

# Design and antiproliferative evaluation of novel sulfanilamide derivatives as potential tubulin polymerization inhibitors

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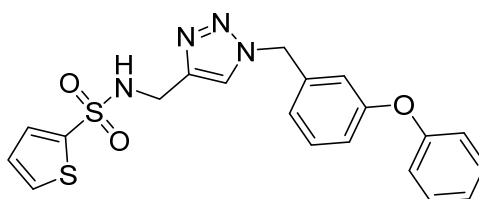
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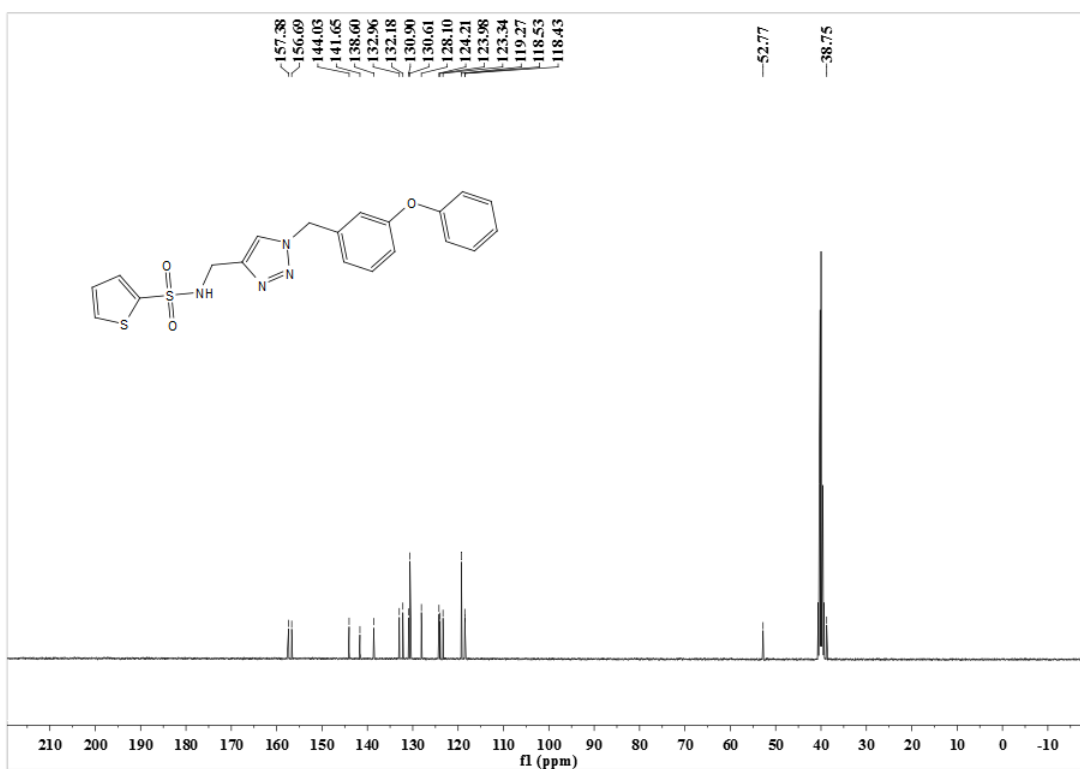
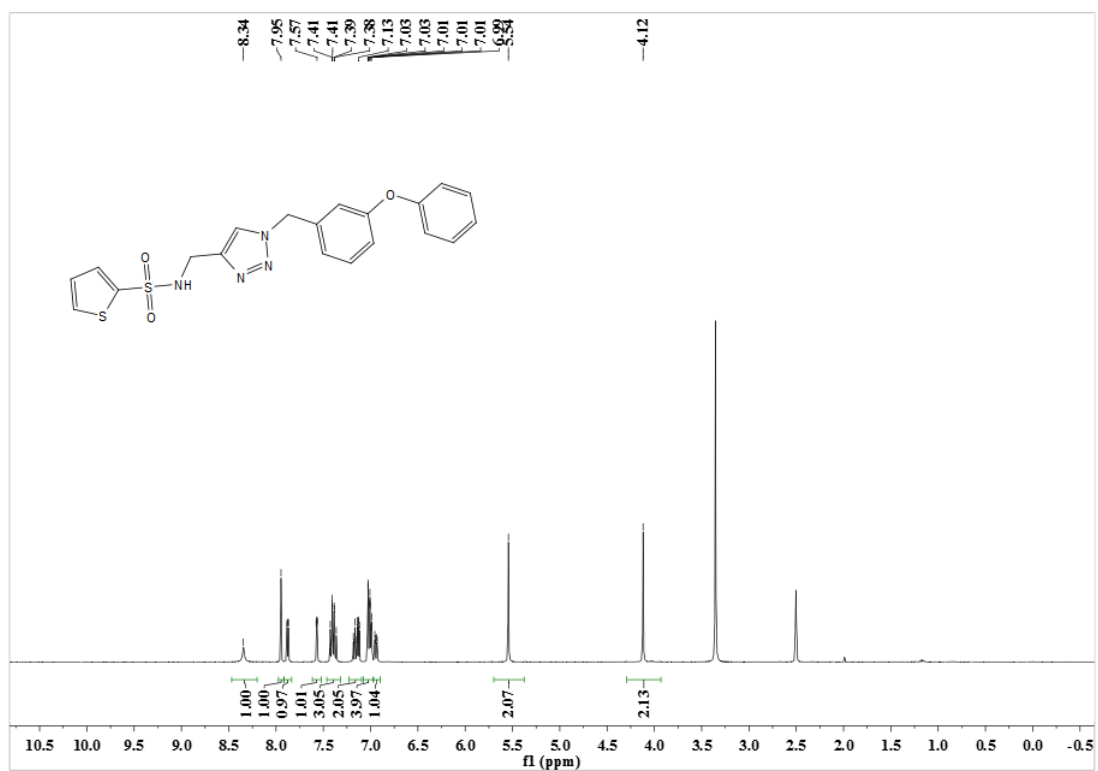
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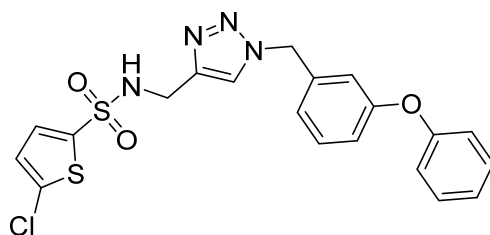
N-((1-(3-phenoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)thiophene-2-sulfonamide (11a)



