Supporting Information

Zafirlukast is a promising scaffold for selectively inhibiting TNFR1 signaling

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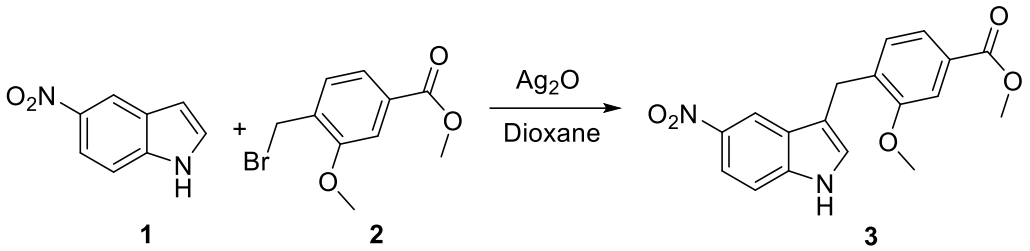
SUPPLEMENTARY METHODS AND MATERIALS

Synthetic procedures for analogs **8a-j**

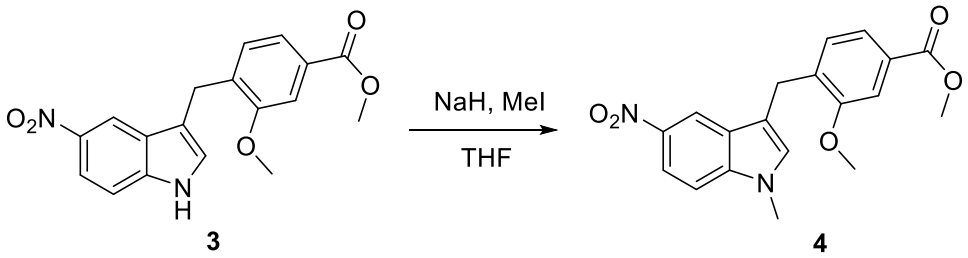
Synthesis of methyl 3-methoxy-4-((5-nitro-1H-indol-3-yl)methyl)benzoate **(3)**



1 2 3

Silver oxide (4.62 g, 20 mmol, 1 eq) was added to a solution of 5-nitroindole **(1)** (3.24 g, 20 mmol, 1 eq) and methyl 4-(bromomethyl)-3-methoxybenzoate **(2)** (5.18 g, 20 mmol, 1 eq) in 40 mL dioxane. The reaction was heated to 60 ^{o}C for 20 hrs. The silver containing precipitate was filtered through a celite pad and the resulting filtrate was concentrated and briefly purified via column chromatography, eluting with 7:3 hexanes:EtOAc. The combined fractions containing mainly the product was recrystallized from DCM and hexanes to give the product **(3)** as yellow crystalline solid (2.77 g, 8.1 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 2.2 Hz, 1H), 8.41 (s, 1H), 8.07 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.35 (d, *J* = 9.0 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 4.14 (s, 2H), 3.93 (s, 3H), 3.88 (s, 3H).

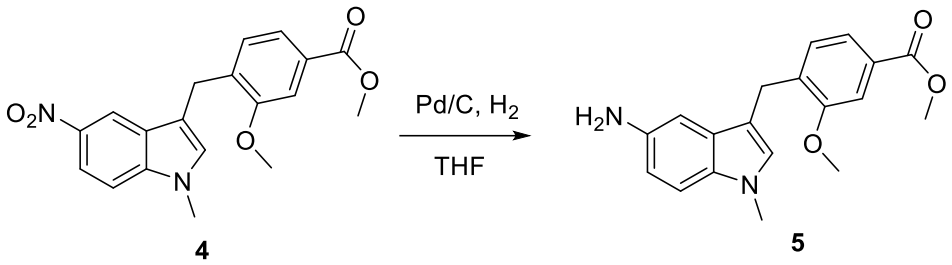
Synthesis of methyl 3-methoxy-4-((1-methyl-5-nitro-1H-indol-3-yl)methyl)benzoate **(4)**



3 4

Methyl 3-methoxy-4-((5-nitro-1H-indol-3-yl)methyl)benzoate **(3)** (1.4 g, 4.14 mmol, 1 eq) was dissolved in 30 mL dry THF and 182 mg of NaH (50% wetted with mineral oil, 1.1 eq) was added. The solution turned red and hydrogen gas formed. Once the bubbling stopped, 0.71 g of MeI (4.97 mmol, 1.2 eq) was added and the reaction was stirred at room temperature for 2 hours while the color faded from dark red to light yellow. Once TLC showed completion of reaction, THF was rotavaped. EtOAc and 1M HCl solution was added. The aqueous phase was extracted with EtOAc and the combined organic phase was dried over $MgSO_4$ and rotavaped to give the product **(4)** as yellow solid (1.02 g, 2.87 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (t, *J* = 1.8 Hz, 1H), 8.09 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.53 (dd, *J* = 6.0, 1.6 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.15 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.90 (s, 1H), 4.11 (s, 2H), 3.94 (d, *J* = 1.5 Hz, 3H), 3.90 – 3.85 (m, 3H), 3.76 (d, *J* = 1.5 Hz, 3H).

