Supporting Information

Chiral Indolylarylsulfone Non-Nucleoside Reverse Transcriptase Inhibitors as New Potent and Broad Spectrum anti-HIV-1 Activity Agents

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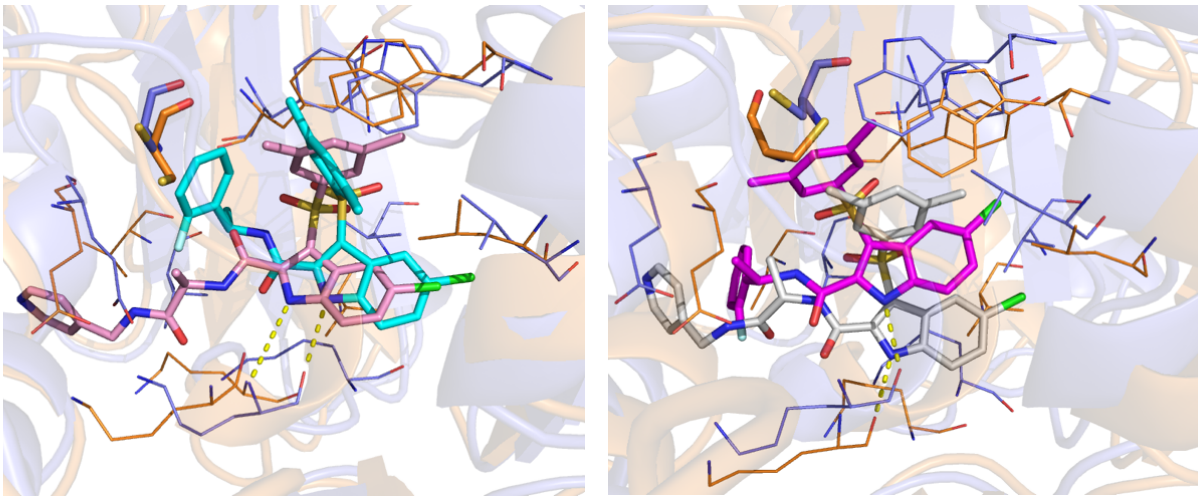

Figure 1S. Left panel: trajectories snapshots of (*R*)-**8** and (*R*)-**23** versus Y181C RT. Right panel: trajectories snapshots of (*S*)-**8** with (*S*)-**23** versus Y181C RT. Residues involved in interactions are reported as lines. Mutated residue is depicted as stick. RT is shown as cartoon. H-bonds are depicted as yellow dotted lines.

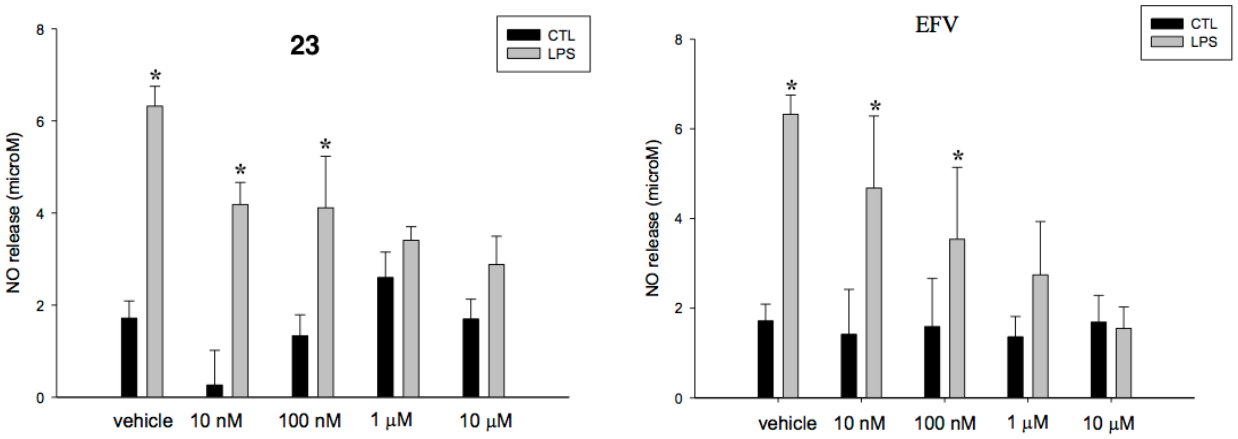

Figure 2S. Compound **23** and EFV treatments reduce NO release induced by LPS on BV2 cells. BV2 cells were treated with 10 nM, 10^2 nM, 10^3 nM or 10^4 nM concentrations of **23** or EFV in the presence or absence of 50 ng/mL LPS for 24 h. NO release was measured by Greiss reaction. Data are expressed as μM. N=3; *p<0,05 vs CTL by Kruskal-Wallis One Way Analysis of Variance (Dunn's method).

