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Article

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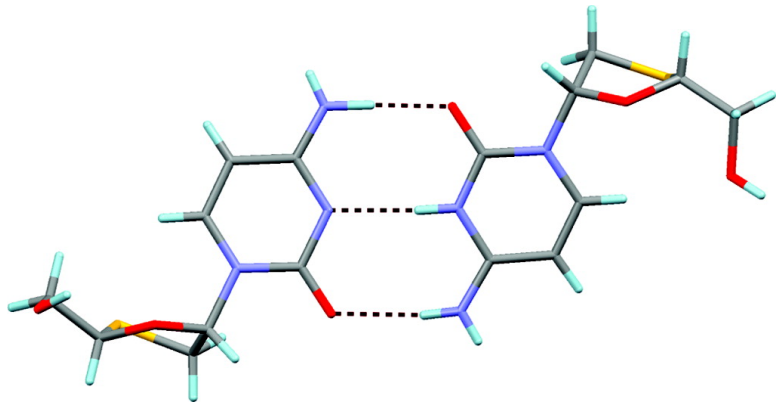

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Co-Crystals of the Anti-HIV Drugs Lamivudine and Zidovudine

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ABSTRACT: Co-crystal forming abilities of the two anti-HIV drugs lamivudine and zidovudine were studied. A study of five crystal structures was carried out to investigate the general applicability of the retrosynthetic approach in the design of new co-crystals. This analysis of co-crystals and salt structures showed a complete to partial success, and in one case, a total failure to obtain the predicted synthon. Both screening strategies and retrosynthetic methods may be appropriate for the discovery of new active pharmaceutical ingredients co-crystals.

Introduction

Co-crystals, or multicomponent molecular crystals,[1,2] attract wide interest in the crystal engineering community because of fundamental and practical reasons.[3,4] Of course, it has been known for more than 150 years that molecular solids may be obtained that contain, within them, two or more distinct chemical compounds,[5−7] and accordingly, co-crystal formation per se is not of intrinsic novelty. However, during the last 25 or so years, there has been a more sharpened focus on the situations when and the reasons why these multicomponent crystals are formed.[8] These define the fundamental reasons why co-crystals are being studied today. The practical reasons have to do with the fact that co-crystals of active pharmaceutical ingredients (API) may be attractive candidates for protection of intellectual property in terms of their particular novelty, utility, and nonobviousness.[9]

An obvious question, in the crystal engineering context, is whether it is easier or more straightforward to design the crystal structure of a multicomponent organic crystal when compared to the crystal structure of a pure compound. The answer to this question is by no means straightforward. Many years ago, one of us wrote[10] that "the very manifestation of co-crystallisation in a particular system implies that it is possible to dissect and analyse a few significant molecular interactions from amongst the larger number that actually determine the stable crystal structure. In other words, it is usually easier to understand why two molecules may co-crystallise rather than why a single molecule adopts a particular crystal structure in preference to another." With the hindsight of the 23 intervening years that have elapsed since that paper was published, it could now be said that the first statement in the quote might equally well apply to crystallization of a single compound as it does to co-crystallization of two compounds: the idea of identifying specific interactions in a crystal structure leads directly to the concept of the supramolecular synthon.[11,12] As for the second statement, it would probably be accepted even today, but understanding a crystal structure is not the same as designing or predicting a structure.

Considerable progress has been made in the definition of protocols for the design of co-crystals, notably by Zaworotko[4] but also by others,[8] using the retrosynthetic approach that is afforded by the concept of the supramolecular synthon. However, there is a difference between designing a crystal structure of a co-crystal by invoking chemically reasonable synthons based on hydrogen bonding and also other significant intermolecular interactions,[13] and actually obtaining such a co-crystal in the laboratory. This difference between expectation and realization is largely a matter of kinetics, solvent choice, and solubility. These are unavoidable issues. More avoidable are issues pertaining to an incomplete understanding of the supramolecular chemistry of the API and the selected co-crystal former. But even here, there are limits. Accordingly, is there a case for adopting a screening approach for new co-crystals?

With these concerns in mind, we studied the co-crystal forming abilities of the APIs lamivudine (2′,3′-dideoxy-3′-thiacytidine) and zidovudine {1-[(2*R*,4*S*,5*S*)-4-azido-5-(hydroxymethyl)tetrahydrofuran-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione} (Scheme 1). These APIs are potent nucleoside analogue reverse transcriptase inhibitors and are commonly used as anti-HIV drugs. Lamivudine can inhibit both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B.[14] It is administered orally being rapidly absorbed with a bioavailability of over 80%. Zidovudine does not destroy the HIV infection, but only delays the progression of the disease and the replication of the virus.[15] The azido group increases the lipophilic nature of the molecule, allowing it to cross cell membranes easily by diffusion and thereby also to cross the blood−brain barrier. Cellular enzymes convert zidovudine into the effective 5′-triphosphate form.

