Homobivalent ligands of the atypical antipsychotic clozapine: Design, synthesis and pharmacological evaluation

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SUPPORTING INFORMATION

Table of Contents

1. Synthesis and Spectroscopic Data of Other Target Compounds

Synthesis of linkers

*Glutaric anhydride (**10b**)*. Glutaric acid (5.06 g, 38.3 mmol) and acetic anhydride (10 mL) were heated at reflux for 1h, cooled and concentrated in vacuo. The resulting oil was distilled affording **10b** (2.95 g, 25.8 mmol, 67%) as a clear oil, which crystallized upon cooling, bp 118-122 °C at 1.5 mmHg (lit.[45] bp 138°C at 7 mmHg), mp 53.4-55.7 °C (lit.[46] mp 53-55 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (t, *J* = 6.7 Hz, 4H, H3, H5), 2.03 (app p, *J* = 6.7 Hz, 2H, H4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0 (C), 29.9 (CH_2), 16.3 (CH_2).

*4,4'-(Piperazine-1,4-diyl)bis(4-oxobutanoic acid) (**11a**).* Following the procedure of Liu et al.,[36] pulverized piperazine (0.508 g, 5.90 mmol) was dissolved in toluene (6 mL). Succinic anhydride (**10a**, 1.16 g, 11.6 mmol) was suspended in toluene (12 mL) and added to the stirred piperazine solution. This solution was heated at reflux for 28 h, then cooled and concentrated in vacuo, yielding a white powder. The product was recrystallized from ethanol, yielding **11a** as off-white crystals (1.02 g, 3.57 mmol, 62%), mp 158.7-160.7 °C (lit.[36] 156.6-158.5 °C). ^{1}H NMR (400 MHz, D_2O) A mixture of amide rotamers.[36] δ 3.72-3.56 (m, 8H, H2′, H3′, H5′, H6′), 2.80-2.72 (m, 4H, H2), 2.69-2.61 (m, 4H, H3). ^{13}C NMR (101 MHz, D_2O) A mixture of amide rotamers.[36] δ 177.4 (C), 172.98 (C), 172.94 (C), 44.9 (CH_2), 44.7 (CH_2), 41.6 (CH_2), 41.4 (CH_2), 29.1 (CH_2), 27.7 (CH_2), 27.6 (CH_2).

*5,5'-(Piperazine-1,4-diyl)bis(5-oxopentanoic acid) (**11b**).* Piperazine (0.247 g, 2.87 mmol) was dissolved in anhydrous dioxane (2 mL), with gentle warming. Glutaric anhydride (**10b**, 0.664 g, 5.82 mmol), suspended in anhydrous dioxane (2 mL), was added to the stirred piperazine solution and heated at reflux for 24 h then cooled to room temperature. The white precipitate was collected by filtration (**11b**, 0.741 g, 2.36 mmol, 82%), mp 157.0-158.1 °C. ^{1}H NMR (400 MHz, D_2O) A mixture of

amide rotamers.[36] δ 3.70-3.55 (m, 8H, H2′, H3′, H5′, H6′), 2.53 (app t, *J* = 7.6 Hz, 4H, H2), 2.44 (t, *J* = 7.2 Hz, 4H, H4), 1.89 (app p, *J* = 7.3 Hz, 4H, H3). ^{13}C NMR (101 MHz, MeOD) A mixture of amide rotamers.[36] δ 176.9 (C), 173.7 (C), 173.6 (C), 46.6 (CH_2), 46.3 (CH_2), 42.8 (CH_2), 42.4 (CH_2), 34.0 (CH_2), 33.2 (CH_2), 33.1 (CH_2), 21.6 (CH_2).

*4,4'-(Ethane-1,2-diylbis(oxy))bis(4-oxobutanoic acid) (**13**).* Following the procedure of Asay et al.,[37] toluene (20 mL) and ethylene glycol (2.1 mL, 37.7 mmol) were combined and a suspension of succinic anhydride (**10a**, 7.58 g, 75.7 mmol) in toluene (20 mL) was added to the stirred solution. The reaction was heated under Dean-Stark conditions overnight, cooled and then concentrated in vacuo. The product was recrystallized from ethyl acetate / hexane, yielding **13** as white crystals (5.45 g, 20.8 mmol, 27%), mp 75.8-76.4 °C (lit.[37] > 80 °C (decomposed)). ^{1}H NMR (400 MHz, D_2O) δ 4.36 (s, 4H, H1′, H2′), 2.70 (s, 8H, H2, H3). ^{13}C NMR (101 MHz, D_2O) δ 176.8 (C), 174.7 (C), 62.8 (CH_2), 28.8 (CH_2), 28.7 (CH_2).

Synthesis of clozapine hydrazine (2) and desmethylclozapine (3)

*8-Chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b,e*][1,4]diazepin-5-amine (**2**).* Following the method of Su et al.,[11] a solution of **1** (1.25 g, 3.82 mmol) in dichloromethane (50 mL) and isoamyl nitrite (25 mL) was stirred at room temperature for 3 h. The solvent was evaporated in vacuo, yielding a pale yellow oil corresponding to the N-nitroso intermediate, 8-chloro-11-(4-methylpiperazin-1-yl)-5-nitroso-5*H*-dibenzo[*b*,*e*][1,4]diazepine. The product was used without further purification. A solution of 8-chloro-11-(4-methylpiperazin-1-yl)-5-nitroso-5*H*-dibenzo[*b*,*e*][1,4]diazepine (1.36 g, 3.82 mmol) in glacial acetic acid (20 mL) was added dropwise to a suspension of zinc metal (6.25 g) in glacial acetic acid (100 mL) over 1 h at 10 to 15 °C. Additional zinc (0.5 g) was added periodically to maintain the green/yellow color of the solution. After 3 h, the solution was filtered and concentrated in vacuo yielding a pale brown residue. Water (25 mL) was added to the residue and the pH was adjusted to 11 using sodium hydroxide pellets. The aqueous layer was extracted with dichloromethane (3 × 50 mL), washed with water (50 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate and evaporated to dryness in vacuo. **2** was purified by flash column chromatography (50% methanol / ethyl acetate) and recrystallized from dichloromethane / hexane (0.635 g, 1.86 mmol, 48%) to yield **2** as beige colored crystals, mp 148-149 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (ddd, *J* = 8.2, 1.0, 1.0 Hz, 1H, H1/H4), 7.37-7.30 (m, 2H, H3/H2, H4/H1), 7.21 (d, *J* = 8.4 Hz, 1H, H6), 7.10 (ddd, *J* = 8.0, 6.1, 1.7 Hz, 1H, H2/H3), 6.86 (d, *J* = 2.2 Hz, 1H, H9), 6.78 (dd, *J* = 8.4, 2.3 Hz, 1H, H7), 4.39 (s, 2H, NH_2), 3.54 (m, 4H, H2′, H6′), 2.66 (m, 4H, H3′, H5′), 2.39 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3 (C), 143.7 (C), 142.0 (C), 133.6 (C), 127.6 (CH), 127.0 (CH), 124.1 (C), 121.5 (CH), 120.0 (CH), 118.2 (CH), 116.8 (CH), 116.0 (C), 110.6 (CH), 54.9 (CH_2), 49.5 (CH_2), 46.4 (CH_3). ESI MS (*m / z*): 342.4 $[M + H]^+$.

*8-Chloro-11-(piperazin-1-yl)-5*H-*dibenzo[*b,e*][1,4]diazepine (*N-*desmethylclozapine, **3**).* According to the procedure by Olofson, R. A. et al.,[35] clozapine (**1**, 2.00 g, 6.13 mmol) was dissolved in anhydrous 1,2-dicholoroethane (30 mL), under nitrogen at room temperature. The reaction mixture was cooled to 0 °C and α-chloroethyl chloroformate (2.64 mL, 24.5 mmol) was added dropwise to the stirred solution over 15 min, (resulting in a yellow precipitate), and maintained at 0 °C for an additional 15 min. The reaction was warmed to room temperature, giving a deep red solution, which was heated at reflux, under nitrogen, for 22 h. The reaction mixture was concentrated in vacuo, the oily brown residue dissolved in methanol (HPLC grade, 30 mL) and heated at 50 °C for 2 h, cooled and concentrated in vacuo. The oily brown residue was partitioned between ethyl acetate (50 mL) and aqueous hydrochloric acid (1 M, 50 mL). The aqueous layer was separated and adjusted to pH 10 using sodium hydroxide pellets. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), the combined organic layers washed with water (2 × 50 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness in vacuo. The yellow foam was purified by column chromatography (10% methanol / chloroform), yielding a yellow foam (**3**, 1.33 g, 4.23 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (ddd, *J* = 7.8, 7.3, 1.6 Hz, 1H, H3), 7.24 (dd, *J* = 7.6, 1.5 Hz, 1H, H1), 7.06 (d, *J* = 2.4 Hz, 1H, H9), 6.99 (ddd, *J* = 7.8, 7.3, 1.1 Hz, 1H, H2), 6.83-6.76 (m, 2H, H4, H7), 6.60 (d, *J* = 8.3 Hz, 1H, H6), 5.06 (s, 1H, H5), 3.42 (m, 4H, H2′, H6′), 2.93 (m, 4H, H3′, H5′), 2.40 (s, 1H, H4′). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (C), 152.8 (C), 141.8 (C), 140.6 (C), 131.9 (CH), 130.2 (CH), 128.9 (C), 126.7 (CH), 123.4 (C), 123.08 (CH), 123.06 (CH), 120.2 (CH), 120.1 (CH), 48.5 (CH_2), 45.9 (CH_2). LCMS (*m / z*): 313.1 $[M + H]^+$.

Synthesis of clozapine N5 acylated bivalent ligands

*1,10-Bis(8-chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b,e*][1,4]diazepin-5-yl)decane-1,10-dione (**7b**).* 1,10-Decanedioic acid (0.087 g, 0.428 mmol) and oxalyl chloride were reacted, followed by the addition of **1** (0.247 g, 0.757 mmol), *N*,*N*-diisopropylethylamine (145 μL, 0.832 mmol) and pyridine (0.095 mL, 1.18 mmol), as per general procedure A. Additional 1,10-decanedioyl dichloride (0.052 g, 0.216 mmol) was added. Column chromatography conditions: column 1 (5% methanol / acetone, until clozapine eluted then 10% methanol / chloroform), column 2 (gradient elution: from 5% methanol / chloroform to 10% methanol / chloroform, increasing in 1% increments), column 3 (1% ammonia / 9 % methanol / chloroform). Yielded **7b** as a white foam (0.115 g, 0.140 mmol, 37%). ^{1}H NMR (400 MHz, $CDCl_3$, 320 K) δ 7.49 (ddd, *J* = 8.0, 7.0, 1.9 Hz, 2H, H3′), 7.41-7.29 (m, 6H, H1′, H2′, H4′), 7.14 (d, *J* = 2.4 Hz, 2H, H9′), 7.10 (d, *J* = 8.2 Hz, 2H, H6′), 6.96 (m, 2H, H7′), 3.73 (m, 4H, H2″a, H6″a), 3.48 (m, 4H, H2″b, H6″b), 2.48 (m, 4H, H3″a, H5″a), 2.37 (m, 4H, H3″b, H5″b), 2.33-2.24 (m, 8H, CH_3, H2a, H9a), 2.13 (m, 2H, H2b, H9b), 1.52 (m, 4H, H3, H8), 1.23-1.12 (m, 8H, H4-H7). ^{13}C NMR (101 MHz, $CDCl_3$, 320 K) δ 173.9 (C), 160.6 (C), 146.5 (C), 145.2 (C), 134.1 (C), 133.8 (C), 132.1 (CH), 129.2 (CH), 127.92 (CH), 127.85 (CH), 127.0 (C), 126.3 (2 × CH), 123.3 (CH), 55.0 (CH_2), 47.0 (CH_2), 46.1 (CH_3), 33.7 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 25.2 (CH_2). HPLC: t_R 12.40 min, 99% purity (Method 2). LCMS (*m / z*): 819.1 $[M + H]^+$, 410.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{46}H_{53}Cl_2N_8O_2^+$ requires $[M + H]^+$ 819.3663; found 819.3694.

