Supporting Information

_Cis_-glycofused benzopyran compounds as new amyloid β peptide ligands

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Synthesis

General Remarks

All solvents were dried with molecular sieves for at least 24 h prior to use. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates (Merck) with detection using UV light when possible, or by charring with a solution of concd. H₂SO₄/EtOH/H₂O (5:45:45) or a solution of (NH₄)₆Mo₇O₂₄ (21 g), Ce(SO₄)₂ (1 g), concd. H₂SO₄ (31 mL) in water (500 mL). Flash column chromatography was performed on silica gel 230-400 mesh (Merck). ¹H and ¹³C NMR spectra were recorded at 25 °C unless otherwise stated, with a Varian Mercury 400 MHz instrument. Chemical shift assignments, reported in ppm, are referenced to the corresponding solvent peaks. HRMS were recorded on a QSTAR elite LC/MS/MS system with a nanospray ion source. Optical rotations were measured at room temperature using an Atago Polax-2L polarimeter and are reported in units of 10⁻¹ deg·cm²·g⁻¹.


A mixture containing the appropriate O-hydroxybenzaldehyde (1-7) (2.5 equiv.), trimethylorthoformiate (2.5 equiv.) and scandium triflate (3% mol) in CH₂Cl₂ is stirred at r.t. for 20 min. The mixture is then cooled at 0°C and the appropriate tri-O-benzyl glycal (8-9) is added. The reaction is then left stirring at r.t. for 30 min. The reaction is then diluted with CH₂Cl₂, washed with water, dried over Na₂SO₄, filtrated and the solvent is removed under reduced pressure. The crude is purified by flash chromatography (eluent Toluene/AcOEt 9.75/0.25) to afford pure compounds 10-19.
(2R,3R,4R,4aS,5R/S,10aR)-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-methoxy-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene (10): yield 59%, C5 R/S 92/8

(5R)

\[\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{)} \delta 7.55 (d, J = 7.6 Hz, 1H, H6), 7.37 – 7.22 (m, 15H, Ar), 7.23 – 7.15 (m, 1H, H8), 6.99 (t, J = 7.5 Hz, 1H, H7), 6.83 (d, J = 8.1 Hz, 1H, H9), 5.66 (d, J = 2.9 Hz, 1H, H10a), 4.96 (d, J = 11.4 Hz, 1H, OCH}_2\text{Ph}), 4.77 (d, J = 4.3 Hz, 1H, H5), 4.62 – 4.31 (m, 5H, OCH}_2\text{Ph}), 4.18 (t, J = 6.4 Hz, 1H, H2), 3.79 (s, 1H, H3), 3.68 – 3.63 (m, 1H, H4), 3.63 – 3.59 (m, 2H, CH}_2\text{O}), 3.58 (s, 3H, OMe), 3.37 – 3.26 (m, 1H, H4a); \text{\textsuperscript{13}C NMR (101 MHz, CDCl}_3\text{)} \delta 152.27, 139.03, 138.89, 138.15, 129.12, 128.62, 128.44, 128.41, 128.38, 128.13, 128.01, 127.95, 127.77, 127.55, 126.26, 122.43, 121.38, 115.59, 97.74, 76.22, 75.62, 75.16, 73.97, 73.71, 72.78, 71.71, 69.13, 57.10, 34.72. [\alpha]_D^{20} = +5.3 (c=1, CHCl}_3). \text{MS: m/z calcd for [M + Na]^+ = 575.2, [M + K]^+ = 591.2; found [M + Na]^+ = 575.3, [M + K]^+ = 591.3.}

(5S)

\[\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{)} \delta 7.39 – 7.24 (m, 13H, Ar), 7.24 – 7.20 (m, 1H, H6), 7.18 (dd, J = 7.0, 2.2 Hz, 2H, Ar), 7.07 (d, J = 7.4 Hz, 1H, H8), 6.88 (m, 2H, H7, H9), 5.71 (d, J = 3.2 Hz, 1H, H10a), 4.92 (d, J = 11.5 Hz, 1H, OCH}_2\text{Ph}), 4.54 (ddd, J = 34.5, 23.4, 11.7 Hz, 5H, OCH}_2\text{Ph}), 4.40 (d, J = 2.1 Hz, 1H, H5), 4.20 (M, 1H, H2), 3.98 (s, 1H, H3), 3.72 – 3.64 (m, 2H, CH}_2\text{O), 3.37 (s, 3H, OMe), 3.32 (dd, J = 11.8, 2.4 Hz, 1H, H4), 3.06 – 2.98 (m, 1H, H4a). \text{\textsuperscript{13}C NMR (101 MHz, CDCl}_3\text{)} \delta 153.89, 138.79, 138.09, 137.76, 131.20, 130.35, 128.67, 128.64, 128.50, 128.25, 128.21, 128.03, 128.01, 127.85, 127.83, 120.81, 118.54, 116.96, 95.00, 75.17, 74.79, 74.77, 73.79, 71.62, 71.53, 71.52, 68.94, 56.38, 37.70, 29.93. [\alpha]_D^{20} = +8.7 (c=1, CHCl}_3). \text{MS: m/z calcd for [M + Na]^+ = 575.2, [M + K]^+ = 591.2; found [M + Na]^+ = 575.3, [M + K]^+ = 591.3.}
(2R,3R,4R,4aR,5R,10aR)-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-methoxy-7-nitro-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene (11): yield 40%, C5 R/S 100/0

\[
\begin{align*}
\text{H NMR} & (400 \text{ MHz, CDCl}_3) \delta 8.44 - 8.41 (m, 1H, H6), 8.08 (dd, J = 9.0, 2.8 Hz, 1H, H8), 7.43 - 7.17 (m, 15H, Ar), 6.87 (d, J = 9.0 Hz, 1H, H9), 5.73 (d, J = 2.9 Hz, 1H, H10a), 4.96 (d, J = 11.3 Hz, 1H, OCH}_2\text{Ph}), 4.73 (t, J = 7.4 Hz, 1H, H5), 4.64 - 4.36 (m, 5H, OCH}_2\text{Ph}), 4.11 (t, J = 6.4 Hz, 1H, H2), 3.86 (s, 1H, H3), 3.64 (dd, J = 9.2, 5.8 Hz, 2H, CH}_2\text{O}), 3.59 (d, J = 7.4 Hz, 3H, OMe), 3.50 (dd, J = 11.1, 2.5 Hz, 1H, H4), 3.41 - 3.32 (m, 1H, H4a). \text{^13C NMR} (101 \text{ MHz, CDCl}_3) \delta 157.58, 142.33, 138.72, 138.01, 137.95, 128.68, 128.53, 128.42, 128.39, 128.23, 128.18, 128.08, 127.94, 127.81, 125.33, 123.31, 123.21, 116.20, 98.87, 75.28, 75.23, 74.68, 73.83, 73.02, 72.39, 72.13, 68.95, 57.10, 33.96. [\alpha]_D^{20} = -4.5 \text{ (c=1, CHCl}_3). \text{MS: m/z calcd for [M + H]^+ = 598.2, [M + Na]^+ = 620.2, [M + K]^+ = 636.2; found [M + H]^+ = 598.3, [M + Na]^+ = 620.4, [M + K]^+ = 636.4.}
\end{align*}
\]

