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Taking advantage of solvate formation to modulate drug-drug ratio in clofaziminium diclofenac salts†

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Non-steroidal anti-inflammatory drugs, such as diclofenac, are gaining attention as repurposed compounds for the treatment of multi-drug resistant tuberculosis. In this study, salts combining diclofenac with clofazimine, are prepared by solvent crystallization and by liquid-assisted grinding. Diclofenac anion possesses an H-bond acceptor which can strongly interact with protic solvent molecules. In this context, selected solvents (protic, aprotic and solvents with increasing molecular volume) are screened in order to investigate solvent impact on crystallization of solvated or unsolvated salt of clofazimine with diclofenac in 1:1 ratio. Five solvated salts and one unsolvated salt were successfully crystallized. The ability of the diclofenac anion to interact with a protic molecule is also exploited in order to crystallize a cocrystal of salt with drug:drug ratio different from 1:1. Structures of two solvated cocrystal of salts (with acetonitrile and ethylacetate) and two polymorphs of an unsolvated cocrystal of salt combining clofazimine with diclofenac in 1:2 ratios are determined.

1 Introduction

Pharmaceutical compounds are often exposed to solvents (or their vapors) during manufacturing (i.e. at the steps of crystallization, wet granulation, spray drying or lyophilization)^{1,2}. Organic compounds including pharmaceuticals are often found in the form of solvates^{3,4}. However, crystalline changes induced by solvate formation or solvent evaporation from the structure can considerably affect the physico-chemical properties of the compounds. Although, in the pharmaceutical industry, solvate formation can sometimes be beneficial to the properties of drugs (e.g., indinavir shows better bioavailability when in the form of a sulfate ethanol solvated form^{1,5,6}), in many other cases it is a nuisance: for instance, if the solvent is toxic or the solvated form exhibits undesired physicochemical and/or

mechanical properties. Thus, selecting a proper solvent which would present a reduced probability of solvate formation is of crucial importance for drug manufacturing⁷.

Several factors have been investigated for their impact on solvate formation. The two most important ones have been identified as solvent-solute affinity and molecular size and shape of the solvent^{8,9}. The first parameter, among other factors, depends on hydrogen bonding and aromatic interaction abilities of the molecule. The second parameter is in correlation with the concept of packing efficiency, since solvent presenting low affinity for a compound can still be incorporated into its structure if it allows a better packing^{8,10}. While various solvents, depending on their molecular volume, size and shape, may lead to different crystal packings, it is also possible that bulky molecules of the compound itself fail to form efficient packing and thus may incorporate solvent molecules in order to improve it. The presence of hydrogen bonding groups tends to promote inclusion of polar solvents by strong and specific interactions¹¹. Despite identification of certain factors contributing to solvate formation, theoretical solvate prediction is challenging and research in this area is still ongoing^{9,10}.

In this study, we focus on the solvated salts of a drug-drug system comprising clofazimine and diclofenac. Clofazimine (CFZ), exhibits antimycobacterial and anti-inflammatory properties and has been recently reevaluated as a potential treatment for

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† Electronic Supplementary Information (ESI) available: Extended table of experimental details for the described structures, table of H-bond parameters, ellipsoids plots of the described structures, powder diffraction patterns of the salts prepared by liquid-assisted grinding, TG/DSC data and variable-temperature powder X-ray diffraction data. Crystallographic information files were deposited on the Cambridge Crystallographic Data Centre (Deposition Number 2032488-2032499). See DOI: 00.0000/00000000.

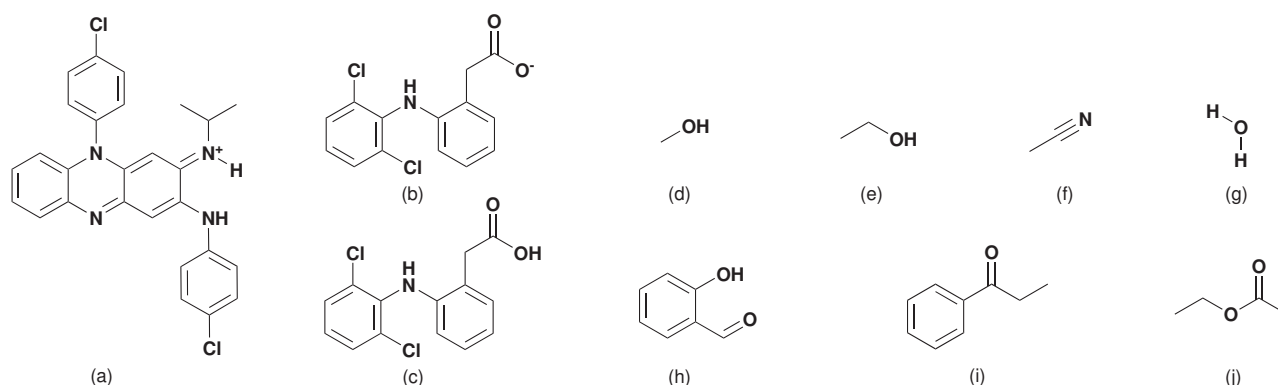


Fig. 1 Scheme of the chemical species observed in the crystal structures of solvated and unsolvated salts/cocrystal of salts: (a) clofaziminium cation, (b) diclofenac anion, (c) diclofenac, (d) methanol, (e) ethanol, (f) acetonitrile, (g) water, (h) salicylaldehyde, (i) propiophenone and (j) ethylacetate.

multidrug-resistant tuberculosis^{12–17}. Diclofenac (DCF) belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs) that has been recently proposed as a host-directed therapy in the treatment of tuberculosis owing to its antitubercular properties^{18–22}. Several studies showing the ability of clofazimine (pKa: 9.29²³) to form salts with organic and inorganic acids^{24–28} point that combining CFZ with DCF in a drug-drug salt should be achievable. Several solvates were previously reported for clofaziminium as well as diclofenac salts^{26,28} and strong H-bond interaction between DCF and solvent molecules have been reported²⁹. Solvate formation is thus also expected with protic solvents during the preparation the drug-drug CFZ-DCF salts.

In our experiments, as expected, diclofenac tended to bind protic solvents and incorporate them into structure, thereby resulting in the solvated form of the CFZ-DCF 1:1 salt. Our further hypothesis was that diclofenac molecule, being also protic, should be able to compete with the solvent molecule for that binding site and thus instead of a solvated 1:1 form lead to a 1:2 CFZ-DCF cocrystal of salt, with diclofenac molecule being connected to diclofenac anion. To verify this and also to see whether an unsolvated 1:1 salt can also be obtained, we have selected a number of aprotic solvents with increasing molecular volume, which due to their chemical nature should have a lower probability of binding to diclofenac. Experimenting with various solvents, we obtained in total five solvated 1:1 forms, two solvated 1:2 forms, one unsolvated 1:1 CFZ-DCF salt and two unsolvated 1:2 cocrystal of salt, thus proving that selecting a proper solvent is essential in crystallization processes and might be key to obtaining desired structures.

2 Materials and methods

2.1 Materials

Clofazimine and diclofenac were respectively purchased from TCI Europe N.V. (Zwinderrecht, Belgium) and Sigma Aldrich (Schnelldorf, Germany). Propiophenone, salicylaldehyde and ethylacetate (Sigma Aldrich, Schnelldorf, Germany), acetonitrile (Thermo Fisher Scientific, Geel, Belgium), methanol (ChemLab, Zedelgem, Belgium), ethanol (Merck, Overijse, Belgium), *N, N*-

dimethylformamide and poly(ethyleneglycol) of average MW 200 (Acros Organics, Geel, Belgium) were used without further purification as crystallization solvents.

2.2 (Solvated/hydrated) clofaziminium diclofenac salts preparation

2.2.1 Liquid-assisted grinding.

CFZNH⁺-DCF⁻-MeOH (1:1:0.74), **CFZNH⁺-DCF⁻-EtOH (1:1:1)** and **CFZNH⁺-DCF⁻ (1:1:1)** can be obtained by grinding 75.0 mg, 0.158 mmol of CFZ with 46.9 mg, 0.158 mmol of DCF in presence of 30 μ L of MeOH, EtOH and EtOAc respectively (liquid-assisted grinding). **CFZNH⁺-DCF⁻-DCF (1:1:1)** (polymorph I), **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)** and **CFZNH⁺-DCF⁻-DCF-EtOAc (1:1:1:1)** are prepared by grinding 75.0 mg (0.158 mmol) of CFZ with 93.8 mg (0.316 mmol) of DCF in presence of 30 μ L of EtOH, MeCN and EtOAc respectively. Crystals of **CFZNH⁺-DCF⁻-DCF (1:1:1)** (polymorph I), **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)** and **CFZNH⁺-DCF⁻-DCF-EtOAc (1:1:1:1)** were obtained by recrystallization of the corresponding powder (CFZ-DCF 1:2 LAG EtOH, LAG MeCN and LAG EtOAc) in ethanol, acetonitrile and ethylacetate respectively (Figure 2). All ball milling experiments were performed at 30 Hz, during 90 minutes (samples were homogenized each 30 minutes) with a Retsch MM 400 Mixer Mill apparatus. Powders were inserted in 2 mL Eppendorf tubes with eight stainless steel balls (7 balls of 2 mm diameter and 1 ball of 3 mm diameter) and were then placed in two grinding jars in which up to 5 Eppendorf tubes can be installed. Powder of **CFZNH⁺-DCF⁻-DCF (1:1:1)** (polymorph II) cocrystal of salt is obtained by desolvation (heating at 130 - 140 °C) of **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)** or of **CFZNH⁺-DCF⁻-DCF-EtOAc (1:1:1:1)** (obtained by liquid-assisted grinding, Figure 2).

2.2.2 Solvent evaporation method.

Powders consisting of an equimolar ratio of clofazimine (37.4 mg, 0.0790 mmol) and diclofenac acid (23.4 mg, 0.0790 mmol) were stirred in the selected solvent (MeCN, MeOH, EtOH, DMF) until complete dissolution and left for slow evaporation at room temperature (20-25 °C). Crystals of **CFZNH⁺-DCF⁻-MeOH**

(1:1:0.74), CFZNH⁺-DCF⁻-EtOH (1:1:1) and CFZNH⁺-DCF⁻-MeCN-H₂O (1:1:1:2) were obtained in MeOH, EtOH and MeCN respectively. Crystals of CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2) and of CFZNH⁺-DCF⁻-DCF (1:1:1) (polymorph II) were obtained in MeCN and PEG 200 respectively, by the same method but from a powder consisting of clofazimine (37.4 mg, 0.0790 mmol) and diclofenac acid (46.8 mg, 0.158 mmol) in 1:2 molar ratio.

Given the low vapor pressure at room temperature (20-25 °C) of propiophenone and salicylaldehyde and the quite good solubility of CFZ and DCF in these solvents, crystallization by solvent evaporation is quite difficult. For this reason, the 1:1 powder mixture of CFZ and DCF was not fully dissolved in these solvent (i.e. an excess powder was placed in the solvent and left at room temperature for crystallization) to give CFZNH⁺-DCF⁻-PPP (2:2:5) and CFZNH⁺-DCF⁻-SAL-H₂O (4:4:9:1).