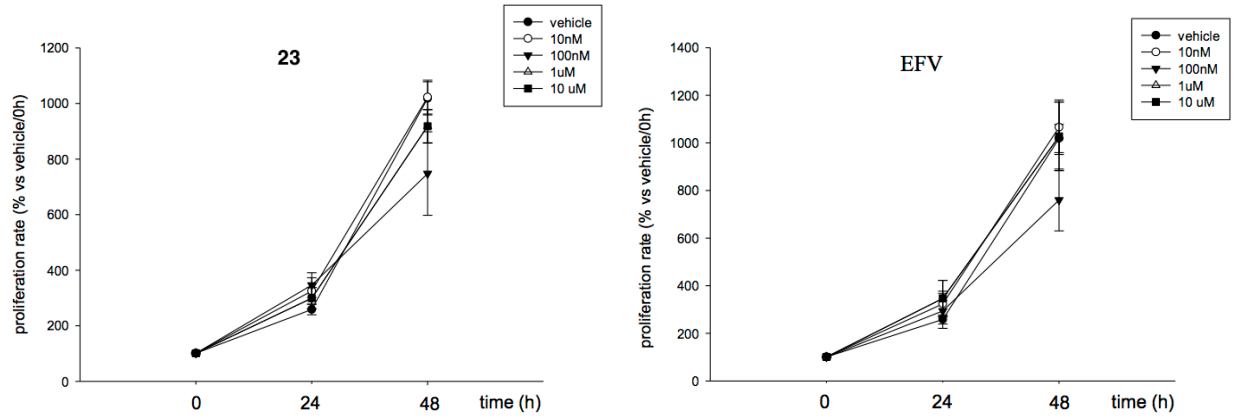

Figure 3S. Compound **23** and EFV treatments do not modify BV2 cell proliferation. BV2 cells were treated with 10 nM, 10^2 nM, 10^3 nM and 10^4 nM of **23** or EFV for 0, 24 and 48 h. Proliferation rate was measured by MTT assay. Data are expressed as % vs vehicle at 0h. N=3.

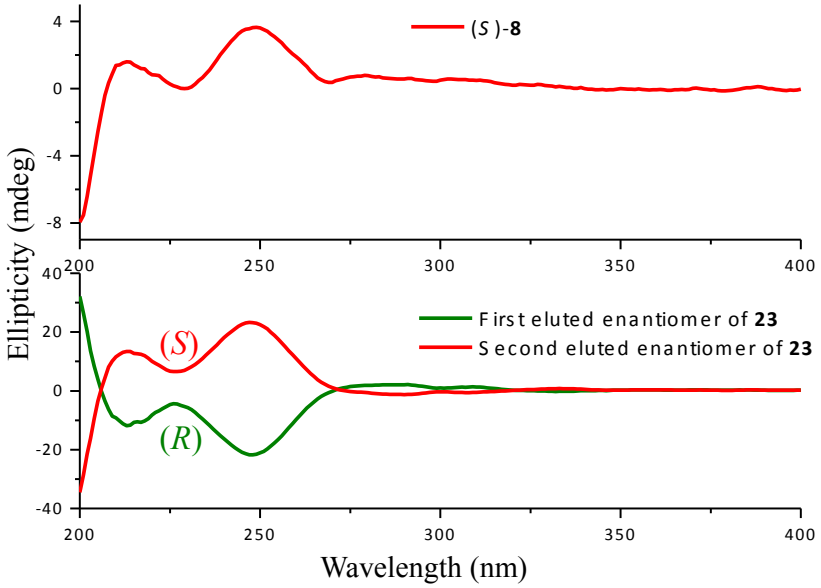

Figure 4S. Comparison of the CD spectra of (*S*)-**8** and the enantiomers of **23** recorded in ethanol.

