

Supplementary material:

$$\log(1/EC_{50}) = 0.489(\pm 0.143)\text{ClogP} + 6.069(\pm 0.177)$$

$$n = 11, r = 0.933, r_{cv}^2 = 0.79, s = 0.26, F_{1,9} = 60.19(10.56) \quad (1)$$

$$\log(1/CC_{50}) = -0.104(\pm 0.101)\text{CMR} + 0.282(\pm 0.136)(\text{ClogP})^2 + 3.391(\pm 1.564)$$

$$n = 10, r = 0.935, r_{cv}^2 = 0.71, s = 0.23, F_{2,7} = 24.19(9.55), (\text{ClogP})_{opt} = 0.0 \quad (2)$$

$$\log(1/EC_{50}) = -0.369(\pm 0.347)\text{ClogP} - 0.571(\pm 0.344)\text{CMR} + 15.159(\pm 3.576)$$

$$n = 14, r = 0.905, r_{cv}^2 = 0.72, s = 0.24, F_{2,11} = 24.92(7.20) \quad (3)$$

$$\log(1/EC_{50}) = 0.595(\pm 0.126)\text{ClogP} - 0.165(\pm 0.045)(\text{ClogP})^2 - 0.177(\pm 0.091)\text{CMR} + 9.010(\pm 1.347)$$

$$n = 25, r = 0.910, r_{cv}^2 = 0.65, s = 0.30, F_{3,21} = 33.69(4.87), (\text{ClogP})_{opt} = 1.80 \quad (4)$$

$$\log(1/CC_{50}) = -0.158(\pm 0.087)\text{CMR} + 0.071(\pm 0.021)(\text{ClogP})^2 + 4.664(\pm 1.279)$$

$$n = 23, r = 0.923, r_{cv}^2 = 0.68, s = 0.30, F_{2,20} = 57.52(5.85), (\text{ClogP})_{opt} = 0.0 \quad (5)$$

$$\log(1/EC_{50}) = 0.761(\pm 0.403)E_s + 0.528(\pm 0.423)B_1 + 0.486(\pm 0.357)I_1 + 5.057(\pm 0.544)$$

$$n = 10, r = 0.925, s = 0.200, F_{3,6} = 11.77(9.78), r_{cv}^2 = 0.48 \quad (6)$$

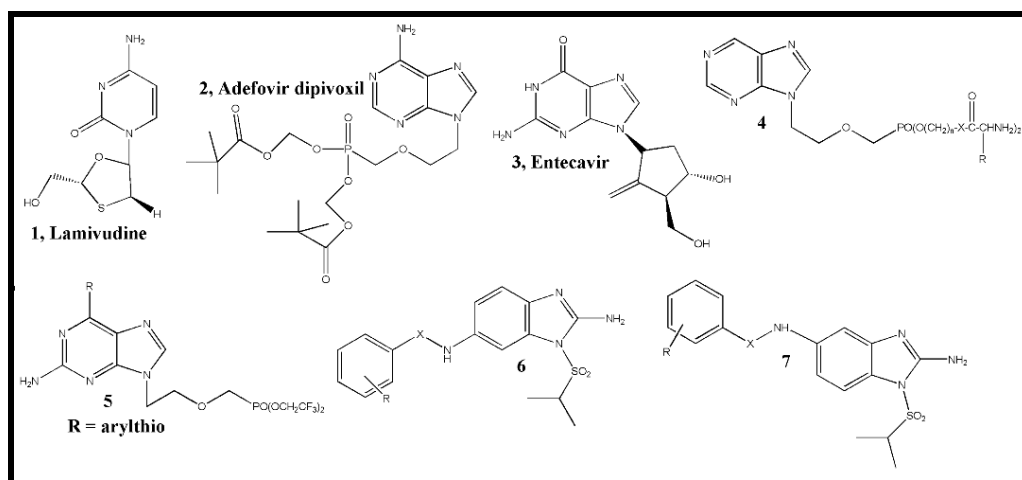


Table 1: Bis (L-amino acid) ester prodrugs of 9-[2-(phosphonomethoxy) ethyl] adenine and their anti-HBV and toxic activities and physicochemical parameters

