

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-5-2	Ph	H	H	CH ₃	CH ₃	H	H	F	OH
XXXII-5-3	Ph	H	H	CH(CH ₃) ₂	CH ₃	H	H	F	OH
XXXII-5-4	Ph	H	H	CH ₂ CH(CH ₃) ₂	CH ₃	H	H	F	OH
XXXII-5-5	Ph	H	H	CH ₂ Ph	CH ₃	H	H	F	OH
XXXII-5-6	Ph	H	H	CH ₂ -indol-3-yl	CH ₃	H	H	F	OH
XXXII-5-7	Ph	H	H	CH ₂ CH ₂ SCH ₃	CH ₃	H	H	F	OH
XXXII-5-8	Ph	*	H	*	CH ₃	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-6.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-6-1	p-Me-Ph	H	H	H	CH ₃	H	H	F	OH
XXXII-6-2	p-Me-Ph	H	H	CH ₃	CH ₃	H	H	F	OH
XXXII-6-3	p-Me-Ph	H	H	CH(CH ₃) ₂	CH ₃	H	H	F	OH
XXXII-6-4	p-Me-Ph	H	H	CH ₂ CH(CH ₃) ₂	CH ₃	H	H	F	OH
XXXII-6-5	p-Me-Ph	H	H	CH ₂ Ph	CH ₃	H	H	F	OH
XXXII-6-6	p-Me-Ph	H	H	CH ₂ -indol-3-yl	CH ₃	H	H	F	OH
XXXII-6-7	p-Me-Ph	H	H	CH ₂ CH ₂ SCH ₃	CH ₃	H	H	F	OH
XXXII-6-8	p-Me-Ph	*	H	*	CH ₃	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-7.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-7-1	p-F-Ph	H	H	H	CH ₃	H	H	F	OH
XXXII-7-2	p-F-Ph	H	H	CH ₃	CH ₃	H	H	F	OH
XXXII-7-3	p-F-Ph	H	H	CH(CH ₃) ₂	CH ₃	H	H	F	OH
XXXII-7-4	p-F-Ph	H	H	CH ₂ CH(CH ₃) ₂	CH ₃	H	H	F	OH
XXXII-7-6	p-F-Ph	H	H	CH ₂ Ph	CH ₃	H	H	F	OH
XXXII-7-7	p-F-Ph	H	H	CH ₂ -indol-3-yl	CH ₃	H	H	F	OH
XXXII-7-8	p-F-Ph	H	H	CH ₂ CH ₂ SCH ₃	CH ₃	H	H	F	OH
XXXII-7-20	p-F-Ph	*	H	*	CH ₃	H	H	F	OH

5 *R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-8.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-8-1	p-Cl-Ph	H	H	H	CH ₃	H	H	F	OH
XXXII-8-2	p-Cl-Ph	H	H	CH ₃	CH ₃	H	H	F	OH
XXXII-8-3	p-Cl-Ph	H	H	CH(CH ₃) ₂	CH ₃	H	H	F	OH
XXXII-8-4	p-Cl-Ph	H	H	CH ₂ CH(CH ₃) ₂	CH ₃	H	H	F	OH
XXXII-8-5	p-Cl-Ph	H	H	CH ₂ Ph	CH ₃	H	H	F	OH
XXXII-8-6	p-Cl-Ph	H	H	CH ₂ -indol-3-yl	CH ₃	H	H	F	OH
XXXII-8-7	p-Cl-Ph	H	H	CH ₂ CH ₂ SCH ₃	CH ₃	H	H	F	OH
XXXII-8-8	p-Cl-Ph	*	H	*	CH ₃	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-9.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-9-1	p-Br-Ph	H	H	H	CH ₃	H	H	F	OH
XXXII-9-2	p-Br-Ph	H	H	CH ₃	CH ₃	H	H	F	OH
XXXII-9-3	p-Br-Ph	H	H	CH(CH ₃) ₂	CH ₃	H	H	F	OH
XXXII-9-4	p-Br-Ph	H	H	CH ₂ CH(CH ₃) ₂	CH ₃	H	H	F	OH
XXXII-9-6	p-Br-Ph	H	H	CH ₂ Ph	CH ₃	H	H	F	OH
XXXII-9-7	p-Br-Ph	H	H	CH ₂ -indol-3-yl	CH ₃	H	H	F	OH
XXXII-9-8	p-Br-Ph	H	H	CH ₂ CH ₂ SCH ₃	CH ₃	H	H	F	OH
XXXII-9-20	p-Br-Ph	*	H	*	CH ₃	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-10.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-10-1	p-I-Ph	H	H	H	CH ₃	H	H	F	OH
XXXII-10-2	p-I-Ph	H	H	CH ₃	CH ₃	H	H	F	OH
XXXII-10-3	p-I-Ph	H	H	CH(CH ₃) ₂	CH ₃	H	H	F	OH
XXXII-10-4	p-I-Ph	H	H	CH ₂ CH(CH ₃) ₂	CH ₃	H	H	F	OH
XXXII-10-5	p-I-Ph	H	H	CH ₂ Ph	CH ₃	H	H	F	OH
XXXII-10-6	p-I-Ph	H	H	CH ₂ -indol-3-yl	CH ₃	H	H	F	OH
XXXII-10-7	p-I-Ph	H	H	CH ₂ CH ₂ SCH ₃	CH ₃	H	H	F	OH
XXXII-10-8	p-I-Ph	*	H	*	CH ₃	H	H	F	OH

5 *R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-11.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-11-1	CH ₃	H	H	H	Et	H	H	F	OH
XXXII-11-2	CH ₃	H	H	CH ₃	Et	H	H	F	OH
XXXII-11-3	CH ₃	H	H	CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-11-4	CH ₃	H	H	CH ₂ CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-11-5	CH ₃	H	H	CH ₂ Ph	Et	H	H	F	OH
XXXII-11-6	CH ₃	H	H	CH ₂ -indol-3-yl	Et	H	H	F	OH
XXXII-11-7	CH ₃	H	H	CH ₂ CH ₂ SCH ₃	Et	H	H	F	OH
XXXII-11-8	CH ₃	*	H	*	Et	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-12.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-12-1	Et	H	H	H	Et	H	H	F	OH
XXXII-12-2	Et	H	H	CH ₃	Et	H	H	F	OH
XXXII-12-3	Et	H	H	CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-12-4	Et	H	H	CH ₂ CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-12-5	Et	H	H	CH ₂ Ph	Et	H	H	F	OH
XXXII-12-6	Et	H	H	CH ₂ -indol-3-yl	Et	H	H	F	OH
XXXII-12-7	Et	H	H	CH ₂ CH ₂ SCH ₃	Et	H	H	F	OH
XXXII-12-8	Et	*	H	*	Et	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

5 Table XXXII-13.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-13-1	ⁱ Pr	H	H	H	Et	H	H	F	OH
XXXII-13-2	ⁱ Pr	H	H	CH ₃	Et	H	H	F	OH
XXXII-13-3	ⁱ Pr	H	H	CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-13-4	ⁱ Pr	H	H	CH ₂ CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-13-5	ⁱ Pr	H	H	CH ₂ Ph	Et	H	H	F	OH
XXXII-13-6	ⁱ Pr	H	H	CH ₂ -indol-3-yl	Et	H	H	F	OH
XXXII-13-7	ⁱ Pr	H	H	CH ₂ CH ₂ SCH ₃	Et	H	H	F	OH
XXXII-13-8	ⁱ Pr	*	H	*	Et	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-14.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-14-1	^t Bu	H	H	H	Et	H	H	F	OH
XXXII-14-2	^t Bu	H	H	CH ₃	Et	H	H	F	OH
XXXII-14-3	^t Bu	H	H	CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-14-4	^t Bu	H	H	CH ₂ CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-14-5	^t Bu	H	H	CH ₂ Ph	Et	H	H	F	OH
XXXII-14-6	^t Bu	H	H	CH ₂ -indol-3-yl	Et	H	H	F	OH
XXXII-14-7	^t Bu	H	H	CH ₂ CH ₂ SCH ₃	Et	H	H	F	OH
XXXII-14-8	^t Bu	*	H	*	Et	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-15.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-15-1	Ph	H	H	H	Et	H	H	F	OH
XXXII-15-2	Ph	H	H	CH ₃	Et	H	H	F	OH
XXXII-15-3	Ph	H	H	CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-15-4	Ph	H	H	CH ₂ CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-15-5	Ph	H	H	CH ₂ Ph	Et	H	H	F	OH
XXXII-15-6	Ph	H	H	CH ₂ -indol-3-yl	Et	H	H	F	OH
XXXII-15-7	Ph	H	H	CH ₂ CH ₂ SCH ₃	Et	H	H	F	OH
XXXII-15-8	Ph	*	H	*	Et	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

5 Table XXXII-16.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-16-1	p-Me-Ph	H	H	H	Et	H	H	F	OH
XXXII-16-2	p-Me-Ph	H	H	CH ₃	Et	H	H	F	OH
XXXII-16-3	p-Me-Ph	H	H	CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-16-4	p-Me-Ph	H	H	CH ₂ CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-16-5	p-Me-Ph	H	H	CH ₂ Ph	Et	H	H	F	OH
XXXII-16-6	p-Me-Ph	H	H	CH ₂ -indol-3-yl	Et	H	H	F	OH
XXXII-16-7	p-Me-Ph	H	H	CH ₂ CH ₂ SCH ₃	Et	H	H	F	OH
XXXII-16-8	p-Me-Ph	*	H	*	Et	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-17.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-17-1	p-F-Ph	H	H	H	Et	H	H	F	OH
XXXII-17-2	p-F-Ph	H	H	CH ₃	Et	H	H	F	OH
XXXII-17-3	p-F-Ph	H	H	CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-17-4	p-F-Ph	H	H	CH ₂ CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-17-5	p-F-Ph	H	H	CH ₂ Ph	Et	H	H	F	OH
XXXII-17-6	p-F-Ph	H	H	CH ₂ -indol-3-yl	Et	H	H	F	OH
XXXII-17-7	p-F-Ph	H	H	CH ₂ CH ₂ SCH ₃	Et	H	H	F	OH
XXXII-17-8	p-F-Ph	*	H	*	Et	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-18.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-18-1	p-Cl-Ph	H	H	H	Et	H	H	F	OH
XXXII-18-2	p-Cl-Ph	H	H	CH ₃	Et	H	H	F	OH
XXXII-18-3	p-Cl-Ph	H	H	CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-18-4	p-Cl-Ph	H	H	CH ₂ CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-18-5	p-Cl-Ph	H	H	CH ₂ Ph	Et	H	H	F	OH
XXXII-18-6	p-Cl-Ph	H	H	CH ₂ -indol-3-yl	Et	H	H	F	OH
XXXII-18-7	p-Cl-Ph	H	H	CH ₂ CH ₂ SCH ₃	Et	H	H	F	OH
XXXII-18-8	p-Cl-Ph	*	H	*	Et	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

5 Table XXXII-19.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-19-1	p-Br-Ph	H	H	H	Et	H	H	F	OH
XXXII-19-2	p-Br-Ph	H	H	CH ₃	Et	H	H	F	OH
XXXII-19-3	p-Br-Ph	H	H	CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-19-4	p-Br-Ph	H	H	CH ₂ CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-19-5	p-Br-Ph	H	H	CH ₂ Ph	Et	H	H	F	OH
XXXII-19-6	p-Br-Ph	H	H	CH ₂ -indol-3-yl	Et	H	H	F	OH
XXXII-19-7	p-Br-Ph	H	H	CH ₂ CH ₂ SCH ₃	Et	H	H	F	OH
XXXII-19-8	p-Br-Ph	*	H	*	Et	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-20.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-20-1	p-I-Ph	H	H	H	Et	H	H	F	OH
XXXII-20-2	p-I-Ph	H	H	CH ₃	Et	H	H	F	OH
XXXII-20-3	p-I-Ph	H	H	CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-20-4	p-I-Ph	H	H	CH ₂ CH(CH ₃) ₂	Et	H	H	F	OH
XXXII-20-5	p-I-Ph	H	H	CH ₂ Ph	Et	H	H	F	OH
XXXII-20-6	p-I-Ph	H	H	CH ₂ -indol-3-yl	Et	H	H	F	OH
XXXII-20-7	p-I-Ph	H	H	CH ₂ CH ₂ SCH ₃	Et	H	H	F	OH
XXXII-20-8	p-I-Ph	*	H	*	Et	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-21.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-21-1	CH ₃	H	H	H	ⁱ Pr	H	H	F	OH
XXXII-21-2	CH ₃	H	H	CH ₃	ⁱ Pr	H	H	F	OH
XXXII-21-3	CH ₃	H	H	CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-21-4	CH ₃	H	H	CH ₂ CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-21-5	CH ₃	H	H	CH ₂ Ph	ⁱ Pr	H	H	F	OH
XXXII-21-6	CH ₃	H	H	CH ₂ -indol-3-yl	ⁱ Pr	H	H	F	OH
XXXII-21-7	CH ₃	H	H	CH ₂ CH ₂ SCH ₃	ⁱ Pr	H	H	F	OH
XXXII-21-8	CH ₃	*	H	*	ⁱ Pr	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

5 Table XXXII-22.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-22-1	Et	H	H	H	ⁱ Pr	H	H	F	OH
XXXII-22-2	Et	H	H	CH ₃	ⁱ Pr	H	H	F	OH
XXXII-22-3	Et	H	H	CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-22-4	Et	H	H	CH ₂ CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-22-5	Et	H	H	CH ₂ Ph	ⁱ Pr	H	H	F	OH
XXXII-22-6	Et	H	H	CH ₂ -indol-3-yl	ⁱ Pr	H	H	F	OH
XXXII-22-7	Et	H	H	CH ₂ CH ₂ SCH ₃	ⁱ Pr	H	H	F	OH
XXXII-22-8	Et	*	H	*	ⁱ Pr	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-23.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-23-1	ⁱ Pr	H	H	H	ⁱ Pr	H	H	F	OH
XXXII-23-2	ⁱ Pr	H	H	CH ₃	ⁱ Pr	H	H	F	OH
XXXII-23-3	ⁱ Pr	H	H	CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-23-4	ⁱ Pr	H	H	CH ₂ CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-23-5	ⁱ Pr	H	H	CH ₂ Ph	ⁱ Pr	H	H	F	OH
XXXII-23-6	ⁱ Pr	H	H	CH ₂ -indol-3-yl	ⁱ Pr	H	H	F	OH
XXXII-23-7	ⁱ Pr	H	H	CH ₂ CH ₂ SCH ₃	ⁱ Pr	H	H	F	OH
XXXII-23-8	ⁱ Pr	*	H	*	ⁱ Pr	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-24.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-24-1	^t Bu	H	H	H	ⁱ Pr	H	H	F	OH
XXXII-24-2	^t Bu	H	H	CH ₃	ⁱ Pr	H	H	F	OH
XXXII-24-3	^t Bu	H	H	CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-24-4	^t Bu	H	H	CH ₂ CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-24-5	^t Bu	H	H	CH ₂ Ph	ⁱ Pr	H	H	F	OH
XXXII-24-6	^t Bu	H	H	CH ₂ -indol-3-yl	ⁱ Pr	H	H	F	OH
XXXII-24-7	^t Bu	H	H	CH ₂ CH ₂ SCH ₃	ⁱ Pr	H	H	F	OH
XXXII-24-8	^t Bu	*	H	*	ⁱ Pr	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

5 Table XXXII-25.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-25-1	Ph	H	H	H	ⁱ Pr	H	H	F	OH
XXXII-25-2	Ph	H	H	CH ₃	ⁱ Pr	H	H	F	OH
XXXII-25-3	Ph	H	H	CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-25-4	Ph	H	H	CH ₂ CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-25-5	Ph	H	H	CH ₂ Ph	ⁱ Pr	H	H	F	OH
XXXII-25-6	Ph	H	H	CH ₂ -indol-3-yl	ⁱ Pr	H	H	F	OH
XXXII-25-7	Ph	H	H	CH ₂ CH ₂ SCH ₃	ⁱ Pr	H	H	F	OH
XXXII-25-8	Ph	*	H	*	ⁱ Pr	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-26.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-26-1	p-Me-Ph	H	H	H	ⁱ Pr	H	H	F	OH
XXXII-26-2	p-Me-Ph	H	H	CH ₃	ⁱ Pr	H	H	F	OH
XXXII-26-3	p-Me-Ph	H	H	CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-26-4	p-Me-Ph	H	H	CH ₂ CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-26-5	p-Me-Ph	H	H	CH ₂ Ph	ⁱ Pr	H	H	F	OH
XXXII-26-6	p-Me-Ph	H	H	CH ₂ -indol-3-yl	ⁱ Pr	H	H	F	OH
XXXII-26-7	p-Me-Ph	H	H	CH ₂ CH ₂ SCH ₃	ⁱ Pr	H	H	F	OH
XXXII-26-8	p-Me-Ph	*	H	*	ⁱ Pr	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-27.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-27-1	p-F-Ph	H	H	H	ⁱ Pr	H	H	F	OH
XXXII-27-2	p-F-Ph	H	H	CH ₃	ⁱ Pr	H	H	F	OH
XXXII-27-3	p-F-Ph	H	H	CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-27-4	p-F-Ph	H	H	CH ₂ CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-27-5	p-F-Ph	H	H	CH ₂ Ph	ⁱ Pr	H	H	F	OH
XXXII-27-6	p-F-Ph	H	H	CH ₂ -indol-3-yl	ⁱ Pr	H	H	F	OH
XXXII-27-7	p-F-Ph	H	H	CH ₂ CH ₂ SCH ₃	ⁱ Pr	H	H	F	OH
XXXII-27-8	p-F-Ph	*	H	*	ⁱ Pr	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

5 Table XXXII-28.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-28-1	p-Cl-Ph	H	H	H	ⁱ Pr	H	H	F	OH
XXXII-28-2	p-Cl-Ph	H	H	CH ₃	ⁱ Pr	H	H	F	OH
XXXII-28-3	p-Cl-Ph	H	H	CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-28-4	p-Cl-Ph	H	H	CH ₂ CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-28-5	p-Cl-Ph	H	H	CH ₂ Ph	ⁱ Pr	H	H	F	OH
XXXII-28-6	p-Cl-Ph	H	H	CH ₂ -indol-3-yl	ⁱ Pr	H	H	F	OH
XXXII-28-7	p-Cl-Ph	H	H	CH ₂ CH ₂ SCH ₃	ⁱ Pr	H	H	F	OH
XXXII-28-8	p-Cl-Ph	*	H	*	ⁱ Pr	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-29.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-29-1	p-Br-Ph	H	H	H	ⁱ Pr	H	H	F	OH
XXXII-29-2	p-Br-Ph	H	H	CH ₃	ⁱ Pr	H	H	F	OH
XXXII-29-3	p-Br-Ph	H	H	CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-29-4	p-Br-Ph	H	H	CH ₂ CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-29-5	p-Br-Ph	H	H	CH ₂ Ph	ⁱ Pr	H	H	F	OH
XXXII-29-6	p-Br-Ph	H	H	CH ₂ -indol-3-yl	ⁱ Pr	H	H	F	OH
XXXII-29-7	p-Br-Ph	H	H	CH ₂ CH ₂ SCH ₃	ⁱ Pr	H	H	F	OH
XXXII-29-8	p-Br-Ph	*	H	*	ⁱ Pr	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-30.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-30-1	p-I-Ph	H	H	H	ⁱ Pr	H	H	F	OH
XXXII-30-2	p-I-Ph	H	H	CH ₃	ⁱ Pr	H	H	F	OH
XXXII-30-3	p-I-Ph	H	H	CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-30-4	p-I-Ph	H	H	CH ₂ CH(CH ₃) ₂	ⁱ Pr	H	H	F	OH
XXXII-30-5	p-I-Ph	H	H	CH ₂ Ph	ⁱ Pr	H	H	F	OH
XXXII-30-6	p-I-Ph	H	H	CH ₂ -indol-3-yl	ⁱ Pr	H	H	F	OH
XXXII-30-7	p-I-Ph	H	H	CH ₂ CH ₂ SCH ₃	ⁱ Pr	H	H	F	OH
XXXII-30-8	p-I-Ph	*	H	*	ⁱ Pr	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

5 Table XXXII-31.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-31-1	CH ₃	H	H	H	ⁿ Bu	H	H	F	OH
XXXII-31-2	CH ₃	H	H	CH ₃	ⁿ Bu	H	H	F	OH
XXXII-31-3	CH ₃	H	H	CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-31-4	CH ₃	H	H	CH ₂ CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-31-5	CH ₃	H	H	CH ₂ Ph	ⁿ Bu	H	H	F	OH
XXXII-31-6	CH ₃	H	H	CH ₂ -indol-3-yl	ⁿ Bu	H	H	F	OH
XXXII-31-7	CH ₃	H	H	CH ₂ CH ₂ SCH ₃	ⁿ Bu	H	H	F	OH
XXXII-31-8	CH ₃	*	H	*	ⁿ Bu	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-32.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-32-1	Et	H	H	H	ⁿ Bu	H	H	F	OH
XXXII-32-2	Et	H	H	CH ₃	ⁿ Bu	H	H	F	OH
XXXII-32-3	Et	H	H	CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-32-4	Et	H	H	CH ₂ CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-32-5	Et	H	H	CH ₂ Ph	ⁿ Bu	H	H	F	OH
XXXII-32-6	Et	H	H	CH ₂ -indol-3-yl	ⁿ Bu	H	H	F	OH
XXXII-32-7	Et	H	H	CH ₂ CH ₂ SCH ₃	ⁿ Bu	H	H	F	OH
XXXII-32-8	Et	*	H	*	ⁿ Bu	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-33.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-33-1	ⁱ Pr	H	H	H	ⁿ Bu	H	H	F	OH
XXXII-33-2	ⁱ Pr	H	H	CH ₃	ⁿ Bu	H	H	F	OH
XXXII-33-3	ⁱ Pr	H	H	CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-33-4	ⁱ Pr	H	H	CH ₂ CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-33-5	ⁱ Pr	H	H	CH ₂ Ph	ⁿ Bu	H	H	F	OH
XXXII-33-6	ⁱ Pr	H	H	CH ₂ -indol-3-yl	ⁿ Bu	H	H	F	OH
XXXII-33-7	ⁱ Pr	H	H	CH ₂ CH ₂ SCH ₃	ⁿ Bu	H	H	F	OH
XXXII-33-8	ⁱ Pr	*	H	*	ⁿ Bu	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

5 Table XXXII-34.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-34-1	^t Bu	H	H	H	ⁿ Bu	H	H	F	OH
XXXII-34-2	^t Bu	H	H	CH ₃	ⁿ Bu	H	H	F	OH
XXXII-34-3	^t Bu	H	H	CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-34-4	^t Bu	H	H	CH ₂ CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-34-5	^t Bu	H	H	CH ₂ Ph	ⁿ Bu	H	H	F	OH
XXXII-34-6	^t Bu	H	H	CH ₂ -indol-3-yl	ⁿ Bu	H	H	F	OH
XXXII-34-7	^t Bu	H	H	CH ₂ CH ₂ SCH ₃	ⁿ Bu	H	H	F	OH
XXXII-34-8	^t Bu	*	H	*	ⁿ Bu	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-35.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-35-1	Ph	H	H	H	ⁿ Bu	H	H	F	OH
XXXII-35-2	Ph	H	H	CH ₃	ⁿ Bu	H	H	F	OH
XXXII-35-3	Ph	H	H	CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-35-4	Ph	H	H	CH ₂ CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-35-5	Ph	H	H	CH ₂ Ph	ⁿ Bu	H	H	F	OH
XXXII-35-6	Ph	H	H	CH ₂ -indol-3-yl	ⁿ Bu	H	H	F	OH
XXXII-35-7	Ph	H	H	CH ₂ CH ₂ SCH ₃	ⁿ Bu	H	H	F	OH
XXXII-35-8	Ph	*	H	*	ⁿ Bu	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-36.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-36-1	p-Mc-Ph	H	H	H	ⁿ Bu	H	H	F	OH
XXXII-36-2	p-Mc-Ph	H	H	CH ₃	ⁿ Bu	H	H	F	OH
XXXII-36-3	p-Mc-Ph	H	H	CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-36-4	p-Mc-Ph	H	H	CH ₂ CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-36-5	p-Mc-Ph	H	H	CH ₂ Ph	ⁿ Bu	H	H	F	OH
XXXII-36-6	p-Mc-Ph	H	H	CH ₂ -indol-3-yl	ⁿ Bu	H	H	F	OH
XXXII-36-7	p-Mc-Ph	H	H	CH ₂ CH ₂ SCH ₃	ⁿ Bu	H	H	F	OH
XXXII-36-8	p-Mc-Ph	*	H	*	ⁿ Bu	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

5 Table XXXII-37.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-37-1	p-F-Ph	H	H	H	ⁿ Bu	H	H	F	OH
XXXII-37-2	p-F-Ph	H	H	CH ₃	ⁿ Bu	H	H	F	OH
XXXII-37-3	p-F-Ph	H	H	CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-37-4	p-F-Ph	H	H	CH ₂ CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-37-5	p-F-Ph	H	H	CH ₂ Ph	ⁿ Bu	H	H	F	OH
XXXII-37-6	p-F-Ph	H	H	CH ₂ -indol-3-yl	ⁿ Bu	H	H	F	OH
XXXII-37-7	p-F-Ph	H	H	CH ₂ CH ₂ SCH ₃	ⁿ Bu	H	H	F	OH
XXXII-37-8	p-F-Ph	*	H	*	ⁿ Bu	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-38.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-38-1	p-Cl-Ph	H	H	H	ⁿ Bu	H	H	F	OH
XXXII-38-2	p-Cl-Ph	H	H	CH ₃	ⁿ Bu	H	H	F	OH
XXXII-38-3	p-Cl-Ph	H	H	CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-38-4	p-Cl-Ph	H	H	CH ₂ CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-38-5	p-Cl-Ph	H	H	CH ₂ Ph	ⁿ Bu	H	H	F	OH
XXXII-38-6	p-Cl-Ph	H	H	CH ₂ -indol-3-yl	ⁿ Bu	H	H	F	OH
XXXII-38-7	p-Cl-Ph	H	H	CH ₂ CH ₂ SCH ₃	ⁿ Bu	H	H	F	OH
XXXII-38-8	p-Cl-Ph	*	H	*	ⁿ Bu	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-39.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-39-1	p-Br-Ph	H	H	H	ⁿ Bu	H	H	F	OH
XXXII-39-2	p-Br-Ph	H	H	CH ₃	ⁿ Bu	H	H	F	OH
XXXII-39-3	p-Br-Ph	H	H	CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-39-4	p-Br-Ph	H	H	CH ₂ CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-39-5	p-Br-Ph	H	H	CH ₂ Ph	ⁿ Bu	H	H	F	OH
XXXII-39-6	p-Br-Ph	H	H	CH ₂ -indol-3-yl	ⁿ Bu	H	H	F	OH
XXXII-39-7	p-Br-Ph	H	H	CH ₂ CH ₂ SCH ₃	ⁿ Bu	H	H	F	OH
XXXII-39-8	p-Br-Ph	*	H	*	ⁿ Bu	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

5 Table XXXII-40.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-40-1	p-I-Ph	H	H	H	ⁿ Bu	H	H	F	OH
XXXII-40-2	p-I-Ph	H	H	CH ₃	ⁿ Bu	H	H	F	OH
XXXII-40-3	p-I-Ph	H	H	CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-40-4	p-I-Ph	H	H	CH ₂ CH(CH ₃) ₂	ⁿ Bu	H	H	F	OH
XXXII-40-5	p-I-Ph	H	H	CH ₂ Ph	ⁿ Bu	H	H	F	OH
XXXII-40-6	p-I-Ph	H	H	CH ₂ -indol-3-yl	ⁿ Bu	H	H	F	OH
XXXII-40-7	p-I-Ph	H	H	CH ₂ CH ₂ SCH ₃	ⁿ Bu	H	H	F	OH
XXXII-40-8	p-I-Ph	*	H	*	ⁿ Bu	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-41.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-41-1	CH ₃	H	H	H	Bz	H	H	F	OH
XXXII-41-2	CH ₃	H	H	CH ₃	Bz	H	H	F	OH
XXXII-41-3	CH ₃	H	H	CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-41-4	CH ₃	H	H	CH ₂ CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-41-5	CH ₃	H	H	CH ₂ Ph	Bz	H	H	F	OH
XXXII-41-6	CH ₃	H	H	CH ₂ -indol-3-yl	Bz	H	H	F	OH
XXXII-41-7	CH ₃	H	H	CH ₂ CH ₂ SCH ₃	Bz	H	H	F	OH
XXXII-41-8	CH ₃	*	H	*	Bz	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-42.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-42-1	Et	H	H	H	Bz	H	H	F	OH
XXXII-42-2	Et	H	H	CH ₃	Bz	H	H	F	OH
XXXII-42-3	Et	H	H	CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-42-4	Et	H	H	CH ₂ CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-42-5	Et	H	H	CH ₂ Ph	Bz	H	H	F	OH
XXXII-42-6	Et	H	H	CH ₂ -indol-3-yl	Bz	H	H	F	OH
XXXII-42-7	Et	H	H	CH ₂ CH ₂ SCH ₃	Bz	H	H	F	OH
XXXII-42-8	Et	*	H	*	Bz	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

5 Table XXXII-43.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-43-1	ⁱ Pr	H	H	H	Bz	H	H	F	OH
XXXII-43-2	ⁱ Pr	H	H	CH ₃	Bz	H	H	F	OH
XXXII-43-3	ⁱ Pr	H	H	CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-43-4	ⁱ Pr	H	H	CH ₂ CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-43-5	ⁱ Pr	H	H	CH ₂ Ph	Bz	H	H	F	OH
XXXII-43-6	ⁱ Pr	H	H	CH ₂ -indol-3-yl	Bz	H	H	F	OH
XXXII-43-7	ⁱ Pr	H	H	CH ₂ CH ₂ SCH ₃	Bz	H	H	F	OH
XXXII-43-8	ⁱ Pr	*	H	*	Bz	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-44.

N _o	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-44-1	^t Bu	H	H	H	Bz	H	H	F	OH
XXXII-44-2	^t Bu	H	H	CH ₃	Bz	H	H	F	OH
XXXII-44-3	^t Bu	H	H	CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-44-4	^t Bu	H	H	CH ₂ CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-44-5	^t Bu	H	H	CH ₂ Ph	Bz	H	H	F	OH
XXXII-44-6	^t Bu	H	H	CH ₂ -indol-3-yl	Bz	H	H	F	OH
XXXII-44-7	^t Bu	H	H	CH ₂ CH ₂ SCH ₃	Bz	H	H	F	OH
XXXII-44-8	^t Bu	*	H	*	Bz	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-45.

N _o	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-45-1	Ph	H	H	H	Bz	H	H	F	OH
XXXII-45-2	Ph	H	H	CH ₃	Bz	H	H	F	OH
XXXII-45-3	Ph	H	H	CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-45-4	Ph	H	H	CH ₂ CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-45-5	Ph	H	H	CH ₂ Ph	Bz	H	H	F	OH
XXXII-45-6	Ph	H	H	CH ₂ -indol-3-yl	Bz	H	H	F	OH
XXXII-45-7	Ph	H	H	CH ₂ CH ₂ SCH ₃	Bz	H	H	F	OH
XXXII-45-8	Ph	*	H	*	Bz	H	H	F	OH

5 *R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-46.

N _o	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-46-1	p-Me-Ph	H	H	H	Bz	H	H	F	OH
XXXII-46-2	p-Me-Ph	H	H	CH ₃	Bz	H	H	F	OH
XXXII-46-3	p-Me-Ph	H	H	CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-46-4	p-Me-Ph	H	H	CH ₂ CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-46-5	p-Me-Ph	H	H	CH ₂ Ph	Bz	H	H	F	OH
XXXII-46-6	p-Me-Ph	H	H	CH ₂ -indol-3-yl	Bz	H	H	F	OH
XXXII-46-7	p-Me-Ph	H	H	CH ₂ CH ₂ SCH ₃	Bz	H	H	F	OH

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-46-8	p-Mc-Ph	*	H	*	Bz	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-47.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-47-1	p-F-Ph	H	H	H	Bz	H	H	F	OH
XXXII-47-2	p-F-Ph	H	H	CH ₃	Bz	H	H	F	OH
XXXII-47-3	p-F-Ph	H	H	CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-47-4	p-F-Ph	H	H	CH ₂ CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-47-5	p-F-Ph	H	H	CH ₂ Ph	Bz	H	H	F	OH
XXXII-47-6	p-F-Ph	H	H	CH ₂ -indol-3-yl	Bz	H	H	F	OH
XXXII-47-7	p-F-Ph	H	H	CH ₂ CH ₂ SCH ₃	Bz	H	H	F	OH
XXXII-47-8	p-F-Ph	*	H	*	Bz	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-48.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-48-1	p-Cl-Ph	H	H	H	Bz	H	H	F	OH
XXXII-48-2	p-Cl-Ph	H	H	CH ₃	Bz	H	H	F	OH
XXXII-48-3	p-Cl-Ph	H	H	CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-48-4	p-Cl-Ph	H	H	CH ₂ CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-48-5	p-Cl-Ph	H	H	CH ₂ Ph	Bz	H	H	F	OH
XXXII-48-6	p-Cl-Ph	H	H	CH ₂ -indol-3-yl	Bz	H	H	F	OH
XXXII-48-7	p-Cl-Ph	H	H	CH ₂ CH ₂ SCH ₃	Bz	H	H	F	OH
XXXII-48-8	p-Cl-Ph	*	H	*	Bz	H	H	F	OH

5 *R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-49.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-49-1	p-Br-Ph	H	H	H	Bz	H	H	F	OH
XXXII-49-2	p-Br-Ph	H	H	CH ₃	Bz	H	H	F	OH
XXXII-49-3	p-Br-Ph	H	H	CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-49-4	p-Br-Ph	H	H	CH ₂ CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-49-5	p-Br-Ph	H	H	CH ₂ Ph	Bz	H	H	F	OH

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-49-6	p-Br-Ph	H	H	CH ₂ -indol-3-yl	Bz	H	H	F	OH
XXXII-49-7	p-Br-Ph	H	H	CH ₂ CH ₂ SCH ₃	Bz	H	H	F	OH
XXXII-49-8	p-Br-Ph	*	H	*	Bz	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

Table XXXII-50.

No	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	R ⁵	R ⁶	X	Y
XXXII-50-1	p-I-Ph	H	H	H	Bz	H	H	F	OH
XXXII-50-2	p-I-Ph	H	H	CH ₃	Bz	H	H	F	OH
XXXII-50-3	p-I-Ph	H	H	CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-50-4	p-I-Ph	H	H	CH ₂ CH(CH ₃) ₂	Bz	H	H	F	OH
XXXII-50-5	p-I-Ph	H	H	CH ₂ Ph	Bz	H	H	F	OH
XXXII-50-6	p-I-Ph	H	H	CH ₂ -indol-3-yl	Bz	H	H	F	OH
XXXII-50-7	p-I-Ph	H	H	CH ₂ CH ₂ SCH ₃	Bz	H	H	F	OH
XXXII-50-8	p-I-Ph	*	H	*	Bz	H	H	F	OH

*R² and R^{3b} joined together by (CH₂)₃ to form five-membered ring.

DOSAGE, ADMINISTRATION, AND USE

- 5 A sixth embodiment of the present invention is directed to a composition for the treatment of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent, and equivalent medium and a compound, that is intended to include its salts (acid or basic addition salts), hydrates, solvates, and crystalline forms can be obtained, represented by
- 10 formula I.

It is contemplated that the formulation of the sixth embodiment can contain any of the compounds contemplated in any of the aspects of the first, second, third, fourth, and fifth embodiments or those specifically recited in the tables above or exemplified herein, either alone or in combination with another compound of the present invention.

- 15 The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms and carriers. Oral administration can be in the form of tablets, coated tablets, hard and soft gelatin capsules, solutions, emulsions, syrups, or

suspensions. Compounds of the present invention are efficacious when administered by suppository administration, among other routes of administration. The most convenient manner of administration is generally oral using a convenient daily dosing regimen which can be adjusted according to the severity of the disease and the patient's response to the
5 antiviral medication.

A compound or compounds of the present invention, as well as their pharmaceutically acceptable salts, together with one or more conventional excipients, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised
10 of conventional ingredients in conventional proportions, with or without additional active compounds and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as
15 suspensions, emulsions, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration. A typical preparation will contain from about 5% to about 95% active compound or compounds (w/w). The term "preparation" or "dosage form" is intended to include both solid and liquid formulations of the active compound and one skilled in the art will appreciate that an active ingredient can exist in different
20 preparations depending on the desired dose and pharmacokinetic parameters.

The term "excipient" as used herein refers to a compound that is used to prepare a pharmaceutical composition, and is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipients that are acceptable for veterinary use as well as human pharmaceutical use. The compounds of this invention can be administered
25 alone but will generally be administered in admixture with one or more suitable pharmaceutical excipients, diluents or carriers selected with regard to the intended route of administration and standard pharmaceutical practice.

A "pharmaceutically acceptable salt" form of an active ingredient may also initially confer a desirable pharmacokinetic property on the active ingredient which were

absent in the non-salt form, and may even positively affect the pharmacodynamics of the active ingredient with respect to its therapeutic activity in the body. The phrase "pharmaceutically acceptable salt" of a compound as used herein means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as glycolic acid, pyruvic acid, lactic acid, malonic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, salicylic acid, muconic acid, and the like or (2) basic addition salts formed with the conjugate bases of any of the inorganic acids listed above, wherein the conjugate bases comprise a cationic component selected from among Na^+ , K^+ , Mg^{2+} , Ca^{2+} , and NH_4^+ , in which R^m is a C_{1-3} alkyl and g is a number selected from among 0, 1, 2, 3, or 4. It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same acid addition salt.

Solid form preparations include powders, tablets, pills, capsules, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. Solid form preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants,

thickeners, solubilizing agents, and the like.

Liquid formulations also are suitable for oral administration include liquid formulation including emulsions, syrups, elixirs and aqueous suspensions. These include solid form preparations which are intended to be converted to liquid form preparations shortly before use. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents.

The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

The compounds of the present invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Suitable formulations along with pharmaceutical carriers, diluents and excipients are described in *Remington: The Science and Practice of Pharmacy 1995*, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania, which is hereby incorporated by reference. The compounds of the present invention can also be encapsulated in liposomes, such as those disclosed in U.S. Patent Nos. 6,180,134, 5,192,549, 5,376,380, 6,060,080, 6,132,763, each of which is incorporated by reference. A skilled formulation scientist may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration without rendering the compositions of the present invention unstable or compromising their therapeutic activity.

The modification of the present compounds to render them more soluble in water or other vehicle, for example, may be easily accomplished by minor modifications (e.g., salt formulation), which are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in patients.

A seventh embodiment of the present invention is directed to a use of the compound represented by formula I in the manufacture of a medicament for the treatment of any condition the result of an infection by any one of the following viral agents: hepatitis C virus, West Nile virus, yellow fever virus, dengue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus and Japanese encephalitis virus.

The term "medicament" means a substance used in a method of treatment and/or prophylaxis of a subject in need thereof, wherein the substance includes, but is not limited to, a composition, a formulation, a dosage form, and the like, comprising the compound of formula I. It is contemplated that the compound of the use of the compound represented by formula I in the manufacture of a medicament for the treatment of any of the antiviral conditions disclosed herein of the seventh embodiment can be any of the compounds contemplated in any of the aspects of the first, second, third, fourth, fifth embodiments or those specifically recited in the tables above or exemplified herein, either alone or in combination with another compound of the present invention. A medicament includes, but is not limited to, any one of the compositions contemplated by the sixth embodiment of the present invention.

A eighth embodiment of the present invention is directed to a method of treatment and/or prophylaxis in a subject in need thereof said method comprises administering a therapeutically effective amount of the compound represented by formula I to the subject.

A first aspect of the eighth embodiment is directed to a method of treatment and/or prophylaxis in a subject in need thereof said method comprises administering a therapeutically effective of at least two or more different compounds falling within the scope of the compound represented by formula I to the subject.

A second aspect of the eighth embodiment is directed to a method of treatment and/or prophylaxis in a subject in need thereof said method comprises alternatively or concurrently administering a therapeutically effective of at least two compounds falling within the scope of the compound represented by formula I to the subject.

- 5 It is intended that a subject in need thereof is one that has any condition the result of an infection by any of the viral agents disclosed herein, which includes, but is not limited to, hepatitis C virus, West Nile virus, yellow fever virus, dengue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus or Japanese encephalitis virus, flaviviridae viruses or pestiviruses or hepaciviruses or a viral agent causing symptoms
10 equivalent or comparable to any of the above-listed viruses.

- The term "subject" means a mammal, which includes, but is not limited to, cattle, pigs, sheep, chicken, turkey, buffalo, llama, ostrich, dogs, cats, and humans, preferably the subject is a human. It is contemplated that in the method of treating a subject thereof of the sixth embodiment can be any of the compounds contemplated in any of the aspects
15 of the first, second, and third embodiments or those specifically recited in the tables above, either alone or in combination with another compound of the present invention.

- The term "therapeutically effective amount" as used herein means an amount required to reduce symptoms of the disease in an individual. The dose will be adjusted to the individual requirements in each particular case. That dosage can vary within wide
20 limits depending upon numerous factors such as the severity of the disease to be treated, the age and general health condition of the patient, other medicaments with which the patient is being treated, the route and form of administration and the preferences and experience of the medical practitioner involved. For oral administration, a daily dosage of between about 0.1 and about 10 g, including all values in between, such as 0.25, 0.5,
25 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, and 9.5, per day should be appropriate in monotherapy and/or in combination therapy. A preferred daily dosage is between about 0.5 and about 7.5 g per day, more preferred 1.5 and about 6.0 g per day. Generally, treatment is initiated with a large initial "loading dose" to rapidly reduce or eliminate the virus following by a decreasing the dose to a level sufficient to prevent

resurgence of the infection. One of ordinary skill in treating diseases described herein will be able, without undue experimentation and in reliance on personal knowledge, experience and the disclosures of this application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease and patient.

5 Therapeutic efficacy can be ascertained from tests of liver function including, but not limited to protein levels such as serum proteins (e.g., albumin, clotting factors, alkaline phosphatase, aminotransferases (e.g., alanine transaminase, aspartate transaminase), 5'-nucleosidase, γ -glutamyltranspeptidase, etc.), synthesis of bilirubin, synthesis of cholesterol, and synthesis of bile acids; a liver metabolic function, including,
10 but not limited to, carbohydrate metabolism, amino acid and ammonia metabolism. Alternatively the therapeutic effectiveness may be monitored by measuring HCV-RNA. The results of these tests will allow the dose to be optimized.

A third aspect of the eighth embodiment, is directed to a method of treatment and/or prophylaxis in a subject in need thereof said method comprises administering to
15 the subject a therapeutically effective of a compound represented by formula I and a therapeutically effective amount of another antiviral agent; wherein the administration is concurrent or alternative. It is understood that the time between alternative administration can range between 1-24 hours, which includes any sub-range in between including, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 23
20 hours. Examples of "another antiviral agents" include, but are not limited to: HCV NS3 protease inhibitors (see WO 2008010921, WO 2008010921, EP 1881001, WO 2007015824, WO 2007014925, WO 2007014926, WO 2007014921, WO 2007014920, WO 2007014922, US 2005267018, WO 2005095403, WO 2005037214, WO 2004094452, US 2003187018, WO 200364456, WO 2005028502, and WO
25 2003006490); HCV NS5B Inhibitors (see US 2007275947, US20072759300, WO2007095269, WO 2007092000, WO 2007076034, WO 200702602, US 2005-98125, WO 2006093801, US 2006166964, WO 2006065590, WO 2006065335, US 2006040927, US 2006040890, WO 2006020082, WO 2006012078, WO 2005123087, US 2005154056, US 2004229840, WO 2004065367, WO 2004003138, WO
30 2004002977, WO 2004002944, WO 2004002940, WO 2004000858, WO 2003105770,

WO 2003010141, WO 2002057425, WO 2002057287, WO 2005021568, WO 2004041201, US 20060293306, US 20060194749, US 20060241064, US 6784166, WO 2007088148, WO 2007039142, WO 2005103045, WO 2007039145, WO 2004096210, and WO 2003037895); HCV NS4 Inhibitors (see WO 2007070556 and WO 2005067900); HCV NS5a Inhibitors (see US 2006276511, WO 2006120252, WO 2006120251, WO 2006100310, WO 2006035061); Toll-like receptor agonists (see WO 2007093901); and other inhibitors (see WO 2004035571, WO 2004014852, WO 2004014313, WO 2004009020, WO 2003101993, WO 2000006529).

10 A fourth aspect of the eighth embodiment, is directed to a method of treatment in a subject in need thereof said method comprises alternatively or concurrently administering a therapeutically effective of a compound represented by formula I and another antiviral agent to the subject. It is understood that the time between alternative administration can range between 1-24 hours, which includes any sub-range in between including, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 23
15 hours.

A fifth aspect of the eighth embodiment, is directed to a method of treatment and/or prophylaxis in a subject in need thereof said method comprises administering to the subject a therapeutically effective of at least one compound represented by formula I and a therapeutically effective amount of another antiviral agent; wherein the
20 administration is concurrent or alternative. It is understood that the time between alternative administration can range between 1-24 hours, which includes any sub-range in between including, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 23 hours.

A sixth aspect of the eighth embodiment, is directed to a method of treatment in a
25 subject in need thereof said method comprises alternatively or concurrently administering a therapeutically effective of at least one compound represented by formula I and another antiviral agent to the subject. It is understood that the time between alternative administration can range between 1-24 hours, which includes any sub-range in between

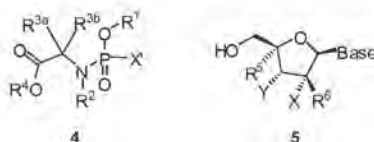
including, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 23 hours.

It is contemplated that the another antiviral agent includes, but is not limited to interferon- α , interferon- β , pegylated interferon- α , ribavirin, levovirin, viramidine, another nucleoside HCV polymerase inhibitor, a HCV non-nucleoside polymerase inhibitor, a HCV protease inhibitor, a HCV helicase inhibitor or a HCV fusion inhibitor. When the active compound or its derivative or salt are administered in combination with another antiviral agent the activity may be increased over the parent compound. When the treatment is combination therapy, such administration may be concurrent or sequential with respect to that of the nucleoside derivatives. "Concurrent administration" as used herein thus includes administration of the agents at the same time or at different times. Administration of two or more agents at the same time can be achieved by a single formulation containing two or more active ingredients or by substantially simultaneous administration of two or more dosage forms with a single active agent.

It will be understood that references herein to treatment extend to prophylaxis as well as to the treatment of existing conditions. Furthermore, the term "treatment" of a HCV infection, as used herein, also includes treatment or prophylaxis of a disease or a condition associated with or mediated by HCV infection, or the clinical symptoms thereof.

PROCESS FOR PREPARATION

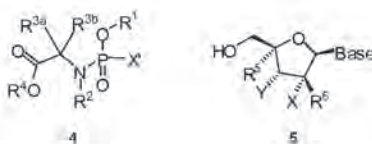
An ninth embodiment of the present invention is directed to a process for preparing the compound of formula I, which comprises reacting a suitably substituted phosphochloridate compound **4** with a nucleoside analog **5**



wherein the substituents R^1 , R^2 , R^{3a} , R^{3b} , R^4 , R^5 , X , Y , R^6 , and base have their meanings as disclosed in the Detailed Description of the Invention and X' is a leaving group, such as Cl, Br, I, tosylate, mesylate, trifluoroacetate, trifluorosulfonate, pentafluorophenoxide, p-NO₂-phenoxide, or other commonly used leaving groups as disclosed in *Advanced Organic Chemistry* by March, Fourth Edition. Leaving groups and methods that can be used to effect the formation of a phosphoramidate nucleoside conjugate are found in US 20060142238 and WO 2007095269. Preferably, the leaving group is Cl.

This reaction is performed in an anhydrous aprotic solvent such tetrahydrofuran, dioxane, or both tetrahydrofuran and dioxane, or any functional equivalent thereof, with tetrahydrofuran being the preferred solvent. The reaction is typically initiated at a temperature range from -78°C to 40°C with the preferred reaction temperature being between 0°C and room temperature. The nucleoside is first stirred with a base (5 to 12 equivalents) such as N-methylimidazole, collidine, pyridine, 2,6-lutidine, 2, 6-*t*Bu-pyridine, etc. a tertiary amine base, such as triethylamine, diisopropylethylamine, etc., or an alkyl Grignard reagent, such as *t*BuMgCl, *t*BuMgBr, MeMgCl, MeMgBr, etc. The phosphorochloridate (3-10 equivalents) is dissolved in the reaction solvent and added to the mixture of the nucleoside and base. The reaction is then allowed to stir over a period of time at a temperature between room temperature and 40°C for a period of 30 min to 24 hr. with the preferred reaction temperature being room temperature and time being 24 hr. The solvent is removed from the reaction mixture and the product is purified by chromatography on silica gel.

A tenth embodiment of the present invention is directed to a product obtained by a process which comprises reacting a suitably substituted phosphochloridate compound **4** with a nucleoside analog **5**



wherein the substituents R^1 , R^2 , R^{3a} , R^{3b} , R^4 , R^5 , X, Y, R^6 , X', and base have their meanings as disclosed in the Detailed Description of the Invention.

This reaction can be performed in an anhydrous aprotic solvent or other suitable solvent, such as tetrahydrofuran, dioxane, or a mixture of tetrahydrofuran and dioxane, with tetrahydrofuran being the preferred solvent. The reaction is typically initiated at a temperature range from -78°C to 40°C with the preferred reaction temperature being between 0°C and room temperature. The nucleoside is first stirred with a base (5 to 12 equivalents) such as N-methylimidazole, a tertiary amine base or tButyl Magnesium Chloride. A phosphorochloridate (3-10 equivalents (or suitable "phosphoro-(leaving group)-date")) is dissolved in the reaction solvent and added to the mixture of the nucleoside and base. The reaction is then allowed to stir over a period of time at a temperature between room temperature and 40°C for a period of 30 min to 24 hr. with the preferred reaction temperature being room temperature and time being 24 hr. The solvent is removed from the reaction mixture and the product is purified by chromatography on silica gel.

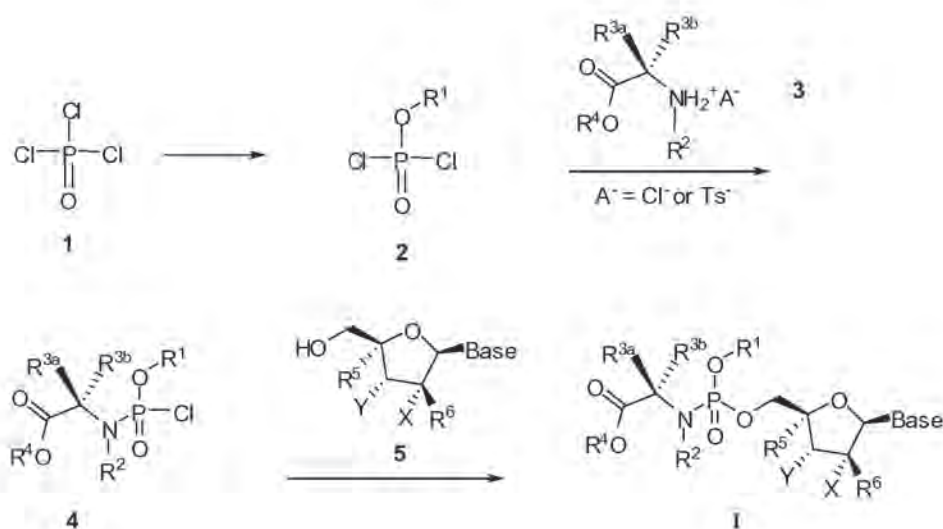
Compounds and Preparation

Phosphoramidate compounds of the present invention can be prepared by condensation of a nucleoside analog **5** with a suitably substituted phosphochloridate compound **4** (Scheme 1). The nucleoside analog is made by conventional procedures disclosed in any one of U.S. Published Application Nos. 2005/0009737, 2006/0199783, 2006/0122146, and 2007/0197463, each of which is incorporated by reference in its entirety.

Disclosed $^1\text{H-NMR}$ values were recorded on a Varian AS-400 instrument. Mass spectral data were obtain using either a Micromass-Quattromicro API or a Waters Acquity.

Thus, by way of example only, a suitably substituted phenol can be reacted with phosphorus oxychloride (**1**) to afford an aryloxy phosphorodichloridate **2** (see Example 1) which is subsequently treated with an acid addition salt of an α -amino acid ester in the presence of TEA to afford an aryloxy phosphorochloridate **4**. This arylalkoxy-amino acid phosphoramidate is reacted with the nucleoside analog to provide the product **I** (for procedure see, e.g., C. McGuigan et al. Antiviral Res. 1992 17:311-321; D. Curley et al. Antiviral Res. 1990 14:345-356; McGuigan et al. Antiviral Chem. Chemother 1990 1(2):107-113).

Scheme 1



The preparation of nucleoside phosphoramidates requires reacting an appropriately substituted phosphochloridate with a nucleoside containing a free 5'-hydroxyl moiety. In cases where only one hydroxyl group is present, preparation of the phosphoramidate usually proceeds smoothly when the phosphochloridate is reacted with

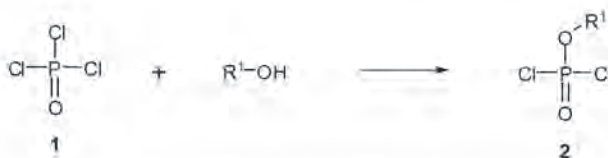
the desired nucleoside. In cases where the nucleoside contains more than one free hydroxyl group, preparation of the appropriately protected nucleoside might be required. Silyl, acetonide or other alcohol protecting groups known in the art might be warranted for protection of the sugar moiety. For protection of the nucleoside base, protecting a
5 free amino group may require amidine protection strategy.

Condensation of the phosphochloridate can be carried out on the unprotected nucleoside. Since the 5'-OH group of a nucleoside is much less hindered than the 3'-OH group, selective phosphoramidation is possible under carefully controlled conditions. After condensation to form a protected phosphoramidate nucleoside, deprotection to
10 obtain the free phosphoramidate nucleoside can be carried out using standard protocols for nucleic acid chemistry. In many cases, the desired product is readily separated from the starting material using column chromatography on silica gel. The synthetic scheme is summarized in Scheme 1.

A further understanding of the disclosed embodiments will be appreciated by
15 consideration of the following examples, which are only meant to be illustrative, and not limit the disclosed invention.

EXAMPLE 1

General Procedure for Preparation of phosphorodichloridates

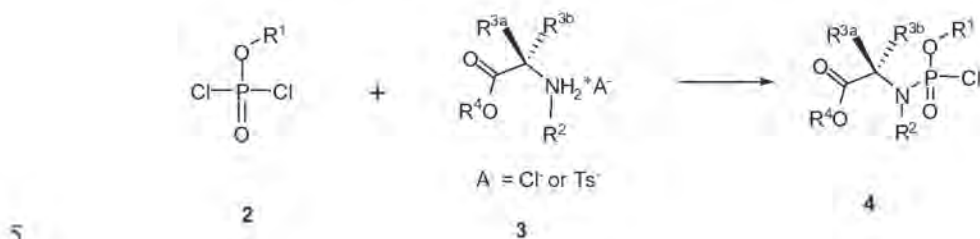


20 A solution of the appropriate phenol **R¹-OH** (1eq) and triethylamine (1 eq.) in anhydrous ether was added dropwise to a stirred solution of phosphoryl trichloride **1** (1eq) at 0 °C over a period of 3 hours under nitrogen. Then the temperature was warmed to room temperature, and the reaction was stirred overnight. The triethylamine salt was

quickly removed with suction filtration and the filtrate concentrated *in vacuo* to dryness to afford **2** as an oil which was used without further purification.

EXAMPLE 2

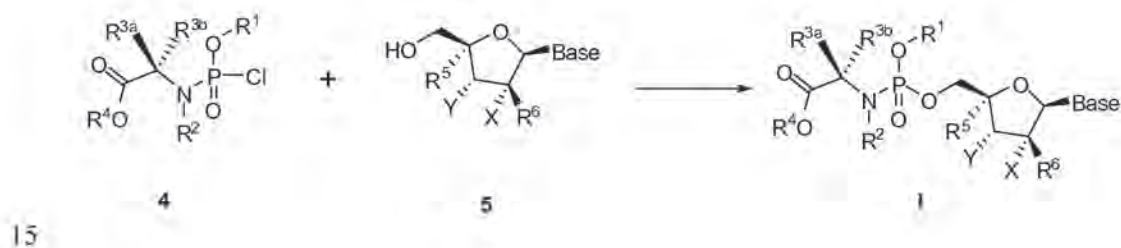
General Procedure for Preparation of phosphorochloridates



A solution of triethylamine (2eq) in anhydrous dichloromethane was added dropwise to a solution of aryloxy-phosphodichloridate **2** (1 eq) and the appropriate amino ester **3** (1 eq) in anhydrous dichloromethane with vigorous stirring at -78 °C over a period of 30 to 120 minutes. Then the reaction temperature was allowed to warm to room temperature and stirred over night. Solvent was removed. The residue was washed with ethyl ether and filtered, the filtrate was dried over reduced pressure to give **4**.

EXAMPLE 3

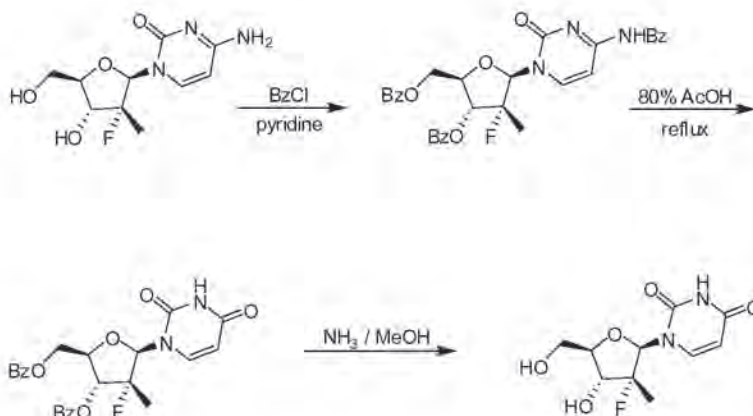
General Procedures for nucleoside phosphoramidate derivatives



A solution of the appropriate phosphorochloridate **4** (6.5 equivalents) in anhydrous tetrahydrofuran (THF) was added to a mixture of nucleoside **5** (1 equivalent) and N-methylimidazole (8 equivalents) in anhydrous THF with vigorous stirring at room temperature and the reaction mixture was stirred overnight. The solvent was removed *in vacuo* and the crude was purified by column chromatography and/or preparative thin layer chromatography to give **1**.

EXAMPLE 4

Preparation of 2'-deoxy-2'-fluoro-2'-C-methyluridine



2'-Deoxy-2'-fluoro-2'-C-methylcytidine (1.0g, 1 eq) (Clark, J., et al., J. Med. Chem., 2005, 48, 5504-5508) was dissolved in 10 ml of anhydrous pyridine and concentrated to dryness *in vacuo*. The resulting syrup was dissolved in 20 ml of anhydrous pyridine under nitrogen and cooled to 0°C with stirring. The brown solution was treated with benzoyl chloride (1.63g, 3eq) dropwise over 10 min. The ice bath was removed and stirring continued for 1.5h whereby thin-layer chromatography (TLC) showed no remaining starting material. The mixture was quenched by addition of water

(0.5 ml) and concentrated to dryness. The residue was dissolved in 50 mL of dichloromethane (DCM) and washed with saturated NaHCO₃ aqueous solution and H₂O. The organic phase was dried over NaSO₄ and filtered, concentrated to dryness to give N⁴,3',5'-tribenzoyl-2'-Deoxy-2'-fluoro-2'-C-methylcytidine (2.0 g, Yield: 91%).

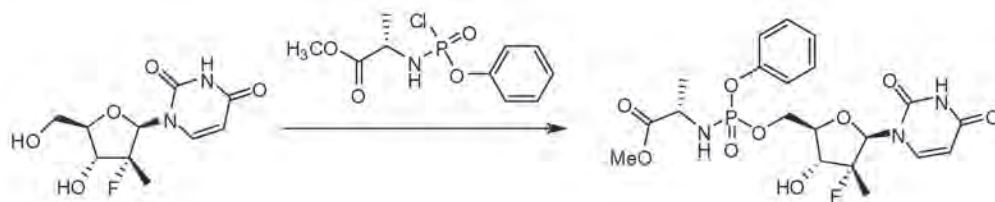
5 N⁴,3',5'-tribenzoyl-2'-Deoxy-2'-fluoro-2'-C-methylcytidine (2.0g, 1 eq) was refluxed in 80% aqueous AcOH overnight. After cooling and standing at room temperature (15 °C), most of the product precipitated and then was filtered through a sintered funnel. White precipitate was washed with water and co-evaporated with toluene to give a white solid. The filtrate was concentrated and co-evaporated with
10 toluene to give additional product which was washed with water to give a white solid. Combining the two batches of white solid gave 1.50g of 3',5'-dibenzoyl-2'-Deoxy-2'-fluoro-2'-C-methyluridine (Yield: 91%).

To a solution of 3',5'-dibenzoyl-2'-Deoxy-2'-fluoro-2'-C-methyluridine (1.5 g, 1eq) in MeOH (10 mL) was added a solution of saturated ammonia in MeOH (20mL).
15 The reaction mixture was stirred at 0 °C for 30 min, and then warmed to room temperature slowly. After the reaction mixture was stirred for another 18 hours, the reaction mixture was evaporated under reduced pressure to give the residue, which was purified by column chromatography to afford pure compound 2'-deoxy-2'-fluoro-2'-C-methyluridine (500 mg, Yield: 60 %).

20

EXAMPLE 5

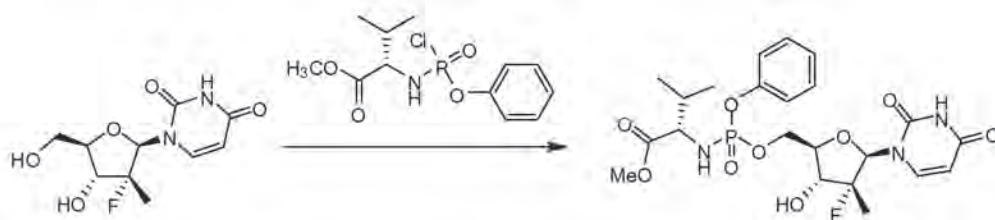
Preparation of 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-alanyl phosphate)



Phenyl methoxyalaninyl phosphorochloridate (1 g, 6.5 eq) dissolved in 3 mL of THF was added to a mixture of 2'-Deoxy-2'-fluoro-2'-C-methyluridine (0.15 g, 1 eq) and N-methylimidazole (0.3 g, 8 eq) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced pressure. The resulting crude product was dissolved in methanol purified by prep-HPLC on a YMC 25x30X2 mm column using a water / acetonitrile gradient elution mobile phase. The acetonitrile and water were removed under reduced pressure to give the desired product (50.1 mg, 15.6%). ¹H NMR (DMSO-*d*₆) δ 1.20-1.27 (m, 6H), 3.58 (d, *J* = 16.0 Hz, 3H), 3.75-3.92 (m, 2H), 4.015-4.379 (m, 2H), 5.54 (t, *J* = 10.2 Hz, 1H), 5.83-5.91 (m, 1H), 6.00-6.16 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.22 (s, 1H), 7.35 (t, *J* = 4.4 Hz, 2H), 7.55 (s, 1H), 11.52 (s, 1H); MS, *m/e* 502 (M+1)⁺.

EXAMPLE 6

Preparation of 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-valyl phosphate)

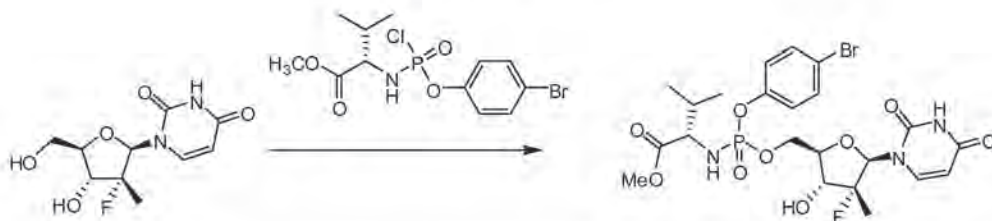


Phenyl methoxy-valyl phosphorochloridate (0.6 g, 3.6 eq) dissolved in 3 mL of THF was added to a mixture of 2'-Deoxy-2'-fluoro-2'-C-methyluridine (0.15 g, 1 eq) and N-methylimidazole (0.44 g, 9 eq) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced

pressure. The resulting crude product was dissolved in methanol purified by prep-HPLC on a YMC 25x30X2 mm column using a water / acetonitrile gradient elution mobile phase. The acetonitrile and water were removed under reduced pressure to give the desired product (60 mg, 20%). ^1H NMR ($\text{DMSO}-d_6$) δ 0.74-0.847 (m, 6H), 1.20-1.28 (m, 3H), 1.89-1.92 (m, 1H), 3.50-3.54 (m, 1H), 3.58 (d, $J = 10.4\text{Hz}$, 3H), 3.72-3.95 (m, 1H), 4.03-4.05 (m, 1H), 4.23-4.43 (m, 2H), 5.56 (t, $J = 16.0\text{ Hz}$, 1H), 5.85-5.92 (m, 1H), 6.01-6.07 (m, 1H), 7.16-7.21 (m, 3H), 7.37 (t, $J = 8\text{ Hz}$, 2H), 7.55-7.60 (m, 1H), 11.52 (s, 1H); MS, m/e 530 ($\text{M}+1$) $^+$.

EXAMPLE 7

10 Preparation of 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate)

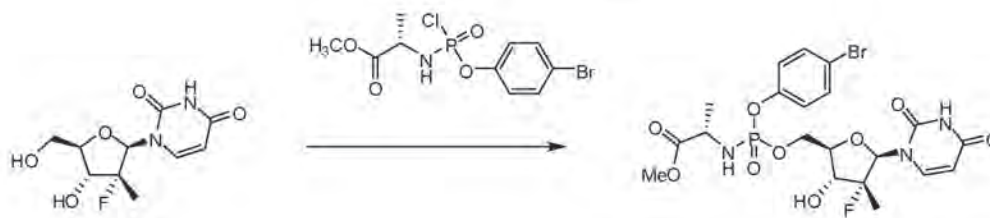


4-Bromophenyl methoxy-valyl phosphorochloridate (1 g, 3.4 eq) dissolved in 3 mL of THF was added to a mixture of 2'-deoxy-2'-fluoro-2'-C-methyluridine (0.2 g, 1 eq) and N-methylimidazole (0.35 g, 6 eq) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced pressure. The resulting crude product was dissolved in methanol purified by prep-HPLC on a YMC 25x30X2 mm column using a water / acetonitrile gradient elution mobile phase. The acetonitrile and water were removed reduced pressure to give the desired product (120 mg, 26%). ^1H NMR ($\text{DMSO}-d_6$) δ 0.72-0.82 (m, 6H), 1.19-1.26 (m, 3H),

1.86-1.92 (m, 1H), 3.48-3.50 (m, 1H), 3.56 (d, $J = 12.0$ Hz, 3H), 3.72-3.89 (m, 1H), 3.96-4.03 (m, 1H), 4.22-4.37 (m, 2H), 5.54-5.60 (m, 1H), 5.85-5.91 (m, 1H), 5.98-6.13 (m, 1H), 7.15 (d, $J = 8.0$ Hz, 2H), 7.49-7.56 (m, 3H), 11.53 (s, 1H); MS, m/e 608 (M+1)⁺.

EXAMPLE 8

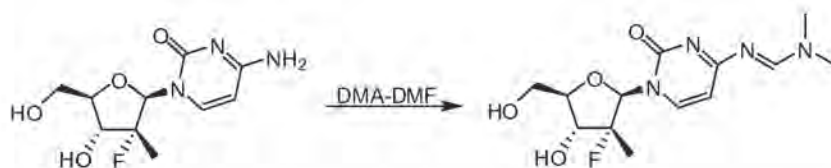
5 **Preparation of 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-alanyl phosphate)**



4-Bromophenyl methoxy-alanyl phosphorochloridate (0.6 g, 5 eq) dissolved in 3 mL of THF was added to a mixture of 2'-deoxy-2'-fluoro-2'-C-methyluridine (0.15 g, 1 eq) and N-methylimidazole (0.3 g, 7.8 eq) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced pressure. The resulting crude product was dissolved in methanol purified by prep-HPLC on a YMC 25x30X2 mm column using a water / acetonitrile gradient elution mobile phase. The acetonitrile and water were removed under reduced pressure to give the desired product (40 mg, 12 %); ¹H NMR (DMSO-*d*₆) δ 1.20-1.26 (m, 6H), 3.57 (d, $J = 2.8$ Hz, 3H), 3.84 (s, 1H), 3.97-4.03 (m, 1H), 4.21-4.25 (m, 1H), 4.33-4.37 (m, 2H), 5.54-5.60 (m, 1H), 5.83-5.89 (m, 1H), 5.98-6.19 (m, 1H), 7.16 (t, $J = 10.2$ Hz, 2H), 7.52-7.57 (m, 3H), 11.52 (s, 1 H); MS, m/e 580(M+1)⁺.

EXAMPLE 9

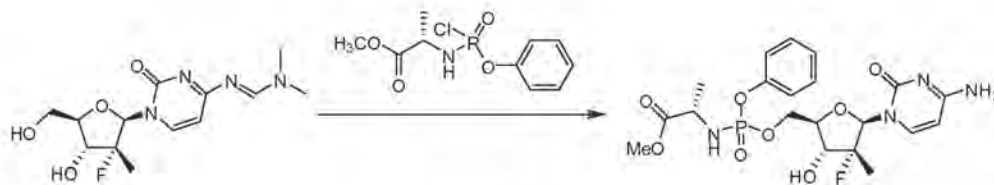
20 **Preparation of N⁴-(N,N-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-C-methylcytidine**



2'-Deoxy-2'-fluoro-2'-C-methylcytidine (500 mg, 1.9 mmol) was stirred with dimethylformamide dimethyl acetal in DMF (10 mL). The resulting mixture was stirred at room temperature overnight. After solvent removal the crude product was used for next step without further purification.

EXAMPLE 10

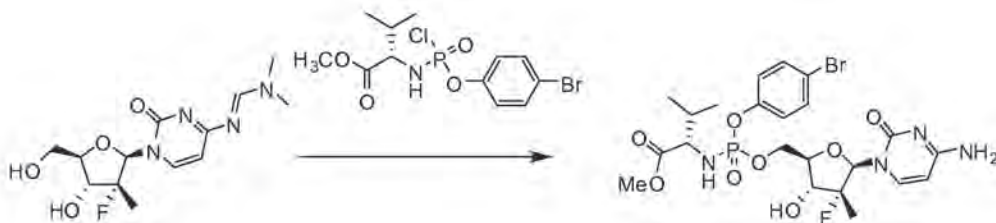
Preparation of 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-alanyl phosphate)



Phenyl methoxyalaninyl phosphorochloridate (0.6 g, 6 eq) dissolved in 3 mL of THF was added to a mixture of N^4 -(*N,N*-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (0.15 g, 1 eq) and *N*-methylimidazole (0.3 g, 7.8 eq) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced pressure. The resulting crude product was dissolved in methanol purified by prep-HPLC on a YMC 25x30X2 mm column using a water / acetonitrile gradient elution mobile phase. The acetonitrile and water were removed under reduced pressure to give the desired product (62 mg, 20.6%). ^1H NMR ($\text{DMSO}-d_6$) δ 1.16 (d, $J = 23.2$ Hz, 3H), 1.22 (d, $J = 7.2$ Hz, 3H), 3.56 (s, 3H), 3.69-3.75 (d, $J = 25.6$ Hz, 1H), 3.82-3.86 (m, 1H), 3.96-3.98 (m, 1H), 4.21-4.34 (m, 2H), 5.68 (d, $J = 7.2$ Hz, 1H), 5.75-5.77 (m, 1H), 6.07-6.16 (m, 1H), 7.15-7.19 (m, 3H), 7.2 (d, $J = 9.2$ Hz, 2H), 7.39 (t, $J = 7.8$ Hz, 2H), 7.48 (d, $J = 9.2$ Hz, 1H); MS, m/e 501($M+1$) $^+$.

EXAMPLE 11

Preparation of 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(4-bromophenyl methoxy-valyl phosphate)

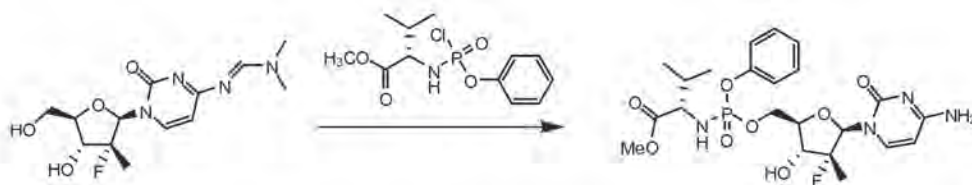


- 5 4-Bromophenyl methoxy-valyl phosphorochloridate (1.0 g, 3.4 eq.) dissolved in 3 mL of THF was added to a mixture of N^4 -(*N,N*-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (0.2 g, 1 eq.) and *N*-methylimidazole (0.35 g, 6 eq.) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced pressure. The resulting crude product was dissolved in
- 10 methanol purified by prep-HPLC on a YMC 25x30X2 mm column using a water / acetonitrile gradient elution mobile phase. The acetonitrile and water were removed under reduced pressure to give the desired product as a white solid (59 mg, 13%); ^1H NMR ($\text{DMSO-}d_6$) δ 0.74-0.83 (m, 6H), 1.12-1.20 (m, 3H), 1.89-1.92 (m, 1H), 3.49-3.51 (m, 1H), 3.55 (s, 3H), 3.59-3.68 (m, 1H), 3.72-.383 (m, 1H), 4.21-4.39 (m, 2H), 5.70-
- 15 5.72 (m, 1H), 5.76-5.83 (m, 1H), 6.04-6.16 (m, 1H), 7.15 (d, $J = 13.0$ Hz, 2H), 7.26 (s, 1H), 7.33 (s, 1H), 7.46-7.55 (m, 1H), 7.56 (d, $J = 4.4$ Hz, 2H) ; MS, m/e 607 ($M+1$) $^+$.

EXAMPLE 12

Preparation of 2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-valyl phosphate)

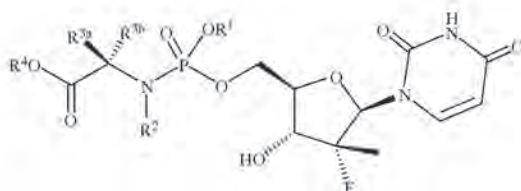
20



- Phenyl methoxy-valyl phosphorochloridate (0.6 g, 6 eq) dissolved in 3 mL of THF was added to a mixture of N⁴-(N,N-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (0.15 g, 1 eq) and N-methylimidazole (0.3 g, 7.8 eq) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced pressure The resulting crude product was dissolved in methanol purified by prep-HPLC on a YMC 25x30X2 mm column using a water / acetonitrile gradient elution mobile phase. The acetonitrile and water were removed under reduced pressure to give the desired product as a white solid (86 mg, 42.9 %). ¹H NMR (DMSO-*d*₆) δ 0.72-0.80 (m, 6H), 1.09-1.18 (m, 3H), 1.87-1.92 (m, 1H), 3.47-3.51 (m, 1H), 3.58 (s, 3H), 3.71-3.75 (m, 1H), 3.97 (t, *J* = 11.2 Hz, 1H), 4.22-4.37 (m, 2H), 5.70 (d, *J* = 8.0 Hz, 1H), 5.76-5.84 (m, 1H), 6.01-6.15 (m, 1H), 7.13-7.18 (m, 3H), 7.27 (s, 2H), 7.34 (d, *J* = 4.0 Hz, 2H), 7.46-7.50 (m, 1H); MS, *m/e* 529 (M+1)⁺.