*1,12-Bis(8-chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b,e*][1,4]diazepin-5-yl)dodecane-1,12-dione (**7c**).* 1,12-Dodecanedioic acid (0.087 g, 0.376 mmol) and oxalyl chloride were reacted, followed by the addition of **1** (0.219 g, 0.671 mmol), *N*,*N*-diisopropylethylamine (163 μL, 0.936 mmol) and pyridine (0.085 mL, 1.05 mmol), as per general procedure A. Additional 1,12-dodecanedioyl dichloride (0.049 g, 0.182 mmol) was added. Column chromatography conditions: column 1 (5% methanol / acetone, until clozapine eluted then 10% methanol / chloroform), column 2 (gradient elution: from 5%

methanol / chloroform to 10% methanol / chloroform, increasing in 1% increments), column 3 (1% ammonia / 9 % methanol / chloroform). Yielded **7c** as a white foam (0.080 g, 0.095 mmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$, 320 K) δ 7.50 (ddd, *J* = 8.0, 7.1, 1.9 Hz, 2H, H3′), 7.42-7.29 (m, 6H, H1′, H2′, H4′), 7.14 (d, *J* = 2.4 Hz, 2H, H9′), 7.10 (d, *J* = 8.3 Hz, 2H, H6′), 6.96 (dd, *J* = 8.3, 2.0 Hz, 2H, H7′), 3.72 (m, 4H, H2″a, H6″a), 3.48 (m, 4H, H2″b, H6″b), 2.47 (m, 4H, H3″a, H5″a), 2.36 (m, 4H, H3″b, H5″b), 2.32-2.23 (m, 8H, CH_3, H2a, H11a), 2.15 (m, 2H, H2b, H11b), 1.53 (m, 4H, H3, H10), 1.25-1.12 (m, 12H, H4-H9). ^{13}C NMR (101 MHz, $CDCl_3$, 320 K) δ 173.9 (C), 160.7 (C), 146.5 (C), 145.2 (C), 134.1 (C), 133.9 (C), 132.1 (CH), 129.2 (CH), 128.0 (CH), 127.9 (CH), 127.1 (C), 126.3 (2 × CH), 123.3 (CH), 55.0 (CH_2), 47.2 (CH_2), 46.2 (CH_3), 33.7 (CH_2), 29.5 (CH_2), 29.4 (2 × CH_2), 25.3 (CH_2). HPLC: t_R 13.04 min, 97% purity (Method 2). LCMS (*m / z*): 847.2 $[M + H]^+$, 424.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{48}H_{57}Cl_2N_8O_2^+$ requires $[M + H]^+$ 847.3976; found 847.4008.

*1,14-Bis(8-chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b,e*][1,4]diazepin-5-yl)tetradecane-1,14-dione (**7d**).* 1,14-Tetradecanedioic acid (0.089 g, 0.343 mmol) and oxalyl chloride were reacted, followed by the addition of **1** (0.205 g, 0.627 mmol), *N*,*N*-diisopropylethylamine (148 μL, 0.850 mmol) and pyridine (0.077 mL, 0.954 mmol), as per general procedure A. Additional 1,14-tetradecanedioyl dichloride (0.046 g, 0.156 mmol) was added. Column chromatography conditions: column 1 (5% methanol / acetone, until clozapine eluted then 10% methanol / chloroform), column 2 (gradient elution: from 5% methanol / chloroform to 10% methanol / chloroform, increasing in 1% increments), column 3 (1% ammonia / 9 % methanol / chloroform). Yielded **7d** as a white foam (0.088 g, 0.101 mmol, 32%). ^{1}H NMR (400 MHz, $CDCl_3$, 320 K) δ 7.49 (ddd, *J* = 8.0, 7.1, 1.9 Hz, 2H, H3′), 7.42-7.29 (m, 6H, H1′, H2′, H4′), 7.14 (d, *J* = 2.4 Hz, 2H, H9′), 7.10 (d, *J* = 8.3 Hz, 2H, H6′), 6.96 (dd, *J* = 8.4, 2.1 Hz, 2H, H7′), 3.72 (m, 4H, H2″a, H6″a), 3.49 (m, 4H, H2″b, H6″b), 2.46 (m, 4H, H3″a, H5″a), 2.37 (m, 4H, H3″b, H5″b), 2.32-2.25 (m, 8H, CH_3, H2a, H13a), 2.16 (m, 2H, H2b, H13b), 1.54 (m, 4H, H3, H12), 1.28-1.13 (m, 16H, H4-H11). ^{13}C NMR (101 MHz, $CDCl_3$, 320 K) δ 174.0 (C), 160.7 (C),

146.5 (C), 145.2 (C), 134.1 (C), 133.8 (C), 132.1 (CH), 129.2 (CH), 128.0 (CH), 127.9 (CH), 127.1 (C), 126.3 (2 × CH), 123.3 (CH), 55.0 (CH_2), 47.2 (CH_2), 46.2 (CH_3), 33.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (2 × CH_2), 25.3 (CH_2). HPLC: t_R 8.69 min, 95% purity (Method 2). LCMS (*m / z*): 875.2 $[M + H]^+$, 438.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{50}H_{61}Cl_2N_8O_2^+$ requires $[M + H]^+$ 875.4289; found 875.4321.

*1,18-Bis(8-chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b,e*][1,4]diazepin-5-yl)octadecane-1,18-dione (**7e**).* 1,18-Octadecanedioic acid (0.118 g, 0.376 mmol) and oxalyl chloride were reacted, followed by the addition of **1** (0.218 g, 0.667 mmol), *N*,*N*-diisopropylethylamine (162 μL, 0.930 mmol) and pyridine (0.084 mL, 1.04 mmol), as per general procedure A. Additional 1,18-octadecanedioyl dichloride (0.059 g, 0.168 mmol) was added. Column chromatography conditions: column 1 (10% methanol / acetone, until clozapine eluted then 5% methanol / chloroform), column 2 (1% ammonia / 4 % methanol / chloroform). Yielded **7e** as a white foam (0.088 g, 0.094 mmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$, 320 K) δ 7.49 (ddd, *J* = 8.0, 7.2, 1.9 Hz, 2H, H3′), 7.42-7.30 (m, 6H, H1′, H2′, H4′), 7.15 (d, *J* = 2.3 Hz, 2H, H9′), 7.10 (d, *J* = 8.3 Hz, 2H, H6′), 6.96 (dd, *J* = 8.4, 2.1 Hz, 2H, H7′), 3.73 (m, 4H, H2″a, H6″a), 3.49 (m, 4H, H2″b, H6″b), 2.47 (m, 4H, H3″a, H5″a), 2.37 (m, 4H, H3″b, H5″b), 2.33-2.24 (m, 8H, CH_3, H2a, H17a), 2.15 (m, 2H, H2b, H17b), 1.55 (m, 4H, H3, H16), 1.29-1.15 (m, 24H, H4-H15). ^{13}C NMR (101 MHz, $CDCl_3$, 320 K) δ 174.0 (C), 160.7 (C), 146.5 (C), 145.2 (C), 134.1 (C), 133.9 (C), 132.1 (CH), 129.2 (CH), 128.0 (CH), 127.9 (CH), 127.1 (C), 126.3 (2 × CH), 123.3 (CH), 55.0 (CH_2), 47.2 (CH_2), 46.2 (CH_3), 33.7 (CH_2), 29.83 (CH_2), 29.81 (CH_2), 29.77 (CH_2), 29.6 (CH_2), 29.43 (CH_2), 29.40 (CH_2), 25.3 (CH_2). HPLC: t_R 12.18 min, 99% purity (Method 1). LCMS (*m / z*): 931.2 $[M + H]^+$, 466.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{54}H_{69}Cl_2N_8O_2^+$ requires $[M + H]^+$ 931.4915; found 931.4922.

*1,20-Bis(8-chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b,e*][1,4]diazepin-5-yl)icosane-1,20-dione (**7f**).* 1,20-Icosanedioic acid (0.129 g, 0.377 mmol) and oxalyl chloride were reacted, followed by the addition of **1** (0.219 g, 0.671 mmol), *N*,*N*-diisopropylethylamine (160 μL, 0.919 mmol) and pyridine (0.084 mL, 1.04 mmol), as per general procedure A. Additional 1,20-icosanedioyl dichloride (0.068 g, 0.180 mmol) was added. Column chromatography conditions: column 1 (10% methanol / acetone, until clozapine eluted then 5% methanol / chloroform), column 2 (1% ammonia / 9 % methanol / chloroform), column 3 (gradient elution: from 5% methanol / chloroform to 10% methanol / chloroform, increasing in 1% increments). Yielded **7f** as a white foam (0.089 g, 0.093 mmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$, 320 K) δ 7.49 (ddd, *J* = 7.9, 7.0, 1.9 Hz, 2H, H3′), 7.41-7.29 (m, 6H, H1′, H2′, H4′), 7.15 (d, *J* = 2.4 Hz, 2H, H9′), 7.10 (d, *J* = 8.3 Hz, 2H, H6′), 6.96 (dd, *J* = 8.4, 2.2 Hz, 2H, H7′), 3.73 (m, 4H, H2″a, H6″a), 3.48 (m, 4H, H2″b, H6″b), 2.47 (m, 4H, H3″a, H5″a), 2.37 (m, 4H, H3″b, H5″b), 2.33-2.23 (m, 8H, CH_3, H2a, H19a), 2.16 (m, 2H, H2b, H19b), 1.54 (m, 4H, H3, H18), 1.29-1.14 (m, 28H, H4-H17). ^{13}C NMR (101 MHz, $CDCl_3$, 320 K) δ 174.0 (C), 160.6 (C), 146.5 (C), 145.2 (C), 134.1 (C), 133.9 (C), 132.1 (CH), 129.2 (CH), 128.0 (CH), 127.8 (CH), 127.1 (C), 126.3 (2 × CH), 123.3 (CH), 55.0 (CH_2), 47.1 (CH_2), 46.2 (CH_3), 33.7 (CH_2), 29.85 (CH_2), 29.84 (CH_2), 29.81 (CH_2), 29.77 (CH_2), 29.6 (CH_2), 29.42 (CH_2), 29.39 (CH_2), 25.3 (CH_2). HPLC: t_R 10.55 min, 97% purity (Method 2). LCMS (*m / z*): 959.3 $[M + H]^+$, 480.3 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{56}H_{73}Cl_2N_8O_2^+$ requires $[M + H]^+$ 959.5228; found 959.5264.

Synthesis of clozapine N5 hydrazide bivalent ligands

N^{1},N^{8}-*Bis(8-chloro-11-(4-methylpiperazin-1-yl)-5*H-*dibenzo[*b,e*][1,4]diazepin-5-yl)octanediamide (**8b**).* 1,8-Octanedioic acid (0.061 g, 0.351 mmol) and oxalyl chloride were reacted using Method B, followed by the addition of **2** (0.210 g, 0.616 mmol) and pyridine (0.080 mL, 0.991 mmol), as per general procedure B. Additional 1,8-octanedioyl dichloride (0.022 g, 0.103 mmol) was added. Column chromatography conditions: column 1 (gradient elution: from 2% methanol / chloroform to 10% methanol / chloroform, increasing in 2% increments), column 2 (gradient elution: from 2% methanol / chloroform to 5% methanol / chloroform, increasing in 1% increments). Yielded **8b** as an off-white foam (0.141 g, 0.171 mmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 2H, NH), 8.56 (d, *J* = 2.3 Hz, 2H, H9′), 7.78 (ddd, *J* = 8.3, 0.9, 0.9 Hz, 2H, H1′/H4′), 7.41-7.33 (m, 4H, H3′/H2′, H4′/H1′), 7.36 (d, *J* = 8.5 Hz, 2H, H6′), 7.13 (dd, *J* = 8.5, 2.4 Hz, 2H, H7′), 7.12 (m, 2H, H2′/H3′), 3.55 (m, 8H, H2″, H6″), 2.66 (m, 8H, H3″, H5″), 2.38 (s, 6H, CH_3), 2.21 (t, *J* = 7.4 Hz, 4H, H2, H7), 1.55 (app p, *J* = 6.9 Hz, 4H, H3, H6), 1.23 (m, 4H, H4, H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1 (C), 153.8 (C), 141.9 (C), 133.9 (C), 132.8 (C), 128.3 (CH), 126.9 (C), 124.7 (CH), 123.7 (CH), 122.7 (CH), 121.8 (CH), 120.7 (CH), 116.2 (C), 110.6 (CH), 54.7 (CH_2), 49.3 (CH_2), 46.3 (CH_3), 38.1 (CH_2), 29.0 (CH_2), 25.3 (CH_2). HPLC: t_R 9.98 min, 95% purity (Method 1). LCMS (*m / z*): 821.2 $[M + H]^+$, 411.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{44}H_{51}Cl_2N_{10}O_2^+$ requires $[M + H]^+$ 821.3568; found 821.3552.

