

Discovery of novel mRNA demethylase FTO inhibitors against esophageal cancer

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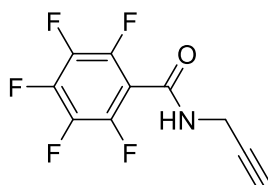
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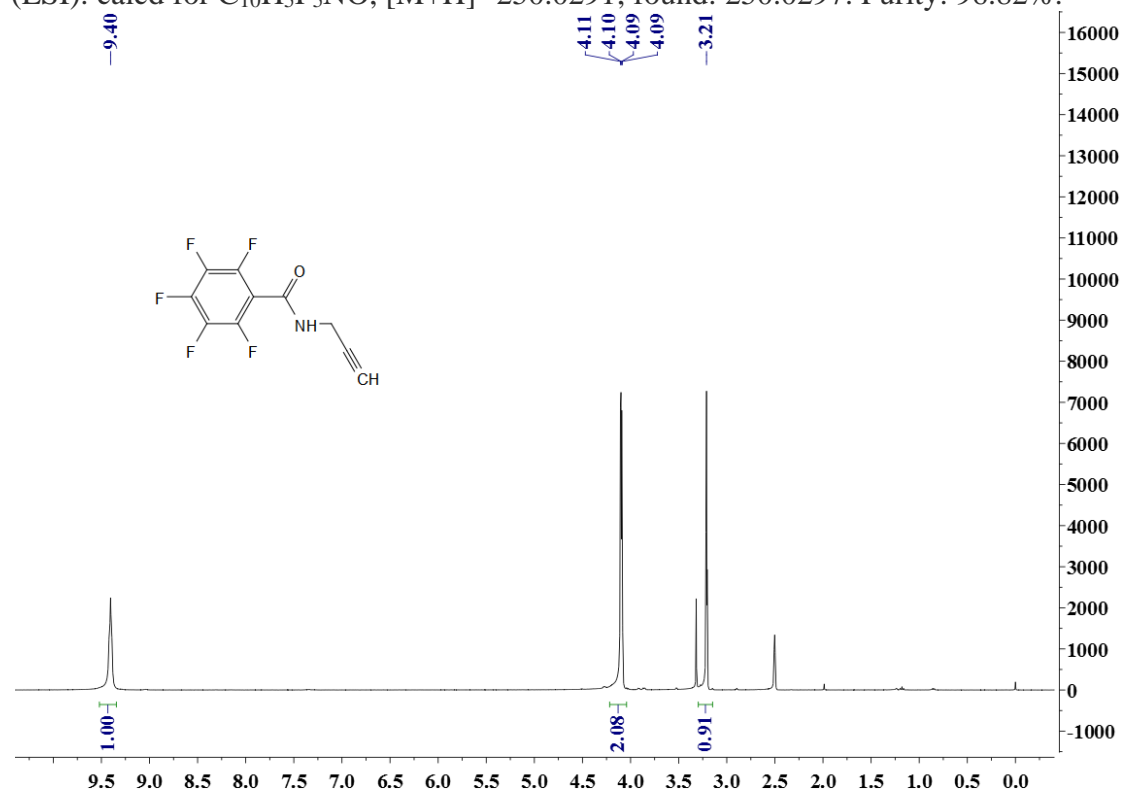
#These authors contributed equally to this work.

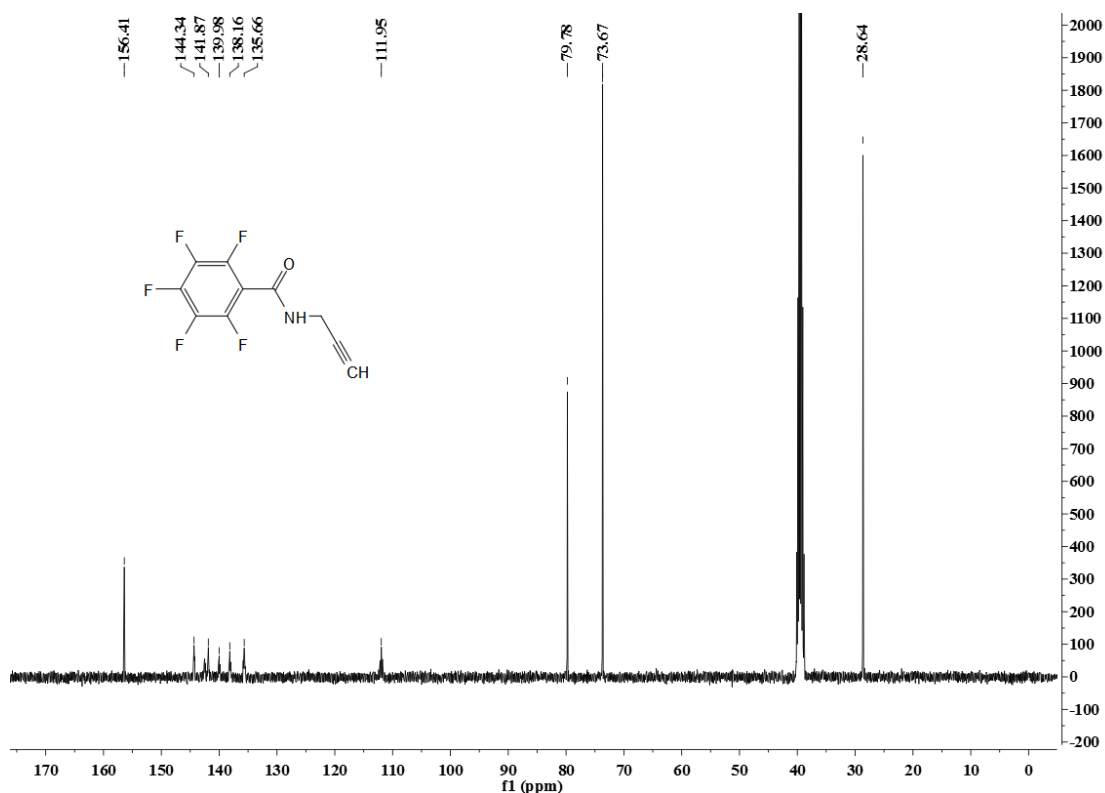
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2,3,4,5,6-Pentafluoro-N-(prop-2-yn-1-yl)benzamide (B)

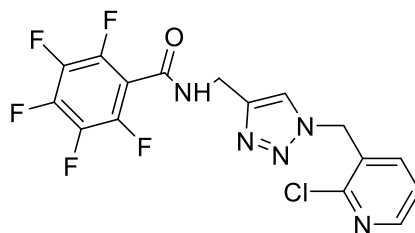


White solid, yield: 79%. Mp: 83-85 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.40 (s, 1H), 4.10 (dd, *J* = 5.5, 2.5 Hz, 2H), 3.21 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 156.41, 144.34, 141.87, 139.98, 138.16, 135.66, 111.95, 79.78, 73.67, 28.64. HR-MS (ESI): calcd for C₁₀H₅F₅NO, [M+H]⁺ 250.0291; found: 250.0297. Purity: 96.82%.