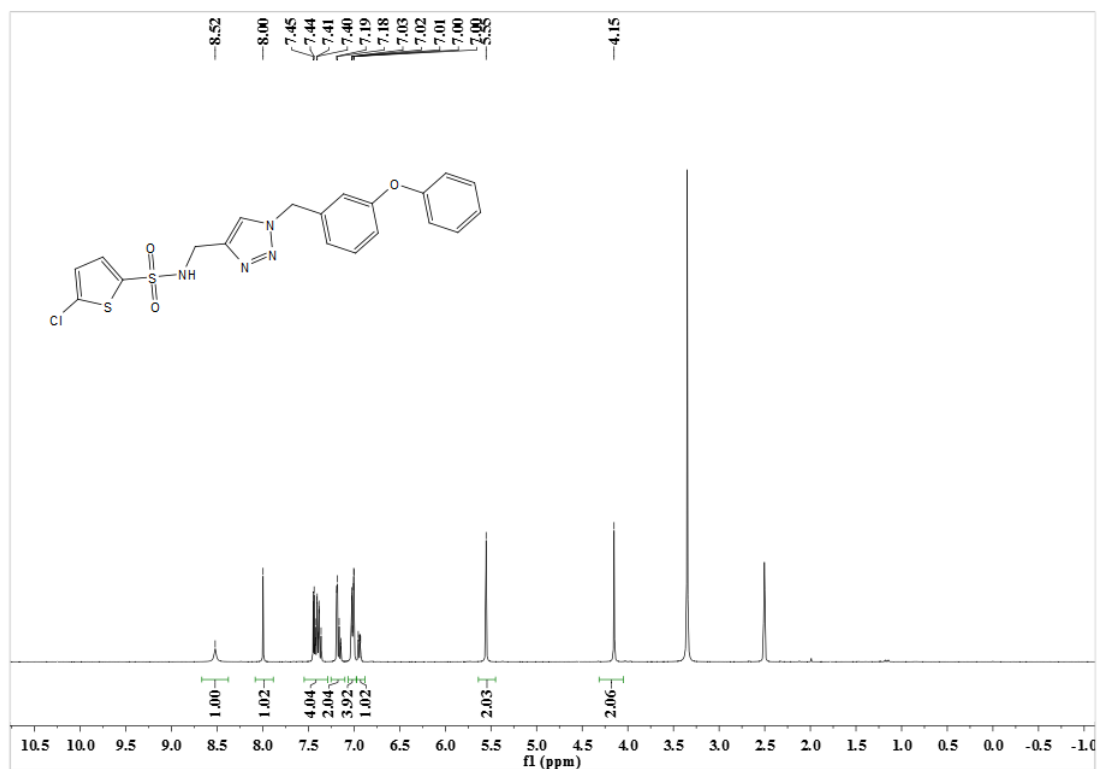
White solid, yield: 60.1%, mp: 104-106°C. <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  8.34 (s, 1H, NH), 7.95 (s, 1H, Ar), 7.88 (dd,  $J = 5.0, 1.3$  Hz, 1H, Ar), 7.57 (dd,  $J = 3.7, 1.3$  Hz, 1H, Ar), 7.40 (tt,  $J = 9.4, 5.1$  Hz, 3H, Ar), 7.15 (ddd,  $J = 11.0, 6.2, 2.3$  Hz, 2H, Ar), 7.08 – 6.97 (m, 4H, Ar), 6.94 (dd,  $J = 8.1, 1.8$  Hz, 1H, Ar), 5.54 (s, 2H, PhCH<sub>2</sub>), 4.12 (s, 2H, NHCH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO)  $\delta$  157.38, 156.69, 144.03, 141.65, 138.60, 132.96, 132.18, 130.90, 130.61, 128.10, 124.21, 123.98, 123.34, 119.27, 118.53, 118.43 (Ar), 52.77 (PhCH<sub>2</sub>), 38.75 (NHCH<sub>2</sub>). HRMS (ESI) calcd for C<sub>20</sub>H<sub>19</sub>N<sub>4</sub>O<sub>3</sub>S<sub>2</sub> [M+H]<sup>+</sup>: 427.0898, found: 427.0899. IR: 3176, 3100, 1489, 1331, 1253, 1215, 1151, 750, 688, 593, 529 cm<sup>-1</sup>.

