Supporting Information

Development of Oseltamivir Phosphonate Congeners as Anti-Influenza Agents

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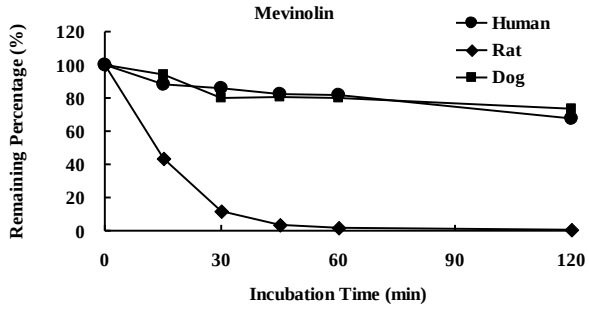

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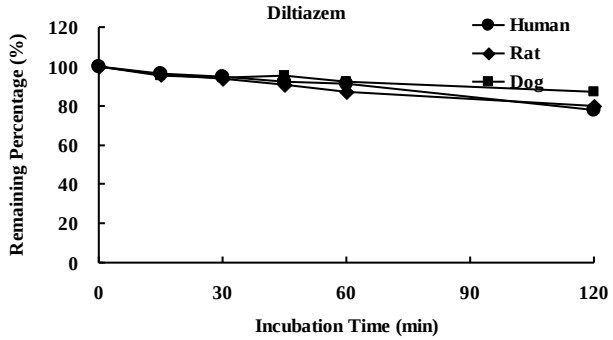

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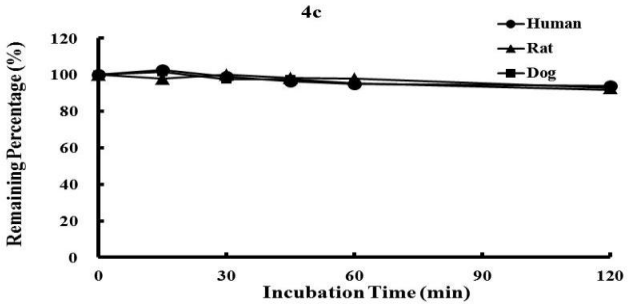


Figure s1. Stability tests. The stability results of control compounds, mevinolin (A) and diltiazem (B), were acceptable. Guanidino-tamiphosphor monoethyl ester **4c** (C) was stable in human, rat and dog whole blood.

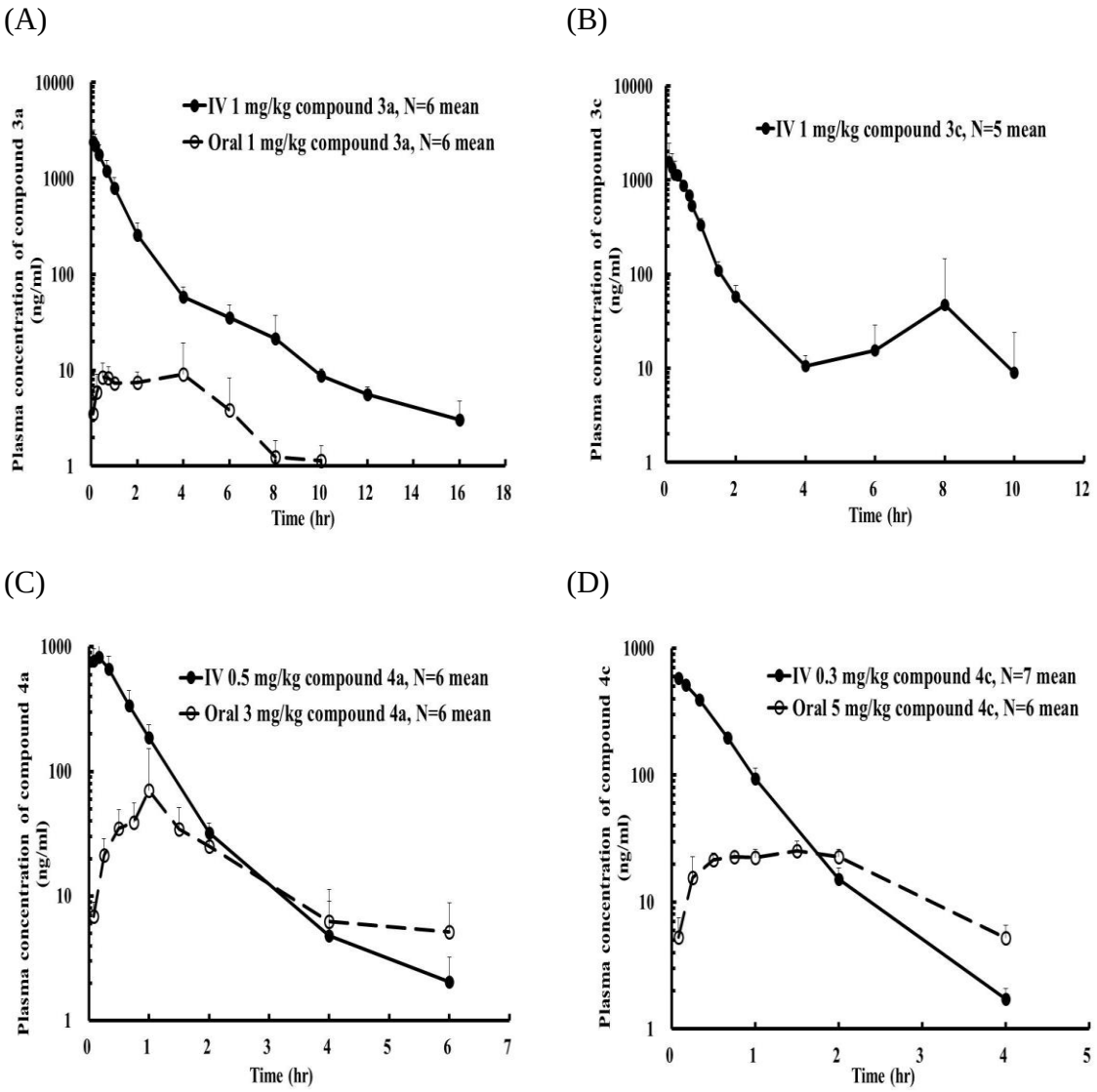
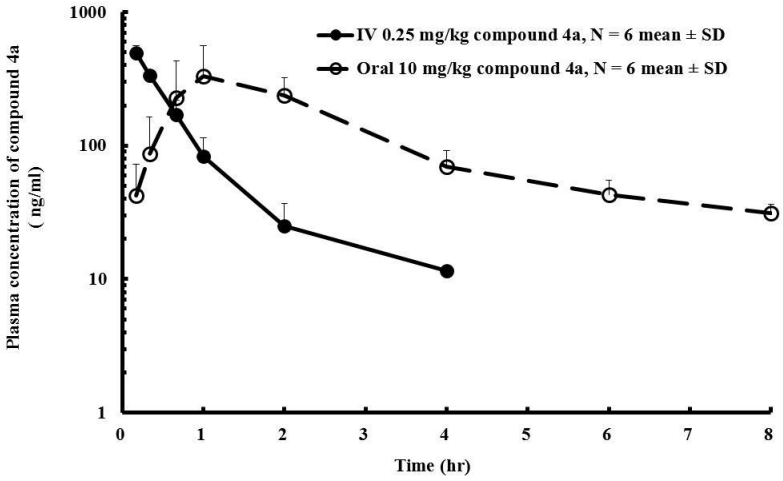


Figure s2. Plasma concentration–time curves after i.v. and oral administration of compounds in normal saline to male rats: (A) **3a**, (B) **3c**, (C) **4a**, and (D) **4c**.

(A)



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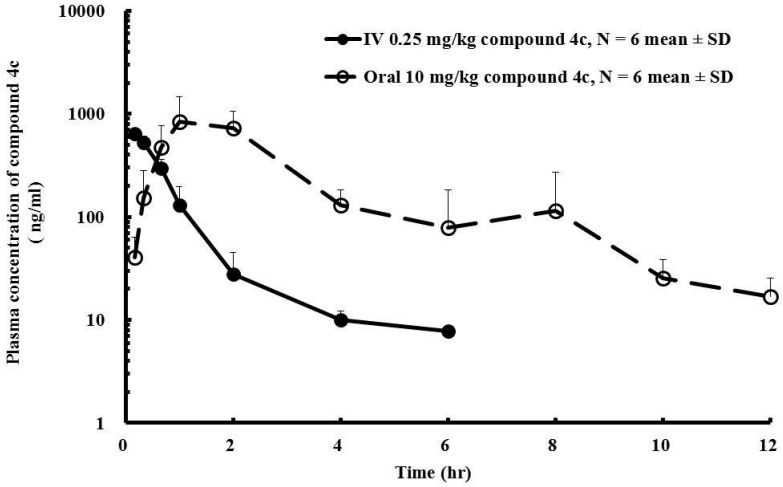


Figure s3. Plasma concentration–time curves after i.v. and oral administration of compounds in normal saline to male mice: (A) **4a** and (B) **4c**.

Table s1. In vitro metabolic stabilities of **4c** and control compounds (testosterone and midazolam) in liver microsomes from various species.

(A) Remaining % at 60 min

	4c	Testosterone	Midazolam
HLM[a]	96.62	35.01	10.91
MRLM[a]	92.54	0.33	1.74
MDLM[a]	104.68	11.34	1.3

(B) Intrinsic clearance (CL_{int}) (μL/min/mg proteins)

	4c	Testosterone	Midazolam
HLM[a]	1.6	35.4	75.2
MRLM[a]	1.8	496.0	135.2
MDLM[a]	~ 0.0	72.6	141.4

(C) In vitro half life ($t_{1/2}$) (min)

	4c	Testosterone	Midazolam
HLM[a]	866.25	39.15	18.43
MRLM[a]	770.00	2.79	10.25
MDLM[a]	∞	19.09	9.80

[a] HLM: pooled human liver microsomes; MRLM: pooled male rat liver microsomes; MDLM pooled male dog liver microsomes.

Table s2. The measured % protein binding of **4c** in plasma from various species.

	Mean% bound measured in plasma		
	4c	Testosterone	Ranitidine
Human plasma	8.93	95.52	21.16
Rat plasma	13.57	92.76	16.80
Dog plasma	12.14	94.01	20.63

Table s3. Recovery of **4c** and **4a** from urine and feces after administration of compound **4c** (5 mg/kg) to Sprague–Dawley rats.

