In Silico and In Vitro Study towards the Rational Design of 4,4′-Disarylbisthiazoles as a Selective α-Synucleinopathy Biomarker

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^{1}H (DMSO-d_6) δ 6.07 (s, 2H), 7.00 (d, J = 5.5 Hz, 1H), 7.61 (dd, J = 4.3, 8.3 Hz, 1H), 7.69 (s, 1H), 8.27 (s, 1H), 9.94 (s, 1H), 10.19 (s, 1H). ^{13}C (DMSO-d_6) δ 39.02, 39.19, 39.35, 39.52, 39.69, 39.85, 40.02, 101.30, 106.77, 108.55, 120.25, 121.60, 127.98, 147.54, 147.86, 155.27, 167.64, 186.46

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^{1}H (DMSO-d_6) δ 8.65 (q, J = 2.4 Hz, 1H), 9.44 (s, 1H), 10.07 (s, 1H), 10.31 (s, 1H). ^{13}C (DMSO-d_6) δ 125.99, 127.09, 127.13, 148.82, 159.47, 159.57, 161.37, 163.08, 169.47, 186.50.

1.1.6. 4-(5-hydroxypyrimidin-2-yl)thiazole-2-carbothioamide, b_{11}

^{1}H (DMSO-d_6) δ 8.43 (d, J = 2.5 Hz, 2H), 8.50 (d, J = 2.5 Hz, 1H), 9.81 (s, 1H), 10.23 (s, 1H), 10.72 (s, 1H). ^{13}C (DMSO-d_6) δ 128.73, 144.52, 150.99, 151.66, 155.06, 168.74, 186.67.

1.1.7. 4-(3-fluoro-4-hydroxyphenyl)thiazole-2-carbothioamide, b_{12}

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1.1.8. 4-(4-hydroxyphenyl)thiazole-2-carbothioamide, b_{13}

^{1}H (DMSO-d_6) δ 6.79 – 6.87 (m, 2H), 7.88 (dd, *J* = 2.2, 8.7 Hz, 2H), 8.14 (d, *J* = 2.1 Hz, 1H), 9.70 (s, 1H), 9.86 (s, 1H), 10.16 (s, 1H). ^{13}C (DMSO-d_6) δ 115.51, 120.45, 124.91, 127.80, 156.03, 157.94, 167.67, 186.61.

1.1.9. 4-(2,4-dihydroxyphenyl)thiazole-2-carbothioamide, b_{16}

^{1}H (DMSO-d_6) δ 6.32 (dd, *J* = 2.3, 8.6 Hz, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 8.14 (s, 1H), 9.56 (d, *J* = 1.4 Hz, 1H), 9.91 (s, 1H), 10.13 (s, 1H), 10.14 (s, 1H). ^{13}C (DMSO-d_6) δ 102.84, 107.08, 111.69, 122.59, 130.19, 153.42, 156.33, 158.64, 166.17, 186.60.

1.2. ^{1}H and ^{13}C spectra of the asymmetric DABTAs, d

1.2.1. 5-(4'-(benzo[d][1,3]dioxol-5-yl)-[2,2'-bithiazol]-4-yl)-2-methoxyphenol, d_1

^{1}H (DMSO-d_6) δ 3.82 (s, 3H), 6.09 (s, 2H), 7.03 (dd, J = 8.3, 10.5 Hz, 2H), 7.43 (dd, J = 22, 8.4 Hz, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 8.11 (s, 1H), 8.21 (s, 1H), 9.21 (s, 1H). ^{13}C (DMSO-d_6) δ 55.65, 101.37, 106.40, 108.69, 112.35, 113.48, 114.94, 115.36, 117.40, 120.30, 126.42, 127.69, 146.71, 147.58, 147.91, 148.20, 155.15, 155.64, 160.03, 160.31.

1.2.2. 4-(benzo[d][1,3]dioxol-5-yl)-4'-(3-fluoro-4-methoxyphenyl)-2,2'-bithiazole, d_2

^{1}H (DMSO-d_6) δ 3.90 (s, 3H), 6.09 (s, 2H), 7.04 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 8.7 Hz, 1H), 7.56 – 7.61 (m, 2H), 7.80 – 7.89 (m, 2H), 8.23 (s, 1H), 8.30 (s, 1H). ^{13}C (DMSO-d_6) 2-δ 56.11, 101.37, 106.39, 108.68, 113.67, 114.13, 115.57, 116.14, 120.29, 122.65, 126.57, 127.64, 147.43, 147.91, 150.65, 152.58, 154.17, 155.20, 160.05, 160.43.

1.2.3. 5-(4'-([1,3]dioxolo[4,5-b]pyridin-6-yl)-[2,2'-bithiazol]-4-yl)-2-methoxyphenol, d_3

^{1}H (DMSO-d_6) δ 9.26 (s, 1H), 8.29 (d, J = 10.6 Hz, 2H), 8.10 (s, 1H), 7.80 (s, 1H), 7.46 (s, 1H), 7.42 (d, J = 7.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.21 (s, 2H), 3.81 (s, 3H). ^{13}C (DMSO-d_6)1-δ 55.72, 100.88, 112.30, 112.40, 113.52, 115.23, 116.65, 117.52, 124.52, 126.45, 136.85, 140.54, 146.77, 148.30, 152.64, 155.75, 158.23, 159.79, 160.95.

1.2.4. 6-(4'-(3-fluoro-4-methoxyphenyl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, d_4

^{1}H (DMSO-d_6/THF-d_8 4:3 vol.) δ 3.92 (s, 3H), 6.22 (s, 2H), 7.25 – 7.33 (m, 1H), 7.82 – 7.89 (m, 3H), 8.29 – 8.38 (m, 3H). ^{13}C (DMSO-d_6/THF-d_8 4:3 vol.) δ 55.90, 100.84, 112.00, 113.45, 113.61, 113.89, 115.99, 116.43, 122.47, 122.50, 124.52, 126.69, 126.74, 136.96, 140.48, 147.57, 147.65, 150.87, 152.80, 152.85, 154.48, 158.26, 160.27, 160.71.

1.2.5. 4-(benzo[d][1,3]dioxol-5-yl)-4'-(6-fluoropyridin-3-yl)-2,2'-bithiazole, d_6

^{1}H (DMSO-d_6) δ 6.07 – 6.12 (m, 2H), 7.04 (dd, J = 2.8, 7.9 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.59 (dd, J = 2.8, 10.5 Hz, 2H), 8.23 – 8.27 (m, 1H), 8.48 – 8.52 (m, 1H), 8.54 – 8.61 (m, 1H), 8.89 (s, 1H). ^{13}C (DMSO-d_6) δ 101.40, 106.40, 108.71, 109.85, 110.15, 115.85, 118.31, 120.32, 127.59, 127.90, 127.94, 139.75, 139.81, 145.23, 145.35, 147.64, 147.93, 151.42, 155.28, 159.80, 161.20, 161.84, 163.73.

1.2.6. 6-(4'-(6-fluoropyridin-3-yl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, d_8

^{1}H (DMSO-d_6/THF-d_8 4:3 vol.) δ 6.23 (s, 2H), 7.29 – 7.35 (m, 1H), 7.85 (d, J = 5.9 Hz, 1H), 8.34 – 8.40 (m, 2H), 8.54 (s, 1H), 8.61 (s, 1H), 8.93 (d, J = 3.9 Hz, 1H). ^{13}C (DMSO-d_6/THF-d_8 4:3 vol.) 1-δ 100.85, 109.59, 109.89, 112.02, 116.75, 118.24, 124.46, 127.97, 136.97, 139.55, 139.62, 140.49, 145.27, 145.40, 151.66, 152.93, 158.29, 160.42, 161.07, 162.03, 163.92.