2.3 Single-crystal X-ray diffraction (SCXRD)

Data collection was performed with an Oxford Diffraction Gemini Ultra R system equipped with a four-circle kappa platform and a Ruby CCD detector, using Cu K α ($\lambda = 1.54184 \text{ \AA}$) radiation. Full data sets were collected either at 295 K (CFZNH⁺-DCF⁻-MeOH (1:1:0.74), CFZNH⁺-DCF⁻ (1:1), CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2), CFZNH⁺-DCF⁻-DCF-EtOAc (1:1:1:1) and CFZNH⁺-DCF⁻-DCF (1:1:1) (polymorphs I and II)), at 100 K (CFZNH⁺-DCF⁻-MeCN-H₂O (1:1:1:2) and CFZNH⁺-DCF⁻-SAL-H₂O (4:4:9:1)) or at both temperatures (CFZNH⁺-DCF⁻-EtOH (1:1:1) and CFZNH⁺-DCF⁻-PPP (2:2:5)). Low-temperature data collection was necessary for CFZNH⁺-DCF⁻-MeCN-H₂O (1:1:1:2) because crystals are unstable at room temperature. Crystals of CFZNH⁺-DCF⁻-SAL-H₂O (4:4:9:1) were stable at room temperature but disorder in the structure could not be resolved without low-temperature data collection. First, analytical numerical absorption correction implemented using a multifaceted crystal model based on expressions derived by Clark & Reid³⁰ was performed using *CrysAlis PRO*³¹. Then, empirical absorption correction was applied, within *CrysAlis PRO*, using spherical harmonics³² as implemented in the SCALE3 ABSPACK scaling algorithm. Dual-space method implemented within *SHELXT*³³ was used for structure solution. Refinement was performed within *Olex*²³⁴ and *ShelXle*³⁵ using the least-square method (*SHELXL-2016/6*³⁶). Anisotropic refinement was performed for non hydrogen atoms. If not involved in strong H-bonds, hydrogen atoms were refined as riding atoms with displacement spheres fixed to 1.2 times that of the parent atom (1.5 for methyl groups). Positions of H atoms involved in strong H-bond were located in Fourier map and refined (except for disordered MeOH molecule in the structure of CFZNH⁺-DCF⁻-MeOH (1:1:0.74), disordered EtOH molecule in the structure of CFZNH⁺-DCF⁻-EtOH (1:1:1) (data collected at 295 K) and for disordered salicylaldehyde molecules and the water molecule in CFZNH⁺-DCF⁻-SAL-H₂O (4:4:9:1)). The solvent molecules are disordered in several structures. More particularly, the methanol molecule in CFZNH⁺-DCF⁻-MeOH (1:1:0.74); all solvent molecules in CFZNH⁺-DCF⁻-PPP (2:2:5) (data collected at

295 K); one molecule of propiophenone (which is located close to an inversion center) in CFZNH⁺-DCF⁻-PPP (2:2:5) (data collection at 100 K); five salicylaldehyde molecules (which are not involved in intermolecular H-bonds) in the structure of CFZNH⁺-DCF⁻-SAL-H₂O (4:4:9:1); the ethanol molecule in the structure of CFZNH⁺-DCF⁻-EtOH (1:1:1) for which data were collected at 295 K and one MeCN molecule in CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2) are disordered.

2.4 Powder X-ray diffraction (PXRD)

Powder diffraction data were collected with Cu K α radiation ($\lambda = 1.54184 \text{ \AA}$) from 4 to 40° 2 θ angle (step size of 0.0167°) on a PANalytical X'PERT PRO Bragg-Brentano diffractometer with an X'Celerator linear detector. Tension and current of the generator were set to 45 kV and 30 mA for data collection.

Variable-temperature PXRD (VT-PXRD) experiments were conducted on the same diffractometer equipped with an Anton-Paar TTK 450 system. Data were collected at 25 °C and then from 30 °C to 140 °C with data collection every 10 °C.

2.5 Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC)

Thermal properties of powders obtained by liquid-assisted grinding and corresponding to determined structures were analysed using a Mettler Toledo TGA/DSC 3+ apparatus. Around 5-10 mg of solid samples were placed in 100 μ L aluminium pans. The analysis was performed from 25 °C to 250 °C with a heating rate of 10 °C/min and using nitrogen (60 mL/min) as purge gas. TGA/DSC results were analysed using the STARE software (version 16.20)

2.6 Structure visualization, crystal packing comparison and solvent molecular volume calculations

Structures and crystal packings were visualized and compared using *Mercury*³⁷. Voids were calculated with the 'Voids' option within *Mercury*³⁷ with a probe radius of 1.2 \AA and an approximated grid spacing of 0.1 \AA . Images were generated with the same program. Crystal packings were more specifically compared using the 'Crystal packing similarity' tool in *Mercury*³⁷. Packing shell size, distance and angle tolerance parameters were set to 15 molecules, 30% and 30° respectively. Moreover, molecular differences and structure inversion were allowed while bond types, H-atom position, atoms' hydrogen counts and atoms bond counts were ignored. As structures contain different solvents, smallest molecular component was ignored for crystal packing comparison. Solvent molecular volumes were determined with the free Molinspiration molecular property calculation service³⁸.

3 Results and discussion

The current work includes two parts. In the first part, we have investigated solvated and unsolvated forms of CFZ-DCF 1:1 salt. The second part is focused on the ability of diclofenac anion to bind diclofenac molecule instead of a solvent molecule (a phenomenon often observed in 1:1 salts) to obtain a 1:2 CFZ-DCF cocrystal of salt. To obtain drug-drug salts, clofazimine and di-

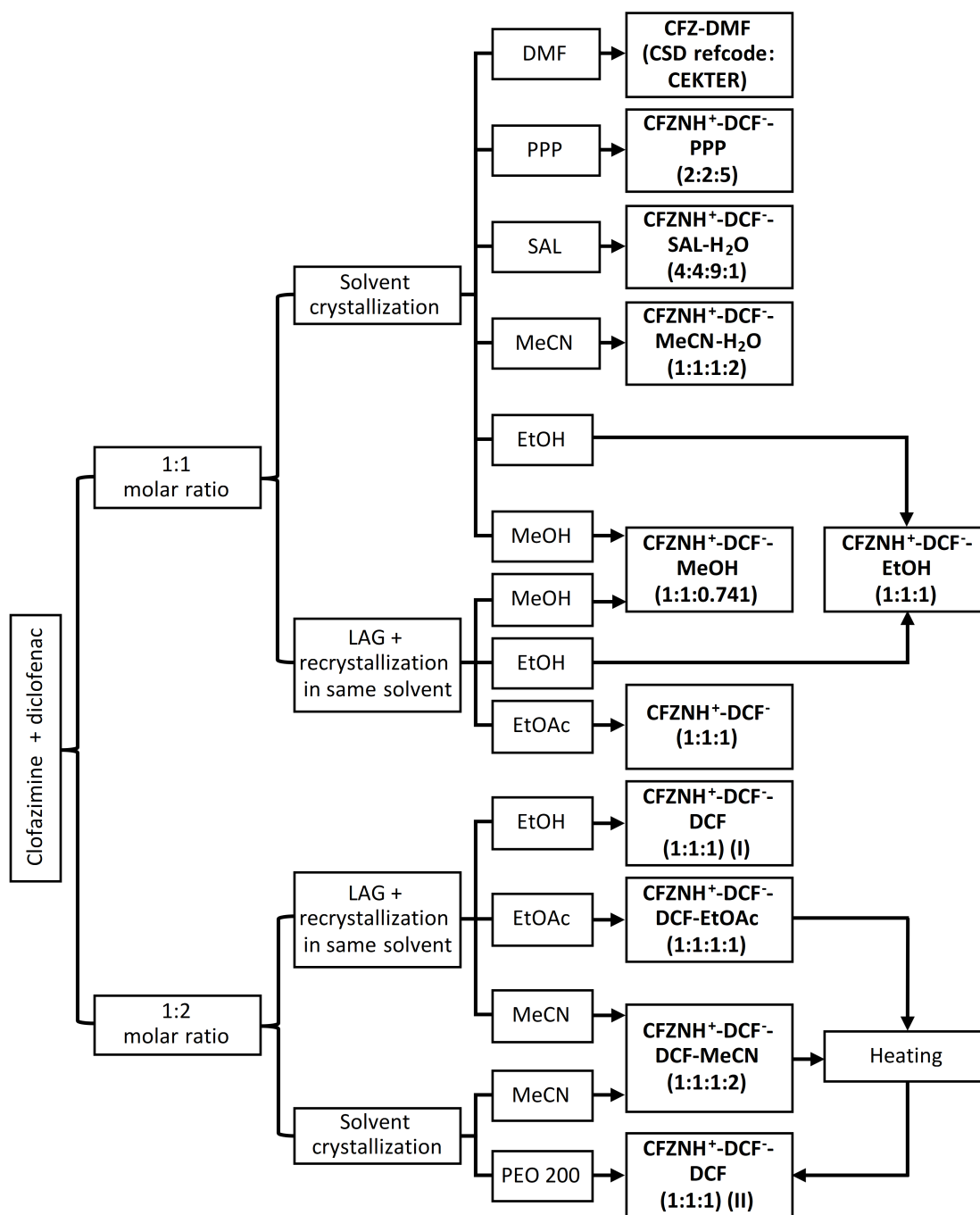


Fig. 2 Summary of performed experiments and associated results. LAG: liquid-assisted grinding, DMF: *N, N'*-dimethylformamide PPP: propiophenone, SAL: salicylaldehyde, MeCN: acetonitrile, EtOH: ethanol, MeOH: methanol, EtOAc: ethyl acetate, PEO: polyethylene glycol.

clofenac were subjected to solvent evaporation crystallization and liquid-assisted grinding (Figure 2). Below and for each part of the work, we will first present structural analysis of the new crystal structures combining clofazimine with diclofenac (Figure 1 and Figures S1 and S2 (labelling)[†]) and discuss the impact of solvent selection on the crystallization outcome.

3.1 Investigation of CFZ-DCF 1:1 salts

The solvents used in the first part of this work were selected based on their ability to interact with the solute (CFZ cations and DCF

anions) *via* hydrogen bonding or other weak interactions and on their molecular size and shape - two main parameters influencing the formation of solvates. First, we selected a series of protic solvents of increasing molecular volume (MeOH, EtOH, salicylaldehyde) in order to investigate the impact on solvate formation of those solvents that are capable of forming H-bond with diclofenac anion. In addition to H-bonds, the aromatic system of salicylaldehyde could also be involved in stacking interactions with clofaziminium cation and/or diclofenac anion. Second, we took aprotic solvents of variable molecular volume (MeCN, DMF, EtOAc, pro-

piophenone) in order to study the effect of solvents that do not have the ability to interact with diclofenac anion through H-bond. Propiophenone, that could potentially interact with CFZNH⁺ and DCF⁻ through stacking has also been included among the selected aprotic solvents. Below we present structural analysis of the 1:1 solvated and unsolvated CFZ-DCF salts that were obtained using aforementioned solvents followed by the discussion of the solvent impact on crystallization outcome.

3.1.1 Structural analysis

3.1.1.1 CFZNH⁺-DCF⁻-MeOH (1:1:0.74) solvated salt crystallizes in *C2/c* space group (Table 1). The asymmetric unit contains one clofaziminium cation, one diclofenac anion and methanol molecule, which is disordered over two positions (one position is located around *C2* axis). A *R*₂¹(7) motif is observed between clofazimine and diclofenac (N4–H4···O1 and N3–H3···O1 charge-assisted H-bonds, Figure 3 (a) and Table S2†). A weaker H-bond is also observed between CFZNH⁺ and DCF⁻ (N4–H4···O2, Figure 3 (a) and Table S2†). Methanol (position with an occupancy of 0.5) interacts with diclofenac through H-bond (O3A–H3OA···O2, Figure 3 (a) and Table S2†). An intramolecular N5–H5···O1 H-bond is also present within the diclofenac anion. A weak C24–H24···O2 H-bond stabilizes dimers of CFZNH⁺-DCF⁻-MeOH trimolecular assemblies (Figure 3 (b)).