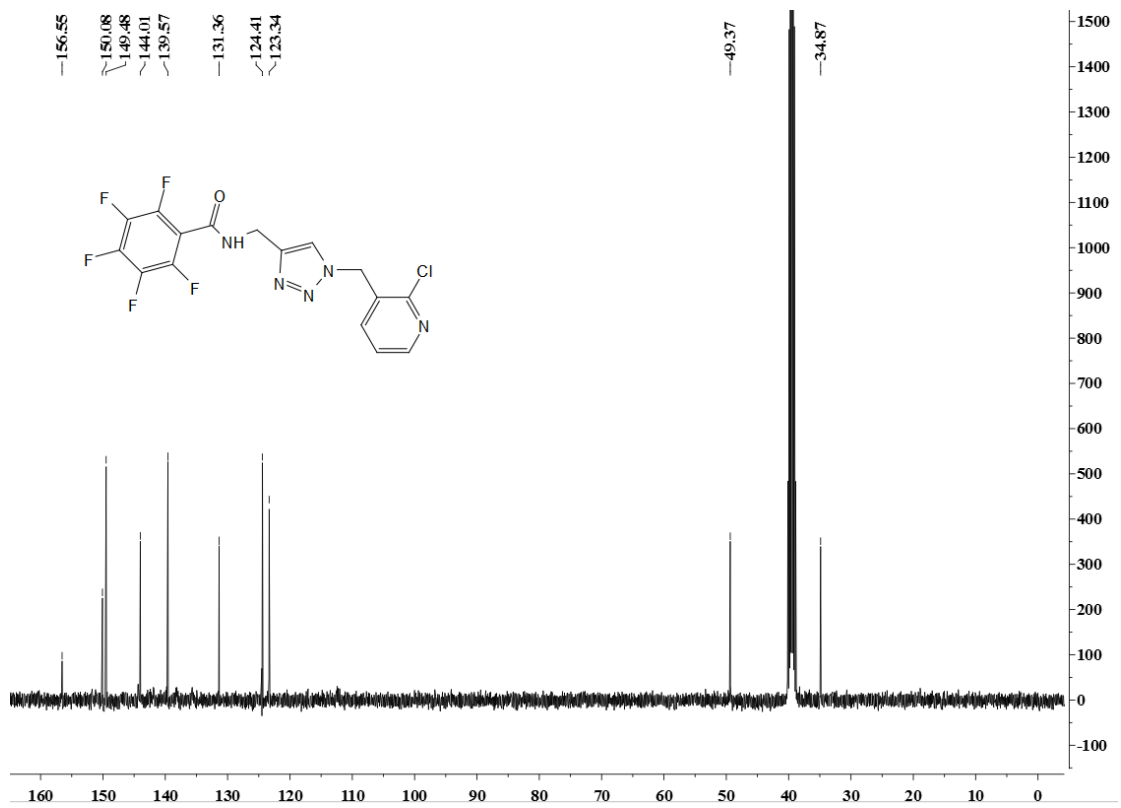
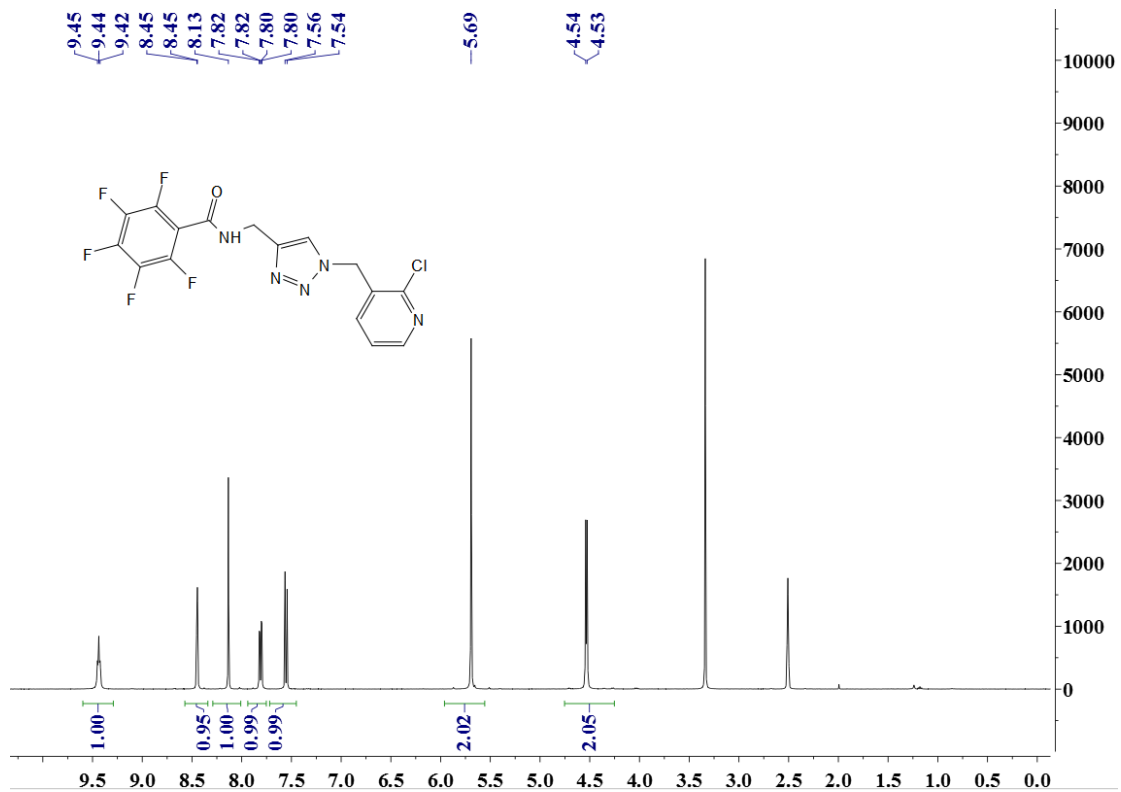




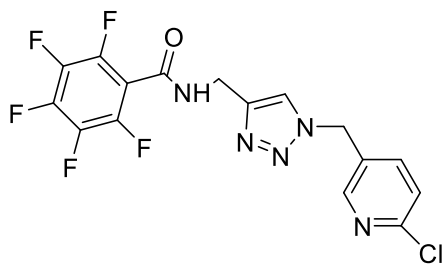
N-((1-((2-chloropyridin-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-2,3,4,5,6-pentafluorobenzamide (C1)