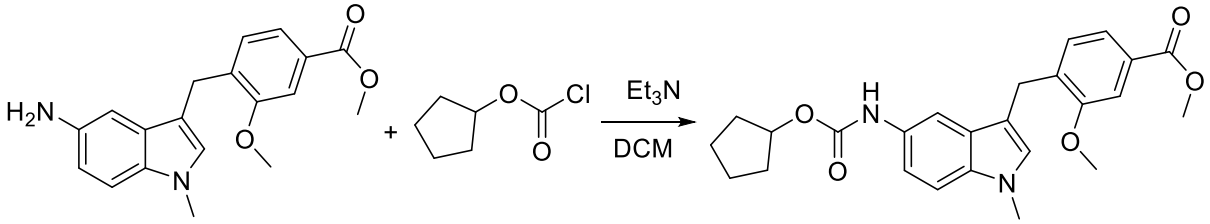
Synthesis of methyl 4-((5-amino-1-methyl-1H-indol-3-yl)methyl)-3-methoxybenzoate **(5)**



4 **5**

Methyl 3-methoxy-4-((1-methyl-5-nitro-1H-indol-3-yl)methyl)benzoate **(4)** (0.22 g, 0.62 mmol, 1 eq) was dissolved in 10 mL THF and added to dry palladium on activated carbon (10% w/w, 0.2 g). The reaction was stirred under hydrogen gas overnight. The reaction was filtered through celite to remove the Pd catalyst and THF was rotavaped to give the product as a foaming solid (144 mg, 0.44 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 2H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.77 (d, *J* = 2.1 Hz, 1H), 6.69 (s, 1H), 6.66 (dd, *J* = 8.6, 2.2 Hz, 1H), 4.01 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.66 (s, 3H).

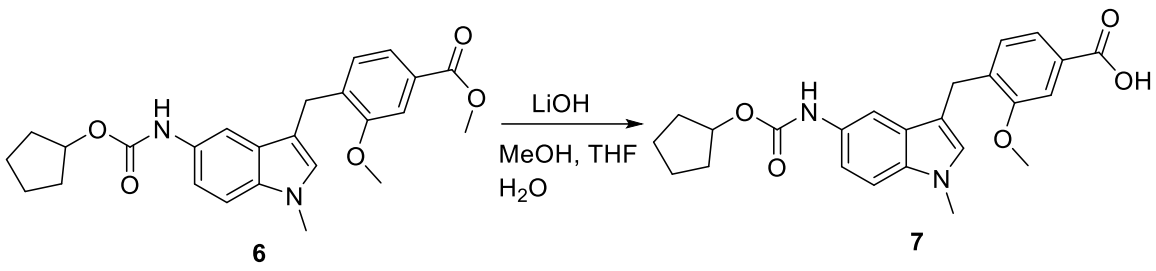
Synthesis of methyl 4-((5-((cyclopentoxycarbonyl)amino)-1-methyl-1H-indol-3-yl)methyl)-3-methoxybenzoate **(6)**



5 **6**

To 220 mg (0.62 mmol) of methyl 4-((5-amino-1-methyl-1H-indol-3-yl)methyl)-3-methoxybenzoate **(5)** in 30 mL DCM, 125 mg (12.4 mmol, 2 eq) of Et_3N was added. The solution was cooled to 0^{o}C. 1 mmol of cyclopentyl chloroformate was diluted in 10 mL of DCM and was transferred to an addition funnel. The chloroformate solution was slowly dropped to the aniline solution. Once the addition was completed, the reaction was warmed up to room temperature and stirred for 1 h. DCM was rotavaped and the residue was purified via flash column chromatography (7:3 hexanes: EtOAc) to give the product **(6)** as white solid (0.176 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 3H), 7.21 – 7.03 (m, 3H), 6.74 (s, 1H), 6.49 – 6.44 (m, 1H), 5.18 (m,1H), 4.05 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.69 (s, 3H), 1.85 (m, 2H), 1.74 (m, 4H), 1.57 (m, 2H).

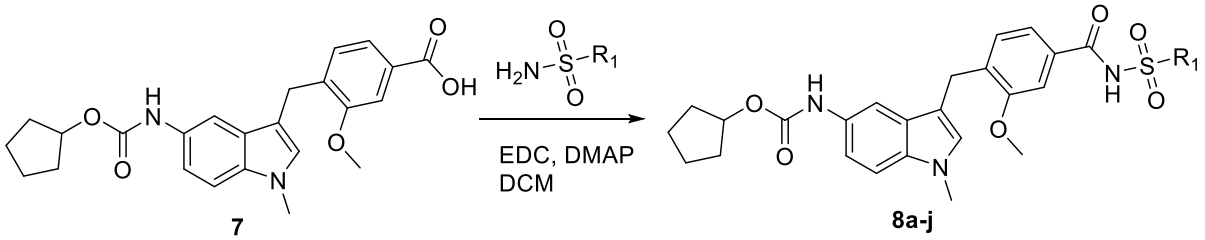
Synthesis of 4-((5-((cyclopentoxycarbonyl)amino)-1-methyl-1H-indol-3-yl)methyl)-3-methoxybenzoic acid



6 **7**

Methyl 4-((5-((cyclopentoxycarbonyl)amino)-1-methyl-1H-indol-3-yl)methyl)-3-methoxybenzoate (0.32 g, 0.78 mmol) **(6)** was dissolved in mixed solvents containing 8 mL of MeOH and 7 mL of THF. LiOH hydrate (0.16 g, 3.9 mmol, 5 eq) was dissolved in 3 mL of water and the solution was added to the solution of the methyl ester. The reaction was allowed to stir at room temperature overnight. MeOH and THF were rotavaped and the resulting suspension was neutralized to pH 3. The solid was collected via filtration and dried to give **(7)** as white solid (0.19 g, 0.48 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 3H), 7.21 – 7.09 (m, 3H), 6.74 (s, 1H), 6.54 (s, 1H), 5.17 (m, 1H), 4.05 (s, 2H), 3.89 (s, 3H), 3.68 (s, 3H), 1.85 (m, 2H), 1.70 (m, 4H), 1.57 (m, 2H).

