**Discovery of novel 3-(piperazin-1-yl)propan-2-ol decorated carbazole derivatives as new membrane-targeting antibacterial agents**

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1. General procedures for the intermediates

All 1H NMR (400 MHz) and 13C NMR (100 MHz) spectra 19F NMR (377 MHz) spectra were recorded on Brucker spectrometers in CDCl3 or DMSO-*d*6. Tetramethylsilane (TMS) served as an internal standard (*δ* = 0) for 1H NMR, and CDCl3 or DMSO-*d*6 was used as internal standard (*δ* = 77.0 or *δ* = 39.5) for 13C NMR. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s =singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad).

1.1 General procedure for the intermediate 1



**Figure S1.** General procedure for the preparation of the intermediate **1**.

As shown in **Figure S1**, for the reaction (1), to a solution of (4-chlorophenyl)methanamine (3.2 mmol, 1.0 equiv.) and K2CO3 (4.8 mmol, 1.5 equiv.) in DCM (10 mL), 2-bromoacetyl bromide (4.8 mmol, equiv.) was added slowly. The reaction mixture was stirred at room temperature for 1 h. After that, the intermediate **1** was obtained through column chromatography with DCM as eluent. A white solid, yield: 50%.

For the reaction (2), to a solution of furan-2-ylmethanamine (4.6 mmol, 1.0 equiv.), K2CO3 (5.8 mmol, 1.5 equiv.) in DCM (10 mL) and 2-bromoacetyl bromide (3.9 mmol, 1.5 equiv.) was added slowly. The reaction mixture was stirred at room temperature for 1 h. After that, the intermediate was obtained through column chromatography with DCM as eluent. A white solid, yield: 29.0%.

1.2 General Procedure for the Preparation of the intermediate 2.

To a 50 mL oven-dried vial containing a magnetic stirring bar, carbazole (29.9 mmol, 1.0 equiv.), and KOH (35.9 mmol, 1.2 equiv.) were dissolved in 15 mL anhydrous DMF, then compound 2-(bromomethyl)oxirane (35.9 mmol, 1.2 equiv.) was added and acted for 6 h at 0 ℃. Upon complete consumption of the starting materials, the reaction mixture was quenched with saturated aqueous solution of NH4Cl (40 mL), extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with NH4Cl, then was concentrated to dryness. The residue was purified by flash chromatography (PE:EA, 180:1, *v/v*) to afford the intermediate **2.**



**Figure S2.** General procedure for the preparation of the intermediate **2**.

1.3 General Procedure for the Preparation of the intermediate 3.

To a 50 mL oven-dried vial containing a magnetic stirring bar, (1) intermediate **2** (18.7 mmol, 1.0 equiv.), and K2CO3 (18.7 mmol, 1.0 equiv.) were dissolved in 30 mL isopropanol, then *tert*-butyl piperazine-1-carboxylate (18.7 mmol, 1.0 equiv.) was added and acted for 6 h at 0 ℃. Upon complete consumption of the starting materials, the reaction mixture was followed by the removal of the solvent under vacuum, added water (25 mL) and extracted with CH2Cl2 (3 × 50 mL). The organic layer was dried with sodium sulfate and the crude product was acquired after the solvent was evaporated under reduced pressure. The crude product was then employed in the next step without further purification. (2) The crude product was dissolved in a 50 mL oven-dried vial containing a magnetic stirring bar by methanol, then the dilute hydrochloric acid was added. After that, the reaction mixture was stirred for 5 h under these conditions until consumption of the material (monitored by TLC), followed by the removal of the solvent under vacuum. The resulting mixture was dissolved in 30 mL water, extracted with ethyl acetate (3 × 20 mL). After that, the aqueous solution was treated with sodium hydroxide saturated solution to adjust pH=7. Then, the intermediate **3** was extracted with CH2Cl2 (3 × 50mL), and the solvent was removed by using rotary evaporation.



**Figure S3.** General procedure for the preparation of the intermediate **3**.

1.4 General procedures for the target compounds A19 and A20.

**Figure S4.** General procedure for the preparation of the compounds **A19** and **A20**.

To a 25 mL oven-dried vial containing a magnetic stirring bar, intermediate **3** (0.7 mmol, 1.0 equiv.) in CH2Cl2 (10 mL), benzoyl chloride (0.8 mmol, 1.1 equiv.) was added dropwise at 0 °C, and triethylamine (0.7 mmol, 1.0 equiv.) was subsequently added. The reaction mixture was then stirred at room temperature for 10 h. When the reaction was completed (monitored by TLC), the solvent was removed and the crude residue was purified by column chromatography (DCM : MeOH, 200:1~140:1, *v/v*) to obtain pure product **A19**. A white solid, yield: 52.9%.

To a 25 mL oven-dried vial containing a magnetic stirring bar, intermediate **3** (0.7 mmol, 1.0 equiv.) in CH2Cl2 (10 mL), benzenesulfonyl chloride (0.8 mmol, 1.1 equiv.) was added at 0 °C, and triethylamine (0.7 mmol, 1.0 equiv.) was added slowly. The reaction mixture was stirred at room temperature for 10 h. When the reaction was completed (monitored by TLC), the solvent was removed and the crude residue was purified by column chromatography (DCM : MeOH, 200:1~150:1, *v/v*) to obtain pure product **A20**. A white solid, yield: 34.7%.

2. Characterization data of target compounds

**2-(4-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)piperazin-1-yl)-N-(4-methoxybenzyl)acetamide (A1)** A yellow oil, yield 40.0%; 1H NMR (400 MHz, DMSO-*d*6, ppm) δ 8.13 (d, *J* = 7.6 Hz, 2H, carbazol-H), 8.10 (s, 1H, N-H), 7.62 (d, *J* = 8.3 Hz, 2H, carbazole-H), 7.47 – 7.39 (m, 2H, carbazole-H), 7.18 (dd, *J* = 7.9, 5.5 Hz, 4H), 6.86 (d, *J* = 8.7 Hz, 2H, benzyl-H), 4.94 (d, *J* = 4.7 Hz, 1H, OH), 4.47 (dd, *J* = 14.8, 4.0 Hz, 1H, carbazole-CH2), 4.28 (dd, *J* = 14.8, 6.8 Hz, 1H, carbazole-CH2), 4.22 (d, *J* = 6.1 Hz, 2H, NH-CH2), 4.06 (m, *J* = 4.7 Hz, 1H, CH2-CH-CH2), 3.71 (s, 3H, O-CH3), 2.95 (s, 2H, piperazine-CH2-amide), 2.49 – 2.31 (m, 8H, piperazine-H);13C NMR (126 MHz, DMSO-*d*6, ppm) δ 169.84, 158.62, 141.17, 132.10, 129.07, 126.00, 122.53, 120.55, 119.16, 114.14, 110.34, 67.64, 62.33, 61.75, 55.53, 53.81, 53.45, 48.02, 41.78; HRMS (ESI) [M+H]+ calcd for C29H35N4O3: 487.2704, found: 487.2700;

