*Electronic Supplementary Information*

# N-Aryl-substituted 3-(β-D-glucopyranosyloxy)-2-methyl-4(1*H*)-pyridinones as agents for Alzheimer's therapy

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**CONTENTS**

**1. Supplementary Methods.**

**1.1. Materials.** All solvents and chemicals (Aldrich, Fisher, Alfa Aesar) were reagent grade and used without further purification. Pyridine was dried over potassium hydroxide and other anhydrous solvents were dried according to standard procedures.[1] Water was purified using an Elgastat Maxima-HPLC reverse osmosis and deionization system (Elga, Bucks, England). Atomic absorption standards $Cu(NO_3)_2$ and $ZnCl_2$ were purchased from Aldrich. Human hepatocellular liver carcinoma cells, HepG2, were provided by UBC Biological Services.

**1.2. Instrumentation.** $^1$H NMR and $^{13}C\{^1H\}$ NMR spectra were recorded at room temperature using a Bruker AV-300 or AV-400 spectrometer, as indicated, at 300.13 (75.48 for $^{13}$C NMR) or 400.13 (100.62 for $^{13}$C NMR) MHz respectively; spectra were calibrated using residual solvent peaks. Low-resolution mass spectra were obtained using a Bruker Esquire Ion Trap ESI-MS spectrometer. Elemental analyses (C, H and N) were performed on a Fisons EA-1108 analyzer. High-resolution mass spectrometry was performed on a Micromass LCT instrument. Melting points were collected using a Fisher Scientific Electrothermal melting point apparatus and are uncorrected. Semi-preparative high-performance liquid chromatography (HPLC) was performed with a Waters W600 solvent gradient controller and a Waters 2487 dual wavelength absorbance detector set to monitor absorbance at 254 nm. Sample volumes of 0.3-1.0 mL were run through a Phenomenex precolumn (LUNA 10u C18(2); 60 x 21.20 mm, 10 μm; part number 398332G) before the main XTerraRP column (187μm. 19 x 300 mm, part number 186000630). Solvent flow rate was 10 mL/min with a 45-minute gradient from 100% $H_2O$ (containing 0.1% trifluoroacetic acid, TFA) to 100% $CH_3CN$. Infrared absorption spectra (4000 – 400 $cm^{-1}$) were collected using a Thermo Scientific Nicolet 6700 attenuated total reflectance FTIR with Smart Orbit attachment. X-band powder EPR spectra were recorded on a Bruker ECS-106 EPR spectrometer in quartz tubes (4 mm diameter). The temperature (130 K) was maintained by liquid nitrogen flowing through a cryostat combined with a Eurotherm B-VT-2000 variable-temperature controller. The microwave frequency (9.4311 x $10^{-9}$ Hz) and magnetic field were calibrated with an EIP 625A microwave frequency counter and a Varian E500 gaussmeter, respectively. 2048 points were taken at 0.2 mW; 2 G amplitude modulation, 40 kHz modulation frequency, 41.9 s sweep time, 5.12 ms time constant, 20.48 ms conversion time. Simulations of the EPR spectra were performed using the WinEPR Simfonia software package.

**1.3. Druglikeness evaluation and Log BB calculation**. Three of the four Lipinski properties (MW, hydrogen bond donors (HBD) and hydrogen bond acceptors (HBA)) as well as Topological Polar Surface Area (TPSA) of all the compounds of this work were evaluated using the Instant Jchem[2] software. The fourth property (clogP parameter) was determined using clogP v.4.0.[3] The clogP and TPSA values were also required for the calculation of log BB.

**1.4. X-ray Crystallography**. The crystals were mounted on glass fibers, and measurements were made on a Bruker X8 APEX II diffractometer at room temperature with graphite-monochromated Mo-Kα radiation. The crystal structures were solved using the Bruker SAINT software package.[4] All data were

processed and corrected by Lorentz and polarization effects and absorption using SADABS program.[5] The structures were solved by direct methods.[6] All hydrogen atoms in all structures were placed in calculated positions. Relevant parameters of crystallization procedures, crystal data, data collection, and refinement are summarized in Tables S1 and S2.

**1.5. Synthesis and characterisation of pyridinone pro-ligands.** All 3-hydroxy-2-methyl-4-pyridinone pro-ligands were synthesized via the 3-benzyloxy- or 3-methoxy-ether protected pyranone (benzyl maltol, **2a**, or methyl maltol, **2b**, respectively); the syntheses of these precursors were performed following a previously described procedures[7, 8] with some variations.

**3-Benzyloxy-2-methyl-1-(4-dimethylaminophenyl)-4(1*H*)-pyridinone (3b). 2a** (1.00 g, 4.63 mmol) and *N,N*-dimethyl-1,4-phenylenediamine (0.55 g, 4.0 mmol) were combined with 2:1 $H_2O$:MeOH (15 mL) in a 20-mL thick-walled glass tube with o-ring-sealing polytetrafluoroethylene (PTFE) stopper. The tube was placed in a metal reactor consisting of a solid metal cylindrical block with a solid lid, both approximately 12 cm in diameter. In both cylinders were bored cylindrical wells large enough to accommodate the glass tubes with approximately 1 mL heating bath oil. Both cylinders also contained four holes for screws reaching from the top of the outer lid down approximately four cm into the bottom piece. The bottom and top were fixed together with four screws such that when assembled, the tubes were held in place and the apparatus was explosion proof. This allowed heating of the entire apparatus to high temperatures (> 165 °C). In this preparation, the tubes and reactor were assembled and heated to 120-130 °C for 96 h. After cooling, the clear orange supernatant was removed and discarded while the darker brown bottom phase was concentrated to yield a brown solid. Column chromatography (silica, 9:1 acetone:MeOH) afforded the product **3b** (1.74 g, 51%). $^1$H NMR (DMSO-$d_6$, 300.13 MHz) δ, ppm: 7.51 (d, $^3J_{6,5}$ = 7.3 Hz, 1H; *H*6), 7.38 (m, 5H; Bn-Ar*H*), 7.15 (d, $^3J$ = 8.9 Hz, 2H, Ar*H*), 6.77 (d, $^3J$ = 8.9 Hz, 2H; Ar*H*), 6.20 (d, $^3J_{6,5}$ = 7.5 Hz, 1H; *H*5), 5.07 (s, 2H, Bn-C$H_2$), 2.95 (s, 6H; N(C$H_3$)$_2$), 1.85 (s, 3H; C2-C$H_3$).

**3-Hydroxy-2-methyl-1-(4-dimethylaminophenyl)-4(1*H*)-pyridinone ($HL_1$).** Hydrobromic acid (HBr, 33% in acetic acid; 18 mL) was added to **3b** (1.3 g, 3.9 mmol) in a round-bottomed flask (50 mL). The residue dissolved upon heating to reflux; the mixture was heated and stirred for 35 min during which time a light-coloured precipitate was formed. Ethyl acetate (20 mL) was added upon cooling and the mixture filtered on a frit. The beige solid was redissolved in dilute HCl (pH 2, 300 mL) and brought to pH 5 with dropwise addition of NaOH (1 M). After further cooling to 4 °C, the solid was isolated by filtration and dried to yield **$HL_1$** (0.77 g, 82% from **3b**, 40% from *N,N*-dimethyl-1,4-benzenediamine)**.** Crystals suitable for X-ray diffraction study were obtained by slow evaporation at 4 °C of a 95% MeOH/5% $CH_2Cl_2$ solution of **$HL_1$**, mp 252-254 °C. Anal. Calcd (found) for $C_{14}H_{16}N_2O_2$: C, 68.83 (68.89); H, 6.60 (6.60); N 11.65 (11.47). Infrared spectrum (cm$^{-1}$, total reflectance): 3153 (br), 1628, 1583, 1522, 1488, 1295. $^1$H NMR (DMSO-$d_6$, 300.13 MHz) δ, ppm: 8.18 (d, $^3J_{6,5}$ = 7.0 Hz, 1H; *H*6), 7.38 (d, $^3J$ = 8.9 Hz, 2H; Ar*H*), 7.26 (d, $^3J_{5,6}$ = 7.0 Hz, 1H; *H*5), 6.92 (d, $^3J$ = 8.9 Hz, 2H; Ar*H*), 3.00 (s, 6H; N(C$H_3$)$_2$), 2.21 (s, 3H; C2-

C$H_3$). $^{13}$C NMR (DMSO-$d_6$, 75.48 MHz) δ, ppm: 169.37 (*C*4), 150.24 (*C*6), 144.91 (*C*3), 138.39 (*C*2), 130.44, 129.30 (Ar*C*), 127.25, 112.08 (Ar*C*H), 110.55 (*C*5), 39.99 (N(*C*H$_3$)$_2$), 13.28 (C2-*C*H$_3$).

**3-Methoxy-2-methyl-1-(4-methylaminophenyl)-4(1*H*)-pyridinone (4b). 2b** (3.00 g, 21.4 mmol) and *N*-methyl-1,4-phenylenediamine dichloride (3.60 g, 18.4 mmol) were combined in 2:3 $H_2O$:MeOH (34 mL) in a round-bottomed flask (100 mL); after adjusting the pH to 7, the mixture was refluxed with stirring for 30 h. The solvent was removed *in vacuo* and the residue taken up in $CH_2Cl_2$ (100 mL) for extraction with pH 5 $H_2O$ (3 x 75 mL). The organic phase was retained and all solvent removed to yield **4b** as a dark purple residue (3.80 g, 85%). $^1$H NMR (DMSO-$d_6$, 300.13 MHz) δ, ppm: 7.47 (d, $^3J_{6,5}$ = 7.5 Hz, 1H; *H*6), 7.10 (d,$^3$ *J* = 8.8 Hz, 2H; Ar*H*), 6.59 (d,$^3$ *J* = 8.8 Hz, 2H; Ar*H*), 6.13 (d, $^3J_{5,6}$ = 7.5 Hz, *H*5), 6.10 (q, 1H; N*H*CH$_3$), 3.73 (s, 3H; C3-OC*H*$_3$), 2.70 (d, $^3J$ = 4.9 Hz, 3H; NHC*H*$_3$), 1.95 (s, 3H; C2-C*H*$_3$).

**3-Hydroxy-2-methyl-1-(4-methylaminophenyl)-4(1*H*)-pyridinone ($HL_2$). 4b** (3.80 g, 15.6 mmol) was dissolved in $CH_2Cl_2$ (90 mL) and stirred at -78 °C (acetone/$CO_{2(s)}$). Boron tribromide ($BBr_3$, 6.0 mL, 63 mmol) was added dropwise and the resultant mixture was stirred for 45 min after which time the flask was transferred to a -12 °C cooling bath (ethylene glycol/$CO_{2(s)}$) and stirred an additional 3 h. The mixture was allowed to warm overnight to room temperature, after which the reaction was quenched by $Et_2O$ addition (10 mL) and all solvents were removed under reduced pressure. The resulting purple solid was dissolved in warm pH 1.5 $H_2O$ (HCl, 250 mL), affording a purple solution; neutralization (to pH 7, dropwise addition of 5 M NaOH) caused black precipitate to form. The solid **$HL_2$** was collected by suction filtration (3.54 g, 83% from *N*-methyl-1,4-phenylenediamine dichloride). Crystals suitable for X-ray diffraction study were obtained by slow evaporation of a 99% MeOH/1% $H_2O$ solution of **$HL_2$** at room temperature, mp 198-200 °C. Anal. Calcd (found) for $C_{13}H_{14}N_2O_2$: C, 67.81 (68.10); H, 6.13 (6.14); N 12.17 (12.17). Infrared spectrum (cm$^{-1}$, total reflectance): 3417, 3046 (br), 1623, 1573, 1513, 1489, 1297. $^1$H NMR (DMSO-$d_6$, 300.13 MHz) δ, ppm: 7.45 (d, $^3J_{6,5}$ = 7.3 Hz, 1H; *H*6), 7.10 (d, $^3J$ = 8.7 Hz, 2H; Ar*H*), 6.60 (d, $^3J$ = 8.8 Hz, 2H; Ar*H*), 6.16 (d, $^3J_{5,6}$ = 7.2 Hz, 1H; *H*5), 6.08 (q, 1H; N*H*CH$_3$), 2.71 (d, $^3J$ = 5.0 Hz, 3H; NHC*H*$_3$), 1.96 (s, 3H; C2-C*H*$_3$). $^{13}$C NMR (DMSO-$d_6$, 75.48 MHz) δ, ppm: 169.31 (*C*4), 150.09 (*C*6), 144.87 (*C*3), 138.44 (*C*2), 129.99, 129.37 (Ar*C*), 127.31, 111.41 (Ar*C*H), 110.47 (*C*5), 29.57 (NH*C*H$_3$), 13.24 (C2-*C*H$_3$).

**3-Benzyloxy-2-methyl-1-(4-nitrophenyl)-4(1*H*)-pyridinone (10b).** In a manner adapted from that already published,[9] **2a** (2.57 g, 11.9 mmol) was combined with *p*-nitroaniline (2.50 g, 18.1 mmol) in 5:1 (3% HCl):MeOH (60 mL) and gently refluxed for 73 h. While still hot, the aqueous phase was decanted. The oil-like phase was dried *in vacuo* and purified by column chromatography (40% $CH_3CN$/60% $CH_2Cl_2$) to yield **10b** (0.78 g, 19%). This was used in the next step without further purification. ESI-MS(+): 337 (M+H$^+$), 359 (M+Na$^+$).

**1-(4-Aminophenyl)-3-hydroxy-2-methyl-4(1*H*)-pyridinone ($HL_3$). 10b** (0.78 g, 2.3 mmol) was combined with MeOH and $H_2O$ (19.6 and 5.0 mL, respectively). The hydrogenation catalyst (10% Pd on C; 0.4 g) was wetted (0.5 mL $H_2O$), added to the mixture, and a small amount of acid was added (0.06 M HCl, 1 mL). After sealing the flask with a rubber septum, an $H_{2(g)}$ balloon was attached to provide positive $H_{2(g)}$ pressure for the 22-h reaction time. The reaction was monitored *via* ESI-MS and once

deemed complete, the mixture was filtered through Celite and concentrated *in vacuo* to yield **$HL_3$** as a pink solid. Recrystallization from 4:1 MeOH:$H_2O$ (200 mL) yielded clear beige crystalline **$HL_3$** (0.24 g, 48%). Crystals suitable for X-ray diffraction study were obtained by slow evaporation at 4 °C of a 4:1 MeOH:$H_2O$ solution of **5c**, mp 185-187 °C. Anal. Calcd (found) for **$HL_3$**•0.5$H_2O$•0.5MeOH; $C_{25}H_{30}N_4O_6$: C, 62.23 (62.66); H, 6.27 (6.35); N 11.61 (11.94). Infrared spectrum ($cm^{-1}$, total reflectance): 3313, 3204 (br), 1622, 1555, 1512, 1487, 1292. $^1$H NMR (DMSO-$d_6$, 300.13 MHz) δ, ppm: 7.46 (d, $^3J_{6,5}$ = 6.4 Hz, 1H; *H*6), 7.01 (d, *J* = 7.4 Hz, 2H; Ar*H*), 6.63 (d, *J* = 7.2 Hz, 2H; Ar*H*), 6.17 (d, $^3J_{5,6}$ = 6.0 Hz, 1H; *H*5), 3.71 (s, 2H; N$H_2$), 1.95 (s, 3H; C2-C$H_3$). $^{13}$C NMR (DMSO-$d_6$, 75.48 MHz) δ, ppm: 169.34 (*C*4), 149.34 (*C*6), 144.91 (*C*3), 138.42 (*C*2), 130.12, 129.45 (Ar*C*), 127.30, 113.67 (Ar*C*H), 110.52 (*C*5), 13.26 (C2-*C*$H_3$).