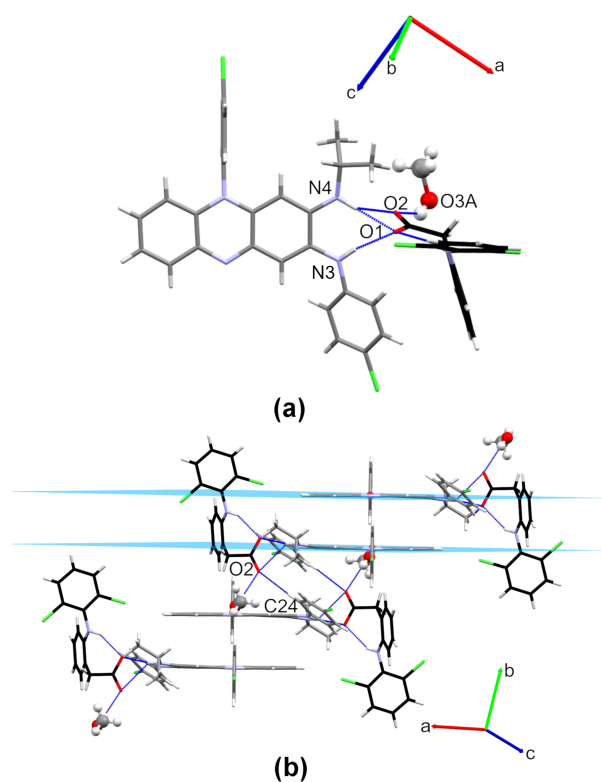


Fig. 3 (a) H-bonds between clofaziminium, diclofenac and methanol in CFZNH⁺-DCF⁻-MeOH (1:1:0.74) (MeOH disorder not shown) and (b) weak C24–H24···O2 H-bond stabilizing dimers of CFZNH⁺-DCF⁻-MeOH trimolecular assemblies and head-to-tail stacking of these assemblies (planes (light blue) and centroids (red) are calculated with C5 C6 C11 and C12 atoms). H-bonds are represented by blue dashed lines.

These dimers are further stacked in a head-to-tail fashion (Fig-

ure 3 (b), centroid-centroid distance of 3.623(2) Å, orthogonal projection distance of 3.378(1) Å and horizontal displacement of 1.311 Å). This salt can also be prepared by liquid-assisted grinding of CFZ with DCF (in 1:1 molar ratio) and with MeOH as solvent (Figure S3 (a)†). TG/DSC analysis of the powder indicates a weight loss of 2.6% between 30 and 150 °C (calculated MeOH content: 2.99%) (Figure S4 †). The powder of CFZNH⁺-DCF⁻-MeOH (1:1:0.74) melts at 118 °C (as confirmed by an analysis performed on a Koffler apparatus). Complete desolvation is difficult to achieve before melting of the powder (at 100 °C, the solvate is still present) and the crystalline phase obtained upon heating of CFZNH⁺-DCF⁻-MeOH (1:1:0.74) at 110 °C could not be identified (Figure S5†).

3.1.1.2 CFZNH⁺-DCF⁻-EtOH (1:1:1) solvated salt crystallizes in *P1* triclinic space group (Table 1). The asymmetric unit consists of the clofaziminium cation, diclofenac anion and one solvent molecule (EtOH). This structure was determined at 295 and 100 K. At 295 K, EtOH molecule is disordered over two

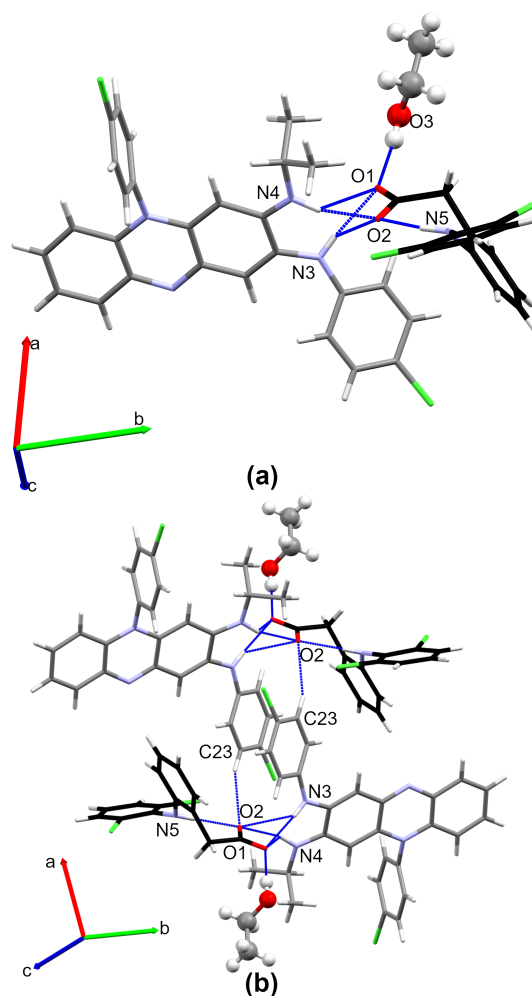


Fig. 4 (a) H-bonds between clofaziminium, diclofenac anion and ethanol in the structure of CFZNH⁺-DCF⁻-EtOH (1:1:1) solvated salt. (b) Weak C23–H23···O2 H-bonds stabilizing dimers of CFZNH⁺-DCF⁻-EtOH three-component assemblies. Ethanol molecules are in ball and stick model, carbon atoms of diclofenac anion are in black and H-bonds are represented by blue dashed lines.

Table 1 Experimental details.

	CFZNH ⁺ -DCF ⁻ - MeOH (1:1:0.74)	CFZNH ⁺ -DCF ⁻ - EtOH (1:1:1)	CFZNH ⁺ -DCF ⁻ - EtOH (1:1:1)	CFZNH ⁺ -DCF ⁻ - MeCN-H ₂ O (1:1:1:2)
Chemical formula	C ₂₇ H ₂₃ Cl ₂ N ₄ · 0.741(CH ₄ O) C ₁₄ H ₁₀ Cl ₂ NO ₂	C ₂₇ H ₂₃ Cl ₂ N ₄ · C ₂ H ₆ O C ₁₄ H ₁₀ Cl ₂ NO ₂	C ₂₇ H ₂₃ Cl ₂ N ₄ · C ₂ H ₆ O C ₁₄ H ₁₀ Cl ₂ NO ₂	C ₂₇ H ₂₃ Cl ₂ N ₄ · C ₂ H ₃ N·2(H ₂ O) MeCN-H ₂ O (1:1:1:2)
<i>Mr</i>	793.42	815.59	815.59	846.61
Crystal system, space group	Monoclinic, C2/c	Triclinic, P $\bar{1}$	Triclinic, P $\bar{1}$	Triclinic, P $\bar{1}$
Temperature (K)	295(2)	295(2)	100(2)	100(2)
<i>a</i> , <i>b</i> , <i>c</i> (Å)	16.7209(3), 27.8319(7)	17.2504(5), 12.5818(4), 13.5318(3)	13.4486(3), 12.5325(5), 13.1773(4)	13.1139(3), 11.6515(3), 16.0793(4)
α , β , γ (°)	90, 93.438(2), 90	80.291(2), 71.638(2), 71.710(2)	82.032(2), 71.833(3), 74.538(3)	103.558(2), 90.461(2), 105.250(2)
<i>V</i> (Å ³)	8013.4(3)	2057.12(10)	1979.61(12)	2052.78(9)
<i>Z</i>	8	2	2	2
No. of measured, independent and observed [<i>I</i> > 2σ(<i>I</i>)] reflections	23679, 7080, 4722	27818, 7236, 6397	21176, 6977, 6386	18621, 7196, 6969
<i>R</i> _{int}	0.040	0.024	0.046	0.019
<i>R</i> [<i>F</i> ² > 2σ(<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.059, 0.193, 1.02	0.050, 0.146, 1.06	0.057, 0.166, 1.07	0.031, 0.080, 1.03
CCDC number	2032488	2032489	2032490	2032491
	CFZNH ⁺ -DCF ⁻ - SAL-H ₂ O (4:4:9:1)	CFZNH ⁺ -DCF ⁻ - PPP (2:2:5)	CFZNH ⁺ -DCF ⁻ - PPP (2:2:5)	CFZNH ⁺ -DCF ⁻ - (1:1)
Chemical formula	4(C ₂₇ H ₂₃ Cl ₂ N ₄)·4(C ₁₄ H ₁₀ Cl ₂ NO ₂)· 9(C ₇ H ₆ O ₂)·H ₂ O	2(C ₂₇ H ₂₃ Cl ₂ N ₄)·2(C ₁₄ H ₁₀ Cl ₂ NO ₂)· 5(C ₉ H ₁₀ O)	2(C ₂₇ H ₂₃ Cl ₂ N ₄)·2(C ₁₄ H ₁₀ Cl ₂ NO ₂)· 5(C ₉ H ₁₀ O)	(C ₂₇ H ₂₃ Cl ₂ N ₄)·(C ₁₄ H ₁₀ Cl ₂ NO ₂)
<i>Mr</i>	4195.16	2209.89	2209.89	769.52
Crystal system, space group	Triclinic, P $\bar{1}$	Triclinic, P $\bar{1}$	Triclinic, P $\bar{1}$	Triclinic, P $\bar{1}$
Temperature (K)	100(2)	295(2)	100(2)	295(2)
<i>a</i> , <i>b</i> , <i>c</i> (Å)	10.4132(5), 25.0657(7)	21.2266(7), 10.7319(4), 21.5496(9)	13.6005(6), 10.5086(4), 21.4224(8)	13.4783(5), 12.4461(6), 13.3667(6)
α , β , γ (°)	66.238(3), 89.969(3), 86.658(3)	73.502(4), 77.404(4), 73.540(4)	73.629(3), 76.913(3), 73.271(3)	84.423(3), 67.963(4), 66.662(4)
<i>V</i> (Å ³)	5060.5(3)	2859.7(2)	2752.92(19)	1876.21(16)
<i>Z</i>	1	1	1	2
No. of measured, independent and observed [<i>I</i> > 2σ(<i>I</i>)] reflections	53166, 17765, 13730	28672, 10049, 6767	28107, 9723, 7857	17078, 6630, 5192
<i>R</i> _{int}	0.069	0.051	0.038	0.037
<i>R</i> [<i>F</i> ² > 2σ(<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.060, 0.171, 1.03	0.052, 0.160, 1.02	0.035, 0.090, 1.03	0.048, 0.141, 1.03
CCDC number	2032492	2032493	2032494	2032495
	CFZNH ⁺ -DCF ⁻ - DCF (1:1:1) (I)	CFZNH ⁺ -DCF ⁻ - DCF-MeCN (1:1:1:2)	CFZNH ⁺ -DCF ⁻ - DCF-EtOAc (1:1:1:1)	CFZNH ⁺ -DCF ⁻ - DCF (1:1:1) (II)
Chemical formula	C ₂₇ H ₂₃ Cl ₂ N ₄ · C ₁₄ H ₁₀ Cl ₂ NO ₂	C ₂₇ H ₂₃ Cl ₂ N ₄ · C ₁₄ H ₁₀ Cl ₂ NO ₂ · C ₁₄ H ₁₁ Cl ₂ NO ₂ ·2(C ₂ H ₃ N)	C ₂₇ H ₂₃ Cl ₂ N ₄ · C ₁₄ H ₁₀ Cl ₂ NO ₂ · C ₁₄ H ₁₁ Cl ₂ NO ₂ ·C ₄ H ₈ O ₂	C ₂₇ H ₂₃ Cl ₂ N ₄ · C ₁₄ H ₁₀ Cl ₂ NO ₂ · C ₁₄ H ₁₁ Cl ₂ NO ₂
<i>Mr</i>	1065.66	1147.77	1153.76	1065.66
Crystal system, space group	Triclinic, P $\bar{1}$	Triclinic, P $\bar{1}$	Triclinic, P $\bar{1}$	Triclinic, P $\bar{1}$
Temperature (K)	295(2)	295(2)	295(2)	295(2)
<i>a</i> , <i>b</i> , <i>c</i> (Å)	10.8837(2), 17.7519(4)	14.4737(3), 15.0694(11), 15.5991(13)	15.2735(10), 15.0569(4), 15.4247(4)	15.3773(4), 11.9326(3), 16.0042(4)
α , β , γ (°)	101.568(2), 105.173(2), 94.286(2)	74.882(7), 61.685(8), 64.227(7)	76.043(2), 61.975(3), 63.541(3)	89.161(2), 70.570(2), 69.693(2)
<i>V</i> (Å ³)	2620.06(10)	2839.6(4)	2820.07(16)	2559.79(12)
<i>Z</i>	2	2	2	2
No. of measured, independent and observed [<i>I</i> > 2σ(<i>I</i>)] reflections	26706, 9218, 8043	27894, 10010, 7543	27162, 9942, 8898	25042, 9036, 7679
<i>R</i> _{int}	0.022	0.032	0.022	0.025
<i>R</i> [<i>F</i> ² > 2σ(<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.050, 0.141, 1.05	0.050, 0.159, 1.08	0.042, 0.122, 1.05	0.045, 0.129, 1.04
CCDC number	2032496	2032497	2032498	2032499

