Supporting Information

Protective activity of (1*S*,2*E*,4*R*,6*R*,7*E*,11*E*)-2,7,11-cembratriene-4,6-diol analogues against diisopropylfluorophosphate neurotoxicity: Preliminary structure-activity relationship and pharmacophore modeling

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Table 1. ^{13}C and ^{1}H NMR Data of Cembranoids **1** and **2**.[a]

position	**1**[1,2]		**2**[2,3]	
	δ_C	δ_H	δ_C	δ_H
1	47.1, CH	1.66, m	48.8, CH	1.70, m
2	131.5, CH	5.24, ddq (15.8, 8.8, 1.8)	128.4, CH	5.52, dd (9.1, 15.4)
3	137.3, CH	5.45, d (15.8)	140.0, CH	5.42, d (15.4)
4	71.1, qC	-	74.2, *q*C	–
5	52.2, CH_2	2.20, m 1.91, m	46.8, CH_2	1.80, dd (2.5, 14.3)
				2.22, dd (5.8, 14.3)
6	64.7, CH	4.85, dd (9.8, 9.0)	68.4, CH	4.60, m
7	130.1, CH	5.47, d (9.8)	128.3, CH	5.56, brd (9.8)
8	136.0, qC	-	136.9, *q*C	–
9	38.2, CH_2	2.25, m, 2.20, m	36.1, CH_2	1.85, m
10	24.5, CH_2	2.13,2H, m	29.4, CH_2	1.82, m; 2.22, m
11	128.2, CH	5.28, m	64.1, CH	4.31, dd (6.2, 9.8)
12	136.8, qC	-	148.0, *q*C	–
13	29.9, CH_2	2.37, m, 1.90, m	34.7, CH_2	1.75, m; 2.15, m
14	31.1, CH_2	1.45, 2H, m	28.6, CH_2	1.35, m; 1.65, m
15	32.1, CH	1.56, m	33.3, CH	1.60, m
16	19.1, CH_3	0.99, 3H, d (6.6)	19.3, CH_3	0.85, 3H,d (6.6)
17	20.8, CH_3	0.84, 3H, d (6.6)	20.9, CH_3	0.88, 3H, d (6.6)
18	28.9, CH_3	1.39, 3H, s	32.4, CH_3	1.26, 3H, s
19	15.2, CH_2	1.55, 3H, s	15.6, CH_3	1.62, 3H, s
20	16.1, CH_3	1.76, 3H, s	16.6, CH_3	1.50, 3H, s

[a] In $CDCl_3$, 400 MHz for ^{1}H and ^{13}C NMR. Coupling constants (*J*) are in Hz. Carbon multiplicities were determined by APT experiments, qC = quaternary, CH = methine, CH_2 = methylene, CH_3 = methyl carbons.

Table 2. ^{13}C and ^{1}H NMR Data of Cembranoids **3** and **4**.[a]