N^{1},N^{10}-*Bis(8-chloro-11-(4-methylpiperazin-1-yl)-5*H-*dibenzo[*b,e*][1,4]diazepin-5-yl)decanediamide (**8c**).* 1,10-Decanedioic acid (0.050 g, 0.246 mmol) and oxalyl chloride were reacted using Method B, followed by the addition of **2** (0.154 g, 0.452 mmol) and pyridine (0.055 mL, 0.681 mmol), as per general procedure B. Additional 1,10-decanedioyl dichloride (0.030 g, 0.124 mmol) was added. Column chromatography conditions: 1% ammonia / 4% methanol / chloroform. Yielded **8c** as an off-white foam (0.111 g, 0.130 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 2H, NH), 8.57 (d, *J* = 2.3 Hz, 2H, H9′), 7.79 (ddd, *J* = 8.2, 0.9, 0.9 Hz, 2H, H1′/H4′), 7.43-7.35 (m, 4H, H3′/H2′, H4′/H1′),

7.36 (d, *J* = 8.5 Hz, 2H, H6′), 7.15 (m, 2H, H2′/H3′), 7.13 (dd, *J* = 8.5, 2.4 Hz, 2H, H7′), 3.55 (m, 8H, H2″, H6″), 2.67 (m, 8H, H3″, H5″), 2.39 (s, 6H, CH_3), 2.24 (t, *J* = 7.4 Hz, 4H, H2, H9), 1.58 (app p, *J* = 7.3 Hz, 4H, H3, H8), 1.26-1.09 (m, 8H, H4-H7). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (C), 153.8 (C), 141.9 (C), 133.9 (C), 132.9 (C), 128.3 (CH), 126.9 (C), 124.7 (CH), 123.7 (CH), 122.7 (CH), 121.9 (CH), 120.8 (CH), 116.3 (C), 110.7 (CH), 54.8 (CH_2), 49.4 (CH_2), 46.4 (CH_3), 38.2 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 25.5 (CH_2). HPLC: t_R 10.45 min, >99% purity (Method 1). LCMS (*m / z*): 849.2 $[M + H]^+$, 425.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{46}H_{56}Cl_2N_{10}O_2^{2+}$ requires $[M + 2H]^{2+}$ 425.1977; found 425.1975.

N^{1},N^{12}-*Bis(8-chloro-11-(4-methylpiperazin-1-yl)-5*H-*dibenzo[*b,e*][1,4]diazepin-5-yl)dodecanediamide (**8d**)*. 1,12-Dodecanedioic acid (0.057 g, 0.248 mmol) and oxalyl chloride were reacted using Method B, followed by the addition of **2** (0.149 g, 0.436 mmol) and pyridine (0.055 mL, 0.681 mmol), as per general procedure B. Additional 1,12-dodecanedioyl dichloride (0.032 g, 0.122 mmol) was added. Column chromatography conditions: gradient elution: from 2% methanol / chloroform to 6% methanol / chloroform, increasing in 1% increments. Yielded **8d** as an off-white foam (0.133 g, 0.151 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 2H, NH), 8.58 (d, *J* = 2.3 Hz, 2H, H9′), 7.79 (ddd, *J* = 8.3, 0.9, 0.9 Hz, 2H, H1′/H4′), 7.44-7.38 (m, 4H, H3′/H2′, H4′/H1′), 7.36 (d, *J* = 8.5 Hz, 2H, H6′), 7.16 (m, 2H, H2′/H3′), 7.14 (dd, *J* = 8.5, 2.4 Hz, 2H, H7′), 3.59 (m, 8H, H2″, H6″), 2.70 (m, 8H, H3″, H5″), 2.42 (s, 6H, CH_3), 2.25 (t, *J* = 7.4 Hz, 4H, H2, H11), 1.61 (app p, *J* = 7.3 Hz, 4H, H3, H10), 1.29-1.07 (m, 12H, H4-H9). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C), 153.7 (C), 142.0 (C), 134.0 (C), 133.0 (C), 128.4 (CH), 127.0 (C), 124.8 (CH), 123.7 (CH), 122.8 (CH), 121.8 (CH), 120.8 (CH), 116.3 (C), 110.8 (CH), 54.7 (CH_2), 49.3 (CH_2), 46.3 (CH_3), 38.4 (CH_2), 29.49 (CH_2), 29.47 (CH_2), 29.3 (CH_2), 25.6 (CH_2). HPLC: t_R 10.93 min, 97% purity (Method 1). LCMS (*m / z*): 877.1 $[M + H]^+$, 439.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{48}H_{59}Cl_2N_{10}O_2^+$ requires $[M + H]^+$ 877.4194; found 877.4188.

N^{1},N^{14}-*Bis(8-chloro-11-(4-methylpiperazin-1-yl)-5*H-*dibenzo[*b,e*][1,4]diazepin-5-yl)tetradecanediamide (**8e**).* 1,14-Tetradecanedioic acid (0.060 g, 0.232 mmol) and oxalyl chloride were reacted using Method B, followed by the addition of **2** (0.145 g, 0.425 mmol) and pyridine (0.055 mL, 0.681 mmol), as per general procedure B. Column chromatography conditions: column 1 (gradient elution: from 2% methanol / chloroform to 10% methanol / chloroform, increasing in 2% increments), column 2 (gradient elution: from 2% methanol / chloroform to 6% methanol / chloroform, increasing in 1% increments). Yielded **8e** as an off-white foam (0.137 g, 0.152 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 2H, NH), 8.58 (d, *J* = 2.3 Hz, 2H, H9′), 7.79 (ddd, *J* = 8.3, 0.9, 0.9 Hz, 2H, H1′/H4′), 7.45-7.38 (m, 4H, H3′/H2′, H4′/H1′), 7.36 (d, *J* = 8.5 Hz, 2H, H6′), 7.15 (m, 2H, H2′/H3′), 7.13 (dd, *J* = 8.5, 2.4 Hz, 2H, H7′), 3.57 (m, 8H, H2″, H6″), 2.69 (m, 8H, H3″, H5″), 2.41 (s, 6H, CH_3), 2.26 (t, *J* = 7.4 Hz, 4H, H2, H13), 1.62 (app p, *J* = 7.3 Hz, 4H, H3, H12), 1.31-1.10 (m, 16H, H4-H11). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C), 153.8 (C), 141.9 (C), 134.0 (C), 132.9 (C), 128.3 (CH), 126.9 (C), 124.7 (CH), 123.6 (CH), 122.7 (CH), 121.8 (CH), 120.8 (CH), 116.3 (C), 110.7 (CH), 54.8 (CH_2), 49.3 (CH_2), 46.3 (CH_3), 38.3 (CH_2), 29.6 (CH_2), 29.52 (CH_2), 29.46 (CH_2), 29.3 (CH_2), 25.6 (CH_2). HPLC: t_R 11.34 min, 95% purity (Method 1). LCMS (*m / z*): 905.2 $[M + H]^+$, 453.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{50}H_{63}Cl_2N_{10}O_2^+$ requires $[M + H]^+$ 905.4507; found 905.4495.

N^{1},N^{18}-*Bis(8-chloro-11-(4-methylpiperazin-1-yl)-5*H-*dibenzo[*b,e*][1,4]diazepin-5-yl)octadecanediamide (**8f**).* 1,18-Octadecanedioic acid (0.078 g, 0.242 mmol) and oxalyl chloride were reacted using Method B, followed by the addition of **2** (0.149 g, 0.436 mmol), *N*,*N*-diisopropylethylamine (105 μL, 0.603 mmol) and pyridine (0.055 mL, 0.681 mmol), as per general procedure B. Additional 1,18-octadecanedioyl dichloride (0.032 g, 0.091 mmol) was added. Column chromatography conditions: gradient elution: from 2% methanol / chloroform to 5% methanol / chloroform, increasing in 1% increments (using a preconditioned column with 0.5% ammonia / 1.5% methanol / chloroform). Yielded **8f** as an off-white foam (0.097 g, 0.101 mmol, 46%). ^{1}H NMR (400

MHz, $CDCl_3$) δ 9.50 (s, 2H, NH), 8.58 (d, *J* = 2.3 Hz, 2H, H9′), 7.80 (ddd, *J* = 8.2, 0.9, 0.9 Hz, 2H, H1′/H4′), 7.44-7.38 (m, 4H, H3′/H2′, H4′/H1′), 7.37 (d, *J* = 8.5 Hz, 2H, H6′), 7.15 (m, 2H, H2′/H3′), 7.13 (dd, *J* = 8.5, 2.4 Hz, 2H, H7′), 3.56 (m, 8H, H2″, H6″), 2.68 (m, 8H, H3″, H5″), 2.40 (s, 6H, CH_3), 2.26 (t, *J* = 7.4 Hz, 4H, H2, H17), 1.63 (app p, *J* = 7.3 Hz, 4H, H3, H16), 1.31-1.13 (m, 24H, H4-H15). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C), 153.8 (C), 142.0 (C), 134.0 (C), 133.0 (C), 128.3 (CH), 126.9 (C), 124.7 (CH), 123.7 (CH), 122.7 (CH), 121.9 (CH), 120.8 (CH), 116.3 (C), 110.7 (CH), 54.8 (CH_2), 49.4 (CH_2), 46.4 (CH_3), 38.4 (CH_2), 29.79 (CH_2), 29.77 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.6 (CH_2). HPLC: t_R 10.09 min, >99% purity (Method 2). LCMS (*m / z*): 961.2 [M + H]$^+$, 481.2 [M + 2H]$^{2+}$. HRMS (*m / z*): $C_{54}H_{72}Cl_2N_{10}O_2^{2+}$ requires [M + 2H]$^{2+}$ 481.2603; found 481.2600.

N^{1},N^{20}-*Bis(8-chloro-11-(4-methylpiperazin-1-yl)-5*H-*dibenzo[*b,e*][1,4]diazepin-5-yl)icosanediamide (**8g**)*. 1,20-Icosanedioic acid (0.084 g, 0.246 mmol) and oxalyl chloride were reacted using Method B, followed by the addition of **2** (0.151 g, 0.441 mmol), *N*,*N*-diisopropylethylamine (105 μL, 0.603 mmol) and pyridine (0.055 mL, 0.681 mmol), as per general procedure B. Additional 1,20-icosanedioyl dichloride (0.047 g, 0.123 mmol) was added. Column chromatography conditions: column 1 (1% ammonia / 2% methanol / chloroform), column 2 (gradient elution: from 2% methanol / chloroform to 6% methanol / chloroform, increasing in 1% increments), column 3 (1% ammonia / 4 % methanol / chloroform). Yielded **8g** as an off-white foam (0.084 g, 0.085 mmol, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 2H, NH), 8.58 (d, *J* = 2.3 Hz, 2H, H9′), 7.80 (ddd, *J* = 8.2, 0.9, 0.9 Hz, 2H, H1′/H4′), 7.45-7.38 (m, 4H, H3′/H2′, H4′/H1′), 7.36 (d, *J* = 8.5 Hz, 2H, H6′), 7.16 (m, 2H, H2′/H3′), 7.13 (dd, *J* = 8.5, 2.4 Hz, 2H, H7′), 3.58 (m, 8H, H2″, H6″), 2.69 (m, 8H, H3″, H5″), 2.41 (s, 6H, CH_3), 2.26 (t, *J* = 7.4 Hz, 4H, H2, H19), 1.63 (app p, *J* = 7.3 Hz, 4H, H3, H18), 1.31-1.14 (m, 28H, H4-H17). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C), 153.8 (C), 141.9 (C), 134.0 (C), 132.9 (C), 128.3 (CH), 126.9 (C), 124.7 (CH), 123.7 (CH), 122.7 (CH), 121.9 (CH), 120.8 (CH), 116.3 (C), 110.7 (CH), 54.8 (CH_2), 49.4

(CH_2), 46.4 (CH_3), 38.4 (CH_2), 29.81 (CH_2), 29.79 (CH_2), 29.76 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.6 (CH_2). HPLC: t_R 10.14 min, 99% purity (Method 2). LCMS (*m / z*): 989.3 $[M + H]^+$, 495.3 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{56}H_{75}Cl_2N_{10}O_2^+$ requires $[M + H]^+$ 989.5446; found 989.5491.

*4,4'-(Piperazine-1,4-diyl)bis(*N*-(8-chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b,e*][1,4]diazepin-5-yl)-4-oxobutanamide) (**12a**).* 4,4'-(Piperazine-1,4-diyl)bis(4-oxobutanoic acid) (**11a**, 0.090 g, 0.316 mmol) and oxalyl chloride were reacted using Method B, followed by the addition of **2** (0.191 g, 0.558 mmol) and pyridine (70 μL, 0.867 mmol), as per general experimental B. Additional 4,4'-(piperazine-1,4-diyl)bis(4-oxobutanoyl chloride) (0.052 g, 0.161 mmol) was added. Column chromatography conditions: 1% ammonia / 4% methanol / chloroform. Yielded **12a** as an off-white foam (0.063 g, 0.067 mmol, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 2H, NH), 8.56 (s, 2H, H9″), 7.79 (ddd, *J* = 8.2, 0.9, 0.9 Hz, 2H, H1″/H4″), 7.42-7.36 (m, 4H, H3″/H2″, H4″/H1″), 7.36 (d, *J* = 8.5 Hz, 2H, H6″), 7.15 (m, 2H, H2″/H3″), 7.13 (dd, *J* = 8.5, 2.4 Hz, 2H, H7″), 3.59 (m, 8H, H2‴, H6‴), 3.55-3.46 (m, 4H, piperazine spacer), 3.42-3.36 (m, 4H, piperazine spacer), 2.69 (m, 8H, H3‴, H5‴), 2.64 (s, 8H, H2′, H3′), 2.40 (s, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) A mixture of amide rotamers.[10] δ 170.3 (C), 170.1 (C), 170.0 (C), 153.9 (C), 141.9 (C), 133.9 (C), 132.9 (C), 128.2 (CH), 126.9 (C), 124.8 (CH), 123.7 (CH), 122.6 (CH), 121.8 (CH), 120.7 (CH), 116.4 (C), 110.7 (CH), 54.8 (CH_2), 49.4 (CH_2), 46.3 (CH_3), 45.2 (CH_2), 45.0 (CH_2), 41.53 (CH_2), 41.45 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 28.0 (CH_2). HPLC: t_R 7.22 min, 96% purity (Method 2). LCMS (*m / z*): 933.2 $[M + H]^+$, 467.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{48}H_{55}Cl_2N_{12}O_4^+$ requires $[M + H]^+$ 933.3841; found 933.3803.

