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# Pharmaceutical Salts of Fluoroquinolone Antibacterial Drugs with Acesulfame Sweetener

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*Novel organic salts of norfloxacin and ciprofloxacin with artificial sweeteners such as saccharin and acesulfame were prepared. The two salts **1** and **2** were characterized by differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). Finally, the crystal structures were solved by single crystal X-ray diffraction data and the structures were analyzed in terms of supramolecular synthons. In norfloxacin acesulfamate **1**, two norfloxacin cations and two acesulfame anions form an eight membered cyclic tetramer supramolecular synthon. The salt, ciprofloxacin acesulfamate **2**, has a similar structure as salt **1**. This study contributes the importance of crystal engineering and supramolecular chemistry to the pharmaceutical applications in terms of interactions and structural correlations in the design of new solid phases.*

*Supplemental materials are available for this article. Go to the publisher's online edition of Molecular Crystals and Liquid Crystals to view the free supplemental file.*

**Keywords** Acesulfame; ciprofloxacin; ciprofloxacin acesulfamate; norfloxacin; norfloxacin acesulfamate; supramolecular cyclic tetramer synthon

## Introduction

Crystal engineering of pharmaceutical cocrystals of active pharmaceutical ingredients (APIs) has attracted great interest in recent years [1,2]. Among various physical forms of APIs (polymorphs, solvates, salts, and cocrystals), cocrystal and salt forms provide a significant advantage in the development of solid dosage forms [3]. Cocrystal or salt formers can extremely affect the crystal packing and improve physicochemical properties of APIs [4]. Although cocrystallization shows exciting advantages, salt formation still represents a widely accepted approach to obtain improved properties of drug [5].

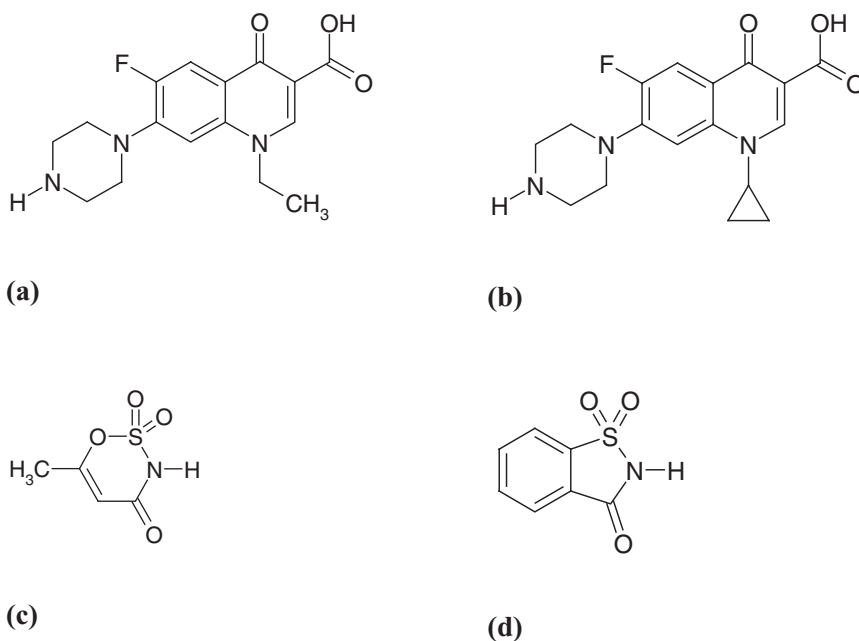
Intermolecular interactions are finally responsible in crystal engineering whereby discrete molecular building blocks are assembled into infinite architectures [6]. Although it is important to recognize that every crystal structure is the result of a subtle balance between a large numbers of noncovalent forces, the hydrogen bond remains a crucial element in

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supramolecular chemistry [7]. Supramolecular synthon strategy has been regarded as a reliable method for the design of crystal structures [8]. Supramolecular heterosynthons based on acid–base chemistry have been exploited for the rational design of organic salts [9].

Norfloxacin, chemically, (1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid) and ciprofloxacin (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid) are widely used fluoroquinolone antibacterial drugs with poor solubility (Scheme 1) [10]. Both are broad-spectrum antibiotics that are active against both Gram-positive and Gram-negative bacteria. They function by inhibiting DNA gyrase, a type II topoisomerase, which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division [11].