**3-Hydroxy-2-methyl-1-(4-nitrophenyl)-4(1*H*)-pyridinone (10c).** The title compound was prepared as previously published from **2a** and *p*-nitroaniline.[9]

**1-(6-Benzothiazolyl)-3-benzyloxy-2-methyl-4(1*H*)-pyridinone (6b). 2a** (0.75 g, 3.5 mmol) and 6-aminobenzothiazole (0.45 g, 3.0 mmol) were combined with 5 mL MeOH and 7 mL $H_2O$ in a 20-mL thick-walled glass tube with o-ring-sealing PTFE stopper in the same apparatus as described in **3b**. Heating to 110-126 °C for 96 h afforded a clear yellow supernatant over an orange viscous liquid. The solvent was removed *in vacuo* and the resultant orange solid dissolved in minimal warm 9:1 acetone:MeOH. A fine white precipitate formed after 2 h at room temperature and was isolated by vacuum filtration to yield **6b** (0.24 g, 23%), mp 193-194 °C. Anal. Calcd (found) for $C_{20}H_{16}N_2O_2S$: C, 68.94 (68.83); H, 4.63 (4.86); N 8.04 (8.03). $^1$H NMR (DMSO-$d_6$, 300.13 MHz) δ, ppm: 9.55 (s, 1H; benzothiazole-*H*2), 8.34 (s, 1H; benzothiazole-*H*7), 8.22 (d, $^3J_{7,8}$ = 8.2 Hz, 1H; benzothiazole-*H*5), 7.70 (d, $^3J_{6,5}$ = 7.5 Hz, 1H; pyrid-*H*6), 7.58 (d, $^3J_{8,7}$ = 8.7 Hz, 1H; benzothiazole-*H*4), 7.38 (m, 5H; Bn-Ar*H*), 7.53 (d, $^3J_{5,6}$ = 7.5 Hz, 1H; pyrid-*H*5), 1.90 (s, 3H; C2-C$H_3$).

**1-(6-Benzothiazolyl)-3-hydroxy-2-methyl-4(1*H*)-pyridinone ($HL_4$).** Acidic debenzylation of **6b** was performed in a similar manner to that of **3b**. Beige solid **$HL_4$** was precipitated from dilute HCl (pH 1.5, 100 mL) by addition of NaOH (1 M, dropwise, to pH 6); further cooling to 4 °C allowed isolation of **$HL_4$** by filtration (1.63 g, 86%). Crystals suitable for X-ray diffraction were obtained by slow evaporation (room temperature) of a methanolic solution of **$HL_4$/$GL_4$**, mp 280-282 °C. Anal. Calcd (found) for $C_{13}H_{10}N_2O_2S$: C, 60.45 (60.70); H, 3.90 (4.04); N, 10.85 (10.78). Infrared spectrum ($cm^{-1}$, total reflectance): 3043 (br), 1624, 1588, 1556, 1493, 1297. $^1$H NMR (DMSO-$d_6$, 300.13 MHz) δ, ppm: 9.55 (s, 1H; benzothiazole-*H*2), 8.36 (s, 1H; benzothiazole-*H*7), 8.23 (d, $^3J_{7,8}$ = 8.2 Hz, 1H; benzothiazole-*H*5), 7.65 (d, $^3J_{6,5}$ = 7.8 Hz, 1H; pyrid-*H*6), 7.62 (m, 1H; benzothiazole-*H*4), 6.24 (d, $^3J_{5,6}$ = 7.3 Hz, 1H; pyrid-*H*5), 1.99 (s, 3H; C2-C$H_3$). $^{13}$C NMR (DMSO-$d_6$, 75.48 MHz) δ, ppm: 161.59 (pyrid-*C*4), 159.49 (*C*11), 153.54 (pyrid-*C*6), 149.10 (pyrid-*C*3), 140.14, 138.94 (benzothiazole-Ar*C*/Ar*C*H), 138.13 (pyrid-*C*2), 134.54, 124.69, 123.96, 121.14 (benzothiazole-Ar*C*/Ar*C*H), 110.59 (pyrid-*C*5), 14.48 (C2-*C*$H_3$).

**1-(2-Benzothiazolyl)-3-benzyloxy-2-methyl-4(1*H*)-pyridinone (7b). 2a** (1.64 g, 7.58 mmol) and 2-aminobenzothiazole (1.25 g, 8.32 mmol) were combined with 5 mL MeOH and 7 mL $H_2O$ in a 20-mL thick-walled glass tube with o-ring-sealing PTFE stopper in the same apparatus as described in **3b**.

Heating to 110-126 °C for 96 h afforded a clear, colorless supernatant over a brown viscous liquid. The entire contents of the tube were transferred to a round-bottomed flask (100 mL) with MeOH (50 mL), concentrated *in vacuo* and extracted with $CH_2Cl_2$ (3 x 25 mL). The organic fraction was dried ($MgSO_4$) and evaporated to dryness whereupon the mixture was separated by column chromatography (silica, 100% EtOAc to 9:2 EtOAc:MeOH). White solid **7b** was obtained (0.22 g, 9%). Anal. Calcd (found) for $C_{20}H_{16}N_2O_2S$: C, 68.94 (68.83); H, 4.63 (4.86); N 8.04 (8.03). $^1$H NMR (DMSO-$d_6$, 300.13 MHz) δ, ppm: 8.22 (m, 1H; benzothiazole-*H*7), 8.08 (m, 1H; benzothiazole-*H*4), 8.01 (d, $^3J_{6,5}$ = 7.5 Hz, 1H; pyrid-*H*6), 7.62 (m, 2H; benzothiazole-*H*5,*H*6), 7.40 (m, 5H; Bn-Ar*H*), 6.36 (d, $^3J_{6,5}$ = 7.8 Hz, 1H; pyrid-*H*5), 5.10 (s, 2H; Bn-C$H_2$), 2.15 (s, 3H; C2-C$H_3$).

**1-(2-Benzothiazolyl)-3-hydroxy-2-methyl-4(1*H*)-pyridinone ($HL_5$).** Acidic debenzylation of **7b** was performed in a similar manner to that of **3b**. Beige solid **7c** was precipitated from aqueous NaOH (pH 13, 10 mL) by addition of HCl (6 M, dropwise, to pH 7); cooling to 4 °C allowed filtration of beige solid **$HL_5$** (0.12 g; 74% yield from **7b**, 6% from 2-aminobenzothiazole). X-ray quality crystals were obtained by slow evaporation of a solution of **$HL_5$** (2:1 MeOH:$CH_2Cl_2$, room temperature), mp 245-247°C. Anal. Calcd (found) for $C_{13}H_{10}N_2O_2S$: C, 60.45 (60.34); H, 3.90 (3.88); N 10.85 (10.82). Infrared spectrum ($cm^{-1}$, total reflectance): 3091 (br), 1624, 1576, 1508, 1483, 1302. $^1$H NMR (DMSO-$d_6$, 300.13 MHz) δ, ppm: 8.23 (m, 1H; benzothiazole-*H*7), 8.09 (m, 1H; benzothiazole-*H*4), 7.98 (d, $^3J_{6,5}$ = 7.5 Hz, 1H; pyrid-*H*6), 7.61 (m, 2H; benzothiazole-*H5,H*6), 6.33 (d, $^3J_{5,6}$ = 7.5 Hz, 1H; pyrid-*H*5), 2.26 (s, 3H; C2-C$H_3$). $^{13}$C NMR (DMSO-$d_6$, 75.48 MHz) δ, ppm: 170.90 (pyrid-*C*4), 160.25 (benzothiazole-*C*2), 149.15 (pyrid-*C*6), 145.09 (pyrid-*C*3), 137.72 (pyrid-*C*2), 135.01, 127.95 (benzothiazole-Ar*C*), 127.28, 126.57, 123.48, 122.79 (benzothiazole-Ar*C*H), 112.25 (pyrid-*C*5), 13.04 (C2-*C*$H_3$).

**3-Benzyloxy-1-[4-(4-bromophenyl)-2-thiazolyl]-2-methyl-4(1*H*)-pyridinone (8b).** A mixture of **2a** (1.3 g; 6.0 mmol) and 2-amino-4-(4-bromophenyl)thiazole (1.68 g; 6.58 mmol) in 15 mL of water/methanol (5:1) was heated in a sealed, thick-walled glass tube in the same apparatus as described in **3b** at 170 °C for 24 h. After cooling to room temperature the reaction mixture was extracted three times with $CHCl_3$. The solvent was removed from the combined organic layers using a rotary evaporator and the residue was purified by column chromatography (silica, EtOAc) to yield **8b** (0.75 g, 28%). Anal. Calcd (found) for $C_{22}H_{17}BrN_2O_2S$: C, 58.28 (58.35); H, 3.78 (3.65); N 6.18 (6.27). $^1$H NMR ($CDCl_3$, 300 MHz) δ, ppm: 7.73 (d, $^3J$ = 8.5 Hz, 2H; ArH), 7.58 (d, $^3J$ = 8.5 Hz, 2H; ArH), 7.56 (s, 1H; thiazole-*H*2), 7.52 (d, $^3J_{5,6}$ = 7.5 Hz, 1H; pyrid-*H*5), 7.44 (dd, $^3J$ = 7.4 Hz, $^3J$ = 1.8 Hz, 2H; benzyl-Ar*H*), 7.37-7.32 (m, 3H, benzyl-Ar*H*), 6.52 (d, $^3J_{6,5}$ = 7.5 Hz, 1H; pyrid-*H*6), 5.24 (s, 2H, benzyl-C$H_2$), 2.12 (s, 3H; C2-C$H_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ, ppm: 174.41 (pyrid-*C*4), 159.97 (thiazole-*C*2), 152.16 (pyrid-*C*6), 145.81 (pyrid-*C*3), 140.19, 137.85 (pyrid-*C*2), 137.36, 131.94, 128.91, 127.71, 123.20, 117.55 (thiazole, phenyl, benzyl-Ar*C*/Ar*C*H), 114.27 (pyrid-C5), 73.38 (O-*C*$H_2$-phenyl), 14.07 (C2-*C*$H_3$).

**1-[4-(4-Bromophenyl)-2-thiazolyl]-3-hydroxy-2-methyl-4(1*H*)-pyridinone ($HL_6$).** Acidic debenzylation of **8b** was performed in a similar manner to that of **3b**. After reaction, beige solid was isolated from the reaction mixture and suspended in water; the mixture was basified (pH 9, dropwise addition of $Na_2CO_3$) and extracted with $CH_2Cl_2$. Removal of the solvent *in vacuo* yielded off-white solid

**$HL_6$** (0.20 g, 83%). Anal. Calcd (found) for $C_{15}H_{11}BrN_2O_2S$: C, 49.60 (50.00); H, 3.05 (3.35); N, 7.71 (7.62). Infrared spectrum ($cm^{-1}$, total reflectance): 3043, 1620, 1574, 1531, 1471, 1243, 1196, 757, 598, 561. $^1$H NMR ($CDCl_3$, 300.13 MHz) δ, ppm: 7.74 (d, $^3J$ = 8.5 Hz, 2H; Ar*H*), 7.58 (m, 4H; pyrid-*H*6, thiazole-*H*, Ar*H*), 6.54 (d, $^3J_{5,6}$ = 7.5 Hz, 1H; pyrid-*H*5), 2.38 (s, 3H; C2-$CH_3$). $^{13}$C NMR ($CDCl_3$, 75.48 MHz) δ, ppm: 170.79 (pyrid-*C*4), 159.78 (thiazole-*C*2), 152.97 (pyrid-*C*6), 145.27 (pyrid-*C*3), 137.24 (pyrid-*C*2), 132.15, 131.86, 128.46, 127.70, 123.25, 114.22 (thiazole, phenyl-Ar*C*/Ar*C*H), 111.87 (pyrid-C5), 13.49 (C2-*C*$H_3$).

**1.6. Synthesis and characterization of glycosylated prodrugs.**

**3-(β-D-Glucopyranosyloxy)-2-methyl-1-(4-dimethylaminophenyl)-4(1*H*)-pyridinone ($GL_1$).** 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**11**, 0.73 g, 1.8 mmol) was dissolved in dry $CH_2Cl_2$ (14 mL). **$HL_1$** (0.34 g, 1.4 mmol) was dissolved in anhydrous KOH/MeOH solution (0.44 M KOH, 7.0 mL MeOH); the pro-ligand solution was added dropwise to the glucose solution. The reaction mixture was stirred (room temperature, 65 h) and monitored by TLC (alumina, 1:1 iPrOH:$H_2O$). The resultant mixture was neutralized (dropwise addition of 12 M HCl), evaporated to dryness, and the residue taken up in dry MeOH (8 mL) for filtration. Column chromatography (alumina, 15% $H_2O$ in iPrOH) yielded **$GL_1$** (0.10 g, 18% from **$HL_1$**). $^1$H NMR (MeOD-$d_4$, 300.13 MHz) δ, ppm: 8.30 (d, $^3J_{6,5}$ = 7.1 Hz, 1H; pyrid-*H*6), 7.31 (overlapping doublets, 3H; Ar*H,* pyrid-*H*5), 6.95 (d, $^3J$ = 9.1 Hz, 2H; Ar*H*), 4.99 (d, $^3J$ = 7.5 Hz, 1H; gluc-*H*1), 3.86 (dd, $^2J_{6a,6b}$ = 12.0 Hz, $^3J_{6a,5}$ = 1.5 Hz, 1H; gluc-*H*6a), 3.68 (dd, $^2J_{6b,6a}$ = 11.7 Hz, $^3J_{6b,5}$ = 5.1 Hz, 1H; gluc-*H*6b), 3.47 (m, 4H; gluc-*H*2,*H*3,*H*4,*H*5), 3.07 (s, 6H; N($CH_3$)$_2$), 2.47 (s, 3H; C2-$CH_3$). $^{13}$C NMR (MeOD-$d_4$ 75.48 MHz) δ, ppm: 166.41 (pyrid-*C*4), 153.87 (pyrid-*C*6), 152.80 (Ar*C*), 145.19 (pyrid-*C*3), 143.18 (pyrid-*C*2), 131.75 (Ar*C*), 127.73 (Ar*C*H), 114.32 (pyrid-*C*5), 114.09 (Ar*C*H), 106.25 (gluc-*C*1), 78.98, 77.81 (gluc-*C*3,*C*5), 75.52 (gluc-*C*2), 71.18 (gluc-*C*4), 62.50 (gluc-*C*6), 40.96 (pyrid-N($CH_3$)$_2$), 16.64 (pyrid-C2-*C*$H_3$). HR-ESIMS *m/z* for $C_{20}H_{26}N_2O_7Na$ ($M+Na^+$) calcd (found): 429.1638 (429.1640).