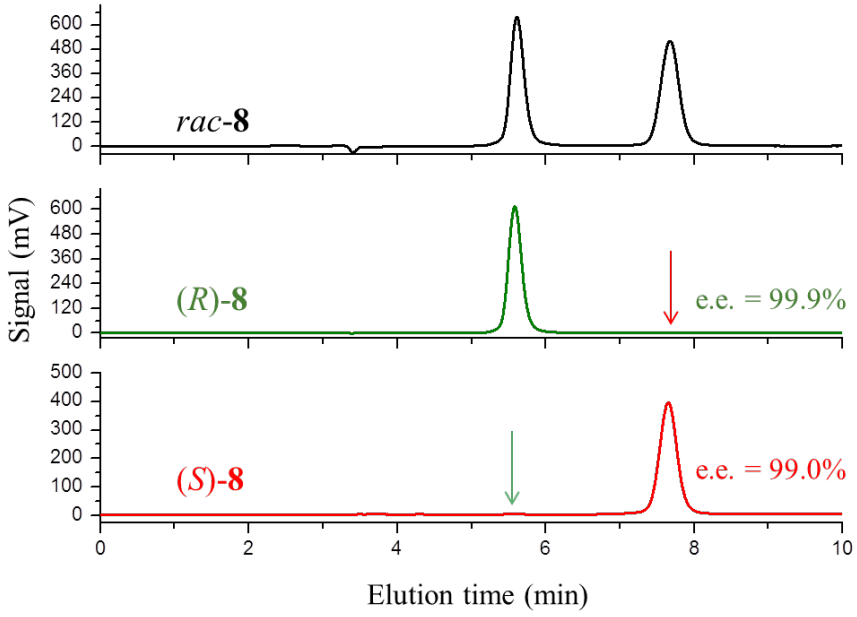

Figure 5S. Enantiomeric purity of the enantiomers of **8** separated at semipreparative scale.

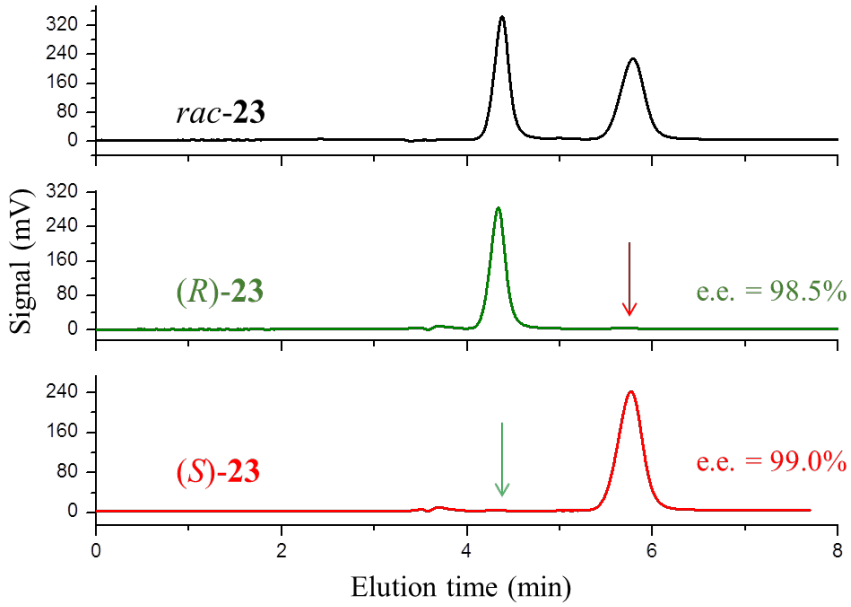

Figure 6S. Enantiomeric purity of the enantiomers of **23** separated at semipreparative scale.