EXAMPLES

- Example numbers **13-54** and **56-66** are prepared using similar procedures described for examples **5-8**. The example number, compound identification, and NMR/MS details are shown below:



Ex.	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	NMR/MS
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Ex.	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	NMR/MS
13	Ph	H	H	Me	Et	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.12-1.16 (m, 3H), 1.20-1.28(m,6H), 3.70-3.90 (m, 2H), 4.00-4.08 (m, 3H), 4.18-4.45 (m, 2H), 5.52-5.58 (m, 1H), 5.85-5.98 (m, 1H), 6.00-6.20 (m, 2H), 7.16-7.23 (m, 3H), 7.37-7.40 (m, 2H), 7.54-7.60 (m, 1H), 11.54 (s, 1H); MS, m/e 516.1 (M+1) ⁺
14	1-Naphth	H	H	Me	Bn	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.18-1.30 (m, 6H), 3.78-4.10 (m, 3H), 4.38-4.49 (m, 2H), 4.99-5.11 (m, 2H), 5.28-5.40 (m, 1H), 5.85-6.10 (m, 2H), 6.30-6.41 (m, 1H), 7.28-7.32 (m, 5H), 7.41-7.60 (m, 5H), 7.73-7.76(m, 1H), 7.94-8.11(m, 1H), 8.13-8.15(m, 1H), 11.50 (s, 1H); MS, m/e 628.4 (M+1) ⁺
15	Ph	H	H	H	Me	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.22 (d, J=22.4 Hz, 3H), 3.59(s, 3H), 3.63-3.69 (m, 2H), 3.74-3.8(m, 1H), 4.02(d, J=11.2 Hz, 1H), 4.23-4.28(m, 1H), 4.40-4.43 (m, 1H), 5.57-5.60 (m, 1H), 5.89(d, J=6.8 Hz, 1H), 6.00-6.06(m, 2H), 7.15-7.23 (m, 3H), 7.35-7.39 (m, 2H), 7.52(d, J=8 Hz, 1H), 11.52(s, 1H); MS, m/e 487.97 (M+1) ⁺
16	2,4-Cl-Ph	H	H	Me	Me	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.22-1.28 (m, 6H), 3.57-3.60 (m, 3H), 3.84-3.92 (m, 2H), 4.00-4.04 (m, 1H), 4.31-4.44 (m, 2H), 5.54-5.61 (m, 1H), 5.85-6.10 (m, 2H), 6.32-6.43 (m, 1H), 7.44-7.54 (m, 3H), 7.72-7.75 (m, 1H), 11.54 (s, 1H); MS, m/e 570.2 (M+1) ⁺
17	1-Naphth	H	H	Me	Me	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.15-1.27 (m, 6H), 3.51-3.55 (d, 3H), 3.85-3.96 (m, 2H), 4.00-4.10(m, 1H), 4.30-4.46 (m, 2H), 5.31-5.39 (m, 1H), 5.89-6.05 (m, 2H), 6.22-6.34 (m, 1H), 7.44-7.60 (m, 5H), 7.73-7.77 (m, 1H), 7.93-7.96 (m, 1H), 8.12-8.14 (m, 1H), 11.50(s, 1H); MS, m/e 552.1 (M+1) ⁺
18	Ph	*	H	*	Me	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.19 (d, J=22.8 Hz, 3H), 1.69-1.84 (m, 3H), 1.99-2.04 (m, 1H), 3.16-3.21 (m, 2H), 3.58 (s, 3H), 3.68-3.8 (m, 1H), 4.00 (m, 1H), 4.01-4.13 (m, 1H), 4.22-4.25 (m, 1H), 4.5 (d, J = 11.2 Hz, 1H), 5.54 (d, J = 8.0 Hz, 1H), 5.86 (s, 1H), 5.6 (d, J = 19.6 Hz, 1H), 7.15-7.2 (m, 3H), 7.34 (t, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 11.38 (s, 1H); MS, m/e 527.93(M+1) ⁺
19	Ph	H	H	Me	n-Bu	¹ H NMR (DMSO- <i>d</i> ₆) δ 0.80-0.90 (m, 3H), 1.20-1.35 (m, 8H), 1.48-1.55 (m, 2H), 3.78-3.88 (m, 2H), 3.95-4.08 (m, 3H), 4.22-4.45 (m, 2H), 5.55-5.57(t, 1H), 5.85-6.18 (m, 3H), 7.14-7.23 (m, 3H), 7.35-7.40 (m, 2H), 7.51-7.60 (d, 1H), 11.50 (s, 1H); MS, m/e 544.2 (M+1) ⁺
20	Ph	H	H	Me	Bn	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.20-1.30 (m, 6H), 3.72-4.05 (m, 3H), 4.23-4.27 (m, 1H), 4.32-4.45 (m, 1H), 5.07-5.10(t, 2H), 5.52-5.56(t, 1H), 5.86-6.10 (m, 2H), 6.13-6.21(m, 1H), 7.15-7.21 (m, 3H), 7.29-7.40 (m, 7H), 7.51-7.56 (d, 1H), 11.50 (s, 1H); MS, m/e 578.2 (M+1) ⁺
21	4-F-Ph	H	H	Me	Me	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.28-1.34 (m, 6H), 3.65(d, J= 4 Hz, 3H), 3.85-3.96 (m, 2H), 4.06-4.12 (m, 1H), 4.30-4.34 (m, 1H), 4.40-4.47 (m, 1H), 5.62-5.67 (m, 1H), 5.94-6.01(m, 1H), 6.09 (d, J=18.8 Hz, 1H), 6.17-6.26 (m, 1H), 7.27-7.33(m, 4H), 7.62 (d, J = 7.6 Hz, 1H), 11.61 (s, 1H); MS, m/e 519.94(M+1) ⁺
22	4-Cl-Ph	H	H	Me	Me	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.22-1.28 (m, 6H), 3.58 (d, 2H), 3.70-3.95(m, 2H), 3.95-4.08 (m, 1H), 4.23-4.45 (m, 2H), 5.55-5.61(t, 1H),

Ex.	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	NMR/MS
23	3,4-Cl-Ph	H	H	Me	Me	5.85-6.10 (m, 2H), 6.15-6.23(m,1H), 7.20-7.26 (m, 2H), 7.43-7.46 (m, 2H), 7.54-7.57 (d, 1H), 11.50 (s,1H) ; MS, m/e 536.1 (M+1) ⁺ 1H NMR (DMSO- <i>d</i> ₆) δ 1.13 (m, 6H), 3.49 (s, 3H), 3.61-3.85 (m, 2H), 3.90-3.93 (m, 1H), 4.16-4.22 (m, 1H), 4.27-4.31 (m, 1H), 5.47-5.52 (m, 1H), 5.82 (d, J = 11.6 Hz, 1H), 5.93(d, J = 19.2 Hz, 1H), 6.15-6.25 (m, 1H), 7.13 (t, J = 9.6 Hz, 1H), 7.43 (d, J = 12Hz, 2H), 7.57 (d, J = 6.0 Hz, 1H), 11.43(s, 1H) ; MS, m/e 569.85 (M+1) ⁺
24	Ph	H	H	Me	2-Bu	1H NMR (DMSO- <i>d</i> ₆) δ 0.83 (d, J = 6.8 Hz, 6H), 1.20-1.26 (m, 6H), 1.79-1.86 (m, 1H), 3.73-3.90 (m, 4H), 4.01 (t, J = 11.2 Hz, 1H), 4.21-4.28 (m, 1H), 4.33-4.42 (m, 1H), 5.54 (t, J = 7.6 Hz, 1H), 5.85-5.92 (m, 1H), 5.99-6.13 (m, 2H), 7.19 (t, J = 8 Hz, 3H), 7.36 (t, J = 7.6 Hz, 2H), 7.53 (d, J = 7.6 Hz, 1H), 11.52 (s, 1H) ; MS, m/e 544.00 (M+1) ⁺
25	Ph	H	H	Me	i-Pr	1H NMR (DMSO- <i>d</i> ₆) δ 1.13-1.28 (m, 12H), 3.74-3.81 (m, 2H), 3.95-4.08 (m,1H), 4.20-4.45 (m, 2H), 4.83-4.87 (m, 1H), 5.52-5.58 (m, 1H), 5.84-6.15 (m, 3H), 7.17-7.23 (m, 3H), 7.35-7.39 (m, 2H), 7.54-7.57 (m, 1H), 11.50 (s,1H) ; MS, m/e 530.2 (M+1) ⁺
26	4-MeO-Ph	H	H	Me	n-Bu	1HNMR (400MHz, DMSO- <i>d</i> ₆): δ =0.78-0.82 (m, 3H), 1.29-1.47 (m, 8H), 1.49-1.54 (m, 2H), 3.66-3.87 (m, 5H), 3.96-4.02 (m, 3H), 4.21-4.39 (m, 2H), 5.57 (t, J= 12.0Hz, 1H), 5.84-6.05 (m, 3H), 6.90 (dd, J1 =8.0Hz, J2=4.0Hz, 2H), 7.09-7.14 (dd, J1=16.0Hz, J2=4.0Hz, 2H), 7.55 (d, J =8.0Hz, 1H), 11.48-11.62 (s, 1H)
27	4-F-Ph	H	H	Me	Et	1H NMR (DMSO- <i>d</i> ₆) δ 1.12-1.28 (m, 9H), 3.72-3.94(m,2H), 3.98-4.10 (m,3H), 4.21-4.42(m,2H), 5.55-5.61 (t, 1H), 5.85-6.20 (m, 3H), 7.18-7.25 (m,4H), 7.55-7.58 (d, 1H), 11.50 (s,1H) ; MS, m/e 533.90 (M+1) ⁺
28	4-F-Ph	H	H	Me	i-Pr	1H NMR (DMSO- <i>d</i> ₆) δ 1.13-1.30 (m, 12H), 3.74-3.85(m,2H), 3.98-4.06 (m,1H), 4.23-4.41(m,2H), 4.83-4.87 (m, 1H), 5.55-5.61 (t, 1H), 5.85-6.12 (m, 3H), 7.18-7.24 (m,4H), 7.55-7.58 (d, 1H), 11.50 (s,1H) ; MS, m/e 547.91 (M+1) ⁺
29	4-F-Ph	H	H	Me	Bn	1H NMR (DMSO- <i>d</i> ₆) δ 1.10-1.23 (m, 6H), 3.65-3.89(m,3H), 4.10-4.30 (m,2H), 4.96-5.00(m,2H), 5.46-5.50 (t, 1H), 5.75-5.96 (m, 2H), 6.04-6.12(m,1H), 7.05-7.11 (m,4H), 7.20-7.24 (d, 5H), 7.42-7.45(d,1H), 11.50 (s,1H) ; MS, m/e 595.94 (M+1) ⁺
30	4-MeO-Ph	H	H	Me	i-Pr	1HNMR (400MHz, DMSO- <i>d</i> ₆): δ=1.15-1.27 (m, 12H), 3.71-3.89 (m, 5H), 3.98-4.02 (m, 1H), 4.22-4.25 (m, 1H), 4.33-4.39 (m, 1H), 4.84-4.87 (m, 1H), 5.57 (t, J= 12.0Hz, 1H), 5.91-6.03 (m, 3H), 6.90 (d, J= 8.0Hz, 2H), 7.09-7.14 (m, 2H), 7.55 (d, J= 8.0Hz, 1H), 11.51 (s, 1H)
31	2-Cl-Ph	H	H	Me	Bn	1H NMR (DMSO- <i>d</i> ₆) δ 1.23 (m, 6 H), 3.93-4.00 (m, 3 H), 4.27-4.40 (m, 2H), 5.0(t, J= 7.2 Hz, 2 H), 5.53 (m, 1 H), 5.80-6.0(m, 2 H), 6.30(m, 1H), 7.15 (d, J= 2.4 Hz, 1 H), 7.27 (m, 6 H), 7.51 (m, 3 H), 11.5 (s, 1 H) ; MS, m/e 579.87(M+1) ⁺ / 596.78 (M+18) ⁺
32	2,4-Cl-Ph	H	H	Me	n-Bu	1H NMR (DMSO- <i>d</i> ₆) δ=0.82 (m, 3 H),1.23 (m, 8 H) , 1.47 (m, 2 H), 3.86 (m, 2 H), 3.84 (m, 3 H),4.27-4.43 (m, 2H), 5.5 (m, 1 H), 6.02 (m, 2 H), 6.35(m, 1H), 7.44 (m, 3 H), 7.77 (m, 1 H), 11.5 (s, 1 H) ; MS, m/e 611.87(M+1) ⁺
33	4-Me-Ph	H	H	Me	i-Pr	1H NMR (DMSO- <i>d</i> ₆) δ 1.14-1.27 (m, 12H), 2.17-2.26 (m, 3H), 3.73-3.82 (m, 1H), 3.99-4.02 (m, 1H), 4.23-4.26 (m, 1H), 4.37-4.40 (m,

Ex.	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	NMR/MS
						1H), 4.82-4.88 (m, 1H), 5.52-5.58 (m, 1H), 5.85-6.07 (m, 3H), 7.01-7.20 (m, 4H), 7.55 (d, J = 16Hz, 1H), 11.51 (s, 1H); MS, m/e 543.98 (M+1) ⁺ ; 1108.86 (2M+23) ⁺
34	4-F-Ph	H	H	Me	n-Bu	1H NMR (DMSO- <i>d</i> ₆) δ 0.82-0.89 (m, 3H), 1.20-1.31 (m, 8H), 1.48-1.53 (m, 2H), 3.77-3.90 (m, 2H), 3.95-4.10 (m, 3H), 4.21-4.45 (m, 2H), 5.56-5.61 (t, 1H), 5.83-6.20 (m, 3H), 7.18-7.25 (m, 4H), 7.55-7.58 (d, 1H), 11.50 (s, 1H); MS, m/e 584.1 (M+23) ⁺
35	3,4-diCl-Ph	H	H	Me	Et	1H NMR (DMSO- <i>d</i> ₆) δ 1.12-1.31 (m, 9H), 3.77-3.92 (m, 2H), 3.95-4.08 (m, 3H), 4.21-4.45 (m, 2H), 5.56-5.62 (t, 1H), 5.80-6.11 (m, 2H), 6.18-6.33 (m, 1H), 7.18-7.25 (m, 1H), 7.49-7.56 (d, 2H), 7.62-7.67 (m, 1H), 11.50 (s, 1H); MS, m/e 606.1 (M+23) ⁺
36	2-Cl-Ph	H	H	Me	i-Pr	1HNMR (400MHz, DMSO- <i>d</i> ₆): δ = 1.12-1.16 (m, 6H), 1.21-1.27 (m, 6H), 3.79-3.85 (m, 2H), 4.00-4.07 (m, 1H), 4.28-4.32 (m, 1H), 4.38-4.43 (m, 1H), 4.83-4.87 (m, 1H), 5.56 (dd, J1=16.0Hz, J2=8.0Hz, 1H), 5.85-6.12 (m, 2H), 6.20-6.33 (m, 1H), 7.19-7.22 (m, 1H), 7.33 (t, J=16.0Hz, 1H), 7.48-7.55 (m, 3H), 11.55 (s, 1H)
37	4-MeO-Ph	H	H	Me	Bn	1HNMR(400MHz, DMSO- <i>d</i> ₆): δ=1.19-1.26 (m, 6H), 3.69-3.70 (s, 3H), 3.87 (m, 2H), 3.99 (m, 1H), 4.20-4.21 (m, 1H), 4.35 (m, 1H), 5.07-5.09 (m, 2H), 5.54 (t, J = 16.0Hz, 1H), 5.85-5.92 (m, 1H), 6.04-6.10 (m, 2H), 6.86 (d, J = 8.0Hz, 2H), 7.09 (dd, J1=16.0Hz, J2=4.0Hz, 2H), 7.30-7.34 (m, 5H), 7.53 (s, 1H), 11.52 (s, 1H)
38	Ph	H	H	Me	n-Pen	1H NMR (DMSO- <i>d</i> ₆) δ 0.79-0.81 (m, 3H), 1.17-1.23 (m, 10H), 3.74-3.81 (m, 2H), 3.94-3.96 (m, 3H), 4.19-4.36 (m, 2H), 5.49-5.54 (m, 1H), 5.87-6.08 (m, 3H), 7.14-7.33 (m, 3H), 7.31-7.35 (m, 2H), 7.51 (d, J = 8Hz, 1H), 11.51 (s, 1H); MS, m/e 557.9 (M+1) ⁺ ; 1136.88 (2M+23) ⁺
39	4-Cl-Ph	H	H	Me	i-Pr	1H NMR (DMSO- <i>d</i> ₆) δ 1.04-1.19 (m, 12H), 3.76-3.80 (m, 2H), 3.98-4.08 (m, 1H), 4.42-4.42 (m, 2H), 4.82-4.85 (m, 1H), 5.55-5.60 (m, 1H), 5.80-6.20 (m, 3H), 7.20-7.25 (m, 2H), 7.43 (d, J = 8.8Hz, 1H), 7.54 (d, J = 8Hz, 1H), 11.51 (s, 1H); MS, m/e 563.88 (M+1) ⁺ ; 1148.73 (2M+23) ⁺
40	4-Cl-Ph	H	H	Me	n-Bu	1H NMR (DMSO- <i>d</i> ₆) δ 0.85 (t, J = 7.2 Hz, 3H), 1.22-1.33 (m, 8H), 1.45-1.53 (m, 2H), 3.80-3.87 (m, 2H), 3.96-4.04 (m, 3H), 4.24-4.27 (m, 1H), 4.35-4.39 (m, 1H), 5.56-5.61 (m, 1H), 5.82-6.11 (m, 2H), 6.15-6.18 (m, 1H), 7.20-7.56 (m, 4H), 7.51-7.57 (m, 1H), 11.54 (s, 1H); MS, m/e 577.95 (M+1) ⁺
41	4-Cl-Ph	H	H	Me	Et	1H NMR (DMSO- <i>d</i> ₆) δ 1.14 (t, J = 7.0Hz, 3H), 1.20-1.28 (m, 6H), 3.77-3.88 (m, 2H), 3.99-4.07 (m, 3H), 4.24-4.28 (m, 1H), 4.34-4.43 (m, 1H), 5.56-5.61 (m, 1H), 5.86-6.13 (m, 2H), 6.15-6.24 (m, 1H), 7.20-7.26 (m, 2H), 7.44 (d, J = 7.6Hz, 2H), 7.55 (d, J = 7.6Hz, 1H), 11.55 (s, 1H); MS, m/e 549.11 (M+1) ⁺
42	4-Me-Ph	H	H	Me	n-Bu	1H NMR (DMSO- <i>d</i> ₆) δ 0.79-0.83 (m, 3H), 1.17-1.28 (m, 8H), 1.45-1.47 (m, 2H), 2.22 (d, J = 2.8Hz, 1H), 3.70-3.90 (m, 2H), 3.95-3.98 (m, 3H), 4.10-4.40 (m, 2H), 5.51 (t, 1H), 5.80-5.90 (m, 1H), 5.95-6.05 (m, 2H), 7.02-7.06 (m, 2H), 7.51 (t, J = 4.2Hz, 4H), 7.51 (d, 1H), 11.51 (s, 1H); MS, m/e 557.99 (M+1) ⁺ ; 1136.84 (2M+23) ⁺

Ex.	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	NMR/MS
43	4-Mc-Phe	H	H	Me	Bn	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.16-1.24 (m, 6H), 2.22 (s, 3H), 3.65-4.03 (m, 3H), 4.11-4.38 (m, 2H), 5.04-5.05 (m, 2H), 5.48-5.50 (m, 1H), 5.77-5.87 (m, 1H), 5.90-6.11 (m, 2H), 6.98-7.10 (m, 4H), 7.28-7.32 (m, 5H), 7.50 (t, 1H), 11.48 (s, 1H); MS, <i>m/e</i> 592.00 (M+1) ⁺ .
44	Ph	H	H	Et	Me	¹ H NMR (DMSO- <i>d</i> ₆) δ 0.70-0.80 (m, 3H), 1.11-1.26 (m, 3H), 1.42-1.61 (m, 2H), 3.50-3.54 (m, 3H), 3.58-3.80 (m, 2H), 3.91-4.02 (m, 1H), 4.12-4.38 (m, 2H), 5.47-5.52 (m, 1H), 5.90-6.03 (m, 2H), 7.08-7.16 (m, 3H), 7.26-7.35 (m, 2H), 7.48 (t, 1H), 11.45 (s, 1H); MS, <i>m/e</i> 515.95 (M+1) ⁺ ; 1052.82 (2M+23) ⁺ .
45	Ph	H	H	Me	4-F-Bn	¹ H NMR (400MHz, DMSO- <i>d</i> ₆) δ 1.20-1.26 (m, 6H), 3.80-3.93 (m, 2H), 3.98 (s, 1H), 4.25-4.26 (m, 1H), 4.36-4.37 (m, 1H), 5.07 (s, 2H), 5.52-5.55 (m, 1H), 5.86-5.87 (m, 1H), 5.98-6.04 (m, 1H), 6.14-6.17 (m, 1H), 7.15-7.20 (m, 5H), 7.36 (dd, <i>J</i> = 20.0, 8.0 Hz, 4H), 7.54 (s, 1H), 11.55 (s, 1H).
46	4-Cl-Ph	H	H	Me	n-Bu	¹ H NMR (400MHz, DMSO- <i>d</i> ₆) δ 1.21-1.28 (m, 6H), 3.71-3.88 (m, 1H), 3.91-3.98 (m, 1H), 4.00-4.01 (m, 1H), 4.23-4.27 (m, 1H), 4.35-4.38 (m, 1H), 5.08 (d, <i>J</i> = 4.0 Hz, 2H), 5.57 (dd, <i>J</i> = 12.0, 8.0 Hz, 1H), 5.91 (d, <i>J</i> = 8.0 Hz, 1H), 6.01 (d, <i>J</i> = 8.0 Hz, 1H), 6.22-6.24 (m, 1H), 7.17-7.23 (m, 2H), 7.31-7.40 (m, 7H), 7.53 (s, 1H), 11.50 (s, 1H).
47	Ph	H	H	Me	3-Mc-1-Bu	¹ H NMR (DMSO- <i>d</i> ₆) δ 0.80-0.82 (m, 6H), 1.18-1.40 (m, 8H), 1.50-1.58 (m, 1H), 3.71-3.82 (m, 3H), 3.97-3.4.01 (m, 3H), 4.21-4.40 (m, 2H), 5.30 (t, <i>J</i> = 8.6 Hz, 1H), 5.81-6.10 (m, 3H), 7.15-7.20 (m, 3H), 7.32-7.36 (m, 2H), 7.48 (d, <i>J</i> = 8.4 Hz, 1H), 11.38 (s, 1H); MS, <i>m/e</i> 557.98 (M+1) ⁺ ; 1136.88 (2M+23) ⁺ .
48	3,4-diCl-Ph	H	H	Me	Bn	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.05-1.37 (m, 6H), 3.71-3.82 (m, 1H), 3.87-4.02 (m, 2H), 4.28-4.29 (m, 1H), 4.36-4.38 (m, 1H), 5.04 (d, <i>J</i> = 5.2 Hz, 2H), 5.55-5.64 (m, 1H), 5.85-5.94 (m, 1H), 6.00-6.05 (m, 1H), 6.29-6.40 (m, 1H), 7.17-7.24 (m, 1H), 7.30-7.41 (m, 5H), 7.45-7.58 (m, 2H), 7.61 (d, <i>J</i> = 4.0 Hz, 1H), 11.53 (s, 1H); MS, <i>m/e</i> 545.80 (M+1) ⁺ .
49	Ph	H	H	Me	c-Hex	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.18-1.41 (m, 12H), 1.59-1.67 (m, 4H), 3.74-13.80 (m, 1H), 3.96-4.02 (m, 1H), 4.19-4.26 (m, 1H), 4.31-4.39 (m, 1H), 4.60 (s, 1H), 5.52 (t, <i>J</i> = 7.8 Hz, 1H), 5.80-6.09 (m, 3H), 7.15-7.20 (m, 3H), 7.32-7.36 (m, 2H), 7.52 (d, <i>J</i> = 8 Hz, 1H), 11.50 (s, 1H); MS, <i>m/e</i> 569.98 (M+1) ⁺ ; 592.14 (M+23) ⁺ .
50	Ph	H	Me	H	n-Bu	¹ H NMR (DMSO- <i>d</i> ₆) δ 0.76 (t, <i>J</i> = 7.2 Hz, 3H), 1.10-1.22 (m, 8H), 1.38-1.43 (m, 2H), 3.72-3.75 (m, 2H), 3.87-3.93 (m, 3H), 4.14-4.21 (m, 1H), 4.23-4.33 (m, 1H), 5.46-5.54 (m, 1H), 5.84-6.11 (m, 3H), 7.09-7.14 (m, 2H), 7.27-7.32 (m, 2H), 7.34-7.51 (m, 1H), 11.47 (s, 1H); MS, <i>m/e</i> 543.98 (M+1) ⁺ .
51	Ph	H	Me	H	i-Pr	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.39 (d, <i>J</i> = 7.2 Hz, 6H), 1.19-1.29 (m, 6H), 3.65-3.75 (m, 2H), 3.95-4.05 (m, 1H), 4.20-4.22 (m, 1H), 4.31-4.33 (m, 1H), 4.79-4.82 (m, 1H), 5.48-5.57 (m, 1H), 5.84-5.91 (m, 1H), 5.96-6.07 (m, 2H), 7.12-7.35 (m, 5H), 7.44-7.54 (m, 1H), 11.49 (s, 1H); MS, <i>m/e</i> 529.96 (M+1) ⁺ .
52	Ph	H	Me	H	Bn	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.18-1.28 (m, 6H), 3.70-3.83 (m, 1H), 3.87-3.94 (m, 1H), 3.99-4.01 (m, 1H), 4.23-4.26 (m, 1H), 4.33-4.37 (m,

Ex.	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	NMR/MS
53	2-Cl-Ph	H	H	Me	n-Bu	¹ H), 5.03-5.12 (m, 2H), 5.51-5.59 (m, 1H), 5.87-5.90 (m, 1H), 5.95-6.07 (m, 1H), 6.10-6.27 (m, 1H), 7.15-7.23 (m, 3H), 7.31-7.38 (m, 7H), 7.47-7.56 (m, 1H), 11.50 (s, 1H); MS, <i>m/e</i> 577.99 (M+1) ⁺ ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ 0.81-0.86 (m, 3H), 1.21-1.31 (m, 8H), 1.46-1.52 (m, 2H), 3.84-3.90 (m, 2H), 3.97-4.04 (m, 3H), 4.27-4.41 (m, 2H), 5.53-5.58 (m, 1H), 5.82-5.95 (m, 1H), 5.96-6.10 (m, 1H), 6.27-6.31 (m, 1H), 7.19-7.22 (m, 1H), 7.34 (dd, <i>J</i> = 8.0, 4.0 Hz, 1H), 7.47-7.55 (m, 3H), 11.55 (s, 1H)
54	4-Br-Ph	H	H	Me	i-Pr	¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ 1.10-1.14 (m, 6H), 1.20-1.27 (m, 6H), 3.74-3.81 (m, 2H), 3.99-4.01 (m, 1H), 4.21-4.25 (m, 1H), 4.37-4.38 (m, 1H), 4.81-4.85 (m, 1H), 5.58 (dd, <i>J</i> = 8.0, 4.0 Hz, 1H), 5.82-5.95 (m, 1H), 5.96-6.09 (m, 1H), 6.10-6.13 (m, 1H), 7.18 (dd, <i>J</i> = 12.0, 8.0 Hz, 2H), 7.53-7.57 (m, 3H), 11.52 (s, 1H)
55	4-F-Ph	H	H	Me	c-Hex	¹ H NMR (DMSO- <i>d</i> ₆): δ 1.20-1.44 (m, 12H), 1.60-1.71 (m, 4H), 3.75-4.02 (m, 2H), 3.94-4.02 (m, 1H), 4.19-4.26 (m, 2H), 4.59-4.61 (m, 1H), 5.57 (t, <i>J</i> = 8.4 Hz, 1H), 5.85-6.06 (m, 3H), 7.17-7.23 (m, 4H), 7.54 (d, <i>J</i> = 8.4 Hz, 1H), 11.50 (s, 1H); MS, <i>m/e</i> 587.92 (M+1) ⁺
56	4-Br-Ph	H	H	Me	c-Hex	¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ 1.18-1.46 (m, 12H), 1.61-1.69 (m, 4H), 3.75-3.82 (m, 2H), 3.95-4.08 (m, 1H), 4.25-4.28 (m, 1H), 4.38 (s, 1H), 4.60-4.62 (m, 1H), 5.56-5.60 (m, 1H), 5.82-5.95 (m, 1H), 6.02-6.20 (m, 2H), 7.09-7.20 (m, 2H), 7.53-7.57 (m, 3H), 11.52 (s, 1H) MS, <i>m/e</i> 650.0 (M+3) ⁺
57	Ph	H	H	Et	i-Pr	¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ 0.75-0.82 (m, 3H), 1.12-1.26 (m, 9H), 1.52-1.59 (m, 2H), 3.55-3.68 (m, 1H), 3.72-3.85 (m, 1H), 3.95-4.08 (m, 1H), 4.18-4.28 (m, 1H), 4.32-4.41 (m, 1H), 4.83-4.86 (m, 1H), 5.55 (m, <i>J</i> = 7.6Hz, 1H), 5.99-6.04 (m, 2H), 6.05-6.10 (m, 1H), 7.14-7.21 (m, 3H), 7.33-7.37 (m, 2H), 7.52-7.54 (m, 1H), 11.53 (s, 1H); MS, <i>m/e</i> 566.07 (M+23) ⁺
58	Ph	H	H	Et	c-Hex	¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ 0.75-0.88 (m, 3H), 1.26-1.46 (m, 9H), 1.52-1.69 (m, 6H), 3.60-3.63 (m, 1H), 3.72-3.90 (m, 1H), 4.02-4.03 (m, 1H), 4.24-4.27 (m, 1H), 4.37-4.38 (m, 1H), 4.63-4.65 (m, 1H), 5.55 (dd, <i>J</i> = 8.0Hz, 4.4Hz, 1H), 5.80-5.95 (m, 1H), 6.00-6.07 (m, 2H), 7.15-7.22 (m, 3H), 7.34-7.38 (m, 2H), 7.54 (d, <i>J</i> = 8.0Hz, 1H), 11.55 (s, 1H); MS, <i>m/e</i> 584.01 (M+1) ⁺ , 606.17 (M+23) ⁺
59	4-F-Ph	H	H	Et	c-Hex	¹ H NMR (DMSO- <i>d</i> ₆): δ 0.75-0.84 (m, 3H), 1.24 (d, <i>J</i> = 22.8Hz, 3H), 1.29-1.47 (m, 6H), 1.51-1.70 (m, 6H), 3.59-3.66 (m, 1H), 3.77-3.84 (m, 1H), 3.98-4.04 (m, 1H), 4.21-4.27 (m, 1H), 4.34-4.41 (m, 1H), 4.60-4.65 (m, 1H), 5.56-5.60 (m, 1H), 5.84-5.90 (m, 1H), 6.00-6.08 (m, 2H), 7.20-7.24 (m, 4H), 7.56 (d, <i>J</i> = 8.0Hz, 1H), 11.49 (s, 1H); MS, <i>m/e</i> 602.00 (M+1) ⁺
60	Ph	H	H	Me	F-CH ₂ -CH ₂ -	¹ H NMR (DMSO- <i>d</i> ₆): δ 1.18-1.25 (m, 6H), 3.71-3.89 (m, 2H), 3.92-3.99 (m, 1H), 4.19-4.27 (m, 4H), 4.48-4.61 (m, 2H), 3.94-3.98 (m, 2H), 4.11-4.23 (m, 4H), 5.47-5.52 (m, 1H), 6.01-6.11 (m, 1H), 5.90-6.14

Ex.	R ¹	R ²	R ^{3a}	R ^{3b}	R ⁴	NMR/MS
						(m, 2H), 7.15-7.21 (m, 3H), 7.32-7.36 (m, 2H), 7.46-7.57 (m, 1H), 11.49 (s, 1H); MS, <i>m/e</i> 533.86 (M+1) ⁺
61	Ph	H	H	Me	F ₂ CH-CH ₂ -	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.17-1.24 (m, 6H), 3.67-3.81 (m, 1H), 3.89-3.98 (m, 2H), 4.21-4.36 (m, 4H), 5.48-5.53 (m, 1H), 5.82-6.05 (m, 2H), 6.18-6.22 (m, 2H), 7.15-7.20 (m, 3H), 7.32-7.36 (m, 2H), 7.51 (s, 1H), 11.50 (s, 1H); MS, <i>m/e</i> 551.92 (M+1) ⁺
62	Ph	H	H	Me	(CF ₃) ₂ -CH-	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.13-1.29 (m, 6H), 3.67-3.81 (m, 1H), 3.94-4.32 (m, 4H), 5.47 (t, <i>J</i> = 8 Hz, 1H), 5.82-6.01 (m, 2H), 6.33-6.36 (m, 1H), 6.70-6.78 (m, 1H), 7.09-7.15 (m, 3H), 7.28-7.32 (m, 2H), 7.43-7.46 (m, 1H), 11.44 (s, 1H); MS, <i>m/e</i> 637.90 (M+1) ⁺
63	Ph	H	H	Me	(CH ₃ F) ₂ -CH-	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.20-1.29 (m, 6H), 3.70-3.90 (m, 1H), 3.91-4.12 (m, 2H), 4.20-4.33 (m, 1H), 4.35-4.48 (m, 1H), 4.52-4.55 (m, 2H), 4.63-4.67 (m, 2H), 5.20-5.35 (m, 1H), 5.56 (t, <i>J</i> = 8.4 Hz, 1H), 5.80-5.95 (m, 1H), 5.95-6.10 (m, 1H), 6.18-6.21 (m, 1H), 7.18-7.23 (m, 3H), 7.35-7.39 (m, 2H), 7.54 (s, 1H), 11.55 (s, 1H); MS, <i>m/e</i> 565.98 (M+1) ⁺
64	Ph	H	H	Me	c-Pr-CH ₂ -	¹ H NMR (DMSO- <i>d</i> ₆) δ 0.20-0.24 (m, 2H), 0.47-0.48 (m, 2H), 0.76-0.84 (m, 3H), 1.03-1.05 (m, 1H), 1.23 (dd, <i>J</i> = 22.4, 6.8 Hz, 3H), 1.55-1.60 (m, 2H), 3.61-3.68 (m, 1H), 3.81-3.89 (m, 3H), 3.98-4.03 (m, 1H), 4.23-4.29 (m, 1H), 4.35-4.41 (m, 1H), 5.56-6.00 (m, 1H), 5.88-5.91 (m, 1H), 6.04-6.10 (m, 2H), 7.20-7.24 (m, 4H), 7.55 (d, <i>J</i> = 7.6 Hz, 1H), 11.53 (s, 1H); MS, <i>m/e</i> 573.17 (M+1) ⁺
65	Ph	H	H	Et	c-Pen	¹ H NMR (DMSO- <i>d</i> ₆) δ 0.75-0.83 (m, 3H), 1.20-1.28 (m, 3H), 1.49-1.63 (m, 8H), 1.76-1.80 (m, 2H), 3.58-3.60 (m, 1H), 3.70-3.82 (m, 1H), 3.98-4.05 (m, 1H), 4.24-4.26 (m, 1H), 4.37-4.42 (m, 1H), 5.03 (s, 1H), 5.54-5.57 (m, 1H), 5.90-6.00 (m, 1H), 6.02-6.07 (m, 2H), 7.15-7.22 (m, 3H), 7.35-7.39 (m, 2H), 7.55 (d, <i>J</i> = 8.0 Hz, 1H), 11.55 (s, 1H); MS, <i>m/e</i> 570.03 (M+1) ⁺

*R² and R^{3b} together are -(CH₂)₃- as derived from L-proline

The purification procedure by Prep-HPLC:

Crude products were dissolved in methanol. Injection volumes of these solutions were 5 mL.

The preparative HPLC system including 2 sets of Gilson 306 pumps, a Gilson 156 UV/Vis detector, a Gilson 215 injector & fraction collector, with Unipoint control software. A Ymc 25×30×2 mm column was used. The mobile phase was HPLC grade

water (A), and HPLC grade acetonitrile (B). Fractions were collected into 100*15mm glass tubes.

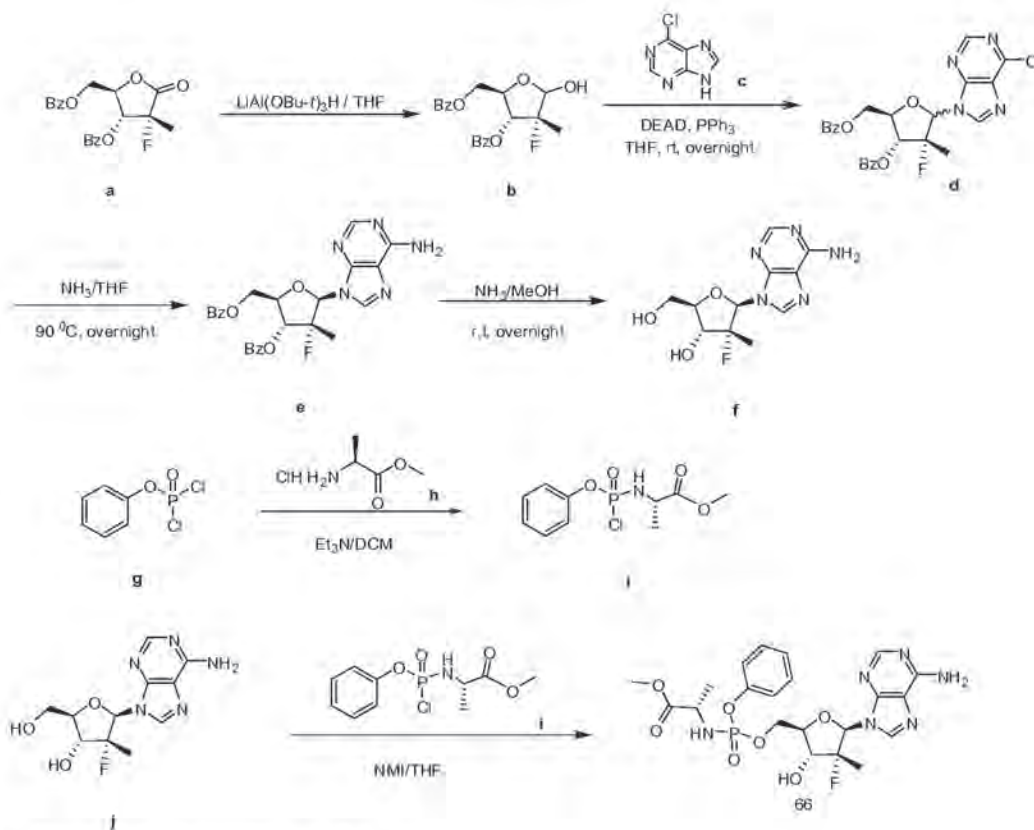
- 5 HPLC gradient is shown in Table 1. Once the gradient was selected, acetonitrile solution was injected into HPLC system, and then fractions collected according to UV peaks. After the separation, each glass tubes were run MS test to collect the desired compounds. The fractions with target MS were combined in a well-weighted flask. Most of acetonitrile was removed under reduce pressure and the remaining solution was freeze-dried to give desired compound.

10 **Table 1:**

Preparative HPLC gradient			
Time (min)	Flow rate (mL/min)	% A	% B
0	15	90	10
30	15	60	40

Preparation of Example 66

Scheme



Preparation of compound (b)

To a solution of compound **a** (1 g, 2.69 mmol) in anhydrous THF (30 mL) was added dropwise 1 M solution of $\text{LiAl}(\text{OBu-}t)_3\text{H}$ in THF (2.69 mL, 2.69 mmol) at -20°C . The reaction mixture was stirred for 2-3 h at the same temperature. EtOAc (100 mL) was added followed by saturated NH_4Cl solution (10 mL) and reaction mixture was slowly brought to room temperature. Reaction mixture was extracted with EtOAc and washed with 1N HCl and water. Combined organic phase was evaporated to give 0.8 g of crude compound **b** as transparent oil, which was used directly for next reaction.

10 Preparation of compound (d)

To a solution of compound **b** (0.8 g, 2.1 mmol), compound **c** (0.45 g, 2.5 mmol) and Ph_3P (0.56 g, 2.1 mmol) in anhydrous THF (20 mL) under nitrogen atmosphere was added DEAD (1.8 mL). The reaction mixture was stirred at room temperature overnight. The reaction solution was concentrated under reduce pressure. The residue was separated

by preparative layer chromatography (hexanes:EtOAc = 3:1) to give crude compound **d** (0.8 g). The crude compound **d** was used to the next step without further purification.

Preparation of compound (e)

Compound **d** (0.8 g, 1.57 mmol) was dissolved in THF (2 mL) and THF saturated with ammonia (5 mL) was then added to this solution. The reaction mixture was heated to 90 °C overnight. After 18 hours, the solution was cooled to room temperature by ice water, then the solvent was removed under reduced pressure and the residue was purified by column to give compound **e** (0.75 g) for the next step.

Preparation of compound (f)

Compound **e** (0.5 g, 1.01 mmol) was dissolved in methanol (2 mL) and methanol was saturated with ammonia (5 mL) was then added to this solution. The reaction mixture was stirred at room temperature overnight. After 18 hours, the solvent was removed under reduced pressure and the residue was purified by column to give crude compound **f** (0.15 g) for the next step.

Preparation of compound (i)

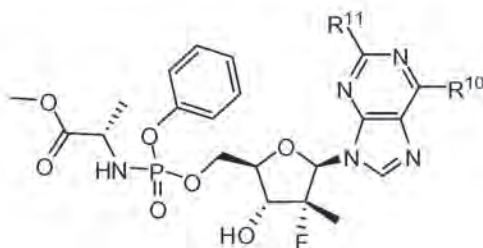
A solution of triethylamine (1.07 g, 10.6 mmol) in anhydrous dichloromethane (15 mL) was added dropwise to a solution of compound **g** (1.16 g, 5.3 mmol) and compound **h** (1.31 g, 5.3 mmol) in dichloromethane (10 mL) with vigorous stirring at -78 °C over a period of 2 hours. After completion of addition, the reaction temperature was allowed to warm to room temperature gradually and stirred over night. Then the solvent was removed under vacuum and anhydrous ether 20 mL was added and the precipitated salt was filtered and the precipitate was washed with ether. The combined organic phase was concentrated to give the colorless oil of compound **i** (1.0 g).

Preparation of Compound 66

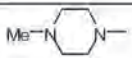
To a solution of compound **j** (0.1 g, 0.35 mmol) dissolved in 10 mL of anhydrous THF, stirred and added 0.4g NMI till the solution became clear, added compound **i** (0.8 g, 2.89 mmol) in 10 mL THF dropwise, stirred at r.t. overnight. Compound purity and identification was confirmed by LCMS. The solvent was evaporated and purified by Prep-HPLC to afford **66**. (25 mg, Yield: 13.6%). ¹H NMR (DMSO-*d*₆) δ 1.08 (d, *J* = 22.8 Hz, 3H), 1.17-1.24 (m, 3H), 3.50-3.52 (m, 3H), 3.78-3.83 (m, 1H), 4.10-4.13 (m,

1H), 4.24-4.44 (m, 2H), 5.85-5.92 (m, 1H), 6.01-6.11 (m, 1H), 6.2-6.27 (m, 1H), 7.08-7.19 (m, 4H), 7.31-7.38 (m, 3H), 8.15 (s, 1H), 8.26 (s, 1H); MS, m/e 525 (M+1)⁺.

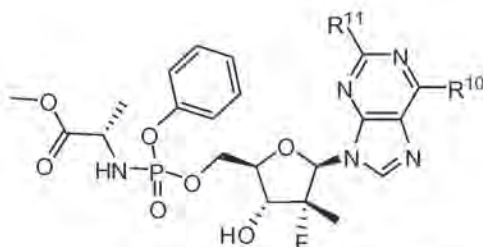
- 5 Example numbers **67-74**, identified below, were prepared using similar procedures disclosed for Example **66**, above.



Example	R ¹¹	R ¹⁰	NMR/MS
67	OH	NH ₂	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.06-1.13 (m, 3H), 1.20-1.24 (m, 3H), 3.27-3.33(m, 3H), 3.56 (s, 1H), 3.82-3.88 (m, 1H), 4.07-4.13 (m, 1H), 4.25-4.40 (m, 2H), 5.85-5.87 (m, 1H), 5.98-6.09 (m, 2H), 6.59 (s, 32H), 7.14-7.37 (m, 3H), 7.35-7.37 (m, 2H), 7.79 (d, <i>J</i> =7.2 Hz, 1H), 10.69 (s, 1H); MS, m/e 541 (M+1) ⁺ ;
68	NH ₂	NH ₂	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.07 (d, <i>J</i> =22.8 Hz, 3H), 1.19 (d, <i>J</i> =7.2 Hz, 3H), 3.51 (s, 3H), 3.62 (s, 1H), 3.75-3.81 (m, 1H), 4.05-4.11 (m, 1H), 4.27-4.42 (m, 2H), 5.79-5.83 (m, 1H), 5.92 (s, 2H), 6.00-6.09 (m, 2H), 6.75 (s, 2H), 7.08-7.17 (m, 3H), 7.31-7.35 (m, 2H), 7.78 (s, 1H); MS, m/e 540 (M+1) ⁺ ;
69	NH ₂	c-Pentyl-NH-	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.05 (d, <i>J</i> =22.8 Hz, 3H), 1.09-1.19 (m, 3H), 1.48 (s, 4H), 1.66 (s, 1H), 1.86 (s, 1H), 3.54 (d, <i>J</i> =14 Hz, 3H), 3.65 (s, 1H), 4.25-4.43 (m, 4H), 5.71-5.82 (m, 1H), 5.94-6.04 (m, 4H), 7.11-7.24 (m, 3H), 7.26-7.34 (m, 2H), 7.77(d, <i>J</i> =3.6 Hz, 1H); MS, m/e 608(M+1) ⁺
70	NH ₂		¹ H NMR (DMSO- <i>d</i> ₆) δ 1.07 (d, <i>J</i> =22.4 Hz, 3H), 2.35-2.38 (m, 2H), 3.54 (d, <i>J</i> =9.2 Hz, 3H), 3.59-3.62 (m, 2H), 3.65 (s, 1H), 3.75-3.82 (m, 1H), 4.01-4.13 (m, 2H), 4.22-4.40 (m, 6H), 5.75-5.85 (m, 1H), 6.00-6.07 (m, 4H), 7.15-7.21 (m, 3H), 7.32-7.35 (m, 2H), 7.79 (d, <i>J</i> =4.0 Hz, 1H); MS, m/e 580 (M+1) ⁺
71	NH ₂	Et ₂ N-	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.06-1.28 (m, 12H), 3.55 (d, <i>J</i> =4.8 Hz, 3H), 3.79-3.87 (m, 4H), 4.07-4.12 (m, 2H), 4.29-4.42 (m,

Example	R ¹¹	R ¹⁰	NMR/MS
			3H), 5.75-5.82 (m, 1H), 5.94 (s, 2H), 6.04-6.10 (m, 2H), 7.14-7.22 (m, 3H), 7.31-7.37 (m, 2H), 7.82 (d, <i>J</i> =4.4 Hz, 1H); MS, <i>m/e</i> 596 (M+1) ⁺
72	NH ₂	n-Propyl-NH-	¹ H NMR (DMSO- <i>d</i> ₆) δ 0.84 (t, <i>J</i> =7.2 Hz, 3H), 1.01-1.01 (m, 3H), 1.09-1.12 (m, 3H), 1.51-1.56 (m, 2H), 3.48 (d, <i>J</i> =15.2 Hz, 3H), 3.79-3.82 (m, 1H), 4.04-4.05 (m, 1H), 4.27-4.38 (m, 3H), 5.72-5.79 (m, 1H), 5.98-6.04 (m, 4H), 7.13-7.20 (m, 3H), 7.26-7.32 (m, 2H), 7.76 (d, <i>J</i> =5.2 Hz, 1H); MS, <i>m/e</i> 582 (M+1) ⁺
73	NH ₂	c-Butyl-NH-	¹ H NMR (DMSO- <i>d</i> ₆) δ 1.02-1.08 (m, 3H), 1.18 (d, <i>J</i> =4.8 Hz, 3H), 1.44-1.61 (m, 2H), 2.02-2.17 (m, 4H), 3.51 (d, <i>J</i> =10.8 Hz, 3H), 3.78-3.83 (m, 1H), 4.03-4.06 (m, 1H), 4.27-4.38 (m, 2H), 4.53-4.62 (m, 1H), 5.68-5.79 (m, 1H), 5.95-6.04 (m, 4H), 7.11-7.18 (m, 3H), 7.29-7.35 (m, 2H), 7.51-7.58 (m, 1H), 7.78 (d, <i>J</i> =5.2 Hz, 1H); MS, <i>m/e</i> 594 (M+1) ⁺
74	NH ₂		¹ H NMR (DMSO- <i>d</i> ₆) δ 0.97-1.20 (m, 6H), 2.18 (s, 3H), 2.19 (s, 4H), 3.43-3.47 (m, 3H), 3.75 (s, 1H), 4.01-4.06 (m, 4 H), 4.22-4.35 (m, 3H), 5.69-5.75 (m, 1H), 5.98-6.05 (m, 3H), 7.09-7.15 (m, 3H), 7.25-7.29 (m, 2H), 7.77 (d, <i>J</i> =3.6 Hz, 1H); MS, <i>m/e</i> 623 (M+1) ⁺

Example numbers 75-80 are prepared using similar procedures disclosed for Example 66, above.



Example	R ¹¹	R ¹⁰
75	H	n-propyl-NH-
76	H	c-Butyl-NH-
77	H	c-Pentyl-NH-
78	H	
79	H	
80	H	

EXAMPLE 81

- Certain exemplified compounds were obtained as mixture of diastereomers because of the chirality at phosphorous. The diastereomers were separated on a Chiralpak-AS-H (2 X 25 cm) column under Supercritical Fluid Chromatography (SFC) conditions using 20% methanol in carbon dioxide as solvent. The absolute stereochemistry of the P-chiral center of the diastereomers were not determined. However, chromatographic resolution of these two diastereomers provides for isomers that are characterized as fast eluting and slow eluting isomers. Some examples are shown below.

Compound	EC ₉₀ (uM)
Example 15 (Diastereomeric mixture)	0.86
Fast Moving isomer of Example 15	1.35
Slow Moving isomer of Example 15	0.26

Compound	EC90 (uM)
Example 39 (Diastereomeric mixture)	0.47
Fast Moving isomer of Example 39	0.78
Slow Moving isomer of Example 39	0.02
Example 49 (Diastereomeric mixture)	0.126
Fast Moving isomer of Example 49	0.03
Slow Moving isomer of Example 49	5.78

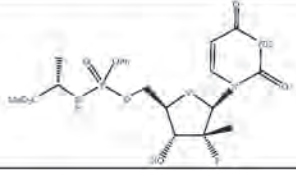
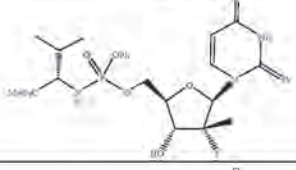
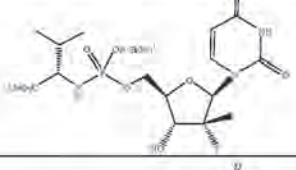
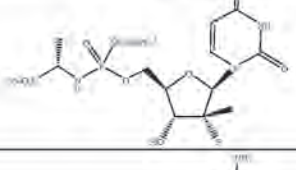
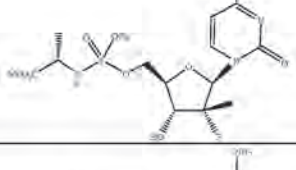
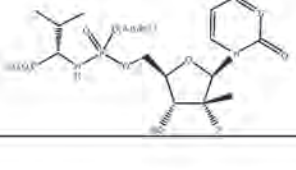
EXAMPLE 82

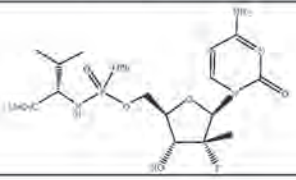
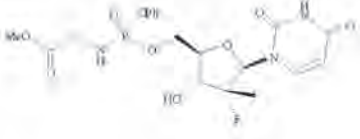
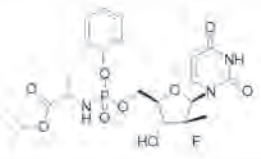
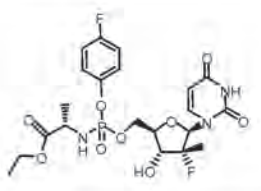
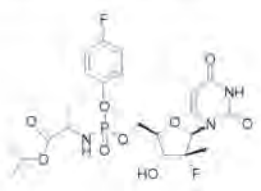
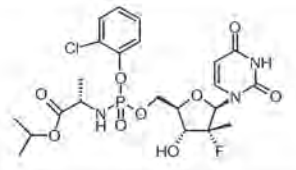
HCV replicon assay. HCV replicon RNA-containing Huh7 cells (clone A cells; Apath, LLC, St. Louis, Mo.) were kept at exponential growth in Dulbecco's modified Eagle's medium (high glucose) containing 10% fetal bovine serum, 4 mM L-glutamine and 1 mM sodium pyruvate, 1× nonessential amino acids, and G418 (1,000 µg/ml). Antiviral assays were performed in the same medium without G418. Cells were seeded in a 96-well plate at 1,500 cells per well, and test compounds were added immediately after seeding. Incubation time 4 days. At the end of the incubation step, total cellular RNA was isolated (RNeasy 96 kit; Qiagen). Replicon RNA and an internal control (TaqMan rRNA control reagents; Applied Biosystems) were amplified in a single-step multiplex RT-PCR protocol as recommended by the manufacturer. The HCV primers and probe were designed with Primer Express software (Applied Biosystems) and covered highly conserved 5'-untranslated region (UTR) sequences (sense primer: 5'-AGCCATGGCGTTAGTA(T)GAGTGT-3' (SEQ ID NO:1); antisense primer: 5'-TTCCGCAGACCACTATGG-3' (SEQ ID NO:2); and probe: 5'-FAM-CCTCCAGGACCCCCCTCCC-TAMRA-3' (SEQ ID NO:3)).

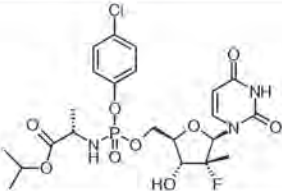
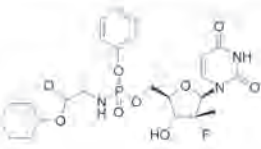
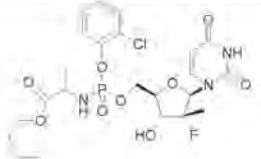
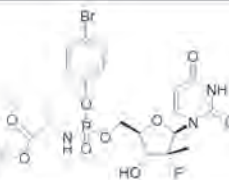
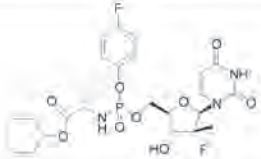
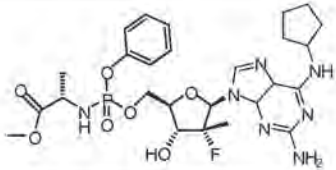
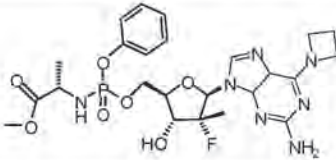
To express the antiviral effectiveness of a compound, the threshold RT-PCR cycle of the test compound was subtracted from the average threshold RT-PCR cycle of the no-drug control (ΔC_{tHCV}). A ΔC_t of 3.3 equals a 1-log 10 reduction (equal to the 90%

effective concentration [EC₉₀]) in replicon RNA levels. The cytotoxicity of the test compound could also be expressed by calculating the $\Delta C_{t_{\text{rRNA}}}$ values. The $\Delta\Delta C_t$ specificity parameter could then be introduced ($\Delta C_{t_{\text{HCV}}} - \Delta C_{t_{\text{rRNA}}}$), in which the levels of HCV RNA are normalized for the rRNA levels and calibrated against the no-drug

5 control.

Ex #	Compound	Log10 Reduction at 50 μ M	EC90 (μ M)
5		-1.21	3.0
6		-0.45	ND
7		0.31	ND
8		-1.48	2.11
10		-1.25	19.15
11		-0.55	ND

Ex #	Compound	Log10 Reduction at 50 μ M	EC90 (μ M)
12		0.31	ND
15		ND	0.86
25		-2.22	0.39
27		-2.25	0.66
28		-2.16	0.75
36		-1.64	21.9

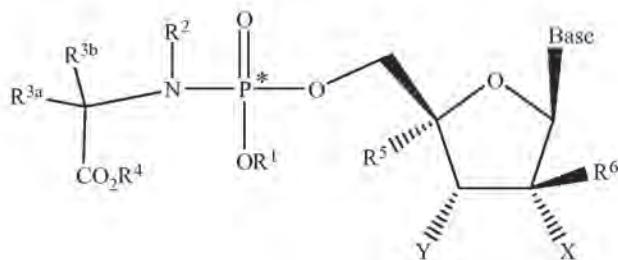
Ex #	Compound	Log10 Reduction at 50µM	EC90 (µM)
39		-1.78	0.47
49		-2.69	0.126
53		-1.33	<0.3
54		-1.55	0.57
55		-2.38	<0.3
69		-2.25	< 0.3
70		-2.25	<0.3

¹(4-BrPh): 4-bromo-phenyl.

The entire contents of U.S. Provisional Application Nos. 60/909,315, filed March 30, 2007, and 60/982,309, filed October 24, 2007, are hereby incorporated by reference
5 in the present application so far as needed to supplement the present disclosure and/or rectify any errors. Moreover, the patent and non-patent references disclosed herein are incorporated by reference. In the event that the incorporated patent and non-patent reference contains a term that conflicts with a term disclosed in either one of the two Provisional Applications or the present application text, the meaning of the term
10 contained in the present application text and the two Provisional Applications controls provided that the overall meaning of the incorporated subject matter is not lost.

We claim:

1. A compound, its stereoisomer, salt, hydrate, solvate, or crystalline form thereof, represented by formula I:



I

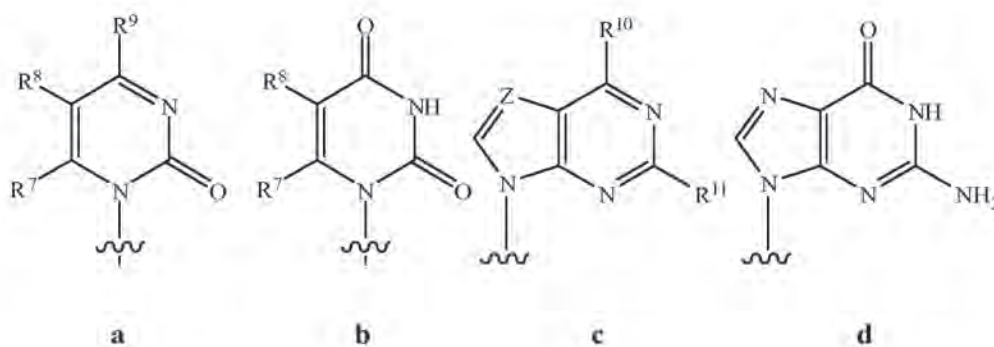
wherein

- (a) R^1 is hydrogen, n-alkyl; branched alkyl; cycloalkyl; or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, F, Cl, Br, I, nitro, cyano, C_{1-6} haloalkyl, $-N(R^{1'})_2$, C_{1-6} acylamino, $-NHSO_2C_{1-6}$ alkyl, $-SO_2N(R^{1'})_2$, $COR^{1''}$, and $-SO_2C_{1-6}$ alkyl; ($R^{1'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{1''}$ is $-OR'$ or $-N(R^{1'})_2$);
- (b) R^2 is hydrogen, C_{1-10} alkyl, R^{3a} or R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, $C(O)CR^{3a}R^{3b}NHR^1$, where n is 2 to 4 and R^1 , R^{3a} , and R^{3b} ;
- (c) R^{3a} and R^{3b} are (i) independently selected from hydrogen, C_{1-10} alkyl, cycloalkyl, $-(CH_2)_c(NR^{3'})_2$, C_{1-6} hydroxyalkyl, $-CH_2SH$, $-(CH_2)_2S(O)_dMe$, $-(CH_2)_3NHC(=NH)NH_2$, (1H-indol-3-yl)methyl, (1H-imidazol-4-yl)methyl, $-(CH_2)_eCOR^{3''}$, aryl and aryl C_{1-3} alkyl, said aryl groups optionally substituted with a group selected from hydroxyl, C_{1-10} alkyl, C_{1-6} alkoxy, halogen, nitro and cyano; (ii) R^{3a} and R^{3b} both are C_{1-6} alkyl; (iii) R^{3a} and R^{3b} together are $(CH_2)_f$ so as to form a spiro ring; (iv) R^{3a} is hydrogen and R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that

- includes the adjoining N and C atoms (v) R^{3b} is hydrogen and R^{3a} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, where c is 1 to 6, d is 0 to 2, e is 0 to 3, f is 2 to 5, n is 2 to 4, and where $R^{3'}$ is independently hydrogen or C_{1-6} alkyl and $R^{3''}$ is $-OR'$ or $-N(R^{3'})_2$; (vi) R^{3a} is H and R^{3b} is H, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph , CH_2 -indol-3-yl, $-CH_2CH_2SCH_3$, CH_2CO_2H , $CH_2C(O)NH_2$, CH_2CH_2COOH , $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, CH_2 -imidazol-4-yl, CH_2OH , $CH(OH)CH_3$, $CH_2((4'-OH)-Ph)$, CH_2SH , or lower cycloalkyl; or (viii) R^{3a} is CH_3 , $-CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph , CH_2 -indol-3-yl, $-CH_2CH_2SCH_3$, CH_2CO_2H , $CH_2C(O)NH_2$, CH_2CH_2COOH , $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, CH_2 -imidazol-4-yl, CH_2OH , $CH(OH)CH_3$, $CH_2((4'-OH)-Ph)$, CH_2SH , or lower cycloalkyl and R^{3b} is H, where $R^{3'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{3''}$ is $-OR'$ or $-N(R^{3'})_2$;
- 15 (d) R^4 is hydrogen, C_{1-10} alkyl, C_{1-10} alkyl optionally substituted with a lower alkyl, alkoxy, di(lower alkyl)-amino, or halogen, C_{1-10} haloalkyl, C_{3-10} cycloalkyl, cycloalkyl alkyl, cycloheteroalkyl, aminoacyl, aryl, such as phenyl, heteroaryl, such as, pyridinyl, substituted aryl, or substituted heteroaryl;
- (e) R^5 is H, a lower alkyl, CN, vinyl, O-(lower alkyl), hydroxyl lower alkyl, i.e., $-(CH_2)_pOH$, where p is 1-6, including hydroxyl methyl (CH_2OH), CH_2F , N_3 , CH_2CN , CH_2NH_2 , CH_2NHCH_3 , $CH_2N(CH_3)_2$, alkyne (optionally substituted), or halogen, including F, Cl, Br, or I, with the provisos that when X is OH, base is cytosine and R^6 is H, R^5 cannot be N_3 and when X is OH, R^6 is CH_3 or CH_2F and B is a purine base, R^5 cannot be H;
- 20 (f) R^6 is H, CH_3 , CH_2F , CHF_2 , CF_3 , F, or CN;
- (g) X is H, OH, F, OMe, halogen, NH_2 , or N_3 ;
- (h) Y is OH, H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, vinyl, N_3 , CN, Cl, Br, F, I, NO_2 , $OC(O)O(C_{1-4}$ alkyl), $OC(O)O(C_{1-4}$ alkyl), $OC(O)O(C_{2-4}$ alkynyl), $OC(O)O(C_{2-4}$
- 25

- alkenyl), OC₁₋₁₀ haloalkyl, O(aminoacyl), O(C₁₋₁₀ acyl), O(C₁₋₄ alkyl), O(C₂₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₂₋₄ alkynyl), S(C₂₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₂₋₄ alkynyl), SO(C₂₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₂₋₄ alkynyl), SO₂(C₂₋₄ alkenyl), OS(O)₂(C₁₋₄ acyl), OS(O)₂(C₁₋₄ alkyl), OS(O)₂(C₂₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₂₋₄ alkenyl), NH(C₂₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₂₋₄ alkynyl), C(O)O(C₂₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₂₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₂₋₄ alkynyl), S(C₂₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₂₋₄ alkynyl), SO(C₂₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₂₋₄ alkynyl), SO₂(C₂₋₄ alkenyl), OS(O)₂(C₁₋₄ acyl), OS(O)₂(C₁₋₄ alkyl), OS(O)₂(C₂₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₂₋₄ alkenyl), NH(C₂₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂;

the base is a naturally occurring or modified purine or pyrimidine base represented by the following structures:



wherein

Z is N or CR¹²;

- R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are independently H, F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆, lower alkenyl of C₂-C₆, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆, lower alkynyl of C₂-

C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, or CH=CHCO₂R',

wherein R' is an optionally substituted alkyl, which includes, but is not limited to,
 5 an optionally substituted C₁₋₂₀ alkyl, an optionally substituted C₁₋₁₀ alkyl, an optionally substituted lower alkyl; an optionally substituted cycloalkyl; an optionally substituted alkynyl of C₂-C₆, an optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl, which includes but is not limited to C(O) alkyl, C(O)(C₁₋₂₀ alkyl), C(O)(C₁₋₁₀ alkyl), or C(O)(lower alkyl) or alternatively, in the instance of NR'₂, each R'
 10 comprise at least one C atom that are joined to form a heterocycle comprising at least two carbon atoms; and

R¹² is an H, halogen (including F, Cl, Br, I), OH, OR', SH, SR', NH₂, NHR', NR'₂, NO₂ lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆, lower alkenyl of C₂-C₆, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆, lower alkynyl of C₂-C₆,
 15 halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, or CH=CHCO₂R'; with the proviso that when base is represented by the structure c with R¹¹ being hydrogen, R¹² is not a: (i) -C≡C-H, (ii) -C=CH₂, or (iii) -NO₂.

2. A compound its stereoisomer, salt, hydrate, solvate, or crystalline form
 20 thereof selected from among

5 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-alanyl phosphate ((S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester);

25 **6** 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-valyl phosphate ((S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-3-methylbutyric acid methyl ester;

- 7 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate ((S)-2-{{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-3-methyl-butyric acid methyl ester);
- 5 8 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-alanyl phosphate (((S)-2-{{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester);
- 10 9 N⁴-(N,N-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-C-methylcytidine;
- 10 10 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-alanyl phosphate (((S)-2-{{(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester);
- 15 11 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(4-bromophenyl methoxy-valyl phosphate (2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate ((S)-2-{{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-3-methyl-butyric acid methyl ester);
- 20 12 2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-valyl phosphate ((S)-2-{{[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-3-methyl-butyric acid methyl ester;
- 25 13 (S)-2-{{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid ethyl ester;
- 30 14 (S)-2-{{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-naphthalen-1-yloxy]-phosphorylamino]-propionic acid benzyl ester;
- 15 {(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-acetic acid methyl ester;

16 (S)-2-{(2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester;

5 17 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-propionic acid methyl ester;

18 (S)-1-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphoryl]-pyrrolidine-2-carboxylic acid methyl ester;

10 19 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid butyl ester;

20 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid benzyl ester;

21 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid methyl ester;

20 22 (S)-2-{(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester;

23 (S)-2-{(3,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester;

25 24 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid sec-butyl ester;

30 25 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid isopropyl ester;

26 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid butyl ester;

27 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid ethyl ester;

28 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid isopropyl ester;

29 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid benzyl ester;

30 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid isopropyl ester;

31 (S)-2-{(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid benzyl ester;

32 (S)-2-{(2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid butyl ester;

33 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino}-propionic acid isopropyl ester;

34 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid butyl ester;

35 (S)-2-{(3,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid ethyl ester;

36 (S)-2-[(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid isopropyl ester;

37 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid benzyl ester;

38 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid pentyl ester;

39 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid isopropyl ester;

40 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid butyl ester;

41 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid ethyl ester;

42 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino]-propionic acid butyl ester;

43 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino]-propionic acid benzyl ester;

44 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-butyric acid methyl ester;

45 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid 4-fluoro-benzyl ester;

46 (S)-2-[(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid butyl ester;

47 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid 3-methyl-butyl ester;

48 (S)-2-[(2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid ethyl ester;

49 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid cyclohexyl ester;

50 (R)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid butyl ester;

51 (R)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid isopropyl ester;

52 (R)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid benzyl ester;

53 (S)-2-[(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid butyl ester;

54 (S)-2-[(4-Bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid isopropyl ester;

55 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid cyclohexyl ester;

56 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-bromo-phenoxy)-phosphorylamino]-propionic acid cyclohexyl ester;

57 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-butyric acid isopropyl ester;

58 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-butyric acid cyclohexyl ester;

59 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-butyric acid cyclohexyl ester;

60 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4 R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-butyric acid isopropyl ester;

61 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid 2,2-difluoro-ethyl ester;

62 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo- 3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid 2,2,2-trifluoro-1-trifluoromethyl-ethyl ester;

63 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid 2-fluoro-1-fluoromethyl-ethyl ester;

64 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo- 3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid cyclopropyl methyl ester;

65 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-butyric acid cyclopentyl ester;

66 (S)-2-([(2R,3R,4R,5R)-5-(6-Amino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

67 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-hydroxy-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic

5 acid methyl ester;

68 (S)-2-((R)-[(2R,3R,4R,5R)-5-(2,6-Diamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

69 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-cyclopentylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

70 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-azetidin-1-yl-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

15 71 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-diethylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

72 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-propylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

20 73 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-cyclobutylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

74 (S)-2-([(2R,3R,4R,5R)-5-[2-Amino-6-(4-methyl-piperazin-1-yl)-purin-9-yl]-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

25 75 (2S)-methyl 2-((((2R,3R,4R,5R)-4-fluoro-3-hydroxy-4-methyl-5-(6-(propylamino)-9H-purin-9-yl)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

76 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(cyclobutylamino)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

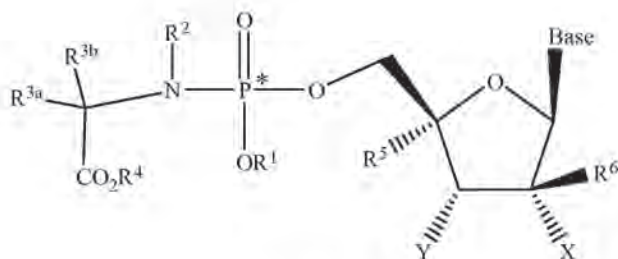
77 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(cyclopentylamino)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

78 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(aziridin-1-yl)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

79 (2S)-methyl 2-((((2R,3R,4R,5R)-4-fluoro-3-hydroxy-4-methyl-5-(6-(piperidin-1-yl)-9H-purin-9-yl)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate; and

80 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(azetidin-1-yl)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate.

3. A composition for the treatment and/or prophylaxis of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent, and equivalent medium and a compound, its stereoisomer, salt, hydrate, solvate, or crystalline form thereof, represented by formula I:



I

wherein

(a) R^1 is hydrogen, n-alkyl; branched alkyl; cycloalkyl; or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, F, Cl, Br, I, nitro, cyano, C_{1-6} haloalkyl, $-N(R^1)_2$, C_{1-6} acylamino, $-NHSO_2C_{1-6}$ alkyl, $-SO_2N(R^1)_2$, $COR^{1'}$, and $-SO_2C_{1-6}$ alkyl; ($R^{1'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{1'}$ is $-OR'$ or $-N(R^1)_2$);

(b) R^2 is hydrogen, C_{1-10} alkyl, R^{3a} or R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, $C(O)CR^{3a}R^{3b}NHR^1$, where n is 2 to 4 and R^1 , R^{3a} , and R^{3b} ;

(c) R^{3a} and R^{3b} are (i) independently selected from hydrogen, C_{1-10} alkyl, cycloalkyl, $-(CH_2)_c(NR^{3'})_2$, C_{1-6} hydroxyalkyl, $-CH_2SH$, $-(CH_2)_2S(O)_dMe$, $-(CH_2)_3NHC(=NH)NH_2$, (1H-indol-3-yl)methyl, (1H-imidazol-4-yl)methyl, $-(CH_2)_eCOR^{3''}$, aryl and aryl C_{1-3} alkyl, said aryl groups optionally substituted with a group selected from hydroxyl, C_{1-10} alkyl, C_{1-6} alkoxy, halogen, nitro and cyano; (ii) R^{3a} and R^{3b} both are C_{1-6} alkyl; (iii) R^{3a} and R^{3b} together are $(CH_2)_f$ so as to form a spiro ring; (iv) R^{3a} is hydrogen and R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms (v) R^{3b} is hydrogen and R^{3a} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, where c is 1 to 6, d is 0 to 2, e is 0 to 3, f is 2 to 5, n is 2 to 4, and where $R^{3'}$ is independently hydrogen or C_{1-6} alkyl and $R^{3''}$ is $-OR'$ or $-N(R^{3'})_2$; (vi) R^{3a} is H and R^{3b} is H, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph , CH_2 -indol-3-yl, $-CH_2CH_2SCH_3$, CH_2CO_2H , $CH_2C(O)NH_2$, CH_2CH_2COOH , $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, CH_2 -imidazol-4-yl, CH_2OH , $CH(OH)CH_3$, $CH_2((4'-OH)-Ph)$, CH_2SH , or lower cycloalkyl; or (viii) R^{3a} is CH_3 , $-CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph , CH_2 -indol-3-yl, $-CH_2CH_2SCH_3$, CH_2CO_2H , $CH_2C(O)NH_2$, CH_2CH_2COOH , $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, CH_2 -imidazol-4-yl, CH_2OH , $CH(OH)CH_3$, $CH_2((4'-OH)-Ph)$, CH_2SH , or lower cycloalkyl and R^{3b} is H, where $R^{3'}$ is independently hydrogen or

alkyl, which includes, but is not limited to, C₁₋₂₀ alkyl, C₁₋₁₀ alkyl, or C₁₋₆ alkyl, R^{3'} is –OR' or –N(R^{3'})₂;

- (d) R⁴ is hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkyl optionally substituted with a lower alkyl, alkoxy, di(lower alkyl)-amino, or halogen, C₁₋₁₀ haloalkyl, C₃₋₁₀ cycloalkyl, cycloalkyl alkyl, cycloheteroalkyl, aminoacyl, aryl, such as phenyl, heteroaryl, such as, pyridinyl, substituted aryl, or substituted heteroaryl;

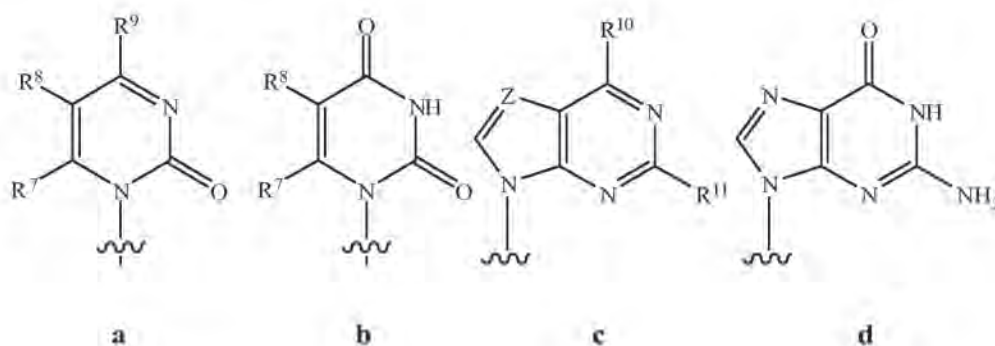
- (e) R⁵ is H, a lower alkyl, CN, vinyl, O-(lower alkyl), hydroxyl lower alkyl, i.e., –(CH₂)_pOH, where p is 1–6, including hydroxyl methyl (CH₂OH), CH₂F, N₃, CH₂CN, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or halogen, including F, Cl, Br, or I, with the provisos that when X is OH, base is cytosine and R⁶ is H, R⁵ cannot be N₃ and when X is OH, R⁶ is CH₃ or CH₂F and B is a purine base, R⁵ cannot be H;

(f) R⁶ is H, CH₃, CH₂F, CHF₂, CF₃, F, or CN;

(g) X is H, OH, F, OMe, halogen, NH₂, or N₃;

- (h) Y is OH, H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, OC(O)O(C₁₋₄ alkyl), OC(O)O(C₁₋₄ alkyl), OC(O)O(C₂₋₄ alkynyl), OC(O)O(C₂₋₄ alkenyl), OC₁₋₁₀ haloalkyl, O(aminoacyl), O(C₁₋₁₀ acyl), O(C₁₋₄ alkyl), O(C₂₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₂₋₄ alkynyl), S(C₂₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₂₋₄ alkynyl), SO(C₂₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₂₋₄ alkynyl), SO₂(C₂₋₄ alkenyl), OS(O)₂(C₁₋₄ acyl), OS(O)₂(C₁₋₄ alkyl), OS(O)₂(C₂₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₂₋₄ alkenyl), NH(C₂₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₂₋₄ alkynyl), C(O)O(C₂₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₂₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₂₋₄ alkynyl), S(C₂₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₂₋₄ alkynyl), SO(C₂₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₂₋₄ alkynyl), SO₂(C₂₋₄ alkenyl), OS(O)₂(C₁₋₄ acyl), OS(O)₂(C₁₋₄ alkyl), OS(O)₂(C₂₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₂₋₄ alkenyl), NH(C₂₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂;

the base is a naturally occurring or modified purine or pyrimidine base represented by the following structures:



5 wherein

Z is N or CR¹²;

R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are independently H, F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆, lower alkenyl of C₂-C₆, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, or CH=CHCO₂R',

10

wherein R' is an optionally substituted alkyl, which includes, but is not limited to, an optionally substituted C₁₋₂₀ alkyl, an optionally substituted C₁₋₁₀ alkyl, an optionally substituted lower alkyl; an optionally substituted cycloalkyl; an optionally substituted alkynyl of C₂-C₆, an optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl, which includes but is not limited to C(O) alkyl, C(O)(C₁₋₂₀ alkyl), C(O)(C₁₋₁₀ alkyl), or C(O)(lower alkyl) or alternatively, in the instance of NR'₂, each R' comprise at least one C atom that are joined to form a heterocycle comprising at least two

15

20 carbon atoms; and

R¹² is an H, halogen (including F, Cl, Br, I), OH, OR', SH, SR', NH₂, NHR', NR'₂, NO₂ lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆, lower alkenyl of C₂-C₆, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆, lower alkynyl of C₂-C₆, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, or CH=CHCO₂R'; with the proviso that when base is represented by the structure c with R¹¹ being hydrogen, R¹² is not a: (i) -C≡C-H, (ii) -C=CH₂, or (iii) -NO₂.

4. A composition for the treatment and/or prophylaxis of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent, and equivalent medium and a compound, its stereoisomer, salt, hydrate, solvate, or crystalline form thereof, selected from among

5 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-alanyl phosphate ((S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester);

6 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-valyl phosphate ((S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-3-methyl-butyric acid methyl ester;

7 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate ((S)-2-{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-3-methyl-butyric acid methyl ester);

8 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-alanyl phosphate (((S)-2-{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester);

9 N⁴-(N,N-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-C-methylcytidine;

- 10** 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-alanyl phosphate
(((S)-2-[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-
methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid
methyl ester);
- 5 **11** 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(4-bromophenyl methoxy-valyl
phosphate (2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl
phosphate ((S)-2-[(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-
yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-3-
methyl-butyric acid methyl ester);
- 10 **12** 2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-valyl phosphate
((S)-2-[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-
methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-3-methyl-butyric
acid methyl ester;
- 15 **13** (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-
fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-
propionic acid ethyl ester;
- 14** (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-
fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-
phosphorylamino]-propionic acid benzyl ester;
- 20 **15** [(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-
hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-acetic
acid methyl ester;
- 16** (S)-2-[(2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-
pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-
phosphorylamino}-propionic acid methyl ester;
- 25 **17** (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-
fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-
phosphorylamino]-propionic acid methyl ester;
- 18** (S)-1-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-
fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphoryl]-
pyrrolidine-2-carboxylic acid methyl ester;
- 30

19 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid butyl ester;

20 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid benzyl ester;

21 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid methyl ester;

10 22 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid methyl ester;

23 (S)-2-[(3,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid methyl ester;

24 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid sec-butyl ester;

25 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester;

26 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid butyl ester;

25 27 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid ethyl ester;

28 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid isopropyl ester;

29 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid benzyl ester;

30 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid isopropyl ester;

31 (S)-2-{(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid benzyl ester;

32 (S)-2-{(2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid butyl ester;

33 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino}-propionic acid isopropyl ester;

34 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid butyl ester;

35 (S)-2-{(3,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid ethyl ester;

36 (S)-2-{(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid isopropyl ester;

37 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid benzyl ester;

38 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid pentyl ester;

39 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid isopropyl ester;

40 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid butyl ester;

41 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid ethyl ester;

42 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino]-propionic acid butyl ester;

43 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino]-propionic acid benzyl ester;

44 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-butyric acid methyl ester;

45 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid 4-fluoro-benzyl ester;

46 (S)-2-[(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid butyl ester;

47 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid 3-methyl-butyl ester;

48 (S)-2-[(2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid ethyl ester;

49 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid cyclohexyl ester;

5 50 (R)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid butyl ester;

51 (R)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester;

10 52 (R)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid benzyl ester;

15 53 (S)-2-((2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino)-propionic acid butyl ester;

54 (S)-2-((4-Bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino)-propionic acid isopropyl ester;

20 55 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid cyclohexyl ester;

56 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-bromo-phenoxy)-phosphorylamino]-propionic acid cyclohexyl ester;

25 57 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-butyric acid isopropyl ester;

30 58 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-butyric acid cyclohexyl ester;

59 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-butyric acid cyclohexyl ester;

60 (S)-2-{(4-Chloro-phenoxy)-[(2R,3R,4 R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-butyric acid isopropyl ester;

61 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 2,2-difluoro-ethyl ester;

62 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo- 3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 2,2,2-trifluoro-1-trifluoromethyl-ethyl ester;

63 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 2-fluoro-1-fluoromethyl-ethyl ester;

64 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo- 3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid cyclopropyl methyl ester;

65 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-butyric acid cyclopentyl ester;

66 (S)-2-[[[(2R,3R,4R,5R)-5-(6-Amino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid methyl ester;

67 (S)-2-[[[(2R,3R,4R,5R)-5-(2-Amino-6-hydroxy-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid methyl ester;

68 (S)-2-{(R)-[(2R,3R,4R,5R)-5-(2,6-Diamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

69 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-cyclopentylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

70 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-azetidin-1-yl-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

71 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-diethylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

72 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-propylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

73 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-cyclobutylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

74 (S)-2-([(2R,3R,4R,5R)-5-[2-Amino-6-(4-methyl-piperazin-1-yl)-purin-9-yl]-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

75 (2S)-methyl 2-((((2R,3R,4R,5R)-4-fluoro-3-hydroxy-4-methyl-5-(6-(propylamino)-9H-purin-9-yl)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

76 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(cyclobutylamino)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

77 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(cyclopentylamino)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

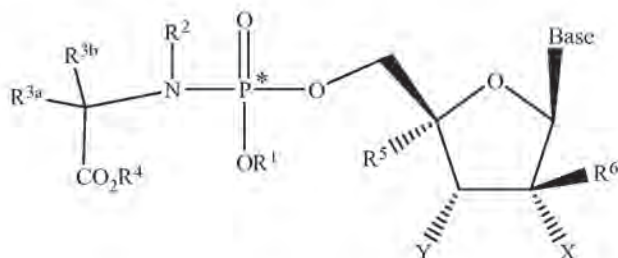
78 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(aziridin-1-yl)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

79 (2S)-methyl 2-(((2R,3R,4R,5R)-4-fluoro-3-hydroxy-4-methyl-5-(6-(piperidin-1-yl)-9H-purin-9-yl)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate; and

80 (2S)-methyl 2-(((2R,3R,4R,5R)-5-(6-(azetidin-1-yl)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate.

5. A use of the compound represented by formula I in the manufacture of a medicament for the treatment of any condition the result of an infection by hepatitis C virus, West Nile virus, yellow fever virus, dengue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus or Japanese encephalitis virus.

wherein the compound, its stereoisomer, salt, hydrate, solvate, or crystalline form thereof, are represented by formula I:



I

wherein

(a) R¹ is hydrogen, n-alkyl; branched alkyl; cycloalkyl; or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of C₁-₆ alkyl, C₂-₆ alkenyl, C₂-₆ alkynyl, C₁-₆ alkoxy, F, Cl, Br, I, nitro, cyano, C₁-₆ haloalkyl, -N(R¹')₂, C₁-₆ acylamino, -NHSO₂C₁-₆ alkyl, -SO₂N(R¹')₂, COR¹'', and -SO₂C₁-₆ alkyl; (R¹' is independently hydrogen or alkyl, which includes, but is not limited to, C₁-₂₀ alkyl, C₁-₁₀ alkyl, or C₁-₆ alkyl, R¹'' is -OR¹ or -N(R¹')₂);

(b) R^2 is hydrogen, C_{1-10} alkyl, R^{3a} or R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, $C(O)CR^{3a}R^{3b}NHR^1$, where n is 2 to 4 and R^1 , R^{3a} , and R^{3b} ;

(c) R^{3a} and R^{3b} are (i) independently selected from hydrogen, C_{1-10} alkyl, cycloalkyl, $-(CH_2)_c(NR^{3'})_2$, C_{1-6} hydroxyalkyl, $-CH_2SH$, $-(CH_2)_2S(O)_dMe$, $-(CH_2)_3NHC(=NH)NH_2$, (1H-indol-3-yl)methyl, (1H-imidazol-4-yl)methyl, $-(CH_2)_eCOR^{3''}$, aryl and aryl C_{1-3} alkyl, said aryl groups optionally substituted with a group selected from hydroxyl, C_{1-10} alkyl, C_{1-6} alkoxy, halogen, nitro and cyano; (ii) R^{3a} and R^{3b} both are C_{1-6} alkyl; (iii) R^{3a} and R^{3b} together are $(CH_2)_f$ so as to form a spiro ring; (iv) R^{3a} is hydrogen and R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms (v) R^{3b} is hydrogen and R^{3a} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, where c is 1 to 6, d is 0 to 2, e is 0 to 3, f is 2 to 5, n is 2 to 4, and where $R^{3'}$ is independently hydrogen or C_{1-6} alkyl and $R^{3''}$ is $-OR^1$ or $-N(R^{3'})_2$; (vi) R^{3a} is H and R^{3b} is H, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph , CH_2 -indol-3-yl, $-CH_2CH_2SCH_3$, CH_2CO_2H , $CH_2C(O)NH_2$, CH_2CH_2COOH , $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, CH_2 -imidazol-4-yl, CH_2OH , $CH(OH)CH_3$, $CH_2((4'-OH)-Ph)$, CH_2SH , or lower cycloalkyl; or (viii) R^{3a} is CH_3 , $-CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph , CH_2 -indol-3-yl, $-CH_2CH_2SCH_3$, CH_2CO_2H , $CH_2C(O)NH_2$, CH_2CH_2COOH , $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, CH_2 -imidazol-4-yl, CH_2OH , $CH(OH)CH_3$, $CH_2((4'-OH)-Ph)$, CH_2SH , or lower cycloalkyl and R^{3b} is H, where $R^{3'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{3''}$ is $-OR^1$ or $-N(R^{3'})_2$;

(d) R^4 is hydrogen, C_{1-10} alkyl, C_{1-10} alkyl optionally substituted with a lower alkyl, alkoxy, di(lower alkyl)-amino, or halogen, C_{1-10} haloalkyl, C_{3-10} cycloalkyl, cycloalkyl alkyl, cycloheteroalkyl, aminoacyl, aryl, such as phenyl, heteroaryl, such as, pyridinyl, substituted aryl, or substituted heteroaryl;

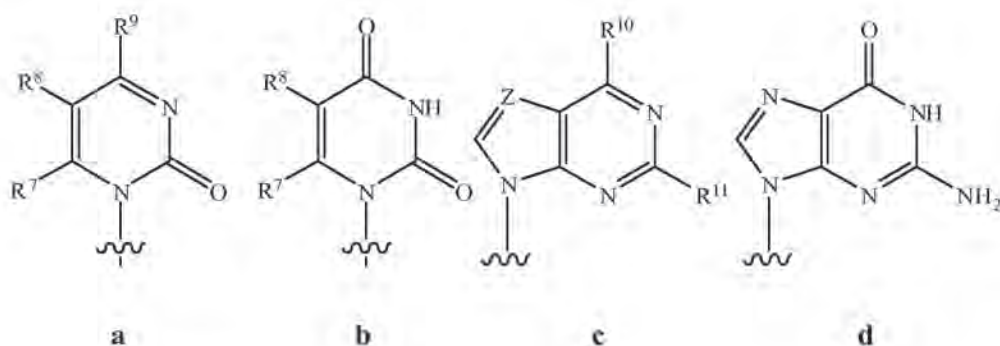
(e) R^5 is H, a lower alkyl, CN, vinyl, O-(lower alkyl), hydroxyl lower alkyl, i.e., $-(CH_2)_pOH$, where p is 1-6, including hydroxyl methyl (CH_2OH), CH_2F , N_3 , CH_2CN , CH_2NH_2 , CH_2NHCH_3 , $CH_2N(CH_3)_2$, alkyne (optionally substituted), or halogen, including F, Cl, Br, or I, with the provisos that when X is OH, base is cytosine and R^6 is H, R^5 cannot be N_3 and when X is OH, R^6 is CH_3 or CH_2F and B is a purine base, R^5 cannot be H;

(f) R^6 is H, CH_3 , CH_2F , CHF_2 , CF_3 , F, or CN;

(g) X is H, OH, F, OMe, halogen, NH_2 , or N_3 ;

(h) Y is OH, H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, vinyl, N_3 , CN, Cl, Br, F, I, NO_2 , $OC(O)O(C_{1-4}$ alkyl), $OC(O)O(C_{1-4}$ alkyl), $OC(O)O(C_{2-4}$ alkynyl), $OC(O)O(C_{2-4}$ alkenyl), OC_{1-10} haloalkyl, O(aminoacyl), O(C_{1-10} acyl), O(C_{1-4} alkyl), O(C_{2-4} alkenyl), S(C_{1-4} acyl), S(C_{1-4} alkyl), S(C_{2-4} alkynyl), S(C_{2-4} alkenyl), SO(C_{1-4} acyl), SO(C_{1-4} alkyl), SO(C_{2-4} alkynyl), SO(C_{2-4} alkenyl), $SO_2(C_{1-4}$ acyl), $SO_2(C_{1-4}$ alkyl), $SO_2(C_{2-4}$ alkynyl), $SO_2(C_{2-4}$ alkenyl), OS(O) $_2$ (C_{1-4} acyl), OS(O) $_2$ (C_{1-4} alkyl), OS(O) $_2$ (C_{2-4} alkenyl), NH_2 , NH(C_{1-4} alkyl), NH(C_{2-4} alkenyl), NH(C_{2-4} alkynyl), NH(C_{1-4} acyl), N(C_{1-4} alkyl) $_2$, N(C_{1-18} acyl) $_2$, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N_3 , CN, one to three halogen (Cl, Br, F, I), NO_2 , C(O)O(C_{1-4} alkyl), C(O)O(C_{1-4} alkyl), C(O)O(C_{2-4} alkynyl), C(O)O(C_{2-4} alkenyl), O(C_{1-4} acyl), O(C_{1-4} alkyl), O(C_{2-4} alkenyl), S(C_{1-4} acyl), S(C_{1-4} alkyl), S(C_{2-4} alkynyl), S(C_{2-4} alkenyl), SO(C_{1-4} acyl), SO(C_{1-4} alkyl), SO(C_{2-4} alkynyl), SO(C_{2-4} alkenyl), $SO_2(C_{1-4}$ acyl), $SO_2(C_{1-4}$ alkyl), $SO_2(C_{2-4}$ alkynyl), $SO_2(C_{2-4}$ alkenyl), OS(O) $_2$ (C_{1-4} acyl), OS(O) $_2$ (C_{1-4} alkyl), OS(O) $_2$ (C_{2-4} alkenyl), NH_2 , NH(C_{1-4} alkyl), NH(C_{2-4} alkenyl), NH(C_{2-4} alkynyl), NH(C_{1-4} acyl), N(C_{1-4} alkyl) $_2$, N(C_{1-4} acyl) $_2$;

the base is a naturally occurring or modified purine or pyrimidine base represented by the following structures:



wherein

Z is N or CR¹²;

R^7 , R^8 , R^9 , R^{10} , and R^{11} are independently H, F, Cl, Br, I, OH, OR', SH, SR', NH₂,
 5 NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆, lower
 alkenyl of C₂-C₆, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆, lower alkynyl of C₂-
 C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-
 C₆, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR',
 CONR'₂, CH=CHCO₂H, or CH=CHCO₂R',

10 wherein R' is an optionally substituted alkyl, which includes, but is not limited to,
 an optionally substituted C₁₋₂₀ alkyl, an optionally substituted C₁₋₁₀ alkyl, an optionally
 substituted lower alkyl; an optionally substituted cycloalkyl; an optionally substituted
 alkynyl of C₂-C₆, an optionally substituted lower alkenyl of C₂-C₆, or optionally
 substituted acyl, which includes but is not limited to C(O) alkyl, C(O)(C₁₋₂₀ alkyl),
 15 C(O)(C₁₋₁₀ alkyl), or C(O)(lower alkyl) or alternatively, in the instance of NR'₂, each R'
 comprise at least one C atom that are joined to form a heterocycle comprising at least two
 carbon atoms; and

R^{12} is an H, halogen (including F, Cl, Br, I), OH, OR', SH, SR', NH₂, NHR', NR'₂,
 NO₂ lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆, lower alkenyl
 20 of C₂-C₆, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆, lower alkynyl of C₂-C₆,
 halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆, halogenated (F,
 Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂,

CH=CHCO₂H, or CH=CHCO₂R'; with the proviso that when base is represented by the structure c with R¹¹ being hydrogen, R¹² is not a: (i) -C≡C-H, (ii) -C=CH₂, or (iii) -NO₂.