1.2.7. 4-(4'-(2-fluoropyrimidin-5-yl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, d_{10}

^{1}H (DMSO-d_6/THF-d_8 4:3 vol.) δ 6.22 (s, 2H), 7.85 (d, J = 6.3 Hz, 1H), 8.38 (d, J = 11.8 Hz, 2H), 8.68 (s, 1H), 9.41 (s, 2H). ^{13}C (DMSO-d_6/THF-d_8 4:3 vol.) δ 100.87, 112.00, 116.97, 119.75, 124.42, 126.46, 137.01, 140.50, 148.63, 153.03, 158.32, 158.82, 158.91, 160.16, 161.18, 161.68, 162.90.

1.2.8. 2-(4'-([1,3]dioxolo[4,5-b]pyridin-6-yl)-[2,2'-bithiazol]-4-yl)pyrimidin-5-ol, d_{11}

^{1}H (DMSO-d_6) δ 6.23 (s, 2H), 7.84 (s, 1H), 8.33 (s, 2H), 8.47 (s, 3H), 10.74 (s, 1H). ^{13}C (DMSO-d_6) δ 100.81, 112.27, 116.90, 122.87, 124.42, 136.83, 140.49, 144.61, 150.96, 151.51, 152.62, 154.94, 158.20, 160.41, 160.84

1.2.9. 2-(4'-(benzo[d][1,3]dioxol-5-yl)-[2,2'-bithiazol]-4-yl)pyrimidin-5-ol, d_{12}

^{1}H (DMSO-d_6) δ 6.09 (s, 2H), 7.04 (d, J = 11.4 Hz, 1H), 7.56 – 7.62 (m, 2H), 8.23 (s, 1H), 8.43 – 8.49 (m, 3H), 10.74 (s, 1H). ^{13}C (DMSO-d_6) 2- δ 101.39, 106.43, 108.71, 115.67, 120.32, 122.65, 127.66, 144.60, 147.61, 147.93, 150.94, 151.54, 154.90, 155.18, 160.27, 160.63.

1.2.10. 4-(4'-([1,3]dioxolo[4,5-b]pyridin-6-yl)-[2,2'-bithiazol]-4-yl)-2-fluorophenol, d_{13}

^{1}H (DMSO-d_6) δ 6.22 (s, 2H), 7.05 (t, J = 8.8 Hz, 1H), 7.68 (dd, J = 2.0, 8.4 Hz, 1H), 7.75 – 7.84 (m, 2H), 8.22 (s, 1H), 8.31 (d, J = 1.9 Hz, 2H), 10.20 (s, 1H). ^{13}C (DMSO-d_6) δ 100.81, 112.22, 113.86, 114.01, 115.59, 116.74, 118.10, 118.13, 122.68, 122.71, 124.42, 125.21, 125.26, 136.80, 140.47, 145.37, 145.47, 150.21, 152.12, 152.61, 154.63, 154.65, 158.17, 160.04, 160.71.

1.2.11. 4-(4'-(benzo[d][1,3]dioxol-5-yl)-[2,2'-bithiazol]-4-yl)phenol, d_{14}

^{1}H (DMSO-d_6) δ 6.09 (s, 2H), 6.87 (d, J = 8.7 Hz, 2H), 7.01 – 7.07 (m, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.85 (d, J = 8.7 Hz, 2H), 8.10 (s, 1H), 8.22 (s, 1H), 9.74 (s, 1H). ^{13}C (DMSO-d_6) δ 101.39, 106.41, 108.71, 114.17, 115.37, 115.66, 120.30, 124.64, 127.67, 127.71, 147.60, 147.93, 155.15, 155.87, 157.94, 160.06, 160.36, 162.35.

1.2.12. 4-(4'-([1,3]dioxolo[4,5-b]pyridin-6-yl)-[2,2'-bithiazol]-4-yl)phenol, d_{15}

^{1}H (DMSO-d_6) δ 6.22 (s, 2H), 6.87 (dd, *J* = 2.8, 8.6 Hz, 2H), 7.80 – 7.87 (m, 3H), 8.11 (d, *J* = 2.7 Hz, 1H), 8.31 (t, *J* = 3.5 Hz, 2H), 9.76 (s, 1H). ^{13}C (DMSO-d_6) δ 100.84, 112.26, 114.42, 115.70, 116.63, 124.49, 124.62, 127.70, 136.82, 140.51, 152.60, 155.93, 157.98, 158.20, 159.85, 160.95.

1.2.13. 4-(4'-([1,3]dioxolo[4,5-b]pyridin-6-yl)-[2,2'-bithiazol]-4-yl)benzene-1,3-diol, d_{22}

^{1}H (DMSO-d6) δ 6.22 (s, 2H), 6.38 (dd, J = 2.3, 8.5 Hz, 1H), 6.45 (d, J = 2.3 Hz, 1H), 7.82 (d, J = 1.9 Hz, 1H), 7.91 (d, J = 8.5 Hz, 1H), 8.12 (s, 1H), 8.27 – 8.35 (m, 2H), 9.59 (s, 1H), 10.31 (s, 1H). ^{13}C (DMSO-d_6) δ 100.77, 102.91, 107.20, 111.52, 112.21, 116.41, 124.48, 129.77, 136.77, 140.44, 152.56, 152.91, 156.31, 158.13, 158.18, 158.63, 161.00.

1.3. ^{1}H and ^{13}C spectra of the fluoroethylated and fluoro- and iodoPEGylated DABTAs

1.3.1. 6-(4'-(5-(2-fluoroethoxy)pyrimidin-2-yl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, f_4

^{1}H (DMSO-d_6) δ 4.52 (d, J = 29.9 Hz, 2H), 4.82 (d, J = 48.5 Hz, 2H), 6.23 (s, 2H), 7.81 – 7.90 (m, 1H), 8.31 – 8.37 (m, 2H), 8.48 – 8.59 (m, 1H), 8.67 – 8.78 (m, 2H). ^{13}C (DMSO-d_6) δ 68.05, 68.20, 81.34, 82.67, 100.81, 112.26, 116.97, 123.84, 124.40, 136.83, 140.48, 144.37, 151.44, 152.65, 152.86, 154.53, 158.20, 160.60, 160.75.

1.3.2. 4-(benzo[d][1,3]dioxol-5-yl)-4'-(5-(2-fluoroethoxy)pyrimidin-2-yl)-2,2'-bithiazole, f_5

^{1}H (DMSO-d6) δ 4.48 (t, J = 3.6 Hz, 1H), 4.54 (t, J = 3.5 Hz, 1H), 4.77 (t, J = 5.0 Hz, 1H), 4.87 (t, J = 3.3 Hz, 1H), 6.09 (s, 2H), 7.04 (dd, J = 3.2, 8.2 Hz, 1H), 7.59 (dd, J = 3.1, 8.3 Hz, 2H), 8.24 (d, J = 3.3 Hz, 1H), 8.54 (s, 1H), 8.71 (s, 2H). ^{13}C (DMSO-d_6) δ 68.05, 68.20, 81.35, 82.67, 101.39, 106.43, 108.70, 115.73, 120.33, 123.61, 127.64, 144.35, 147.62, 147.92, 151.43, 152.89, 154.50, 155.21, 160.18, 160.82.