positions, both of which allow O3–H···O1 interaction between EtOH and diclofenac anion while at 100 K the same interaction is observed but EtOH is not disordered. At both temperatures, diclofenac anion and clofaziminium interact through bifurcated charge-assisted H-bonds (N4–H4···O2, N3–H3···O2, N4–H4···O1 and N3–H3···O1, Table S2† and Figure 4 (a)). A *D*₁¹(2) motif between ethanol and diclofenac anion as well as an intramolecular H-bond (*S*₁¹(7) motif) in diclofenac anion are also observed (O3–H3OB···O1 and N5–H5···O2 respectively, Table S2† and Figure 4 (a)). Dimers of CFZNH⁺-DCF⁻-EtOH three-component assemblies are stabilized through weak H-bonds (C23–H23···O2, Table S2† and Figure 4 (b)). PXRD pattern of the powder obtained by liquid-assisted grinding of CFZ with DCF (in 1:1 molar ratio) and with EtOH as solvent corresponds to the calculated pattern of CFZNH⁺-DCF⁻-EtOH (1:1:1) (Figure S3 (b)†). This powder was analyzed by TG/DSC (Figure S4†) that revealed a weight loss of 5.6% which is consistent with calculated EtOH content (5.6%). Only one endothermic event, associated with salt melting and solvent evaporation was observed at 113 °C. Such a high temperature of desolvation suggests that EtOH is strongly bound to diclofenac anion (Figure S4† and Ta-

ble 2). This is in accordance with the O3···O1 distance (between 2.672(3) and 2.82(1) Å) observed in the structure, which is characteristic of strong H-bond, as defined by Desiraju and Steiner³⁹.

Table 2 Melting point temperatures of reported crystalline phases. Powders were obtained by LAG. *Value obtained from desolvated powder of CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2).

Compound	Transition onset (°C)	Melting onset (°C)
CFZ	/	218
DCF	/	177
CFZNH ⁺ -DCF ⁻ - EtOH (1:1:1)	Desolvation at melting	113
CFZNH ⁺ -DCF ⁻ (1:1)	/	186
CFZNH ⁺ -DCF ⁻ -DCF (1:1:1) (polymorph I)	/	171
CFZNH ⁺ -DCF ⁻ -DCF- MeCN (1:1:1:2)	93	157
CFZNH ⁺ -DCF ⁻ -DCF- EtOAc (1:1:1:1)	93	157
CFZNH ⁺ -DCF ⁻ -DCF (1:1:1) (polymorph II)	/	157*

3.1.1.3 CFZNH⁺-DCF⁻-MeCN-H₂O (1:1:1:2) solvated dihydrated salt crystallizes in space group $P\bar{1}$ (Tables 1 and S1†). One clofaziminium cation, one diclofenac anion, two water and one acetonitrile molecules constitute the asymmetric unit. A $R_2^1(7)$ motif is observed between clofaziminium and diclofenac (N4–H4...O1 and N3–H3...O1 charge-assisted H-bonds, Table S2†, Figure 5 (a)). An intramolecular N5–H5...O1 H-bond is also present within the diclofenac anion. Water molecules bridge diclofenac anion and clofaziminium through O3–H3OA...O2, O4–H4OB...O3 and O4–H4OA...N2 H-bonds (Table S2†), forming 8-component clusters (2 clofaziminium cations, 2 diclofenac anions and 4 water molecules, Figure 5 (b) and (c)). These 8-component clusters are extended along *a*-axis thanks to water tetramers ($R_4^1(8)$ motif, O3–H3OB...O4 and O4–H4OB...O3, Table S2†, Figure 5 (c)).

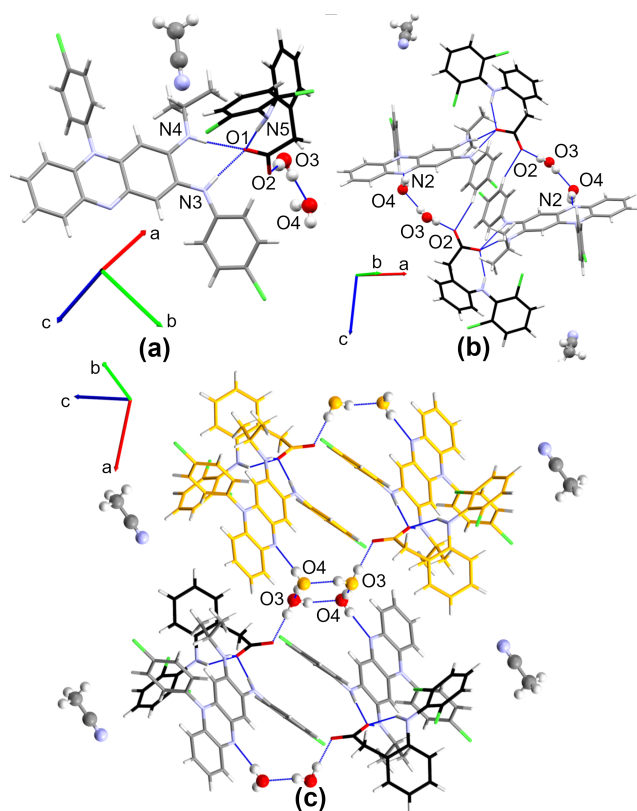


Fig. 5 (a) H-bonds between clofaziminium, diclofenac and water in **CFZNH⁺-DCF⁻-MeCN-H₂O (1:1:1:2)**, (b) 8-component clusters stabilized by O3–H3OA...O2, O4–H4OB...O3 and O4–H4OA...N2 H-bonds and (c) chains of 8-component clusters along *a*-axis (one 8-component cluster is colored in orange). H-bonds are represented by blue dashed lines.

3.1.1.4 CFZNH⁺-DCF⁻-SAL-H₂O (4:4:9:1) solvated hydrated salt crystallizes in $P\bar{1}$ space group (Tables 1 and S1†). The asymmetric unit contains two clofaziminium cations, two diclofenac anions, 4.5 salicylaldehyde and a half water molecules (one salicylaldehyde and the water are located on an inversion center). Clofaziminium cations interact with diclofenac anions through charge-assisted H-bonds ($R_2^1(7)$ motif, N4–H4...O1 and N3–H3...O1, as well as N8–H8...O3 and

N9–H9...O3, Table S2† and Figure 6 (a)). Intramolecular H-bonds are observed within diclofenac anions (N5–H5...O1 and N10–H10...O3, Table S2†). Two salicylaldehyde molecules are H-bonded, through their phenol moiety, to diclofenac anion (O5S–H5OS...O2 as well as O7T–H7OT...O4, Table S2† and Figure 6 (a)). Other solvent molecules are disordered and have their phenol moiety oriented to allow intramolecular H-bonds (O9U–H9OU...O10U, O9V–H9OV...O10V; O11W–H11W...O12W, O11X–H11X...O12X and O13Y–H13Y...O14Y, Table S2† and Figure 6 (b)). The water molecule interacts with the salicylaldehyde molecule located on an inversion center through O15–H15O...O13Y (Table S2†), which is H-bonded to diclofenac anion (C29–H29B...O13Y, Table S2†). Chains along *a*-axis are stabilized by weak

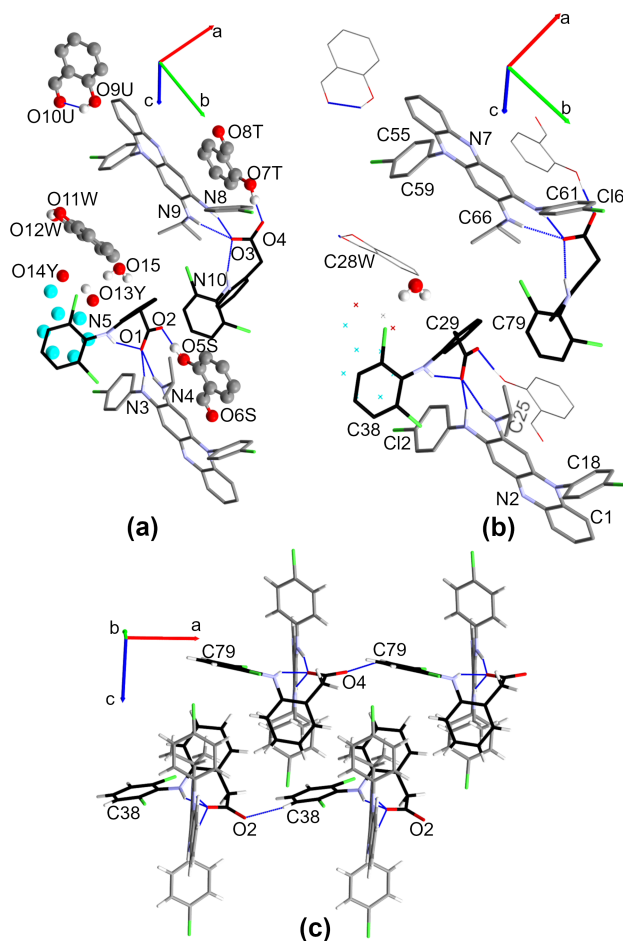


Fig. 6 (a) H-bonds between clofaziminium, diclofenac anion and salicylaldehyde molecules. H atoms not involved in strong H-bonds are omitted for clarity. Salicylaldehyde molecules are in ball and stick model, carbon atoms of the salicylaldehyde molecule located on an inversion center are coloured in cyan (other disordered SAL molecule are omitted). (b) Labelling of atoms involved in weak H-bonds in the structure of **CFZNH⁺-DCF⁻-SAL-H₂O (4:4:9:1)** (salicylaldehyde molecules are represented in wireframe model and H atoms not involved in strong H-bonds are omitted for clarity). (c) Weak H-bonds between diclofenac anions (C38–H38...O2 and C79–H79...O4) stabilize chains along *a*-axis (salicylaldehyde molecules are omitted for clarity). Carbon atoms of diclofenac anion are in black and H-bonds are represented by blue dashed lines.

