niflumic acid molecules and the consequent difference in the outer surface of the tubes (Supporting Information, Figure S13).

A possible reason why tolfenamic and mefenamic acids do not form similar 1:1 cocrystals can be inferred from the structures of **1·6** and **2·6**. A short C–H…O contact is formed between the 2'-H atom of the acids and an amide O atom in the 1:1 cocrystals, which stabilizes the amide chains (Figure 2). The 2'-methyl substituent of tolfenamic acid and mefenamic acid, which replaces this H atom, would most likely not fit in this space. Therefore, the presence of the 2'-methyl substituent would add steric strain to the hydrogen bond network of a hypothetical 1:1 cocrystal for these acids, were it to adopt the same structure as the other 1:1 cocrystals.



(a) (b)

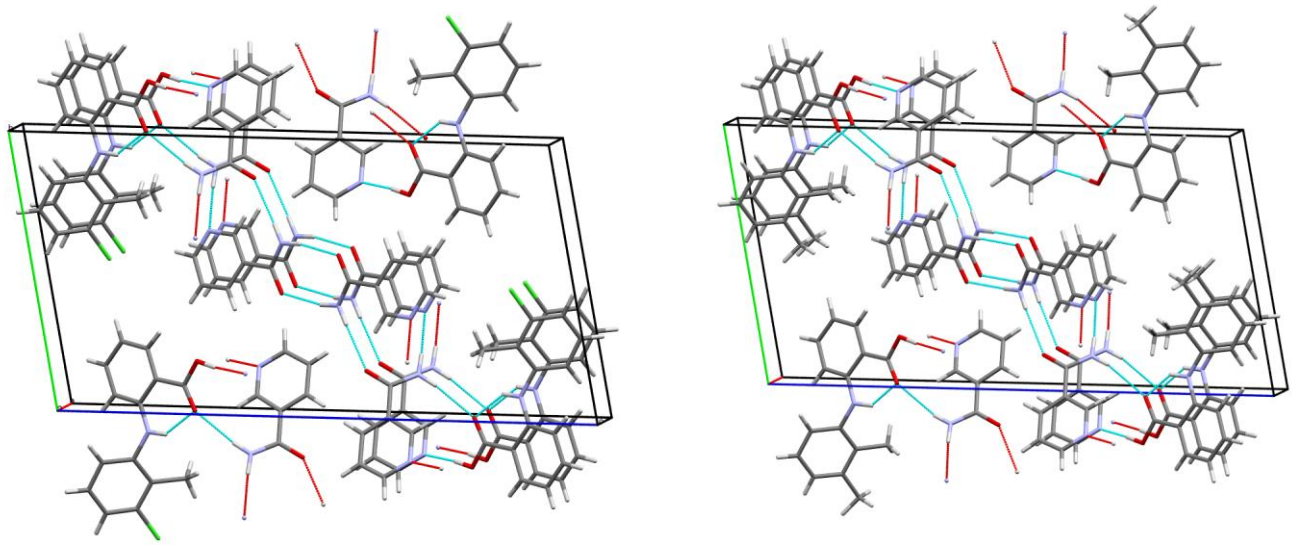
Figure 1. Packing diagram of the 1:1 cocrystals (a) flufenamic acid / nicotinamide, **1·6**, and (b) niflumic acid / nicotinamide, **2·6**. Atom colors: C – grey, H – white, N – blue, O – red, F – lime green.

(a) (b)

Figure 2. Short C–H…O contacts (green line) in the cocrystals (a) **1·6** ($d_{H...O}$ = 2.62 Å, $\alpha_{C–H...O}$ = 167°), and (b) **2·6** ($d_{H...O}$ = 2.48 Å, $\alpha_{C–H...O}$ = 124°). Hydrogen bonds are shown as light blue lines.

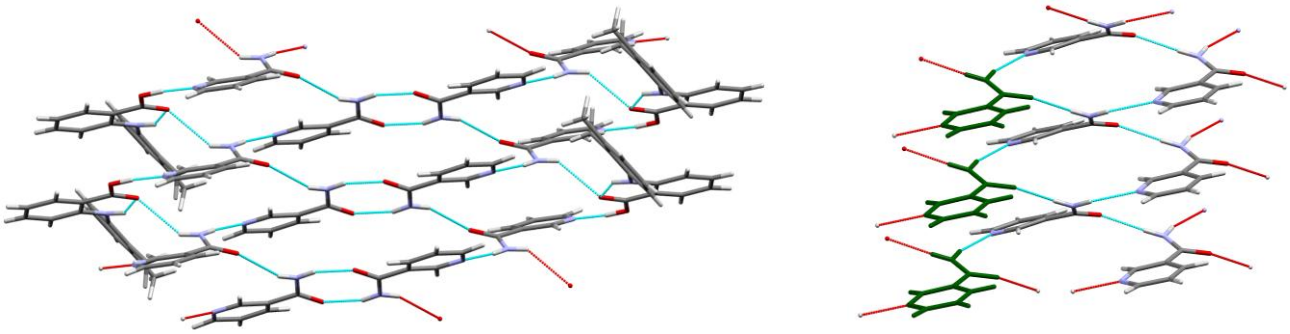
As a consequence, the acid:amide ratio is 1:2 in the cocrystals of tolfenamic acid and mefenamic acid with nicotinamide (**3·6** and **4·6**). Both of these cocrystals show the same hydrogen bonding interactions and packing arrangements, *i.e.*, they are isostructural (Figure 3). The isostructurality index calculated from the volume overlap of the two structures[41] is high, I_v = 95%.