No co-crystals of lamivudine and zidovudine have been reported so far in the literature. As a design strategy, one may

Scheme 1. Co-Crystals and Salts Studied in This Paper

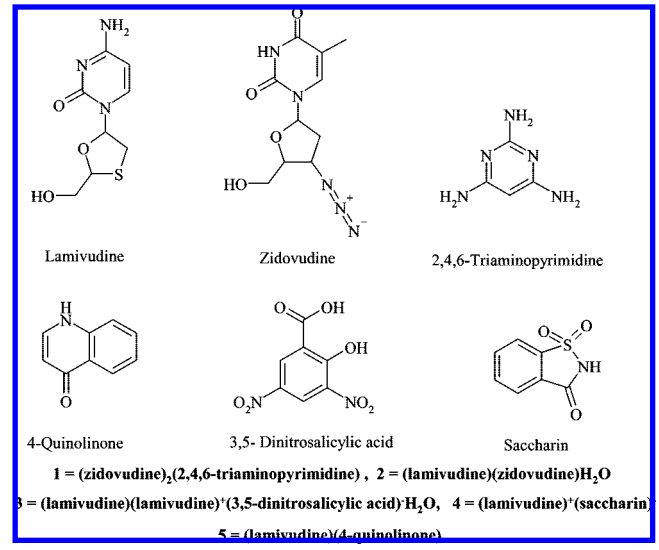

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Table 1. Crystallographic Data and Structure Refinement Parameters

co-crystal/salt	**1**	**2**[a]	**3**	**4**[a]	**5**
structural formula	$2(C_{10}H_{13}N_5O_4)$ $(C_4H_7N_5)$	$(C_{10}H_{13}N_5O_4)$ $(C_8H_{11}N_3O_3S)$ (H_2O)	$(C_8H_{11}N_3O_3S)$ $(C_8H_{12}N_3O_3S)$ $(C_7H_4N_2O_7)$ H_2O	$(C_8H_{12}N_3O_3S)$ $(C_7H_4NO_3S)$	$(C_8H_{11}N_3O_3S)$ (C_9H_7NO)
formula weight	659.63	514.54	705.6	412.44	538.47
crystal system	monoclinic	monoclinic	monoclinic	orthorhombic	monoclinic
space group	*C*2	$P2_1$	$P2_1$	$P2_12_12_1$	$P2_1$
T (K)	298(2)	298(2)	298(2)	100(2)	298(2)
a (Å)	22.737(5)	8.6899(10)	7.719(4)	5.3464(6)	12.312(4)
b (Å)	8.422(2)	7.2501(9)	9.124(5)	13.7459(14)	5.0847(15)
c (Å)	19.036(5)	18.504(2)	21.059(12)	22.738(2)	14.444(4)
α (°)	90	90	90	90	90
β (°)	125.881(3)	92.506(2)	93.296(8)	90	93.955(5)
γ (°)	90	90	90	90	90
V (Å^3)	2953.5(12)	1164.7(2)	1480.7(14)	1671.1(3)	902.1(4)
Z	2	2	2	2	2
ρ_{calc} (g/cm^3)	1.477	1.394	1.578	1.639	1.394
μ (mm^{-1})	0.115	0.201	0.263	0.364	0.213
R_1 [$I > 2\sigma(I)$]	0.0918	0.0378	0.0596	0.0257	0.0777
wR_2	0.2914	0.1006	0.1760	0.0676	0.1853
goodness-of-fit	1.060	1.034	1.032	1.051	1.006
reflns collected	13213	11952	7342	6667	9390
unique reflns	4964	4557	4705	3197	3540
observed reflns	2120	4206	3981	3117	2102
CCDC no.	694082	687160	694083	VAWPIT	694084

[a] Reported in earlier studies. See refs 34 and 35, respectively.

note that these API molecules have multiple hydrogen bond donor and acceptor groups so that multipoint synthons are conceivable.[16,17]

Experimental Section

Sample Preparation and Crystallization. (Zidovudine)$_2$(2,4,6-triaminopyrimidine) (1). Equimolar quantities of zidovudine (53.4 mg) and 2,4,6-triaminopyrimidine (25 mg) were ground together for 10 min in a mortar and pestle with the addition of a few drops of MeOH. The resulting material was dissolved in 15 mL of MeOH. The solution was allowed to evaporate for 2 days. A single crystal was selected for single crystal X-ray diffraction from the resulting crystalline material.

(Lamivudine)(zidovudine)H$_2$O (2). Lamivudine (22.9 mg) and zidovudine (26.7 mg) were taken in equimolar quantity and dissolved in 10 mL of EtOH. The solution was allowed to evaporate for 2 days. Single crystals were obtained easily.