position	**3**[4,5]		**4**[4,5]	
	δ_C, mult.	δ_H (J, Hz)	δ_C, mult.	δ_H (J, Hz)
1	46.3 CH	1.68, m	46.4 CH	1.64, m
2	132.1 CH	5.23, dd (15.8,9.0)	131.8 CH	5.41, dd (15.8, 8.1)
3	134.0 CH	5.07, d (15.8)	133.2 CH	5.28, d (15.8)
4	75.5 qC	-	77.1 qC	-
5	52.8 CH_2	2.07, dd (13.9, 1.8) 1.77, dd (13.9, 3.7)	55.1 CH_2	2.82, d (11.7) 2.45, d (11.7)
6	63.5 CH	4.79, ddd (9.6, 3.7, 2.2)	200.1 qC	-
7	133.0 CH	5.25, dq (9.6, 1.8)	127.4 CH	6.13, s
8	135.0 qC	-	156.1 qc	-
9	38.3 CH_2	2.0, 2H, m	40.3 CH_2	2.10, 2H, m
10	22.9 CH_2	1.68, 2H, m	23.9 CH_2	2.22, 2H, m
11	128.3 CH	5.24, m	123.7 CH	5.00, m
12	133.1 qC	-	134.2 qC	-
13	37.3, CH_2	2.20, m 1.93, m	37.1 CH_2	2.11, 2H, m
14	22.1, CH_2	1.42, 2H, m	27.6 CH_2	1.44, 2H, m
15	32.9, CH	1.51, m	32.8 CH	1.55, m
16	20.2 CH_3	0.84, 3H, d (6.25)	19.3 CH_3	0.80, 3H, d (6.6)
17	20.4 CH_3	0.85, 3H, d (6.25)	20.5 CH_3	0.83, 3H, d (6.6)
18	22.9 CH_3	1.26, 3H, s	24.7 CH_3	1.31, 3H, s
19	16.0 CH_3	1.64, 3H, d (1.8)	18.4 CH_3	2.02, 3H, d (1.1)
20	15.1 CH_3	1.50, 3H, s	15.6 CH_3	1.56, 3H, s
21	50.2 CH_3	3.12, 3H, s	50.2 CH_3	3.24 3H, s

[a]In $CDCl_3$, 400 MHz for ^{1}H and ^{13}C NMR. Coupling constants (J) are in Hz. Carbon multiplicities were determined by APT experiments, qC = quaternary, CH = methine, CH_2 = methylene, CH_3 = methyl carbons.

Table 3. ^{13}C and ^{1}H NMR Data of Cembranoids **5** and **6**.[a]

position	**5**[4]		**6**[4]	
	δ_C, mult.	δ_H (J, Hz)	δ_C, mult.	δ_H (J, Hz)
1	47.1 CH	1.65, m	47.0 CH	1.64, 1H, m
2	133.4 CH	5.17, dd (15.8,8.0)	133.7 CH	5.16, 1H, dd (15.8,8.0)
3	135.1 CH	5.22, d (15.8)	137.9 CH	5.24, d (15.8)
4	75.7 qC	-	75.5 qC	-
5	52.6 CH_2	2.07, dd (13.9, 1.8)	49.7 CH_2	2.09, dd (13.9, 1.8) 1.84, m
		1.92, dd (13.9, 3.7)		
6	64.2 CH	4.82, ddd (9.4, 3.7, 1.8)	68.0 CH	5.83, dt (8.8, 1.6)
7	133.3 CH	5.31, d (9.9)	129.4 CH	5.21, 1H, d (9.9)
8	133.0 qC	-	137.4 qC	-
9	35.8 CH_2	2.19, 2H, m	35.9 CH_2	1.84, 2H, m
10	25.0 CH_2	2.27, 2H, dt, (10.6, 2.5)	25.1 CH_2	1.48, 2H, m
11	61.0 CH	2.82, dd (7.7, 2.5)	61.1 CH	2.81, dd (8.0, 1.5)
12	59.5 qC	-	59.5 qC	-
13	36.6 CH_2	2.19, 2H, m	36.7 CH_2	2.20, 2H, m
14	28.3 CH_2	1.46, 2H, m	28.3 CH_2	1.57, 2H, m
15	33.8 CH	1.56, m	33.9 CH	1.60, m
16	20.0 CH_3	0.82, 3H, d (6.5)	18.9 CH_3	0.79, 3H, d (7.0)
17	20.6 CH_3	0.86, 3H, d (6.5)	20.6 CH_3	0.83, 3H, d (7.0)
18	22.2 CH_3	1.23, 3H, s	22.2 CH_3	1.23, 3H, s
19	16.2 CH_3	1.78, 3H, s	16.1 CH_3	1.87, 3H, d (1.2)
20	16.3 CH_3	1.19, 3H, s	16.6 CH_3	1.19, 3H, s
21	50.3 CH_3	3.14 3H, s	50.4 CH_3	3.13 3H, s
CO	-	-	170.1 qC	-
CH_3	-	-	21.6	2.00, 3H, s

[a]In $CDCl_3$, 400 MHz for ^{1}H and ^{13}C NMR. Coupling constants (J) are in Hz. Carbon multiplicities were determined by APT experiments, qC = quaternary, CH = methine, CH_2 = methylene, CH_3 = methyl carbons.

