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Supplementary material:**Table 1.** Anti-HIV, anti-HBV and anti-HSV activities of 2'-deoxy-2',2''-difluoro-L-nucleosides.

Compound #	HIV-1 EC ₅₀ (μM)	HBV (2.2.15) (μM)	HSV (1 and 2) (μM)	Toxicity (calorimetric assay)		
				Vero (IC ₅₀ , μM)	CEM (IC ₅₀ , μM)	PBM (IC ₅₀ , μM)
AZT	0.004	>10	>100	29.0	13.0	>100
31	>100	ND	ND	>100	>100	>100
32	>100	ND	ND	>100	>100	>100
33	>100	>10	>100	>100	>100	>100
34	>100	>10	>100	>100	>100	>100
37	>100	>10	>100	>100	>100	>100
38	>100	>10	>100	>100	>100	>100
39	>100	>10	>100	>100	>100	>100
40	>100	>10	>100	>100	>100	>100
41	>100	>10	>100	>100	>100	>100
42	>100	>10	>100	>100	>100	>100
43	>100	>10	>75	>100	>100	>100
44	>100	>10	>100	>100	>100	>100
45	>100	>10	>100	>100	>100	>100
46	>100	>10	>100	>100	>100	>100
47	>100	>10	>100	>100	>100	>100
48	>100	>10	>100	>100	>100	>100
49	>100	>10	>100	>100	>100	>100
50	>100	>10	>100	>100	>100	>100
59	>100	>10	>100	>100	>100	>100
60	>100	>10	>100	>100	>100	>100
63	>100	>10	>100	>100	>100	>100
64	>100	>10	>100	>100	>100	>100

Supplementary material:

Table 2. ¹H NMR Data.

#	Solvent					
2	DMSO-d ₆	5.83 (s, 2-OH)	5.38 (s, 3-OH)	3.74-4.42 (m, 6H)	1.28, 1.33 (2s, 2CH ₃)	
3	CDCl ₃	9.71 (d, 1H, CHO)	5.31 (d, H-2)	4.12 (dd, 2H, H-3)	2.05, 1.26 (2s, 2CH ₃)	
4(R)	CDCl ₃	3.88-4.42 (m, 6H)	2.87 (d, J=8.38, 3-OH, D ₂ O exchangeable)	1.35-1.45 (2s, 2CH ₃)		
4(S)	CDCl ₃	3.88-4.41 (m, 6H)	2.46 (d, J=4.19, 3-OH, D ₂ O exchangeable)	1.38-1.41 (2s, 2CH ₃)		
6a	CDCl ₃	7.36-8.01 (m, 10H, aromatic)	5.68 (m, 1H, H-3)	4.92 (m, 1H, H-4)	4.60-4.71 (m, 2H, H-5')	
7a	CDCl ₃	7.39-8.20 (m, 10H, aromatic)	5.49, 5.72 (2m, 1H, H-1, 1:4)	4.44-4.79 (m, 4H, H-3, H-4, H-5)		
8a (β)	CDCl ₃	7.43-8.09 (m, 10H, aromatic)	6.04 (d, J=6.46, H-1)	5.95 (m, 1H, H-3)	4.73 (dd, J ₁ =2.74, J ₂ =2.18, H-4)	4.62 (m, 2H, H-5)
8a (α)	CDCl ₃	7.42-8.08 (m, 10H, aromatic)	6.13 (d, J=5.81, H-1)	5.56 (dd, J ₁ =4.30, J ₂ =6.47, H-3)	4.83 (m, 1H, H-4)	4.64-4.82 (m, 2H, H-5)

Table 2 contd.