*5,5'-(Piperazine-1,4-diyl)bis(*N*-(8-chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b,e*][1,4]diazepin-5-yl)-5-oxopentanamide) (**12b**).* 5,5'-(Piperazine-1,4-diyl)bis(5-oxopentanoic acid) (**11b**, 0.099 g, 0.315 mmol) and oxalyl chloride were reacted using Method B, followed by the addition of **2** (0.200 g,

0.584 mmol) and pyridine (72 μL, 0.892 mmol), as per general experimental B. Column chromatography conditions: column 1 (gradient elution: from 2% methanol / chloroform to 10% methanol / chloroform, increasing in 2% increments), column 2 (1% ammonia / 4% methanol / chloroform). Yielded **12b** as an off-white foam (0.101 g, 0.105 mmol, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (br s, 1H, NH), 9.63 (br s, 1H, NH), 8.55 (d, *J* = 2.4 Hz, 2H, H9″), 7.79 (ddd, *J* = 8.2, 0.9, 0.9 Hz, 2H, H1″/H4″), 7.45-7.37 (m, 4H, H3″/H2″, H4″/H1″), 7.38 (d, *J* = 8.6 Hz, 2H, H6″), 7.18-7.13 (m, 4H, H2″/H3″, H7″), 3.57 (m, 8H, H2‴, H6‴), 3.52-3.43 (m, 4H, piperazine spacer), 3.34-3.25 (m, 4H, piperazine spacer), 2.71 (m, 8H, H3‴, H5‴), 2.44-2.31 (m, 14H, CH_3, H2′, H4′), 1.98 (app p, *J* = 7.1 Hz, 4H, H3′). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 (C), 170.7 (C), 153.8 (C), 141.8 (C), 133.6 (C), 132.8 (C), 128.3 (CH), 127.0 (C), 124.6 (CH), 123.8 (CH), 122.7 (CH), 121.9 (CH), 120.8 (CH), 116.3 (C), 110.6 (CH), 54.7 (CH_2), 49.3 (CH_2), 46.3 (CH_3), 45.3 (CH_2), 45.1 (CH_2), 41.5 (CH_2), 41.3 (CH_2), 36.7 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 20.6 (CH_2), 20.5 (CH_2). HPLC: t_R 9.72 min, 98% purity (Method 1). LCMS (*m / z*): 961.1 $[M + H]^+$, 481.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{50}H_{60}Cl_2N_{12}O_4^{2+}$ requires $[M + 2H]^{2+}$ 481.2113; found 481.2122.

*Ethane-1,2-diyl bis(4-((8-chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b,e*][1,4]diazepin-5-yl)amino)-4-oxobutanoate) (**14**).* 4,4'-(Ethane-1,2-diylbis(oxy))bis(4-oxobutanoic acid) (**13**, 0.090 g, 0.343 mmol) and oxalyl chloride were reacted using Method B, followed by the addition of **2** (0.204 g, 0.596 mmol) and pyridine (76 μL, 0.942 mmol) as per general experimental B. Column chromatography conditions: column 1 (0.5% ammonia / 2.5% methanol / chloroform), column 2 (gradient elution: from 2% methanol / chloroform to 5% methanol / chloroform, increasing in 1% increments). Yielded **14** as an off-white foam (0.124 g, 0.136 mmol, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 2H, NH), 8.52 (d, *J* = 2.3 Hz, 2H, H9″), 7.78 (ddd, *J* = 8.3, 0.9, 0.9 Hz, 2H, H1″/H4″), 7.43-7.36 (m, 4H, H3″/H2″, H4″/H1″), 7.36 (d, *J* = 8.5 Hz, 2H, H6″), 7.14 (ddd, *J* = 8.1, 6.3, 1.8 Hz, 2H, H2″/H3″), 7.12 (dd, *J* = 8.5, 2.4 Hz, 2H, H7″), 4.16 (s, 4H, H1, H2), 3.58 (m, 8H,

H2‴, H6‴), 2.72 (m, 8H, H3‴, H5‴), 2.66 (m, 4H, H2′/H3′), 2.57 (m, 4H, H3′/H2′), 2.42 (s, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (C), 169.4 (C), 153.7 (C), 141.8 (C), 133.6 (C), 132.7 (C), 128.3 (CH), 126.9 (C), 124.6 (CH), 123.7 (CH), 122.6 (CH), 121.8 (CH), 120.7 (CH), 116.3 (C), 110.6 (CH), 62.3 (CH_2), 54.6 (CH_2), 49.2 (CH_2), 46.1 (CH_3), 32.2 (CH_2), 28.9 (CH_2). HPLC: t_R 10.17 min, >99% purity (Method 1). LCMS (*m / z*): 909.1 $[M + H]^+$, 455.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{46}H_{51}Cl_2N_{10}O_6^+$ requires $[M + H]^+$ 909.3365; found 909.3328.

Synthesis of clozapine N4′ propylamine bivalent ligands

N^{1},N^{8}-*Bis(3-(4-(8-chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)piperazin-1-yl)propyl)octanediamide (**9b**).* 1,8-Octanedioic acid (0.030 g, 0.169 mmol) and oxalyl chloride were reacted, followed by the addition of **5** (0.127 g, 0.343 mmol) and pyridine (0.039 mL, 0.483 mmol), as per general procedure C. Column chromatography conditions: 10% methanol / chloroform. Yielded **9b** as a yellow foam (0.062 g, 0.071 mmol, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 2H, H3‴), 7.24 (dd, *J* = 7.7, 1.4 Hz, 2H, H1‴), 7.05 (d, *J* = 2.4 Hz, 2H, H9‴), 7.03-6.97 (m, 4H, H2‴, CONH), 6.85 (dd, *J* = 7.9, 0.8 Hz, 2H, H4‴), 6.82 (dd, *J* = 8.3, 2.4 Hz, 2H, H7‴), 6.65 (d, *J* = 8.3 Hz, 2H, H6‴), 5.21 (s, 2H, H5‴), 3.45 (s, 8H, H3″, H5″), 3.32 (td, *J* = 5.9, 5.9 Hz, 4H, H1′), 2.57 (s, 8H, H2″, H6″), 2.52 (t, *J* = 6.3 Hz, 4H, H3′), 2.11 (m, 4H, H2, H7), 1.69 (app p, *J* = 6.3 Hz, 4H, H2′), 1.59 (app p, *J* = 7.0 Hz, 4H, H3, H6), 1.31 (m, 4H, H4, H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (C), 163.1 (C), 153.1 (C), 141.8 (C), 140.8 (C), 132.2 (CH), 130.3 (CH), 129.0 (C), 126.8 (CH), 123.43 (CH), 123.36 (C), 123.2 (CH), 120.35 (CH), 120.33 (CH), 57.6 (CH_2), 53.2 (CH_2), 47.5 (CH_2), 39.4 (CH_2), 37.0 (CH_2), 29.1 (CH_2), 25.9 (CH_2), 25.2 (CH_2). HPLC: t_R 7.94 min, >99% purity (Method 1). LCMS (*m / z*): 877.2 $[M + H]^+$, 439.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{48}H_{59}Cl_2N_{10}O_2^+$ requires $[M + H]^+$ 877.4194; found 877.4199.

N^{1},N^{10}-*Bis(3-(4-(8-chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)piperazin-1-yl)propyl)decanediamide (**9c**).* 1,10-Decanedioic acid (0.036 g, 0.176 mmol) and oxalyl chloride were reacted, followed by the

addition of **5** (0.131 g, 0.354 mmol) and pyridine (0.040 mL, 0.496 mmol), as per general procedure C. Additional 1,10-decanedioyl dichloride (0.023 g, 0.094 mmol) was added. Column chromatography conditions: column 1 (10% methanol / chloroform), column 2 (1% ammonia / 4% methanol / chloroform), column 3 (10% methanol / chloroform). Yielded **9c** as a yellow foam (0.071 g, 0.078 mmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (ddd, *J* = 7.8, 7.3, 1.5 Hz, 2H, H3‴), 7.24 (dd, *J* = 7.7, 1.5 Hz, 2H, H1‴), 7.06 (d, *J* = 2.4 Hz, 2H, H9‴), 7.00 (ddd, *J* = 7.7, 7.4, 1.1 Hz, 2H, H2‴), 6.94 (br t, *J* = 5.0 Hz, 2H, CONH), 6.85 (dd, *J* = 8.0, 0.8 Hz, 2H, H4‴), 6.82 (dd, *J* = 8.3, 2.4 Hz, 2H, H7‴), 6.65 (d, *J* = 8.3 Hz, 2H, H6‴), 5.20 (s, 2H, H5‴), 3.43 (m, 8H, H3″, H5″), 3.35 (td, *J* = 5.9, 5.8 Hz, 4H, H1′), 2.55 (m, 8H, H2″, H6″), 2.51 (t, *J* = 6.3 Hz, 4H, H3′), 2.11 (m, 4H, H2, H9), 1.69 (app p, *J* = 6.2 Hz, 4H, H2′), 1.58 (app p, *J* = 7.1 Hz, 4H, H3, H8), 1.32-1.23 (m, 8H, H4-H7). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (C), 163.1 (C), 153.2 (C), 141.8 (C), 140.8 (C), 132.1 (CH), 130.3 (CH), 129.0 (C), 126.9 (CH), 123.5 (C), 123.4 (CH), 123.1 (CH), 120.32 (CH), 120.28 (CH), 57.8 (CH_2), 53.3 (CH_2), 47.6 (CH_2), 39.6 (CH_2), 37.1 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.0 (CH_2), 25.3 (CH_2). HPLC: t_R 8.45 min, >99% purity (Method 1). LCMS (*m / z*): 905.2 $[M + H]^+$, 453.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{50}H_{63}Cl_2N_{10}O_2^+$ requires $[M + H]^+$ 905.4507; found 905.4550.

N^{1},N^{12}-*Bis(3-(4-(8-chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)piperazin-1-yl)propyl)dodecanediamide (**9d**)*. 1,12-Dodecanedioic acid (0.040 g, 0.173 mmol) and oxalyl chloride were reacted, followed by the addition of **5** (0.131 g, 0.354 mmol) and pyridine (0.040 mL, 0.496 mmol), as per general procedure C. Additional 1,12-dodecanedioyl dichloride (0.021 g, 0.091 mmol) was added. Column chromatography conditions: column 1 (10% methanol / chloroform), column 2 (1% ammonia / 4% methanol / chloroform), column 3 (10% methanol / chloroform). Yielded **9d** as a yellow foam (0.059 g, 0.063 mmol, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 2H, H3‴), 7.25 (dd, *J* = 7.7, 1.6 Hz, 2H, H1‴), 7.06 (d, *J* = 2.4 Hz, 2H, H9‴), 7.00 (ddd, *J* = 7.8, 7.4, 1.1 Hz, 2H, H2‴), 6.91 (br t, *J* = 4.9 Hz, 2H, CONH), 6.85 (dd, *J* = 8.0, 0.9 Hz, 2H, H4‴), 6.82 (dd, *J* = 8.3, 2.4 Hz, 2H, H7‴),

6.64 (d, *J* = 8.3 Hz, 2H, H6‴), 5.15 (s, 2H, H5‴), 3.44 (m, 8H, H3″, H5″), 3.36 (td, *J* = 6.0, 5.9 Hz, 4H, H1′), 2.55 (m, 8H, H2″, H6″), 2.52 (t, *J* = 6.3 Hz, 4H, H3′), 2.12 (m, 4H, H2, H11), 1.70 (app p, *J* = 6.3 Hz, 4H, H2′), 1.59 (app p, *J* = 7.4 Hz, 4H, H3, H10), 1.28-1.21 (m, 12H, H4-H9). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (C), 163.1 (C), 153.1 (C), 141.8 (C), 140.8 (C), 132.1 (CH), 130.3 (CH), 129.1 (C), 126.9 (CH), 123.43 (C), 123.39 (CH), 123.1 (CH), 120.32 (CH), 120.25 (CH), 57.8 (CH_2), 53.4 (CH_2), 47.5 (CH_2), 39.6 (CH_2), 37.2 (CH_2), 29.44 (CH_2), 29.40 (CH_2), 29.38 (CH_2), 26.0 (CH_2), 25.3 (CH_2). HPLC: t_R 6.32 min, >99% purity (Method 2). LCMS (*m / z*): 933.2 $[M + H]^+$, 467.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{52}H_{67}Cl_2N_{10}O_2^+$ requires $[M + H]^+$ 933.4820; found 933.4854.