**2-(4-(3-(9H-carbazol-9-yl)-2-hydroxypropyl)piperazin-1-yl)-*N*-(4-methylbenzyl)aetamide (A2)** A yellow oil, yield 49.0%; 1H NMR (400 MHz, DMSO-*d*6, ppm) δ 8.16 (s, 1H, N-H), 8.13 (d, *J* = 7.9 Hz, 2H, carbazole-H), 7.62 (d, *J* = 8.3 Hz, 2H, carbazole-H), 7.43 (t, *J* = 7.7 Hz, 2H, carbazole-H), 7.18 (t, *J* = 7.2 Hz, 2H, carbazole-H), 7.12 (q, *J* = 8.2 Hz, 4H, benzyl-H), 4.93 (d, *J* = 4.9 Hz, 1H, OH), 4.47 (dd, *J* = 14.8, 4.0 Hz, 1H, carbazole-CH2), 4.33 – 4.26 (m, 1H, carbazole-CH2), 4.25 (d, *J* = 6.1 Hz, 2H, NH-CH2), 4.06 (d, *J* = 4.8 Hz, 1H, CH2-CH-CH2), 2.96 (s, 2H, piperazine-CH2-amide), 2.50 (s, 2H, CH-CH2-piperazine), 2.47 – 2.31 (m, 8H, piperazine-H), 2.26 (s, 3H, benzyl-CH3); 13C NMR (101 MHz, DMSO-*d*6, ppm) δ 169.81, 141.10, 136.99, 136.27, 129.28, 127.63, 125.96, 122.48, 120.50, 119.13, 110.27, 67.43, 62.08, 61.53, 53.61, 53.16, 47.92, 42.03, 21.11; HRMS (ESI) [M+H]+ calcd for C29H35N4O2: 471.2755, found: 471.2751.

**2-(4-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)piperazin-1-yl)-*N*-benzylacetamide (A3)** A yellow oil, yield 75.13%, 1H NMR (400 MHz, CDCl3) δ 8.09 (d, *J* = 7.7 Hz, 2H, carbazole-H), 7.47 (t, *J* = 2.7 Hz, 2H, carbazole-H), 7.46 – 7.45 (m, 2H, carbazole-H), 7.34 (d, *J* = 1.6 Hz, 1H, benzyl-H), 7.33 – 7.29 (m, 2H, benzyl-H), 7.28 (d, *J* = 1.5 Hz, 1H, benzyl-H), 7.24 (d, *J* = 2.4 Hz, 2H, carbazole-H), 7.23 (d, *J* = 2.6 Hz, 1H, carbazole-H), 4.45 (d, *J* = 6.0 Hz, 2H, carbazol-CH2), 4.38 (dd, *J* = 5.4, 2.6 Hz, 2H, NH-CH2), 4.21 (td, *J* = 9.5, 5.3 Hz, 1H, CH2-CH-CH2), 3.04 (s, 2H, piperazine-CH2-amide), 2.55 (d, *J* = 12.8 Hz, 2H, CH-CH2-piperazine), 2.55 – 2.33 (m, 8H, piperazine-H); 13C NMR (101 MHz, CDCl3) δ 168.28, 139.35, 136.73, 127.12, 125.91, 124.14, 121.38, 118.68, 117.57, 107.46, 75.61, 64.66, 60.04, 59.78, 51.86, 45.41, 41.32, 28.09; HRMS (ESI) [M+H]+ calcd for C28H33N4O2: 457.2598, found: 457.2592.

**2-(4-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)piperazin-1-yl)-*N*-(2-fluorobenzyl)actamide (A4)** A yellow oil, yield 32.0%; 1H NMR (400 MHz, DMSO-*d*6, ppm) δ 8.20 (t, *J* = 6.0 Hz, 1H, N-H), 8.13 (d, *J* = 7.7 Hz, 2H, carbazol-H), 7.63 (d, *J* = 8.3 Hz, 2H, carbazol-H), 7.46 – 7.40 (m, 2H, carbazol-H), 7.33 – 7.26 (m, 2H, benzyl-H), 7.18 (t, *J* = 5.3 Hz, 2H, carbazol-H), 7.17 – 7.13 (m, 2H, benzyl-H), 4.95 (s, 1H, OH), 4.47 (dd, *J* = 14.8, 4.1 Hz, 1H, carbazol-CH2), 4.35 (d, *J* = 6.0 Hz, 2H, NH-CH2), 4.28 (dd, *J* = 14.8, 6.8 Hz, 1H, carbazol-CH2), 4.07 (s, 1H, CH2-CH-CH2), 2.99 (s, 2H, piperazine-CH2-amide), 2.50 (s, 2H, CH-CH2-piperazine), 2.49 – 2.30 (m, 8H, piperazin-H); 13C NMR (101 MHz, DMSO-*d*6, ppm) δ 169.98, δ 160.46 (d, 1*J*C-F = 244.1 Hz), 159.25, 141.17, 129.81, 129.71, 129.24 (d, 3*J*C-F = 8.0 Hz), 126.77, 126.62, 125.91, 124.75 (d, 4*J*C-F = 3.5 Hz), 122.52, 120.48, 119.06, 115.50 (d, 2*J*C-F = 21.2 Hz), 110.31, 67.66, 62.37, 61.68, 53.86, 53.48, 48.05, 36.23, 36.19; 19F NMR (377 MHz, DMSO-*d*6, ppm) δ -119.17; HRMS (ESI) [M+H]+ calcd for C28H32N4O2F: 475.2504, found: 475.2500.