Table 4. ^{13}C and ^{1}H NMR Data of Cembranoids **7** and **8**.[a]

position	**7**[4]		**8**[1,6,7]	
	δ_C, mult.	δ_H (*J*, Hz)	δ_C, mult.	δ_H (*J*, Hz)
1	46.9 CH	1.47, m	46.4 CH	1.64, m
2	134.6 CH	5.18, dd (15.8, 7.3)	131.8 CH	5.41, dd (15.8, 8.1)
3	135.0 CH	5.24, d (15.8)	133.2 CH	5.28, d (15.8)
4	76.8 qC	-	77.2 qC	-
5	49.9 CH_2	2.10, dd (15.0, 3.0) 1.82, dd (15.0, 5.1)	55.6 CH_2	2.84, d (11.6) 2.42, d (11.6)
6	64.8 CH	3.95, ddd (8.2, 5.1, 3.0)	201.2 qC	-
7	69.4 CH	2.82, d (9.1)	127.2 CH	6.13, s
8	63.5 qC	-	155.1 qc	-
9	36.7 CH_2	1.98, 2H, m	40.1 CH_2	2.12, 2H, m
10	23.0 CH_2	2.07, 2H, m	23.7 CH_2	2.24, 2H, m
11	123.7 CH	5.02, m	123.1 CH	5.02, m
12	134.6 qC	-	134.0 qC	-
13	36.4 CH_2	1.89, 2H, m	37.1 CH_2	2.12, 2H, m
14	28.2 CH_2	1.63, 2H, m	27.6 CH_2	1.46, 2H, m
15	33.0 CH	1.69, m	32.8 CH	1.59, m
16	19.7 CH_3	0.82, 3H, d (6.6)	19.1 CH_3	0.81, 3H, d (6.6)
17	21.0 CH_3	0.87, 3H, d (6.6)	20.0 CH_3	0.85, 3H, d (6.6)
18	23.0 CH_3	1.32, 3H, s	24.2 CH_3	1.31, 3H, s
19	17.7 CH_3	1.34, 3H, s	18.1 CH_3	2.00, 3H, d (1.1)
20	14.7 CH_3	1.51, 3H, s	15.6 CH_3	1.59, 3H, s
21	50.8 CH_3	3.16 3H, s	-	-

[a]In $CDCl_3$, 400 MHz for ^{1}H and ^{13}C NMR. Coupling constants (*J*) are in Hz. Carbon multiplicities were determined by APT experiments, qC = quaternary, CH = methine, CH_2 = methylene, CH_3 = methyl carbons.

Table 5. ^{13}C and ^{1}H NMR Data of Cembranoids **9- 11**.[a]