#	Solvent	H-1'	H-3'	H-4'	H-5'	Other
11	CDCl ₃	6.39 (dd, J ₁ =6.13, J ₂ =11.73)	5.67 (m)	4.59 (brs)	4.67-4.85 (2m)	8.36 (brs, NH), 7.39 (d, 1H, J=8.14, H-6), 7.45-8.36 (m, 10H, aromatic), 5.67 (d, 1H, J=8.12, H-5)
23	CDCl ₃	6.54 (dd, J ₁ =5.26, J ₂ =11.83)	5.60 (m, 2H, H-3', NH)	4.57 (m)	4.76 (m)	7.45-8.09 (m, 12H, aromatic, H-6, NH)
24	CDCl ₃	6.62 (t, J=6.99)	5.80 (m)	4.85 (pd)	4.62 (m)	5.60 (brs, 1H, NH), 7.43-8.07 (m, 12H, aromatic, NH, H-6)
25	CDCl ₃	6.54 (dd, J ₁ =5.64, J ₂ =11.84)	5.63 (m)	4.59 (m)	4.77 (m)	8.20 (brs, 1H, NH), 7.45-8.09 (m, 11H, aromatic, H-6), 5.87 (brs, 1H, NH)
26	CDCl ₃	6.62 (dd, J ₁ =5.14, J ₂ =5.14)	5.80 (m)	4.91 (m)	4.64 (m)	8.81 (brs, 1H, NH), 7.44-8.08 (m, 11 H, aromatic, H-6), 5.95 (brs, 1H, NH)
27	CDCl ₃	6.55 (dd, J ₁ =5.35, J ₂ =12.12)	5.62 (m)	4.59 (m)	4.78 (2m)	7.45-8.09 (m, 12H, aromatic, H-6, NH), 5.78 (brs, 1H, NH)
28	CDCl ₃	6.62 (dd, J ₁ =4.93, J ₂ =8.42)	5.80 (m)	4.91 (m)	4.64 (m)	7.44-8.08 (m, 11 H, aromatic, H-6), 8.28 (brs, 1H, NH), 5.86 (brs, 1H, NH)
29	CDCl ₃	6.54 (dd, J ₁ =5.47, J ₂ =12.00)	5.62 (m)	4.58 (m)	4.78 (2m)	7.46-8.09 (m, 12H, aromatic, H-6, NH), 5.69 (brs, 1H, NH)

Table 2 contd.

30	CDCl ₃	6.62 (dd, J ₁ =4.75, J ₂ =9.02)	5.79 (m)	4.91 (m)	4.64 (m)	7.44-8.09 (m, 11 H, aromatic, H-6), 8.23 (brs, 1H, NH), 5.72 (brs, 1H, NH)
31	DMSO- <i>d</i> ₆	6.03 (t, J=8.0)	4.02 (m)	3.63 (m)	3.77 (m)	11.55 (s, 1H, NH), 7.64 (s, 1H, H-6), 6.33 (d, 1H, 3'-OH), 5.33 (t, 1H, 5'-OH), 1.76 (s, 3H, CH ₃)
32	DMSO- <i>d</i> ₆	6.22 (dd, J ₁ =6.5, J ₂ =11.0)	4.40 (m)	4.27 (m)	3.56 (m)	11.54 (s, 1H, NH), 7.45 (s, 1H, H-6), 6.36 (d, 1H, 3'-OH), 5.09 (t, 1H, 5'-OH), 1.80 (s, 3H, CH ₃)
33	DMSO- <i>d</i> ₆	6.08 (t, J=7.78)	4.19 (brt)	4.84 (pt)	3.61-3.78 (2m)	11.57 (brs, 1H, NH, D ₂ O exch), 7.79 (d, 1H, J=8.12, H-6), 6.33 (d, 3'-OH, D ₂ O exch), 5.70 (d, 1H, J=8.15, H-5), 5.29 (t, 5'-OH, D ₂ O exch)
34	DMSO- <i>d</i> ₆	6.20 (dd, J ₁ =6.83, J ₂ =9.56)	5.35 (pt)	5.23 (brd)	3.58 (2m)	11.55 (brs, 1H, NH, D ₂ O exch), 7.60 (d, 1H, J=8.13, H-6), 6.40 (d, 3'-OH, D ₂ O exch), 5.70 (d, 1H, J=8.13, H-5), 5.10 (brs, 1H, 5'-OH, D ₂ O exch)
37	DMSO- <i>d</i> ₆	6.03 (t, J=7.11)	4.26 (m)	3.87 (pd)	3.62-3.81 (2m)	12.14 (brs, 1H, NH, D ₂ O exch), 8.30 (s, 1H, H-6), 6.34 (d, 3'-OH, D ₂ O exch), 5.47 (t, 1H, 5'-OH, D ₂ O exch)
38	DMSO- <i>d</i> ₆	6.19 (dd, J ₁ =8.80, J ₂ =6.93)	4.37 (brd, 2H)		3.46-3.64 (2m)	12.12 (brs, 1H, NH, D ₂ O exch), 7.95 (s, 1H, H-6), 6.42 (d, 3'-OH, D ₂ O exch), 5.09 (t, 1H, 5'-OH, D ₂ O exch)
39	DMSO- <i>d</i> ₆	6.02 (t, J=6.90)	4.22 (m)	3.85 (brd)	3.61-3.80 (2m)	12.07 (brs, 1H, NH, D ₂ O exch), 8.36 (s, 1H, H-6), 6.32 (d, 3'-OH, D ₂ O exch), 5.47 (t, 1H, 5'-OH, D ₂ O exch)