**Scheme 1.** Molecular structures of (a) Norfloxacin (b) Ciprofloxacin (c) Acesulfame (d) Saccharin.

Norfloxacin possess an acidic  $-\text{COOH}$  group with a  $\text{pK}_a$  of 6.34 and a basic  $\text{N-H}$  group with a  $\text{pK}_a$  of 8.75 and in aqueous solution, norfloxacin essentially exist in a zwitterionic form, due to the acid/base interaction between the basic nitrogen of the piperazine and the carboxylic acid group. Therefore, the aqueous solubility of norfloxacin at a pH close to 7 (isoelectric point of the molecule) is low ( $0.28\text{--}0.40\text{ mg mL}^{-1}$ ) [12]. We have previously reported one cocrystal (with isonicotinamide) and three organic salts with various dicarboxylic acids of norfloxacin showing increased solubility [13]. Ciprofloxacin also possess an acidic  $-\text{COOH}$  group with a  $\text{pK}_a$  of 6.09 and a basic  $\text{N-H}$  group with a  $\text{pK}_a$  of 8.62 and also exhibits the remaining above said properties as norfloxacin.

As a follow-up to the earlier studies, we are interested in employing artificial sweeteners that are FDA approved (GRAS, generally recognized as safe) salt/cocrystal formers [14]. In this paper, we report the crystal structures of saccharin and acesulfame salts of norfloxacin that are obtained by different methods. In addition, we have introduced a completely new salt/cocrystal former, acesulfame [15], which has similar functional groups

(O<sub>2</sub>S–NH–C=O) to saccharin [16] (Scheme 1) and prepared pharmaceutical salts with norfloxacin and ciprofloxacin. We characterized these salts by differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). Crystal structures of these compounds were obtained from the single crystal X-ray diffraction. The crystal structures (**1–2**) were thoroughly discussed in terms of supramolecular synthons and their role in building up of crystal structure. It was also our aim to compare and contract various structures and understand the role of supramolecular interactions in the formation of salts or cocrystals.

## Experimental

### Chemicals

Norfloxacin (EuPhar grade) and solvents (purity > 99.8%) were obtained from Sigma Aldrich, Stockholm, Sweden. Ciprofloxacin (≥98.0%) and Acesulfame-K (≥99.0%) were sourced from Fluka, Sweden. MilliQ water was used in the crystallization.

### Preparation and Isolation of Salts

*Preparation of Norfloxacin Acesulfamate, 1.* An equimolar mixture of norfloxacin and acesulfame-K was suspended in 10 mL water in a 25 mL conical flask. The suspension was titrated by drop wise addition of concentrated HCl, until complete solubility. Heating was applied if necessary. The solution was allowed to cool and evaporate slowly in a controlled fume hood temperature (22.5°C ± 0.5°C, air flow 0.54 m s<sup>-1</sup>). Scale up was carried out to produce 2 g of the material.

*Preparation of Ciprofloxacin Acesulfamate, 2.* An equimolar mixture of ciprofloxacin and acesulfame-K was suspended in 10 mL water in 25 mL conical flask. The suspension was titrated by drop wise addition of concentrated HCl, until complete solubility with heating to aid dissolution. The solution was left to cool and evaporate slowly in a controlled fume hood temperature (22.5°C ± 0.5°C, air flow 0.54 m s<sup>-1</sup>). Scale up was carried out to produce 2 g of the material.

*Preliminary Characterization.* The shapes of the crystals of the salts **1–2** were observed under the Leica MZ6 polarizing microscope.

*Differential Scanning Calorimetry.* Thermal analyses of the samples were performed on a Thermal Advantage DSC Q1000 V9.8Build 296 (TA instrument-waters, LLC) module which was calibrated for temperature and cell constants using indium and sapphire. Samples (3–5 mg) were crimped in nonhermetic aluminum pans (30 μL) and scanned at a heating rate of 10°C min<sup>-1</sup> in the range 30°C–300°C under a continuously purged dry nitrogen atmosphere, (flow rate 50 mL min<sup>-1</sup>). The instrument was equipped with a refrigerated cooling system. The data were collected in triplicate for each sample and were analyzed using TA Instruments Universal Analysis 2000 V4.3A software.

*Powder X-Ray Diffraction (PXRD).* PXRD patterns were collected on a Siemens DIFFRACplus 5000 powder diffractometer with a Cu Kα radiation (1.54056 Å). The tube voltage and amperage were set at 40 kV and 40 mA, respectively. The divergence slit and antiscattering slit settings were variable for the illumination on the 20 mm sample size.