6. A use of

5 a compound, its stereoisomer, salt, hydrate, solvate, or crystalline form thereof, selected from among

5 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-alanyl phosphate ((S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester);

6 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-valyl phosphate ((S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-3-methylbutyric acid methyl ester);

15 7 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate ((S)-2-{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-3-methylbutyric acid methyl ester);

8 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-alanyl phosphate (((S)-2-{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester);

9 N⁴-(N,N-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-C-methylcytidine;

25 10 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-alanyl phosphate (((S)-2-{[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester);

30 11 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(4-bromophenyl methoxy-valyl phosphate (2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate ((S)-2-{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-

yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-3-methyl-butyrlic acid methyl ester);

12 2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-valyl phosphate ((S)-2-([(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-3-methyl-butyrlic acid methyl ester;

13 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid ethyl ester;

10 14 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-propionic acid benzyl ester;

15 15 {(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-acetic acid methyl ester;

16 (S)-2-((2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino)-propionic acid methyl ester;

20 17 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-propionic acid methyl ester;

18 (S)-1-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphoryl)-pyrrolidine-2-carboxylic acid methyl ester;

25 19 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid butyl ester;

30 20 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid benzyl ester;

21 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid methyl ester;

22 (S)-2-{(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester;

23 (S)-2-{(3,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester;

24 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid sec-butyl ester;

25 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester;

26 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid butyl ester;

27 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid ethyl ester;

28 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid isopropyl ester;

29 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid benzyl ester;

30 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid isopropyl ester;

31 (S)-2-[(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid benzyl ester;

32 (S)-2-[(2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid butyl ester;

33 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino]-propionic acid isopropyl ester;

34 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid butyl ester;

35 (S)-2-[(3,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid ethyl ester;

36 (S)-2-[(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid isopropyl ester;

37 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid benzyl ester;

38 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid pentyl ester;

39 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid isopropyl ester;

40 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid butyl ester;

- 41 (S)-2-{{(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid ethyl ester;
- 42 (S)-2-{{(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino}-propionic acid butyl ester;
- 43 (S)-2-{{(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino}-propionic acid benzyl ester;
- 44 (S)-2-{{(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-butyric acid methyl ester;
- 45 (S)-2-{{(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 4-fluoro-benzyl ester;
- 46 (S)-2-{{(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid butyl ester;
- 47 (S)-2-{{(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 3-methyl-butyl ester;
- 48 (S)-2-{{(2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid ethyl ester;
- 49 (S)-2-{{(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid cyclohexyl ester;
- 50 (R)-2-{{(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid butyl ester;

51 (R)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester;

52 (R)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid benzyl ester;

53 (S)-2-[(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid butyl ester;

54 (S)-2-[(4-Bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid isopropyl ester;

55 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid cyclohexyl ester;

56 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-bromo-phenoxy)-phosphorylamino]-propionic acid cyclohexyl ester;

57 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-butyric acid isopropyl ester;

58 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-butyric acid cyclohexyl ester;

59 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-butyric acid cyclohexyl ester;

60 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4 R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-butyric acid isopropyl ester;

61 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 2,2-difluoro-ethyl ester;

62 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 2,2,2-trifluoro-1-trifluoromethyl-ethyl ester;

63 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 2-fluoro-1-fluoromethyl-ethyl ester;

64 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid cyclopropyl methyl ester;

65 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-butyric acid cyclopentyl ester;

66 (S)-2-([(2R,3R,4R,5R)-5-(6-Amino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

67 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-hydroxy-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

68 (S)-2-((R)-[(2R,3R,4R,5R)-5-(2,6-Diamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

69 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-cyclopentylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

70 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-azetidin-1-yl-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

71 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-diethylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

72 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-propylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

73 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-cyclobutylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

74 (S)-2-([(2R,3R,4R,5R)-5-[2-Amino-6-(4-methyl-piperazin-1-yl)-purin-9-yl]-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

75 (2S)-methyl 2-((((2R,3R,4R,5R)-4-fluoro-3-hydroxy-4-methyl-5-(6-(propylamino)-9H-purin-9-yl)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

76 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(cyclobutylamino)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

77 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(cyclopentylamino)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

78 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(aziridin-1-yl)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

79 (2S)-methyl 2-((((2R,3R,4R,5R)-4-fluoro-3-hydroxy-4-methyl-5-(6-(piperidin-1-yl)-9H-purin-9-yl)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate; and

80 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(azetidin-1-yl)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate

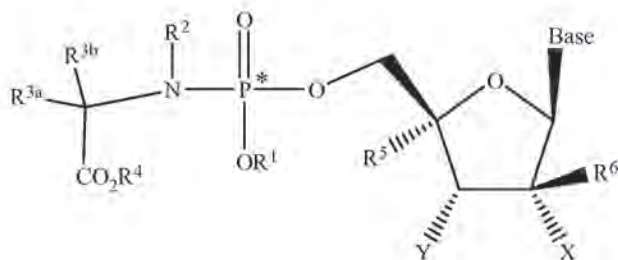
in the manufacture of a medicament for the treatment of any condition the result of an infection by hepatitis C virus, West Nile virus, yellow fever virus, dengue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus or Japanese encephalitis virus.

5

7. A method of treatment in a subject in need thereof, which comprises:

administering a therapeutically effective amount of the compound represented by formula I to the subject;

wherein the compound or its stereoisomer, salt, hydrate, solvate, or crystalline form thereof represented by formula I:



I

wherein

(a) R^1 is hydrogen, n-alkyl; branched alkyl; cycloalkyl; or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, F, Cl, Br, I, nitro, cyano, C_{1-6} haloalkyl, $-N(R^{1'})_2$, C_{1-6} acylamino, $-NHSO_2C_{1-6}$ alkyl, $-SO_2N(R^{1'})_2$, $COR^{1''}$, and $-SO_2C_{1-6}$ alkyl; ($R^{1'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{1''}$ is $-OR^1$ or $-N(R^{1'})_2$);

(b) R^2 is hydrogen, C_{1-10} alkyl, R^{3a} or R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, $C(O)CR^{3a}R^{3b}NHR^1$, where n is 2 to 4 and R^1 , R^{3a} , and R^{3b} ;

(c) R^{3a} and R^{3b} are (i) independently selected from hydrogen, C_{1-10} alkyl, cycloalkyl, $-(CH_2)_c(NR^{3'})_2$, C_{1-6} hydroxyalkyl, $-CH_2SH$, $-(CH_2)_2S(O)_dMe$, $-(CH_2)_3NHC(=NH)NH_2$, (1H-indol-3-yl)methyl, (1H-imidazol-4-yl)methyl, $-(CH_2)_eCOR^{3''}$, aryl and aryl C_{1-3} alkyl, said aryl groups optionally substituted with a group selected from hydroxyl, C_{1-10} alkyl, C_{1-6} alkoxy, halogen, nitro and cyano; (ii) R^{3a} and R^{3b} both are C_{1-6} alkyl; (iii) R^{3a} and R^{3b} together are $(CH_2)_f$ so as to form a spiro ring; (iv) R^{3a} is hydrogen and R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms (v) R^{3b} is hydrogen and R^{3a} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, where c is 1 to 6, d is 0 to 2, e is 0 to 3, f is 2 to 5, n is 2 to 4, and where $R^{3'}$ is independently hydrogen or C_{1-6} alkyl and $R^{3''}$ is $-OR^1$ or $-N(R^{3'})_2$; (vi) R^{3a} is H and R^{3b} is H, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph , CH_2 -indol-3-yl, $-CH_2CH_2SCH_3$, CH_2CO_2H , $CH_2C(O)NH_2$, CH_2CH_2COOH , $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, CH_2 -imidazol-4-yl, CH_2OH , $CH(OH)CH_3$, $CH_2((4'-OH)-Ph)$, CH_2SH , or lower cycloalkyl; or (viii) R^{3a} is CH_3 , $-CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph , CH_2 -indol-3-yl, $-CH_2CH_2SCH_3$, CH_2CO_2H , $CH_2C(O)NH_2$, CH_2CH_2COOH , $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, CH_2 -imidazol-4-yl, CH_2OH , $CH(OH)CH_3$, $CH_2((4'-OH)-Ph)$, CH_2SH , or lower cycloalkyl and R^{3b} is H, where $R^{3'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{3''}$ is $-OR^1$ or $-N(R^{3'})_2$;

(d) R^4 is hydrogen, C_{1-10} alkyl, C_{1-10} alkyl optionally substituted with a lower alkyl, alkoxy, di(lower alkyl)-amino, or halogen, C_{1-10} haloalkyl, C_{3-10} cycloalkyl, cycloalkyl alkyl, cycloheteroalkyl, aminoacyl, aryl, such as phenyl, heteroaryl, such as, pyridinyl, substituted aryl, or substituted heteroaryl;

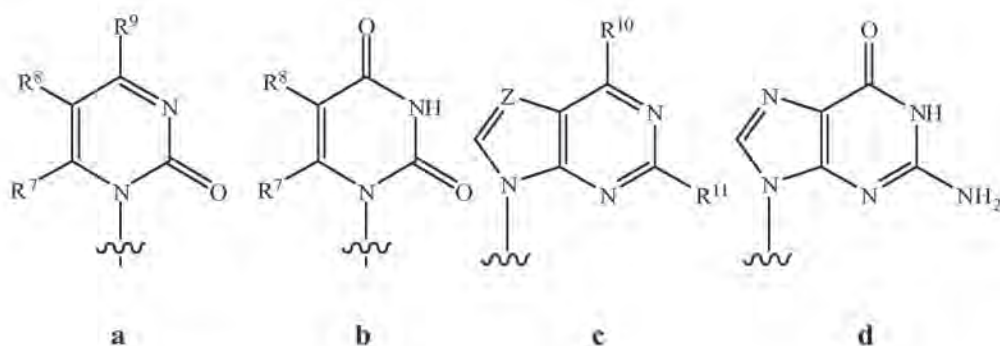
(e) R^5 is H, a lower alkyl, CN, vinyl, O-(lower alkyl), hydroxyl lower alkyl, i.e., $-(CH_2)_pOH$, where p is 1-6, including hydroxyl methyl (CH_2OH), CH_2F , N_3 , CH_2CN , CH_2NH_2 , CH_2NHCH_3 , $CH_2N(CH_3)_2$, alkyne (optionally substituted), or halogen, including F, Cl, Br, or I, with the provisos that when X is OH, base is cytosine and R^6 is H, R^5 cannot be N_3 and when X is OH, R^6 is CH_3 or CH_2F and B is a purine base, R^5 cannot be H;

(f) R^6 is H, CH_3 , CH_2F , CHF_2 , CF_3 , F, or CN;

(g) X is H, OH, F, OMe, halogen, NH_2 , or N_3 ;

(h) Y is OH, H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, vinyl, N_3 , CN, Cl, Br, F, I, NO_2 , $OC(O)O(C_{1-4}$ alkyl), $OC(O)O(C_{1-4}$ alkyl), $OC(O)O(C_{2-4}$ alkynyl), $OC(O)O(C_{2-4}$ alkenyl), OC_{1-10} haloalkyl, O(aminoacyl), O(C_{1-10} acyl), O(C_{1-4} alkyl), O(C_{2-4} alkenyl), S(C_{1-4} acyl), S(C_{1-4} alkyl), S(C_{2-4} alkynyl), S(C_{2-4} alkenyl), SO(C_{1-4} acyl), SO(C_{1-4} alkyl), SO(C_{2-4} alkynyl), SO(C_{2-4} alkenyl), $SO_2(C_{1-4}$ acyl), $SO_2(C_{1-4}$ alkyl), $SO_2(C_{2-4}$ alkynyl), $SO_2(C_{2-4}$ alkenyl), OS(O) $_2$ (C_{1-4} acyl), OS(O) $_2$ (C_{1-4} alkyl), OS(O) $_2$ (C_{2-4} alkenyl), NH_2 , NH(C_{1-4} alkyl), NH(C_{2-4} alkenyl), NH(C_{2-4} alkynyl), NH(C_{1-4} acyl), N(C_{1-4} alkyl) $_2$, N(C_{1-18} acyl) $_2$, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N_3 , CN, one to three halogen (Cl, Br, F, I), NO_2 , C(O)O(C_{1-4} alkyl), C(O)O(C_{1-4} alkyl), C(O)O(C_{2-4} alkynyl), C(O)O(C_{2-4} alkenyl), O(C_{1-4} acyl), O(C_{1-4} alkyl), O(C_{2-4} alkenyl), S(C_{1-4} acyl), S(C_{1-4} alkyl), S(C_{2-4} alkynyl), S(C_{2-4} alkenyl), SO(C_{1-4} acyl), SO(C_{1-4} alkyl), SO(C_{2-4} alkynyl), SO(C_{2-4} alkenyl), $SO_2(C_{1-4}$ acyl), $SO_2(C_{1-4}$ alkyl), $SO_2(C_{2-4}$ alkynyl), $SO_2(C_{2-4}$ alkenyl), OS(O) $_2$ (C_{1-4} acyl), OS(O) $_2$ (C_{1-4} alkyl), OS(O) $_2$ (C_{2-4} alkenyl), NH_2 , NH(C_{1-4} alkyl), NH(C_{2-4} alkenyl), NH(C_{2-4} alkynyl), NH(C_{1-4} acyl), N(C_{1-4} alkyl) $_2$, N(C_{1-4} acyl) $_2$;

the base is a naturally occurring or modified purine or pyrimidine base represented by the following structures:



wherein

Z is N or CR¹²;

R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are independently H, F, Cl, Br, I, OH, OR', SH, SR', NH₂,
 5 NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆, lower
 alkenyl of C₂-C₆, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆, lower alkynyl of C₂-
 C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-
 C₆, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR',
 CONR'₂, CH=CHCO₂H, or CH=CHCO₂R',

10 wherein R' is an optionally substituted alkyl, which includes, but is not limited to,
 an optionally substituted C₁₋₂₀ alkyl, an optionally substituted C₁₋₁₀ alkyl, an optionally
 substituted lower alkyl; an optionally substituted cycloalkyl; an optionally substituted
 alkynyl of C₂-C₆, an optionally substituted lower alkenyl of C₂-C₆, or optionally
 substituted acyl, which includes but is not limited to C(O) alkyl, C(O)(C₁₋₂₀ alkyl),
 15 C(O)(C₁₋₁₀ alkyl), or C(O)(lower alkyl) or alternatively, in the instance of NR'₂, each R'
 comprise at least one C atom that are joined to form a heterocycle comprising at least two
 carbon atoms; and

R¹² is an H, halogen (including F, Cl, Br, I), OH, OR', SH, SR', NH₂, NHR', NR'₂,
 NO₂ lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆, lower alkenyl
 20 of C₂-C₆, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆, lower alkynyl of C₂-C₆,
 halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆, halogenated (F,
 Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂,

CH=CHCO₂H, or CH=CHCO₂R'; with the proviso that when base is represented by the structure c with R¹¹ being hydrogen, R¹² is not a: (i) -C≡C-H, (ii) -C=CH₂, or (iii) -NO₂.

8. A method of treatment in a subject in need thereof, which comprises:

5 administering a therapeutically effective amount of a compound, its stereoisomer, salt, hydrate, solvate, or crystalline form thereof, selected from among

5 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-alanyl phosphate ((S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester);

6 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-valyl phosphate ((S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-3-methyl-butyric acid methyl ester);

15 7 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate ((S)-2-{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-3-methyl-butyric acid methyl ester);

20 8 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-alanyl phosphate (((S)-2-{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester);

9 N⁴-(N,N-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-C-methylcytidine;

25 10 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-alanyl phosphate (((S)-2-{[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester);

30 11 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(4-bromophenyl methoxy-valyl phosphate (2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate ((S)-2-{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-

yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-3-methyl-butyrac acid methyl ester);

12 2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-valyl phosphate ((S)-2-([(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-3-methyl-butyrac acid methyl ester;

13 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid ethyl ester;

10 14 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-propionic acid benzyl ester;

15 15 {(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-acetic acid methyl ester;

16 (S)-2-((2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino)-propionic acid methyl ester;

20 17 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-propionic acid methyl ester;

18 (S)-1-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphoryl)-pyrrolidine-2-carboxylic acid methyl ester;

25 19 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid butyl ester;

30 20 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid benzyl ester;

21 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid methyl ester;

22 (S)-2-{(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester;

23 (S)-2-{(3,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester;

24 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid sec-butyl ester;

25 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester;

26 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid butyl ester;

27 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid ethyl ester;

28 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid isopropyl ester;

29 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid benzyl ester;

30 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid isopropyl ester;

31 (S)-2-[(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid benzyl ester;

32 (S)-2-[(2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid butyl ester;

33 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino]-propionic acid isopropyl ester;

34 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid butyl ester;

35 (S)-2-[(3,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid ethyl ester;

36 (S)-2-[(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid isopropyl ester;

37 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid benzyl ester;

38 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid pentyl ester;

39 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid isopropyl ester;

40 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid butyl ester;

- 41 (S)-2-{{(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid ethyl ester;
- 42 (S)-2-{{(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino}-propionic acid butyl ester;
- 43 (S)-2-{{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino}-propionic acid benzyl ester;
- 44 (S)-2-{{(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-butyric acid methyl ester;
- 45 (S)-2-{{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 4-fluoro-benzyl ester;
- 46 (S)-2-{{(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid butyl ester;
- 47 (S)-2-{{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 3-methyl-butyl ester;
- 48 (S)-2-{{(2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid ethyl ester;
- 49 (S)-2-{{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid cyclohexyl ester;
- 50 (R)-2-{{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid butyl ester;

51 (R)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester;

52 (R)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid benzyl ester;

53 (S)-2-[(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid butyl ester;

54 (S)-2-[(4-Bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid isopropyl ester;

55 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid cyclohexyl ester;

56 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-bromo-phenoxy)-phosphorylamino]-propionic acid cyclohexyl ester;

57 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-butyric acid isopropyl ester;

58 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-butyric acid cyclohexyl ester;

59 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-butyric acid cyclohexyl ester;

60 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4 R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-butyric acid isopropyl ester;

61 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 2,2-difluoro-ethyl ester;

5 62 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 2,2,2-trifluoro-1-trifluoromethyl-ethyl ester;

63 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 2-fluoro-1-fluoromethyl-ethyl ester;

10 64 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid cyclopropyl methyl ester;

65 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-butyric acid cyclopentyl ester;

66 (S)-2-([(2R,3R,4R,5R)-5-(6-Amino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

67 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-hydroxy-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

68 (S)-2-((R)-[(2R,3R,4R,5R)-5-(2,6-Diamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

69 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-cyclopentylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

70 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-azetidin-1-yl-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

71 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-diethylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

72 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-propylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

73 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-cyclobutylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

74 (S)-2-([(2R,3R,4R,5R)-5-[2-Amino-6-(4-methyl-piperazin-1-yl)-purin-9-yl]-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

75 (2S)-methyl 2-((((2R,3R,4R,5R)-4-fluoro-3-hydroxy-4-methyl-5-(6-(propylamino)-9H-purin-9-yl)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

76 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(cyclobutylamino)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

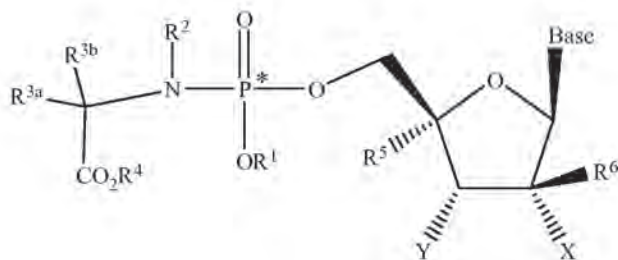
77 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(cyclopentylamino)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

78 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(aziridin-1-yl)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

79 (2S)-methyl 2-((((2R,3R,4R,5R)-4-fluoro-3-hydroxy-4-methyl-5-(6-(piperidin-1-yl)-9H-purin-9-yl)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate; and

80 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(azetidin-1-yl)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate.

9. A process for preparing a compound, its stereoisomer, salt, hydrate, solvate, or crystalline form thereof, represented by formula I:



I

wherein

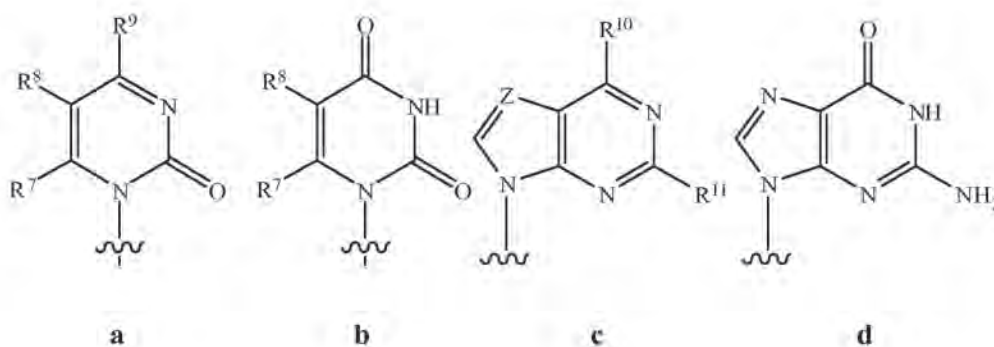
- (a) R^1 is hydrogen, n-alkyl; branched alkyl; cycloalkyl; or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, F, Cl, Br, I, nitro, cyano, C_{1-6} haloalkyl, $-N(R^{1'})_2$, C_{1-6} acylamino, $-NHSO_2C_{1-6}$ alkyl, $-SO_2N(R^{1'})_2$, $COR^{1''}$, and $-SO_2C_{1-6}$ alkyl; ($R^{1'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{1''}$ is $-OR'$ or $-N(R^{1'})_2$);
- (b) R^2 is hydrogen, C_{1-10} alkyl, R^{3a} or R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, $C(O)CR^{3a}R^{3b}NHR^1$, where n is 2 to 4 and R^1 , R^{3a} , and R^{3b} ,
- (c) R^{3a} and R^{3b} are (i) independently selected from hydrogen, C_{1-10} alkyl, cycloalkyl, $-(CH_2)_c(NR^{3'})_2$, C_{1-6} hydroxyalkyl, $-CH_2SH$, $-(CH_2)_2S(O)_dMe$, $-(CH_2)_3NHC(=NH)NH_2$, (1H-indol-3-yl)methyl, (1H-imidazol-4-yl)methyl, $-(CH_2)_eCOR^{3''}$, aryl and aryl C_{1-3} alkyl, said aryl groups optionally substituted with a group selected from hydroxyl, C_{1-10} alkyl, C_{1-6} alkoxy, halogen, nitro and cyano; (ii) R^{3a} and R^{3b} both are C_{1-6} alkyl; (iii) R^{3a} and R^{3b} together are $(CH_2)_f$ so as to form a spiro ring; (iv) R^{3a} is hydrogen and R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that

- includes the adjoining N and C atoms (v) R^{3b} is hydrogen and R^{3a} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, where c is 1 to 6, d is 0 to 2, e is 0 to 3, f is 2 to 5, n is 2 to 4, and where $R^{3'}$ is independently hydrogen or C_{1-6} alkyl and $R^{3''}$ is $-OR'$ or $-N(R^{3'})_2$; (vi) R^{3a} is H and R^{3b} is H, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph , CH_2 -indol-3-yl, $-CH_2CH_2SCH_3$, CH_2CO_2H , $CH_2C(O)NH_2$, CH_2CH_2COOH , $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, CH_2 -imidazol-4-yl, CH_2OH , $CH(OH)CH_3$, $CH_2((4'-OH)-Ph)$, CH_2SH , or lower cycloalkyl; or (viii) R^{3a} is CH_3 , $-CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph , CH_2 -indol-3-yl, $-CH_2CH_2SCH_3$, CH_2CO_2H , $CH_2C(O)NH_2$, CH_2CH_2COOH , $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, CH_2 -imidazol-4-yl, CH_2OH , $CH(OH)CH_3$, $CH_2((4'-OH)-Ph)$, CH_2SH , or lower cycloalkyl and R^{3b} is H, where $R^{3'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{3''}$ is $-OR'$ or $-N(R^{3'})_2$;
- 15 (d) R^4 is hydrogen, C_{1-10} alkyl, C_{1-10} alkyl optionally substituted with a lower alkyl, alkoxy, di(lower alkyl)-amino, or halogen, C_{1-10} haloalkyl, C_{3-10} cycloalkyl, cycloalkyl alkyl, cycloheteroalkyl, aminoacyl, aryl, such as phenyl, heteroaryl, such as, pyridinyl, substituted aryl, or substituted heteroaryl;
- (e) R^5 is H, a lower alkyl, CN, vinyl, O-(lower alkyl), hydroxyl lower alkyl, i.e., $-(CH_2)_pOH$, where p is 1-6, including hydroxyl methyl (CH_2OH), CH_2F , N_3 , CH_2CN , CH_2NH_2 , CH_2NHCH_3 , $CH_2N(CH_3)_2$, alkyne (optionally substituted), or halogen, including F, Cl, Br, or I, with the provisos that when X is OH, base is cytosine and R^6 is H, R^5 cannot be N_3 and when X is OH, R^6 is CH_3 or CH_2F and B is a purine base, R^5 cannot be H;
- 20 (f) R^6 is H, CH_3 , CH_2F , CHF_2 , CF_3 , F, or CN;
- (g) X is H, OH, F, OMe, halogen, NH_2 , or N_3 ;
- (h) Y is OH, H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, vinyl, N_3 , CN, Cl, Br, F, I, NO_2 , $OC(O)O(C_{1-4}$ alkyl), $OC(O)O(C_{1-4}$ alkyl), $OC(O)O(C_{2-4}$ alkynyl), $OC(O)O(C_{2-4}$

- alkenyl), OC₁₋₁₀ haloalkyl, O(aminoacyl), O(C₁₋₁₀ acyl), O(C₁₋₄ alkyl), O(C₂₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₂₋₄ alkynyl), S(C₂₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₂₋₄ alkynyl), SO(C₂₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₂₋₄ alkynyl), SO₂(C₂₋₄ alkenyl), OS(O)₂(C₁₋₄ acyl), OS(O)₂(C₁₋₄ alkyl), OS(O)₂(C₂₋₄ alkenyl), NH₂,
 5 NH(C₁₋₄ alkyl), NH(C₂₋₄ alkenyl), NH(C₂₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₂₋₄ alkynyl), C(O)O(C₂₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₂₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₂₋₄ alkynyl), S(C₂₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₂₋₄ alkynyl), SO(C₂₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₂₋₄ alkynyl), SO₂(C₂₋₄ alkenyl), OS(O)₂(C₁₋₄ acyl), OS(O)₂(C₁₋₄ alkyl), OS(O)₂(C₂₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₂₋₄ alkenyl), NH(C₂₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂;

the base is a naturally occurring or modified purine or pyrimidine base represented by the following structures:

15



wherein

Z is N or CR¹²;

- R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are independently H, F, Cl, Br, I, OH, OR', SH, SR', NH₂,
 20 NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆, lower alkenyl of C₂-C₆, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆, lower alkynyl of C₂-

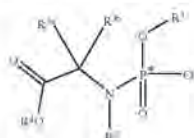
C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, or CH=CHCO₂R',

wherein R' is an optionally substituted alkyl, which includes, but is not limited to,
 5 an optionally substituted C₁₋₂₀ alkyl, an optionally substituted C₁₋₁₀ alkyl, an optionally substituted lower alkyl; an optionally substituted cycloalkyl; an optionally substituted alkynyl of C₂-C₆, an optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl, which includes but is not limited to C(O) alkyl, C(O)(C₁₋₂₀ alkyl), C(O)(C₁₋₁₀ alkyl), or C(O)(lower alkyl) or alternatively, in the instance of NR'₂, each R'
 10 comprise at least one C atom that are joined to form a heterocycle comprising at least two carbon atoms; and

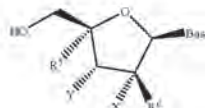
R¹² is an H, halogen (including F, Cl, Br, I), OH, OR', SH, SR', NH₂, NHR', NR'₂, NO₂ lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆, lower alkenyl of C₂-C₆, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆, lower alkynyl of C₂-C₆,
 15 halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, or CH=CHCO₂R'; with the proviso that when base is represented by the structure c with R¹¹ being hydrogen, R¹² is not a: (i) -C≡C-H, (ii) -C=CH₂, or (iii) -NO₂;

said process comprising:

20 reacting a substituted phosphochloridate compound **4** with a nucleoside analog **5**



4



5

10. A process for preparing a compound, its stereoisomer, salt, hydrate, solvate, or crystalline form thereof, selected from among

5 **5** 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-alanyl phosphate ((S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester);

5 **6** 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-valyl phosphate ((S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-3-methyl-butyrlic acid methyl ester);

10 **7** 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate ((S)-2-{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-3-methyl-butyrlic acid methyl ester);

15 **8** 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-alanyl phosphate (((S)-2-{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester);

9 N⁴-(N,N-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-C-methylcytidine;

20 **10** 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-alanyl phosphate (((S)-2-{[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester);

25 **11** 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(4-bromophenyl methoxy-valyl phosphate (2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate ((S)-2-{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-3-methyl-butyrlic acid methyl ester);

30 **12** 2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-valyl phosphate ((S)-2-{[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-3-methyl-butyrlic acid methyl ester);

13 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid ethyl ester;

14 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-propionic acid benzyl ester;

15 {[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-acetic acid methyl ester;

16 (S)-2-((2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino)-propionic acid methyl ester;

17 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-propionic acid methyl ester;

18 (S)-1-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphoryl)-pyrrolidine-2-carboxylic acid methyl ester;

19 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid butyl ester;

20 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid benzyl ester;

21 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid methyl ester;

22 (S)-2-((4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino)-propionic acid methyl ester;

23 (S)-2-{(3,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester;

24 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid sec-butyl ester;

25 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester;

26 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid butyl ester;

27 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid ethyl ester;

28 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid isopropyl ester;

29 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid benzyl ester;

30 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid isopropyl ester;

31 (S)-2-{(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid benzyl ester;

32 (S)-2-{(2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid butyl ester;

33 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino}-propionic acid isopropyl ester;

5 34 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid butyl ester;

35 (S)-2-{(3,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid ethyl ester;

10 36 (S)-2-{(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid isopropyl ester;

15 37 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid benzyl ester;

38 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid pentyl ester;

20 39 (S)-2-{(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid isopropyl ester;

40 (S)-2-{(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid butyl ester;

25 41 (S)-2-{(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid ethyl ester;

30 42 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino}-propionic acid butyl ester;

43 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino}-propionic acid benzyl ester;

5 44 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-butyric acid methyl ester;

45 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 4-fluoro-benzyl ester;

10 46 (S)-2-((2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino)-propionic acid butyl ester;

15 47 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 3-methyl-butyl ester;

48 (S)-2-((2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino)-propionic acid ethyl ester;

20 49 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid cyclohexyl ester;

50 (R)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid butyl ester;

25 51 (R)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester;

30 52 (R)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid benzyl ester;

53 (S)-2-[(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid butyl ester;

54 (S)-2-[(4-Bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid isopropyl ester;

55 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid cyclohexyl ester;

56 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-bromo-phenoxy)-phosphorylamino]-propionic acid cyclohexyl ester;

57 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-butyric acid isopropyl ester;

58 (S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-butyric acid cyclohexyl ester;

59 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-butyric acid cyclohexyl ester;

60 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-butyric acid isopropyl ester;

61 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid 2,2-difluoro-ethyl ester;

62 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino]-propionic acid 2,2,2-trifluoro-1-trifluoromethyl-ethyl ester;

63 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 2-fluoro-1-fluoromethyl-ethyl ester;

64 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid cyclopropyl methyl ester;

65 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-butyric acid cyclopentyl ester;

66 (S)-2-([(2R,3R,4R,5R)-5-(6-Amino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

67 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-hydroxy-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

68 (S)-2-((R)-[(2R,3R,4R,5R)-5-(2,6-Diamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

69 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-cyclopentylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

70 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-azetidin-1-yl-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

71 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-diethylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

72 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-propylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

73 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-cyclobutylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

74 (S)-2-([(2R,3R,4R,5R)-5-[2-Amino-6-(4-methyl-piperazin-1-yl)-purin-9-yl]-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

75 (2S)-methyl 2-((((2R,3R,4R,5R)-4-fluoro-3-hydroxy-4-methyl-5-(6-(propylamino)-9H-purin-9-yl)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

76 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(cyclobutylamino)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

77 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(cyclopentylamino)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

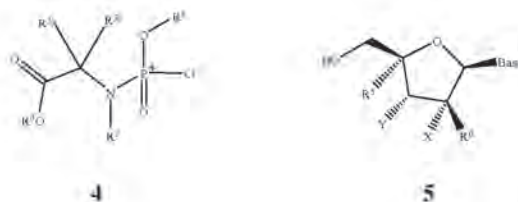
78 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(aziridin-1-yl)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

79 (2S)-methyl 2-((((2R,3R,4R,5R)-4-fluoro-3-hydroxy-4-methyl-5-(6-(piperidin-1-yl)-9H-purin-9-yl)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate; and

80 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(azetidin-1-yl)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate

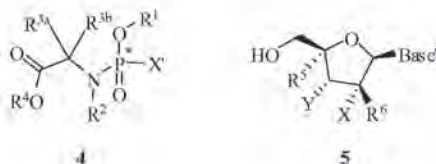
said process comprising:

reacting a substituted phosphochloridate compound 4 with a nucleoside analog 5



11. A product its stereoisomer, salt, hydrate, solvate or crystalline form thereof, prepared a process comprising:

- 5 reacting a substituted phosphochloridate compound **4** with a nucleoside analog **5**



wherein

- (a) R^1 is hydrogen, n-alkyl; branched alkyl; cycloalkyl; or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, F, Cl, Br, I, nitro, cyano, C_{1-6} haloalkyl, $-N(R^{1'})_2$, C_{1-6} acylamino, $-NHSO_2C_{1-6}$ alkyl, $-SO_2N(R^{1'})_2$, $COR^{1''}$, and $-SO_2C_{1-6}$ alkyl; ($R^{1'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{1''}$ is $-OR^1$ or $-N(R^{1'})_2$);
- 15 (b) R^2 is hydrogen, C_{1-10} alkyl, R^{3a} or R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, $C(O)CR^{3a}R^{3b}NHR^1$, where n is 2 to 4 and R^1 , R^{3a} , and R^{3b} ,
- (c) R^{3a} and R^{3b} are (i) independently selected from hydrogen, C_{1-10} alkyl, cycloalkyl, $-(CH_2)_6(NR^3)_2$, C_{1-6} hydroxyalkyl, $-CH_2SH$, $-(CH_2)_2S(O)_dMe$, -
- 20 $(CH_2)_3NHC(=NH)NH_2$, (1H-indol-3-yl)methyl, (1H-imidazol-4-yl)methyl, -

- (CH₂)_cCOR^{3''}, aryl and aryl C₁₋₃ alkyl, said aryl groups optionally substituted with a group selected from hydroxyl, C₁₋₁₀ alkyl, C₁₋₆ alkoxy, halogen, nitro and cyano; (ii) R^{3a} and R^{3b} both are C₁₋₆ alkyl; (iii) R^{3a} and R^{3b} together are (CH₂)_f so as to form a spiro ring; (iv) R^{3a} is hydrogen and R^{3b} and R² together are (CH₂)_n so as to form a cyclic ring that includes the adjoining N and C atoms (v) R^{3b} is hydrogen and R^{3a} and R² together are (CH₂)_n so as to form a cyclic ring that includes the adjoining N and C atoms, where c is 1 to 6, d is 0 to 2, e is 0 to 3, f is 2 to 5, n is 2 to 4, and where R^{3'} is independently hydrogen or C₁₋₆ alkyl and R^{3''} is -OR' or -N(R^{3'})₂; (vi) R^{3a} is H and R^{3b} is H, CH₃, CH₂CH₃, CH(CH₃)₂, CH₂CH(CH₃)₂, CH(CH₃)CH₂CH₃, CH₂Ph, CH₂-indol-3-yl, -CH₂CH₂SCH₃, CH₂CO₂H, CH₂C(O)NH₂, CH₂CH₂COOH, CH₂CH₂C(O)NH₂, CH₂CH₂CH₂CH₂NH₂, -CH₂CH₂CH₂NHC(NH)NH₂, CH₂-imidazol-4-yl, CH₂OH, CH(OH)CH₃, CH₂((4'-OH)-Ph), CH₂SH, or lower cycloalkyl; or (viii) R^{3a} is CH₃, -CH₂CH₃, CH(CH₃)₂, CH₂CH(CH₃)₂, CH(CH₃)CH₂CH₃, CH₂Ph, CH₂-indol-3-yl, -CH₂CH₂SCH₃, CH₂CO₂H, CH₂C(O)NH₂, CH₂CH₂COOH, CH₂CH₂C(O)NH₂, CH₂CH₂CH₂CH₂NH₂, -CH₂CH₂CH₂NHC(NH)NH₂, CH₂-imidazol-4-yl, CH₂OH, CH(OH)CH₃, CH₂((4'-OH)-Ph), CH₂SH, or lower cycloalkyl and R^{3b} is H, where R^{3'} is independently hydrogen or alkyl, which includes, but is not limited to, C₁₋₂₀ alkyl, C₁₋₁₀ alkyl, or C₁₋₆ alkyl, R^{3''} is -OR' or -N(R^{3'})₂;

- (d) R⁴ is hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkyl optionally substituted with a lower alkyl, alkoxy, di(lower alkyl)-amino, or halogen, C₁₋₁₀ haloalkyl, C₃₋₁₀ cycloalkyl, cycloalkyl alkyl, cycloheteroalkyl, aminoacyl, aryl, such as phenyl, heteroaryl, such as, pyridinyl, substituted aryl, or substituted heteroaryl;

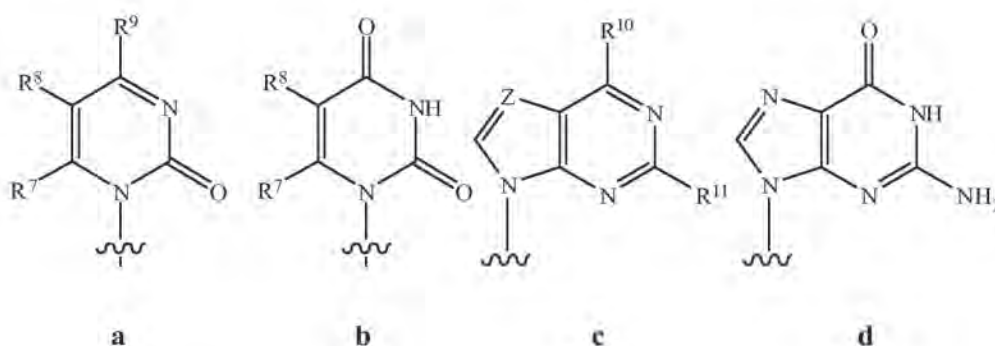
- (e) R⁵ is H, a lower alkyl, CN, vinyl, O-(lower alkyl), hydroxyl lower alkyl, i.e., -(CH₂)_pOH, where p is 1 -6, including hydroxyl methyl (CH₂OH), CH₂F, N₃, CH₂CN, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or halogen, including F, Cl, Br, or I, with the provisos that when X is OH, base is cytosine and R⁶ is H, R⁵ cannot be N₃ and when X is OH, R⁶ is CH₃ or CH₂F and B is a purine base, R⁵ cannot be H;

- (f) R⁶ is H, CH₃, CH₂F, CHF₂, CF₃, F, or CN;

(g) X is H, OH, F, OMe, halogen, NH₂, or N₃;

(h) Y is OH, H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, OC(O)O(C₁₋₄ alkyl), OC(O)O(C₁₋₄ alkyl), OC(O)O(C₂₋₄ alkynyl), OC(O)O(C₂₋₄ alkenyl), OC₁₋₁₀ haloalkyl, O(aminoacyl), O(C₁₋₁₀ acyl), O(C₁₋₄ alkyl), O(C₂₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₂₋₄ alkynyl), S(C₂₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₂₋₄ alkynyl), SO(C₂₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₂₋₄ alkynyl), SO₂(C₂₋₄ alkenyl), OS(O)₂(C₁₋₄ acyl), OS(O)₂(C₁₋₄ alkyl), OS(O)₂(C₂₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₂₋₄ alkenyl), NH(C₂₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₂₋₄ alkynyl), C(O)O(C₂₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₂₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₂₋₄ alkynyl), S(C₂₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₂₋₄ alkynyl), SO(C₂₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₂₋₄ alkynyl), SO₂(C₂₋₄ alkenyl), OS(O)₂(C₁₋₄ acyl), OS(O)₂(C₁₋₄ alkyl), OS(O)₂(C₂₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₂₋₄ alkenyl), NH(C₂₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂;

the base is a naturally occurring or modified purine or pyrimidine base represented by the following structures:



20 wherein

Z is N or CR¹²;

- R^7 , R^8 , R^9 , R^{10} , and R^{11} are independently H, F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆, lower alkenyl of C₂-C₆, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, or CH=CHCO₂R',

- wherein R' is an optionally substituted alkyl, which includes, but is not limited to, an optionally substituted C₁₋₂₀ alkyl, an optionally substituted C₁₋₁₀ alkyl, an optionally substituted lower alkyl; an optionally substituted cycloalkyl; an optionally substituted alkynyl of C₂-C₆, an optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl, which includes but is not limited to C(O) alkyl, C(O)(C₁₋₂₀ alkyl), C(O)(C₁₋₁₀ alkyl), or C(O)(lower alkyl) or alternatively, in the instance of NR'₂, each R' comprise at least one C atom that are joined to form a heterocycle comprising at least two carbon atoms; and

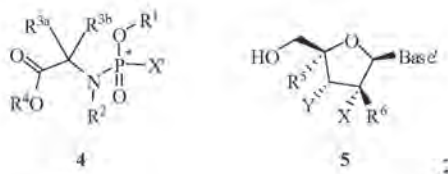
- R^{12} is an H, halogen (including F, Cl, Br, I), OH, OR', SH, SR', NH₂, NHR', NR'₂, NO₂ lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆, lower alkenyl of C₂-C₆, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆, lower alkynyl of C₂-C₆, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, or CH=CHCO₂R'; with the proviso that when base is represented by the structure c with R¹¹ being hydrogen, R¹² is not a: (i) -C≡C-H, (ii) -C=CH₂, or (iii) -NO₂

and

wherein X' is a leaving group, such as, Cl,

12. A product its stereoisomer, salt, hydrate, solvate or crystalline form thereof, prepared a process comprising:

reacting a substituted phosphochloridate compound 4 with a nucleoside analog 5



wherein the product comprises a compound, its stereoisomer, salt, hydrate, solvate, or crystalline form thereof, selected from among

5 **5** 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-alanyl phosphate ((S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester);

6 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(phenyl methoxy-valyl phosphate ((S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-3-methyl-
10 butyric acid methyl ester);

7 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate ((S)-2-{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-3-methyl-butyric acid methyl ester);
15

8 2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-alanyl phosphate (((S)-2-{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester);
20

9 N⁴-(N,N-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-C-methylcytidine;

10 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-alanyl phosphate (((S)-2-{[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester);
25

11 2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(4-bromophenyl methoxy-valyl phosphate (2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate ((S)-2-{(4-bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-

yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-3-methyl-butyrac acid methyl ester);

12 2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-valyl phosphate ((S)-2-{[(2R,3R,4R,5R)-5-(2-oxo-3-amino-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-3-methyl-butyrac acid methyl ester;

13 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid ethyl ester;

10 14 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-propionic acid benzyl ester;

15 15 {(S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-acetic acid methyl ester;

16 (S)-2-{(2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester;

20 17 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-propionic acid methyl ester;

18 (S)-1-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphoryl}-pyrrolidine-2-carboxylic acid methyl ester;

25 19 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid butyl ester;

30 20 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid benzyl ester;

21 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid methyl ester;

22 (S)-2-{(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester;

23 (S)-2-{(3,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid methyl ester;

24 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid sec-butyl ester;

25 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester;

26 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid butyl ester;

27 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid ethyl ester;

28 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid isopropyl ester;

29 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid benzyl ester;

30 (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid isopropyl ester;

31 (S)-2-{(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid benzyl ester;

5 **32** (S)-2-{(2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid butyl ester;

33 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino}-propionic acid isopropyl ester;

10 **34** (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid butyl ester;

35 (S)-2-{(3,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid ethyl ester;

36 (S)-2-{(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid isopropyl ester;

20 **37** (S)-2-[[[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-methoxy-phenoxy)-phosphorylamino]-propionic acid benzyl ester;

38 (S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid pentyl ester;

25 **39** (S)-2-{(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid isopropyl ester;

40 (S)-2-{(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid butyl ester;

- 41 (S)-2-{{(4-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid ethyl ester;
- 42 (S)-2-{{(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino}-propionic acid butyl ester;
- 43 (S)-2-{{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-p-tolyloxy-phosphorylamino}-propionic acid benzyl ester;
- 44 (S)-2-{{(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-butyric acid methyl ester;
- 45 (S)-2-{{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 4-fluoro-benzyl ester;
- 46 (S)-2-{{(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid butyl ester;
- 47 (S)-2-{{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 3-methyl-butyl ester;
- 48 (S)-2-{{(2,4-Dichloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid ethyl ester;
- 49 (S)-2-{{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid cyclohexyl ester;
- 50 (R)-2-{{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid butyl ester;

51 (R)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester;

52 (R)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid benzyl ester;

53 (S)-2-[(2-Chloro-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid butyl ester;

10 54 (S)-2-[(4-Bromo-phenoxy)-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-propionic acid isopropyl ester;

55 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-propionic acid cyclohexyl ester;

56 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-bromo-phenoxy)-phosphorylamino]-propionic acid cyclohexyl ester;

57 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-butyric acid isopropyl ester;

58 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-butyric acid cyclohexyl ester;

25 59 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-(4-fluoro-phenoxy)-phosphorylamino]-butyric acid cyclohexyl ester;

60 (S)-2-[(4-Chloro-phenoxy)-[(2R,3R,4 R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino]-butyric acid isopropyl ester;

61 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 2,2-difluoro-ethyl ester;

62 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 2,2,2-trifluoro-1-trifluoromethyl-ethyl ester;

63 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid 2-fluoro-1-fluoromethyl-ethyl ester;

64 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid cyclopropyl methyl ester;

65 (S)-2-([(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-butyric acid cyclopentyl ester;

66 (S)-2-([(2R,3R,4R,5R)-5-(6-Amino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

67 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-hydroxy-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

68 (S)-2-((R)-[(2R,3R,4R,5R)-5-(2,6-Diamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

69 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-cyclopentylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

70 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-azetidin-1-yl-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

71 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-diethylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

72 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-propylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

73 (S)-2-([(2R,3R,4R,5R)-5-(2-Amino-6-cyclobutylamino-purin-9-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

74 (S)-2-([(2R,3R,4R,5R)-5-[2-Amino-6-(4-methyl-piperazin-1-yl)-purin-9-yl]-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino)-propionic acid methyl ester;

75 (2S)-methyl 2-((((2R,3R,4R,5R)-4-fluoro-3-hydroxy-4-methyl-5-(6-(propylamino)-9H-purin-9-yl)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

76 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(cyclobutylamino)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

77 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(cyclopentylamino)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

78 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(aziridin-1-yl)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate;

79 (2S)-methyl 2-((((2R,3R,4R,5R)-4-fluoro-3-hydroxy-4-methyl-5-(6-(piperidin-1-yl)-9H-purin-9-yl)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate; and

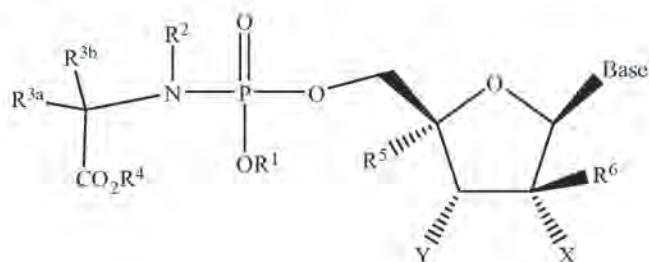
80 (2S)-methyl 2-((((2R,3R,4R,5R)-5-(6-(azetidin-1-yl)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate

wherein Base' is as recited in each of compounds 5-74; and

wherein X' is a leaving group, such as, Cl.

ABSTRACT

Disclosed herein are phosphoramidate prodrugs of nucleoside derivatives for the treatment of viral infections in mammals, which is a compound, its stereoisomer, salt (acid or basic addition salt), hydrate, solvate, or crystalline form thereof, represented by the following structure:



Also disclosed are methods of treatment, uses, and processes for preparing each of which utilize the compound represented by formula **I**.

Electronic Acknowledgement Receipt	
EFS ID:	13952856
Application Number:	13609614
International Application Number:	
Confirmation Number:	5143
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Michael Joseph Sofia
Customer Number:	104538
Filer:	Erin Julia Daida Austin/DAVID NGUY
Filer Authorized By:	Erin Julia Daida Austin
Attorney Docket Number:	03956.053800.2
Receipt Date:	10-OCT-2012
Filing Date:	11-SEP-2012
Time Stamp:	16:07:52
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		039560538002_SuppPrelimAmendment.PDF	174728 8f0eb3d394f9604c5bd6a0c94c19cc09a2 =A16ed	yes	7

	Multipart Description/PDF files in .zip description				
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	Claims		2	6	
	Applicant Arguments/Remarks Made in an Amendment		7	7	
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2		039560538002_Response.PDF	97299	yes	5
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	Applicant Response to Pre-Exam Formalities Notice		1	1	
	Specification		2	3	
	Applicant Arguments/Remarks Made in an Amendment		4	5	
Warnings:					
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3		039560538002_Marked-UpSubstituteSpec.PDF	3450915	yes	752
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	Specification		1	679	
	Claims		680	751	
	Abstract		752	752	
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4		039560538002_CleanSubstituteSpec.PDF	3440066	yes	752
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Information:					
5	Sequence Listing (Text File)	039560538002_ST25.TXT	1091	no	0
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Information:					
Total Files Size (in bytes):			7164099		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875					Application or Docket Number 13/609,614		Filing Date 09/11/2012		☐ To be Mailed			
APPLICATION AS FILED – PART I												
(Column 1)			(Column 2)		SMALL ENTITY ☐		OR		OTHER THAN SMALL ENTITY			
FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)	RATE (\$)	FEE (\$)	RATE (\$)	FEE (\$)	RATE (\$)	FEE (\$)		
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A		N/A		N/A	380				
☒ SEARCH FEE (37 CFR 1.16(k), (j), or (m))	N/A	N/A	N/A		N/A		N/A	620				
☒ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A		N/A		N/A	250				
TOTAL CLAIMS (37 CFR 1.16(i))	12 minus 20 =	- 0	X \$ =		OR	X \$60 =	0					
INDEPENDENT CLAIMS (37 CFR 1.16(h))	12 minus 3 =	- 9	X \$ =		OR	X \$250 =	2250					
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).											
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))												
* If the difference in column 1 is less than zero, enter "0" in column 2.												
			TOTAL				TOTAL	3500				
APPLICATION AS AMENDED – PART II												
(Column 1)			(Column 2)		(Column 3)		SMALL ENTITY		OR		OTHER THAN SMALL ENTITY	
AMENDMENT	09/11/2012	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)
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	Independent (37 CFR 1.16(h))	+ 12	Minus	*** 12	= 0	X \$ =		OR	X \$250 =	0		
	☐ Application Size Fee (37 CFR 1.16(s))											
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))											
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AMENDMENT	10/10/2012	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)
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	Independent (37 CFR 1.16(h))	+ 1	Minus	*** 12	= 0	X \$ =		OR	X \$250 =	0		
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	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))											
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0		
<p>* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.</p> <p>** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".</p> <p>*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".</p> <p>The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.</p>												

Legal Instrument Examiner:
/ROBERT TALBERT/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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217-9197 (toll free).

Reviewer: Durreshwar Anjum

Timestamp: [year=2012; month=10; day=19; hr=13; min=6; sec=59; ms=534;]

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Validated By CRFValidator v 1.0.4

Application No: 13609614 Version No: 1.0

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<110> Sofia, Michael
Du, Jinfa
Wang, Peiyuan
Nagarathnam, Dhanapalan

<120> NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

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<150> US 13/099,671

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<151> 2008-03-21

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<151> 2007-10-24

<150> US 60/909,315

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY DOCKET NO.	TOT CLAIMS	IND CLAIMS
13/609,614	09/11/2012	1629	6600	03956.053800.2	13	1

CONFIRMATION NO. 5143

UPDATED FILING RECEIPT

104538

Fitzpatrick Cella Harper & Scinto (Gilead)
1290 Avenue of the Americas
New York, NY 10104



0000000057253300

Date Mailed: 10/24/2012

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Michael Joseph Sofia, Doylestown, PA;
Jinfa Du, New Hope, PA;
Peiyuan Wang, Totowa, NJ;
Dhanapalan Nagarathnam, Bethany, CT;

Applicant(s)

Michael Joseph Sofia, Doylestown, PA;
Jinfa Du, New Hope, PA;
Peiyuan Wang, Totowa, NJ;
Dhanapalan Nagarathnam, Bethany, CT;

Assignment For Published Patent Application

GILEAD PHARMASSET LLC, Foster City, CA

Power of Attorney: The patent practitioners associated with Customer Number 104538

Domestic Priority data as claimed by applicant

This application is a CON of 13/099,671 05/03/2011
which is a CON of 12/053,015 03/21/2008 PAT 7964580
which claims benefit of 60/982,309 10/24/2007
and claims benefit of 60/909,315 03/30/2007

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.)

If Required, Foreign Filing License Granted: 09/21/2012

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/609,614**

Projected Publication Date: 01/31/2013

Non-Publication Request: No

Early Publication Request: No
Title

NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

Preliminary Class

514

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 13/609,614			
APPLICATION AS FILED - PART I									
(Column 1)		(Column 2)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY			
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)		
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	390		
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	620		
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250		
TOTAL CLAIMS (37 CFR 1.16(i))	13	minus 20 =				x 62 =	0.00		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1	minus 3 =				x 250 =	0.00		
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						3200		
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00		
				TOTAL		TOTAL	4460		
* If the difference in column 1 is less than zero, enter "0" in column 2.									
APPLICATION AS AMENDED - PART II									
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)	
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	Independent (37 CFR 1.16(h))	* Minus ***	=	x =			x =		
	Application Size Fee (37 CFR 1.16(s))								
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
				TOTAL ADD'L FEE		TOTAL ADD'L FEE			
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)	
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	Independent (37 CFR 1.16(h))	* Minus ***	=	x =			x =		
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	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
				TOTAL ADD'L FEE		TOTAL ADD'L FEE			
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.									

Doc code: IDS

Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)

Approved for use through 07/31/2012. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		13609614
	Filing Date		2012-09-11
	First Named Inventor	Michael Joseph Sofia	
	Art Unit	1623	
	Examiner Name	Unassigned	
	Attorney Docket Number	03956.053800.2	

U.S. PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	1	RE29835	A	1978-11-14	Wilkowski et al.	
	2	3798209	A	1974-03-19	Wilkowski et al.	
	3	3852267	A	1974-12-03	Meyer, Jr. et al.	
	4	4814477	A	1989-03-21	Wijnberg et al.	
	5	4957924	A	1990-09-18	Beauchamp	
	6	5026687	A	1991-06-25	Yarchoan et al.	
	7	5118820	A	1992-06-02	Hertel	
	8	5149794	A	1992-09-22	Yatvin et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	13609614
Filing Date	2012-09-11
First Named Inventor	Michael Joseph Sofia
Art Unit	1623
Examiner Name	Unassigned
Attorney Docket Number	03956.053800.2

9	5157027	A	1992-10-20	Biller et al.	
10	5192549	A	1993-03-09	Barenolz et al.	
11	5194654	A	1993-03-16	Hostetler et al.	
12	5223263	A	1993-06-29	Hostetler et al.	
13	5256641	A	1993-10-26	Yatvin et al.	
14	5256798	A	1993-10-26	Chou et al.	
15	5372808	A	1994-12-13	Blatt et al.	
16	5376380	A	1994-12-27	Kikuchi et al.	
17	5405598	A	1995-04-11	Schinazi et al.	
18	5411947	A	1995-05-02	Hostetler et al.	
19	5420266	A	1995-05-30	Britton et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	13609614
Filing Date	2012-09-11
First Named Inventor	Michael Joseph Sofia
Art Unit	1623
Examiner Name	Unassigned
Attorney Docket Number	03956.053800.2

20	5426183	A	1995-06-20	Kjell	
21	5453499	A	1995-09-26	Chou et al.	
22	5462724	A	1995-10-31	Schinazi et al.	
23	5463092	A	1995-10-31	Hostetler et al.	
24	5496546	A	1996-03-05	Wang et al.	
25	5538865	A	1996-07-23	Reyes et al.	
26	5543389	A	1996-08-06	Yatvin et al.	
27	5543390	A	1996-08-06	Yatvin et al.	
28	5543391	A	1996-08-06	Yatvin et al.	
29	5554728	A	1996-09-10	Basava et al.	
30	5610054	A	1997-03-11	Draper	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		13609614
Filing Date		2012-09-11
First Named Inventor	Michael Joseph Sofia	
Art Unit	1623	
Examiner Name	Unassigned	
Attorney Docket Number	03956.053800.2	

31	5633358	A	1997-05-27	Gruetzke et al.	
32	5633388	A	1997-05-27	Diana et al.	
33	5676942	A	1997-10-14	Testa et al.	
34	5703058	A	1997-12-30	Schinazi et al.	
35	5711944	A	1998-01-27	Gilbert et al.	
36	5725859	A	1998-03-10	Omer	
37	5738845	A	1998-04-14	Imakawa	
38	5738846	A	1998-04-14	Greenwald et al.	
39	5747646	A	1998-05-05	Hakimi et al.	
40	5767097	A	1998-06-16	Tam	
41	5792834	A	1998-08-11	Hakimi et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	13609614
Filing Date	2012-09-11
First Named Inventor	Michael Joseph Sofia
Art Unit	1623
Examiner Name	Unassigned
Attorney Docket Number	03956.053800.2

42	5830455	A	1998-11-03	Valtuna et al.	
43	5830905	A	1998-11-03	Diana et al.	
44	5834594	A	1998-11-10	Hakimi et al.	
45	5837257	A	1998-11-17	Tsai et al.	
46	5846964	A	1998-12-08	Ozeki	
47	5849696	A	1998-12-15	Chretien et al.	
48	5869253	A	1999-02-09	Draper	
49	5891874	A	1999-04-06	Colacino et al.	
50	5905070	A	1999-05-18	Schinazi et al.	

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Application Number	13609614
Filing Date	2012-09-11
First Named Inventor	Michael Joseph Sofia
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	1	101108870	CN	A	2008-01-23	Yixin Leng		☐
	2	199 14 474	DE	A1	1999-10-07	Hoffmann La-Roché AG		☐
	3	0 180 276	EP	A1	1986-05-07	OCE ANDENO BV		☐
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	Filing Date		2012-09-11
	First Named Inventor	Michael Joseph Sofia	
	Art Unit	1623	
	Examiner Name	Unassigned	
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31	International Search Report issued in International Application No. PCT/US2004/012472 mailed December 30, 2004 (4 pages)	☐
32	International Search Report issued in International Application No. PCT/US2005/025916 mailed June 15, 2006 (2 pages)	☐
33	International Search Report issued in International Application No. PCT/EP2006/069060 mailed January 30, 2007 (4 pages)	☐
34	International Search Report issued in International Application No. PCT/US2005/032406 mailed May 8, 2008 (3 pages)	☐

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(Not for submission under 37 CFR 1.99)

Application Number	13609614
Filing Date	2012-09-11
First Named Inventor	Michael Joseph Sofia
Art Unit	1623
Examiner Name	Unassigned
Attorney Docket Number	03956.053800.2

35	Bartenschlager et al., "Nonstructural Protein 3 of the Hepatitis C Virus Encodes a Serine-Type Proteinase Required for Cleavage at the NS3/4 and NS4/5 Junctions," J. Virol., Vol. 67, No. 7, pages 3835 - 3844 (1993)	☐
36	Bartenschlager et al., "Kinetic and Structural Analyses of Hepatitis C Virus Polyprotein Processing," J. Virol., Vol. 68, No. 8, pages 5045 - 5055 (1994)	☐
37	Bazan et al., "Detection of a Trypsin-like Serine Protease Domain in Flaviviruses and Pestiviruses," Virology, Vol. 171, pages 637 - 639 (1989)	☐
38	Beaulieu et al., "Inhibitors of the HCV NS5B polymerase: New hope for the treatment of hepatitis C infections," Current Opinion in Investigational Drugs, Vol. 5, No. 8, pages 838 - 850 (2004)	☐
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44	Rice, C. M., "Flaviviridae: The Viruses and Their Replication," Fields Virology, 3rd Edition, Vol. 1, pages 931 - 959 (1996)	☐
45	Gorbalenya et al., "A conserved NTP-motif in putative helicases," Nature, Vol. 333, page 22 (1988)	☐

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46	Gorbalenya et al., "N-terminal domains of putative helicases of flavi- and pestiviruses may be serine proteases," Nucleic Acids Research, Vol. 17, No. 10, pages 3889 - 3897 (1989)	☐
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48	Grakoui et al., "A second hepatitis C virus-encoded proteinase," Proc. Natl. Acad. Sci., Vol. 90, pages 10583 - 10587 (1993)	☐
49	Griffith et al., "HCV Anti-viral Agents," Annual Reports in Medicinal Chemistry, Vol. 39, pages 223 - 237 (2004)	☐
50	Halstead, S. B., "Selective Primary Health Care: Strategies for Control of Disease in the Developing World. XI. Dengue," Review of Infectious Diseases, Vol. 6, No. 2, pages 251 - 263 (1984)	☐

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STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	13609614
Filing Date	2012-09-11
First Named Inventor	Michael Joseph Sofia
Art Unit	1623
Examiner Name	Unassigned
Attorney Docket Number	03956.053800.2

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2012-11-13
Name/Print	Alicia A. Russo	Registration Number	46192

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
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	Filing Date		2012-09-11	
	First Named Inventor	Michael Joseph Sofia		
	Art Unit	1623		
	Examiner Name	Unassigned		
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	2	7390791	B2	2008-06-24	Gilead Sciences, Inc.	
	3	7879815	B2	2011-02-01	Merck Sharp & Dohme Corp., Istituto di Ricerche di	
	4	7964580	B2	2011-06-21	Pharmasset, Inc.	
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	1	20020198173	A1	2002-12-26	Schirazi et al.	

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Examiner Name	Unassigned
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2	20020058635	A1	2002-05-16	Averett	
3	20010034440	A1	2001-10-25	Shepard et al.	
4	20100137576	A1	2010-06-03	Stec et al.	
5	20100152128	A1	2010-06-17	Attenni et al.	
6	20100173863	A1	2010-07-08	Schinazi et al.	
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- ☐ See attached certification statement.
- ☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.
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Signature	/Alicia A. Russo/	Date (YYYY-MM-DD)	2012-11-13
Name/Print	Alicia A. Russo	Registration Number	46192

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EFS ID:	14209238
Application Number:	13609614
International Application Number:	
Confirmation Number:	5143
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Michael Joseph Sofia
Customer Number:	104538
Filer:	Erin Julia Daida Austin/DAVID NGUY
Filer Authorized By:	Erin Julia Daida Austin
Attorney Docket Number:	03956.053800.2
Receipt Date:	13-NOV-2012
Filing Date:	11-SEP-2012
Time Stamp:	10:26:49
Application Type:	Utility under 35 USC 111(a)

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	:	Examiner: Unassigned
MICHAEL JOSEPH SOFIA ET AL.	)	
	:	Group Art Unit: 1623
Application No.: 13/609,614	)	
	:	Confirmation No.: 5143
Filed: September 11, 2012	)	
	:	
For: NUCLEOSIDE	)	
PHOSPHORAMIDATE	:	
PRODRUGS	)	
	:	November 13, 2012

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P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56 and in accordance with the practice under 37 C.F.R. §§ 1.97 and 1.98, the Examiner's attention is directed to the documents listed on the concurrently submitted Forms PTO/SB/08a. The references listed on the concurrently submitted Forms PTO/SB/08a were cited by the Examiner and/or the Applicants during prosecution of related U.S. Patent No. 7,964,580 B2 and U.S. Application No. 13/099,671. Pursuant to 37 CFR § 1.98(a)(2)(ii) and MPEP 609.02(A)(2), copies of U.S. patent documents and other documents considered by the Office during examination of related U.S. Patent No. 7,964,580 B2 and U.S. Application No. 13/099,671 are not provided. Applicants note that more than one e-IDS is necessary to file a complete IDS

listing all of the references cited during prosecution of U.S. Patent No. 7,964,580 B2 and U.S. Application No. 13/099,671. Applicants submit the concurrently filed Forms PTO/SB/08a in order to have the information printed on any patent resulting from the present application pursuant to MPEP 609.02(A)(2). It is respectfully requested that the above-referenced information be considered by the Examiner and that an initialed copy of the concurrently submitted Forms PTO/SB/08a be returned indicating that such information has been considered.

In accordance with 37 C.F.R. § 1.97(h) and MPEP 2129, applicants make no admission regarding whether the references listed on the concurrently submitted Forms PTO/SB/08a are, or are considered to be, material to patentability.

Pursuant to 37 C.F.R. § 1.97(b), no fee is believed due in connection with this paper. Should the Office determine that any fee is due, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 50-3939.

Applicants' undersigned attorneys may be reached in their New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to the address given below.

Respectfully submitted,

/Alicia A. Russo/
Alicia A. Russo
Registration No.: 46,192

Erin J.D. Austin
Registration No.: 66,532

Attorneys for Applicants

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		13609614	
	Filing Date		2012-09-11	
	First Named Inventor	Michael Joseph Sofia		
	Art Unit	1623		
	Examiner Name	Unassigned		
	Attorney Docket Number	03956.053800.2		

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	First Named Inventor	Michael Joseph Sofia		
	Art Unit	1623		
	Examiner Name	Patrick T. Lewis		
	Attorney Docket Number	03956.053800.2		

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5	20110251152	A1	2011-10-13	PHARMASSET, INC.	
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2	SIDDIQUI, Adam Q., et al., "The Presence of Substituents on the Aryl Moiety of the Aryl Phosphoramidate Derivatives of d4T Enhances Anti-HIV Efficacy in Cell Culture: A Structure-Activity Relationship," J. Med. Chem. (1999) 42:393-399.	☐
3	DUMEZ, Darin, et al., "Large-Scale Synthesis and Formulation of GMP-Grade Stampidine, a New Anti-HIV Agent," Arzneim.-Forsch./Drug Res. (2006) 56(2a):136-151.	☐
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5	NAKAYAMA, Kensaku, et al., "A Highly Enantioselective Synthesis of Phosphate Triesters," J. Am. Chem. Soc. (1990) 112:6936-6942.	☐
6	WOZNIAK, Lucyna A., et al., "The stereospecific synthesis of P-chiral biophosphates and their analogues by the Stec reaction," Chem. Soc. Rev. (2003) 32:158-169.	☐
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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
11 May 2006 (11.05.2006)

PCT

(10) International Publication Number
WO 2006/050161 A2

(51) International Patent Classification:
A61K 31/7076 (2006.01)

(74) Agents: HARRIS, Robert, J. et al.; Viksnins Harris & Padys PLLP, P.O. Box 111098, St. Paul, MN 55111-1098 (US).

(21) International Application Number:
PCT/US2005/039072

(22) International Filing Date: 28 October 2005 (28.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/623,065 29 October 2004 (29.10.2004) US
60/641,754 7 January 2005 (07.01.2005) US
60/665,832 29 March 2005 (29.03.2005) US
60/692,572 22 June 2005 (22.06.2005) US
60/728,215 19 October 2005 (19.10.2005) US

(71) Applicant (for all designated States except US):
BIOCRIST PHARMACEUTICALS, INC. [US/US];
2190 Parkway Lake Drive, Birmingham, Alabama 35244 (US).

(71) Applicants and

(72) Inventors: **BABU, Yarlagaadda, S.** [IN/US]; 3441 Strollway Drive, Birmingham, Alabama 35226 (US). **CHAND, Pooran** [US/US]; 509 Creekwood Place, Birmingham, Alabama 35226 (US). **WU, Minwan** [CN/US]; 2709 Paden Trail, Vestavia Hills, Alabama 35226 (US). **KOTIAN, Pravin, L.** [US/US]; 1313 Atkins Trimm Blvd., Hoover, Alabama 35226 (US). **KUMAR, V., Satish** [IN/US]; 809 Mayapple Court, Birmingham, Alabama 35244 (US). **LIN, Tsu-hsing** [US/US]; 1848 Arbor Lane, Vestavia Hills, Alabama 35226 (US). **EL-KATTAN, Yahya** [US/US]; 3336 Castle Crest Drive, Vestavia Hills, Alabama 35216 (US). **GHOSH, Ajit, K.** [IN/US]; 3119 Crossings Drive, Birmingham, Alabama 35242 (US).

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(54) Title: THERAPEUTIC EUROPYRIMIDINES AND THIENOPYRIMIDINES

(57) Abstract: The invention provides compounds of formula I, II, and III as described herein, as well as pharmaceutical compositions comprising the compounds, and synthetic methods and intermediates that are useful for preparing the compounds. The compounds of formula I, II, and III are useful as anti-viral agents and/or as anti-cancer agents.

WO 2006/050161 A2

THERAPEUTIC FUROPYRIMIDINES AND THIENOPYRIMIDINES

Priority

This application claims priority from US Provisional Patent Application Nos. 60/623,065, filed October 29, 2004; 60/641,754, filed January 7, 2005; 60/665,832, filed March 29, 2005; and 60/692,572, filed June 22, 2005.

Background of the Invention

Viral diseases are a major cause of death and economic loss in the world. The *Flaviviridae* family of viruses consists of three genera: the flaviviruses (including dengue, West Nile, and yellow fever viruses), hepacivirus (HCV), and the pestiviruses (including bovine viral diarrhoea virus, BVDV). The disease states and conditions caused by members of this family include yellow fever, dengue, Japanese encephalitis, St. Louis encephalitis, Hepatitis B and C, West Nile disease, and AIDS. Currently, human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are responsible for the largest number of viral related deaths worldwide. Although there are some drugs useful for treating HIV, there are only a few drugs useful for treating HBV, and no drugs that are broadly useful for treating HCV.

Ribavirin (1- β -D-ribofuranosyl-1-1,2,4-triazole-3-carboxamide) is a synthetic, non-interferon-inducing, broad spectrum antiviral nucleoside. Ribavirin is structurally similar to guanosine, and has in vitro activity against several DNA and RNA viruses including *Flaviviridae* (Davis. *Gastroenterology* 118:S104-S114, 2000). Ribavirin reduces serum amino transferase levels to normal in 40% of patients, but it does not lower serum levels of HCV-RNA (Davis. *Gastroenterology* 118:S104-S114, 2000). Thus, ribavirin alone is not effective in reducing viral RNA levels. Additionally, ribavirin has significant toxicity and is known to induce anemia.

Interferons (IFNs) are compounds which have been commercially available for the treatment of chronic hepatitis for nearly a decade. IFNs are glycoproteins produced by immune cells in response to viral infection. IFNs inhibit viral replication of many viruses, including HCV. When used as the sole treatment for hepatitis C infection, IFN suppresses serum HCV-RNA to undetectable levels. Additionally, IFN normalizes

serum amino transferase levels. Unfortunately, the effects of IFN are temporary and a sustained response occurs in only 8%-9% of patients chronically infected with HCV (Davis, Gastroenterology 118:S104-S114, 2000).

HCV is a positive stranded ss RNA virus with a well characterized RNA-
5 dependent RNA polymerase (RdRp) and a well characterized disease progression. HCV has infected an estimated 170 million people worldwide, leading to a major health crisis as a result of the disease. Indeed, during the next few years the number of deaths from HCV-related liver disease and hepatocellular carcinoma may overtake those caused by AIDS. Egypt is the hardest hit country in the world, with 23% of the
10 population estimated to be carrying the virus; whereas, in the USA the prevalence of chronic infections has recently been determined to be around 1.87% (2.7 million persons). HCV infections become chronic in about 50% of cases. Of these, about 20% develop liver cirrhosis that can lead to liver failure, including hepatocellular carcinoma.

The NS5B region of HCV encodes a 65 KDa RdRp thought to be responsible
15 for viral genome replication. RdRps function as the catalytic subunit of the viral replicase required for the replication of all positive-strand viruses. The NS5B protein has been well characterized, shown to possess the conserved GDD motif of RdRps and *in vitro* assay systems have been reported. Cellular localization studies revealed that NS5B is membrane-associated in the endoplasmic reticulum like NS5A, suggesting
20 that those two proteins may remain associated with one another after proteolytic processing. Additional evidence suggests that NS3, NS4A and NS5B interact with each other to form a complex that functions as part of the replication machinery of HCV.

The X-ray crystal structure of NS5B apoenzyme has been determined and three
25 very recent publications describe the unusual shape of the molecule. This unique shape for a polymerase, resembling a flat sphere, is attributed to extensive interactions between the fingers and thumb subdomains in such a way that the active site is completely encircled, forming a cavity 15 Å across and 20 Å deep. Modeling studies showed that the NS5B apoenzyme can accommodate the template-primer without large
30 movement of the subdomains, suggesting that the structure is preserved during the polymerization reaction. The RdRp polypeptides from various members of the

Flaviviridae family and other viral families have been shown to be conserved (J.A. Bruenn, Nucleic Acids Research, Vol. 19, No. 2 p. 217, 1991).

Currently, there are no safe and effective therapeutic agents on the market that target HCV polymerase. There is currently a need for therapeutic agents and
5 therapeutic methods that are useful for treating viral infections, such as HCV, HIV, and HBV.

In addition, there is also a current need for therapeutic agents and therapeutic methods that are useful for treating cancer. Even though significant advances have occurred in the treatment of cancer, it still remains a major health concern. It has been
10 reported that cancer is the cause of death of up to one of every four Americans. Notwithstanding the advances in treatments for cancer and other diseases there is still a need for novel drugs that are effective to treat cancer.

Summary of the Invention

The present invention provides compounds that are inhibitors of viral RNA and
15 DNA polymerases (e.g. polymerases from hepatitis B, hepatitis C, human immunodeficiency virus, Polio, Coxsackie A and B, Rhino, Echo, small pox, Ebola, and West Nile virus) and that are useful for treating HCV, as well as other viral infections (e.g. flaviviral infections), and cancer.

Accordingly, the invention provides novel compounds of formulae I, II, and III
20 as described herebelow, or a pharmaceutically acceptable salt or prodrug thereof.

The invention also provides a pharmaceutical composition comprising a compound of formula I, II, or III, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier. The composition can optionally comprise one or more additional anti-viral or anti-cancer agents.

25 The invention also provides a method for treating a viral infection in an animal comprising administering to the animal an effective amount of a compound of formula I, II, or III, or a pharmaceutically acceptable salt or prodrug thereof.

The invention also provides a method for inhibiting a viral RNA or DNA polymerase comprising contacting the polymerase (*in vitro* or *in vivo*) with an effective
30 inhibitory amount of a compound of formula I, II, or III, or a pharmaceutically acceptable salt or prodrug thereof.

The invention also provides a method for treating cancer in an animal comprising administering to the animal an effective amount of a compound of formula I, II, or III, or a pharmaceutically acceptable salt or prodrug thereof.

The invention also provides a compound of formula I, II, or III, or a
5 pharmaceutically acceptable salt or prodrug thereof, for use in medical therapy (e.g. for use in treating a viral infection or for use in treating cancer).

The invention also provides the use of a compound of formula I, II, or III, or a pharmaceutically acceptable salt or prodrug thereof, to prepare a medicament useful for treating a viral infection in an animal (e.g. a human).

10 The invention also provides the use of a compound of formula I, II, or III, or a pharmaceutically acceptable salt or prodrug thereof, to prepare a medicament useful for treating cancer in an animal (e.g. a human).

The invention also provides novel synthetic intermediates and synthetic methods that are disclosed herein as being useful for preparing compounds of formula
15 I, II, or III. Some compounds of formula I, II, and III may be useful as synthetic intermediates for preparing other compounds of formula I, II, and III.

Detailed Description of the Invention

Definitions

20 The term "pharmaceutically acceptable salt" as used herein refers to a compound of the present disclosure derived from pharmaceutically acceptable bases, inorganic or organic acids. Examples of suitable acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric,
25 methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, trifluoroacetic and benzenesulfonic acids. Salts derived from appropriate bases include, but are not limited to, alkali such as sodium and ammonia.

The terms "treat", "treating" and "treatment" as used herein include administering a compound prior to the onset of clinical symptoms of a disease
30 state/condition so as to prevent any symptom, as well as administering a compound after the onset of clinical symptoms of a disease state/condition so as to reduce or

eliminate any symptom, aspect or characteristic of the disease state/condition. Such treating need not be absolute to be useful.

The term "animal " as used herein refers to any animal, including mammals, such as, but not limited to, mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, and primates. In one specific embodiment of the invention the animal is a human.

The term "therapeutically effective amount", in reference to treating a disease state/condition, refers to an amount of a compound either alone or as contained in a pharmaceutical composition that is capable of having any detectable, positive effect on any symptom, aspect, or characteristics of a disease state/condition when administered as a single dose or in multiple doses. Such effect need not be absolute to be beneficial.

The term "alkyl" as used herein refers to alkyl groups having from 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl and the like. In a specific embodiment, the alkyl groups have from 1-4 carbon atoms and are referred to as lower alkyl.

The term "substituted alkyl" as used herein refers to an alkyl group having from 1 to 3 substituents, said substituents being selected from the group consisting of alkoxy, substituted alkoxy, acyl, substituted acyl, acylamino, acyloxy, oxyacyl, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, N₃, carboxyl, carboxyl esters, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic.

The terms "alkenyl" or "alkene" as used herein refers to an alkenyl group having from 2 to 10 carbon atoms and having at least 1 site of alkenyl unsaturation. Such groups are exemplified by vinyl(ethen-1-yl), allyl, but-3-en-1-yl, and the like.

The term "substituted alkenyl" as used herein refers to alkenyl groups having from 1 to 3 substituents, said substituents being selected from those describe above for a substituted alkyl.

The term "alkynyl" or "alkyne" as used herein refers to an alkynyl group having from 2-10 carbon atoms and having at least 1 site of alkynyl unsaturation. Such groups are exemplified by, but not limited to, ethyn-1-yl, propyn-1-yl, propyn-2-yl, 1-methylprop-2-yn-1-yl, butyn-1-yl, butyn-2-yl, butyn-3-yl, and the like.

5 The term "substituted alkynyl" as used herein refers to alkynyl groups having from 1 to 3 substituents, said substituents being selected those describe above for a substituted alkyl.

The term "alkoxy" refers to the group alkyl-O-.

10 The term "substituted alkoxy" as used herein refers to the group substituted alkyl-O-.

The term "acyl" as used herein refers to the groups alkyl-C(O) -, alkenyl-C(O) -, alkynyl-C(O) -, cycloalkyl-C(O) -, aryl-C(O) -, heteroaryl-C(O) -, and heterocyclic-C(O).

15 The term "substituted acyl" as used herein refers to the groups substituted alkyl-C(O)-, substituted alkenyl-C(O) -, substituted alkynyl-C(O) -, substituted cycloalkyl-C(O) -, substituted aryl-C (O)-, substituted heteroaryl-C(O), and substituted heterocyclic-C(O) -.

20 The term "acylamino" as used herein refers to the group-C(O)NZ₁Z₂ where each Z₁ and Z₂ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl, and the substituents described above in the definition of substituted alkyl.

25 The term "acyloxy" as used herein refers to the groups alkyl-C(O)O-, substituted alkyl- C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O-.