**3-(β-D-Glucopyranosyloxy)-2-methyl-1-(4-methylaminophenyl)-4(1*H*)-pyridinone ($GL_2$). 11** (0.36 g, 0.88 mmol) was dissolved in dry $CH_2Cl_2$ (7 mL). **$HL_2$** (0.17 g, 0.72 mmol) was dissolved in anhydrous KOH/MeOH solution (0.44 M KOH, 3.5 mL MeOH); the pro-ligand solution was added dropwise to the stirred glucose solution. The reaction mixture was stirred (room temperature, 70 h) and monitored by TLC (7:2:1 iPrOH:$H_2O$:$NH_3$). The resultant mixture was neutralized (dropwise addition of 12 M HCl), evaporated to dryness, and the residue taken up in dry MeOH (5 mL) for filtration. Semi-preparative HPLC (100% $H_2O$ to 100% ACN over 45 min) allowed collection of **$GL_2$** (0.08 g, 28% from **$HL_2$**). $^1$H NMR (MeOD-$d_4$, 400.13 MHz) δ, ppm: 8.29 (d, $^3J_{6,5}$ = 7.2 Hz, 1H; pyrid-*H*6), 7.23 (overlapping doublets, 3H; Ar*H,* pyrid-*H*5), 6.77 (d, $^3J$ = 8.9 Hz, 2H; Ar*H*), 4.96 (d, $^3J$ = 7.9 Hz, 1H; gluc-*H*1), 3.86 (dd, $^2J_{6a,6b}$ = 12.0 Hz, $^3J_{6a,5}$ = 2.1 Hz, 1H; gluc-*H*6a), 3.67 (dd, $^2J_{6b,6a}$ = 12.0 Hz, $^3J_{6b,5}$ = 5.5 Hz, 1H; gluc-*H*6b), 3.57, 3.46, 3.38, 3.34 (m, 4H; gluc-*H*2,*H*3,*H*4,*H*5), 2.84 (s, 3H; NHC$H_3$), 2.47 (s, 3H; C2-C$H_3$). $^{13}$C NMR (DMSO-$d_6$ 100.62 MHz) δ, ppm: 167.92 (pyrid-*C*4), 150.67 (pyrid-*C*6), 148.12 (pyrid-*C*3), 142.76 (Ar*C*), 142.48 (pyrid-*C*2), 129.45 (Ar*C*H), 126.92 (Ar*C*), 113.82 (pyrid-*C*5), 111.57 (Ar*C*H), 105.00 (gluc-*C*1), 77.52, 76.56 (gluc-*C*3,*C*5), 74.04 (gluc-*C*2), 69.63 (gluc-*C*4), 60.98 (gluc-*C*6), 29.60 (pyrid-

N($CH_3$)$_2$), 15.46 (pyrid-C2-$CH_3$). HR-ESIMS *m/z* for $C_{19}H_{24}N_2O_7Na$ ($M+Na^+$) calcd (found): 415.1481 (415.1474).

**3-(β-D-Glucopyranosyloxy)-2-methyl-1-(4-nitrophenyl)-4(1*H*)-pyridinone (10d). 11** (1.6 g, 3.8 mmol) was dissolved in dry $CH_2Cl_2$ (28 mL). **10c** (0.76 g, 3.1 mmol) was dissolved in anhydrous KOH/MeOH solution (0.44 M KOH, 14 mL); the pro-ligand solution was added dropwise to the stirred glucose solution. The reaction mixture was stirred (room temperature, 44 h) and monitored by TLC (9:1 EtOAc:MeOH). The resultant mixture was neutralized (dropwise addition of 12 M HCl), evaporated to dryness, and the residue taken up in dry MeOH (5 mL) for filtration. Column chromatography (alumina, 15% $H_2O$ in iPrOH) yielded light yellow solid **10d** (0.26 g, 21% from **10c**). $^1$H NMR (MeOD-$d_4$, 300.13 MHz) δ, ppm: 8.46 (d, $^3J$ = 9.1 Hz, 2H; Ar*H*), 7.81 (d, $^3J_{6,5}$ = 7.5 Hz, 1H; pyrid-*H*6), 7.76 (d, $^3J$ = 9.0 Hz, 2H; Ar*H*), 6.60 (d, $^3J_{6,5}$ = 7.5 Hz, 1H; pyrid-*H*5), 4.77 (d, $^3J$ = 7.5 Hz, 1H; gluc-*H*1), 3.86 (2 overlapping dd, 2H; gluc-*H*6a,b), 3.69, 3.65, 3.45 (m, 4H; gluc-*H*2,*H*3,*H*4,*H*5), 2.29 (s, 3H; C2-C$H_3$). $^{13}$C NMR (MeOD-$d_4$, 75.48 MHz) δ, ppm: 175.38 (pyrid-*C*4), 149.98 (pyrid-*C*6), 147.70 (pyrid-*C*3), 146.22 (pyrid-*C*2), 141.90 (Ar*C*), 129.94, 126.48 (Ar*C*H), 117.39 (pyrid-*C*5), 106.95 (Ar*C*), 105.56 (gluc-*C*1), 78.56, 78.10 (gluc-*C*3,*C*5), 75.66 (gluc-*C*2), 71.25 (gluc-*C*4), 62.88 (gluc-*C*6), 15.90 (pyrid-C2-*C*$H_3$). HR-ESIMS *m/z* for $C_{18}H_{20}N_2O_9Na$ ($M+Na^+$) calcd (found): 431.1067 (431.1077).

**1-(4-Aminophenyl)-3-(β-D-glucopyranosyloxy)-2-methyl-4(1*H*)-pyridinone (GL$_3$). 10d** (0.02 g, 0.05 mmol) was dissolved in MeOH (1.2 mL). Pd (10% on activated charcoal, 0.05 g) was first wetted ($H_2O$, 0.5 mL) and added to the reaction flask. The reaction mixture was stirred under positive $H_{2(g)}$ pressure for 9 h, whereupon the reaction mixture was filtered and evaporated to dryness *in vacuo*. **GL$_3$** was obtained as a beige solid (0.010 g, 54% from **10d**). $^1$H NMR (DMSO-$d_6$, 400.13 MHz) δ, ppm: 7.81 (d, $^3J_{6,5}$ = 7.5 Hz, 1H; pyrid-*H*6), 7.10 (d, $^3J$ = 8.2 Hz, 2H; Ar*H*), 6.68 (d, $^3J$ = 8.5 Hz, 2H; Ar*H*), 6.53 (d, $^3J_{5,6}$ = 7.5 Hz, 1H; pyrid-*H*5), 4.56 (d, $^3J$ = 7.2 Hz, 1H; gluc-*H*1), 3.65 (d, $^2J_{6a,6b}$ = 10.2 Hz, 1H; gluc-*H*6a), 3.44 (dd, $^2J_{6b,6a}$ = 12.0 Hz, $^3J_{6b,5}$ = 5.5 Hz, 1H; gluc-*H*6b), 3.20, 3.12 (m, 4H; gluc-*H*2,*H*3,*H*4,*H*5), 2.17 (s, 3H; C2-C$H_3$). $^{13}$C NMR (DMSO-$d_6$, 100.62 MHz) δ, ppm: 170.69 (pyrid-*C*4), 145.50 (pyrid-*C*6), 143.66 (pyrid-*C*3), 141.95 (pyrid-*C*2), 130.02, 127.15, 125.68, (2Ar*C*, 1Ar*C*H), 114.73 (pyrid-*C*5), 114.06 (Ar*C*H), 105.96 (gluc-*C*1), 77.46, 76.78 (gluc-*C*3,*C*5), 74.03 (gluc-*C*2), 69.53 (gluc-*C*4), 60.99 (gluc-*C*6), 15.03 (pyrid-C2-*C*$H_3$). HR-ESIMS *m/z* for $C_{18}H_{22}N_2O_7Na$ ($M+Na^+$) calcd (found): 401.1325 (401.1318).

**1-(6-Benzothiazolyl)-3-(β-D-glucopyranosyloxy)-2-methyl-4(1*H*)-pyridinone (GL$_4$). 11** (0.72 g, 1.7 mmol) was dissolved in dry $CH_2Cl_2$ (14 mL). **HL$_4$** (0.37 g, 1.4 mmol) was dissolved in anhydrous KOH/MeOH solution (0.22 M KOH, 6.8 mL); the pro-ligand solution was added dropwise to the stirred glucose solution. The reaction mixture was stirred (room temperature, 72 h) and monitored by TLC (10% MeOH in acetone). The resultant mixture was neutralized (dropwise addition of 12 M HCl), evaporated to dryness, the residue taken up in dry MeOH (5 mL) and filtered. Semi-preparative HPLC (100% $H_2O$ to 100% ACN over 45 min) allowed collection of **GL$_4$** (0.07 g, 12% from **HL$_4$**). $^1$H NMR (DMSO-$d_6$, 400.13 MHz) δ, ppm: 9.59 (s, 1H; benzothiazole-*H*2), 8.43 (s, 1H; benzothiazole-*H*7), 8.27 (d, $^3J$ = 8.9 Hz, 1H; benzothiazole-*H*5), 8.04 (d, $^3J_{6,5}$ = 7.2 Hz, 1H; pyrid-*H*6), 7.70 (d, $^3J$ = 8.8 Hz, 1H;

benzothiazole-*H*4), 6.66 (d, $^{3}J_{5,6}$ = 7.2 Hz, 1H; pyrid-*H*5), 4.65 (d, $^{3}J$ = 7.2 Hz, 1H; gluc-*H*1), 3.66 (d, $^{2}J_{6a,6b}$ = 11.3 Hz, 1H; gluc-*H*6a), 3.46 (dd, $^{2}J_{6b,6a}$ = 11.3 Hz, $^{3}J_{6b,5}$ = 5.4 Hz, 1H; gluc-*H*6b), 3.24, 3.15 (m, 4H; gluc-*H*2,*H*3,*H*4,*H*5), 2.21 (s, 3H; C2-C$H_3$). $^{13}$C NMR (DMSO-$d_6$, 100.62 MHz) δ, ppm: 170.89 (pyrid-*C*4), 159.21 (benzothiazole-*C*2), 153.28 (pyrid-*C*6), 145.35 (pyrid-*C*3), 143.59 (pyrid-*C*2), 141.71, 138.31, 134.57, 125.26, 123.89, 121.59 (benzothiazole-Ar*C*/Ar*C*H), 114.88 (pyrid-*C*5), 105.76 (gluc-*C*1), 77.52, 76.76 (gluc-*C*3,*C*5), 74.09 (gluc-*C*2), 69.56 (gluc-*C*4), 61.00 (gluc-*C*6), 15.26 (pyrid-C2-*C*$H_3$). HR-ESIMS *m/z* for $C_{19}H_{20}N_2O_7SNa$ (M+$Na^+$) calcd (found): 443.0889 (443.0895).

**1-(2-Benzothiazolyl)-3-(β-D-glucopyranosyloxy)-2-methyl-4(1*H*)-pyridinone ($GL_5$). 11** (0.78 g, 1.9 mmol) was dissolved in dry $CH_2Cl_2$ (14 mL). **$HL_5$** (0.40 g, 1.5 mmol) was dissolved in an anhydrous KOH/MeOH solution (0.44 M KOH, 6.7 mL); the pro-ligand solution was added dropwise to the stirred glucose solution. The reaction mixture was stirred (room temperature, 24 h) and monitored by TLC (9:1 EtOAc:MeOH). The resultant mixture was neutralized (dropwise addition of 12 M HCl), evaporated to dryness and the residue taken up in dry MeOH (5 mL) for filtration. Semi-preparative HPLC (100% $H_2O$ to 100% ACN over 45 min) allowed collection of **$GL_5$** (0.15 g, 24% from **7c**). $^{1}$H NMR (MeOD-$d_4$, 400.13 MHz) δ, ppm: 8.28 (d, $^{3}J_{6,5}$ = 7.5 Hz, 1H; pyrid-*H*6), 8.10 (overlapping doublets, 2H; benzothiazole-*H*4,*H*7), 7.62 (m, 2H; benzothiazole-*H*5,*H*6), 6.88 (d, $^{3}J_{5,6}$ = 7.5 Hz, 1H; pyrid-*H*5), 4.90 (d, $^{3}J$ = 7.5 Hz, 1H; gluc-*H*1), 3.86 (dd, $^{2}J_{6a,6b}$ = 12.0 Hz, $^{3}J_{6a,5}$ = 2.1 Hz, 1H; gluc-*H*6a), 3.69 (dd, $^{2}J_{6b,6a}$ = 12.0 Hz, $^{3}J_{6b,5}$ = 5.5 Hz, 1H; gluc-*H*6b), 3.50, 3.39, 3.34 (m, 4H; gluc-*H*2,*H*3,*H*4,*H*5), 2.54 (s, 3H; C2-C$H_3$). $^{13}$C NMR (DMSO-$d_6$ 100.62 MHz) δ, ppm: 173.34 (pyrid-*C*4), 159.64 (benzothiazole-*C*2), 148.97 (pyrid-*C*6), 144.07 (pyrid-*C*3), 142.87 (pyrid-*C*2), 140.24, 135.38, 127.43, 126.91, 123.69, 122.94 (benzothiazole-Ar*C*/Ar*C*H), 116.13 (pyrid-*C*5), 105.64 (gluc-*C*1), 77.50, 76.74 (gluc-*C*3,*C*5), 74.10 (gluc-*C*2), 69.60 (gluc-*C*4), 61.05 (gluc-*C*6), 14.50 (pyrid-C2-*C*$H_3$). HR-ESIMS *m/z* for $C_{19}H_{20}N_2O_7SNa$ (M+$Na^+$) calcd (found): 443.0889 (443.0897).

