Electronic Supplementary Information

Why lamivudine assembles into double-stranded helices in crystals? Salt heterosynthon *versus* base-pairing homosynthon

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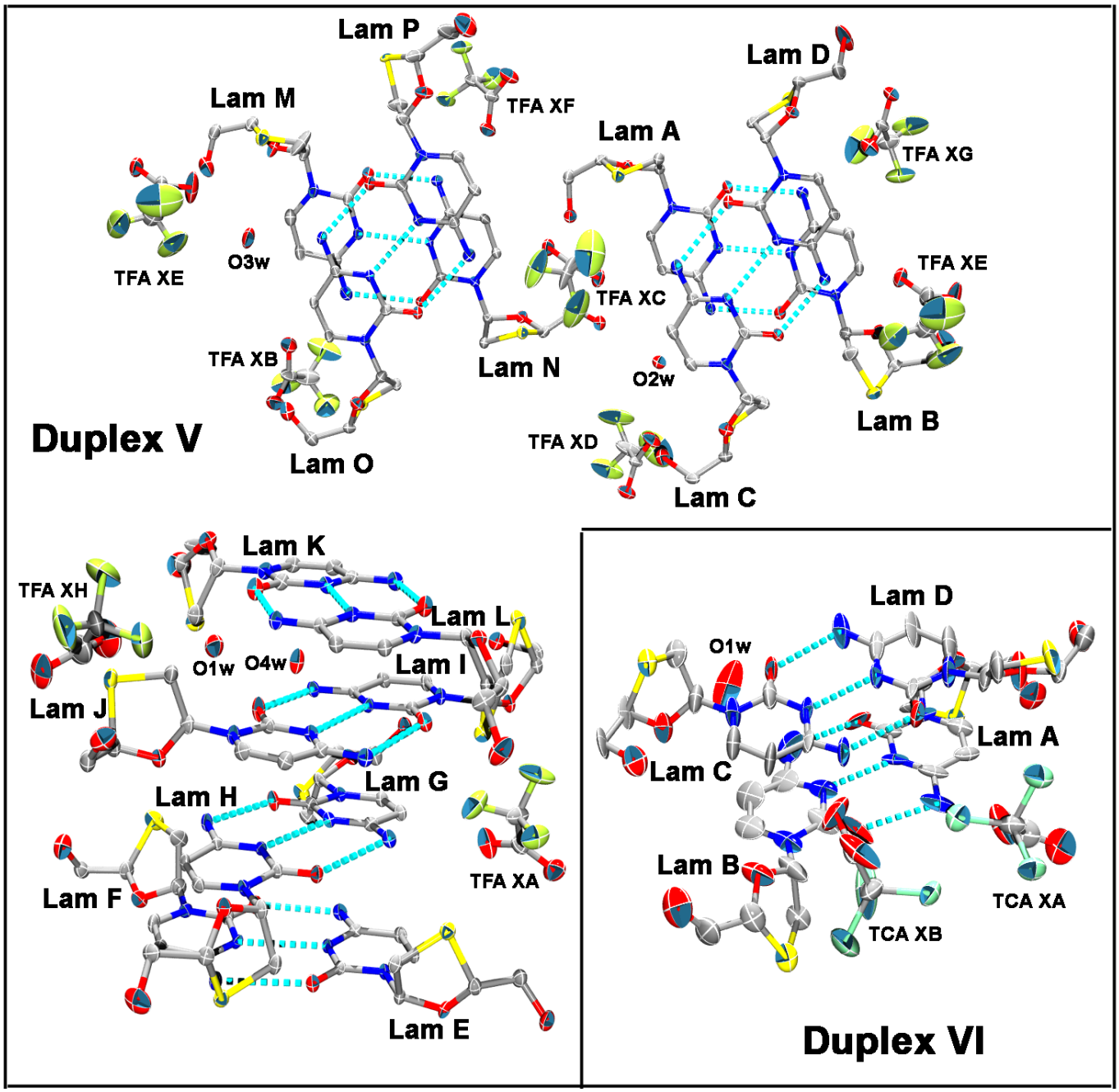

Figure S1. 30% Ellipsoid plot of non-hydrogen atoms present in the asymmetric units of lamivudine duplex V and lamivudine duplex VI Cyan dashed lines are highlighting base pairing hydrogen bonds to facilitate the identification of stacked lamivudine units.