Table 2 contd.

40	DMSO- d_6	6.20 (t, J=7.80)	4.35 (brs, 2H)		3.51-3.64 (2m)	12.08 (brs, 1H, NH, D ₂ O exch), 7.99 (s, 1H, H-6), 6.42 (d, 3'-OH, D ₂ O exch), 5.09 (t, 1H, 5'-OH, D ₂ O exch)
41	DMSO- d_6	6.02 (t, J=7.05)	4.23 (m)	3.86 (m)	3.61-3.81 (2m)	11.95 (s, 1H, NH, D ₂ O exch), 8.37 (s, 1H, H-6), 6.33 (d, 3'-OH, D ₂ O exch), 5.48 (t, 1H, 5'-OH, D ₂ O exch)
42	DMSO- d_6	6.19 (t, J=7.98)	4.34 (brs, 2H)		3.50-3.64 (2m)	11.95 (s, 1H, NH, D ₂ O exch), 7.95 (s, 1H, H-6), 6.42 (d, 3'-OH, D ₂ O exch), 5.10 (t, 1H, 5'-OH, D ₂ O exch)
43	DMSO- d_6	6.12 (t, J=8.2)	4.12 (m)	3.59-3.78 (m, 3H)		7.69 (d, J=7.4, H-6), 7.34, 7.37 (2 brs, 2H, NH ₂), 6.42 (brs, 3'-OH), 5.77 (d, J=7.5, H-5), 5.33 (brs, 5'-OH)
44	DMSO- d_6	6.26 (dd, J ₁ =6.6, J ₂ =10.6)		4.13 (m)	3.48-3.62 (m)	7.52 (d, J=7.5, H-6), 7.36, 7.30 (2 brs, 2H, NH ₂), 6.51 (brs, 3'-OH), 5.77 (d, J=7.5, H-5), 5.17 (brs, 1H, 5'-OH)
45	DMSO- d_6	6.12 (t, J=7.27)	4.25 (pd)	3.68-3.88 (m, 3H)		8.11 (d, 1H, J=7.21, H-6), 8.09, 7.83 (2s, 2H, NH ₂ , D ₂ O exch), 6.34 (brs, 3'-OH, D ₂ O exch), 5.42 (brs, 1H, 5'-OH, D ₂ O exch)
46	DMSO- d_6	6.21 (t, J=7.97)	4.32 (m)	4.25 (brd)	3.48-3.63 (2m)	7.79 (d, 1H, J=6.92, H-6), 8.00, 7.74 (2s, 2H, NH ₂ , D ₂ O exch), 6.33 (d, 3'-OH, D ₂ O exch), 5.06 (t, 1H, 5'-OH, D ₂ O exch)
47	DMSO- d_6	6.07 (t, J=7.36)	4.20 (m)	3.62-3.83 (2m, 3H)		8.14 (s, 1H, H-6), 8.12, 7.47 (2s, 2H, NH ₂ , D ₂ O exch), 6.27 (d, 3'-OH, D ₂ O exch), 5.39 (t, 1H, 5'-OH, D ₂ O exch)
48	DMSO- d_6	6.23 (dd, J ₁ =6.89, J ₂ =9.07)	4.33 (m)	4.28 (brd)	3.49-3.54 (2m)	7.82 (s, 1H, H-6), 8.10, 7.47 (2s, 2H, NH ₂ , D ₂ O exch), 6.35 (d, 3'-OH, D ₂ O exch), 5.08 (t, 1H, 5'-OH, D ₂ O exch)

Table 2 contd.