(Lamivudine)(lamivudine)$^+$(3,5-dinitrosalicylic acid)$^-$H$_2$O (3). Lamivudine (22.9 mg) and 3,5-dinitrosalicylic acid (22.8 mg) were taken in equimolar quantity and dissolved in 10 mL of 1:1 MeOH−DMF. The solution was allowed to evaporate for few days to yield single crystals of the hydrate.

(Lamivudine)$^+$(saccharin)$^-$ (4). Lamivudine (45.8 mg) and saccharin (36.6 mg) were taken in equimolar quantity and ground together for 10 min in a mortar and pestle. The resulting material was dissolved in 10 mL of 1:1 $CHCl_3$−MeOH. The solution was allowed to evaporate for 2 days and suitable single crystals were obtained.

(Lamivudine)(4-quinolinone) (5). Lamivudine (22.9 mg) and 4-quinolinone (14.5 mg) were taken in equimolar quantity and dissolved in 10 mL of EtOH. The solution was allowed to evaporate for 2 days to give crystals of the 1:1 adduct.

X-ray Crystallography. X-ray diffraction intensities for all the co-crystals reported in this paper were collected at 298 K on a Bruker SMART 4K CCD diffractometer (Bruker Systems Inc.) using Mo *K*α X-radiation.[18] Data were processed using the Bruker *SAINT* package[19] with structure solution and refinement using *SHELX97* (Sheldrick, 1997).[20] The structures of all the co-crystals were solved by direct methods and refined by full-matrix least-squares on F^2. H-atoms were located from the difference Fourier map in both the structures and refined freely with isotropic displacement parameters. Crystal data and details of data collections, structure solutions and refinements are summarized in Tables 1 and 2. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as deposition nos. CCDC 694082−694084 (see also Table 1). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 lEZ UK (fax: + 44 (1223) 336 033; e-mail: deposit@ccdc.cam.ac.uk.

Table 2. Hydrogen Bond Metrics for the Co-Crystals and Salts Reported in This Study

co-crystal	interaction	*d*/Å (H···A)	*D*/Å (X···A)	*θ*/deg X−H···A
1	$N_{(10)}$−H···$N_{(15)}$	2.02	2.978 (4)	158
	$N_{(11)}$−H···$O_{(4)}$	2.22	3.213 (5)	169
	$N_{(14)}$−H···$O_{(8)}$	2.16	3.094(5)	154
	$N_{(5)}$−H···$N_{(12)}$	2.04	3.000(5)	159
	$O_{(6)}$−H···$N_{(3)}$	2.40	2.944(4)	114
	$N_{(13)}$−H···$O_{(3)}$	1.78	2.791(4)	178
	$N_{(13)}$−H···$O_{(4)}$	2.07	3.049(5)	164
	$N_{(16)}$−H···$O_{(7)}$	1.86	2.851(4)	168
	$N_{(16)}$−H···$O_{(8)}$	2.05	3.049(5)	169
	$O_{(2)}$−H···$O_{(3)}$	2.35	2.851(4)	111
2	$N_{(8)}$−H···$O_{(4)}$	1.97	2.830(3)	159
	$O_{(8)}$−H···$N_{(7)}$	1.78	2.755(2)	173
	$O_{(2)}$−H···$O_{(6)}$	1.94	2.890(3)	163
	$N_{(8)}$−H···$O_{(3)}$	2.12	2.902(3)	132
	$O_{(8)}$−H···$O_{(1)}$	2.06	2.893(3)	142
	$N_{(5)}$−H···$O_{(8)}$	1.84	2.843(2)	171
	$O_{(6)}$−H···$O_{(7)}$	1.71	2.688(2)	175
3	$N_{(1)}$−H···$O_{(14)}$	1.88	2.839(7)	158
	$N_{(4)}$−H···$O_{(12)}$	2.12	2.983(7)	142
	$N_{(1)}$−H···$O_{(6)}$	1.79	2.797(6)	177
	$N_{(4)}$−H···$O_{(3)}$	2.03	2.853(6)	137
	$N^{(+)}{}_{(5)}$−H···$N_{(2)}$	1.83	2.836(5)	175
	$O_{(5)}$−H···$O_{(6)}$	2.27	2.916(6)	122
	$O_{(14)}$−H···$O_{(3)}$	1.89	2.860(5)	167
4	$N_{(4)}$−H···$O_{(1)}$	1.85	2.838(2)	165
	$N_{(4)}$−H···$N_{(1)}{}^{(-)}$	1.94	2.946(2)	171
	$N^{(+)}{}_{(3)}$−H···$O_{(6)}$	1.64	2.644(2)	170
	$O_{(2)}$−H···$O_{(4)}$	1.96	2.928(2)	169
5	$N_{(3)}$−H···$O_{(4)}$	1.98	2.934(7)	163
	$N_{(3)}$−H···$O_{(2)}$	1.92	2.828(6)	155
	$N_{(4)}$−H···$O_{(3)}$	2.01	2.827(7)	170
	$O_{(2)}$−H···$O_{(4)}$	1.81	2.633(3)	159

Results and Discussion

Both lamivudine and zidovudine contain multiple hydrogen bond donor and acceptor groups. These groups can be used for designing co-crystals of the two APIs. The cytosine fragment of lamivudine and the thymine fragment of zidovudine also appear to be able to form synthons with compounds containing complementary hydrogen bonding groups.