1.3.3. 4-(benzo[d][1,3]dioxol-5-yl)-4'-(5-(2-(2-fluoroethoxy)ethoxy)pyrimidin-2-yl)-2,2'-bithiazole, f_6

^{1}H (DMSO-d6) δ 3.71 (t, J = 3.7 Hz, 1H), 3.75 – 3.80 (m, 1H), 3.82 – 3.87 (m, 2H), 4.34 – 4.40 (m, 2H), 4.49 – 4.54 (m, 1H), 4.61 (t, J = 3.6 Hz, 1H), 6.10 (s, 2H), 7.04 (d, J = 15.6 Hz, 1H), 7.56 – 7.61 (m, 2H), 8.24 (s, 1H), 8.53 (s, 1H), 8.70

(s, 2H). ^{13}C (DMSO-d_6) δ 68.23, 68.81, 69.76, 69.91, 82.41, 83.72, 101.40, 106.43, 108.72, 115.74, 120.34, 123.48, 127.65, 144.30, 147.63, 147.93, 151.71, 152.68, 154.57, 155.22, 160.20, 160.80.

1.3.4. 4-(benzo[d][1,3]dioxol-5-yl)-4'-(5-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)pyrimidin-2-yl)-2,2'-bithiazole, f_7

^{1}H (DMSO-d_6) δ 3.56 – 3.67 (m, 5H), 3.67 – 3.71 (m, 1H), 3.79 – 3.84 (m, 2H), 4.33 – 4.38 (m, 2H), 4.44 – 4.50 (m, 1H), 4.54 – 4.59 (m, 1H), 6.10 (s, 2H), 7.01 – 7.07 (m, 1H), 7.59 (d, J = 7.7 Hz, 2H), 8.24 (s, 1H), 8.53 (s, 1H), 8.69 (s, 2H). ^{13}C (DMSO-d_6) δ 30.75, 68.25, 68.82, 69.66, 69.81, 69.85, 69.95, 82.43, 83.75, 101.41, 106.44, 108.72, 115.74, 120.33, 123.46, 127.65, 144.28, 147.63, 147.94, 151.73, 152.65, 154.58, 155.21, 160.21, 160.79.

1.3.5. 6-(4'-(5-(2-(2-fluoroethoxy)ethoxy)pyrimidin-2-yl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, f_8

^{1}H (DMSO-d_6) δ 3.69 – 3.74 (m, 1H), 3.75 – 3.80 (m, 1H), 3.82 – 3.88 (m, 2H), 4.35 – 4.41 (m, 2H), 4.49 – 4.54 (m, 1H), 4.58 – 4.64 (m, 1H), 6.23 (s, 2H), 7.85 (d, J = 1.9 Hz, 1H), 8.31 – 8.37 (m, 2H), 8.56 (s, 1H), 8.70 (s, 2H). ^{13}C (DMSO-d_6) δ 68.24, 68.82, 69.76, 69.91, 82.42, 83.74, 100.84, 112.29, 116.99, 123.73, 124.43, 136.85, 140.51, 144.32, 151.74, 152.66, 154.61, 158.22, 160.59, 160.79.

1.3.6. 6-(4'-(3-(2-(2-fluoroethoxy)ethoxy)-4-methoxyphenyl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, f_9

^{1}H (DMSO-d_6) δ 3.70 – 3.76 (m, 1H), 3.76 – 3.86 (m, 6H), 4.18 – 4.24 (m, 2H), 4.50 – 4.55 (m, 1H), 4.59 – 4.65 (m, 1H), 6.22 (s, 2H), 7.08 (d, J = 8.4 Hz, 1H), 7.57 – 7.64 (m, 2H), 7.82 (d, J = 1.9 Hz, 1H), 8.27 (s, 1H), 8.32 (d, J = 1.5 Hz, 2H). ^{13}C (DMSO-d_6) δ 55.60, 68.04, 69.05, 69.78, 69.93, 82.49, 83.80, 100.81, 111.19, 112.18, 112.22, 115.51, 116.66, 119.32, 124.44, 126.24, 136.80, 140.48, 148.10, 149.52, 152.59, 155.60, 158.17, 159.90, 160.80.

1.3.7. 6-(4'-(3-fluoro-4-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)phenyl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, f_{10}

^{1}H (DMSO-d_6) δ 3.71 (t, J = 3.7 Hz, 1H), 3.75 – 3.80 (m, 1H), 3.82 – 3.87 (m, 2H), 4.34 – 4.40 (m, 2H), 4.49 – 4.54 (m, 1H), 4.61 (t, J = 3.6 Hz, 1H), 6.10 (s, 2H), 7.04 (d, J = 15.6 Hz, 1H), 7.56 – 7.61 (m, 2H), 8.24 (s, 1H), 8.53 (s, 1H), 8.70 (s, 2H). ^{13}C (DMSO-d_6) δ 68.23, 68.81, 69.76, 69.91, 82.41, 83.72, 101.40, 106.43, 108.72, 115.74, 120.34, 123.48, 127.65, 144.30, 147.63, 147.93, 151.71, 152.68, 154.57, 155.22, 160.20, 160.80.

1.3.8. 4-(benzo[d][1,3]dioxol-5-yl)-4'-(4-(2-fluoroethoxy)phenyl)-2,2'-bithiazole, f_{11}

^{1}H (DMSO-d_6) δ 4.24 – 4.29 (m, 1H), 4.30 – 4.35 (m, 1H), 4.70 – 4.75 (m, 1H), 4.80 – 4.85 (m, 1H), 6.09 (s, 2H), 7.04 (d, J = 7.9 Hz, 1H), 7.09 (d, J = 8.9 Hz, 2H), 7.59 (d, J = 8.2 Hz, 2H), 7.97 (d, J = 8.8 Hz, 2H), 8.22 (d, J = 4.5 Hz, 2H). ^{13}C (DMSO-d_6) δ 67.09, 67.24, 81.53, 82.86, 101.40, 106.41, 108.71, 114.87, 115.17, 115.46, 120.31, 126.48, 127.65, 127.70, 147.60, 147.93, 155.18, 155.30, 158.46, 160.27.

1.3.9. 6-(4'-(4-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)phenyl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, f_{12}

^{1}H (DMSO-d6) δ 3.56 – 3.61 (m, 2H), 3.61 – 3.66 (m, 3H), 3.66 – 3.72 (m, 1H), 3.75 – 3.81 (m, 2H), 4.13 – 4.18 (m, 2H), 4.45 – 4.50 (m, 1H), 4.54 – 4.60 (m, 1H), 6.23 (s, 2H), 7.03 – 7.10 (m, 2H), 7.83 (d, J = 1.8 Hz, 1H), 7.92 – 7.99 (m, 2H), 8.22 (s, 1H), 8.32 (d, J = 2.4 Hz, 2H). ^{13}C (DMSO-d_6) δ 67.24, 68.97, 69.67, 69.82, 69.87, 69.97, 82.43, 83.75, 100.82, 112.24, 114.83, 115.25, 116.69, 124.45, 126.13, 127.61, 136.81, 140.49, 152.62, 155.43, 158.18, 158.82, 160.00, 160.85.