Each sample was scanned between 5° and 50° in 2θ with a step size of 0.02° and 3.2 steps sec<sup>-1</sup>. The instrument had previously been calibrated using a silicon standard.

*X-Ray Crystallography.* The single crystal X-ray diffraction data of the crystals **1–2** were collected on a Bruker Nonius Kappa CCD at 293(2) K using Mo Kα radiation (λ = 0.71073 Å). The crystal structures were solved by direct methods using SHELXS-97 and refined by full matrix least-squares refinement on *F*<sup>2</sup> with anisotropic displacement parameters for non-H atoms, using SHELXL-97 [17]. N–H and O–H hydrogens were located from difference Fourier maps. Aromatic and aliphatic C–H hydrogens were generated by the riding model in idealized geometries. Table 1 gives the pertinent crystallographic data, and Table 2 gives hydrogen bond parameters.

### Results and Discussion

The salts **1** and **2** were obtained as needle shaped crystals. These crystals were used for various analyses.

**Table 1.** Salient crystallographic data and structure refinement parameters of salts 1–2

	<b>1</b>	<b>2</b>
Empirical formula	C <sub>24</sub> H <sub>24</sub> N <sub>3</sub> O <sub>6</sub> SF	C <sub>21</sub> H <sub>23</sub> N <sub>4</sub> O <sub>7</sub> SF
Formula weight	482.49	494.50
Crystal system	Monoclinic	Monoclinic
Space group	<i>C2/c</i>	<i>P2<sub>1</sub>/c</i>
<i>T</i> /K	293 (2)	293 (2)
<i>a</i> /Å	36.7720 (4)	16.4456 (8)
<i>b</i> /Å	7.13700 (10)	7.1089 (13)
<i>c</i> /Å	17.9460 (2)	19.225 (2)
α/°	90	90
β/°	116.4550 (10)	93.786 (5)
γ/°	90	90
<i>Z</i>	8	4
<i>V</i> /Å <sup>3</sup>	4216.59 (10)	2242.7 (5)
<i>D</i> <sub>calc</sub> /g cm <sup>-3</sup>	1.520	1.465
<i>F</i> (000)	2016	1032
μ/mm <sup>-1</sup>	0.215	0.204
θ/° range, °	3.28 to 30.32	3.06 to 30.75
Index ranges	–51 ≤ <i>h</i> ≤ 52 –10 ≤ <i>k</i> ≤ 10 –25 ≤ <i>l</i> ≤ 25	–22 ≤ <i>h</i> ≤ 23 0 ≤ <i>k</i> ≤ 9 –26 ≤ <i>l</i> ≤ 27
N-total	11,907	10,936
N-independent	6317	7004
N-observed	5314	3375
Parameters	306	319
<i>R</i> <sub>1</sub> ( <i>I</i> > 2σ( <i>I</i> ))	0.0409	0.0774
<i>wR</i> <sub>2</sub> (all data)	0.1082	0.1714
GOF	1.061	1.122
CCDC	704016	704015

**Table 2.** Geometrical parameters of hydrogen bonds in 1–2

Salt	D–H...A <sup>a</sup>	D...A (Å)	H...A (Å)	D–H...A (°)	Symmetry code
1	N3 <sup>+</sup> –H17...O4	2.7393 (17)	1.88 (2)	158.6 (19)	$x, 1 - y, -1/2 + z$
	N3 <sup>+</sup> –H19...O4	2.7230 (15)	1.840 (19)	157.3 (18)	$1/2 - x, -1/2 + y, 1/2 - z$
2	Intra O2–H18...O3	2.5339 (16)	1.66	154	–
	N3 <sup>+</sup> –H17...O4	2.745 (4)	1.78	159	$x, 3/2 - y, 1/2 + z$
	N3 <sup>+</sup> –H17...N4 <sup>–</sup>	3.370 (4)	2.56	137 <sup>°</sup>	$x, 3/2 - y, 1/2 + z$
	N3–H18...O4	2.796 (4)	1.86	152	$1 - x, -1/2 + y, 1/2 - z$
	Intra O2–H19...O3	2.540 (4)	1.67	145	–

<sup>a</sup>All of the N–H, and O–H distances are neutron normalized to 1.009 and 0.983 Å. C–H geometries are not given for the clarity.