	Recovered amount (μg)		
	4c	**4a**	**4c** + **4a**
Urine	20.1 ± 4.8 μg	5.7 ± 2.5 μg	25.7 ± 6.8 μg
	(1.5 ± 0.4 %)[a]	(0.4 ± 0.2 %)[a]	(1.9 ± 0.5)[a]
Feces	582.9 ± 161.6 μg	364.4 ± 39.9 μg	947.3 ± 163.9 μg
	(43.2 ± 12.0 %)[a]	(27.0 ± 3.0 %)[a]	(70.2 ± 12.1 %)[a]
Urine +	603.0 ± 164.1 μg	370.1 ± 38.0 μg	973.0 ± 165.3 μg
Feces	(44.7 ± 12.2 %)[a]	(27.4 ± 2.8 %)[a]	(72.1 ± 12.2 %)[a]

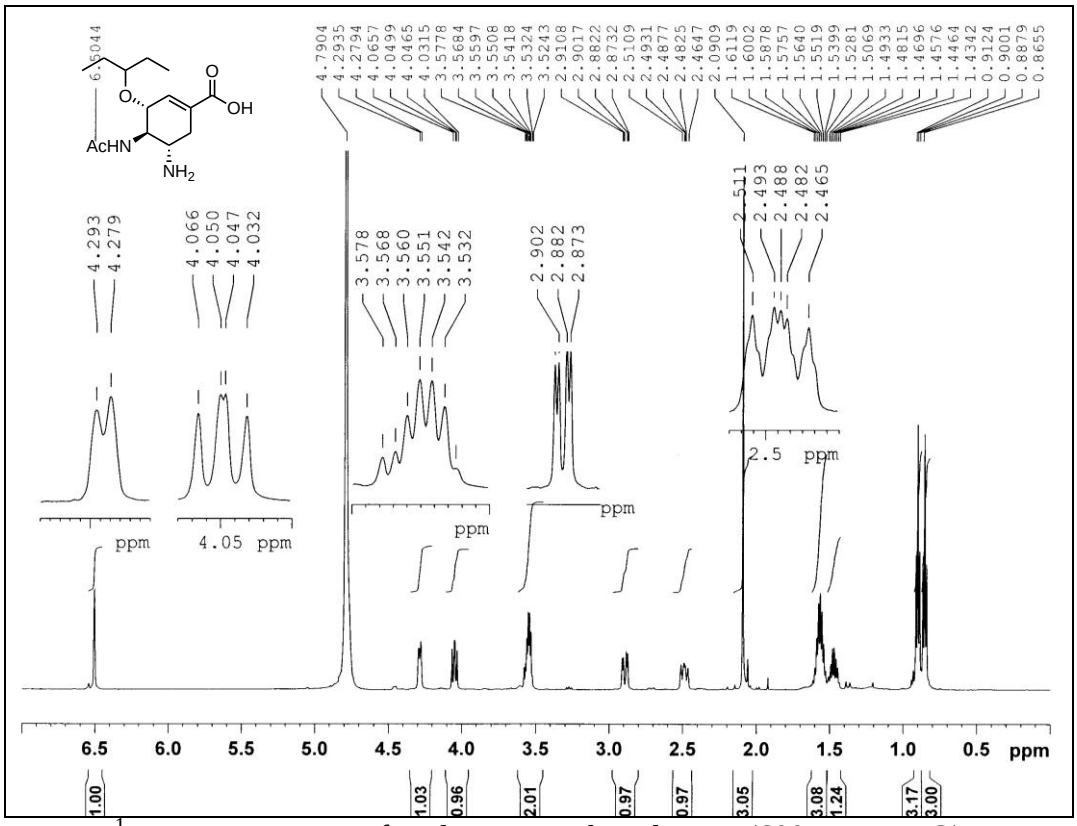
[a] The number in parenthesis indicates the percentage recovery.

Table s4. Clinical observation on treatment of mice with compounds **3a** and **3c**.

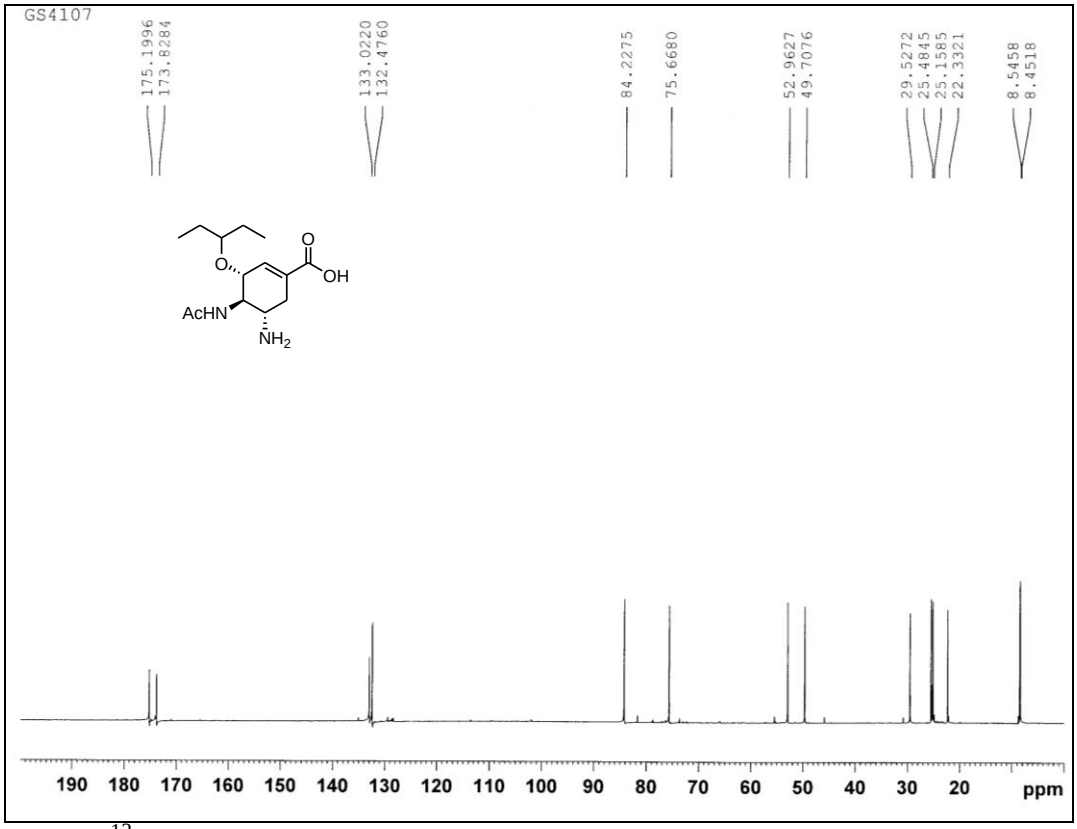
Dose (mg/kg)	Motality	Tremor	Convulsion	Body jerks	Hypoactivity	Hunched posture	Piloerection
Compound **3a**							
300	–	–	–	–			
500	–	+ (1/1)	–	–			
750	+ (1/4)	+ (3/4)	+ (3/4)	+ (1/4)			
800	+ (1/1)	–	–	–			
1000	+ (1/1)	–	–	–			
Compound **3c**							
300	–	–	–	–	–	–	–
600	–	–	–	–	–	–	–
900	–	+ (3/3)	–	–	+ (3/3)[a]	+ (3/3)[a]	+ (3/3)[a]
1500	–	+ (1/1)	+ (1/1)	+ (1/1)	+ (1/1)[a]	+ (1/1)[a]	+ (1/1)[a]
2000	+ (1/1)[b]	+ (1/1)	+ (1/1)	+ (1/1)	+ (1/1)	+ (1/1)	+ (1/1)

[a] The clinical sign was observed till to the second day after dosing.

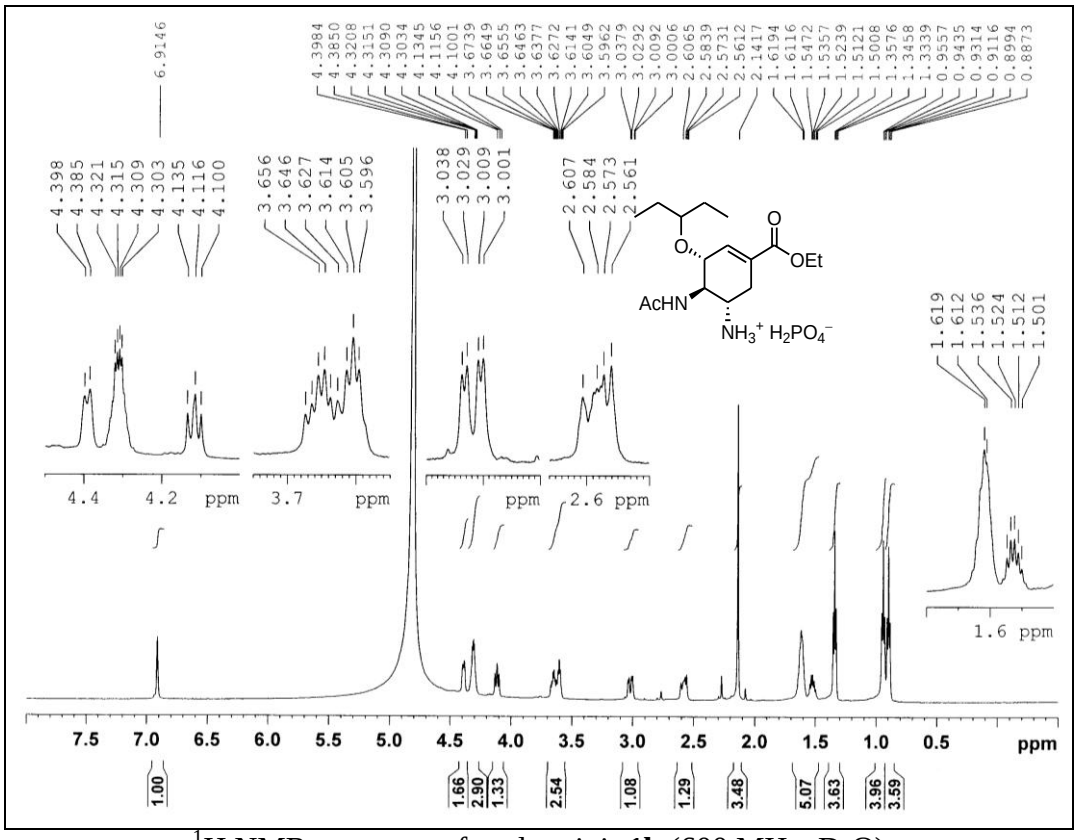
[b] This animal was found dead in half hour later after dosing.