Synthesis of cyclopentyl (3-(2-methoxy-4-(((4-(trifluoromethyl)phenyl)sulfonyl)carbamoyl)benzyl)-1-methyl-1H-indol-5-yl)carbamate **(8a-j)**



7 **8a-j**

General procedure

The carboxylic acid **(7)**, EDC (2.1 eq) and DMAP (1.05 eq) were dissolved in DCM and the reaction was carried out at room temperature overnight. The reaction mixture was washed with 0.1 M HCl. The aqueous layer was extracted with DCM 2 times. Combined organic layers was concentrated to give the crude product, which was recrystallized in DCM/hexanes to give the product as white to light yellow crystalline solid. Alternatively, the crude product can also be purified via flash chromatography with 70/30/1 hexanes/EtOAc/HOAc as the mobile phase. After the desired fractions were concentrated, 10mL of EtOAc was added and rotavaped again to facilitate the evaporation of HOAc.

8a: 66% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.39 (s, 1H), 9.17 (s, 1H), 7.75 (s, 2H), 7.55 (s, 1H), 7.48 (q, J = 2.3 Hz, 2H), 7.44 (s, 1H), 7.33 (dd, J = 8.0, 2.2 Hz, 1H), 7.22 (dd, J = 8.8, 2.2 Hz, 1H), 7.09 (d, J = 8.9 Hz, 1H), 7.07 – 7.02 (m, 1H), 6.98 (s, 1H), 5.02 (tt, J = 6.0, 2.7 Hz, 1H), 3.90 (s, 2H), 3.88 (s, 3H), 3.64 (s, 3H), 2.37 (s, 3H), 1.80 (s, 2H), 1.68 – 1.44 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.38, 157.07, 154.10, 139.92, 139.22, 135.75, 134.70, 133.68,

131.49, 130.57, 129.77, 129.42, 128.88, 128.16, 127.63, 125.28, 121.16, 114.77, 111.35, 110.49, 109.93, 108.49, 76.65, 56.13, 32.80, 32.74, 25.10, 23.70, 21.28. $[M-H]^-$ = 574.2012; found 574.2036

8b: 87% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.37 (s, 1H), 9.19 (s, 1H), 7.85 (d, *J* = 7.9 Hz, 2H), 7.57 (s, 1H), 7.45 (s, 1H), 7.41 (d, *J* = 7.9 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.11 (s, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.99 (s, 1H), 5.03 (td, *J* = 6.2, 3.1 Hz, 1H), 3.91 (s, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 2.37 (s, 3H), 1.81 (s, 2H), 1.68 – 1.47 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.40, 157.05, 154.10, 144.57, 137.14, 135.63, 133.68, 131.49, 130.71, 129.93, 129.74, 128.87, 128.19, 127.63, 121.11, 114.76, 111.36, 110.46, 109.92, 108.53, 76.65, 56.11, 32.80, 32.74, 25.09, 23.70, 21.52. $[M-H]^-$ = 574.2012; found 574.2037

8c: 58% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.38 (s, 1H), 9.18 (s, 1H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.57 (s, 1H), 7.46 (s, 1H), 7.35 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 7.16 – 7.09 (m, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.99 (s, 1H), 5.02 (m, 1H), 3.91 (s, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 1.88 – 1.76 (m, 2H), 1.72 – 1.47 (m, 6H), 1.28 (s, 9H). ^{13}C NMR (151 MHz, dmso) δ 165.36, 157.14, 157.07, 154.09, 137.09, 135.72, 133.68, 131.49, 130.56, 129.77, 128.88, 128.05, 127.62, 126.43, 121.16, 114.77, 111.34, 110.48, 109.93, 108.45, 76.64, 56.13, 35.42, 32.79, 32.75, 31.17, 25.10, 23.70. $[M-H]^-$ = 616.2481; found 616.2499

8d: 62% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.54 (s, 1H), 9.25 – 9.11 (m, 1H), 7.97 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.56 (s, 1H), 7.45 (d, *J* = 1.8 Hz, 1H), 7.35 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.15 – 7.09 (m, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.00 (s, 1H), 5.03 (m, 1H), 3.92 (s, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 1.81 (m, 2H), 1.73 – 1.47 (m, 6H). ^{13}C NMR (151 MHz, dmso) δ 165.62, 157.07, 154.09, 138.98, 138.82, 135.83, 133.68, 131.49, 130.52, 130.13, 129.77, 129.72, 128.88, 127.62, 121.20, 114.77, 111.33, 110.51, 109.93, 108.47, 76.64, 56.12, 32.80, 32.75, 25.11, 23.70. $[M-H]^-$ = 594.1466; found 594.1494