N^{1},N^{14}-*Bis(3-(4-(8-chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)piperazin-1-yl)propyl)tetradecanediamide (**9e**).* 1,14-Tetradecanedioic acid (0.048 g, 0.184 mmol) and oxalyl chloride were reacted, followed by the addition of **5** (0.131 g, 0.354 mmol), anhydrous potassium carbonate (0.050 g, 0.362 mmol) and pyridine (0.100 mL, 1.24 mmol), as per general procedure C. Additional 1,14-tetradecanedioyl dichloride (0.027 g, 0.093 mmol) was added. Column chromatography conditions: column 1 (gradient elution: from 2% methanol / chloroform to 5% methanol / chloroform, increasing in 1% increments, using a column preconditioned with 1% ammonia / 2% methanol / chloroform), column 2 (10% methanol / chloroform). Yielded **9e** as a yellow foam (0.064 g, 0.066 mmol, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 2H, H3‴), 7.25 (dd, *J* = 7.7, 1.4 Hz, 2H, H1‴), 7.06 (d, *J* = 2.4 Hz, 2H, H9‴), 7.00 (m, 2H, H2‴), 6.88-6.83 (m, 4H, CONH, H4‴), 6.82 (dd, *J* = 8.3, 2.4 Hz, 2H, H7‴), 6.64 (d, *J* = 8.3 Hz, 2H, H6‴), 5.11 (s, 2H, H5‴), 3.45 (m, 8H, H3″, H5″), 3.35 (td, *J* = 5.9, 5.9 Hz, 4H, H1′), 2.55 (m, 8H, H2″, H6″), 2.51 (t, *J* = 6.3 Hz, 4H, H3′), 2.13 (m, 4H, H2, H13), 1.69 (app p, *J* = 6.2 Hz, 4H, H2′), 1.60 (app p, *J* = 7.3 Hz, 4H, H3, H12), 1.32-1.16 (m, 16H, H4-H11). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (C), 163.0 (C), 153.1 (C), 141.8 (C), 140.7 (C), 132.1 (CH), 130.3 (CH), 129.1 (C), 126.9 (CH), 123.43 (C), 123.37 (CH), 123.1 (CH), 120.3 (CH), 120.2 (CH), 57.8 (CH_2), 53.4 (CH_2), 47.6 (CH_2), 39.5 (CH_2), 37.2 (CH_2), 29.6 (CH_2),

29.52 (CH_2), 29.45 (CH_2), 29.4 (CH_2), 26.0 (CH_2), 25.4 (CH_2). HPLC: t_R 6.66 min, >99% purity (Method 2). LCMS (*m / z*): 961.2 $[M + H]^+$, 481.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{54}H_{71}Cl_2N_{10}O_2^+$ requires $[M + H]^+$ 961.5133; found 961.5139.

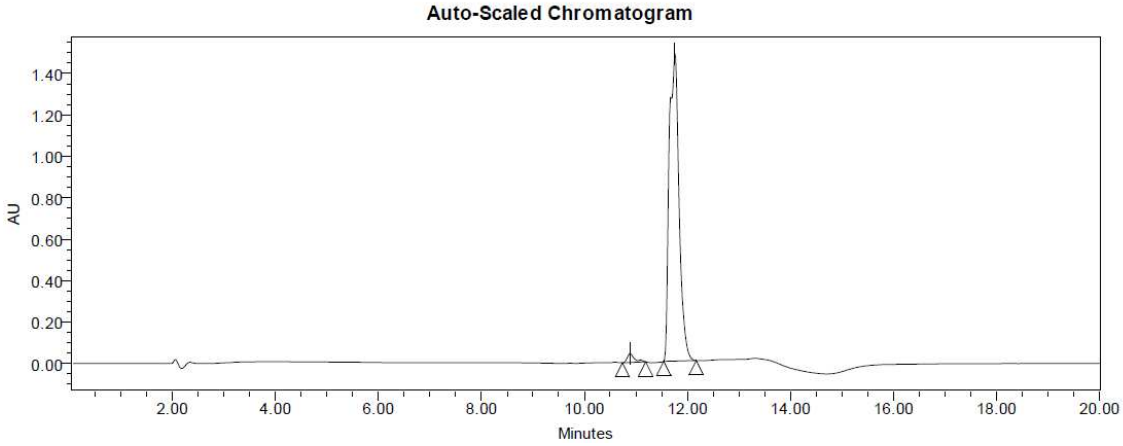
N^1,N^{18}-*Bis(3-(4-(8-chloro-5*H-*dibenzo[*b,e*][1,4]diazepin-11-yl)piperazin-1-yl)propyl)octadecanediamide (**9f**).* 1,18-Octadecanedioic acid (0.057 g, 0.182 mmol) and oxalyl chloride were reacted, followed by the addition of **5** (0.132 g, 0.357 mmol), anhydrous potassium carbonate (0.050 g, 0.362 mmol) and pyridine (0.100 mL, 1.24 mmol), as per general procedure C. Additional 1,18-octadecanedioyl dichloride (0.026 g, 0.073 mmol) was added. Column chromatography conditions: column 1 (gradient elution: from 2% methanol / chloroform to 5% methanol / chloroform, increasing in 1% increments, using a column preconditioned with 1% ammonia / 2% methanol / chloroform), column 2 (10% methanol / chloroform). Yielded **9f** as a yellow foam (0.074 g, 0.072 mmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 2H, H3‴), 7.25 (dd, *J* = 7.7, 1.5 Hz, 2H, H1‴), 7.06 (d, *J* = 2.4 Hz, 2H, H9‴), 7.00 (ddd, *J* = 7.7, 7.4, 1.1 Hz, 2H, H2‴), 6.86-6.82 (m, 4H, CONH, H4‴), 6.82 (dd, *J* = 8.3, 2.4 Hz, 2H, H7‴), 6.63 (d, *J* = 8.3 Hz, 2H, H6‴), 5.06 (s, 2H, H5‴), 3.45 (m, 8H, H3″, H5″), 3.35 (td, *J* = 5.9, 5.9 Hz, 4H, H1′), 2.55 (m, 8H, H2″, H6″), 2.50 (t, *J* = 6.3 Hz, 4H, H3′), 2.13 (m, 4H, H2, H17), 1.69 (app p, *J* = 6.3 Hz, 4H, H2′), 1.61 (app p, *J* = 7.4 Hz, 4H, H3, H16), 1.34-1.18 (m, 24H, H4-H15). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (C), 162.9 (C), 153.0 (C), 141.8 (C), 140.7 (C), 132.1 (CH), 130.3 (CH), 129.1 (C), 126.9 (CH), 123.42 (C), 123.36 (CH), 123.1 (CH), 120.3 (CH), 120.2 (CH), 57.7 (CH_2), 53.3 (CH_2), 47.5 (CH_2), 39.5 (CH_2), 37.2 (CH_2), 29.72 (2 × CH_2), 29.68 (CH_2), 29.6 (CH_2), 29.52 (CH_2), 29.46 (CH_2), 26.0 (CH_2), 25.4 (CH_2). HPLC: t_R 7.64 min, 99% purity (Method 2). LCMS (*m / z*): 509.2 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{58}H_{79}Cl_2N_{10}O_2^+$ requires $[M + H]^+$ 1017.5759; found 1017.5789.

N^{1},N^{20}-*Bis(3-(4-(8-chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)piperazin-1-yl)propyl)icosanediamide (**9g**)*. 1,20-Icosanedioic acid (0.062 g, 0.182 mmol) and oxalyl chloride were reacted, followed by the addition of **5** (0.132 g, 0.357 mmol), *N*,*N*-diisopropylethylamine (78 μL, 0.448 mmol) and pyridine (0.040 mL, 0.0496 mmol), as per general procedure C. Additional 1,20-icosanedioyl dichloride (0.025 g, 0.067 mmol) was added. Column chromatography conditions: gradient elution: from 2% methanol / chloroform to 5% methanol / chloroform, increasing in 1% increments (using a column preconditioned with 1% ammonia / 2% methanol / chloroform). Yielded **9g** as a yellow foam (0.123 g, 0.118 mmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (ddd, *J* = 7.9, 7.4, 1.6 Hz, 2H, H3‴), 7.24 (dd, *J* = 7.8, 1.5 Hz, 2H, H1‴), 7.06 (d, *J* = 2.4 Hz, 2H, H9‴), 7.00 (ddd, *J* = 7.7, 7.4, 1.1 Hz, 2H, H2‴), 6.88-6.83 (m, 4H, CONH, H4‴), 6.81 (dd, *J* = 8.3, 2.4 Hz, 2H, H7‴), 6.63 (d, *J* = 8.3 Hz, 2H, H6‴), 5.13 (s, 2H, H5‴), 3.45 (m, 8H, H3″, H5″), 3.35 (td, *J* = 5.9, 5.9 Hz, 4H, H1′), 2.54 (m, 8H, H2″, H6″), 2.49 (t, *J* = 6.4 Hz, 4H, H3′), 2.13 (m, 4H, H2, H19), 1.69 (app p, *J* = 6.3 Hz, 4H, H2′), 1.61 (app p, *J* = 7.3 Hz, 4H, H3, H18), 1.34-1.17 (m, 28H, H4-H17). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (C), 162.9 (C), 153.0 (C), 141.8 (C), 140.7 (C), 132.1 (CH), 130.3 (CH), 129.0 (C), 126.8 (CH), 123.4 (C), 123.3 (CH), 123.1 (CH), 120.3 (CH), 120.2 (CH), 57.6 (CH_2), 53.3 (CH_2), 47.5 (CH_2), 39.4 (CH_2), 37.1 (CH_2), 29.72 (CH_2), 29.70 (2 × CH_2), 29.66 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 26.0 (CH_2), 25.4 (CH_2). HPLC: t_R 8.06 min, >99% purity (Method 2). LCMS (*m / z*): 523.4 $[M + 2H]^{2+}$. HRMS (*m / z*): $C_{60}H_{83}Cl_2N_{10}O_2^+$ requires $[M + H]^+$ 1045.6072; found 1045.6104.

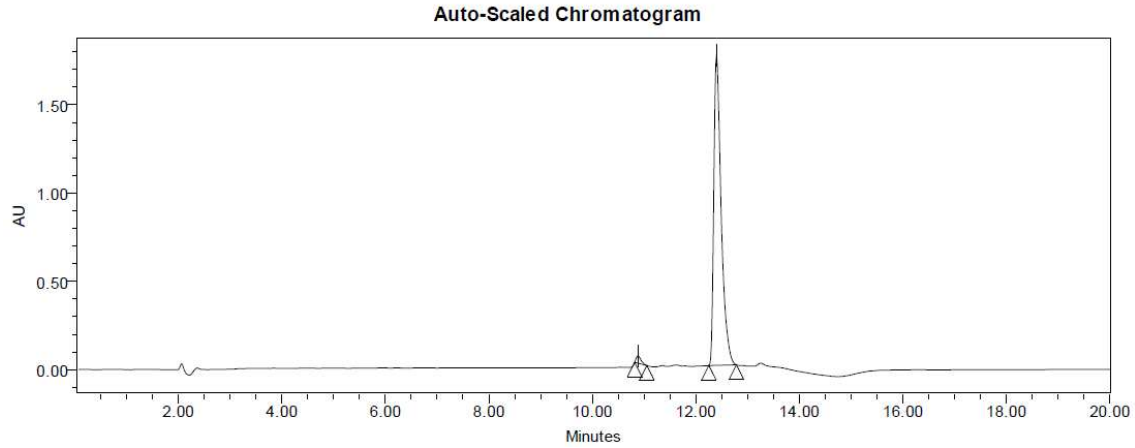
2. HPLC Chromatograms for the Target Compounds