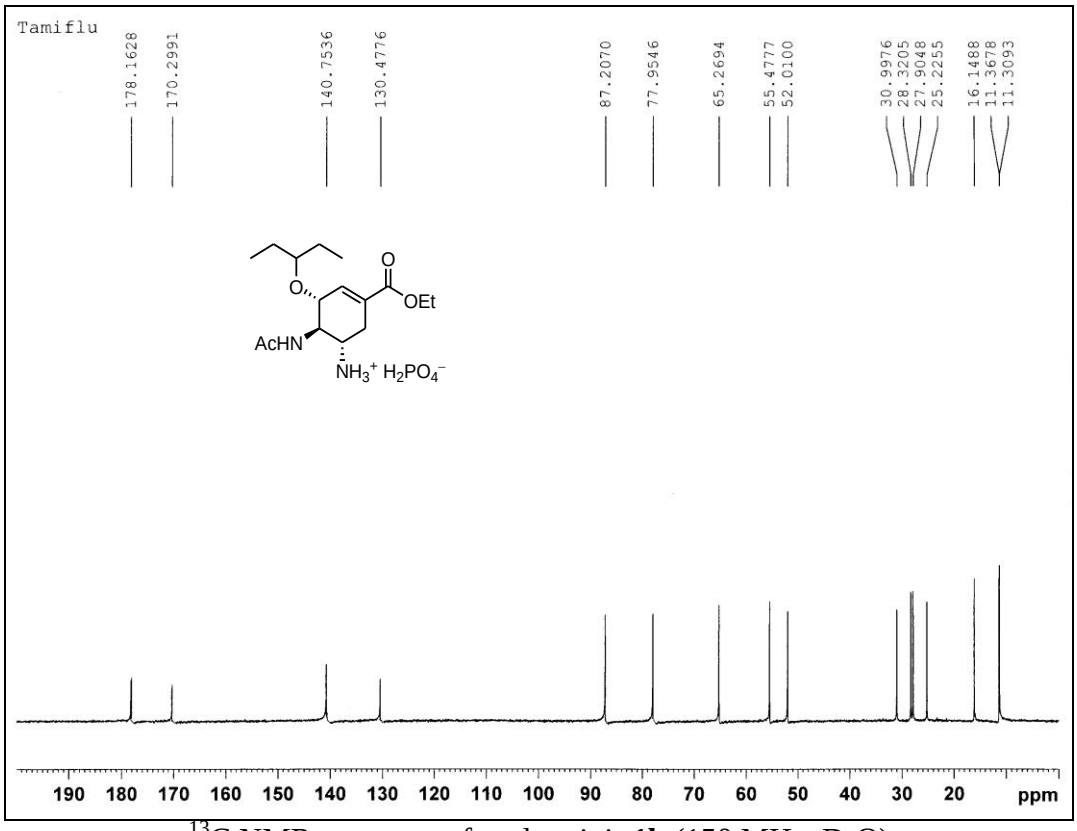
^{1}H NMR spectrum of oseltamivir carboxylate **1a** (600 MHz, D_2O)



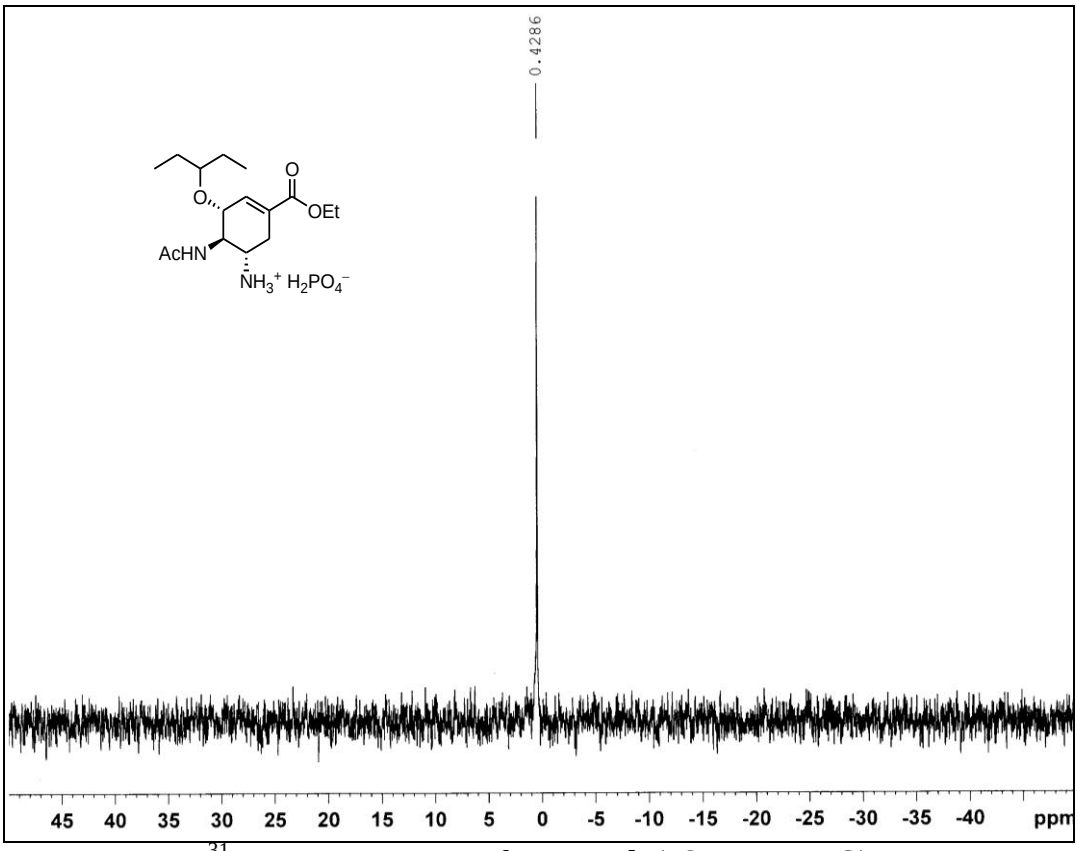
^{13}C NMR spectrum of oseltamivir carboxylate **1a** (150 MHz, D_2O)



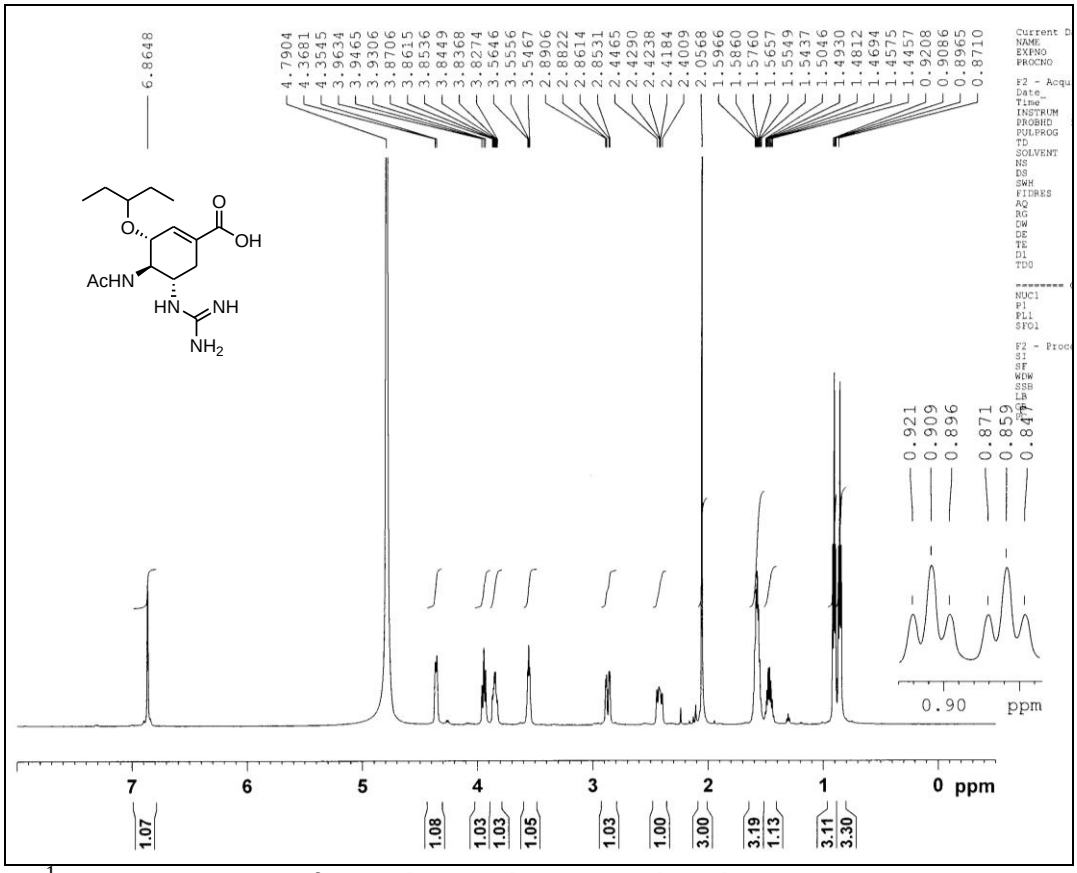
^{1}H NMR spectrum of oseltamivir **1b** (600 MHz, D_2O)