Position	**9**[2]		**10**[2]		**11**[2]	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	46.1, CH	1.50, m	46.0, CH	1.55, m	46.5, CH	1.51, m
2	130.3, CH	5.17, dd (15.8, 9.2)	130.1, CH	5.16, dd, (15.4, 9.2)	131.8, CH	5.21, dd (15.8, 8.8)
3	136.3, CH	5.36, d, (15.8)	136.5, CH	5.36, d, (15.4)	136.3, CH	5.35, d (15.8)
4	70.9, qC	-	70.8, qC	-	71.5, qC	-
5	51.4, CH_2	2.00, m	51.7, CH_2	2.05, m	52.2, CH_2	2.00, m 1.88, m
6	69.3, CH	5.60, dd (9.5, 9.0)	68.7, CH	5.57, dd (9.4, 9.0)	64.4, CH	4.86, dd (9.6, 9.2)
7	127.1, CH	5.27, d (9.9)	127.3, CH	5.24, d (9.9)	126.4, CH	5.62, d (9.9)
8	139.6, qC	-	139.3, qC	-	133.2, qC	-
9	38.9, CH_2	2.05, m 2.20, m	38.9, CH_2	2.10, m 2.25, m	70.9, CH	4.23, brs
10	76.1, CH	4.10, brd (7.7)	75.2, CH	3.92, ddd (10.9, 5.3, 2.9)	38.1, CH_2	2.40, m 2.32, m
11	124.0, CH	4.91, m	124.2, CH	4.90, m	124.7, CH	4.99, brt (3.6)
12	133.5, qC	-	133.1, qC	-	136.8, qC	-
13	36.5, CH_2	1.90, m 2.05, m	35.9, CH_2	1.90, m	27.9, CH_2	2.04, m, 1.66, m
14	27.5, CH_2	1.25, m 1.60, m	27.4, CH_2	1.20, m 1.55, m	32.0, CH_2	1.40, m 1.31, m
15	33.2, CH	1.55, m	33.1, CH	1.50, m	32.8, CH	1.51, m
16	19.5, CH_3	0.79, d (6.6)	19.5, CH_3	0.79, d (6.6)	19.2, CH_3	0.78, 3H, d (6.6)
17	20.5, CH_3	0.82, d (6.6)	20.4, CH_3	0.80, d (6.6)	20.7, CH_3	0.81, 3H, d (6.6)
18	28.3, CH_3	1.36, s	28.2, CH_3	1.36, s	28.9, CH_3	1.41, 3H, s
19	16.0, CH_3	1.48, s	15.9, CH_3	1.48, s	15.1, CH_3	1.53, 3H, s
20	15.0, CH_3	1.72, s	15.0, CH_3	1.71, s	16.1, CH_3	1.69, 3H, s

[a]In $CDCl_3$, 400 MHz for ^{1}H and ^{13}C NMR. Coupling constants (*J*) are in Hz. Carbon multiplicities were determined by APT experiments, qC = quaternary, CH = methine, CH_2 = methylene, CH_3 = methyl carbons.

Table 6. ^{13}C and ^{1}H NMR Data of Cembranoids **12** and **13.**[a.]

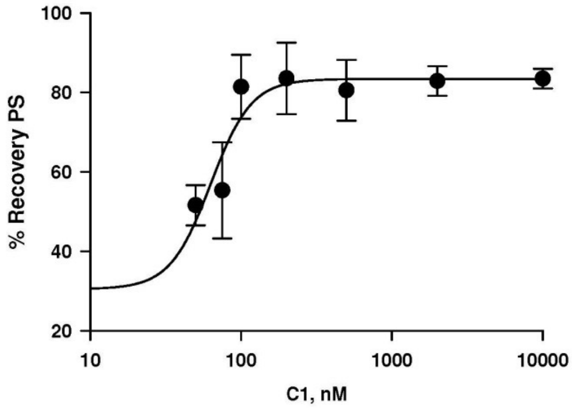
position	**12**[2]		**13**[2]	
	δ_C	δ_H	δ_C	δ_H
1	47.5, CH	1.63, m	46.5, CH	1.51, m
2	131.8, CH	5.24, ddq (15.8, 8.8, 1.8)	131.8, CH	5.21, dd (15.8, 8.8)
3	137.3, CH	5.40, d (15.8)	136.3, CH	5.35, d (15.8)
4	72.1, qC	-	71.5, qC	-
5	52.2, CH_2	2.15, m 1.95, m	52.2, CH_2	2.00, m 1.88, m
6	64.4, CH	4.82, dd (9.8, 9.0)	64.4, CH	4.86, dd (9.6, 9.2)
7	130.2, CH	5.47, d (9.8)	126.4, CH	5.62, d (9.9)
8	136.2, qC	-	133.2, qC	-
9	38.0, CH_2	2.25, m, 2.20, m	70.9, CH	4.23, brs
10	22.5, CH_2	2.33,2H, m	38.1, CH_2	2.40, m 2.32, m
11	128.0, CH	5.28, m	124.7, CH	4.99, brt (3.6)
12	136.2, qC	-	134.8, qC	-
13	27.9, CH_2	2.27, m, 1.90, m	27.9, CH_2	2.04, m, 1.66, m
14	32.0, CH_2	1.42, 2H, m	32.0, CH_2	1.40, m 1.31, m
15	32.8, CH	1.51, m	32.8, CH	1.51, m
16	19.2, CH_3	0.79, 3H, d (6.6)	19.2, CH_3	0.78, 3H, d (6.6)
17	20.7, CH_3	0.84, 3H, d (6.6)	20.7, CH_3	0.81, 3H, d (6.6)
18	28.9, CH_3	1.39, 3H, s	28.9, CH_3	1.41, 3H, s
19	60.0, CH_2	3.57, d (11.1), 3.51, d (11.1)	15.1, CH_3	1.53, 3H, s
20	16.1, CH_3	1.76, 3H, s	60.1, CH_3	3.67, d (11.2), 3.61, d (11.2)