8e: 32% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.68 (d, *J* = 4.7 Hz, 1H), 8.13 (d, *J* = 4.4 Hz, 2H), 7.69 (h, *J* = 4.3 Hz, 1H), 7.58 (s, 1H), 7.50 (s, 1H), 7.36 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 1H), 7.00 (s, 1H), 5.03 (tt, *J* = 8.8, 4.3 Hz, 1H), 3.92 (s, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 1.85 – 1.77 (m, 2H), 1.70 – 1.47 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.51, 156.61, 153.67, 150.02, 138.69, 135.35, 133.24, 131.07, 129.33, 128.44, 127.75, 127.20, 123.23, 120.83, 114.35, 110.92, 110.19, 109.49, 108.08, 103.42, 103.04, 76.21, 62.94, 55.67, 32.36, 32.31, 24.68, 23.26. $[M-H]^-$ = 561.1808; found 561.1829

8f: 47% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.34 (s, 1H), 9.26 (s, 1H), 8.39 (s, 1H), 7.65 (s, 1H), 7.54 (s, 1H), 7.43 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 7.08 (s, 1H), 5.11 (td, *J* = 6.3, 3.2 Hz, 1H), 3.99 (s, 2H), 3.97 (s, 3H), 3.86 (s, 3H), 3.73 (s, 3H), 2.38 (s, 3H), 1.91 – 1.84 (m, 2H), 1.77 – 1.53 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.40, 157.04, 154.10, 147.50, 136.55, 135.47, 133.68, 131.49, 130.89, 129.72, 128.88, 127.64, 121.03, 118.17, 114.78, 111.39, 110.41, 109.93, 108.55, 76.64, 56.12, 39.14, 32.80, 32.75, 25.08, 23.70, 12.56. $[M-H]^-$ = 578.2073; found 578.2101

8g: 41% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.86 (s, 1H), 9.19 (s, 1H), 7.59 (s, 1H), 7.53 (t, *J* = 2.3 Hz, 1H), 7.42 (d, *J* = 7.9Hz, 1H), 7.24 (d, *J* = 8.8Hz, 1H), 7.14 – 7.07 (m, 2H), 7.01 (s, 1H), 6.59 (s, 1H), 5.03 (tq, *J* = 5.8, 2.8 Hz, 1H), 3.93 (s, 2H), 3.91 (s, 3H), 3.66 (s, 3H), 3.55 (tq, *J* = 12.0, 3.6 Hz, 1H), 2.08 – 1.98 (m, 2H), 1.84 – 1.72 (m, 4H), 1.71 – 1.51 (m, 6H), 1.50 – 1.39 (m, 2H), 1.35 – 1.18 (m, 3H), 1.14 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.40, 157.04, 154.11, 135.66, 133.69, 131.50, 130.76, 129.76, 128.88, 127.64, 121.26, 114.77, 111.39, 110.60, 109.93, 108.53, 76.65, 61.76, 60.39, 56.13, 32.80, 32.75, 25.83, 25.12, 24.87, 23.70. $[M-H]^-$ = 566.2325; found 566.2350

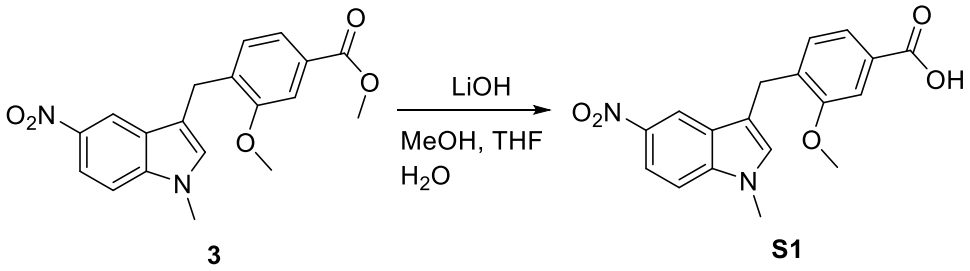
8h: 83% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.18 (d, *J* = 8.2 Hz, 2H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.56 (s, 1H), 7.45 (d, *J* = 1.6 Hz, 1H), 7.35 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 1H), 7.00 (s, 1H), 5.02 (m, 1H), 3.91 (s, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 1.86 – 1.76 (m, 2H), 1.70 – 1.48 (m, 6H).^{13}C NMR (151 MHz, DMSO-d_6) δ 165.79, 157.08, 154.10, 143.87, 135.96, 133.68, 133.51 (q, $^{2}J_{C-F}$=32.4Hz), 131.48, 130.39, 129.79, 129.13, 128.89, 127.61, 126.84 (q, $^{3}J_{C-F}$=3.34Hz), 123.81 (q, $^{1}J_{C-F}$=273Hz), 121.28, 114.74, 111.31, 110.55, 109.94, 108.51, 76.65, 56.12, 40.36, 32.79, 32.75, 25.11, 23.69. HRMS (ESI-): m/z calc for $[M-H]^-$ = 628.1729; found 628.1456

8i: 33% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.26 (s, 1H), 8.22 – 8.15 (m, 4H), 7.64 (s, 1H), 7.53 (s, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.07 (s, 1H), 5.10 (tt, *J* = 5.7, 2.7 Hz, 1H), 3.99 (s, 2H), 3.96 (s, 3H), 3.73 (s, 2H), 1.88 (m, 2H), 1.78 – 1.57 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.43, 165.82, 157.08, 154.09, 144.01, 135.98, 133.74, 133.68, 131.49, 130.37, 129.79, 128.85, 127.62, 121.30, 118.02, 116.34, 114.73, 111.31, 110.56, 109.93, 108.51, 76.64, 56.13, 32.80, 32.75, 25.12, 23.70. $[M-H]^-$ = 585.1808; found 585.1838