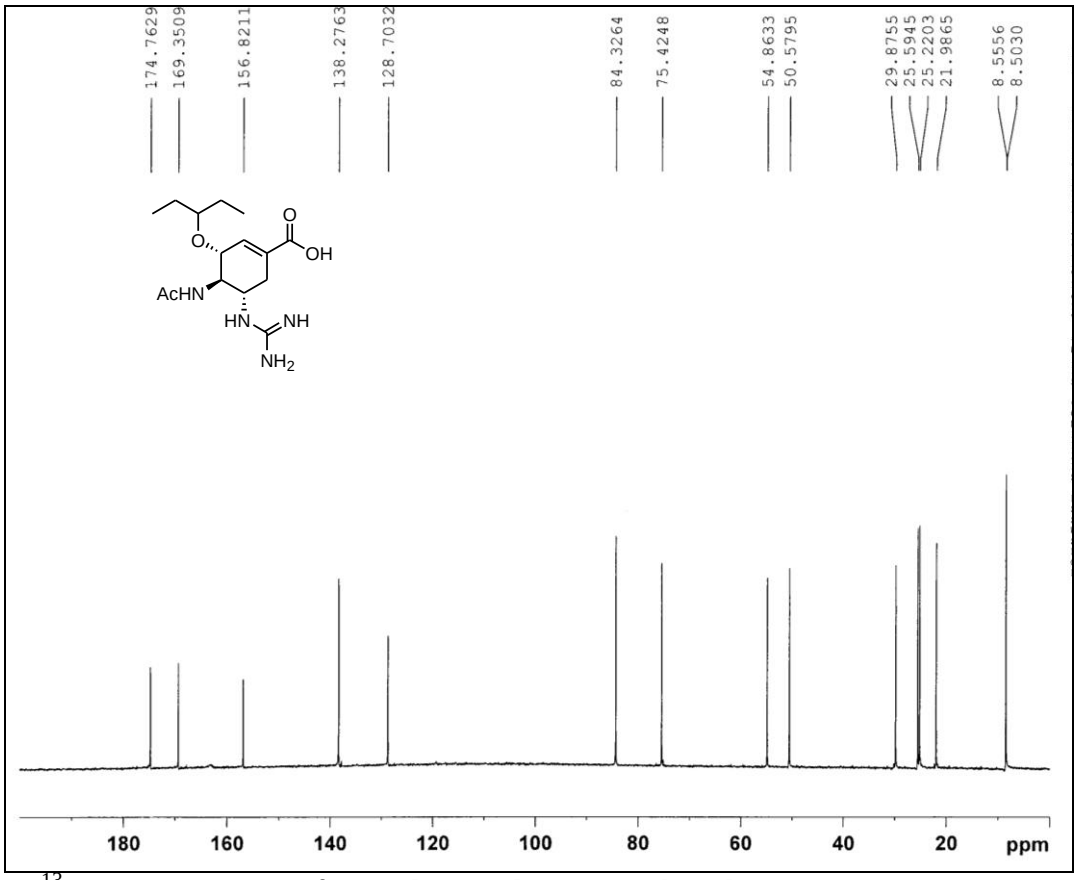
^{13}C NMR spectrum of oseltamivir **1b** (150 MHz, D_2O)



^{31}P NMR spectrum oseltamivir **1b** (162 MHz, D_2O)



^{1}H NMR spectrum of guanidino-oseltamivir carboxylate **2a** (600 MHz, D_2O)



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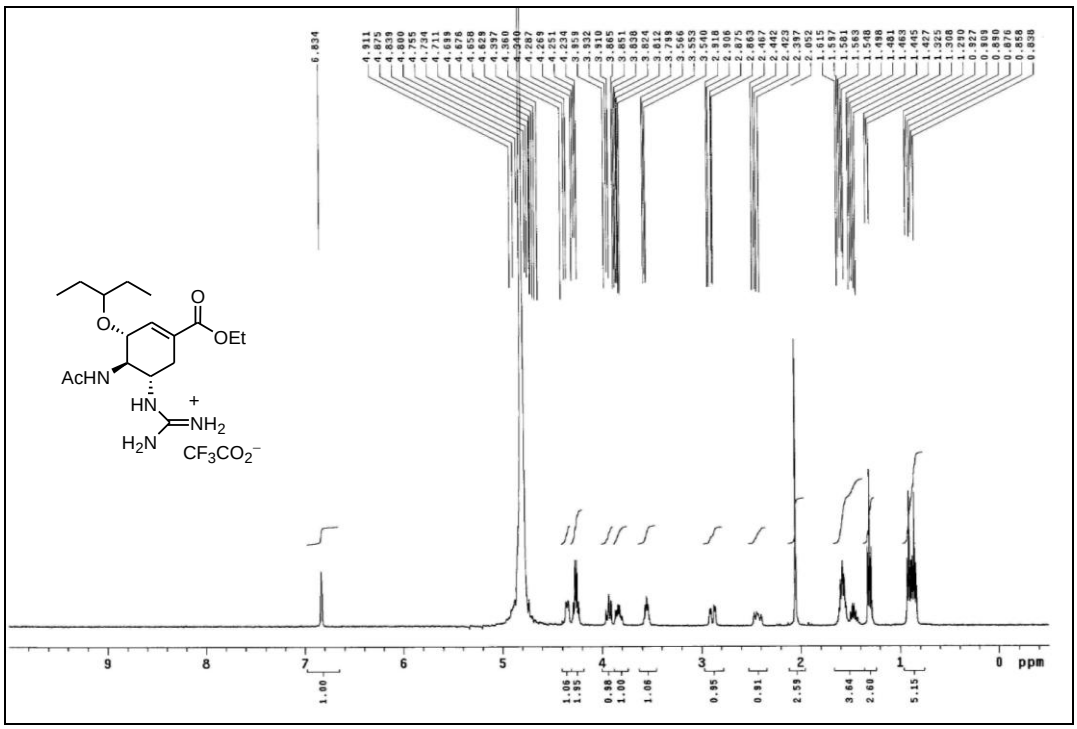
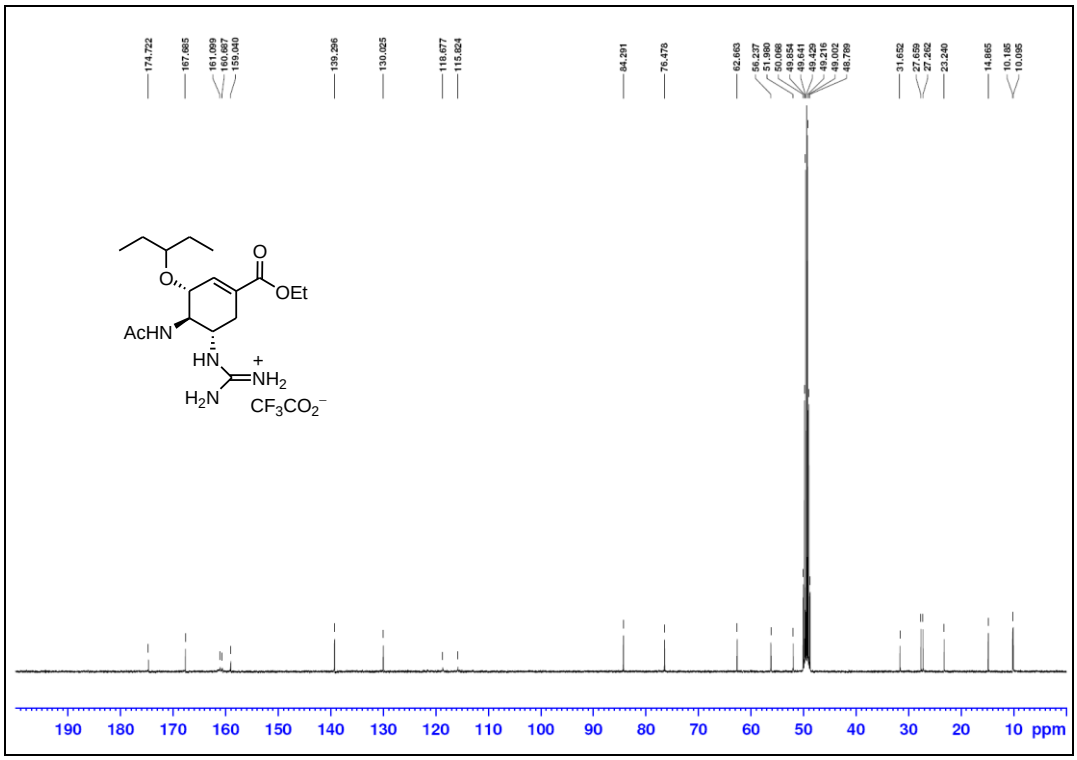


^{1}H NMR spectrum of guanidino-oseltamivir **2b** (as the TFA salt, 400 MHz, in D_2O)