HPLC chromatograms for clozapine N5 bivalent ligands

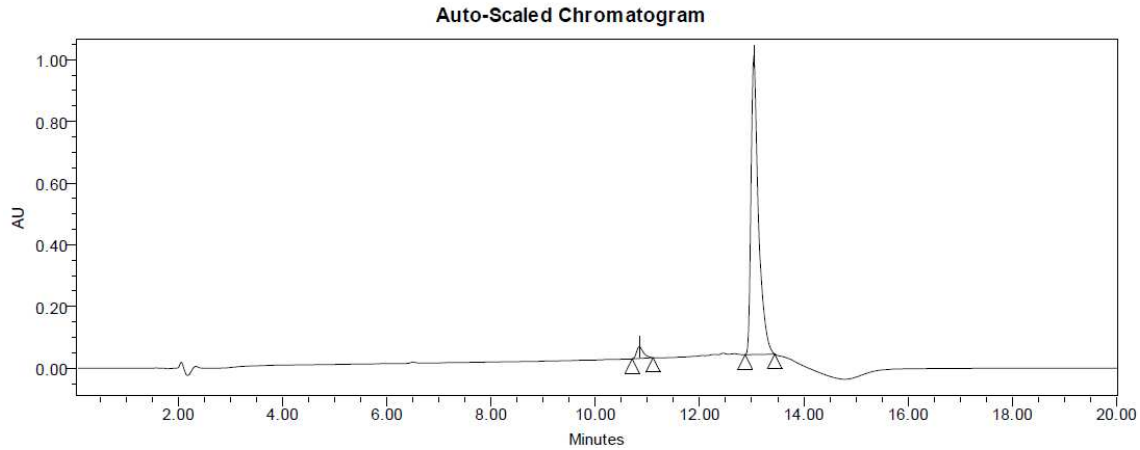
Compound **7a**



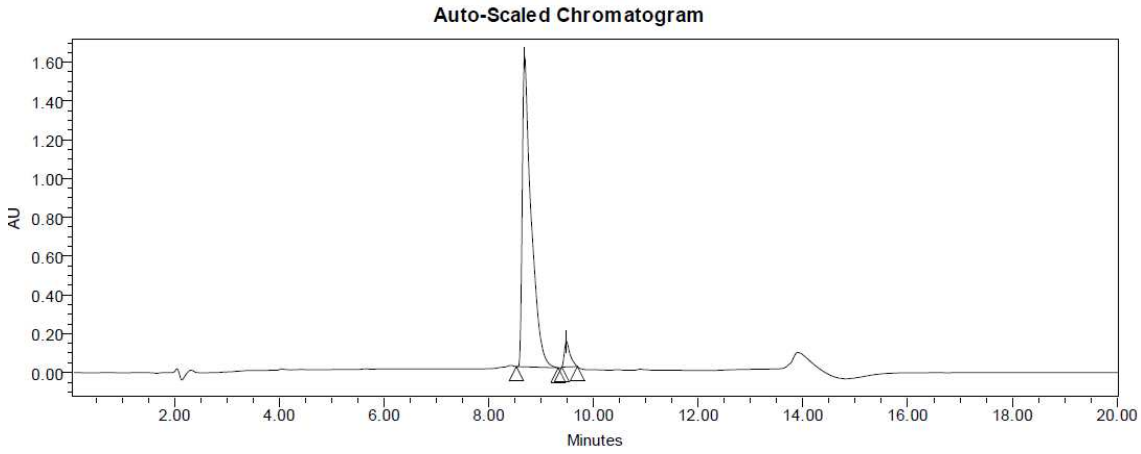
Compound **7b**



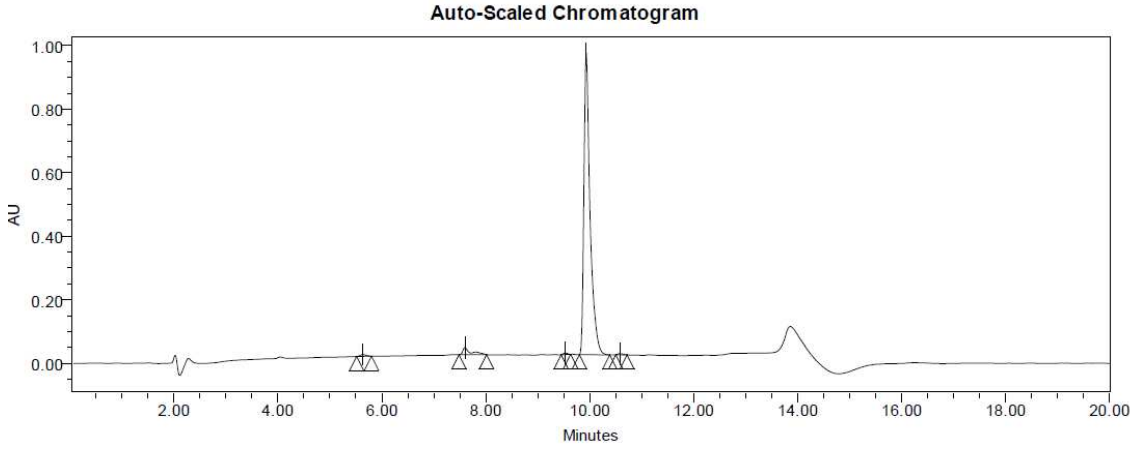
Compound **7c**



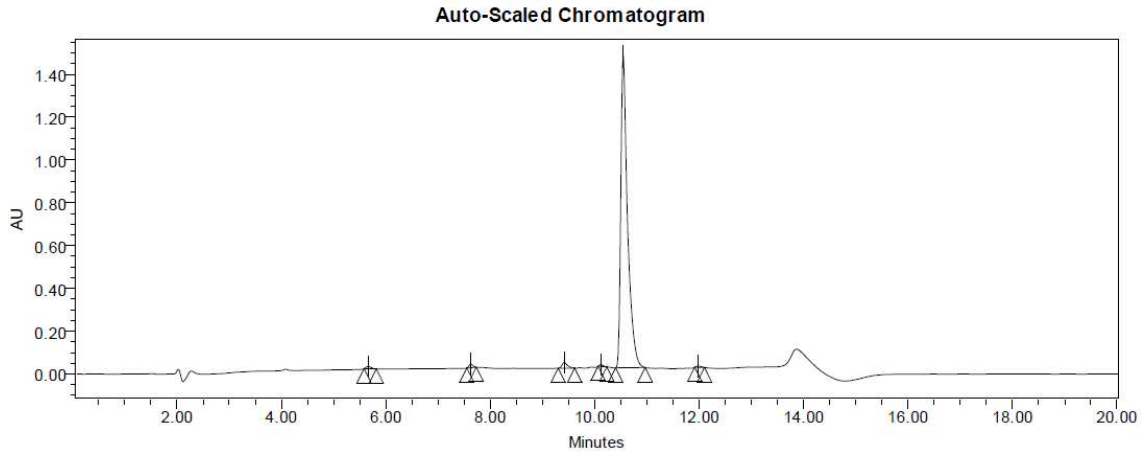
Compound **7d**



Compound **7e**

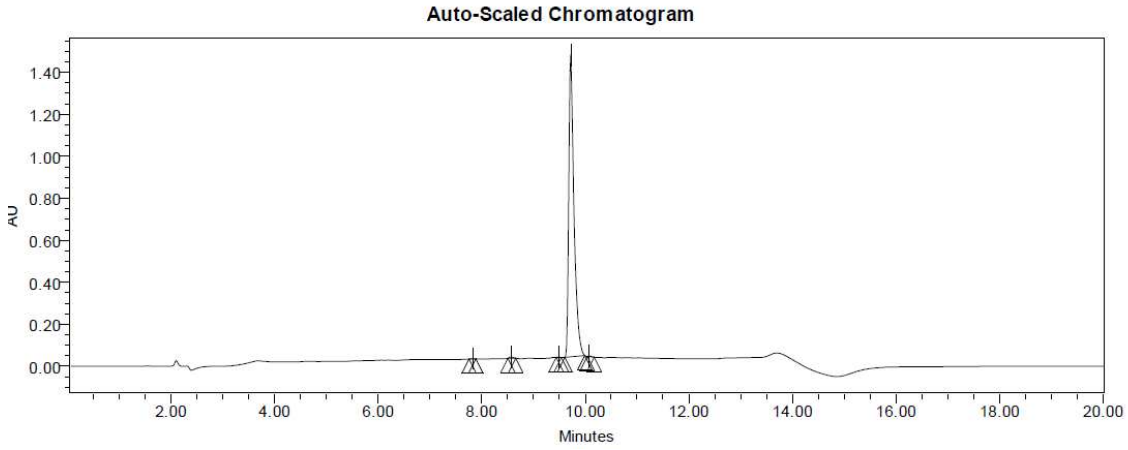


Compound **7f**

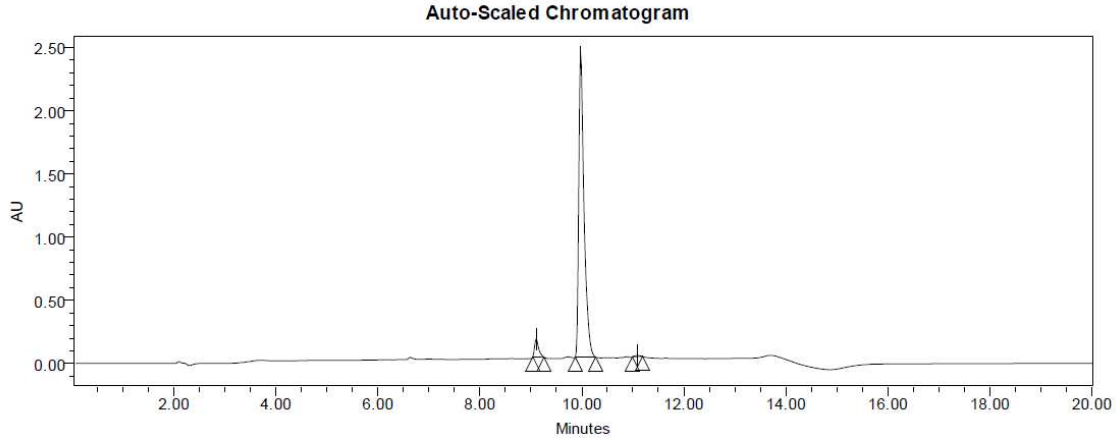


HPLC chromatograms for clozapine N5 hydrazide bivalent ligands

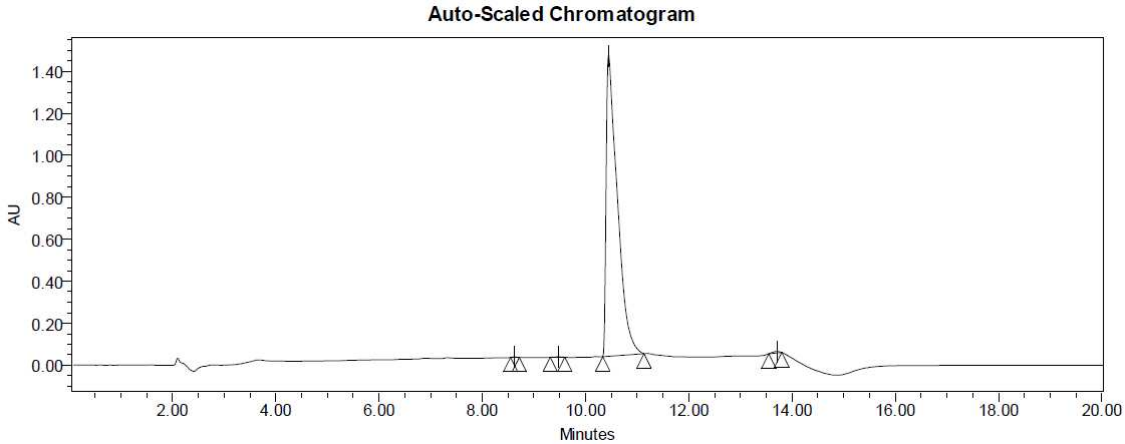
Compound **8a**



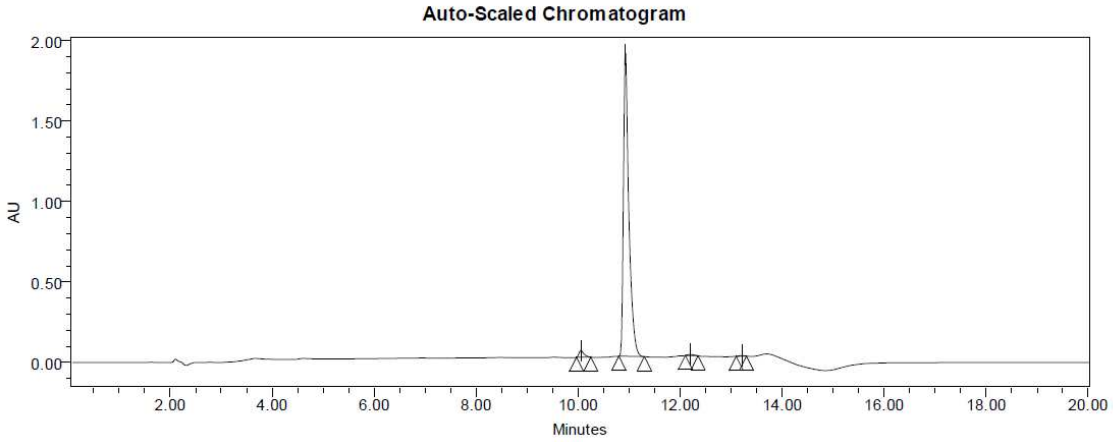