1.3.10. 6-(4'-(5-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)pyrimidin-2-yl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, f_{13}

^{1}H (DMSO-d_6) δ 3.58 – 3.64 (m, 5H), 3.66 – 3.71 (m, 1H), 3.79 – 3.84 (m, 2H), 4.33 – 4.39 (m, 2H), 4.44 – 4.50 (m, 1H), 4.54 – 4.59 (m, 1H), 6.23 (s, 2H), 7.84 (d, *J* = 1.8 Hz, 1H), 8.33 (d, *J* = 1.9 Hz, 1H), 8.34 (s, 1H), 8.55 (s, 1H), 8.69 (s, 2H). ^{13}C (DMSO-d_6) δ 68.27, 68.83, 69.67, 69.82, 69.87, 69.96, 82.44, 83.76, 100.84, 112.29, 116.99, 123.71, 124.43, 136.85, 140.51, 144.31, 151.76, 152.63, 152.66, 154.62, 158.22, 160.59, 160.79.

1.3.11. 4-(benzo[d][1,3]dioxol-5-yl)-4'-(3-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)-4-methoxyphenyl)-2,2'-bithiazole, f_{14}

^{1}H (DMSO-d_6) δ 3.60 (dt, *J* = 2.0, 6.0 Hz, 2H), 3.61 – 3.67 (m, 3H), 3.67 – 3.72 (m, 1H), 3.77 – 3.84 (m, 5H), 4.17 – 4.23 (m, 2H), 4.43 – 4.49 (m, 1H), 4.52 – 4.59 (m, 1H), 6.10 (s, 2H), 7.01 – 7.06 (m, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.65 (m, 4H), 8.24 (d, *J* = 11.8 Hz, 2H). ^{13}C (DMSO-d_6) δ 55.59, 68.01, 69.05, 69.68, 69.83, 69.90, 69.98, 82.44, 83.76, 101.41, 106.41, 108.73, 111.13, 112.16, 115.30, 115.45, 119.27, 120.30, 126.28, 127.70, 147.61, 147.94, 148.14, 149.48, 155.17, 155.58, 160.15, 160.25.

1.3.12. 4-(benzo[d][1,3]dioxol-5-yl)-4'-(5-methoxypyrimidin-2-yl)-2,2'-bithiazole, f_{15}

^{1}H (DMSO-d_6) δ 3.99 (s, 3H), 6.10 (s, 2H), 7.02 – 7.08 (m, 1H), 7.57 – 7.63 (m, 2H), 8.25 (s, 1H), 8.54 (s, 1H), 8.68 (s, 2H). ^{13}C (DMSO-d_6) δ 56.29, 101.39, 106.42, 108.71, 115.72, 120.32, 123.44, 127.64, 143.85, 147.62, 147.93, 152.30, 152.65, 154.58, 155.20, 160.19, 160.79.

1.3.13. 5-(4'-(5-methoxypyrimidin-2-yl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, f_{16}

^{1}H (DMSO-d_6) δ 4.01 (s, 3H), 6.22 (s, 2H), 7.85 (d, *J* = 3.8 Hz, 1H), 8.33 – 8.43 (m, 2H), 8.53 (t, *J* = 2.9 Hz, 1H), 8.68 (t, *J* = 3.0 Hz, 2H). ^{13}C (DMSO-d_6) δ 56.44, 100.03, 111.31, 117.52, 120.71, 123.64, 140.92, 142.11, 142.22, 148.29, 150.03, 151.62, 153.87, 153.89, 160.40, 161.89.

1.3.14. 6-(4'-(4-methoxyphenyl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, f_{17}

^{1}H (DMSO-d_6) δ 3.82 (s, 3H), 6.23 (s, 2H), 7.03 – 7.09 (m, 2H), 7.84 (d, *J* = 1.9 Hz, 1H), 7.94 – 7.99 (m, 2H), 8.22 (s, 1H), 8.33 (d, *J* = 2.6 Hz, 2H). ^{13}C (DMSO-d_6) δ 55.28, 100.83, 112.25, 114.34, 115.26, 116.70, 118.19, 124.46, 126.09, 127.61, 136.81, 140.50, 152.62, 155.47, 158.20, 159.60, 160.01, 160.86.

1.3.15. 6-(4'-(3,4-dimethoxyphenyl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, f_{18}

^{1}H (DMSO-d_6) δ 3.71 (s, 1H), 3.83 (s, 4H), 6.23 (s, 3H), 7.07 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.84 (d, *J* = 1.9 Hz, 1H), 8.28 (s, 1H), 8.32 – 8.37 (m, 3H).

1.3.16. 6-(4'-(2,4-dimethoxyphenyl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, f_{19}

^{1}H (DMSO-d_6) δ 3.84 (s, 3H), 3.95 (s, 3H), 6.23 (s, 2H), 6.67 – 6.74 (m, 2H), 7.83 (d, *J* = 2.0 Hz, 1H), 8.09 – 8.17 (m, 2H), 8.29 – 8.34 (m, 2H). ^{13}C (DMSO-d_6) δ 55.41, 55.73, 98.66, 100.82, 105.61, 112.24, 114.79, 116.54, 118.28, 124.49, 130.21, 136.79, 140.49, 151.52, 152.58, 157.88, 158.17, 158.32, 160.68, 161.06.

1.3.17. 6-(4'-(2,4-bis(2-(2-fluoroethoxy)ethoxy)phenyl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, f_{20}

^{1}H (DMSO-d_6) δ 3.68 – 3.86 (m, 6H), 3.89 – 3.97 (m, 2H), 4.17 – 4.23 (m, 2H), 4.25 – 4.35 (m, 2H), 4.47 – 4.59 (m, 2H), 4.59 – 4.68 (m, 2H), 6.23 (s, 2H), 6.68 – 6.81 (m, 2H), 7.83 (d, *J* = 1.9 Hz, 1H), 8.14 (d, *J* = 8.7 Hz, 1H), 8.26 – 8.34 (m, 3H). ^{13}C (DMSO-d_6) δ 67.33, 67.51, 68.77, 68.98, 69.63, 69.77, 69.92, 82.47, 83.79, 100.01, 100.81, 106.49, 112.24, 115.08, 116.53, 118.19, 124.49, 130.15, 136.79, 140.49, 151.55, 152.58, 157.00, 158.17, 158.22, 159.73, 161.07.

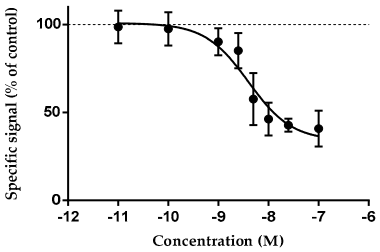
1.3.18. 6-(4'-(5-(2-(2-(2-iodoethoxy)ethoxy)ethoxy)pyrimidin-2-yl)-[2,2'-bithiazol]-4-yl)-[1,3]dioxolo[4,5-b]pyridine, h_{13}

^{1}H (DMSO-d_6) δ 3.33 (d, *J* = 6.4 Hz, 2H), 3.58 – 3.70 (m, 6H), 3.78 – 3.86 (m, 2H), 4.33 – 4.40 (m, 2H), 6.23 (s, 2H), 7.85 (d, *J* = 1.8 Hz, 1H), 8.31 – 8.37 (m, 2H), 8.55 (s, 1H), 8.70 (d, *J* = 2.6 Hz, 2H). ^{13}C (DMSO-d_6) δ 5.51, 68.28, 68.85, 69.34, 69.96, 71.02, 100.83, 112.28, 116.98, 123.70, 124.42, 136.84, 140.50, 144.32, 151.76, 152.61, 152.65, 154.62, 158.21, 160.57, 160.78.