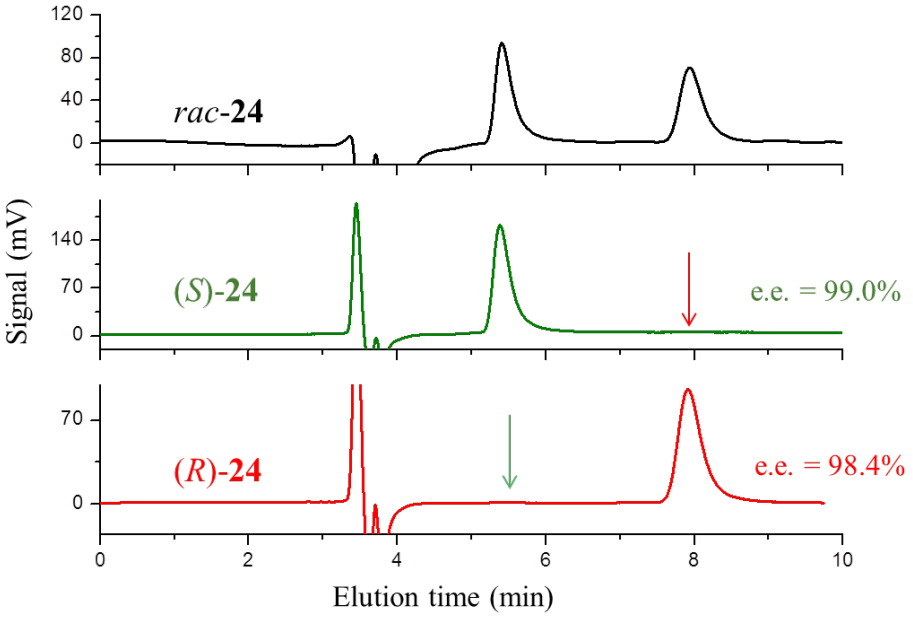

Figure 7S. Enantiomeric purity of the enantiomers of **24** separated at semipreparative scale.

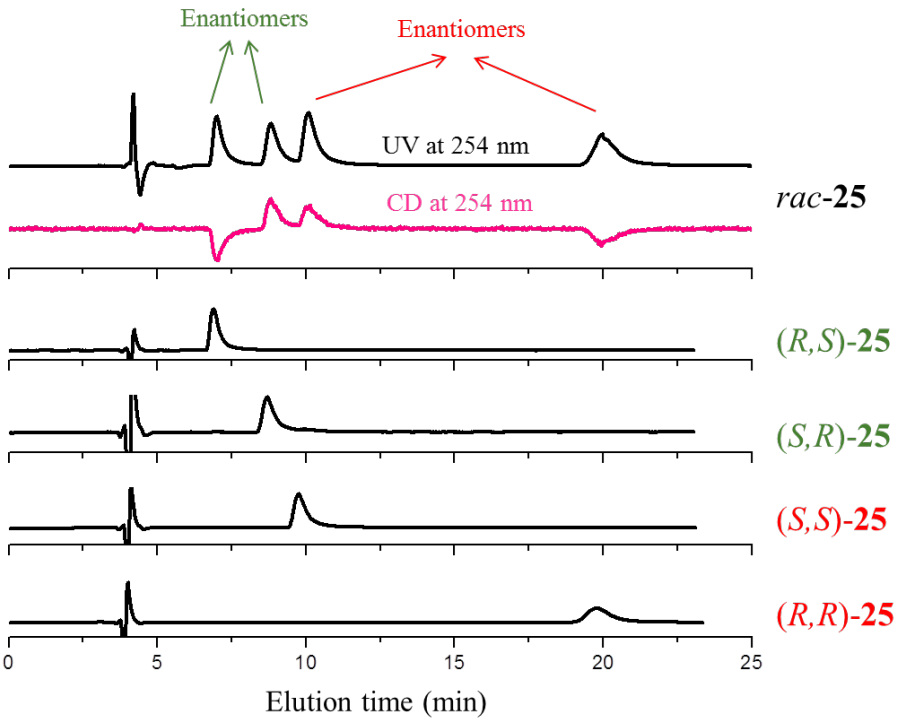

Figure 8S. Enantiomeric purity of the enantiomers of **25** separated at semipreparative scale.