**1-[4-(4-Bromophenyl)-2-thiazolyl]-3-(β-D-glucopyranosyloxy)-2-methyl-4(1*H*)-pyridinone ($GL_6$).** 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2.74 g, 6.7 mmol) was stirred in dry $CH_2Cl_2$ (15 mL). A suspension of **$HL_6$** (2.00 g, 5.5 mmol) in anhydrous KOH/MeOH solution (0.44 M KOH, 12.5 mL) was added dropwise and the reaction mixture was stirred (room temperature, 24 h). More KOH was added to fully deprotect the sugar (0.50 g, 8.9 mmol) and the mixture stirred for another 3 h before neutralizing (dropwise addition of 12 M HCl). The solvent was then removed and the residue extracted with MeOH (5 mL). The solution was concentrated *in vacuo* and column chromatography (silica; EtOAc:MeOH 4:1) afforded the white crystalline product (1.2 g, 42%). Anal. Calcd (found) for $C_{21}H_{21}BrN_2O_7S{\cdot}CH_3OH$: C, 47.40 (47.30); H, 5.03 (5.14); N, 4.52 (4.41). $^{1}$H NMR (MeOD-$d_4$, 300.13 MHz) δ, ppm: 8.11 (s, 1H; thiazole-Ar*H*), 7.98 (d, $^{3}J_{6,5}$ = 7.6 Hz, 1H; pyrid-*H*6), 7.86 (d, $^{3}J$ = 6.7 Hz, 2H; Ar*H*), 7.60 (d, $^{3}J$ = 6.7 Hz, 2H; Ar*H*), 6.56 (d, $^{3}J_{5,6}$ = 7.6 Hz, 1H; pyrid-*H*5), 4.79 (d, $^{3}J$ = 7.6 Hz, 1H; gluc-*H*1), 3.83 (dd, $^{2}J_{6a,6b}$ = 11.8 Hz, $^{3}J_{6a,5}$ = 1.9 Hz, 1H; gluc-*H*6a), 3.65 (dd, $^{2}J_{6b,6a}$ = 11.9 Hz, $^{3}J_{6b,5}$ = 5.3 Hz, 1H; gluc-*H*6b), 3.41-3.45 (m, 2H; gluc-C*H*), 3.3-3.4 (m, 2H; gluc-C*H*), 2.45 (s, 3H; C2-C$H_3$). $^{13}$C NMR (MeOD-$d_4$, 100.05 MHz) δ, ppm: 176.46 (pyrid-*C*4), 157.92 (thiazole-*C*2), 153.67 (thiazole-*C*5), 146.61, 146.17 (Ar*C*, pyrid-*C*2), 142.20 (pyrid-*C*6), 136.69 (Ar*C*H), 133.59 (pyrid-*C*3), 129.48 (Ar*C*H),

124.28 (Ar*C*-Br), 118.51 (pyrid-*C*5), 117.69 (thiazole-*C*4), 107.02 (gluc-*C*1), 79.14, 78.82 (gluc-*C*3, *C*5), 76.02 (gluc-*C*2), 71.51 (gluc-*C*4), 63.02 (gluc-*C*6), 15.61 (pyrid-C2-*C*$H_3$).

**3-(β-D-Glucopyranosyloxy)-1-[4-(4-iodophenyl)-2-thiazolyl]-2-methyl-4(1*H*)-pyridinone ($GL_7$).**

***1-[4-(4-Bromophenyl)-3-(2,3,4,6-tetra-O-acetyl-b-D-glucopyranosyloxy)-2-thiazolyl]-2-methyl-4(1H)-pyridinone* (8f).** $GL_6$ was acetylated by suspending $GL_6$ (1.2 g, 2.3 mmol) in dry pyridine (22 mL) and carefully adding acetic anhydride (5 mL). The reaction mixture was stirred overnight (room temperature), quenched by pouring into $H_2O$ (200 mL), and the acetylated product extracted with EtOAc. After washing the organic layer with sodium bisulfate (aqueous, 2 M) to remove most of the pyridine the solvent was removed *in vacuo*. The resultant residue was repeatedly taken up in $CH_2Cl_2$ and dried to remove the residual pyridine, yielding a white crystalline solid **8f** which was used in the following step without further purification (1.24 g, 78%).

***3-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-1-[4-(4-tributylstannylphenyl)-2-thiazolyl]-2-methyl-4(1H)-pyridinone* (12).** To a stirred solution of **8f** (1.37 g, 1.98 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.23 g, 0.200 mmol) in degassed toluene, hexabutylditin (5.8 g; 5.0 mL; 10 mmol) was added. The reaction mixture was stirred overnight at 120 °C under an argon atmosphere. After cooling to room temperature the reaction mixture was filtered through Celite® and concentrated *in vacuo*. Column chromatography (silica; ethyl acetate/methanol 50:1) yielded the tributylstannyl compound **12** as a white crystalline solid (0.722 g, 40%). In some cases, triphenylphosphine oxide was found as an impurity which was removed by semi preparative HPLC chromatography. Anal. Calcd (found) for $C_{41}H_{56}N_2O_{11}SSn$: C, 54.49 (54.61); H, 6.25 (6.24); N, 3.10 (3.13). $^1$H NMR (MeOD-$d_4$, 300.13 MHz) δ, ppm: 8.05 (s, 1H, thiazole-*H*5), 7.95 (d, $^3J$ = 7.6 Hz, 1H; pyrid-*H*6), 7.89 (d, $^3J$ = 7.8 Hz, 2H; Ar*H*), 7.55 (d, $^3J_{6,5}$ = 7.9 Hz, 2H; Ar*H*), 6.52 (d, $^3J_{5,6}$ = 7.6 Hz, 1H; pyrid-*H*5), 5.49 (d, $^3J$ = 7.8 Hz, 1H; gluc-*H*1), 5.36 (dd, $^3J_{3,2}$ = 9.4 Hz, $^3J_{3,4}$ = 9.5 Hz, 1H; gluc-*H*3), 5.16 (dd, $^3J_{2,3}$ = 9.4 Hz, $^3J_{2,1}$ = 8.0 Hz, 1H; gluc-*H*2), 5.07 (dd, $^3J_{4,3}$ = 9.7 Hz, $^3J_{4,5}$ = 9.8 Hz, 1H; gluc-*H*4), 4.29 (dd, $^2J_{6a,6b}$ = 12.4 Hz, $^3J_{6a,5}$ = 5.2 Hz, 1H; gluc-*H*6a), 4.13 (dd, $^2J_{6b,6a}$ = 12.2 Hz, $^3J_{6b,5}$ = 2.0 Hz, 1H; gluc-*H*6b), 3.86, (ddd, $^3J_{5,6a}$ = 4.9 Hz, $^3J_{5,6b}$ = 2.2 Hz, $^3J_{5,4}$ = 9.8 Hz, 1H; gluc-*H*5), 2.34 (s, 3H; pyrid-C$H_3$), 2.06 (s, 3H; Ac-C$H_3$), 2.02 (s, 3H; Ac-C$H_3$), 2.00 (s, 3H; Ac-C$H_3$), 2.00 (s, 3H; Ac-C$H_3$), 1.55 (m, 6H, C$H_2$), 1.35 (m, 6H, C$H_2$), 1.06 (m, 6H, C$H_2$), 0.87 (m, 9H, C$H_3$). $^{13}$C NMR (MeOD-$d_4$, 100.05 MHz) δ, ppm: 173.93 (pyrid-*C*4), 170.92, 170.53, 170.42, 170.16, (CO*CH*$_3$), 159.37 (thiazole-*C*2), 153.38 (thiazole-*C*5), 144.38 (pyrid-*C*2), 143.04 (Ar*C*-Sn(Bu)$_3$), 142.54 (Ar*C*), 140.09 (pyrid-*C*6), 136.78 (Ar*C*H), 133.02 (pyrid-*C*3), 125.43 (Ar*C*H), 116.58 (pyrid-*C*5), 115.87 (thiazole-*C*4) 99.43 (gluc-*C*1), 72.87 (gluc-*C*3), 71.82 (gluc-*C*5), 71.86 (gluc-*C*2), 68.69 (gluc-*C*4), 61.55 (gluc-*C*6), 29.10 (Sn*C*H$_2$), 27.09 (SnCH$_2$*C*H$_2$), 19.65, 19.51, 19.34 (CO*C*H$_3$), 13.77 (pyrid-C2-*C*H$_3$), 12.79, (Sn(CH$_2$)$_3$*C*H$_3$), 9.18 (Sn(CH$_2$)$_2$*C*H$_2$). HR-ESIMS *m/z* for $C_{41}H_{56}N_2O_{11}S^{120}SnNa$ (M+Na$^+$) calcd (found): 927.2525 (927.2513).

***3-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-1-[4-(4-iodophenyl)-2-thiazolyl]-2-methyl-4(1H)-pyridinone (9f).*** To a stirred solution of **12** (0.11 g, 0.122 mmol) in chloroform (15 mL) a solution of

iodine in chloroform (0.1 M) was added until iodine color persisted. The solution was stirred overnight at room temperature. A solution of potassium fluoride in methanol (1 M; 0.4 mL) and an aqueous solution of sodium bisulfite (5%; 1.5 mL) were added sequentially to the reaction mixture causing the iodine color to disappear. The products were extracted with ethyl acetate and the solvent removed from the combined organic layers *in vacuo*. The residue was dissolved in acetonitrile and washed with hexanes several times to remove tributyltin side products. Removal of the solvent yielded pure compound **9f** as a yellow crystalline solid (0.09 g, 99%). Anal. Calcd (found) for $C_{29}H_{31}IN_2O_{11}S\cdot H_2O$: C, 45.80 (45.88); H, 4.37 (4.07); N, 3.68 (3.48). $^1$H NMR (MeOD-$d_4$, 300.13 MHz) δ, ppm: 8.11 (s, 1H, thiazole-*H*5), 7.94 (d, $^3J$ = 7.6 Hz, 1H; pyrid-*H6*), 7.81 (d, $^3J$ = 8.4 Hz, 2H; Ar*H*), 7.73 (d, $^3J$ = 8.4 Hz, 1H; Ar*H*), 6.51 (d, $^3J_{5,6}$ = 7.6 Hz, 1H; pyrid-*H*5), 5.49 (d, $^3J$ = 7.9 Hz, 1H; gluc-*H*1), 5.36 (dd, $^3J_{3,2}$ = 9.4 Hz, $^3J_{3,4}$ = 9.5 Hz, 1H; gluc-*H*3), 5.16 (dd, $^3J_{2,3}$ = 9.5 Hz, $^3J_{2,1}$ = 8.1 Hz, 1H; gluc-*H*2), 5.07 (dd, $^3J_{4,3}$ = 9.6 Hz, $^3J_{4,5}$ = 9.8 Hz, 1H; gluc-*H*4), 4.29 (dd, $^2J_{6a,6b}$ = 12.2 Hz, $^3J_{6a,5}$ = 5.0 Hz, 1H; gluc-*H*6a), 4.12 (dd, $^2J_{6b,6a}$ = 12.2 Hz, $^3J_{6b,5}$ = 1.8 Hz, 1H; gluc-*H*6b), 3.86, (m, 1H; gluc-*H*5), 2.33 (s, 3H; pyrid-C$H_3$), 2.12 (s, 3H; Ac-C$H_3$), 2.02 (s, 3H; Ac-C$H_3$), 2.00 (s, 3H; Ac-C$H_3$), 2.00 (s, 3H; Ac-C$H_3$). $^{13}$C NMR (MeOD-$d_4$, 100.05 MHz) δ, ppm: 173.93 (pyrid-*C*4), 170.82, 170.39, 170.28, 170.02, (CO*C*$H_3$), 159.64 (thiazole-*C*2), 152.05 (thiazole-*C*5), 144.32 (pyrid-*C*2), 142.53 (Ar*C*), 140.09 (pyrid-*C*6), 138.00 (Ar*C*H), 132.98 (pyrid-*C*3), 127.84 (Ar*C*H), 116.70 (pyrid-*C*5), 116.55 (thiazole-*C*4), 99.40 (gluc-*C*1), 94.00 (Ar*C*-I), 72.83 (gluc-*C*3), 71.96 (gluc-*C*5), 71.84 (gluc-*C*2), 68.66 (gluc-*C*4), 61.48 (gluc-*C*6), 19.58, 19.43, 19.27 (CO*C*$H_3$), 13.71 (pyrid-C2-*C*$H_3$).

***3-(β-D-glucopyranosyloxy)-1-[4-(4-iodophenyl)-2-thiazolyl]-2-methyl-4(1H)-pyridinone*** **(GL$_7$).** Compound **9f** (0.09 g, 0.12 mmol) was dissolved in dry methanol (5 mL); sodium methoxide (0.01 g, 0.24 mmol) was added while stirring. After 2 h, Rexyn ($H^+$ form) was added to the cloudy reaction mixture. The mixture was stirred until clear (~20 min) and then filtered. *In vacuo* solvent removal yielded compound **GL$_7$** as an off-white solid (0.07 g, 99%). $^1$H NMR (MeOD-$d_4$, 300.13 MHz) δ, ppm: 8.14 (s, 1H, thiazole-*H*5), 8.00 (d, $^3J_{6,5}$ = 7.6 Hz, 1H; pyrid-*H*6), 7.81 (d, $^3J$ = 8.4 Hz, 2H; Ar*H*), 7.72 (d, $^3J$ = 8.5 Hz, 2H; Ar*H*), 6.59 (d, $^3J_{5,6}$ = 7.6 Hz, 1H; pyrid-*H*5), 4.80 (partially obscured by water peak, 1H; gluc-*H*1), 3.85 (dd, $^2J_{6a,6b}$ = 10.0 Hz, $^3J_{6a,5}$ = 2.0 Hz, 1H; gluc-*H*6a), 3.69 (dd, $^2J_{6b,6a}$ = 11.9 Hz, $^3J_{6b,5}$ = 5.3 Hz, 1H; gluc-*H*6b), 3.33-3.50 (m, 4H, gluc-*H*2,*H*3,*H4*,*H*5), 2.46 (s, 3H; pyrid-C$H_3$). $^{13}$C NMR (MeOD-$d_4$, 75.48 MHz) δ, ppm: 174.75 (pyrid-*C*4), 159.57 (thiazole-*C*2), 152.05 (thiazole-*C*5), 144.93 (Ar*C*), 144.39 (pyrid-*C*2), 140.52 (pyrid-*C*6), 138.02 (Ar*C*H), 132.97 (pyrid-*C*3), 127.83 (Ar*C*H), 116.89 (pyrid-*C*5), 116.06 (thiazole-*C*4), 105.29d (gluc-*C*1), 94.04 (Ar*C*-I), 77.42, 77.09 (gluc-*C*3, *C*5), 74.29 (gluc-*C*2), 69.83 (gluc-*C*4), 61.30 (gluc-*C*6), 13.95 (pyrid-C2-*C*$H_3$). HR-ESIMS *m/z* for $C_{21}H_{21}IN_2O_7SNa$ ($M+Na^+$) calcd (found): 595.0012 (595.0004).