(2R,3R,4R,4aR,5R,10aR)-3,4,7-tris(benzyloxy)-2-benzyloxymethyl-5-methoxy-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene (12): yield 35%, C5 R/S 100/0

\[
\begin{align*}
\text{H NMR} & (400 \text{ MHz, CDCl}_3) \delta 7.52 - 7.25 (m, 20H, Ar), 7.23 (d, J = 2.2 Hz, 1H, H6), 6.86 (dd, J = 8.8, 3.0 Hz, 1H, H8), 6.81 - 6.74 (m, 1H, H9), 5.64 (d, J = 2.9 Hz, 1H, H10a), 5.10 - 4.95 (m, 3H, OCH}_2\text{Ph}), 4.76 (d, J = 4.4 Hz, 1H, H5), 4.64-4.34 (m, 5H, OCH}_2\text{Ph}), 4.20 (t, J = 6.5 Hz, 1H, H2), 3.83 (s, 1H, H3), 3.67 (dd, J = 11.1, 2.6 Hz, 1H, H4), 3.65 - 3.61 (m, 2H, CH}_2\text{O}), 3.58 (s, 3H, OMe), 3.36 - 3.25 (m, 1H, H4a). \text{^13C NMR} (101 \text{ MHz, CDCl}_3) \delta 149.98, 139.05, 138.93, 138.16, 130.59, 129.64, 128.61, 128.43, 128.40, 128.36, 128.13, 127.97, 127.94, 127.75, 127.52, 126.52, 121.97, 115.37, 97.62, 76.33, 75.66, 75.16, 73.93, 73.71, 72.69, 71.65, 69.15, 57.11, 34.78, 20.99. [\alpha]_D^{20} = -5.5 \text{ (c=1, CHCl}_3); \text{MS: m/z calcd for [M + Na]^+ = 681.3, [M + K]^+ = 697.3; found [M + Na]^+ = 681.5, [M + K]^+ = 697.4.}
\end{align*}
\]
(2R,3R,4R,4aR,5R/S,10aR)-3,4-bis(benzyloxy)-2-benzyloxymethyl-5,7-dimethoxy-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene (13): yield 73%, C5 R/S 85/15

(5R)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.37 – 7.21 (m, 15H, Ar), 7.11 (d, $J$ = 0.9 Hz, 1H, H6), 6.76 (d, 2H, H8 and H9), 5.61 (d, $J$ = 2.9 Hz, 1H, H10a), 4.96 (d, $J$ = 11.4 Hz, 1H, OCH$_2$Ph), 4.74 (d, $J$ = 4.4 Hz, 1H, H5), 4.60-4.36 (m, 5H, OCH$_2$Ph), 4.18 (t, $J$ = 6.4 Hz, 1H, H2), 3.80 (s, 4H, ArOMe and H3), 3.66 (dd, $J$ = 11.1, 2.6 Hz, 1H, H4), 3.61 (dt, $J$ = 7.0, 3.4 Hz, 2H, CH$_2$O), 3.57 (s, 3H, OMe), 3.33 – 3.24 (m, 1H, H4a). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 154.39, 146.10, 139.05, 138.92, 138.16, 128.62, 128.44, 128.38, 128.14, 127.97, 127.95, 127.76, 127.54, 123.12, 116.33, 115.18, 110.81, 97.61, 75.76, 75.16, 73.92, 73.72, 72.77, 71.65, 69.14, 57.07, 56.06, 34.72. $\left[\alpha\right]_D^{20} = +7.1$ (c=1, CHCl$_3$); MS: m/z calcd for [M + K]$^+$ = 621.2; found [M + K]$^+$ = 621.5.

(5S)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.15 (m, 15H, Ar), 6.84 – 6.76 (m, 2H, H8 and H9), 6.58 (s, 1H, H6), 5.64 (d, $J$ = 3.1 Hz, 1H, H10a), 4.91 (d, $J$ = 11.5 Hz, 1H, OCH$_2$Ph), 4.66 – 4.40 (m, 5H, OCH$_2$Ph), 4.35 (d, $J$ = 2.0 Hz, 1H, H5), 4.26 – 4.17 (m, 1H, H2), 4.00 (s, 1H, H3), 3.76 (s, 3H, ArOMe), 3.70 – 3.63 (m, 2H, CH$_2$O), 3.40 (s, 3H, OMe), 3.34 (dd, $J$ = 11.8, 2.3 Hz, 1H, H4), 3.03 – 2.94 (m, 1H, H4a). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 153.63, 147.66, 138.79, 138.10, 137.74, 128.63, 128.50, 128.46, 128.42, 128.25, 128.21, 128.03, 128.03, 127.97, 127.89, 127.83, 127.72, 127.50, 119.01, 117.67, 116.63, 115.27, 99.18, 94.88, 74.97, 74.80, 73.79, 71.60, 71.49, 71.42, 70.65, 70.02, 69.88, 68.96, 56.57, 55.96, 37.60. $\left[\alpha\right]_D^{20} = +6.6$ (c=1, CHCl$_3$); MS: m/z calcd for [M + K]$^+$ = 621.2; found [M + K]$^+$ = 621.6.
(2R,3R,4R,4aR,5R/S,10aR)-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-methoxy-7-methyl-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene (14): yield 91%, C5 R/S 95/5

(5R)