### DSC Analysis

DSC thermograms showing the thermal behavior of the salts **1** and **2** in this study are shown in supplementary information (Figs S1a–S2a). The melting range of norfloxacin at 221°C is in agreement with the reported melting point of the norfloxacin, and an endothermic peak at 90°C signifying that the norfloxacin used in this study was indeed norfloxacin dihydrate (Fig. S1a) [18]. The thermal behavior of acesulfame-K and ciprofloxacin are in agreement with the reported values (Fig. S2a) [19,20]. The exothermic peaks of norfloxacin acesulfamate, **1** and ciprofloxacin acesulfamate, **2** at 240°C and 235°C shows their melting points (Figs S1a and S2a). Thermograms of salts of **1–2** without endothermic peaks at 90–120°C evidenced that the salts have no solvent molecules in their crystal structures (Figs S1a and S2a).

### PXRD Analysis

The PXRD patterns for salts **1–2** are shown in supplementary information (Figs. S1b and S2b). The PXRD pattern for norfloxacin was identical to that of the reported patterns of the norfloxacin dihydrate. The distinct nature of PXRD patterns of salts **1–2** compared to norfloxacin dihydrate, ciprofloxacin and acesulfame-K indicates the generation of new solid phases.

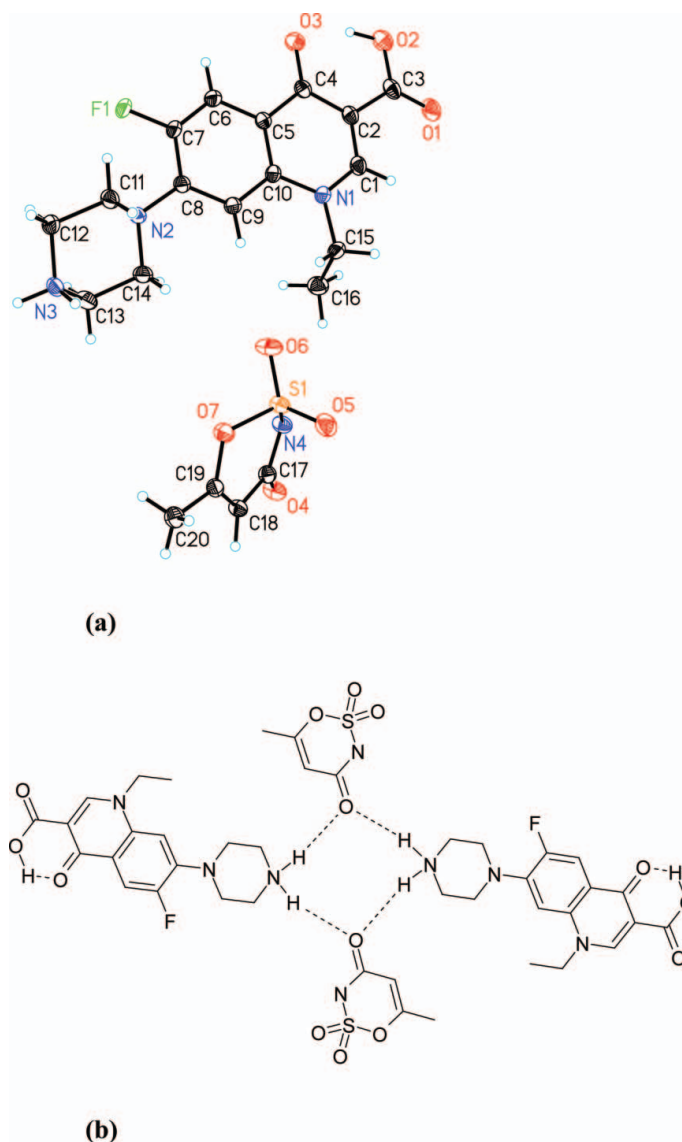
### Design of Salts 1–2

Norfloxacin and Ciprofloxacin are structurally very similar compounds and they vary in at N1 atom with ethyl group and cyclopropyl groups respectively. Based on the reported literature on the norfloxacin saccharinate salt [16a] it can be assumed that the saccharin and acesulfame are also have similar functional groups (O<sub>2</sub>S–NH–C=O) in their chemical structures. These similarities promote us to carry out the cocrystallization experiments expecting the similar structures in their crystals. However, due to the differences between the pK<sub>a</sub> values of APIs (norfloxacin pK<sub>a</sub> = 8.75 and ciprofloxacin pK<sub>a</sub> = 8.62) and salt/cocrystal former (acesulfame pK<sub>a</sub> = 2.0), the new phases **1** and **2** were crystallized as salts with similar synthons in their crystal structures.