**1.7. Radiolabeling of $GL_7$. 3-(β-D-glucopyranosyloxy)-1-[4-(4-[$^{125}$I]iodophenyl)-2-thiazolyl]-2-methyl-4(1*H*)-pyridinone ([$^{125}$I]-$GL_7$).**

To a sample of Na[$^{125}$I]I (0.5 mCi) was added $H_3PO_4$ (2.5 μL, 0.05 N) before transfer to an ethanolic solution of the tributylstannyl precursor **12** (0.001 g, 200 μL). A freshly prepared aqueous solution of Chloramine-T (1 mg, 100 μL) was then added to the reaction mixture and stirred (room temperature, 20 min). The reaction was quenched by the addition of aqueous NaCl (100 μL, 20% w/v) and the radioiodination products were extracted with EtOAc. The solvent was removed from the combined organic layers under a stream of air and the residue dissolved in MeOH (200 μL) for subsequent deprotection of the glucose moiety. Sodium methoxide was added (1 mg in 50 μL 1:1 MeOH/$H_2O$) and the reaction mixture was stirred (room temperature, 15 min). After addition of Amberlite$^{TM}$ resin ($H^+$-form) and stirring for another 7 min at room temperature, the solution was diluted with $H_2O$ (5 mL) and passed through a C-18 Sep-Pak® cartridge. The cartridge was washed ($H_2O$, 5 mL) and finally the product eluted with MeOH (2.5 mL). Analysis *via* TLC indicated the radiolabeled product was obtained in a radiochemical purity of ≥ 97%. Its identity was confirmed by comparing $R_f$-values of labeled *vs.* cold compound **[$^{125}$I]-$GL_7$** (0.31, on silica, 4:1 EtOAc:MeOH).

**1.8. Synthesis and Characterisation of Cu(II) complexes. General Procedure for the Synthesis of Cu(II) complexes.** To a concentrated solution (1:9 $CH_2Cl_2$:MeOH) containing 2 equivalents of protonated ligand, 2 equivalents of $NEt_3$ were added. The reaction mixture was stirred at room temperature for ~5 min and added dropwise to a previously prepared 4 mL solution of copper(II) perchlorate (1 equivalent) in the same solvent solution. The resultant mixture was stirred for ~1 h and the solid obtained was isolated and purified according to the procedure described below for each compound under the corresponding heading.

***Bis*(1-(4-dimethylaminophenyl)-2-methyl-3-oxy-4-pyridonato)copper(II) ([Cu($L_1$)$_2$]). $HL_1$** (0.062 g, 0.25 mmol) and copper(II) perchlorate hexahydrate (0.046 g, 0.12 mmol) were used as described above. A fine light green precipitate was collected by filtration and washed with 1:9 $CH_2Cl_2$:MeOH and dried *in vacuo* to afford **[Cu($L_1$)$_2$]** (0.050 g, 74%). Liquid-liquid diffusion between $CHCl_3$ and $Et_2O$ afforded dark green blade-shaped crystals suitable for X-ray diffraction. Anal. Calcd (found) for $C_{28}H_{30}CuN_4O_4$: C, 61.13 (60.79); H, 5.50 (5.38); N 10.18 (10.08). Infrared spectrum ($cm^{-1}$, total reflectance): 1607, 1519, 1504, 1463, 1296, 726, 574, 537. EPR (130 K, powder): $A_\perp$ = 150 x $10^{-3}$ $cm^{-1}$, $g_\perp$ = 2.063, $A_\parallel$ = 202 x $10^{-4}$ $cm^{-1}$, $g_\parallel$ = 2.263.

***Bis*(1-(4-methylaminophenyl)-2-methyl-3-oxy-4-pyridonato)copper(II) ([Cu($L_2$)$_2$]). $HL_2$** (0.057 g, 0.25 mmol) and copper(II) perchlorate hexahydrate (0.045 g, 0.12 mmol) were used as described above. The precipitate was collected by filtration and washed with 1:9 $CH_2Cl_2$:MeOH and dried *in vacuo* to afford **[Cu($L_2$)$_2$]** as a fine green solid (0.040 g, 64%). Anal. Calcd (found) for $C_{26}H_{26}CuN_4O_4$: C, 59.82 (59.49); H, 5.02 (5.16); N 10.73 (10.60). Infrared spectrum ($cm^{-1}$, total reflectance): 3337, 1608, 1504, 1459, 1293, 725, 583, 538.

***Bis*(1-(4-aminophenyl)-2-methyl-3-oxy-4-pyridonato)copper(II) ([Cu(L$_3$)$_2$]). HL$_3$** (0.055 g, 0.25 mmol) and copper(II) perchlorate hexahydrate (0.045 g, 0.12 mmol) were used as described above. The resultant precipitate was filtred and washed with 1:9 $CH_2Cl_2$:MeOH and dried *in vacuo* to afford **[Cu(L$_3$)$_2$]** as a fine green solid (0.042 g, 70%). Green plate crystals suitable for X-ray analysis were grown from slow evaporation of a solution of 3:1 MeOH:DMSO. Anal. Calcd (found) for $C_{24}H_{22}CuN_4O_4$: C, 58.35 (58.02); H, 4.49 (4.52); N 11.34 (11.21). Infrared spectrum ($cm^{-1}$, total reflectance): 3314, 3213, 1607, 1538, 1502, 1462, 1281, 737, 575, 539.

***Bis*(1-(6-benzothiazolyl)-2-methyl-3-oxy-4-pyridonato)copper(II) ([Cu(L$_4$)$_2$]). HL$_4$** (0.072 g, 0.28 mmol) and copper(II) perchlorate hexahydrate (0.050 g, 0.14 mmol) were used as described above. The precipitate was collected by filtration and washed with 1:9 $CH_2Cl_2$:MeOH and dried *in vacuo* to afford **[Cu(L$_4$)$_2$]** as a fine green solid (0.039 g, 50%). Anal. Calcd (found) for $C_{26}H_{18}CuN_4O_4S_2$: C, 54.02 (53.67); H, 3.14 (3.17); N 9.69 (9.58). Infrared spectrum ($cm^{-1}$, total reflectance): 1586, 1536, 1507, 1460, 1288, 723, 573, 533.

***Bis*(1-(2-benzothiazolyl)-2-methyl-3-oxy-4-pyridonato)copper(II) ([Cu(L$_5$)$_2$]). HL$_5$** (0.018 g, 0.070 mmol) and copper(II) perchlorate hexahydrate (0.013 g, 0.035 mmol) were used as described above. A fine light green precipitate was collected by filtration and washed with 1:9 $CH_2Cl_2$:MeOH and dried *in vacuo* to afford **[Cu(L$_5$)$_2$]** (0.014 g, 35%). Anal. Calcd (found) for $C_{26}H_{18}CuN_4O_4S_2$•MeOH: C, 53.15 (53.00); H, 3.63 (3.28); N 9.18 (9.33). Infrared spectrum ($cm^{-1}$, total reflectance): 1586, 1545, 1500, 1456, 1299, 727, 564, 543.

***Bis*(1-[4-(4-bromophenyl)-2-thiazolyl]-2-methyl-3-oxy-4-pyridonato)copper(II) ([Cu(L$_6$)$_2$]). ([Cu(L$_6$)$_2$])** was prepared in a slightly different manner from those of the previous complexes: **HL$_6$** (0.036 g, 0.1 mmol) was dissolved in 2:1 $CH_2Cl_2$:MeOH (6 mL) resulting in a yellowish solution. After addition of copper(II) perchlorate hexahydrate (0.019 g, 0.05 mmol) the reaction mixture was stirred for 5 min after which $NEt_3$ was added to the mixture (14 µL, 0.1 mmol) and the solution is heated to reflux for a few seconds. After filtration, vapor diffusion of diethyl ether into the green solution affords green crystals of the copper complex that are suitable for X-ray crystallography. Anal. Calcd (found) for $C_{30}H_{20}Br_2CuN_4O_4S_2$: C, 45.73 (45.39); H, 2.56 (2.62); N 7.11 (6.75). Infrared spectrum ($cm^{-1}$, total reflectance): 1592, 1549, 1489, 1471, 1283, 1236, 737, 536. CCDC 247601.

**1.9. Antioxidant Studies.** The antioxidant capacity of all 3-hydroxy-4-pyridinone pro-ligands were determined by the trolox equivalent antioxidant capacity (TEAC) assay using 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox) as a standard and α-tocopherol (vitamin E) and butylated hydroxytoluene (BHT) as reference compounds. TEAC values were calculated according to an improved 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulphonic acid diammonium salt (ABTS) radical cation decolorization assay.[10] The radical was generated by dissolving ABTS (0.0387 g, 7.05 µmol, 7 mM) in water (10 mL) and exposing the solution to potassium persulphate (0.0066 g, 24.4 µmol, 2.45 mM). After incubation (dark, room temperature, 16 h), the resultant solution was diluted with HPLC-grade methanol such that the absorbance of the solution at 745 nm was 0.7 ± 0.2 (*i.e.* 2.5 mL diluted to 200 mL). Both the $ABTS^{\bullet+}$ solution and the test solutions were maintained at 30 °C using a water bath.

$ABTS^{\bullet+}$ solution (2 mL) was loaded into a cuvette and the absorbance was recorded at 745 nm prior to addition of the test compounds and then at times 1, 3 and 6 min following addition. Test solutions were prepared such that the addition of 20 μL to the radical would provide a reduction in absorbance by 20-80%; this resulted in solutions ranging in concentration from 0.25-16 μM. Upon addition of 20 μL of test solution to the cuvette, the contents were mixed thoroughly by vigorously pipetting the mixture for twenty seconds. A new blank spectrum (MeOH) was collected before each sample run.

Solution absorbance was plotted *vs.* test compound concentration; each resultant slope was normalized with respect to that obtained for Trolox to give the Trolox-equivalence (TEAC) value for each time point (1, 3, 6 min). The error in each slope was calculated using linear regression techniques, and then statistically carried through calculation to the final values for the TEAC. Controls for test compound and standard absorption were performed: separate solutions were prepared and their absorption (745 nm) monitored; all compounds displayed insignificant absorption at this wavelength.

**1.10. Cytotoxicity (MTT) Assay.** Human hepatocytes (cell line: HepG2) were cultured according to standard procedures.[11] Cells were harvested for use by first removing excess culture media and adding trypsin (~ 4 mL) to the culture flask to release the cells from the wall of the dish. The cells were incubated (37 °C, 5 min), after which 10% fetal bovine serum (FBS) media (~ 4 mL) was added to quench the trypsin. The cells were suspended in solution, centrifuged (800 rpm, 3 min), and diluted to a concentration of $10^4$ cells per 100 μL media. Cells were allotted to the wells of a 96-well plate ($10^4$ cells or 100 μL per well) and incubated (37 °C, 24 h). Test compounds were dissolved in 10% FBS media and 1% DMSO/media solution, and filtered through a 0.2 μM "Milex" polyethersulphone syringe filter for sterilization. The initial solutions were diluted with 10% FBS media (with 1% DMSO for the less soluble compounds) to extend across a range of concentrations from 1 to 1000 μM. Cisplatin was used as a positive control for cell death. Cells were incubated with test compounds for 72 h; after incubation 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; 50 μL of 2.5 g/L in PBS) was added and cells were incubated for an additional 3 h. Supernatant was removed and the cells were dissolved in DMSO (150 μL). Absorbance was measured at 577 nm and referenced to the control and blank wells to find the relative cell viabilities for each assay condition ($n \geq 4$).

**1.11. $A\beta_{1\text{-}40}$ Turbidity Assay.** Synthetic $A\beta_{1\text{-}40}$ peptide was obtained from Bachem (Torrance, CA, USA). 4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffer was prepared and Chelex resin was added to the solution to rid the buffer of any residual transition metal ions; the pH was adjusted to 6.6 for $Cu^{2+}$ and to 7.4 for $Zn^{2+}$ studies. After removal of Chelex *via* filtration (Millipore 0.22-μm acetate filter), these buffer solutions were used in the subsequent preparation of metal, ligand and test solutions. Lyophilized synthetic human $A\beta_{1\text{-}40}$ amyloid peptide was prepared as a ~ 200-μM solution in distilled, deionized water. Intermittent sonication (1 min on, 30 s off) was applied for 3 min through a water bath to achieve full peptide dissolution. Next, the peptide solution was filtered through a 0.2-μm nylon syringe filter (Whatman; Kent, UK) to remove any microparticulate protein matter. A bicinchoninic acid (BCA, 4,4'-dicarboxy-2,2'-biquinoline) assay was performed to assess the concentration of the Aβ peptide, and was used to ensure that the concentration of Aβ peptide stayed consistent over all assays.[12] Stock

solutions of $Cu^{2+}$ and $Zn^{2+}$ were prepared from AAS standards to final concentrations of 200 μM using pH 6.6 and 7.4 buffers respectively, and solutions of the free ligands were prepared in HEPES buffer of the appropriate pH. Turbidity assays were performed in flat-bottomed 96-well microtitre plates (Falcon) with 200 μL of assay solution per well. Generally, to evaluate the effects of the pyridinone pro-ligands, $A\beta_{1\text{-}40}$ peptide (~ 25 μM) was co-incubated with either $Zn^{2+}$ or $Cu^{2+}$ (25 μM) for two minutes before the pro-ligand of interest was added (150 μM). Similar trials were performed with DTPA (50 μM) as a reference chelator with a high affinity for $Zn^{2+}$ and $Cu^{2+}$. After a 45-minute incubation at 22 ˚C, the 405-nm absorbances of all test solutions were measured using a Labsystems iEMS or Molecular Devices Thermomax microplate reader. Wells containing either Aβ peptide or the respective test ligand in the metal-containing HEPES buffer at the appropriate pH were used as blanks for spectrophotometric analysis, and MALDI-TOF spectroscopy was used to confirm the presence of intact Aβ peptide before and after the metal/chelator trials (for a representative MALDI-TOF spectrum see Figure S9).

**1.12. *In Vivo* Brain Uptake Assay.**

Male Fischer-344 rats (220-330 g; Charles River Labs, Kingston, N.Y.) were anesthetized with sodium pentobarbital (50 mg/kg). A PE-60 catheter filled with heparinized saline (100 units/mL) was placed into the left common carotid artery after ligation of the left external carotid, occipital and common carotid arteries (common carotid artery ligation is accomplished caudal to the catheter implantation site). The pterygopalatine artery was left open during the experiments. Rat rectal temperature was monitored and maintained at 37 °C by a heating pad connected to a feedback device (YSI Indicating Controller, Yellow Springs, Ohio). The catheter to the left common carotid artery was then connected to a syringe containing a physiologic perfusion fluid with 1.0 μCi/mL 3H-choline, and **[$^{125}$I]-GL$_7$** as described above. Perfusion fluid was filtered, warmed to 37 °C and gassed with 95% air and 5% $CO_2$. The perfusion fluid was infused into the left carotid artery with an infusion pump for 60 s at 10 mL/min (Harvard Apparatus, South Natick, MA). This perfusion rate maintained a carotid artery pressure of 120 mm Hg. Rats were then decapitated and cerebral samples obtained; the brains were removed from the skull, and the perfused cerebral hemisphere dissected on ice after removal of the arachnoid membrane and meningeal vessels. Brain regions were placed in scintillation vials and weighed. In addition, a 50-μL aliquot of the perfusion fluid was transferred to a scintillation vial and weighed. The brain and perfusion fluid samples were digested overnight at 50 °C in 1 mL of 1M piperidine. 10 mL of Fisher Chemical scintillation cocktail (Beckman, Fullerton, CA) was then added to each vial and the tracer contents assessed by dual-label liquid scintillation counting. Dual labeled scintillation counting of brain and perfusate samples was accomplished with correction for quench, background and efficiency. Brain vascular space was estimated from separate experiments and used to correct for radiotracer remaining within brain capillaries; apparent permeability surface-area coefficients (PA; BBB "permeability") were determined using the Crone-Renkin equation [$PA = -F \ln (1- K_{in}/F)$].