30 The term "oxyacyl" as used herein refers to the groups alkyl-OC(O) -, substituted alkyl-OC(O)-, alkenyl-OC(O)-, substituted alkenyl-OC(O) -, alkynyl-OC(O) -, substituted alkynyl-OC(O)-, aryl-OC(O)-, substituted aryl-OC(O)-, cycloalkyl-OC(O)-, substituted cycloalkyl-OC(O)-, heteroaryl-OC(O) -, substituted heteroaryl-OC(O) -, heterocyclic- OC(O)-, and substituted heterocyclic-OC(O)-.

The term "amino" as used herein refers to the group -NH_2 .

The term "substituted amino" as used herein refers to the group $\text{-N Z}_1\text{Z}_2$ where Z_1 and Z_2 are as described above in the definition of acylamino, provided that Z_1 and Z_2 are both not hydrogen.

5 The term "aminoacyl" as used herein refers to the groups $\text{-NZ}_3\text{C(O)alkyl}$, $\text{-NZ}_3\text{C(O)substituted alkyl}$, $\text{-NZ}_3\text{C(O)cycloalkyl}$, $\text{-NZ}_3\text{C(O)substituted cycloalkyl}$, $\text{-NZ}_3\text{C(O)alkenyl}$, $\text{-NZ}_3\text{C(O)substituted alkenyl}$, $\text{-NZ}_3\text{C(O)alkynyl}$, $\text{-NZ}_3\text{C(O)substituted alkynyl}$, $\text{-NZ}_3\text{C(O)aryl}$, $\text{-NZ}_3\text{C(O)substituted aryl}$, $\text{-NZ}_3\text{C(O)heteroaryl}$, $\text{-NZ}_3\text{C(O)substituted heteroaryl}$, $\text{-NZ}_3\text{C(O)heterocyclic}$, and $\text{-NZ}_3\text{C(O)substituted heterocyclic}$, where NZ_3 is hydrogen or alkyl.

The term "aryl" as used herein refers to a monovalent aromatic cyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) which condensed rings may or may not be aromatic. Exemplary aryls include, but are not limited to, phenyl and naphthyl.

15 The term "substituted aryl" as used herein refers to aryl groups which are substituted with from 1 to 3 substituents selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl, and those substituents described above in the definition of substituted alkyl.

The term "aryloxy" as used herein refers to the group aryl-O- that includes, by way of example but not limitation, phenoxy, naphthoxy, and the like.

The term "substituted aryloxy" as used herein refers to substituted aryl-O- groups.

The term "carboxyl" as used herein refers to -COOH or salts thereof.

25 The term "carboxyl esters" as used herein refers to the groups -C(O)O-alkyl , $\text{-C(O)O-substituted alkyl}$, -C(O)O-aryl , and $\text{-C(O)O-substituted aryl}$.

The term "cycloalkyl" as used herein refers to a saturated or unsaturated cyclic hydrocarbon ring systems, such as those containing 1 to 3 rings and 3 to 7 carbons per ring. Exemplary groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and adamantyl.

30 The term "substituted cycloalkyl" as used herein refers to a cycloalkyl having from 1 to 5 substituents selected from the group consisting of oxo ($=\text{O}$), thioxo ($=\text{S}$),

alkyl, substituted alkyl, and those substituents described in the definition of substituted alkyl.

The term "cycloalkoxy" as used herein refers to -O-cycloalkyl groups.

The term "substituted cycloalkoxy" as used herein refers to -O-substituted
5 cycloalkyl groups.

The term "formyl" as used herein refers to HC(O)-.

The term "halogen" as used herein refers to fluoro, chloro, bromo and iodo.

The term "heteroaryl" as used herein refers to an aromatic group of from 1 to
10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen,
10 nitrogen, sulfur in the ring. The sulfur and nitrogen heteroatoms atoms may also be
present in their oxidized forms. Such heteroaryl groups can have a single ring (e. g. ,
pyridyl or furyl) or multiple condensed rings (e. g. , indoliziny or benzothienyl)
wherein the condensed rings may or may not be aromatic and/or contain a heteroatom.
Exemplary heteroaryl groups include, but are not limited to, heteroaryls include
15 pyridyl, pyrrolyl, thienyl, indolyl, thiophenyl, and furyl.

The term "substituted heteroaryl" as used herein refers to heteroaryl groups that
are substituted with from 1 to 3 substituents selected from the same group of
substituents defined for substituted aryl.

The term "heteroaryloxy" as used herein refers to the group -O-heteroaryl.

The term "substituted heteroaryloxy" as used herein refers to the group -O-
20 substituted heteroaryl.

The term "heterocycle" or "heterocyclic" or "heterocycloalkyl" refers to a
saturated or unsaturated group (but not heteroaryl) having a single ring or multiple
condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from
25 the group consisting of nitrogen, oxygen, sulfur, within the ring wherein, in fused ring
systems, one or more the rings can be cycloalkyl, aryl or heteroaryl provided that the
point of attachment is through the heterocyclic ring. The sulfur and nitrogen
heteroatoms atoms may also be present in their oxidized forms.

The term "substituted heterocycle" or "substituted heterocyclic" or "substituted
30 heterocycloalkyl" refers to heterocycle groups that are substituted with from 1 to 3 of
the same substituents as defined for substituted aryl.

Examples of heterocycles and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2, 3,4-tetrahydroisoquinoline, 4,5, 6,7-tetrahydrobenzo [b] thiophene, thiazole, thiazolidine, thiophene, benzo [b] thiophene, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), piperidinyl, pyrrolidine, tetrahydrofuranlyl, and the like.

The term "heterocyclyloxy" as used herein refers to the group -O-heterocyclic.

The term "substituted heterocyclyloxy" as used herein refers to the group-O-substituted heterocyclic.

The term "phosphate" as used herein refers to the groups -OP(O)(OH)₂ (monophosphate or phospho), -OP(O)(OH)OP(O)(OH)₂ (diphosphate or diphospho) and -OP(O)(OH)OP(O)(OH)OP(O)(OH)₂ (triphosphate or triphospho) or salts thereof including partial salts thereof. It is understood that the initial oxygen of the mono-, di-, and triphosphate may include the oxygen atom of a sugar.

The term "phosphate esters" as used herein refers to the mono-, di- and tri-phosphate groups described above wherein one or more of the hydroxyl groups is replaced by an alkoxy group.

The term "phosphonate" refers to the groups -OP(O)(Z₄)(OH) or -OP(O)(Z₄)(OZ₄) or salts thereof including partial salts thereof, wherein each Z₄ is independently selected from hydrogen, alkyl, substituted alkyl, carboxylic acid, and carboxyl ester. It is understood that the initial oxygen of the phosphonate may include the oxygen of a sugar.

The term "thiol" as used herein refers to the group -SH.

The term "thioalkyl" or "alkylthioether" or "thioalkoxy" refers to the group -S-alkyl.

The term "substituted thioalkyl" or "substituted alkylthioether" or "substituted thioalkoxy" refers to the group -S-substituted alkyl.

The term "thiocycloalkyl" as used herein refers to the group -S-cycloalkyl.

The term "substituted thiocycloalkyl" as used herein refers to the group -S-substituted cycloalkyl.

The term "thioaryl" as used herein refers to the group -S-aryl.

5 The term "substituted thioaryl" as used herein refers to the group -S-substituted aryl.

The term "thioheteroaryl" as used herein refers to the group -S-heteroaryl.

The term "substituted thioheteroaryl" as used herein refers to the group -S-substituted heteroaryl.

10 The term "thioheterocyclic" as used herein refers to the group -S-heterocyclic.

The term "substituted thioheterocyclic" as used herein refers to the group -S-substituted heterocyclic.

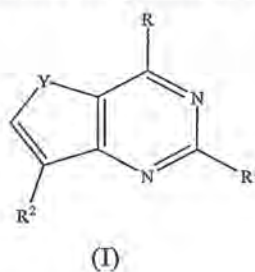
The term "amino acid sidechain" refers to the Z_7 substituent of α -amino acids of the formula $Z_6\text{NHCH}(Z_7)\text{COOH}$ where Z_7 is selected from the group consisting of hydrogen, alkyl, substituted alkyl and aryl and Z_6 is hydrogen or together with Z_7 and the nitrogen and carbon atoms bound thereto respectively form a heterocyclic ring. In one embodiment, the α -amino acid sidechain is the sidechain one of the twenty naturally occurring L amino acids.

Sugars described herein may either be in D or L configuration.

20

Compounds of formula I

Compounds of the invention include compounds of formula I:



25 wherein:

Y is O or S;

R is OR₃, SR₃, NR₃R₄, NR₃NR₄R₅, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, (CH₂)_n-CH(NHR₃)CO₂R₄, Cl, F, Br, I, CN, COOR₃, CONR₃R₄, NHC(=NR₃)NHR₄, NR₃OR₄, NR₃NO, NHCONHR₃, NR₃N=NR₄, NR₃N=CHR₄, NR₃C(O)NR₄R₅, NR₃C(S)NR₄R₅,
 5 NR₃C(O)OR₄, CH=N-OR₃, NR₃C(=NH)NR₄R₅, NR₃C(O)NR₄NR₅R₆, O-C(O)R₃, OC(O)-OR₃, ONH-C(O)O-alkyl, ONHC(O)O-aryl, ONR₃R₄, SNR₃R₄, S-ONR₃R₄, or SO₂NR₃R₄;

n is 0-5;

R¹ is H, NR₃R₄, Cl, F, OR₃, SR₃, NHCOR₃, NHSO₂R₃, NHCONHR₃, CN,
 10 alkyl, aryl, ONR₃R₄, or NR₃C(O)OR₄;

R² is a nucleoside sugar group; and

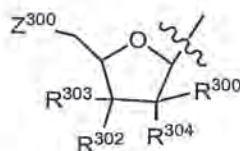
R₃, R₄, R₅, and R₆ are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, heterocyclic, aryl, substituted aryl, acyl, substituted acyl, SO₂-alkyl and
 15 NO; or R₃ and R₄ together with the nitrogen to which they are attached form a pyrrolidino, piperidino, piperazino, azetidino, morpholino, or thiomorpholino ring; or R₄ and R₅ together with the nitrogen to which they are attached form a pyrrolidino, piperidino, piperazino, azetidino, morpholino, or thiomorpholino ring;
 or a pharmaceutically acceptable salt or prodrug thereof;

20 United States Patent 4,584,369 relates to certain specific nucleosides.

Accordingly, in one embodiment, the invention excludes compounds of formula I wherein Y is S; when R is -NH₂, -OH, -SH, or -SCH₃; R¹ is hydrogen; and R² is non-phosphorylated ribose; as well as compounds of formula I wherein Y is O; when R is -NH₂; R¹ is hydrogen; and R² is non-phosphorylated ribose.

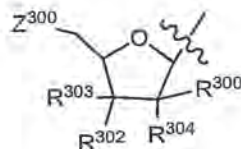
25 In another embodiment the invention excludes compounds of formula I wherein Y is S; R is -NH₂, -OH, -SH, or -SCH₃; R¹ is hydrogen; and R² is ribose; as well as compounds of formula I wherein Y is O; R is -NH₂; R¹ is hydrogen; and R² is ribose.

In another embodiment, the invention excludes compounds of formula I wherein R is -SH, -OH, -S-alkyl, -O-alkyl, or NR₃R₄; R₃ and R₄ are each H or alkyl;
 30 and R² has the following formula:



wherein: one of R^{300} and R^{304} is H and the other is H or OH; R^{302} is OH, alkyl-O-, alkylC(=O)O-, alkyl-S-, or alkylC(=O)-S-; R^{303} is H; and Z^{300} is OH, alkyl-O-, alkylC(=O)O-, alkyl-S-, or alkylC(=O)-S-.

- 5 In another embodiment, the invention excludes compounds of formula I wherein R^2 has the following formula:



- 10 wherein: one of R^{300} and R^{304} is H and the other is H or OH; R^{302} is OH, alkyl-O-, alkylC(=O)O-, alkyl-S-, or alkylC(=O)-S-; R^{303} is H; and Z^{300} is OH, alkyl-O-, alkylC(=O)O-, alkyl-S-, or alkylC(=O)-S-.

In one embodiment the invention provides a compound of formula I as described above, wherein Y is O; or a pharmaceutically acceptable salt or prodrug thereof.

- 15 In one embodiment the invention provides a compound of formula I as described above, wherein Y is S; or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment the invention provides a compound of formula I as described above, wherein R is OR_3 , Cl, SR_3 , NR_3R_4 , or $NR_3NR_4R_5$; or a

- 20 pharmaceutically acceptable salt or prodrug thereof.

In one embodiment the invention provides a compound of formula I as described above, wherein R is NR_3R_4 ; R_3 is selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, heterocyclic, aryl, substituted aryl, acyl, substituted acyl, SO_2 -alkyl and

- 25 NO; and R_4 is selected from the group consisting of H, alkyl, substituted alkyl, alkenyl,

substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, heterocyclic, aryl, substituted aryl, acyl, substituted acyl, SO₂-alkyl and NO; or R₃ and R₄ together with the nitrogen to which they are attached form a pyrrolidino, piperidino, piperazino, azetidino, morpholino, or thiomorpholino ring; or R₄ and R₅ together with the nitrogen to which they are attached form a pyrrolidino, piperidino, piperazino, azetidino, morpholino, or thiomorpholino ring.

In one embodiment the invention provides a compound of formula I as described above, wherein R is NR₃NR₄R₅, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, (CH₂)_n-CH(NHR₃)CO₂R₄, Cl, F, Br, I, CN, COOR₃, CONR₃R₄, NHC(=NR₃)NHR₄, NR₃OR₄, NR₃NO, NHCONHR₃, NR₃N=NR₄, NR₃N=CHR₄, NR₃C(O)NR₄R₅, NR₃C(S)NR₄R₅, NR₃C(O)OR₄, CH=N-OR₃, NR₃C(=NH)NR₄R₅, NR₃C(O)NR₄NR₅R₆, O-C(O)R₃, OC(O)-OR₃, ONH-C(O)O-alkyl, ONHC(O)O-aryl, ONR₃R₄, SNR₃R₄, S-ONR₃R₄, or SO₂NR₃R₄.

In one embodiment the invention provides a compound of formula I as described above, wherein R₁ is H or NR₃R₄; or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment the invention provides a compound of formula I as described above, wherein R² is a nucleoside sugar group of Group A, B, C, D, E, or F described hereinbelow; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula I as described above, wherein R² is ribose, 2-deoxyribose; 2-deoxy-2-fluororibose; arabinose; 2-deoxy-2-fluoroarabinose; 2,3-dideoxyribose; 2,3-dideoxy-2-fluoroarabinose; 2,3-dideoxy-3-fluororibose; 2,3-dideoxy-2,3-didehydroribose; 2,3-dideoxy-3-azidoribose; 2,3-dideoxy-3-thiaribose; or 2,3-dideoxy-3-oxaribose; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula I as described above, wherein R² is ribose, 2-methylribose, 2-deoxyribose; 2-deoxy-2-fluororibose; arabinose; 2-deoxy-2-fluoroarabinose; 2,3-dideoxyribose; 2,3-dideoxy-2-fluoroarabinose; 2,3-dideoxy-3-fluororibose; 2,3-dideoxy-2,3-didehydroribose; 2,3-

dideoxy-3-azidoribose; 2,3-dideoxy-3-thiaribose; or 2,3-dideoxy-3-oxaribose; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula I as described above, wherein R^2 is thioribose; 2-deoxythioribose; 2-deoxy-2-fluorothioribose; thioarabinose; 2-deoxy-2-fluorothioarabinose; 2,3-dideoxythioribose; 2,3-dideoxy-2-fluorothioarabinose; 2,3-dideoxy-3-fluorothioribose; 2,3-dideoxy-2,3-didehydrothioribose; or 2,3-dideoxy-3-azidothioribose; or a pharmaceutically acceptable salt or prodrug thereof.

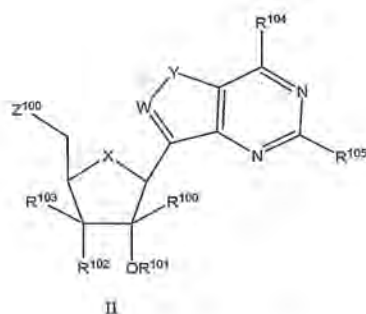
In another embodiment the invention provides a compound of formula I as described above, wherein R^2 is 4-hydroxymethylcyclopent-2-ene; 2,3-dihydroxy-4-hydroxymethylcyclopent-4-ene; 3-hydroxy-4-hydroxymethylcyclopentane; 2-hydroxy-4-hydroxymethylcyclopentene; 2-fluoro-3-hydroxy-4-hydroxymethylcyclopentane; 2,3-dihydroxy-4-hydroxymethyl-5-methylenecyclopentane; 4-hydroxymethylcyclopentane, 2,3-dihydroxy-4-hydroxymethylcyclopentane; or 2,3-dihydroxymethylcyclobutane; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula I as described above, wherein R^2 is 4-hydroxymethylpyrrolidine; 2,3-dihydroxy-4-hydroxymethylpyrrolidine; 2/3-hydroxy-4-hydroxymethylpyrrolidine; 2-fluoro-3-hydroxy-4-hydroxymethylpyrrolidine; or 3-fluoro-2-hydroxy-4-hydroxymethylpyrrolidine; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula I as described above, wherein R_3 , R_4 , R_5 , and R_6 are independently selected from the group consisting of H, alkyl, and substituted alkyl; or R_3 and R_4 together with the nitrogen to which they are attached form a pyrrolidino, piperidino, piperazino, azetidino, morpholino, or thiomorpholino ring; or R_4 and R_5 together with the nitrogen to which they are attached form a pyrrolidino, piperidino, piperazino, azetidino, morpholino, or thiomorpholino ring.

Compounds of formula II

The invention also provides novel compounds of formula II:



wherein:

- R^{100} is alkyl (1-4 carbon atom), alkenyl, or alkynyl, which R^{100} may be unsubstituted or substituted;
- 5 R^{101} is H, alkyl, $-C(O)alkyl$, or $aryl-C(=O)-$;
- R^{102} is H, OH, $-Oalkyl$, $-OC(O)alkyl$, $aryl-C(=O)-O-$, $-CH_2OH$, CH_2NH_2 , N_3 , CH_2N_3 , or NH_2 ;
- R^{103} is H, OH, or NH_2 ; provided both R^{102} and R^{103} cannot be the same group except hydrogen;
- 10 R^{104} is $NR^{110}R^{111}$, $NR^{110}-NR^{111}R^{112}$, $NR^{110}N=NR^{111}$, $NR^{110}N=CHR^{111}$, $NR^{110}N=O$, $NR^{110}C(O)NR^{111}R^{112}$, $NR^{110}C(S)NR^{111}R^{112}$, $NR^{110}C(=NH)NR^{111}R^{112}$, $NR^{110}C(O)NR^{111}NR^{112}R^{113}$, $NR^{110}OR^{111}$, $O-C(O)R^{110}$, $OC(O)-OR^{110}$, $O-NH-C(O)Oalkyl$, $ONHC(O)Oaryl$, $ONR^{110}R^{111}$, $S-NR^{110}R^{111}$, $S-ONR^{110}R^{111}$, or $SO_2NR^{110}R^{111}$;
- 15 R^{105} is H, halogen, N_3 , $NHC(O)R^{106}$, $NR^{110}R^{111}$, $NHSO_2R^{106}$, $NHCONHR^{106}$, $NH-C(S)NHR^{106}$, CH_2NHR^{106} , $NHNH_2$, CN , alkyl, alkynyl, CH_2aryl , OH, or SR^{106} ;
- R^{106} is H or alkyl;
- Z^{100} is OH, $-O-[P(=O)(OH)O-]_n-H$, $-CH_2-[P(=O)(OH)O-]_n-H$, $-O-P(=O)(R^{107})R^{108}$, $-CH_2-P(=O)(R^{107})R^{108}$, $-O-[P(=O)(R^{109})O-]_n-H$, or
- 20 $-CH_2-[P(=O)(R^{109})O-]_n-H$;
- R^{107} and R^{108} in phosphonic acid or phosphoric acid independently represent a protected or unprotected substituted or unsubstituted hydroxyl group to be decomposed under physiological conditions;
- R^{109} is a hydroxyl group that may be protected or substituted with a group to be
- 25 decomposed under physiological conditions;

R^{110} , R^{111} , R^{112} and R^{113} are independently H, alkyl, substituted alkyl, cycloalkyl, heterocyclic, alkoxy, aryl, substituted aryl, acyl, substituted acyl, SO_2 -alkyl, NH_2 , OH or NO;

R^{114} is H, alkyl, substituted alkyl, $C(O)R^{109}$, aryl, substituted aryl, or
 5 heterocycle;

n is 0-3;

X is O, S, NH, or CH_2 ;

W is CHR^{114} , N, or CH-halo;

Y is O, S, or NR^{114} ; and

10 or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment the invention provides a compound of formula II as described above, wherein Y is O or S; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula II as
 15 described above, wherein R^{101} is H, alkyl, $-C(O)$ alkyl, or benzoyl; and R^{102} is H, OH, Oalkyl, $-OC(O)$ alkyl, benzoyl-O-, $-CH_2OH$, CH_2NH_2 , N_3 , CH_2N_3 , or NH_2 ; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula II as described above, wherein Y is O or S; R^{101} is H, alkyl, $-C(O)$ alkyl, or benzoyl; and R^{102}
 20 is H, OH, Oalkyl, $-OC(O)$ alkyl, benzoyl-O-, $-CH_2OH$, CH_2NH_2 , N_3 , CH_2N_3 , or NH_2 ; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula II as described above, wherein Y is O or S; and W is CR^{114} , N, or C-halo; or a pharmaceutically acceptable salt or prodrug thereof.

25 In another embodiment the invention provides a compound of formula II as described above wherein Y is O or S; Z^{100} is OH, $-O-[P(=O)(OH)O-]_n-H$, $-CH_2-[P(=O)(OH)O-]_n-H$, $-O-P(=O)(R^{107})R^{108}$, $-CH_2-P(=O)(R^{107})R^{108}$, $-O-[P(=O)(R^{109})O-]_n-H$, or $-CH_2-[P(=O)(R^{109})O-]_n-H$; and R^{107} and R^{108} are each H; or a pharmaceutically acceptable salt or prodrug thereof.

30 In another embodiment the invention provides a compound of formula II as described above wherein Y is O or S; Z^{100} is OH, $-O-[P(=O)(OH)O-]_n-H$, $-CH_2-$

$[P(=O)(OH)O-]_n-H$, $-O-P(=O)(R^{107})R^{108}$, $-CH_2-P(=O)(R^{107})R^{108}$, $-O-[P(=O)(R^{109})O-]_n-H$, or $-CH_2-[P(=O)(R^{109})O-]_n-H$; W is CR^{114} , N, or C-halo; and R^{107} and R^{108} are each H; or a pharmaceutically acceptable salt or prodrug thereof.

- In another embodiment the invention provides a compound of formula II as described above wherein R^{100} is alkyl; R^{101} is H; R^{102} is OH; R^{103} is H; R^{104} is $NR^{110}R^{111}$ or $NR^{110}-NR^{111}R^{112}$; R^{105} is H or NH_2 ; R^{110} , R^{111} , R^{112} and R^{113} are independently H, alkyl, substituted alkyl, or cycloalkyl; and Z^{100} is OH.

For a compound of formula II, a specific value for R^{100} is alkyl.

For a compound of formula II, a specific value for R^{101} is H.

- 10 For a compound of formula II, a specific value for R^{102} is OH.

For a compound of formula II, a specific value for R^{103} is H.

For a compound of formula II, a specific value for R^{104} is $NR^{110}R^{111}$ or $NR^{110}-NR^{111}R^{112}$.

For a compound of formula II, a specific value for R^{105} is H or NH_2 .

- 15 For a compound of formula II, a specific value for R^{107} is OH.

For a compound of formula II, a specific value for R^{108} is OH.

For a compound of formula II, a specific value for R^{110} , R^{111} , R^{112} and R^{113} are independently H, alkyl, substituted alkyl, or cycloalkyl.

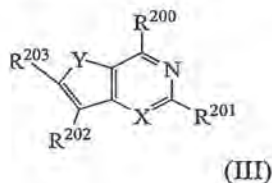
For a compound of formula II, a specific value for Z^{100} is OH.

- 20 For a compound of formula II, a specific value for Z^{100} is $-O-[P(=O)(OH)O-]_n-H$, $-O-P(=O)(R^{107})R^{108}$, or $-O-[P(=O)(R^{109})O-]_n-H$.

For a compound of formula II, a specific value for Z^{100} is $-CH_2-[P(=O)(R^{109})O-]_n-H$.

25 Compounds of formula III

The invention also provides novel compounds of formula III:



wherein:

X is N or CH;

Y is O, S or N-R²⁰⁴;

R²⁰⁰ is OR²⁰⁵, OH, NHR²⁰⁴, NR²⁰⁴R²⁰⁵, NHNHR²⁰⁴, NR²⁰⁴NHR²⁰⁵, SR²⁰⁵, SH, alkyl, aryl, Cl, NR²⁰⁴OR²⁰⁵, NR²⁰⁴NO, or NHCONHR²⁰⁴;

5 R²⁰¹ is H, NHR²⁰⁴, Cl, F, OR²⁰⁴, SR²⁰⁴, NHCOR²⁰⁴, NHSO₂R²⁰⁴, NHCONHR²⁰⁴, CN, alkyl, aryl, or NR²⁰⁴R²⁰⁵;

R²⁰² is a substituted alkyl, moiety from a sugar with the proviso that when Y= NH or S and R²⁰⁰ is NH₂, OH, SH, alkylamino, alkylloxy, or alkylthio, the sugar moiety can not be from ribose or 2-deoxyribose; a moiety from a thio sugar; hydroxyl
10 substituted cycloalkanes; or hydroxyl substituted 5-pyrrolidine moieties;

R²⁰³ is H, alkyl, aryl, F, Cl, CN, CO₂H or NH₂;

R²⁰⁴ is H, OH, alkyl, aryl, -COO-alkyl, CONH₂, CONH-alkyl, O-C(O)-alkyl, O-C(O)-aryl or alkoxy; and

R²⁰⁵ is alkyl, aryl, OH or alkoxy;

15 and pharmaceutically acceptable salts thereof and prodrugs thereof.

In one embodiment the invention provides a compound of formula III as described above, wherein Y is O or S; or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment the invention provides a compound of formula III as
20 described above, wherein R²⁰⁰ is OR²⁰⁵, NHR²⁰⁴, NR²⁰⁴R²⁰⁵, NHNHR²⁰⁴, NR²⁰⁴NHR²⁰⁵, SR²⁰⁵, alkyl, aryl, Cl, NR²⁰⁴OR²⁰⁵, NR²⁰⁴NO, or NHCONHR²⁰⁴.

In one embodiment the invention provides a compound of formula III as described above, wherein R²⁰² is a nucleoside sugar group; or a pharmaceutically acceptable salt or prodrug thereof.

25 In another embodiment the invention provides a compound of formula III as described above, wherein R²⁰² is ribose, 2-deoxyribose; 2-deoxy-2-fluororibose; arabinose; 2-deoxy-2-fluoroarabinose; 2,3-dideoxyribose; 2,3-dideoxy-2-fluoroarabinose; 2,3-dideoxy-3-fluororibose; 2,3-dideoxy-2,3-didehydroribrose; 2,3-dideoxy-3-azidoribose; 2,3-dideoxy-3-thiaribose; or 2,3-dideoxy-3-oxaribose.

30 In another embodiment the invention provides a compound of formula III as described above, wherein R²⁰² is ribose, 2-methylribose, 2-deoxyribose; 2-deoxy-2-

fluororibose; arabinose; 2-deoxy-2-fluoroarabinose; 2,3-dideoxyribose; 2,3-dideoxy-2-fluoroarabinose; 2,3-dideoxy-3-fluororibose; 2,3-dideoxy-2,3-didehydroribose; 2,3-dideoxy-3-azidoribose; 2,3-dideoxy-3-thiaribose; or 2,3-dideoxy-3-oxaribose.

In another embodiment the invention provides a compound of formula III as
5 described above, wherein R^{202} is thioribose, 2-deoxythioribose; 2-deoxy-2-fluorothioribose; thioarabinose; 2-deoxy-2-fluorothioarabinose; 2,3-dideoxythioribose; 2,3-dideoxy-2-fluorothioarabinose; 2,3-dideoxy-3-fluorothioribose; 2,3-dideoxy-2,3-didehydrothioribose; or 2,3-dideoxy-3-azidothioribose.

In another embodiment the invention provides a compound of formula III as
10 described above, wherein R^{202} is 4-hydroxymethylcyclopent-2-ene; 2,3-dihydroxy-4-hydroxymethylcyclopent-4-ene; 3-hydroxy-4-hydroxymethylcyclopentane; 2-hydroxy-4-hydroxymethylcyclopentene; 2-fluoro-3-hydroxy-4-hydroxymethylcyclopentane; 2,3-dihydroxy-4-hydroxymethyl-5-methylenecyclopentane; 4-hydroxymethylcyclopentane, 2,3-dihydroxy-4-hydroxymethylcyclopentane; or 2,3-dihydroxymethylcyclobutane.
15

In another embodiment the invention provides a compound of formula III as described above, wherein R^{202} is 4-hydroxymethylpyrrolidine; 2,3-dihydroxy-4-hydroxymethylpyrrolidine; 2/3-hydroxy-4-hydroxymethylpyrrolidine; 2-fluoro-3-hydroxy-4-hydroxymethylpyrrolidine; or 3-fluoro-2-hydroxy-4-hydroxymethylpyrrolidine.
20

In another embodiment the invention provides a compound of formula III as described above, wherein X is N; Y is NH; R^{200} is NH_2 ; R^{201} is H; and R^{203} is H; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula III as
25 described above, wherein X is N; Y is NH; R^{200} is OH; R^{201} is H; and R^3 is H; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula III as described above, wherein X is N; Y is S; R^{200} is NH_2 ; R^{201} is H; and R^{203} is H; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula III as described above, wherein X is N; Y is O; R²⁰⁰ is NH₂; R²⁰¹ is H; and R²⁰³ is H; or a pharmaceutically acceptable salt or prodrug thereof.

5 In another embodiment the invention provides a compound of formula III as described above, wherein X is N; Y is O; R²⁰⁰ is Cl, SH or S-alkyl; R²⁰¹ is H; and R²⁰³ is H; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula III as described above, wherein X is N; Y is O; R²⁰⁰ is Cl; R²⁰¹ is H; and R²⁰³ is H; or a pharmaceutically acceptable salt or prodrug thereof.

10 In another embodiment the invention provides a compound of formula III as described above, wherein X is N; Y is O, S or NH; R²⁰⁰ is OH; R²⁰¹ is NH₂; and R²⁰³ is H; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula III as described above, wherein X is N; Y is O, S or NH; R²⁰⁰ is NHR²⁰⁴, NR²⁰⁴R²⁰⁵, aryl, 15 NR²⁰⁴OR²⁰⁵, NR²⁰⁴NHR²⁰⁵, NHNHR²⁰⁴, SR²⁰⁵ or OR²⁰⁵; R²⁰¹ is H, and R²⁰³ is H; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula III as described above, wherein X is CH; Y is O, NH or S; R²⁰⁰ is Cl, aryl, NHR²⁰⁴, NR²⁰⁴R²⁰⁵, OR²⁰⁵, SR²⁰⁵, NHNHR²⁰⁴, NR²⁰⁴NHR²⁰⁵, or NR²⁰⁴OR²⁰⁵; R²⁰¹ is H, and R²⁰³ 20 is H; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula III as described above, wherein X is N; Y is O, S or NH; R²⁰⁰ is NH₂; R²⁰¹ is H, R²⁰² is any alkyl group containing hydroxyl; and R²⁰³ is H; or a pharmaceutically acceptable salt or prodrug thereof.

25 In another embodiment the invention provides a compound of formula III as described above, wherein: X is N; Y is O or S; R²⁰⁰ is OR²⁰⁵, NHR²⁰⁴, NR²⁰⁴R²⁰⁵, NHNHR²⁰⁴, NR²⁰⁴NHR²⁰⁵, SR²⁰⁵, or Cl; R²⁰¹ is H or NHR²⁰⁴; R²⁰² is a substituted alkyl, moiety from a sugar with the proviso that when Y= NH or S and R²⁰⁰ is NH₂, OH, SH, alkylamino, alkyloxy, or alkylthio, the sugar moiety can not be from ribose or 30 2-deoxyribose; a moiety from a thio sugar; hydroxyl substituted cycloalkanes; or

hydroxyl substituted 5-pyrrolidine moieties; R^{203} is H; R^{204} is H, or alkyl; and R^{205} is alkyl; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of formula III as described above, wherein: X is N; Y is O or S; R^{200} is OR^{205} , NHR^{204} , $NR^{204}R^{205}$, $NHNHR^{204}$, $NR^{204}NHR^{205}$, SR^{205} , or Cl; R^{201} is H or NHR^{204} ; R^{202} is a nucleoside sugar group with the proviso that when Y=NH or S and R^{200} is NH_2 , OH, SH, alkylamino, alkyloxy, or alkylthio, the sugar moiety is not ribose or 2-deoxyribose; R^{203} is H; R^{204} is H, or alkyl; and R^{205} is alkyl; or a pharmaceutically acceptable salt or prodrug thereof.

10 For a compound of formula III, a specific value for X is N.

For a compound of formula III, a specific value for Y is O or S.

For a compound of formula III, a specific value for R^{200} is OR^{205} , NHR^{204} , $NR^{204}R^{205}$, $NHNHR^{204}$, $NR^{204}NHR^{205}$, SR^{205} , or Cl.

For a compound of formula III, a specific value for R^{201} is H or NHR^{204} .

15 For a compound of formula III, a specific value for R^{202} is a substituted alkyl, moiety from a sugar.

For a compound of formula III, a specific value for R^{203} is H, alkyl, aryl, F, Cl, CN, CO_2H or NH_2 .

20 Prodrugs

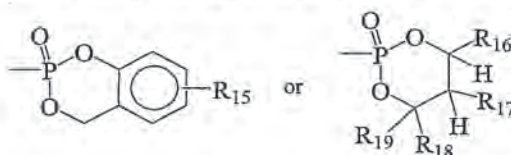
The term "prodrug" as used herein refers to a compound that can be metabolized *in vivo* to provide a compound of formula I, II, or III. Thus prodrugs include compounds that can be prepared by modifying one or more functional groups in a compound of formula I, II, or II, to provide a corresponding compound that can be metabolized *in vivo* to provide a compound of formula I, II, or III. Such modifications are known in the art. For example, one or more hydroxy groups or amine groups in a compound of formula I, II, or III, can be acylated with alkyl-C(=O)-groups or with residues from amino acids to provide a prodrug. Alternatively, one or more pendent hydroxyl groups from a mono-, di-, or tri-phosphate functionality in a compound of formula I, II, or III can be converted to an alkoxy, substituted alkoxy, aryloxy, or substituted aryloxy group.

In one embodiment, the term prodrug includes a compound wherein one or more hydroxy groups on a nucleoside sugar group (e.g. a 2', 3', or 5' hydroxy group) have been converted to a group that can be metabolized *in vivo* to provide a compound of formula I, II, or III. For example, the invention provides a compound wherein one or more hydroxy groups on a nucleoside sugar group (e.g. a 2', 3', or 5' hydroxy group) have been converted to an acyloxy, acylamino or R-O group, wherein R is a carboxy-linked amino acid.

In one embodiment, the term prodrug includes a compound wherein one or more pendent hydroxyl groups from a mono-, di-, or tri-phosphate functionality in a compound of formula I, II, or III is converted to a group R_y-O-; wherein each R_y is independently a 1-20 carbon branched or unbranched, saturated or unsaturated chain, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced with -O- or -S- and wherein one or more of the carbon atoms is optionally substituted with oxo (=O) or thioxo (=S) (See Lefebvre et al., J. Med. Chem. 1995, 38, 3941-50).

In another embodiment, the term prodrug includes a compound wherein one or more pendent hydroxyl groups from a mono-, di-, or tri-phosphate functionality in a compound of formula I, II, or III is converted to a group R_z-N-; wherein each R_z is a residue of an amino acid. Thus, in the methods of treatment of the present invention, the term "administering" includes administration of a compound of formula I, II, or III, as well as administration of a prodrug which converts to a compound of formula I, II, or III or a salt thereof *in vivo*. Conventional procedures for the selection and preparation of prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985; and in International Patent Application Publication Number WO 2005/084192. A variety of prodrugs are also described in International Patent Application Number PCT US2004/013063, which was published as International Publication Number WO 2004/096286.

In another embodiment the prodrug comprises one of more groups of formula:



wherein:

R₁₅ is H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, and an amino acid;

- 5 R₁₆ is H, optionally substituted monocyclic aryl, or optionally substituted monocyclic heteroaryl; and R₁₇ is H, halogen, CN, -CO-R₂₀, -CON(R₂₁)₂, -CO₂R₂₀, -SO₂R₂₀, -SO₂N(R₂₁)₂, -OR₂₁, -SR₂₁, -R₂₁, -N(R₂₁)₂, -O-COR₂₀, -O-CO₂R₂₀, -SCOR₂₀, -S-CO₂R₂₀, -NHCOR₂₁, -NHCO₂R₂₁, -(CH₂)_p-OR₂₂, or -(CH₂)_p-SR₂₂; or R₁₆ and R₁₇ are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one
10 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus; or R₁₇ and R₁₈ are connected as described below;

- R₁₈ and R₁₉ are each independently H, alkyl, aryl, heterocycloalkyl, aralkyl, optionally substituted monocyclic aryl or optionally substituted monocyclic heteroaryl; or R₁₈ and R₁₉ are connected via an additional 2-5 atoms to form a cyclic group,
15 optionally containing 0-2 heteroatoms; or R₁₇ and R₁₈ are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom and R₁₉ is H, alkyl, aryl, heterocycloalkyl, aralkyl, optionally substituted monocyclic aryl or optionally substituted monocyclic heteroaryl; and

- R₂₀ is alkyl, aryl, heterocycloalkyl, or arylalkyl;
20 R₂₁ is H, alkyl, aryl, heterocycloalkyl, or arylalkyl;
R₂₂ is H or lower acyl;
n is an integer from 2-5;
m is an integer from 10-20; and
p is an integer from 2-3.

- 25 Prodrug forms of a compound bearing various nitrogen functions (amino, hydroxyamino, amide, etc.) may include the following types of derivatives where each R_p group individually may be hydrogen, substituted or unsubstituted alkyl, aryl, alkenyl, alkynyl, heterocycle, alkylaryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl or cycloalkenyl groups as defined earlier.

- 30 (a) Carboxamides, represented as -NHC(O)R_p
(b) Carbamates, represented as -NHC(O)OR_p

- (c) (Acyloxy)alkyl Carbamates, represented as NHC(O)OROC(O)R_p
- (d) Enamines, represented as $-\text{NHCR}(=\text{CHCO}_2\text{R}_p)$ or $-\text{NHCR}(=\text{CHCONR}_p\text{R}_p)$
- (e) Schiff Bases, represented as $-\text{N}=\text{CR}_p\text{R}_p$
- 5 (f) Mannich Bases (from carboximide compounds), represented as $\text{RCONHCH}_2\text{NR}_p\text{R}_p$

Preparations of such prodrug derivatives are discussed in various literature sources (examples are: Alexander *et al.*, J. Med. Chem. 1988, 31, 318; Aligas-Martin *et al.*, PCT WO0041531, p.30).

- 10 Prodrug forms of carboxyl-bearing compounds include esters $(-\text{CO}_2\text{R}_m)$ where the R_m group corresponds to any alcohol whose release in the body through enzymatic or hydrolytic processes would be at pharmaceutically acceptable levels. Another prodrug derived from a carboxylic acid form of the disclosure may be a quaternary salt type of structure described by Bodor *et al.*, J. Med.
- 15 Chem. 1980, 23, 469.



25

Nucleoside Sugar Groups

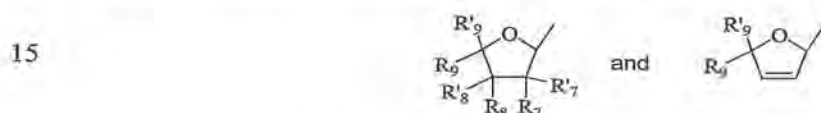
- The term "nucleoside sugar group" as used herein includes cyclic and acyclic groups that can be included as the sugar portion of a nucleoside analog of formula I, II, or III. Many examples of such groups are known in the field of nucleoside chemistry
- 30 (See for example Antiviral Drugs by John S. Driscoll (2002) published by Ashgate Publishing Ltd.).

- The term nucleoside sugar group includes substituted and unsubstituted tetrahydrofuranyl and dihydrofuranyl compounds including those set forth in group (A) below, substituted and unsubstituted tetrahydrothiophenyl and dihydrothiophenyl
- 35 compounds including those set forth in group (B) below, substituted and unsubstituted

alkyl compounds including those set forth in group (C) below, substituted and unsubstituted cycloalkyl and cycloalkenyl compounds including those set forth in group (D) below, substituted and unsubstituted dihydropyrrolidinyl and tetrahydropyrrolidinyl compounds including those set forth in group (E) below, and substituted and unsubstituted dioxolane, substituted and unsubstituted thioxolane, and substituted and unsubstituted dithiolane compounds including those set forth in group (F) below.

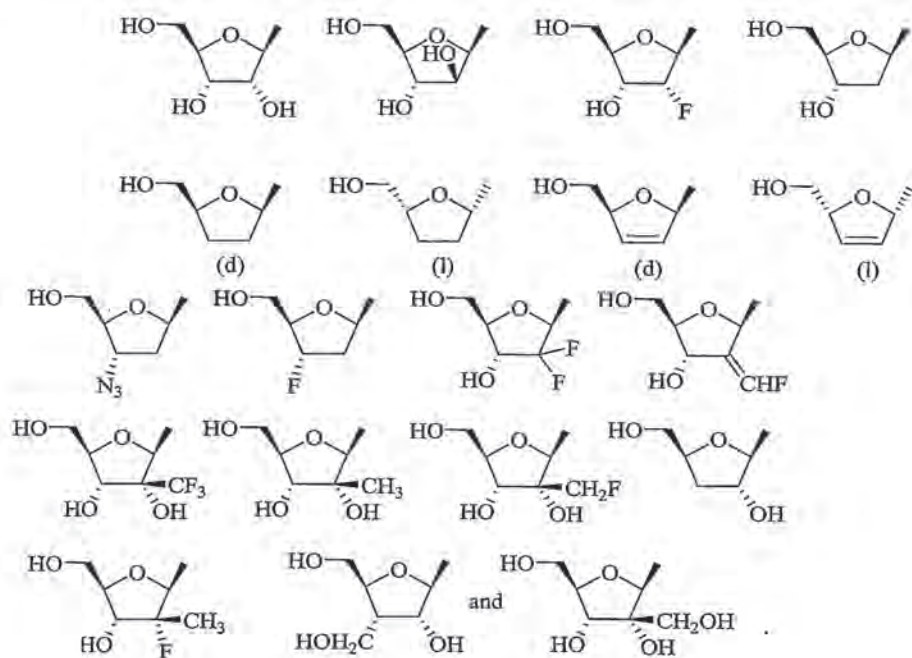
Group A

Examples of substituted tetrahydro and dihydrofuranyl compounds include those compounds represented by the general structures:



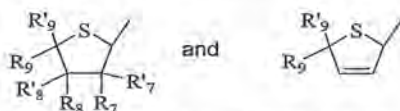
Specific examples include, but are not limited to, the following compounds:

20

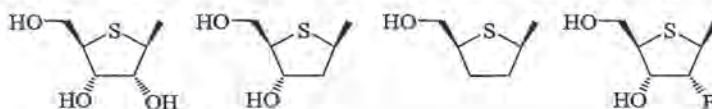
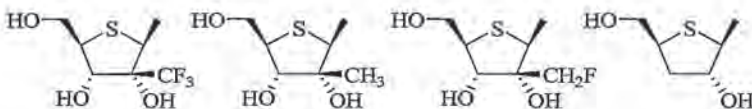
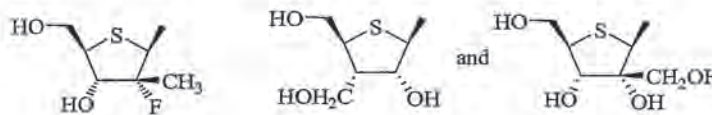


Group B

Examples of substituted tetrahydrothiophenyl and dihydrothiophenyl compounds include those compounds represented by the general structures:

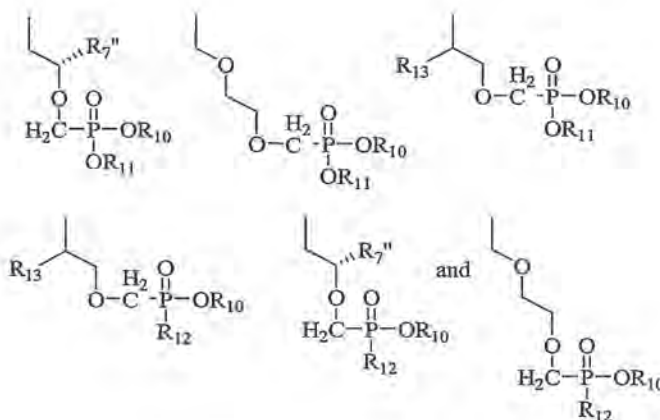


10 Specific examples include, but are not limited to, the following compounds:

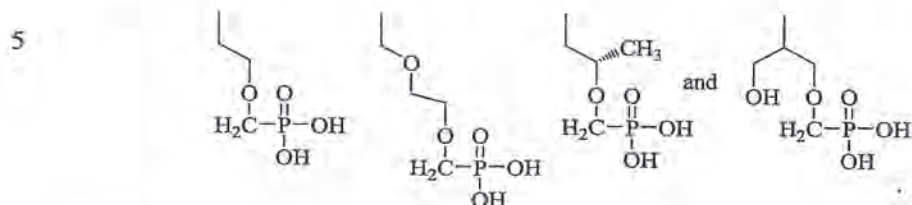


Group C

30 Examples of substituted alkyl compounds include those compounds represented by:

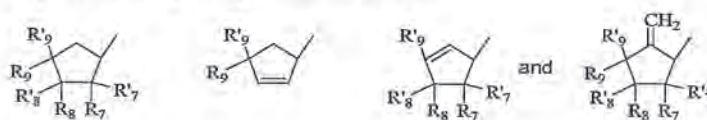


Specific examples include, but are not limited to, the following compounds:

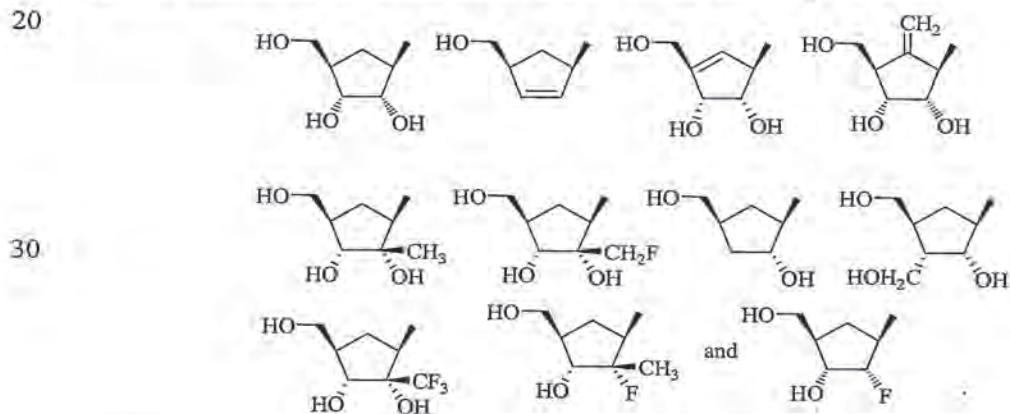


Group D

15 Examples of substituted cycloalkyl and cycloalkenyl compounds include those compounds represented by the general structures:

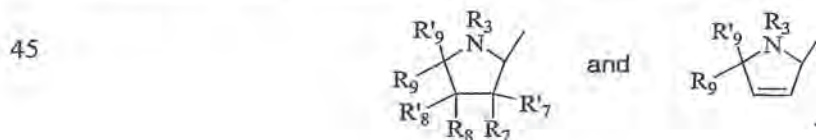


Specific examples include, but are not limited to, the following compounds:

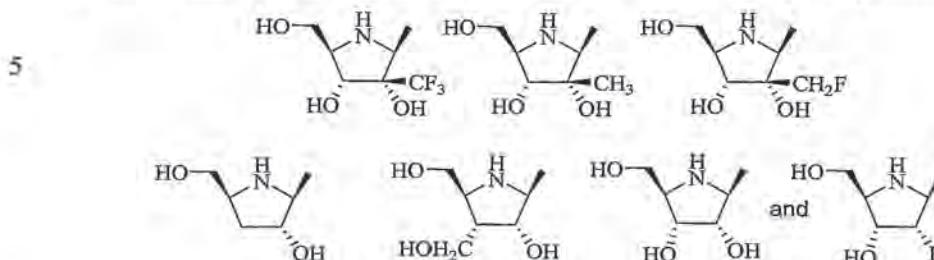


Group E

40 Examples of substituted dihydropyrrolidinyl and tetrahydropyrrolidinyl compounds include those compounds represented by the general structures:

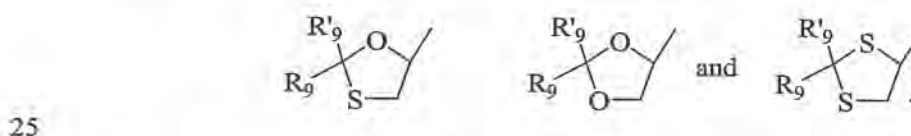


Specific examples include, but are not limited to, the following compounds:

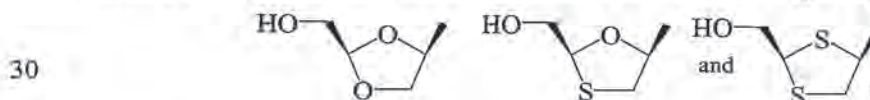


15 Group F

Examples of substituted dioxolane, substituted thioxolane and substituted dithiolane compounds include those compounds represented by the general structures:



Specific examples include, but are not limited to, the following compounds:



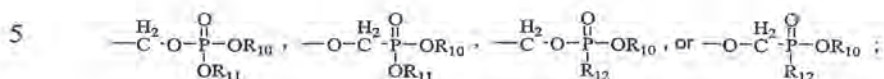
For the structures in Groups A-F, the following definitions apply:

35 R_7 is H, OR_{14} , N_3 , NH_2 , or F; and R'_7 is H, F, OH, O-alkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl; or R_7 and R'_7 together may be $=CH_2$, $=CHF$; wherein both R_7 and R'_7 are not OH; and when one of R_7 and R'_7 is NH_2 , the other is not OH; and when one of R_7 and R'_7 is N_3 , the other is not OH; R_7'' is alkyl or substituted alkyl.

40 R_8 is H, OR_{14} , N_3 , NH_2 , or F; and R'_8 is H, F, OH, O alkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl; or R_8 and R'_8 together may be $=CH_2$, $=CHF$; wherein both R_8 and R'_8 are not OH; and when one of R_8 and R'_8 is NH_2 , the other is not OH; and when one of R_8 and R'_8 is N_3 , the other is not OH;

R_9 is H, CH_3 , C_2H_5 , or N_3 ;

R'_9 is $\text{CH}_2\text{OR}_{14}$, CH_2F , CH_2SH , CHFOH , CF_2OH ,



R_{10} and R_{11} are each independently H, alkyl, aryl, substituted aryl, acyloxyalkyl, or $(\text{CH}_2)_n\text{-O-(CH}_2)_m\text{CH}_3$;

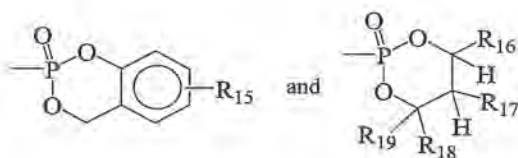
10 R_{12} is an N-linked amino acid residue (e.g. $-\text{NH-CH}(\text{CH}_3)\text{CO}_2\text{alkyl}$ or $-\text{NH-CH}(\text{isopropyl})\text{-CO}_2\text{alkyl}$);

R_{13} is H, CH_3 , C_2H_5 , CH_2F , CH_2OH , $\text{CH}_2\text{CH}_2\text{F}$, $\text{CH}_2\text{CH}_2\text{OH}$, CH_2N_3 , $\text{CH}_2\text{CH}_2\text{N}_3$, CH_2NH_2 , or $\text{CH}_2\text{CH}_2\text{NH}_2$; and

R_{14} is H.

15 In one embodiment, for a compound of formula I, R_{14} is replaced to form a pharmaceutically acceptable prodrug, for example, a prodrug selected from the group consisting of: acyl, oxyacyl, phosphonate, phosphate, phosphate esters, phosphoramidate, phosphorodiamidate, phosphoramidate mono ester, cyclic phosphoramidate, cyclic phosphorodiamidate, phosphoramidate diester, $\text{C}(\text{O})$

20 $\text{CHR}_{15}\text{NH}_2$,



wherein:

R_{15} is H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, or

25 an amino acid;

R_{16} is H, optionally substituted monocyclic aryl, or optionally substituted monocyclic heteroaryl; and R_{17} is H, halogen, CN, $-\text{CO-R}_{20}$, $-\text{CON}(\text{R}_{21})_2$, $-\text{CO}_2\text{R}_{20}$, $-\text{SO}_2\text{R}_{20}$, $-\text{SO}_2\text{N}(\text{R}_{21})_2$, $-\text{OR}_{21}$, $-\text{SR}_{21}$, $-\text{R}_{21}$, $-\text{N}(\text{R}_{21})_2$, $-\text{O-COR}_{20}$, $-\text{O-CO}_2\text{R}_{20}$, $-\text{SCOR}_{20}$, $-\text{S-CO}_2\text{R}_{20}$, $-\text{NHCOR}_{21}$, $-\text{NHCO}_2\text{R}_{21}$, $-(\text{CH}_2)_p\text{-OR}_{22}$, or $-(\text{CH}_2)_p\text{-SR}_{22}$; or R_{16} and R_{17} are

30 connected via an additional 3-5 atoms to form a cyclic group, optionally containing one

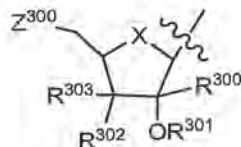
heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus; or R₁₇ and R₁₈ are connected as described below;

R₁₈ and R₁₉ are each independently H, alkyl, aryl, heterocycloalkyl, aralkyl, optionally substituted monocyclic aryl or optionally substituted monocyclic heteroaryl;

- 5 or R₁₈ and R₁₉ are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms; or R₁₇ and R₁₈ are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom and R₁₉ is H, alkyl, aryl, heterocycloalkyl, aralkyl, optionally substituted monocyclic aryl or optionally substituted monocyclic heteroaryl; and

- 10 R₂₀ is alkyl, aryl, heterocycloalkyl, or arylalkyl;
 R₂₁ is H, alkyl, aryl, heterocycloalkyl, or arylalkyl;
 R₂₂ is H or lower acyl;
 n is an integer from 2-5;
 m is an integer from 10-20; and
 15 p is an integer from 2-3.

In one embodiment of the invention, R² has the following formula:

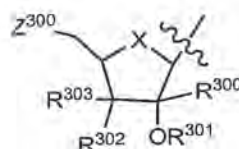


wherein:

- 20 R³⁰⁰ is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;
 R³⁰¹ is H, alkyl, -C(O)alkyl, or aryl-C(=O)-;
 R³⁰² is H, OH, -Oalkyl, -OC(O)alkyl, benzoyloxy, -CH₂OH, CH₂NH₂, N₃, CH₂N₃, or NH₂;
 25 R³⁰³ is H, OH, or NH₂; provided both R³⁰² and R³⁰³ cannot be the same group except hydrogen;
 X is O, S, NH or CH₂;

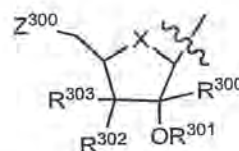
Z^{300} is $-O-[P(=O)(R^{307})O-]_n-R^{308}$, or $-CH_2-[P(=O)(R^{307})O-]_n-R^{308}$;
 each R^{307} is independently OH, -Oalkyl, or -OC(O)alkyl;
 each R^{308} is independently H, alkyl, or -C(O)alkyl; and
 n is 0, 1, 2, or 3.

5 In one embodiment of the invention, R^2 has the following formula:



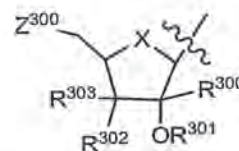
wherein: R^{300} is H or methyl; R^{301} is H; R^{302} is OH; R^{303} is H; X is O, S, NH or CH_2 ; Z^{300}
 is $-O-[P(=O)(R^{307})O-]_n-R^{308}$, or $-CH_2-[P(=O)(R^{307})O-]_n-R^{308}$, each R^{307} is OH; each R^{308}
 10 is H; and n is 0, 1, 2, or 3.

In another embodiment of the invention, R^2 has the following formula:



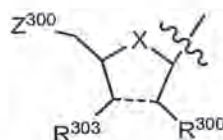
wherein: R^{300} is H or alkyl; R^{301} is H, alkyl, or benzoyl; R^{302} is OH, or benzyloxy, R^{303}
 15 is H; X is O, S, NH or CH_2 ; Z^{300} is $-O-[P(=O)(R^{307})O-]_n-R^{308}$, or $-CH_2-[P(=O)(R^{307})O-]_n-$
 R^{308} , each R^{307} is OH; each R^{308} is H; and n is 0, 1, 2, or 3.

In another embodiment of the invention, R^2 has the following formula:



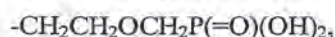
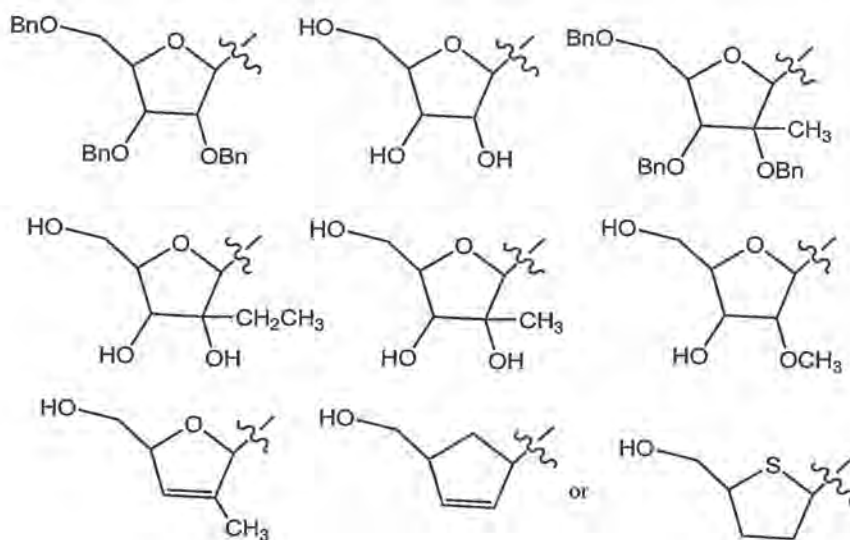
20 wherein: R^{300} is H or methyl; R^{301} is H, methyl, or benzoyl; R^{302} is OH, or benzyloxy,
 R^{303} is H; X is O, S, NH or CH_2 ; Z^{300} is $-O-[P(=O)(R^{307})O-]_n-R^{308}$, or
 $-CH_2-[P(=O)(R^{307})O-]_n-R^{308}$; each R^{307} is OH; each R^{308} is H; and n is 0, 1, 2, or 3.

In another embodiment of the invention, R^2 has the following formula:



- wherein: R^{300} is H or alkyl; R^{303} is H or alkyl; the bond represented by --- is a single or a double bond; X is O, S, NH or CH_2 ; Z^{300} is $-O-[P(=O)(R^{307})O-]_n-R^{308}$, or
- 5 $-CH_2-[P(=O)(R^{307})O-]_n-R^{308}$; each R^{307} is OH; each R^{308} is H; and n is 0, 1, 2, or 3.

In another embodiment of the invention, R^2 has the formula:



10

Synthetic Processes

- Processes for preparing compounds of formula I, II, and III or pharmaceutically acceptable salts or prodrugs thereof, as well as processes for preparing intermediate
- 15 compounds that can be used to prepare compounds of formula I, II, or III or pharmaceutically acceptable salts or prodrugs thereof are provided as further embodiments of the invention. For example in one embodiment the invention provides

a method for preparing a pharmaceutically acceptable salt of compound of formula I, II, or III, comprising converting a corresponding compound of formula I, II, or III to the salt.

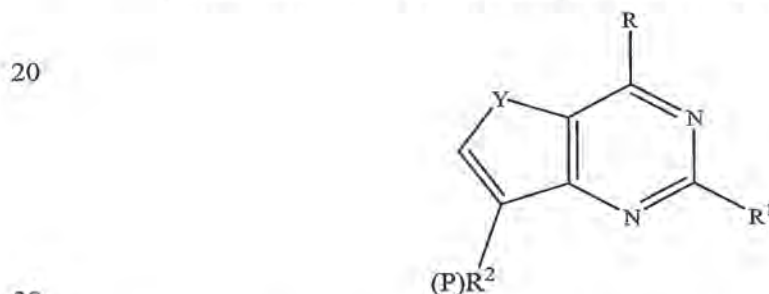
In another embodiment the invention provides a method for preparing a prodrug of a compound of formula I, II, or III, comprising converting a corresponding compound of formula I, II, or III to the prodrug.

In another embodiment the invention provides a method for preparing a compound of formula I, II, or III, comprising deprotecting a corresponding compound of formula I, II, or III that comprises one or more protecting groups to provide the compound of formula I, II, or III.

Synthetic Intermediates

The invention also provides synthetic intermediates that are useful for preparing compounds of formula I, II, or III. For example, the invention provides novel synthetic intermediates such as those described in the Examples herein.

In one embodiment the invention provides a compound of formula:



wherein: R is chloro or bromo; R¹ and Y have any of the values defined herein; and (P)R² is a nucleoside sugar group bearing one or more protecting groups.

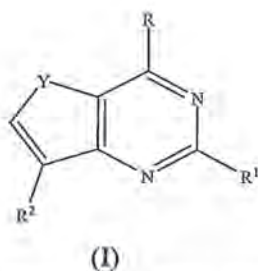
In one embodiment, the invention provides the compound: 2-(3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-tetrahydrofuran-2-yl)acetonitrile; 2-(6-((tert-Butyldiphenylsilyloxy)methyl)-2,2,3a-trimethyl-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)acetonitrile; 2-(3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methyl-tetrahydrofuran-2-yl)acetonitrile;

- 2-(3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methyl-tetrahydrofuran-2-yl)acetonitrile; 2-(4-(Benzyloxy)-5-(benzyloxymethyl)-3-methoxy-tetrahydrofuran-2-yl)acetonitrile; 2-(3-Methyl-5-(trityloxymethyl)-2,5-dihydrofuran-2-yl)acetonitrile; 2-(3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-3-ethyl-tetrahydrofuran-2-yl)acetonitrile;
- 5 Ethyl 3-amino-4-(3,4-bis(benzyloxy)-5-(benzyloxymethyl)-tetrahydrofuran-2-yl)furan-2-carboxylate; 3-Amino-4-(3,4-bis(benzyloxy)-5-(benzyloxymethyl)-tetrahydrofuran-2-yl)furan-2-carbonitrile; Ethyl 3-amino-4-(3,4-bis(benzyloxy)-5-(benzyloxymethyl)-3-methyl-tetrahydrofuran-2-yl)furan-2-carboxylate; 3-Amino-4-(3,4-bis(benzyloxy)-5-(benzyloxymethyl)-3-methyl-tetrahydrofuran-2-yl)furan-2-carbonitrile; 3-Amino-4-
- 10 (3,4-bis(benzyloxy)-5-(benzyloxymethyl)-3-vinyl-tetrahydrofuran-2-yl)furan-2-carbonitrile; 3-Amino-4-(3,4-bis(benzyloxy)-5-(benzyloxymethyl)-3-ethyl-tetrahydrofuran-2-yl)furan-2-carbonitrile; 3-Amino-4-(3,4-bis(benzyloxy)-5-(benzyloxymethyl)-3-(hydroxymethyl)-tetrahydrofuran-2-yl)furan-2-carbonitrile; 3-Amino-4-(3-methyl-5-(trityloxymethyl)-2,5-dihydrofuran-2-yl)furan-2-carbonitrile; 3-
- 15 Amino-4-(3,4-bis(benzyloxy)-5-(benzyloxymethyl)-2,5-dihydrofuran-2-yl)thiophene-2-carbonitrile; 3-Amino-4-(3,4-bis(benzyloxy)-5-(benzyloxymethyl)-3-methyl-tetrahydrofuran-2-yl)thiophene-2-carbonitrile; 3-Amino-4-(4-(benzyloxy)-5-(benzyloxymethyl)-3-methoxy-tetrahydrofuran-2-yl)furan-2-carbonitrile; 3-Amino-4-(3,4-bis(benzyloxy)-5-(benzyloxymethyl)-3-methyl-tetrahydrofuran-2-yl)furan-2-
- 20 carboxamide; 3-Amino-4-(3,4-bis(benzyloxy)-5-(benzyloxymethyl)-tetrahydrofuran-2-yl)furan-2-carboxamide; 3-Amino-4-(3,4-bis(benzyloxy)-5-(benzyloxymethyl)-3-methyl-tetrahydrofuran-2-yl)furan-2-carbothioamide; 3-Amino-4-(3,4-bis(benzyloxy)-5-(benzyloxymethyl)-tetrahydrofuran-2-yl)furan-2-carbothioamide; 3-Amino-4-(4-(trityloxymethyl)cyclopent-2-enyl)furan-2-carbonitrile; 3-Amino-4-(5-
- 25 (trityloxymethyl)-tetrahydrothiophen-2-yl)furan-2-carbonitrile; 3-Amino-4-(2-(trityloxy)ethyl)furan-2-carbonitrile; 2-Amino-7-(3,4-dihydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl)furo[3,2-*d*]pyrimidin-4(3*H*)-one; or
- 7-(3,4-Dihydroxy-5-(hydroxymethyl)-3-methyl-tetrahydrofuran-2-yl)furo[3,2-*d*]pyrimidin-4(3*H*)-one; 7- β -(2',3',5'-Tri-O-benzyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidin-4(3*H*)-one; 4-Chloro-7- β -(2',3',5'-tri-O-benzyl-D-ribofuranosyl)-furo[3,2-
- 30 *d*]pyrimidine; 7- β -(2',3',5'-Tri-O-benzyl-2'-C-methyl-D-ribofuranosyl)-furo[3,2-

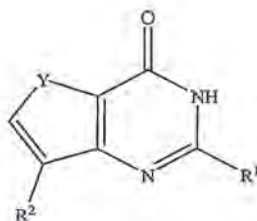
d]pyrimidin-4(3*H*)-one; 4-Chloro-7- β -(2',3',5'-tri-O-benzyl-2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; or 7-(2-(Trityloxy)ethyl)furo[3,2-*d*]pyrimidin-4-amine.

5 Isomers and Physical Forms

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, tautomeric,
 10 or stereoisomeric form, or mixtures thereof, of a compound of the invention (e.g. a compound of formula I, II, or III), which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic
 15 separation using a chiral stationary phase) and how to determine anti-viral or anti-cancer activity using the standard tests described herein, or using other similar tests which are well known in the art. Although the invention includes all isomeric forms of the compounds described herein, one embodiment of the invention provides compounds having the absolute stereochemistry depicted in the Examples hereinbelow.
 20 For example, it would be known in the field of chemistry that a compound of formula I:



wherein R is OH would form a tautomer of the following formula:



Accordingly, the invention includes all tautomeric forms of the compounds of formulae I, II, and III.

Pharmaceutical Compositions, Modes of Administration and Methods of Treatment

5 The present disclosure provides compounds of the general formula (I, II, and III) as detailed above which are inhibitors of DNA and/or RNA viral polymerases and anticancer agents. Various forms of DNA and RNA viral polymerases are inhibited by the compounds disclosed, such as but not limited to viral RdRps. The compounds of the present disclosure therefore have utility in treating and/or preventing viral
10 infections in a host and in treatment and/or preventing a variety of disease states and/or conditions caused by or related to such viral infections. In one embodiment, the compounds are useful in the above mentioned treating and/or preventing by inhibiting a viral RNA and DNA polymerases. Such viral agents include, but are not limited to, hepatitis B, hepatitis C, human immunodeficiency virus, Polio, Coxsackie A and B,
15 Rhino, Echo, small pox, Ebola, and West Nile virus. In a particular embodiment, the causative agent of the viral infection is a flavivirus.

 The present disclosure provides for a compound of the general formula (I, II, and III) and a pharmaceutical composition comprising a pharmaceutically effective amount of at least one compound of general formula (I, II, or III) as described herein.
20 Such compounds and/or pharmaceutical compositions may be used in the manufacture of a medicament for treating and/or preventing a disease or condition in which it is desirable to inhibit a viral RNA and DNA polymerases. Such pharmaceutical compositions may also comprise a pharmaceutically acceptable carrier and other ingredients known in the art, or may comprise solely a compound of the general
25 formula (I, II, and III).

 The pharmaceutically acceptable carriers described herein, including, but not limited to, vehicles, adjuvants, excipients, or diluents, are well-known to those who are

skilled in the art. Typically, the pharmaceutically acceptable carrier is chemically inert to the active compounds and has no detrimental side effects or toxicity under the conditions of use. The pharmaceutically acceptable carriers can include polymers and polymer matrices.

5 The compounds described in the instant disclosure can be administered by any conventional method available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in combination with additional therapeutic agents.

 The compounds described are administered in a pharmaceutically effective amount. The pharmaceutically effective amount of the compound and the dosage of the
10 pharmaceutical composition administered will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the severity and stage of the disease state or condition; the kind of concurrent treatment; the frequency of treatment; and the effect desired.

15 A daily dosage of active ingredient can be expected to be about 0.001 to 1000 milligrams (mg) per kilogram (kg) of body weight per day. In one embodiment, the total amount is between about 0.1 mg/kg and about 100 mg/kg of body weight per day; in an alternate embodiment between about 1.1 mg/kg and about 50 mg/kg of body weight per day; in yet another alternate embodiment between 0.1 mg/kg and about 30
20 mg/kg of body weight per day. The above described amounts may be administered as a series of smaller doses over a period of time if desired. The pharmaceutically effective amount can be calculated based on the weight of the parent compound to be delivered. If the salt or prodrug exhibits activity in itself, the pharmaceutically effective amount can be estimated as above using the weight of the salt or prodrug, or by other
25 means known to those skilled in the art. The dosage of active ingredient may be given other than daily if desired.

 The total amount of the compound administered will also be determined by the route, timing and frequency of administration as well as the existence, nature, and extent of any adverse side effects that might accompany the administration of the
30 compound and the desired physiological effect. It will be appreciated by one skilled in

the art that various conditions or disease states, in particular chronic conditions or disease states, may require prolonged treatment involving multiple administrations.

Dosage forms of the pharmaceutical compositions described herein (forms of the pharmaceutical compositions suitable for administration) contain from about 0.1 mg to about 3000 mg of active ingredient (i.e. the compounds disclosed) per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5-95% weight based on the total weight of the composition. Multiple dosage forms may be administered as part of a single treatment. The active ingredient may be administered to achieve peak plasma concentrations of the active ingredient of from about 0.2 to 70 μ M, or from about 1.0 to 10 μ M.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups and suspensions. It can also be administered parenterally, in sterile liquid dosage forms. The active ingredient can also be administered intranasally (nose drops) or by inhalation via the pulmonary system, such as by propellant based metered dose inhalers or dry powders inhalation devices. Other dosage forms are potentially possible such as administration transdermally, via patch mechanisms or ointment.

Formulations suitable for oral administration can include (a) liquid solutions, such as a pharmaceutically effective amount of the compound dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined pharmaceutically effective amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, propylene glycol, glycerin, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and corn starch. Tablet forms can include one or more of the following: lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium

stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, and gels containing, in addition to the active ingredient, such carriers as are known in the art.

Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the patient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The compound can be administered in a physiologically acceptable diluent in a pharmaceutically acceptable carrier, such as a sterile liquid or mixture of liquids, including water, saline, aqueous dextrose and related sugar solutions, an alcohol, such as ethanol, isopropanol, or hexadecyl alcohol, glycols, such as propylene glycol or polyethylene glycol such as poly(ethyleneglycol) 400, glycerol ketaIs, such as 2,2-dimethyl-1,3-dioxolane-4-methanol, ethers, an oil, a fatty acid, a fatty acid ester or glyceride, or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant, such as a soap or a detergent, suspending agent, such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agents and other pharmaceutical adjuvants.

Oils, which can be used in parenteral formulations, include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters. Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyldialkylammonium halides, and alkylpyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin,

ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylene polypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl .beta.-aminopropionates, and 2-alkylimidazoline quaternary ammonium salts, and (e) mixtures thereof.

The parenteral formulations typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Suitable preservatives and buffers can be used in such formulations. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations ranges from about 5% to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

Pharmaceutically acceptable excipients are also well-known to those who are skilled in the art. The choice of excipient will be determined in part by the particular compound, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical composition of the present invention. The following methods and excipients are merely exemplary and are in no way limiting. The pharmaceutically acceptable excipients preferably do not interfere with the action of the active ingredients and do not cause adverse side-effects. Suitable carriers and excipients include solvents such as water, alcohol, and propylene glycol, solid absorbants and diluents, surface active agents, suspending agent, tableting binders, lubricants, flavors, and coloring agents.

The compounds of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, and nitrogen. Such aerosol formulations may be administered by metered dose inhalers. They also may be

formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer.

The formulations can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets. The requirements for effective pharmaceutically acceptable carriers for injectable compositions are well known to those of ordinary skill in the art. See *Pharmaceutics and Pharmacy Practice*, J.B. Lippincott Co., Philadelphia, Pa., Banker and Chalmers, Eds., 238-250 (1982) and *ASHP Handbook on Injectable Drugs*, Toissel, 4th ed., 622-630 (1986).

Formulations suitable for topical administration include pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, as well as creams, emulsions, and gels containing, in addition to the active ingredient, such carriers as are known in the art. Furthermore, transdermal patches can be prepared using methods known in the art.

Additionally, formulations suitable for rectal administration may be presented as suppositories by mixing with a variety of bases such as emulsifying bases or water-soluble bases. Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulas containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

One skilled in the art will appreciate that suitable methods of administering a compound of the present invention to a patient are available, and, although more than one route can be used to administer a particular compound, a particular route can provide a more immediate and more effective reaction than another route.

Useful embodiments of pharmaceutical dosage forms for administration of the compounds according to the present invention can be illustrated as follows.

A large number of hard-shell capsules are prepared by filling standard two-piece hard gelatine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture
5 of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to
10 increase palatability, improve elegance and stability or delay absorption.

Immediate release tablets/capsules are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These
15 liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

Moreover, the compounds of the present invention can be administered in the
20 form of nose drops, or metered dose and a nasal or buccal inhaler. The drug is delivered from a nasal solution as a fine mist or from a powder as an aerosol.

In one embodiment, the teachings of the present disclosure provide for the use of such pharmaceutical compositions and medicaments in a method of treating a viral infection or treating a disease state and/or condition caused by or related to such viral
25 infection. In one embodiment, the treatment is the result of the inhibition of a viral RNA or DNA polymerase, such as but not limited to a RdRp. Such treatment or inhibition need not be complete to be useful. The method of treatment comprises the steps of: (i) identifying a patient in need of such treatment; (ii) providing such pharmaceutical composition containing at least one compound of the invention; and
30 (iii) administering such pharmaceutical composition in a therapeutically effective

amount to treat the viral infection in a patient in need of such treatment or to inhibit the activity of a viral RNA or DNA polymerase in a patient in need of such treatment.

In one embodiment, the teachings of the present disclosure provide for the use of such pharmaceutical compositions and medicaments in a method of preventing or suppressing a viral infection or preventing or suppressing a disease state and/or condition caused by or related to such viral infection. In one embodiment, the prevention or suppression is the result of the inhibition of a viral RNA or DNA polymerase, such as but not limited to a RdRp. Such prevention, suppression or inhibition need not be complete to be useful. The method of preventing or suppressing comprises the steps of: (i) identifying a patient in need of such prevention; (ii) providing such pharmaceutical composition containing at least one compound of the general formula (I, II, or III); and (iii) administering such pharmaceutical composition in a therapeutically effective amount to prevent or suppress the viral infection in a patient in need of such treatment or to inhibit the activity of a viral RNA and DNA polymerase in a patient in need of such treatment.

The methods of the treating and preventing a viral infection or a disease state and/or condition caused by or related to said viral infection may further comprise administering a therapeutically effective amount of a compound of the present invention in combination with a therapeutically effective amount of another anti-viral agent which, in particular, may be active against HCV. Agents active against HCV include, but are not limited to, ribavirin, levovirin, viramidine, thymosin alpha-1, an inhibitor of HCV NS3 serine protease, an inhibitor of inosine monophosphatedehydrognease, interferon- α , pegylated interferon- α (peginterferon- α), a combination of interferon- α and ribavirin, a combination of peginterferon- α and ribavirin, a combination of interferon- α and levovirin, and a combination of peginterferon- α and levovirin. Interferon- α includes, but is not limited to, recombinant interferon- α 2a, interferon- α 2b, a consensus interferon, and a purified interferon- α product.

The compounds and pharmaceutical compositions of the present disclosure can be administered to patients to prevent and/or treat a number of cancers. Cancers include, but are not limited to, leukemias and lymphomas such as acute lymphocytic

leukemia, acute nonlymphocytic leukemias, chronic lymphocytic leukemia, chronic myelogenous leukemia, Hodgkin's Disease, non-Hodgkin's lymphomas, and multiple myeloma, childhood solid tumors such as brain tumors, neuroblastoma, retinoblastoma, Wilms Tumor, bone tumors, and soft-tissue sarcomas, common solid tumors of adults
5 such as lung cancer, colon and rectum cancer, breast cancer, prostate cancer, urinary cancers, uterine cancers, oral cancers, pancreatic cancer, melanoma and other skin cancers, stomach cancer, ovarian cancer, brain tumors, liver cancer, laryngeal cancer, thyroid cancer, esophageal cancer, and testicular cancer. The cancer may be related to a viral infection or an activity of a viral DNA or RNA polymerase.

10 The methods of the treating and preventing cancer may also comprises further administering of a chemotherapeutic agent in combination with any of the compounds or pharmaceutical compositions of the present disclosure. Any suitable chemotherapeutic agent can be employed for this purpose. The chemotherapeutic agent is typically selected from the group consisting of alkylating agents, antimetabolites,
15 natural products, hormonal agents, and miscellaneous agents.

Examples of alkylating chemotherapeutic agents include carmustine, chlorambucil, cisplatin, lomustine, cyclophosphamide, melphalan, mechlorethamine, procarbazine, thiotepa, uracil mustard, triethylenemelamine, busulfan, pipobroman, streptozocin, ifosfamide, dacarbazine, carboplatin, and hexamethylmelamine.

20 Examples of chemotherapeutic agents that are antimetabolites include cytosine arabinoside, fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, azaserine, thioguanine, floxuridine, fludarabine, cladribine and L-asparaginase.

Examples of chemotherapeutic agents that are natural products include actinomycin D, bleomycin, camptothecins, daunomycin, doxorubicin, etoposide,
25 mitomycin C, TAXOLTM (paclitaxel), taxotere, teniposide, vincristine, vinorelbine, mithramycin, idarubicin, MITHRACINTM (plicamycin), and deoxycoformycin.

An example of a hormonal chemotherapeutic agent includes tamoxifen. Examples of the aforesaid miscellaneous chemotherapeutic agents include mitotane, mitoxantrone, vinblastine, and levamisole.

The ability of a compound to inhibit viral polymerases can be evaluated using known assays. The ability of a compound to inhibit HCV NS5B polymerase can be evaluated using the following assay.

HCV NS5B Polymerase Assay

- 5 Antiviral activity of the test compounds was assessed (Okuse *et al.*, Antiviral Res. 2005, **65**, 23-34) in the stably HCV RNA-replicating cell line, AVA5, derived by transfection of the human hepatoblastoma cell line, Huh7 (Blight *et al.*, Sci. 2000, **290**, 1972). Compounds were added to dividing cultures once daily for three days. Media was changed with each addition of compound. Cultures generally started the assay at
10 30-50% confluence and reached confluence during the last day of treatment. Intracellular HCV RNA levels and cytotoxicity were assessed 24 hours after the last dose of compound.

- Triplicate cultures for HCV RNA levels (on 48-well and 96-well plates) and cytotoxicity (on 96-well plates) were used. A total of six untreated control cultures, and
15 triplicate cultures treated with α -interferon and ribavirin served as positive antiviral and toxicity controls.

- Intracellular HCV RNA levels were measured using a conventional blot hybridization method in which HCV RNA levels are normalized to the levels of B-actin RNA in each individual culture (Okuse *et al.*, Antivir. Res. 2005, **65**, 23-34).
20 Cytotoxicity was measured using a neutral red dye uptake assay (Korba and Gerin, Antivir. Res. 1992, **19**, 55). HCV RNA levels in the treated cultures are expressed as a percentage of the mean levels of RNA detected in untreated cultures.

 Representative compounds of formulae I, II, and III demonstrated significant activity in this assay.

25 Compound Synthesis

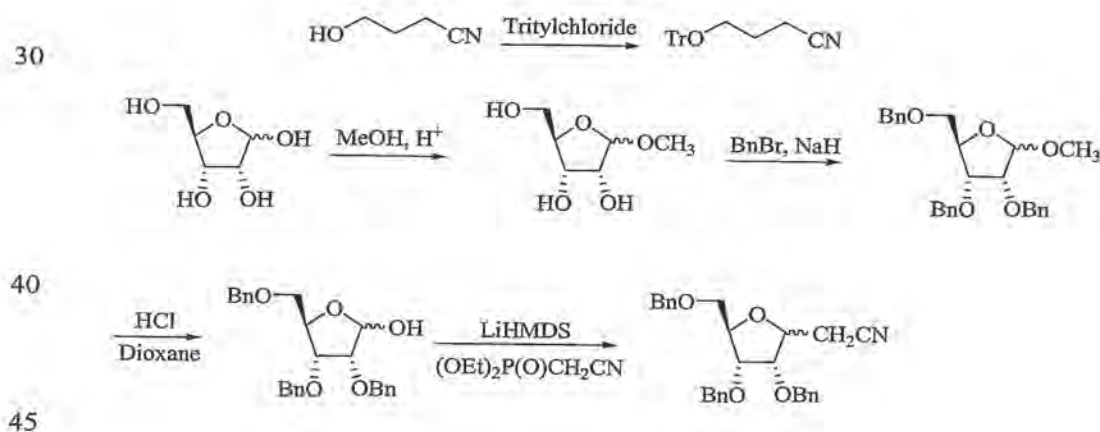
- Compound of formula I, II, and III can be prepared using synthetic intermediates and synthetic procedures that are known, or they can be prepared using the synthetic intermediates and synthetic procedures identified in Schemes A1-D2, and the accompanying Examples herein. The following abbreviations are used herein.