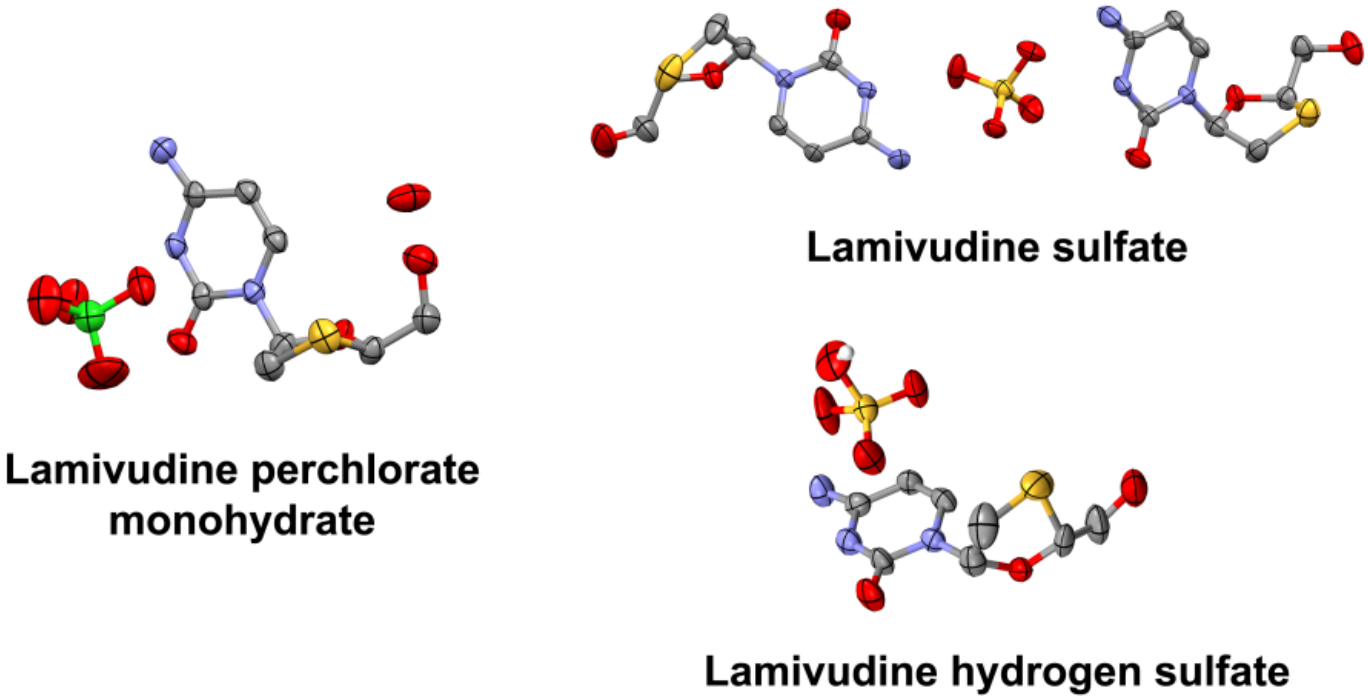

Figure S2. 50% Ellipsoid plot of lamivudine perchlorate, sulfate and hydrogen sulfate. Only non-hydrogen atoms are shown, except for the hydrogen of the hydrogen sulfate anion. The disordered oxygen atoms of perchlorate and hydrogen sulfate were modeled over two sets of 50% occupancy. For clarity reasons, only the atoms of one set were depicted.

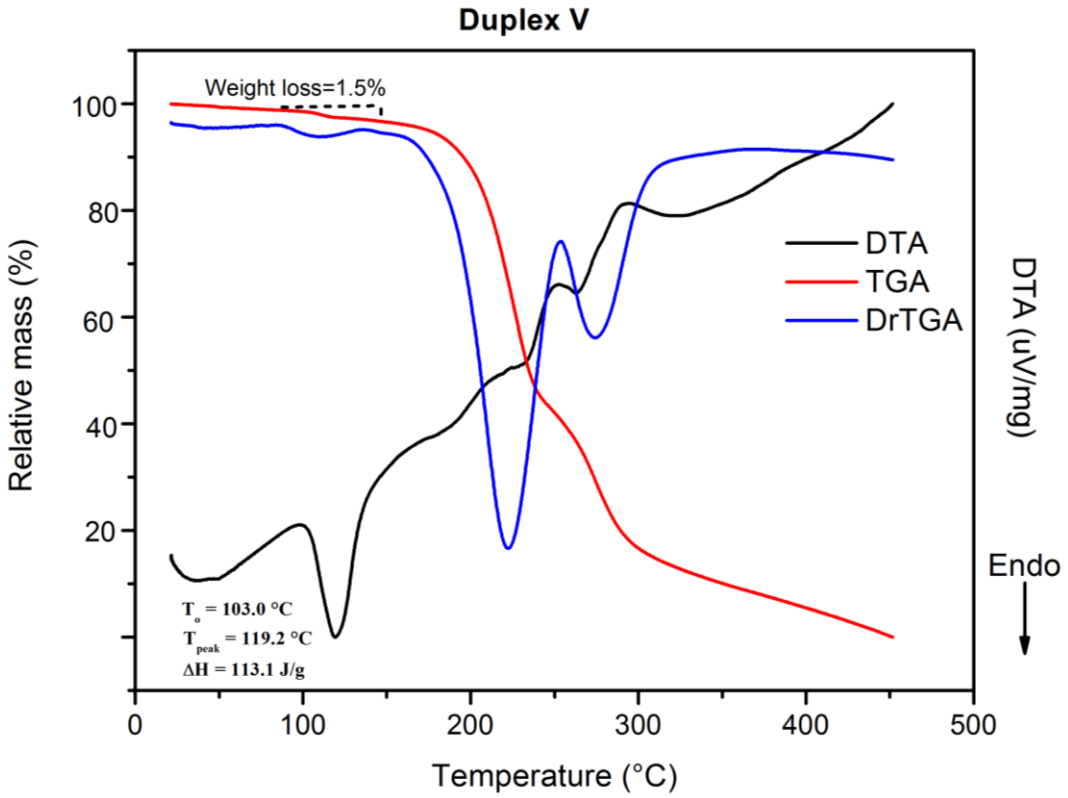

Figure S3. TG curve (red line), its derivative (blue line) and DTA curve (black line) of lamivudine duplex V.