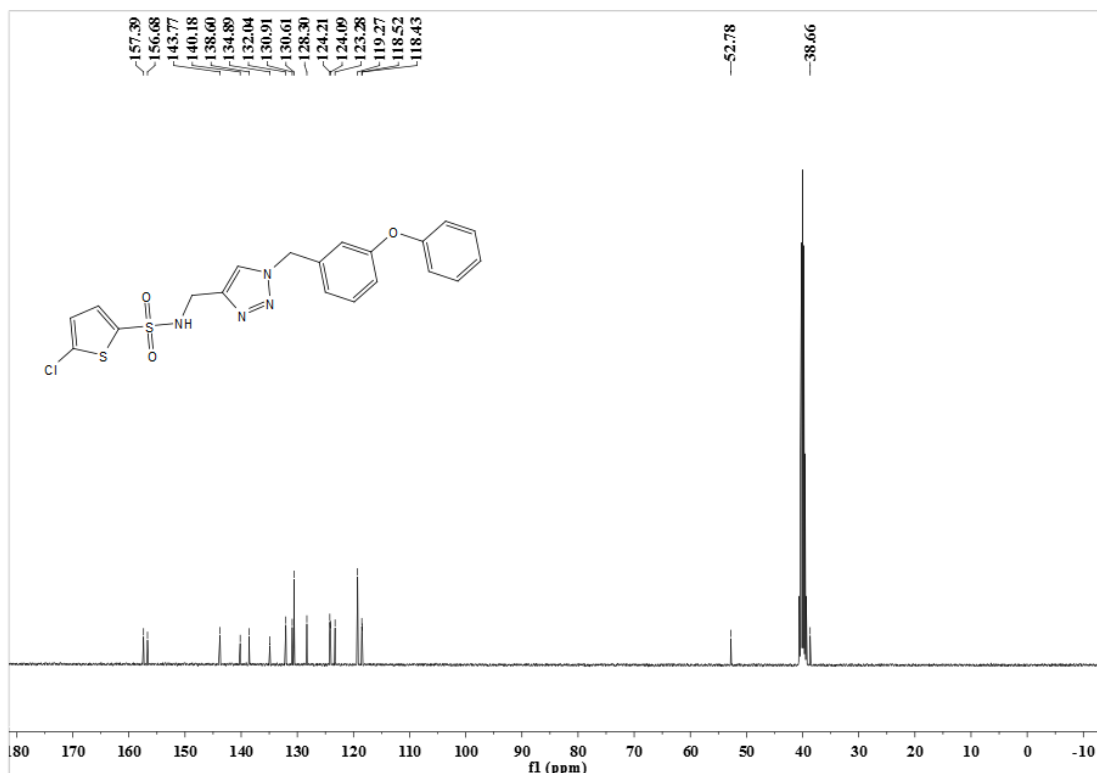


5-chloro-N-((1-(3-phenoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)thiophene-2-sulfonamide (11b)