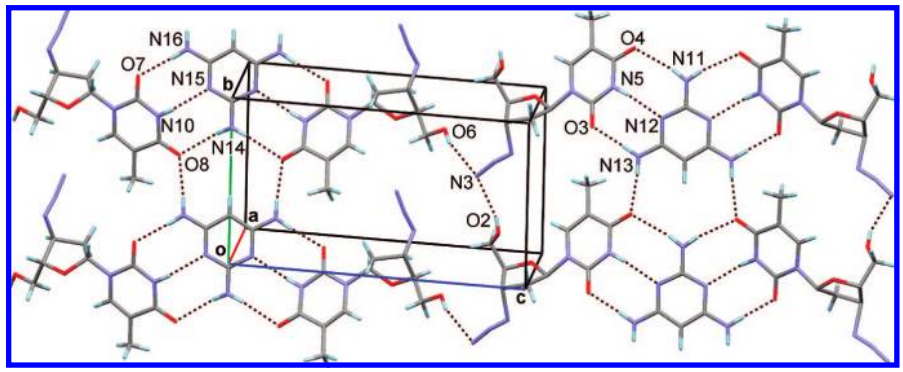


Figure 1. 2D arrangement of molecules in co-crystal **1** showing synthon **I**. Notice that two of these synthons constitute a trimer made up of two zidovudine molecules and one 2,4,6-triaminopyrimidine molecule, accounting for the 2:1 stoichiometry of the co-crystal.

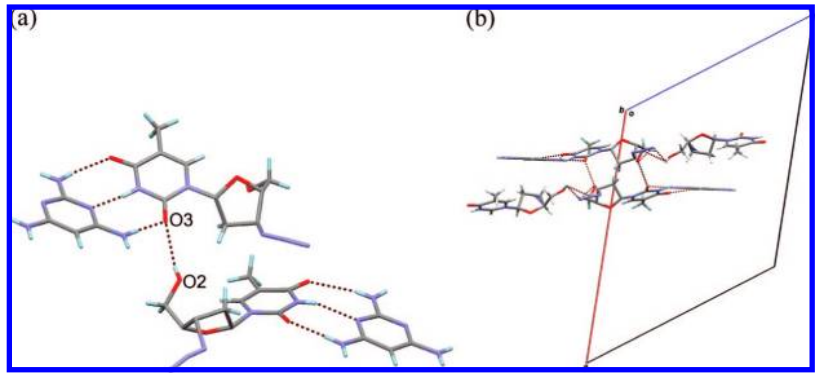


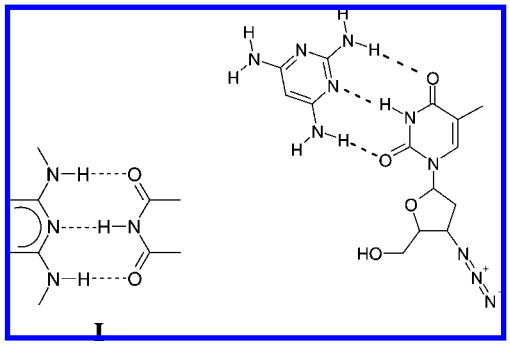
Figure 2. (a) O−H···O hydrogen bond between zidovudine molecules of different layers and (b) two layers held together by O−H···O hydrogen bonds.

Co-Crystal 1. (Zidovudine)$_2$(2,4,6-triaminopyrimidine). It appeared that the zidovudine molecule should form the three-point synthon **I** with suitable molecules (Scheme 2). Synthon **I** is very robust and reliable. It has been used in crystal engineering for many years. There are 76 cases of this synthon in the Cambridge Structural Database (CSD). Allen and co-workers reported that synthon **I** occurs in 97% of the cases where the requisite molecular components are available.[21] Whitesides prepared many molecular aggregates (rods, tapes, and rosettes) using this synthon and employing derivatives of cyanuric acid and melamine.[22] Lehn,[23] Reinhoudt,[24] and many others have also used this synthon in supramolecular design. Synthon **I** has been also used in applications such as supramolecular catalysis of photoinduced dimerization of fullerene.[25]

Co-crystal **1** takes space group *C*2 with two molecules of zidovudine and two half molecules of 2,4,6-triaminopyrimidine in the asymmetric unit. The trimer is made up of two zidovudine molecules and one molecule of 2,4,6-triaminopyrimidine and is held together by the expected three-point synthon **I**, which is a basic part of the crystal structure. These trimers are joined by two N−H···O hydrogen bonds to form an infinite 1D arrangement. This is further extended in two dimensions by O−H···N hydrogen bonds as shown in Figure 1. Additional O−H···O bonds between zidovudine molecules in adjacent 2D layers extends the structure to the third dimension (Figure 2).