8j: 60% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.29 – 8.10 (m, 4H), 7.56 (s, 1H), 7.46 (d, *J* = 1.7 Hz, 1H), 7.37 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 1H), 7.00 (s, 1H), 5.02 (m, 1H), 3.92 (s, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 1.81 (m, 2H), 1.72 – 1.47 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.86, 157.10, 156.05, 154.09, 143.58, 136.02, 133.69, 131.50, 130.32, 129.80, 129.48, 128.89, 127.61, 127.56, 121.33, 114.77, 111.30, 110.59, 109.93, 108.47, 76.64, 56.13, 32.79, 32.75, 25.12, 23.69. $[M-H]^-$ = 686.1418; found 686.1446

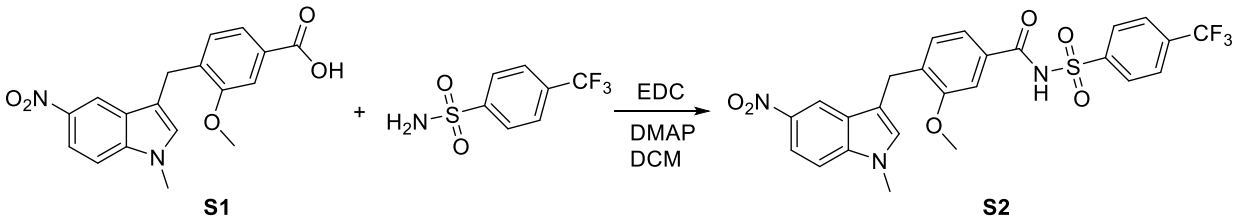
Synthetic procedures of **9a-f**

Synthesis of 3-methoxy-4-((1-methyl-5-nitro-1H-indol-3-yl)methyl)benzoic acid **(S1)**



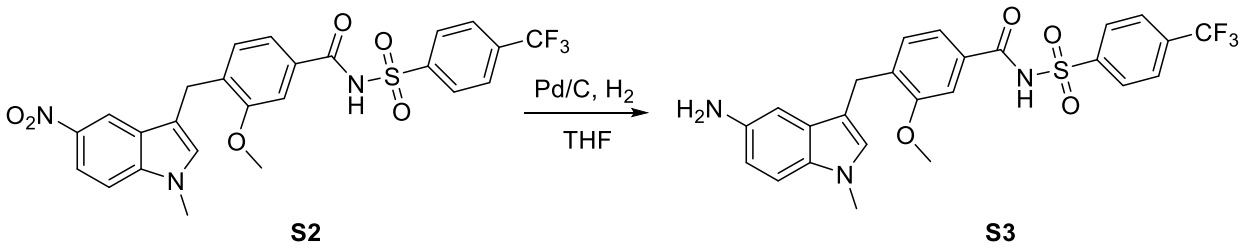
Methyl 3-methoxy-4-((1-methyl-5-nitro-1H-indol-3-yl)methyl)benzoate **(3)** (3.3 g, 9.4 mmol, 1 eq) was dissolved in mixed solvents containing 80 mL of MeOH and 70 mL of THF. LiOH hydrate (1.18 g, 28.2 mmol, 3 eq) was dissolved in 30 mL of water and the solution was added to the solution of the methyl ester. The reaction was allowed to stir at room temperature overnight. MeOH and THF were rotavaped and the resulting suspension was neutralized to pH 3. The solid was collected via filtration and dried to give the carboxylic acid product **(S1)** as white solid (2.91 g, 8.55 mmol, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 2.3 Hz, 1H), 7.98 (dd, J = 9.1, 2.3 Hz, 1H), 7.55 (d, J = 9.1 Hz, 1H), 7.46 (s, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.33 (s, 1H), 7.22 (d, J = 7.7 Hz, 1H), 4.07 (s, 2H), 3.88 (s, 3H), 3.78 (s, 3H).

Synthesis of 3-methoxy-4-((1-methyl-5-nitro-1H-indol-3-yl)methyl)-N-((4-(trifluoromethyl)phenyl) sulfonyl)benzamide **(S2)**



3-methoxy-4-((1-methyl-5-nitro-1H-indol-3-yl)methyl)benzoic acid **(S1)** (2.91 g, 8.55 mmol), trifluoromethylphenyl sulfonamide (2.25 g, 10 mmol, 1.2 eq), EDC (1.92 g, 10 mmol, 1.2 eq) and DMAP (1.22 g, 10 mmol, 1.2 eq) were dissolved in 100 mL of DCM and the reaction was carried out at room temperature overnight. The reaction was washed with 1 M HCl. The aqueous layer was extracted with DCM 2 times. Organic layers were combined and concentrated to give the crude product, which was recrystallized in DCM/hexanes to give **(S2)** as white solid (3.8 g, 6.9 mmol, 80.7% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 2.2 Hz, 1H), 8.16 (d, J = 8.2 Hz, 2H), 8.06 – 7.94 (m, 3H), 7.55 (d, J = 9.0 Hz, 1H), 7.46 (s, 1H), 7.37 (dd, J = 7.9, 1.7 Hz, 2H), 7.31 (s, 1H), 7.22 (d, J = 7.9 Hz, 1H), 4.05 (s, 2H), 3.88 (s, 3H), 3.77 (s, 3H).

