



Cocrystals of Lamotrigine Based on Coformers Involving Carbonyl Group Discovered by Hot-Stage Microscopy and DSC Screening

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Supporting Information



ABSTRACT: Four novel lamotrigine cocrystals, namely, 1:1 lamotrigine:phthalimide (1), 1:1:1 lamotrigine:pyromellitic diimide:DMF (2), 2:1:0.64 lamotrigine:caffeine:3-pentanone (3), and 1:1 lamotrigine:isophthaldehyde (4), were discovered using a combined hot-stage thermomicroscopy and differential-scanning calorimetry screening technique. The utilized cocrystal screening method is rapid, requires the use of small amounts of material, and is highly suitable for compounds that are prone to solvate formation. The structurally characterized cocrystals were prepared in an attempt to develop lamotrigine cocrystals based on cocrystal formers involving carbonyl and amide functional groups. The prepared cocrystals are sustained by $N-H(amide)\cdots N(pyridyl)$, $N-H(amino)\cdots O(amide)$, and $N-H(amino)\cdots O(carbonyl)$ hydrogen bonds.

1. INTRODUCTION

Lamotrigine (i.e., 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine, **lam**; Scheme 1) is an anticolvulsant¹ that exhibits very

Scheme 1. Chemical diagrams of lam and four cocrystal formers; ptl, pmd, caf and ipa



poor solubility in water. This active pharmaceutical ingredient (API) was primarily developed for treatments of epilepsy and bipolar disorders, but it has also been reported as beneficial in the treatment of specific cluster headaches and migraines.²

The poor aqueous solubility of lam may be attributed to its tendency to form an extensively hydrogen-bonded network in the solid state.³ Within the network, the lam molecules are held together by strong N-H(amino)...N(pyridyl) hydrogen bonds that participate in the formation of both $R_2^2(8)$ and $R_3^2(8)$ homosynthons (Figure 1). Numerous attempts have so far been made to obtain crystalline lam phases wherein lam forms crystalline architectures that are more soluble in aqueous media. These attempts yielded, cited by reference codes or their working titles, so far 8 solvates; (KADPAG,⁴ WUVLIJ,⁵ XUVLOP,⁶ WUVLOP,⁵ OVUNAV,⁷ YERTAR,⁸ IJAHOR,⁹ OVOMUO⁷), 17 salts (YUCRAQ,³ YUCREV,³ WUVKUU,⁵ WUVLAB,⁵ WUVLEF,⁵ OVUMOI,⁷ OVUMEY,⁷ GAVLEV,¹⁰ YEXFUD,¹¹ FOXLUA,¹² FUHVOU,¹² FOXMEL,¹² WUVKOO,¹² lam:acetate,¹³ lam:4-hydroxy benzoate,¹³ KUZMUO,¹⁴ QEJHUI¹⁵), 4 cocrystals (WUVKEE/WUVKEE01,⁵ WUVKII,⁵ lam:acetamide¹³), and notably, no lam polymorphs.

Crystal engineering and cocrystals have recently emerged as viable means to design and fabricate APIs with enhanced

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Figure 1. Hydrogen-bonding motifs observed in the crystal structure of ${\rm lam.}^3$

physicochemical properties (e.g., solubility,¹⁶ stability,¹⁷ compressibility,¹⁸ etc.). With this in mind, a study of supramolecular synthons and understanding the hierarchy in **lam** multicomponent solids is required. Our working hypothesis is based on the presumption that **lam** cocrystals with disrupted aminopyridine homosynthons may exhibit better solubility profiles in aqueous media. Because of the literature data, it has been shown so far that carboxylic acids are suitable salt formers with **lam** but not cocrystal formers.

Considering the relatively small number of carboxylic acids in the GRAS and EAFUS lists,¹⁹ as well as the large abundance of aldehydes, ketones and amides in these lists, we recognized the need to develop **lam** cocrystals based on supramolecular synthons involving carbonyl and amide groups. That ketones are indeed worthwhile being considered as suitable cocrystal formers for **lam** was shown in a Cambridge Structural Database (CSD)²⁰ survey (Supporting Information Table S1). Specifically, there are two polymorphs of **lam** cocrystals with methylparaben; one with disrupted both motifs 1 and 2, and the other with preserved motif 1.⁵ The crystal structure of **lam**: nicotinamide cocrystal also disrupts motif 2,⁵ while acetamide cocrystal preserves motif 1.¹³

We have, therefore, preformed a cocrystal screen involving various carbonyls and amides shown in Scheme 1. Although cocrystal formers used in this study are mainly not listed as GRAS and EAFUS compounds, they still represent valuable model compounds for the development of **lam** cocrystals involving on coformers based on carbonyl and amide functionalities. The cocrystal formers were selected based on their presumed inability to form salts. Both phthalimide and piromellitic diimide exhibit pK_a values (i.e., 8.3 and 8.5, respectively) that do not support salt formation with **lam** $(pK_a($ **lam**) = 5.7) since the cocrystal components exhibit a negative ΔpK_a value.²¹

To screen for **lam** cocrystal formation, we used hot-stage microscopy (HSM)²² and differential scanning calorimetry (DSC).²³ Thermomicroscopy of organic compounds is one of the oldest and simplest methods suitable for screening purposes. This fast technique allows the fast identification of polymorphs, solvates and hydrates, as well as the study of material decomposition and phase transitions.²⁴ The microscopic observation of thermally treated binary systems was initially described by Lehmann²⁵ and later on refined by Kofler.²⁶ This

method, also commonly called contact method by McCrone,²⁷ is nowadays widely used for fast cocrystal screens of binary system. On the basis of known melting points of the cocrystal components, the Kofler contact method provides information about the formation of new solid phases or eutectic mixtures formation. DSC²³ is also a powerful and rapid cocrystal screening method, and is particularly useful if utilized in combination with HSM as presented in this work. Both screening methods are solvent free and, therefore, sustainable and require only very small quantities of the cocrystal components.