**2-(4-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)piperazin-1-yl)-*N*-(3-fluorobenzyl)actamide (A5)** A yellow oil, yield 60.0%; 1H NMR (400 MHz, DMSO-*d*6, ppm) δ 8.29 (t, *J* = 6.2 Hz, 1H, N-H), 8.12 (d, *J* = 7.7 Hz, 2H, 2H, carbazol-H), 7.62 (d, *J* = 8.3 Hz, 2H, carbazol-H), 7.42 (t, *J* = 7.7 Hz, 2H, carbazol-H), 7.34 (dd, *J* = 14.5, 7.1 Hz, 1H, benzyl-H), 7.18 (t, *J* = 7.4 Hz, 2H, carbazol-H), 7.09 (d, *J* = 8.1 Hz, 1H, benzyl-H), 7.04 (t, *J* = 8.4 Hz, 2H, benzyl-H), 4.93 (s, 1H, OH), 4.47 (dd, *J* = 14.8, 4.1 Hz, 1H, carbazol-CH2), 4.30 (d, *J* = 6.2 Hz, 2H, NH-CH2), 4.29 – 4.24 (m, 1H, carbazol-CH2), 4.06 (s, 1H, CH2-CH-CH2), 2.98 (s, 2H, piperazine-CH2-amide), 2.50 (d, *J* = 1.5 Hz, 2H, CH-CH2-piperazine), 2.48 – 2.31 (m, 8H, piperazin-H); 13C NMR (101 MHz, DMSO-*d*6, ppm) δ 170.03, 162.66 (d, 1*J*C-F = 243.0 Hz), 143.36, 143.29, 141.17, 130.63 (d, 3*J*C-F = 8.2 Hz), 125.90, 123.61 (d, 4*J*C-F = 2.5 Hz), 122.52, 120.48, 119.06, 114.28 (d, 2*J*C-F = 21.3 Hz), 113.99, 113.78, 110.31, 67.67, 62.38, 61.77, 53.82, 53.52, 48.06, 41.86; 19F NMR (377 MHz, DMSO-*d*6, ppm) δ -113.59; HRMS (ESI) [M+H]+ calcd for C28H32O2N4F: 475.2504; found: 475.2501.

**2-(4-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)piperazin-1-yl)-*N*-(4-fluorobenzyl)actamide (A6)** A yellow oil, yield 74.3%;1H NMR (400 MHz, DMSO-*d*6, ppm) δ 8.24 (t, *J* = 6.2 Hz, 1H, N-H), 8.13 (d, *J* = 7.7 Hz, 2H, carbazol-H), 7.62 (d, *J* = 8.3 Hz, 2H, carbazol-H), 7.46 – 7.39 (m, 2H, carbazol-H), 7.31 – 7.26 (m, 2H, benzyl-H), 7.18 (t, *J* = 7.2 Hz, 2H, carbazol-H), 7.12 (t, *J* = 8.9 Hz, 2H, benzyl-H), 4.96 (s, 1H, OH), 4.46 (dd, *J* = 14.8, 4.1 Hz, 1H, carbazol-CH2), 4.30 (d, *J* = 6.8 Hz, 1H, NH-CH2), 4.27 (d, *J* = 6.2 Hz, 2H, carbazol-CH2), 4.07 (s, 1H, CH2-CH-CH2), 2.97 (s, 2H, piperazine-CH2-amide), 2.51 (d, *J* = 1.7 Hz, 2H, CH-CH2-piperazine), 2.49 – 2.31 (m, 8H, piperazine-H); 13C NMR (101 MHz, DMSO-*d*6, ppm) δ 169.84, 161.57 (d, 1*J*C-F = 241.9 Hz), 141.16, 136.44, 129.64 (d, 3*J*C-F = 8.0 Hz), 125.91, 122.52, 120.48, 119.07, 115.41 (d, 2*J*C-F = 21.1 Hz), 110.30, 67.62, 62.32, 61.73, 55.38, 53.78, 53.44, 48.04, 41.62; 19F NMR (377 MHz, DMSO) δ -73.43, -116.28; HRMS (ESI) [M+H]+ calcd for C28H32O2N4F: 475.2504; found: 475.2491.

**2-(4-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)piperazin-1-yl)-*N*-(2-chlorobenzyl)acetamide (A7)** A yellow oil, yield 40.0%; 1H NMR (400 MHz, CDCl3) δ 8.12 (d, *J* = 7.7 Hz, 2H, carbazol-H), 7.63 (t, *J* = 5.7 Hz, 1H, N-H), 7.51 (t, *J* = 3.0 Hz, 2H, carbazol-H), 7.48 (dd, *J* = 8.3, 0.9 Hz, 2H, carbazol-H), 7.40 – 7.36 (m, 2H, carbazol-H), 7.30 – 7.27 (m, 2H, benzyl-H), 7.25 (dd, *J* = 5.1, 2.8 Hz, 2H, benzyl-H), 4.54 (d, *J* = 6.2 Hz, 2H, carbazol-CH2), 4.40 (d, *J* = 5.6 Hz, 2H, NH-CH2), 4.28 – 4.20 (m, 1H, CH2-CH-CH2), 3.02 (s, 2H, piperazine-CH2-amide), 2.60 (s, 2H, CH-CH2-piperazine), 2.52 – 2.44 (m, 6H, piperazin-H), 2.44 – 2.31 (m, 2H, piperazin-H); 13C NMR (101 MHz, CDCl3) δ 170.02, 141.02, 135.68, 133.64, 130.34, 129.59, 129.03, 127.16, 125.77, 123.01, 120.30, 119.19, 109.15, 66.37, 61.66, 61.32, 53.50, 47.11, 41.18; HRMS (ESI) [M+H]+ calcd for C28H32O2N4Cl: 491.2208; found: 491.2205.