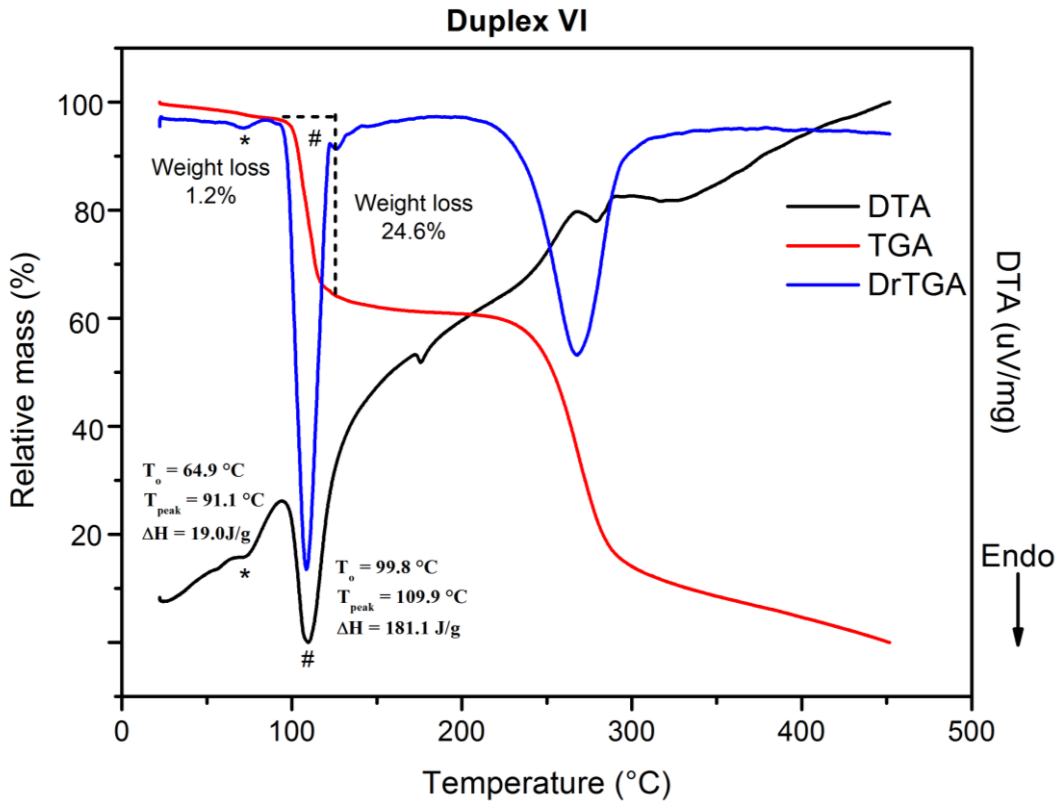

Figure S4. TG curve (red line), its derivative (blue line) and DTA curve (black line) of lamivudine duplex VI. Asterisks and hashtags mark the water and trichloroacetic acid elimination events, respectively.

Table S1. Crystal data and Refinement Parameters for the crystal structures of lamivudine reported in this work.