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{H} & \quad \text{O} & \quad \text{Bn} \\
\text{MeO} & \quad \text{OBn} & \quad \text{OBn} & \quad \text{OBn} \\
\end{align*}
\]

\[\text{1H NMR (400 MHz, CDCl}_3\text{) } \delta 7.33 (d, J = 7.1 Hz, 1H, H6), 7.31 – 7.21 (m, 15H, Ar), 6.99 (d, J = 7.3 Hz, 1H, H8), 6.72 (d, J = 8.2 Hz, 1H, H9), 5.61 (d, J = 2.9 Hz, 1H, H10a), 4.96 (d, J = 11.4 Hz, 1H, OCH}_2\text{Ph), 4.74 (d, J = 4.5 Hz, 1H, H5), 4.62 – 4.33 (m, 5H, OCH}_2\text{Ph), 4.18 (t, J = 6.4 Hz, 1H, H2), 3.80 (s, 1H, H3), 3.66 (dd, J = 11.2, 2.6 Hz, 1H, H4), 3.61 (dd, J = 6.3, 4.1 Hz, 2H, CH}_2\text{O), 3.57 (s, 3H, OMe), 3.33 – 3.23 (m, 1H, H4a), 2.31 (s, 3H, Me). 13C NMR (101 MHz, CDCl}_3\text{) } \delta 149.98, 139.05, 138.93, 138.16, 130.59, 129.64, 128.61, 128.43, 128.40, 128.36, 128.13, 127.97, 127.75, 127.52, 126.52, 121.97, 115.37, 97.63, 76.92, 76.33, 75.66, 75.16, 73.93, 73.71, 72.69, 71.65, 69.15, 57.1, 34.78, 20.99. [\alpha]_D^{20}\text{ = -5.2 (c=1, CHCl}_3\text{); MS: m/z calcd for [M + H]^+ = 567.3, [M + Na]^+ = 589.3, [M + K]^+ = 605.2; found [M + H]^+ = 567.6, [M + Na]^+ = 589.5, [M + K]^+ = 605.6. }
\]

(5S)

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{H} & \quad \text{O} & \quad \text{Bn} \\
\text{MeO} & \quad \text{OBn} & \quad \text{OBn} & \quad \text{OBn} \\
\end{align*}
\]

\[\text{1H NMR (400 MHz, CDCl}_3\text{) } \delta 7.40 – 7.13 (m, 15H, Ar), 7.01 (dd, J = 8.3, 1.7 Hz, 1H, H8), 6.82 (s, 1H, H6), 6.75 (d, J = 8.3 Hz, 1H, H9), 5.66 (d, J = 3.2 Hz, 1H, H10a), 4.92 (d, J = 11.5 Hz, 1H, OCH}_2\text{Ph), 4.65 – 4.42 (m, 5H, OCH}_2\text{Ph), 4.37 – 4.30 (d, J = 2.0 Hz, 1H, H5), 4.26 – 4.17 (m, 1H, H2), 3.98 (s, 1H, H3), 3.72 – 3.63 (m, 2H, CH}_2\text{O), 3.38 (s, 3H, ArOMe), 3.36 – 3.29 (dd, J = 2.38, 11.78 Hz, 1H, H4), 3.06 – 2.93 (m, 1H, H4a), 2.26 (s, 3H, Me). 13C NMR (101 MHz, CDCl}_3\text{) } \delta 151.53, 138.81, 138.10, 137.77, 131.35, 131.03, 129.91, 128.64, 128.60, 128.54, 128.49, 128.26, 128.21, 128.01, 127.93, 127.82, 118.18, 116.64, 94.89, 75.00, 74.84, 74.80, 73.79, 71.55, 71.47, 71.35, 68.96, 56.42, 37.60, 29.93, 20.77. [\alpha]_D^{20}\text{ = -2.1 (c=1, CHCl}_3\text{); MS: m/z calcd for [M + H]^+ = 567.3, [M + Na]^+ = 589.3, [M + K]^+ = 605.2; found [M + H]^+ = 567.6, [M + Na]^+ = 589.5, [M + K]^+ = 605.6. }
\]
(2R,3R,4R,4aR,5R/S,10aR)-3,4-bis(benzyloxy)-2-benzyloxymethyl-5,8-dimethoxy-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene (15): yield 64%, C5 R/S 53/47

(5R)

\[
\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{) } &\delta 7.42 (d, \ J = 8.6 \text{ Hz}, 1\text{H}, H6), 7.37 - 7.21 (m, 15\text{H}, \text{Ar}), 6.56 (dd, \ J = 8.5, 2.4 \text{ Hz}, 1\text{H}, H7), 6.39 (d, \ J = 2.4 \text{ Hz}, 1\text{H}, H8), 5.62 (d, \ J = 2.8 \text{ Hz}, 1\text{H}, H10a), 4.96 (d, \ J = 11.4 \text{ Hz}, 1\text{H}, \text{OCH}_2\text{Ph}), 4.71 (d, \ J = 4.4 \text{ Hz}, 1\text{H}, H5), 4.60 - 4.35 (m, 5\text{H}, \text{OCH}_2\text{Ph}), 4.19 (t, \ J = 6.4 \text{ Hz}, 1\text{H}, H2), 3.80 (s, 1\text{H}, H3), 3.78 (s, 3\text{H}, \text{ArOme}), 3.66 (dd, \ J = 11.1, 2.4 \text{ Hz}, 1\text{H}, H4), 3.60 (t, \ J = 6.3 \text{ Hz}, 2\text{H}, \text{CH}_2\text{O}), 3.55 (s, 3\text{H}, \text{Ome}), 3.31 - 3.24 (m, 1\text{H}, H4a). \\
\text{13C NMR (101 MHz, CDCl}_3\text{) } &\delta 160.56, 153.13, 139.03, 138.97, 138.15, 128.61, 128.43, 128.40, 128.12, 127.96, 127.75, 127.52, 127.14, 114.73, 107.86, 100.74, 97.96, 76.04, 75.67, 75.16, 74.05, 73.72, 72.86, 71.82, 69.18, 56.99, 55.55, 34.91, 29.92. \end{align*}
\]

\[
\alpha\text{D}_20 = -2.2 (c=1, \text{CHCl}_3); \text{ MS: m/z calcd for [M + Na]^+ = 605.3, [M + K]^+ = 621.2}; \text{ found [M + Na]^+ = 605.6, [M + K]^+ = 621.5.}
\]