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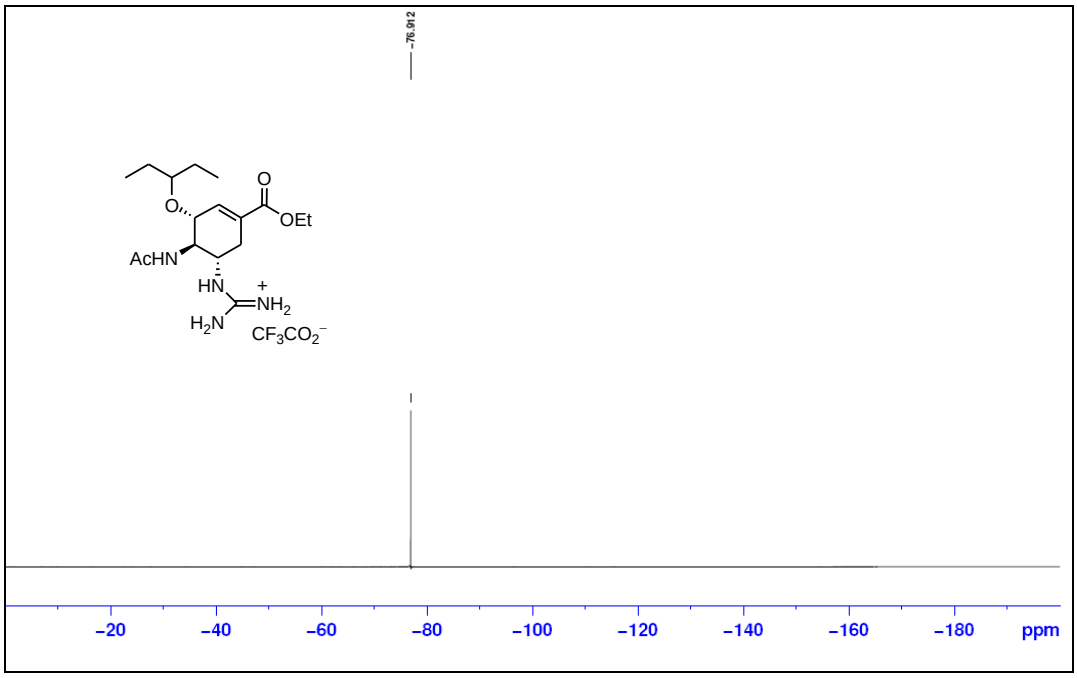
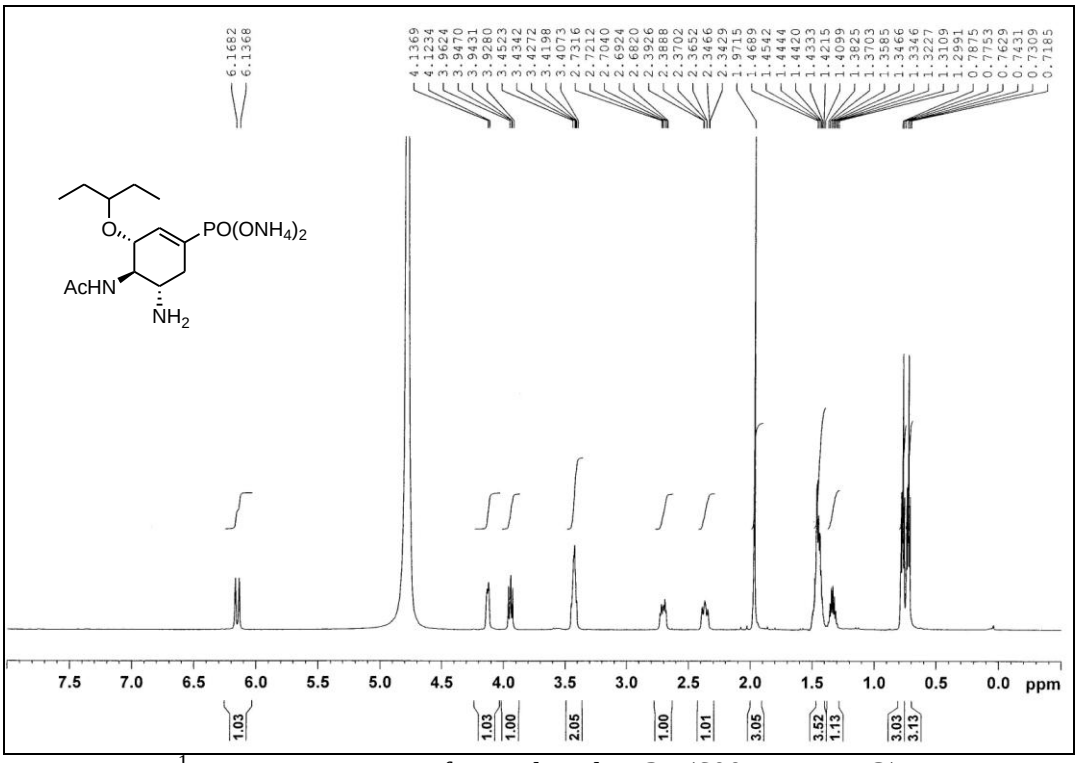
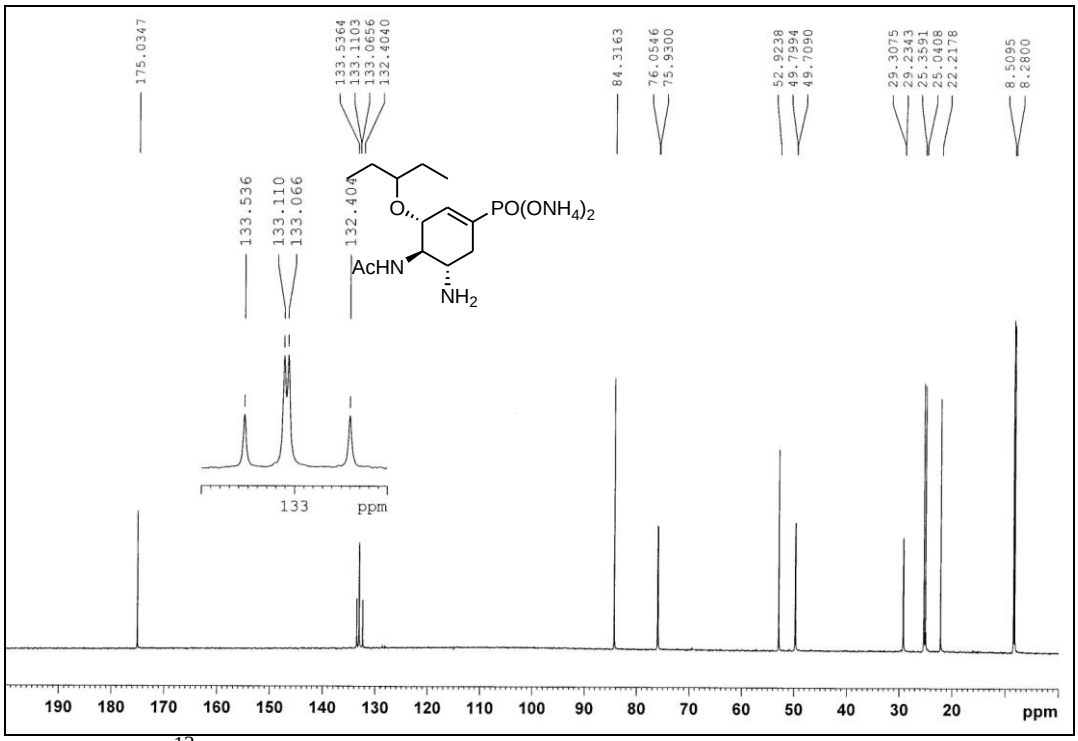


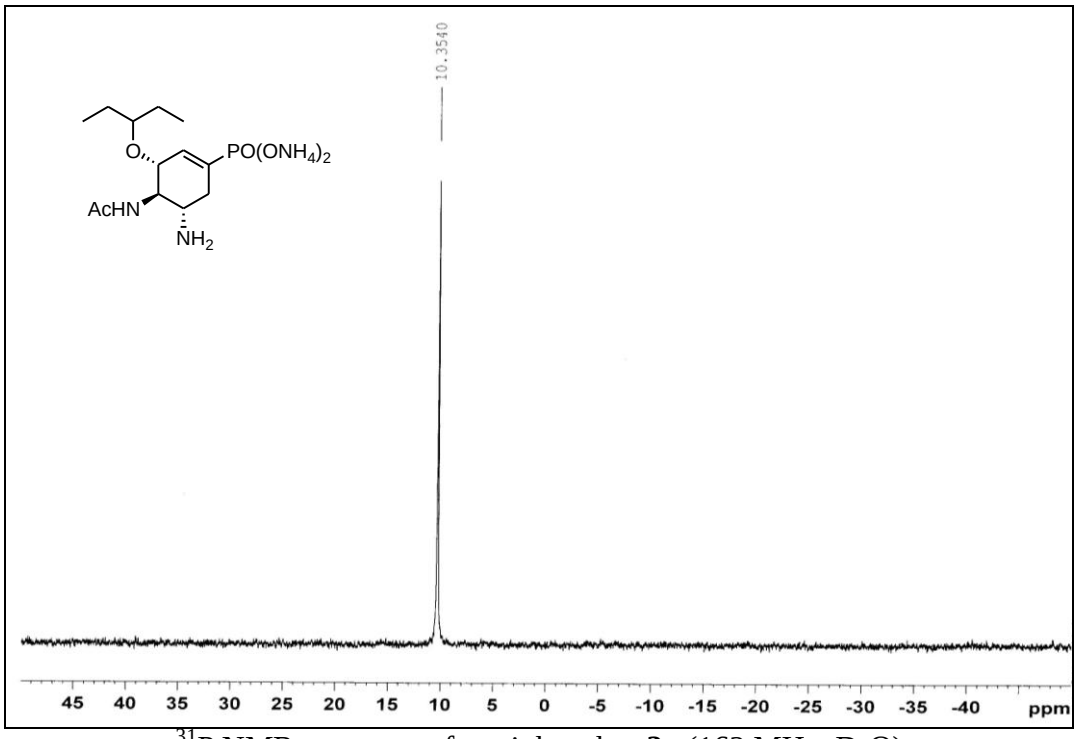
^{19}F NMR spectrum of guanidino-oseltamivir **2b** (as the TFA salt, 400 MHz, in CD_3OD)



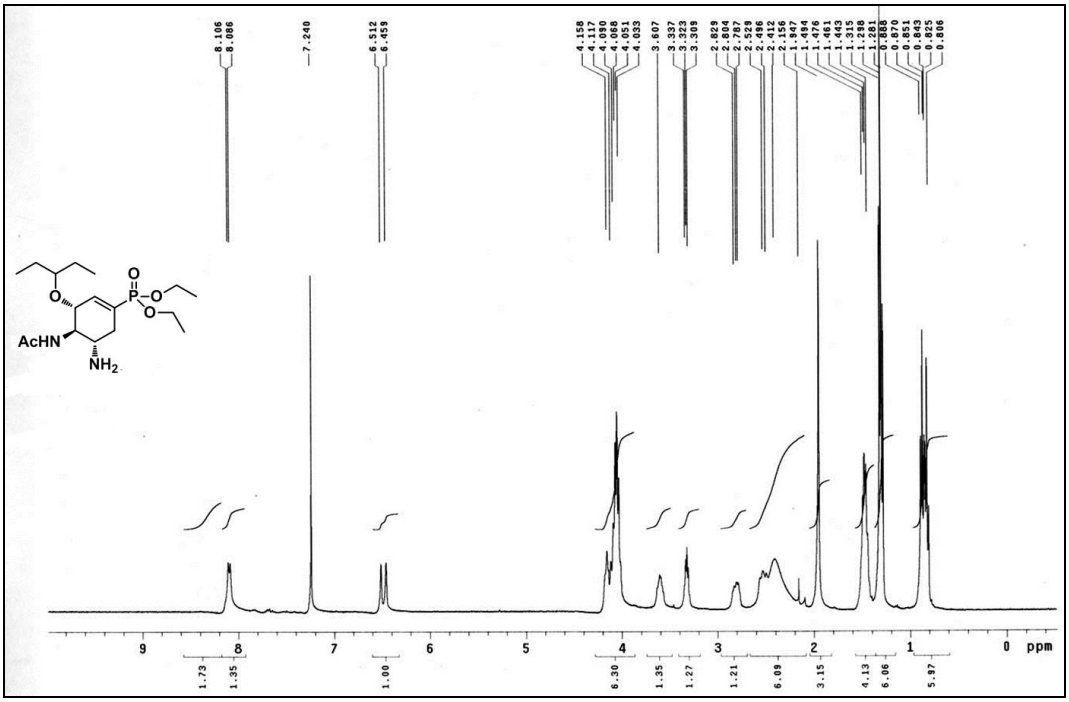
^{1}H NMR spectrum of tamiphosphor **3a** (600 MHz, D_2O)



^{13}C NMR spectrum of tamiphosphor **3a** (150 MHz, D_2O)



^{31}P NMR spectrum of tamiphosphor **3a** (162 MHz, D_2O)