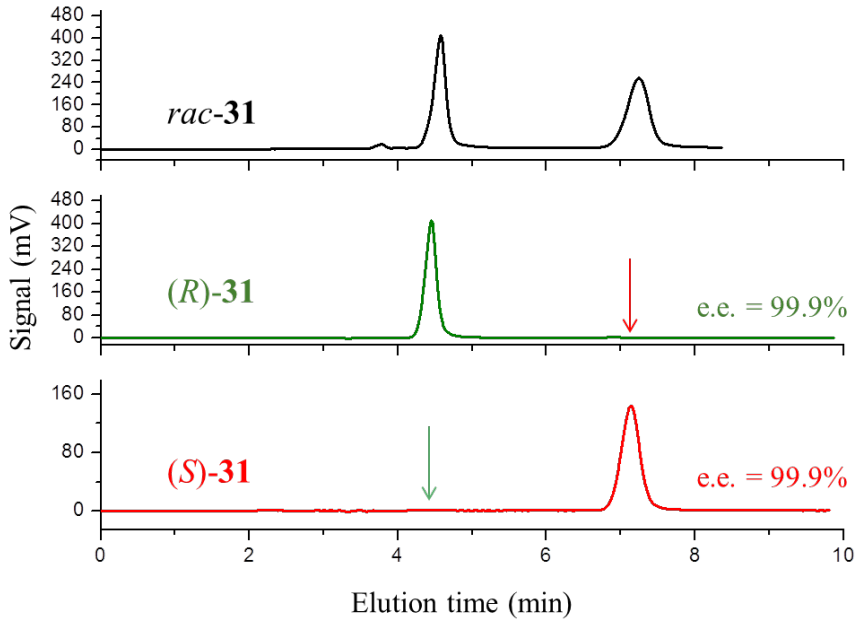

Figure 9S. Enantiomeric purity of the enantiomers of **31** separated at semipreparative scale.

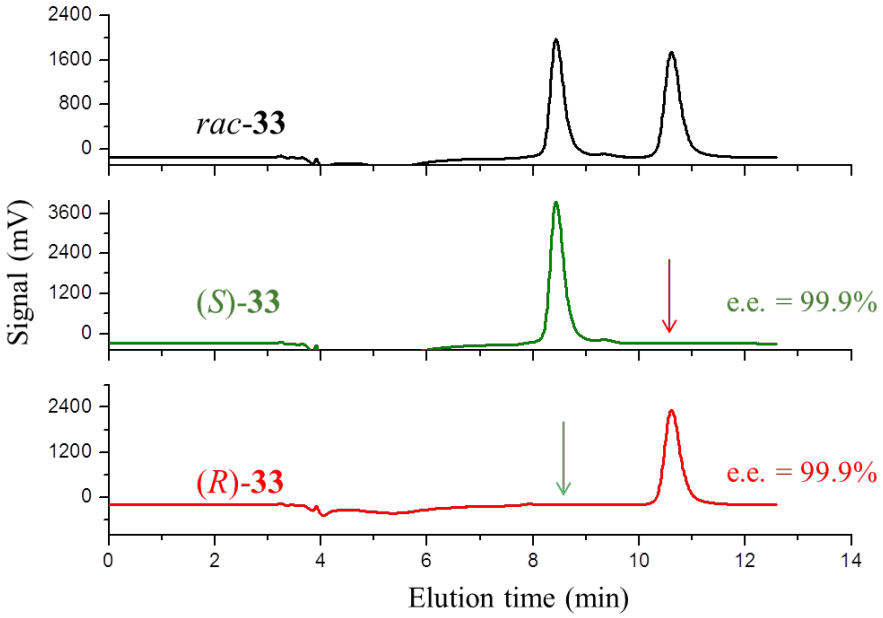

Figure 10S. Enantiomeric purity of the enantiomers of **33** separated at semipreparative scale.

Table 1S. In silico physicochemical properties of **9-22, 24** and **26-37**.

Cmpd	LogP[a]	TPSA[b]	H-bond Acc.[c]	H-bond Don.[d]	MW[e]	QPP Caco[f]	QPP MDCK[g]
9	2.70	100.55	4	2	456.94	1359.11	1719.66
10	4.75	87.41	3	2	527.46	1390.83	4295.93
11	3.71	96.64	5	2	500.97	1702.21	3131.21
12	4.62	87.41	5	2	502.96	1430.99	5407.89
13	3.99	87.41	4	2	484.97	1184.16	2460.85
14	4.42	87.41	5	2	488.94	1093.77	3640.43
15	2.00	124.09	5	2	478.95	148.66	153.92
16	2.00	124.09	5	2	478.95	131.72	134.9
17	3.14	113.43	3	3	467.97	275.47	299.61
18	2.97	142.11	4	4	507.99	74.95	74.46
19	3.22	116.09	4	3	492.98	378.62	431.52
20	3.01	116.51	4	3	524.04	305.67	603.56
21	3.21	116.51	4	3	538.08	555.98	882.22
22	1.82	129.40	5	3	511.00	140.77	269.22
24	2.03	129.40	5	3	525.03	214.84	388.32
26	2.65	144.75	4	3	530.07	235.21	725.6
27	2.85	144.75	4	3	544.10	347.91	1050.92
28	1.50	180.15	7	3	573.03	301.56	943.23
29	1.70	180.15	7	3	587.05	190.26	201.45
30	1.25	141.29	6	3	511.99	135.68	258.24
31	1.45	142.29	6	3	526.02	176.09	279.78
32	1.65	129.65	5	3	499.98	197.37	372.13
33	1.86	129.65	5	3	514.00	277.73	554.97
34	3.18	116.51	5	3	528.00	240.43	688.91
35	3.38	116.51	5	3	542.03	464.70	1224.57
36	3.38	116.51	5	3	542.03	400.35	860.26
37	3.57	116.51	5	3	556.06	627.59	1446.23