H-bonds between diclofenac anions (C38–H38...O2 and C79–H79...O4, Table S2† and Figure 6 (c)). Several weak H-bonds are also observed between clofazimine and salicylaldehyde molecules (C1–H1...O12W, C18–H18...O6S, C55–H55...O8T, C61–H61A...O7T and C28W–H28W...O5S, Table S2†). Weak H-bonds are also observed between two CFZNH⁺ cations (C14–H14...N2, C25–H25...Cl6, C59–H59...N7 and C66–H66...Cl2, Table S2†).

3.1.1.5 CFZNH⁺-DCF⁻-PPP (2:2:5) solvated salt crystallizes in *P* $\bar{1}$ space group (Tables 1 and S1†). The asymmetric unit contains one clofaziminium cation, one diclofenac anion, and 2.5 propiophenone molecules (one PPP is located on an inversion center). The structure of this solvated salt was determined at 295 K and at 100 K. Same interactions are observed at both temperatures, but PPP molecules are disordered at 295 K. Clofaziminium cation and diclofenac anion interact through N3–H3...O1 and N4–H4...O1 charge-assisted H-bonds (Table S2† and Figure 7 (a)). Two propiophenone molecules interact with clofaziminium through weak H-bonds (C15–H15...O3 and C18–H18...O4, Table S2† and Figure 7(a)). Clofaziminium

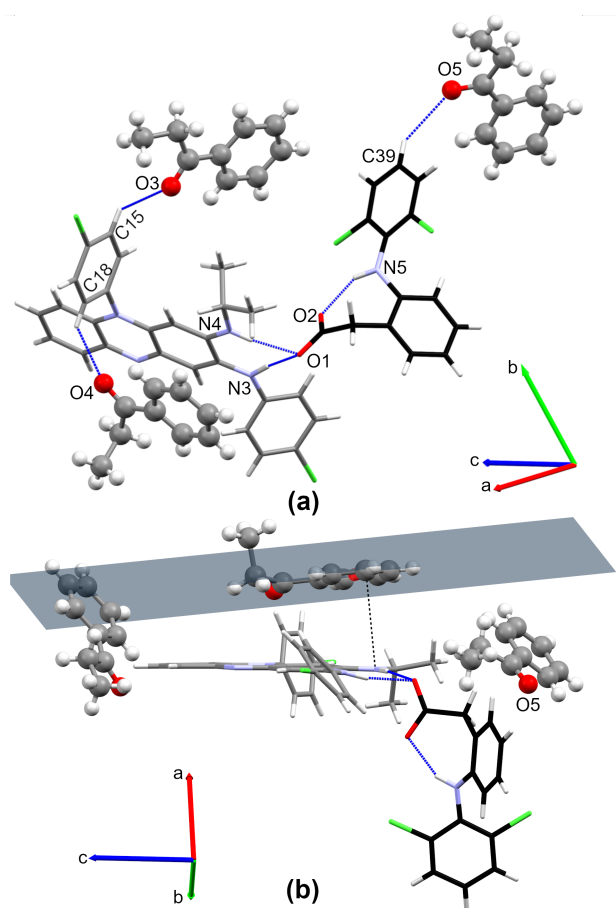


Fig. 7 (a) H-bonds (blue dashed lines) between clofaziminium, diclofenac anion and propiophenone molecules (PPP whose oxygen atom is labelled O5 is located on an inversion center) and (b) π -cation interaction (black dashed line) between clofazimine and PPP (centroid in red and plane in blue). PPP molecules are in ball and stick model, carbon atoms of diclofenac anion are in black.

cations are stacked in a head-to-tail fashion (centroid-centroid distance of 3.519(1) Å, interplanar distance of 3.430(1) Å and horizontal displacement of 0.788 Å (planes and centroids were calculated using atoms C5 C6 C11 C12)). Moreover, a cation- π interaction is observed between iminium moiety of CFZNH⁺ and one propiophenone molecule (vertical distance: 3.719 Å (between N4⁺ and the plane passing through C54 C55 C56 C57 C58 and C59) and horizontal displacement of 0.837 Å, Figure 7(b)).

3.1.1.6 CFZNH⁺-DCF⁻ (1:1) salt crystallizes in space group *P* $\bar{1}$ (Tables 1 and S1†) with one clofaziminium cation and one diclofenac anion in the asymmetric unit. Clofaziminium interacts with diclofenac anion through charge-assisted H-bond (*R*₂¹(7) motif, N4–H4...O1 and N3–H3...O1, Table S2†, Figure 8). An intramolecular H-bond is observed N5–H5...O2, Table S2† within diclofenac anion. Interestingly, in this structure, the carboxylate of diclofenac anion is almost coplanar to the iminophenazine moiety of clofazimine (angle between planes passing through N4–C9–C8–N3 and O1–C28–O2–C29 is only 14.3°, Table 3) which is not the case in solvated structures (angles between the same planes are comprised between 83.2° and 62.5°, Table 3). This orientation results in a supplementary H-bond between clofaziminium and diclofenac (N3–H3...O2 Table S2†, Figure 8). Clofaziminium cations are stacked in a head-to-tail fashion (Figure 8, centroid-centroid distance: 3.592(2) Å, orthogonal projection distance: 3.443(1) Å and horizontal offset of 1.026 Å, with centroids and planes calculated from C5 C6 C11 and C12 atoms). This crystalline phase can also be obtained by liquid-assisted grinding of CFZ with DCF (in 1:1 molar ratio) with EtOAc as solvent (Figure S3 (c)†).

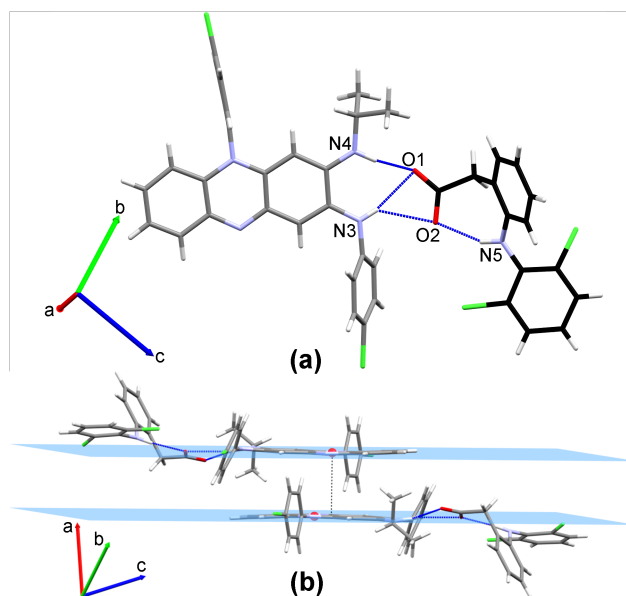


Fig. 8 (a) H-bonds between clofaziminium and diclofenac anion in **CFZNH⁺-DCF⁻ (1:1)** and (b) π - π stacking between clofaziminium (centroids in red and planes in blue). H-bonds are represented by blue dashed lines.

Melting point of this unsolvated salt was determined as 186 °C by DSC analysis (Figure S4† and Table 2). Interestingly, this unsolvated salt has a smaller packing coefficient than the solvated 1:1

Table 3 Packing coefficient of the determined structures (at 295 K unless stated otherwise in the table) and angles between planes passing through N4-C9-C8-N3 atoms of clofaziminium cations and O1-C28-O2-C29 atoms of diclofenac anions.*Angle between planes passing through N8-C49-C50-N9 atoms of second clofaziminium cation and O3-C69-O4-C70 atoms of second diclofenac anion.

Structure	Packing coefficient	Angle between N4-C9-C8-N3 and O1-C28-O2-C29 planes (°)
CFZNH⁺-DCF⁻-MeOH (1:1:0.74)	0.661	83.0
CFZNH⁺-DCF⁻-EtOH (1:1:1)	0.658	73.3
CFZNH⁺-DCF⁻-EtOH (1:1:1) (100 K)	0.675	72.2
CFZNH⁺-DCF⁻-MeCN-H₂O (1:1:1:2) (100 K)	0.677	64.9
CFZNH⁺-DCF⁻-SAL-H₂O (4:4:9:1) (100 K)	0.700	74.5; 83.2*
CFZNH⁺-DCF⁻-PPP (2:2:5)	0.698	81.3
CFZNH⁺-DCF⁻-PPP (2:2:5) (100 K)	0.696	80.9
CFZNH⁺-DCF⁻ (1:1)	0.653	14.3
CFZNH⁺-DCF⁻-DCF (1:1:1) (polymorph I)	0.642	66.8
CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)	0.665	63.4
CFZNH⁺-DCF⁻-DCF-EtOAc (1:1:1:1)	0.657	62.5
CFZNH⁺-DCF⁻-DCF (1:1:1) (polymorph II)	0.660	46.4

salts (Table 3). This is in accordance with the presence of voids (15.41 Å³, 0.8% of the unit cell volume). This lower packing efficiency could explain solvent insertion (and so solvate crystallization) when diclofenac anion-solvent or clofaziminium cation-solvent interactions are possible.

3.1.2 Impact of solvent on crystallization of 1:1 salts

Salts combining clofazimine with diclofenac are, as initially expected, prone to solvate formation as indicated by the majority of the structures described in this work. First determined structure (**CFZNH⁺-DCF⁻-MeOH (1:1:0.74)**) contains toxic solvent (MeOH), which is H-bonded to diclofenac anion.

To avoid presence of toxic solvent, several options can be considered. The most evident ones, would be salt preparation without solvent (neat grinding) or with non-toxic/pharmaceutically accepted solvents (water, ethanol⁴⁰) or desolvation of solvated salts. Grinding clofazimine with diclofenac in 1:1 molar ratio in absence of solvent as well as in presence of water (LAG H₂O) resulted in a physical mixture of clofazimine with diclofenac (Figure S3 (h)†), thus not yielding any reaction. Moreover, crystallization experiment in only water as solvent was unsuccessful because of the low aqueous solubility of clofazimine. Since water as a solvent turned out to be unsuccessful and complete desolvation of **CFZNH⁺-DCF⁻-MeOH (1:1:0.74)** is difficult to achieve before melting of the powder, another pharmaceutically accepted solvent, namely ethanol, was chosen. In this case, solvent crystallization experiment as well as liquid-assisted ball milling, led to the same solvated salt: **CFZNH⁺-DCF⁻-EtOH (1:1:1)**, in which, as expected, ethanol interacted with DCF⁻ through H-bond.