[a] In $CDCl_3$, 400 MHz for ^{1}H and ^{13}C NMR. Coupling constants (*J*) are in Hz. Carbon multiplicities were determined by APT experiments, qC = quaternary, CH = methine, CH_2 = methylene, CH_3 = methyl carbons.

Table 7. [13]C and [1]H NMR Data of Cembranoids **14** and **15**.[a]

position	**14**[4]		**15**[4]	
	δ_C, mult.	δ_H (*J*, Hz)	δ_C, mult.	δ_H (*J*, Hz)
1	46.1 CH	1.62, m	41.6 CH	2.17, m
2	133.7 CH	5.42, dd (8.8, 7.0)	42.7 CH	2.75, dd (7.3, 4.0)
3	135.4 CH	5.44, d (8.8)	115.3 CH	5.45, d (7.3)
4	76.3 qC	-	131.9 qC	-
5	57.1 CH_2	2.83, d (11.7)	122.7 CH	5.97, s
		2.46, d (11.7)		
6	199.0 qC	-	132.3 qC	-
7	126.6 CH	6.02, s	126.8 CH	5.56, s
8	157.2 qC	-	137.8 qC	-
9	40.7 CH_2	2.13, 2H, m	31.4 CH_2	1.93, m 2.74, m
10	23.9 CH_2	2.26, 2H, m	25.4 CH_2	1.95, m 2.03, m
11	123.1 CH	4.89, dd (7.7, 7.7)	126.9 CH	5.18, dd (7.7, 7.7)
12	134.2 qC	-	134.4 qC	-
13	37.0 CH_2	2.01, 2H, m	39.2 CH_2	1.27, 2H, m
14	27.6 CH_2	1.39, 2H, m	22.9 CH_2	1.57, 2H, m
15	33.3 CH	1.82, m	27.9 CH	2.00, m
16	19.3 CH_3	0.84, 3H, d (6.6)	17.2 CH_3	0.81, 3H, d (7.0)
17	20.2 CH_3	0.86, 3H, d (6.6)	21.6 CH_3	0.92, 3H, d (7.0)
18	21.0 CH_3	1.29, 3H, s	22.0 CH_3	1.83, 3H, (1.4)
19	18.7 CH_3	2.13, 3H, d (1.1)	24.1 CH_3	1.84, 3H, d (1.5)
20	15.7 CH_3	1.56, 3H, s	16.8 CH_3	1.63, 3H, s
21	49.8 CH_3	3.13, 3H, s	-	-

[a]In $CDCl_3$, 400 MHz for [1]H and [13]C NMR. Coupling constants (*J*) are in Hz. Carbon multiplicities were determined by APT experiments, qC = quaternary, CH = methine, CH_2 = methylene, CH_3 = methyl carbons.