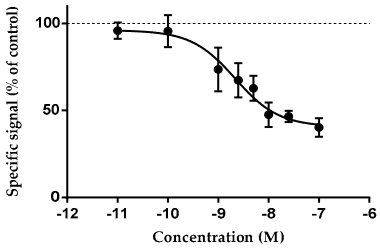
2. Competition binding assays with [^{3}H]DCVJ

2.1. Alpha-synuclein fibrils

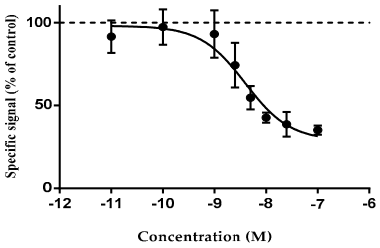
d_2



d_4



d_6



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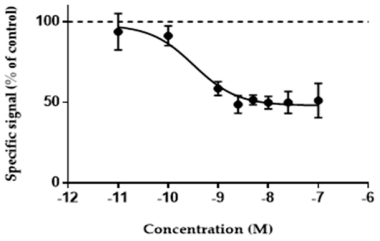


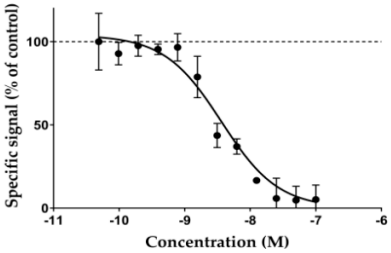
d_{10}

f_4

f_5

f_6

f_7



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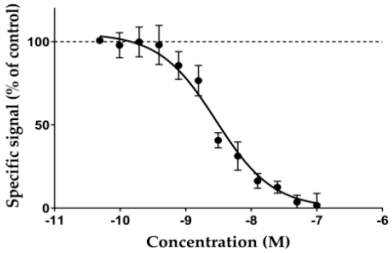


f_{10}

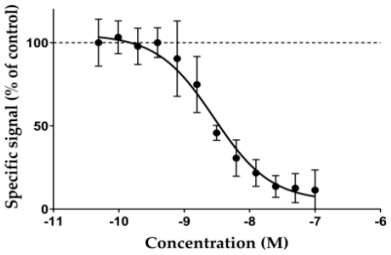
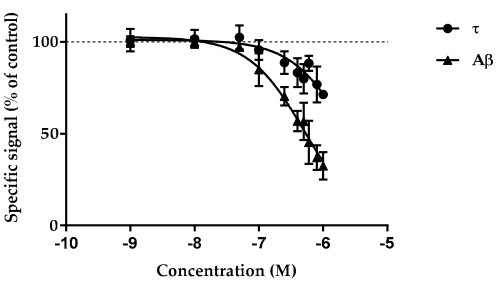


Figure S1. α-Syn displacement binding curves of the some DABTAs against [^{3}H]DCVJ

2.2. Beta-amyloid and tau fibrils

d_2



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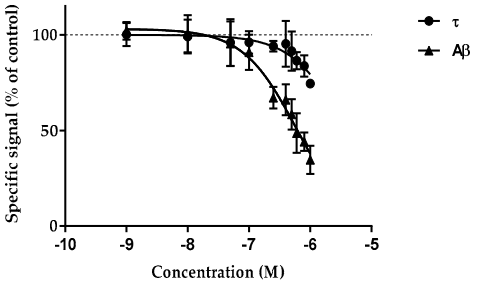

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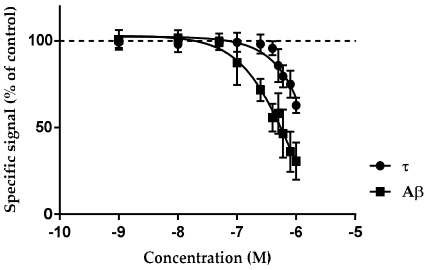

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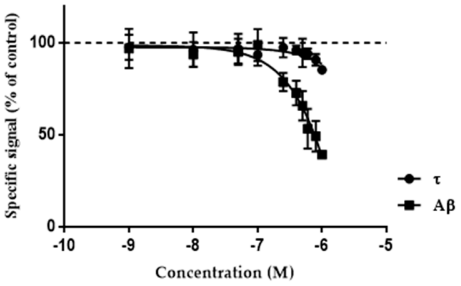


d_{10}

f_4

f_5

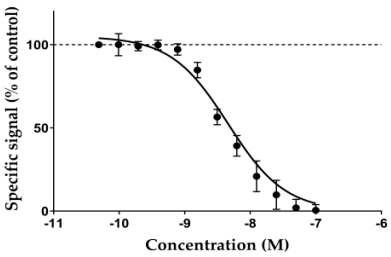
f_6

Figure S2. β-amyloid and tau fibrils displacement binding curves of the some DABTAs against [^{3}H]DCVJ

3. Competition binding assays with [^{3}H]PIB

3.1. Alpha-synuclein fibrils

d_2



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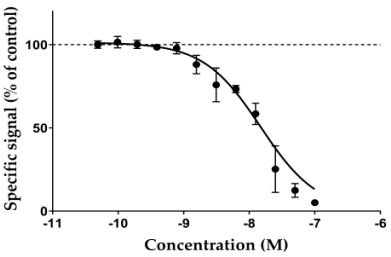

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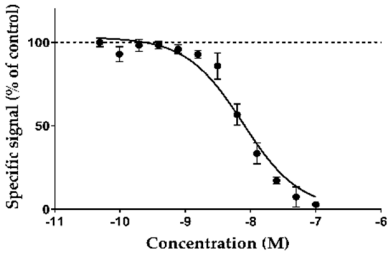
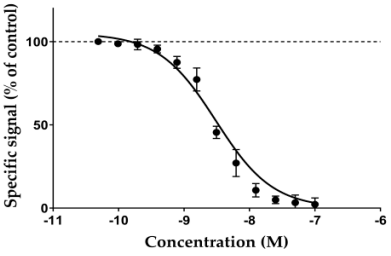
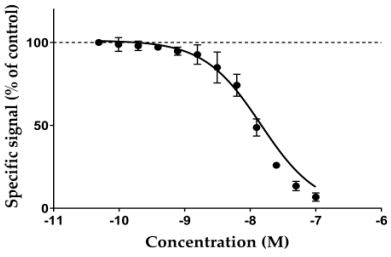


d_8



d_{10}



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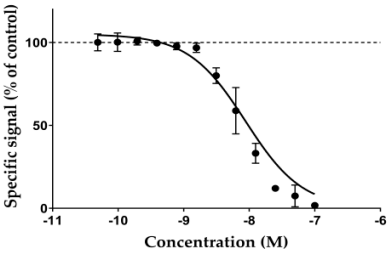

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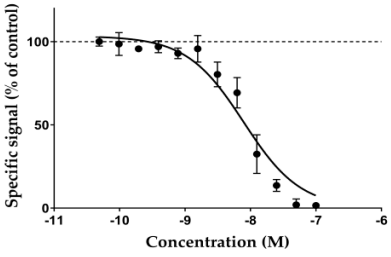

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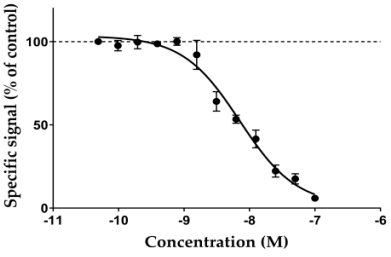