**2-(4-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)piperazin-1-yl)-*N*-(3-chlorobenzyl)acetamide (A8)** A yellow oil, yield 59.2%; 1H NMR (DMSO-*d*6, ppm) δ 8.31 (t, *J* = 6.2 Hz, 1H, N-H), 8.13 (d, *J* = 7.7 Hz, 2H, carbazol-H), 7.63 (d, *J* = 8.2 Hz, 2H, carbazol-H), 7.43 (dd, *J* = 11.3, 4.0 Hz, 2H, carbazol-H), 7.33 (dd, *J* = 13.2, 5.6 Hz, 2H, benzyl-H), 7.30 – 7.27 (m, 1H, benzyl-H), 7.19 (dd, *J* = 16.1, 8.4 Hz, 3H, carbazol-H), 4.94 (d, *J* = 5.1 Hz, 1H, OH), 4.47 (dd, *J* = 14.8, 4.0 Hz, 1H, carbazol-CH2), 4.30 (d, *J* = 6.1 Hz, 2H, benzyl-CH2), 4.27 (d, *J* = 6.8 Hz, 1H, carbazol-CH2), 4.13 – 4.03 (m, 1H, CH2-CH-CH2), 2.98 (s, 2H, piperazine-CH2-amide), 2.50 (m, 2H, CH-CH2-piperazine), 2.47 – 2.32 (m, 8H, piperazin-H); 13C NMR (101 MHz, DMSO-*d*6, ppm) δ 170.34, 142.71, 141.08, 133.37, 130.64, 127.42, 127.14, 126.31, 125.97, 122.47, 120.49, 119.14, 110.26, 67.49, 62.18, 61.57, 53.63, 53.27, 47.90, 41.79; HRMS (ESI) [M+H]+ calcd for C28H32O2N4Cl: 491.2208; found: 491.2201.

**2-(4-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)piperazin-1-yl)-*N*-(4-chlorobenzyl)acetamide (A9)** A yellow oil, yield 54.0%; 1H NMR (400 MHz, DMSO-*d*6, ppm) δ 8.27 (t, *J* = 6.2 Hz, 1H, N-H), 8.13 (d, *J* = 7.7 Hz, 2H, carbazol-H), 7.62 (d, *J* = 8.3 Hz, 2H, carbazol-H), 7.47 – 7.39 (m, 2H, carbazol-H), 7.36 (d, *J* = 8.4 Hz, 2H, benzyl-H), 7.28 (t, *J* = 7.6 Hz, 2H, benzyl-H), 7.18 (t, *J* = 7.4 Hz, 2H, carbazol-H), 4.94 (d, *J* = 5.0 Hz, 1H, OH), 4.47 (dd, *J* = 14.8, 4.0 Hz, 1H, carbazol-CH2), 4.30 (d, *J* = 6.8 Hz, 1H, NH-CH2), 4.27 (d, *J* = 6.1 Hz, 2H, carbazol-CH2), 4.12 – 4.02 (m, 1H, CH2-CH-CH2), 2.97 (s, 2H, piperazine-CH2-amide), 2.50 (d, *J* = 1.3 Hz, 2H, CH-CH2-piperazine), 2.47 – 2.30 (m, 8H, piperazine-H); 13C NMR (101 MHz, DMSO-*d*6, ppm) δ 170.10, 141.17, 139.31, 131.74, 129.60, 128.71, 126.01, 122.54, 120.56, 119.16, 110.34, 67.59, 62.30, 61.71, 53.77, 53.42, 48.02, 41.73; HRMS (ESI) [M+H]+ calcd for C28H32N4O2Cl: 491.2208, found: 491.2202.

**2-(4-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)piperazin-1-yl)-*N*-(4-(trifluoromethyl)benzyl)acetamide (A10)** A yellow oil, yield 31.2%; 1H NMR (400 MHz, DMSO-*d*6, ppm) δ 8.36 (t, *J* = 6.2 Hz, 1H, N-H), 8.13 (d, *J* = 7.7 Hz, 2H, carbazol-H), 7.67 (d, *J* = 8.1 Hz, 2H, benzyl-H), 7.63 (d, *J* = 8.3 Hz, 2H, carbazol-H), 7.46 (d, *J* = 8.2 Hz, 2H, carbazol-H), 7.45 – 7.41 (m, 2H, benzyl-H), 7.18 (t, *J* = 7.3 Hz, 2H, carbazol-H), 4.94 (d, *J* = 5.1 Hz, 1H, OH), 4.47 (dd, *J* = 14.7, 4.1 Hz, 1H, carbazol-CH2), 4.38 (d, *J* = 6.1 Hz, 2H, ), 4.28 (dd, *J* = 14.8, 6.7 Hz, 1H, carbazol-CH2), 4.07 (dd, *J* = 10.3, 5.0 Hz, 1H, CH2-CH-CH2), 2.99 (s, 2H, piperazine-CH2-amide), 2.50 (s, 2H, CH-CH2-piperazine), 2.50 – 2.32 (m, 8H, piperazin-H); 13C NMR (101 MHz, DMSO-*d*6, ppm) δ 170.24, 145.05, 141.10, 128.27, 127.83 (d, 2*J*C-F = 31.6 Hz), 125.96, 125.64, 125.59 (d, 3*J*C-F = 3.8 Hz), 125.53, 125.42 (d, 1*J*C-F = 272.7 Hz), 122.49, 120.50, 119.13, 110.27, 67.41, 62.08, 61.52, 53.60, 53.19, 47.92, 42.01; 19F NMR (376 MHz, DMSO-*d*6, ppm) δ -60.76; HRMS (ESI) [M+H]+ calcd for C29H32O2N4F3: 525.2472; found: 525.2465.

**2-(4-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)piperazin-1-yl)-*N*-(2,4-dichlorobenzyl)acetamide (A11)** A yellow oil, yield 36.2%; 1H NMR (500 MHz, DMSO-*d*6, ppm) δ 8.30 (t, *J* = 6.1 Hz, 1H, N-H), 8.13 (d, *J* = 7.7 Hz, 2H, carbazol-H), 7.63 (d, *J* = 8.2 Hz, 2H, carbazol-H), 7.60 (d, *J* = 2.1 Hz, 1H, benzyl-H), 7.43 (t, *J* = 6.7 Hz, 2H, carbazol-H), 7.42 – 7.39 (m, 1H, benzyl-H), 7.30 (d, *J* = 8.3 Hz, 1H, benzyl-H), 7.18 (t, *J* = 7.4 Hz, 2H, carbazol-H), 4.97 (d, *J* = 5.0 Hz, 1H, OH), 4.47 (dd, *J* = 14.8, 4.0 Hz, 1H, carbazol-CH2), 4.33 (d, *J* = 6.1 Hz, 2H, NH-CH2), 4.28 (dd, *J* = 14.8, 6.8 Hz, 1H, carbazol-CH2), 4.07 (dd, *J* = 10.3, 5.1 Hz, 1H, CH2-CH-CH2), 3.01 (s, 2H, piperazine-CH2-amide), 2.50 (s, 2H, CH-CH2-piperazine), 2.37 (ddd, *J* = 18.1, 12.6, 6.3 Hz, 8H, piperazin-H); 13C NMR (126 MHz, DMSO-*d*6, ppm) δ 170.30, 141.21, 136.27, 133.32, 132.62, 130.59, 129.06, 127.81, 125.97, 122.56, 120.56, 119.12, 110.37, 67.72, 62.43, 61.73, 55.46, 53.93, 53.62, 48.10; HRMS (ESI) [M+H]+ calcd for C28H31O2N4Cl2: 525.1819; found: 525.1812.