To further investigate the parameters influencing the crystallization of (un)solvated salts, another protic solvent of higher molecular volume, salicylaldehyde (111 Å³³⁸) was selected. Despite their high molecular volume, salicylaldehyde molecules are included in the structure of **CFZNH⁺-DCF⁻-SAL-H₂O (4:4:9:1)**. Interestingly more than one salicylaldehyde molecule as well as one water molecule have been accommodated in the structure

probably to allow a good packing (this structure turned to have the best packing coefficient, Table 3). The existence of this solvate proves that the ability of solvent to interact with solute via weak interactions may be one of the factors explaining why even bulky solvents can still be trapped in the crystal.

High molecular volume did not hamper solvent insertion in the structure, at least for protic solvents that are able to interact with the solute through H-bond. We then focused on aprotic solvents. First, we selected acetonitrile (molecular volume of 46 Å³³⁸). However crystals obtained in these conditions corresponded to **CFZNH⁺-DCF⁻-MeCN-H₂O (1:1:1:2)**, a solvated hydrated salt, unstable at room temperature. Three other aprotic solvents (N,N-dimethylformamide, 78 Å³, ethylacetate, 91 Å³ and propiophenone, 136 Å³³⁸) with larger molecular volumes were then selected to perform crystallization experiments of CFZ and DCF in 1:1 molar ratio. A larger molecular volume could potentially hamper solvent inclusion in the structure. However, we still observed solvate formation: crystals obtained from DMF corresponded to the known clofazimine solvate **CFZ-DMF** (CSD ref-code: CEKTER⁴¹); crystallization experiments performed in propiophenone led to a solvated salt, **CFZNH⁺-DCF⁻-PPP (2:2:5)**, despite the absence of H-bond donor on propiophenone. The formation of the propiophenone solvate highlights again the fact that the molecular volume is not the only parameter affecting solvate formation, and that the interactions between the solvent and the solute are of crucial importance as well. In this case, propiophenone interacts with clofaziminium through π -cation interaction. Very interestingly, crystals of **CFZNH⁺-DCF⁻ (1:1)** unsolvated salt could however be obtained in ethylacetate, an aprotic molecule with a smaller molecular volume than propiophenone. The absence of the aromatic ring in ethylacetate, in contrast to propiophenone, results in a smaller number of potential interactions that it can form with clofazimine and thus may explain why ethylacetate is not incorporated into the structure. This unsolvated salt does not correspond to the crystalline phase appearing upon desolvation of **CFZNH⁺-DCF⁻-MeOH (1:1:0.74)**, which could indicate the existence of another polymorph of **CFZNH⁺-DCF⁻ (1:1)**.

3.2 Investigation of CFZ-DCF 1:2 cocrystal of salts

The second part of this work is dedicated to studying whether diclofenac molecule can bind diclofenac anion instead of the solvent molecule via O-H...O bond. We followed the same solvent selection criteria as in the first part and chose the solvents that would be less likely to be incorporated into the structure. The addition of a second diclofenac molecule in the system is expected to generate other types of crystal packings than those obtained for salts in a 1:1 molar ratio. Therefore, solvents leading to unsolvated form(s) in the case of 1:1 salts could potentially lead to solvated salts in a 1:2 molar ratio and *vice versa*. The solvents selected for this second part of the study were therefore restricted to low-boiling aprotic (EtOAc and MeCN) and non-toxic protic (EtOH) solvents. Indeed, MeCN and EtOAc could potentially be included in the system if they allow a more efficient packing, however these two solvents should not normally interact with the solute (CFZNH⁺, DCF⁻ and DCF) through H-bond or stacking. These solvents should therefore not be strongly bound within the crystal structure and, due to their low boiling point, may easily evaporate from the solvated structure if the latter is formed. When a diclofenac molecule is available in the solution, it should compete with protic solvents for the diclofenac anion binding site, potentially leading to 1:2 CFZ-DCF forms. However, inclusion of a protic solvent could still be possible (if its shape and size can be accommodated in the crystal packing) because DCF molecule also possesses H-bond acceptor. Although, the potential O-H...O interaction between DCF molecule and the solvent would be expected to be less strong with diclofenac molecule than with the anion.

3.2.1 Structural analysis

3.2.1.1 CFZNH⁺-DCF⁻-DCF (1:1:1) cocrystal of salt (polymorph I) crystallizes in *P* $\bar{1}$ space group (Tables 1 and S1†). The asymmetric unit comprises one clofaziminium cation, one diclofenac anion and one diclofenac molecule. Clofaziminium interacts with diclofenac anion through charge-assisted H-bond ($R_2^2(9)$ motif, N4–H4...O1 and N3–H3...O2, Table S2†, Figure 9 (a)). Intramolecular H-bonds are observed within diclofenac anion and molecule (N5–H5...O1 and N6–H6...O4, Table S2†, Figure 9 (a)). Diclofenac anion and molecule interact together through O3–H3O...O2 H-bond (Table S2†). This interaction is very similar to the one between diclofenac anion and ethanol in **CFZNH⁺-DCF⁻-EtOH (1:1:1)**. Indeed, even if these two structures are not isostructural, when clofaziminium and diclofenac anion are overlaid it can be observed that EtOH has a conformation similar to the first atoms (H3O, O3, C42 and C43) of diclofenac molecule (Figure 9 (d)).

All previously described interactions stabilize CFZNH⁺-DCF⁻-DCF assemblies. Two types of dimers of these assemblies, which are respectively stabilized by C31–H31...O3 and C3–H3A...O3 weak H-bonds (Table S2†, Figure 9 (b) and (c)), are also observed in the structure of **CFZNH⁺-DCF⁻-DCF (1:1:1)** cocrystal of salt. π - π stacking interactions are also observed between clofaziminium cations. The first one occurs between the phenazine core of two CFZNH⁺, with a centroid-centroid

distance of 3.669(1) Å, an orthogonal projection distance of 3.413(1) Å and an horizontal offset of 1.345 Å (planes and centroid calculated using C5 C6 C11 and C12 atoms, Figure 9 (e)). This stacking is further stabilized by C3–H3A...O3 (Figure 9 (c)) weak H-bonds. A second π - π stacking interaction is also observed between two C19 C20 C21 C22 C23 C24 aromatic rings of clofaziminium with a centroid-centroid distance of 3.801(1) Å, an orthogonal projection distance of 3.357(1) Å and an horizontal offset of 1.781 Å (Figure 9 (f)). Finally a C–H... π interaction is observed between C18–H18 of clofaziminium and diclofenac molecule (C44 C45 C46 C47 C48 C49) with a H...centroid distance of 2.59 Å, a C...centroid distance of 3.443(3) Å and a C–H...centroid angle of 153° (Figure 9 (g)).

The powder pattern calculated from SCXRD data corresponds to the one of the batch powder prepared by LAG EtOH (Figure S3 (d)†). This cocrystal of salt melts at 171 °C (Figure S4† and Table 2).

3.2.1.2 CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2) solvated cocrystal of salt also crystallizes in space group *P* $\bar{1}$ (Tables 1 and S1†). The asymmetric unit contains one clofaziminium cation, one diclofenac anion, one diclofenac molecule and two acetonitrile molecules (one MeCN molecule is disordered). Clofaziminium and diclofenac anion interact through charge-assisted H-bonds ($R_2^1(7)$ motif, N4–H4...O1 and N3–H3...O1, Table S2†, Figure 10 (a)). In both diclofenac (anion and molecule) an intramolecular H-bond is observed (N5–H5...O2 and N6–H6...O4, Table S2†). Molecular diclofenac and diclofenac anion interact through O3–H3B...O2 H-bond (Table S2†, Figure 10 (a)). Such H-bonds (N4–H4...O1, N3–H3...O1 and O3–H3B...O2) stabilize CFZNH⁺-DCF⁻-DCF assemblies, which further form dimers through C38–H38...O4 (Figure 10 (b)). A weak H-bond, stabilizing chains along *a*-axis, is also observed between diclofenac molecules (C43–H43A...O3, Figure 10 (c) and (d)). This crystalline phase can also be obtained from liquid-assisted grinding of CFZ and DCF in 1:2 molar ratio and with MeCN as solvent (LAG) (Figure S3 (e)†).

TG/DSC analysis of **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)** (powder obtained by liquid-assisted grinding experiment) reveals a 6.2% weight loss between 50 and 140 °C on the TG curve (Figure S4†) which is associated with an endothermic event on the DSC curve (onset: 93 °C) (Figure S4† and Table 2). These events can be attributed to desolvation (calculated MeCN content of 7.2% in **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)**). The endothermic event observed at 157 °C corresponds to the melting of the desolvated phase and suggests the formation of either an eutectic mixture or of an unsolvated crystalline phase combining CFZ and DCF (Figure S4† and Table 2). A variable-temperature PXRD experiment performed on **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)** confirmed the formation of a new crystalline phase upon heating which does not correspond to **CFZNH⁺-DCF⁻-DCF (1:1:1)** polymorph I (Figure S6†). Results from variable-temperature PXRD experiment and DSC/TG analyses suggest the formation of a second polymorph of **CFZNH⁺-DCF⁻-DCF (1:1:1)**.