Compound **8b**



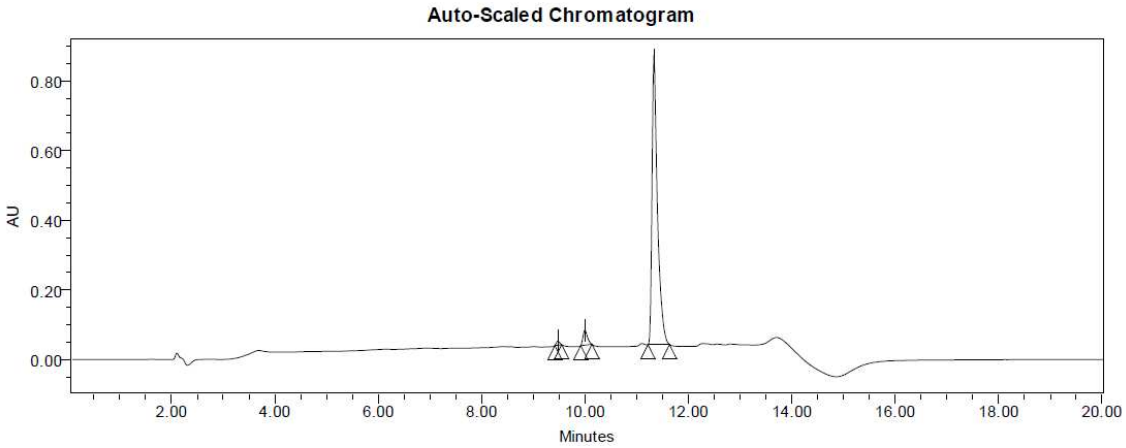
Compound **8c**



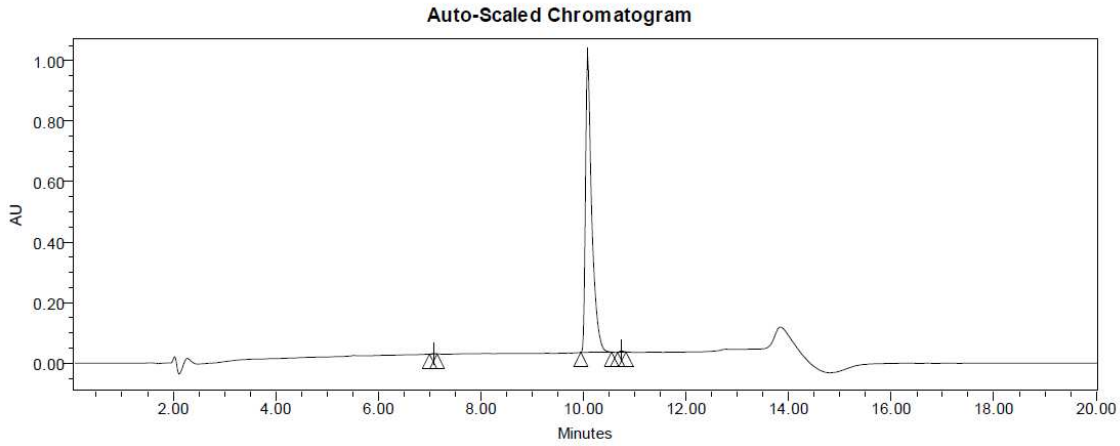
Compound **8d**



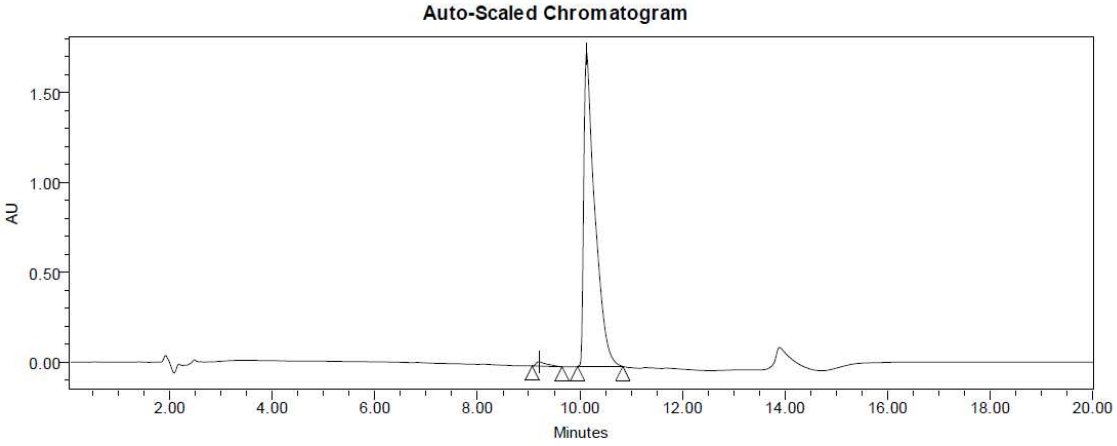
Compound **8e**



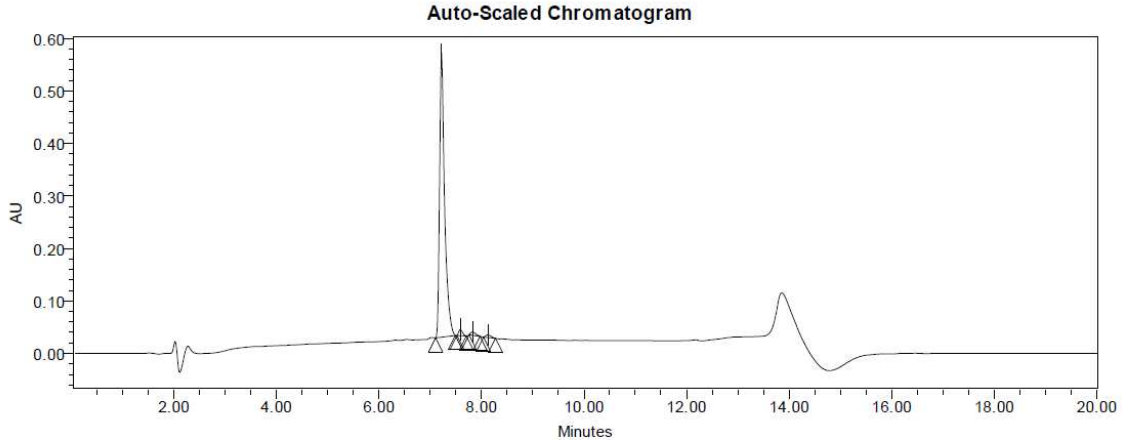
Compound **8f**



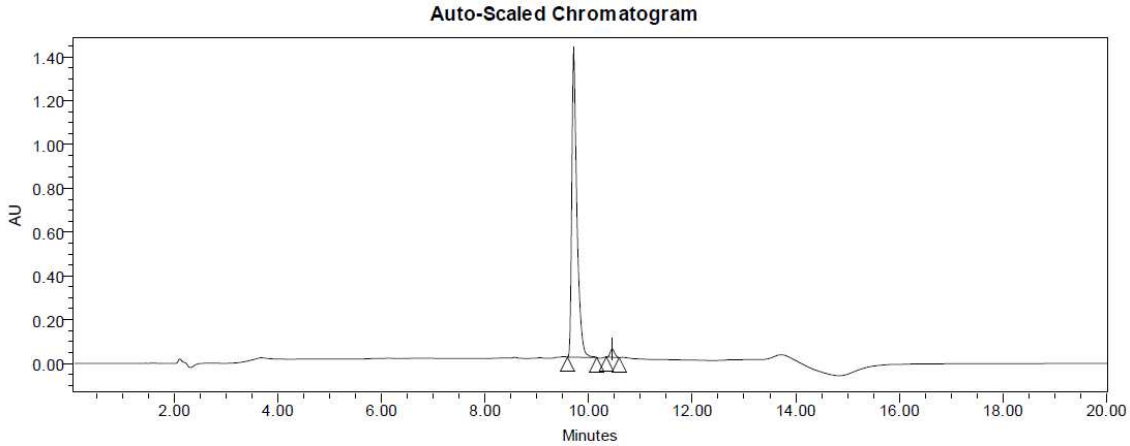
Compound **8g**



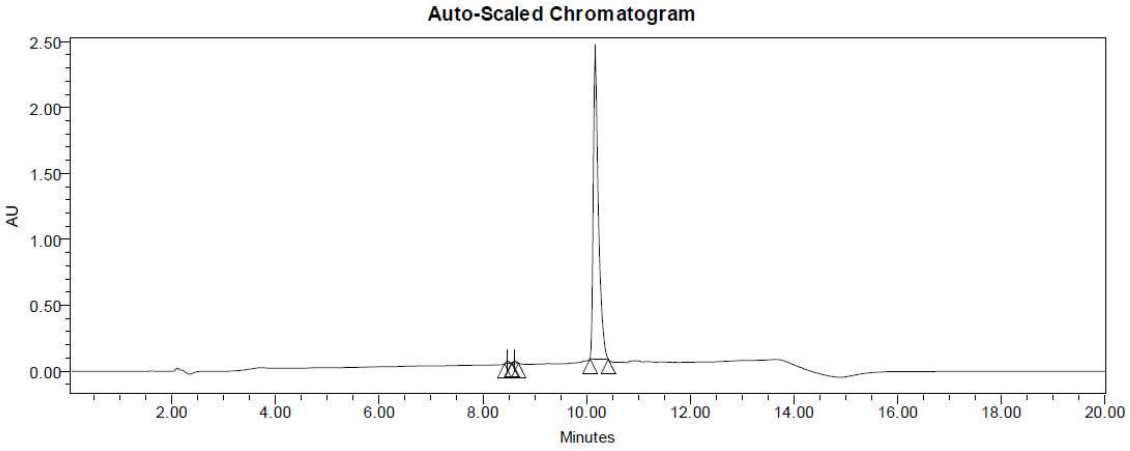
Compound **12a**



Compound **12b**

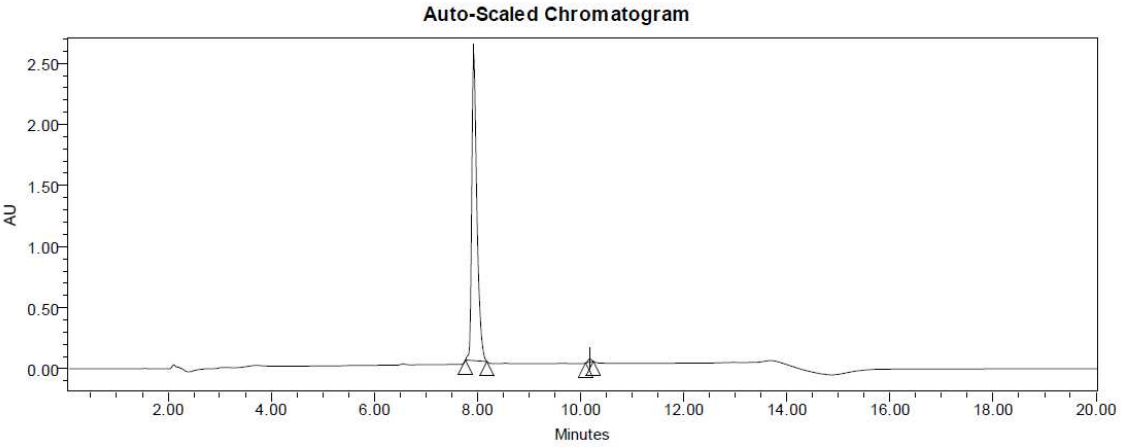


Compound **14**

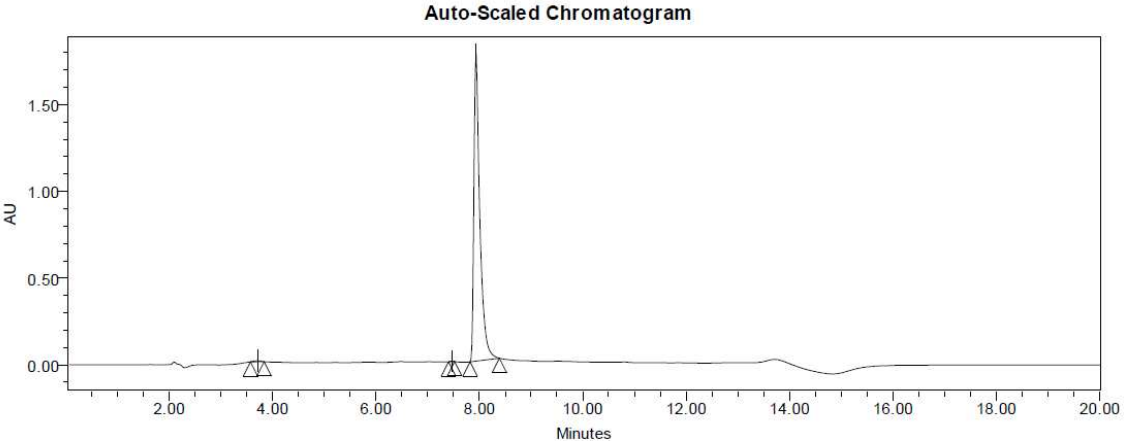


HPLC chromatograms for clozapine N4′ propyl amine bivalent ligands

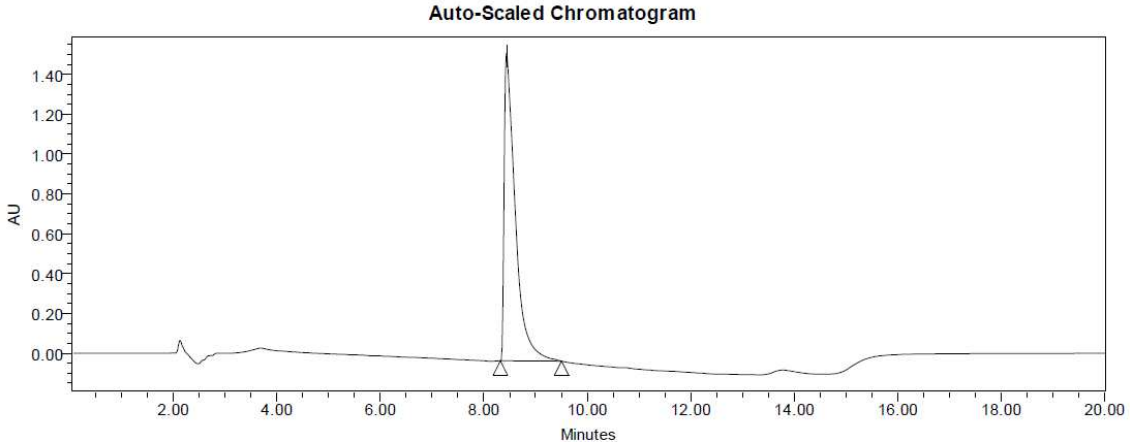