**2-(4-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)piperazin-1-yl)-*N*-(furan-2-ylmethyl)acetamide (A12)** A yellow oil, yield 56.8%; 1H NMR (400 MHz, DMSO-*d*6, ppm) δ 8.13 (d, *J* = 7.7 Hz, 2H, carbazol-H), 8.09 (d, *J* = 5.9 Hz, 1H, N-H), 7.63 (d, *J* = 8.2 Hz, 2H, carbazol-H), 7.55 (d, *J* = 0.9 Hz, 1H, furan-H), 7.44 (dd, *J* = 11.3, 4.0 Hz, 2H, carbazol-H), 7.18 (t, *J* = 7.4 Hz, 2H, carbazol-H), 6.38 (dd, *J* = 3.0, 1.9 Hz, 1H, furan-H), 6.20 (d, *J* = 3.1 Hz, 1H, furan-H), 4.94 (d, *J* = 3.9 Hz, 1H, OH), 4.47 (dd, *J* = 14.7, 4.0 Hz, 1H, carbazol-CH2), 4.30 (d, *J* = 5.8 Hz, 3H, NH-CH2-furan), 4.26 (d, *J* = 6.8 Hz, 1H, carbazol-CH2), 4.07 (s, 1H, CH2-CH-CH2), 2.96 (s, 1H, piperazine-CH2-amide), 2.50 (d, *J* = 3.4 Hz, 2H, CH-CH2-piperazine), 2.48 – 2.31 (m, 8H, piperazin-H); 13C NMR (101 MHz, DMSO) δ 169.66, 152.96, 142.42, 141.17, 125.90, 122.52, 120.48, 119.06, 110.90, 110.31, 106.97, 67.67, 62.37, 61.64, 53.86, 53.42, 48.06, 35.75; HRMS (ESI) [M+H]+ calcd for C26H31O3N4: 447.2391; found: 447.2385.

**2-(4-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)piperazin-1-yl)-*N*-(thiophen-2-ylmethyl)acetamide (A13)** A yellow oil, yield 58.7%; 1H NMR (400 MHz, DMSO-*d*6, ppm) δ 8.28 (t, *J* = 6.1 Hz, 1H, N-H), 8.13 (d, *J* = 7.7 Hz, 2H, carbazol-H), 7.63 (d, *J* = 8.2 Hz, 2H, carbazol-H), 7.43 (t, *J* = 7.6 Hz, 2H, carbazol-H), 7.36 (dd, *J* = 4.4, 1.9 Hz, 1H, thiophene-H), 7.18 (t, *J* = 7.4 Hz, 2H, carbazol-H), 6.95 (s, 1H, thiophene-H), 6.93 (d, *J* = 3.4 Hz, 1H, thiophene-H), 4.94 (d, *J* = 4.8 Hz, 1H, OH), 4.49 (d, *J* = 4.1 Hz, 1H, carbazol-CH2), 4.46 (d, *J* = 6.0 Hz, 2H, NH-CH2), 4.28 (dd, *J* = 14.8, 6.7 Hz, 1H, carbazol-CH2), 4.07 (d, *J* = 4.9 Hz, 1H, CH2-CH-CH2), 2.95 (s, 2H, piperazine-CH2-amide), 2.50 (s, 2H, CH-CH2-piperazine), 2.38 (ddd, *J* = 23.8, 19.6, 9.9 Hz, 8H, piperazin-H); 13C NMR (101 MHz, DMSO-*d*6, ppm) δ 169.65, 143.28, 141.17, 127.09, 125.91, 125.63, 125.30, 122.52, 120.48, 119.06, 110.31, 67.66, 62.38, 61.69, 53.84, 53.44, 48.06, 37.44; HRMS (ESI) [M+H]+ calcd for C26H31O2N4S: 463.2162; found: 463.2159.

**1-(9*H*-carbazol-9-yl)-3-(4-methylpiperazin-1-yl)propan-2-ol (A14)** A yellow oil, yield 59.2%; 1H NMR (400 MHz, DMSO-*d*6, ppm) δ 8.13 (d, *J* = 7.7 Hz, 2H, carbazol-H), 7.62 (d, *J* = 8.3 Hz, 2H, carbazol-H ), 7.43 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 2H, carbazol-H), 7.18 (dd, *J* = 11.0, 3.8 Hz, 2H, carbazol-H), 4.96 (d, *J* = 4.1 Hz, 1H, OH), 4.46 (dd, *J* = 14.8, 4.0 Hz, 1H, carbazol-CH2), 4.27 (dd, *J* = 14.8, 6.8 Hz, 1H, carbazol-CH2), 4.05 (s, 1H, CH2-CH-CH2), 3.43 (s, 2H, CH-CH2-piperazine), 2.55 (dd, *J* = 9.8, 6.1 Hz, 1H, piperazine-H), 2.39 (dd, *J* = 12.5, 6.9 Hz, 3H, piperazine-H), 2.31 (dd, *J* = 12.5, 5.8 Hz, 4H, piperazine-H), 2.14 (s, 3H, piperazine-CH3); 13C NMR (101 MHz, DMSO-*d*6, ppm) δ 141.16, 125.90, 122.50, 120.49, 119.06, 110.29, 67.69, 62.34, 55.26, 53.90, 48.05, 46.23; HRMS (ESI) [M+H]+ calcd for C20 H26ON3: 324.2070; found: 324.2065.