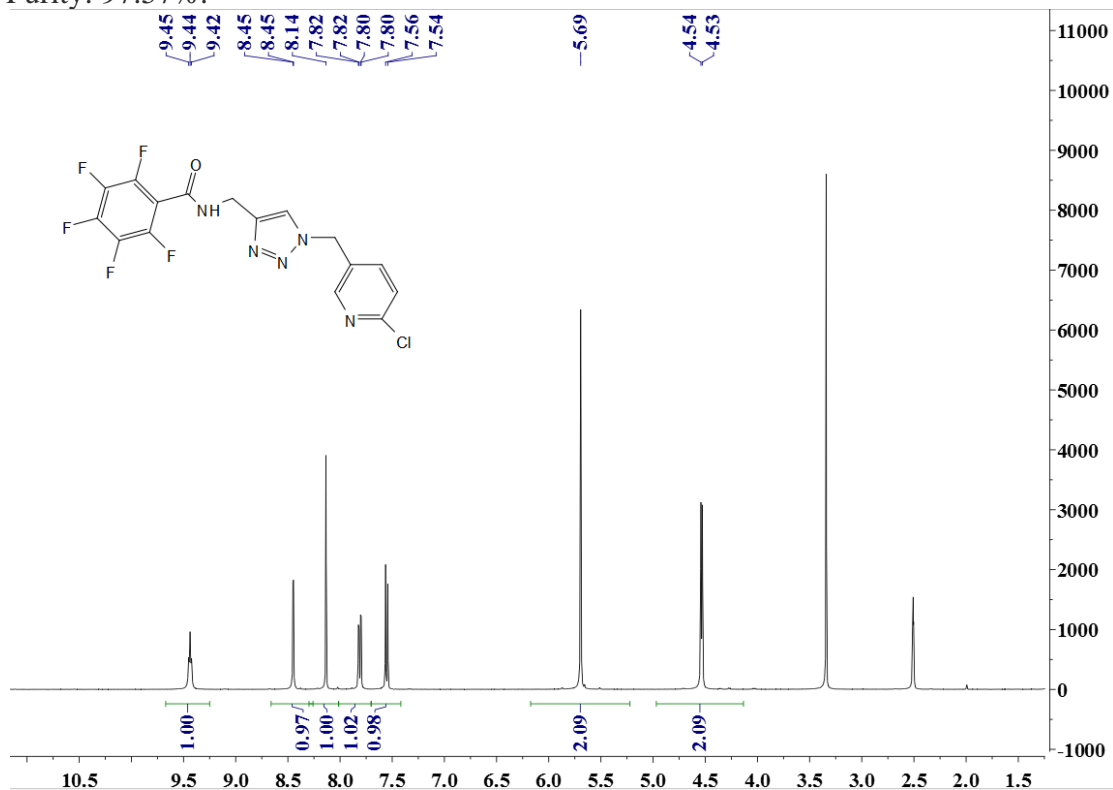
White solid, yield: 83%. Mp: 152-154 °C. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.44 (t, $J = 5.4$ Hz, 1H), 8.45 (d, $J = 2.3$ Hz, 1H), 8.13 (s, 1H), 7.81 (dd, $J = 8.3, 2.5$ Hz, 1H), 7.55 (d, $J = 8.2$ Hz, 1H), 5.69 (s, 2H), 4.53 (d, $J = 5.6$ Hz, 2H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 156.55, 150.08, 149.48, 144.01, 139.57, 131.36, 124.41, 123.34, 49.37, 34.87. HR-MS (ESI): calcd for $\text{C}_{16}\text{H}_{10}\text{ClF}_5\text{N}_5\text{O}$, $[\text{M}+\text{H}]^+$ 418.0494; found: 418.0498. Purity: 97.43%.

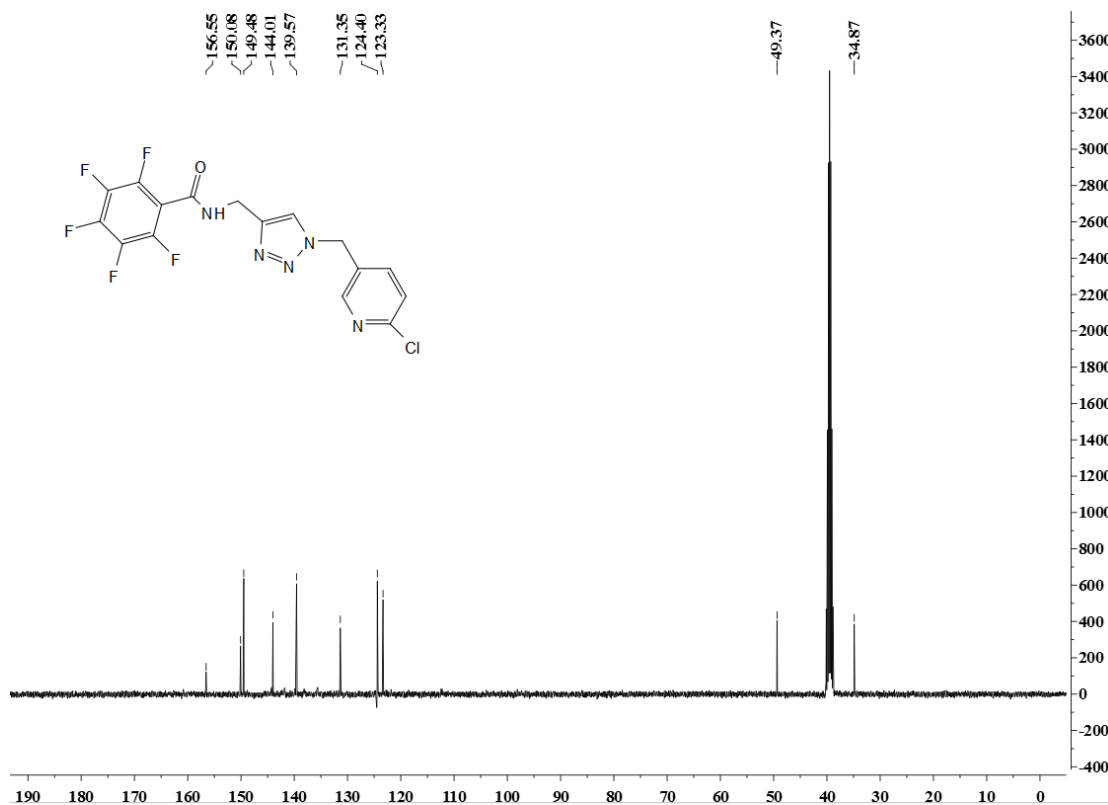


N-((1-((6-chloropyridin-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-2,3,4,5,6-pentafluorobenzamide (C2)

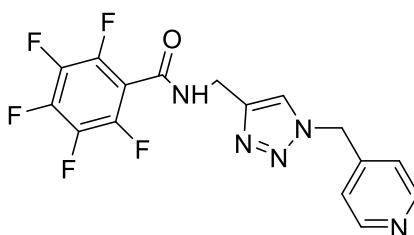


White solid, yield: 80%. Mp: 148-150 °C. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.44 (t, $J = 5.4$ Hz, 1H), 8.45 (d, $J = 2.3$ Hz, 1H), 8.14 (s, 1H), 7.81 (dd, $J = 8.3, 2.5$ Hz, 1H), 7.55 (d, $J = 8.2$ Hz, 1H), 5.69 (s, 2H), 4.53 (d, $J = 5.6$ Hz, 2H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 156.55, 150.08, 149.48, 144.01, 139.57, 131.35, 124.40, 123.33, 49.37, 34.87. HR-MS (ESI): calcd for $\text{C}_{16}\text{H}_{10}\text{ClF}_5\text{N}_5\text{O}$, $[\text{M}+\text{H}]^+$ 418.0494; found: 418.0498. Purity: 97.57%.