## 2. Supplementary Figures

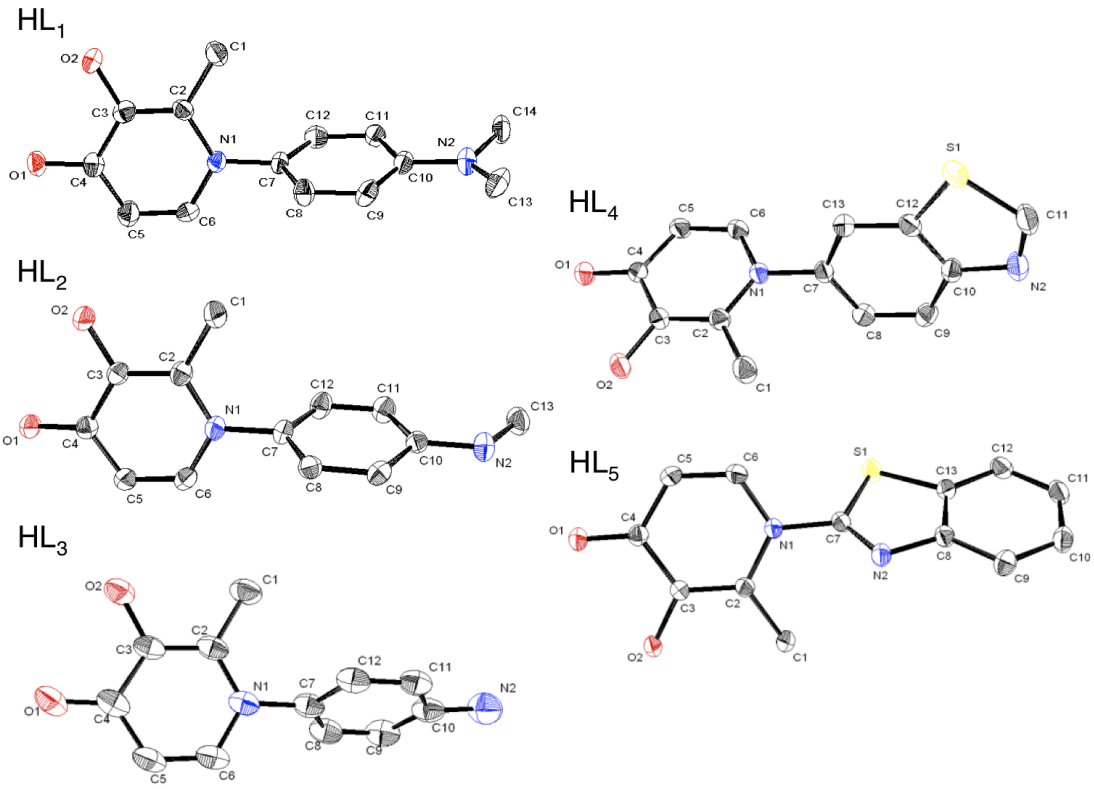



**Fig. S1** X-ray structures of pyridinone pro-ligands

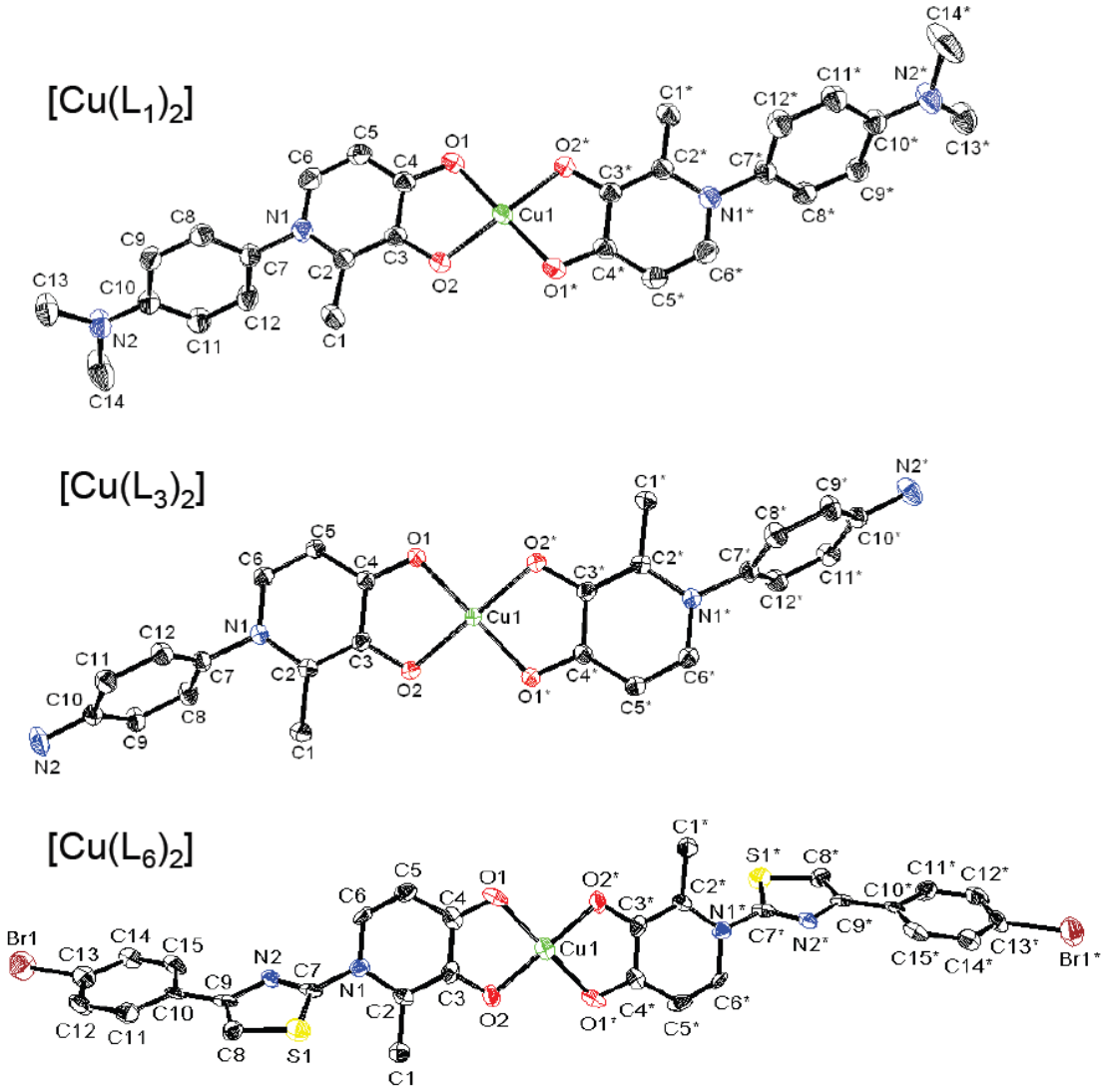



**Fig. S2** X-ray structures of Cu(II) complexes

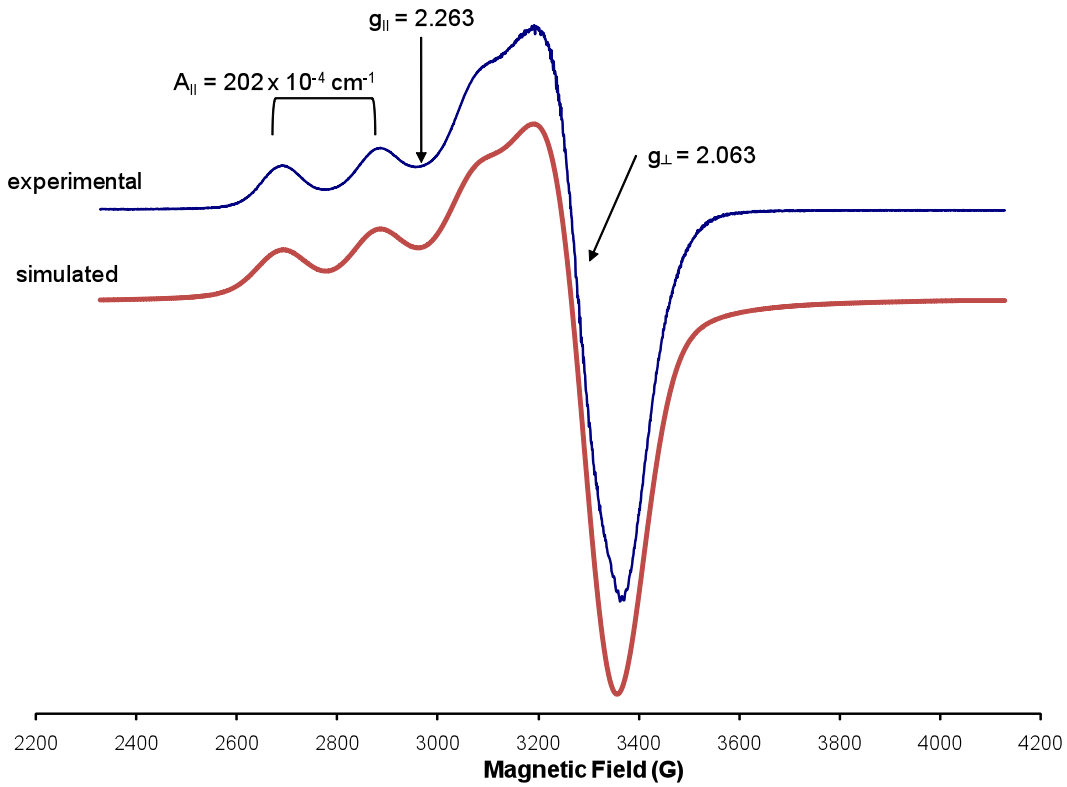
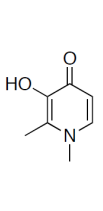
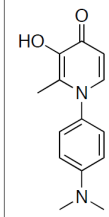
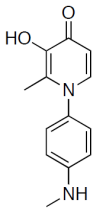
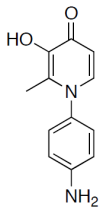
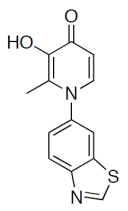
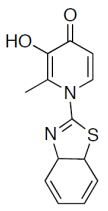
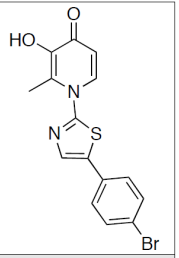



**Fig. S3** Experimental and simulated EPR powder spectra of [**Cu(L$_1$)$_2$**] (130 K)

**Fig. S4** Drug-likeness and log BB calculated values. All the parameters are defined in the manuscript

| |  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|---|
| ID | $HL_0$ | $HL_1$ | $HL_2$ | $HL_3$ | $HL_4$ | $HL_5$ | $HL_6$ |
| MW | 139 | 244 | 230 | 216 | 258 | 260 | 363 |
| cLogP | -0.90 | 1.19 | 0.70 | -0.18 | 1.00 | 0.85 | 2.45 |
| HBA | 3 | 4 | 4 | 4 | 4 | 4 | 4 |
| HBD | 1 | 1 | 2 | 2 | 1 | 1 | 1 |
| Lipinski's rules | passed | passed | passed | passed | passed | passed | passed |
| TPSA | 40.54 | 43.78 | 52.57 | 66.56 | 53.43 | 52.9 | 53.43 |
| Log BB | -0.59 | -0.32 | -0.53 | -0.87 | -0.49 | -0.51 | -0.27 |

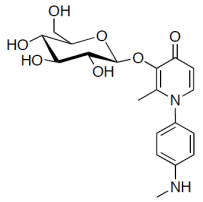
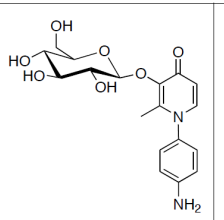
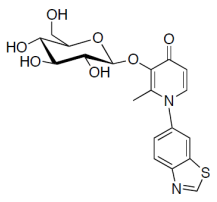
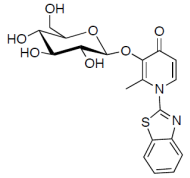
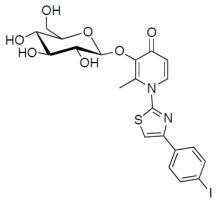
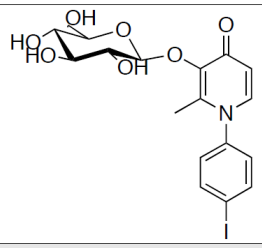
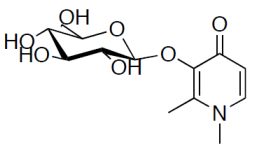
| |  |  |  |  |  |  |
|---|---|---|---|---|---|---|
| ID | $GL_1$ | $GL_2$ | $GL_3$ | $GL_4$ | $GL_5$ | $GL_7$ |
| MW | 406 | 392 | 378 | 420 | 420 | 572 |
| cLogP | -0.49 | -1.04 | -1.79 | -0.78 | -0.71 | 0.91 |
| HBA | 9 | 9 | 9 | 9 | 9 | 9 |
| HBD | 4 | 5 | 5 | 4 | 4 | 4 |
| Lipinski's rules | passed | passed | passed | passed | passed | passed |
| TPSA | 122.93 | 131.72 | 145.71 | 132.58 | 132.58 | 132.58 |
| Log BB | -1.75 | -1.96 | -2.28 | -1.94 | -1.94 | -1.68 |

**Fig. S4** (con't.) Drug-likeness and log BB calculated parameters. All the parameters are defined in the manuscript

| |  |  |
|---|---|---|
| ID | 1 | 2 |
| MW | 489 | 301 |
| cLogP | 0.32 | -2.68 |
| HBA | 8 | 8 |
| HBD | 4 | 4 |
| Lipinski's rules | passed | passed |
| TPSA | 119.69 | 119.69 |
| Log BB | -1.58 | -2.04 |