(5S)

\[
\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{) } &\delta 7.39 - 7.16 (m, 15\text{H}, \text{Ar}), 6.97 (d, \ J = 8.4 \text{ Hz}, 1\text{H}, H6), 6.47 (dd, \ J = 8.3, 2.5 \text{ Hz}, 1\text{H}, H7), 6.43 (d, \ J = 2.3 \text{ Hz}, 1\text{H}, H8), 5.71 (d, \ J = 3.2 \text{ Hz}, 1\text{H}, H10a), 4.97 - 4.87 (d, \ J = 11.4 \text{ Hz}, 1\text{H}, \text{OCH}_2\text{Ph}), 4.65 - 4.43 (m, 5\text{H}, \text{OCH}_2\text{Ph}), 4.37 (d, \ J = 2.1 \text{ Hz}, 1\text{H}, H5), 4.19 (d, \ J = 5.5 \text{ Hz}, 1\text{H}, H2), 3.98 (s, 1\text{H}, H3), 3.77 (s, 3\text{H}, \text{ArOme}), 3.70 - 3.63 (m, 2\text{H}, \text{CH}_2\text{O}), 3.35 (s, 3\text{H}, \text{Ome}), 3.32 (d, \ J = 2.4 \text{ Hz}, 1\text{H}, H4), 3.00 (m, 1\text{H}, H4a). \\
\text{13C NMR (101 MHz, CDCl}_3\text{) } &\delta 161.44, 155.01, 138.80, 138.10, 137.84, 131.97, 128.67, 128.65, 128.50, 128.25, 128.20, 128.03, 128.02, 127.84, 111.11, 108.00, 101.38, 95.17, 75.34, 74.78, 74.35, 73.79, 71.70, 71.60, 71.57, 69.00, 56.13, 55.54, 37.84, 29.93. \end{align*}
\]

\[
\alpha\text{D}_20 = -4.6 (c=1, \text{CHCl}_3); \text{ MS: m/z calcd for [M + Na]^+ = 605.3, [M + K]^+ = 621.2}; \text{ found [M + Na]^+ = 605.7, [M + K]^+ = 621.6.}
\]
(2R,3R,4R,4aR,5R,10aR)-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-methoxy-8-methyl-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene (16): yield 45%, C5 R/S 100/0

\[\text{1H NMR (400 MHz, CDCl}_3\text{)}\ \delta \ 7.42 \ (d, \ J = 7.8 \ Hz, \ 1H, \ H6), \ 7.37 – 7.20 \ (m, \ 15H, \ Ar), \ 6.81 \ (d, \ J = 7.8 \ Hz, \ 1H, \ H7), \ 6.66 \ (s, \ 1H, \ H9), \ 5.63 \ (d, \ J = 2.8 \ Hz, \ 1H, \ H10a), \ 4.97 \ (d, \ J = 11.4 \ Hz, \ 1H, \ OCH}_2\text{Ph}, \ 4.74 \ (d, \ J = 4.2 \ Hz, \ 1H, \ H5), \ 4.62 – 4.34 \ (m, \ 5H, \ OCH}_2\text{Ph}, \ 4.19 \ (t, \ J = 6.3 \ Hz, \ 1H, \ H2), \ 3.81 \ (s, \ 1H, \ H3), \ 3.66 \ (dd, \ J = 11.1, \ 2.6 \ Hz, \ 1H, \ H4), \ 3.62 \ (dd, \ J = 6.2, \ 4.6 \ Hz, \ 2H, \ CH}_2\text{O}, \ 3.56 \ (s, \ 3H, \ OMe), \ 3.34 – 3.21 \ (m, \ 1H, \ H4a), \ 2.31 \ (s, \ 3H, \ Me). \ \text{13C NMR (101 MHz, CDCl}_3\text{)} \ \delta \ 152.11, \ 139.20, \ 139.07, \ 139.00, \ 138.19, \ 128.61, \ 128.44, \ 128.41, \ 128.37, \ 128.12, \ 127.97, \ 127.94, \ 127.75, \ 127.51, \ 126.10, \ 122.28, \ 119.48, \ 116.04, \ 97.74, \ 76.22, \ 75.74, \ 75.16, \ 74.03, \ 73.70, \ 72.84, \ 71.69, \ 69.16, \ 57.06, \ 34.89, \ 21.41. \ [\alpha]_D^{20} = -6.2 \ (c=1, \ CHCl}_3). \ MS: \ m/z \ \text{calcd for [M + K]}^+ = 605.2; \ \text{found [M + K]}^+ = 605.2.

(2R,3S,4R,4aR,5R,10aR)-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-methoxy-7-methyl-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene (17): yield 66%, C5 R/S 100/0

\[\text{1H NMR (400 MHz, CDCl}_3\text{)}\ \delta \ 7.43 – 7.18 \ (m, \ 14H, \ Ar \text{ and } H6), \ 7.09 \ (dd, \ J = 6.7, \ 2.7 \ Hz, \ 2H, \ Ar), \ 6.99 \ (d, \ J = 6.3 \ Hz, \ 1H, \ H8), \ 6.72 \ (d, \ J = 8.2 \ Hz, \ 1H, \ H9), \ 5.60 \ (d, \ J = 3.0 \ Hz, \ 1H, \ H10a), \ 4.82 \ (d, \ J = 10.7 \ Hz, \ 1H, \ OCH}_2\text{Ph}, \ 4.74 \ (d, \ J = 4.4 \ Hz, \ 1H, \ H5), \ 4.71 – 4.44 \ (m, \ 5H, \ OCH}_2\text{Ph}, \ 4.07 \ (d, \ J = 9.9 \ Hz, \ 1H, \ H2), \ 3.86 – 3.79 \ (m, \ 2H, \ CH}_2\text{O}, \ 3.74 \ (dd, \ J = 10.8, \ 1.9 \ Hz, \ 1H, \ H3), \ 3.72 – 3.65 \ (m, \ 1H, \ H4), \ 3.55 \ (s, \ 3H, \ OMe), \ 2.83 \ (dd, \ J = 10.5, \ 4.4, \ 3.2 \ Hz, \ 1H, \ H4a), \ 2.30 \ (s, \ 3H, \ Me). \ \text{13C NMR (101 MHz, CDCl}_3\text{)} \ \delta \ 149.83, \ 139.14, \ 138.40, \ 138.19, \ 130.78, \ 129.78, \ 128.61, \ 128.58, \ 128.44, \ 128.17, \ 128.01, \ 127.91, \ 127.89, \ 127.55, \ 126.48, \ 121.83, \ 115.50, \ 97.17, \ 78.56, \ 78.54, \ 76.43, \ 75.60, \ 74.92, \ 73.77, \ 72.55, \ 68.67, \ 57.39, \ 40.09, \ 20.98. \ [\alpha]_D^{20} = +3.7 \ (c=1, \ CHCl}_3). \ MS: \ m/z \ \text{calcd for [M + Na]}^+ = 589.3, \ [M + K]^{1+} = 605.2; \ \text{found [M + Na]}^+ = 589.4, \ [M + K]^{1+} = 605.3.
(2R,3S,4R,4aR,5R,10aR)-3,4-bis(benzyloxy)-2-benzyloxymethyl-5,8-dimethoxy-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene (18): yield 37%, C5 R/S 100/0