		Duplex V	Duplex VI	Lamivudine sulfate	Lamivudine hydrogen sulfate	Lamivudine perchlorate monohydrate
Chemical formula		$C_{36}H_{48}F_6N_{12}O_{17}S_4$	$C_{36}H_{48}Cl_6N_{12}O_{17}S_4$	$C_{16}H_{24}N_6O_{10}S_3$	$C_8H_{13}N_3O_7S_2$	$C_8H_{14}ClN_3O_8S$
Fw ($g.mol^{-1}$)		1163.10	1261.80	556.59	327.33	347.73
Cryst syst		Trigonal	Hexagonal	Orthorhombic	Orthorhombic	Orthorhombic
Space group		*P* 3_2	*P* 6_1	*P* $2_12_12_1$	*P* $2_12_12_1$	*P* $2_12_12_1$
Z		12	6	4	4	4
T (K)		296(2)	296(2)	296(2)	296(2)	296(2)
Unit cell dimensions	*a* (Å)	29.3603(5)	14.8380(10)	6.7148(14)	6.756(2)	6.2322(7)
	b (Å)	29.3603(5)	14.8380(10)	17.982(6)	10.726(3)	13.2055(15)
	c (Å)	20.4187(4)	42.003(3)	19.374(5)	23.809(8)	17.424(2)
	α (°)	90	90	90	90	90
	β (°)	90)	90	90	90	90
	γ (°)	120	120	90	90	90
V ($Å^3$)		15243.3(7)	8008.7(14)	2339.3(11)	1725.3(9)	1434.0(3)
ρ_{calc} ($g.cm^{-3}$)		1.520	1.570	1.580	1.260	1.611
Absorption coefficient μ (mm^{-1})		0.289	0.556	0.383	0.336	0.455
absorption correc. (multi-scan) T_{min}/T_{max}		0.771/0.977	0.854/0.973	0.779/0.974	0.623/0.977	0.862/0.978
ϑ range for data collection (°)		1.387 - 25.376	1.585 - 25.073	2.388/25.459	1.711/25.528	1.935/25.072
index ranges	*h*	-35 to 35	-16 to 17	-8 to 4	-8 to 6	-5 to 7
	k	-35 to 35	-17 to 17	-13 to 21	-10 to 12	-14 to 15
	l	-24 to 18	-49 to 48	-9 to 23	-26 to 27	-20 to 20
Data collected		115389	84541	6148	5046	5157
Unique reflections		29358	9364	3786	2833	2506
Symmetry factor (R_{int})		0.066	0.1232	0.0393	0.0407	0.0398
Completeness to θ_{max} (%)		99.9	99.7	98.3	94.8	99.5
F(000)		7224	3900	1160	680	720
Refined parameters		2756	677	317	190	217
Goodness-of-fit on F^2 $(S)^a$		1.001	1.243	1.024	1.042	1.032
Final $R_1{}^b$ factor [$I > 2\sigma(I)$]		0.0649	0.1421	0.0488	0.0839	0.0469
$wR_2{}^c$ factor (all data)		0.1863	0.4163	0.1141	0.2463	0.1194
Largest diff. peak / hole (*e* $Å^{-3}$)		0.661/-0.302	1.043/-0.526	0.268/-0.312	0.984/-0.374	0.214/-0.225
CCDC deposit no.		1580051	1580052	1580054	1580055	1580053

Table S2. Hydrogen-bond geometry found in lamivudine duplex V.

D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A(°)
		Base Pairing		
N_{3a}—H_{3a}···N_{3b}	0.86	1.98	2.830(9)	172
N_{4a}—H_{4a1}···O_{2b}	0.86	1.88	2.749(9)	173
N_{4b}—H_{4b1}···O_{2a}	0.86	2.08	2.928(17)	171
N_{4c}—H_{4c1}···O_{2d}	0.86	2.21	3.048(17)	166
N_{3d}—H_{3d}···N_{3c}	0.86	2.01	2.859(14)	172
N_{4d}—H_{4d1}···O_{2c}	0.86	1.83	2.692(14)	174
N_{3e}—H_{3e}···N_{3f}	0.86	1.98	2.830(9)	170
N_{4e}—H_{4e1}···O_{2f}	0.86	1.87	2.721(10)	172
N_{4f}—H_{4f1}···O_{2e}	0.86	2.11	2.956(13)	166
N_{4g}—H_{4g1}···O_{2h}	0.86	2.16	2.984(14)	160
N_{3h}—H_{3h}···N_{3g}	0.86	1.98	2.833(14)	170
N_{4h}—H_{4n1}···O_{2g}	0.86	1.89	2.743(14)	170
N_{3i}—H_{3i}···N_{3j}	0.86	2.00	2.849(9)	171
N_{4i}—H_{4n1}···O_{2j}	0.86	1.92	2.778(9)	172
N_{4j}—H_{4j1}···O_{2i}	0.86	2.17	3.005(11)	164
N_{4k}—H_{4k1}···O_{2l}	0.86	2.11	2.961(16)	172
N_{3l}—H_{3l}···N_{3k}	0.86	1.97	2.828(14)	173
N_{4l}—H_{4l1}···O_{2k}	0.86	1.86	2.720(16)	175
N_{4m}—H_{4m1}···O_{2n}	0.86	2.15	2.999(17)	170
N_{3n}—H_{3n}···N_{3m}	0.86	1.98	2.833(9)	176
N_{4n}—H_{4n1}···O_{2m}	0.86	1.87	2.73(10)	174
N_{3o}—H_{3o}···N_{3p}	0.86	1.94	2.793(14)	169
N_{4o}—H_{4p1}···O_{2p}	0.86	1.88	2.732(14)	171
N_{4p}—H_{4p1}···O_{2o}	0.86	2.08	2.920(17)	166
		Primary Amines		
N_{4a}—H_{4a2}···O_{2w}	0.86	2.01	2.858(13)	169
N_{4b}—H_{4b2}···O_{2xg}	0.86	2.30	3.116(2)	158
N_{4c}—H_{4c2}···O_{2xc}	0.86	2.26	3.089(19)	162
N_{4d}—H_{4d2}···O_{1xe}	0.86	2.01	2.852(18)	165
N_{4e}—H_{4e2}···O_{1xd}	0.86	2.03	2.858(17)	162
N_{4f}—H_{4f2}···O_{1xg}	0.86	2.06	2.909(11)	168
N_{4g}—H_{4g2}···O_{2xa}	0.86	2.19	3.02(2)	163
N_{4h}—H_{4h2}···O_{2xh}	0.86	1.95	2.80(2)	167
N_{4i}—H_{4i2}···O_{4w}	0.86	1.97	2.820(14)	170
N_{4j}—H_{4j2}···O_{1xb}	0.86	2.38	3.202(16)	160
N_{4k}—H_{4k2}···O_{1xa}	0.86	2.19	3.036(14)	170
N_{4l}—H_{4l2}···O_{1w}	0.86	2.03	2.880(12)	170
N_{4m}—H_{4m2}···O_{2xb}	0.86	2.14	2.98(2)	167
N_{4n}—H_{4n2}···O_{1xf}	0.86	1.95	2.794(17)	166
N_{4o}—H_{4o2}···O_{3w}	0.86	2.00	2.848(18)	168
N_{4p}—H_{4p2}···O_{1xc}	0.86	2.21	3.048(17)	166
		Hydroxyl Fragment		
$O_{5'a}$—$H_{5'a}$···O_{1xc}	0.82	2.04	2.705(13)	137
$O_{5'c}$—$H_{5'c}$···O_{2xd}	0.82	1.91	2.681(14)	155
$O_{5'e}$—$H_{5'e}$···$O_{5'g}$	0.82	1.98	2.771(14)	161
$O_{5'f}$—$H_{5'f}$···$O_{5'j}$	0.82	2.10	2.81(2)	144
$O_{5'g}$—$H_{5'g}$···$O_{5'c}$	0.82	1.93	2.707(13)	159
$O_{5'i}$—$H_{5'i}$···O_{2xa}	0.82	2.44	3.013(16)	128
$O_{5'i}$—$H_{5'i}$···O_{1xa}	0.82	2.20	2.993(16)	162
$O_{5'j}$—$H_{5'j}$···O_{1xh}	1.00	2.22	2.966(3)	130
$O_{5'k}$—$H_{5'k}$···O_{2xf}	0.82	2.20	2.75(2)	125