49	DMSO- d_6	6.07 (t, J=7.32)	4.19 (m)	3.63 (m)	3.81 (m)	8.21 (s, 1H, H-6), 8.13, 7.26 (2s, 2H, NH ₂ , D ₂ O exch), 6.27 (d, 3'-OH, D ₂ O exch), 5.41 (t, 1H, 5'-OH, D ₂ O exch)
50	DMSO- d_6	6.24 (t, J=7.71)	4.34 (brd)	4.28 (brs)	3.50-3.63 (2m)	7.86 (s, 1H, H-6), 8.11, 7.25 (2s, 2H, NH ₂ , D ₂ O exch), 6.34 (brs, 3'-OH, D ₂ O exch), 5.08 (brs, 1H, 5'-OH, D ₂ O exch)
53a	CDCl ₃	6.55 (dd, J ₁ =6.40, J ₂ =11.30)	5.98 (m)	4.72 (brd)	4.75-4.90 (m)	8.75 (s, 1H, H-8), 8.31 (s, 1 H, H-2), 7.42-8.12 (m, 10H, aromatic)
53b	CDCl ₃	6.27 (dd, J ₁ =6.2, J ₂ =8.9)	4.43 (m)	3.72-3.99 (m, 3H, H-4', H-5')		8.65 (s, 1 H, H-8), 8.30 (s, 1 H, H-2), 0.79-0.90 (m, 18 H), 0.00-0.05 (m, 12 H)
54a	CDCl ₃	6.76 (dd, J ₁ =5.06, J ₂ =8.48)	5.93 (m)	5.12 (m)	4.73 (m)	8.80 (s, 1H, H-8), 8.39 (s, 1H, H-2), 7.45-8.10 (m, 10H, aromatic)
54b	CDCl ₃	6.51 (dd, J ₁ =5.1, J ₂ =0.6)	4.61 (m)	4.38 (m)	3.82 (m)	8.76 (s, 1H, H-8), 8.44, 1H, H-2), 0.92-1.00 (m, 18 H), 0.09-0.16 (m, 12 H)
59	DMSO- d_6	6.29 (dd, J ₁ =4.08, J ₂ =10.93)	4.48 (pt)	3.96 (brd)	3.65-3.82 (m)	12.53 (s, 1 H, NH, D ₂ O exch), 8.35 (s, 1H, H-8), 8.13 (s, 1 H, H-2), 6.40 (d, 1 H, 3'-OH, D ₂ O exch), 5.27 (t, 1 H, 5'-OH, D ₂ O exch)
60	DMSO- d_6	6.43 (t, J=8.16)	4.45 (m)	4.40 (brs)	3.56-3.76 (2m)	12.50 (s, 1H, NH, D ₂ O exch), 8.25 (s, 1H, H-8), 8.12 (s, 1H, H-2), 6.49 (d, 1H, 3'-OH, D ₂ O exch), 5.13 (t, 1H, 5'-OH, D ₂ O exch)

Table 2 contd.