It is of high importance to state that cocrystal screening involving **lam**, based on liquid evaporation technique, could be misleading because of **lam**'s tendency for solvates formation or to its relatively low solubility in organic solvents. The results of experiments obtained by combination of HSM and DSC experiments indicated that cocrystal phase must exist and that under suitable crystallization conditions cocrystal phase can be isolated by solvent evaporation.

We herein reported the results of our cocrystal screen, as well as four cocrystal structures of lamotrigine, namely the **lam:ptl** cocrystal (1:1) (1), the **lam:pmd**:DMF solvate cocrystal (1:1:1) (2), the **lam:caf**:3-pentanone solvate cocrystal (2:1:0.64) (3) and the **lam:ipa** cocrystal (1:1) (4) (Scheme 1).

2. MATERIALS AND METHODS

2.1. Materials. Lamotrigine was supplied from the *in-house* source with purity of 99.9%. Pyromellitic diimide (97%) has been supplied by Alfa Aeser. Anhydrous caffeine (99%) has been supplied by Fluca while phthalimide (98%) and isophthaldehyde (97%) have been supplied by Sigma-Aldrich. All chemicals were used without further purification.

2.2. Synthesis of the 1:1 lam:ptl Cocrystal, 1. lam (0.064 g, 0.25 mmol) was dissolved in 5 mL of hot 3-pentanone. The hot solution was subsequently filtered into a glass vial, and a 3-pentanone solution (2 mL) of ptl (0.037 g (0.25 mmol) was added to the lam solution. The obtained solution was filtered and left to evaporate slowly at room temperature. The crystallization vial was covered with perforated paraffin film. Colorless and hexagonal crystalline plates suitable for single crystal X-ray diffraction emerged after 6 days.

2.3. Synthesis of the lam:pmd:DMF Solvate Cocrystal (1:1:1), 2. lam (0.128 g, 0.50 mmol) was dissolved in 2 mL of hot dimethylformamide DMF, while **pmd** (0.108 g, 0.50 mmol) was dissolved in 3 mL of hot DMF. The solutions were hot-filtered and mixed in a glass vial. The obtained solution was left to evaporate at room temperature. After 3 days, white crystals of pyromellitic diimide appeared. Yellow prisms of **2** were isolated after 14 days as a second fraction.

2.4. Synthesis of lam:caf:3-Pentanone Solvate Cocrystal (2:1:0.64), 3. lam (0.128 g, 0.50 mmol) was dissolved in 15 mL of hot 3-penthanone, whereas caf (0.097 g, 0.50 mmol) was solubilized in 12 mL of the same solvent. The solutions were filtered while still hot and subsequently combined in a glass vial that was covered by paraffin in order to slow down the solvent evaporation. After 10 days of solvent evaporation, colorless prisms were isolated from the crystallization vial. The harvested crystals were small in size and were, thus, used as seeds in other crystallization trials. To prepare a single crystal of 3, a concentrated suspension of 3 was prepared. The suspension was hotfiltered and cooled to room temperature and then filtered once more. Several previously obtained small single crystals of 3 were added to the filtrate to seed the formation of sizable single crystals. Slow evaporation at room temperature was achieved by covering the glass vial with a paraffin film with a small hole. Single crystals of 3 suitable for single crystal X-ray diffraction were obtained after 7 days.

2.5. Synthesis of the lam:ipa Cocrystal (1:1), 4. lam (0.05 g, 0.20 mmol) was dissolved in 4 mL of methyl—ethyl ketone by heating. The solution was filtered while hot and added to a glass vial containing ipa (0.027 g, 0.20 mmol). The obtained suspension was mixed until all

	1	2	3	4
chemical formula	$C_{17}H_{12}Cl_2N_6O_2$	$C_{22}H_{18}Cl_2N_8O_5$	$C_{29.20}H_{29.40}Cl_4N_{14}O_{2.64}$	$C_{17}H_{12}Cl_2N_5O_2$
stoichiometry	1:1	1:1:1	2:1:0.64	1:1
M _r	403.23	545.34	760.51	389.22
crystal system, color and habit	monoclinic, colorless hexagonal plate	triclinic, yellow prism	monoclinic, colorless prism	monoclinic, colorless plate
crystal dimensions (mm ³)	$0.55 \times 0.48 \times 0.24$	$0.52 \times 0.44 \times 0.39$	$0.58 \times 0.34 \times 0.22$	$0.35\times0.28\times0.11$
space group	$P2_{1}/c$	$P\overline{1}$	$P2_1/n$	$P2_{1}/c$
Ζ	4	2	4	4
a (Å)	15.4408(4)	8.5495(2)	10.6828(3)	16.8971(10)
b (Å)	7.9449(2)	10.9017(3)	14.0628(3)	8.0443(4)
c (Å)	14.8452(4)	13.8187(4)	23.7907(5)	13.4064(7)
α (deg)		91.066(2)		
β (deg)	105.774(3)	107.330(2)	95.746(2)	97.556(5)
γ (deg)		94.090(2)		
V (Å ³)	1752.56(8)	1225.29(6)	3556.12(15)	1806.45(17)
$ ho(calcd)/g \ cm^{-3}$	1.528	1.478	1.420	1.431
T (K)	296(2)	296(2)	105(2)	296(2)
reflus collected, unique, R_{int} , observed $[I \ge 2\sigma(I)]$	4794 (0.1028) 2620, 1997	18987 (0.0206) 4376, 3706	22415 (0.0331) 6347, 5506	5145 (0.0278) 2697, 1578
$R_1 \left[I \ge 2\sigma(I) \right]$	0.0706	0.0447	0.0582	0.0463
R_2 (all data)	0.1795	z0.1367	0.1722	0.1164
GOF on F^2 , S	0.973	1.132	1.029	0.831
max. and min. electron density (e $Å^{-3}$)	0.637, -0.52	0.411, -0.55	1.014, -0.54	0.33, -0.22