Physicochemical properties predicted by SwissADME:[1S] [a]Octanol-water partition coefficient predictor by topological method implemented from Moriguchi;[2S,3S] [b]Molecular polar surface area: this parameter correlates with human intestinal absorption (<140).[4S] [c]Number of H-bond acceptors; [d]Number of H-bond donors; [e]Molecular Weight. Physicochemical properties predicted by QikProp:[5S] [f]QPP Caco - Apparent Caco-2 permeability (nm/sec) (<25 poor, >500 great); [g]QPP MDCK - Apparent MDCK permeability (nm/sec) (<25 poor, >500 great).

Table 2S. Elemental analyses of compounds 8-37.

compd	Calculated (%)	Found (%)
8	C, 61.91; H, 4.57; Cl, 7.31; F, 3.92; N, 5.78; S, 6.61	C, 61.76; H, 4.52; Cl, 7.11; F, 3.80; N, 5.62; S, 6.42
9	C, 60.46; H, 4.63; Cl, 7.76; N, 6.13; S, 7.02	C, 60.25; H, 4.59; Cl, 7.62; N, 6.02; S, 6.88
10	C, 61.48; H, 4.59; Cl, 13.44; N, 5.31; S, 6.08	C, 61.37; H, 4.54; Cl, 13.36; N, 5.22; S, 5.90
11	C, 59.94; H, 4.43; Cl, 7.08; F, 3.79; N, 5.59; S, 6.40	C, 59.85; H, 4.39; Cl, 6.91; F, 3.65; N, 5.48; S, 6.32
12	C, 59.70; H, 4.21; Cl, 7.05; F, 7.55; N, 5.57; S, 6.38	C, 59.59; H, 4.17; Cl, 6.88; F, 7.37; N, 5.68; S, 6.19
13	C, 61.91; H, 4.40; Cl, 7.31; F, 3.92; N, 5.78; S, 6.61	C, 61.84; H, 4.44; Cl, 7.19; F, 3.75; N, 5.69; S, 6.48
14	C, 58.96; H, 3.92; Cl, 7.25; F, 7.77; N, 5.73; S, 6.56	C, 58.68; H, 3.88; Cl, 7.13; F, 7.58; N, 5.61; S, 6.88
15	C, 59.42; H, 3.69; Cl, 7.63; N, 12.05; S, 6.90	C, 59.26; H, 3.61; Cl, 7.40; N, 11.95; S, 6.78
16	C, 59.42; H, 3.69; Cl, 7.63; N, 12.05; S, 6.90	C, 59.34; H, 3.61; Cl, 7.51; N, 11.88; S, 6.71
17	C, 61.60; H, 4.74; Cl, 7.58; N, 8.98; S, 6.85	C, 61.50; H, 4.68; Cl, 7.48; N, 8.81; S, 6.78
18	C, 59.11; H, 4.37; Cl, 6.98; N, 13.79; S, 6.31	C, 58.89; H, 4.32; Cl, 6.88; N, 13.68; S, 6.20
19	C, 60.51; H, 4.46; Cl, 7.24; N, 11.44; S, 6.55	C, 60.42; H, 4.42; Cl, 7.13; N, 11.29; S, 6.31
20	C, 61.88; H, 5.00; Cl, 6.77; N, 8.02; S, 6.12	C, 61.73; H, 4.98; Cl, 6.64; N, 7.92; S, 5.97
21	C, 62.50; H, 5.25; Cl, 6.59; N, 7.81; S, 5.96	C, 62.42; H, 5.16; Cl, 6.42; N, 7.70; S, 5.85
22	C, 58.76; H, 4.54; Cl, 6.94; N, 10.96; S, 6.28	C, 58.59; H, 4.48; Cl, 6.78; N, 10.82; S, 6.07
23	C, 59.48; H, 4.80; Cl, 6.75; N, 10.67; S, 6.11	C, 59.31; H, 4.72; Cl, 6.69; N, 10.58; S, 5.93