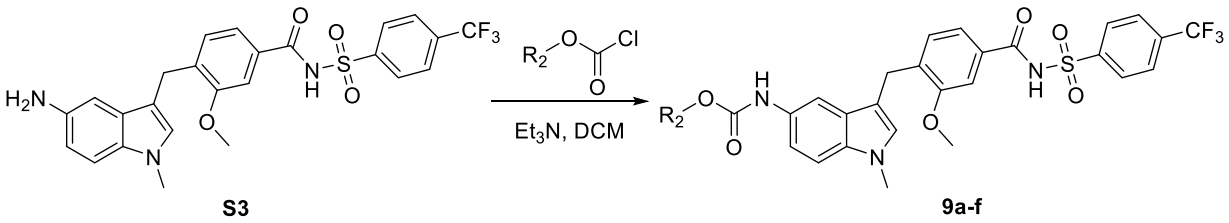
Synthesis of 4-((5-amino-1-methyl-1H-indol-3-yl)methyl)-3-methoxy-N-((4-(trifluoromethyl)phenyl) sulfonyl)benzamide **(S3)**



S2 **S3**

3-methoxy-4-((1-methyl-5-nitro-1H-indol-3-yl)methyl)-N-((4-(trifluoromethyl)phenyl)sulfonyl)benzamide **(S2)** (2.9 g, 5.3 mmol) was dissolved in 100 mL THF and added to dry palladium on activated carbon (10% w/w, 0.35 g). The reaction was stirred under hydrogen gas overnight until TLC indicated complete conversion. Palladium on carbon was filtered through celite and THF was rotavaped to give **(S3)** as a white solid that quickly turns dark (2 g, 3.87 mmol, 73%).[1]H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 8.1 Hz, 2H), 7.48 (s, 1H), 7.39 (d, J = 8.6 Hz, 1H), 7.36 (dt, J = 7.8, 1.4 Hz, 1H), 7.15 (s, 2H), 6.94 (d, J = 6.9 Hz, 2H), 3.92 (s, 2H), 3.83 (s, 3H), 3.71 (s, 3H).

Synthesis of **9a-f**



S3 **9a-f**

General procedure

To the amino intermediate in DCM, 1.5 eq of Et_3N was added. The solution was cooled to 0°C. 1 eq of chloroformate was diluted in DCM and transferred to an addition funnel. The chloroformate solution was slowly dropped to the aniline solution. Once the addition was completed, the reaction was warmed up to room temperature and stirred for 1 h. The reaction mixture was washed with 0.1 M HCl. The aqueous layer was extracted with DCM 2 times. Combined organic layers was concentrated to give the crude product, which was recrystallized in DCM/hexanes to give the product as white to light yellow crystalline solid. Alternatively, the crude product can also be purified via flash chromatography with 70/30/1 hexanes/EtOAc/HOAc as the mobile phase. After the desired fractions were concentrated, 10mL of EtOAc was added and rotavaped again to facilitate the evaporation of HOAc.

9a: 94% yield. [1]H NMR (600 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.18 (d, J = 8.2 Hz, 2H), 8.02 (d, J = 8.3 Hz, 2H), 7.53 (s, 1H), 7.45 (d, J = 1.9 Hz, 1H), 7.36 (dd, J = 7.9, 1.8 Hz, 1H), 7.26 (d, J = 8.7 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 7.08 (d, J = 7.9 Hz, 1H), 7.01 (s, 1H), 3.92 (s, 2H), 3.89 (s,

3H), 3.66 (s, 3H), 3.60 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.80, 157.08, 154.73, 143.89, 135.93, 133.79, 133.50 (q, $^{2}J_{C-F}$=32.4Hz), 131.30, 130.44, 129.82, 129.13, 128.96, 127.62, 126.85 (q, $^{3}J_{C-F}$=3.34Hz), 123.81 (q, $^{1}J_{C-F}$=273Hz), 121.29, 114.81, 111.35, 110.57, 110.00, 108.68, 56.13, 51.76, 32.76, 25.12. HRMS (ESI-): m/z calc for $[M-H]^-$ = 574.1260; found 574.1051

9b: 70% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.18 (d, *J* = 8.3 Hz, 2H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.55 (s, 1H), 7.45 (d, *J* = 1.4 Hz, 1H), 7.36 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 7.00 (s, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.78, 157.08, 154.27, 143.87, 135.96, 133.74, 133.51 (q, $^{2}J_{C-F}$=32.4Hz), 131.40, 130.38, 129.83, 129.13, 128.91, 127.61, 126.85 (q, $^{3}J_{C-F}$=3.34Hz), 123.81 (q, $^{1}J_{C-F}$=273Hz), 121.28, 114.82, 111.35, 110.57, 109.97, 108.62, 60.17, 56.13, 32.75, 25.12, 15.07. HRMS (ESI-): m/z calc for $[M-H]^-$ = 588.1416; found 588.1139