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Table 1. Crystallographic Data for 1, 2, 3, and 4

particles were dissolved. The solution was covered by a perforated paraffin film and let to evaporate at room temperature. The solution yielded colorless crystalline plates of **4** after 1 day. Noteworthy, crystals of **4** were observed to form only on the walls of the vial, while the bottom of the vial held a physical mixture of the starting materials.

2.6. Desolvatation of 3. The unsolvated lam:caf cocrystal was obtained by either (a) heating the 3 to a temperature of 184 $^{\circ}$ C in the DSC, and (b) by heating a milled 2:1 physical mixture of lam and caf. The transformations of the two solids into the unsolvated lam:caf cocrystal were monitored by XRPD.

2.7. Mechanochemical Experiments. Solid-state grinding performed using binary mixtures containing **lam** and one of the studied cocrystal formers. About 1 g of the physical mixture (1:1) was ground in a Pulverisettte 7 planetary ball mill. Samples were grounded in 12 mL SiN jars with 7 SiN balls (10 mm in diameter) with 600 rpm for either 30 and 60 min. Solvent-drop grinding was performed under the same conditions with the addition of about 3 drops of the same solvent from which single crystals were isolated. All obtained solids were characterized by XRPD.

2.8. Hot-Stage Optical Microscopy. Thermomicroscopic experiments were performed with an optical polarizing microscope (*Olympus BX51*) equipped with a *Linkam* hot-stage microscope *THMS 600* being connected to a *TMS 94* temperature controller. The micrographs were recorded at 50× magnification using a *JVS* camera being attached to the microscope. Samples were heated with constant heating rate of 10 and 20 °C/min over a temperature range from 25 °C until the melting of substance with higher melting point. The samples were discontinued upon melting. The hot-stage was controlled by the Lynksys 32 software package (version 1.96).²⁸

2.8.1. Mixed Fusion (Contact) Method. Two components under observation are brought in physical contact by melting them between a glass microscope slide and a coverslip. Small quantity of powder of the component with higher melting point is placed on one side of covered glass slide and heated on Kofler bench. The liquid passes within the slide and coverslip and fulfils one-half of the glass surface. After the solidification of the component on the opposite glass side, component with lower melting point is placed and heated until it is melted and spread within the glass slide and a coverslip. When the second molten component is being brought into the contact with the first component it causes partial solubility of the first component. By solidification mixing zone is created and it is observed during heating in hot-stage experiments.

2.9. Thermal Analysis (DSC). DSC profiles were generated in the range of 30-250 °C using a *TA Instrument Q1000*. About 3-5 mg of the sample was encapsulated in a pierced Al pan. The same empty pan was used as reference. A nitrogen purge at 50 mL/min was employed. The resulting data were analyzed using the *TA Instruments Universal Analysis 2000* software (version 4.7A).²⁹

2.10. Single Crystal X-ray Diffraction. Single-crystal analyses of 1–4 were performed on a *Oxford Xcalibur Gemini* diffractometer equipped with a *Sapphire* CCD detector and graphite-monochromated Cu K_{α} radiation ($\lambda = 1.5418$ Å). The diffraction data for 1, 2, and 4 were collected at 296(2) K, while the data for 3 was collected at 105(2) K. All diffraction frames were collected using ω -scans (Table 1).

The CrysAlis CCD and CrysAlis RED (Version 1.171.33.66) programs were employed for data collection, cell refinement and data reduction.³⁰ The Lorentz-polarization effect was corrected and the diffraction data have been scaled for absorption effects by the multiscanning method. The structures were solved by direct methods and refined on F^2 by weighted full-matrix least-squares. SHELXS97³¹ and SHELXL97³¹ (being integrated in the WinGX version 1.80.05 software package) were used to solve and refine the structures. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms belonging to $C(sp^2)$ and $C(sp^3)$ carbon atoms were placed in geometrically idealized positions with isotropic displacement parameters fixed at 1.2 times U_{eq} (for C(sp²) carbon atoms) or 1.5 times U_{eq} (for methyl groups) of the atoms to which they were attached and they were constrained to ride on their parent atoms. Hydrogen atoms of the lam amino groups (belonging to the N3 and N5 nitrogen atoms) or of coformers ptl in 1 and pmd in 2 were located in difference Fourier maps as small electron densities at final stages of the refinement procedures. These H-atom coordinates were refined freely with isotropic displacement parameters being set at 1.2 U_{eq} of the corresponding nitrogen atoms. In the structure of 2, the DMF molecule were found to exhibit positional disorder (53:47) with C=O distances restrained by DFIX instruction to 1.22(1) Å. The occupancies of atoms belonging to 3-pentanone solvent molecule in 3 were refined as free variables and fixed at 0.64 at the end of the refinement in order to shorten the molecular formula of 3. One of the aldehyde groups in the ipa coformer molecule in 4 exhibits a stacking