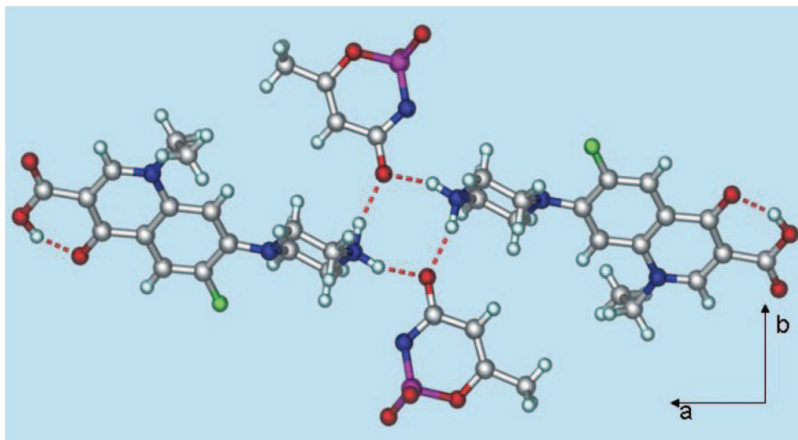
## Crystal Structure Analysis

### *Norfloxacin Acesulfamate, 1*

The acesulfame neutralizes with HCl (see experimental section) and subsequently the piperazinyl ring N-atom of norfloxacin protonated and forms salt **1**. The salt **1** crystallizes in the monoclinic  $C2/c$  space group with one norfloxacin cation and one acesulfamate anion in the asymmetric unit (Fig. 1a). The carboxylic group of norfloxacin is involved in intramolecular O–H...O hydrogen bonding with the quinolone oxygen atom

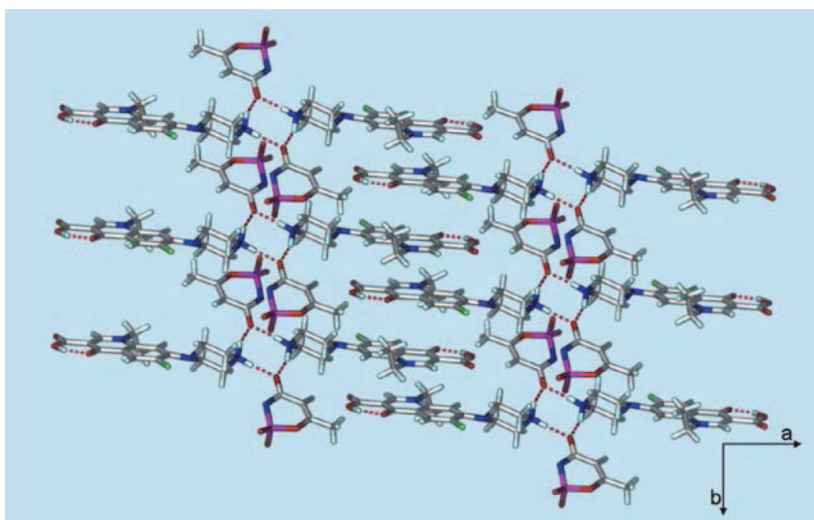


**Figure 1.** (a) ORTEP representation of the norfloxacin acesulfamate, **1**. Thermal ellipsoids are drawn at 50% probability level. (b) Molecular diagram showing interactions in the crystal.



**Figure 2.** Cyclic tetramer synthon formed with norfloxacin and acesulfamate ions via  $\text{N}^+-\text{H}\cdots\text{O}$  interactions in salt **1**.

( $\text{O2}\cdots\text{O3} = 2.5339(16) \text{ \AA}$ ,  $154^\circ$ ). The two norfloxacin cations and two acesulfamate anions form an eight membered cyclic tetramer synthon with two types  $\text{N}^+-\text{H}\cdots\text{O}$  hydrogen bonds ( $\text{N3}\cdots\text{O4} = 2.7393(17) \text{ \AA}$ ,  $158.6(19)^\circ$ ;  $\text{N3}\cdots\text{O4} = 2.7230(15) \text{ \AA}$ ,  $157.3(18)^\circ$ ) (Figs 1b and 2). After the formation of cyclic tetramers the quinolone moieties of norfloxacin molecules stack with  $\pi$ - $\pi$  interactions along the  $b$ -axis (centroid $\cdots$ centroid =  $3.617 \text{ \AA}$ ,  $4.001 \text{ \AA}$ ) (Fig. 3). Surprisingly the N-atom of the acesulfamate ion has not participated in any of the strong interactions but it is involved in a weak  $\text{C}-\text{H}\cdots\text{O}$  hydrogen bond [21].