R	Rsqr	Adj Rsqr	Standard Error of Estimate
0.97	0.94	0.90	6.44

	Coefficient	Std. Error	t	P
min	30	6	5	0.009
max	83	3	24	<0.0001
EC_{50}	63	9	7	0.0025
Hillslope	3	1	2	0.0855

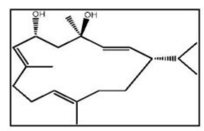
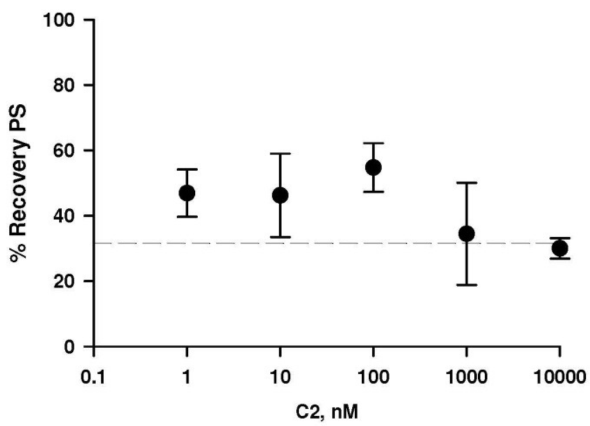


Figure S1. EC_{50} data of **1**.



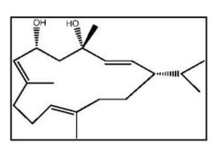
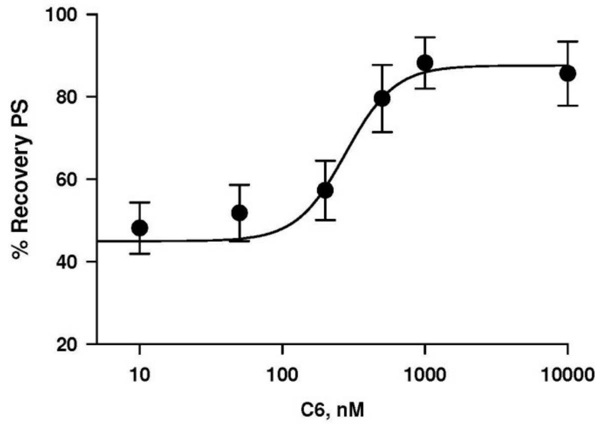


Figure S2. EC_{50} data of **2**.



R	Rsqr	Adj Rsqr	Standard Error of Estimate
0.97	0.94	0.89	6.81

	Coefficient	Std. Error	t	P
min	45	4	11	0.0016
max	88	6	15	0.0006
EC_{50}	277	87	3	0.0492
Hillslope	3	2	2	0.2123

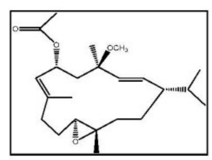
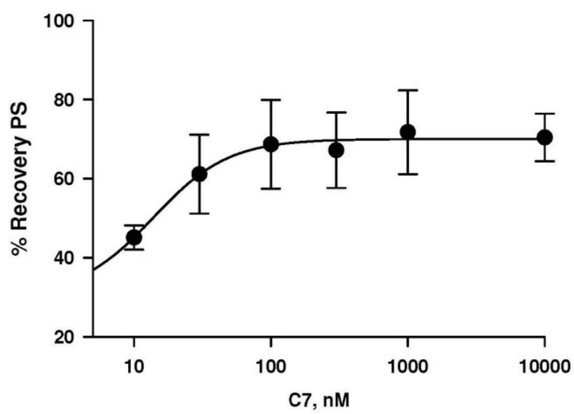


Figure S3. EC_{50} data of **6**.