$O_{5'l}$—$H_{5'l}$···O_{2xb}	1.00	2.11	2.768(18)	122
$O_{5'm}$—$H_{5'm}$···O_{2xe}	0.82	1.94	2.69(3)	150
$O_{5'n}$—$H_{5'n}$···O_{2xc}	0.86	1.91	2.762(15)	167
$O_{5'o}$—$H_{5'o}$···O_{1xb}	1.00	1.91	2.76(2)	142
$O_{5'o}$—$H_{5'o}$···O_{2xb}	1.00	2.63	2.64(10)	150
		Water molecules		
O_{1w}—H_{11w}···$O_{5'f}$	0.85	2.41	2.94(2)	121
O_{1w}—H_{21w}···O_{1xh}	0.85	2.18	3.01(5)	166
O_{2w}—H_{12w}···$O_{5'n}$	0.85	2.23	2.99(10)	149
O_{2w}—H_{22w}···$S_{3'c}$	0.85	2.91	3.73(10)	162
O_{3w}—H_{23w}···O_{2xe}	0.99	1.95	2.82(2)	145
O_{3w}—H_{13w}···$O_{5'l}$	0.99	2.49	3.17(2)	125
O_{4w}—H_{14w}···O_{2xf}	0.85	2.26	2.92(2)	134
O_{4w}—H_{24w}···$O_{5'e}$	0.85	2.25	2.84(10)	127

Table S3. Hydrogen-bond geometry in lamivudine duplex VI.

D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A(°)
		Base Pairing		
N_{3a}—H_{3a}···N_{3b}	0.86	1.89	2.74(3)	170
N_{4a}—H_{4a1}···O_{2b}	0.86	2.06	2.88(4)	161
N_{4b}—H_{4b1}···O_{2a}	0.86	1.82	2.65(3)	163
N_{4c}—H_{4c1}···O_{2d}	0.86	2.12	2.88(4)	163
N_{3d}—H_{3d}···N_{3c}	0.86	1.95	2.80(3)	172
N_{4d}—H_{4d1}···O_{2c}	0.86	2.03	2.96(4)	177
		Primary Amines		
N_{4a}—H_{4a2}···O_{2xa}	0.86	1.45	2.30(7)	177
N_{4b}—H_{4b2}···O_{1w}	0.86	2.11	2.92(8)	154
		Hydroxyl Fragment		
$O_{5'a}$—$H_{5'a}$···O_{2xb}	0.82	1.60	2.35(5)	151
$O_{5'b}$—$H_{5'b}$···$O_{5'c}$	0.82	2.19	2.96(6)	158
$O_{5'c}$—$H_{5'c}$···$O_{5'd}$	0.82	1.88	2.46(6)	128
$O_{5'd}$—$H_{5'd}$···O_{1xa}	0.82	2.31	3.03(5)	148
		Water molecules		
O_{1w}—H_{11w}···Cl_{3a}	0.99	2.46	3.43(4)	166
O_{1w}—H_{21w}···$S_{3'c}$	1.00	2.65	3.56(5)	152

Table S4. Hydrogen-bond geometry in lamivudine sulfate.