Table 2. Synthon Types (Denoted as A, B, C, D, or Their Combination) Established in lam Structures and Its Derivatives



disorder in the crystal structure. The disorder has been modeled into two alternating positions in a 0.57:0.43 ratio, thus indicating differently stacked **ipa** molecules within the crystal structure of **4**. ORTEP views (Supporting Information Figures S8–S11) of the molecular structures show the major occupation site of the aldehyde group denoted as A, and minor one as B. Molecular geometry calculations (including H-bonding and noncovalent interactions) were performed using the PLATON³² and PARST³³ programs being integrated in the WinGX software system.³⁴ ORTEP-3³⁵ was used for molecular visualization. Packing diagrams were generated using Mercury.³⁶

2.11. Cambridge Structural Database Survey. The Cambridge Structural Database (CSD)²⁰ (version 5.32, update of Nov 2011) was surveyed for structures containing 1,3-diaminotriazine (Scheme 1), and was carried out using ConQuest³⁷ (version 1.13) and performed without the use of any filters (e.g., organic compounds, determined 3D-coordinates, etc.). CSD was in addition surveyed to examine the number of cocrystals containing carbonyl group according to the applied filters and by hand selection.³⁸

3. RESULTS AND DISCUSSION

3.1. Synthon Analysis. A combined literature and CSD survey were performed to evaluate the feasibility of using ketones and amides as cocrystal formers for the synthesis of **lam** cocrystals. The survey of CSD base revealed 35 entries

with a 1,3-diaminotriazine moiety, whereof 30 related to a **lam** structure and another 5 to a **lam** analogue (i.e., **BEZGUI**, **CIQLET**, **LINFOD**, **TEKWAH**, and **WINMIP**). Including the literature search a total of 38 structures containing a 1,3-diaminotriazine structure were found.¹³ Among the 38 multicomponent structures, we identified various structural motifs, which we divided in five classes (i.e., A, B, C, D or their combination (AB), Table 2) in contrast to motif 1 and motif 2 that relate to lamotrigine structure itself.

Structural motif A is a $R_4^2(16)$ synthon that can be regarded as a combination of the aminopyiridine $R_2^2(8)$ homosynthon (motif 1 in lam)³ that is based on N–H(amino)····N(pyridyl) hydrogen bonds, and a $R_3^2(8)$ synthon based on N–H(amino)····N(pyridyl) and N–H(amino)····O hydrogen bonds, whereby the hydrogen-bond-accepting O-atom belongs to either water,⁶ DMF,⁸ acetamide¹³ or an alcohol.^{4,5,7,9} Based on this observation, we proposed that oxygen atoms belonging to the carbonyl groups of aldehydes and ketones could potentially participate in the formation of motif **A**. Such proposition is additionally supported by the large number of crystal structures deposited in the CSD that entail functional groups analogous to amino-triazine ring being bound to carbonyl moieties via

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 $N-H(amino)\cdots O(carbonyl)$ hydrogen bonds (Supporting Information Table S1).

Structural motif B is heterosynthon $R_2^2(8)$ based on charge assisted N⁺-H(amino)····O⁻(carboxy) hydrogen bonds. This structural motif was found in **lam** salts involving carboxylic acids. It is presumed that other strong hydrogen-bonding functionalities, such as amides, might be able to be bounded to the 1,3-diaminotriazine **lam** ring.

Besides described motifs two other, motif C and motif D, have been recognized among structures and could be utilized in further crystal engineering approach in cocrystal design.

3.2. Screening and Characterization. Thermomicroscopy was employed to evaluate the potential **ptl**, **caf**, **pmd** and **ipa** to form cocrystals with **lam**. Samples for the microscopic examinations were prepared by the Kofler contact method.^{22a} Additional DSC measurements were performed for each binary 1:1 homogenized mixture to gain a better understanding of the thermal events revealed by HSM.

Visual investigations of samples containing lam and ptl showed a solid phase of ptl and the amorphous lam phase being divided by the mixing zone. The amorphous state of lam was supported with a series of combined XRPD and DSC measurements. The mixing zone is formed by melting ptl in lam on a Kofler's bench and is in a glassy state. It was observed that the mixing zone turns into a liquid at 177 °C whereby at the same time lam starts to crystallize. No other thermal events were observed until the melting point of lam (217.1 °C). Once the heating was stopped at about 190 °C and the sample was allowed to cool down to room temperature, the liquid mixing zone solidified with a different molar ratio (as compared to the initial glass formation) and a new phase becomes visible on the lam side of the glass slide. When a new cycle of heating is applied, the new phase serves as a nucleus in a crystallization event that starts at about 125 °C from the residual glassy phase of the mixing zone. At about 200 °C the new phase completely fulfils the gap between the lam and ptl phases. The melting points of two eutectics were shown to be close to the melting points of the new phase. At about 205 °C the liquid zone is visible between the new phase and lam (Figure 2). The new phase melts about 207 °C (Figure 3).



Figure 2. Contact area of lam-pht system at 205 $^{\circ}$ C in second heating cycle. Cocrystal phase (C) is placed centric. Eutectic lam:cocrystal starts to melt (D) on the board with solid lam (B). Ptl is in the solid state (A).



Figure 3. Contact area of lam:ptl system at 207 $^{\circ}$ C in second heating cycle. Cocrystal phase (C) melting is ongoing and solid phase is placed between two liquid zones, presenting eutectic melts (D). Lam (B) and ptl (A) are in the solid state and melt at the end in accordance to their melting point temperatures.

The process described above was shown to be reversible in numerous heating/cooling cycles. The DSC profile of the physical mixture of **lam** and **ptl** revealed an endothermic peak at 177.0 $^{\circ}$ C that was attributed to the fusion of eutectic mixtures (Figure 4).



Figure 4. DSC profiles of caf (1), lam (2), ipa (3), ptl (4), binary mixture of lam and ptl (5), binary mixture of lam and caf (6), and binary mixture of lam and ipa (7) (endothermic signal down).