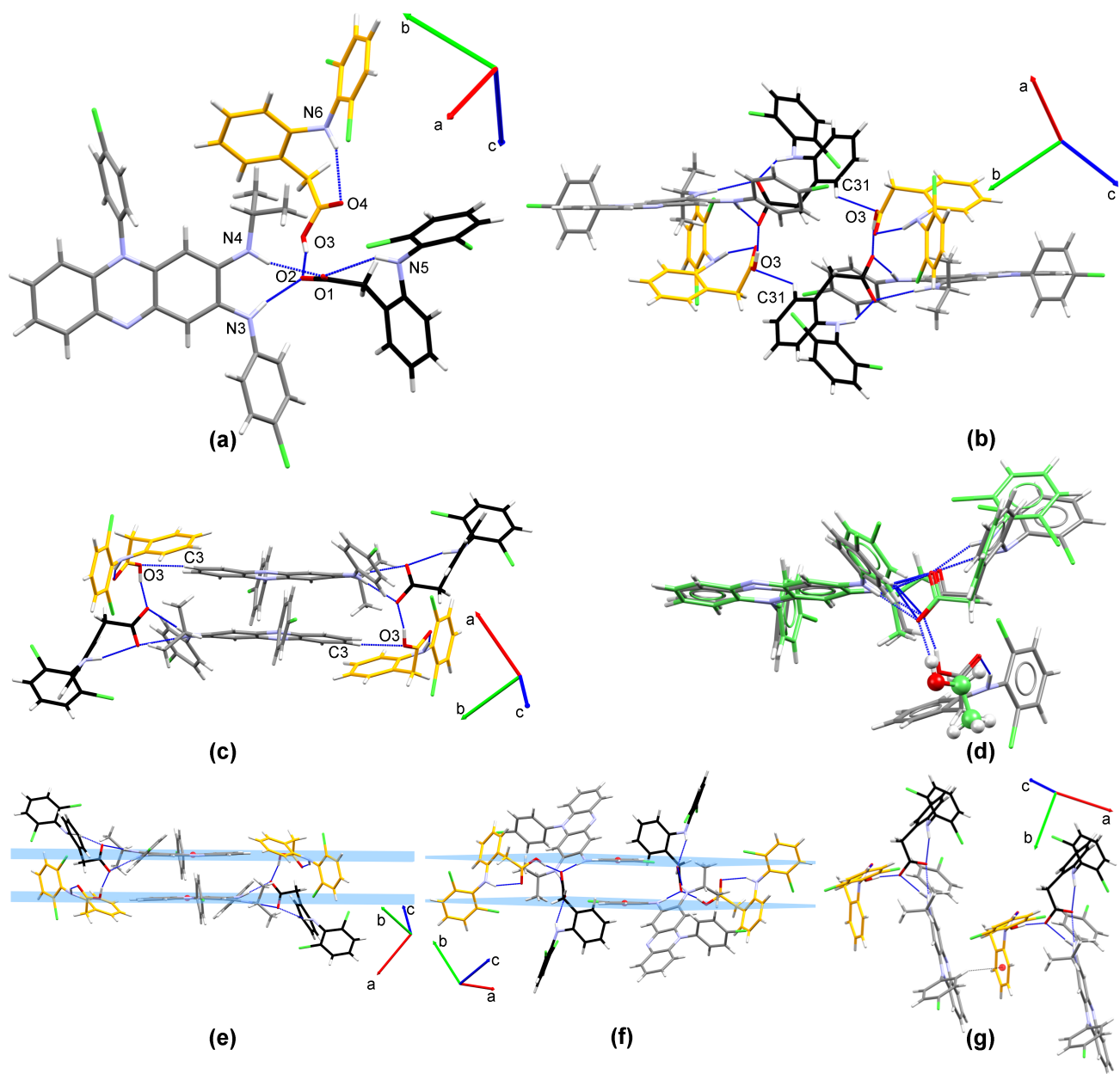


Fig. 9 H-bonds between clofaziminium, diclofenac anion and diclofenac molecule in **CFZNH⁺-DCF⁻-DCF (1:1:1)** polymorph I (a), dimers of **CFZNH⁺-DCF⁻-DCF** assemblies stabilized through C31–H31...O3 (b) and through C3–H3A...O3 (c). Interaction between DCF molecule and DCF anion in **CFZNH⁺-DCF⁻-DCF (1:1:1)** polymorph I (grey) is similar to the one between DCF anion and EtOH in **CFZNH⁺-DCF⁻-EtOH (1:1:1)** (green) (d). π - π stacking between clofaziminium cations (e) and (f) and C–H... π interaction between **CFZNH⁺** and DCF molecule (g). Carbon atoms of diclofenac anion are in black while those of diclofenac molecule are in orange. H-bonds are represented by blue dashed lines.

3.2.1.3 CFZNH⁺-DCF⁻-DCF-EtOAc (1:1:1:1) solvated cocrystal of salt crystallizes in $P\bar{1}$ space group (Tables 1 and S1†). The asymmetric unit contains one clofaziminium cation, one diclofenac anion, one diclofenac molecule and one ethylacetate molecule. **CFZNH⁺-DCF⁻-DCF-EtOAc (1:1:1:1)** is isostructural to **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)** and the same interactions are observed in both structures (Figure 10(e) and (f)). **CFZNH⁺-DCF⁻-DCF-EtOAc (1:1:1:1)** is prepared by ball-milling CFZ and DCF in 1:2 molar ratio in presence of few drops of EtOAc (Figure S3 (f)†). TG/DSC analysis of the CFZ-DCF 1:2 LAG EtOAc powder reveals a 5.6% weight loss between 50 and 140 °C, asso-

ciated to an endothermic event on the DSC curve (onset: 73 °C), indicating desolvation of **CFZNH⁺-DCF⁻-DCF-EtOAc (1:1:1:1)** (expected solvent content from SCXRD data: 7.6%). The single endothermic event observed at 157 °C corresponds to the melting of the desolvated phase (Figure S4† and Table 2). A PXRD experiment performed on heated powder (130 °C) of **CFZNH⁺-DCF⁻-DCF-EtOAc (1:1:1:1)** confirmed the formation of a new crystalline phase, identical to the one obtained by heating **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)** (Figure S3 (g)†).

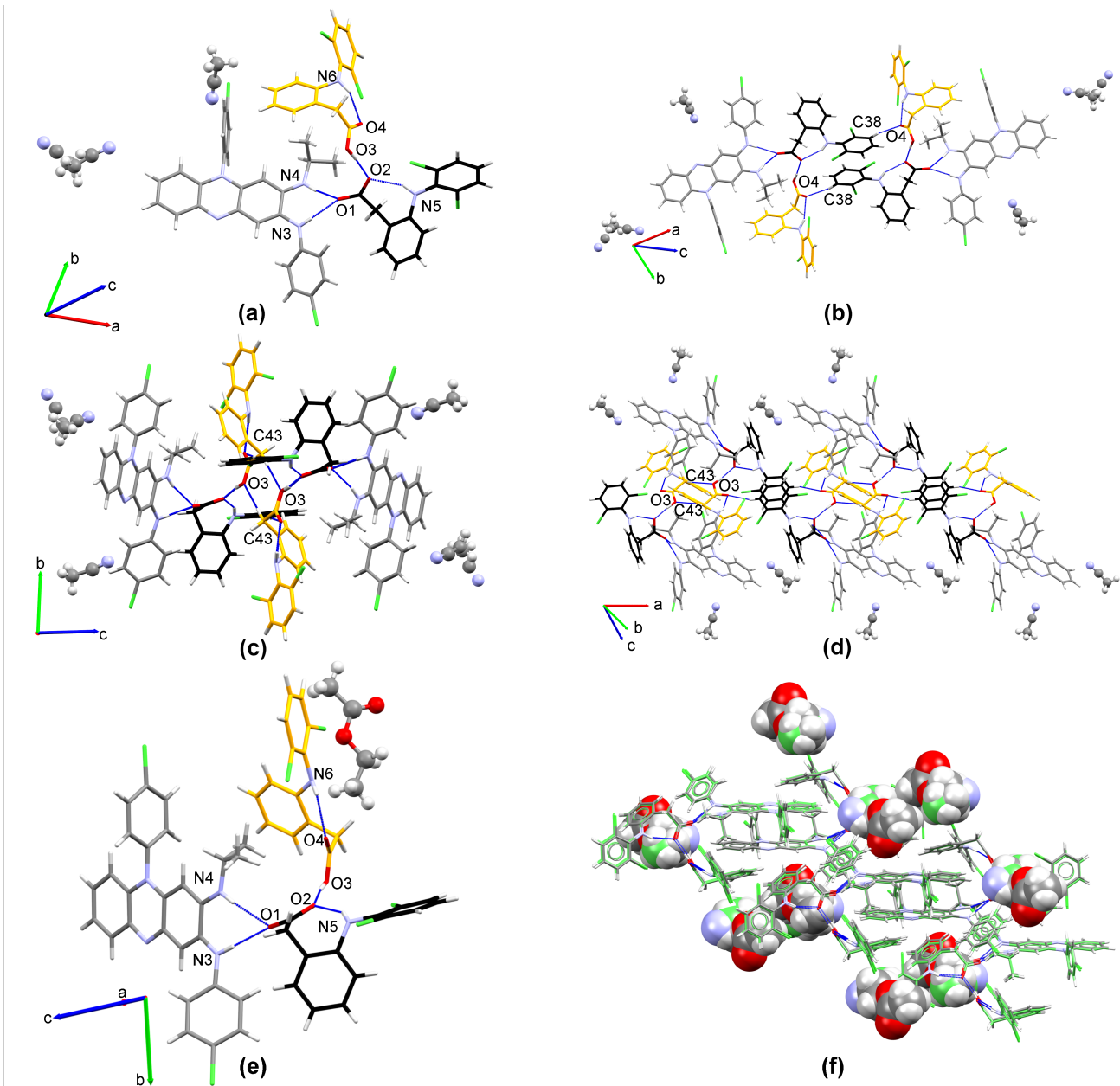


Fig. 10 (a) H-bonds between clofaziminium, diclofenac anion and diclofenac molecule in **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)**, (b) dimers of CFZNH⁺-DCF⁻-DCF assemblies (c) diclofenac molecules interact through C43–H43A...O3 H-bond and (d) C43–H43A...O3 H-bond between diclofenac molecules stabilizes chains along *a*-axis. Carbon atoms of diclofenac anion are in black while those of diclofenac molecule are in orange. Solvent is in ball and stick model. H-bonds are represented by blue dashed lines.

3.2.1.4 CFZNH⁺-DCF⁻-DCF (1:1:1) cocrystal of salt (polymorph II) crystallizes in triclinic $P\bar{1}$ space group (Tables 1 and S1[†]). Single crystals of this unsolvated cocrystal of salt were obtained by recrystallization of CFZ-DCF 1:2 powder (physical mixture) in PEG 200. Charge-assisted H-bonds ($R_2^1(7)$, N3–H3...O1 and N4–H4...O1, Table S2[†]) are observed between clofaziminium and diclofenac anion. The second oxygen atom of DCF⁻ is involved in a $D_1^1(2)$ H-bond with diclofenac molecule (O3–H3O...O2, Table S2[†]). These H-bonds ($R_2^1(7)$ and $D_1^1(2)$) stabilize CFZNH⁺-DCF⁻-DCF assemblies (Figure 11 (a)). Weak H-bonds between CFZNH⁺ and DCF molecule (C4–H4...O3, Table S2[†]) stabilize dimers of CFZNH⁺-DCF⁻-DCF assemblies (Fig-

ure 11 (b)). A second type of such dimers is stabilized by a weak H-bond between DCF⁻ and DCF molecule (C38–H38...O4, Table S2[†] and Figure 11 (c)). Intramolecular H-bonds in DCF⁻ and DCF are also observed (N5–H5...O2 and N6–H6...O4, Table S2[†] and Figure 11 (a)). In comparison with **CFZNH⁺-DCF⁻-DCF (1:1:1)** polymorph I, π - π stacking contribution to crystal packing stabilization is less important as there is no stacking between clofaziminium nor C–H... π interactions between clofaziminium and diclofenac molecule. There is however one π - π stacking interaction between two diclofenac anions with a centroid-centroid distance of 3.506(1) Å, an orthogonal projection distance of 3.355(1) Å and an horizontal offset of 1.017 Å (Figure 11(d), planes and