D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A(°)
		$R^2_2(8)$		
N_{3a}—H_{3a}···O_1	0.86	1.89	2.711(6)	159
N_{4a}—H_{4a1}···O_4	0.86	1.95	2.806(6)	171
N_{3b}—H_{3b}···O_2	0.86	1.96	2.798(6)	166
N_{4b}—H_{4b1}···O_3	0.86	1.97	2.819(7)	168
		Primary Amines		
N_{4a}—H_{4a2}···O_3	0.86	1.98	2.754(7)	149
N_{4b}—H_{4b2}···O_4	0.86	1.99	2.821(6)	164
		Hydroxyl Fragment		
$O_{5'a}$—$H_{5'a}$···$O_{5'b}$	0.82	2.03	2.753(8)	147
$O_{5'b}$—$H_{5'b}$···O_1	0.82	2.04	2.737(8)	142
$O_{5'b}$—$H_{5'b}$···O_2	0.82	2.56	3.307(7)	152

Table S5. Hydrogen-bond geometry in lamivudine hydrogen sulfate.

D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A(°)
		$R^2_2(8)$		
N_3—H_3···O_{4x}	0.86	1.90	2.753(9)	168
N_4—H_{4a}···O_{2x}	0.86	2.12	2.961(9)	165
		Primary Amines		
N_4—H_{4b}···O_{1x}	0.86	2.25	3.039(10)	153
N_4—H_{4b}···O_{4x}	0.86	2.57	3.316(9)	146
		Hydroxyl Fragment		
$O_{5'}$—$H_{5'}$···O_{2x}	0.82	2.26	2.819(10)	125

Table S6. Hydrogen-bond geometry in lamivudine perchlorate monohydrate.

D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A(°)
		$R^1_2(6)$		
N_3—H_3···O_2	0.86	1.98	2.795(6)	157
N_4—H_{4a}···O_2	0.86	2.34	3.067(6)	141
		Primary Amines		
N_4—H_{4a}···O_{3x}	0.86	2.34	2.959(2)	130
N_4—H_{4b}···O_{1w}	0.86	1.92	2.779(7)	172
		Hydroxyl Fragment and Water molecule		
$O_{5'}$—$H_{5'}$···O_{2x}	0.82	2.17	2.853(7)	141
O_{1w}—H_{11w}···$O_{5'}$	0.99	1.99	2.818(7)	140
O_{1w}—H_{21w}···O_{2x}	0.99	2.12	2.877(7)	131

Table S7. Synthon energy calculated at the M06-2X/6-31+G** level of theory without optimization for lamivudinium ($3TC^+$) or lamivudine (3TC) and the listed counterions used to assemble the $R_2^2(8)$ heterosynton. Some aggregates were extracted out from crystal structures obtained from CSD data base while others were created using Chimera since they were not available in crystal structures of lamivudine.

Dimer[#]	Counterion	SCF (kcal/mol)
20	phthalate	-205.0
34	malonate	-203.7
21	4,5-dichlorophthalate	-197.6
18	fumarate	-193.6
16	L-tartrate	-191.9
19	maleate	-191.4
22	pimelate	-188.4
12	**oxalate**	**-173.0**
4	salicylate	-152.2
23	hydrogen pimelate	-151.9
9	**D-tartrate**	**-150.7**
17	D-hidrogen tartrate	-145.6
10	L-hydrogen tartrate	-145.3
3	hydrogen phthalate	-144.4
35	hydrogen malonate	-143.0
7	**hydrogen maleate**	**-142.4**
5	R-mandelate	-132.2
14	**trichloroacetate**	**-101.2**
11	hydrogen oxalate	-100.9
6	S-mandelate	-98.8
13	**trifluoracetate**	**-95.6**
8	**hydrogen fumarate**	**-95.6**
1a	3,5-dinitrosalicylate	-90.1
1b	3,5-dinitrosalicylate	-87.9
2	4,5-dichlorohydrogen phthalate	-86.0
30	oxalic acid	-19.1
28	D-tartaric acid	-19.0
33	malonic acid	-18.4
31	trifluoracetic acid	-16.7
27	fumaric acid	-14.8
24	4,5-dichlorophthalic acid	-14.7
32	trichloroacetic acid	-14.6
26	maleic acid	-13.7
29	L-tartaric acid	-13.7
15	pimelic acid	-13.5
25	Phthalic acid	-12.3

[#] The lines in bold concerns the counterions that are found in lamivudine duplexes already reported in the literature.[S1] The dimers 1a, 1b, 6, 8-10, 13-14, 16-35 were created using Chimera.[S2] Dimers 1a, 1b, 2-8,10-11, 13-14, 17,23 and 35 are assembled with monovalent anions, while dimers 9, 12, 16, 18-22 and 34 have divalent anions.

Table S8. Synthon energy calculated at the M06-2X/6-31+G** level of theory after partial geometric optimization for lamivudinium ($3TC^+$) or lamivudine (3TC) and the listed counterions used to assemble the $R_2^2(8)$ heterosynton. Some aggregates were extracted out from crystal structures obtained from CSD data base while others were created using Chimera since they were not available in crystal structures of lamivudine.