R	Rsqr	Adj Rsqr	Standard Error of Estimate
1.00	0.99	0.99	1.81

	Coefficient	Std. Error	t	P
min	30	2	17	0.0005
max	70	1	67	<0.0001
EC_{50}	14	2	8	0.0041
Hillslope	2	0	5	0.0132

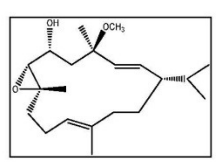
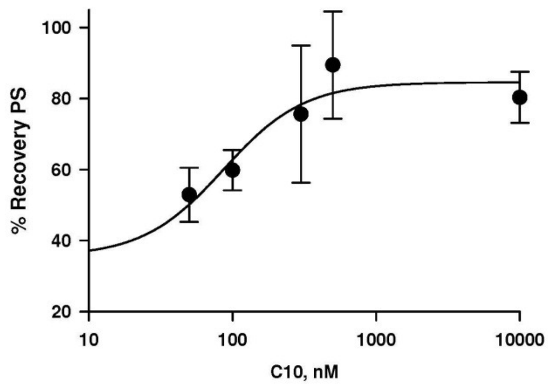


Figure S4. EC_{50} data of **7**.



R	Rsqr	Adj Rsqr	Standard Error of Estimate
0.97	0.95	0.87	7.23

	Coefficient	Std. Error	t	P
min	35	7	5	0.038
max	85	7	13	0.006
EC_{50}	87	36	2	0.138
Hillslope	2	1	2	0.238

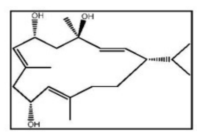
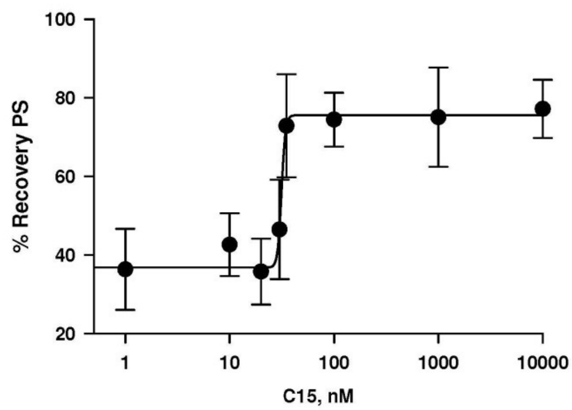


Figure S5. EC_{50} data of **10**.



R	Rsqr	Adj Rsqr	Standard Error of Estimate
0.99	0.98	0.97	3.37

	Coefficient	Std. Error	t	P
min	37	2	22	<0.0001
max	76	2	39	<0.0001
EC_{50}	31	1	40	<0.0001
Hillslope	24.0	10.2	2	0.0659

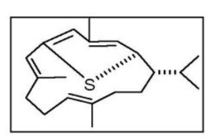
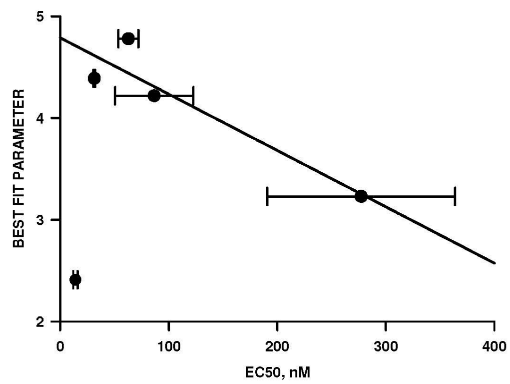


Figure S6. EC_{50} data of **15**.



	R	Rsqr	Adj Rsqr	Standard Error of Estimate
	0.93	0.87	0.80	0.30

	Coefficient	Std. Error	t	P
y0	4.8	0.2	20.8	0.0023
a	-0.0055	0.0015	-3.6	0.0691

Figure S7. Validation of EC_{50} values using QSAR data.

ERROR: undefined
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