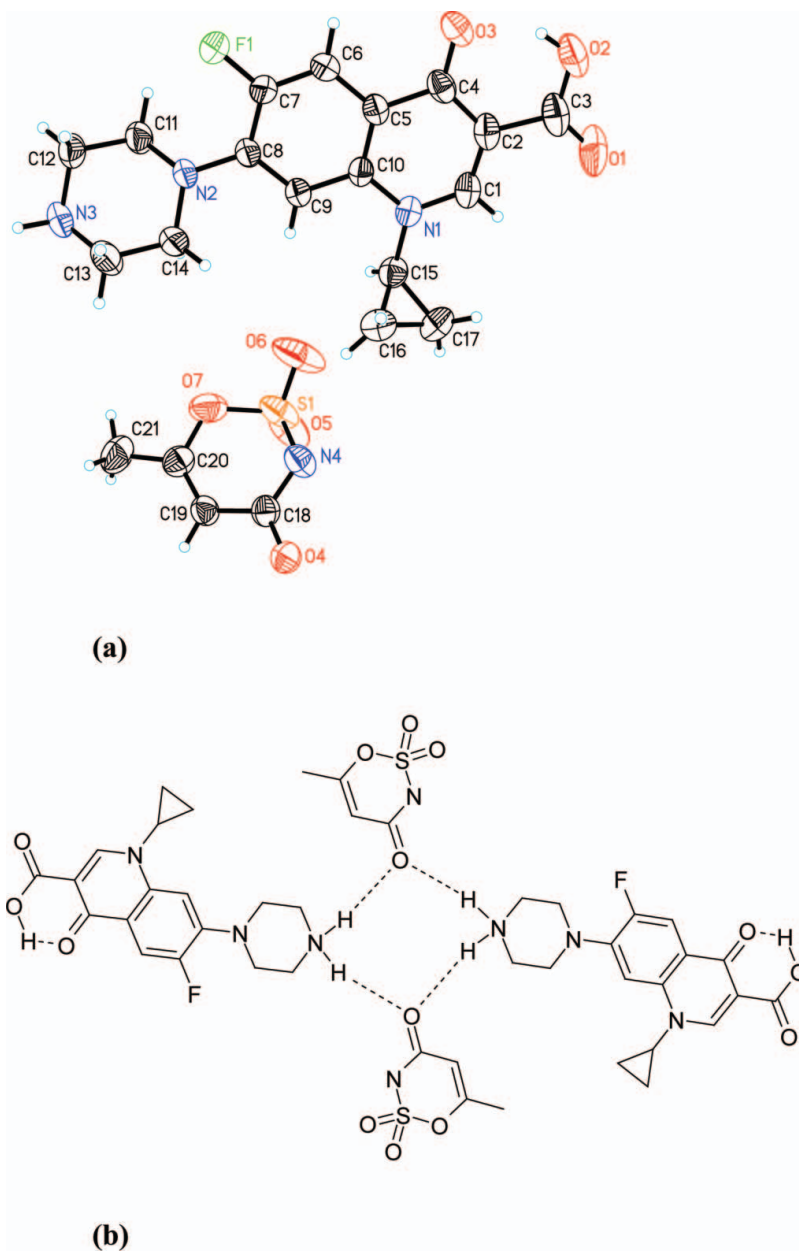


**Figure 3.** Packing diagram of salt **1** shows the  $\pi$ -stacked layers of quinolone moieties of norfloxacin ions.

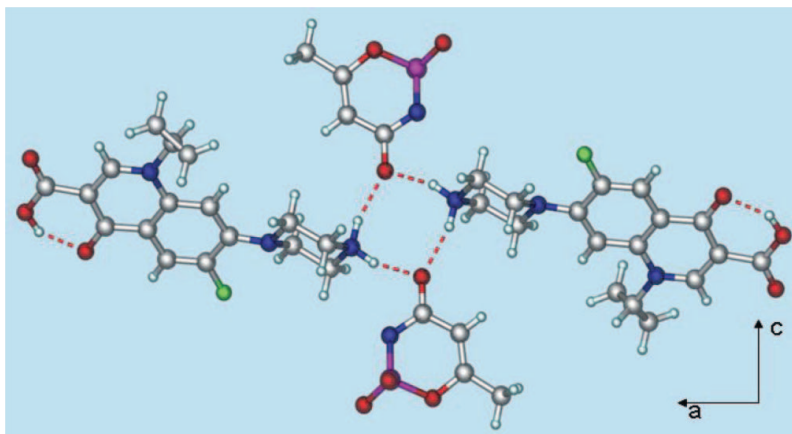


**Ciprofloxacin Acesulfamate, 2**

The acesulfame neutralizes with HCl (see experimental section) and subsequently the piperazinyl ring N-atom of ciprofloxacin protonated and forms salt **2**. The salt **2** crystallizes in the monoclinic  $P2_1/c$  space group with one ciprofloxacin cation and one acesulfamate anion in the asymmetric unit (Fig. 4a). The carboxylic acid group of norfloxacin involved

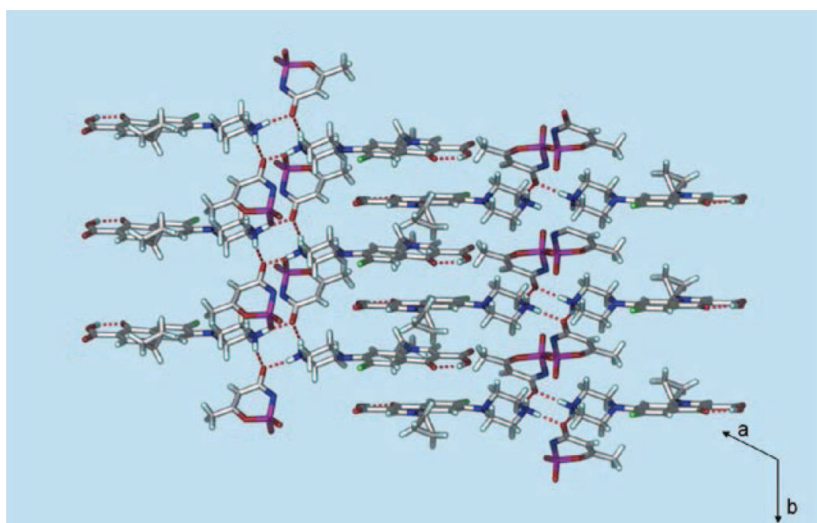


**Figure 4.** (a) ORTEP representation of the ciprofloxacin acesulfamate, **2**. Thermal ellipsoids are drawn at 50% probability level. (b) Molecular diagram showing interactions in the crystal.



**Figure 5.** Cyclic tetramer synthon formed with ciprofloxacin and acesulfamate ions via  $N^+ \cdots H \cdots O$  interactions in salt **1**.

in intramolecular  $O-H \cdots O$  hydrogen bonding with the quinolone oxygen atom ( $O2 \cdots O3 = 2.540(4) \text{ \AA}$ ,  $145^\circ$ ). The crystal structure analysis reveals that as in salt **1** a similar eight membered supramolecular synthon is formed in salt **2** with  $N-H \cdots O$  hydrogen bonds ( $N3 \cdots O4 = 2.796(4) \text{ \AA}$ ,  $152^\circ$ ;  $N3 \cdots O4 = 2.745(4) \text{ \AA}$ ,  $159^\circ$ ) (Figs. 4a and 5). The quinolone moieties of ciprofloxacin form  $\pi$ - $\pi$  interactions (centroid $\cdots$ centroid =  $3.702 \text{ \AA}$ ) along the  $b$ -axis as in all the remaining structures (Fig. 6). Unlike in salt **1**, the N-atom of the acesulfamate ion participated in a weak  $N^+ \cdots H \cdots N^-$  interaction.



**Figure 6.** Packing diagram of salt **2** shows the  $\pi$ -stacked layers of quinolone moieties of ciprofloxacin ions.

### Structural Correlation Between the Salts 1 and 2

It could be noted that in norfloxacin acesulfamate **1** and ciprofloxacin acesulfame **2**, the short is *b*-axis [7.13690(10) Å in salt **1** and 7.1089(13) Å in salt **2**]. And also, the norfloxacin ion (in salt **1**) and ciprofloxacin ions (in salt **2**) lie along the *b*-axis. However, the crystal structure of salts **1** and **2**. In the case of salt **1**, two norfloxacin ions and two acesulfamate ions form an eight membered cyclic tetramer synthon. But salt **2** forms an exactly similar cyclic eight membered supramolecular tetramer synthon with N–H...O hydrogen bonds when compared to salt **1**.