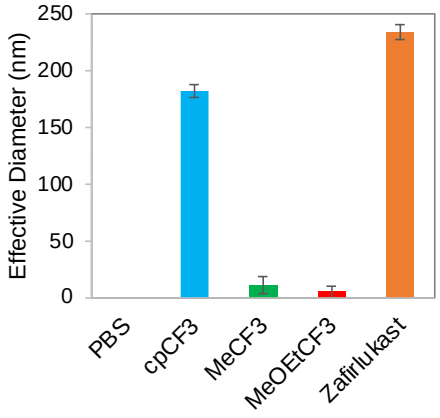
9c: 95% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.18 (d, *J* = 8.0 Hz, 2H), 8.02 (d, *J* = 8.0 Hz, 2H), 7.56 (s, 1H), 7.45 (s, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 7.00 (s, 1H), 4.14 (t, *J* = 4.5 Hz, 2H), 3.92 (s, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 3.52 (t, *J* = 4.5 Hz, 2H), 3.25 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.80, 157.08, 154.16, 143.89, 135.94, 133.75, 133.50 (q, $^{2}J_{C-F}$=32.4Hz), 131.31, 130.44, 129.83, 129.13, 128.92, 127.61, 126.84 (q, $^{3}J_{C-F}$=3.34Hz), 123.81 (q, $^{1}J_{C-F}$=273Hz), 121.28, 114.77, 111.39, 110.57, 109.98, 108.59, 70.66, 63.37, 58.39, 56.12, 32.75, 25.12. HRMS (ESI-): m/z calc for $[M-H]^-$ = 618.1522; found 618.1247

9d: 46% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.28 (s, 1H), 8.17 (d, *J* = 8.1 Hz, 2H), 8.02 (d, *J* = 8.1 Hz, 2H), 7.54 (s, 1H), 7.45 (s, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.00 (s, 1H), 4.87 (p, *J* = 7.5 Hz, 1H), 3.91 (s, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 2.25 (m, 2H), 1.99 (m, 2H), 1.71 (m, 1H), 1.56 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.81, 157.07, 153.48, 143.90, 135.93, 133.74, 133.49 (q, $^{2}J_{C-F}$=32.4Hz), 131.28, 130.44, 129.81, 129.13, 128.92, 127.61, 126.83 (q, $^{3}J_{C-F}$=3.34Hz), 123.81 (q, $^{1}J_{C-F}$=273Hz), 121.28, 114.77, 111.36, 110.56, 109.97, 108.59, 68.12, 56.12, 32.75, 30.59, 25.10, 13.35. HRMS (ESI-): m/z calc for $[M-H]^-$ = 614.1573; found 614.1303

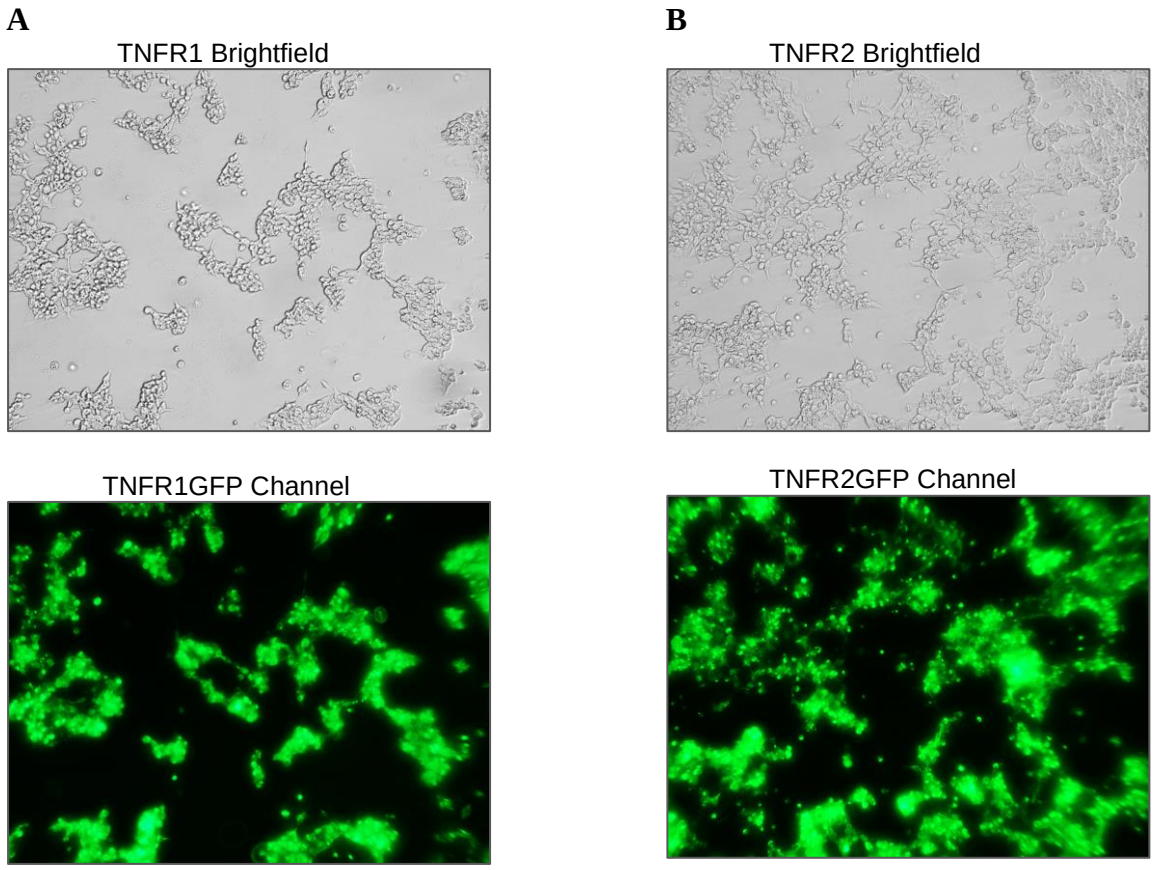
9e: Boc_2O was used instead to build the t-butyl carbomate. 88% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.18 (d, *J* = 8.2 Hz, 2H), 8.02 (d, *J* = 8.1 Hz, 2H), 7.57 (s, 1H), 7.46 (d, *J* = 1.8 Hz, 1H), 7.36 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.09 (m, 8.5 Hz, 2H), 6.98 (s, 1H), 3.92 (s, 2H), 3.90 (s, 3H), 3.65 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.73, 157.08, 153.53, 143.81, 136.06, 133.54 (q, $^{2}J_{C-F}$=32.4Hz), 133.58, 131.73, 130.31, 129.88, 129.15, 128.75, 127.60, 126.86 (q, $^{3}J_{C-F}$=3.34Hz), 123.80 (q, $^{1}J_{C-F}$=273Hz), 121.30, 114.82, 111.38, 110.56, 109.84, 108.40, 78.74, 56.12, 32.74, 28.68, 27.31, 25.08. HRMS (ESI-): m/z calc for $[M-H]^-$ = 616.1729; found 616.1770