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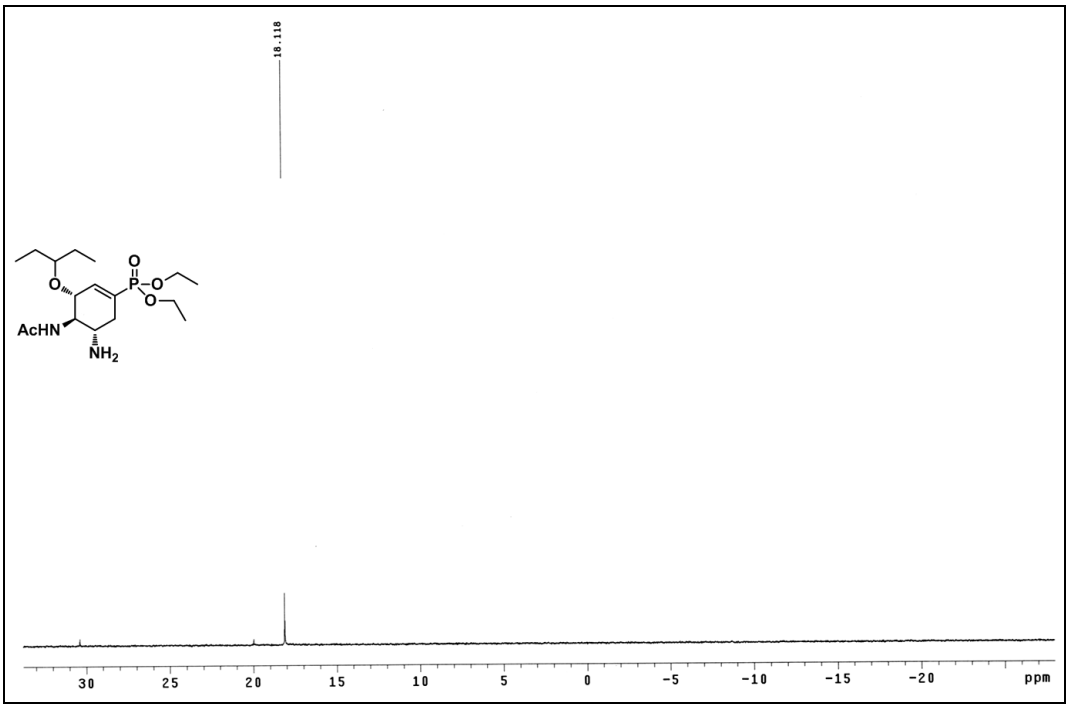

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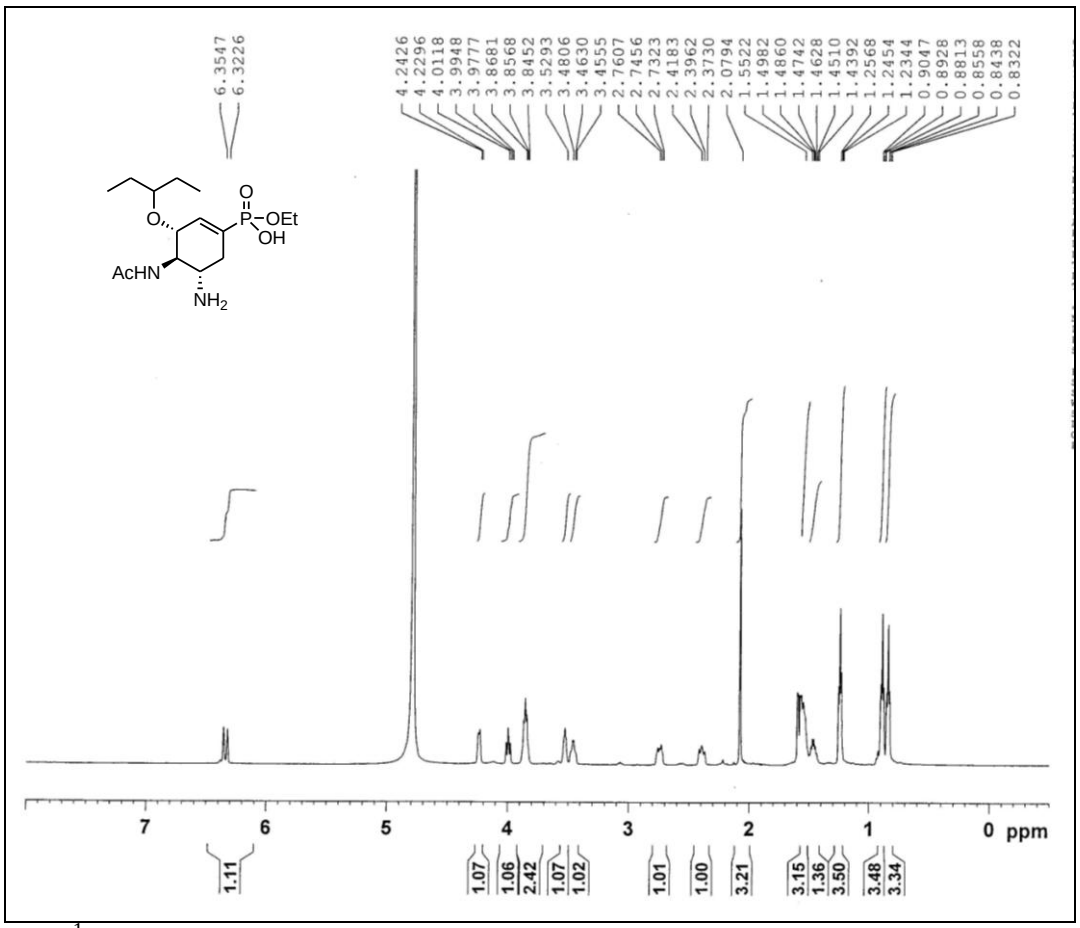

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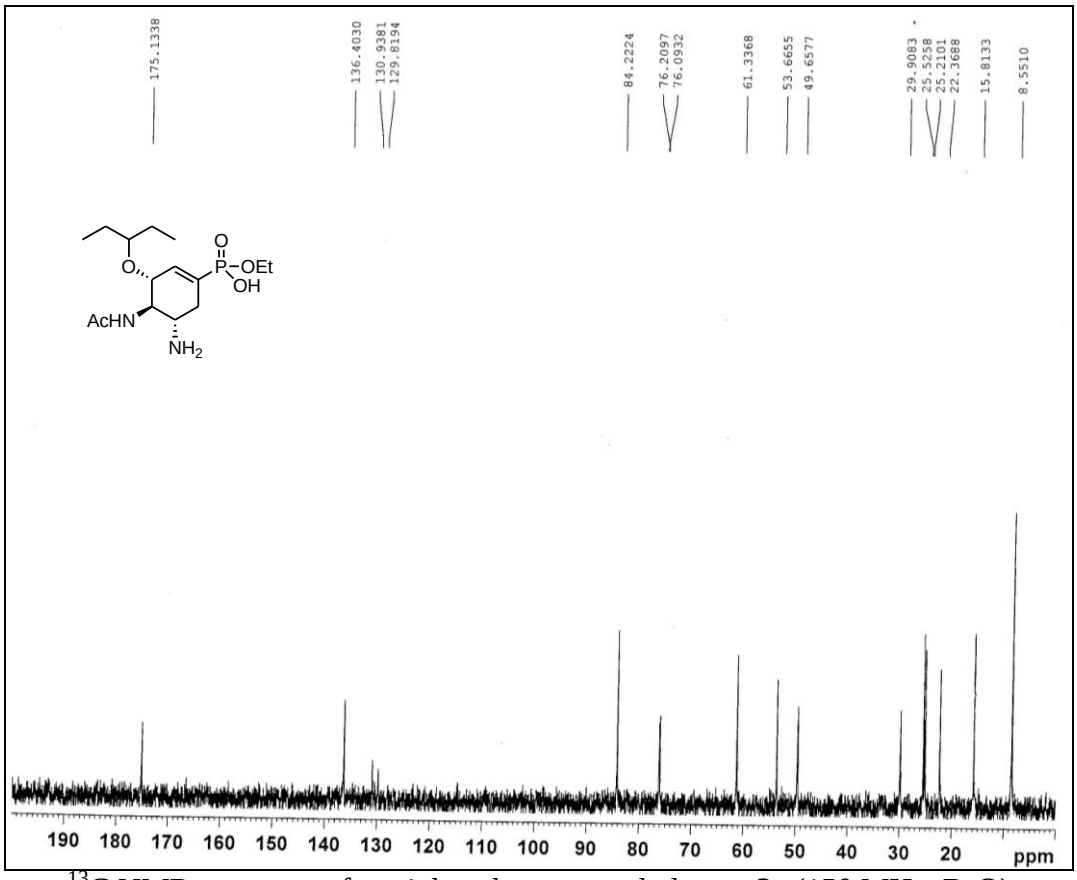

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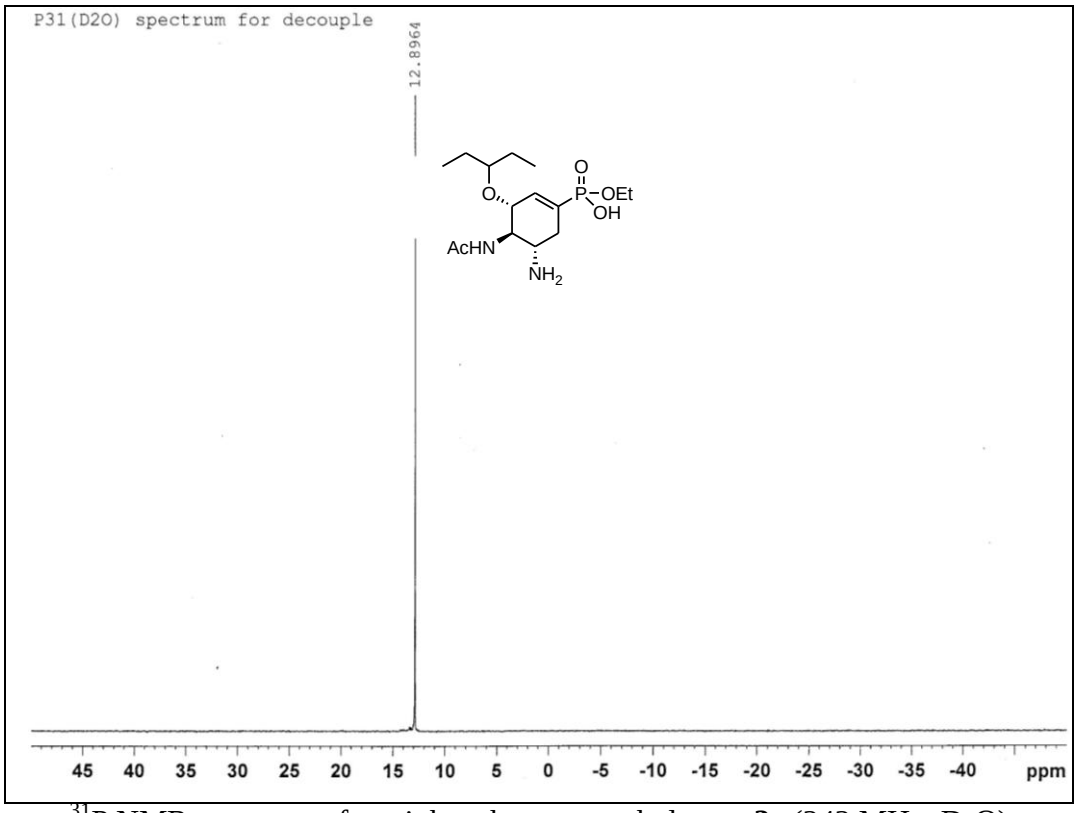