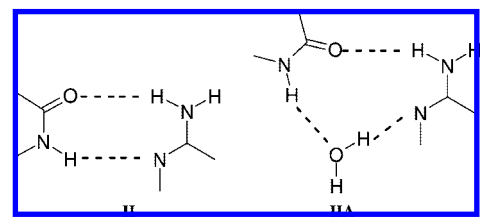
To summarize, rational design of this co-crystal based on retrosynthetic analysis works very well, and the expected synthon **I** is observed in the crystal structure. As a cautionary note, however, it should be stated that a co-crystallization experiment with zidovudine and melamine (2,4,6-triaminotriazine) did not yield any co-crystals.

Scheme 2. Three-Point Synthon I and Possibility of This Synthon between Zidovudine and 2,4,6-Triaminopyrimidine



Co-Crystal 2. (Lamivudine)(zidovudine)H_2O. Lamivudine and zidovudine molecules can, in principle, form synthon **II** with each other (Scheme 3). There are 78 hits for this synthon

Scheme 3. Predicted Two-Point Synthon II between Lamivudine and Zidovudine and Observed Synthon IIA in the Hydrated Co-Crystal



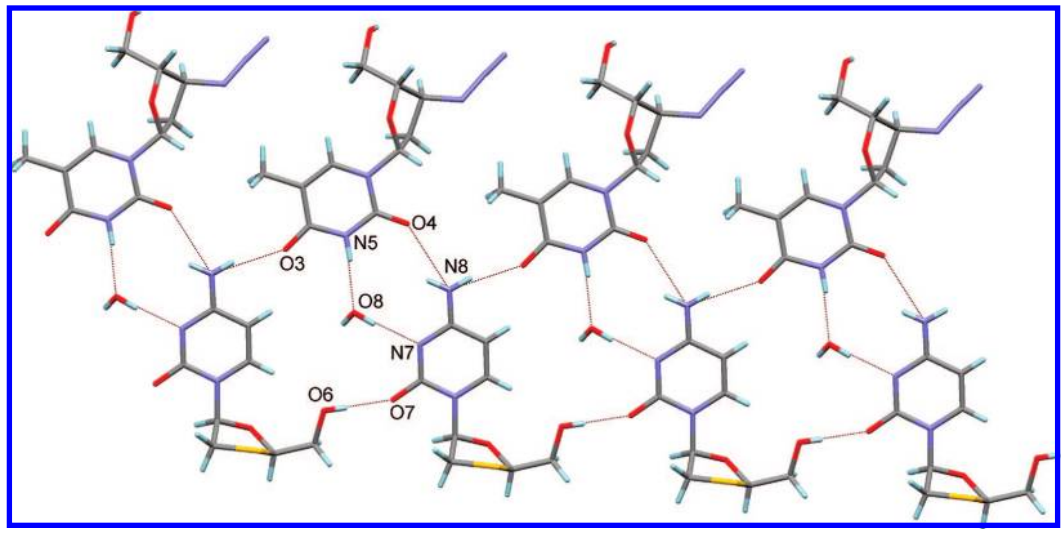


Figure 3. 1D ribbon type arrangement of lamivudine and zidovudine molecules in the crystal structure of co-crystal **2**.

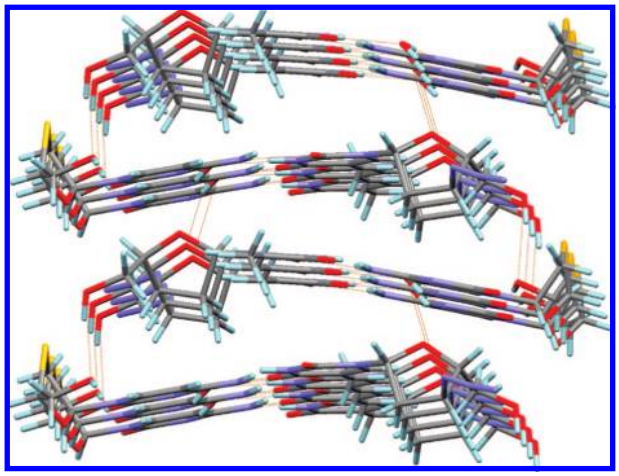


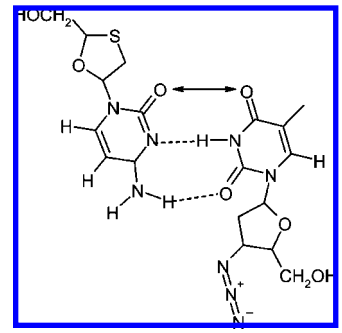
Figure 4. 1D ribbons from perpendicular view and interconnectivity between them in the crystal structure of co-crystal **2**.