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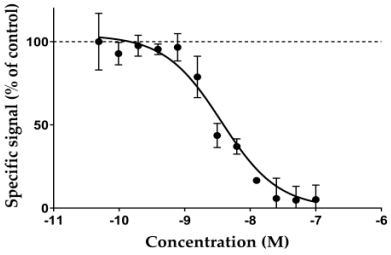

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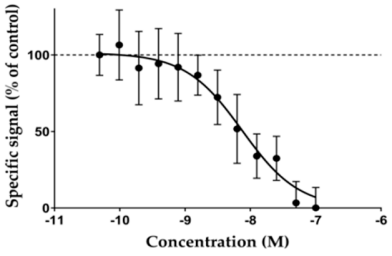

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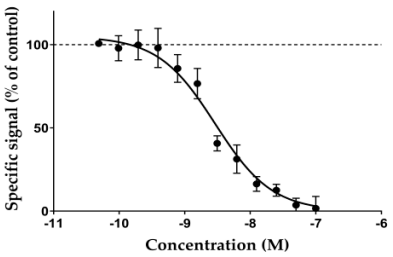

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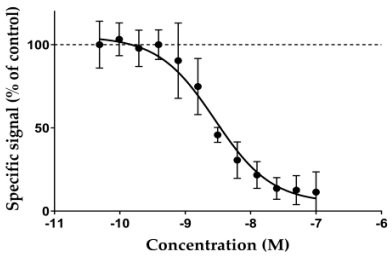

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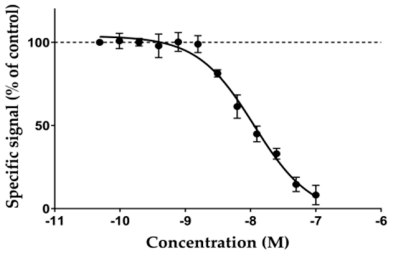

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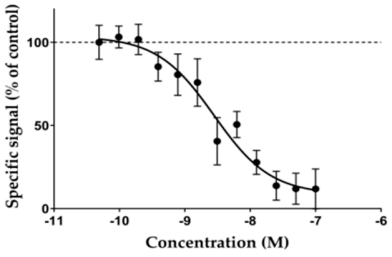

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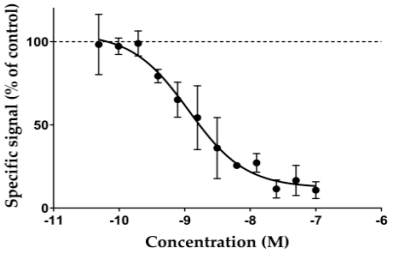

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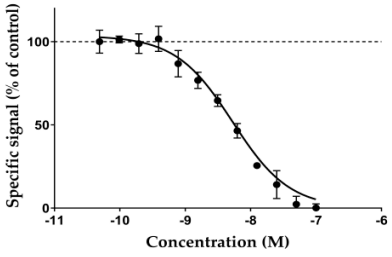

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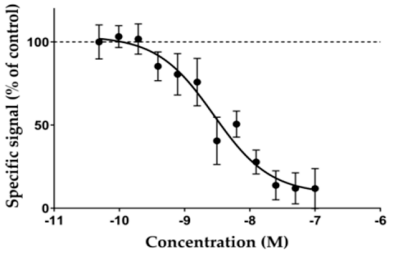

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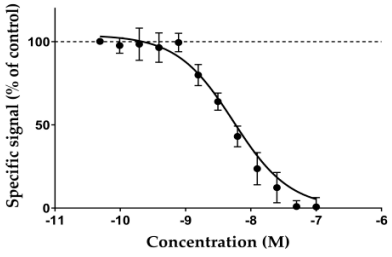

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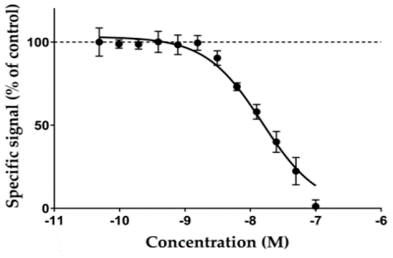

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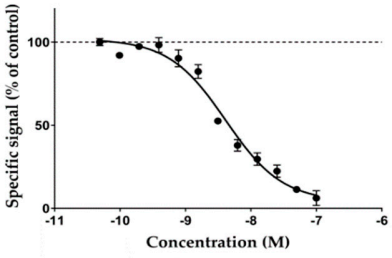
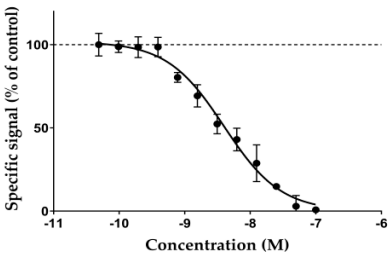


f_{20}



h_{13}

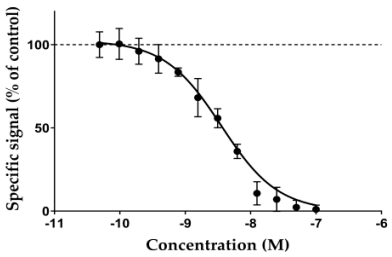
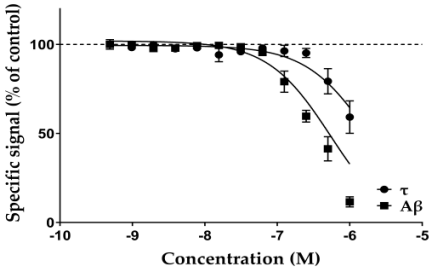


Figure S3. α-Syn displacement binding curves of the all the DABTAs against [^{3}H]PIB

3.2. Beta-amyloid and tau fibrils

d_2



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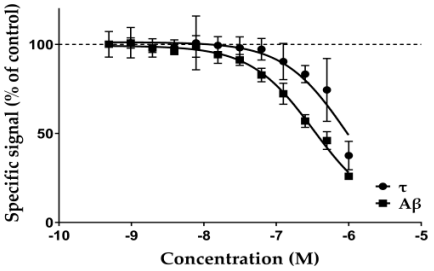
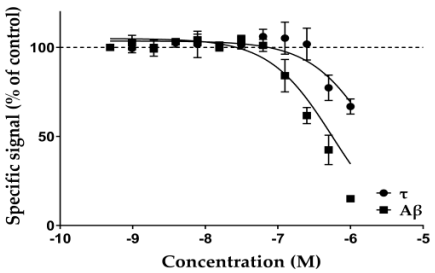


d_6



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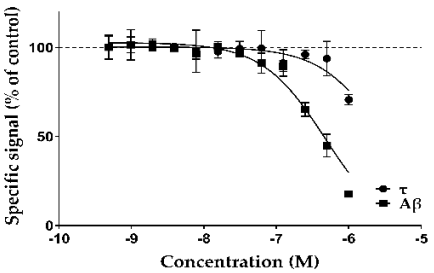

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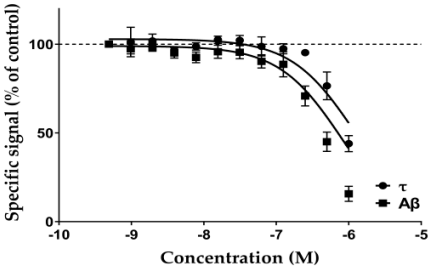