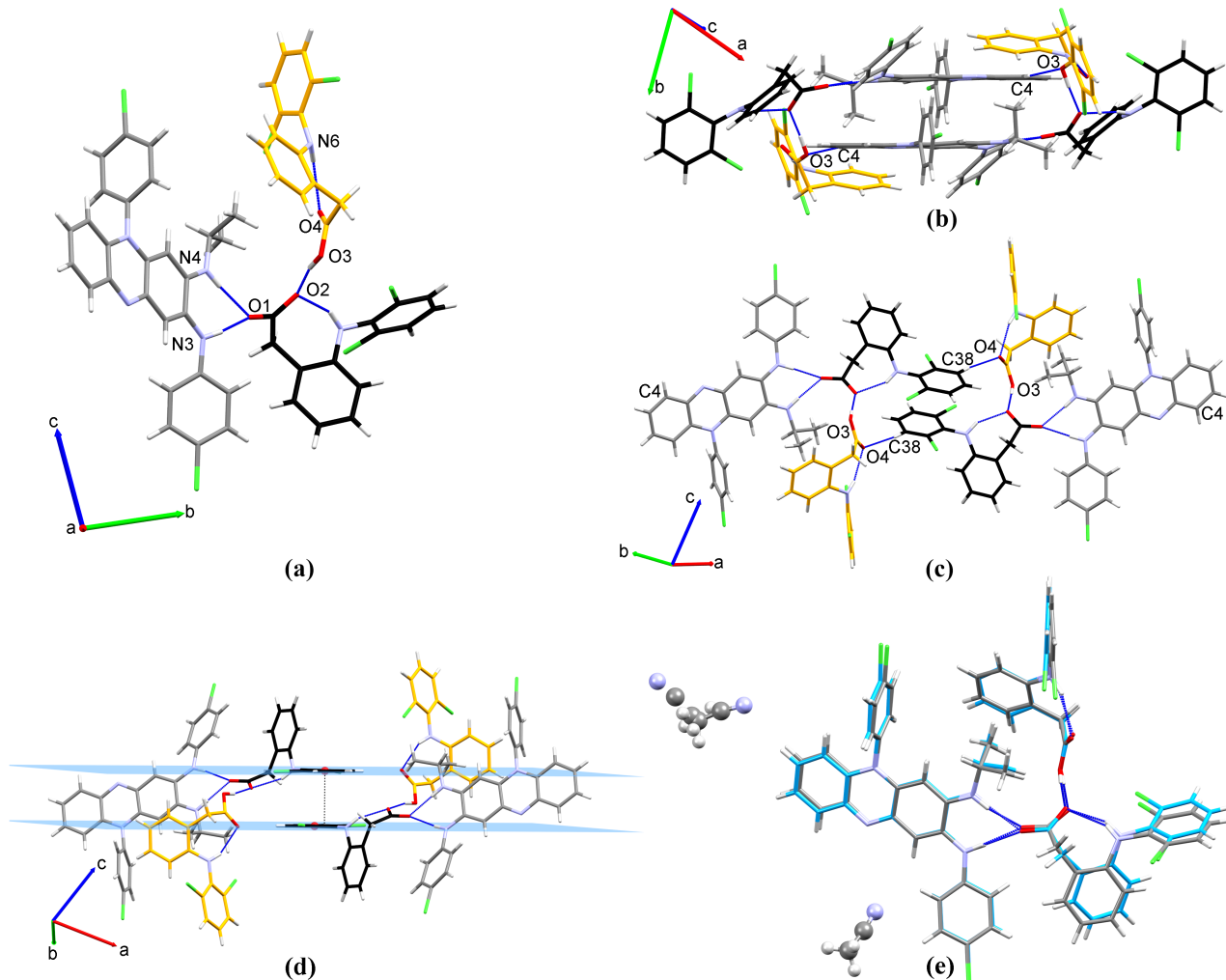


Fig. 11 (a) H-bonds between clofaziminium, diclofenac anion and diclofenac molecule in **CFZNH⁺-DCF⁻-DCF (1:1:1)** (polymorph II), (b) clofaziminium and diclofenac molecule interact through C4–H4...O3, stabilizing a dimer of CFZNH⁺-DCF⁻-DCF assemblies (c) diclofenac anion and diclofenac molecule assemblies and (d) π - π stacking between two DCF⁻ anions. (e) Asymmetric unit overlay of **CFZNH⁺-DCF⁻-DCF (1:1:1)** (carbon atoms in blue) and of **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)** (carbons atoms in grey). Carbon atoms of diclofenac anion are in black while those of diclofenac molecule are in orange (except for part (e) of the Figure). H-bonds are represented by blue dashed lines.

centroids calculated with C36 C37 C38 C39 C40 and C41).

Despite a quite good overlay of the molecules constituting their asymmetric unit (Figure 11 (e)), **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)** and **CFZNH⁺-DCF⁻-DCF (1:1:1)** are not isostructural as revealed by the crystal packing comparison performed with *Mercury* (only 9 molecules over 15 overlay despite distance and angle tolerance of 30% and 30°). Diclofenac anion orientation is slightly modified in the unsolvated cocrystal of salt in comparison to the one observed in **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)**. Indeed, the angle between the planes passing through N4-C9-C8-N3 atoms of CFZNH⁺ and through O1-C28-O2-C29 of DCF⁻ is different in the two structures (63.44° in **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)** vs. 46.41° in **CFZNH⁺-DCF⁻-DCF (1:1:1)**).

VT-PXRD and PXRD data measured after heating **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)** and **CFZNH⁺-DCF⁻-DCF-EtOAc (1:1:1:1)** indicate a phase transformation from the solvated cocrystal of salts to the **CFZNH⁺-DCF⁻-DCF (1:1:1)** unsolvated cocrystal of salt (polymorph II) (Figures S3 (g)† and

S6†). TG/DSC data obtained from **CFZNH⁺-DCF⁻-DCF-MeCN (1:1:1:2)** indicate that **CFZNH⁺-DCF⁻-DCF (1:1:1)** polymorph II melts at 157 °C (Figure S4† and Table 2). The difference in melting point observed between polymorph I (171 °C) and polymorph II (157 °C), can be partially explained by the fact that there are more π interactions in polymorph I while intermolecular H-bonds are of comparable strength in both polymorphs. It is interesting to notice that polymorph II has however a better packing (higher density) than polymorph I (packing coefficient of 0.660 vs. 0.642, density of 1.383 g.cm⁻³ vs. 1.351 g.cm⁻³ (data collected at 295 K for both structures)) (Table 3).

3.2.2 Impact of solvent on crystallization of 1:2 cocrystal of salts

Changing the clofazimine-diclofenac molecular ratio during crystallization experiment allowed the crystallization of a 1:2 unsolvated cocrystal of salt in EtOH, while this solvent previously led to a solvated 1:1 salt. This result indicates that diclofenac molecule

can successfully compete with the solvent for the interaction site with diclofenac anion. However, preparation of 1:2 cocrystal of salts did not completely rule out crystallization of solvated forms, as two solvated phases were obtained in acetonitrile and ethylacetate. Interestingly, crystallization of a 1:2 cocrystal of salt in EtOAc leads to a solvated form while the same solvent previously lead to an unsolvated $\text{CFZNH}^+\text{-DCF}^-$ (1:1) salt. EtOAc and MeCN both have a small molecular volume that can be accommodated in the structure if packing allows. However, as expected no strong interactions exist between EtOAc or MeCN and the solutes (CFZNH^+ , DCF^- and DCF).

TG/DSC analysis of these two solvated cocrystal of salts ($\text{CFZNH}^+\text{-DCF}^- \text{-DCF-MeCN}$ (1:1:1:2), $\text{CFZNH}^+\text{-DCF}^- \text{-DCF-EtOAc}$ (1:1:1:1)) revealed a weight loss between 50 and 100 °C and a melting point around 157 °C (Figure S4†). A phase transformation, probably associated with desolvation (and formation of an unsolvated cocrystal of salt combining CFZ and DCF), was identified by PXRD experiments (Figures S6† and S3 (g)†). The powder diffraction pattern obtained after desolvation of $\text{CFZNH}^+\text{-DCF}^- \text{-DCF-MeCN}$ (1:1:1:2) or $\text{CFZNH}^+\text{-DCF}^- \text{-DCF-EtOAc}$ (1:1:1:1) does not correspond to the one of $\text{CFZNH}^+\text{-DCF}^- \text{-DCF}$ (1:1:1) (polymorph I) (Figures S6† and S3 (g)†), which could be the indication of the existence of a second polymorph of $\text{CFZNH}^+\text{-DCF}^- \text{-DCF}$ (1:1:1). To verify this hypothesis, we have tried to obtain single crystals of this new unsolvated crystalline phase using other solvents that cannot be incorporated into the structure. We selected short chain polymers such as PEG (average MW: 200 g/mol and 400 g/mol) and polycaprolactone triol (average MW: 300 g/mol) as recrystallization solvents because of their higher molecular weight and also because of their molecular ‘flexibility’ in comparison to salicylaldehyde and propiophenone which previously led to solvated salts. Few single crystals of $\text{CFZNH}^+\text{-DCF}^- \text{-DCF}$ (1:1:1) (polymorph II) cocrystal of salt were obtained in PEG (average MW: 200 g/mol). Comparison of the calculated powder pattern of $\text{CFZNH}^+\text{-DCF}^- \text{-DCF}$ (1:1:1) (polymorph II) with the one obtained after variable-temperature PXRD experiment performed on $\text{CFZNH}^+\text{-DCF}^- \text{-DCF-MeCN}$ (1:1:1:2) confirmed desolvation and phase transformation that were inferred from VT-PXRD and TG/DSC experiments.

4 Conclusions

Clofaziminium : diclofenac system is a great example of structural variety that can be reached when a clever solvent selection is applied to explore various crystalline forms. As expected, diclofenac anion is able to interact with protic solvent molecules through H-bonds, leading to the crystallization of solvated drug-drug salts of clofazimine and diclofenac. Protic and aprotic solvents of increasing molecular volumes were taken in order to understand how solvent impacts crystallisation of clofazimine and diclofenac.

When facing probable solvate formation, the potential solute-solvent interactions can be more relevant than the size of the solvent. For example, the unsolvated $\text{CFZNH}^+\text{-DCF}^-$ (1:1) salt crystallized only in ethylacetate, an aprotic solvent having a lower molecular volume than another selected solvent, propiophenone. Despite its high molecular volume, propiophenone

was incorporated into the structure owing to π interactions, resulting in the corresponding solvated salt. A particular feature of the $\text{CFZNH}^+\text{-DCF}^-$ (1:1) unsolvated structure is that the carboxylate of DCF^- is almost coplanar to CFZNH^+ . It is, to the best of our knowledge, the first time that this specific carboxylate orientation is reported in a clofaziminium salt. These results highlight the importance of considering potential solute-solvent interactions not only in terms of H-bond interactions, but also other weak interactions such as probable π interactions.

Changing the clofazimine to diclofenac ratio from 1:1 to 1:2 allowed an extra diclofenac molecule to compete for the binding site with the protic solvent molecules. More particularly, diclofenac anion successfully beat EtOH for the H-bond interaction on diclofenac anion resulting in an unsolvated cocrystal of salt ($\text{CFZNH}^+\text{-DCF}^- \text{-DCF}$ (1:1:1) polymorph I) with the 1:2 clofazimine to diclofenac molar ratio. The second polymorph of $\text{CFZNH}^+\text{-DCF}^- \text{-DCF}$ (1:1:1) emerged from desolvation of $\text{CFZNH}^+\text{-DCF}^- \text{-DCF-MeCN}$ (1:1:1:2) and $\text{CFZNH}^+\text{-DCF}^- \text{-DCF-EtOAc}$ (1:1:1:1). The latter underlines that undesired solvated forms can potentially give access to other desired structures. Recrystallization using unconventional solvents such as short chain polymers exhibiting good fluidity, high molecular flexibility and high molecular weight can also be an option to avoid solvent inclusion into the structure, as illustrated by the successful growth of $\text{CFZNH}^+\text{-DCF}^- \text{-DCF}$ (1:1:1) (polymorph II) in PEG 200.

Changing the drug:drug ratio in the structure expectedly affects the physico-chemical properties of the corresponding solid forms, for instance, the melting point of the $\text{CFZNH}^+\text{-DCF}^-$ (1:1), 186 °C whereas those of $\text{CFZNH}^+\text{-DCF}^- \text{-DCF}$ (1:1:1) polymorph I and II are 171 °C and 157 °C respectively.

Conflicts of interest

There are no conflicts to declare. The European Commission’s support for the production of this publication does not constitute an endorsement of the contents, which reflect the views only of the authors, and the Commission cannot be held responsible for any use which may be made of the information contained therein.

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