in the CSD. Synthon **II** is also observed in the co-crystal of 4-amino-2-oxopyrimidine and 2,4-dioxo-5-fluoropyrimidine (CYTFUR01), which are model compounds for lamivudine and zidovudine respectively. Accordingly, we predicted a co-crystal between lamivudine and zidovudine based on the occurrence and reliability of synthon **II**.

Lamivudine and zidovudine indeed form a 1:1 co-crystal, **2**, in space group $P2_1$ but it is hydrated and the synthon formed is the extended **IIA** rather than **II**. These modules are connected through N−H···O and O−H···O hydrogen bonds to form a 1D ribbon as shown in Figure 3. The ribbons are further connected by O−H···O interactions between zidovudine and lamivudine as shown in Figure 4.

In this case, co-crystal formation occurs, but the observed synthon (**IIA**) is slightly different from the expected one (**II**) in that a molecule of water intervenes in the hydrogen bond pattern of the synthon. It is not really possible to confidently predict hydrate formation or solvate formation despite many rationalizations and correlations in this regard.[26] However, it is important to note here that a number of co-crystallization attempts from water free media resulted in no co-crystal formation. Clearly, hydration is a dominant theme here. It is difficult to rationalize the nonoccurrence of synthon **II**. Perhaps it could be argued that formation of **II** would result in

Scheme 4. Possible Carbonyl···Carbonyl Repulsion in the Putative Lamivudine−Zidovudine Co-Crystal with Non-Hydrated Synthon II



unacceptably large repulsions between the carbonyl groups in the two API fragments (Scheme 4).

Synthons **II** and **IIA** are broadly similar. In the CSD, there are five hits for synthon **IIA**. The strongest interaction (N−H···O) in the predicted synthon **II** is also observed in the experimental synthon **IIA**. The intermediacy of water in a hydrogen bonded array is a common theme in structural chemistry. Synthon **IIA** resembles water or alcohol bridged carboxylic acid dimer synthons, which are quite common in the literature.[27] Water is also inserted in many hydrogen bonded arrays in biological structures.[28] To summarize, synthons **II** and **IIA**, while not identical, are equivalent and in this respect synthon theory is moderately successful in this case.

Apart from the structural features one should also appreciate that co-crystal **2** is constituted with two APIs. A combination of these two drugs is marketed as a physical mixture under the trade name Combivir, which is claimed to be more effective than the individual drugs.[29] Generally, combinations of two or more drugs are not preferred because of possible mismatches of their physical properties which could lead to problems in drug delivery. It is not known if any such problems have arisen with Combivir. However, its marketing as a co-crystal instead of a physical mixture might be useful in as yet unforeseen situations.

Co-Crystal 3. (Lamivudine)(lamivudine)$^+$(3,5-dinitrosalicylic acid)$^-$H$_2$O. Hydrogen bonded synthons formed between carboxylic acids and 2-aminopyridines (or 2-aminopyrimidines) are very common.[30] It was expected therefore that lamivudine