### Conclusions

This study reveals that the design and preparation of new solids (salts or cocrystals) based on structural similarities. The molecular geometry of APIs and salt/cocrystal formers may be the driving force to crystallize with similar supramolecular synthons in their crystal structures. It can be understood from the salts **1–2** having similar supramolecular synthons that we can design the new organic solids based on supramolecular synthons with more predictability.

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### References

- [1] Trask, A. V., Motherwell, W. D., & Jones, W. (2006). *Int. J. Pharm.*, 320, 114.
- [2] Childs, S. L., Chyall, L. J., Dunlap, J. T., Smolenskaya, V. N., Stahly, B. C., & Stahly, G. P. (2004). *J. Am. Chem. Soc.*, 126, 13335.
- [3] McNamara, D. P., Childs, S. L., Giordano, J., Iarriccio, A., Cassidy, J., Shet, M. S., Mannion, R., O'Donnell, E., & Park, A. (2006). *Pharm. Res.*, 23, 1888.
- [4] Almarsson, Ö., & Zaworotko, M. J. (2004). *Chem. Commun. (Camb.)*, 1889.
- [5] (a) Byrn, S. R., Pfeiffer, R. P., & Stowell, J. G. (1999). *Solid State Chemistry of Drugs*, SSCI Inc.: West Lafayette, IN; (b) Berge, S. M., Bighley, L. D., & Monkhouse, D. C. (1977). *J. Pharm. Sci.*, 66, 1; (c) Stahl, P. H., & Wermuth, C. G. (2002). *Handbook of pharmaceutical salts*, Verlag Helvetica Chimica Acta; Zurich and Wiley-VCH: Weinheim.
- [6] Etter, M. C. (1990). *J. Phys. Chem.*, 95, 601.
- [7] Aakeröy, C. B. (2004). In *Encyclopedia of Supramolecular Chemistry*, Atwood, J. L., & Steed, J. W. (Eds.). Marcel Dekker, New York, 1379.
- [8] Desiraju, G. R. (1995). *Angew. Chem., Int. Ed. Engl.*, 34, 2311.
- [9] Bis, J. A., & Zaworotko, M. J. (2005). *Cryst. Growth Des.*, 5(3), 1169.
- [10] King, A., & Ian, P. (1986). *J. Antimicrob. Chemother.*, 18(Suppl. D), 1.
- [11] Rose, D. L., & Riley, C. M. (1990). *Int. J. Pharm.*, 63, 237.
- [12] Tackás, N. K., Noszál, B., Hermecz, I., Kersztúri, G., Podanyi, B., & Szasz, G. (1990). *J. Pharm. Sci.*, 79, 1023.
- [13] Basavoju, S., Boström, D., & Velaga, S. P. (2006). *Cryst. Growth Des.*, 6(12), 2699.
- [14] Bhatt, P. M., Ravindra, N. V., Banerjee, R., & Desiraju, G. R. (2005). *Chem. Commun.*, 1073.
- [15] Mathlouthi, M., & Portmann, M. O. (1990). *J. Mol. Struct.*, 237, 327.
- [16] (a) Velaga, S. P., Basavoju, S., & Boström, D. (2008). *J. Mol. Struct.*, 889, 150; (b) Chen, A. M., Ellison, M. E., Peresypkin, A., Wenslow, R. M., Variankaval, N., Savarin, C. G., Natishan, T. K., Mathre, D. J., Dormer, P. G., Euler, D. H., Ball, R. G., Ye, Z., Wang, Y., & Santos, I. (2007). *Chem. Commun.*, 4, 419.

- [17] Sheldrick, G. M. (1997). *SHELX-97: Program for the Solution and refinement of Crystal Structures*, University of Göttingen: Germany.
- [18] Katdate, A. V., Ryan, J. A., Bavitz, J. F., Erb, D. M., & Guillory, J. K. (1986). *Microchemical Acta.*, 90, 1.
- [19] Melting point of acesulfame-K was obtained from MSDS. URL link for MSDS: [http://www.sciencelab.com/xMSDS-Acesulfame\\_Potassium-9922767](http://www.sciencelab.com/xMSDS-Acesulfame_Potassium-9922767)
- [20] Dorofeev, V. L., Aszamastev, A. P., & Veselova, O. M. (2004). *Pharm. Chem. J.*, 38(6), 333.
- [21] Desiraju, G. R., & Steiner, T. (1999). *The weak hydrogen bond in structural chemistry and biology*, Oxford University Press: Oxford.