24	C, 59.48; H, 4.80; Cl, 6.75; N, 10.67; S, 6.11	C, 59.26; H, 4.71; Cl, 6.66; N, 10.39; S, 5.90
25	C, 60.16; H, 5.05; Cl, 6.58; N, 10.39; S, 5.95	C, 59.98; H, 4.99; Cl, 6.42; N, 10.25; S, 5.72
26	C, 56.65; H, 4.56; Cl, 6.69; N, 7.93; S, 12.10	C, 56.51; H, 4.49; Cl, 6.45; N, 7.81; S, 11.95
27	C, 57.40; H, 4.82; Cl, 6.52; N, 7.72; S, 11.79	C, 57.27; H, 4.80; Cl, 6.48; N, 7.52; S, 11.54
28	C, 52.40; H, 4.40; Cl, 6.19; N, 14.67; S, 5.60	C, 52.12; H, 4.34; Cl, 5.98; N, 14.42; S, 5.46
29	C, 53.19; H, 4.64; Cl, 6.04; N, 14.32; S, 5.46	C, 53.04; H, 4.58; Cl, 5.89; N, 14.15; S, 5.21
30	C, 56.30; H, 4.33; Cl, 6.92; N, 13.68; S, 6.26	C, 56.21; H, 4.29; Cl, 6.78; N, 13.38; S, 6.07
31	C, 57.08; H, 4.60; Cl, 6.74; N, 13.31; S, 6.10	C, 56.91; H, 4.52; Cl, 6.51; N, 13.05; S, 5.88
32	C, 57.66; H, 4.44; Cl, 7.09; N, 8.40; S, 6.41	C, 57.48; H, 4.37; Cl, 6.95; N, 8.21; S, 6.25
33	C, 58.42; H, 4.71; Cl, 6.90; N, 8.18; S, 6.24	C, 58.25; H, 4.68; Cl, 6.75; N, 7.92; S, 6.11
34	C, 59.14; H, 4.39; Cl, 6.71; F, 3.60; N, 7.96; S, 6.07	C, 58.92; H, 4.28; Cl, 6.64; F, 3.49; N, 7.72; S, 5.87
35	C, 59.83; H, 4.65; Cl, 6.54; F, 3.51; N, 7.75; S, 5.92	C, 59.55; H, 4.59; Cl, 6.28; F, 3.42; N, 7.51; S, 5.70
36	C, 59.83; H, 4.65; Cl, 6.54; F, 3.51; N, 7.75; S, 5.92	C, 59.61; H, 4.54; Cl, 6.37; F, 3.40; N, 7.49; S, 5.78
37	C, 60.48; H, 4.89; Cl, 6.38; F, 3.42; N, 7.56; S, 5.77	C, 60.37; H, 4.82; Cl, 6.25; F, 3.28; N, 7.38; S, 5.41

References of Supporting Information

(1S) SwissADME website for computation of physicochemical descriptors and ADME parameterrs prediction, Swiss Institute of Bioinformatics (SIB), www.swissadme.ch.

(2S) Moriguchi, I.; Hirono, S.; Liu, Q.; Nakagome, I.; Matsushita, Y. Simple method of calculating octanol/water partition coefficient. Chem. *Pharm. Bull.* **1992** 40, 127-130.

(3S) Moriguchi, I.; Hirono, S.; Liu, Q.; Nakagome, I.; Hirano, H. Comparison of reliability of log P values for drugs calculated by several methods. *Chem. Pharm. Bull.* **1994** 42, 976-978.

(4S) Pajouhesh, H.; Lenz, G. R. Medicinal chemical properties of successful central nervous system drugs. NeuroRx **2015**, *2*, 541-553.

(5S) QikProp Schrödinger Release 2015-1: QikProp, Schrödinger, LLC, New York, NY, 2017.