The small exothermic peak at 178.9 °C suggests both the clustering of molecules in the eutectic melt and a recrystallization event indicating interaction between **lam** and **ptl**. The DSC thermogram revealed three additional endothermic signals at 198.2 °C, 202.6 °C (weak), and 206.7 °C (strong) that corresponds to the melting of the eutectic mixture (**lam/ptl**), the melting of a mixture of the eutectic and the new phase, and the melting of the new phase, respectively. Notably, the melting point of the new phase (i.e., 206.7 °C) was found to be in good agreement with the melting point of solid **1** (i.e., 205.5 °C) that has been determined by DSC using a batch of single crystals (Figure 5).



Figure 5. DSC profiles of cocrystals 1, 2, 3, and 4 (endothermic signal down).

A physical mixture of lam and ptl 1:1 was melted on Kofler's bench and XRPD pattern was compared with the XRPD pattern of batch of single crystals. Two examined patterns proved the same crystalline cocrystal form. In addition, mechanochemical experiments showed that the same polymorph form can be obtained by milling in a ball without using any solvents to facilitate cocrystal formation. Noteworthy, the reaction mixture undergoes a phase transformation after 30 min of grinding to result in the formation of an amorphous solid. Further grinding resulted in partial cocrystal formation, as evidenced by PXRD (Supporting Information Figure S1). A DSC curve of the milled sample revealed only the crystallization of the amorphous lam phase and the melting of 1: no signs of fusion of the eutectic mixture were observed. Solvent drop grinding with 3-penthanone, on the other hand, significantly enhanced the mechanochemical reaction yields. The increase of the reaction yield was attributed to the increased molecular mobility of lam through the presence of 3-pentanone, a fairly good solvent for lam.

In the case of **lam** and **caf**, the sample prepared by the Kofler contact method clearly shows the formation of a mixing zone between the solid **caf** phase and the amorphous **lam** phase. Heating of the initially prepared sample allows the observation of two thermal events occurring at the same time. Specifically, a strong strip in the range of the mixing zone appears at about 130 °C, indicating the formation of a new phase. Second event relates to the crystallization of amorphous **lam** influenced by heat. The first eutectic (**caf**/cocrystal) melts at about 190 °C (Figure 6).

At about 196 °C, the new phase is completely melted (Figure 7). DSC experiment on the physical mixture shows a broad endothermic peak at 175.8 °C (Figure 4). This peak corresponds to the melting of the eutectic (lam/caf). This was evidenced by XRPD experiments on a sample obtained by heating the physical mixture of lam and caf (2:1) up to 168 °C in the calorimeter. Besides physical mixture, XRPD evidenced traces of new crystalline phase crystallized from melt (the solid is described below as unsolvated form of 3, Supporting Information Figures S2 and S3). Single crystals of 3 were isolated from 3-pentanone in the form of solvate. The DSC profile shows three thermal events (Figure 5). The first endothermic peak was observed at 177.6 °C and was attributed the desolvatation process (Figure 8), as demonstrated



Figure 6. Contact area of lam-caf system at 190 °C. Eutectic caf:cocrystal (D) is melted. Lam (B) still undergoes crystallization. The new cocrystal phase (C), in the middle of lam (B) and eutectic melt (D) is visible.



Figure 7. Contact area of lam-caf system at 200 °C. Lam (B) and caf (A) exist in solid state, while the cocrystal phase is completely melted.

by a mass loss in related TGA measurements (Supporting Information Figure S4).

The desolvation is followed by a small exothermic peak indicating the recrystallization of initial solvated phase and a new phase formation. The new unsolvated form melts at 194.9 °C. The reversible transformation to 3 was proved by slurring the unsolvated form in 3-pentanone. The preparation of 3 was also attempted mechanochemically. In particular, **lam** and **caf** 2:1 was ground in a ball mill and the resulting solid was shown to be amorphous, as revealed by XRPD. Solvent drop grinding was shown to enhance cocrystal formation (Supporting Information Figure S5), and the observed reaction yields were proportional to the amounts of solvent (i.e., 3-pentanone) added to reaction mixture. The dependence of reaction yields on the amount of solvent is not surprising considering that 3-pentanone is built into the **lam:caf** crystal lattice.

Microscopic observations of **lam** and **ipa** physical mixtures revealed no interaction between the two compounds prior to heating. The mixing zone does not even appear when the prepared sample is isothermally treated at 60 °C on Kofler's bench. We also note that heating at lower rates (i.e., 1-10 °C/min)

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Figure 8. Desolvatation of 3. Crystals 3 at room temperature (A), losing the transparency at about 182 °C (B), and crystal melting at 188 °C (C).

allows to observe melting of **ipa**, which is being followed by the melting of **lam**. We found that the DSC trace of the physical mixture (ground for 1 min) consists of two close endothermic peaks, one corresponding to the melting of **ipa** at 87.4 °C and the another one relating to the formation of the new solid form at 115.0 °C (Figure 4). The same HSM experiment were also performed using increased heating rate, that is, 20 °C/min and lead to the observation of two eutectic melting points, as well as the formation of a new phase. We found that the first eutectic (**ipa**/cocrystal) melts at a temperature close to the melting point of **ipa** (i.e., ~86 °C) (Figure 9).



Figure 9. Contact area of lam-ipa system at 86 °C. Cocrystal phase (C) is visible attached to the solid lam phase (B). ipa (A) is almost melted.

The second eutectic (lam/cocrystal) melted completely at about 100 °C, as shown in Figure 10.