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.43 (d, $J = 8.6$ Hz, 1H, H6), 7.38 – 7.19 (m, 10H, Ar), 7.15 – 7.05 (m, 2H, Ar), 6.56 (dd, $J = 8.5$, 2.3 Hz, 1H, H7), 6.40 (t, $J = 5.9$ Hz, 1H, H9), 5.61 (d, $J = 2.8$ Hz, 1H, H10a), 4.83 (d, $J = 10.6$ Hz, 1H, H4a), 4.72 (d, $J = 4.4$ Hz, 1H, OCH$_2$Ph), 4.70-4.44 (m, 5H, OCH$_2$Ph), 4.08 (d, $J = 10.0$ Hz, 1H, H2), 3.88 – 3.73 (m, 3H, H3 and CH$_2$O), 3.79 (s, 3H, OMe), 3.73 – 3.65 (m, 1H, H4), 3.52 (s, 3H, OMe), 2.89 – 2.75 (m, 1H, H4a). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 160.66, 152.96, 139.13, 138.37, 138.18, 128.62, 128.60, 128.44, 128.18, 128.15, 128.02, 127.93, 127.91, 127.56, 127.12, 114.56, 108.09, 100.84, 97.50, 78.51, 78.45, 76.18, 75.63, 74.97, 73.78, 72.70, 68.67, 57.29, 55.57, 40.20. [α]$_D^{20}$ = +11.6 (c=1, CHCl$_3$). MS: m/z calcd for [M + Na]$^+$ = 605.3, [M + K]$^+$ = 621.2; found [M + Na]$^+$ = 605.6, [M + K]$^+$ = 621.4.

(2R,3S,4R,4aR,5R,10aR)-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-methoxy-8-methyl-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene (19): yield 21%, C5 R/S 100/0

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.41 (d, $J = 7.9$ Hz, 1H, H6), 7.39 – 7.18 (m, 13H, Ar), 7.14 – 7.03 (m, 2H, Ar), 6.80 (d, $J = 7.7$ Hz, 1H, H7), 6.65 (s, 1H, H9), 5.62 (d, $J = 2.7$ Hz, 1H, H10a), 4.82 (d, $J = 10.6$ Hz, 1H, OCH$_2$Ph), 4.74 (d, $J = 3.8$ Hz, 1H, H5), 4.72 – 4.39 (m, 5H, OCH$_2$Ph), 4.07 (d, $J = 10.0$ Hz, 1H, H2), 3.89 – 3.72 (m, 3H, H3 and CH$_2$O), 3.68 (t, $J = 9.7$ Hz, 1H, H4), 3.53 (s, 3H, OMe), 2.87 – 2.78 (m, 1H, H4a), 2.30 (s, 3H, Me). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 151.94, 139.37, 139.14, 138.39, 138.20, 128.62, 128.59, 128.44, 128.17, 128.02, 127.92, 127.90, 127.55, 126.05, 122.43, 119.33, 116.17, 97.28, 78.52, 76.93, 76.34, 75.61, 74.96, 73.77, 72.58, 68.68, 57.33, 40.17, 21.38. [α]$_D^{20}$ = +8.3 (c=1, CHCl$_3$). MS: m/z calcd for [M + Na]$^+$ = 589.3, [M + K]$^+$ = 605.2; found [M + Na]$^+$ = 589.5, [M + K]$^+$ = 605.2.
General synthetic strategy for the deprotection of compounds 10-19 (C7 R only) to afford compounds 20-29. To a 6 mM solution of the protected compound in AcOEt/MeOH 1:1, previously degassed, Pd(OH)$_2$ 5% mol is added and the reaction mixture is stirred under H$_2$ atmosphere for 45 min.-1.5 h. Then the catalyst is removed by filtration and the solvent evaporated under reduced pressure to afford pure compounds 20-29.

(2R,3R,4R,4aS,5R,10aR)-2-hydroxymethyl-5-methoxy-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene-3,4-diol (20): yield 97%

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.45 (d, $J = 7.7$ Hz, 1H, H$_6$), 7.18 (t, $J = 7.7$ Hz, 1H, H$_8$), 6.94 (dd, $J = 17.4$, 9.9 Hz, 1H, H$_7$), 6.78 (d, $J = 8.2$ Hz, 1H, H$_9$), 5.62 (d, $J = 3.1$ Hz, 1H, H$_{10a}$), 4.91 (d, $J = 2.4$ Hz, 1H, H$_5$), 3.99 (t, $J = 6.0$ Hz, 1H, H$_2$), 3.81 (s, 2H, H$_3$ and H$_4$), 3.80 – 3.74 (m, 2H, CH$_2$O), 3.69 (s, 3H, OMe), 3.00 – 2.92 (m, 1H, H$_{4a}$). $^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 156.35, 132.98, 130.04, 125.32, 124.83, 119.22, 100.69, 81.51, 76.68, 71.54, 71.23, 65.57, 61.65, 38.46. $[\alpha]_D^{20} = -7.6$ (c=1, CHCl$_3$); MS: m/z calcld for [M + Na]$^+$ = 305.1, [M + K]$^+$ = 321.1; found [M + Na]$^+$ = 305.3, [M + K]$^+$ = 321.2.
(2R,3R,4R,4aS,5R,10aR)-7-amino-2-hydroxymethyl-5-methoxy-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene-3,4-diol (21): yield 94%

\[
\begin{align*}
\text{H NMR (400 MHz, CD}_3\text{OD)} & \delta 6.89 (s, 1H, H6), 6.65-6.55 (m, 2H, H8 and H9), 5.52 (d, J = 3.0 Hz, 1H, H10a), 4.83 (d, J = 4.9 Hz, 1H, H5), 3.98 (t, J = 5.8 Hz, 1H, H2), 3.87 – 3.78 (m, 2H, H3 and H4), 3.79 – 3.73 (m, 1H, CH2O), 3.67 (s, 3H, OMe), 2.96 – 2.85 (m, 1H, H4a). \\
\text{13C NMR (101 MHz, CD}_3\text{OD)} & \delta 149.10, 144.77, 125.69, 121.06, 119.69, 118.60, 117.30, 114.55, 100.39, 81.79, 80.99, 76.53, 71.56, 71.43, 65.59, 61.71, 38.72. \left[\alpha\right]_{D}^{20} = +13.3 \text{ (c=1, CHCl}_3\right). \text{ MS: m/z calcd for } [M + H]^+ = 298.1 \text{ [M + Na]}^+ = 320.1, \text{ [M + K]}^+ = 336.1; \text{ found } [M + H]^+ = 298.3, [M + Na]^+ = 320.3, \text{ [M + K]}^+ = 336.3.
\end{align*}
\]