**1-(4-(benzo[*d*][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-3-(9*H*-carbazol-9-yl)propan-2-ol (A15)** A white solid, yield 49.0%; m. p. 151.4-152.4 oC; 1H NMR (500 MHz, DMSO-*d*6, ppm) δ 8.15 – 8.10 (m, 2H, carbazol-H), 7.62 (d, *J* = 8.3 Hz, 2H, carbazol-H), 7.42 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 2H, carbazol-H), 7.18 (ddd, *J* = 7.9, 7.3, 0.9 Hz, 2H, carbazol-H), 6.84 (s, 1H, benzo[*d*][1,3]dioxol-5-ylmethyl-H, 6.84 (d, 1H, *J* = 6.5 Hz, benzo[*d*][1,3]dioxol-5-ylmethyl-H, 6.74 (dd, 1H, *J* = 7.9, 1.6 Hz, 2H, benzo[*d*][1,3]dioxol-5-ylmethyl-H, 5.98 (s, 2H, benzo[*d*][1,3]dioxol-CH2), 4.94 (d, *J* = 5.1 Hz, 1H, OH), 4.46 (dd, *J* = 14.8, 3.9 Hz, 1H, carbazol-CH2), 4.27 (dd, *J* = 14.8, 6.9 Hz, carbazol-CH2), 4.09 – 4.00 (m, 1H, CH2-CH-CH2), 3.36 (s, 1H, piperazine-CH2-benzo[*d*][1,3]dioxol), 2.35 (ddd, *J* = 18.2, 12.5, 6.4 Hz, 8H, piperazine-H); 13C NMR (101 MHz, DMSO-*d*6, ppm) δ 147.64, 146.57, 141.17, 132.48, 125.90, 122.51, 122.45, 120.47, 119.06, 110.29, 109.54, 108.28, 101.21, 67.70, 62.36, 62.23, 53.99, 52.98, 48.07. HRMS (ESI) [M+H]+ calcd for C27H30O3N3: 444.2282; found: 444.2273.

**1-(9*H*-carbazol-9-yl)-3-(4-phenylpiperazin-1-yl)propan-2-ol (A16)** A white solid, yield 75.3%; m. p. 166.5-167.5 oC; 1H NMR (500 MHz, DMSO-*d*6, ppm) δ 8.13 (d, *J* = 7.6 Hz, 2H, carbazol-H), 7.65 (d, *J* = 8.3 Hz, 2H, carbazol-H), 7.46 – 7.41 (m, 2H, carbazol-H), 7.21 (dd, *J* = 5.9, 4.5 Hz, 2H, phenyl-H), 7.18 (t, *J* = 4.6 Hz, 2H, carbazol-H), 6.92 (d, *J* = 8.0 Hz, 1H, phenyl-H), 6.77 (t, *J* = 7.3 Hz, 1H, phenyl-H), 5.02 (d, *J* = 5.1 Hz, 1H, OH), 4.51 (dd, *J* = 14.8, 4.2 Hz, 1H, carbazol-CH2), 4.32 (dd, *J* = 14.8, 6.8 Hz, carbazol-CH2), 4.16 – 4.08 (m, 1H, CH2-CH-CH2), 3.17 – 3.07 (m, 4H, 4-phenylpiperazine-H), 2.62 – 2.51 (m, 4H, CH-CH2-piperazine + 4-phenylpiperazine-H), 2.43 (ddd, *J* = 18.3, 12.6, 6.2 Hz, 2H, 4-phenylpiperazine-H); 13C NMR (126 MHz, DMSO-*d*6, ppm) δ 151.55, 141.22, 129.44, 125.99, 122.58, 120.56, 119.27, 119.14, 115.82, 110.39, 67.80, 62.40, 54.06, 48.73, 48.14; HRMS (ESI) [M+H]+ calcd for C25H28ON3: 386.2227; found: 386.2220.

**1-(9*H*-carbazol-9-yl)-3-(4-(2-chlorobenzyl)piperazin-1-yl)propan-2-ol (A17)**

A white solid, yield 34.3%; m. p. 100.9-101.9 oC; 1H NMR (500 MHz, DMSO-*d*6, ppm) δ 8.12 (d, *J* = 7.7 Hz, 2H, carbazol-H), 7.63 (d, *J* = 8.3 Hz, 2H, carbazol-H), 7.44 – 7.42 (m, 2H, carbazol-H), 7.41 (t, *J* = 1.4 Hz, 1H, benzyl-H), 7.34 – 7.30 (m, 1H, benzyl-H), 7.27 (td, *J* = 7.6, 1.9 Hz, 1H, benzyl-H), 7.20 – 7.16 (m, 2H, carbazol-H), 4.97 (d, *J* = 5.1 Hz, 1H, OH), 4.47 (dd, *J* = 14.8, 3.9 Hz, 1H, carbazol-CH2), 4.27 (dd, *J* = 14.8, 6.9 Hz, 1H, carbazol-CH2), 4.10 – 4.02 (m, 1H, CH2-CH-CH2), 3.55 (s, 2H, 2-chlorobenzyl-CH2-piperazine), 2.51 (d, *J* = 1.8 Hz , 2H, CH-CH2-piperazine), 2.48 – 2.31 (m, 8H, piperazin-H); 13C NMR (101 MHz, DMSO-*d*6, ppm) δ 141.16, 125.90, 122.50, 120.49, 119.06, 110.29, 67.69, 62.34, 55.26, 53.90, 48.05, 46.23; HRMS (ESI) [M+H]+ calcd for C26H29ON3Cl: 434.1994; found: 434.1987.

**1-(9*H*-carbazol-9-yl)-3-(4-(4-chlorobenzyl)piperazin-1-yl)propan-2-ol (A18)**

A white solid, yield 76.3%; m. p. 155.5-156.1 oC; 1H NMR (500 MHz, DMSO-*d*6, ppm) δ 8.12 (d, *J* = 7.6 Hz, 2H, carbazol-H), 7.62 (d, *J* = 8.3 Hz, 2H, carbazol-H), 7.42 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 2H, carbazol-H), 7.38 – 7.36 (m, benzyl-2H), 7.32 – 7.30 (m, benzyl-2H), 7.19 – 7.15 (m, 2H, carbazol-H), 4.95 (d, *J* = 5.1 Hz, 1H, OH), 4.46 (dd, *J* = 14.8, 3.9 Hz, 1H, carbazol-CH2), 4.27 (dd, *J* = 14.8, 6.9 Hz, 1H, carbazol-CH2), 4.08 – 4.01 (m, 1H, CH2-CH-CH2), 3.44 (s, piperazine-CH2-4-chlorobenzyl), 3.42 (m, 2H, CH-CH2-piperazine), 2.39 (dd, *J* = 12.5, 7.0 Hz, 4H, piperazine-H), 2.32 (dd, *J* = 12.5, 5.7 Hz, 4H, piperazine-H); 13C NMR (126 MHz, DMSO-*d*6, ppm) δ 141.22, 137.86, 131.91, 131.11, 128.65, 125.95, 122.56, 120.54, 119.11, 110.36, 67.76, 62.42, 61.67, 54.07, 53.16, 48.14; HRMS (ESI) [M+H]+ calcd for C26H29ON3Cl: 434. 1994; found: 434. 1989.