- 30 Tr : trityl
 Bn: benzyl

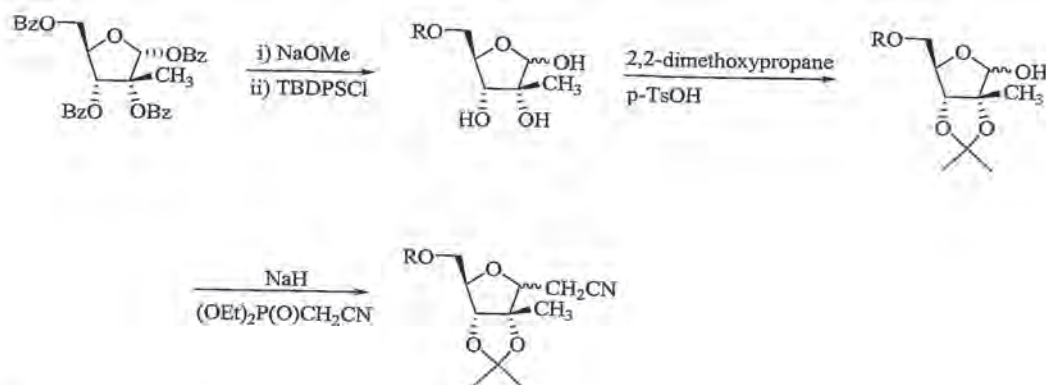
	TBDPS:	<i>tert</i> -butyldiphenylsilyl
	m-CPBA :	3-chloroperoxybenzoic acid
	TFA :	trifluoroacetic acid
	TBDMSCl :	<i>tert</i> -butyldimethylsilyl chloride
5	DMF:	dimethylformamide
	THF:	tetrahydrofuran
	LDA:	lithium diisopropylamine
	TEAB:	triethylammonium bicarbonate
	mMTrCl:	monomethoxytrityl chloride
10	DMAP:	dimethylaminopyridine
	DEAE :	diethylaminoethyl-sepharose
	CMA-80 :	Chloroform 80:MeOH 18: NH ₄ OH :2
	CMA-50 :	Chloroform 50:MeOH 40: NH ₄ OH :10
	Bz:	benzoyl
15	BnBr:	benzyl bromide
	LiHMDS :	lithium hexamethyldisilazane
	TBDPSCl:	<i>tert</i> -butyldiphenylsilyl chloride
	DMSO:	dimethylsulfoxide
	RMgBr:	alkyl magnesium bromide
20	DIBAL:	diisobutylaluminum hydride
	DBN:	1,5-diazabicyclo[4.3.0]non-5-ene
	DBU:	1,8-diazabicyclo[5.4.0]undec-7-ene
	MeMgBr :	methylmagnesium bromide

25 PREPARATION OF R²-CH₂CN COMPOUNDS:

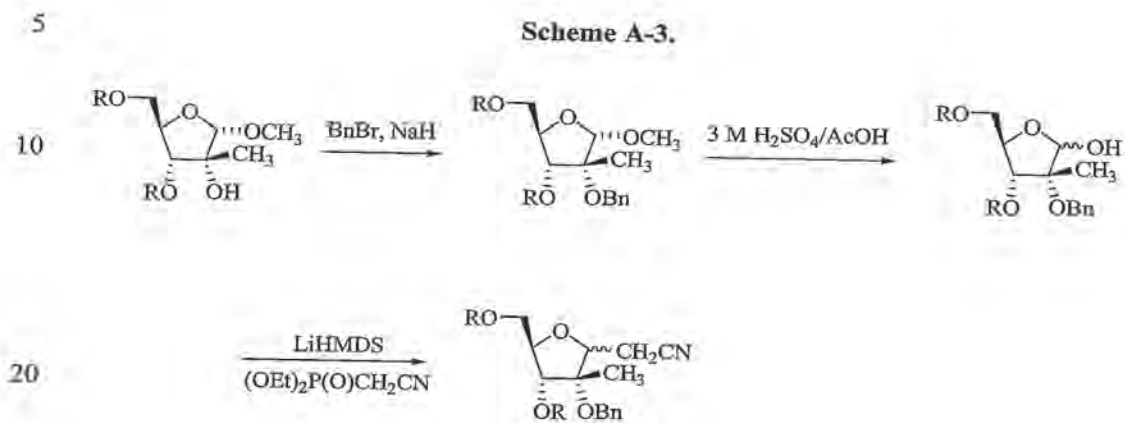
Scheme A-1.



Scheme A-2.

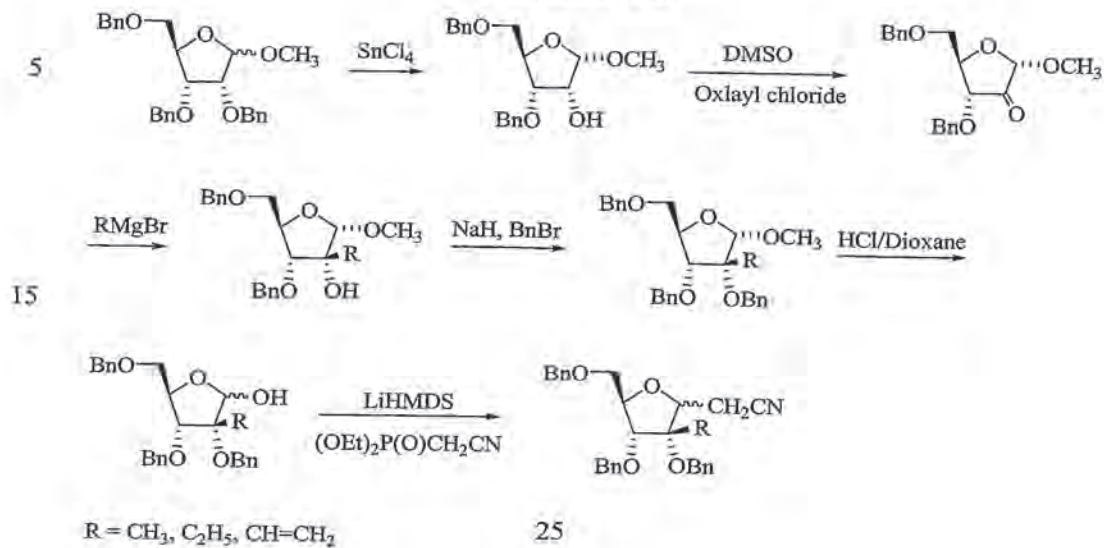
R = *tert*-butyldiphenylsilyl

Scheme A-3.

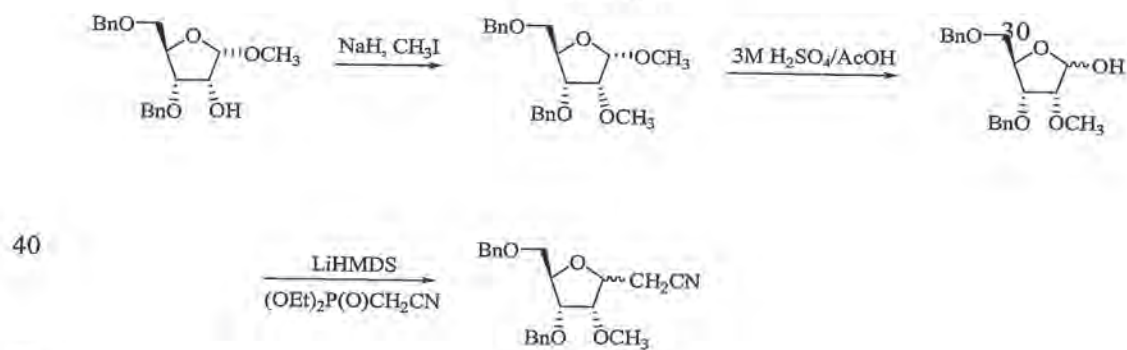


R = 2,4-dichlorobenzyl

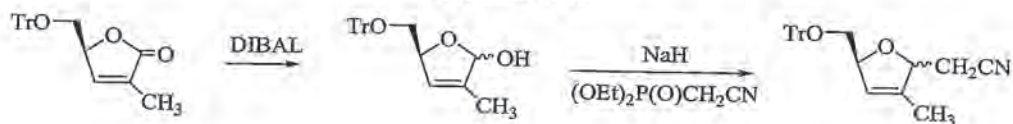
Scheme A-4.



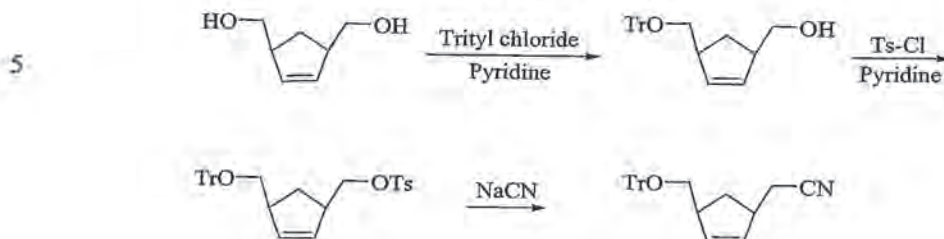
Scheme A-5.



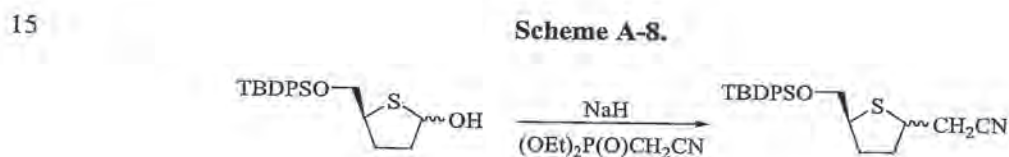
Scheme A-6.



Scheme A-7.



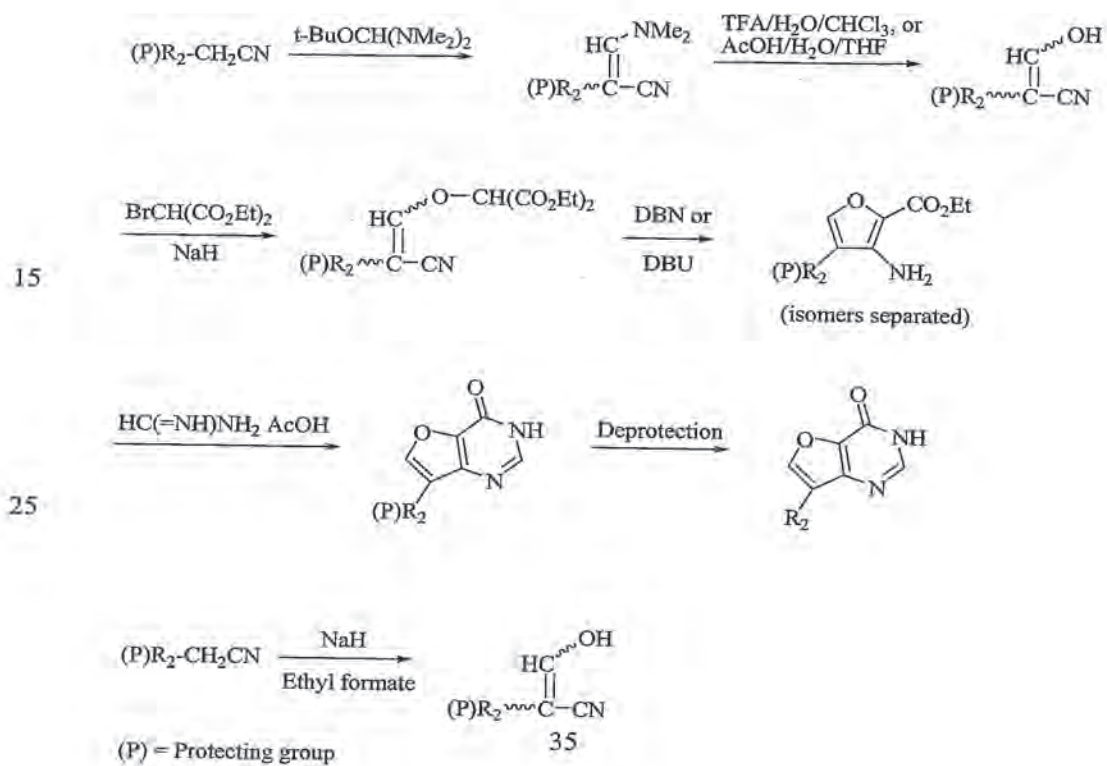
Scheme A-8.



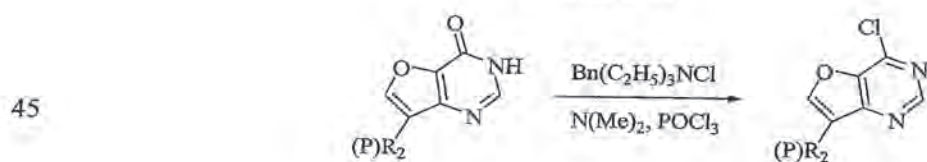
PREPARATION OF COMPOUNDS OF THE INVENTION FROM R^2CH_2CN INTERMEDIATES

25 In the following schemes, R^2 is a nucleoside sugar group (e.g. a substituted tetrahydro or dihydrofuranyl; a substituted tetrahydro or dihydrothiophenyl; a substituted alkyl, substituted cycloalkyl or cycloalkenyl; a substituted pyrrolidinyl; or a substituted dioxolanyl, thioxolanyl or dithiolanyl). $(P)R^2$ is a nucleoside sugar group bearing one or more protecting groups.

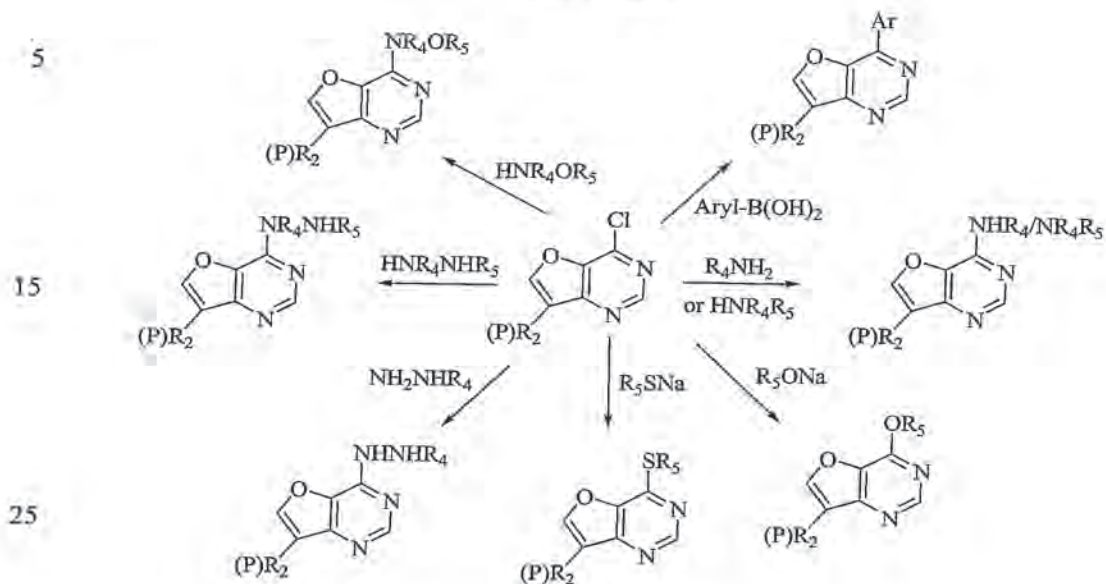
Scheme B-1.



Scheme B-2.



Scheme B-3.

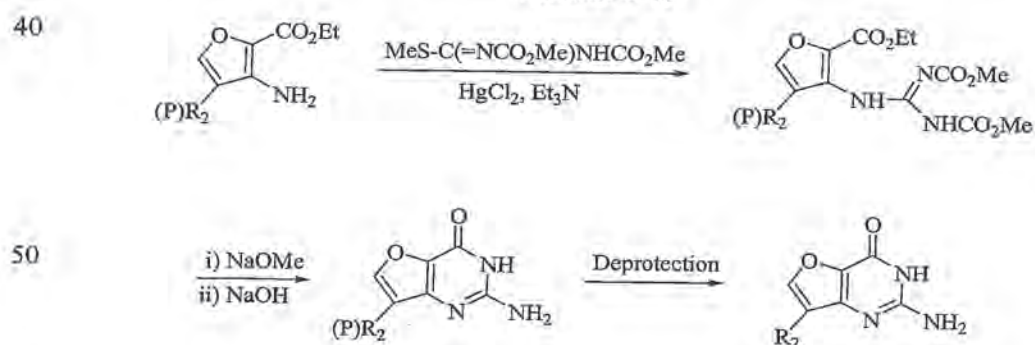


Deprotection of protecting groups in R_2 gives the target molecules

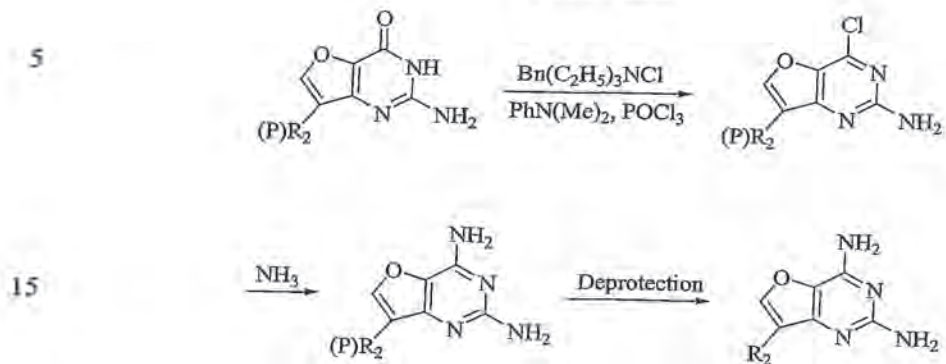
NR_4R_5 = Azetidine, pyrrolidine

35 R_4, R_5 = H, CH_3 , C_2H_5 , $n-C_3H_7$, $i-C_3H_7$, ; CH_2CH_2OH , $CH_2CH_2NH_2$, $NH_2(CH_2)_nNH_2$

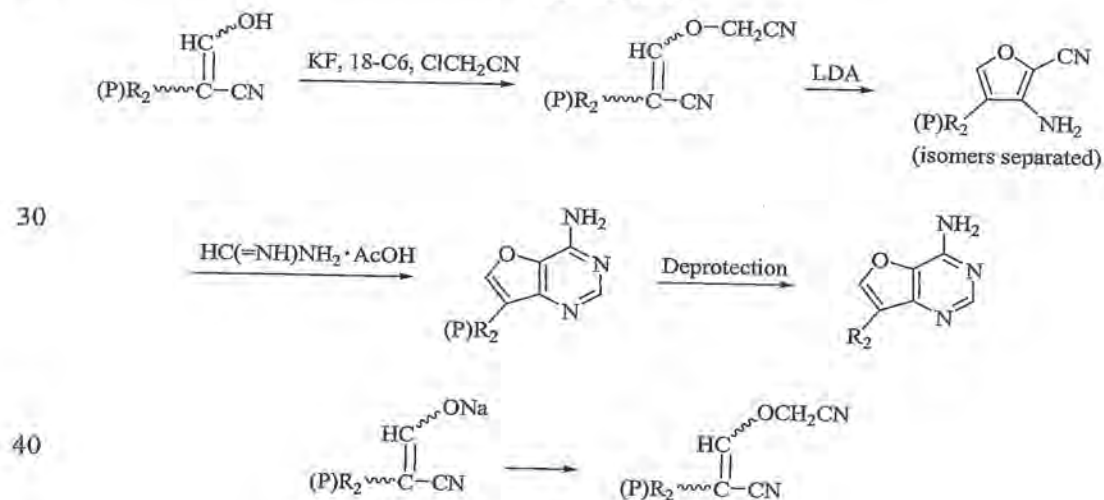
Scheme B-4.



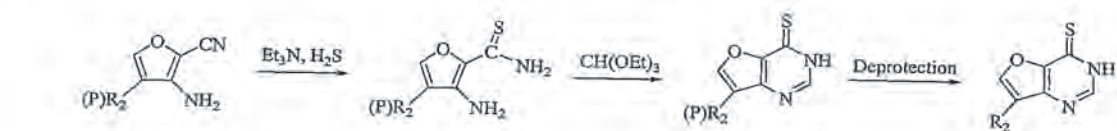
Scheme B-5.

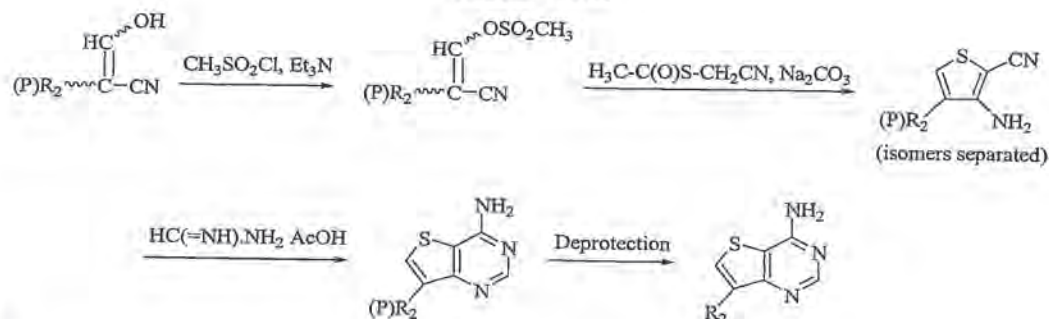


Scheme B-6.



Scheme B-7.



Scheme B-8.

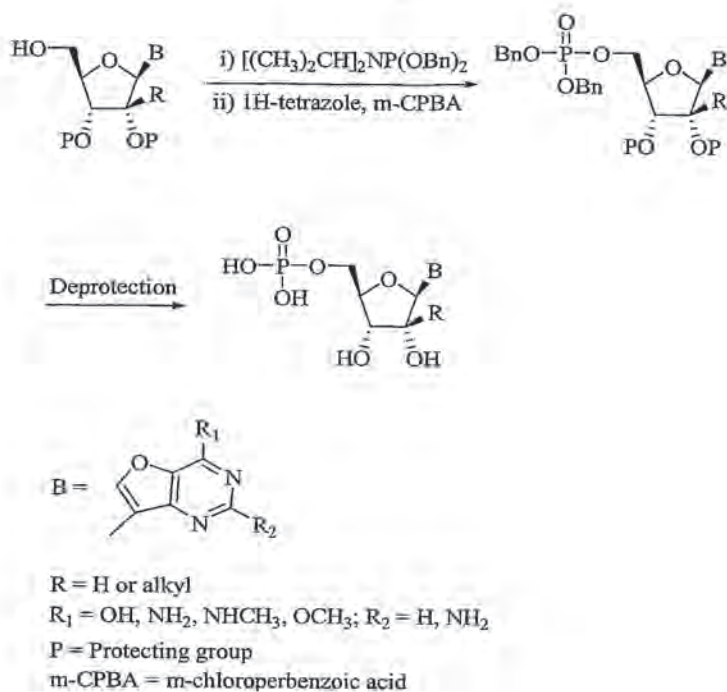
15

PREPARATION OF MONOPHOSPHATES AND TRIPHOSPHATES OF NUCLEOSIDES (represented by Examples C-1 to C-6)

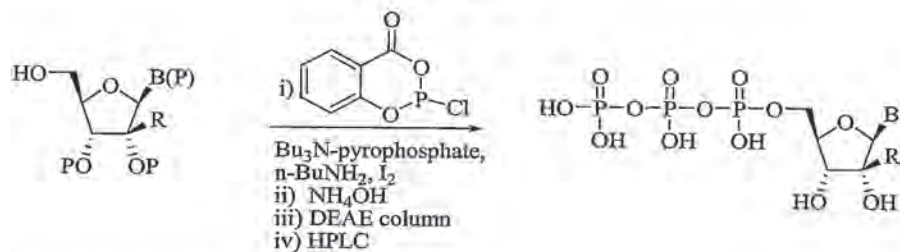
20 The following Schemes illustrate the preparation of compounds of formula I, II, and III that have one or more phosphate groups. In these Schemes, B represents the furopyrimidine or thienopyrimidine base of formula I, and B(P) represents the furopyrimidine or thienopyrimidine base of formula I, bearing one or more protecting groups.

25

Scheme C-1.

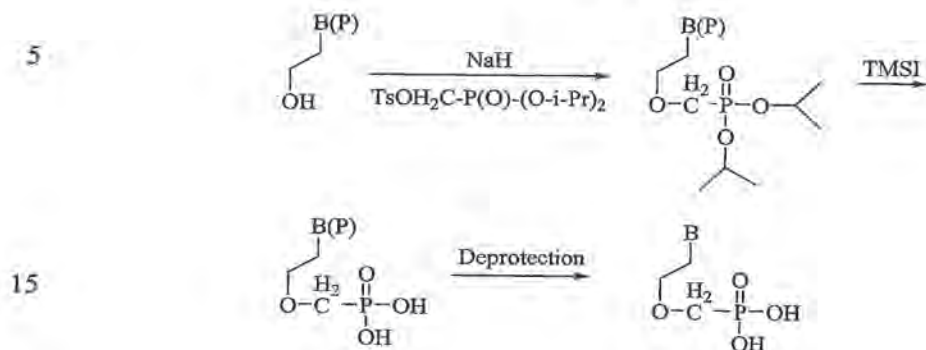


Scheme C-2.



B and R are the same as in Scheme C-1

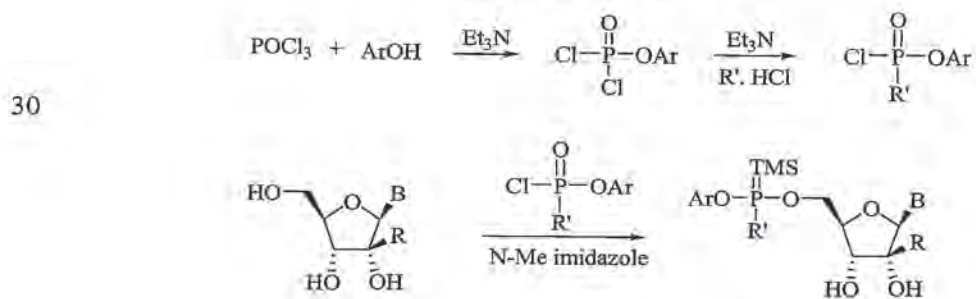
Scheme C-3.



PREPARATION OF PRODRUGS

20 The following Schemes illustrate the preparation of prodrugs of the invention.

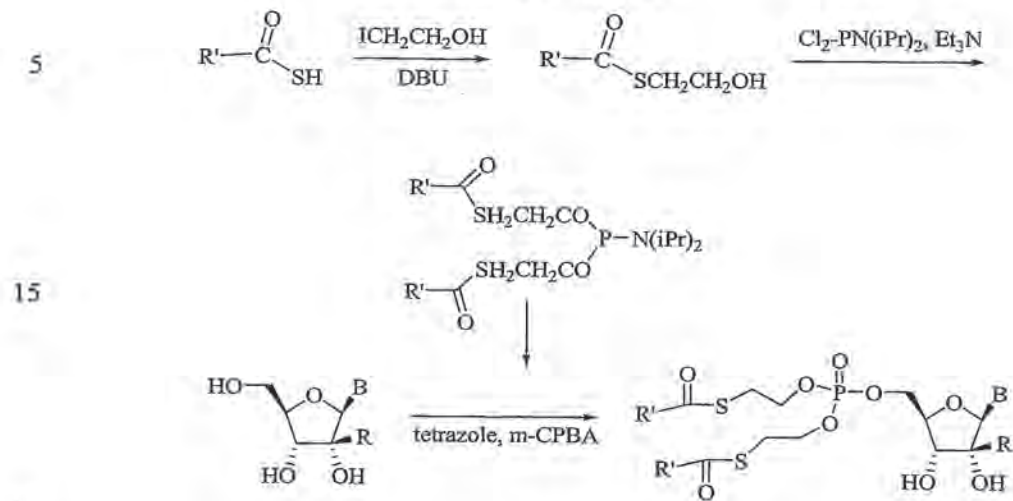
Scheme D-1.



B and R are the same as in scheme C-1

R' = aminoacid ester

Scheme D-2.

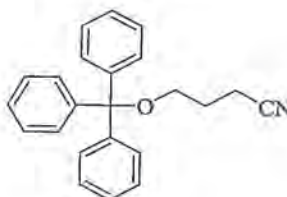


B and R are the same as in scheme C-1

R' = CH₃, C(CH₃)₃

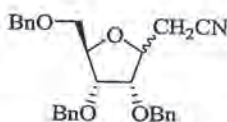
30

The invention will now be illustrated by the following non-limiting Examples.

Examples**Example A-1****4-(Trityloxy)butanenitrile (Scheme A-1).**

To a solution of 3-cyano-1-*n*-propanol (16.85 g, 198 mmol, prepared by method of Blicke, et al., J. Org. Chem., 1961, 26, 3685) in dichloromethane (250 mL) were added triethylamine (80.1 g, 792 mmol) and trityl chloride (82.8 g, 297 mmol) at room temperature and the mixture was stirred for 16 h. To the reaction mixture was added methanol (25 mL) and stirred for 1 h. After concentration, the residue was purified on a column of silica gel using ethyl acetate and hexanes as eluent to give 40 g (61.7%) of the desired product.

¹HNMR (DMSO-*d*₆): δ 7.15-7.40 (m, 15H), 3.01-3.12 (m, 2H), 2.51-2.64 (m, 2H), 1.75-1.90 (m, 2H).

Example A-2**2-(3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-tetrahydrofuran-2-yl)acetonitrile (Scheme A-1).**

Step 1: To a solution of D-ribose (61 g, 406.66 mmol) in methanol (1 L) was added conc. sulfuric acid (6.1 mL) and stirred at 4 °C for 16 h. The reaction mixture was neutralized using triethylamine (40 mL), concentrated to dryness and co-distilled twice

with 200 mL of toluene to remove trace amount of water. This furnished 72 g of crude *O*-methyl-D-ribofuranose, which was used as such for next step.

5 Step 2: To a slurry of NaH (65 g, 60%, 1.626 mol) in DMF (200 mL) was added crude compound from Step 1 (72 g, 406.66 mmol) in DMF (800 mL) over a period of 0.5 h, maintaining the temperature below 5 °C. The anion formed was stirred at room temperature for 30 min. Benzyl bromide (219.1 g, 1280.9 mmol) was added dropwise over a period of 1 h maintaining temperature between 0-5 °C. The reaction was stirred at room temperature for 12 h (TLC analysis in 30% ethyl acetate/hexane showed
10 complete disappearance of starting material), was diluted with water (500 mL) and extracted with ethyl acetate (2 x 1 L). The combined organic extracts were washed twice with water (1 L), brine (500 mL), and dried over MgSO₄ and filtered. The filtrate was concentrated under vacuum to furnish crude residue. The crude residue was purified by flash chromatography (silica gel 1 kg), eluting with ethyl acetate in hexanes
15 to furnish 112 g (63.3%) of desired product as an oil.

¹H NMR (DMSO-*d*₆): δ 7.36-7.27 (m, 15H), 4.92 (s, 1H), 4.66-4.44 (m, 6H), 4.12-4.07 (m, 1H), 3.97 (dd, *J* = 6.78 and 4.5 Hz, 1H), 3.91 (d, *J* = 4.5 Hz, 1H), 3.55 (dd, *J* = 10.73 and 3.4 Hz, 1H), 3.42 (dd, *J* = 10.7 and 6.0 Hz, 1H), 3.21 (s, 3H).

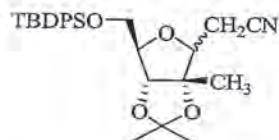
20 Step 3: To a solution of product from Step 2 (114 g, 262.35 mmol) in dioxane (250 mL) was added 4 N HCl (250 mL) and heated at reflux for 4 h. The reaction mixture was allowed to attain room temperature and diluted with ethyl acetate (1.5 L). The aqueous layer was separated and extracted with ethyl acetate (3 x 1 L). The organic layers were combined, washed with water (2 x 500 mL), saturated aqueous NaHCO₃
25 (250 mL), water (500 mL), and brine (250 mL), and dried over MgSO₄ and filtered. The filtrate was concentrated under vacuum to furnish crude product. The crude product was purified by flash chromatography (silica gel 1.5 kg, eluting with ethyl acetate in hexanes 0 to 30%) to furnish starting material (9.9 g,) and 85.3 g (45%) of desired product (mixture of isomers) as an oil.

30 ¹H NMR (DMSO-*d*₆): δ 7.32-7.25 (m, 15H), 6.57 (d, *J* = 4.8 Hz, 0.7H, D₂O exchangeable), 5.82 (d, *J* = 7.7 Hz, 0.3H), 5.26 (dd, *J* = 7.7, 3.5 Hz, 0.3H), 5.21 (dd, *J*

= 4.8, 1.3 Hz, 0.7H), 4.70-4.43 (m, 6H), 4.16 (q, J = 4.1 Hz, 0.3H), 4.06-3.96 (m, 1.3H), 3.93-3.87 (m, 0.7H), 3.80 (dd, J = 4.3, 1.5 Hz, 0.7H), 3.58-3.41 (m, 2H);

Step 4: To a stirred solution of product from Step 3 (15 g, 35.67 mmol) in THF (150 mL) was added diethyl (cyanomethyl)phosphonate (6.95 g, 39.23 mmol) at room temperature followed by lithium bis(trimethylsilyl)amide (39.2 mL, 1M solution in THF) addition at -78 °C. The reaction mixture was stirred at -78 °C for about 20 min and at 0 °C for 1.5 h and then was quenched by adding water (50 mL). The reaction was extracted with ether (2 x 200 mL), washed with water (2 x 50 mL), brine (1 x 50 mL), and dried over Mg SO₄. After filtration, the filtrate was concentrated and purified by flash chromatography using 0 to 30% ethyl acetate in hexanes to give 10.79 g (68.2%) of desired compound as a mixture of isomers as an oil.
MS (ES⁺) 444.33 (M+1).

15

Example A-3

2-(6-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2,3a-trimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)acetonitrile (Scheme A-2).

Step 1: A solution of 2'-C-methyl-1,3,5-tribenzoylribofuranose (19.1 g, 40.09 mmol, prepared according to literature procedures (a) Harry-O'kuru et. al., J. Org. Chem. 1997, **62**, 1754-1759 and (b) Du, J. et. al. Nucleosides & Nucleotides, 1999, **18**, 187-195) in MeOH (850 mL) was treated with NaOMe (25 wt % in MeOH, 55 mL, 240.35 mmol) followed by stirring at room temperature for 2.5 h. The reaction mixture was neutralized with conc. HCl until pH reached between 7 and 8 and concentrated to dryness. The residue was treated with MeOH (300 mL), stirred, filtrated to remove insolubles, and the filtrate was concentrated. The residue was treated with water (400 mL) and extracted with EtOAc (2 x 200 mL). The aqueous phase was concentrated to

dryness to give 11.64 g of yellow syrup. Part of the syrup (474 mg) was treated with DMF (6 mL), imidazole (325 mg, 4.77 mmol), and TBDPSCl (0.50 mL, 1.92 mmol) followed by stirring at room temperature for 22 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with water (2 x 50 mL), brine (50 mL), and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using hexanes:ethyl acetate (1:0 to 1:1) as eluent to give 293 mg (45%, two steps) of product as a colorless oil.

¹H NMR (a mixture of anomeric isomers, ratio = 1:3, CDCl₃): δ 7.70-7.62 (m, 4H), 7.45-7.34 (m, 6H), 5.07, 5.03 (s, s, 1H), 4.15-3.69 (m, 4H), 1.36, 1.31 (s, s, 3H), 1.07, 1.05 (s, s, 9H). MS (ES⁺) 425.41 (M+Na).

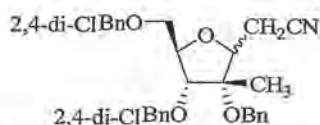
Step 2: A mixture of compound from Step 1 (7.2 g, 17.89 mmol), dimethoxypropane (27 mL, 98%, 0.22 mol), *p*-TsOH (160 mg, 0.84 mmol) in acetone (80 mL) was stirred at room temperature for 1 h. The reaction mixture was treated with EtOAc (800 mL), water (500 mL), saturated NaHCO₃ (30 mL), and the organic layer was separated. The aqueous phase was further extracted with EtOAc (500 mL). The combined organic extracts were washed with water (2 x 300 mL), brine (300 mL), and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using hexanes:ethyl acetate (1:0 to 10:1) as eluent to give 6.16 g (58%) of desired product with some inseparable undesired compound as a colorless oil which was used as such for the next step.

Step 3: A suspension of NaH (60%, 760 mg, 19 mmol) in DME (65 mL) was cooled to 0 °C and treated with diethyl cyanomethylphosphonate (3.1 mL, 19 mmol) dropwise. After stirring for 10 min at about 0 °C, the mixture was treated dropwise with a solution of product from Step 2 (4.2 g, 9.49 mmol) in DME (25 mL) followed by stirring at room temperature for 2 h. The reaction mixture was treated with ether (500 mL) and water (250 mL) and organic layer was separated. The aqueous phase was further extracted with ether (250 mL) and the combined organic extracts were washed with water (2 x 250 mL), and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using hexanes:ethyl

acetate (1:0 to 10:1) as eluent to give 2.84 g (50%, two steps) of 2-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,2,3a-trimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)acetonitrile as a colorless oil.

¹H NMR (CDCl₃): δ 7.76-7.60 (m, 4H), 7.59-7.49 (m, 6H), 4.59 (bs, 1H), 4.15-4.03 (m, 2H), 3.84-3.73 (m, 2H), 2.93 (dd, *J* = 16.8, 4.5 Hz, 1H), 2.70 (dd, *J* = 16.7, 8.1 Hz, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.08 (s, 9H). MS (ES⁺) 488.35 (M+Na).

Example A-4



2-(3-(Benzyloxy)-4-(2,4-dichlorobenzyloxy)-5-((2,4-dichlorobenzyloxy)methyl)-3-methyl-tetrahydrofuran-2-yl)acetonitrile (Scheme A-3).

Step 1: A solution of 3,5-bis-O-(2,4-dichlorophenylmethyl)-2-C-β-methyl-1-O-methyl-α-D-ribofuranose (20.11 g, 40.53 mmol, prepared according to literature procedures a) Martin, P., *Helvetica Chimica Acta*, 1995, **78**, 486-504 and b) Eldrup et al., *J. Med. Chem.* 2004, **47**, 5284-5297) in THF (500 mL) was treated with NaH (60%, 6.45 g, 161.25 mmol) and stirred at room temperature for 0.5 h followed by addition of BnBr (14.6 mL, 122.74 mmol) over 10 min. The reaction mixture was stirred at 70 °C overnight and diluted with EtOAc (2 L), washed with water (2 x) and brine, and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using hexanes:ethyl acetate (1:0 to 4:1) as eluent to give 16.2 g (68%) of desired product as a yellow oil.

¹H NMR (DMSO-*d*₆): δ 7.70-7.25 (m, 11H), 4.85-4.50 (m, 7H), 4.20-4.13 (m, 1H), 3.76-3.67 (m, 3H), 3.37 (s, 3H), 1.40 (s, 3H); IR (neat, cm⁻¹) 2904, 1591, 1472, 1199, 1102; Anal. Calcd for C₂₈H₂₈Cl₄O₅: C, 57.36; H, 4.81; Cl, 24.19. Found: C, 57.23; H, 4.65; Cl, 24.32; MS (ES⁺) 609.07 (M+Na).

Step 2: A mixture of product from Step 1 (15.19 g, 25.91 mmol) and 3M H₂SO₄/HOAc (1:4, 150 mL) was heated at 70 °C for 9 h. The reaction mixture was diluted with

chloroform (500 mL) and washed with water (2 x), 1M NaHCO₃, water, and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using hexanes:ethyl acetate (1:0 to 4:1) as eluent to give 8.6 g (58%) of desired product as a light yellow oil.

- 5 ¹H NMR (a mixture of anomeric isomers, ratio = 5:4, DMSO-*d*₆): δ 7.80-7.40 (m, 11H), 6.86 and 6.23 (2d, *J* = 4.8 and 6.3 Hz, 1H), 6.23 (*J* = 6.3 Hz) (2d, 1H), 5.25-5.19 (m, 1H), 4.95-4.70 (m, 6H), 4.42-3.75 (m, 4H), 1.55, 1.53 (2s, 3H); IR (neat, cm⁻¹) 3435, 2916, 2873, 1591, 1472, 1384, 1095; MS (ES⁺) 593.03 (M+Na); Anal. Calcd for C₂₇H₂₆Cl₄O₅: C, 56.66; H, 4.58; Cl, 24.78. Found: C, 56.44; H, 4.48; Cl, 24.76.

10

Step 3. A solution of product from Step 2 (4.25 g, 7.43 mmol) in THF (35 mL) was cooled to -78 °C and treated with diethyl cyanomethylphosphonate (3.6 mL, 22.25 mmol) followed by addition of 1M lithium bis(trimethylsilyl)amide (9 mL). The reaction mixture was warmed to room temperature and stirred for 21 h. It was diluted with ether (400 mL) and water (200 mL) and the organic layer was separated. The aqueous phase was further extracted with ether (200 mL). The combined organic extracts were washed with water (2 x) and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using hexanes:ethyl acetate (1:0 to 4:1) as eluent to give 3.9 g (88%) of desired product as a colorless oil.

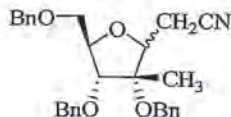
15

¹H NMR (a mixture of anomeric isomers, ratio = 3:2, DMSO-*d*₆): δ 7.53-7.10 (m, 11H), 4.71-4.43 (m, 7H), 4.07-3.75 (m, 2H), 3.62-3.48 (m, 2H), 2.77-2.54 (m, 2H), 1.35, 1.21 (2s, 3H); IR (neat, cm⁻¹) 2879, 2252, 1591, 1472, 1383, 1095; MS (ES⁺) 618.13 (M+Na) Anal. Calcd for C₂₉H₂₇Cl₄NO₄: C, 58.51; H, 4.57; N, 2.35. Found: C, 58.31; H, 4.49; N, 2.27.

20

25

Example A-5



2-(3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methyl-tetrahydrofuran-2-yl)acetonitrile (Scheme A-4).

Step 1: To a solution of the compound from Step 2 of Example A-2 (111 g, 255.45 mmol) in CH_2Cl_2 (800 mL) at -20°C was added dropwise a solution of stannic chloride (280.99 mL, 1M solution in CH_2Cl_2 , 280.99 mmol) over a period of 30 min while stirring and maintaining the temperature between -20 and -10°C . After the solution was kept at 0°C for 23 h, the reaction mixture was quenched carefully by the addition of saturated NaHCO_3 solution (1 L) over a 10-min period. Tin salts were removed via filtration through Celite[®], and from the filtrate the organic phase was separated. The aqueous layer was extracted with chloroform (1000 mL). The combined organic extracts were washed twice with water (500 mL) and brine (200 mL), and dried over MgSO_4 . After filtration, the filtrate was concentrated to furnish crude product as dark yellow oil. The crude oil was purified by flash chromatography (silica gel 1 kg, eluting with ethyl acetate in hexanes) to furnish 78.7 g (89.5%) of 4-(benzyloxy)-5-(benzyloxymethyl)-2-methoxy-tetrahydrofuran-3-ol as an oil.

^1H NMR ($\text{DMSO}-d_6$): δ 7.35- 7.26 (m, 10H), 4.77 (d, $J = 4.3$ Hz, 1H), 4.56 (dd, $J = 42.8$ and 12.4 Hz, 2H), 4.46 (bs, 2H), 4.06 (dd, $J = 8.3$ and 4.3 Hz, 1H), 3.98 (dd, $J = 6.6$ and 4.7 Hz, 1H), 3.68 (dd, $J = 6.6$ and 3.8 Hz, 1H), 3.44 (d, $J = 4.5$ Hz, 2H), 3.30 (bs, 3H); IR (neat) 3554.8, 3030.7, 2926.0, 2912.0, 2863.2, 1957.1, 1732.1, 1650.4, 1494.8, 1452.4, 1414.7, 1362.0, 1323.2, 1269.2, 1187.7, 1124.5, 1095.7, 1040.0, 914.4, 853.3, 738.8 and 698.5 cm^{-1} ; MS (ES^+) 367.38 ($\text{M}+\text{Na}$); Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{O}_5$: C, 69.74; H, 7.02. Found: C, 69.84; H, 7.00.

Step 2: A solution of DMSO (45.05 g, 576.66 mmol) in anhydrous CH_2Cl_2 (150 mL) was added dropwise to a solution of oxalylchloride (36.88 g, 290.5 mmol) at -78°C with stirring over a period of 30 min (maintaining the internal temperature below -65°C

°C during addition). To this was added dropwise a solution of compound from Step 1 in CH₂Cl₂ (150 mL) over a period of 30 min. The reaction mixture was stirred at -70 °C for 3.5 h and quenched by dropwise addition of triethylamine (113.08 g, 1117.5 mmol) at -70 °C over 30 min. The reaction mixture was allowed to warm to room temperature and diluted with water (500 mL). The organic layer was separated and aqueous layer was extracted with chloroform (2 x 500 mL). The combined organic layers were washed with water (1 L), brine (1 L), and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was dried under vacuum to furnish 79 g of the product as a light yellow syrup. This compound was used as such without further purification for the next step.

Step 3: A solution of MeMgBr (3M in ether, 263.5 mL, 790.5 mmol) was added dropwise to a solution of compound from Step 2 (76.4 g, 223.5 mmol) in anhydrous diethyl ether at -70°C over a period of 2 h (maintaining the inside temperature around -70 °C). The reaction was stirred at the same temperature for 2.5 h (TLC analysis using 30% ethyl acetate in hexanes of an aliquot showed completion of reaction). The reaction mixture was quenched by pouring into ice cold water (3 L) and neutralized with 1N HCl (750 mL) to pH 6-7. The aqueous layer was separated and extracted once with ethyl acetate (2 L). The combined organic layers were washed with water (2 x 1 L), saturated NaHCO₃ (2 x 200 mL) and brine (250 mL), and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column (1 kg silica gel) and eluted with ethyl acetate in hexanes (0 to 25%) to furnish 41 g (50%) of desired product which was used in the next reaction without further purification.

Step 4: To a solution of compound from Step 3 (40 g, 111.6 mmol) in DMF (250 mL) at 0 °C was added 60% NaH (17.85 g, 446.4 mmol) and the mixture was stirred at 20 °C for 30 min. To this mixture at 0 °C was added benzyl bromide (23.86 g, 139.5 mmol) dropwise over a period of 30 min and was heated at 70 °C for 19 h. After cooling to room temperature, the reaction mixture was diluted with water (100 mL) and acidified with acetic acid to pH 7-8. The reaction mixture was extracted with ethyl

acetate (2 x 500 mL) and the combined organic layers were washed with water (1 L), brine (1 L), and dried over MgSO_4 (200 g). After filtration, the filtrate was concentrated and the residue was purified by flash chromatography (1 kg silica gel, eluting with ethyl acetate in hexanes 0 to 20%) to furnish 33.78 g (67.4%) of desired product as an oil.

^1H NMR ($\text{DMSO}-d_6$): δ 7.39-7.23 (m, 15H), 4.72 (s, 1H), 4.64 (dd, $J=15.4$ and 11.6 Hz, 2H), 4.55-4.44 (m, 4H), 4.06 (dd, $J=9.4$ and 4.9 Hz, 1H), 3.61-3.51 (m, 3H), 3.30 (s, 3H), 1.32 (s, 3H); IR (neat) 3427, 3063, 3030, 2901, 1952, 1495, 1453, 1369, 1200, 1103, 1028, 736 and 698 cm^{-1} ; MS (ES^+) 471.38 ($\text{M}+\text{Na}$). Anal. Calcd for $\text{C}_{28}\text{H}_{32}\text{O}_5$: C, 74.97; H, 7.19. Found: C, 74.87; H, 7.22.

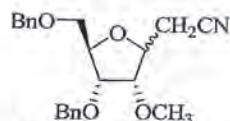
Step 5: To a solution of product from Step 4 (33.5 g, 74.77 mmol) in dioxane (250 mL) was added 2 N HCl (250 mL) and heated at reflux for 20 h. The reaction mixture was allowed to attain room temperature and diluted with ethyl acetate (1 L) and organic layer was collected. The aqueous layer was further extracted with ethyl acetate (1 L). The combined organic layers were washed with water (2 x 500 mL), saturated aqueous NaHCO_3 (150 mL), and brine (500 mL), and dried over MgSO_4 . After filtration, the filtrate was concentrated and the residue was purified by flash chromatography (1.5 kg silica gel, eluting with ethyl acetate in hexanes) to furnish 14.52 g (45%) of desired product, 3,4-bis(benzyloxy)-5-(benzyloxymethyl)-3-methyl-tetrahydrofuran-2-ol, as an oil which is a mixture of isomers.

^1H NMR ($\text{DMSO}-d_6$): δ 7.38-7.24 (m, 15H), 6.60 (bs, 1H, D_2O exchangeable), 5.00 (s, 0.7H), 4.99 (s, 0.3H), 4.73-4.47 (m, 6H), 4.19-4.14 (m, 0.3H), 4.06-4.00 (m, 0.7H), 3.79 (d, $J=7.5$ Hz, 0.7H), 3.67 (d, $J=6.2$ Hz, 0.3H), 3.61-3.49 (m, 2H), 1.34 (s, 2H), 1.32 (s, 1H); IR (neat): 3425, 3064, 3031, 2926, 2870, 1954, 1878, 1812, 1735, 1603, 1497, 1454, 1364, 1311, 1252, 1202, 1094, 1028, 910, 855, 814, 737, 698 cm^{-1} ; MS (ES^+) 457.38 (100% $\text{M}+\text{Na}$).

Step 6: To a stirred solution of compound from Step 5 (14.06 g, 32.37 mmol) in THF (150 mL) was added diethyl (cyanomethyl)phosphonate (6.30 g, 35.60 mmol) and cooled to -78°C . To this cooled solution, lithium bis(trimethylsilyl)amide (35.60 mL,

35.60 mmol, 1M solution in THF) was added over a period of 15 min. The temperature of the reaction mixture was brought to 20 °C over a period of 4 h and further stirred for another 16 h. The reaction mixture was again cooled to -78 °C and to this were added diethyl (cyanomethyl)-phosphonate (8.6 g, 48.55 mmol) and lithium bis(trimethylsilyl)amide (16.18 mL, 16.18 mmol, 1M solution in THF) and stirred for 24 h at 20 °C. The reaction was quenched by adding water (50 mL), stirred for 30 min and extracted with ethyl acetate (2 x 1000 mL). The combined organic extracts were washed with water (1 x 500 mL), brine (1 x 250 mL), and dried (MgSO₄). After filtration, the filtrate was concentrated to afford 14.7 g (98.6%) of the product, which was used as such for next step.

Example A-6



20 **2-(4-(Benzyloxy)-5-(benzyloxymethyl)-3-methoxy-tetrahydrofuran-2-yl)acetonitrile (Scheme A-5).**

Step 1: A solution of compound from Example A-5, Step 1 (4 g, 11.61 mmol) in DMF (95 mL) was treated with NaH (60%, 1.86 g, 46.5 mmol) and stirred at room temperature for 1 h followed by addition of MeI (0.87 mL, 13.84 mmol) in DMF (15 mL). The reaction mixture was stirred at room temperature for 23 h and was diluted with EtOAc (600 mL), neutralized with HOAc, washed with water (2 x 300 mL) and brine (200 mL), and dried over MgSO₄. After filtration and concentration of the filtrate, the residue (5.8 g, light yellow oil) was used as such for next step.

30 MS (ES⁺) 381.46 (M+Na).

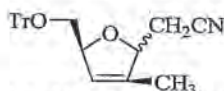
Step 2: A solution of product from Step 1 (5.8 g crude) in a mixture of 3M H₂SO₄/HOAc (1:4, 60 mL) was heated at 70 °C for 2 h. The reaction mixture was diluted with chloroform (300 mL) and washed with water (2 x 200 mL), 1M NaHCO₃ (200 mL), water again (200 mL), and dried over MgSO₄. After filtration and

concentration of the filtrate, the residue (4.5 g, yellow oil) was used as such for next step.

MS (ES^+) 367.48 ($M+Na$).

- 5 Step 3: A solution of product from Step 2 (3.5 g) in THF (42 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ and treated with diethyl (cyanomethyl)phosphonate (4.2 mL, 25.96 mmol) followed by addition of 1M lithium bis(trimethylsilyl)amide in THF (10.5 mL, 10.5 mmol). The reaction mixture was warmed to room temperature and stirred for 18 h and was diluted with ether (400 mL) and water (200 mL). The aqueous phase was extracted further with ether (200 mL). The combined organic extracts were washed with water (2 x 200 mL) and dried over $MgSO_4$. After filtration and concentration of the filtrate, the residue was purified on a silica gel column using hexanes:ethyl acetate (1:0 to 2:1) as eluent to give 2.4 g (a mixture of anomeric isomers, 72% for three steps) of 2-(4-(benzyloxy)-5-(benzyloxymethyl)-3-methoxy-tetrahydrofuran-2-yl)acetonitrile as a colorless oil.
- 10
- 15 MS (ES^+): 390.43 ($M+Na$)⁺.

Example A-7



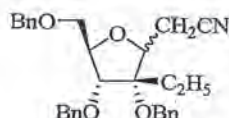
2-(3-Methyl-5-(trityloxymethyl)-2,5-dihydrofuran-2-yl)acetonitrile (Scheme A-6).

- 25 Step 1: To a solution of 3-methyl-5-trityloxymethyl-5*H*-furan-2-one (1.85 g, 5 mmol, prepared by the method of Lopez-Herrera et. al., *J. Carbohydrate Chem.* 1994, **13**, 767) in toluene (25 mL) under N_2 atmosphere at $-78\text{ }^{\circ}\text{C}$ was added dropwise with stirring DiBAL (10 mL, 10 mmol, 1M solution in toluene). The addition rate was maintained to keep the temperature of the reaction below $-70\text{ }^{\circ}\text{C}$. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h and
- 30 quenched with ethyl acetate (4 mL) at that temperature. The reaction mixture was allowed to warm to room temperature and concentrated under vacuum to dryness. The residue obtained was purified by flash chromatography on silica gel eluting with 20% ethyl acetate in hexanes to furnish 1.65 g (88%) of 3-methyl-5-trityloxymethyl-2,5-dihydrofuran-2-ol (a mixture of isomers) as a white solid; mp $100\text{--}102\text{ }^{\circ}\text{C}$.

¹H NMR (DMSO-*d*₆): δ 7.43-7.23 (m, 15H), 6.31 (dd, *J* = 2.8 and 7.3 Hz, 1H), 5.74-5.65 (m, 2H), 4.85 (bs, 0.4H), 4.65 (bs, 0.6H), 3.06 (dd, *J* = 6.8 and 9.1 Hz, 0.6H), 2.95-2.83 (m, 1.4H), 1.69, 1.66 (2s, 3H); IR (KBr) 3414, 3058, 3028, 2918, 2869, 1962, 1737, 1597, 1489, 1445, 1222, 1069, 1033, 985, 747, 702 cm⁻¹; Anal. Calcd for C₂₅H₂₄O₃: C, 80.61; H, 6.50. Found: C, 80.15; H, 6.39.

Step 2: To a slurry of NaH (0.19 g, 4.8 mmol, 60%) in DME (24 mL) cooled to 0 °C was added dropwise diethyl (cyanomethyl)phosphonate (0.96 mL, 6 mmol). The solution became homogenous on completion of addition and was stirred at 0 °C for 30 min. To this solution was added dropwise a solution of product from Step 6, 3-methyl-5-trityloxymethyl-2,5-dihydro-furan-2-ol (1.85 g, 5 mmol) in DME (15 mL). The reaction mixture was allowed to warm to room temperature, stirred overnight, diluted with water (50 mL) and was extracted with ether (2 x 50 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was purified by flash chromatography (25 g silica gel) eluting with ethyl acetate in hexanes to furnish 1.06 g (90%) of 2-(3-methyl-5-trityloxymethyl-2,5-dihydro-furan-2-yl)-acetonitrile (a mixture of isomers), as a colorless oil.

¹H NMR (CDCl₃): δ 7.47-7.41 (m, 6H), 7.33-7.19 (m, 9H), 5.64 (s, 0.6H), 5.53 (s, 0.4H), 5.10 (m, 0.4H), 4.96-4.83 (m, 1.6H), 3.26 (dd, *J* = 5.6 and 9.7 Hz, 0.4H), 3.18-3.05 (m, 1.6H), 2.83-2.53 (m, 2H), 1.79 (m, 3H); IR (KBr) 3430, 3059, 2917, 2865, 2363, 2249, 1967, 1735, 1491, 1445, 1242, 1074, 993, 748, 704 cm⁻¹; Anal. Calcd for C₂₇H₂₅NO₂: C, 81.07; H, 6.43; N, 3.50. Found: C, 81.37; H, 6.25; N, 3.49.

Example A-8

2-(3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-3-ethyl-tetrahydrofuran-2-yl)acetonitrile (Scheme A-4).

Step 1: A solution of oxalylchloride (4 mL, 0.04 mol) was added dropwise to a solution of DMSO (6.18 mL, 0.087 mol) in anhydrous CH_2Cl_2 (100 mL) at -78°C with stirring over a period of 30 min. To this was added dropwise a solution of product from Step 1 of Example A-5 (10 g, 0.029 mol) in CH_2Cl_2 (25 mL) over a period of 30 min. The reaction mixture was stirred at -70°C for 3.5 h and quenched by dropwise addition of triethylamine (5 mL) at -70°C over 30 min. The reaction mixture was allowed to warm to room temperature and diluted with water (200 mL). The organic layer was separated and aqueous layer was extracted with chloroform (2 x 200 mL). The combined organic layers were washed with water (200 mL), brine (200 mL), and dried over MgSO_4 . After filtration, the filtrate was concentrated and the residue was dissolved in *tert*-butyl dimethyl ether (150 mL), and cooled to -78°C . To this cooled solution was added dropwise a solution of ethyl magnesium bromide (43.5 mL, 1M in THF, 0.043 mol). The reaction was further stirred at -78°C for 2.5 h and poured into ice cold water (200 mL) and neutralized with 1N HCl (300 mL) to pH 6-7. The organic layer was collected and the aqueous layer was extracted with ethyl acetate (200 mL). The combined organic layers were washed with water (2 x 200 mL), saturated NaHCO_3 (2 x 200 mL), water (100 mL) and brine (200 mL), and dried over MgSO_4 . After filtration, the filtrate was concentrated and the residue was purified on silica gel column using gradient 0 to 25% EtOAc in hexanes to give 3.0 g (30%) of desired product.

Step 2: To a solution of the product from Step 1 (3 g, 8 mmol) in THF (100 mL) at 0°C was added NaH (0.5 g, 12 mmol) and the mixture was stirred at 20°C for 30 min. After cooling to 0°C , benzyl bromide (1.5 mL, 12 mmol) was added dropwise and heated to 70°C for 16 h. After cooling, the reaction mixture was diluted with water

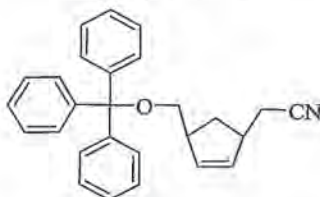
(100 mL), acidified with acetic acid to pH 7-8 and was extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with water (200 mL), brine (200 mL), and dried over MgSO_4 . After filtration, the filtrate was concentrated and the residue was purified by flash chromatography (gradient 0 to 20% EtOAc in hexanes) to give 1.3 g (86%) of 3,4-bis-benzyloxy-5-benzyloxymethyl-3-ethyl-2-methoxy-tetrahydro-furan.

MS (ES^+) 463.25 (M+1).

Step 3: To a solution of the product from Step 2 (3.2 g, 6.9 mmol) in dioxane (50 mL) was added 2 N HCl (50 mL) and heated at reflux for 20 h. The reaction mixture was allowed to attain room temperature and diluted with ethyl acetate (100 mL). The organic layer was collected and the aqueous layer was further extracted with ethyl acetate (100 mL). The combined organic layers were washed with water (2 x 100 mL), saturated aqueous NaHCO_3 (50 mL), water (50 mL) and brine (50 mL), and dried over MgSO_4 . After filtration, the filtrate was concentrated and the residue was purified by flash chromatography (gradient 0 to 20% EtOAc in hexanes) to furnish 1.2 g (30%) of 3,4-bis-benzyloxy-5-benzyloxymethyl-3-ethyl-tetrahydro-furan-2-ol, as an oil.

Step 4: To a stirred solution of sodium hydride (0.18 g, 5.4 mmol) and diethyl (cyanomethyl)-phosphonate (0.85 mL, 5.4 mmol) in DME (20 mL) was added product from Step 3 (2.7 mmol, 1.2 g) and the reaction was stirred at room temperature for 16 h. The reaction was then diluted with diethyl ether (100 mL), washed with water (100 mL) and brine (100 mL). The organic layer was collected, dried over MgSO_4 , filtered and the filtrate was concentrated to give 1.5 g of crude 3,4-bis-benzyloxy-5-benzyloxymethyl-3-ethyl-tetrahydro-furan-2-yl)-acetonitrile, as an oil, which was used as such for the next step.

Example A-9



10

2-(4-(Trityloxymethyl)cyclopent-2-enyl)acetonitrile (Scheme A-7).

- 15 **Step 1:** To a stirred solution of (4-hydroxymethyl-cyclopent-2-enyl)-methanol (13.8 g, 107.81 mmol, prepared by method of Mekrami et al., *Tetrahedron: Asymmetry* 1992, 3, 431) in methylene chloride (100 mL) was added pyridine (25.5 g, 118.59 mmol) and trityl chloride (33.06 g, 118.59 mmol) at room temperature and the mixture was stirred for 18 h. After addition of water (50 mL), the reaction mixture was diluted with
- 20 methylene chloride (100 mL) and the organic layer was separated. The aqueous layer was further extracted with methylene chloride (100 mL). The combined organic layers were washed with water (100 mL), brine (50 mL), and dried (MgSO₄). After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using ethyl acetate in hexanes (0 to 30%), which afforded 18.25 g (45.7%) of desired
- 25 product, (4-trityloxymethyl-cyclopent-2-enyl)-methanol.

¹HNMR (DMSO-*d*₆): δ 7.39-7.22 (m, 15H), 5.77-5.72 (m, 2H), 4.53 (t, *J* = 5.4 Hz, 1H, D₂O exchangeable), 3.22-3.18 (m, 2H), 2.93-2.84 (m, 3H), 2.74-2.69 (m, 1H), 2.10 (m, 1H), 1.12-1.03 (m, 1H); MS (ES⁺) 393.47 (M+23).

- 30 **Step 2:** To a stirred solution of product from Step 1 (18 g, 48.45 mmol) in pyridine (50 mL) was added *p*-toluenesulfonyl chloride at room temperature and the mixture was stirred for 48 h. After concentration, the residue was dissolved in ethylacetate (200 mL), washed with water (2 x 100 mL), brine (50 mL), and dried (MgSO₄). After filtration, the filtrate was concentrated and the residue was purified on silica gel
- 35 column using ethyl acetate in hexanes (0 to 30%), which afforded 21.45 g (84.4%) of

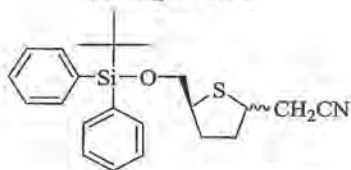
desired product, toluene-4-sulfonic acid 4-trityloxymethyl-cyclopent-2-enylmethyl ester.

¹HNMR (DMSO-*d*₆): δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.38-7.22 (m, 15H), 5.79 (d, *J* = 5.4 Hz, 1H), 5.57 (d, *J* = 5.6 Hz, 1H), 3.91-3.77 (m, 2H), 2.94-2.83 (m, 4H), 2.37 (s, 3H), 2.09-1.98 (m, 1H), 1.08-0.99 (m, 1H).

Step 3: To a stirred solution of compound from Step 2, toluene-4-sulfonic acid 4-trityloxymethyl-cyclopent-2-enylmethyl ester (21.3 g, 40.59 mmol) in dimethylformamide (150 mL) was added sodium cyanide (3.58 g, 73.18 mmol) at room temperature and the reaction was stirred at 70 °C for 48 h. After cooling, the reaction mixture was extracted with ethyl acetate (2 x 250 mL), washed with water (2 x 100 mL), brine (50 mL) and dried (MgSO₄). After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using ethyl acetate in hexanes (0 to 30%), which afforded 14.96 g (97.1%) of desired product, (4-trityloxymethyl-cyclopent-2-enyl)-acetonitrile, as a colorless solid.

¹HNMR (DMSO-*d*₆): δ 7.40-7.23 (m, 15H), 5.84 (d, *J* = 5.1 Hz, 1H), 5.69 (d, *J* = 5.4 Hz, 1H), 3.00-2.90 (m, 4H), 2.53 (d, *J* = 6.4 Hz, 2H), 2.30-2.20 (m, 1H), 1.16-1.07 (m, 1H).

Example A-10

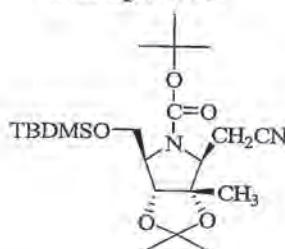


2-(5-((*tert*-Butyldiphenylsilyloxy)methyl)-tetrahydrothiophen-2-yl)acetonitrile (Scheme A-8).

It was prepared from 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-4-thioribofuranose (Secrist III et al., J. Med. Chem. 1992, 35, 533) by following the same method used in Example A-3, Step 3.

^1H NMR (CDCl_3) δ in ppm 7.70-7.40 (m, 10H), 4.10 (m, 1H), 3.65 (m, 3H), 3.60 (m, 2H), 2.10 (m, 2H), 1.80 (m, 2H), 1.10 (s, 9H).

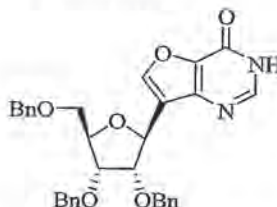
Example A-11



tert-Butyl 6-((*tert*-butyl dimethylsilyloxy)methyl)-4-(cyanomethyl)-2,2,3a-trimethyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate.

This was prepared by following the method reported in Application Ser. No. 11/157,867 filed on June 22, 2005.

Example B-1



7-β-(2',3',5'-Tri-O-benzyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidin-4(3*H*)-one (Scheme B-1).

Step 1: To a stirred solution of compound from Step 4 of example A-2, (3*S*,4*R*,5*R*)-(3,4-bis-benzyloxy-5-benzyloxymethyl-tetrahydro-furan-2-yl)-acetonitrile (10.7 g, 24.12 mmol) in DMF (150 mL) was added *tert*-butoxybis(dimethylamino)methane (21.02 g, 120.62 mmol) at room temperature and stirred for 12 h. The reaction mixture was diluted with toluene (700 mL) and washed with water (2 x 250 mL), brine (1 x 50 mL) and dried (MgSO_4). After filtration, the filtrate was concentrated to give (13.8 g) of desired product, which was used as such for next step.

Step 2: The compound from Step 1 (13.8 g, 24.12 mmol) was dissolved in chloroform (250 mL), trifluoroacetic acid (4.59 g, 40.29 mmol) and water (137 mL) at room temperature and stirred for 18 h. The organic layer was separated and the aqueous layer
5 was extracted with chloroform (2 x 200 mL). The combined organic extracts were washed with water (2 x 200 mL), brine (1 x 100 mL), and dried (MgSO₄). After filtration, the filtrate was concentrated to afford 12.59 g of desired product. A small amount was taken out and purified on silica gel column using ethyl acetate and hexanes.

10 MS (ES⁺) 494.20 (M+23), (ES⁻) 470.28 (M-1); Anal. Calcd for C₂₉H₂₉NO₅•0.75 H₂O: C, 71.80; H, 6.33; N, 2.88. Found: C, 71.95; H, 6.04; N, 2.88.

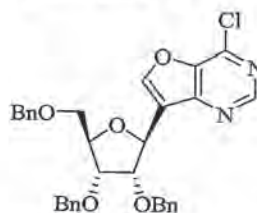
Step 3: To a stirred solution of product from Step 2, (186.5 g, 395.4 mmol) in DMF (1500 mL) was added sodium hydride (19.7 g, 60%, 494.3 mmol) in four portions at 0
15 °C over a period of 1.5 h followed by 2-bromodiethylmalonate (118.1 g, 494.3 mmol) over a period of 30 min at 0 °C and stirred at room temperature for 12 h. After diluting with water (1000 mL), the reaction mixture was extracted with ethyl acetate (3 x 2000 mL). The combined organic extracts were washed with water (2 x 1000 mL), brine (1 x 200 mL), and dried (MgSO₄). After filtration, the filtrate was concentrated to give 296
20 g of crude desired product, which was used in the next reaction without further purification.

Step 4: To a compound from Step 3 (296 g, crude) in EtOH (1000 mL) was added 1,5-diazabicyclo[4.3.0]non-5-ene (58.9 g, 474.48 mmol) at room temperature and stirred
25 for 18 h. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate (4000 mL), washed with water (2 x 1000 mL), brine (2 x 500 mL), and dried (MgSO₄). After filtration, the filtrate was concentrated and the crude residue was purified by flash chromatography on silica gel using ethyl acetate and hexanes to afford
30 29 g, (13.1%) of the desired product as light brown oil.

Step 5: To a stirred solution of compound from Step 4 (29.0 g, 52.04 mmol) in EtOH (600 mL) was added formamidine acetate (135 g, 1301 mmol) at room temperature and heated at reflux for four days and the solid material was removed by filtration and filtrate was concentrated. The residue was dissolved in chloroform (400 mL), washed with water (2 x 100 mL), brine (1 x 100 mL), and dried (MgSO₄). The crude residue was purified by flash chromatography on silica gel using CMA-80 in chloroform (0 to 20%) to afford 12 g (42.8%) of the desired product (12 g, 42.8%) as a colorless crystalline solid; mp 88-100 °C.

¹H NMR (DMSO-*d*₆): δ 12.66 (bs, 1H, D₂O exchangeable), 8.11 (s, 1H), 8.05 (d, *J* = 2.8 Hz, 1H), 7.33-7.25 (m, 15H), 5.11 (d, *J* = 4.8 Hz, 1H), 4.61 (s, 2H), 4.58-4.48 (m, 4H), 4.4 (t, *J* = 4.7 Hz, 1H), 4.19-4.12 (m, 2H), 3.63 (ddd, *J* = 23.3, 10.7, 3.2 Hz, 2H); MS (ES⁺) 539.43 (M+1), 561.42 (M+23), (ES⁻) 537.44 (M-1); Anal. Calcd for C₃₂H₃₀N₂O₆: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.30; H, 5.54; N, 5.10.

15

Example B-2

25

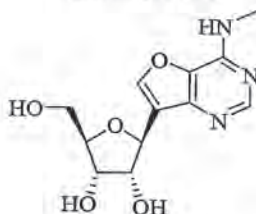
4-Chloro-7-β-(2',3',5'-tri-O-benzyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine (Scheme B-2).

To a stirred solution of compound from Example B-1, Step 5, (6.26 g, 11.62 mmol), benzyltriethylammonium chloride (5.29 g, 23.24 mmol), *N,N*-dimethylaniline (2.12 g, 17.43 mmol) in acetonitrile (50 mL) was added phosphorous oxychloride (10.69 g, 69.74 mmol) at 80 °C and further stirred at 80 °C for 30 min. Then the reaction was concentrated to dryness, dissolved in chloroform (100 mL) and quenched with water (50 mL). The organic layer was separated and aqueous layer was further extracted with chloroform (2 x 50 mL). The combined chloroform extracts were washed with water (2 x 100 mL), sat. NaHCO₃ (1 x 50 mL), water (1 x 100 mL), and brine (1 x 50 mL), and

dried (MgSO₄). After filtration, the filtrate was concentrated and the residue was purified by flash chromatography on silica gel column using ethyl acetate in hexanes (0 to 25%) to afford 5.62 g (86.8%) of desired product as a colorless crystalline solid.

¹H NMR (DMSO-*d*₆): δ 8.87 (s, 1H), 8.54 (s, 1H), 7.33-7.19 (m, 15H), 5.21 (d, *J* = 5.1 Hz, 1H), 4.66-4.47 (m, 7H), 4.24-4.18 (m, 2H), 3.66 (ddd, *J* = 23.1, 10.5, 3.5 Hz, 2H); Anal. Calcd for C₃₂H₂₉ Cl N₂O₅: C, 68.99; H, 5.24; Cl, 6.36; N, 5.02. Found: C, 69.12; H, 5.19; Cl, 6.30; N, 5.04.

Example B-3



4-Methylamino-7-β-(D-ribofuranosyl)-furo[3,2-*d*]pyrimidine (Scheme B-3).

Step 1: To a stirred solution of product from Example B-2 (0.5 g, 0.897 mmol), methylamine hydrochloride (0.36 g, 5.38 mmol) in EtOH (10 mL) was added triethylamine (1.815 g, 17.94 mmol) at room temperature and stirred at 45 °C for 5 h and at room temperature for 12 h. The reaction mixture was concentrated to dryness, dissolved in chloroform (100 mL), washed with water (2 x 25 mL), brine (1 x 20 mL), and dried (MgSO₄). After filtration, the filtrate was concentrated and the residue was purified on silica gel column using ethyl acetate in hexanes (0 to 50%) which afforded 0.266 g (53.7%) of desired product as a colorless solid.

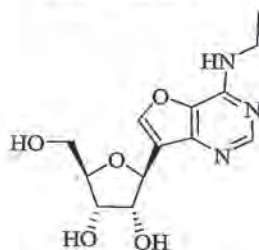
MS (ES⁺) 574.42 (M+23), (ES⁻) 550.72 (M-1).

Step 2: To a stirred solution of product from Step 1 (0.258 g, 0.468 mmol) in methylene chloride (20 mL) was added boron trichloride (4.68 mL, 4.68 mmol, 1M solution in methylene chloride) at -78 °C and stirred at the same temperature for 1 h. Then the reaction was brought to -30 °C over a period of 30 min, and quenched by adding a mixture of methanol:chloroform (2:1, 5 mL). After the reaction mixture

reached to room temperature, it was neutralized with aqueous NH_3 in MeOH (10%, 5 mL) and was concentrated to dryness. The solid obtained was suspended in MeOH (15 mL) and 4N HCl in dioxane (2 mL) was added and reaction mixture was concentrated. The residue was purified by flash chromatography on silica gel using CMA-80 in chloroform (0 to 100%) which afforded 118 mg (89.6%) of the desired product as a colorless crystalline solid; mp 88-100 °C.

^1H NMR ($\text{DMSO}-d_6$): δ 8.30 (s, 1H), 8.21(s, 1H), 7.93 (d, $J = 4.7$ Hz, 1H, D_2O exchangeable), 5.80 (dd, $J = 9.4, 3.3$ Hz, 1H, D_2O exchangeable), 5.05 (d, $J = 6.4$ Hz, 1H, D_2O exchangeable), 4.88 (d, $J = 4.3$ Hz, 1H), 4.77 (d, $J = 7.3$ Hz, 1H, D_2O exchangeable), 4.35-4.29 (m, 1H), 1.04-4.00 (m, 1H), 3.89 (dd, $J = 5.4, 2.6$ Hz, 1H), 3.63 (td, $J = 12.0, 3.0$ Hz, 1H), 3.52-3.44 (m, 1H), 2.97 (d, $J = 4.5$ Hz, 3H); IR (KBr) 3324.6, 2931.8, 1649.4, 1557.1, 1520.0, 1442.4, 1403.8, 1332.5, 1221.1, 1180.1, 1101.5, 1080.1, 1021.9, 956.9, 892.8, 821.7, 787.4, 742.6, 586.4 and 524.6 cm^{-1} ; MS (ES^+) 282.51 ($\text{M}+1$); Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_5 \cdot 0.6 \text{ H}_2\text{O}$: C, 49.34; H, 5.59; N, 14.38. Found: C, 49.41; H, 5.46; N, 14.06.

Example B-4



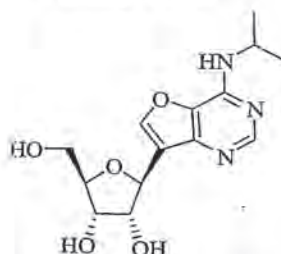
4-Ethylamino-7- β -(D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-3).

This was prepared according to the procedure used for Example B-3, and using ethylamine instead of methylamine, mp 76-88 °C, yield 32% in two steps.

^1H NMR ($\text{DMSO}-d_6$): δ 8.27 (s, 1H), 8.21 (s, 1H), 8.00 (t, $J = 5.8$ Hz, 1H, D_2O exchangeable), 5.81 (d, $J = 10.1$ Hz, 1H, D_2O exchangeable), 5.04 (d, $J = 7.62$ Hz, 1H, D_2O exchangeable), 4.68 (d, $J = 6.2$ Hz, 1H, D_2O exchangeable), 4.76 (d, $J = 7.3$ Hz, 1H), 4.35-4.29 (m, 1H), 4.04-4.00 (m, 1H), 3.89 (dd, $J = 5.4, 2.8$ Hz, 1H), 3.63 (d, $J =$

13.1 Hz, 1H), 3.54-3.46 (m, 3H), 1.18 (t, $J = 7.15$ Hz, 3H); IR (KBr) 3427.5, 3249.4, 3110.9, 2926.5, 2874.6, 2779.2, 2618.3, 2525.0, 1640.4, 1558.5, 1502.9, 1419.6, 1330.9, 1249.9, 1224.2, 1171.3, 1118.7, 1082.5, 1014.6, 900.8, 853.2, 749.5, 653.9, 653.6, 588.3 and 547.8 cm^{-1} ; MS (ES^+) 296.52 ($\text{M}+1$); Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_5 \cdot \text{H}_2\text{O} \cdot 0.25 \text{ CH}_3\text{OH}$: C, 49.52; H, 6.27; N, 13.07. Found: C, 49.83; H, 5.99; N, 12.80.

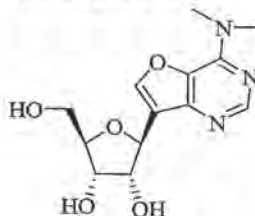
Example B-5



4-Isopropylamino-7- β -(D-ribofuranosyl)-furo[3,2-*d*]pyrimidine (Scheme B-3).

This was prepared according to the procedure used for Example B-3, and using isopropylamine instead of methylamine, mp 58-80 $^{\circ}\text{C}$, yield 32% in two steps.

^1H NMR ($\text{DMSO}-d_6$): δ 8.27 (s, 1H), 8.21 (s, 1H), 7.84 (d, $J = 8.1$ Hz, 1H, D_2O exchangeable), 5.83 (bs, 1H, D_2O exchangeable), 5.03 (d, $J = 6.4$ Hz, 1H, D_2O exchangeable), 4.88 (d, $J = 4.3$ Hz, 1H, D_2O exchangeable), 4.76 (d, $J = 7.3$ Hz, 1H), 4.45-4.29 (m, 2H), 4.04-4.00 (m, 1H), 3.89 (dd, $J = 5.2, 2.6$ Hz, 1H), 3.63 (dd, $J = 12.0, 2.6$ Hz, 1H), 3.53-3.44 (m, 1H), 1.21 (d, $J = 6.5$ Hz, 6H); IR (KBr) 3300.2, 2973.9, 2928.4, 1637.7, 1557.4, 1502.5, 1450.5, 1423.5, 1332.4, 1217.8, 1176.6, 1120.7, 1086.5, 1020.8, 892.4, 821.7, 700.4, 588.3 and 537.6 cm^{-1} ; MS (ES^-) 308 ($\text{M}-1$); Anal. Calcd for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_5 \cdot 0.8 \text{ H}_2\text{O}$: C, 51.94; H, 6.41; N, 12.98. Found: C, 52.24; H, 6.41; N, 12.50.

Example B-6

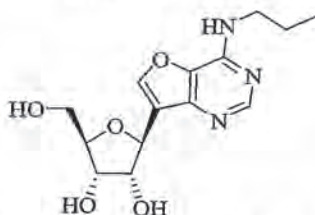
10

4-Dimethylamino-7-β-(D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-3).

15 This was prepared according to the procedure used for Example B-3, and using dimethylamine instead of methylamine, mp 210 °C, yield 45% in two steps.

¹H NMR (DMSO-*d*₆): δ 8.29 (s, 1H), 8.24 (s, 1H), 5.76 (dd, *J* = 9.4, 3.4 Hz, 1H, D₂O exchangeable), 5.05 (d, *J* = 6.2 Hz, 1H, D₂O exchangeable), 4.88 (d, *J* = 4.5 Hz, 1H, D₂O exchangeable), 4.78 (d, *J* = 7.3 Hz, 1H), 4.35-4.29 (m, 1H), 4.04-4.00 (m, 1H),
20 3.89 (dd, *J* = 5.8, 3.0 Hz, 1H), 3.63 (dd, *J* = 12.4, 3.4 Hz, 1H), 3.52-3.44 (m, 1H), 3.33 (s, 6H); IR (KBr) 3361.4, 3120.5, 2972.9, 2930.6, 2865.1, 1627.5, 1515.9, 1428.7, 1406.1, 1368.8, 1348.9, 1304.8, 1275.0, 1224.0, 1115.1, 1098.3, 1081.7, 1018.5, 869.3, 848.3, 748.2 and 593.3 cm⁻¹; MS (ES⁺) 296.51 (M+1); Anal. Calcd for C₁₃H₁₇N₃O₅: C, 52.87; H, 5.80; N, 14.23. Found: C, 52.80; H, 5.87; N, 14.07.

25

Example B-7

30

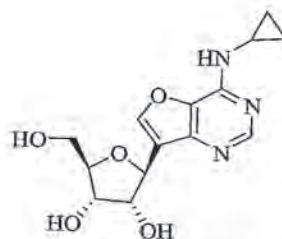
4-n-Propylamino-7-β-(D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-3).

This was prepared according to the procedure used for Example B-3, and using
40 propylamine instead of methylamine, mp 58-80 °C, yield 21% in two steps.

¹H NMR (DMSO-*d*₆): δ 8.27 (s, 1H), 8.21 (s, 1H), 8.03 (bs, 1H, D₂O exchangeable), 5.81 (dd, *J* = 9.8, 3.4 Hz, 1H, D₂O exchangeable), 5.04 (d, *J* = 6.4 Hz, 1H, D₂O

exchangeable), 4.88 (d, $J = 4.3$ Hz, 1H, D₂O exchangeable), 4.76 (d, $J = 7.3$ Hz, 1H), 4.36-4.29 (m, 1H), 4.04-4.00 (m, 1H), 3.89 (dd, $J = 5.4, 2.6$ Hz, 1H), 3.65-3.60 (m, 1H), 3.52-3.40 (m, 3H), 1.65-1.54 (m, 2H), 0.90 (t, $J = 7.3$ Hz, 3H); IR (KBr) 3310.5, 2931.8, 2207.9, 1911.5, 1640.7, 1557.6, 1510.3, 1422.2, 1333.6, 1304.4, 1238.3, 1170.5, 1116.8, 1082.1, 1020.2, 891.1, 821.7, 746.4 and 586.4 cm^{-1} ; MS (ES^+) 310 (M+1), (ES^-) 308.48 (M-1); Anal. Calcd for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_5 \cdot 0.75 \text{H}_2\text{O}$: C, 52.08; H, 6.40; N, 13.01. Found: C, 52.10; H, 6.08; N, 12.62.

Example B-8

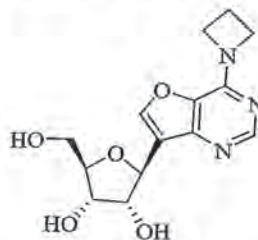


4-Cyclopropylamino-7-β-(D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-3).

