SUPPORTING INFORMATION

The Elusive Crystal Structure of the Neuraminidase Inhibitor Tamiflu (Oseltamivir Phosphate): Molecular Details of Action

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Table S1. Intermolecular interactions in the crystal structure of oseltamivir phosphate

Cation	D—H•••A[a]	H•••A /Å	D•••A / Å	<DHA / °
Ester group				
1†	C32—H32A•••O10$^{\#3}$	2.31	3.252(6)	162.0
2‡	C16—H16A•••O14$^{\#2}$	2.57	3.432(6)	147.1
Ammonium group				
1	N1—H1A•••*O2*$^{\#7}$	1.89	2.745(4)	154.6
1	N1—H1B•••*O4*$^{\#4}$	1.97	2.801(4)	150.2
1	N1—H1C•••*O5*	1.82	2.722(5)	170.6
1[b]	N1—H1B•••*O7*$^{\#4}$	2.43	2.938(5)	115.3
2	N3—H3B•••*O1*	2.13	2.940(5)	147.4
2	N3—H3C•••*O2*$^{\#4}$	1.84	2.735(5)	168.1
2	N3—H3D•••*O5*$^{\#5}$	1.94	2.781(4)	152.1
2	N3—H3B•••*O6*	2.38	3.003(4)	125.6
Amide group				
1	N2—H2•••*O3*$^{\#4}$	2.25	3.125(5)	176.3
1	N2—H2•••*O4*$^{\#4}$	2.62	3.194(5)	124.0
1	*O3—H3*•••O12$^{\#6}$	1.86	2.691(4)	168.5
1‡	C16—H16A•••O14	2.57	3.432(6)	147.1
2	N4—H4A•••*O8*	2.13	2.976(4)	162.1
2	*O8—H8*•••O16$^{\#1}$	1.81	2.633(4)	164.4
2[b]	C32—H32C•••*O1*	2.68	3.240(6)	116.5
2†	C32—H32A•••O10	2.31	3.252(6)	162.0
Other interactions				
2	C25—H25C•••O16$^{\#1}$	2.64	3.437(8)	138.8
2[b]	C17—H17•••*O6*	2.48	3.087(5)	119.0

[a] Symmetry operators: $^{\#1}$*x*, *y*, *z*+1; $^{\#2}$*x*-1/2, -*y*+1/2, -*z*+1; $^{\#3}$-*x*+1/2, *y*+1/2, -*z*+1; $^{\#4}$-*x*, -*y*+1, *z*; $^{\#5}$*x*, *y*, *z*-1; $^{\#6}$-*x*, -*y*+1, *z*-1; $^{\#7}$-*x*, -*y*+1, *z*+1. The atoms in italic belong to the phosphate groups. †,‡Common bonds for the ester group and amide group.

[b] A recent analysis (P. A. Wood, F. H. Allen, E. Pidcock, *CrystEngComm*, **2009**, *11*, 1563) has established that interactions with angles smaller than 120° are unlikely to contribute to stabilization with hydrogen bonding. For consistency with the older literature, we list these cases here, however, we note that their contribution to the hydrogen bonding network is probably minor.

Materials and crystallization: Oseltamivir phosphate powder (Toronto Research Chemicals) was screened for crystals by slow evaporation, at room temperature, of nearly-saturated solutions in over 15 organic solvents and their mixtures. The compound is well soluble in water, methanol and polar solvents (the dissolution in solvents less polar than water can be further enhanced by vigorous mixing or shaking), but it is very sparingly soluble in solvents that are less polar than water (alcohols), and practically insoluble in non-polar solvents (chloroform, dichloromethane, toluene, benzene). Saturated solutions were prepared and kept in siliconized glass well plates until the solvent evaporated completely. In all cases, the compound was recovered as white amorphous powder.

In another set of series of experiments, the crystallization was performed by diffusing vapors of organic solvents into a water solution of the compound, which is stable at room temperature. In each case, a small open vial containing nearly saturated solution of the salt was places inside a larger closed vial containing organic solvent or solvent mixtures. In the screening experiments, both the concentration of the solute and the organic solvent were varied. In most cases, either white amorphous powders were obtained, or, when the concentration as low, the increased volume of the solution prevented the crystallization. Ultimately, by using this method and letting vapors of ethyl acetate diffuse very slowly into an aqueous solution of the salt over a period of four months, a couple of batches were obtained that contained at the bottom of the vial very small, colorless, many of which were aggregated into bunches. The yield of the crystals is very low. The crystals were extremely weakly diffracting with laboratory Mo source and structure determination as not possible. Several single crystals were also found in these experiments around the crystal aggregates, and a needle crystal was mechanically separated from the bottom of the container and used for X-ray data collection.