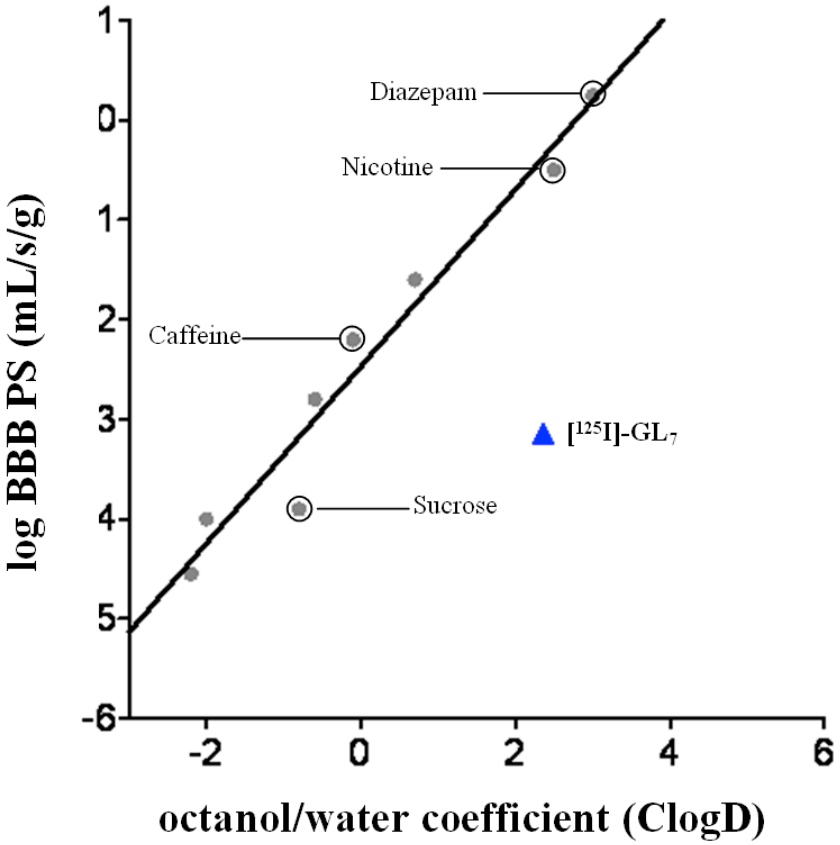



**Fig. S5** Plot of observed BBB permeation vs. calculated octanol/water partition coefficient. ClogD is calculated octanol/water partition coefficient at pH 7.4; log BBB PS is log BBB permeability-surface area coefficient

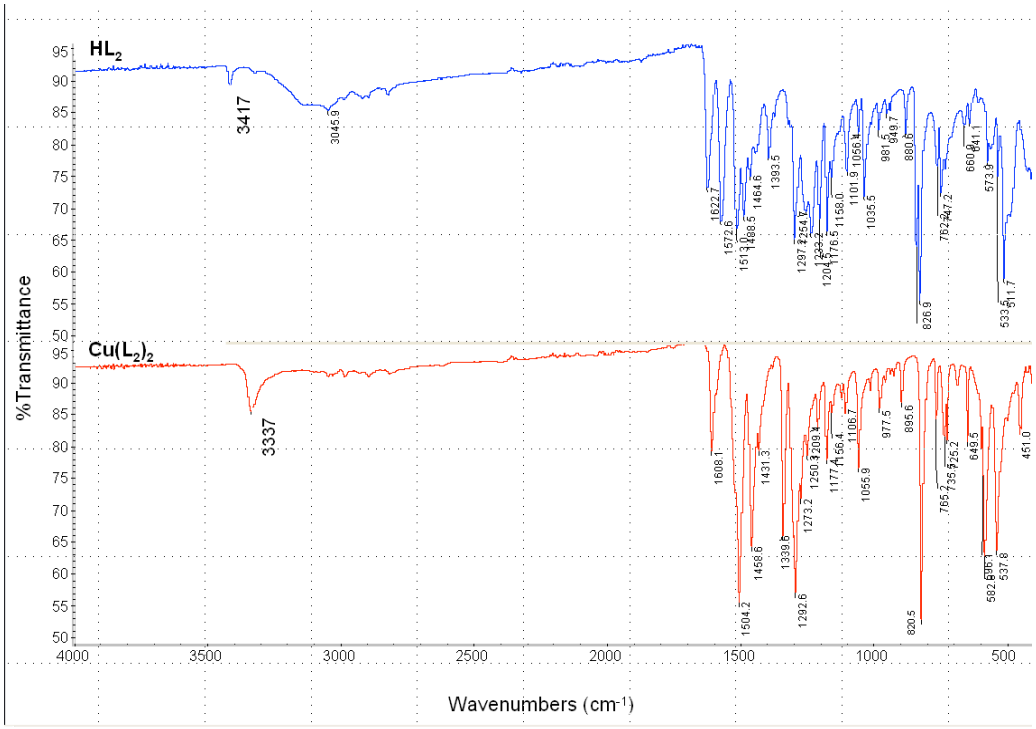



**Fig. S6** IR spectra for $\mathbf{HL_2}$ pro-ligand (upper) and corresponding $\mathbf{[Cu(L_2)_2]}$ complex (lower), 4000-400 $cm^{-1}$

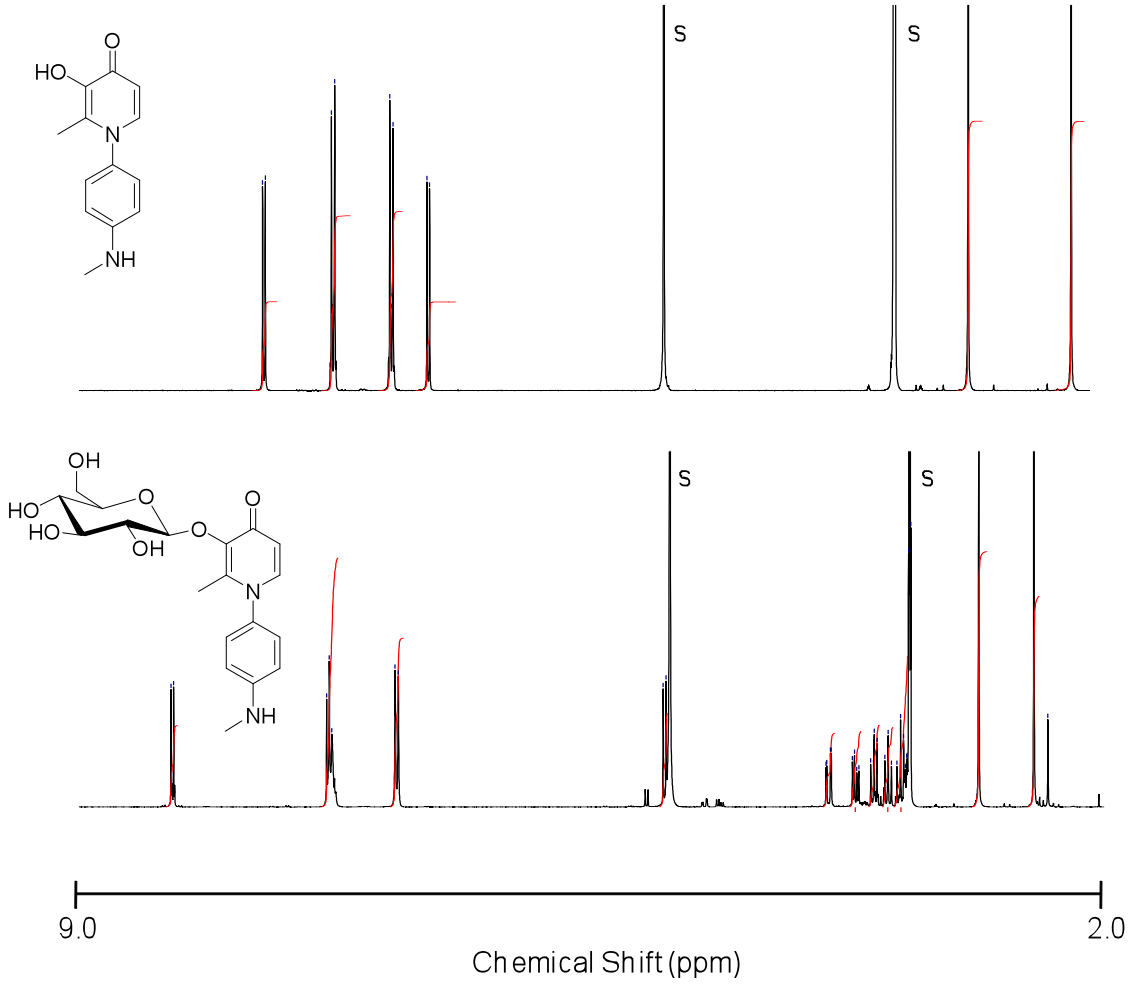



**Fig. S7** NMR $^{1}$H NMR ($CD_3OD$, 400.13 MHz, room temperature) spectra of $\mathbf{HL_2}$ (upper) and $\mathbf{GL_2}$ (lower), from 9.0 – 2.0 ppm; s indicates solvent peaks

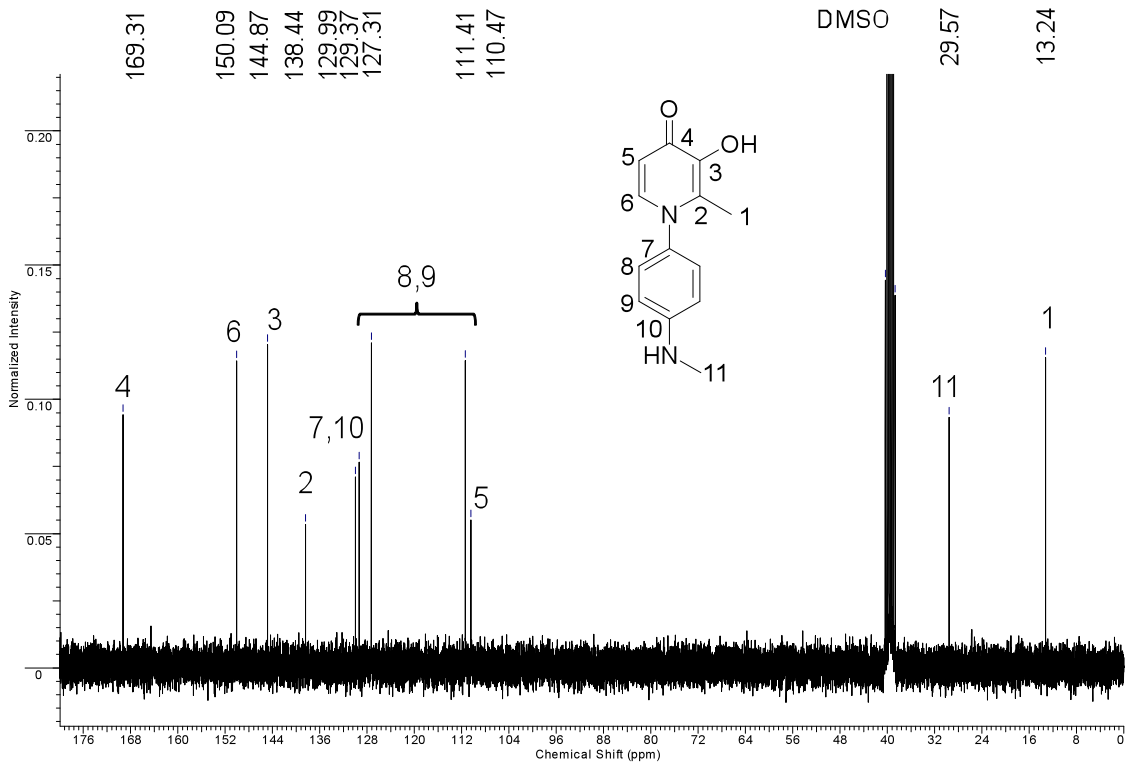



**Fig. S8** Representative $^{13}$C NMR spectrum (DMSO-*d6*, 75.48 MHz, room temperature) for pyridinone pro-ligand $\mathbf{HL_2}$

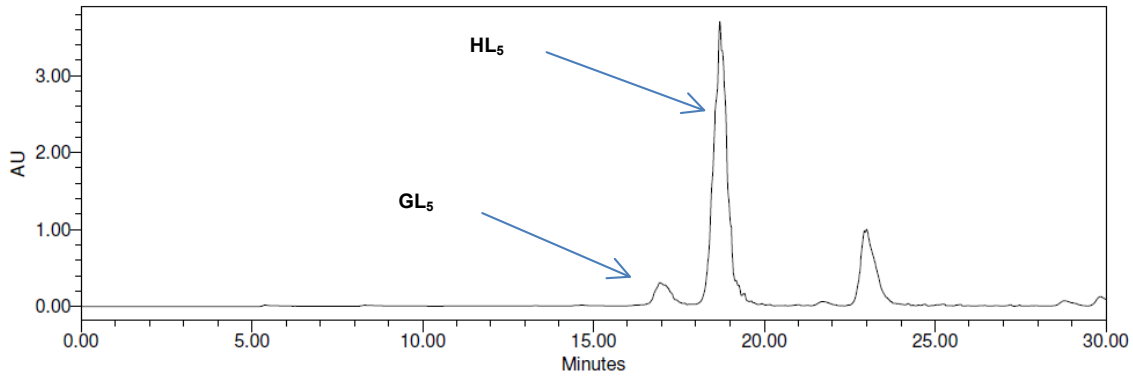



**Fig. S9** Representative semi-preparative HPLC trace for purification of $\mathbf{GL_5}$

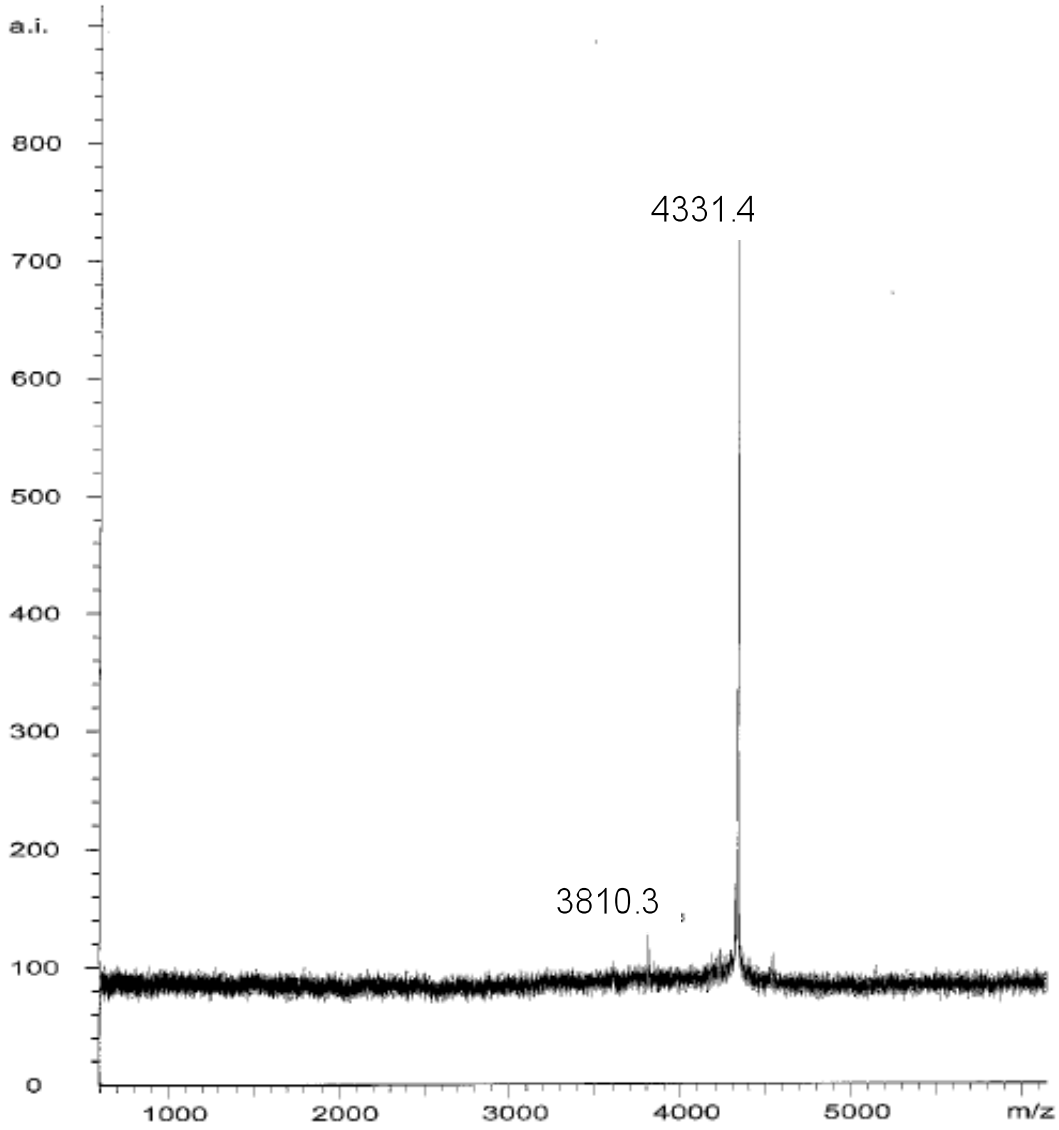



**Fig. S10** Representative MALDI-TOF mass spectrum confirming the presence of $A\beta_{1\text{-}40}$ (MW = 4329.9 g/mol) in solution after turbidity assay at pH 7.4; $Zn^{2+}$ addition was followed by $\mathbf{HL_1}$ addition