(2R,3R,4R,4aS,5R,10aR)-2-hydroxymethyl-5-methoxy-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene-3,4,7-triol (22): yield 100%

\[
\begin{align*}
\text{H NMR (400 MHz, CD}_3\text{OD)} & \delta 6.88 (s, 1H, H6), 6.62 (s, 2H, H8 and H9), 5.54 (d, J = 2.8 Hz, 1H, H10a), 4.84 (d, J = 4.8 Hz, 1H, H5), 3.98 (t, J = 5.9 Hz, 1H, H2), 3.84 (d, J = 2.7 Hz, 1H, H4), 3.81 (s, 1H, H3), 3.76 (dd, J = 5.8, 2.3 Hz, 2H, CH2O), 3.68 (s, 3H, OMe), 2.98 – 2.84 (m, 1H, H4a). \text{13C NMR (101 MHz, CD}_3\text{OD)} & \delta 155.33, 149.19, 125.97, 121.06, 119.88, 119.77, 116.18, 116.06, 100.47, 81.66, 76.55, 71.57, 71.35, 65.59, 61.67, 38.61. \left[\alpha\right]_{D}^{20} = +11.1 \text{ (c=1, CHCl}_3\right); \text{ MS: m/z calcd for } [M + Na]^+ = 321.1; \text{ found } [M + Na]^+ = 321.2.
\end{align*}
\]

(2R,3R,4R,4aS,5R,10aR)-2-hydroxymethyl-5,7-dimethoxy-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene-3,4-diol (23): yield 96%

\[
\begin{align*}
\text{H NMR (400 MHz, CD}_3\text{OD)} & \delta 7.00 (d, J = 2.1 Hz, 1H, H6), 6.77 (dd, J = 8.9, 2.3 Hz, 1H, H8), 6.71 (d, J = 8.8 Hz, 1H, H9), 5.57 (d, J = 3.0 Hz, 1H, H10a), 4.87 (s, 1H, H5), 3.98 (t, J = 6.0 Hz, 1H, H2), 3.83 – 3.79 (m, 2H, H3 and H4), 3.76 (dd, J = 6.1, 3.0 Hz, 2H, CH2O), 3.74 (s, 3H, OMe),
\end{align*}
\]

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3.68 (s, 3H, OMe), 2.98 - 2.89 (m, 1H, H4a). $^{13}\text{C}$ NMR (101 MHz, CD$_3$OD) $\delta$ 158.33, 150.09, 125.97, 119.98, 118.90, 114.61, 100.59, 81.54, 76.60, 71.60, 71.26, 65.57, 61.52, 58.83, 38.47. $\alpha_d^{20} = +8.9$ (c=1, CHCl$_3$); MS: m/z calcd for [M + Na]$^+$ = 335.1; found [M + Na]$^+$ = 335.3.

(2R,3R,4R,4aS,5R,10aR)-2-hydroxymethyl-5-methoxy-7-methyl-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene-3,4-diol (24): yield 95%

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.24 (s, 1H, H6), 6.98 (d, $J$ = 8.2 Hz, 1H, H8), 6.66 (d, $J$ = 8.3 Hz, 1H, H9), 5.57 (d, $J$ = 3.0 Hz, 1H, H10a), 3.98 (t, $J$ = 6.0 Hz, 1H, H2), 3.83 – 3.78 (m, 2H, H3 and H4), 3.77 (dd, $J$ = 6.0, 2.9 Hz, 2H, CH$_2$O), 3.68 (s, 3H, OMe), 2.96 - 2.89 (m, 1H, H4a), 2.26 (s, 3H, Me). $^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 150.14, 130.22, 129.54, 126.29, 120.97, 115.09, 96.65, 77.67, 72.66, 67.62, 67.37, 61.64, 57.73, 34.59, 19.57. $\alpha_d^{20} = +13.3$ (c=1, CHCl$_3$); MS: m/z calcd for [M + Na]$^+$ = 319.1, [M + K]$^+$ = 335.1; found [M + Na]$^+$ = 319.4, [M + K]$^+$ = 335.4.

(2R,3R,4R,4aS,5R,10aR)-2-hydroxymethyl-5,8-dimethoxy-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene-3,4-diol (25): yield 97%

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.32 (d, $J$ = 8.6 Hz, 1H, H6), 6.54 (dd, $J$ = 8.6, 2.4 Hz, 1H, H7), 6.35 (d, $J$ = 2.4 Hz, 1H, H9), 5.58 (d, $J$ = 3.0 Hz, 1H, H10a), 4.84 (d, $J$ = 4.9 Hz, 1H, H5), 4.00 (t, $J$ = 6.0 Hz, 1H, H2), 3.86 – 3.79 (m, 2H, H3 and H4), 3.77 (dd, $J$ = 6.0, 3.3 Hz, 2H, CH$_2$O), 3.74 (s, 3H, OMe), 3.67 (s, 3H, OMe), 2.96-2.86 (m, 1H, H4a). $^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 160.95, 153.28, 126.97, 113.53, 107.31, 100.40, 96.94, 77.53, 72.80, 67.62, 67.29, 61.64, 55.61, 54.54, 34.63. $\alpha_d^{20} = -7.6$ (c=1, CHCl$_3$); MS: m/z calcd for [M + Na]$^+$ = 335.1, [M + K]$^+$ = 351.1; found [M + Na]$^+$ = 335.4, [M + K]$^+$ = 351.3.
(2R,3R,4R,4aS,5R,10aR)-2-hydroxymethyl-5-methoxy-8-methyl-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene-3,4-diol (26): yield 97%

1H NMR (400 MHz, CD3OD) δ 7.29 (d, J = 7.8 Hz, 1H, H6), 6.76 (d, J = 7.8 Hz, 1H, H7), 6.60 (s, 1H, H9), 5.57 (d, J = 3.0 Hz, 1H, H10a), 4.85 (d, J = 4.7 Hz, 1H, H5), 3.98 (t, J = 5.9 Hz, 1H, H3), 3.83 – 3.73 (m, 4H, CH2O, H2, H4), 3.67 (s, 3H, OMe), 2.96 – 2.85 (m, 1H, H4a), 2.25 (s, 3H, Me).