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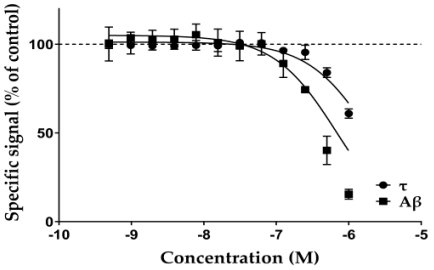

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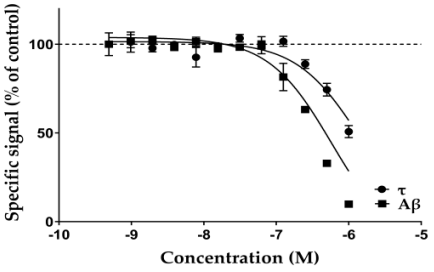

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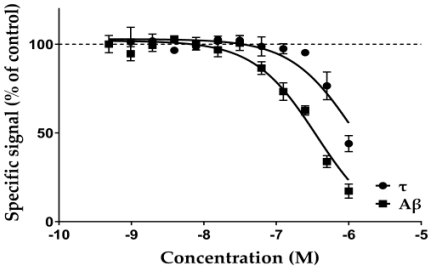

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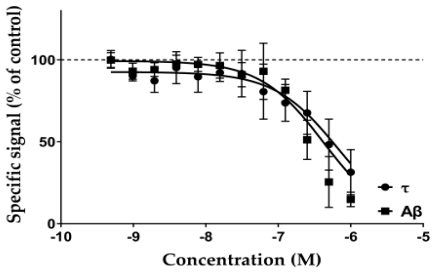

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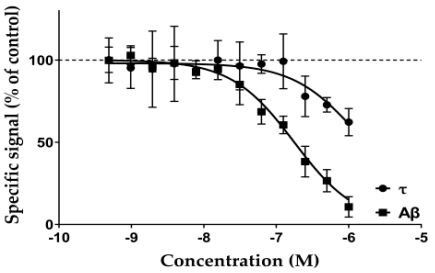

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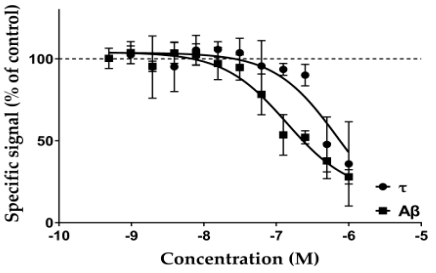

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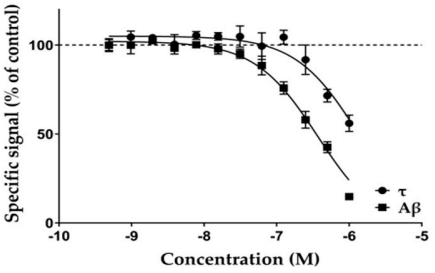

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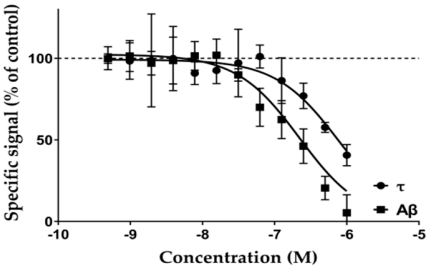

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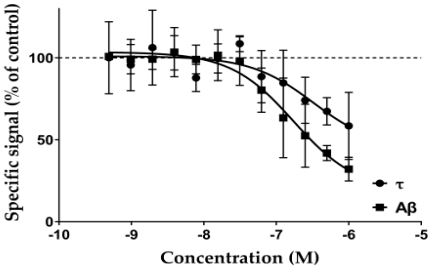

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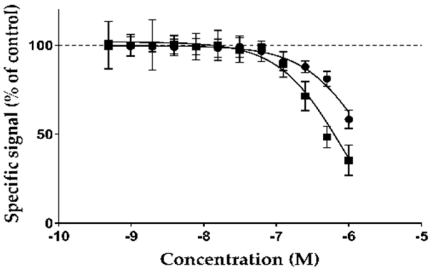

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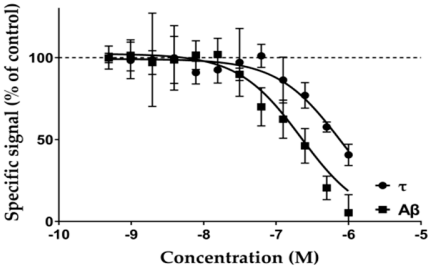

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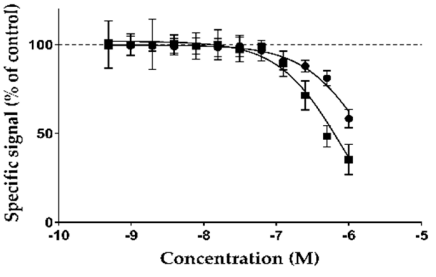

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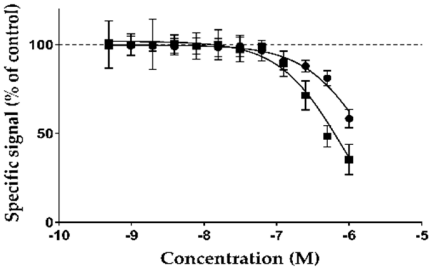

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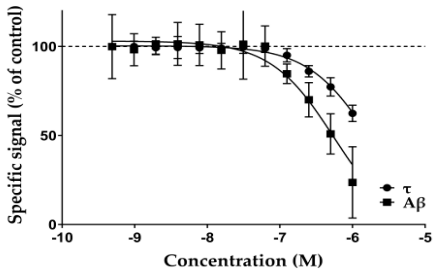

Figure S4. β-amyloid and tau fibrils displacement binding curves all the DABTAs against [^{3}H]PIB

4. In silico studies

	Average over 100-ns				Averaged over top-50 snapshots			
	Site 1	Site 2	Site 3	Site 4	Site 1	Site 2	Site 3	Site 4
f4	8.3	8.7	2.8	14.1	14.5	14.3	5.2	21.5
f5	4.3	8.1	2.7	10.9	8.5	17.9	3.5	22.5
f6	11.3	7.1	3.5	4.6	14.9	13.9	5.5	7.3
f7	10.4	9.7	2.9	5.2	18.6	14.6	4.3	7.2
f8	7.0	10.0	4.6	10.4	8.7	16.0	11.1	19.4
f9	6.1	5.9	3.7	13.5	10.9	8.0	4.8	21.5
f10	5.7	11.5	4.5	11.7	11.9	16.1	5.7	18.8
f11	5.7	10.6	3.5	2.3	13.3	23.1	5.0	3.2
f12	5.4	9.7	4.5	7.7	9.2	16.7	5.2	12.2
f13	7.5	10.0	2.5	8.6	10.9	12.7	3.2	13.7
f14	10.7	7.2	4.9	8.5	16.9	15.8	6.3	12.5
f15	7.5	9.7	4.3	5.5	12.6	15.7	7.7	8.7
f16	6.2	6.1	4.5	15.7	17.3	10.6	5.7	25.7
f17	6.6	4.3	6.3	8.4	15.4	8.6	9.5	11.6
f18	7.1	12.1	2.3	8.9	11.8	17.1	3.9	18.5
f19	5.6	5.7	2.1	4.7	12.4	9.1	3.8	10.7
f20	6.4	7.9	3.8	6.2	8.5	13.1	4.7	8.9
h13	7.5	4.8	5.3	14.8	11.3	11.3	6.1	24.7
d2	7.4	8.1	2.6	14.0	13.4	11.3	3.4	22.0
d4	9.9	3.1	3.4	4.7	16.6	7.7	4.6	7.0
d6	4.6	11.6	7.9	5.1	7.9	23.3	10.2	15.3
d8	9.0	11.8	3.4	11.6	17.1	21.3	4.2	18.8
d10	7.4	5.0	3.0	20.6	13.1	8.9	4.8	26.9