Compd	R	X	n	ClogP	CMR	log(1/EC <sub>50</sub> ) <sup>a</sup>			log(1/CC <sub>50</sub> ) <sup>a</sup>		
						Obsd	Cald, Eq. 1	Pred, LOO	Obsd	Cald, Eq. 2	Pred, LOO
4a	Me	O	2	-1.75	11.94	4.90	5.21	5.34	2.73	3.01	3.15
4b	Isopropyl	O	2	0.10	13.79	5.88	6.12	6.14	2.59 <sup>c</sup>	1.96	-
4c	2-Me-Pr	O	2	1.16	14.72	7.02	6.64	6.56	2.18	2.32	2.25
4d	Bz	O	2	1.08	16.96	6.51	6.60	6.61	2.59 <sup>c</sup>	1.96	-
4e	H	S	2	-2.16	12.14	4.99	5.01	5.02	3.59	3.44	3.24
4f	Me	S	2	-1.54	13.24	5.81	5.31	5.15	2.62	2.63	2.69
4g	Isopropyl	S	2	0.31	15.10	6.12	6.22	6.23	1.54	1.82	1.92
4h	2-Me-Pr	S	2	1.37	16.02	6.67	6.74	6.75	2.47	2.32	2.20
4i	Bz	S	2	1.29	18.26	6.68	6.70	6.70	1.96	1.93	1.98
4j	Isopropyl	O	1	-0.46	12.86	6.52 <sup>b</sup>	5.84	-	2.47	2.10	1.90
4k	2-Me-Pr	O	1	0.59	13.79	6.47	6.36	6.34	2.07	2.10	2.06
4l	Bz	O	1	0.51	16.03	6.18	6.32	6.33	1.81	1.75	1.79

<sup>a</sup>Taken from ref [9]. <sup>b</sup>Not included in the derivation of Eq. 1. <sup>c</sup>Not included in the derivation of Eq. 2.

Table 2: 2-Amino-6-arythio-9-[2-(phosphonomethoxy) ethyl]purine bis(2,2,2-trifluoroethyl) esters and their anti-HBV and toxic activities and physicochemical parameters.

Compd	R	ClogP	CMR	log(1/EC <sub>50</sub> )			log(1/CC <sub>50</sub> )
				Obsd <sup>a</sup>	Cald Eq. 3	Pred LOO	Obsd <sup>b</sup>
5a	SPh	2.95	11.45	7.30	7.54	7.62	NA <sup>b</sup>
5b	SPh(4-Me)	3.45	11.91	7.22	7.09	7.07	3.96
5c	SPh(3-Me)	3.45	11.91	7.04	7.09	7.10	3.82
5d	SPh(2-Me)	3.45	11.91	7.10	7.09	7.09	3.47

5e	SPh(4-Et)	3.98	12.38	6.40	6.63	6.67	3.77
5f	SPh(4-iPr)	4.38	12.84	6.01	6.22	6.29	3.77
5g	SPh(4-NO <sub>2</sub> )	2.70	12.06	6.28 <sup>a</sup>	7.28	–	3.42
5h	SPh(4-Cl)	3.67	11.94	6.92	6.99	7.00	4.21
5i	SPh(4-OMe)	2.87	12.06	7.52	7.22	7.15	NA
5j	SPh(3-OMe)	2.87	12.06	7.40	7.22	7.19	NA
5k	SPh(2-OMe)	2.47	12.06	7.10	7.37	7.56	NA
5l	SPh(4-OEt)	3.40	12.53	6.19 <sup>a</sup>	6.75	–	NA
5m	SPh(4-O-nPr)	3.93	12.99	6.06	6.30	6.35	3.60
5n	SPh(4-O-iPr)	3.71	12.99	6.54	6.38	6.34	3.45
5o	SPh(4-O-nBu)	4.46	13.46	NA	NA	–	3.58
5p	SPh(4-O-iBu)	4.11	13.46	6.07	5.96	5.89	4.00
5q	SPh(4-O-CF <sub>3</sub> )	3.98	12.11	7.22	6.78	6.66	3.09
5r	S-(2-naphthyl)	4.13	13.14	7.04 <sup>c</sup>	6.13	–	3.70

<sup>a</sup>Taken from ref [10]. <sup>b</sup>NA: Not available. <sup>c</sup>Not included in the derivation of Eq. 3.