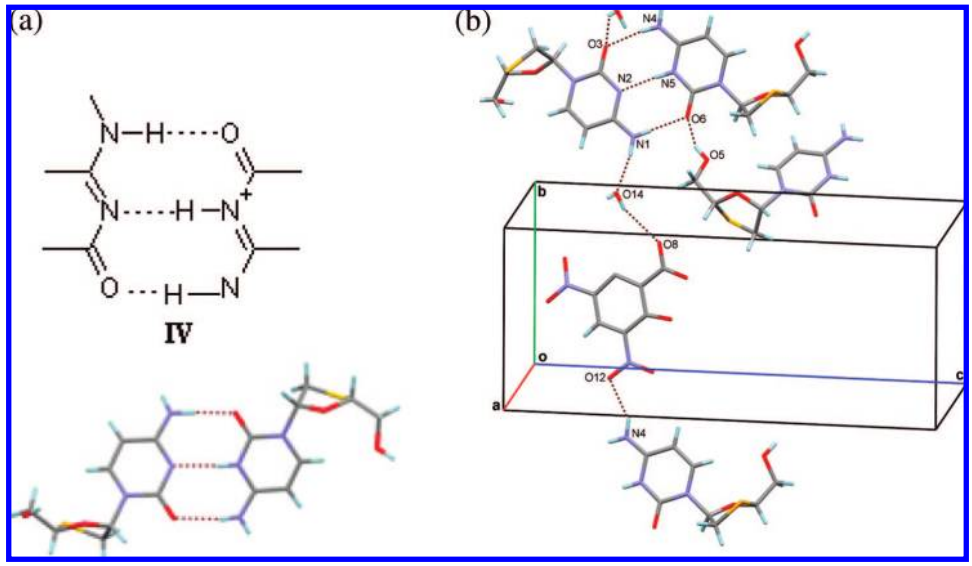


Figure 5. (a) Dimer made up of neutral and charged lamivudine molecules through a three-point synthon **IV**. (b) Important hydrogen bonds in co-crystal **3**.

would form a synthon such as **IIIA** with acids. Proton transfer is also common in such cases[31] and would lead to a synthon such as **IIIB** (Scheme 5). There are 124 and 351 hits for synthons **IIIA** and **IIIB** in the CSD. It was noted that cytosine which is a model compound for lamivudine forms a salt with 3,5-dinitrosalicylic acid with synthon **IIIB**.[32] Accordingly, co-crystallization of lamivudine with 3,5-dinitrosalicylic acid was attempted.

Co-crystal **3** adopts space group $P2_1$ with one $(\text{lamivudine})^+$ cation, one $(\text{3,5-dintrosalicylate})^-$ anion, one neutral molecule of lamivudine, and one water molecule in the asymmetric unit. The structure contains a very complex hydrogen bonding pattern with multiple hydrogen bonding donors and acceptors. Rather than forming synthons such as **IIIA** or **IIIB**, the important synthon here (**IV**) is formed by three-point assembly between neutral and cationic lamivudine fragments (Figure 5a). These dimers give rise to a complex 3D hydrogen bonded structure (Figure 5b).

The structure of co-crystal **3** is very different from the predicted one. Of course, it would have been difficult to predict partial protonation of lamivudine which is a prerequisite for the observed three-point synthon **IV** of which there are 16 occurrences in the CSD,[33] all of which occur between neutral and protonated cytosine fragments.

Salt 4. $(\text{Lamivudine})^+(\text{saccharin})^-$. It is not difficult to predict that lamivudine would also form a salt with the moderately acidic saccharin (pK_a 2.2). Lamivudine saccharinate, **4**, crystallizes in the space group $P2_12_12_1$ with one $(\text{lamivudine})^+$ cation and one $(\text{saccharin})^-$ anion in the asymmetric unit.[35] The saccharinate fragments form a layered structure which is characterized by a very stable two-point synthon constituted with $N^{(+)}-H\cdots O$ and $N-H\cdots N^{(-)}$ hydrogen bonds (Figure 6). These dimers are further linked with $N-H\cdots O{=}C$ and $O-H\cdots O{=}S$ hydrogen bonds to form a layer-like structure.

Unlike co-crystal **3**, there is complete rather than partial protonation of lamivudine in **4**. Accordingly, synthon **IV** is not observed. Rather, a two-point synthon (**V**) constituted with $N^{(+)}-H\cdots O$ and $N-H\cdots N^{(-)}$ hydrogen bonds is observed. Synthon **V** was not specifically designed but if it is given that complete proton transfer will occur, this particular outcome looks quite reasonable and perhaps it might even have been

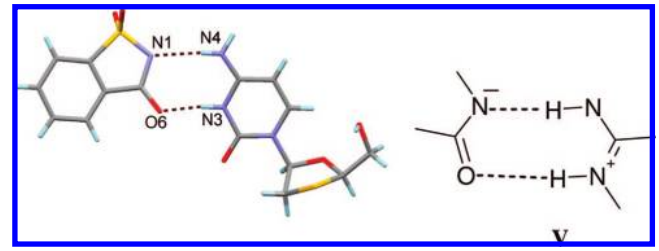


Figure 6. Two-point synthon observed in lamivudine saccharinate.

predicted in advance. The difficulty in all these examples that involve acid−base equilibria is that there is no way of controlling and/or predicting partial versus complete protonation of the base (lamivudine in this case) without careful monitoring of the pH of the solution, and this seems to dramatically influence the outcome of crystallization.

Ab initio calculations performed using the Gaussian-03 software at the HF/6-31+G(d,p) level of theory gave a hydrogen bond stabilization energy of −96.99 kcal/mol for the model $(\text{lamivudine})^+(\text{saccharin})^-$ system having the two-point synthon **V**. This supersedes the net hydrogen bond stabilization energy in the model $(\text{lamivudine})(\text{lamivudine})^+$ system with the three-point synthon **IV** by about −56.45 kcal/mol. This suggests that there is an energetic preference for the more stable two-point synthon **V** over the three-point synthon **IV**, and that such a preference favors the complete protonation of lamivudine in the $(\text{lamivudine})^+(\text{saccharin})^-$ system.