The melting of the new solid phase was completed at about 115 °C. We have also preformed mechanochemical screens that demonstrated cocrystal formation *in traces* when dry- and solvent-drop grinding conditions were applied (Supporting Information Figure S6). Anhydrous single crystals of 4 were, however, isolated from MEK. DSC experiments involving these single crystals revealed an endothermic at 127.2 °C (Figure 5).

Pyrommelitic diimine has a high melting point (i.e., > $350 \,^{\circ}\text{C}$ as determined by DSC) and exhibits low solubility in most solvents. For that reason, we found the Kofler contact method as unsuitable for screening experiments. DSC thermogram of the physical mixture did not show any thermal events but the lamotrigine melting. In spite of that fact and due to fragment molecular similarity with **ptl**, we expected existence of cocrystals with **pmd**. Dry grinding experiments did not yield the cocrystal, as the mechanochemical treatment of the **lam:pmd** mixtures results in the formation of an amorphous phase. Nevertheless, we were able to form compound **2** after 30 min of solvent drop



Figure 10. Contact area of **lam–ipa** at about 100 °C. Eutectic (D) is completely melted making cocrysatlline phase (C) separated from **lam** solid (B). **ipa** is present in liquid state (A).

grinding involving DMF as solvent. The reaction yields were also found to be proportional with the amounts of DMF used, as DMF is built into the crystal lattice during cocrystal formation (Figure S7). Single crystals of 2 were also isolated from DMF. DSC thermogram exhibits a broad endothermic peak at 188.0 °C that corresponds to the desolvation of DMF (Figure 5).

3.3.1. Crystal Structure Analysis. Lam:Ptl (1:1) Cocrystal, **1**. The asymmetric unit of **1** comprises one **lam** and **ptl** molecule (Supporting Information Figure S8). The basic supramolecular unit is built up of **lam**—**lam** homosynthon via N—H…N hydrogen bond between N5 amino group of one **lam** and the triazine N4 atom of the other **lam** molecule (Supporting Information Table S2, Figure 11a).

Therefore, $R_2^2(8)$ ring motif is formed (aminopyridine dimer or motif 1 in lam structure itself,³ Figure 1). The lam dimers are further conjugated by both sides via noncentrosymmetric $R_3^2(8)$ heterosynthon formed between the other disposable N5 amino hydrogen atom and the ptl keto O2 atom and between the amino N3 group of another lam and the ptl keto O2 atom leading to the O2 atom acting as double proton acceptor. The combination of these two supramolecular units produces a $R_4^2(16)$ motif. Contrary to O2, the other **ptl** keto O1 atom participates in hydrogen bond formation as a single proton acceptor shaping $R_2^2(8)$ noncentrosymmetric heterosynthon with the N3 amino group and via N6-H1N6...N2 hydrogen bond between the ptl N6-H1N6 group and triazine N2 atom as a proton acceptor. Therefore, hydrogen-bonded zig-zag ribbons are formed spreading along c axis in alternating ABA fashion (A = ptl coformer molecule, B = lam molecule) (Figure 11b).

The **ptl** N6–H1N6 group forms at the same time N–H \cdots N hydrogen bond with the triazine N1 atom, but comparably



Figure 11. (a) Partial packing diagram of 1 showing supramolecular synthons with applied graph-set analysis. (b) Packing diagram of 1 viewed in *ac* plane. Hydrogen-bonded *zig-zag* ribbons are formed spreading along *c* axis in alternating ABA fashion (A = ptl coformer molecule, B = lam molecule).



Figure 12. Packing diagram of 2 showing chains of rings with the alternating $R_4^2(16)$ synthon and $R_2^2(8)$ heterosynthons in ABC fashion along *a* axis $(A = R_2^2(8)$ heterosynthon between two **pmd** molecules, $B = R_2^2(8)$ heterosynthon between **pmd** and **lam** molecules, $C = R_4^2(16)$ synthon between **pmd** and **lam** molecules).



Figure 13. Packing diagram of 3 showing chains of rings established by $R_4^2(16)$ and $R_2^2(8)$ N-H…N homosynthons with inserted layers which contains AAB array of dichlorophenyl **lam** rings and **caf** molecules. The chains of rings and non-hydrogen bonded layers spread along *c* axis in an alternating fashion.

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weaker than N6–H1N6…N2 hydrogen bond. The **lam** and **ptl** coformer molecule are further interlinked via C4–H4…O2 and C14–H14…Cl2 hydrogen bonds (Supporting Information Table S2). The **lam** molecules are mutually joined via C5–H5…Cl1 and C6–H6…Cl1 intermolecular hydrogen bonds.³⁹

3.3.2. Lam:Pmd:DMF Solvate Cocrystal (1:1:1), 2. The asymmetric unit of 2 consists of lam molecule, pmd coformer molecule and DMF solvent molecule (Supporting Information Figure S9). The disorder of DMF keto and methyl group is described in section 2.10. Both conjugated structural motifs $R_2^2(8)$ homosynthon (formed via N5–H2N5…N4 hydrogen bond, Supporting Information Table S2) and noncentrosymmetric $R_2^2(8)$ heterosynthon (formed via N3-H2N3...O5 and N5-H1N5...O5 hydrogen bonds, Supporting Information Table S2) forming $R_4^2(16)$ basic supramolecular unit are preserved in 2. But, unlike in 1, the heterosynthon in 2 originates from the keto oxygen double acceptor O5 atom of the solvent DMF molecule via N5-H1N5-05 (Supporting Information Table S2). The $R_4^2(16)$ synthon alternates with $R_2^2(8)$ synthon (formed via N3-H1N3····O2 and N7-H1N7...N2 hydrogen bonds between lam and pmd molecules) and $R_2^2(8)$ synthon (formed via N6–H1N6…O3 bond) between two **pmd** molecules in ABC fashion into ribbons spanning along a axis (Figure 12).