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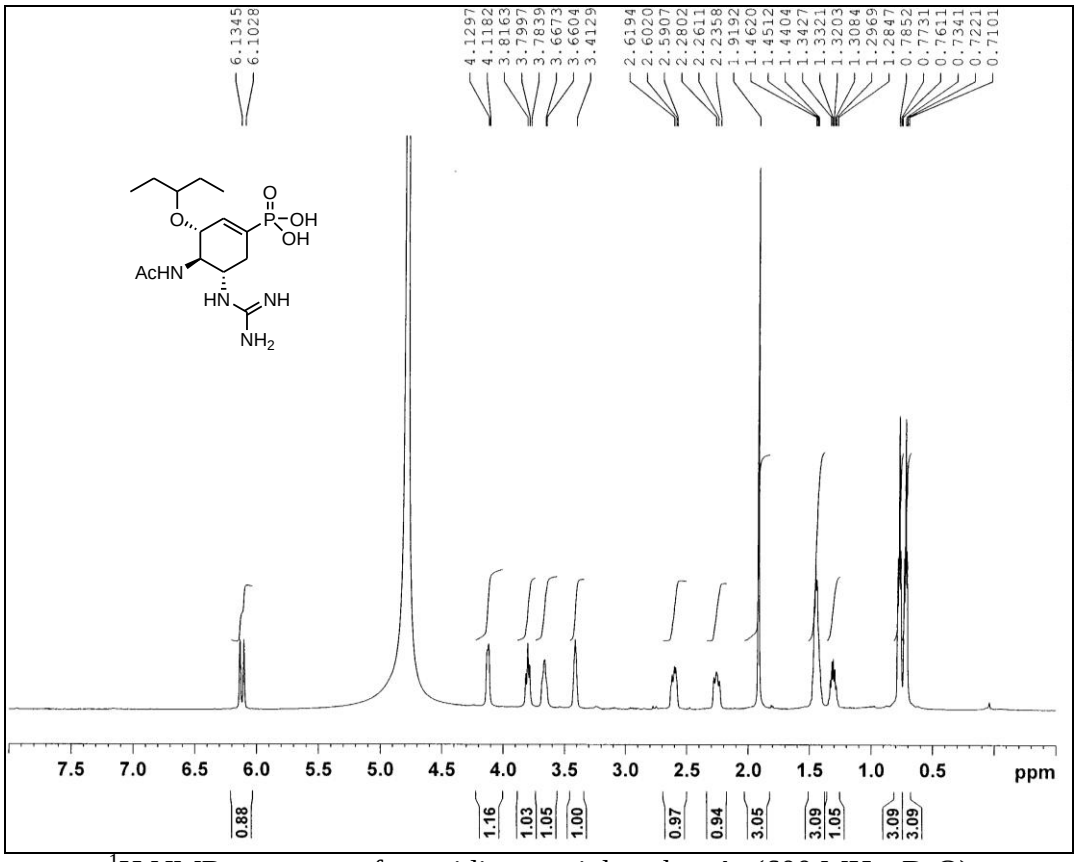

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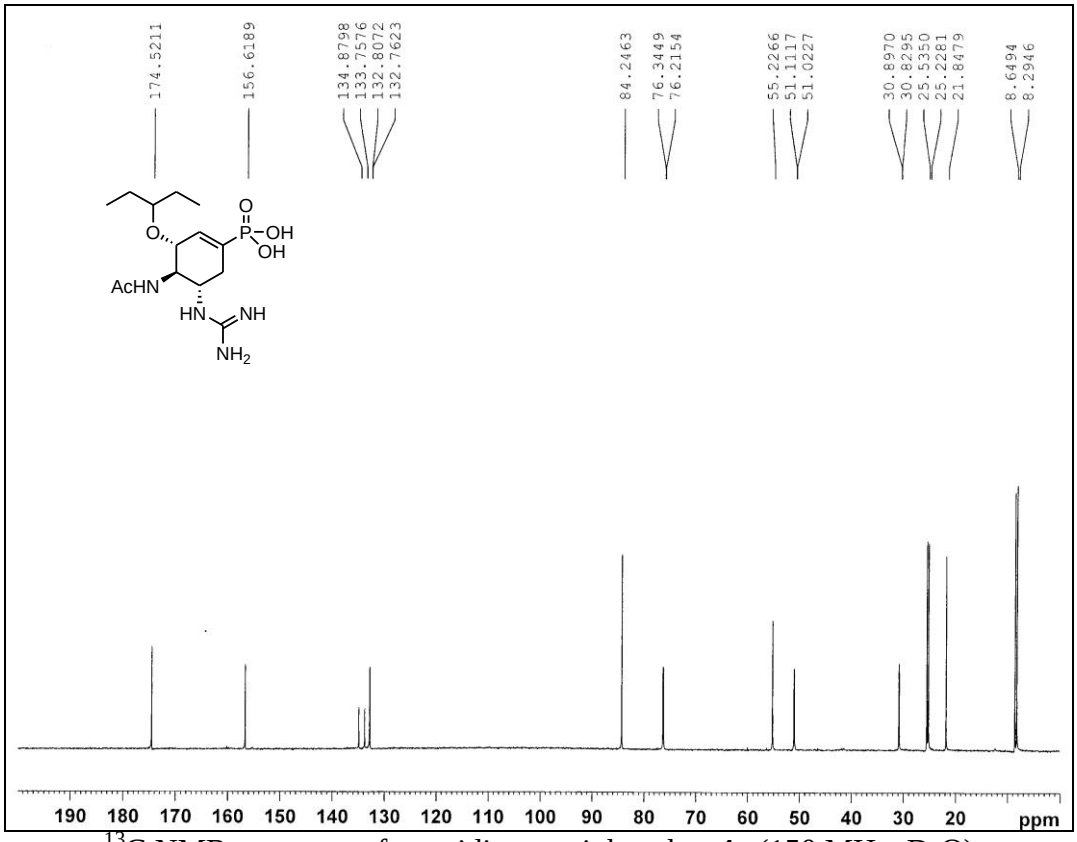

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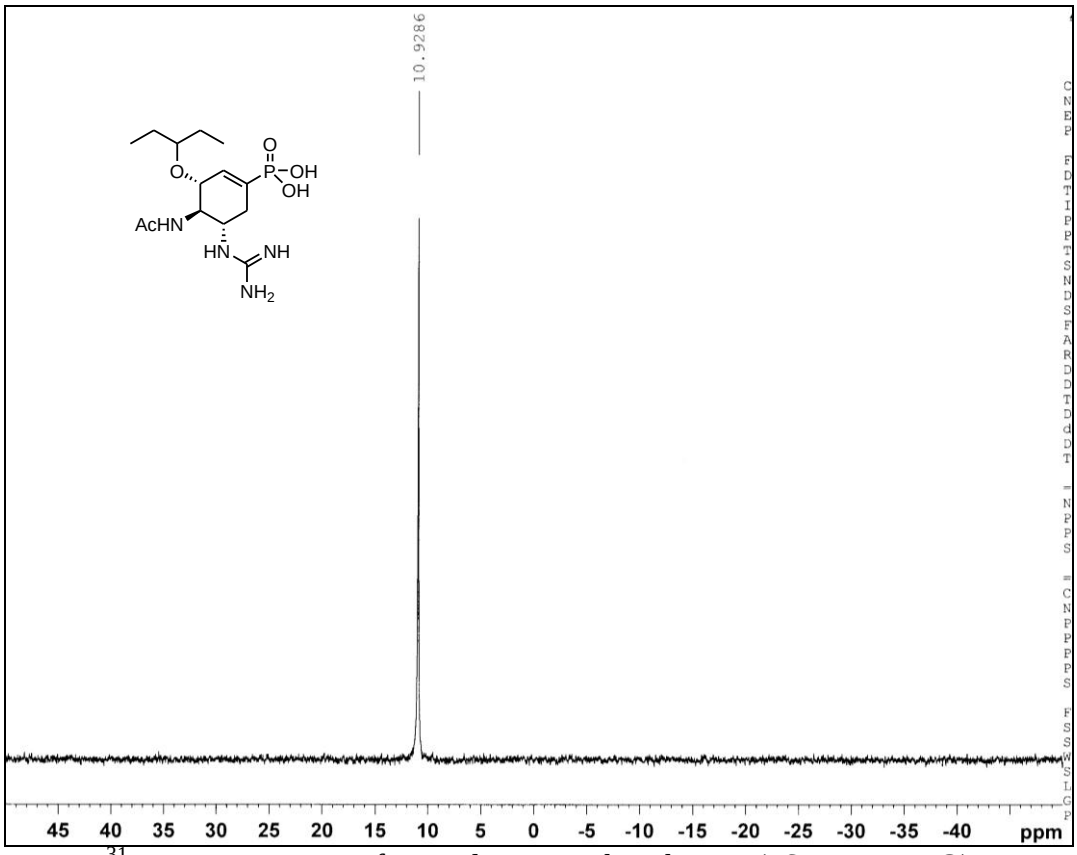