55	DMSO- d_6	6.51 (dd, $J_1=4.1$, $J_2=10.6$)	4.60 (m)	4.01 (m)	3.73-3.82 (m)	8.96 (s, 1H, H-8), 8.88 (s, 1H, H-2), 6.45 (d, 3'-OH), 5.29 (t, 5'-OH)
56	DMSO- d_6	6.65 (t, $J=7.0$)	4.51 (m, 2 H)		3.65 (m)	8.88 (s, 1H, H-8), 8.85 (s, 1 H, H-2), 6.50 (d, 1 H, 3'-OH), 5.14 (t, 1 H, 5'-OH)
61	CDCl ₃	6.76 (dd, $J_1=5.27$, $J_2=10.78$)	5.75 (m)	4.69 (m)	4.83 (2m)	8.36 (s, 1H, H-8), 7.46-8.10 (m, 10H, aromatic), 5.13 (brs, 2H, NH ₂)
62	CDCl ₃	6.87 (dd, $J_1=2.53$, $J_2=7.83$)	5.88 (brd)	5.02 (brs)	4.74 (m)	8.36 (s, 1H, H-8), 7.46-8.11 (m, 10H, aromatic), 5.14 (brs, 2H, NH ₂)
63	DMSO- d_6	6.45 (brt, 4H, H-1', 3'-OH, NH ₂)	4.38 (m)	3.88 (brd)	3.57-3.81 (2m)	11.35 (brs, 1H, NH, D ₂ O exch), 8.42 (s, 1H, H-8), 5.40 (brs, 1H, 5'-OH, D ₂ O exch)
64	DMSO- d_6	6.66 (t, $J=7.40$)	4.40 (m)	4.32 (brs)	3.54-3.66 (2m)	11.06 (brs, 1H, NH, D ₂ O exch), 8.15 (s, 1H, H-8), 6.45 (d, 1H, 3'-OH, D ₂ O exch), 5.14 (t, 1H, 5'-OH, D ₂ O exch)

Supplementary material:

Table 3. ^{13}C NMR Data.

#	δ ppm
6a	166.11, 165.04, 162.93 (t, $J=32.59$), 134.91, 134.15, 130.21, 129.21, 129.02, 127.81, 111.87 (dd, $J_1=262.85$, $J_2=257.95$), 78.85, 77.76, 77.44, 77.12, 70.06, 69.83 (dd, $J_1=15.77$, $J_2=30.98$), 62.60
37	159.64, 150.10, 137.64, 123.64 (t, $J=258.42$), 108.91, 84.28 (t, $J=33.08$), 81.78, 68.59 (t, $J=22.32$), 59.19
38	160.37, 150.69, 138.45, 123.98 (t, $J=258.87$), 109.03, 85.29 (d, $J=6.8$), 84.98 (t, $J=20.60$), 70.30 (dd, $J_1=19.40$, $J_2=40.27$), 60.75
39	160.24, 150.65, 140.23, 123.80 (t, $J=259.35$), 97.63, 84.47 (t, $J=32.02$), 81.90, 68.75 (t, $J=22.18$), 59.29
40	160.25, 150.75, 140.69, 123.92 (t, $J=259.78$), 97.36, 85.25 (d, $J=6.9$ Hz), 84.80 (t, $J=20.42$), 70.27 (dd, $J_1=18.08$, $J_2=26.15$), 60.70
41	161.23, 150.78, 144.81, 123.75 (t, $J=258.29$), 84.25 (t, $J=33.08$), 81.75, 70.93, 68.60 (t, $J=22.21$), 59.10
42	161.67, 151.23, 145.57, 124.18 (t, $J=259.45$), 85.55 (d, $J=6.14$), 84.98 (dd, $J_1=19.40$, $J_2=40.27$), 70.94, 70.58 (dd, $J_1=18.42$, $J_2=26.37$), 60.99
47	162.17, 154.01, 139.29, 123.62 (t, $J=258.45$), 100.64, 84.48 (t, $J=31.05$), 81.25, 68.85 (t, $J=22.27$), 59.13
48	162.44, 154.50, 139.97, 123.87 (t, $J=259.03$), 100.74, 85.13 (t, $J=19.94$), 84.71 (d, $J=6.42$), 70.40 (dd, $J_1=18.29$, $J_2=26.17$), 60.57
49	162.52, 153.73, 141.68, 123.44 (t, $J=257.94$), 87.68, 84.20 (t, $J=31.82$), 81.07 (d, $J=4.44$), 68.50 (t, $J=22.44$), 58.97
50	162.91, 154.56, 142.58, 123.88 (t, $J=258.91$), 87.86, 84.75 (d, $J=6.86$), 85.10 (t, $J=19.24$), 70.42 (dd, $J_1=18.50$, $J_2=26.45$), 60.60
59	157.38, 149.16, 147.40, 139.40, 124.90, 123.55 (dd, $J_1=255.5$, $J_2=261.38$), 83.80 (dd, $J_1=23.57$, $J_2=40.60$), 82.33 (d, $J=8.3$ Hz), 69.26 (dd, $J_1=17.95$, $J_2=26.08$), 60.25