The ribbons are interlinked along c axis by C20A-H20A···O3 hydrogen bond between aldehyde C-H group and the diimide keto oxygen atom O3 as well as by C4-H4…O4 hydrogen bond formed between dichlorophenyl C-H group of lam molecule and diimide keto O4 atom (Supporting Information Table S2). It is interesting that diimide keto O1 atom does not participate in the hydrogen bond formation with lam molecule. It only forms hydrogen bonds with methyl and methylene groups of DMF molecule (with both major A and minor B component). By a careful inspection of Supporting Information Table S2, one can observe that the assembling of DMF molecule with pmd molecule is not the same for the A and B components (C20A-H20A···O3, C22A-H22A···O1, and C22A-H22B···N1 bonds versus C21B-H21F···O1, C22B-H22F…O3, and C21B-H21D…Cl2 bonds). The latter hydrogen bond is at the same time the only hydrogen bond with the lam chlorine atom acting as a proton acceptor.

3.3.3. Lam:Caf:3-Pentanone Solvate Cocrystal (2:1:0.64), 3. The asymmetric unit of 3 contains two crystallographically independent lam molecules (denoted as A and B), one caf coformer molecule and 3-pentanone solvent molecule (Supporting Information Figure S10). Hydrogen bonding architecture is the most complex in 3 in comparison with other three cocyrstal structures. This cocrystal structure imitates the basic supramolecular unit $R_4^2(16)$ like in 1 formed between two lam molecules mutually and their assemblies with caf molecule. That includes both supramolecular units: $R_2^2(8)$ homosynthon and $R_3^2(8)$ heterosynthon (Figure 13 and Supporting Information Table S2).

The additional feature of homosynthon is that does not shape the centrosymmetric dimer, since it occurs between conformationally different **lam** molecules A and B (N5A–H5A1…N4B and N5B–H5B2…N4A hydrogen bonds). The heterosynthon $R_3^2(8)$ (N3B–H3B2…O1 and N5A–H5A2…O1, as well as N3A-H3B1…O2 and N5B–H5B1…O2 hydrogen bonds) is formed like in 1 and unlike in 2 with **caf** coformer molecule and not with 3-pentanone solvent molecule. The feasible reason for that is owing to steric demands of 3-pentanone solvent molecule. The ribbons (or chains of rings) spreading along *a*



Figure 14. (a) Packing diagram of 4 showing supramolecular unit spreading along c axis. (b) Packing diagram of 4 viewed in ac plane. The chain of triazine **lam** rings parallel to c axis interchanges with the layer of hydrogen bonded dichlorophenyl rings and **ipa** molecules along a axis. **ipa** and dichlorophenyl rings are almost perpendicularly oriented in relation to triazine rings.

axis are formed by an alternated array of supramolecular assembly denoted as $R_4^2(16)$ and noncentrosymmetric $R_2^2(8)$ homosynthon shaped between A and B lam molecules (via N3B-H3B2...N2A and N3A-H3A1...N2B hydrogen bonds). Since the caffeine keto atoms O1 and O2 act as a double proton acceptor in the $R_3^2(8)$ heterosynthon formation they simultaneously act as a span between ribbons. Thus, caf coformer molecules are sandwiched between dichlorophenyl lam rings in a AAB fashion (A = dichlorophenyl ring, B = caf molecule). Final supramolecular assembling can be described as a chains of rings established by $R_4^2(16)$ and $R_2^2(8)$ synthons with inserted layers which contains AAB array of dichlorophenyl lam rings and caf molecule. Such formed 3D hydrogen pattern propagates along c axis in an alternating fashion (Figure 12). Hydrogen bonding patterns that include 3-pentanone solvent molecule includes keto O3 atom acting as a the double proton acceptor in two hydrogen bonds C7-H7A···O3 and C8-H8C···O3 (Supporting Information Table S2) with caf methyl groups, and



Scheme 2. Supramolecular Synthons Found in lam Cocrystals (1-4) and Their Correlation with A, B, C, and D Motif Notation

several hydrogen bonds of C–H···N type between methyl C9 and methylene C12 groups of lower Lewis acidity and triazine nitrogen atoms of both lamotrigine molecules A and B (C9–H9B···N1A, C9–H9B···N2A, C12–H12B···N2A, C9– H9C···N4B; Supporting Information Table S2). Thus, 3-pentanone molecule is not included in hydrogen bonded lam:caf 3D network. Two chlorine atoms are involved in C–H···Cl hydrogen bonds generating C6B–H6B···Cl1B and C8–H8A···Cl2A hydrogen bonds with the caf C6 and C8 methyl group (Supporting Infromation Table S2).

3.3.4. Lam:lpa Cocrystal (1:1), 4. Asymmetric unit of 4 involves one lam molecule and one ipa molecule (Supporting Information Figure S11). The orientational disorder of one of the aldehyde groups (possible positions are denoted as A and B) is described in section 2.10. This different spatial orientation of the aldehyde group within the crystal structure can result in different hydrogen bonding patterns with A and B aldehyde positions i.e. their supramolecular assembling is different. Basic supramolecular $R_2^2(8)$ homosynthon designed by the N4 triazine acceptor atom and the N3 amino group of centrosymmetrically related lam molecule presenting in all 1 - 3 structures (in 1 - 3 between amino N5 group and the N4 triazine atom) is found in 4, too (via hydrogen bond N3–H2N3…N4; Supporting Information Table S2 and Figure 14a).