This was prepared according to the procedure used for Example B-3, and using cyclopropylamine instead of methylamine, mp 88-100 °C, yield 44% in two steps.

^1H NMR ($\text{DMSO}-d_6$): δ 8.31 (s, 1H), 8.23 (s, 1H), 8.14 (d, $J = 3.5$ Hz, 1H, D₂O exchangeable), 5.77 (dd, $J = 9.4, 3.4$ Hz, 1H, D₂O exchangeable), 5.05 (d, $J = 6.4$ Hz, 1H, D₂O exchangeable), 4.88 (d, $J = 4.3$ Hz, 1H, D₂O exchangeable), 4.77 (d, $J = 7.3$ Hz, 1H), 4.36-4.29 (m, 1H), 4.04-4.00 (m, 1H), 3.89 (dd, $J = 5.8, 3.2$ Hz, 1H), 3.63-3.44 (m, 2H), 3.01-2.92 (m, 1H), 0.79-0.73 (m, 2H), 0.62-0.57 (m, 2H); IR (KBr) 3295.5, 2924.1, 2189.0, 1640.2, 1557.4, 1502.5, 1425.4, 1354.4, 1300.6, 1227.4, 1120.1, 1086.2, 1022.1, 892.7, 824.1, 787.0, 744.3, 702.1, 589.2 and 534.3 cm^{-1} ; MS (ES^+) 308.52 (M+1), (ES^-) 306.46 (M-1); Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_5 \cdot \text{H}_2\text{O}$: C, 51.68; H, 5.88; N, 12.91. Found: C, 51.89; H, 5.80; N, 12.59.

Example B-9

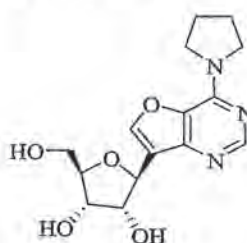


4-Azetidino-7-β-(D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-3).

This was prepared according to the procedure used for Example B-3, and using azetidine instead of methylamine, mp 192 °C, yield 56% in two steps.

¹H NMR (DMSO-*d*₆): δ 8.28 (s, 1H), 8.23 (s, 1H), 5.72 (dd, *J* = 9.2, 3.2 Hz, 1H, D₂O exchangeable), 5.04 (d, *J* = 6.4 Hz, 1H, D₂O exchangeable), 4.88 (d, *J* = 4.5 Hz, 1H, D₂O exchangeable), 4.77 (d, *J* = 7.3 Hz, 1H), 4.35-4.28 (m, 5H), 4.03-3.99 (m, 1H), 3.88 (dd, *J* = 5.8, 3.0 Hz, 1H), 3.65-3.44 (m, 2H), 2.49-2.40 (m, 2H); IR (KBr) 3413.0, 3211.5, 3062.0, 2943.4, 2879.7, 2650.0, 1896.7, 1633.2, 1592.4, 1547.5, 1508.3, 1440.8, 1401.7, 1340.3, 1296.8, 1244.1, 1213.4, 1171.9, 1118.7, 1082.1, 1013.0, 974.1, 904.6, 866.0, 818.3, 787.4, 748.4, 687.9, 663.5 and 590.1 cm⁻¹; MS (ES⁺) 308.52 (M+1); Anal. Calcd for C₁₄H₁₇N₃O₅•0.15 H₂O: C, 54.24; H, 5.62; N, 13.55. Found: C, 54.27; H, 5.56; N, 13.41.

Example B-10

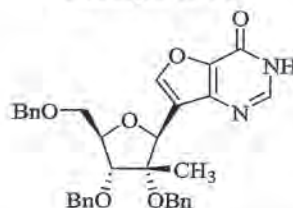


4-Pyrrolidino-7-β-(D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-3).

This was prepared according to the procedure used for Example B-3, and using pyrrolidine instead of methylamine, mp 198 °C, yield 54% in two steps.

¹H NMR (DMSO-*d*₆): δ 8.33 (s, 1H), 8.29 (s, 1H), 5.91 (bs, 1H, D₂O exchangeable), 5.11 (d, *J* = 6.2 Hz, 1H, D₂O exchangeable), 4.95 (d, *J* = 4.3 Hz, 1H, D₂O exchangeable), 4.84 (d, *J* = 7.3 Hz, 1H), 4.41-4.35 (m, 1H), 4.10-4.01 (m, 1H), 3.96 (dd, *J* = 5.8, 3.0 Hz, 1H), 3.94-3.67 (m, 5H), 3.58-3.51 (m, 1H), 2.07-1.97 (bs, 4H); IR (KBr) 3456.4, 3261.6, 3113.1, 2949.2, 2914.8, 2871.0, 2794.8, 2629.6, 1624.6, 1544.8, 1501.3, 1456.3, 1345.9, 1325.1, 1252.8, 1229.2, 1188.3, 1117.7, 1087.7, 1014.5, 980.4, 901.1, 846.7, 787.1, 748.4, 633.4, 588.3 and 545.9 cm⁻¹; MS (ES⁺) 322.54 (M+1);
 10 Anal. Calcd for C₁₅H₁₉N₃O₅•0.25 H₂O: C, 55.29; H, 6.03; N, 12.89. Found: C, 55.53; H, 6.01; N, 12.72.

Example B-11

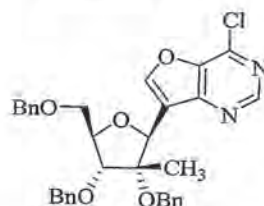


25 7-β-(2',3',5'-Tri-O-benzyl-2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidin-4(3*H*)-one (Scheme B-1).

This was prepared according to the procedure used for Example B-1, starting from Example A-5 instead of A-2.

30 ¹H NMR (DMSO-*d*₆): δ 12.67 (bs, 1H, D₂O exchangeable), 8.14 (s, 1H), 8.09 (s, 1H), 7.38-7.25 (m, 15H), 5.21 (s, 1H), 4.75-4.52 (m, 6H), 4.2-4.15 (m, 1H), 4.05 (d, *J* = 7.72 Hz, 1H), 3.78-3.68 (m, 2H), 1.21 (s, 3H); MS (ES⁺) 553.37 (M+1); Anal. Calcd for C₃₃H₃₂N₂O₆: C, 71.72; H, 5.84; N, 5.07. Found: C, 71.51; H, 5.89; N, 5.07.

Example B-12



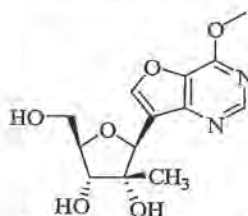
4-Chloro-7-β-(2',3',5'-tri-O-benzyl-2'-C-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-2).

15 This was prepared according to the procedure used for Example B-2, using starting material from Example B-11 instead of B-1, yield 92%.

¹H NMR (DMSO-*d*₆): δ 8.98 (s, 1H), 8.57 (s, 1H), 7.38-7.24 (m, 15H), 5.31 (s, 1H), 4.70 (dd, *J* = 16.7, 11.6 Hz, 2H), 4.67-4.53 (m, 4H), 4.24-4.19 (m, 1H), 4.10 (d, *J* = 7.5 Hz, 1H), 3.75 (ddd, *J* = 21.8, 10.9, 3.2 Hz, 2H), 1.21 (s, 3H); Anal. Calcd for

20 C₃₃H₃₁ClN₂O₅: C, 69.40; H, 5.47; N, 4.90. Found: C, 69.65; H, 5.48; N, 4.92.

Example B-13



30 4-Methoxy-7-β-(2'-C-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-3).

35

Step 1: To a stirred solution of freshly prepared sodium methoxide {prepared from Na (0.022 g, 3.27 mmol) in MeOH (5 mL)} was added compound from Example B-12 (0.187 g, 0.327 mmol) in methanol (5 mL) at room temperature and further stirred for 2 h. After concentrating the reaction mixture, the residue was suspended in water (15 mL) and extracted with ethylacetate (2 x 50 mL). The combined organic extracts were
40 washed with water (2 x 20 mL), brine (20 mL), and dried (MgSO₄). After filtration, the

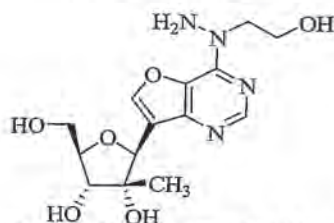
filtrate was concentrated and the residue was purified on a silica gel column, which gave 157 mg (84%) of desired product as a colorless sticky material.

^1H NMR ($\text{DMSO}-d_6$): δ 8.65 (s, 1H), 8.30 (d, $J = 0.5$ Hz, 1H), 7.40-7.25 (m, 15H), 5.29 (d, $J = 0.5$ Hz, 1H), 4.71 (dd, $J = 15.6, 11.6$ Hz, 2H), 4.63 (dd, $J = 15.4, 11.5$ Hz, 2H), 4.57 (dd, $J = 16.4, 11.8$ Hz, 2H), 4.23-4.18 (m, 1H), 4.12 (d, $J = 7.9$ Hz, 1H), 4.10 (s, 3H), 3.79 (dd, $J = 10.9, 3.2$ Hz, 1H), 3.71 (dd, $J = 10.7, 4.5$ Hz, 1H), 1.19 (s, 3H); MS (ES^+) 567.39 ($\text{M}+1$), 589.37 ($\text{M}+23$).

Step 2: To a suspension of 10% Pd-C (0.05 g) in methanol (3 mL) was added a solution of compound from Step 1 (0.15 g, 0.264 mmol) in MeOH (10 mL) followed by 1N HCl (0.79 mL, 0.79 mmol). The mixture was hydrogenated at 60 psi for 6 h and filtered through a small pad of Celite and the filtrate was concentrated to dryness. The residue was purified on a column of silica gel using CMA-80 in chloroform (0 to 10%), which afforded 65 mg (83.1%) of desired product as a colorless solid.

^1H NMR ($\text{DMSO}-d_6$): δ 8.64 (s, 1H), 8.37 (d, $J = 0.8$ Hz, 1H), 5.02 (d, $J = 0.8$ Hz, 1H), 5.01 (d, 1H, D_2O exchangeable), 4.88 (dd, $J = 6.0, 4.7$ Hz, 1H, D_2O exchangeable), 4.78 (s, 1H, D_2O exchangeable), 4.10 (s, 3H), 3.88-3.83 (m, 1H), 3.81-3.72 (m, 2H), 3.64-3.57 (m, 1H), 0.90 (s, 3H); IR (KBr): 3399.7, 2926.2, 1623.4, 1552.7, 1486.2, 1444.1, 1371.7, 1321.0, 1226.8, 1184.9, 1154.3, 1105.2, 1076.1, 1045.8, 925.4, 870.1, 835.2, 796.6, 698.3, 642.4 and 591.1 cm^{-1} ; MS (ES^+) 297.44 ($\text{M}+1$); Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_6 \cdot 0.25 \text{H}_2\text{O}$: C, 51.91; H, 5.52; N, 9.31. Found: C, 52.09; H, 5.65; N, 9.09.

Example B-14



4-[(N-1-Hydroxyethyl)hydrazino]-7-β-(2'-C-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-3).

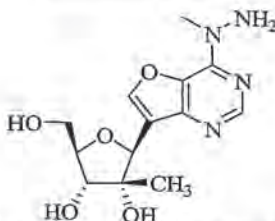
Step 1: To a stirred solution of compound from Example **B-12** (0.2 g, 0.35 mmol) in ethanol (10 mL) and chloroform (5 mL) was added *N*-hydroxyethylhydrazine (0.079 g, 1.05 mmol) at room temperature and stirred for 48 h. After concentrating the reaction mixture, the residue was diluted with water (10 mL) and extracted with chloroform (3 x 20 mL). The combined organic extracts were washed with brine (10 mL) and dried (MgSO₄). After filtration, the filtrate was concentrated and the residue was purified on silica gel column using methanol in chloroform (0 to 5%), which afforded 186 mg (87.1%) of desired product.

¹H NMR (DMSO-*d*₆): δ 8.29 (s, 1H), 8.13 (s, 1H), 7.39-7.25 (m, 15H), 5.26 (s, 1H), 5.13 (s, 2H, D₂O exchangeable), 4.75 (t, *J* = 5.4 Hz, 1H, D₂O exchangeable), 4.73-4.53 (m, 6H), 4.20-4.11 (m, 2H), 3.88 (t, *J* = 6.4 Hz, 2H), 3.78 (dd, *J* = 10.9, 2.6 Hz, 1H), 3.72-3.67 (m, 3H), 1.20 (s, 3H); MS, (ES⁺) 609.28 (M-1).

Step 2: To a stirred solution of compound from Step 1 (180 mg, 0.29 mmol) in methylene chloride (20 mL) was added 1M solution of boron trichloride in dichloromethane (2.95 mL, 2.95 mmol) at -78 °C and stirred further at this temperature for 1.5 h. After the temperature became 0 °C, it was quenched by adding chloroform (2 mL) and methanol (3 mL). To the mixture was added aqueous saturated ammonia (5 mL) and it was stirred for 30 min at room temperature. After concentration, the residue was dissolved in methanol (10 mL), treated with 1M dry HCl in methanol (2 mL) and stirred for 1 h. The resultant suspension was concentrated to dryness and the residue was purified on a silica gel column using CMA-80 in chloroform (0 to 10%), which afforded 68 mg (68.8%) of desired product as a colorless solid; mp 84-92 °C.

¹H NMR (DMSO-*d*₆): δ 8.25 (s, 1H), 8.17 (s, 1H), 5.16 (bs, 3H, D₂O exchangeable), 4.99-4.95 (m, 2H, D₂O exchangeable), 4.80 (s, 1H), 4.77-4.73 (m, 1H, D₂O exchangeable), 3.92-3.86 (m, 3H), 3.80-3.66 (m, 4H), 3.63-3.55 (m, 1H), 0.89 (s, 3H); IR (KBr) 3412.8, 2926.0, 1612.5, 1577.1, 1539.9, 1487.4, 1437.0, 1352.1, 1305.8, 1072.4, 1045.4, 830.3, 788.9, 634.6 and 588.3 cm⁻¹; MS (ES⁺) 341.39 (M+1), 363.37 (M+23), (ES⁻) 339.36 (M-1); Anal. Calcd for C₁₄H₂₀N₄O₆•0.25 H₂O: C, 48.76; H, 5.99; N, 16.24. Found: C, 49.01; H, 6.08; N, 15.71.

Example B-15



4-[(*N*-1-Methyl)hydrazino]-7-β-(2'-*C*-methyl-*D*-ribofuranosyl)-furo[3,2-*d*]pyrimidine (Scheme B-3).

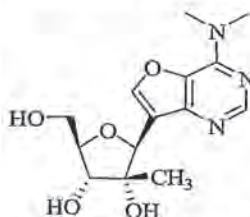
Step-1: This was prepared according to the procedure used for Example B-14 (Step 1), using *N*-methylhydrazine instead of *N*-hydroxyethylhydrazine, yield 89%.

¹H NMR (DMSO-*d*₆): δ 8.29 (s, 1H), 8.12 (d, *J* = 0.7 Hz, 1H), 7.38-7.25 (m, 15H), 5.25 (s, 1H), 5.20 (s, 2H, D₂O exchangeable), 4.72 (s, 2H), 4.68-4.53 (m, 4H), 4.20-4.10 (m, 2H), 3.74 (ddd, *J* = 23.7, 10.7, 2.6 Hz, 2H), 3.37 (s, 3H), 1.19 (s, 3H); MS (ES⁺) 581.36 (M+1), 603.31 (M+23).

Step 2: This was prepared according to the procedure used for Example B-2 (Step 2), using product from Step 1; mp 70-84 °C, yield 87%.

¹H NMR (DMSO-*d*₆): δ 8.25 (d, *J* = 0.56 Hz, 1H), 8.16 (s, 1H), 5.23 (s, 2H, D₂O exchangeable), 5.06 (dd, *J* = 6.7, 4.7 Hz, 1H, D₂O exchangeable), 4.96 (d, *J* = 7.5 Hz, 2H, D₂O exchangeable), 4.80 (s, 1H), 3.90 (dd, *J* = 8.66, 6.9 Hz, 1H), 3.80-3.71 (m, 2H), 3.64-3.56 (m, 1H), 3.37 (s, 3H), 0.88 (s, 3H); IR (KBr): 3821.1, 2926.6, 1663.4, 1615.1, 1581.2, 1537.3, 1497.4, 1441.6, 1413.8, 1355.9, 1306.4, 1109.1, 1074.3, 1041.6, 957.8, 868.0, 835.2, 790.1, 636.5 and 589.0 cm⁻¹; M; MS (ES⁺) 311.49 (M+1), 333.45 (M+23), (ES⁻) 309.45 (M-1); Anal. Calcd for C₁₃H₁₈N₄O₅I•0.25 H₂O: C, 49.59; H, 5.92; N, 17.79. Found: C, 49.76; H, 6.13; N, 16.97.

Example B-16



4-Dimethylamino-7-β-(2'-C-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-3).

15 Step 1: To a stirred solution of compound from Example B-12 (0.11 g, 0.19 mmol) was added 40% solution of *N,N*-dimethylamine in water (5 mL) at room temperature and was stirred at same temperature for 18 h. After concentrating the reaction mixture, the residue was purified on a column of silica gel using ethyl acetate and hexanes mixture as eluent to afford 106 mg (96.3%) of desired product.

20 ¹H NMR (DMSO-*d*₆): δ 8.32 (s, 1H), 8.14 (s, 1H), 7.37-7.25 (m, 15H), 5.25 (s, 1H), 4.72-4.52 (m, 6H), 4.19-4.11 (m, 2H), 3.78 (dd, *J* = 10.7, 2.6 Hz, 1H), 3.69 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.30 (bs, 6H), 1.20 (s, 3H); MS (ES⁺) 580.34 (M+1), 602.40 (M+23); Anal. Calcd for C₃₅H₃₇N₃O₅: C, 72.51; H, 6.43; N, 7.24. Found: C, 72.42; H, 6.56; N, 7.17.

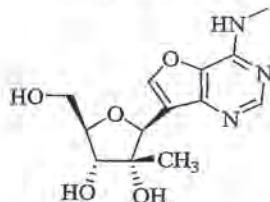
25

Step 2: To a suspension of 10% Pd-C (20 mg) in methanol (3 mL) was added a solution of compound from Step 1 (0.09 g, 0.155 mmol) in MeOH (20 mL) followed by 1N HCl (1 mL, 1 mmol). The mixture was hydrogenated at 70 psi for 3 h and filtered through a small pad of Celite and the filtrate was concentrated to dryness. The residue was dissolved in methanol (2 mL) and triturated with ether (2 x 3 mL). The solid was separated and collected by filtration to afford 40 mg (83.4%) of desired product as a colorless solid.

30 ¹H NMR (DMSO-*d*₆-D₂O): δ 8.57 (s, 1H), 8.41 (s, 1H), 4.99 (s, 1H), 3.84-3.60 (m, 4H), 3.45 (bs, 6H), 0.87 (s, 3H); MS (ES⁺) 310.38 (M+1); Anal. Calcd for C₁₄H₁₉N₃O₅•3 HCl•1.5 H₂O•0.15 Et₂O: C, 38.38; H, 5.84; N, 9.19. Found: C, 38.29; H, 5.50; N, 8.95.

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Example B-17

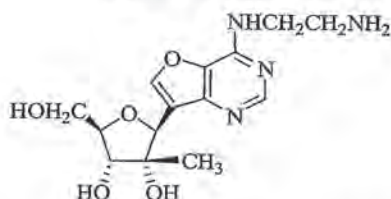


4-Methylamino-7-β-(2'-C-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-3).

This was prepared according to the procedure used for Example B-16, using methylamine instead of dimethylamine, yield 63% in two steps.

¹H NMR (DMSO-*d*₆): δ 8.30 (s, 1H), 8.16(s, 1H), 7.84 (d, 1H, D₂O exchangeable), 5.07 (dd, *J* = 6.5, 4.5 Hz, 1H, D₂O exchangeable), 4.97 (d, *J* = 6.5 Hz, 1H, D₂O exchangeable), 4.96 (s, 1H), 4.77 (s, 1H, D₂O exchangeable), 3.92 (dd, *J* = 8.4, 6.9 Hz, 1H), 3.80-3.72 (m, 2H), 3.64-3.56 (m, 1H), 2.95 (d, *J* = 4.5 Hz, 3H), 0.89 (s, 3H); MS (ES⁺) 296.51 (M+1), 318.45 (M+23), (ES⁻) 294.47 (M-1).

Example B-18



4-Aminoethylamino-7-β-(2'-C-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-3).

Step 1: A solution of compound from Example B-12 (212 mg, 0.37 mmol) in ethanol (15 mL) and chloroform (15 mL) was treated with ethane-1,2-diamine (0.5 mL, 7.4 mmol) followed by stirring at room temperature for 16 h. Additional ethane-1,2-diamine (0.25 mL, 3.7 mmol) was added and stirring was continued for 6 h. The reaction mixture was concentrated and purified on a silica gel column using

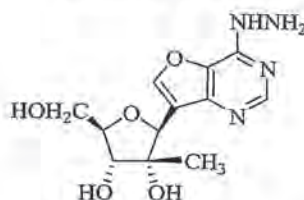
chloroform/CMA-80 (1:0 to 0:1) as eluent to give 157 mg (71%) of desired product as a light yellow oil.

¹H NMR (MeOH-*d*₄): δ 8.31 (s, 1H), 8.05 (d, *J* = 0.7 Hz, 1H), 7.44-7.20 (m, 15H), 5.37 (d, *J* = 0.7 Hz, 1H), 4.79 (s, 2H), 4.64 (s, 2H), 4.64-4.50 (m, 2H), 4.34-4.26 (m, 1H),
5 4.15 (d, *J* = 7.9 Hz, 1H), 3.88-3.60 (m, 2H), 3.65 (t, *J* = 6.2 Hz, 2H), 2.93 (t, *J* = 6.2 Hz, 2H), 1.19 (s, 3H); IR (neat, cm⁻¹): 3363, 2867, 1635, 1497, 1090; MS (ES⁺) 595.46 (M+H)⁺ Anal. Calcd for C₃₅H₃₈N₄O₅•0.5 H₂O: C, 69.63; H, 6.51; N, 9.28. Found: C, 69.59; H, 6.46; N, 9.22.

10 Step 2: A solution of product from Step 1 (120 mg, 0.20 mmol) in dichloromethane (3.7 mL) was cooled to -78 °C and treated with BCl₃ dropwise (1M in dichloromethane, 2.0 mL) followed by stirring at -78 °C for 2 h and at -25 °C for 2 h. The reaction mixture was treated with CH₂Cl₂:MeOH (1:1, 2.2 mL) and stirred at -15 °C for 0.5 h. It was then neutralized with conc. NH₄OH at 0 °C and stirred at room
15 temperature for 15 min followed by concentration under vacuum. The residue was treated with MeOH (12 mL) and 20% HCl in MeOH (15 mL) and stirred at room temperature for 1 h followed by concentration. The residue was purified on a silica gel column using CMA-80:CMA-50 (1:0 to 1:1) as eluent to give 62 mg (96%) of desired product as a yellow solid.

20 ¹H NMR (MeOH-*d*₄): δ 8.39 (s, 1H), 8.09 (d, *J* = 0.9 Hz, 1H), 5.12 (d, *J* = 0.9 Hz, 1H), 4.04-3.78 (m, 4H), 3.91 (t, *J* = 5.8 Hz, 2H), 3.28 (t, *J* = 5.8 Hz, 2H), 1.02 (s, 3H); IR (KBr, cm⁻¹) 3367, 1642, 1507, 1410, 1075; MS (ES⁺) 325.46 (M+H)⁺.

Example B-19



4-Hydrazino-7-β-(2'-C-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-3).

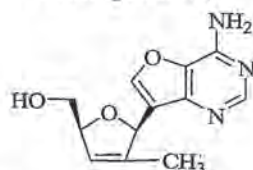
Step 1: A solution of compound from Example B-12 (219 mg, 0.38 mmol) in ethanol (15 mL) and chloroform (15 mL) was treated with hydrazine (98%, 0.05 mL, 1.56 mmol) followed by stirring at room temperature for 16 h. Additional hydrazine (0.10 mL, 3.12 mmol) was added and stirring was continued for 23 h. The reaction mixture was concentrated and purified on a silica gel column using chloroform/CMA-80 (1:0 to 2:1) as eluent to give 129 mg (60%) of desired product as an off-white solid.

¹H NMR (MeOH-*d*₄): δ 8.37 (s, 1H), 8.07 (d, *J* = 0.9 Hz, 1H), 7.45-7.20 (m, 15H), 5.39 (d, *J* = 0.9 Hz, 1H), 4.81 (s, 2H), 4.70-4.54 (m, 4H), 4.34-4.27 (m, 1H), 4.17 (d, *J* = 7.9 Hz, 1H), 3.90-3.71 (m, 2H), 1.21 (s, 3H); IR (neat, cm⁻¹) 3316, 3030, 2895, 1624, 1453, 1088; MS (ES⁺) 567.44 (M+H)⁺; Anal. Calcd for C₃₃H₃₄N₄O₅: C, 69.95; H, 6.05; N, 9.89. Found: C, 69.86; H, 6.02; N, 9.69.

Step 2: A solution of compound from Step 1 (98 mg, 0.17 mmol) in dichloromethane (3.1 mL) was cooled to -78 °C and treated with BCl₃ (1M in dichloromethane, 1.7 mL) dropwise followed by further stirring at -78 °C for 2 h and at -25 °C for 2 h. The reaction mixture was treated with CH₂Cl₂/MeOH (1:1, 1.9 mL) and stirred at -15 °C for 0.5 h. It was then neutralized with conc. NH₄OH at 0 °C and stirred at room temperature for 15 min followed by concentration under vacuum. The residue was treated with MeOH (10 mL) and 20% HCl in MeOH (12.5 mL) and stirred at room temperature for 1 h followed by concentration. The residue was purified on a silica gel column using chloroform/CMA-80 (1:0 to 0:1) as eluent to give 32 mg (64%) of desired product as a light brown solid.

¹H NMR (MeOH-*d*₄): δ 8.04 (s, 1H), 7.79 (s, 1H), 4.94 (s, 1H), 3.92-3.64 (m, 4H), 0.82 (s, 3H); IR (KBr, cm⁻¹): 3316, 2927, 1634, 1072; MS (ES⁺): 297.47 (M+H)⁺.

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Example B-20

15 **((2*S*,5*R*)-(5-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)-4-methyl-2,5-dihydrofuran-2-yl)methanol (Scheme B-6).**

Step 1: To a solution of compound from Example A-7 (Step 7) (55 g, 0.139 mmol) in DMF (695 mL) was added *tert*-butoxybis(dimethylamino)methane (73g, 0.417 mmol) and heated at 60 °C for 6 h. After evaporating most of the solvent under reduced pressure, the residue was suspended in water (500 mL) and extracted with Et₂O (3 x 350 mL). Combined organic extracts were washed with water (2 x 250 mL), dried over MgSO₄, filtered and the filtrate was concentrated to give 72 g of desired product, dimethyl-[2-(3-methyl-5-trityloxymethyl-2,5-dihydro-furan-2-yl)-propenyl]-amine, which was used as such for the next step.

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Step 2: To a solution of compound from Step 1 (70 g crude) in CHCl₃ (1200 mL), was added water (750 mL) followed by trifluoroacetic acid (17 mL). The reaction mixture was stirred at room temperature for 17 h and the organic layer was separated. The aqueous layer was further extracted with CHCl₃ (200 mL) and the combined organic layers were washed with water (500 mL), sat. NaHCO₃ (200 mL), and dried over MgSO₄. After filtration, the filtrate was concentrated to give 48 g of the corresponding enol. This was used as such in the next step.

Step 3: To a stirring suspension of the compound obtained from Step 2 (47 g crude), DMF (1000 mL), KF (12.8 g, 0.22 mol) and 18-crown-6 (23 g, 0.088 mol) was added chloroacetonitrile (25 g, 0.333 mol) and the reaction mixture was stirred for 24 h at

35

room temperature. After removing most of the solvent under reduced pressure, water (1000 mL) was added and the mixture was extracted with Et₂O (2 x 700 mL). The combined organic extracts were washed with water (2 x 250 mL), dried over MgSO₄, and filtered. The filtrate was concentrated and the residue was purified on a column of silica gel (450 g) using 10 to 40% EtOAc in hexanes to give 21 g (32% in three steps) of corresponding cyanomethyl enol ether.
MS (ES⁺) 485.21 (M+Na).

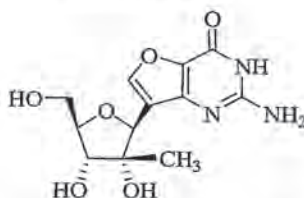
Step 4: To a cold solution (-78 °C) of the compound obtained from Step 3 in THF (530 mL) was added LDA (2M in THF, 65 mL) at such a rate that the reaction temperature never exceeded above -70 °C. After another 0.5 h stirring at -78 °C, the reaction mixture was quenched with water (50 mL) and allowed to attain room temperature. After removing the solvent, the residue was purified on a silica gel column (450 g) using 0 to 20% EtOAc in hexanes as eluent. Two more successive column chromatography were needed to purify the compound and to give 3.02 g (15%) of 3-amino-4-((2*S*)-3-methyl-5-(trityloxymethyl)-2,5-dihydrofuran-2-yl)furan-2-carbonitrile, as a white solid; mp 68 °C (R_f = 0.5 in 30% EtOAc in hexanes).
¹H NMR (DMSO-*d*₆): 7.62 (s, 1H), 7.23-7.42 (m, 15H), 5.56-5.68 (m, 4H), 5.07 (m, 1H), 2.96 (m, 2H), 1.62 (s, 3H).); IR (KBr): 3357, 2864, 2203, 1635, 1444, 1071, 704 cm⁻¹; MS (ES⁺) 485.34 (M+Na); Anal. Calcd for C₃₀H₂₆N₂O₃: C, 77.90; H, 5.66; N, 6.05. Found: C, 77.59; H, 5.75; N, 5.85.

Further elution provided 2.17 g (11%) of 3-amino-4-((2*R*)-3-methyl-5-(trityloxymethyl)-2,5-dihydrofuran-2-yl)furan-2-carbonitrile as a white solid, mp 138-144 °C (R_f = 0.48 in 30% EtOAc in hexanes).
¹H NMR (DMSO-*d*₆): 7.20-7.40 (m, 16H), 5.87 (br, 2H), 5.65 (m, 1H), 5.53 (m, 1H), 4.86 (m, 1H), 3.06 (dd, *J* = 9.6 and 6.7 Hz, 1H), 2.9 (dd, *J* = 9.6 and 3.0 Hz, 1H) 1.66 (s, 3H); IR (KBr): 3361, 2868, 2201, 1637, 1444, 1085, 700 cm⁻¹; MS (ES⁺) 485.28 (M+Na); Anal. Calcd for C₃₀H₂₆N₂O₃: C, 77.90; H, 5.66; N, 6.05. Found: C, 77.72; H, 5.75; N, 5.93.

- Step 5: A mixture of compound from Step 4, 3-amino-4-((2*R*)-3-methyl-5-(trityloxymethyl)-2,5-dihydrofuran-2-yl)furan-2-carbonitrile (1.45 g, 3.13 mol) and formamidine acetate (6.5 g, 62.69 mmol) in EtOH (25 mL) was heated at reflux for 24 h. Additional formamidine acetate (3.25 g, 31.34 mmol) was added and continued heating for further 40 h. Most of the solvent was evaporated, water (100 mL) was added and the mixture was extracted with EtOAc (2 x 75 mL). The combined organic extracts were washed with water (2 x 50 mL), dried over MgSO₄ and filtered. The filtrate was concentrated and the residue was purified on a silica gel column (40 g) using 0 to 10% EtOAc in hexanes as eluent to give 1.2 g (78%) of 7-((2*R*)-3-methyl-5-(trityloxymethyl)-2,5-dihydrofuran-2-yl)furo[3,2-*d*]pyrimidin-4-amine as a white solid; mp 128-132 °C (*R*_f = 0.67 in 10% MeOH in CHCl₃).
- ¹H NMR (DMSO-*d*₆): 8.06 (s, 1H), 7.97 (s, 1H), 7.16-7.37 (m, 17H), 5.77 (m, 1H), 5.64(s, 1H), 4.96 (m, 1H), 3.30 (m, 1H), 2.98 (m, 1H), 1.61 (s, 3H); IR (KBr): 3328, 1645, 1438, 704 cm⁻¹; MS (ES⁺) 512.32 (M+Na); Anal. Calcd for C₃₁H₂₇N₃O₃•0.5 H₂O: C, 74.67; H, 5.66; N, 8.42. Found: C, 74.53; H, 5.53; N, 8.25.

- Step 6: To a solution of compound from Step 6, 7-((2*R*)-3-methyl-5-(trityloxymethyl)-2,5-dihydrofuran-2-yl)furo[3,2-*d*]pyrimidin-4-amine (40 mg, 0.082 mmol) in dioxane (4 mL) was added 4N aqueous HCl (0.125 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min and the mixture was evaporated, redissolved in MeOH (3 mL) and neutralized with 0.1 N NaOH. The solution was purified on a silica gel column using 0 to 10% of MeOH in CHCl₃ to give 12 mg (23%) of desired target, ((2*S*,5*R*)-5-(4-aminofuro[3,2-*d*]pyrimidin-7-yl)-4-methyl-2,5-dihydrofuran-2-yl)methanol as a thick oil.
- ¹H NMR (DMSO-*d*₆): 8.16 (s, 1H), 8.04 (s, 1H), 5.75-5.79 (m, 1H), 5.61-5.65 (m, 1H), 4.90-4.96 (m, 1H), 3.87 (dd, *J* = 12.4 and 2.0 Hz, 1H), 3.70 (dd, *J* = 12.4 and 2.8 Hz, 1H) and 1.58 (s, 3H); MS (ES⁺) 248.45 (M+H).

Example B-21



2-Amino-7-β-(2'-C-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidin-4(3H)-one
(Scheme B-4).

Steps 1 through 4 were carried out the same way as in Example B-1 starting from A-5 instead of A-2.

Step 4 product: ^1H NMR ($\text{DMSO}-d_6$): δ 7.50 (d, $J = 0.8$ Hz, 1H), 7.39-7.25 (m, 15H), 5.29 (bs, 2H), 4.88 (1, 1H), 4.64-4.53 (m, 6H), 4.30-4.15 (m, 3H), 3.92 (d, $J = 5$ Hz, 1H), 3.73-3.67 (m, 2H), 1.24 (t, 3H), 1.15 (s, 3H); IR (KBr) 3462, 3349, 2871, 1705, 1672, 1632, 1591, 1537, 1455, 1369, 1323, 1107, 1026 cm^{-1} ; MS (ES^+) 572.31 ($\text{M}+\text{Na}$); Anal. Calcd for $\text{C}_{34}\text{H}_{37}\text{NO}_7$: C, 71.43; H, 6.52; N, 2.45. Found: C, 71.15; H, 6.50; N, 2.26.

Step 5: To a solution of product from Step 4 (0.8 g, 1.4 mmol) in pyridine (14 mL) was added triethylamine (0.98 mL, 7 mmol), mercury (II) chloride (0.76 g, 2.8 mmol), 1,3 dicarbomethoxy-2-methyl-2-thiopsuedourea (0.58 g, 2.8 mmol) and the reaction mixture was stirred at room temperature overnight. Solvent was removed under vacuum and the residue was triturated with ethyl acetate (100 mL) and filtered through a pad of Celite[®] to remove insoluble impurities. The filtrate was concentrated under vacuum and the residue obtained was purified by column chromatography (silica gel 40 g, eluting with 0-75% ethyl acetate in hexanes) to furnish 0.44 g (10%) of desired product as yellow oil.

^1H NMR ($\text{DMSO}-d_6$): δ 11.20 (s, 1H), 9.82 (s, 1H), 7.78 (d, $J = 0.9$ Hz, 1H), 7.35-7.22 (m, 15H), 5.25 (s, 1H), 4.60-4.35 (m, 7H), 4.22-4.11 (m, 2H), 3.79 (d, $J = 4.5$ Hz, 1H), 3.64 (m, 2H), 3.60 (s, 3H), 3.49 (s, 3H), 1.20 (t, 3H), 1.07 (s, 3H); IR (KBr) 3439, 3285, 3152, 2951, 2363, 1810, 1734, 1629, 1449, 1409, 1271, 1225, 1184, 1111, 1067,

737, 698 cm^{-1} ; MS (ES^+) 730.42 ($\text{M}+1$); Anal. Calcd for $\text{C}_{39}\text{H}_{43}\text{N}_3\text{O}_{11} \cdot 0.5 \text{H}_2\text{O}$: C, 63.39; H, 6.01; N, 5.69. Found: C, 63.04; H, 5.94; N, 5.97.

Step 6: To a solution of product from Step 5 (0.4 g, 0.55 mmol) in methanol (6 mL) was added sodium methoxide (5.4M solution in methanol, 0.126 mL) and stirred at room temperature overnight. After 24 h, additional sodium methoxide (5.4M in methanol, 0.126 mL) was added and stirred for 6 h. The reaction was quenched with glacial acetic acid (0.09 mL, 1.5 mmol) and concentrated under vacuum to dryness. The residue obtained was purified by column chromatography (silica gel 10g, eluting with 0-25% CMA-80 in chloroform) to furnish 0.304 g (89%) of desired product, 2-methoxycarbonylamino-7-(3,4-bis-benzyloxy-5-benzyloxymethyl-3-methyl-tetrahydrofuran-2-yl)-3H-furo[3,2-*d*]pyrimidin-4-one, as yellow oil.

Step 7: To the product from Step 6 (0.3 g, 0.49 mmol) in methanol (2.5 mL) was added 1N NaOH (2.5 mL, 2.5 mmol) and heated at 50 °C for 3 h. Additional 1N NaOH (2.5 mL, 2.5 mmol) was added and continued heating at 50 °C for 3 h. The reaction mixture was cooled to room temperature and pH adjusted to 6 using glacial acetic acid (0.3 mL). The reaction mixture was concentrated under vacuum to remove methanol and the yellow solid obtained was collected by filtration, washed with water and hexane to furnish 0.25 g (90%) of desired product as a yellow solid; mp 80-84 °C.

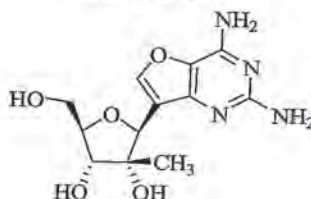
^1H NMR ($\text{DMSO}-d_6$): δ 11.11 (bs, 1H), 7.89 (s, 1H), 7.38-7.25 (m, 15H), 6.38 (bs, 2H), 5.04 (s, 1H), 4.75-4.52 (m, 6H), 4.16-4.11 (m, 1H), 4.05 (d, $J = 7.5 \text{ Hz}$, 1H), 3.80-3.67 (m, 2H), 1.22 (s, 3H); IR (KBr) 3324, 3144, 3030, 2897, 2869, 1696, 1643, 1532, 1496, 1453, 1364, 1317, 1099, 1026, cm^{-1} ; MS (ES^+) 568.38 ($\text{M}+1$), (ES^-): 566.22 ($\text{M}-1$); Anal. Calcd for $\text{C}_{33}\text{H}_{33}\text{N}_3\text{O}_6 \cdot 0.5 \text{H}_2\text{O}$: C, 68.72; H, 5.95; N, 7.29. Found: C, 68.94; H, 5.75; N, 7.21.

Step 8: A mixture of compound from Step 7 (0.2 g, 0.35 mmol) in ethanol (5 mL) containing Pd-C (10%, 40 mg) and 1N HCl (1.75 mL) was hydrogenated at 70 psi for 12 h. The reaction mixture was filtered through Celite to remove catalyst and the filtrate was concentrated under vacuum to dryness. The residue was purified by column

chromatography (silica gel 4 g, eluting with 0-25% methanol in chloroform) to furnish 0.082 g (67%) of desired product as an off-white solid.

¹HNMR (DMSO-*d*₆): δ 11.02 (bs, 1H, D₂O exchangeable), 7.93 (d, *J* = 0.7 Hz, 1H), 6.39 (bs, 2H, D₂O exchangeable), 4.96-4.82 (m, 2H, D₂O exchangeable), 4.81 (d, *J* = 0.7 Hz, 1H), 4.77-4.60 (m, 1H, D₂O exchangeable), 3.76-3.66 (m, 3H), 3.61-3.53 (m, 1H), 0.94 (s, 3H); ¹³CNMR (DMSO-*d*₆/D₂O): δ 153.75, 147.28, 132.59, 121.66, 82.45, 80.57, 78.23, 74.27, 73.92, 61.22, 22.07; IR (KBr) 3381.5, 2926.8 1699.64, 1645.5, 1533.4, 1490.0, 1373.3, 1179.2, 1118.7, 1075.0, 1040.3, 881.6, 822.0, 781.2, 673.4, 582.5 and 492.1 cm⁻¹; MS (ES⁺) 298.37 (M+1), (ES⁻) 296.35 (M-1).

Example B-22



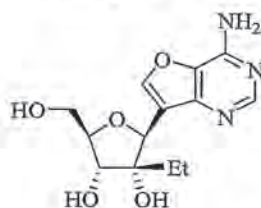
2,4-Diamino-7-β-(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine (Scheme B-5).

Step 1: To a solution of compound from Example B-21, Step 7 (0.5 g, 0.85 mmol) in CH₃CN (5 mL) was added benzyl triethylammonium chloride (0.38 g, 1.7 mmol) and *N,N* dimethylaniline (0.16 mL, 1.28 mmol). After the reaction mixture was heated to 80°C, phosphorus oxychloride (0.5 mL, 5.1 mmol) was added and maintained at this temperature for 1 h. The reaction mixture was concentrated, ice cold water (20 mL) was added to it and was extracted with CHCl₃ (50 mL). The organic layer was separated, washed with aqueous sodium bicarbonate solution (2 x 20 mL) and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using 0 to 10% MeOH in CHCl₃ to give 0.41 g (81%) of the desired product.

MS (ES⁻) 585.20 (M-1).

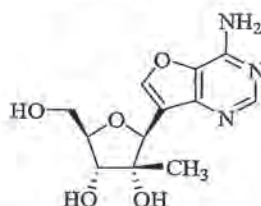
- Step 2: Compound from Step 1 (0.35 g, 0.59 mmol) was taken in a pressure vessel with methanol saturated with ammonia (20 mL) and the vessel was heated to 100 °C for 12 h. After evaporation of the solvent, the residue was partitioned between CHCl₃ (50 mL) and water (50 mL). The organic layer was collected, dried over MgSO₄, filtered and the filtrate was concentrated. The residue was dissolved in EtOH (20 mL) and 10% Pd-C (50 mg) and 1N HCl (0.2 mL) were added to it. The reaction was shaken under hydrogen atmosphere (70 psi) for 18 h and filtered through Celite. The filtrate was concentrated and the residue was purified on a column of silica gel using 0 to 50% CMA-50 in CMA-80 to give 81 mg (61%) of the desired target.
- 15 ¹H NMR (CD₃OD) δ in ppm 7.60 (s, 1H), 4.80 (s, 1H), 3.85 (m, 1H), 3.75 (m, 2H), 3.60 (m, 1H), 0.80 (s, 3H); MS (ES⁺) 297.50 (M+H)⁺.

Example B-23



4-Amino-7-β-(2'-C-ethyl-D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-6).

- 25 This compound was prepared from the product of Example A-8 according to the procedures used for Example B-20 except at the last step of deprotection. The last step of deprotection was achieved through catalytic hydrogenation in the presence of 10% Pd-C in ethanol containing two equivalents of HCl.
- 30 ¹H NMR (DMSO-*d*₆) δ 8.30 (s, 1H), 8.25 (s, 1H), 7.45 (brs, 2H), 5.1 (m, *J* = 5.0 Hz, 1H), 5.00 (m, 1H), 4.50 (m, 1H), 4.12 (m, 3H), 8.80-3.60 (m, 3H), 3.10 (m, 1H), 1.20 (m, 2H), 0.70 (t, *J* = 7.1 Hz, 1H); MS (ES⁺) 296.49 (M+H)⁺; Anal. Calcd for C₁₃H₁₇N₃O₅•HCl•H₂O: C, 44.68; H, 5.77; N, 12.0. Found: C, 44.78; H, 5.44; N, 11.34.

Example B-24**4-Amino-7-β-(2'-C-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-6).**

Step 1: A solution of compound from Example A-3, Step 3 (4.02 g, 8.63 mmol) in DMF (45 mL) was treated with *t*-BuOCH(NMe₂)₂ (12.07 g, 69.25 mmol) and stirred at room temperature overnight. The reaction mixture was diluted with toluene (800 mL) and washed with water (2 x 400 mL) and brine (300 mL), and dried over MgSO₄. After filtration the filtrate was concentrated to give 5.01 g of the desired product as a light yellow oil, which was used as such for the next step.

Step 2: The product from Step 1 (4.98 g) was dissolved in chloroform (150 mL) and treated with a solution of TFA (2.25 mL) in water (100 mL) and stirred vigorously at room temperature for 17 h. The organic layer was separated and washed with water (2 x), and dried over MgSO₄. After filtration, the filtrate was concentrated to give 4.26 g of the desired product as light yellow oil, and was used as such for next step.

Step 3: A mixture of compound from Step 2 (1.55 g), 18-crown-6 (0.66 g, 2.5 mmol) and KF (365 mg, 6.28 mmol) in DMF (30 mL) was treated dropwise with chloroacetonitrile (709 mg, 9.39 mmol) followed by stirring at room temperature for 14 h (TLC showed that TBDPS group was lost). After concentration, the residue was taken in pyridine (10 mL) and treated with trityl chloride (1.35 g, 4.75 mmol) followed by stirring at 70 °C for 19 h. The reaction mixture was diluted with EtOAc (150 mL) and washed with water (2 x 70 mL) and brine (70 mL), then dried over MgSO₄. After filtration and concentration of the filtrate, the residue was purified on a silica gel column using hexanes:ethyl acetate (1:0 to 2:1) as eluent to give 727 mg (43%, three

steps) of desired product as a mixture of *Z*, *E*, α , and β isomers, as a white foam, which was used as such for the next step.

MS (ES⁺) 559.30 (M+Na)⁺.

- 5 Step 4: A solution of above mixture from Step 3 (520 mg, 0.97 mmol) in THF (15 mL) was cooled to -78 °C and treated with LDA dropwise (2M in THF/heptane/ethylbenzene, 1.95 mL, 3.9 mmol) followed by stirring at -78 °C for 2 h. The reaction was quenched with water (320 μ L) and stirred at room temperature for 1 h. After concentration, the residue was purified on a silica gel column using
10 hexanes:ethyl acetate (1:0 to 3:1) as eluent to give 15 mg (2.9%) of desired product as a light yellow syrup.

¹H NMR (CDCl₃): δ 7.50-7.18 (m, 16H), 4.71 (s, 1H), 4.35-4.25 (m, 2H), 3.42-3.30 (m, 2H), 1.59 (s, 3H), 1.39 (s, 3H), 1.22 (s, 3H); MS (ES⁺) 559.26 (M+Na)⁺.

- 15 Step 5: A mixture of compound from Step 4 (23 mg, 0.043 mmol) and formamidine acetate (45 mg, 0.43 mmol) in EtOH (5 mL) was refluxed for 23 h. It was then refluxed for five additional days with addition of formamidine acetate (total of 300 mg added, 2.88 mmol, 100 mg every day for first three days). The reaction mixture was concentrated and purified on a silica gel column using chloroform:methanol (1:0 to
20 95:5) as eluent to give 14 mg (58%) of desired product as a colorless oil.

¹H NMR (MeOH-*d*₄): δ 8.14 (s, 1H), 7.78 (s, 1H), 7.45-7.37 (m, 6H), 7.28-7.10 (m, 9H), 5.07 (s, 1H), 4.20 (d, *J* = 3.0 Hz, 1H), 4.17-4.11 (m, 1H), 3.27 (d, *J* = 5.0 Hz, 2H), 1.53 (s, 3H), 1.27 (s, 3H), 1.06 (s, 3H); MS (ES⁺) 586.39 (M+Na)⁺.

- 25 Step 6: A solution of compound from Step 5 (14 mg, 0.025 mmol) in MeOH (2 mL) was treated with 20% HCl in MeOH (2.5 mL) and stirred at room temperature for 1 h followed by concentration. The residue was redissolved in a small amount of MeOH and treated with ether to precipitate the desired compound, which was collected by filtration to give 3 mg (43%) of desired product as hydrochloride.

- 30 ¹H NMR (MeOH-*d*₄): δ 8.45 (s, 1H), 8.25 (s, 1H), 5.03 (s, 1H), 4.05-3.81 (m, 3H), 3.76 (d, *J* = 7.3 Hz, 1H), 0.96 (s, 3H); MS (ES⁺) 282.41 (M+H)⁺.

Alternate synthesis:

This compound was also prepared from the benzyl protected tetrahydrofuran derivative:

5

Step 1: A solution of compound from Example A-4, Step 3 (3.8 g, 6.38 mmol) in DMF (50 mL) was treated with *t*-BuOCH(NMe₂)₂ (4.33 g, 24.86 mmol) and stirred at room temperature overnight. The reaction mixture was diluted with toluene (100 mL) and washed with water (75 mL). The aqueous phase was extracted further with toluene (50 mL) and the combined extracts were washed with water (2 x) and dried over MgSO₄. After filtration, the filtrate was concentrated to give 5.0 g of the desired product which was used as such for the next step.

Step 2: The product from Step 1 (4.9 g) was treated with a solution of THF/HOAc/H₂O (1:1:1, 30 mL) and stirred at room temperature for 3 h. The reaction mixture was diluted with chloroform (100 mL) and water (100 mL). The organic layer was separated and washed with water (1 x), sat. NaHCO₃ (2 x), water (1 x), and dried over MgSO₄. After filtration, the filtrate was concentrated to give 3.08 g of the desired product, which was used as such for next step.

20

Step 3: A mixture of product from Step 2 (3.0 g), 18-crown-6 (1.02 g, 3.86 mmol) and KF (0.56 g, 4.83 mmol) in DMF (40 mL) was treated dropwise with chloroacetonitrile (1.1 g, 14.49 mmol) followed by stirring at room temperature for 18 h. After concentration, the residue was taken in EtOAc and filtered through Celite. The filtrate was concentrated and the residue was purified on a silica gel column using hexanes:ethyl acetate (1:0 to 2:1) as eluent to give 1.41 g (33%, three steps) of desired product (a mixture of *Z*, *E*, α , and β isomers) as a light colorless oil, which was used as such for the next step.

25

MS (ES⁺) 685.25 (M+Na)⁺.

30

Step 4: A solution of above mixture from Step 3 (817 mg, 1.23 mmol) in THF (19 mL) was cooled to -78 °C and treated with LDA dropwise (1M in THF, 4.92 mL) followed by further stirring at -78 °C for 2 h. The reaction was quenched with water (405 µL) and stirred at room temperature for 1 h. After concentration, the residue was purified on a silica gel column using hexanes:ethyl acetate (1:0 to 3:1) as eluent to give 79 mg (9.7%) of desired product as a light yellow syrup.

¹H NMR (CDCl₃): δ 7.42-7.14 (m, 12H), 4.94 (d, *J* = 1.2 Hz, 1H), 4.76-4.50 (m, 6H), 4.37-4.29 (m, 1H), 3.95-3.68 (m, 3H), 1.23 (s, 3H); MS (ES⁻) 659.68 (M-H)⁻.

Step 5: A mixture of compound from Step 4 (75 mg, 0.113 mmol) and formamidine acetate (300 mg, 2.85 mmol) in EtOH (10 mL) was refluxed for 21 h. Additional formamidine acetate (200 mg, 1.90 mmol) was added and it was refluxed again for 19 h. The reaction mixture was concentrated and purified on a silica gel column using chloroform:methanol (1:0 to 95:5) as eluent to give 62 mg (80%) of desired product as a light yellow syrup.

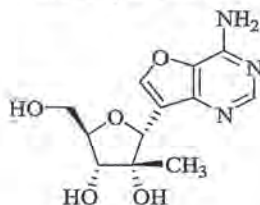
¹H NMR (MeOH-*d*₄): δ 8.45 (s, 1H), 8.29 (d, *J* = 0.7 Hz, 1H), 7.74-7.40 (m, 11H), 5.58 (d, *J* = 0.7 Hz, 1H), 5.15-4.79 (m, 6H), 4.55-4.49 (m, 1H), 4.44 (d, *J* = 7.6 Hz, 1H), 4.16-4.00 (m, 2H), 1.51 (s, 3H); MS (ES⁺) 710.29 (M+Na)⁺.

Step 6: A solution of compound from Step 5 (58 mg, 0.084 mmol) in dichloromethane (1.5 mL) was cooled to -78 °C and treated with BCl₃ dropwise (1M in dichloromethane, 0.84 mL) followed by stirring at -78 °C for 2 h and at -25 °C for 2.5 h. The reaction mixture was treated with CH₂Cl₂/MeOH (1:1, 0.9 mL) and stirred at -15 °C for 0.5 h. It was then neutralized with conc. NH₄OH at 0 °C and stirred at room temperature for 15 min followed by concentration under vacuum. The residue was treated with MeOH (6 mL) and 20% HCl in MeOH (7.5 mL) and stirred at room temperature for 1 h followed by concentration. The residue was purified on a silica gel column using chloroform:methanol (1:0 to 3:1) as eluent to give the product, which was treated with MeOH (5 mL) and 20% HCl in MeOH (0.5 mL), then stirred for 10 min. After concentration, the residue was re-dissolved in a small amount of MeOH and

treated with ether to precipitate the desired compound as HCl salt. The filtration and washing with ether provided 20 mg (75%) of desired product.

^1H NMR matched with the compound obtained from the previous approach; IR (KBr, cm^{-1}) 3380, 3113, 2693, 1678, 1611, 1079; MS (ES^+) 304.36 ($\text{M}+\text{Na}$) $^+$.

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Example B-25

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4-Amino-7- α -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine (Scheme B-6).

Step 1: When Example B-24 was prepared from Example A-3, at Step 4 in the first approach, another isomer was isolated during chromatography, which corresponded to the α isomer (86 mg, 17%).

^1H NMR (CDCl_3): δ 7.48-7.20 (m, 16H), 4.71 (s, 1H), 4.47 (d, $J = 1.2$ Hz, 1H), 4.33-4.26 (m, 1H), 3.36-3.22 (m, 2H), 1.48 (s, 3H), 1.42 (s, 3H), 1.42 (s, 3H); MS (ES^+) 559.94 ($\text{M}+\text{Na}$) $^+$.

25

Step 2: A mixture of compound from Step 1 (65 mg, 0.12 mmol) and formamidine acetate (130 mg, 99%, 1.24 mmol) in EtOH (5 mL) was refluxed for 22 h. Additional formamidine acetate (100 mg) was added and the reaction mixture was refluxed for 7 h followed by concentration. The residue was purified on a silica gel column using chloroform:methanol (1:0 to 95:5) as eluent to give 60 mg (89%) of desired compound, as a light yellow oil.

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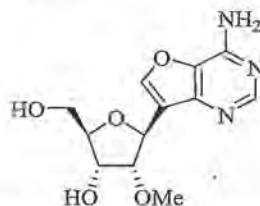
^1H NMR (CDCl_3): δ 8.43 (s, 1H), 7.94 (s, 1H), 7.51-7.20 (m, 15H), 5.68 (bs, 2H), 5.17 (s, 1H), 4.49 (s, 1H), 4.35 (t, $J = 6.3$ Hz, 1H), 3.38-3.22 (m, 2H), 1.52 (s, 3H), 1.49 (s, 3H), 1.39 (s, 3H); MS (ES^+): 564.49 ($\text{M}+\text{H}$) $^+$.

35

Step 3: A solution of compound from Step 2 (55 mg, 0.10 mmol) in MeOH (2 mL) was treated with 20% HCl in MeOH (2.5 mL) and stirred at room temperature for 1 h followed by concentration. The residue was redissolved in a small amount of MeOH and treated with ether to precipitate the desired HCl salt, which was collected by filtration to give 19 mg (54%) of desired product as hydrochloride, as yellow solid.

^1H NMR (MeOH- d_4): δ 8.71 (s, 1H), 8.55 (d, $J = 0.4$ Hz, 1H), 5.17 (s, 1H), 4.45-4.37 (m, 1H), 4.29 (d, $J = 8.3$ Hz, 1H), 4.12-3.87 (m, 2H), 1.45 (s, 3H); IR (KBr, cm^{-1}): 3409, 3132, 1677, 1036; MS (ES^+) 304.37 ($\text{M}+\text{Na}$) $^+$.

Example B-26



4-Amino-7-β-(2'-O-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidine (Scheme B-6).

Step 1: A solution of anomeric isomers from Example A-6, Step 3 (3.07 g, 8.36 mmol) in DMF (48 mL) was treated with *t*-BuOCH(NMe₂)₂ (10 mL, 48.43 mmol) and stirred at room temperature for 15 h. The reaction mixture was diluted with toluene (300 mL), washed with water (2 x 150 mL) and brine (150 mL), and dried over MgSO₄. After filtration, the filtrate was concentrated to give 3.75 g of desired product as yellow oil, which was used as such for next step.

MS (ES^+) 445.48 ($\text{M}+\text{Na}$) $^+$.

Step 2: The product from Step 1 (3.7 g crude) was dissolved in chloroform (75 mL) and treated with a solution of TFA (1.1 mL) in H₂O (50 mL) followed by vigorous stirring at room temperature for 20 h. The reaction mixture was diluted with chloroform (75 mL) and was washed with water (75 mL). The organic layer was separated and dried over MgSO₄. After filtration, the filtrate was concentrated to give 3.67 g of desired product as a yellow oil, which was used as such for next step.

MS (ES⁺) 396.45 (M+H)⁺.

5 Step 3: A mixture of compound from Step 2 (3.62 g), 18-crown-6 (1.78 g, 6.73 mmol) and KF (0.97 g, 16.7 mmol) in DMF (75 mL) was treated dropwise with chloroacetonitrile (1.6 mL, 25 mmol) followed by stirring at room temperature for 23 h. The reaction mixture was diluted with EtOAc (200 mL), washed with water (2 x 100 mL) and brine (100 mL), and dried over MgSO₄. After filtration, the filtrate was concentrated to give 3.24 g of desired product as brown oil, which was used as such for next step.

10 MS (ES⁺) 457.40 (M+Na)⁺.

Step 4: A solution of compound from Step 3 (3.19 g) in THF (95 mL) was cooled to -78 °C and treated with LDA (2M in heptane/THF/ethylbenzene, 14.5 mL) dropwise followed by stirring at -78 °C for 3 h. The reaction was quenched with water (2.4 mL) and stirred at room temperature for 1 h. After concentration, the residue was purified on a silica gel column using hexanes:ethyl acetate (1:0 to 2:1) as eluent to give 863 mg (24% for four steps, R_f = 0.50, hexanes/EtOAc = 2:1) of desired product as a brown oil. ¹H NMR (DMSO- *d*₆): δ 7.64 (s, 1H), 7.40-7.28 (m, 10H), 5.79 (s, 2H), 4.74 (d, *J* = 7.3 Hz, 1H), 4.60-4.46 (m, 4H), 4.20-3.95 (m, 2H), 3.88 (dd, *J* = 7.4, 5.1 Hz, 1H), 3.65-3.45 (m, 2H), 3.30 (s, 3H); MS (ES⁺) 435.44 (M+H)⁺.

25 Step 5: A mixture of compound from Step 4 (404 mg, 0.93 mmol) and formamidine acetate (1.96 g, 18.6 mmol) in EtOH (14 mL) was refluxed for 40 h. The reaction mixture was concentrated and purified on a silica gel column using chloroform:methanol (1:0 to 96:4) as eluent to give 317 mg (74%) of desired product as a light brown oil.

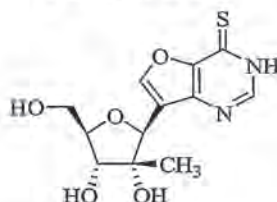
¹H NMR (CDCl₃): δ 8.40 (s, 1H), 7.82 (d, *J* = 0.9 Hz, 1H), 7.36-7.26 (m, 10H), 5.54 (bs, 2H), 5.28 (dd, *J* = 3.4, 0.8 Hz, 1H), 4.68-4.49 (m, 4H), 4.35-4.28 (m, 1H), 4.22-4.15 (m, 2H), 3.84-3.60 (m, 2H), 3.53 (s, 3H); MS (ES⁺) 462.43 (M+H)⁺.

30

Step 6: A solution of compound from Step 5 (161 mg, 0.35 mmol) in MeOH (15 mL) was treated with 1N aqueous HCl (1 mL) and Pd-C (10%, 60 mg) followed by hydrogenation (~50 psi) for 6 h. After filtration and concentration, the residue was purified on a silica gel column using chloroform/MeOH (1:0 to 4:1) as eluent to give 57 mg (58%) of desired product.

^1H NMR (MeOH- d_4): δ 8.25 (s, 1H), 8.08 (d, J = 0.4 Hz, 1H), 5.03 (d, J = 8.0 Hz, 1H), 4.43 (dd, J = 4.9, 2.2 Hz, 1H), 4.18 (dd, J = 7.9, 4.9 Hz, 1H), 4.12 (dd, J = 4.5, 2.2 Hz, 1H), 3.90-3.67 (m, 2H), 3.39 (s, 3H); IR (KBr, cm^{-1}) 3419, 2925, 1656, 1438, 1090; MS (ES^+) 282.54 ($\text{M}+\text{H}^+$); Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_5 \cdot 0.75 \text{ MeOH} \cdot 0.25 \text{ H}_2\text{O}$: C, 49.43; H, 6.02; N, 13.56. Found: C, 49.02; H, 5.77; N, 13.31.

Example B-27



7-β-(2'-C-Methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidin-4(3H)-thione (Scheme B-7).

Step 1: To a solution of compound from Example B-1, Step 2 (17 g, 35.01 mmol) in DMF (250 mL) was added potassium fluoride (4.06 g, 70.02 mmol), 18-crown-6 (7.31 g, 27.65 mmol) followed by chloroacetonitrile (7.93 g, 105.03 mmol) and the mixture was stirred for 18 h at room temperature. The reaction was diluted with ethylacetate (1 L) and washed with water (2 x 200 mL), brine (1 x 200 mL) and dried (MgSO_4). After filtration, the filtrate was concentrated to afford 16.5 g of desired product, which was used in the next reaction without further purification.

MS (ES^+) 525.28 ($\text{M}+1$).

Step 2: To a stirred solution of product from Step 1 (15 g, 28.62 mmol) in THF (450 mL) was added lithiumdiisopropylamide (57.2 mmol, 114.5 mmol, 2M solution in

THF) at -78 °C over a period of 30 min and stirred further at same temperature for 30 min. After quenching the reaction mixture with water (10 mL), it was concentrated and the residue was purified on a column of silica gel using ethyl acetate:hexanes (0 to 20%) as eluent to afford 2.8 g (18.5%) of desired product.

- 5 ¹H NMR (DMSO-*d*₆): δ 7.52 (d, *J* = 0.9 Hz, 1H), 7.38-7.26 (m, 15H), 5.63 (bs, 2H, D₂O exchangeable), 4.83 (d, *J* = 0.9 Hz, 1H), 4.62-4.54 (m, 6H), 4.17 (q, *J* = 4.7 Hz, 1H), 3.89 (d, *J* = 4.9 Hz, 1H), 3.69-3.59 (m, 2H), 1.15 (s, 3H); IR (neat): 3446.8, 3344.5, 3233.6, 3063.0, 3031.6, 2977.6, 2871.3, 2202.3, 1955.7, 1879.2, 1814.9, 1766.3, 1726.9, 1636.1, 1551.5, 1494.8, 1450.5, 1364.0, 1260.6, 1176.7, 1093.6, 1027.6, 912.4, 873.6, 819.6, 787.0, 737.7 and 698.3 cm⁻¹; MS (ES⁺) 547.33 (M+23), (ES⁻): 523.24 (M-1); Anal. Calcd for C₃₂H₃₂N₂O₅: C, 73.26; H, 6.14; N, 5.33. Found: C, 73.67; H, 6.33; N, 4.90.
- 10

Step 3: To a stirred solution of compound from Step 2 (2.8 g, 5.34 mmol) in pyridine (100 mL) was added triethylamine (35 mL) and H₂S gas was bubbled for 30 min. The reaction mixture was transferred to a steel bomb and stirred at 60 °C for 16 h. After concentration, the residue was purified on a column of silica gel using ethyl acetate:hexanes as eluent to provide 2.35 g (78.8%) of desired product as a yellow brown solid.

- 15 ¹H NMR (DMSO-*d*₆): δ 8.48 (bs, 1H, D₂O exchangeable), 8.32 (bs, 1H, D₂O exchangeable), 7.43 (s, 1H), 7.37-7.25 (15H), 6.46 (bs, 2H, D₂O exchangeable), 4.89 (s, 1H), 4.65 (m, 6H), 4.17 (dd, *J* = 9.0, 4.3 Hz, 1H), 3.92 (d, *J* = 5.3 Hz, 1H), 3.71 (dd, *J* = 10.7, 4.1 Hz, 1H), 3.65 (dd, *J* = 10.7, 4.3 Hz, 1H), 1.16 (s, 3H); MS (ES⁺) 559.27 (M+1), 581.23 (M+23).
- 20

Step 4: A mixture of product from Step 3 (2.3 g, 4.12 mmol) and triethylorthoformate (100 mL) was heated at 100 °C for 18 h. After concentration, the residue was purified on a column of silica gel using ethyl acetate:hexanes as eluent to afford 1.32 g (56.5%) of desired product along with some unidentified products.

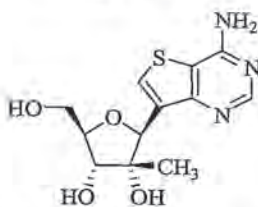
- 25 ¹H NMR (DMSO-*d*₆): δ 14.10 (bs, 1H, D₂O exchangeable), 8.34 (s, 1H), 8.26 (s, 1H), 7.38-7.25 (m, 15H), 5.21 (s, 1H), 4.73-4.52 (m, 6H), 4.20-4.15 (m, 1H), 4.03 (d, *J* =
- 30

7.5 Hz, 1H), 3.79-3.66 (m, 2H), 1.20 (s, 3H); MS (ES^+) 569.74 (M+1), 591.37 (M+23); Anal. Calcd for $C_{33}H_{32}N_2O_5S$: C, 69.69; H, 5.67; N, 4.92. Found: C, 69.94; H, 5.70; N, 4.88.

- 5 Step 5: To a stirred solution of product from Step 4 (0.1 g, 0.176 mmol) in dichloromethane (10 mL) was added BCl_3 (1.7 mL, 1.7 mmol, 1M solution in dichloromethane) at $-78^\circ C$ and further stirred at this temperature for 30 min and at $-30^\circ C$ for another 30 min. The reaction was quenched by adding water (1.5 mL) and brought to room temperature over a period of 30 min. After neutralization with
10 aqueous NH_3 and concentrating, the residue was purified on a column of silica gel using methanol and chloroform (0 to 30%) as eluent to afford 10 mg (19%) of product as a colorless solid.

^1H NMR ($DMSO-d_6$): δ 14.00 (bs, 1H, D_2O exchangeable), 8.39 (s, 1H), 8.26 (s, 1H), 5.00 (d, $J = 4.8$ Hz, 1H, D_2O exchangeable), 4.94 (s, 1H), 4.82 (t, $J = 5.4$ Hz, 1H, D_2O
15 exchangeable), 4.75 (s, 1H, D_2O exchangeable), 3.77-3.70 (m, 3H), 3.63-3.54 (m, 1H), 0.92 (s, 3H); MS (ES^+) 321.26 (M+1), (ES^-) 297.30 (M+35); Anal. Calcd for $C_{12}H_{14}N_2O_5S \cdot 0.75 H_2O$: C, 46.22; H, 5.01; N, 8.98. Found: C, 46.85; H, 5.24; N, 8.36.

Example B-28



- 30 **4-Amino-7- β -(2'-C-methyl-D-ribofuranosyl)-thieno[3,2-*d*]pyrimidine (Scheme B-8).**

Step 1: A solution of compound from Example B-24, Step 2 (1.23 g, 2.49 mmol) in dichloromethane (10 mL) at $0^\circ C$ was treated with triethylamine (0.44 mL) followed by
35 addition of methyl sulfonyl chloride (343 mg, 3.0 mmol) in dichloromethane (6 mL) over a period of 10 min. The reaction mixture was stirred at $0^\circ C$ for 1 h and diluted

with chloroform (20 mL) and was washed with brine (2 x) and dried over MgSO_4 . After filtration, the filtrate was concentrated to give desired product (1.43 g) and used as such for next step.

MS (ES^+) 594.28 ($\text{M}+\text{Na}$)⁺.

5

Step 2: A mixture of the product from Step 1 (1.43 g), acetylthioacetoneitrile (575 mg, 5.0 mmol), and anhydrous Na_2CO_3 (530 mg, 5.0 mmol) in absolute ethanol (30 mL) was refluxed for 6 h and concentrated to dryness. The residue was partitioned between chloroform and water. The organic layer was separated and further washed with water and dried over MgSO_4 . After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using hexanes:ether (1:0 to 7:3) as eluent to give 140 mg (10% for two steps) of desired product as an oil.

10

^1H NMR ($\text{DMSO}-d_6$): δ 7.54-7.47 (m, 4H), 7.35-7.26 (m, 6H), 7.09 (d, $J = 1.2$ Hz, 1H), 5.86 (bs, 2H), 4.53 (s, 1H), 4.30 (d, $J = 2.3$ Hz, 1H), 4.04-3.99 (m, 1H), 3.68 (t, $J = 4.4$ Hz, 2H), 1.40 (s, 3H), 1.20 (s, 3H), 0.85 (bs, 12H); MS (ES^+) 571.37 ($\text{M}+\text{Na}$)⁺.

15

Step 3: A mixture of compound from Step 2 (120 mg, 0.22 mmol) and formamidine acetate (227 mg, 2.16 mmol) in EtOH (5 mL) was refluxed for 16 h. Additional formamidine acetate (227 mg, 2.16 mmol) was added followed by reflux for 16 h. After concentration, the residue was taken in chloroform and washed with water and dried over MgSO_4 . After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using hexanes:ether (1:0 to 1:1) as eluent to give 11 mg (9%) of desired product as an oil.

20

^1H NMR (CDCl_3): δ 8.65 (s, 1H), 7.80-7.70 (m, 4H), 7.64 (d, $J = 1.2$ Hz, 1H), 7.50-7.36 (m, 6H), 5.56 (s, 1H), 5.38 (bs, 2H), 4.51 (d, $J = 3.1$ Hz, 1H), 4.25 (dd, $J = 7.2$, 3.8 Hz, 1H), 4.00-3.92 (m, 2H), 1.75 (s, 3H), 1.45 (s, 3H), 1.12 (s, 3H), 1.10 (s, 9H); MS (ES^+) 576.49 ($\text{M}+\text{H}$)⁺.

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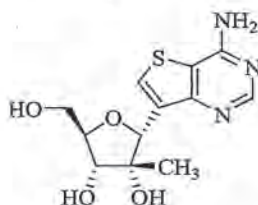
Step 4: A solution of compound from Step 3 (28 mg, 0.049 mmol) in 12% dry HCl/MeOH (2 mL) was stirred at room temperature for 0.5 h followed by concentration. The residue was treated with 12% dry HCl/MeOH (2 mL) again and

30

stirred at room temperature for 15 min followed by concentration. This process was repeated once more with 1 mL of dry 12% HCl/MeOH. The residue was washed with ether (2 x) and dried under vacuum to afford 16 mg (88%) of desired product as hydrochloride.

- 5 ^1H NMR (D_2O): δ 8.45 (s, 1H), 8.18 (s, 1H), 5.14 (s, 1H), 3.98-3.75 (m, 4H), 0.80 (s, 3H); MS (ES^+) 298.41 ($\text{M}+\text{H}$) $^+$.

Example B-29



- 20 **4-Amino-7- α -(2'-C-methyl-D-ribofuranosyl)-thieno[3,2-*d*]pyrimidine (Scheme B-8).**

- Step 1: Under Example B-28 in Step 2, another product alpha isomer was also isolated. ^1H NMR ($\text{DMSO}-d_6$): δ 7.49-7.42 (m, 4H), 7.34-7.20 (m, 7H), 5.99 (s, 2H), 4.61 (s, 1H), 4.25 (s, 1H), 3.92 (t, $J = 6.8$ Hz, 1H), 3.59-3.53 (m, 2H), 1.19 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 0.83 (s, 9H); IR (neat, cm^{-1}) 3473, 3359, 2932, 2858, 2198, 1428, 1109; Anal. Calcd for $\text{C}_{30}\text{H}_{36}\text{N}_2\text{O}_4\text{Si}$: C, 65.66; H, 6.61; N, 5.10. Found: C, 65.42; H, 6.68; N, 4.94; MS (ES^+): 571.49 ($\text{M}+\text{Na}$) $^+$.
- 25

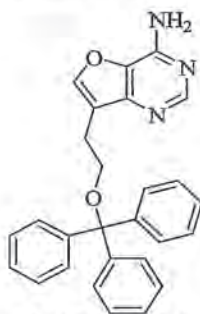
- Step 2: A mixture of compound from Step 1 (230 mg, 0.42 mmol) and formamidine acetate (437 mg, 4.20 mmol) in EtOH (6 mL) was refluxed for 6 h. Additional formamidine acetate (437 mg, mmol) was added followed by reflux for 18 h. The reaction mixture was concentrated and the residue was taken in chloroform, washed with water, and dried over MgSO_4 . After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using hexanes:EtOAc (1:0 to 1:1) as eluent to give 195 mg (81%) of desired product as an oil.
- 30
- 35

¹H NMR (DMSO-*d*₆): 8.40 (s, 1H), δ 7.99 (s, 1H), 7.78-7.41 (m, 10H), 5.43 (s, 1H), 4.63 (s, 1H), 4.24 (t, *J* = 5.5 Hz, 1H), 3.86 (d, *J* = 5.3 Hz, 2H), 1.55 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H), 1.09 (s, 9H); IR (neat, cm⁻¹) 3450, 3337, 2932, 2858, 1636, 1573, 1513, 1109; MS (ES⁺) 598.40 (M+Na)⁺; Anal. Calcd for C₃₁H₃₇N₃O₄SSi•H₂O: C, 62.70; H, 6.62; N, 7.08. Found: C, 62.40; H, 6.37; N, 6.99.

Step 3: Compound from Step 2 (90 mg, 0.16 mmol) was treated the same way as Step 4 in Example B-28. It gave 43 mg (74%) of desired product as hydrochloride.

¹H NMR (MeOH-*d*₄): δ 9.54 (bs, 2H), 8.74 (s, 1H), 8.43 (s, 1H), 5.13 (s, 1H), 4.27-4.17 (m, 1H), 4.00 (d, *J* = 8.0 Hz, 1H), 3.76-3.52 (m, 2H), 1.16 (s, 3H); IR (KBr, cm⁻¹) 3367, 1661, 1607, 1568, 1036; MS (ES⁺) 298.41 (M+H)⁺; Anal. Calcd for C₁₂H₁₅N₃O₄S•HCl•1.5 H₂O: C, 39.95; H, 5.31; N, 11.65. Found: C, 40.48; H, 5.37; N, 11.24.

Example B-30

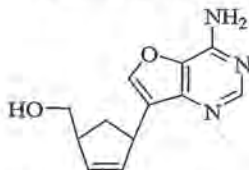


7-(2-(Trityloxy)ethyl)furo[3,2-d]pyrimidin-4-amine (Scheme B-6).

It was prepared by following the method (alternate approach, Steps 1-5) used for compound B-24 starting from Example A-1.

¹H NMR (DMSO-*d*₆): δ 8.18 (s, 1H), 8.02 (s, 1H), 7.32-7.22 (m, 15H), 3.25 (t, *J* = 6.6 Hz, 2H), 2.87 (t, *J* = 6.6 Hz, 2H).

Example B-31

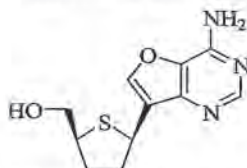


5
10 (cis)-(4-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)cyclopent-2-en-1-yl)methanol (Scheme B-6).

It was prepared by following the method used for compound **B-24** starting from Example A-9.

15 ¹H NMR (CDCl₃): δ 8.42 (s, 1H), 7.58 (s, 1H), 5.89 (td, *J* = 5.4, 2.3 Hz, 1H), 5.76 (td, *J* = 5.4, 2.3 Hz, 1H), 5.22 (bs, 2H, D₂O exchangeable), 4.54 (bs, 1H, D₂O exchangeable), 4.18-4.10 (m, 1H), 3.88 (dd, *J* = 10.9, 3.7 Hz, 1H), 3.76 (dd, *J* = 10.7, 3.0 Hz, 1H), 3.22-3.13 (m, 1H), 2.64 (td, *J* = 13.9, 9.7 Hz, 1H), 2.07 (td, *J* = 13.9, 6.4 Hz, 1H); MS (ES⁺) 254.52 (M+23).

Example B-32

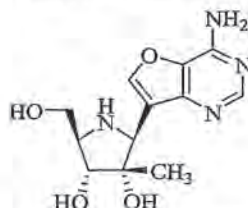


25
30 (5-(4-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)-2-thienyl)methyl)tetrahydrothiophen-2-yl)methanol (Scheme B-6).

It was prepared by following the method used for compound **B-24** starting from Example A-10.

35 ¹H NMR (CD₃OD): δ 8.58 (s, 1H), 8.32 (s, 1H), 4.70 (t, *J* = 6.4 Hz, 1H), 3.85 (t, *J* = 6.5 Hz, 1H), 3.65 (m, 2H), 2.50 (m, 1H), 2.20 (m, 2H), 1.95 (m, 1H); MS (ES⁺) 252.53 (M+H)⁺.

Example B-33



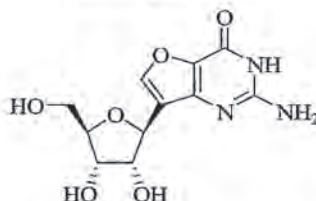
2-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)-5-(hydroxymethyl)-3-methylpyrrolidine-3,4-diol (Scheme B-6).

It was prepared by following the method used for compound **B-24** starting from Example **A-11**.

^1H NMR (D_2O): 8.58 (s, 1H), 8.53 (s, 1H), 5.05 (s, 1H), 4.51 (d, $J = 9.2$ Hz, 1H), 4.10-4.12 (m, 2H), 3.80-3.90 (m, 1H), 1.17 (s, 3H); ^{13}C NMR (D_2O): 152.16, 148.59, 147.63, 143.90, 133.77, 113.80, 78.89, 73.45, 63.16, 60.67, 57.82, 19.51; MS (ES^+)

281.41.

Example B-34



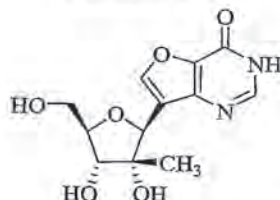
2-Amino-7-β-(D-ribofuranosyl)-furo[3,2-*d*]pyrimidin-4(3*H*)-one (Scheme B-4).

It was prepared from Example **A-2** by following the same procedure used for Example **B-21**.

^1H NMR ($\text{DMSO}-d_6$): δ 8.11 (s, 1H), 4.69 (d, $J = 6.9$ Hz, 1H), 4.05-4.01 (m, 1H), 3.97-3.95 (m, 1H), 3.89-3.86 (m, 1H), 3.80-3.63 (m, 2H); MS (ES^-) 282.34 ($\text{M}-1$).

Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_5 \cdot 2 \text{HCl} \cdot 1.5 \text{H}_2\text{O}$: C, 34.55; H, 4.75; N, 10.99. Found: C, 34.37; H, 4.98; N, 10.87.

Example B-35

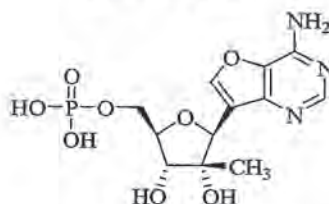


7-β-(2'-C-Methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidin-4(3H)-one (Scheme B-1).

It was prepared by deprotection of Example B-11 by hydrogenation under the same conditions used with Example B-16.

¹H NMR (DMSO-*d*₆): δ 12.42 (bs, 1H, D₂O exchangeable), 8.20 (s, 1H), 8.08 (s, 1H), 4.98 (d, *J* = 6.4 Hz, 1H), 4.93 (s, 1H), 4.83 (t, *J* = 5.0 Hz, 1H, D₂O exchangeable), 4.73 (s, 1H, D₂O exchangeable), 3.78-3.70 (m, 2H), 3.64-3.54 (m, 1H), 0.93 (s, 3H); MS (ES⁻) 281.34 (M-1); Anal. Calcd for C₁₂H₁₄N₂O₆•CH₄O: C, 49.66; H, 5.77; N, 8.91. Found: C, 49.63; H, 5.61; N, 8.26.

Example C-1



4-Amino-7-β-(2'-C-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidine-5'-monophosphate (Scheme C-1).

Step 1: A solution of Example B-24 (50 mg, 0.18 mmol) in THF (6 mL) was treated with 1-*H*-tetrazole (39 mg, 98%, 0.55 mmol) and cooled with ice/water followed by dropwise addition of dibenzyl *N,N*-diisopropylphosphoramidite (75 μL, 0.22 mmol). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. Additional dibenzyl *N,N*-diisopropylphosphoramidite (25 μL, 0.075 mmol) was added and the mixture was stirred at room temperature further for 1 h. The reaction mixture

was cooled to -40 °C, and treated with *m*-CPBA (82 mg, max. 77%) followed by stirring at 0 °C for 2 h. After diluting with chloroform (100 mL), the mixture was washed with 5% Na₂SO₃ (2 x 30 mL), sat. NaHCO₃ (2 x 30 mL) and water (2 x 30 mL), and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using chloroform/MeOH (1:0 to 10:1) as eluent to give 40 mg (41%) of desired product as a white solid.

¹H NMR (DMSO-*d*₆): δ 8.22 (s, 1H), 8.10 (s, 1H), 7.39 (bs, 2H), 7.36-7.27 (m, 10H), 5.23 (d, *J* = 6.4 Hz, 1H), 5.02 (s, 2H), 5.00 (s, 2H), 4.99 (s, 1H), 4.91 (s, 1H), 4.34-4.26 (m, 2H), 4.12-3.96 (m, 2H), 0.92 (s, 3H); MS (ES⁺) 542.31 (M+H)⁺.

10

Step 2: A mixture of product from Step 1 (35 mg, 0.065 mmol) and Pd-C (10%, 20 mg) in MeOH (15 mL) was hydrogenated for 16 h (~50 psi). After removing the catalyst by filtration, the filtrate was concentrated and the residue was treated with water (10 mL) and washed with EtOAc (2 x 10 mL) and chloroform (2 x 10 mL). The aqueous phase was concentrated to dryness. The residue was dissolved in 2 mL of H₂O and filtered, which gave a 24.4 mM (measured by UV at 274 nM) solution of desired monophosphate.

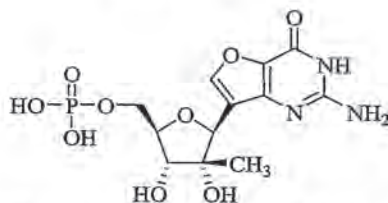
15

¹H NMR (D₂O): δ 8.13 (bs, 1H), 8.03 (s, 1H), 5.03 (s, 1H), 4.20-4.08 (m, 1H), 4.06-3.85 (m, 3H), 0.88 (s, 3H); ³¹P NMR (D₂O): δ 0.83 (bs, 1P); MS (ES⁺) 362.42 (M+H)⁺.