Similarly to the 1:1 cocrystals, the carboxyl group of mefenamic and tolfenamic acid donates a hydrogen bond to the aromatic N atom of a nicotinamide molecule. However, in the 1:2 stoichiometry cocrystals an acid donor is available for only one of the nicotinamide molecules, while the other aromatic N accepts a hydrogen bond from the amido group of the acid-bound nicotinamide molecule. A helix of nicotinamide molecules is linked by the alternation of this NH…N interaction and NH…O(amide) hydrogen bonds (Figure 4a). A similar helical arrangement is present in the stable polymorph of nicotinamide (Figure 4b).[40] In nicotinamide, the helix is part of a two-dimensional grid motif, while in the cocrystals two of these helices are linked into a pair by the amide–amide dimer (**IV**) motif. The acid molecules connect subsequent turns of each helix via a pair of acid–aromatic N and amide–acid hydrogen bonds, capping the outside of the helix pair. Therefore, the complete hydrogen bond motif is infinite only along the axis of the helices, and, similarly to the 1:1 cocrystals, a columnar assembly of the molecules is obtained.



(a) (b)

Figure 3. Crystal structures of the 1:2 cocrystals (a) tolfenamic acid/nicotinamide, **3·6**, and (b) mefenamic acid nicotinamide, **4·6**.



(a) (b)

Figure 4. Hydrogen bond network in (a) **4·6** and (b) nicotinamide (**6**) form I. The common helical assembly of nicotinamide molecules is highlighted in (b).

This similarity in the overall construction of the 1:1 and 1:2 cocrystals is in contrast with their different hydrogen bond motifs. Presumably, the sizeable hydrophobic region of the fenamic acid molecules limits the extension of hydrogen bonds into two- or three-dimensional networks, while favorable stacking interactions between the fenamic acid molecules help the formation of molecular

columns. With regard to hydrogen bonding, the 1:2 cocrystals show more structural resemblance to nicotinamide than to the 1:1 cocrystals (Figure 1). In effect, the only shared motif between all four cocrystals is the acid–aromatic N synthon.

The cocrystal structures give little indication why 1:1 fenamic acid:nicotinamide stoichiometry is preferred over 1:2. The packing coefficient of each cocrystal is 0.70–0.71, so improvements in space filling cannot be used as an adequate explanation. These cocrystals are formed because the acid–aromatic N synthon is energetically more favorable than any of the interactions possible in the one-component crystals. The relative weight of this interaction is higher in the 1:1 cocrystals. The similarity of the 1:2 cocrystals to nicotinamide may further reduce their kinetic stability, by facilitating the formation of nicotinamide crystals during cocrystal decomposition.

There is no obvious reason why flufenamic acid and niflumic acid could not form 1:2 cocrystals similar to those of tolfenamic and mefenamic acid. It is, however, clear from the relative difficulty of their preparation that the 1:2 cocrystals are less stable than the 1:1 cocrystals. Therefore, it is reasonable to assume that when starting from a 1:2 mixture of flufenamic or niflumic acid and nicotinamide, the mixture of a 1:1 cocrystal and nicotinamide is a more stable product of the cocrystallization reaction than a pure 1:2 cocrystal.

The failure to form meclofenamic acid/nicotinamide cocrystals is also hard to explain. For example, comparison with the **3·6** structure shows that the additional 6'-Cl atom would be positioned on the outside of the hydrogen-bonded helices. While such a substitution may render close packing less optimal, it is not in obvious conflict with the hydrogen bond network. Presumably, the failure of cocrystallisation is determined by interactions between the hydrophobic fragments of the molecules, which are much less predictable than hydrogen bonds.

Conclusion

Of the five fenamic acids investigated, four formed cocrystals with nicotinamide, demonstrating the robustness of the carboxylic acid–aromatic N heterosynthon. The acid:amide stoichiometry of the

cocrystals was either 1:1 or 1:2, depending on the acid involved. The 1:1 cocrystals were more stable, and were formed with the lowest melting, most soluble fenamic acids. The structure of the 1:1 cocrystals suggests that steric conflict involving the 2'-substituents in the other three acids prevents them from forming 1:1 cocrystals.

Obtaining the two 1:2 cocrystals in sufficient purity for structure determination was only possible using grinding and sonication, implying that scale-up of these cocrystals using solution based methods would require a detailed knowledge of the ternary phase diagram. Analysis of the structures of the 1:2 cocrystals does not provide a clear explanation for why only two of the five fenamic acids formed cocrystals with this stoichiometry.

Although all four cocrystals utilize a predictable supramolecular synthon and similar hydrogen bonds are present in related structures, the extended hydrogen bond motifs and the different compositions of the cocrystals would be difficult to predict. Some physicochemical properties of the fenamic acids, related to the stability of the acid crystals, could be correlated with the stability of the cocrystals. Yet other properties, also associated with the stability of the acid crystals, showed no such correlation. Similar studies on groups of related cocrystals will be required to confirm whether the correlations discussed in this work are of general utility.

Acknowledgment. This publication has emanated from research conducted with the financial support of Science Foundation Ireland, under Grant nos. 05/PICA/B802 TIDA 09, 05/PICA/B802/EC07 and 08/RFP/MTR1664. We gratefully acknowledge Jana Cairns, Lorraine Donaghy and Tracy Walker for the preparation and analysis of cocrystals. We are grateful to Fabia Gozzo (Paul Scherrer Institute) for collecting synchrotron data.

Supporting Information Available. Solubility data, hydrogen bond tables, PXRD and DSC data for the cocrystals, Rietveld refinement plots and CIF files. This information is available free of charge via the Internet at http://pubs.acs.org/.

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SYNOPSIS TOC