On the contrary to 1-3 structures, the supramolecular $R_3^2(8)$ homosynthon in 4 which is abutted on the $R_2^2(8)$ both sides, is built up via N5–H1N5…N2 and N3–H1N3…N2 hydrogen bonds. Therefore, the motif D in Table 2, which is characteristic for crystal structure of **lam** molecule itself, is accomplished in 4. The H1N3 atom of the N3 amino group takes part in bifurcated hydrogen bond with N2, but also with the N1 triazine atom. Taking into account N3–H1N3…N1 hydrogen bond the synthon $R_3^2(8)$ can be described as $R_3^2(9)$ one. The combination of $R_2^2(8)$ and $R_3^2(8)$ synthons results in $R_4^2(16)$ supramolecular unit spreading along c axis. The **ipa**

molecule is clasped to this 2D chain of rings by the N5– H2N5…O1, C17A–H17A…Cl2, C13–H13…Cl2, and C11– H11…N1 hydrogen bonds (Supporting Information Table S2). Two different orientations of the aldehyde group denoted as A and B form different types of hydrogen bonds: O2A acts as a proton acceptor, forming interaction with **lam** aromatic C4–H4 group, while O2B participates into C15–H15…O2B acting between two **ipa** molecules. There is another hydrogen bond between two **ipa** molecules C17B–H17B…O1. Thus, the chain of the triazines **lam** rings parallel to *c* axis interchanges along *a* axis with the layer of hydrogen bonded dichlorophenyl rings and **ipa** molecules almost perpendicularly oriented in relation to the triazine rings (Figure 14b).

Correlating (Scheme 2) synthons found in 1-4 with motifs 1 and 2 in lam structure itself, as well as with established synthons by CSD survey, in all four cocrystal structures (1-4) robust amino pyrimidine lam dimer retains showing that breaking the robust dimer synthon is not a demand for the lam cocrystals design and their formation.

The role of carbonyl group in supramolecular synthons formation in structures 1–4 is different. While it is demonstrated that carbonyl group participates in formation of motif A (in structure 3), motif B (in structure 2) and motif AB (in structure 1), structure 4 preserves motif D which does not include participation of carbonyl group. In addition, the N–H group of the coformers participates in the formation of strong hydrogen bond establishing robust synthon described as the N–H(amino)···O(carbonyl) (denoted as motif B) which is analogous to the N⁺–H(amino)···O⁻(carboxy) found in salts. Regarding synthon hierarchy in **Iam** multicomponent solids we conclude that motif B is dominant in comparison to motif A. The presumption for motif AB formation is first generation of motif B containing strong N–H(amino)···O(carbonyl) hydrogen bond following by motif A emergence (Scheme 2).

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4. CONCLUSION

Lam is a relevant API, and its poor aqueous solubility stressed the need for the development of lam-based salts and cocrystals with enhanced solubility. In this context, lam has been previously subjected to cocrystal formation using carboxylic acids as cocrystal formers. Considering the relatively low number of pharmaceutically acceptable carboxylic acids, as well as the high number of amides, aldehydes and ketones listed in the GRAS and EAFUS lists, we turned to explore the utility of later classes of compounds in the preparation of lam cocrystal. Our efforts resulted in the formation of four novel lam cocrystals based on amides and aldehydes, namely lam:ptl cocrystal (1:1) 1, lam:pmd:DMF solvate cocrystal (1:1:1) 2, lam:caf:3-pentanone solvate cocrystal (2:1:0.64) 3 and lam:ipa cocrystal (1:1) 4.

The cocrystals were discovered using a screening method based on HSM and DSC. The results obtained using the combined HSM/DSC screening methods were also compared to those obtained during mechanochemical cocrystal screens. Notably, the HSM/DSC screening method was shown to be as sufficient as neat and solvent-drop grinding: two mechanochemical screening methods being generally regarded as highly efficient and suitable for cocrystal screening. Considering the small amounts of material required for HSM/DSC cocrystal screens, it appears reasonable to suggest the use of this method as standard when only small amounts of material are available for screening purposes, or when safety considerations do not allow the use of larger quantities.

Screening of **lam** cocrystals based on solvent evaporation technique from water and common organic solvents resulted in numerous solved **lam** crystalline structures (solvates) and not the cocrystals. This negative result in cocrystal formation emphasizes the valuable screening results based on HSM and DSC showing that under specific crystallization conditions cocrystals can be isolated.

Structural studies of the cocrystals revealed that carbonyl and amide functionalities participate in the formation of supramolecular motifs that have so far been observed in **lam** multicomponent solids. In all four cocrystal structures robust amino pyrimidine **lam** dimer retain showing that breaking the robust dimer synthon is not a demand for **lam** cocrystals design and their formation.

Finally, the **lam:caf** cocrystal represents a solids containing two APIs that are used for the same indication treatment of headaches. Since it has been recently shown recently fix-dose⁴⁰ combinations have a greater therapeutic effect in comparison to separately administrated components,⁴¹ it appears that the preparation of the **lam:caf** cocrystal provides a new alternative for solid-dosage-form formulations for the treatment of headaches.

ASSOCIATED CONTENT

S Supporting Information

Details relating to the CSD survey, table of hydrogen bonds and interactions geometry, TGA thermogram of the lam:caf:3pentanone solvate, FT-IR of desolvated form of lam:caf cocrystal and its XRPD, XRPDs of ground physical mixtures, ORTEP views for all cocrystal structures 1–4. This material is available free of charge via the Internet at http://pubs.acs.org. The CIFs of compounds 1-4 (CCDC deposition numbers 844580 – 844583) can be obtained free of charge at www.ccdc. cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223–336033; email: deposit@ccdc.cam.ac.uk]. Tables of structure factors are available from the authors by request.

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Notes

The authors declare no competing financial interest.

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