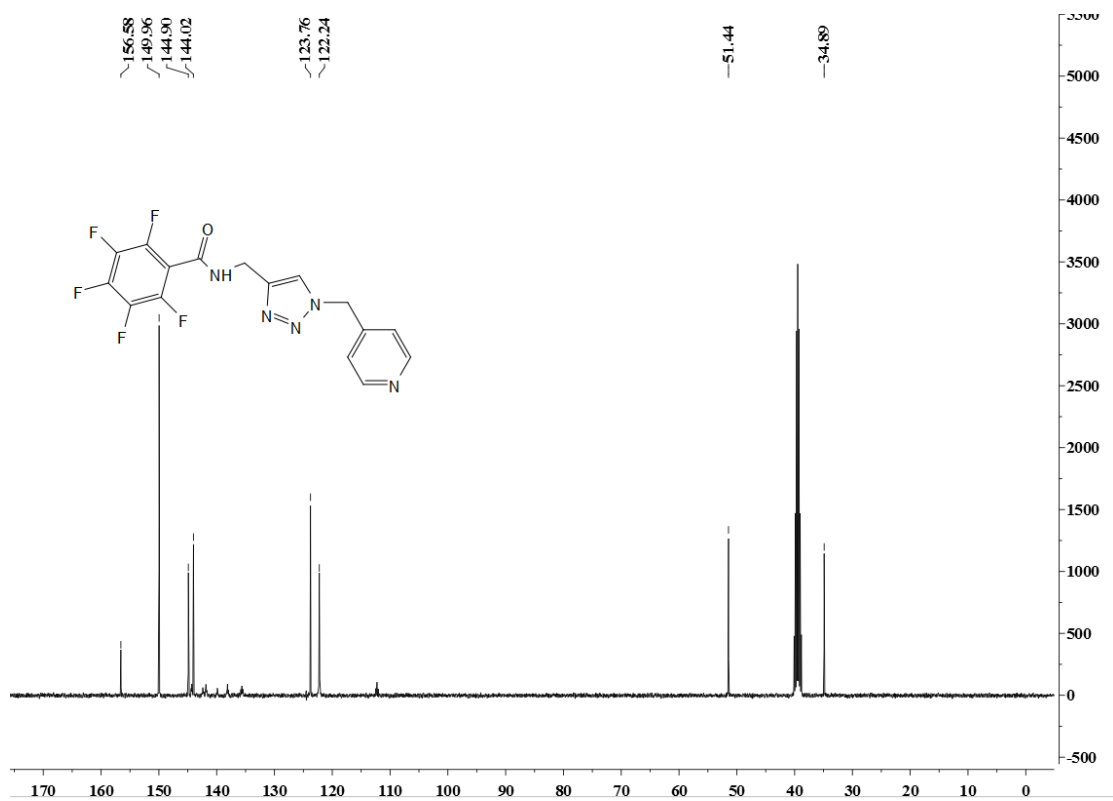
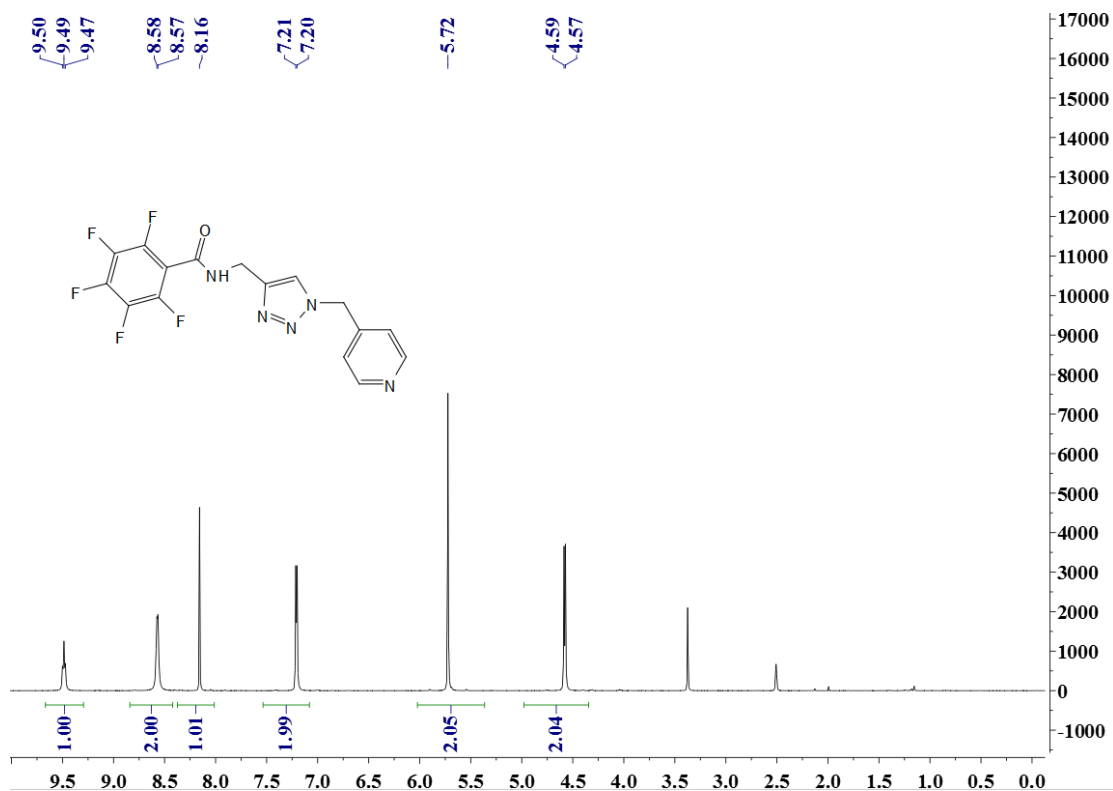




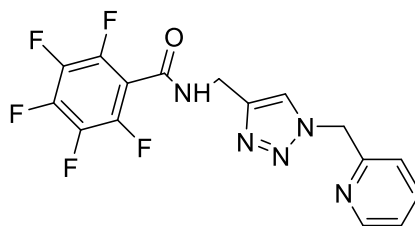
2,3,4,5,6-pentafluoro-N-((1-(pyridin-4-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)benzamide (C3)