Compound **9a**



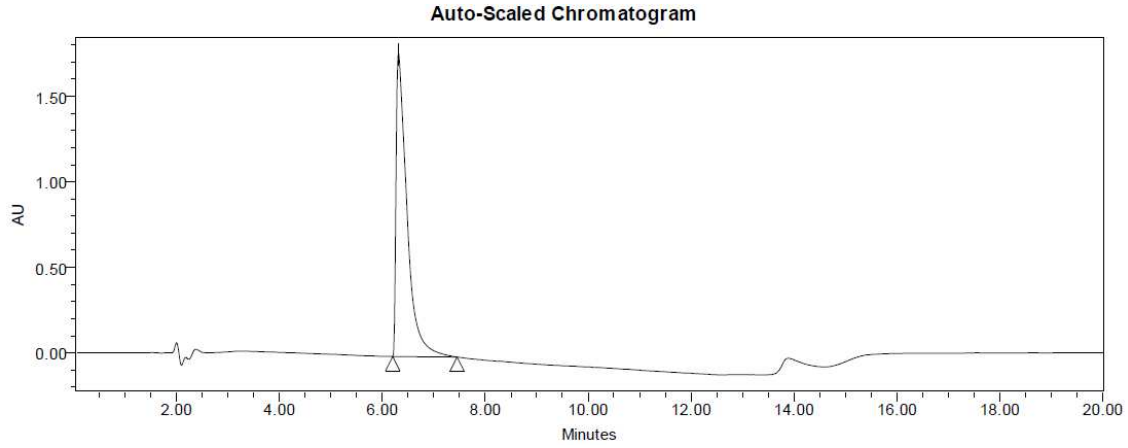
Compound **9b**



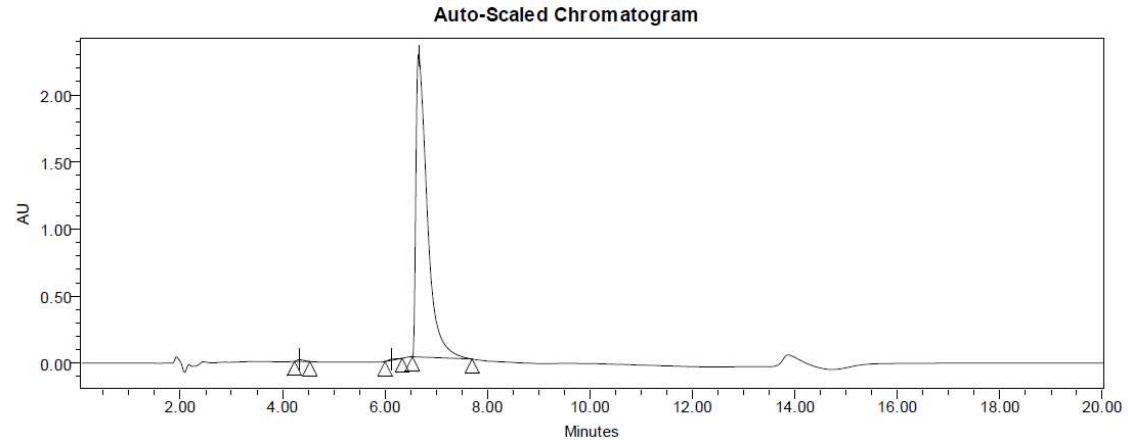
Compound **9c**



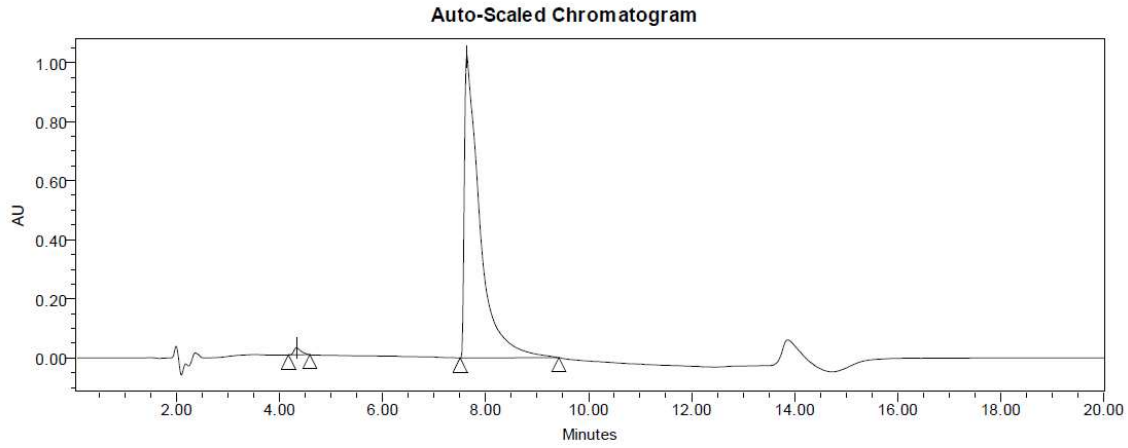
Compound **9d**



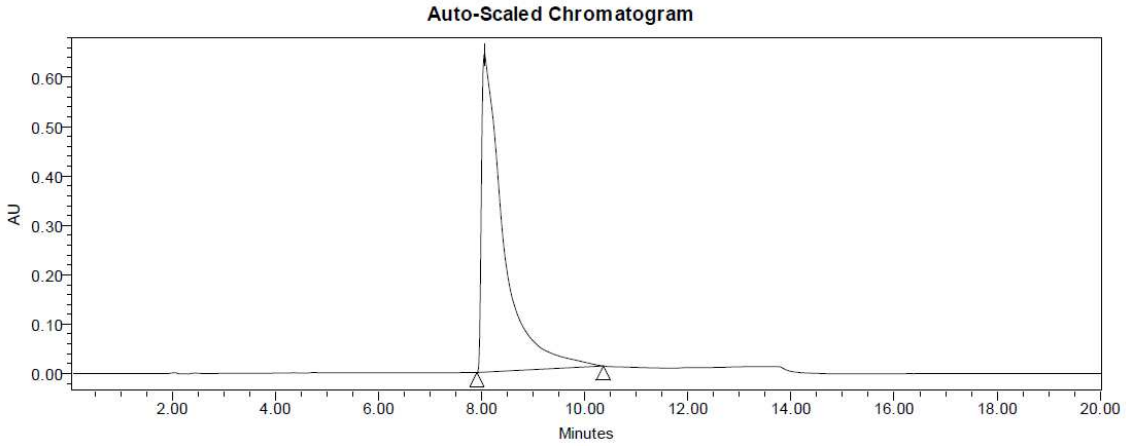
Compound **9e**



Compound **9f**

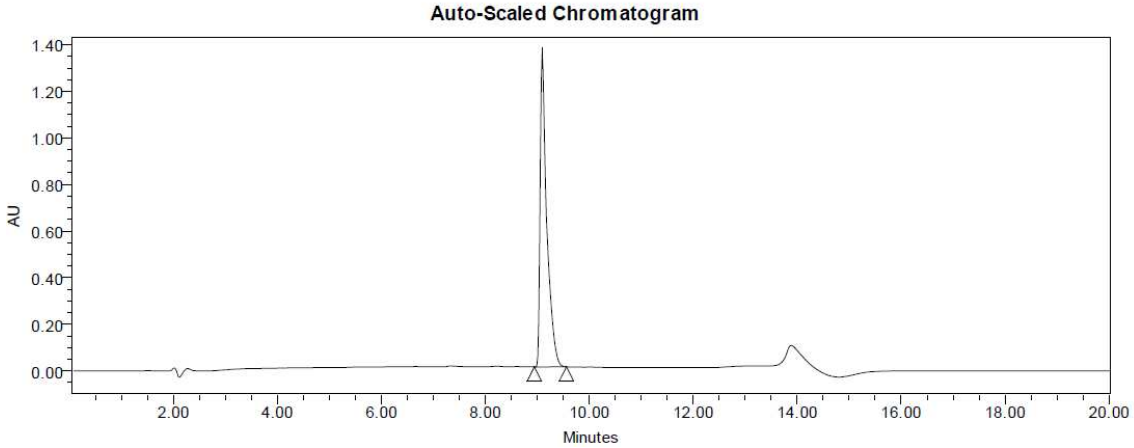


Compound **9g**

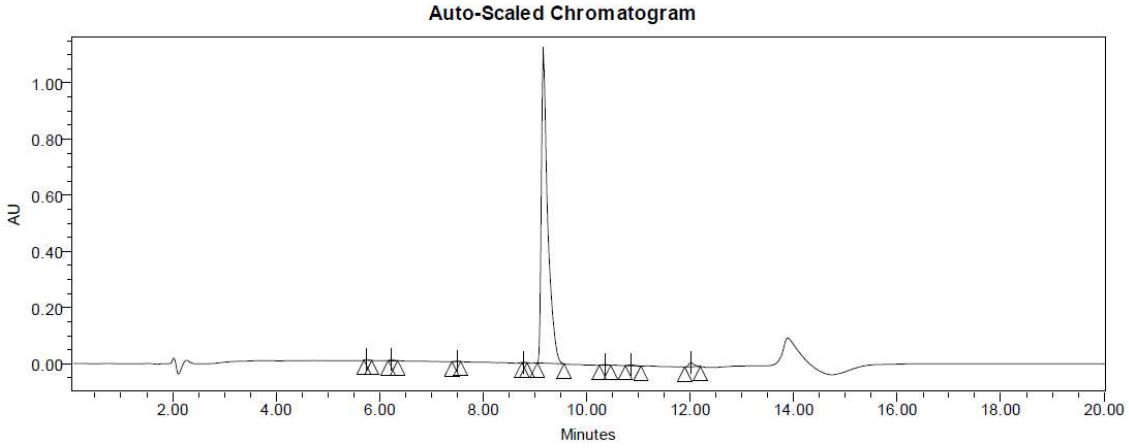


HPLC chromatograms for monovalent ligands

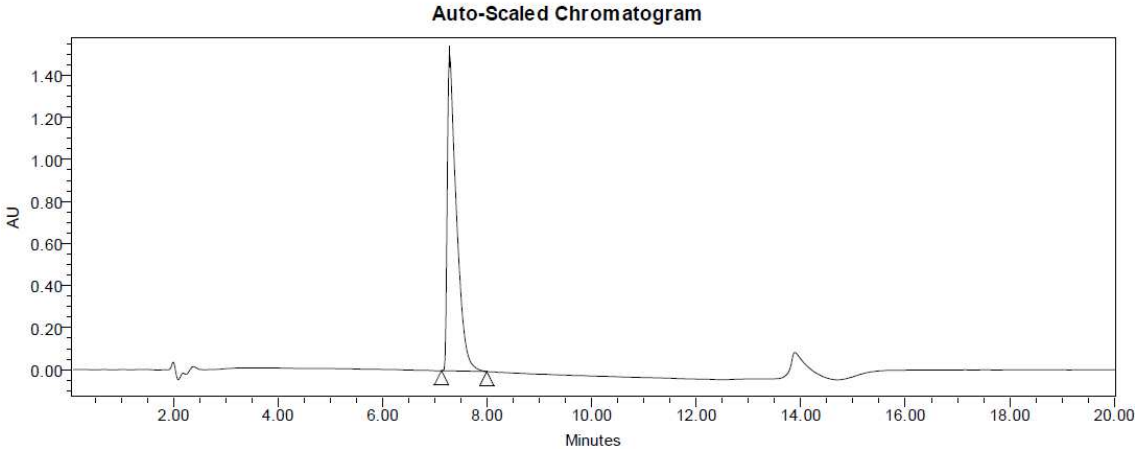
Compound **15**



Compound **16**



Compound **17**



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