Dimer[#]	Counterion	SCF (kcal/mol)
12	**oxalate**	**-211.2**
20	phthalate	-191.0
16	L-tartrate	-175.5
34	malonate	-170.3
9	**D-tartrate**	**-166.5**
21	4,5-dichlorophthalate	-165.4
19	maleate	-161.4
18	fumarate	-159.1
22	pimelate	-152.9
23	hydrogen pimelate	-113.8
14	**trichloroacetate**	**-113.2**
11	hydrogen oxalate	-110.2
5	R-mandelate	-109.7
6	S-mandelate	-109.4
4	salicylate	-109.4
13	**trifluoracetate**	**-106.8**
8	**hydrogen fumarate**	**-104.8**
17	D-hidrogen tartrate	-103.7
7	**hydrogen maleate**	**-99.7**
35	hydrogen malonate	-98.0
10	L-hydrogen tartrate	-97.6
2	4,5-dichlorohydrogen phthalate	-92.8
1a	3,5-dinitrosalicylate	-91.1
1b	3,5-dinitrosalicylate	-81.1
3	hydrogen phthalate	-71.0
32	trichloroacetic acid	-22.2
30	oxalic acid	-21.5
15	pimelic acid	-21.0
24	4,5-dichlorophthalic acid	-20.9
33	malonic acid	-20.6
31	trifluoracetic acid	-20.4
29	L-tartaric acid	-19.4
28	D-tartaric acid	-19.4
27	fumaric acid	-19.1
26	maleic acid	-19.0
25	Phthalic acid	-16.3

[#] The lines in bold concerns the counterions that can form lamivudine duplexes.[S1] The dimers 1a, 1b, 6, 8-10, 13-14, 16-35 were created using Chimera.[S2] Dimers 1a, 1b, 2-8,10-11, 13-14, 17,23 and 35 are assembled with monovalent anions, while dimers 9, 12, 16, 18-22 and 34 have divalent anions.

Table S9. Synthon energy calculated at the M06-2X/6-31+G** level of theory after full geometric optimization for lamivudinium ($3TC^+$) or lamivudine (3TC) and the listed counterions used to assemble the $R_2^2(8)$ heterosynton. Some aggregates were extracted out from crystal structures obtained from CSD data base while others were created using Chimera since they were not available in crystal structures of lamivudine.

Dimer[#]	Counterion	SCF (kcal/mol)
34	malonate	-222.0
12	**oxalate**	**-219.5**
19	maleate	-217.2
20	phthalate	-209.1
21	4,5-dichlorophthalate	-207.4
22	pimelate	-196.0
18	fumarate	-193.1
16	L-tartrate	-187.1
9	**D-tartrate**	**-186.0**
23	hydrogen pimelate	-128.6
8	**hydrogen fumarate**	**-122.3**
11	hydrogen oxalate	-119.8
6	S-mandelate	-117.4
5	R-mandelate	-113.7
4	salicylate	-112.5
13	**trifluoracetate**	**-112.5**
17	D-hidrogen tartrate	-112.1
14	**trichloroacetate**	**-110.2**
10	L-hydrogen tartrate	-108.4
35	hydrogen malonate	-102.4
7	**hydrogen maleate**	**-102.2**
3	hydrogen phthalate	-100.3
2	4,5-dichlorohydrogen phthalate	-93.4
1a	3,5-dinitrosalicylate	-88.1
1b	3,5-dinitrosalicylate	-87.8
24	4,5-dichlorophthalic acid	-23.8
31	trifluoracetic acid	-21.8
32	trichloroacetic acid	-21.2
30	oxalic acid	-20.0
27	fumaric acid	-19.8
25	Phthalic acid	-19.6
33	malonic acid	-19.3
29	L-tartaric acid	-19.1
26	maleic acid	-18.8
15	pimelic acid	-17.9
28	D-tartaric acid	-15.4

[#] The lines in bold concerns the counterions that can form lamivudine duplexes.[S1] The dimers 1a, 1b, 6, 8-10, 13-14, 16-35 were created using Chimera.[S2] After full optimization there was proton migration from lamivudinium to counterion in the dimers 3-8, 10, 11, 13, 14, 16-23 and 34-35. Dimers 1a, 1b, 2-8,10-11, 13-14, 17,23 and 35 were assembled with monovalent anions, while dimers 9, 12, 16, 18-22 and 34 were built with divalent anions.

Table S10. Gibbs and Enthalpy energies of the $R_2^2(8)$ heterosynton between lamivudinium ($3TC^+$) or lamivudine (3TC) and the listed counterions calculated at the M06-2X/6-31+G** level of theory after full geometric optimization of the heterodimers.