Figure S5. Root mean square deviations (RMSDs) of ligand (non-hydrogen atoms) in the 23x4 trajectories

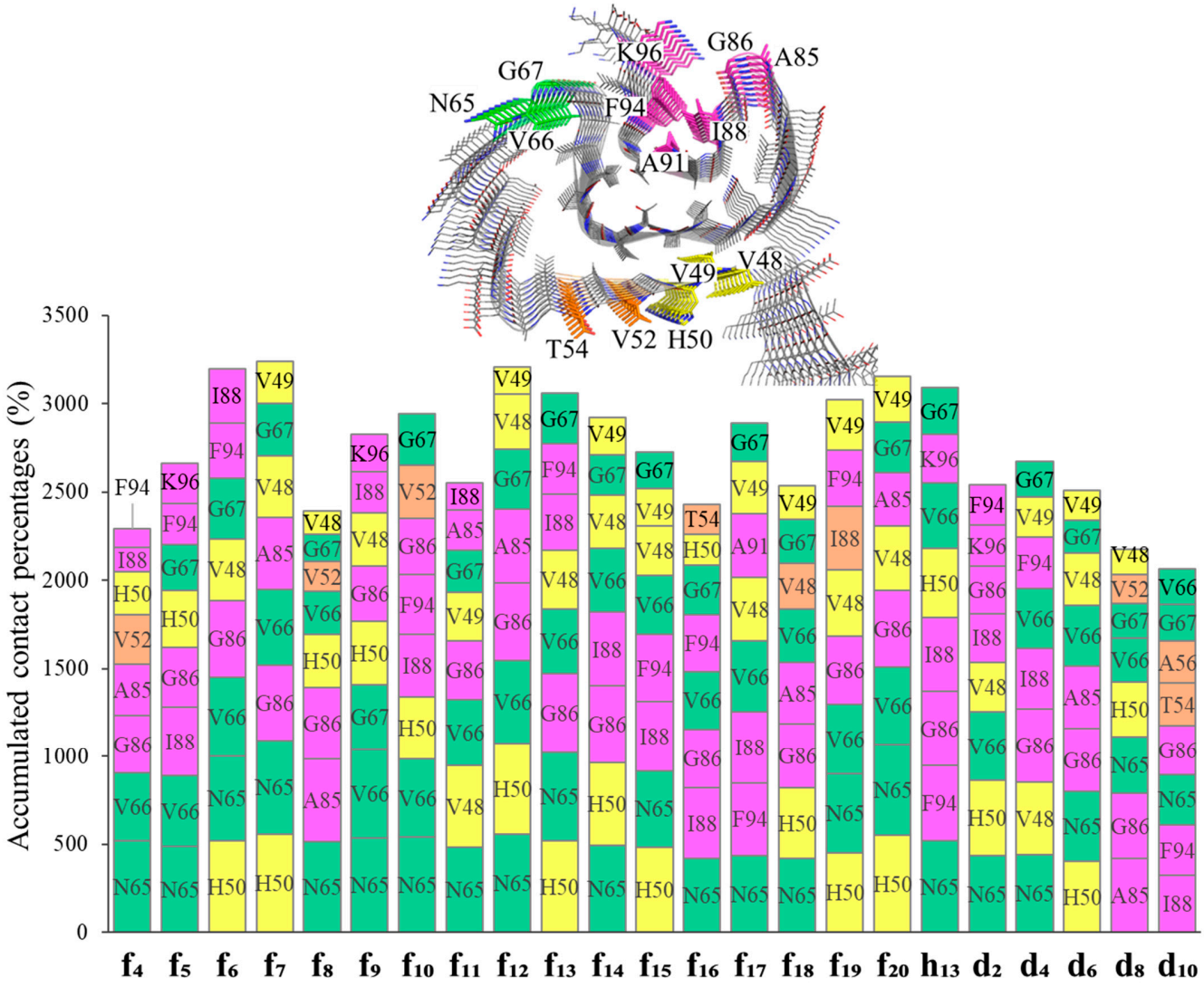

Figure S6. Top-8 most contacted surface residues for each compound on α-Syn protofibril throughout 69 (23 compounds * 3 initial surface sites) 100-ns MD simulations.

4.1. Molecular docking and binding free energy calculations

We adopted the binding sites detected from our previous study with the labels of sites 1-4 [1], in which site-3 is the inner cavity site. The 9-chain protofibril, as it is in the PDB structure, was used and prepared as descripted in previous work [1]. The Glide module in Schrödinger Suite (version 2021-4) was used with the grid center setting to the geometrical center of the residues on the fifth chain of α-Syn protofibril (PDB: 2N0A). To define the grid centers for docking, the geometrical center of the key fifth-chain's residues was adopted for each site, i.e. G67, G68 and K97 for site-1, G86, I88, F94 and K96 for site-2, E61, T72, G73, A53, V55, T59 and E61 for site-3, and K45, V48 and H50 for site-4. The grid size is assigned to 20 Å.

The docked complexes were subjected to the Prime module implemented in Schrödinger Suite (version 2021-4) for MM/GBSA (molecular mechanics, the generalized Born model, and solvent accessibility) binding free energy calculations. The residues within 8 Å of ligand atoms were energy-minimized by the OPLS4 force field in a VSGB (variable dielectric surface generalized Born) continuum solvation model.

4.2. Molecular dynamics simulations

Molecular dynamics (MD) simulations were carried out for the 92 complexes (23 ligands on each of the 4 sites). 100-ns MD simulation was performed for each complex using the Desmond package (version 2021-4) with the similar parameterization of settings to our previous work [2]. Briefly, the OPLS4 force field was used for all the atoms in a solvation box with 10 Å buffering area to the protofibril, which is filled by numbers of sodium/chloride ions (for charge neutralization and a salt concentration of 0.15 M). The Nose-Hoover thermostat and Martyna-Bobias-Klein barostat models were used to maintain the simulations in the NPT ensemble at 300K and 1 atm. Visual Molecular Dynamics (VMD, version 1.9.4a57) and the simulation interaction diagram scripts (implemented in Schrödinger Suite) were used to analyze the trajectories of each system.

References

1. Kuang, G.; Murugan, N.A.; Ågren, H. Mechanistic Insight into the Binding Profile of DCVJ and α-Synuclein Fibril Revealed by Multiscale Simulations. *ACS Chem. Neurosci.* **2019**, *10*, 610–617, doi:10.1021/acschemneuro.8b00465.
2. Li, J.; Kumar, A.; Långström, B.; Nordberg, A.; Ågren, H. Insight into the Binding of First- and Second-Generation PET Tracers to 4R and 3R/4R Tau Protofibrils. *ACS Chem. Neurosci.* **2023**, *14*, 3528–3539, doi:10.1021/acschemneuro.3c00437.