Table 3: A combine of Tables 1 and 2

Compd	ClogP	CMR	log(1/EC <sub>50</sub> )			log(1/CC <sub>50</sub> )		
			Obsd	Cald	Pred	Obsd	Cald	Pred
4a	-1.75	11.94	4.90	5.35	5.53	2.73	2.99	3.05
4b	0.10	13.79	5.88 <sup>a</sup>	6.63	–	2.59	2.49	2.48
4c	1.16	14.72	7.02	6.87	6.66	2.18	2.44	2.46
4d	1.08	16.96	6.51	6.45	6.45	2.59	2.07	1.92
4e	-2.16	12.14	4.99	4.81	4.66	3.59	3.07	3.02
4f	-1.54	13.24	5.81	5.36	5.23	2.62	2.74	2.76
4g	0.31	15.10	6.12	6.50	6.54	1.54 <sup>c</sup>	2.29	–
4h	1.37	16.02	6.67	6.68	6.68	2.47	2.27	2.24
4i	1.29	18.26	6.68	6.27	6.03	1.96	1.90	1.86
4j	-0.46	12.86	6.52	6.42	6.40	2.47	2.65	2.69
4k	0.59	13.79	6.47	6.86	6.91	2.07	2.51	2.57
4l	0.51	16.03	6.18	6.43	6.46	1.81	2.16	2.21
5a	2.95	11.45	7.30	7.30	7.31	NA	NA	NA
5b	3.45	11.91	7.22	6.99	6.98	3.96	3.63	2.85
5c	3.45	11.91	7.04	6.99	6.99	3.82	3.63	3.61
5d	3.45	11.91	7.10	6.99	6.98	3.47	3.63	3.65
5e	3.98	12.38	6.40	6.58	6.59	3.77	3.83	3.83
5f	4.38	12.84	6.01	6.18	6.25	3.77	3.99	4.05
5g	2.70	12.06	6.28 <sup>a</sup>	7.29	–	3.42	3.28	3.26
5h	3.67	11.94	6.92	6.86	6.85	4.21	3.74	3.68
5i	2.87	12.06	7.52	7.22	7.19	NA	NA	NA
5j	2.87	12.06	7.40	7.22	7.20	NA	NA	NA
5k	2.47	12.06	7.10	7.34	7.38	NA	NA	NA
5l	3.40	12.53	6.19 <sup>a</sup>	6.90	–	NA	NA	NA
5m	3.93	12.99	6.06	6.51	6.58	3.60	3.71	3.72
5n	3.71	12.99	6.54	6.65	6.29	3.45	3.59	3.60
5o	4.46	13.46	NA <sup>b</sup>	NA	NA	3.58	3.95	4.04
5p	4.11	13.46	6.07	6.29	6.36	4.00	3.74	3.71
5q	3.98	12.11	7.22	6.63	6.56	3.09	3.88 <sup>c</sup>	–
5r	4.13	13.14	7.04 <sup>a</sup>	6.34	–	3.70	3.80	3.82

<sup>a</sup>Not included in the derivation of Eq. 4. <sup>b</sup>NA: Not available. <sup>c</sup>Not included in the derivation of Eq. 5.

Table 4: 1-Isopropylsulfonyl-2-amine benzimidazoles and their anti-HBV and toxic activities and physicochemical parameters

Compd	X	R	E <sub>s</sub>	B <sub>1</sub>	I <sub>1</sub>	log(1/EC <sub>50</sub> )		
						Obsd <sup>a</sup>	Calcd	Pred
6a <sup>b</sup>	CO	H	0.00	1.00	1.00	4.47	6.07	–
6b	CO	2-F	-0.46	1.35	1.00	6.03	5.91	5.88
6c	CO	4-F	-0.46	1.35	1.00	5.92	5.91	5.90
6d	CO	2,6-DiF	-0.92	2.70	1.00	6.15	6.27	7.53
6e	CO	2-Cl	-0.97	1.80	1.00	6.09	5.75	5.68
6f	CO	4-CH <sub>3</sub>	-1.24	1.52	1.00	5.38	5.40	5.41
6g	SO <sub>2</sub>	H	0.00	1.00	1.00	5.82	6.07	6.28
6h	SO <sub>2</sub>	4-CH <sub>3</sub>	-1.24	1.52	1.00	5.32	5.40	5.44
6i <sup>b</sup>	SO <sub>2</sub>	3-NO <sub>2</sub>	-1.01	1.70	1.00	4.98	5.67	–
7a	CO	H	0.00	1.00	0.00	5.70	5.85	5.47
7b	CO	4-F	-0.46	1.35	0.00	5.43	5.42	5.41

<sup>a</sup>Taken from ref [11]. <sup>b</sup>Not included in the derivation of Eq. 6.