13C NMR (101 MHz, CD3OD) δ 156.14, 143.22, 133.19, 129.62, 125.66, 122.29, 119.72, 100.65, 81.54, 76.64, 71.24, 65.63, 61.61, 38.51, 23.91. [α]D20 = +8,3 (c=1, CHCl3); MS: m/z calcd for [M + Na]+ = 319.1; found [M + Na]⁺ = 319.3.

(2R,3S,4R,4aS,5R,10aR)-2-(hydroxymethyl)-5-methoxy-7-methyl-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene-3,4-diol (27): yield 98%

1H NMR (400 MHz, CD3OD) δ 7.12 (s, 1H, H6), 6.85 (d, J = 8.3 Hz, 1H, H8), 6.54 (d, J = 8.3 Hz, 1H, H9), 5.38 (d, J = 2.9 Hz, 1H, H10a), 3.75 – 3.59 (m, 3H, CH2O and H2), 3.53 (s, 4H, H3 and OMe), 3.34 (t, J = 8.9 Hz, 1H, H4), 2.50 – 2.40 (m, 1H, H4a), 2.13 (s, 3H, Me). 13C NMR (101 MHz, CD3OD) δ 150.01, 130.29, 129.54, 126.43, 121.13, 115.15, 96.39, 77.56, 73.82, 70.37, 70.10, 61.29, 57.52, 40.03, 19.56. [α]D20 = +13,3 (c=1, CHCl3); MS: m/z calcd for [M + K]+ = 335.1; found [M + K]+ = 335.3.

(2R,3S,4R,4aS,5R,10aR)-2-hydroxymethyl-5,8-dimethoxy-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene-3,4-diol (28): yield 97%

1H NMR (400 MHz, CD3OD) δ 7.33 (d, J = 8.6 Hz, 1H, H6), 6.54 (dd, J = 8.6, 2.4 Hz, 1H, H7), 6.36 (d, J = 2.4 Hz, 1H, H9), 5.51 (t, J = 6.6 Hz, 1H, H10a), 4.83 (d, J = 4.8 Hz, 1H, H5), 3.87 – 3.66 (m, 6H, CH2O and H4 and OMe), 3.66 (d, J = 6.3 Hz, 3H, OMe), 3.48 (t, J = 9.2 Hz, 1H, H3), 2.25 (s, 3H, Me).
2.57 (ddd, \(J = 10.3, 4.9, 3.1\) Hz, 1H, H4a). \(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta\) 160.95, 153.13, 127.12, 113.68, 107.43, 100.38, 96.66, 77.40, 73.93, 70.26, 70.02, 61.24, 57.39, 54.54, 40.05. \([\alpha]_D^{20} = +11.6\) (c=1, CHCl\(_3\)); MS: m/z calcd for \([M + Na]^+ = 335.1, [M + K]^+ = 351.1\); found \([M + Na]^+ = 335.5, [M + K]^+ = 351.5\).

\((2R,3S,4R,4aS,5R,10aR)-2\)-hydroxymethyl-5-methoxy-8-methyl-2,3,4,4a,5,10a-hexahydropyrano[2,3-b]chromene-3,4-diol (29): yield 98%

\[
\begin{align*}
\text{H NMR (400 MHz, CD\(_3\)OD) } \delta &\ 7.31 (d, J = 7.8\ Hz, 1H, H6), 6.78 (d, J = 7.7\ Hz, 1H, H7), 6.62 (s, 1H, H9), 5.52 (d, J = 2.9\ Hz, 1H, H10a), 4.85 (d, J = 4.7\ Hz, 1H, H5), 3.85 (dd, J = 13.7, 4.5\ Hz, 1H, CH\(_2\)O), 3.76 (q, J = 4.2\ Hz, 2H, CH\(_2\)O and H2), 3.68 – 3.62 (m, 4H, H4 and OMe), 3.48 (t, J = 9.0\ Hz, 1H, H3), 2.58 (ddd, J = 10.4, 4.9, 3.1\ Hz, 1H, H4a), 2.27 (s, 3H, Me). \(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta\) 152.07, 139.31, 126.11, 121.84, 118.54, 115.68, 96.45, 77.50, 73.84, 70.30, 70.04, 61.25, 57.47, 40.04, 19.99. \([\alpha]_D^{20} = -7.8\) (c=1, CHCl\(_3\)); MS: m/z calcd for \([M + Na]^+ = 319.1, [M + K]^+ = 335.1\); found \([M + Na]^+ = 319.4, [M + K]^+ = 335.3\).
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Peptide synthesis and purification

Procedure

Aβ1-42 was prepared by solid-phase peptide synthesis on a 433A synthesizer (Applied Biosystems) using Fmoc-protected L-amino acid derivatives, NOVASYN-TGA resin on a 0.1 mM scale. Peptide was cleaved from the resin as previously described and purified by reverse phase HPLC on a semi-preparative C4 column (Waters) using water:acetonitrile gradient elution. Peptide identity was confirmed by MALDI-TOF analysis (model Reflex III, Bruker). Peptide purity was always above 95%.

NMR spectroscopy binding studies

Material and Methods

NMR experiments were recorded on a Varian 400-MHz Mercury. A batch of Aβ1-42 was selected that contained pre-amyloidogenic seeds highly toxic to N2a cells. Immediately before use, lyophilized Aβ1-42 was dissolved in 10 mM NaOD in D2O at a concentration of 160 μM, then diluted 1:1 with 10 mM phosphate buffer saline, pH 7.4 containing 100 mM NaCl (PBS) and one of the tested compounds. Compounds 20-29 were dissolved in PBS, pH 7.4, and added to the peptide solution. The pH of each sample was verified with a Microelectrode (Mettler Toledo) for 5 mm NMR tubes and adjusted with NaOD or DCl. All pH values were corrected for isotope effect. Basic sequences were employed for 2D-TOCSY, 2D-NOESY and STD experiments. For STD, a train of Gaussian-shaped pulses each of 50 ms was employed to saturate selectively the protein envelope; the total saturation time of the protein envelope was adjusted by the number of shaped pulses and was varied between 5 s and 0.5 s.
Supporting Figures