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Example C-2

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2-Amino-7-β-(2'-C-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidin-4(3H)-one-5'-monophosphate (Scheme C-1).

Step 1: A mixture of Example B-21 (48 mg, 0.15 mmol), 2,2-dimethoxypropane (0.34 mL, 98%, 2.72 mmol), and *p*-toluenesulfonic acid monohydrate (40 mg, 0.21 mmol) in

acetone (2 mL) and DMF (2 mL) was stirred at room temperature of 2 h followed by neutralization with 0.5 N aqueous NaOH. The mixture was concentrated to dryness and used as such for the next step.

MS (ES⁺) 338.37 (M+H)⁺.

5

Step 2: The product from Step 1 was mixed with imidazole (60 mg, 0.88 mmol) and TBDMSCl (45 mg, 0.30 mmol) in DMF (3 mL) and stirred at room temperature for 8 h. Additional imidazole (120 mg) and TBDMSCl (90 mg) were added and the reaction mixture was further stirred at room temperature for 17 h followed by concentration to dryness. The residue was purified on a silica gel column using chloroform/MeOH (1:0 to 95:5) as eluent to give 50 mg (74% for two steps) of desired product as a colorless film.

¹H NMR (MeOH-*d*₄): δ 7.58 (d, *J* = 1.0 Hz, 1H), 4.91 (s, 1H), 4.29 (d, *J* = 2.9 Hz, 1H), 4.02-3.95 (m, 1H), 3.78-3.66 (m, 2H), 1.49 (s, 3H), 1.28 (s, 3H), 1.11 (s, 3H), 0.81 (s, 9H), 0.00 (s, 6H); MS (ES⁺) 452.44 (M+H)⁺.

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Step 3: A mixture of compound from Step 2 (50 mg, 0.11 mmol) and 4-methoxytrityl chloride (70 mg, 0.22 mmol) in pyridine (3 mL) was stirred at 70 °C for 13 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with water (2 x 50 mL), brine (50 mL), and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using hexanes/EtOAc (1:0 to 1:1) as eluent to give 45 mg (57%) of desired product as a colorless film.

¹H NMR (CDCl₃): δ 9.91 (bs, 1H), 7.36-7.00 (m, 13H), 6.90 (bs, 1H), 6.68 (d, *J* = 8.8 Hz, 2H), 4.72 (s, 1H), 4.23 (d, *J* = 3.2 Hz, 1H), 4.00-3.94 (m, 1H), 3.68 (d, *J* = 4.0 Hz, 2H), 3.66 (s, 3H), 1.38 (s, 3H), 1.28 (s, 3H), 0.99 (s, 3H), 0.82 (s, 9H), 0.00 (s, 6H); MS (ES⁺) 746.31 (M+Na)⁺.

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Step 4: A solution of product from Step 3 (45 mg, 0.062 mmol) in THF (3 mL) was treated with Bu₄NF (1M in THF, 0.12 mL) followed by stirring at room temperature for 2.5 h. The reaction mixture was concentrated and the residue was purified on a

25

silica gel column using hexanes/EtOAc/MeOH (1:1:0 to 1:1:0.1) as eluent to give 39 mg (100%) of desired product as a colorless film.

¹H NMR (CDCl₃): δ 7.77 (bs, 1H), 7.60 (s, 1H), 7.40-7.20 (m, 12H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.30 (s, 1H), 5.17 (s, 1H), 4.64 (d, *J* = 1.4 Hz, 1H), 4.34 (bs, 1H), 4.03-3.68 (m, 2H), 3.80 (s, 3H), 1.60 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H); (MS (ES⁺) 632.28 (M+Na)⁺.

Step 5: A solution of product from Step 4 (39 mg, 0.62 mmol) in dichloromethane (2 mL) was treated with 1-*H*-tetrazole (14 mg, 98%, 0.20 mmol) and the suspension was stirred at room temperature for 5 min followed by addition of dibenzyl *N,N*-diisopropylphosphoramidite (35 μL, 0.1 mmol). The reaction mixture was stirred at room temperature for 3.5 h, cooled to -40 °C, and treated with a solution of *m*-CPBA (30 mg, max. 77%) in dichloromethane (1 mL) followed by stirring at 0 °C for 2 h. The reaction mixture was diluted with chloroform (50 mL) and washed with 5% Na₂SO₃ (2 x 15 mL), NaHCO₃ (2 x 15 mL), water (2 x 20 mL), and dried over MgSO₄. After filtration, the filtrate was concentrated, and the residue was purified on a silica gel column using hexanes/EtOAc/MeOH (1:1:0 to 1:1:0.1) as eluent to give 38 mg (70% for two steps) of desired product as a white solid.

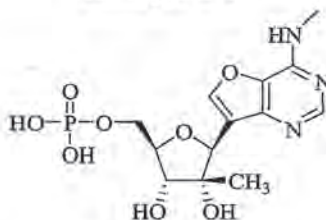
¹H NMR (DMSO-*d*₆): δ 10.88 (s, 1H), 7.69 (s, 1H), 7.44-7.10 (m, 23H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.06 (s, 2H), 5.03 (s, 2H), 4.51 (s, 1H), 4.12 (d, *J* = 2.3 Hz, 1H), 4.05-3.95 (m, 3H), 3.69 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 0.81 (s, 3H); IR (KBr, cm⁻¹) 3339, 2984, 1699, 1611, 1252, 1017; MS (ES⁺) 870.30 (M+H)⁺; Anal. Calcd for C₄₉H₄₈N₃O₁₀P•0.75 H₂O: C, 66.62; H, 5.65; N, 4.76. Found: C, 66.68; H, 5.64; N, 4.80.

Step 6: A mixture of product from Step 5 (30 mg, 0.034 mmol) and Pd-C (10%, 20 mg) in MeOH (15 mL) was hydrogenated for 20 h (~50 psi). After removing the catalyst by filtration, the filtrate was concentrated, and the residue was treated with TFA (3 mL) and stirred at room temperature for 1 h followed by concentration to dryness. The residue was stirred with EtOAc (20 mL), water (20 mL), and TEAB (pH=8.0, 1M, 2 mL) for 30 min. The organic layer was collected, the aqueous phase was further

extracted with EtOAc (2 x 20 mL) and the combined organic extracts were concentrated to dryness. The residue was treated with MeOH (6 mL) and 20% dry HCl in MeOH (7.5 mL) followed by stirring at room temperature for 1.2 h. The reaction mixture was concentrated to dryness and purified by HPLC (CH₃CN/1M TEAB buffer, pH = 8.0, 0-20 min, 0-35% CH₃CN; 20-22 min, 35-60% CH₃CN, monitoring at 260 nm) to give the desired product (*t_R* = 14.1 min). All the fractions containing product were pooled together and reconstituted to 2 mL with water, which gave 6.1 mM (measured by UV at 288 nm) solution of desired monophosphate.

¹H NMR (D₂O): δ 7.78 (d, *J* = 0.7 Hz, 1H), 4.91 (d, *J* = 0.6 Hz, 1H), 4.15-4.07 (m, 1H), 4.04-3.86 (m, 3H), 0.95 (s, 3H); ³¹P NMR (D₂O): 1.81 (s, 1P); MS (ES⁺) 378.30 (M+H)⁺.

Example C-3



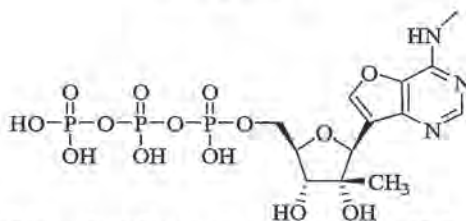
4-Methylamino-7-β-(2'-C-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidine-5'-monophosphate (Scheme C-1).

A solution of Example B-17 (50 mg, 0.17 mmol) in THF (5 mL) was cooled to 0 °C and to this were added, tetrazole (0.51 mmol, 35 mg) and dibenzyl diisopropylphosphoramidate (0.17 mmol, 61 μL) and the mixture was stirred for 1 h. Additional 0.2 equivalents of the phosphorylating reagents were added and stirring continued for 2 h at room temperature. The reaction was then cooled to -40 °C and m-chloroperbenzoic acid (80 mg, 0.34 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was quenched by the addition of 10% aqueous sodium sulfite (3 mL), and diluted with CHCl₃ (20 mL). The organic layer was washed with water (20 mL), aqueous saturated sodium bicarbonate solution (2 x 20 mL), and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was

purified on a silica gel column using 0 to 5% MeOH in chloroform as eluent to give 70 mg of desired product. This product was dissolved in MeOH (10 mL) and to the solution was added 10% Pd-C (50 mg). The suspension was hydrogenated for 18 h at 50 psi, the catalyst was removed by filtration through Celite and the residue was taken in water and ethyl acetate (20 mL each). The organic layer was removed, and the aqueous layer was concentrated and purified by HPLC (gradient 0 to 100% CH₃CN in water on reverse phase C18 column, *t_R*-7.8 min). The desired fractions were collected and concentrated to give 46 mg (70%) of desired phosphate.

¹H NMR (D₂O δ in ppm) 8.05 (s, 1H), 8.04 (s, 1H), 5.20 (s, 1H), 3.90 (m, 4H), 2.90 (s, 3H), 0.90 (s, 3H). ³¹P NMR 4.7 ppm. MS (ES⁺) 376 (M+H)⁺, 398 (M+Na)⁺, MS (ES⁻) 374.30 (M-H)⁻.

Example C-4



4-Methylamino-7-β-(2'-C-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidine-5'-triphosphate (Scheme C-2).

Step 1: A mixture of Example B-17 (95 mg, 0.32 mmol), MMTrCl (550 mg, 98%, 1.75 mmol), DMAP (25 mg, 0.20 mmol), and pyridine (3.2 mL) in DMF (2 mL) was stirred at room temperature for 19 h followed by addition of triethylamine (2.4 mL, 17.22 mmol), DMAP (20 mg, 0.16 mmol), and 4-nitrobenzoyl chloride (1.22 g, 98%, 6.44 mmol) and stirred at room temperature for five days. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (2 x 50 mL), brine (50 mL), and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using hexanes/EtOAc (1:0 to 1:1) as eluent to give 110 mg (34%) of desired product as a brown syrup.

^1H NMR (CDCl_3): δ 8.88 (s, 1H), 7.89 (s, 1H), 8.51-7.20 (m, 24H), 6.85 (d, $J = 9.0$ Hz, 2H), 5.95 (d, $J = 4.0$ Hz, 1H), 5.65 ($J = 0.8$ Hz, 1H), 4.27 (dd, $J = 8.0, 4.2$ Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.66-3.62 (m, 2H), 1.48 (s, 3H).

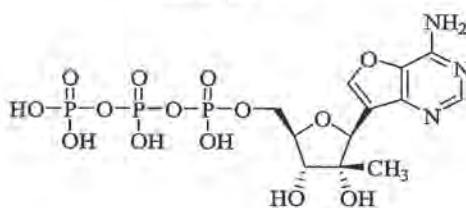
- 5 Step 2: A solution of product from Step 1 (105 mg, 0.1 mmol) in acetonitrile (10 mL) was treated with 0.2 N aqueous HCl (0.5 mL) and stirred at room temperature for 2 h. The reaction mixture was neutralized with 0.5 N aqueous NaOH to pH = 5 followed by dilution with water (20 mL) and concentration to remove most of acetonitrile. The aqueous mixture was extracted with chloroform (2 x 50 mL) and EtOAc (2 x 25 mL).
- 10 The combined organic extracts were dried over MgSO_4 . After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using hexanes/EtOAc/MeOH (1:0:0 to 1:1:0.1) as eluent to give 600 mg (81%) of desired product as a yellow solid.

- ^1H NMR ($\text{DMSO}-d_6$): δ 9.13 (s, 1H), 8.46 (d, $J = 0.8$ Hz, 1H), 8.41-7.66 (m, 12H),
15 5.72 (d, $J = 3.2$ Hz, 1H), 5.60 (s, 1H), 5.18 (t, $J = 6.0$ Hz, 1H), 4.25 (dd, $J = 6.8, 3.6$ Hz, 1H), 3.85-3.79 (m, 2H), 3.66 (s, 3H), 1.37 (s, 3H); MS (ES^+): 743.26 ($\text{M}+\text{H}$) $^+$.

- Step 3: A suspension of product from Step 2 (50 mg, 0.067 mmol) in a mixture of pyridine (75 μL) and dioxane (220 μL) was treated with a freshly prepared solution of
20 chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one (1M in dioxane, 80 μL) and was stirred at room temperature for 20 min followed by treatment with a solution of tributylammonium pyrophosphate (1.6 $\text{Bu}_3\text{N}\cdot 1.0 \text{H}_4\text{P}_2\text{O}_7$, 51 mg, 0.11 mmol) in DMF (220 μL) and *n*-butylamine (70 μL) simultaneously. A clear solution formed which was stirred at room temperature for 30 min and treated with 2.8 mL of 1% I_2 in Py/ H_2O
25 (98/2). Excess iodine was reduced by addition of 5% aqueous sodium thiosulphate (230 μL) and the resulting solution was concentrated to dryness. The residue was treated with conc. NH_4OH (20 mL) and was stirred at room temperature overnight followed by concentration to dryness. The residue was dissolved in H_2O (20 mL) and washed with CH_2Cl_2 (2 x 15 mL). The aqueous phase was concentrated under vacuum for a short
30 period of time to remove the trace of CH_2Cl_2 and purified by DEAE ion exchange column chromatography with a linear gradient of TEAB buffer (1M TEAB buffer, pH

= 8.0/H₂O, 250 mL/250 mL, 0:1 to 1:0). The fractions containing the desired nucleotide were combined and concentrated. The residue was redissolved in H₂O and purified further by HPLC (CH₃CN/0.1M TEAB buffer, pH = 8.0, 0-20 min, 0-35% CH₃CN; 20-28 min, 35-100% CH₃CN, monitoring at 260 nm) to give the product (*t_R* = 15.6 min). The desired fractions were pooled together and re-dissolved in 2 mL of water to give 3.3 mM (measured by UV at 278 nm) solution of desired triphosphate.
¹H NMR (D₂O): δ 8.17 (s, 1H), 8.04 (s, 1H), 5.11 (s, 1H), 4.30-4.10 (m, 2H), 4.02 (s, 2H), 2.95 (s, 3H), 0.98 (s, 3H); ³¹P NMR (D₂O): δ -8.20 (d, *J* = 17.8 Hz, 1P), -9.86 (d, *J* = 17.3, 1P), -21.50 (t, *J* = 17.9 Hz, 1P); MS (ES⁻) 534.14 (M-1).

Example C-5



4-Amino-7-β-(2'-C-methyl-D-ribofuranosyl)-furo[3,2-d]pyrimidine-5'-triphosphate (Scheme C-2).

Step 1: A mixture of Example B-24 (138 mg, 0.49 mmol) and imidazole (175 mg, 2.57 mmol) in DMF (5 mL) was treated with TBDMSCl (130 mg, 0.86 mmol) followed by stirring at room temperature for 17 h. To this mixture were added triethylamine (3.2 mL), DMAP (30 mg, 0.25 mmol), 4-nitrobenzoyl chloride (1.66 g, 98%, 8.76 mmol), and DMF (3 mL) and stirring was continued for another 24 h. The reaction mixture was diluted with EtOAc (150 mL), washed with water (2 x 75 mL), brine (75 mL), and dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was purified by column chromatography on a silica gel column using hexanes/ethyl acetate (1:0 to 1:1) as eluent to give 266 mg of product, which was used as such for next step. MS (ES⁻) 841.47 (M-1).

Step 2: A solution of compound from Step 1 (260 mg) in THF (25 mL) was treated with tetrabutyl ammonium fluoride (1M in THF, 0.4 mL). The reaction mixture was stirred at room temperature for 2 h and additional tetrabutyl ammonium fluoride (1 mL) was added followed by stirring at room temperature for 5 h and concentration. The residue was purified by column chromatography on silica gel (hexanes/ethyl acetate/methanol, 1:1:0 to 1:1:0.1) to give 40 mg (11% for two steps) of desired product.

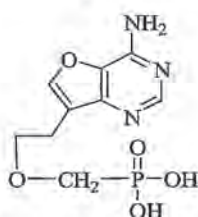
¹H NMR (DMSO-*d*₆): δ 11.96 (s, 1H), 9.25 (s, 1H), 8.60 (s, 1H), 8.50-8.17 (m, 12H), 5.78 (d, *J* = 3.3 Hz, 1H), 5.71 (s, 1H), 4.30 (m, 1H), 3.89-3.83 (m, 2H), 1.52 (s, 3H); MS (ES⁺) 727.58 (M-1).

Step 3: A suspension of product from Step 2 (37 mg, 0.051 mmol) in a mixture of pyridine (55 μL) and dioxane (165 μL) was treated with a freshly prepared solution of chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one (1M in dioxane, 60 μL). The reaction mixture was stirred at room temperature for 20 min followed by treatment with a solution of tributylammonium pyrophosphate (1.6 Bu₃N·1.0 H₄P₂O₇, 39 mg, 0.082 mmol) in DMF (165 μL) and *n*-butylamine (55 μL) simultaneously. A clear solution formed which was stirred at room temperature for 30 min followed by treatment with 2.1 mL of 1% I₂ in Py/H₂O (98/2). Excess iodine was reduced by addition of 5% aqueous sodium thiosulphate (175 μL) and the resulting solution was concentrated to dryness. The residue was treated with conc. NH₄OH (15 mL) and was stirred at room temperature overnight followed by concentration to dryness. The residue was dissolved in H₂O (20 mL) and washed with CH₂Cl₂ (2 x 15 mL). The aqueous phase was concentrated under vacuum for a short period of time to remove the trace of CH₂Cl₂ and purified by DEAE ion exchange column chromatography with a linear gradient of TEAB buffer (1M TEAB buffer, pH = 8.0/H₂O, 0:1 to 1:0). The fractions containing the desired nucleotide were combined and concentrated and the residue was redissolved in H₂O and purified further by HPLC (CH₃CN/0.1M TEAB buffer, pH = 8.0, 0-20 min, 0-35% CH₃CN; 20-28 min, 35-100% CH₃CN, monitoring at 260 nm) to give desired triphosphate (*t*_R = 14.7 min). The fractions containing desired product

were pooled together, concentrated and re-dissolved in 2 mL of water to give 1.38 mM (measured by UV at 274 nM) solution of triphosphate.

^1H NMR (D_2O): δ 8.15 (s, 1H), 8.09 (s, 1H), 5.12 (s, 1H), 4.29-4.10 (m, 2H), 4.02 (bs, 2H), 0.97 (s, 3H); ^{31}P NMR (D_2O): δ -8.50 (d, J = 15.8 Hz, 1P), -9.88 (d, J = 16.8, 4.5 Hz, 1P), -21.5 (dd, J = 15.8, 16.8 Hz, 1P); MS (ES $^-$) 520.53 (M-1).

Example C-6



(2-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)ethoxy)methylphosphonic acid (Scheme C-3).

Step 1: To a stirred solution of compound from Example B-30, 7-(2-trityloxyethyl)-furo[3,2-*d*]pyrimidin-4-ylamine (0.52 g, 1.23 mmol) in pyridine (20 mL) was added triphenylchloromethane (0.68 g, 2.46 mmol) at room temperature and the mixture was stirred at 70 °C for 16 h. Additional triphenylchloromethane (6.8 g, 24.6 mmol) was added and again stirred at 70 °C for 48 h. To the reaction mixture was added MeOH (50 mL) and stirred for 1 h at 70 °C. The reaction mixture was concentrated and the residue was dissolved in chloroform (100 mL), washed with water (2 x 50 mL), brine (50 mL), and dried (MgSO_4). After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using ethyl acetate in hexanes (0 to 50%), which afforded 0.788 g (96.5%) of desired trityl-[7-(2-trityloxyethyl)-furo[3,2-*d*]pyrimidin-4-yl]-amine, as a colorless solid.

^1H NMR ($\text{DMSO}-d_6$): δ 8.20 (s, 1H, D_2O exchangeable), 8.09 (s, 1H), 7.88 (s, 1H), 7.70-7.14 (m, 30H), 3.22 (t, J = 6.6 Hz, 2H), 5.87 (t, J = 6.4 Hz, 2H); MS (ES $^+$) 664.64 (M+1).

Step 2: A solution of compound from Step 1 (753 mg, 1.13 mmol) in acetonitrile (130 mL) was treated with aqueous 0.2 N HCl (6.5 mL, 1.3 mmol) followed by stirring at room temperature for 8 h. The reaction mixture was neutralized with aqueous 0.5 N NaOH, diluted with 150 mL of water, and concentrated under vacuum to remove most of the acetonitrile. The aqueous residue was extracted with chloroform (200 mL) and ethyl acetate (200 mL, 100 mL). The combined organic extracts were dried over MgSO₄. After filtration and concentration, the residue was purified on a silica gel column using hexanes:ethyl acetate:methanol (1:1:0 to 1:1:0.1) as eluent to give 394 mg (83%) of desired product as a white solid.

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10 ¹H NMR (DMSO-*d*₆): δ 8.18 (s, 1H), 8.04 (s, 1H), 7.95 (s, 1H), 7.40-7.14 (m, 15H), 4.80 (t, *J* = 5.5 Hz, 1H), 3.72-3.62 (m, 2H), 2.72 (t, *J* = 6.8 Hz, 2H); MS (ES⁺) 422.43 (M+H)⁺.

Step 3: A solution of product from Step 2 (345 mg, 0.82 mmol) in DMF (7 mL) was treated with sodium hydride (60%, 132 mg, 3.3 mmol) at room temperature and the mixture was stirred for 1 h. To this solution was added a solution of (di-isopropoxyphosphono)methyl tosylate (345 mg, 0.98 mmol) in DMF (1 mL) and the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with ethyl acetate (100 mL), neutralized with acetic acid and washed with water (2 x) and brine and the organic layer was dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using ethyl acetate:hexanes:methanol (1:1:0 to 1:1:0.1), then CMA-80 as eluents to give 160 mg (33%) of desired product as a colorless film.

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MS (ES⁺) 622.43 (M+Na)⁺.

25 Another compound with loss of one isopropyl group, 170 mg (37%) was isolated as a white solid.

MS (ES⁺) 558.43 (M+H)⁺.

The mixture of both compounds was used for the next step.

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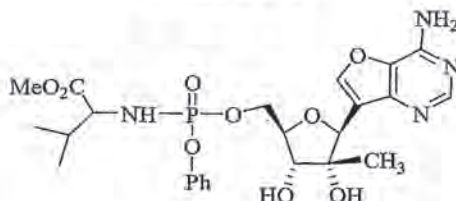
Step 4: A solution of products from Step 3, (139 mg, 0.23 mmol) and (142 mg, 0.25 mmol), in DMF (4.8 mL) was treated with triethylamine (0.42 mL) followed by trimethylsilyliodide (0.69 mL, 4.83 mmol) and the reaction mixture flask was covered with aluminum foil to protect from light and stirred for 24 h at room temperature. It was then diluted with TEAB buffer (13 mL), water (50 mL) and chloroform (85 mL) and stirred for 1 h. The organic phase was collected and the aqueous phase was re-extracted with chloroform (3 x 50 mL). The combined organic extracts were dried over MgSO₄. After filtration, the filtrate was concentrated and the residue was used as such for next step.

10 MS (ES⁺) 516.40 (M+H)⁺.

Step 5: A solution of compound from Step 4 in MeOH (21 mL) was treated with conc. HCl (21 mL) and stirred at room temperature for 20 h. The reaction mixture was concentrated to dryness and treated with 10 mL of water followed by extraction with ethyl acetate (2 x 10 mL). The aqueous layer was concentrated to about 5 mL, filtered (0.2 μm), and purified by HPLC (CH₃CN/0.1 M TEAB buffer, pH = 8.0, 0-20 min, 0-35% CH₃CN; 20-28 min, 35-100% CH₃CN, monitoring at 260 nm) to give the desired product (*t_R* = 14.74 min). Fractions containing the desired product were pooled together, concentrated and re-dissolved in 2 mL of H₂O and give 10.48 mM (measured by UV at 274 nm) solution of the monophosphate.

¹H NMR (H₂O-*d*₂): δ 8.10 (s, 1H), 7.78 (s, 1H), 3.74 (t, *J* = 6.2 Hz, 2H), 3.53 (d, *J* = 8.5 Hz, 2H), 2.79 (t, *J* = 6.2 Hz, 2H); ³¹P NMR (H₂O-*d*₂): 17.02 (bs, 1P); MS (ES⁺): 274.46 (M + H)⁺.

Example D-1



Methyl 2-(((5-(4-aminofuro[3,2-*d*]pyrimidin-7-yl)-3,4-dihydroxy-4-methyl-tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)-3-methylbutanoate (Scheme D-1).

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Step 1: To a solution of POCl_3 (10 mL, 107 mmol) in CH_2Cl_2 (30 mL) at -50°C (dry ice/acetone) was added a solution of phenol (2.86 g, 30.3 mmol) and Et_3N (4.25 mL, 30.4 mmol) in CH_2Cl_2 (25 mL) over a period of 15 min. The temperature was allowed to go to 10°C over a period of 1.5 h and stirred at room temperature overnight. The white solid was removed by filtration under nitrogen atmosphere and the filtrate was evaporated to dryness. To the residue, Et_2O (20 mL) was added and the white solid was removed again by filtration. The concentration of the filtrate provided 8.1 g of phenyl phosphorodichloridate, which was used as such for the next step.

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Step 2: To a solution of L-valine-methyl ester hydrochloride (2.4 g, 14.36 mmol) and phenyl phosphorodichloridates from Step 1 (3.02 g) in CH_2Cl_2 (60 mL) at -78°C (dry ice/acetone) was added a solution of Et_3N (4.02 mL, 28.72 mmol) in CH_2Cl_2 (20 mL) over a period of 30 min. The reaction mixture was further stirred at -50 to -30°C for 4.5 h and then evaporated to dryness. To the residue was added Et_2O (20 mL) and the white solid was removed under nitrogen. The filtrate was concentrated to give 3.0 g (68%) of phenyl methylvaline phosphorochloridate, which was used as such for the next step.

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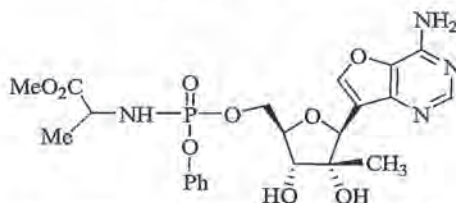
Step 3: To a solution of Example B-24 (63 mg, 0.225 mmol) and *N*-methyl imidazole (74 mg, 0.9 mmol) in THF (1 mL) was added a solution of phosphorochloridate from Step 2 (137 mg, 0.45 mmol) in THF (1 mL) at room temperature and the mixture was

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stirred for 4 h. Additional phosphorochloridate (137 mg, 0.45 mmol) and *N*-methyl imidazole (74 mg, 0.9 mmol) were added and stirred for 17 h at room temperature. The reaction mixture was concentrated and the residue was purified on a column of silica gel using 0 to 5% MeOH in CHCl₃ to give 28 mg (23%) of desired product as a white solid, mp 58-62 °C.

¹H NMR (DMSO-*d*₆): 8.23 (s, 1H), 8.08 (s, 1H), 7.00-7.40 (m, 7H), 5.85-6.00 (m, 1H), 5.17 (brs, 1H, D₂O exchangeable), 4.99 and 4.97 (2s, 1H), 4.89 (brs, 1H, D₂O exchangeable), 3.92-4.35 (m, 3H), 3.66 and 3.57 (2s, 3H), 3.33-3.68 (m, 2H), 1.78-1.96 (m, 1H), 0.92 (s, 3H), 0.80 (d, *J* = 6.8 Hz, 3H) and 0.73 (d, *J* = 6.8 Hz, 3H); IR (KBr) 3341, 3205, 2965, 1739, 1653, 1491, cm⁻¹; MS (ES⁺) 573.30 (M+Na); Anal. Calcd for C₂₄H₃₁N₄O₉P•2 H₂O: C, 49.14; H, 6.01; N, 9.55. Found: C, 49.24; H, 5.78; N, 9.33.

Example D-2



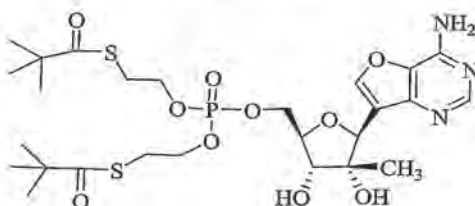
Methyl 2-(((5-(4-Aminofuro[3,2-d]pyrimidin-7-yl)-3,4-dihydroxy-4-methyl-tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (Scheme D-1).

This compound was prepared the same way as Example D-1 except that L-alanine-methyl ester hydrochloride was used in this preparation instead of L-valine-methyl ester hydrochloride, yield (48%).

¹H NMR (DMSO-*d*₆): 8.24 and 8.23 (2s, 1H, for both isomers), 8.08 and 8.07 (2s, 1H, both isomers), 7.10-7.40 (m, 7H, ArH and NH₂), 5.94-6.00 (m, 1H), 5.14-5.20 (m, 1H), 4.96 and 4.99 (2s, 1H), 4.90 (s, 1H), 4.14-4.35 (m, 2H), 3.94-4.02 (m, 2H), 3.78-3.89 (m, 1H), 3.52 and 3.56 (2s, 3H), 1.15 and 1.23 (2d, *J* = 7.34 and 6.94 Hz, 3H), 0.92 (s, 3H); IR (KBr): 3335, 3201, 1741, 1653, 1489, 1213, 935 cm⁻¹; MS (ES⁺) 545.28

(M+Na); Anal. Calcd for $C_{22}H_{27}N_4O_9P \cdot 0.75 H_2O$: C, 49.30; H, 5.35; N, 10.45. Found: C, 49.51; H, 5.18; N, 9.94.

Example D-3

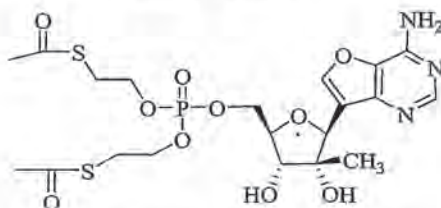


S,S'-2,2'-(((5-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)-3,4-dihydroxy-4-methyl-tetrahydrofuran-2-yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,1-diyl) bis(2,2-dimethylpropanethioate) (Scheme D-2).

To a solution of Example **B-24** (0.16 g, 0.6 mmol) in THF (20 mL) at 0 °C were added tetrazole (120 mg, 1.8 mmol) and 2,2-dimethyl-thiopropionic acid S-{diisopropylamino-[2-(2,2-dimethyl-propionylsulfanyl)-ethoxy]-phosphanyloxymethyl} ester (0.51 g, 1.2 mmol) dropwise followed by stirring for 2 h at room temperature. After the reaction mixture was cooled to -40° C, 70% m-chloroperbenzoic acid (0.27 g, 0.7 mmol) was added and the reaction was allowed to warm to room temperature and was quenched by the addition of aqueous 10% sodium sulfite (3 mL) and diluted with $CHCl_3$ (20 mL). The organic layer was washed with water (20 mL), aqueous saturated sodium bicarbonate solution (2 x 20 mL) and dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using 0 to 10% MeOH in chloroform as eluent to give 90 mg (20%) of desired product.

^1H NMR ($DMSO-d_6$ δ in ppm) 8.25 (s, 1H), 8.15 (s, 1H), 7.40 (br s, 2H), 5.20 (m, 1H), 4.90 (m, 2H), 4.20 (m, 2H), 4.00 (m, 6H), 3.10 (m, 4H), 1.15 (m, 18H), 0.90 (s, 3H); ^{31}P NMR 0.68 ppm; MS (ES^+) 650.32 ($M+H^+$); Anal. Calcd for $C_{26}H_{40}N_3O_{10}PS_2$: C, 48.05; H, 6.20; N, 6.47. Found: C, 48.02; H, 6.37; N, 6.23.

Example D-4

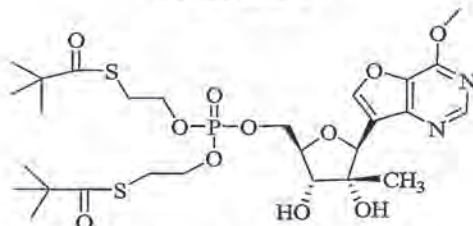


S,S'-2,2'-(((5-(4-Aminofuro[3,2-d]pyrimidin-7-yl)-3,4-dihydroxy-4-methyl-tetrahydrofuran-2-yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,1-diyl) diethanethioate (Scheme D-2).

This compound was prepared the same way as Example D-3 using, compound from Example B-24 and thioacetic acid *S*-{2-[(2-acetylsulfanyl-ethoxy)-diisopropylamino-phosphanyloxy]-ethyl} ester, yield 8.6 mg (3%).

¹H NMR (DMSO-*d*₆ δ in ppm) 8.26 (s, 1H), 8.12 (s, 1H), 7.35 (br s, 2H), 5.20 (m, 1H), 4.95 (m, 2H), 4.30 (m, 2H), 4.00 (m, 6H), 3.20 (m, 4H), 2.30 (m, 6H), 0.90 (s, 3H); ³¹P NMR 0.61 ppm; MS (ES⁺) 566.28 (M+H)⁺.

Example D-5



S,S'-2,2'-(((3,4-Dihydroxy-5-(4-methoxyfuro[3,2-d]pyrimidin-7-yl)-4-methyl-tetrahydrofuran-2-yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,1-diyl) bis(2,2-dimethylpropanethioate) (Scheme D-2).

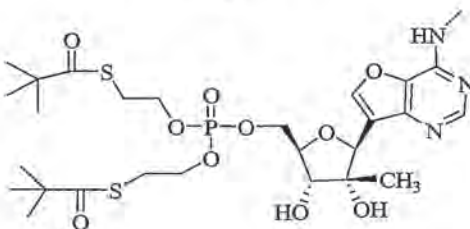
This compound was prepared the same way as Example D-3 using compound from Example B-13 and 2,2-dimethyl-thiopropionic acid *S*-{diisopropylamino-[2-(2,2-dimethyl-propionylsulfanyl)-ethoxy]-phosphanyloxymethyl} ester, yield 15 mg (13%).

^1H NMR (CDCl_3 , δ in ppm) 8.60 (s, 1H), 7.90 (s, 1H), 5.20 (m, 1H), 4.40 (m, 3H), 4.25 (s, 3H), 4.20 (m, 6H), 3.90 (m, 1H), 3.20 (m, 4H), 1.20 (m, 18H), 1.00 (s, 3H); ^{31}P NMR 0.0 ppm; MS (ES^+) 665.28 ($\text{M}+\text{H}^+$), MS (ES^-) ($\text{M}+\text{Cl}$) $^-$ 699.19.

5

Example D-6

15

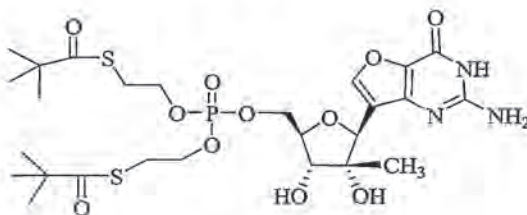


S,S'-2,2'-(((3,4-Dihydroxy-4-methyl-5-(4-(methylamino)furo[3,2-*d*]pyrimidin-7-yl)-tetrahydrofuran-2-yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,1-diyl) bis(2,2-dimethylpropanethioate) (Scheme D-2).

This compound was prepared the same way as Example D-3 using compound from Example B-17 and 2,2-dimethyl-thiopropionic acid S-{diisopropylamino-[2-(2,2-dimethyl-propionylsulfanyl)-ethoxy]-phosphanyloxymethyl} ester, yield 107 mg (48%).

^1H NMR ($\text{DMSO}-d_6$, δ in ppm) 8.35 (s, 1H), 8.00 (s, 1H), 7.80 (br s, 1H), 5.20 (d, $J = 6.5$ Hz, 1H), 4.97 (m, 1H), 4.90 (m, 1H), 4.26 (m, 2H), 3.99 (m, 6H), 3.00 (m, 4H), 2.96 (m, 3H), 1.14 (m, 18H), 0.91 (s, 3H); ^{31}P NMR 0.60 ppm; MS (ES^+) 686.27 ($\text{M}+\text{Na}^+$), MS (ES^-) ($\text{M}-\text{H}^-$) 662.30; Anal. Calcd for $\text{C}_{27}\text{H}_{42}\text{N}_3\text{O}_{10}\text{PS}_2$: C, 47.24; H, 6.54; N, 6.12. Found: C, 47.16; H, 6.27; N, 6.10.

40

Example D-7

S,S'-2,2'-((5-(2-Amino-4-oxo-3,4-dihydrofuro[3,2-*d*]pyrimidin-7-yl)-3,4-dihydroxy-4-methyl-tetrahydrofuran-2-yl)methoxy)phosphoryl)-bis(oxy)bis(ethane-2,1-diyl) bis(2,2-dimethylpropanethioate) (Scheme D-2).

- 5 This compound was prepared the same way as Example D-3 using compound from Example B-21 and 2,2-dimethyl-thiopropionic acid S-{diisopropylamino-[2-(2,2-dimethyl-propionylsulfanyl)-ethoxy]-phosphanyloxymethyl} ester, yield 28 mg (33%).
¹H NMR (DMSO-*d*₆ δ in ppm) 10.90 (br s, 1H), 7.80 (s, 1H), 6.30 (br s, 2H), 5.12 (m, 1H), 4.80 (m, 2H), 4.20 (m, 2H), 4.00 (m, 4H), 3.80 (m, 2H), 3.00 (m, 4H), 1.12 (m, 10 18H), 0.91 (s, 3H); ³¹P NMR 0.50 ppm; MS (ES⁺) 666.36 (M+H)⁺, MS (ES⁻) (M-H)⁻ 664.33.

Example D-8

- The following illustrate representative pharmaceutical dosage forms, containing
 15 a compound of formula I, II, or III, or a pharmaceutically acceptable salt or prodrug thereof ('Compound X'), for therapeutic or prophylactic use in humans.

	<u>(i) Tablet 1</u>	<u>mg/tablet</u>
	Compound X=	100.0
20	Lactose	77.5
	Povidone	15.0
	Croscarmellose sodium	12.0
	Microcrystalline cellulose	92.5
	Magnesium stearate	<u>3.0</u>
25		300.0
	<u>(ii) Tablet 2</u>	<u>mg/tablet</u>
	Compound X=	20.0
	Microcrystalline cellulose	410.0
30	Starch	50.0
	Sodium starch glycolate	15.0
	Magnesium stearate	<u>5.0</u>
		500.0

	<u>(iii) Capsule</u>	<u>mg/capsule</u>
	Compound X=	10.0
	Colloidal silicon dioxide	1.5
	Lactose	465.5
5	Pregelatinized starch	120.0
	Magnesium stearate	<u>3.0</u>
		600.0
	<u>(iv) Injection 1 (1 mg/ml)</u>	<u>mg/ml</u>
10	Compound X= (free acid form)	1.0
	Dibasic sodium phosphate	12.0
	Monobasic sodium phosphate	0.7
	Sodium chloride	4.5
	1.0 N Sodium hydroxide solution	
15	(pH adjustment to 7.0-7.5)	q.s.
	Water for injection	q.s. ad 1 mL
	<u>(v) Injection 2 (10 mg/ml)</u>	<u>mg/ml</u>
	Compound X= (free acid form)	10.0
20	Monobasic sodium phosphate	0.3
	Dibasic sodium phosphate	1.1
	Polyethylene glycol 400	200.0
	0.1 N Sodium hydroxide solution	
	(pH adjustment to 7.0-7.5)	q.s.
25	Water for injection	q.s. ad 1 mL
	<u>(vi) Aerosol</u>	<u>mg/can</u>
	Compound X=	20.0
	Oleic acid	10.0
30	Trichloromonofluoromethane	5,000.0
	Dichlorodifluoromethane	10,000.0
	Dichlorotetrafluoroethane	5,000.0

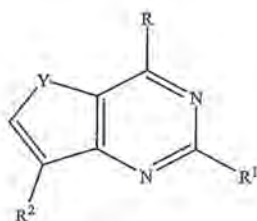
The above formulations may be obtained by conventional procedures well known in the pharmaceutical art.

All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

CLAIMS

What is claimed:

1. A compound of formula I:



(I)

wherein:

Y is O or S;

R is OR₃, SR₃, NR₃R₄, NR₃NR₄R₅, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, (CH₂)_n-CH(NHR₃)CO₂R₄, (CH₂)_n-S-alkyl, (CH₂)_n-S-aryl, Cl, F, Br, I, CN, COOR₃, CONR₃R₄, NHC(=NR₃)NHR₄, NR₃OR₄, NR₃NO, NHCONHR₃, NR₃N=NR₄, NR₃N=CHR₄, NR₃C(O)NR₄R₅, NR₃C(S)NR₄R₅, NR₃C(O)OR₄, CH=N-OR₃, NR₃C(=NH)NR₄R₅, NR₃C(O)NR₄NR₅R₆, O-C(O)R₃, OC(O)-OR₃, ONH-C(O)O-alkyl, ONHC(O)O-aryl, ONR₃R₄, SNR₃R₄, S-ONR₃R₄, or SO₂NR₃R₄;

- 15 n is 0-5;

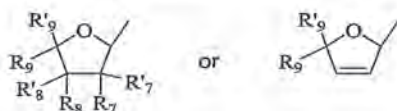
R¹ is H, NR₃R₄, Cl, F, OR₃, SR₃, NHCOR₃, NHSO₂R₃, NHCONHR₃, CN, alkyl, aryl, ONR₃R₄, or NR₃C(O)OR₄;

R² is a nucleoside sugar group; and

- 20 R₃, R₄, R₅, and R₆ are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, heterocyclic, aryl, substituted aryl, acyl, substituted acyl, SO₂-alkyl and NO; or R₃ and R₄ together with the nitrogen to which they are attached form a pyrrolidino, piperidino, piperazino, azetidino, morpholino, or thiomorpholino ring; or R₄ and R₅ together with the nitrogen to which they are attached form a pyrrolidino, 25 piperidino, piperazino, azetidino, morpholino, or thiomorpholino ring; or a pharmaceutically acceptable salt or prodrug thereof;

provided Y is not S when R is -NH₂, -OH, -SH, or -SCH₃; R¹ is hydrogen; and R² is non-phosphorylated ribose; and provided Y is not O when R is -NH₂; R¹ is hydrogen; and R² is non-phosphorylated ribose.

- 5 2. The compound of claim 1 wherein Y is O.
3. The compound of claim 1 wherein Y is S.
4. The compound of any one of claims 1-3 wherein R is OR₃, Cl, SR₃, NR₃R₄, or
- 10 NR₃NR₄R₅.
5. The compound of any one of claims 1-3 wherein R is hydroxy, chloro, methoxy, mercapto, amino, methylamino, isopropylamino, propylamino, ethylamino, dimethylamino, cyclopropylamino, 2-aminoethylamino, 1-(2-hydroxyethyl)hydrazino,
- 15 hydrazino, 1-methylhydrazino, azetidino, or pyrrolidino.
6. The compound of any one of claims 1-5 wherein R¹ is H or NR₃R₄.
7. The compound of any one of claims 1-6 wherein R² is



20

wherein:

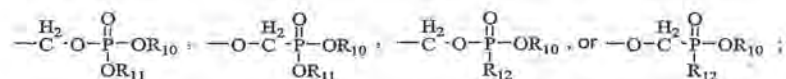
- R₇ is H, OR₁₄, N₃, NH₂, or F; and R'₇ is H, F, OH, O-alkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl; or R₇ and R'₇ together may be =CH₂, =CHF; wherein both R₇ and R'₇ are not OH; and when one of R₇ and R'₇ is
- 25 NH₂, the other is not OH; and when one of R₇ and R'₇ is N₃, the other is not OH;

R₈ is H, OR₁₄, N₃, NH₂, or F; and R'₈ is H, F, OH, O alkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl; or R₈ and R'₈ together may be =CH₂, =CHF; wherein both R₈ and R'₈ are not OH; and when one of

R_8 and R'_8 is NH_2 , the other is not OH; and when one of R_8 and R'_8 is N_3 , the other is not OH;

R_9 is H, CH_3 , C_2H_5 , or N_3 ;

R'_9 is CH_2OR_{14} , CH_2F , CH_2SH , $CHFOH$, CF_2OH ,



5

R_{10} and R_{11} are each independently H, alkyl, aryl, substituted aryl, acyloxyalkyl, or $(CH_2)_n-O-(CH_2)_mCH_3$;

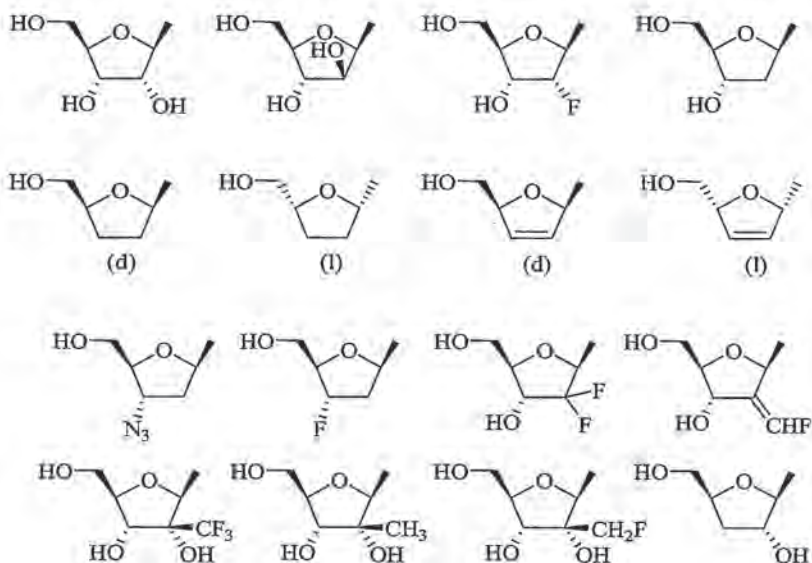
R_{12} is an N-linked amino acid residue (e.g. $-NH-CH(CH_3)CO_2$ alkyl or $-NH-CH(isopropyl)-CO_2$ alkyl); and

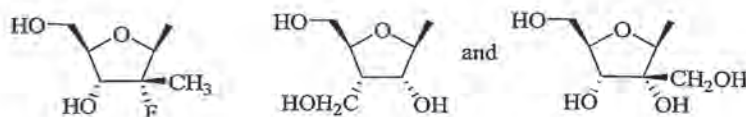
R_{14} is H;

n is 2-5; and

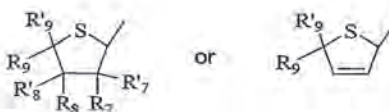
m is 10-20.

15 8. The compound of any one of claims 1-6 wherein R^2 is selected from:





9. The compound of any one of claims 1-6 wherein R^2 is:



10

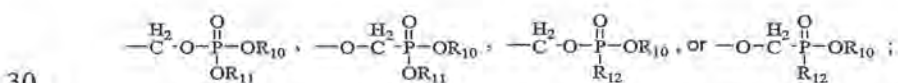
wherein:

R_7 is H, OR_{14} , N_3 , NH_2 , or F; and R'_7 is H, F, OH, O-alkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl; or R_7 and R'_7 together may be $=CH_2$, $=CHF$; wherein both R_7 and R'_7 are not OH; and when one of R_7 and R'_7 is NH_2 , the other is not OH; and when one of R_7 and R'_7 is N_3 , the other is not OH;

R_8 is H, OR_{14} , N_3 , NH_2 , or F; and R'_8 is H, F, OH, O alkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl; or R_8 and R'_8 together may be $=CH_2$, $=CHF$; wherein both R_8 and R'_8 are not OH; and when one of R_8 and R'_8 is NH_2 , the other is not OH; and when one of R_8 and R'_8 is N_3 , the other is not OH;

R_9 is H, CH_3 , C_2H_5 , or N_3 ;

R'_9 is CH_2OR_{14} , CH_2F , CH_2SH , $CHFOH$, CF_2OH ,



30

R_{10} and R_{11} are each independently H, alkyl, aryl, substituted aryl, acyloxyalkyl, or $(CH_2)_n-O-(CH_2)_mCH_3$;

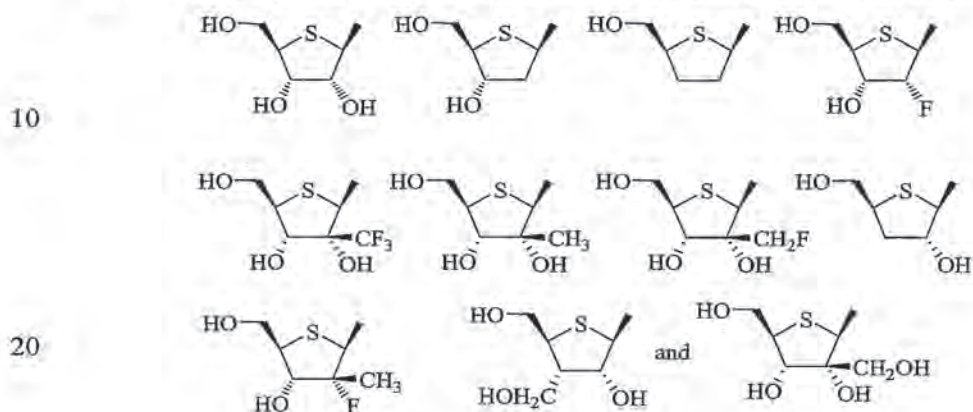
R_{12} is an N-linked amino acid residue (e.g. $-NH-CH(CH_3)CO_2alkyl$ or $-NH-CH(isopropyl)-CO_2alkyl$);

35 R_{14} is H;

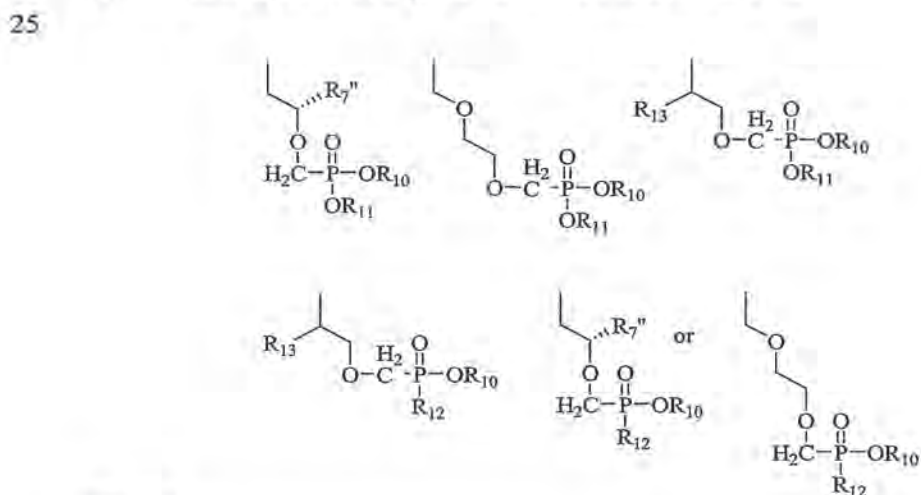
n is 2-5; and

m is 10-20.

10. The compound of any one of claims 1-6 wherein R^2 is selected from:



11. The compound of any one of claims 1-6 wherein R^2 is:



wherein

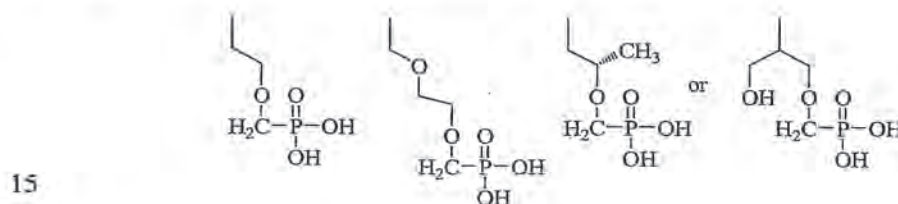
R_7'' is alkyl or substituted alkyl;

R_{10} and R_{11} are each independently H, alkyl, aryl, substituted aryl, acyloxyalkyl, or $(CH_2)_n-O-(CH_2)_mCH_3$;

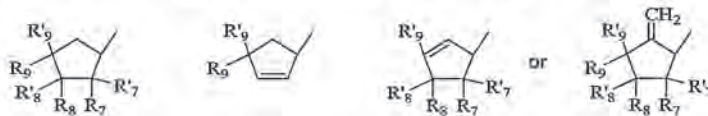
30 R_{12} is an N-linked amino acid residue (e.g. $-NH-CH(CH_3)CO_2alkyl$ or $-NH-CH(isopropyl)-CO_2alkyl$);

R_{13} is H, CH_3 , C_2H_5 , CH_2F , CH_2OH , CH_2CH_2F , CH_2CH_2OH , CH_2N_3 , $CH_2CH_2N_3$, CH_2NH_2 , or $CH_2CH_2NH_2$; and
 R_{14} is H.

12. The compound of any one of claims 1-6 wherein R^2 is:



13. The compound of any one of claims 1-6 wherein R^2 is:



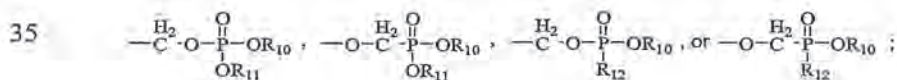
wherein:

20 R_7 is H, OR_{14} , N_3 , NH_2 , or F; and R'_7 is H, F, OH, O-alkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl; or R_7 and R'_7 together may be $=CH_2$, $=CHF$; wherein both R_7 and R'_7 are not OH; and when one of R_7 and R'_7 is NH_2 , the other is not OH; and when one of R_7 and R'_7 is N_3 , the other is not OH;

25 R_8 is H, OR_{14} , N_3 , NH_2 , or F; and R'_8 is H, F, OH, O alkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl; or R_8 and R'_8 together may be $=CH_2$, $=CHF$; wherein both R_8 and R'_8 are not OH; and when one of R_8 and R'_8 is NH_2 , the other is not OH; and when one of R_8 and R'_8 is N_3 , the other is not OH;

30 R_9 is H, CH_3 , C_2H_5 , or N_3 ;

R'_9 is CH_2OR_{14} , CH_2F , CH_2SH , $CHFOH$, CF_2OH ,

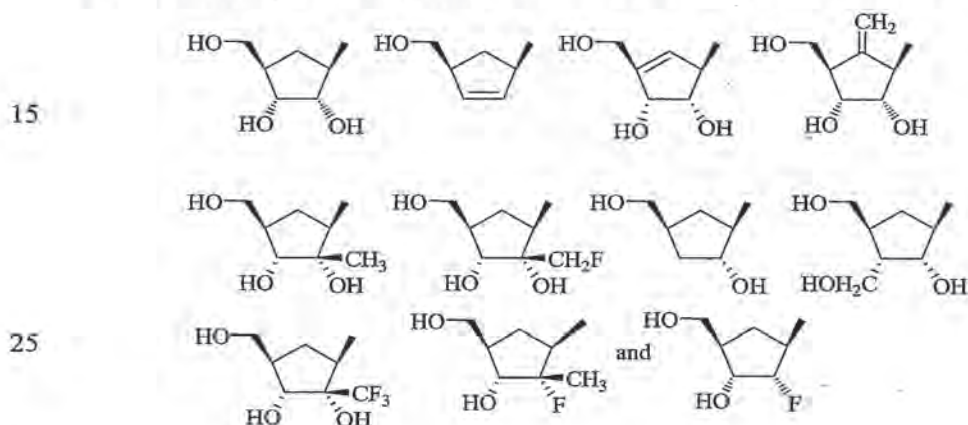


R_{10} and R_{11} are each independently H, alkyl, aryl, substituted aryl, acyloxyalkyl, or $(CH_2)_n-O-(CH_2)_mCH_3$;

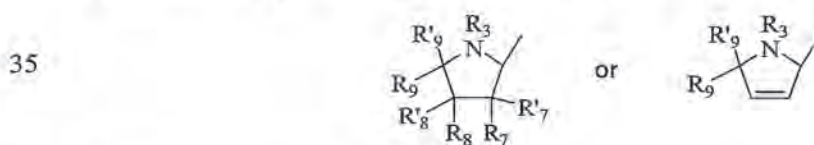
R_{12} is an N-linked amino acid residue (e.g. $-NH-CH(CH_3)CO_2alkyl$ or $-NH-CH(isopropyl)-CO_2alkyl$); and

- 5 R_{14} is H;
 n is 2-5; and
 m is 10-20.

14. The compound of any one of claims 1-6 wherein R^2 is selected from:



15. The compound of any one of claims 1-6 wherein R^2 is:



wherein:

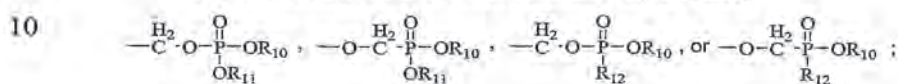
R_7 is H, OR_{14} , N_3 , NH_2 , or F; and R'_7 is H, F, OH, O-alkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl; or R_7 and R'_7 together may be $=CH_2$, $=CHF$; wherein both R_7 and R'_7 are not OH; and when one of R_7 and R'_7 is NH_2 , the other is not OH; and when one of R_7 and R'_7 is N_3 , the other is not OH;

45 not OH;

- R_8 is H, OR_{14} , N_3 , NH_2 , or F; and R'_8 is H, F, OH, O alkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl; or R_8 and R'_8 together may be $=CH_2$, $=CHF$; wherein both R_8 and R'_8 are not OH; and when one of R_8 and R'_8 is NH_2 , the other is not OH; and when one of R_8 and R'_8 is N_3 , the other is not OH;

R_9 is H, CH_3 , C_2H_5 , or N_3 ;

R'_9 is CH_2OR_{14} , CH_2F , CH_2SH , $CHFOH$, CF_2OH ,



R_{10} and R_{11} are each independently H, alkyl, aryl, substituted aryl, acyloxyalkyl, or $(CH_2)_n-O-(CH_2)_mCH_3$;

- 15 R_{12} is an N-linked amino acid residue (e.g. $-NH-CH(CH_3)CO_2$ alkyl or $-NH-CH(isopropyl)-CO_2$ alkyl); and

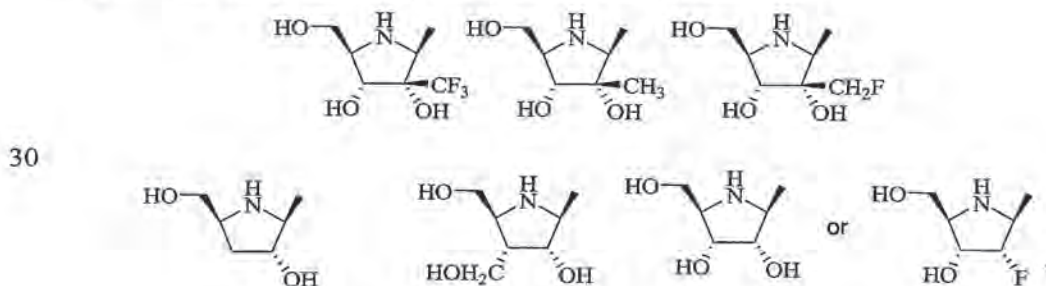
R_{14} is H;

n is 2-5; and

m is 10-20.

20

16. The compound of any one of claims 1-6 wherein R^2 is:



17. The compound of any one of claims 1-6 wherein R^2 is:

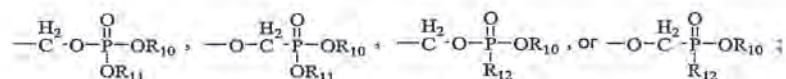


45

wherein

R₉ is H, CH₃, C₂H₅, or N₃;

R'₉ is CH₂OR₁₄, CH₂F, CH₂SH, CHFOH, CF₂OH,



- 5 R₁₀ and R₁₁ are each independently H, alkyl, aryl, substituted aryl, acyloxyalkyl, or (CH₂)_n-O-(CH₂)_mCH₃;

R₁₂ is an N-linked amino acid residue (e.g. -NH-CH(CH₃)CO₂alkyl or -NH-CH(isopropyl)-CO₂alkyl);

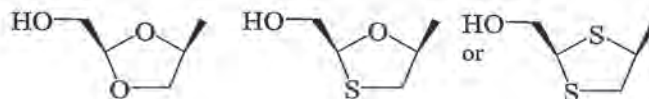
- 10 R₁₃ is H, CH₃, C₂H₅, CH₂F, CH₂OH, CH₂CH₂F, CH₂CH₂OH, CH₂N₃, CH₂CH₂N₃, CH₂NH₂, or CH₂CH₂NH₂;

R₁₄ is H;

n is 2-5; and

m is 10-20.

- 15 18. The compound of any one of claims 1-6 wherein R² is:



19. The compound of any one of claims 1-6 wherein R² is ribose, 2-methylribose,
25 2-deoxyribose; 2-deoxy-2-fluororibose; arabinose; 2-deoxy-2-fluoroarabinose; 2,3-dideoxyribose; 2,3-dideoxy-2-fluoroarabinose; 2,3-dideoxy-3-fluororibose; 2,3-dideoxy-2,3-didehydroribose; 2,3-dideoxy-3-azidoribose; 2,3-dideoxy-3-thiaribose; or 2,3-dideoxy-3-oxaribose; or a pharmaceutically acceptable salt or prodrug thereof.

- 30 20. The compound of any one of claims 1-6 wherein R² is thioribose, 2-deoxythioribose; 2-deoxy-2-fluorothioribose; thioarabinose; 2-deoxy-2-fluorothioarabinose; 2,3-dideoxythioribose; 2,3-dideoxy-2-fluorothioarabinose; 2,3-

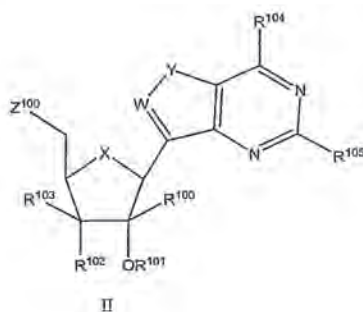
dideoxy-3-fluorothioribose; 2,3-dideoxy-2,3-didehydrothioribose; or 2,3-dideoxy-3-azidothioribose; or a pharmaceutically acceptable salt or prodrug thereof.

21. The compound of any one of claims 1-6 wherein R² is 4-hydroxymethyl-
5 cyclopent-2-ene; 2,3-dihydroxy-4-hydroxymethylcyclopent-4-ene; 3-hydroxy-4-
hydroxymethylcyclopentane; 2-hydroxy-4-hydroxymethylcyclopentene; 2-fluoro-3-
hydroxy-4-hydroxymethylcyclopentane; 2,3-dihydroxy-4-hydroxymethyl-5-
methylenecyclopentane; 4-hydroxymethylcyclopentane, 2,3-dihydroxy-4-
hydroxymethylcyclopentane; or 2,3-dihydroxymethylcyclobutane; or a
10 pharmaceutically acceptable salt or prodrug thereof.

22. The compound of any one of claims 1-6 wherein R² is 4-hydroxymethyl-
pyrrolidine; 2,3-dihydroxy-4-hydroxymethylpyrrolidine; 2/3-hydroxy-4-
hydroxymethylpyrrolidine; 2-fluoro-3-hydroxy-4-hydroxymethylpyrrolidine; or 3-
15 fluoro-2-hydroxy-4-hydroxymethyl-pyrrolidine; or a pharmaceutically acceptable salt
or prodrug thereof.

23. The compound of any one of claims 1-22 wherein R₃, R₄, R₅, and R₆ are
independently selected from the group consisting of H, alkyl, and substituted alkyl; or
20 R₃ and R₄ together with the nitrogen to which they are attached form a pyrrolidino,
piperidino, piperazino, azetidino, morpholino, or thiomorpholino ring; or R₄ and R₅
together with the nitrogen to which they are attached form a pyrrolidino, piperidino,
piperazino, azetidino, morpholino, or thiomorpholino ring.

24. A compound of formula II:



wherein:

- 5 R^{100} is alkyl, alkenyl, or alkynyl, which R^{100} may be unsubstituted or substituted;
- R^{101} is H, alkyl, $-C(O)alkyl$, or benzoyl;
- R^{102} is H, OH, Oalkyl, $-OC(O)alkyl$, $-Obenzoyl$, $-CH_2OH$, CH_2NH_2 , N_3 , CH_2N_3 , or NH_2 ;
- 10 R^{103} is H, OH, or NH_2 ; provided both R^{102} and R^{103} cannot be the same group except hydrogen;
- R^{104} is $NR^{110}R^{111}$, $NR^{110}-NR^{111}R^{112}$, $NR^{110}N=NR^{111}$, $NR^{110}N=CHR^{111}$, $NR^{110}N=O$, $NR^{110}C(O)NR^{111}R^{112}$, $NR^{110}C(S)NR^{111}R^{112}$, $NR^{110}C(=NH)NR^{111}R^{112}$, $NR^{110}C(O)NR^{111}NR^{112}R^{113}$, $NR^{110}OR^{111}$, $O-C(O)R^{110}$, $OC(O)-OR^{110}$, $O-NH-C(O)Oalkyl$, $ONHC(O)Oaryl$, $ONR^{110}R^{111}$, $S-NR^{110}R^{111}$, $S-ONR^{110}R^{111}$, or $SO_2NR^{110}R^{111}$;
- 15 R^{105} is H, NH_2 , halogen, N_3 , NHR^{106} , $NHC(O)R^{106}$, $NR^{110}R^{111}$, $NHSO_2R^{106}$, $NHCONHR^{106}$, $NH-C(S)NHR^{106}$, CH_2NHR^{106} , $NHNH_2$, CN , alkyl, alkynyl, CH_2aryl , OH, or SR^{106} ;
- 20 R^{106} is H or alkyl;
- Z^{100} is OH, $-O-[P(=O)(OH)O-]_n-H$, $-CH_2-[P(=O)(OH)O-]_n-H$, $-O-P(=O)(R^{107})R^{108}$, $-CH_2-P(=O)(R^{107})R^{108}$, $-O-[P(=O)(R^{109})O-]_n-H$, or $-CH_2-[P(=O)(R^{109})O-]_n-H$;

R^{107} and R^{108} in phosphonic acid or phosphoric acid independently represent a protected or unprotected substituted or unsubstituted hydroxyl group to be decomposed under physiological conditions;

R^{109} is a hydroxyl group that may be protected or substituted with a group to be decomposed under physiological conditions;

R^{110} , R^{111} , R^{112} and R^{113} are independently H, alkyl, substituted alkyl, cycloalkyl, heterocyclic, alkoxy, aryl, substituted aryl, acyl, substituted acyl, SO_2 -alkyl, NH_2 , OH or NO;

R^{114} is H, alkyl, substituted alkyl, $C(O)R^{109}$, aryl, substituted aryl, or heterocycle;

n is 0-3;

X is O, S, NH, or CH_2 ;

W is CR^{114} , N, or C-halo; and

Y is O, S, or NR^{114} ;

or a pharmaceutically acceptable salt or prodrug thereof.

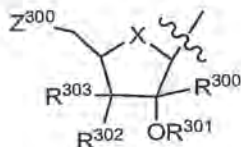
25. The compound of claim 24 wherein Y is O or S.

26. The compound of claim 24 wherein Y is O or S; Z^{100} is OH, $-O-[P(=O)(OH)O-]_n-H$, $-CH_2-[P(=O)(OH)O-]_n-H$, $-O-P(=O)(R^{107})R^{108}$, $-CH_2-P(=O)(R^{107})R^{108}$, $-O-[P(=O)(R^{109})O-]_n-H$, or $-CH_2-[P(=O)(R^{109})O-]_n-H$; and R^{107} and R^{108} are each H.

27. The compound of claim 24 wherein R^{100} is alkyl; R^{101} is H; R^{102} is OH; R^{103} is H; R^{104} is $NR^{110}R^{111}$ or $NR^{110}-NR^{111}R^{112}$; R^{105} is H or NH_2 ; R^{110} , R^{111} , R^{112} and R^{113} are independently H, alkyl, substituted alkyl, or cycloalkyl; and Z^{100} is OH.

28. The compound of claim 1 wherein R^2 has the following formula:

30



wherein:

R^{300} is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;

R^{301} is H, alkyl, $-C(O)alkyl$, or $aryl-C(=O)-$;

5 R^{302} is H, OH, $-Oalkyl$, $-OC(O)alkyl$, benzoyloxy, $-CH_2OH$, CH_2NH_2 , N_3 , CH_2N_3 , or NH_2 ;

R^{303} is H, OH, or NH_2 ; provided both R^{302} and R^{303} cannot be the same group except hydrogen;

X is O, S, NH or CH_2 ;

10 Z^{300} is $-O-[P(=O)(R^{307})O-]_n-R^{308}$, or $-CH_2-[P(=O)(R^{307})O-]_n-R^{308}$;

each R^{307} is independently OH, $-Oalkyl$, or $-OC(O)alkyl$;

each R^{308} is independently H, alkyl, or $-C(O)alkyl$; and

n is 0, 1, 2, or 3.

15 29. The compound of claim 1 which is 4-methylamino-7- β -(D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Ethylamino-7- β -(D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Isopropylamino-7- β -(D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Dimethylamino-7- β -(D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; or 4-*n*-Propylamino-7- β -(D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; or a pharmaceutically acceptable salt or prodrug thereof.

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30. The compound of claim 1 which is 4-Cyclopropylamino-7- β -(D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Azetidino-7- β -(D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Pyrrolidino-7- β -(D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Methoxy-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-[(*N*-1-Hydroxyethyl)hydrazino]-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-[(*N*-1-Methyl)hydrazino]-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Dimethylamino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Methylamino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Aminoethylamino-7- β -(2'-C-methyl-D-

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- ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Hydrazino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; ((2*S*,5*R*)-(5-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)-4-methyl-2,5-dihydrofuran-2-yl)methanol; 2-Amino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidin-4(3*H*)-one; 2,4-Diamino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Amino-7- β -(2'-C-ethyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Amino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Amino-7- α -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Amino-7- β -(2'-O-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 7- β -(2'-C-Methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidin-4(3*H*)-thione; 4-Amino-7- β -(2'-C-methyl-D-ribofuranosyl)-thieno[3,2-*d*]pyrimidine; 4-Amino-7- α -(2'-C-methyl-D-ribofuranosyl)-thieno[3,2-*d*]pyrimidine; (*cis*)-(4-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)cyclopent-2-enyl)methanol; (5-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)-tetrahydrothiophen-2-yl)methanol; 2-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)-5-(hydroxymethyl)-3-methylpyrrolidine-3,4-diol; 2-Amino-7- β -(D-ribofuranosyl)-furo[3,2-*d*]pyrimidin-4(3*H*)-one; 7- β -(2'-C-Methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidin-4(3*H*)-one; 4-Amino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine-5'-monophosphate; 2-Amino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidin-4(3*H*)-one-5'-monophosphate; 4-Methylamino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine-5'-monophosphate; 4-Methylamino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine-5'-triphosphate; 4-Amino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine-5'-triphosphate; (2-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)ethoxy)methylphosphonic acid; Methyl 2-(((5-(4-aminofuro[3,2-*d*]pyrimidin-7-yl)-3,4-dihydroxy-4-methyl-tetrahydrofuran-2-yl)methoxy)(phenoxy)-phosphorylamino)-3-methylbutanoate; Methyl 2-(((5-(4-aminofuro[3,2-*d*]pyrimidin-7-yl)-3,4-dihydroxy-4-methyl-tetrahydrofuran-2-yl)methoxy)(phenoxy)-phosphorylamino)propanoate; S,S'-2,2'-(((5-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)-3,4-dihydroxy-4-methyl-tetrahydrofuran-2-yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,1-diyl) bis(2,2-dimethylpropanethioate); S,S'-2,2'-(((5-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)-3,4-dihydroxy-4-methyl-tetrahydrofuran-2-yl)methoxy)phosphoryl)bis(oxy)-bis(ethane-2,1-diyl) diethanethioate; S,S'-2,2'-(((3,4-Dihydroxy-5-(4-methoxyfuro[3,2-*d*]pyrimidin-7-yl)-4-methyl-tetrahydrofuran-2-yl)methoxy)phosphoryl)bis-(oxy)bis(ethane-2,1-diyl)

bis(2,2-dimethylpropanethioate); S,S'-2,2'-(((3,4-Dihydroxy-4-methyl-5-(4-(methylamino)furo[3,2-*d*]pyrimidin-7-yl)-tetrahydrofuran-2-yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,1-diyl) bis(2,2-dimethylpropanethioate); S,S'-2,2'-((5-(2-Amino-4-oxo-3,4-dihydrofuro[3,2-*d*]pyrimidin-7-yl)-3,4-dihydroxy-4-methyl-tetrahydrofuran-2-yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,1-diyl) bis(2,2-dimethylpropanethioate); or a pharmaceutically acceptable salt or prodrug thereof.

31. The compound of claim 28 which is 4-Methoxy-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-[(*N*-1-Hydroxyethyl)hydrazino]-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-[(*N*-1-Methyl)hydrazino]-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Dimethylamino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Methylamino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Aminoethylamino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Hydrazino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 2-Amino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidin-4(3*H*)-one; 2,4-Diamino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Amino-7- β -(2'-C-ethyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Amino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 4-Amino-7- α -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine; 7- β -(2'-C-Methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidin-4(3*H*)-thione; 4-Amino-7- β -(2'-C-methyl-D-ribofuranosyl)-thieno[3,2-*d*]pyrimidine; 4-Amino-7- α -(2'-C-methyl-D-ribofuranosyl)-thieno[3,2-*d*]pyrimidine; 2-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)-5-(hydroxymethyl)-3-methylpyrrolidine-3,4-diol; 7- β -(2'-C-Methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidin-4(3*H*)-one; 4-Amino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine-5'-monophosphate; 2-Amino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidin-4(3*H*)-one-5'-monophosphate; 4-Methylamino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine-5'-monophosphate; 4-Methylamino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine-5'-triphosphate; 4-Amino-7- β -(2'-C-methyl-D-ribofuranosyl)-furo[3,2-*d*]pyrimidine-5'-triphosphate; Methyl 2-(((5-(4-aminofuro[3,2-*d*]pyrimidin-7-yl)-3,4-dihydroxy-4-methyl-tetrahydrofuran-2-yl)methoxy)(phenoxy)-phosphorylamino)-3-methylbutanoate; Methyl 2-(((5-(4-aminofuro[3,2-*d*]pyrimidin-7-

- yl)-3,4-dihydroxy-4-methyl-tetrahydrofuran-2-yl)methoxy)(phenoxy)-
phosphorylamino)propanoate; S,S'-2,2'-(((5-(4-Aminofuro[3,2-*d*]pyrimidin-7-yl)-3,4-
dihydroxy-4-methyl-tetrahydrofuran-2-yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,1-
diyl) bis(2,2-dimethylpropanethioate); S,S'-2,2'-(((5-(4-Aminofuro[3,2-*d*]pyrimidin-7-
5 yl)-3,4-dihydroxy-4-methyl-tetrahydrofuran-2-yl)methoxy)phosphoryl)bis(oxy)-
bis(ethane-2,1-diyl) diethanethioate; S,S'-2,2'-(((3,4-Dihydroxy-5-(4-methoxyfuro[3,2-
d]pyrimidin-7-yl)-4-methyl-tetrahydrofuran-2-yl)methoxy)phosphoryl)bis-
(oxy)bis(ethane-2,1-diyl) bis(2,2-dimethylpropanethioate); S,S'-2,2'-(((3,4-Dihydroxy-
4-methyl-5-(4-(methylamino)furo[3,2-*d*]pyrimidin-7-yl)-tetrahydrofuran-2-
10 yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,1-diyl) bis(2,2-dimethylpropanethioate);
S,S'-2,2'-(((5-(2-Amino-4-oxo-3,4-dihydrofuro[3,2-*d*]pyrimidin-7-yl)-3,4-dihydroxy-4-
methyl-tetrahydrofuran-2-yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,1-diyl) bis(2,2-
dimethylpropanethioate); or a pharmaceutically acceptable salt or prodrug thereof.
- 15 32. The compound of any one of claims 1-31 which is a prodrug.
33. The compound of any one of claims 1-31 which comprises one or more mono-,
di-, or tri-phosphate groups.
- 20 34. The compound of any one of claims 1-31 which comprises one or more
mono-phosphate groups.
35. The compound of claim 33 or 34 which is a prodrug.
- 25 36. The compound of claim 35 wherein one or more pendent hydroxyl groups from
the mono-, di-, or tri-phosphate group has been converted to an alkoxy, substituted
alkoxy, aryloxy, or substituted aryloxy group.
- 30 37. The compound of claim 35 wherein one or more pendent hydroxyl groups from
the mono-, di-, or tri-phosphate group has been converted to a group R_y-O-; wherein
each R_y is independently a 1-20 carbon branched or unbranched, saturated or

unsaturated chain, wherein one or more of the carbon atoms is optionally replaced with -O- or -S- and wherein one or more of the carbon atoms is optionally substituted with oxo (=O) or thioxo (=S).

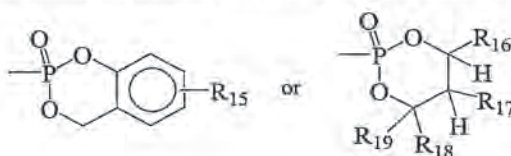
38. The compound of claim 35 wherein one or more pendent hydroxyl groups from the mono-, di-, or tri-phosphate group has been converted to a group R_z-N- ; wherein each R_z is a residue of an amino acid.

39. The compound of claim 38 wherein the amino acid is a natural amino acid.

10

40. The compound of claim 35 which comprises one or more groups of formula:

15



20 wherein:

R_{15} is H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, or an amino acid;

R_{16} is H, optionally substituted monocyclic aryl, or optionally substituted monocyclic heteroaryl; and R_{17} is H, halogen, CN, $-CO-R_{20}$, $-CON(R_{21})_2$, $-CO_2R_{20}$, $-SO_2R_{20}$, $-SO_2N(R_{21})_2$, $-OR_{21}$, $-SR_{21}$, $-R_{21}$, $-N(R_{21})_2$, $-O-COR_{20}$, $-O-CO_2R_{20}$, $-SCOR_{20}$, $-S-CO_2R_{20}$, $-NHCOR_{21}$, $-NHCO_2R_{21}$, $-(CH_2)_p-OR_{22}$, or $-(CH_2)_p-SR_{22}$; or R_{16} and R_{17} are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus; or R_{17} and R_{18} are connected as described below;

R_{18} and R_{19} are each independently H, alkyl, aryl, heterocycloalkyl, aralkyl, optionally substituted monocyclic aryl or optionally substituted monocyclic heteroaryl; or R_{18} and R_{19} are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms; or R_{17} and R_{18} are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom and R_{19} is H,

alkyl, aryl, heterocycloalkyl, aralkyl, optionally substituted monocyclic aryl or optionally substituted monocyclic heteroaryl;

R₂₀ is alkyl, aryl, heterocycloalkyl, or arylalkyl;

R₂₁ is H, alkyl, aryl, heterocycloalkyl, or arylalkyl;

5 R₂₂ is H or lower acyl;

n is an integer from 2-5;

m is an integer from 10-20; and

p is an integer from 2-3.

10 41. A pharmaceutical composition comprising a compound as described in any one of claims 1-40 and a pharmaceutically acceptable carrier.

42. The composition of claim 41 which further comprises one or more additional anti-viral agents.

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43. The composition of claim 42 wherein the one or more anti-viral agents are selected from ribavirin, levovirin, viramidine, thymosin alpha-1, an inhibitor of a serine proteases, an inhibitor of inosine monophosphatedehydrognease, interferon- α , and pegylated interferon- α (peginterferon- α).

20

44. The composition of any one of claims 41-43 which further comprises one or more additional HCV polymerase inhibitors.

25 45. The composition of any one of claims 41-44 which further comprises one or more protease inhibitors.

46. The composition of any one of claims 41-45 which further comprises ribavirin.

30 47. The composition of any one of claims 41-46 which further comprises interferon- α or pegylated interferon- α (peginterferon- α).

48. The composition of claim 41 which further comprises one or more anti-cancer agents.
49. The composition of claim 48 wherein the one or more anti-cancer agents are
5 selected from alkylating agents, antimetabolites, natural products, and hormonal agents.
50. A method for treating a viral infection in an animal comprising administering to the animal an effective amount of a compound as described in any one of claims 1-40,
10 or a composition as described in any one of claims 41-47.
51. The method of claim 50 wherein the viral infection is selected from the group consisting of: hepatitis B, hepatitis C, human immunodeficiency virus, Polio, Coxsackie A and B, Rhino, Echo, small pox, Ebola, and West Nile virus.
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52. The method of claim 50 wherein the viral infection is HCV.
53. The method of any one of claims 50-52 which further comprises administering to the animal one or more additional HCV polymerase inhibitors.
20
54. The method of any one of claims 50-53 which further comprises administering to the animal, one or more protease inhibitors.
55. The method of any one of claims 50-54 which further comprises administering
25 ribavirin to the animal.
56. The method of any one of claims 50-55 which further comprises administering interferon- α or pegylated interferon- α (peginterferon- α) to the animal.

57. A method for treating cancer in an animal comprising administering to the animal an effective amount of a compound as described in any one of claims 1-40, or a composition as described in any one of claims 41 and 48-49.
- 5 58. The method of claim 57 wherein one or more additional anti-cancer compounds are administered.
59. The method of any one of claims 50-58 wherein the animal is a human.
- 10 60. A method for inhibiting a viral RNA or DNA polymerase comprising contacting the polymerase *in vitro* or *in vivo* with an effective inhibitory amount of a compound as described in any one of claims 1-40.
61. The method of claim 60 wherein the viral polymerase is an RdRp.
- 15 62. A compound as described in any one of claims 1-40 for use in medical therapy.
63. The use of a compound as described in any one of claims 1-40 to prepare a medicament useful for treating a viral infection in an animal.
- 20 64. The use of a compound as described in any one of claims 1-40 to prepare a medicament useful for treating cancer in an animal.

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
23 August 2007 (23.08.2007)

PCT

(10) International Publication Number
WO 2007/095269 A2(51) International Patent Classification: **Not classified**[DE/IT]; Via Pontina KM. 30,600, I-00040 Pomezia (IT).
PACINI, Barbara [IT/IT]; Via Pontina KM. 30,600,
I-00040 Pomezia (IT).(21) International Application Number:
PCT/US2007/003862(74) Common Representative: **MERCK & CO., INC.**; 126
East Lincoln Avenue, Rahway, New Jersey 07065-0907
(US).(22) International Filing Date:
12 February 2007 (12.02.2007)

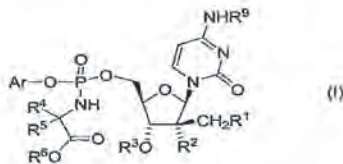
(25) Filing Language: English

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS,
LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY,
MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS,
RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(26) Publication Language: English

(30) Priority Data:
60/773,009 14 February 2006 (14.02.2006) US
60/832,832 24 July 2006 (24.07.2006) US(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).(71) Applicants (for all designated States except US):
MERCK & CO., INC. [US/US]; 126 East Lincoln Ave-
nue, Rahway, New Jersey 07065-0907 (US). **ISTITUTO
DI RICERCHE DI BIOLOGIA MOLECOLARE P.
ANGELETTI S.P.A.** [IT/IT]; Via Pontina KM. 30,600,
I-00040 Pomezia (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MACCOSS, Mal-**
colm [GB/US]; 126 East Lincoln Avenue, Rahway, NJ
07065-0907 (US). **OLSEN, David, B.** [US/US]; 126
East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
DONGHI, Monica [IT/IT]; Via Pontina KM. 30,600,
I-00040 Pomezia (IT). **GARDELLI, Cristina** [IT/IT]; Via
Pontina KM. 30,600, I-00040 Pomezia (IT). **HARPER,**
Steven [GB/IT]; Via Pontina KM. 30,600, I-00040
Pomezia (IT). **MEPPEN, Malte** [DE/IT]; Via Pontina
KM. 30,600, I-00040 Pomezia (IT). **NARJES, Frank****Published:**— without international search report and to be republished
upon receipt of that reportFor two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.(54) Title: NUCLEOSIDE ARYL PHOSPHORAMIDATES FOR THE TREATMENT OF RNA-DEPENDENT RNA VIRAL IN-
FECTION

(57) Abstract: The present invention provides nucleoside aryl phosphoramidates of structural formula (I) which are precursors to inhibitors of RNA-dependent RNA viral polymerase. These compounds are precursors to inhibitors of RNA-dependent RNA viral replication and are useful for the treatment of RNA-dependent RNA viral infection. They are particularly useful as precursors to inhibitors of hepatitis C virus (HCV) NS5B polymerase, as precursors to inhibitors of HCV replication, and/or for the treatment of hepatitis C infection. The invention also describes pharmaceutical compositions containing such nucleoside aryl phosphoramidates alone or in combination with other agents active against RNA-dependent RNA viral infection, in particular HCV infection. Also disclosed are methods of inhibiting RNA-dependent RNA polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection with the nucleoside aryl phosphoramidates of the present invention.