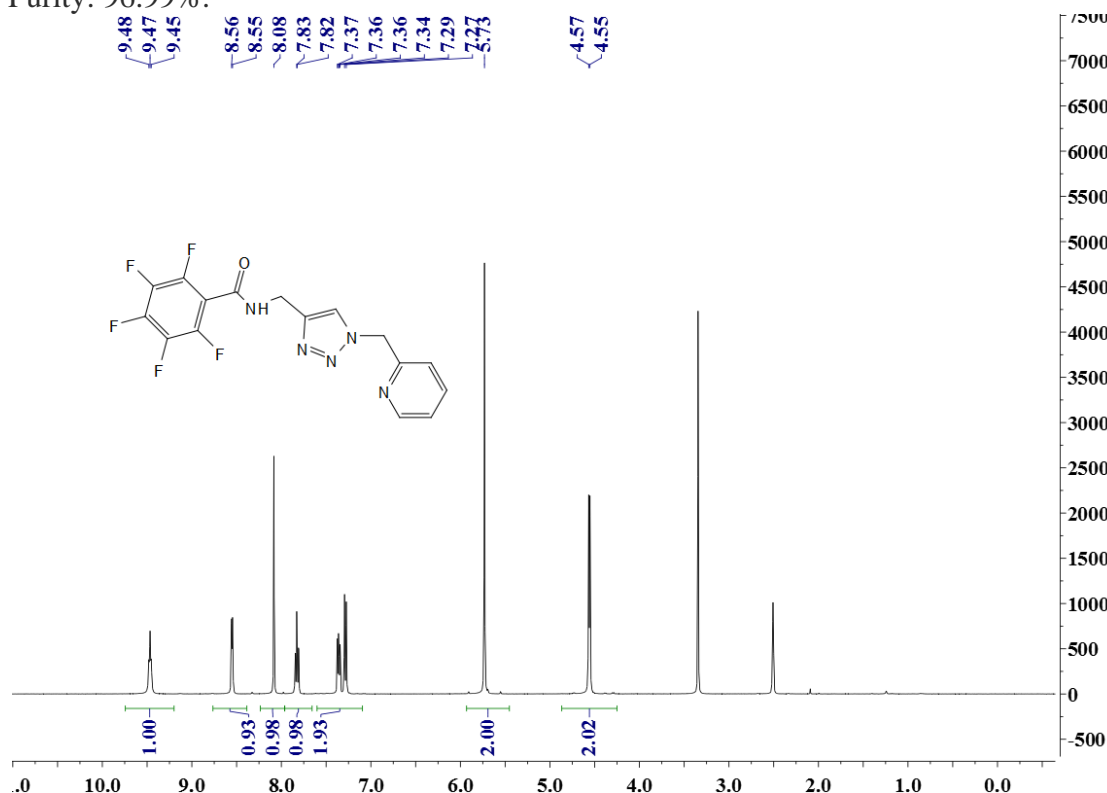
White solid, yield: 72%. Mp: 108-110 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.49 (t, *J* = 5.4 Hz, 1H), 8.57 (d, *J* = 3.8 Hz, 2H), 8.16 (s, 1H), 7.21 (d, *J* = 5.6 Hz, 2H), 5.72 (s, 2H), 4.58 (d, *J* = 5.6 Hz, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 156.58, 149.96, 144.90, 144.02, 123.76, 122.24, 51.44, 34.89. HR-MS (ESI): calcd for C₁₆H₁₁F₅N₅O, [M+H]⁺ 384.0884; found: 384.0889. Purity: 98.06%.

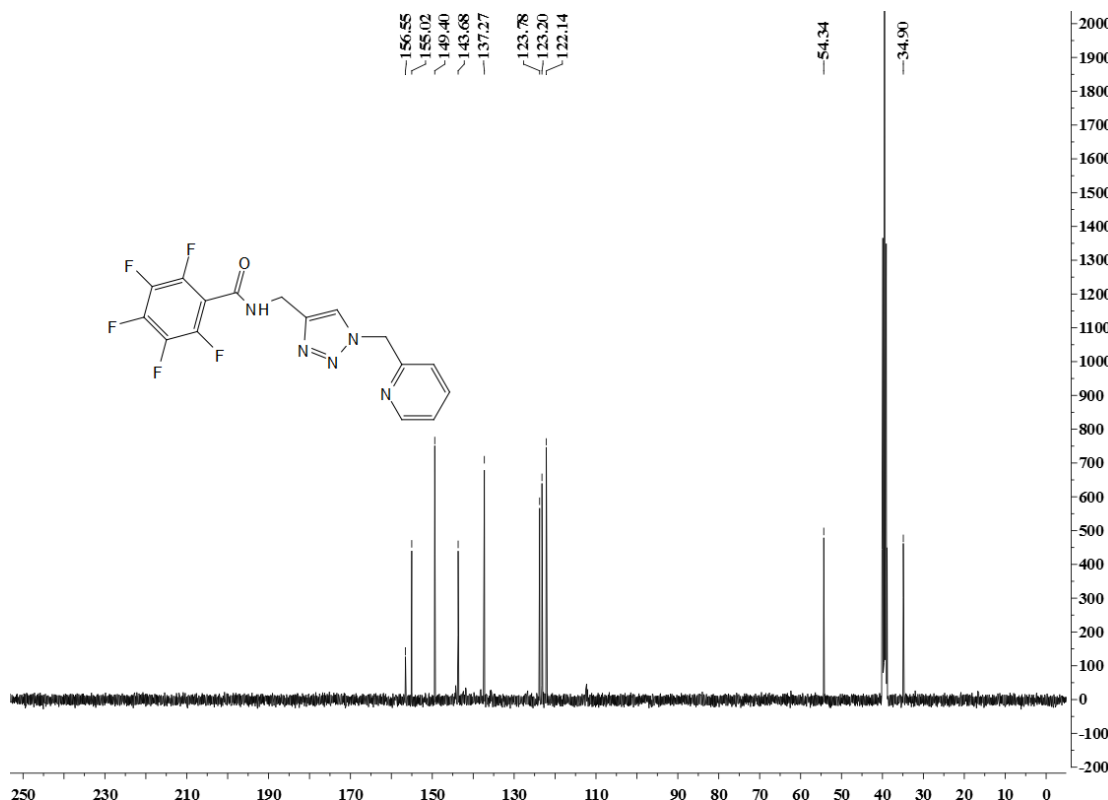


2,3,4,5,6-pentafluoro-N-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)benzamide (C4)

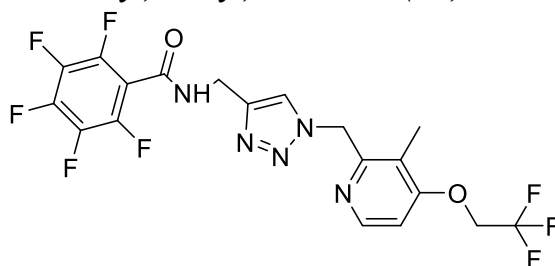


White solid, yield: 88%. Mp: 149-151 °C. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.47 (t, $J = 5.3$ Hz, 1H), 8.55 (d, $J = 4.2$ Hz, 1H), 8.08 (s, 1H), 7.83 (td, $J = 7.7, 1.7$ Hz, 1H), 7.60 – 7.09 (m, 2H), 5.73 (s, 2H), 4.56 (d, $J = 5.6$ Hz, 2H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 156.55, 155.02, 149.40, 143.68, 137.27, 123.78, 123.20, 122.14, 54.34, 34.90. HR-MS (ESI): calcd for $\text{C}_{16}\text{H}_{11}\text{F}_5\text{N}_5\text{O}$, $[\text{M}+\text{H}]^+$ 384.0884; found: 384.0887. Purity: 96.99%.