**(4-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)piperazin-1-yl)(phenyl)methanone (A19)** A white solid, yield 52.9%; m. p. 91-92 oC; 1H NMR (500 MHz, DMSO-*d*6, ppm) δ 8.13 (d, *J* = 7.4 Hz, 2H, carbazol-H), 7.63 (d, *J* = 8.0 Hz, 2H, carbazol-H), 7.43 (t, *J* = 4.9 Hz, 2H, carbazol-H), 7.40 – 7.35 (m, 5H, phenyl-H), 7.18 (t, *J* = 7.1 Hz, 2H, carbazol-H), 5.01 (d, *J* = 4.9 Hz, 1H, OH), 4.51 – 4.46 (m, 1H, carbazol-CH2), 4.30 (dd, *J* = 14.7, 6.6 Hz, 1H, carbazol-CH2), 4.11 (s, 1H, CH2-CH-CH2), 3.62 (s, 2H, piperazine-H), 3.30 (s, 2H, piperazine-H), 2.41 (ddd, *J* = 26.4, 12.5, 6.1 Hz, 6H, piperazin-H + CH-CH2-piperazine); 13C NMR (126 MHz, DMSO-*d*6, ppm) δ 169.43, 141.20, 136.46, 129.99, 128.94, 127.41, 126.01, 122.59, 120.55, 119.14, 110.39, 67.62, 62.23, 55.44, 48.09; HRMS (ESI) [M+H]+ calcd for C26H28O2N3: 414.2176; found: 414.2166.

**1-(9*H*-carbazol-9-yl)-3-(4-(phenylsulfonyl)piperazin-1-yl)propan-2-ol(A20)**

A white solid, yield 34.7%; m. p. 142.2-143 oC; 1H NMR (500 MHz, DMSO-*d*6, ppm) δ 8.01 (d, *J* = 7.0 Hz, 2H, carbazol-H), 7.78 (d, *J* = 4.0 Hz, 1H, phenyl-H), 7.71 (s, 4H, phenyl-H), 7.52 (d, *J* = 7.6 Hz, 2H, carbazol-H), 7.32 (t, *J* = 6.9 Hz, 2H, carbazol-H), 7.12 (t, *J* = 6.9 Hz, 2H, carbazol-H), 4.98 (s, 1H, OH), 4.35 (d, *J* = 14.8 Hz, 2H, carbazol-CH2), 4.23 (dd, *J* = 14.7, 5.7 Hz, 1H, carbazol-CH2), 4.01 (s, 1H, CH2-CH-CH2), 2.73 (s, 4H, CH-CH2-piperazine + 4-(phenylsulfonyl)piperazine-3H), 2.40 – 2.29 (m, 6H, CH-CH2-piperazine + piperazin-5H); 13C NMR (101 MHz, DMSO-*d*6, ppm) δ 141.04, 135.13, 133.77, 129.90, 128.06, 125.78, 122.45, 120.39, 118.99, 110.20, 67.09, 61.97, 52.74, 48.09, 46.18. HRMS (ESI) [M+H]+ calcd for C25H28O3N3S: 450.1846; found: 450.1835.

3. 1H NMR, 13C NMR, and HRMS spectra for the target compounds

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**Figure S5.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A1**

****

**Figure S6.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A1**



Figure S7. HRMS spectrum of target compound A1



**Figure S8.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A2**



**Figure S9.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A2**



Figure S10. HRMS spectrum of target compound A2.



**Figure S11.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A3**



**Figure S12.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A3**



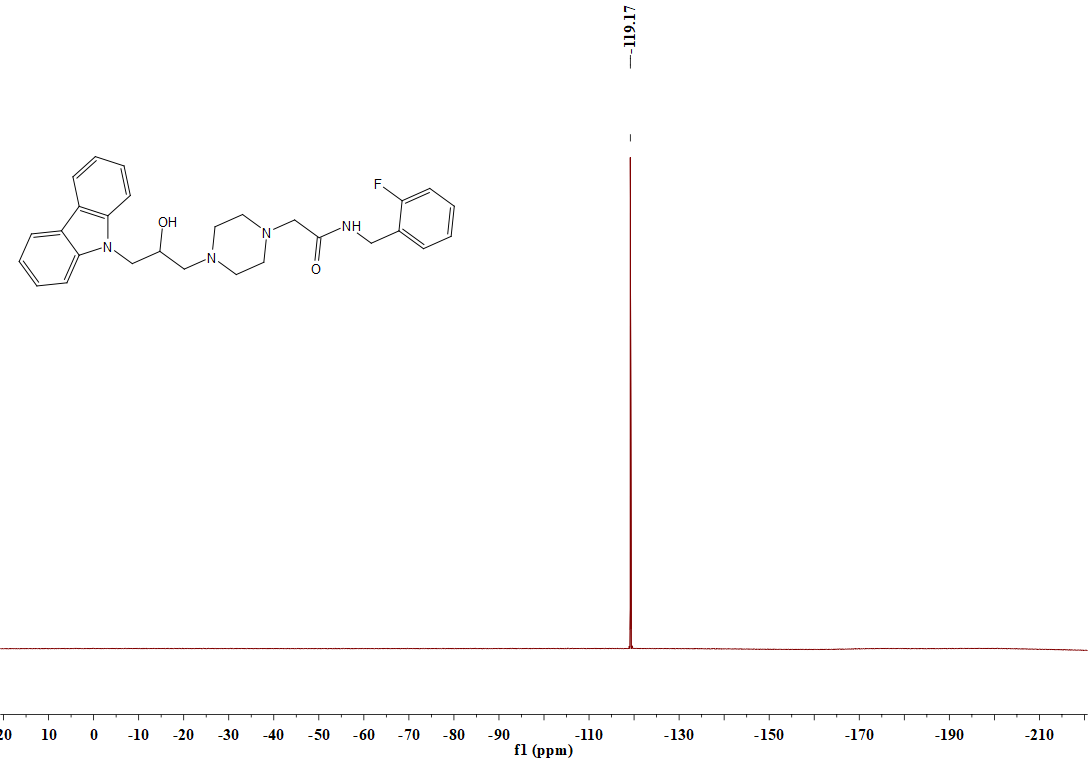
Figure S13. HRMS spectrum of target compound A3