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TITLE OF THE INVENTION

NUCLEOSIDE ARYL PHOSPHORAMIDATES FOR THE TREATMENT OF RNA-DEPENDENT RNA VIRAL INFECTION

5 FIELD OF THE INVENTION

The present invention is concerned with nucleoside aryl phosphoramidates, their synthesis, and their use as precursors to inhibitors of RNA-dependent RNA viral polymerase. The compounds of the present invention are precursors to inhibitors of RNA-dependent RNA viral replication and are therefore useful for the treatment of RNA-dependent RNA viral infection. They are particularly
10 useful as precursors to inhibitors of hepatitis C virus (HCV) NS5B polymerase, as precursors to inhibitors of HCV replication, and for the treatment of hepatitis C infection.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver
15 disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be 2-15% of the world's population. There are an estimated 4.5 million infected people in the United States alone, according to the U.S. Center for Disease Control. According to the World Health Organization, there are more than 200 million infected individuals worldwide, with at least 3 to 4 million people being infected each year. Once infected, about 20% of people clear the virus, but the rest
20 harbor HCV the rest of their lives. Ten to twenty percent of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. The viral disease is transmitted parenterally by contaminated blood and blood products, contaminated needles, or sexually and vertically from infected mothers or carrier mothers to their off-spring. Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon- α alone or in combination with the nucleoside analog
25 ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine for HCV. Consequently, there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection. The state of the art in the treatment of HCV infection has been reviewed, and reference is made to the following publications: B. Dymock, et al., "Novel approaches to the treatment of hepatitis C virus infection," Antiviral Chemistry & Chemotherapy, 11: 79-96 (2000); H. Rosen, et al., "Hepatitis C
30 virus: current understanding and prospects for future therapies," Molecular Medicine Today, 5: 393-399 (1999); D. Moradpour, et al., "Current and evolving therapies for hepatitis C," European J. Gastroenterol. Hepatol., 11: 1189-1202 (1999); R. Bartenschlager, "Candidate Targets for Hepatitis C Virus-Specific Antiviral Therapy," Intervirology, 40: 378-393 (1997); G.M. Lauer and B.D. Walker, "Hepatitis C Virus Infection," N. Engl. J. Med., 345: 41-52 (2001); B.W. Dymock, "Emerging therapies for hepatitis C virus
35 infection," Emerging Drugs, 6: 13-42 (2001); and C. Crabb, "Hard-Won Advances Spark Excitement about Hepatitis C," Science: 506-507 (2001); the contents of all of which are incorporated by reference herein in their entirety.

Different approaches to HCV therapy have been taken, which include the inhibition of viral serine proteinase (NS3 protease), helicase, and RNA-dependent RNA polymerase (NS5B), and the development of a vaccine.

The HCV virion is an enveloped positive-strand RNA virus with a single
5 oligoribonucleotide genomic sequence of about 9600 bases which encodes a polyprotein of about 3,010 amino acids. The protein products of the HCV gene consist of the structural proteins C, E1, and E2, and the non-structural proteins NS2, NS3, NS4A and NS4B, and NS5A and NS5B. The nonstructural (NS) proteins are believed to provide the catalytic machinery for viral replication. The NS3 protease releases NS5B, the RNA-dependent RNA polymerase from the polyprotein chain. HCV NS5B polymerase is
10 required for the synthesis of a double-stranded RNA from a single-stranded viral RNA that serves as a template in the replication cycle of HCV. NS5B polymerase is therefore considered to be an essential component in the HCV replication complex [see K. Ishi, et al., "Expression of Hepatitis C Virus NS5B Protein: Characterization of Its RNA Polymerase Activity and RNA Binding," Hepatology, 29: 1227-1235 (1999) and V. Lohmann, et al., "Biochemical and Kinetic Analyses of NS5B RNA-Dependent RNA
15 Polymerase of the Hepatitis C Virus," Virology, 249: 108-118 (1998)]. Inhibition of HCV NS5B polymerase prevents formation of the double-stranded HCV RNA and therefore constitutes an attractive approach to the development of HCV-specific antiviral therapies.

The development of inhibitors of HCV NS5B polymerase with potential for the treatment of HCV infection has been reviewed in M.P. Walker et al., "Promising candidates for the
20 treatment of chronic hepatitis C," Expert Opin. Invest. Drugs, 12: 1269-1280 (2003) and in P. Hoffmann et al., "Recent patents on experimental therapy for hepatitis C virus infection (1999-2002)," Expert Opin. Ther. Patents, 13: 1707-1723 (2003). The activity of purine ribonucleosides against HCV polymerase was reported by A.E. Eldrup et al., "Structure-Activity Relationship of Purine Ribonucleosides for Inhibition of HCV RNA-Dependent RNA Polymerase," J. Med. Chem., 47: 2283-2295 (2004). There is
25 a continuing need for structurally diverse nucleoside derivatives as inhibitors of HCV polymerase as therapeutic approaches for HCV therapy.

It has now been found that nucleoside aryl phosphoramidates of the present invention are precursors to potent inhibitors of RNA-dependent RNA viral replication and in particular HCV
30 replication. The phosphoramidates are converted *in vivo* into their nucleoside 5'-phosphate (nucleotide) derivatives which are converted into the corresponding nucleoside 5'-triphosphate derivatives which are inhibitors of RNA-dependent RNA viral polymerase and in particular HCV NS5B polymerase. The instant nucleoside phosphoramidates are useful to treat RNA-dependent RNA viral infection and in particular HCV infection.

It is therefore an object of the present invention to provide nucleoside aryl
35 phosphoramidates which are useful as precursors to inhibitors of RNA-dependent RNA viral polymerase and in particular as precursors to inhibitors of HCV NS5B polymerase.

It is another object of the present invention to provide nucleoside aryl phosphoramidates which are useful as precursors to inhibitors of the replication of an RNA-dependent RNA virus and in particular as precursors to inhibitors of the replication of hepatitis C virus.

5 It is another object of the present invention to provide nucleoside aryl phosphoramidates which are useful in the treatment of RNA-dependent RNA viral infection and in particular in the treatment of HCV infection.

It is another object of the present invention to provide pharmaceutical compositions comprising the nucleoside aryl phosphoramidates of the present invention in association with a pharmaceutically acceptable carrier.

10 It is another object of the present invention to provide pharmaceutical compositions comprising the nucleoside aryl phosphoramidates of the present invention for use as precursors to inhibitors of RNA-dependent RNA viral polymerase and in particular as precursors to inhibitors of HCV NS5B polymerase.

15 It is another object of the present invention to provide pharmaceutical compositions comprising the nucleoside aryl phosphoramidates of the present invention for use as precursors to inhibitors of RNA-dependent RNA viral replication and in particular as precursors to inhibitors of HCV replication.

20 It is another object of the present invention to provide pharmaceutical compositions comprising the nucleoside aryl phosphoramidates of the present invention for use in the treatment of RNA-dependent RNA viral infection and in particular in the treatment of HCV infection.

It is another object of the present invention to provide pharmaceutical compositions comprising the nucleoside aryl phosphoramidates of the present invention in combination with other agents active against an RNA-dependent RNA virus and in particular against HCV.

25 It is another object of the present invention to provide methods for the inhibition of RNA-dependent RNA viral polymerase and in particular for the inhibition of HCV NS5B polymerase.

It is another object of the present invention to provide methods for the inhibition of RNA-dependent RNA viral replication and in particular for the inhibition of HCV replication.

30 It is another object of the present invention to provide methods for the treatment of RNA-dependent RNA viral infection and in particular for the treatment of HCV infection.

It is another object of the present invention to provide methods for the treatment of RNA-dependent RNA viral infection in combination with other agents active against RNA-dependent RNA virus and in particular for the treatment of HCV infection in combination with other agents active against HCV.

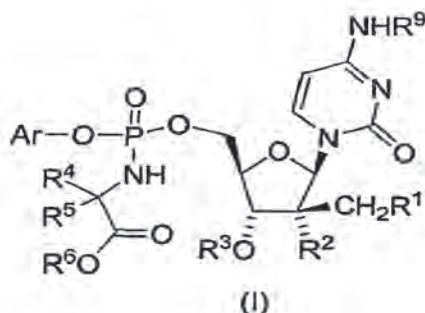
35 It is another object of the present invention to provide nucleoside aryl phosphoramidates and their pharmaceutical compositions for use as a medicament for the inhibition of RNA-dependent RNA viral replication and/or the treatment of RNA-dependent RNA viral infection and in particular for the inhibition of HCV replication and/or the treatment of HCV infection.

It is another object of the present invention to provide for the use of the nucleoside aryl phosphoramidates of the present invention and their pharmaceutical compositions for the manufacture of a medicament for the inhibition of RNA-dependent RNA viral replication and/or the treatment of RNA-dependent RNA viral infection and in particular for the inhibition of HCV replication and/or the treatment of HCV infection.

These and other objects will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention relates to compounds of structural formula I of the indicated stereochemical configuration:



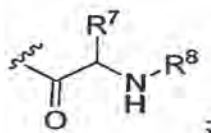
and pharmaceutically acceptable salts thereof; wherein
n is 0, 1, or 2;

Ar is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, or isoquinolinyl, wherein Ar is optionally substituted with one to five substituents independently selected from the group consisting of halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, cyano, nitro, amino, carboxy, trifluoromethyl, trifluoromethoxy, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ alkylcarbonyl, C₁₋₄ alkylcarbonyloxy, and C₁₋₄ alkyloxycarbonyl;

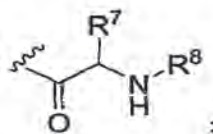
R¹ is hydrogen or fluoro;

R² is fluoro, methoxy, or OR¹⁰;

R³ is selected from the group consisting of hydrogen, C₁₋₁₆ alkylcarbonyl, C₂₋₁₈ alkenylcarbonyl, C₁₋₁₀ alkyloxycarbonyl, C₃₋₆ cycloalkylcarbonyl, C₃₋₆ cycloalkyloxycarbonyl, and an amino acyl residue of structural formula:



R¹⁰ is selected from the group consisting of hydrogen, C₁₋₁₆ alkylcarbonyl, C₂₋₁₈ alkenylcarbonyl, C₁₋₁₀ alkyloxycarbonyl, C₃₋₆ cycloalkylcarbonyl, C₃₋₆ cycloalkyloxycarbonyl, and an amino acyl residue of structural formula:



5 or R³ and R¹⁰ together with the oxygen atoms to which they are attached form a five-membered cyclic carbonate;

R⁴ is hydrogen, C₁₋₅ alkyl, phenyl, or benzyl;

10 wherein alkyl is optionally substituted with one substituent selected from the group consisting of fluorine, hydroxy, methoxy, amino, carboxy, carbamoyl, guanidino, mercapto, methylthio, 1*H*-imidazolyl, and 1*H*-indol-3-yl; and wherein phenyl and benzyl are optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, and methoxy;

R⁵ is hydrogen or methyl;

15 or R⁴ and R⁵ together with the carbon atom to which they attached form a 3- to 6-membered aliphatic spirocyclic ring system;

R⁶ is hydrogen, C₁₋₁₆ alkyl, C₂₋₂₀ alkenyl, (CH₂)_nC₃₋₆ cycloalkyl, phenyl, benzyl, or adamantyl;

20 wherein alkyl, alkenyl, cycloalkyl, and adamantyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄ alkoxy; and wherein phenyl and benzyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, cyano, C₁₋₄ alkoxy, trifluoromethyl, and trifluoromethoxy;

R⁷ is hydrogen, C₁₋₅ alkyl, or phenyl C₀₋₂ alkyl;

R⁸ is hydrogen, C₁₋₄ alkyl, C₁₋₄ acyl, benzoyl, C₁₋₄ alkyloxycarbonyl,

phenyl C₀₋₂ alkyloxycarbonyl, C₁₋₄ alkylaminocarbonyl, phenyl C₀₋₂ alkylaminocarbonyl, C₁₋₄ alkylsulfonyl, or phenyl C₀₋₂ alkylsulfonyl; and

25 R⁹ is hydrogen, C₁₋₈ alkylcarbonyl, or C₁₋₈ alkyloxycarbonyl.

30 The compounds of formula I are useful as precursors to inhibitors of RNA-dependent RNA viral polymerase and in particular of HCV NS5B polymerase. They are also precursors to inhibitors of RNA-dependent RNA viral replication and in particular of HCV replication and are useful for the treatment of RNA-dependent RNA viral infection and in particular for the treatment of HCV infection.

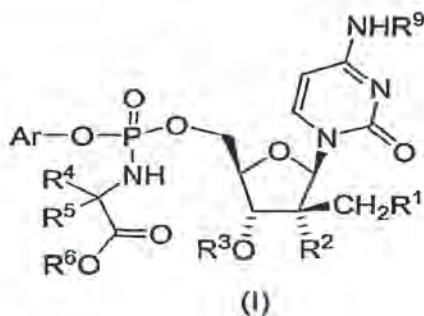
Without limitation as to their mechanism of action, the aryl phosphoramidates of the present invention act as precursors of the corresponding nucleoside 5'-monophosphates. Endogenous kinase enzymes convert the 5'-monophosphates into their 5'-triphosphate derivatives which are the inhibitors of the RNA-dependent RNA viral polymerase. Thus, the aryl phosphoramidates may provide

for more efficient target cell penetration than the nucleoside itself, may be less susceptible to metabolic degradation, and may have the ability to target a specific tissue, such as the liver, resulting in a wider therapeutic index allowing for lowering the overall dose of the antiviral agent.

- Also encompassed within the present invention are pharmaceutical compositions
 5 containing the compounds alone or in combination with other agents active against RNA-dependent RNA virus and in particular against HCV as well as methods for the inhibition of RNA-dependent RNA viral replication and for the treatment of RNA-dependent RNA viral infection.

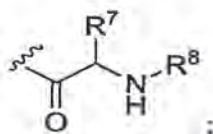
DETAILED DESCRIPTION OF THE INVENTION

- 10 The present invention relates to compounds of structural formula I of the indicated stereochemical configuration:



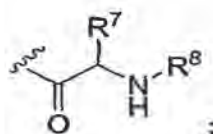
and pharmaceutically acceptable salts thereof; wherein

- n is 0, 1, or 2;
 15 Ar is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinoliny, or isoquinoliny, wherein Ar is optionally substituted with one to five substituents independently selected from the group consisting of halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, cyano, nitro, amino, carboxy, trifluoromethyl, trifluoromethoxy, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ alkylcarbonyl, C₁₋₄ alkylcarbonyloxy, and C₁₋₄ alkyloxycarbonyl;
 20 R¹ is hydrogen or fluoro;
 R² is fluoro, methoxy, or OR¹⁰;
 R³ is selected from the group consisting of hydrogen, C₁₋₁₆ alkylcarbonyl, C₂₋₁₈ alkenylcarbonyl, C₁₋₁₀ alkyloxycarbonyl, C₃₋₆ cycloalkylcarbonyl, C₃₋₆ cycloalkyloxycarbonyl, and an amino acyl residue of structural formula:



25

R¹⁰ is selected from the group consisting of hydrogen, C₁₋₁₆ alkylcarbonyl, C₂₋₁₈ alkenylcarbonyl, C₁₋₁₀ alkyloxycarbonyl, C₃₋₆ cycloalkylcarbonyl, C₃₋₆ cycloalkyloxycarbonyl, and an amino acyl residue of structural formula:



5 or R³ and R¹⁰ together with the oxygen atoms to which they are attached form a five-membered cyclic carbonate;

R⁴ is hydrogen, C₁₋₅ alkyl, phenyl, or benzyl;

wherein alkyl is optionally substituted with one substituent selected from the group consisting of fluorine, hydroxy, methoxy, amino, carboxy, carbamoyl, guanidino, mercapto, methylthio, 1*H*-imidazolyl, and 1*H*-indol-3-yl; and wherein phenyl and benzyl are optionally substituted with one
10 to two substituents independently selected from the group consisting of halogen, hydroxy, and methoxy;

R⁵ is hydrogen or methyl;

or R⁴ and R⁵ together with the carbon atom to which they attached form a 3- to 6-membered aliphatic
15 spirocyclic ring system;

R⁶ is hydrogen, C₁₋₁₆ alkyl, C₂₋₂₀ alkenyl, (CH₂)_nC₃₋₆ cycloalkyl, phenyl, benzyl, or adamantyl;

wherein alkyl, alkenyl, cycloalkyl, and adamantyl are optionally substituted with one to three
substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄ alkoxy; and wherein
phenyl and benzyl are optionally substituted with one to three substituents independently
20 selected from halogen, hydroxy, cyano, C₁₋₄ alkoxy, trifluoromethyl, and trifluoromethoxy;

R⁷ is hydrogen, C₁₋₅ alkyl, or phenyl C₀₋₂ alkyl;

R⁸ is hydrogen, C₁₋₄ alkyl, C₁₋₄ acyl, benzoyl, C₁₋₄ alkyloxycarbonyl,
phenyl C₀₋₂ alkyloxycarbonyl, C₁₋₄ alkylaminocarbonyl, phenyl C₀₋₂ alkylaminocarbonyl, C₁₋₄
alkylsulfonyl, or phenyl C₀₋₂ alkylsulfonyl; and

25 R⁹ is hydrogen, C₁₋₈ alkylcarbonyl, or C₁₋₈ alkyloxycarbonyl.

The compounds of formula I are useful as precursors to inhibitors of RNA-dependent RNA viral polymerase. They are also precursors to inhibitors of RNA-dependent RNA viral replication and are useful for the treatment of RNA-dependent RNA viral infection.

In one embodiment of the compounds of the present invention, R¹ is hydrogen or fluoro,
30 R² is hydroxy, and R³ is hydrogen. In a class of this embodiment, R¹ is hydrogen.

In a second embodiment of the compounds of the present invention, R¹ is hydrogen or fluoro, R² is fluoro, and R³ is hydrogen. In a class of this embodiment, R¹ is hydrogen.

In a third embodiment of the compounds of the present invention, Ar is phenyl optionally substituted with one to five substituents independently selected from the group consisting of halogen, C₁₋

4 alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, cyano, nitro, amino, carboxy, trifluoromethyl, trifluoromethoxy, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ alkylcarbonyl, C₁₋₄ alkylcarbonyloxy, and C₁₋₄ alkyloxycarbonyl. In a class of this embodiment, Ar is phenyl substituted with three to five substituents independently selected from the group consisting of halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, cyano, nitro, amino, carboxy, trifluoromethyl, trifluoromethoxy, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ alkylcarbonyl, C₁₋₄ alkylcarbonyloxy, and C₁₋₄ alkyloxycarbonyl. In a subclass of this class, Ar is phenyl substituted with three substituents independently selected from the group consisting of halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, cyano, nitro, amino, carboxy, trifluoromethyl, trifluoromethoxy, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ alkylcarbonyl, C₁₋₄ alkylcarbonyloxy, and C₁₋₄ alkyloxycarbonyl. In another class of this third embodiment, Ar is unsubstituted phenyl.

In a fourth embodiment of the compounds of the present invention, Ar is unsubstituted 1-naphthyl.

In a fifth embodiment of the compounds of the present invention, Ar is indolyl. In a class of this embodiment, Ar is 1*H*-indol-5-yl.

In a sixth embodiment of the compounds of the present invention, R⁵ is hydrogen and R⁴ is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, isopropyl, isobutyl, 2-methyl-1-propyl, hydroxymethyl, fluoromethyl, mercaptomethyl, carboxymethyl, carbamoylmethyl, 1-hydroxyethyl, 2-carboxyethyl, 2-carbamoyl-ethyl, 2-methylthioethyl, 4-amino-1-butyl, 3-amino-1-propyl, 3-guanidino-1-propyl, 1*H*-imidazol-4-ylmethyl, phenyl, benzyl, 4-hydroxybenzyl, and 1*H*-indol-3-ylmethyl. In a class of this embodiment, R⁴ is methyl or benzyl. In a subclass of this class, R⁴ is methyl.

In a seventh embodiment of the compounds of the present invention, R⁶ is C₁₋₈ alkyl, cyclohexyl, or cyclopentyl. In a class of this embodiment, R⁶ is ethyl or butyl. In a another class of this embodiment, Ar is indolyl.

In an eighth embodiment of the compounds of the present invention, R⁶ is C₇₋₁₆ alkyl.

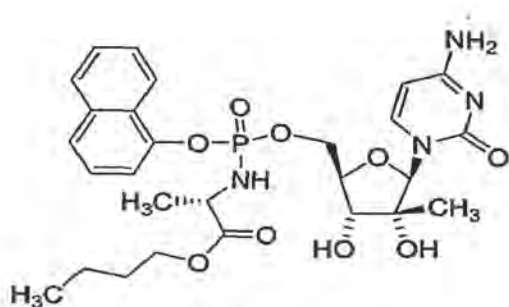
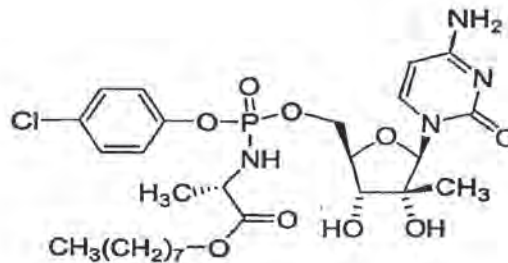
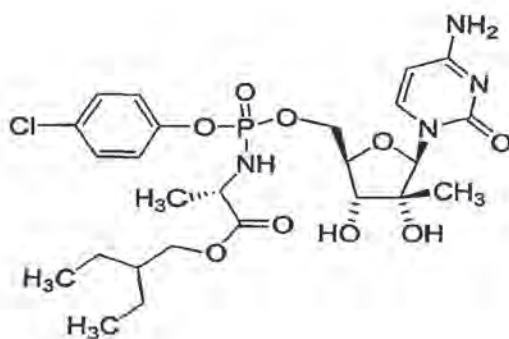
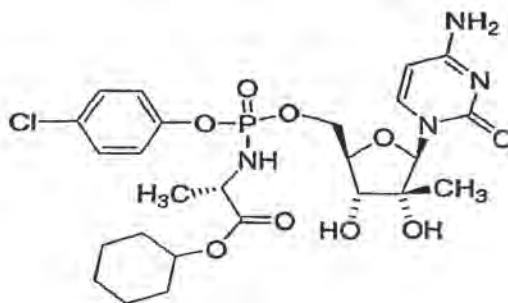
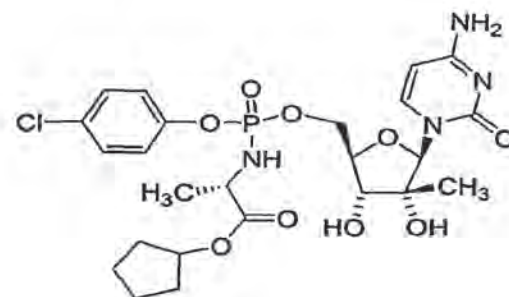
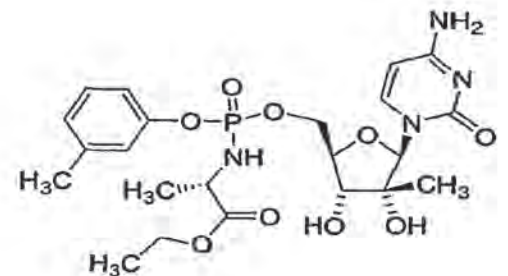
In a class of this embodiment, R⁶ is C₈₋₁₂ alkyl. In a subclass of this class, R⁶ is C₈ alkyl. In a subclass of this subclass, R⁶ is 2-*n*-propyl-pent-1-yl.

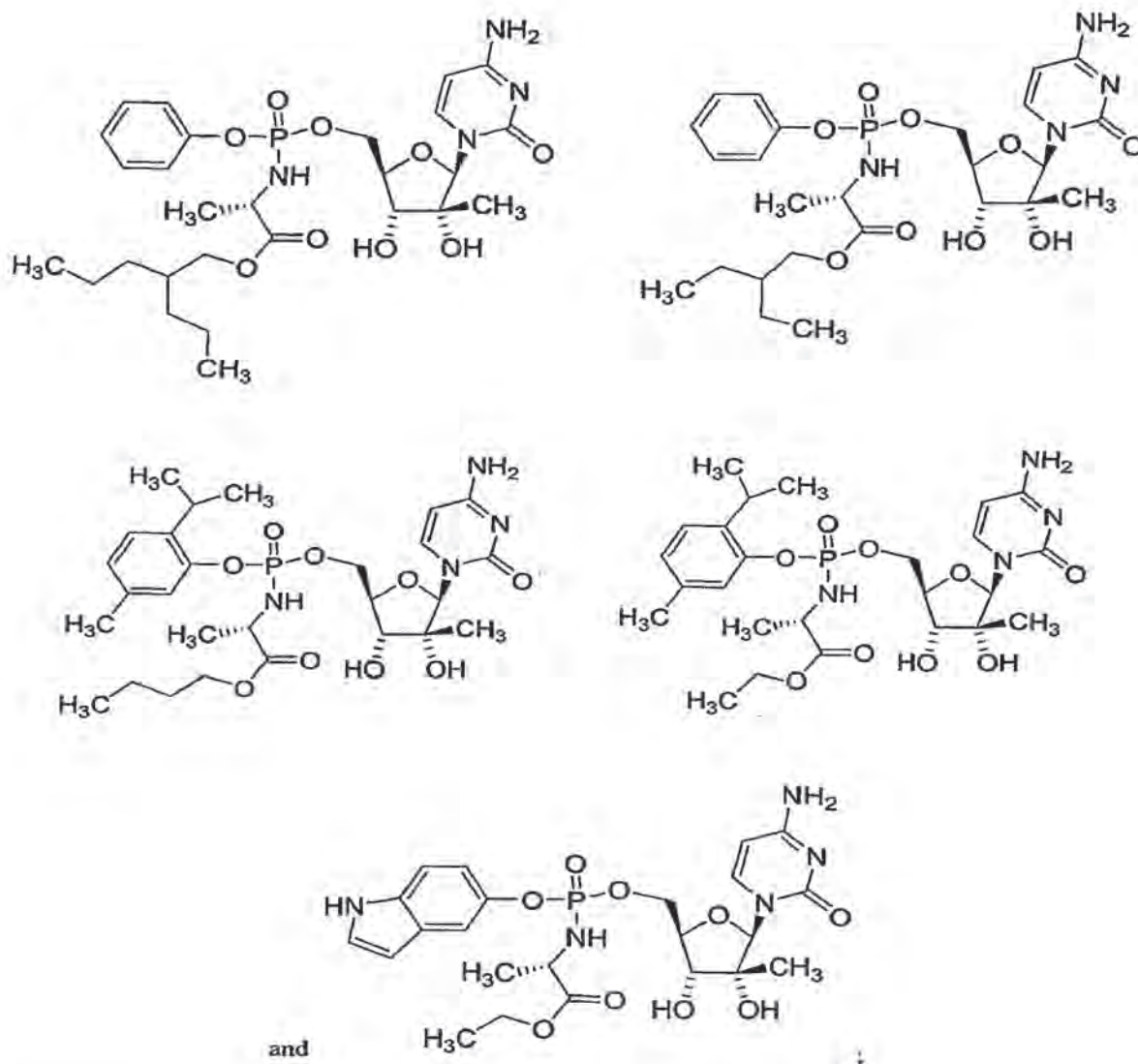
In a ninth embodiment of the compounds of the present invention, Ar is phenyl or indolyl each of which is optionally substituted with one to three substituents selected from halogen and C₁₋₄ alkyl; R⁴ is methyl; R⁶ is ethyl or butyl; and R⁵ is hydrogen. In a class of this embodiment, Ar is indolyl.

In a tenth embodiment of the compounds of the present invention, R⁴ and R⁵ are both methyl.

In an eleventh embodiment of the compounds of the present invention, Ar is unsubstituted phenyl and R⁶ is C₈ alkyl. In a class of this embodiment, R⁶ is 2-*n*-propyl-pent-1-yl.

Illustrative but nonlimiting examples of compounds of the present invention of structural formula I which are useful as precursors to inhibitors of RNA-dependent RNA viral polymerase are the following:





5 and pharmaceutically acceptable salts thereof.

In one embodiment of the present invention, the nucleoside aryl phosphoramidates of the present invention are useful as precursors to inhibitors of positive-sense single-stranded RNA-dependent RNA viral polymerase, inhibitors of positive-sense single-stranded RNA-dependent RNA viral replication, and/or for the treatment of positive-sense single-stranded RNA-dependent RNA viral infection. In a class of this embodiment, the positive-sense single-stranded RNA-dependent RNA virus is a *Flaviviridae* virus or a *Picornaviridae* virus. In a subclass of this class, the *Picornaviridae* virus is a

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rhinovirus, a poliovirus, or a hepatitis A virus. In a second subclass of this class, the *Flaviviridae* virus is selected from the group consisting of hepatitis C virus, yellow fever virus, dengue virus, West Nile virus, Japanese encephalitis virus, Banzi virus, and bovine viral diarrhea virus (BVDV). In a subclass of this subclass, the *Flaviviridae* virus is hepatitis C virus.

5 Another aspect of the present invention is concerned with a method for inhibiting RNA-dependent RNA viral polymerase, a method for inhibiting RNA-dependent RNA viral replication, and/or a method for treating RNA-dependent RNA viral infection in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of a compound of structural formula I.

In one embodiment of this aspect of the present invention, the RNA-dependent RNA
10 viral polymerase is a positive-sense single-stranded RNA-dependent RNA viral polymerase. In a class of this embodiment, the positive-sense single-stranded RNA-dependent RNA viral polymerase is a *Flaviviridae* viral polymerase or a *Picornaviridae* viral polymerase. In a subclass of this class, the *Picornaviridae* viral polymerase is rhinovirus polymerase, poliovirus polymerase, or hepatitis A virus polymerase. In a second subclass of this class, the *Flaviviridae* viral polymerase is selected from the
15 group consisting of hepatitis C virus polymerase, yellow fever virus polymerase, dengue virus polymerase, West Nile virus polymerase, Japanese encephalitis virus polymerase, Banzi virus polymerase, and bovine viral diarrhea virus (BVDV) polymerase. In a subclass of this subclass, the *Flaviviridae* viral polymerase is hepatitis C virus polymerase.

In a second embodiment of this aspect of the present invention, the RNA-dependent
20 RNA viral replication is a positive-sense single-stranded RNA-dependent RNA viral replication. In a class of this embodiment, the positive-sense single-stranded RNA-dependent RNA viral replication is *Flaviviridae* viral replication or *Picornaviridae* viral replication. In a subclass of this class, the *Picornaviridae* viral replication is rhinovirus replication, poliovirus replication, or hepatitis A virus replication. In a second subclass of this class, the *Flaviviridae* viral replication is selected from the
25 group consisting of hepatitis C virus replication, yellow fever virus replication, dengue virus replication, West Nile virus replication, Japanese encephalitis virus replication, Banzi virus replication, and bovine viral diarrhea virus replication. In a subclass of this subclass, the *Flaviviridae* viral replication is hepatitis C virus replication.

In a third embodiment of this aspect of the present invention, the RNA-dependent RNA
30 viral infection is a positive-sense single-stranded RNA-dependent viral infection. In a class of this embodiment, the positive-sense single-stranded RNA-dependent RNA viral infection is *Flaviviridae* viral infection or *Picornaviridae* viral infection. In a subclass of this class, the *Picornaviridae* viral infection is rhinovirus infection, poliovirus infection, or hepatitis A virus infection. In a second subclass of this class, the *Flaviviridae* viral infection is selected from the group consisting of hepatitis C virus infection,
35 yellow fever virus infection, dengue virus infection, West Nile virus infection, Japanese encephalitis virus infection, Banzi virus infection, and bovine viral diarrhea virus infection. In a subclass of this subclass, the *Flaviviridae* viral infection is hepatitis C virus infection.

Throughout the instant application, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

The term "naphthyl" encompasses both 1-naphthyl (α -naphthyl) and 2-naphthyl (β -naphthyl).

The term "adamantyl" encompasses both 1-adamantyl and 2-adamantyl.

By the term "optionally substituted benzyl" is meant $-\text{CH}_2\text{Phenyl}$ wherein the phenyl moiety is optionally substituted.

The term "alkenyl" shall mean straight or branched chain alkenes of two to twenty total carbon atoms, or any number within this range (e.g., ethenyl, propenyl, butenyl, pentenyl, oleyl, etc.).

The term "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms, or any number within this range (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl).

The term "alkoxy" refers to straight or branched chain alkoxides of the number of carbon atoms specified (e.g., C_{1-4} alkoxy), or any number within this range [i.e., methoxy ($\text{MeO}-$), ethoxy, isopropoxy, etc.].

The term "alkylthio" refers to straight or branched chain alkylsulfides of the number of carbon atoms specified (e.g., C_{1-4} alkylthio), or any number within this range [i.e., methylthio ($\text{MeS}-$), ethylthio, isopropylthio, etc.].

The term "alkylamino" refers to straight or branched alkylamines of the number of carbon atoms specified (e.g., C_{1-4} alkylamino), or any number within this range [i.e., methylamino, ethylamino, isopropylamino, t-butylamino, etc.].

The term "alkylsulfonyl" refers to straight or branched chain alkylsulfones of the number of carbon atoms specified (e.g., C_{1-6} alkylsulfonyl), or any number within this range [i.e., methylsulfonyl (MeSO_2-), ethylsulfonyl, isopropylsulfonyl, etc.].

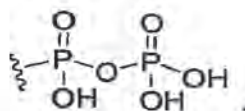
The term "alkyloxycarbonyl" refers to straight or branched chain esters of a carboxylic acid or carbamic acid group present in a compound of the present invention having the number of carbon atoms specified (e.g., C_{1-8} alkyloxycarbonyl), or any number within this range [i.e., methyloxycarbonyl ($\text{MeOCO}-$), ethyloxycarbonyl, or butyloxycarbonyl].

The term "alkylcarbonyl" refers to straight or branched chain alkyl acyl group of the specified number of carbon atoms (e.g., C_{1-8} alkylcarbonyl), or any number within this range [i.e., methyloxycarbonyl ($\text{MeOCO}-$), ethyloxycarbonyl, or butyloxycarbonyl].

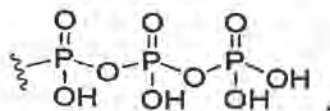
The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

The term "phosphoryl" refers to $-\text{P}(\text{O})(\text{OH})_2$.

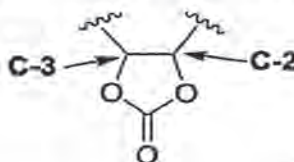
The term "diphosphoryl" refers to the radical having the structure:



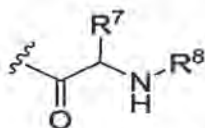
The term "triphosphoryl" refers to the radical having the structure:



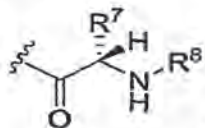
- 5 The term "five-membered cyclic carbonate ring" denotes the following ring system formed at the C-2 and C-3 positions of the furanose ring of the nucleoside by acylating the C-2 and C-3 hydroxyls with a carbonylating reagent, such as phosgene and 1,1'-carbonyldiimidazole:



- 10 When R⁷ in the amino acyl residue embodiment of R³ and R¹⁰ is a substituent other than hydrogen in the formula



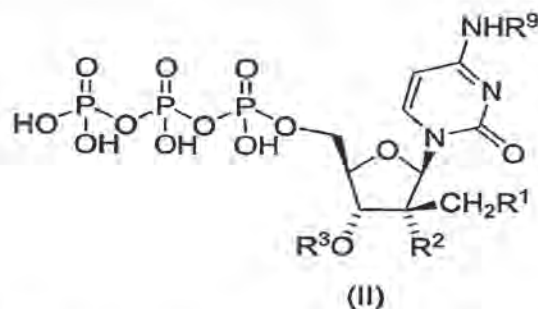
- the amino acyl residue contains an asymmetric center and is intended to include the individual *R*- and *S*-stereoisomers as well as *RS*-diastereoisomeric mixtures. In one embodiment, the stereochemistry at the stereogenic carbon corresponds to that of an *S*-amino acid, that is, the naturally occurring alpha-amino acid stereochemistry, as depicted in the formula:
- 15



The term "substituted" shall be deemed to include multiple degrees of substitution by a named substituent. Where multiple substituent moieties are disclosed or claimed, the substituted

compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally.

The term "5'-triphosphate" refers to a triphosphoric acid ester derivative of the 5'-hydroxyl group of a nucleoside compound of the present invention having the following general structural formula II:



wherein R¹, R², R³, and R⁹ are as defined above.

The term "composition", as in "pharmaceutical composition," is intended to encompass a product comprising the active ingredient(s) and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The terms "administration of" and "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need.

Another aspect of the present invention is concerned with a method of inhibiting HCV NS5B polymerase, inhibiting HCV replication, or treating HCV infection with a compound of the present invention in combination with one or more agents useful for treating HCV infection. Such agents active against HCV include, but are not limited to, ribavirin, levovirin, viramidine, nitazoxanide, thymosin alpha-1, interferon-β, interferon-α, pegylated interferon-α (peginterferon-α), a combination of interferon-α and ribavirin, a combination of peginterferon-α and ribavirin, a combination of interferon-α and levovirin, and a combination of peginterferon-α and levovirin. Interferon-α includes, but is not limited to, recombinant interferon-α2a (such as Roferon interferon available from Hoffmann-LaRoche, Nutley, NJ), pegylated interferon-α2a (PegasysTM), interferon-α2b (such as Intron-A interferon available from Schering Corp., Kenilworth, NJ), pegylated interferon-α2b (PegIntronTM), a recombinant consensus interferon (such as interferon alphacon-1), and a purified interferon-α product. Amgen's recombinant consensus interferon has the brand name Infergen®. Levovirin is the L-enantiomer of ribavirin which

has shown immunomodulatory activity similar to ribavirin. Viramidine represents an analog of ribavirin disclosed in WO 01/60379 (assigned to ICN Pharmaceuticals). In accordance with this method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment, and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating HCV infection includes in principle any combination with any pharmaceutical composition for treating HCV infection. When a compound of the present invention or a pharmaceutically acceptable salt thereof is used in combination with a second therapeutic agent active against HCV, the dose of each compound may be either the same as or different from the dose when the compound is used alone.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS3 serine protease. HCV NS3 serine protease is an essential viral enzyme and has been described to be an excellent target for inhibition of HCV replication. Both substrate and non-substrate based inhibitors of HCV NS3 protease inhibitors are disclosed in WO 98/22496, WO 98/46630, WO 99/07733, WO 99/07734, WO 99/38888, WO 99/50230, WO 99/64442, WO 00/09543, WO 00/59929, GB-2337262, WO 02/18369, WO 02/08244, WO 02/48116, WO 02/48172, WO 05/037214, and U.S. Patent No. 6,323,180. HCV NS3 protease as a target for the development of inhibitors of HCV replication and for the treatment of HCV infection is discussed in B.W. Dymock, "Emerging therapies for hepatitis C virus infection," Emerging Drugs, 6: 13-42 (2001). Specific HCV NS3 protease inhibitors combinable with the compounds of the present invention include BILN2061, VX-950, SCH6, SCH7, and SCH-503034.

Ribavirin, levovirin, and viramidine may exert their anti-HCV effects by modulating intracellular pools of guanine nucleotides via inhibition of the intracellular enzyme inosine monophosphate dehydrogenase (IMPDH). IMPDH is the rate-limiting enzyme on the biosynthetic route in *de novo* guanine nucleotide biosynthesis. Ribavirin is readily phosphorylated intracellularly and the monophosphate derivative is an inhibitor of IMPDH. Thus, inhibition of IMPDH represents another useful target for the discovery of inhibitors of HCV replication. Therefore, the compounds of the present invention may also be administered in combination with an inhibitor of IMPDH, such as VX-497, which is disclosed in WO 97/41211 and WO 01/00622 (assigned to Vertex); another IMPDH inhibitor, such as that disclosed in WO 00/25780 (assigned to Bristol-Myers Squibb); or mycophenolate mofetil [see A.C. Allison and E.M. Eugui, Agents Action, 44 (Suppl.): 165 (1993)].

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with the antiviral agent amantadine (1-aminoadamantane) [for a comprehensive description of this agent, see J. Kirschbaum, Anal. Profiles Drug Subs. 12: 1-36 (1983)].

The compounds of the present invention may also be combined for the treatment of HCV infection with antiviral 2'-C-branched ribonucleosides disclosed in R. E. Harry-O'kuru, et al., J. Org.

Chem., 62: 1754-1759 (1997); M. S. Wolfe, et al., Tetrahedron Lett., 36: 7611-7614 (1995); U.S. Patent No. 3,480,613 (Nov. 25, 1969); US Patent No. 6,777,395 (Aug. 17, 2004); US Patent No. 6,914,054 (July 5, 2005); International Publication Numbers WO 01/90121 (29 November 2001); WO 01/92282 (6 December 2001); WO 02/32920 (25 April 2002); WO 02/057287 (25 July 2002); WO 02/057425 (25 July 2002); WO 04/002422 (8 Jan. 2004); WO 04/002999 (8 January 2004); WO 04/003000 (8 January 2004); WO 04/002422 (8 January 2004); US Patent Application Publications 2005/0107312; US 2005/0090463; US 2004/0147464; and US 2004/0063658; the contents of each of which are incorporated by reference in their entirety. Such 2'-C-branched ribonucleosides include, but are not limited to, 2'-C-methylcytidine, 2'-fluoro-2'-C-methylcytidine 2'-C-methyluridine, 2'-C-methyladenosine, 2'-C-methylguanosine, and 9-(2-C-methyl- β -D-ribofuranosyl)-2,6-diaminopurine; the corresponding amino acid esters of the furanose C-2', C-3', and C-5' hydroxyls (such as 3'-O-(L-valyl)-2'-C-methylcytidine dihydrochloride, also referred to as valopicitabine dihydrochloride or NM-283 and 3'-O-(L-valyl)-2'-fluoro-2'-C-methylcytidine), and the corresponding optionally substituted cyclic 1,3-propanediol esters of their 5'-phosphate derivatives.

The compounds of the present invention may also be combined for the treatment of HCV infection with other nucleosides having anti-HCV properties, such as those disclosed in US Patent No. 6,864,244 (Mar. 8, 2005); WO 02/51425 (4 July 2002), assigned to Mitsubishi Pharma Corp.; WO 01/79246, WO 02/32920, and WO 02/48165 (20 June 2002), assigned to Pharmasset, Ltd.; WO 01/68663 (20 September 2001), assigned to ICN Pharmaceuticals; WO 99/43691 (2 Sept. 1999); WO 02/18404 (7 March 2002), assigned to Hoffmann-LaRoche; U.S. 2002/0019363 (14 Feb. 2002); WO 02/100415 (19 Dec. 2002); WO 03/026589 (3 Apr. 2003); WO 03/026675 (3 Apr. 2003); WO 03/093290 (13 Nov. 2003); US 2003/0236216 (25 Dec. 2003); US 2004/0006007 (8 Jan. 2004); WO 04/011478 (5 Feb. 2004); WO 04/013300 (12 Feb. 2004); US 2004/0063658 (1 Apr. 2004); and WO 04/028481 (8 Apr. 2004).

In one embodiment, nucleoside HCV NS5B polymerase inhibitors that may be combined with the nucleoside derivatives of the present invention are selected from the following compounds: 4'-azido-cytidine; 4-amino-7-(2-C-methyl- β -D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-hydroxymethyl- β -D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-fluoromethyl- β -D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-5-fluoro-7-(2-C-methyl- β -D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-7-(2-C-methyl- β -D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one; 4-amino-7-(2-C,2-O-dimethyl- β -D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; and pharmaceutically acceptable salts and prodrugs thereof.

The compounds of the present invention may also be combined for the treatment of HCV infection with non-nucleoside inhibitors of HCV polymerase such as those disclosed in WO 01/77091 (18 Oct. 2001), assigned to Tularik, Inc.; WO 01/47883 (5 July 2001), assigned to Japan Tobacco, Inc.; WO 02/04425 (17 January 2002), assigned to Boehringer Ingelheim; WO 02/06246 (24 Jan. 2002), assigned to Istituto di Ricerche di Biologia Molecolare P. Angeletti S.P.A.; WO 02/20497 (3 March

2002); WO 2005/016927 (in particular JTK003), assigned to Japan Tobacco, Inc.; the contents of each of which are incorporated herein by reference in their entirety; and HCV-796 (Viropharma Inc.).

In one embodiment, non-nucleoside HCV NS5B polymerase inhibitors that may be combined with the nucleoside derivatives of the present invention are selected from the following compounds:

5 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; methyl ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-yl)carbonyl]amino} sulfonyl)acetate; ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-yl)carbonyl]amino} sulfonyl)acetic acid; 14-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxamide; 3-chloro-14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; *N*-(11-carboxy-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-7-yl)-*N,N*-dimethylethane-1,2-diaminium bis(trifluoroacetate); 14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic acid; 14-cyclohexyl-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[3-(dimethylamino)propyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(diethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(1-methylpiperidin-4-yl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxamide; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-*N*-[(dimethylamino)sulfonyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxamide; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 6-allyl-14-cyclohexyl-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 13-cyclohexyl-5-methyl-4,5,6,7-tetrahydrofuro[3',2':6,7][1,4]diazocino[1,8-*a*]indole-10-carboxylic acid; 15-cyclohexyl-6-[2-

(dimethylamino)ethyl]-7-oxo-6,7,8,9-tetrahydro-5*H*-indolo[2,1- α][2,6]benzodiazonine-12-carboxylic acid; 15-cyclohexyl-8-oxo-6,7,8,9-tetrahydro-5*H*-indolo[2,1- α][2,5]benzodiazonine-12-carboxylic acid; 13-cyclohexyl-6-oxo-6,7-dihydro-5*H*-indolo[1,2- d][1,4]benzodiazepine-10-carboxylic acid; and pharmaceutically acceptable salts thereof.

5 By "pharmaceutically acceptable" is meant that the carrier, diluent, or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Also included within the present invention are pharmaceutical compositions comprising the nucleoside aryl phosphoramidates of the present invention in association with a pharmaceutically acceptable carrier. Another example of the invention is a pharmaceutical composition made by
10 combining any of the compounds described above and a pharmaceutically acceptable carrier. Another illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

Also included within the present invention are pharmaceutical compositions useful for inhibiting RNA-dependent RNA viral polymerase in particular HCV NS5B polymerase comprising an
15 effective amount of a compound of the present invention and a pharmaceutically acceptable carrier. Pharmaceutical compositions useful for treating RNA-dependent RNA viral infection in particular HCV infection are also encompassed by the present invention as well as a method of inhibiting RNA-dependent RNA viral polymerase in particular HCV NS5B polymerase and a method of treating RNA-dependent viral replication and in particular HCV replication. Additionally, the present invention is
20 directed to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention in combination with a therapeutically effective amount of another agent active against RNA-dependent RNA virus and in particular against HCV. Agents active against HCV include, but are not limited to, ribavirin, levovirin, viramidine, thymosin α -1, an inhibitor of HCV NS3 serine protease, interferon- α , pegylated interferon- α (peginterferon- α), a combination of interferon- α and
25 ribavirin, a combination of peginterferon- α and ribavirin, a combination of interferon- α and levovirin, and a combination of peginterferon- α and levovirin. Interferon- α includes, but is not limited to, recombinant interferon- α 2a (such as Roferon interferon available from Hoffmann-LaRoche, Nutley, NJ), interferon- α 2b (such as Intron-A interferon available from Schering Corp., Kenilworth, NJ), a consensus interferon, and a purified interferon- α product. For a discussion of ribavirin and its activity against HCV, see J.O. Saunders and S.A. Raybuck, "Inosine Monophosphate Dehydrogenase: Consideration of
30 Structure, Kinetics, and Therapeutic Potential," *Ann. Rep. Med. Chem.*, 35: 201-210 (2000).

Another aspect of the present invention provides for the use of the nucleoside aryl phosphoramidates and their pharmaceutical compositions for the manufacture of a medicament for the inhibition of RNA-dependent RNA viral replication, in particular HCV replication, and/or the treatment
35 of RNA-dependent RNA viral infection, in particular HCV infection. Yet a further aspect of the present invention provides for the nucleoside aryl phosphoramidates and their pharmaceutical compositions for

use as a medicament for the inhibition of RNA-dependent RNA viral replication, in particular HCV replication, and/or for the treatment of RNA-dependent RNA viral infection, in particular HCV infection.

The pharmaceutical compositions of the present invention comprise a compound of structural formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also
5 contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active
10 ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of structural formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of
15 preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders,
20 disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed.
25 If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be
30 administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in
35 addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may

contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of structural formula I may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

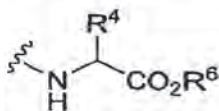
The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of structural formula I are administered orally.

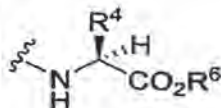
For oral administration to humans, the dosage range is 0.01 to 1000 mg/kg body weight in divided doses. In one embodiment the dosage range is 0.1 to 100 mg/kg body weight in divided doses. In another embodiment the dosage range is 0.5 to 20 mg/kg body weight in divided doses. For oral administration, the compositions are preferably provided in the form of tablets or capsules containing 1.0 to 1000 milligrams of the active ingredient, particularly, 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art. This dosage regimen may be adjusted to provide the optimal therapeutic response.

The compounds of the present invention contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereoisomeric mixtures and individual diastereoisomers. When R⁵ is hydrogen and R⁴ in the amino acyl residue attached to the phosphorus atom in structural formula I is a substituent other than hydrogen in the formula



the amino acid residue contains an asymmetric center and is intended to include the individual *R*- and *S*-stereoisomers as well as *RS*-stereoisomeric mixtures. In one embodiment, the stereochemistry at the stereogenic carbon corresponds to that of an *S*-amino acid, that is, the naturally occurring alpha-amino acid stereochemistry, as depicted in the formula:

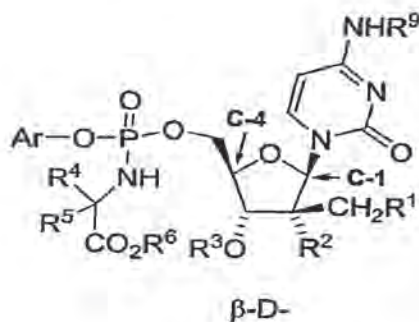


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The tetrasubstituted phosphorus in compounds of structural formula I constitutes another asymmetric center, and the compounds of the present invention are intended to encompass both stereochemical configurations at the phosphorus atom.

The present invention is meant to comprehend nucleoside aryl phosphoramidates having the β -D stereochemical configuration for the five-membered furanose ring as depicted in the structural formula below, that is, nucleoside aryl phosphoramidates in which the substituents at C-1 and C-4 of the five-membered furanose ring have the β -stereochemical configuration ("up" orientation as denoted by a bold line).

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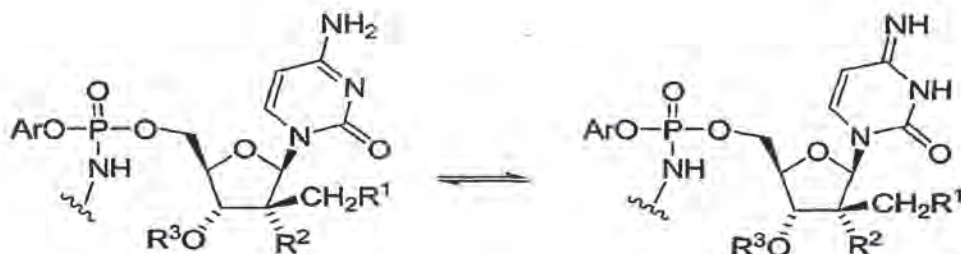


15

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both *E* and *Z* geometric isomers.

Some of the compounds described herein may exist as tautomers such as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of structural formula I. Example of keto-enol tautomers which are intended to be encompassed within the compounds of the present invention are illustrated below:

20



Compounds of structural formula I may be separated into their individual diastereoisomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof, or via chiral chromatography using an optically active stationary phase.

Alternatively, any stereoisomer of a compound of the structural formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts of basic compounds encompassed within the term "pharmaceutically acceptable salt" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts of basic compounds of the present invention include, but are not limited to, the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate; maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof include, but are not limited to, salts derived from inorganic bases including aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, mangamous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, cyclic amines, and basic ion-exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine,

lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

Also, in the case of a carboxylic acid (-COOH) or hydroxyl group being present in the compounds of the present invention, pharmaceutically acceptable prodrug esters of carboxylic acid derivatives, such as methyl, ethyl, or pivaloyloxymethyl esters or prodrug acyl derivatives of the ribose C-2', C-3', and C-5' hydroxyls, such as *O*-acetyl, *O*-pivaloyl, *O*-benzoyl and *O*-aminoacyl, can be employed. Included are those esters and acyl groups known in the art for modifying the bioavailability, tissue distribution, solubility, and hydrolysis characteristics for use as sustained-release or prodrug formulations. The contemplated derivatives are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the terms "administering" and "administration" is meant to encompass the treatment of the viral infections described with a compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the mammal, including a human patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985, which is incorporated by reference herein in its entirety.

Preparation of the Nucleoside Aryl Phosphoramidates of the Invention:

2'-C-Methylcytidine was prepared as described in the literature by C. Pierra et al., *Nucleosides, Nucleotides and Nucleic Acids*, 24: 767 (2005) or J.A. Piccirilli et al., *J. Org. Chem.*, 64: 747 (1999). 2'-Deoxy-2'-fluoro-2'-C-methylcytidine is prepared as described in *J. Med. Chem.*, 48: 5504-5508 (2005). The aryl phosphorochloridates for the phosphorylation reactions were prepared according to the methods described in U.S. Patent No. 6,455,513, the contents of which are incorporated by reference herein in their entirety. The phosphorylation reactions to generate the aryl phosphoroamidates of the present invention were carried out following the methods described in U.S. Patent No. 6,455,513 and C. McGuigan, et al., *J. Med. Chem.*, 36: 1048 (1993). For example, phenol or 1-naphthol was reacted with phosphorus oxychloride which was followed by coupling with different amino acid salts to give phenoxy or 1-naphthyloxy phosphorochloridates which were generally purified by flash chromatography and then coupled with the nucleoside in the presence of a suitable base, such as *t*-butylmagnesium chloride (see M. Uchiyama et al., *J. Org. Chem.*, 58: 373 (1993) and Scheme 1).

General Procedures:

All solvents were obtained from commercial sources and were used without further purification. Reactions were carried out under an atmosphere of nitrogen in oven dried (110 °C) glassware. Organic extracts were dried over sodium sulfate (Na₂SO₄), and were concentrated (after filtration of the drying agent) on rotary evaporators operating under reduced pressure. Flash chromatography was carried out on silica gel following published procedures (W.C. Still et al., *J. Org.*

Chem., 43: 2923 (1978)) or on commercial flash chromatography systems (Biotage corporation and Jones Flashmaster II) utilising pre-packed columns.

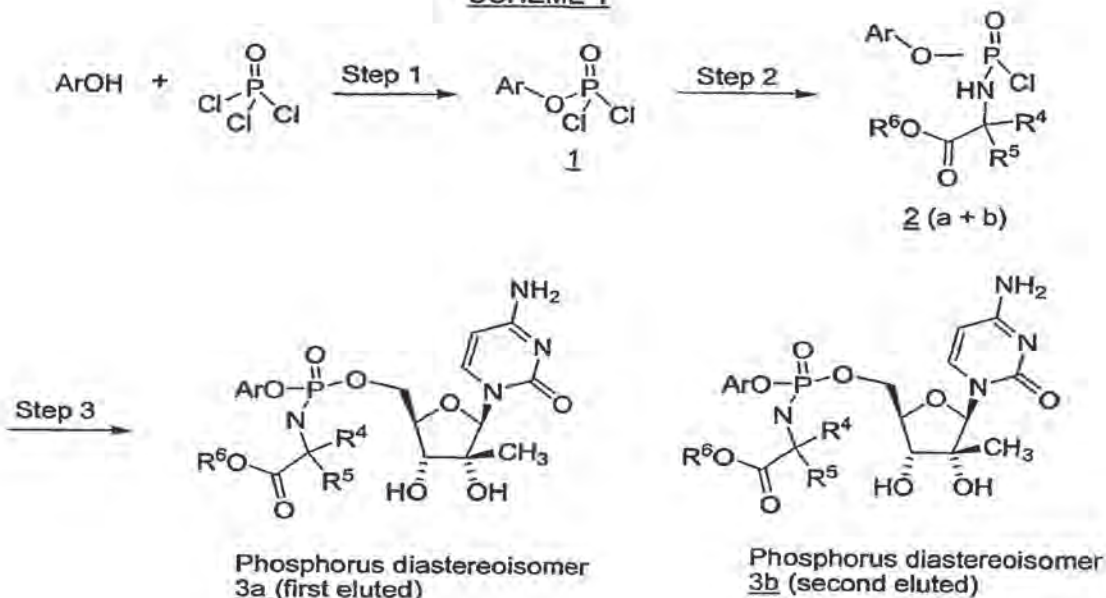
Reagents were usually obtained directly from commercial suppliers (and used as supplied) or are readily accessible using routine synthetic steps that are either reported in the scientific literature or are known to those skilled in the art.

^1H and ^{31}P NMR spectra were recorded on Bruker AM series spectrometers operating at (reported) frequencies between 300 and 600 MHz. Chemical shifts (δ) for signals corresponding to non-exchangeable protons (and exchangeable protons where visible) are recorded in parts per million (ppm) relative to tetramethylsilane and are measured using the residual solvent peak as reference. Signals are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad, and combinations thereof); coupling constant(s) in hertz (Hz); number of protons. Mass spectral (MS) data were obtained on a Perkin Elmer API 100, or Waters MicroMass ZQ, operating in negative (ES^-) or positive (ES^+) ionization mode and results are reported as the ratio of mass over charge (m/z) for the parent ion only. Preparative scale HPLC separations were carried out on a Waters 2525 pump, equipped with a 2487 dual absorbance detector, on a TSP Spectra system P4000 equipped with a UV1000 absorption module or on a automated, mass-triggered Waters Micromass system incorporating a 2525 pump module, a Micromass ZMD detector and a 2525 collection module. Compounds were eluted with linear gradients of water and MeCN both containing 0.1% trifluoroacetic acid or formic acid using flow rates between 10 and 40 mL/min. Symmetry C18 columns (7 μM , 19 x 300 mm) were used as stationary phase.

The following abbreviations are used in the examples, the schemes and the tables: aq.: aqueous; Ar: aryl; atm: atmosphere; CCl_4 : carbon tetrachloride; DCM: dichloromethane; DMF: *N,N*-dimethylformamide; DMSO: dimethylsulfoxide; eq.: equivalent(s); Et_3N : triethylamine; EtOAc: ethyl acetate; Et_2O : diethyl ether; h: hour(s); Me: methyl; MeCN: acetonitrile; MeOH: methanol; min: minutes; MS: mass spectrum; *N,N*-DMA: *N,N*-dimethylacetamide; PE: petroleum ether; Py: pyridine; quant.: quantitative; RP-HPLC: reversed phase high-performance liquid chromatography; RT: room temperature; sec: second(s); TFA: trifluoroacetic acid; and THF: tetrahydrofuran.

The Examples below provide illustrations of the conditions used for the preparation of the compounds of the present invention. These Examples are not intended to be limitations on the scope of the instant invention in any way, and they should not be so construed. Those skilled in the art of nucleoside and nucleotide synthesis will readily appreciate that known variations of the conditions and processes of the following preparative procedures can be used to prepare these and other compounds of the present invention. All temperatures are degrees Celsius unless otherwise noted.

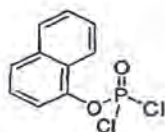
SCHEME 1



EXAMPLE 1

5'-O-[[[(1S)-2-n-butoxy-1-methyl-2-oxoethyl]amino](1-naphthalenyloxy)phosphinyl]-2'-C-methylcytidine

Step 1: 1-Naphthyl dichlorophosphate

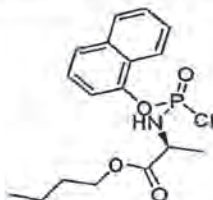


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To 1-naphthol in Et₂O (0.23 M) was added phosphorus oxychloride (1.0 eq.) and the solution was cooled to -78°C. Neat Et₃N (1.0 eq) was added and the resulting solution was left to warm to RT overnight. The white slurry was filtered under an inert atmosphere and all volatiles were removed to yield the title compound as a colorless liquid that was used without further purification in the next step.

10 ³¹P NMR (400 MHz, CDCl₃): δ 3.93 ppm.

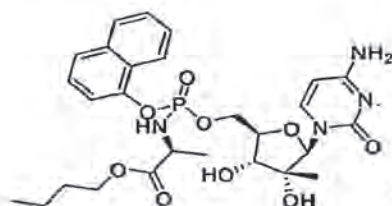
Step 2: n-Butyl N-[chloro(1-naphthyloxy)phosphoryl]-L-alaninate



To 1-naphthyl dichlorophosphate in DCM (0.086 M) was added (2*S*)-1-butoxy-1-oxopropan-2-aminium chloride (1.0 eq.). After cooling to -78 °C, neat Et₃N (2.0 eq.) was added and the reaction was left to warm to RT overnight. All volatiles were removed and the resulting white solid was washed with Et₂O, filtered and evaporated *in vacuo* to obtain a colorless oil as a 1:1 mixture of

5 diastereoisomers. ³¹P NMR (400 MHz, CDCl₃): δ 8.39 and 8.11 ppm.

Step 3: 5'-O-[[[(1*S*)-2-*n*-butoxy-1-methyl-2-oxoethyl]amino](1-naphthalenyloxy)phosphinyl]-2'-C-methylcytidine



2'-C-Methylcytidine was diluted with THF (0.097 M). The resulting slurry was cooled to -78°C, then *tert*-butylmagnesium chloride (as 1.0 M solution in THF, 2.2 eq.) was added. The mixture was immediately warmed to 0°C, stirred for thirty min and again cooled to -78 °C, then butyl *N*-[chloro(1-naphthyloxy)phosphoryl]-L-alaninate (as 1.0 M solution in THF, 2.2 eq.) was added dropwise. The reaction was allowed to reach RT overnight, and then was quenched by the addition of water. The

15 aqueous phase was extracted three times with EtOAc, the combined organic phases were washed with brine and dried over Na₂SO₄. The crude was purified by column chromatography on silica gel (DCM/MeOH gradient from 90:10 to 80:20), and the resulting off white solid was dissolved in DMSO and purified by RP-HPLC. Fractions containing the pure diastereoisomers were combined and freeze-dried to afford the title compounds as their white TFA salts.

First-Eluting Diastereoisomer:

¹H NMR (400 MHz, CD₃OD) δ 8.24-8.22 (m, 1H), 8.00 (d, *J* = 8.09 Hz, 1H), 7.95-7.93 (m, 1H), 7.76 (d, *J* = 8.09 Hz, 1H), 7.61-7.56 (m, 2H), 7.52 (d, *J* = 7.84 Hz, 1H), 7.48 (t, *J* = 8.08 Hz, 1H), 6.01 (s, 1H), 5.91 (d, *J* = 7.83 Hz, 1H), 4.68 (ddd, *J* = 11.75, 5.05, 1.89 Hz, 1H), 4.57 (ddd, *J* = 11.88, 6.07, 3.28 Hz, 1H), 4.22 (dd, *J* = 9.1, 2.27 Hz, 1H), 4.12-4.03 (m, 3H), 3.84 (d, *J* = 9.1 Hz), 1.63-1.56 (m, 2H), 1.42-1.33

25 (m, 5H), 1.18 (s, 3H), 0.93 (t, *J* = 7.33 Hz, 3H), NH₂, NH, 2 x OH not visible, ³¹P NMR: (400 MHz, CD₃OD) δ: 2.77; MS (ES+) *m/z* 591 (M+H)⁺

Second-Eluting Diastereoisomer:

¹H NMR (400 MHz, CD₃OD): δ 8.28-8.22 (m, 1H), 7.99-7.92 (m, 2H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.65-7.69 (m, 2H), 7.59-7.55 (m, 1H), 7.50 (t, *J* = 8.1 Hz, 1H), 6.00 (s, 1H), 5.86 (d, *J* = 7.83 Hz, 1H), 4.65

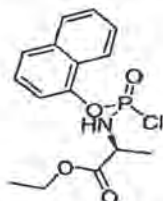
30 (ddd, *J* = 11.7 Hz, *J* = 6.3 Hz, *J* = 1.6 Hz, 1H), 4.53-4.46 (m, 1H), 4.24-4.17 (m, 1H), 4.10-4.00 (m, 3H),

3.83 (d, $J = 9.3$ Hz, 1H), 1.62–1.53 (m, 2H), 1.41–1.32 (m, 5H), 1.17 (s, 3H), 0.93 (t, $J = 7.4$ Hz, 3H); ^{31}P NMR: (300 MHz, CD_3OD) δ : 4.33; MS (ES^+) m/z 591 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 2

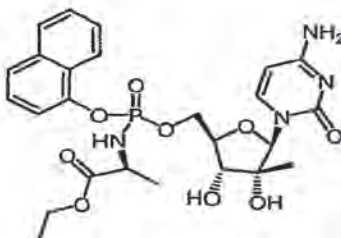
5 5'-O-[[[(1S)-2-ethoxy-1-methyl-2-oxoethyl]amino](1-naphthalenyloxy)phosphinyl]-2'-C-methylcytidine

Step 2: Ethyl N-[chloro(1-naphthyloxy)phosphoryl]-L-alaninate



Following the procedure described for Example 1, step 2, treatment of a solution in DCM (0.144 M) of 1-naphthyl dichlorophosphate with L-alanine ethyl ester hydrochloride (1.0 eq.) and Et_3N (2.0 eq.) provided the title compound as a colorless oil as a 1:1.1 * mixture of diastereoisomers. ^{31}P NMR (300 MHz, CDCl_3) δ : 9.47 and 9.14 * .

Step 3: 5'-O-[[[(1S)-2-ethoxy-1-methyl-2-oxoethyl]amino](1-naphthalenyloxy)phosphinyl]-2'-C-methylcytidine



Following the procedure described for Example 1, step 3, 2'-C-methylcytidine in THF (0.097 M) was cooled to -78°C , then *tert*-butylmagnesium chloride (as 1.0 M solution in THF, 2.2 eq.) was added, followed by the addition of ethyl N-[chloro(1-naphthyloxy)phosphoryl]-L-alaninate (as a 1.0 M solution in THF, 2.2 eq.). The crude product was purified by column chromatography on silica gel (DCM:MeOH=92:8). The resulting solid was dissolved in DMSO and purified by RP-HPLC to afford the title compounds as their white TFA salts.

Second-eluting Diastereoisomer:

^1H NMR (400 MHz, CD_3OD): δ 8.27–8.22 (m, 1H), 7.98–7.94 (m, 1H), 7.92 (d, $J = 7.83$ Hz, 1H), 7.79 (d, $J = 7.83$ Hz, 1H), 7.65–7.55 (m, 3H), 7.50 (t, $J = 7.95$ Hz, 1H), 6.01 (s, 1H), 5.85 (d, $J = 7.83$ Hz, 1H), 4.65 (ddd, $J = 11.81$ Hz, $J = 6.12$ Hz, $J = 1.83$ Hz, 1H), 4.49 (ddd, $J = 11.87$ Hz, $J = 5.81$ Hz, $J = 3.53$ Hz,

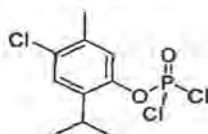
1H), 4.23-4.17 (m, 1H), 4.11 (q, J = 7.07 Hz, 2H), 4.07-3.99 (m, 1H), 3.84 (d, J = 9.09 Hz, 1H), 1.36 (dd, J = 6.69 Hz, J = 0.37 Hz, 3H), 1.22 (t, J = 7.07 Hz, 3H), 1.17 (s, 3H); ³¹P NMR (400 MHz, CD₃OD): δ 4.35; MS (ES⁺) m/z 563 (M+H)⁺

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EXAMPLE 3

5'-O-[[4-chloro-5-methyl-2-(1-methylethyl)phenoxy]][(1S)-2-ethoxy-1-methyl-2-oxoethyl]amino]phosphinyl]-2'-C-methylcytidine

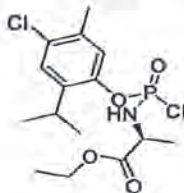
Step 1: 4-Chloro-2-isopropyl-5-methylphenyl dichlorophosphate



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Following the procedure described for Example 1, Step 1, treatment of a solution (0.174 M) in Et₂O of 4-chloro-2-isopropyl-5-methyl-phenol with phosphorus oxychloride (1.0 eq.) and Et₃N (1.0 eq.) provided the title compound as a colorless oil. ³¹P NMR (300 MHz, CD₃OD): δ 4.54.

Step 2: Ethyl N-[chloro(4-chloro-2-isopropyl-5-methylphenoxy)phosphoryl]-L-alaninate

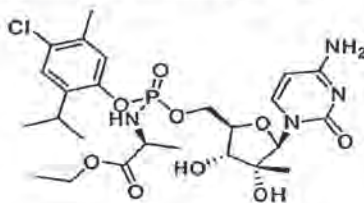


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Following the procedure described for Example 1, step 2, treatment of a solution in DCM (0.098 M) of 4-chloro-2-isopropyl-5-methylphenyl dichlorophosphate with L-alanine ethyl ester hydrochloride (1.0 eq.) and Et₃N (2.0 eq.) provided the title compound as a colorless oil as a 1:1.35⁺ mixture of diastereoisomers. ³¹P NMR (300 MHz, CD₃OD): δ 8.5 and 8.8⁺.

20

Step 3: 5'-O-[[4-chloro-5-methyl-2-(1-methylethyl)phenoxy]][(1S)-2-ethoxy-1-methyl-2-oxoethyl]amino]phosphinyl]-2'-C-methylcytidine



Following the procedure described for Example 1, step 3, 2'-C-methylcytidine in THF (0.097 M) was cooled to -78°C, then *tert*-butylmagnesium chloride (as 1.0 M solution in THF, 2.2 eq.) was added, followed by the addition of ethyl *N*-[chloro(4-chloro-2-isopropyl-5-methylphenoxy)phosphoryl]-L-alaninate (as a 1.0 M solution in THF, 2.2 eq.). The crude product was purified by column chromatography on silica gel (DCM:MeOH gradient from 90:10 to 80:20), the resulting solid was redissolved in DMSO and purified by RP-HPLC to afford the title compounds as their white TFA-salts.

First-eluting diastereoisomer:

¹H NMR (300 MHz, CD₃OD): δ 8.03 (d, J = 7.96 Hz, 1H), 7.31 (s, 2H), 6.07 (d, J = 7.96 Hz, 1H), 6.01 (s, 1H), 4.61 (ddd, J = 11.66, 5.2, 1.54 Hz, 1H), 4.49 (ddd, J = 11.72, 5.86, 3.76 Hz, 1H), 4.24-4.16 (m, 3H), 4.01 (dt, J = 16.14, 7.3 Hz, 1H), 3.83 (d, J = 9.28 Hz, 1H), 2.33 (s, 3H), 1.43 (d, J = 7.08 Hz, 3H), 1.31-1.23 (m, 12H), NH₂, NH, 2 x OH not visible; ³¹P NMR: (300 MHz CD₃OD): δ 5.03; MS (ES+) m/z 625 and 627 (M+Na⁺).

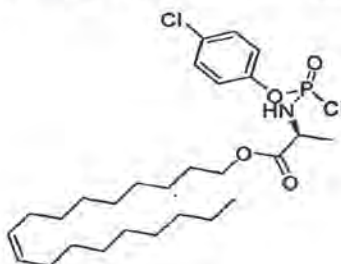
Second-eluting diastereoisomer:

¹H NMR (300 MHz, CD₃OD) δ 7.96 (d, J = 7.83 Hz, 1H), 7.37 (s, 1H), 7.33 (s, 1H), 6.02 (s, 1H), 6.00 (d, J = 7.83 Hz, 1H), 4.57 (ddd, J = 11.88, 6.45, 1.77 Hz, 1H), 4.41 (ddd, J = 11.81, 6.45, 4.04 Hz, 1H), 4.20-4.14 (m, 3H), 4.00 (dt, J = 17.18, 7.33 Hz, 1H), 3.80 (d, J = 9.34 Hz, 1H), 2.34 (s, 3H), 1.43 (d, J = 7.08 Hz, 3H), 1.29-1.25 (m, 9H), 1.20 (s, 3H), NH₂, NH, 2 x OH not visible; ³¹P NMR: (300 MHz, CD₃OD): δ 5.026; MS (ES+) m/z 625 and 627 (M+Na⁺).

EXAMPLE 4

5'-O-[(4-chlorophenoxy)][[(1*S*)-1-methyl-2-[(9*Z*)-9-octadecenyl-2-oxoethyl]amino]phosphinyl]-2'-C-methylcytidine

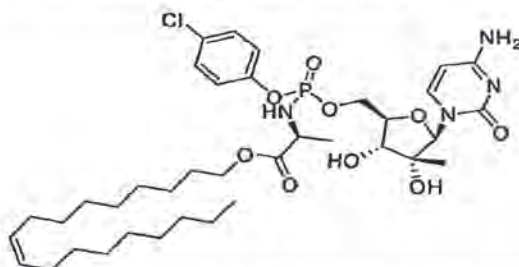
Step 2: (9*Z*)-octadec-9-en-1-yl *N*-[chloro(4-chlorophenoxy)phosphoryl]-L-alaninate



Following the procedure described for Example 1, step 2, treatment of a solution in DCM (0.116 M) of (9*Z*)-octadec-9-en-1-yl *N*-[chloro(4-chlorophenoxy)phosphoryl]-L-alaninate with 4-chlorophenyl dichlorophosphate (1.0 eq.) and with Et₃N (2.0 eq.) provided the title compound as a colorless oil as 1.2*:1 mixture of diastereoisomers.

³¹P NMR (400 MHz, CDCl₃): δ 8.31* and 7.97.

Step 3: 5'-O-[(4-chlorophenoxy)][[(1S)-1-methyl-2-[(9Z)-9-octadecenyoxy]-2-oxoethyl]amino]phosphiny]-2'-C-methylcytidine



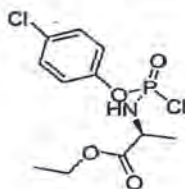
5 Following the procedure described for Example 1, step 3, 2'-C-methylcytidine in THF (0.097 M) was cooled to -78°C, then *tert*-butylmagnesium chloride (as 1.0 M solution in THF, 2.2 eq.) was added followed by the addition of (9Z)-octadec-9-en-1-yl *N*-[chloro(4-chlorophenoxy)phosphoryl]-L-alaninate. The crude mixture was purified by column chromatography on silica gel (DCM:MeOH gradient from 90:10 to 80:20), the resulting solid was redissolved in DMSO and purified by RP-HPLC to afford the title compound as white powders. A 1:1.4^{*} mixture of diastereoisomers at phosphorus was observed by ¹H NMR.

15 ¹H NMR (300 MHz, CD₃OD): δ 8.03 and 8.02^{*} (d, J = 7.74 Hz and J^{*} = 7.96 Hz, 1H), 7.43-7.39 (m, 2H), 7.32-7.26 (m, 2H), 6.11 and 6.09^{*} (d, J = 7.3 Hz and J^{*} = 7.52 Hz, 1H), 6.02 and 6.01^{*} (s, 1H), 5.43-5.33 (m, 2H), 4.65-4.54 (m, 1H), 4.51-4.39 (m, 1H), 4.22-4.07 (m, 2H), 4.05-3.95 (m, 1H), 3.83 and 3.82^{*} (d, J = 9.07 Hz and J^{*} = 9.07 Hz, 1H), 2.07-2.00 (m, 4H), 1.66-1.62 (m, 2H), 1.42-1.33 (m, 26H), 1.22 (s, 3H), 0.94 (t, J = 6.2 Hz, 3H), NH₂, NH, 2 x OH not visible; ³¹P NMR: (300 MHz, CD₃OD): δ 5.15 and 5.12^{*} (s, 1P). MS (ES+) m/z 769 and 771 (M+H)⁺.

EXAMPLE 5

20 5'-O-[(4-chlorophenoxy)][[(1S)-2-ethoxy-1-methyl-2-oxoethyl]amino]phosphiny]-2'-C-methylcytidine

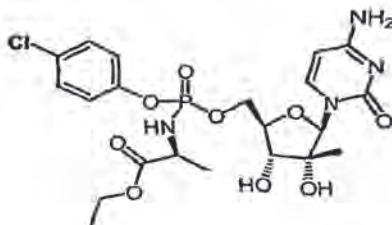
Step 2: Ethyl *N*-[chloro(4-chlorophenoxy)phosphoryl]-L-alaninate



25 Following the procedure described for Example 1, step 2, treatment of a solution in DCM (0.090 M) of 4-chlorophenyl dichlorophosphate with L-alanine ethyl ester hydrochloride (1.0 eq.) and Et₃N (2.0 eq.) provided the title compound as a colorless oil as a 1:1^{*} mixture of diastereoisomers.

^{31}P NMR (300 MHz, CDCl_3): δ 9.43 and 9.11*.

Step 3: 5'-O-[(4-chlorophenoxy)[[(1S)-2-ethoxy-1-methyl-2-oxoethyl]amino]phosphinyl]-2'-C-methylcytidine



5

Following the procedure described for Example 1, step 3, 2'-C-methylcytidine in THF (0.097 M) was cooled to -78°C , then *tert*-butylmagnesium chloride (as 1.0 M solution in THF, 2.2 eq.) was added, followed by the addition of ethyl N-[chloro(4-chlorophenoxy)phosphoryl]-L-alaninate (as a 1.0 M solution in THF, 2.2 eq.). The crude was purified by column chromatography on silica gel (DCM:MeOH=92:8), the resulting solid was redissolved in DMSO and purified by RP-HPLC to afford the title compounds as their white TFA-salts.

10

Second-Eluting Diastereoisomer:

^1H NMR (300 MHz, CD_3OD): δ 8.01 (d, $J = 7.74$ Hz, 1H), 7.43 (d, $J = 8.85$ Hz, 2H), 7.31 (d, $J = 8.85$ Hz, 2H), 6.06 (d, $J = 7.74$ Hz, 1H), 6.02 (s, 1H), 4.58 (ddd, $J = 11.89$ Hz, $J = 6.25$ Hz, $J = 1.82$ Hz, 1H), 4.47-4.38 (m, 1H), 4.24-4.12 (m, 3H), 4.06-3.92 (m, 1H), 3.81 (d, $J = 9.28$ Hz, 1H), 1.41 (d, $J = 6.85$ Hz, 3H), 1.27 (t, $J = 7.18$ Hz, 3H), 1.21 (s, 3H); ^{31}P NMR (300 MHz, CD_3OD): δ 5.10; MS (ES^+) m/z 547 ($\text{M}+\text{H}$) $^+$

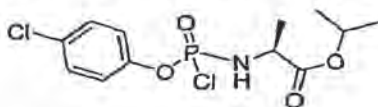
15

EXAMPLE 6

5'-O-[(4-chlorophenoxy)[[(1S)-1-methyl-2-(1-methylethoxy)-2-oxoethyl]amino]phosphinyl]-2'-C-methylcytidine

20

Step 2: Isopropyl-N-[chloro(4-chlorophenoxy)phosphoryl]-L-alaninate

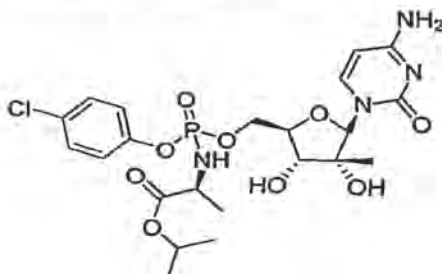


Following the procedure described for Example 1, step 2, the title compound was isolated as a yellow oil and as a mixture of two diastereoisomers at phosphorus.

25

^{31}P NMR (300 MHz, CDCl_3): δ 9.61, 9.35.

Step 3: 5'-O-[(4-chlorophenoxy)[[(1S)-1-methyl-2-(1-methylethoxy)-2-oxoethyl]amino]phosphinyl]-2'-C-methylcytidine



Following the procedure described for Example 1, step 3, the title compound was isolated as a single diastereoisomer at phosphorus and as its TFA salt.

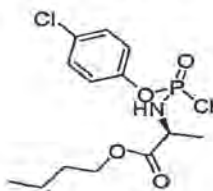
Second-eluting diastereoisomer:

¹H NMR (300 MHz, CD₃OD): δ 8.0 (d, J = 7.7 Hz, 1H), 7.41 (d, J = 8.7 Hz, 2H), 7.3 (d, J = 8.7 Hz, 2H), 6.05 (d, J = 7.96 Hz, 1H), 6.0 (s, 1H), 5.02-4.94 (m, 1H), 4.56 (ddd, J = 11.7, 6.4, 1.7 Hz, 1H), 4.41 (ddd, J = 11.8, 6.35, 3.7 Hz, 1H), 4.21-4.14 (m, 1H), 3.99-3.89 (m, 1H), 3.80 (d, J = 9.2 Hz, 1H), 1.39 (d, J = 7.1 Hz, 3H), 1.25 (d, J = 6.2 Hz, 6H), 1.20 (s, 3H). ³¹P NMR (400 MHz, CD₃OD): δ 5.13. MS (ES⁺) m/z 561 (M+H)⁺.

EXAMPLE 7

5'-O-[[[(1S)-2-n-butoxy-1-methyl-2-oxoethyl]amino](4-chlorophenoxy)phosphinyl]-2'-C-methylcytidine

Step 2: n-Butyl N-[chloro(4-chlorophenoxy)phosphoryl]-L-alaninate



Following the procedure described for Example 1, step 2, treatment of a solution in DCM (0.090 M) of the commercially available 4-chlorophenyl dichlorophosphate with L-alanine ethyl ester hydrochloride (1.0 eq.) and Et₃N (2.0 eq.) provided the title compound as a colorless oil as a 1.1:1* mixture of diastereoisomers. ³¹P NMR (400 MHz, CDCl₃): δ: 9.52 and 9.28*

Step 3: 5'-O-[[[(1S)-2-n-butoxy-1-methyl-2-oxoethyl]amino](4-chlorophenoxy)phosphinyl]-2'-C-methylcytidine