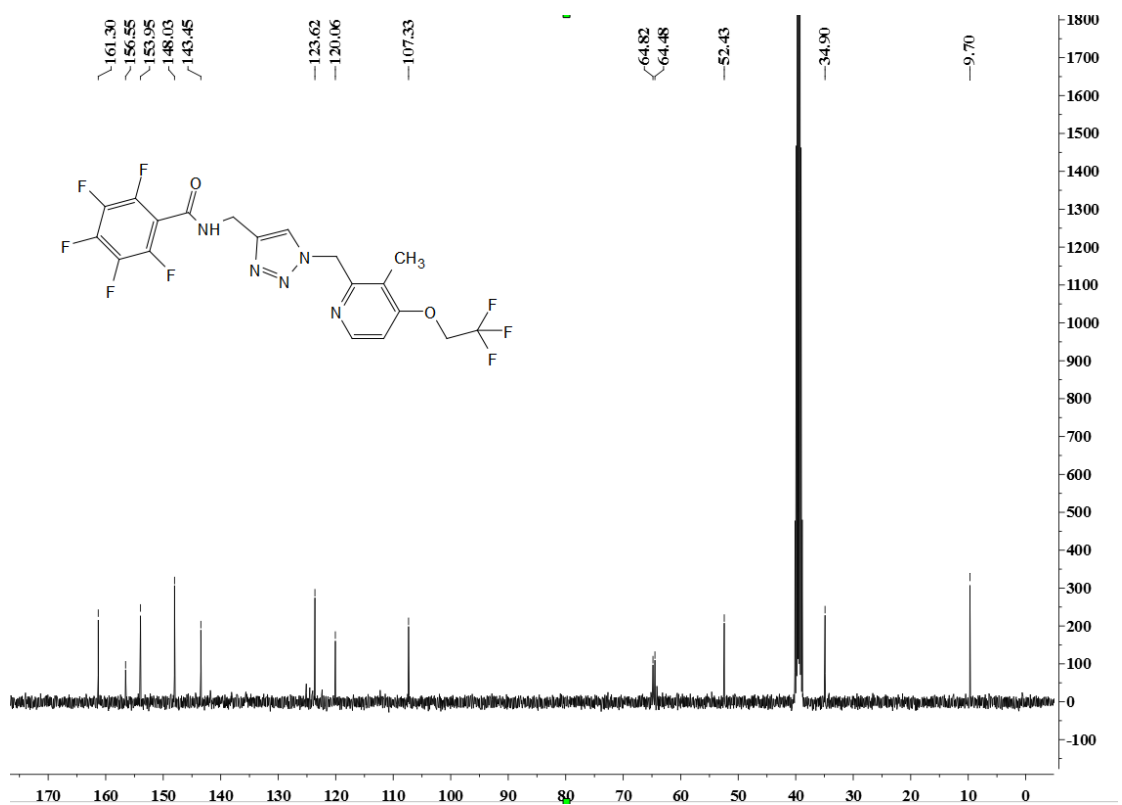
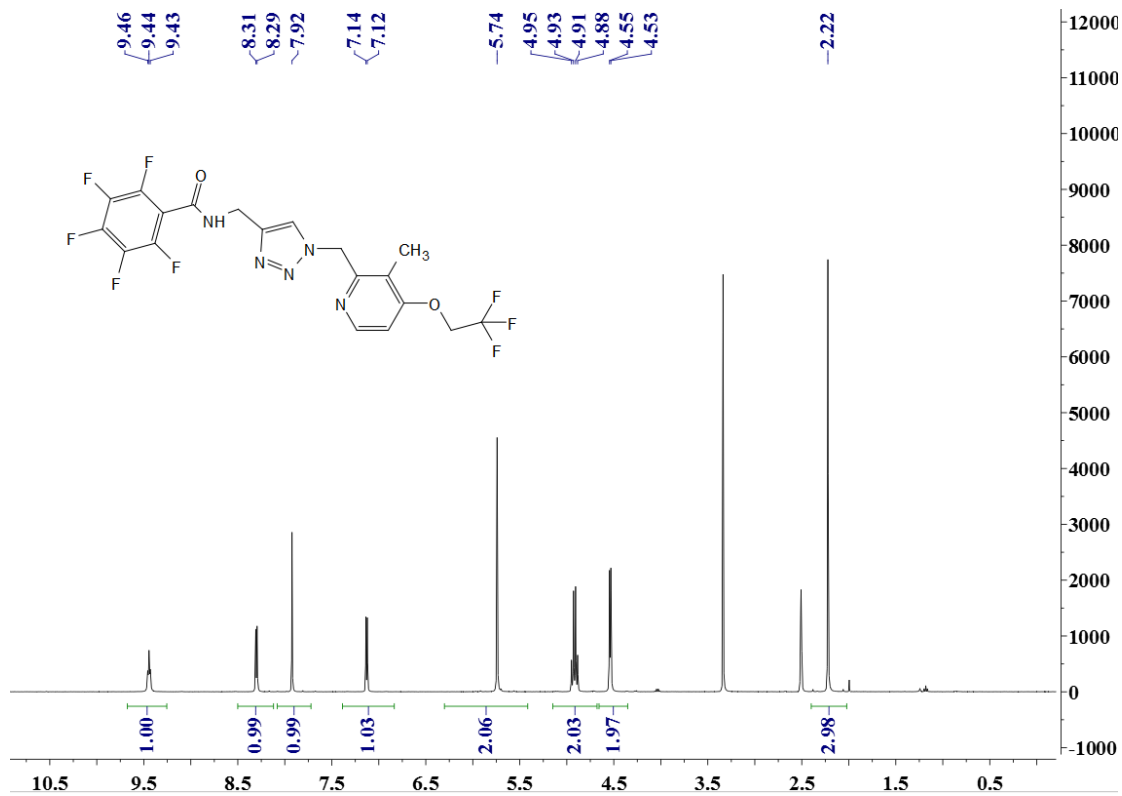




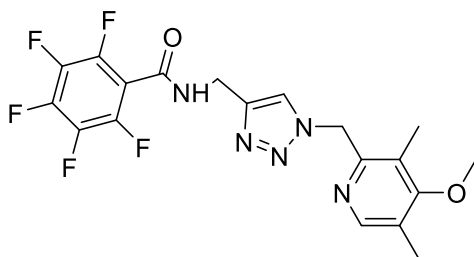
2,3,4,5,6-pentafluoro-N-((1-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)-1,2,3-triazol-4-yl)methyl)benzamide (C5)