**3. Supplementary Tables.**

**Table S1** Crystallographic data for **$HL_1$, $HL_2$, $HL_3$, $HL_4$**, and **$HL_5$**

| **crystal data** | **$HL_1$• MeOH** | **$HL_2$ • $H_2O$** | **2[$HL_3$]• MeOH•$H_2O$** | **$HL_4$ • MeOH** | **$HL_5$** |
|---|---|---|---|---|---|
| empirical formula | $C_{15}H_{20}N_2O_3$ | $C_{13}H_{16}N_2O_3$ | $C_{25}H_{30}N_4O_6$ | $C_{14}H_{14}N_2O_3S$ | $C_{13}H_{10}N_2O_2S$ |
| fw | 276.15 | 248.28 | 482.52 | 290.33 | 258.29 |
| crystal system, space group | triclinic, *P* -1 (#2) | monoclinic, *P* $2_1$ (#4) | monoclinic, *P* $2_1/n$ (#14) | triclinic, *P* -1 (#2) | monoclinic, *P* $2_1/c$ (#14) |
| *a* (Å) | 7.5438(8) | 8.2835(4) | 12.9650(17) | 11.368(2) | 10.3006(12) |
| *b* (Å) | 9.0878(9) | 13.9790(7) | 14.3780(18) | 11.457(2) | 7.8737(10) |
| *c* (Å) | 11.3719(12) | 10.5581(5) | 12.9795(16) | 12.809(2) | 13.7999(16) |
| α (deg) | 85.485(6) | 90.0 | 90.0 | 67.68(1) | 90.0 |
| β (deg) | 78.375(6) | 90.255(2) | 90.445(8) | 76.79(1) | 93.837(4) |
| γ (deg) | 69.760(5) | 90.0 | 90.0 | 74.17(1) | 90.0 |
| *V* [Å3] | 716.44(13) | 1222.56(10) | 2419.4(5) | 1470.0(5) | 1116.7(2) |
| *Z*, $D_{calcd}$ (g/cm3) | 2, 1.281 | 4, 1.349 | 4, 1.325 | 4, 1.312 | 4, 1.536 |
| $\mu$(Mo Kα), (cm-1) | 0.90 | 0.97 | 0.96 | 2.28 | 2.84 |
| $F_{000}$ | 296.00 | 528.00 | 1024.00 | 608.00 | 536.00 |
| temp. (K) | 173(2) | 173(2) | 173(2) | 173(2) | 173(2) |
| reflns collcd / unique | 14 829/3490 ($R_{int}$ = 0.032) | 12 253/5314 ($R_{int}$ = 0.023) | 20 588/4455 ($R_{int}$ = 0.044) | 26 978/6723 ($R_{int}$ = 0.036) | 16 448/2541 ($R_{int}$ = 0.022) |
| residuals (*F*2, all data) | $wR_2$ = 0.128 | $wR_2$ = 0.093 | $wR_2$ = 0.112 | $wR_2$ = 0.095 | $wR_2$ = 0.088 |
| residuals (*F*, $I > 2\sigma(I)$) | $R_1$ = 0.046 | $R_1$ = 0.037 | $R_1$ = 0.043 | $R_1$ = 0.039 | $R_1$ = 0.033 |

**Table S2** Selected bond lengths (Å) and angles (°) in **$HL_1$, $HL_2$, $HL_3$, $HL_4$**, and **$HL_5$**

| **$HL_1$ • MeOH** | | **$HL_2$ • MeOH** | | **2[$HL_3$] • MeOH•$H_2O$** | |
|---|---|---|---|---|---|
| **Atoms** | **Distance** | **Atoms** | **Distance** | **Atoms** | **Distance** |
| C(3)-O(2) | 1.3544(16) | C(3)-O(2) | 1.360(2) | C(3)-O(2) | 1.358(2) |
| C(4)-O(1) | 1.2721(16) | C(4)-O(1) | 1.270(2) | C(4)-O(1) | 1.281(2) |
| N(1)-C(2) | 1.3788(17) | N(1)-C(2) | 1.383(2) | N(1)-C(2) | 1.378(2) |
| C(2)-C(3) | 1.3644(19) | C(2)-C(3) | 1.375(2) | C(2)-C(3) | 1.363(3) |
| C(3)-C(4) | 1.431(2) | C(3)-C(4) | 1.440(3) | C(3)-C(4) | 1.419(3) |
| C(4)-C(5) | 1.410(2) | C(4)-C(5) | 1.413(3) | C(4)-C(5) | 1.410(3) |
| C(5)-C(6) | 1.358(2) | C(5)-C(6) | 1.355(3) | C(5)-C(6) | 1.353(3) |
| C(6)-N(1) | 1.3518(18) | C(6)-N(1) | 1.356(3) | C(6)-N(1) | 1.355(2) |
| | | | | | |
| **Atoms** | **Angle** | **Atoms** | **Angle** | **Atoms** | **Angle** |
| C(8)-C(7)-N(1)-C(6) | -71.69(18) | C(8)-C(7)-N(1)-C(6) | -74.2(2) | C(8)-C(7)-N(1)-C(6) | -113.4(2) |
| C(12)-C(7)-N(1)-C(6) | 110.09(16) | C(12)-C(7)-N(1)-C(6) | 103.6(2) | C(12)-C(7)-N(1)-C(6) | 66.3(2) |
| C(8)-C(7)-N(1)-C(2) | 104.81(15) | C(8)-C(7)-N(1)-C(2) | 105.2(2) | C(8)-C(7)-N(1)-C(2) | 68.2(2) |
| C(12)-C(7)-N(1)-C(2) | -73.41(17) | C(12)-C(7)-N(1)-C(2) | -76.9(2) | C(12)-C(7)-N(1)-C(2) | -112.1(2) |
| | | | | | |

**Table S2 (con't.)** Selected bond lengths (Å) and angles (°) in **$HL_1$, $HL_2$, $HL_3$, $HL_4$**, and **$HL_5$**

| **$HL_4$ • MeOH** | | **$HL_5$** | |
|---|---|---|---|
| **Atoms** | **Distance** | **Atoms** | **Distance** |
| C(3)-O(2) | 1.3794(17) | C(3)-O(2) | 1.3536(17) |
| C(4)-O(1) | 1.2993(18) | C(4)-O(1) | 1.2585(17) |
| N(1)-C(2) | 1.4065(18) | N(1)-C(2) | 1.3944(17) |
| C(2)-C(3) | 1.398(2) | C(2)-C(3) | 1.3706(19) |
| C(3)-C(4) | 1.460(2) | C(3)-C(4) | 1.4462(19) |
| C(4)-C(5) | 1.443(2) | C(4)-C(5) | 1.429(2) |
| C(5)-C(6) | 1.386(2) | C(5)-C(6) | 1.352(2) |
| C(6)-N(1) | 1.382(2) | C(6)-N(1) | 1.3686(18) |
| | | | |
| **Atoms** | **Angle** | **Atoms** | **Angle** |
| C(8)-C(7)-N(1)-C(6) | -108.98(16) | N(2)-C(7)-N(1)-C(6) | 124.06(15)- |
| C(13)-C(7)-N(1)-C(6) | 71.98(18) | S(1)-C(7)-N(1)-C(6) | 55.93(16) |
| C(8)-C(7)-N(1)-C(2) | 73.44(18) | N(2)-C(7)-N(1)-C(2) | -55.57(19) |
| C(13)-C(7)-N(1)-C(2) | -105.59(16) | S(1)-C(7)-N(1)-C(2) | 124.44(12) |

**Table S3** Crystallographic data for **$[Cu(L_1)_2]$, $[Cu(L_3)_2]$, $[Cu(L_6)_2]$**

| **crystal data** | **$[Cu(L_1)_2]$** •$2CHCl_3$ | **$[Cu(L_3)_2]$** •2DMSO | **$[Cu(L_6)_2]$** |
|---|---|---|---|
| Formula | $C_{28}H_{30}N_4O_4Cu$ .$2CHCl_3$ | $C_{24}H_{22}N_4O_4Cu$ .2DMSO | $C_{30}H_{20}Br_2CuN_4O_4S_2$ |
| fw | 788.84 | 650.25 | 787.98 |
| crystal system, space group | monoclinic, *P* $2_1/c$ (#14) | monoclinic, *P* $2_1/c$ (#14) | monoclinic, *P* $2_1/n$ (#14) |
| *a* (Å) | 12.9970(12) | 7.7458(9) | 17.027(3) |
| *b* (Å) | 15.3280(17) | 16.433(2) | 9.524(2) |
| *c* (Å) | 9.0063(8) | 12.0999(14) | 18.442(4) |
| α (deg) | 90.0 | 90.0 | 90.0 |
| β (deg) | 110.181(4) | 103.182(4) | 104.05(3) |
| γ (deg) | 90.0 | 90.0 | 90.0 |
| *V* [Å3] | 1684.1(3) | 1499.6(3) | 2901(1) |
| *Z*, $D_{calcd}$ (g/cm3) | 2, 1.556 | 2, 1.440 | 4, 1.804 |
| $\mu$(Mo Kα), (cm-1) | 11.66 | 9.15 | 3.696 |
| $F_{000}$ | 806.00 | 678.00 | 1564 |
| temp. (K) | 173(2) | 173(2) | 173(2) |
| reflns collcd / unique | 17 601/4105 ($R_{int}$ = 0.035) | 17 254/3618 ($R_{int}$ = 0.045) | 6289/6289 ($R_{int}$ = 0.2553) |
| residuals (*F*2, all data) | $wR_2$ = 0.100 | $wR_2$ =0.098 | $wR_2$ = 0.1182 |
| residuals (*F*, *I* > 2σ(*I*)) | $R_1$ = 0.038 | $R_1$ = 0.035 | $R_1$ = 0.0497 |

**Table S4** Selected bond lengths (Å) and angles (°) in **$[Cu(L_1)_2]$, $[Cu(L_3)_2]$, $[Cu(L_6)_2]$**

| **$[Cu(L_1)_2]$** • $2CHCl_3$ | | **$[Cu(L_3)_2]$** • 2DMSO | | **$[Cu(L_6)_2]$** | |
|---|---|---|---|---|---|
| **Atoms** | **Distance** | **Atoms** | **Distance** | **Atoms** | **Distance** |
| C(3)-O(2) | 1.321(3) | C(3)-O(2) | 1.328(2) | C(3)-O(2) | 1.301(7) |
| C(4)-O(1) | 1.295(3) | C(4)-O(1) | 1.298(2) | C(4)-O(1) | 1.274(7) |
| N(1)-C(2) | 1.369(3) | N(1)-C(2) | 1.384(2) | N(1)-C(2) | 1.373(7) |
| C(2)-C(3) | 1.376(3) | C(2)-C(3) | 1.380(2) | C(2)-C(3) | 1.395(8) |
| C(3)-C(4) | 1.431(3) | C(3)-C(4) | 1.427(2) | C(3)-C(4) | 1.437(9) |
| C(4)-C(5) | 1.389(3) | C(4)-C(5) | 1.403(2) | C(4)-C(5) | 1.412(8) |
| C(5)-C(6) | 1.359(3) | C(5)-C(6) | 1.364(3) | C(5)-C(6) | 1.280(8) |
| C(6)-N(1) | 1.352(3) | C(6)-N(1) | 1.356(2) | C(6)-N(1) | 1.361(7) |
| Cu(1)-O(2) | 1.9085(14) | Cu(1)-O(2) | 1.9113(12) | Cu(1)-O(2) | 1.917(4) |
| Cu(1)-O(1) | 1.9191(16) | Cu(1)-O(1) | 1.9311(12) | Cu(1)-O(1) | 1.946(4) |
| | | | | | |
| **Atoms** | **Angle** | **Atoms** | **Angle** | **Atoms** | **Angle** |
| O(1)-Cu(1)-O(2) | 87.76(6) | O(1)-Cu(1)-O(2) | 86.03(5) | O(1)-Cu(1)-O(2) | 85.9(2) |
| O(1)-Cu(1)-O(2*) | 93.24(6) | O(1)-Cu(1)-O(2*) | 93.97(5) | O(1)-Cu(1)-O(2*) | 94.2(2) |
| C(8)-C(7)-N(1)-C(6) | -65.3(3) | C(8)-C(7)-N(1)-C(6) | 109.8(2) | S(1)-C(7)-N(1)-C(2) | 58.40(3) |
| C(12)-C(7)-N(1)-C(6) | 113.3(3) | C(12)-C(7)-N(1)-C(6) | -71.9(2) | S(1)-C(7)-N(1)-C(6) | -116.14(2) |
| C(8)-C(7)-N(1)-C(2) | 117.6(3) | C(8)-C(7)-N(1)-C(2) | -73.6(2) | N(2)-C(7)-N(1)-C(2) | -131.50(3) |
| C(12)-C(7)-N(1)-C(2) | -63.7(3) | C(12)-C(7)-N(1)-C(2) | 104.7(2) | N(2)-C(7)-N(1)-C(6) | 53.95(3) |

**4. Supplementary Notes.**

1. D. D. Perrin, W. L. F. Armarego and D. R. Perrin, *Purification of laboratory chemicals*, Pergamon Press, Oxford, 1980.
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