**Figure S14.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A4**

****

**Figure S15.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A4**



**Figure S16.** 19F NMR spectrum (DMSO-*d*6, 377 MHz) of **A4**



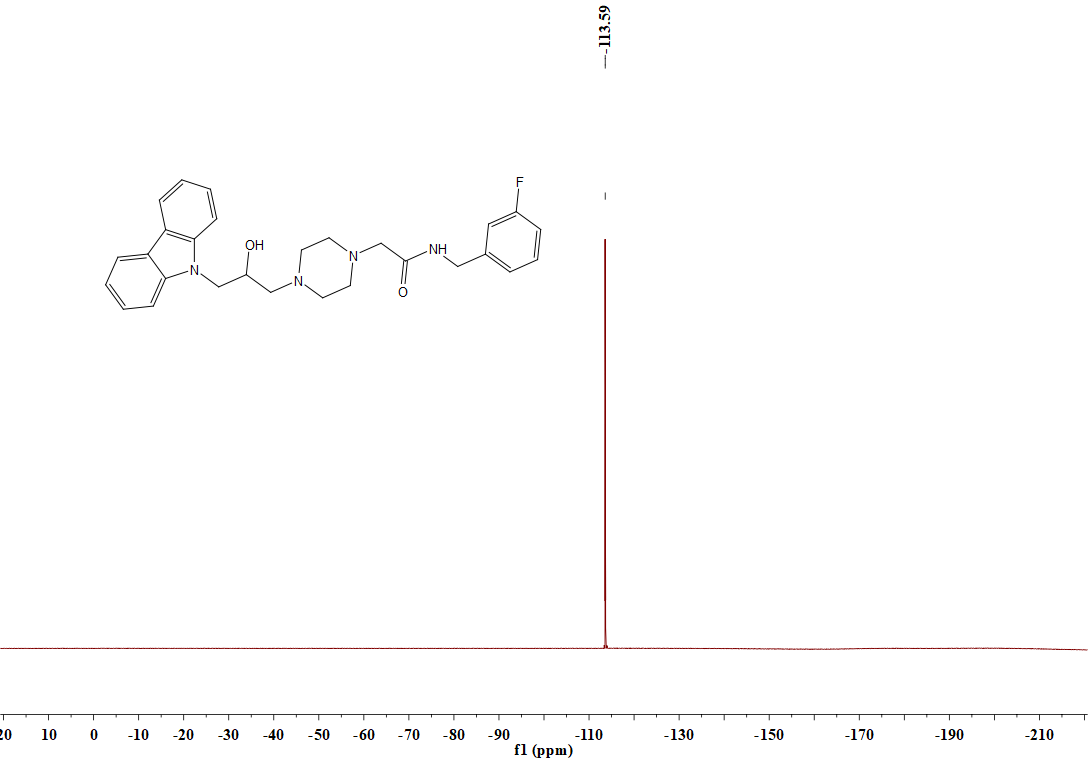
Figure S17. HRMS spectrum of target compound A4

**

**Figure S18.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A5**



**Figure S19.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A5**

****

**Figure S20.** 19F NMR spectrum (DMSO-*d*6, 377 MHz) of **A5**



Figure S21. HRMS spectrum of target compound A5



**Figure S22.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A6**



**Figure S23.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A6**

****

**Figure S24.** 19F NMR spectrum (DMSO-*d*6, 377 MHz) of **A6**



Figure S25. HRMS spectrum of target compound A6



**Figure S26.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A7**



**Figure S27.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A7**



Figure S28. HRMS spectrum of target compound A7



**Figure S29.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A8**



**Figure S30.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A8**



Figure S31. HRMS spectrum of target compound A8



**Figure S32.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A9**



**Figure S33.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A9**



Figure S34. HRMS spectrum of target compound A9



**Figure S35.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A10**



**Figure S36.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A10**

****

**Figure S37.** 19F NMR spectrum (DMSO-*d*6, 377 MHz) of **A10**



Figure S38. HRMS spectrum of target compound A10



**Figure S39.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A11**



**Figure S40.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A11**



Figure S41. HRMS spectrum of target compound A11



**Figure S42.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A12**



**Figure S43.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A12**



Figure S44. HRMS spectrum of target compound A12



**Figure S45.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A**13



**Figure S46.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A**13



Figure S47. HRMS spectrum of target compound A13



**Figure S48.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A14**



**Figure S49.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A14**



Figure S50. HRMS spectrum of target compound A14



**Figure S51.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A15**



**Figure S52.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A15**



Figure S53. HRMS spectrum of target compound A15



**Figure S54.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A16**



**Figure S55.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A16**



Figure S56. HRMS spectrum of target compound A16



**Figure S57.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A17**



**Figure S58.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A17**



Figure S59. HRMS spectrum of target compound A1**7**



**Figure S60.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A18**



**Figure S61.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A18**



Figure S62. HRMS spectrum of target compound A18



**Figure S63.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A19**



**Figure S64.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A19**



Figure S65. HRMS spectrum of target compound A19



**Figure S66.** 1H NMR spectrum (DMSO-*d*6, 400 MHz) of **A20**



**Figure S67.** 13C NMR spectrum (DMSO-*d*6, 101 MHz) of **A20**



Figure S68. HRMS spectrum of target compound A20

4. The metabolism property of compound A9.

**Table S1** The metabolism property of compound **A9** through the online prediction tool ADMETlab 2.0.

|  |  |  |
| --- | --- | --- |
| Metabolism Property Value Decision | Value | Decision |
| Metabolism |  |  |
| CYP1A2 inhibitor | 0.651 |  |
| CYP1A2-substrate | 0.513 |  |
| CYP2C19-inhibitor | 0.93 |  |
| CYP2C19-substrate | 0.795 |  |
| CYP2C9-inhibitor | 0.634 |  |
| CYP2C9-substrate | 0.32 |  |
| CYP2D6-inhibitor | 0.978 |  |
| CYP2D6-substrate | 0.857 |  |
| CYP3A4-inhibitor | 0.403 |  |
| CYP3A4-substrate | 0.916 |  |