Co-Crystal 5. (Lamivudine)(4-quinolinone). Co-crystal **5** was not designed with a retrosynthetic approach but obtained during screening.[36] It crystallizes in space group $P2_1$ with one molecule of lamivudine and one molecule of 4-quinolinone in the asymmetric unit. The structure is stabilized by multiple $N-H\cdots O$ and $O-H\cdots O$ hydrogen bonds (Figure 7). The amino group of lamivudine forms $N-H\cdots O$ hydrogen bonds with the carbonyl O-atom of 4-quinolinone and the OH group of another lamivudine molecule. This latter lamivudine molecule forms an $O-H\cdots O$ hydrogen bond with the carbonyl O-atom of yet another 4-quinolinone molecule resulting in a helical arrangement of hydrogen bonds. From an inspection of the

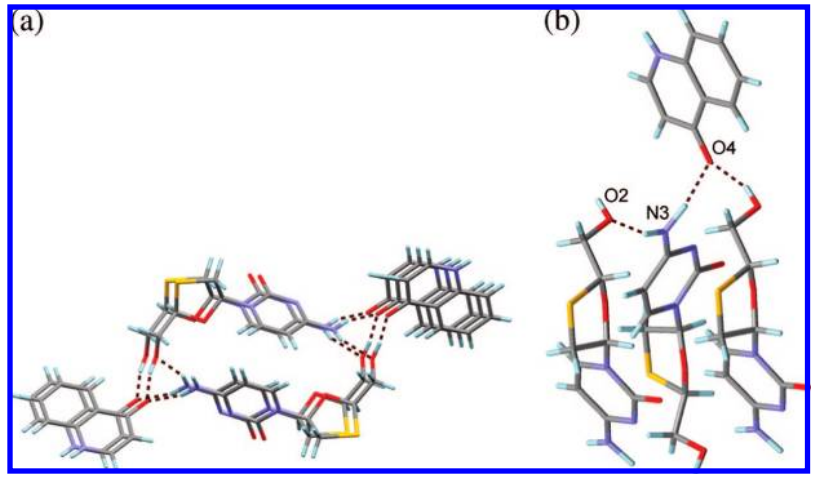
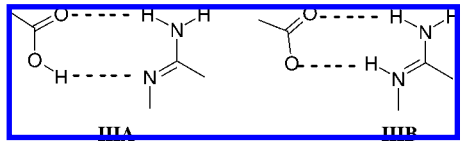


Figure 7. Helical arrangement of N−H···O and O−H···O hydrogen bonds in co-crystal **5** seen from different orientations.

Scheme 5. Carboxylic Acid−Aminopyridine Synthons



crystal structure of **5**, it would appear that it would be difficult to predict in advance.

This example emphasizes the importance of co-crystal screening in obtaining new co-crystals of APIs. If one were to rely only on synthon theory, it is highly unlikely that 4-quinolinone would be selected as a co-crystal former for lamivudine.

All five co-crystals and salts **1**−**5** described here represent chemical extensions of lamivudine and/or zidovudine. The five crystal structures are very different from one another, and when taken together they address the pertinent question as to the general applicability of the retrosynthetic approach for the design of API co-crystals.

Co-crystal **1** is formed successfully based on retrosynthetic analysis and the predicted synthon is observed in the experimental structure; the API is equivalent to the model compound. Co-crystal **2** was designed on the basis of a two-point dimer synthon but was actually obtained as a hydrate with the predicted synthon being slightly modified by the water molecule, the presence of which is largely unpredictable. This example can be treated as a moderate success of synthon theory. Co-crystal **3**, which is an example of an acid−base interaction, is distinct. The predicted structure is quite different from the observed one and synthon theory fails in this case. Salt **4** is another example of an acid−base interaction, but unlike **3**, protonation of the base by the acid is complete and the outcome is different from that in **3**. Co-crystal **5** was not planned on the basis of retrosynthetic analysis but was obtained during a screening of the API with various compounds containing hydrogen bond acceptors and donors. Although this structure was not predicted, the hydrogen bonding and other structural features are entirely reasonable.

Conclusions

Synthon theory works well for the prediction of co-crystals of simple compounds. However, in the case of a more complex molecule such as the API lamivudine the presence of multiple hydrogen bonding donors and acceptors creates difficulties in crystal structure prediction. Partial protonation of the API, which is hardly predictable, is also a complicating factor. Screening methods provided a co-crystal, the crystal structure of which, although reasonable, was not predictable. A balance between the retrosynthetic approach and co-crystal screening might well offer the best strategy to rapidly obtain a large number of API co-crystals.

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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