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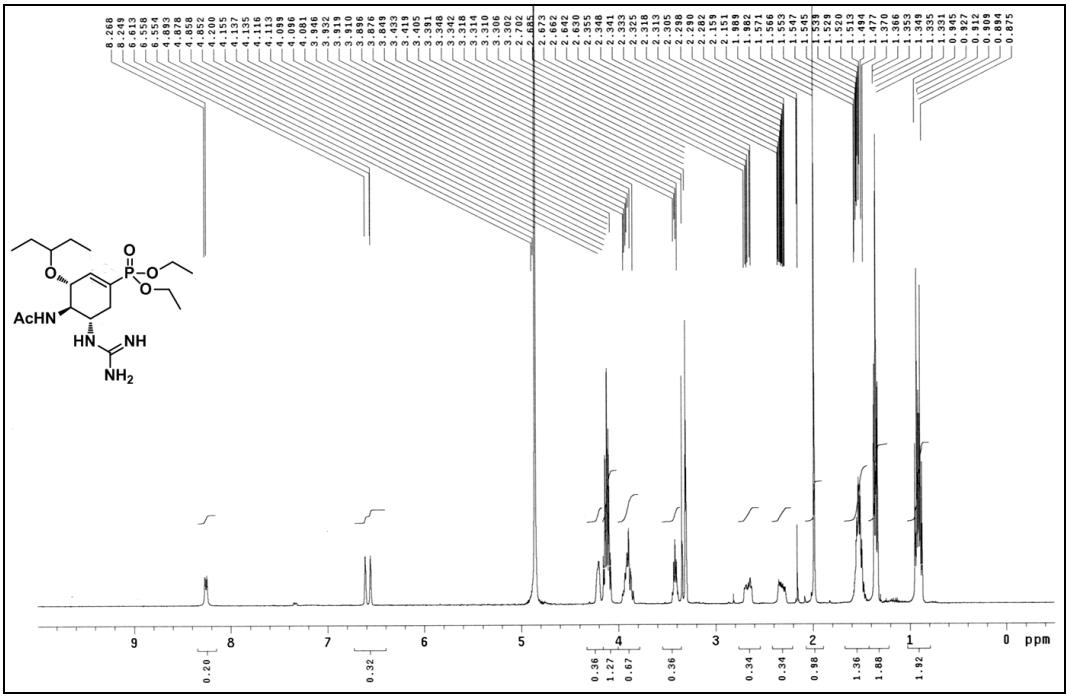
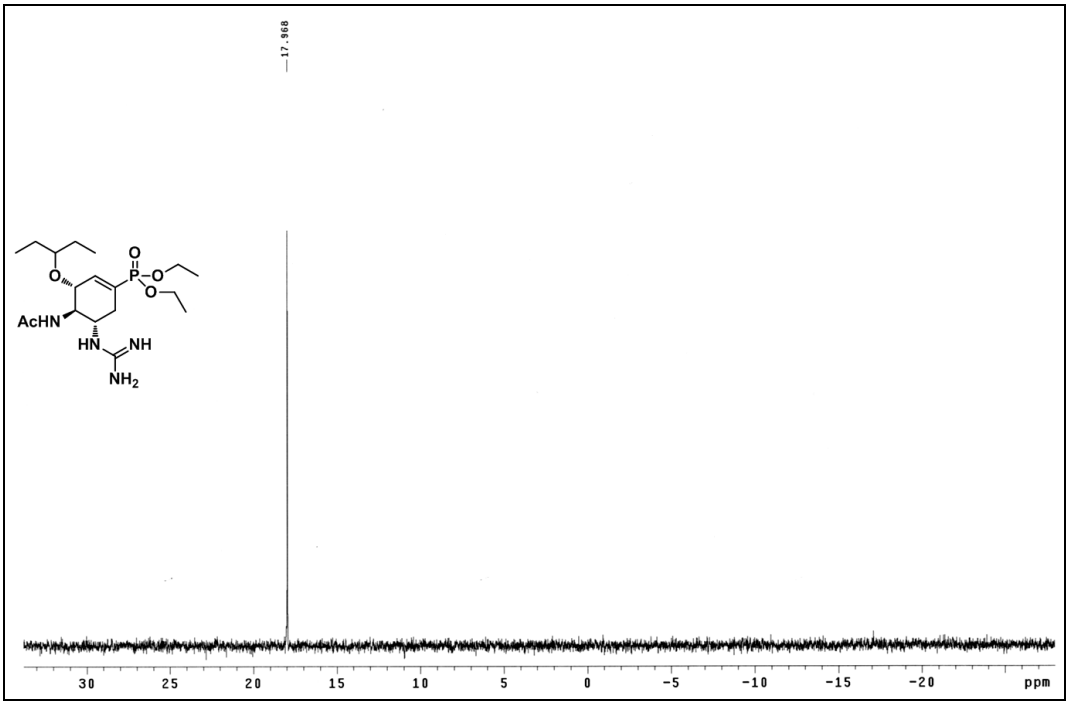


^{1}H NMR spectrum of guanidino-tamiphosphor diethyl ester **4b** (400 MHz, in CD_3OD)



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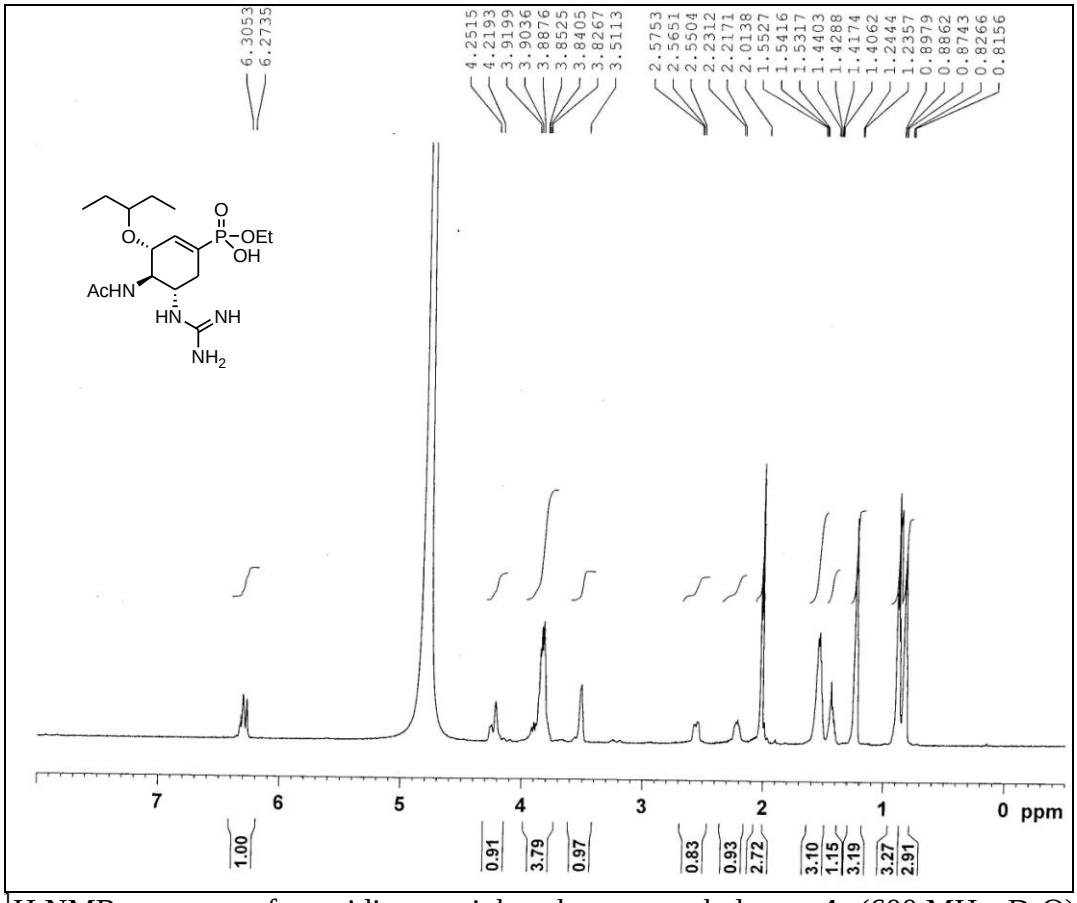

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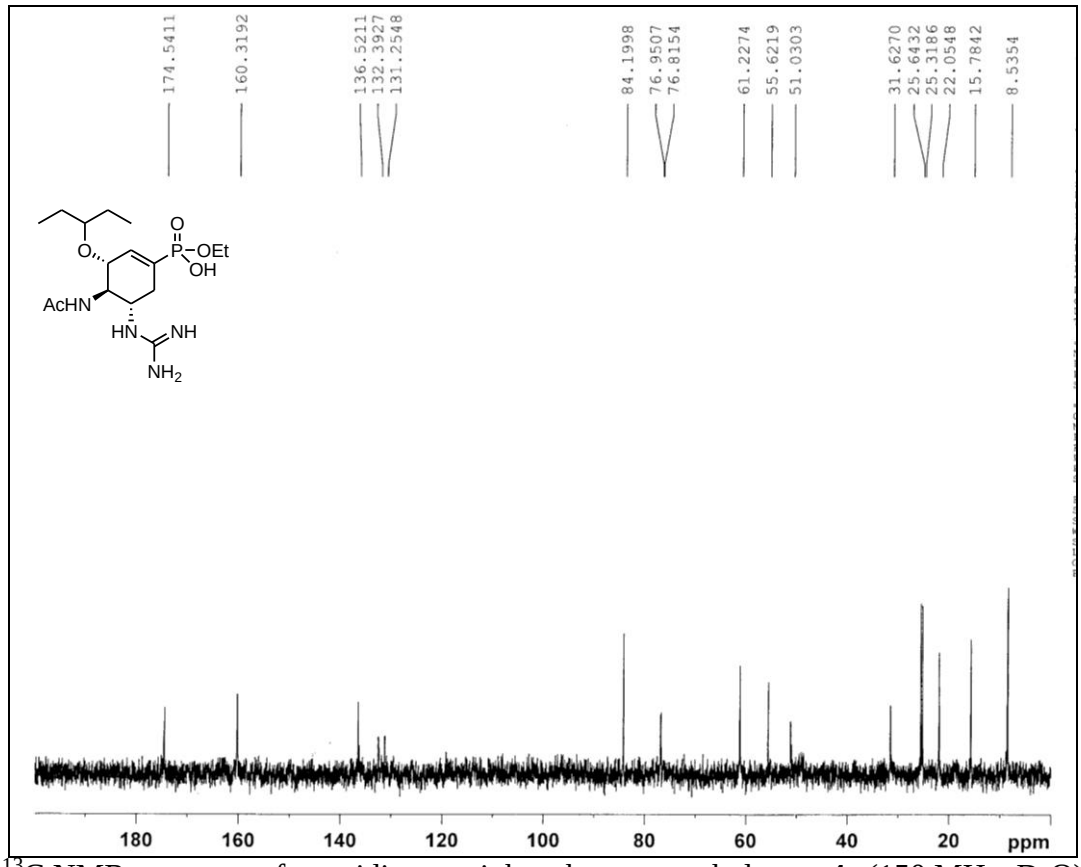

^{13}C NMR spectrum of guanidino-tamiphosphor monoethyl ester **4c** (150 MHz, D_2O)