9f: 71% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.18 (d, *J* = 8.1 Hz, 2H), 8.02 (d, *J* = 8.2 Hz, 2H), 7.57 (s, 1H), 7.46 (s, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 7.00 (s, 1H), 4.83 (m, 1H), 3.92 (s, 2H), 3.89 (s,

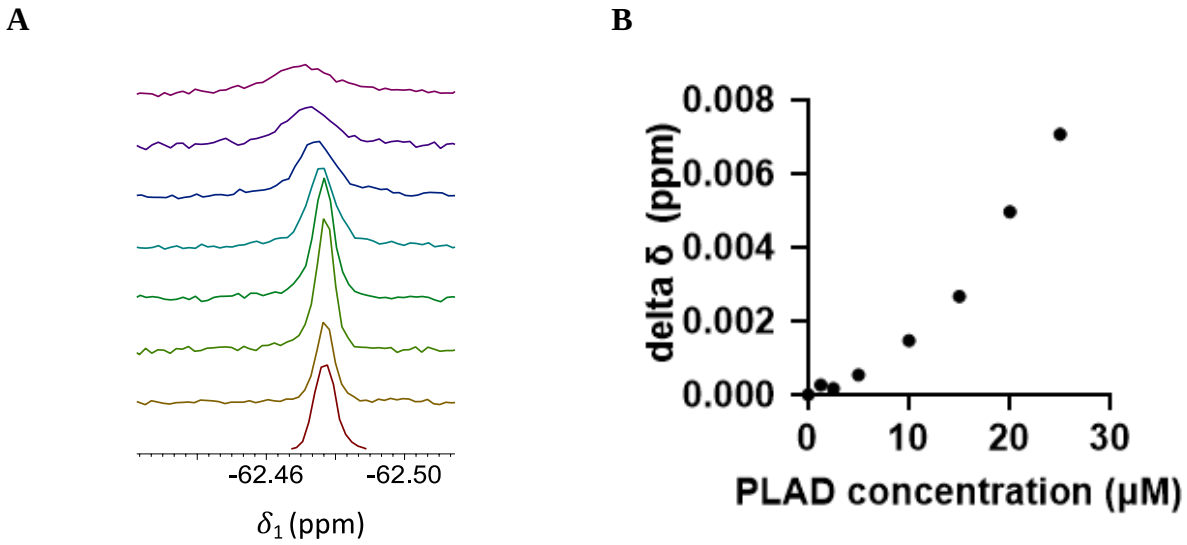
3H), 3.66 (s, 3H), 1.20 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.79, 157.08, 153.87, 143.88, 135.97, 133.69, 133.51 (q, $^{2}J_{C-F}$=32.4Hz), 131.49, 130.41, 129.83, 129.14, 128.87, 127.61, 126.84 (q, $^{3}J_{C-F}$=3.34Hz), 123.81 (q, $^{1}J_{C-F}$=273Hz), 121.29, 114.82, 111.36, 110.57, 109.93, 108.52, 67.31, 56.13, 32.75, 25.11, 22.51. HRMS (ESI-): m/z calc for $[M-H]^-$ = 602.1573; found 602. 1313



Supplementary Figure 1. Solubility of Zafirlukast and its analogs. Solubility of zafirlukast and its analogs at 200 μM in phosphate buffer saline at physiological pH 7.4. Dynamic light scattering measurements were taken at room temperature.



Supplementary Figure 2. Fluorescent microscopy images of HEK293T cells transiently transfected with TNFR1ΔCD-GFP (A) or TNFR2ΔCD-GFP (B) plasmids**.**



Supplementary Figure 3. Binding cpCF3 to TNFR1-PLAD. (A) ^{19}F-NMR ligand observed NMR experiments for 25 μM analog cpCF$_3$ in PBS with recombinant PLAD. PLAD was titrated into solutions of 25 μM cpCF$_3$ to give final concentrations of 0, 1.25, 2.5, 5, 10, 15, and 20 μM PLAD (concentration increases from bottom to top). Resonances were referenced to an internal TFA control. (B) Change in chemical shift plotted against PLAD concentration.