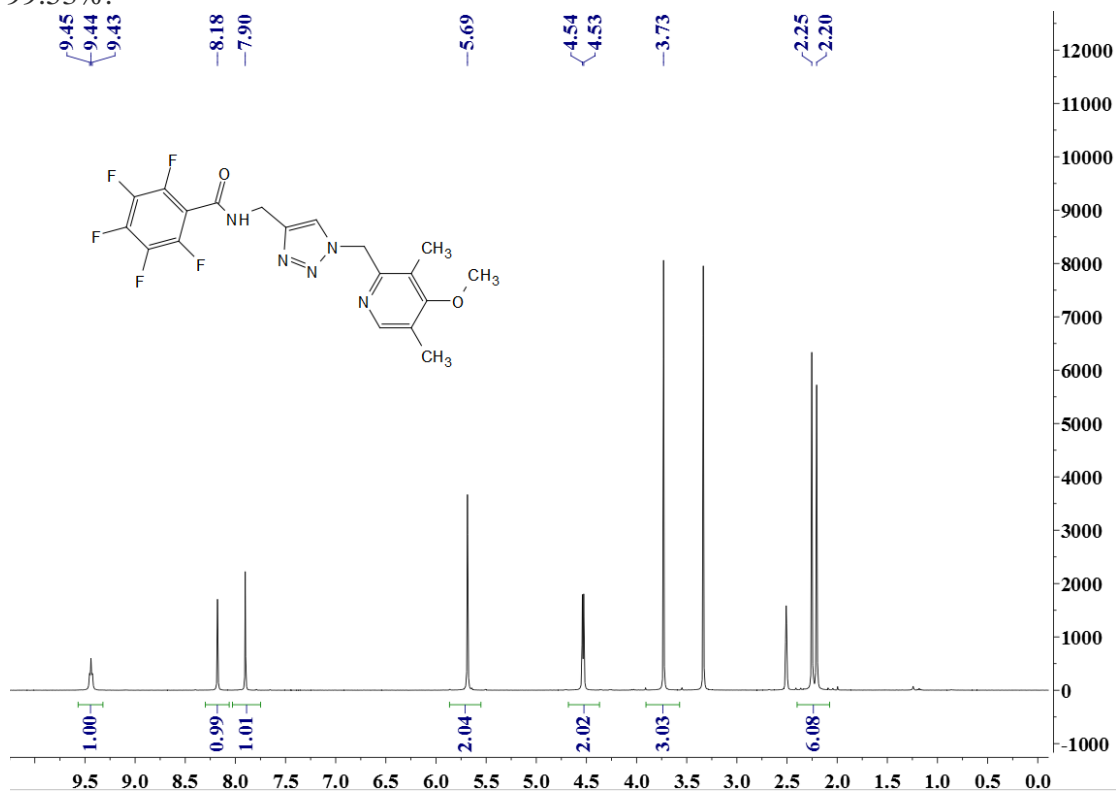
White solid, yield: 69%. Mp: 156-158 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.44 (t, *J* = 5.5 Hz, 1H), 8.30 (d, *J* = 5.6 Hz, 1H), 7.92 (s, 1H), 7.13 (d, *J* = 5.7 Hz, 1H), 5.74 (s, 2H), 4.92 (q, *J* = 8.7 Hz, 2H), 4.54 (d, *J* = 5.6 Hz, 2H), 2.22 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 161.30, 156.55, 153.95, 148.03, 143.45, 123.62, 120.06, 107.33, 64.82, 64.48, 52.43, 34.90, 9.70. HR-MS (ESI): calcd for C₁₉H₁₄F₈N₅O₂, [M+H]⁺ 496.1020; found: 496.1025. Purity: 97.43%.

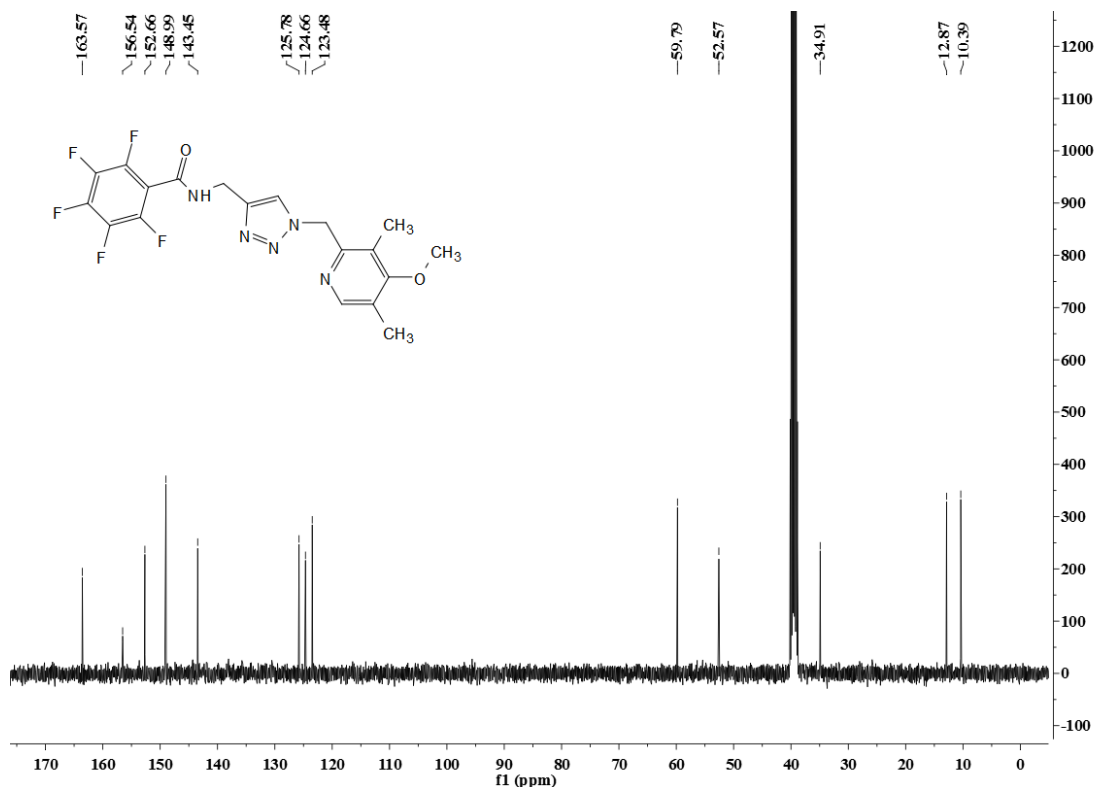


2,3,4,5,6-pentafluoro-N-((1-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)benzamide (C6)

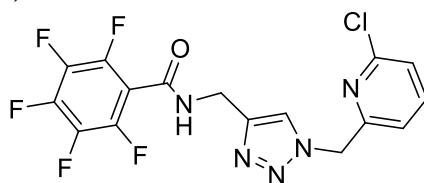


White solid, yield: 62%. Mp: 135-137 °C. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.44 (t, $J = 5.3$ Hz, 1H), 8.18 (s, 1H), 7.90 (s, 1H), 5.69 (s, 2H), 4.53 (d, $J = 5.6$ Hz, 2H), 3.73 (s, 3H), 2.23 (d, $J = 19.3$ Hz, 6H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 163.57, 156.54, 152.66, 148.99, 143.45, 125.78, 124.66, 123.48, 59.79, 52.57, 34.91, 12.87, 10.39. HR-MS (ESI): calcd for $\text{C}_{19}\text{H}_{17}\text{F}_5\text{N}_5\text{O}_2$, $[\text{M}+\text{H}]^+$ 442.1302; found: 442.1307. Purity: 99.53%.