Dimer[#]	Counterion	Gibbs (kcal/mol)	Enthalpy (kcal/mol)
34	malonate	-209.8	-220.8
12	**oxalate**	**-208.9**	**-218.9**
19	maleate	-200.0	-215.4
20	phthalate	-194.6	-207.2
21	4,5-dichlorophthalate	-190.1	-205.9
22	pimelate	-179.3	-194.0
18	fumarate	-181.5	-191.9
16	L-tartrate	-175.3	-185.9
9	**D-tartrate**	**-174.3**	**-185.1**
23	hydrogen pimelate	-116.0	-127.0
8	**hydrogen fumarate**	**-109.8**	**-121.0**
11	hydrogen oxalate	-106.8	-118.4
6	S-mandelate	-105.0	-116.1
5	R-mandelate	-102.2	-112.6
17	D-hidrogen tartrate	-100.8	-111.2
13	**trifluoracetate**	**-101.3**	**-111.1**
4	salicylate	-99.5	-110.2
14	**trichloroacetate**	**-99.2**	**-108.8**
10	L-hydrogen tartrate	-96.4	-107.3
35	hydrogen malonate	-89.6	-101.3
7	**hydrogen maleate**	**-89.3**	**-99.5**
3	hydrogen phthalate	-85.9	-97.4
2	4,5-dichlorohydrogen phthalate	-80.3	-91.5
1b	3,5-dinitrosalicylate	-74.9	-88.7
1a	3,5-dinitrosalicylate	-76.3	-88.0
24	4,5-dichlorophthalic acid	-9.3	-22.7
31	trifluoracetic acid	-9.3	-20.9
32	trichloroacetic acid	-9.5	-20.3
30	oxalic acid	-7.6	-19.1
27	fumaric acid	-7.3	-18.6
25	Phthalic acid	-6.8	-18.5
29	L-tartaric acid	-7.0	-18.4
33	malonic acid	-7.4	-18.1
26	maleic acid	-7.5	-17.8
15	pimelic acid	-5.4	-16.3
28	D-tartaric acid	-1.7	-13.9

[#] The lines in bold refers to counterions that can form lamivudine duplexes.[S1] The dimers 1a, 1b, 6, 8-10, 13-14, 16-35 were created using Chimera.[S2] After full optimization there was proton migration from lamivudinium to counterion in the dimers 3-8, 10, 11, 13, 14, 16-23 and 34-35. Dimers 1a, 1b, 2-8,10-11, 13-14, 17,23 and 35 were assembled with monovalent anions, while dimers 9, 12, 16, 18-22 and 34 were built with divalent anions.

Table S11. Entropy of the $R_2^2(8)$ heterosynton between lamivudinium ($3TC^+$) or lamivudine (3TC) and the listed counterions calculated at the M06-2X/6-31+G** level of theory after full geometric optimization of the heterodimers.

Dimer[#]	Counterion	Entropy (kcal/K.mol)
21	4,5-dichlorophthalate	-0.053
19	maleate	-0.052
22	pimelate	-0.049
1b	3,5-dinitrosalicylate	-0.046
24	4,5-dichlorophthalic acid	-0.045
20	phthalate	-0.042
28	D-tartaric acid	-0.041
1a	3,5-dinitrosalicylate	-0.039
25	Phthalic acid	-0.039
31	trifluoracetic acid	-0.039
35	hydrogen malonate	-0.039
11	hydrogen oxalate	-0.039
30	oxalic acid	-0.039
3	hydrogen phthalate	-0.039
29	L-tartaric acid	-0.038
27	fumaric acid	-0.038
2	4,5-dichlorohydrogen phthalate	-0.038
8	**hydrogen fumarate**	**-0.038**
6	S-mandelate	-0.037
34	malonate	-0.037
23	hydrogen pimelate	-0.037
15	pimelic acid	-0.037
10	L-hydrogen tartrate	-0.037
32	trichloroacetic acid	-0.036
9	**D-tartrate**	**-0.036**
33	malonic acid	-0.036
4	salicylate	-0.036
16	L-tartrate	-0.035
18	fumarate	-0.035
5	R-mandelate	-0.035
17	D-hidrogen tartrate	-0.035
26	maleic acid	-0.035
7	**hydrogen maleate**	**-0.034**
12	**oxalate**	**-0.033**
13	**trifluoracetate**	**-0.033**
14	**trichloroacetate**	**-0.032**

[#] The lines in bold concerns the counterions that can form lamivudine duplexes.[S1] The dimers 1a, 1b, 6, 8-10, 13-14, 16-35 were created using Chimera.[S2] After full optimization there was proton migration from lamivudinium to counterion in the dimers 3-8, 10, 11, 13, 14, 16-23 and 34-35. Dimers 1a, 1b, 2-8,10-11, 13-14, 17,23 and 35 were assembled with monovalent anions, while dimers 9, 12, 16, 18-22 and 34 were built with divalent anions.

Table S12. Pka of organic acids used as counterions in lamivudine crystal structures.

Acid	Pka*	ΔPka
trifluoracetic acid	**0.52**	**3.78**
trichloroacetic acid	**0.66**	**3.64**
oxalic acid	**1.25**	**3.05**
maleic acid	**1.92**	**2.47**
3,5-dinitrosalicyllic acid	**2.18**	**2.12**
phthalic acid	2.95	1.35
salicylic acid	2.97	1.33
L-tartaric acid	2.98	1.32
D-tartaric acid	**2.98**	**1.32**
fumaric	**3.02**	**1.28**
R-mandelic acid	3.37	0.93
pimelic acid	4.71	-0.18
4,5-dichlorophthalic acid	not available	not available

* The Pka values were obtained from Lange's Handbook of Chemistry.[S3] The lines in bold concerns the counterions that can form lamivudine duplex or where the three-point synthon (3,5-dinitrosalicylic acid) is observed in lamivudine crystal structures.[S1,S4]

Supporting References

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