Figure 1S. $^1$H spectra (A, C, E, G, I, M, O, Q, S and U) and 1D-STD spectra (B, D, F, H, L, N, P, R, T and V) of mixtures dissolved in deuterated PBS at 25°C containing Aβ1-42 (80 μM) and a test molecule (1.6 mM) (A and B, compound 13; C and D, compound 14; E and F, compound 15; G and H, compound 16; I and L, compound 17; M and N, compound 18; O and P, compound 19; Q and R, compound 20; S and T, compound 21 e U and V, compound 22). $^1$H spectra were acquired with 64 scans, 1D-STD spectra with 512 scans and 2 s of saturation time.
Figure 2S. 2D-NOESY spectra of compounds 21 (A) c 24 (C) dissolved in deuterated PBS, pH 7.5, 25°C, mixing time 0.9 s. trNOESY of mixture containing Aβ1-42 (80 uM) and compound 21 (B) or compound 24 (D) dissolved in deuterated PBS, pH 7.5, 25°C, mixing time 0.3 s. Positive cross-peak are blue, negative ones red.
Figure 3S. A) $^1$H NMR spectrum of the mixture containing Aβ1-42 (80 uM) and compound 24 (1.6 mM) in PBS, pH=7.5, 25°C; B-F STD-NMR spectra of the same mixture acquired with different saturation times. (B, 0.5 s; C, 1.2 s; D, 2.0 s; E 3.0 s; F, 5.0 s).
Molecular Mechanics (MM) and Molecular Dynamics (MD) calculations

**Material and Methods**

Molecular mechanics and dynamics studies were conducted with MacroModel 9.8.207\(^3\) as implemented in version 9.1.207 of the Maestro suite,\(^4\) using MM3* force field.\(^5\) The starting coordinates for dynamics calculations were those obtained after energy minimization of the structures, followed by conformational search. In particular, a systematic variation of the torsional degrees of freedom of the molecules permitted different starting structures to be constructed that were further minimized to provide the corresponding local minima. For each compound the conformer with the lowest energy was considered. Simulations were carried out over 5 ns at 298 K with a 0.25 fs time step and a 20 ps equilibration step; 100 structures were sampled and minimized for further analysis. The continuum GB/SA solvent model\(^6\) was employed and the general PRCG (Polak–Ribiere Conjugate Gradient) method for energy minimization was used. An extended cut-off was applied and the SHAKE procedure for bonds was not selected.

The values of the key proton-proton distances H2-H3, H2-H4, H3-H4, H4a-H10a, H4a-H5 and H5-H10a as well as the values of the dihedral angle H2-C2-C3-H3, H3-C3-C4-H4, H4a-C4a-C10a-H10a and H4a-C4a-C5-H5 were monitored during the MD and are reported in supporting information. All compounds showed the same values of H2-H4, H4a-H5, H4a-H10a, and H5-H10a distances (Fig. 4S), and of the dihedral angles H4a-C4a-C10a-H10a (average value $\theta = 62^\circ$) and H4a-C4a-C5-H5 (average value $\theta = -53^\circ$), which are the diagnostic parameters to identify molecule conformation. On the other hand, on the basis of the distances H2-H3 and H3-H4 (Fig. 6S) and the dihedral angles H2-C2-C3-H3 and H3-C3-C4-H4, molecules 20-29 could be clustered into two groups (20-26, with average $\theta_{H2-C2-C3-H3} = -60^\circ$, $\theta_{H3-C3-C4-H4} = 60^\circ$ and 27-29, with average $\theta_{H2-C2-C3-H3} = -180^\circ$, average $\theta_{H3-C3-C4-H4} = 180^\circ$), depending on C3 stereochemistry (Fig.s 7S-16S).
Supporting Figures

**Figure 4S.** Superimposition of the 30 structures with the lowest energy calculated through MD simulations in water, 298K; A, compound 20; B, compound 21; C, compound 22; D, compound 23; E, compound 24; F, compound 25; G, compound 26; H, compound 27; I, compound 28; L, compound 29.
**Fig. 5S.** Superimposition of the 30 structures with the lowest energy calculated through MD simulations in water, 298K; A, compound 21; B, compound 24

**Fig. 6S.** Average values for H2-H3, H2-H4, H3-H4, H4a-H10a and H5-H10a interproton distances. Concerning H2-H3 and H3-H4, compounds 20-29 can be clustered into two groups (bottom).
Figure 7S. H2-H3 distance (Å). A, compound 20; B, compound 21; C, compound 22; D, compound 23; E, compound 24; F, compound 25; G, compound 26; H, compound 27; I, compound 28; J, compound 29.
Figure 8S. H2-H4 distance (Å). A, compound 20; B, compound 21; C, compound 22; D, compound 23; E, compound 24; F, compound 25; G, compound 26; H, compound 27; I, compound 28; L, compound 29.
Figura 9S. H3-H4 distance (Å). A, compound 20; B, compound 21; C, compound 22; D, compound 23; E, compound 24; F, compound 25; G, compound 26; H, compound 27; I, compound 28; L, compound 29.
Figure 10S. H4a-H10a distance (Å). A, compound 20; B, compound 21; C, compound 22; D, compound 23; E, compound 24; F, compound 25; G, compound 26; H, compound 27; I, compound 28; L, compound 29.
Figure 11S. H4a-H5 distance (Å). A, compound 20; B, compound 21; C, compound 22; D, compound 23; E, compound 24; F, compound 25; G, compound 26; H, compound 27; I, compound 28; L, compound 29.
Figure 12S. H10a-H5 distance (Å). A, compound 20; B, compound 21; C, compound 22; D, compound 23; E, compound 24; F, compound 25; G, compound 26; H, compound 27; I, compound 28; L, compound 29.
Figure 13S. H2-C2-C3-H3 dihedral angle (°). A, compound 20; B, compound 21; C, compound 22; D, compound 23; E, compound 24; F, compound 25; G, compound 26; H, compound 27; I, compound 28; L, compound 29.
Figure 14S. H3-C3-C4-H4 dihedral angle (°). A, compound 20; B, compound 21; C, compound 22; D, compound 23; E, compound 24; F, compound 25; G, compound 26; H, compound 27; I, compound 28; L, compound 29.
Figure 1S8. H4a-C4a-C10a-H10a dihedral angle (°). A, compound 20; B, compound 21; C, compound 22; D, compound 23; E, compound 24; F, compound 25; G, compound 26; H, compound 27; I, compound 28; L, compound 29.
Figure 16S. H4a-C4a-C5-H5 dihedral angle (°). A, compound 20; B, compound 21; C, compound 22; D, compound 23; E, compound 24; F, compound 25; G, compound 26; H, compound 27; I, compound 28; J, compound 29.