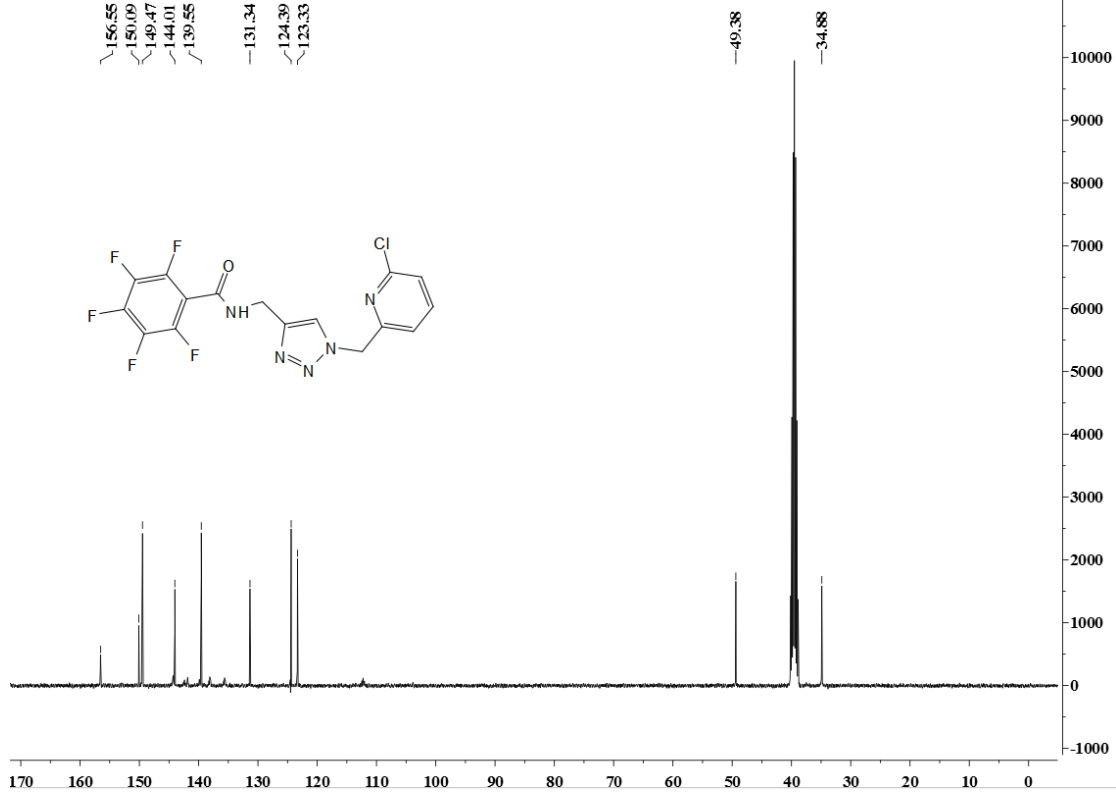
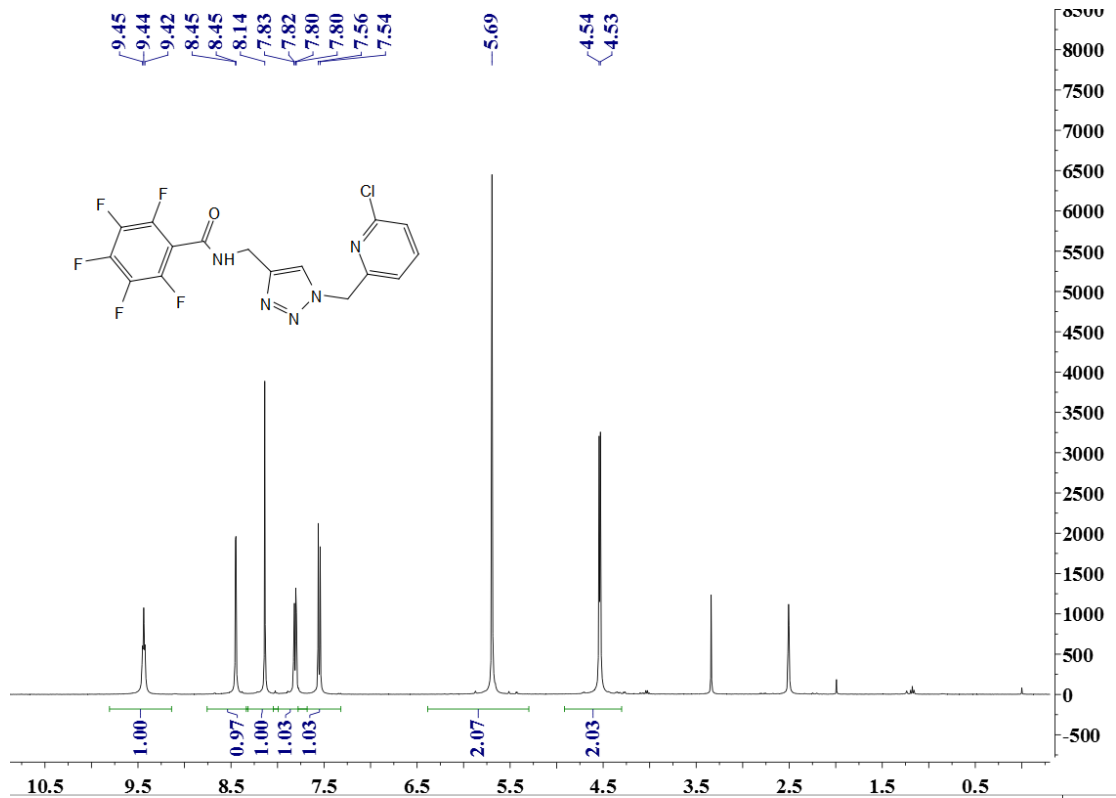




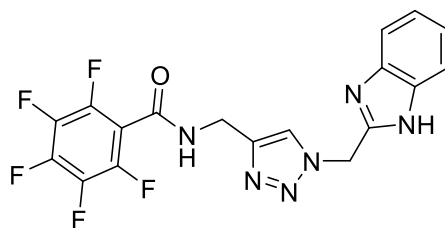
***N*-((1-((6-chloropyridin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-2,3,4,5,6-pentafluorobenzamide (C7)**



White solid, yield: 88%. Mp: 148-150 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.44 (t, *J* = 5.3 Hz, 1H), 8.45 (d, *J* = 2.3 Hz, 1H), 8.14 (s, 1H), 7.81 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 5.69 (s, 2H), 4.54 (d, *J* = 5.5 Hz, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 156.55, 150.09, 149.47, 144.01, 139.55, 131.34, 124.39, 123.33, 49.38, 34.88. HR-MS (ESI): calcd for C₁₆H₁₀ClF₅N₅O, [M+H]⁺ 418.0494; found: 418.0497. Purity: 98.24%.



N-((1-((1H-benzod[j]imidazol-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-2,3,4,5,6-pentafluorobenzamide (C8)



White solid, yield: 73%. Mp: 232-234 °C. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 12.68 (s, 1H), 9.46 (t, $J = 5.4$ Hz, 1H), 8.13 (s, 1H), 7.55 (dd, $J = 35.7, 7.6$ Hz, 2H), 7.34 – 6.97 (m, 2H), 5.88 (s, 2H), 4.57 (d, $J = 5.6$ Hz, 2H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 156.59, 148.24, 143.84, 123.66, 47.24, 34.89. HR-MS (ESI): calcd for $\text{C}_{18}\text{H}_{12}\text{F}_5\text{N}_6\text{O}$, $[\text{M}+\text{H}]^+$ 423.0993; found: 423.0998. Purity: 98.15%.