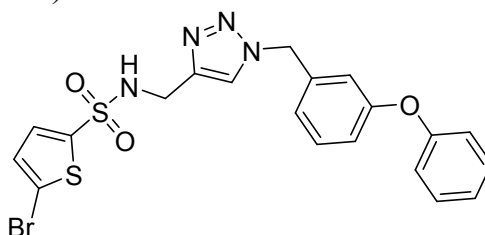


White solid, yield: 68.3%, mp: 110-111°C.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.52 (s, 1H, NH), 8.00 (s, 1H, Ar), 7.55 – 7.29 (m, 4H, Ar), 7.25 – 7.10 (m, 2H, Ar), 7.07 – 6.97 (m, 4H, Ar), 6.98 – 6.88 (m, 1H, Ar), 5.55 (s, 2H,  $\text{PhCH}_2$ ), 4.15 (s, 2H,  $\text{NHCH}_2$ ).  $^{13}\text{C}$  NMR (100 MHz, DMSO)  $\delta$  157.39, 156.68, 143.77, 140.18, 138.60, 134.89, 132.04, 130.91, 130.61, 128.30, 124.21, 124.09, 123.28, 119.27, 118.52, 118.43 (Ar), 52.78 ( $\text{PhCH}_2$ ), 38.66 ( $\text{NHCH}_2$ ). HRMS (ESI) calcd for  $\text{C}_{20}\text{H}_{18}\text{ClN}_4\text{O}_3\text{S}_2$   $[\text{M}+\text{H}]^+$ : 461.0512, found: 461.0509. IR: 3120, 1488, 1412, 1328, 1252, 1159, 786, 685, 612, 523  $\text{cm}^{-1}$ .

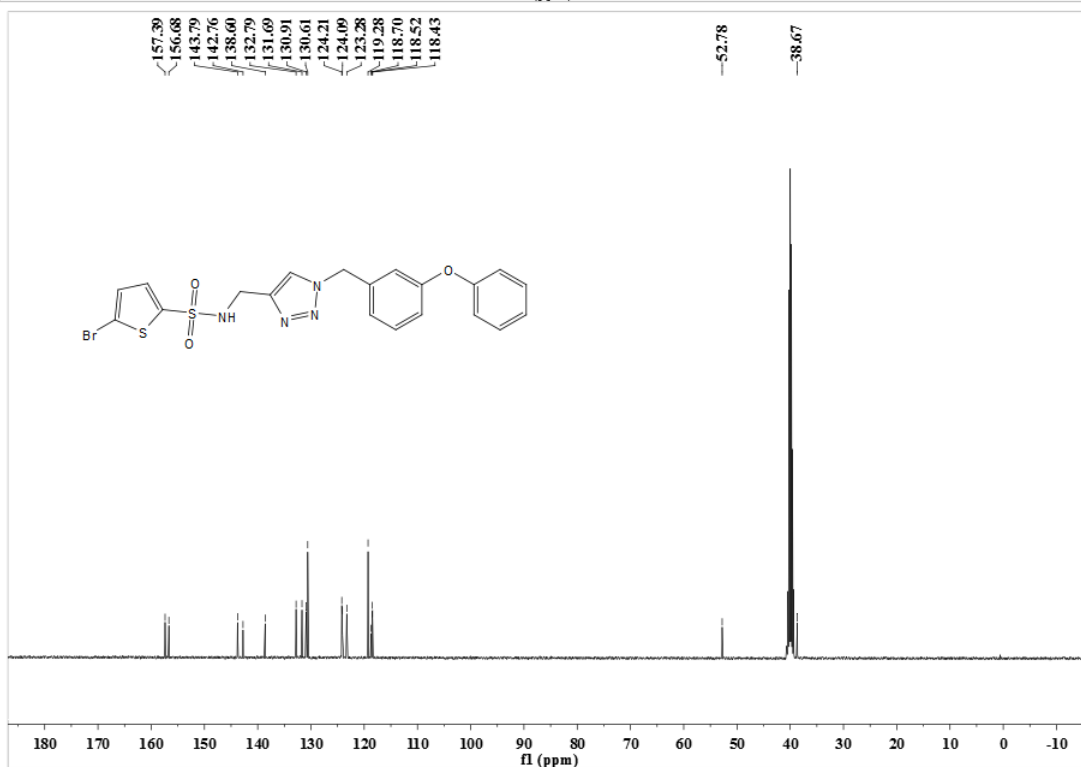
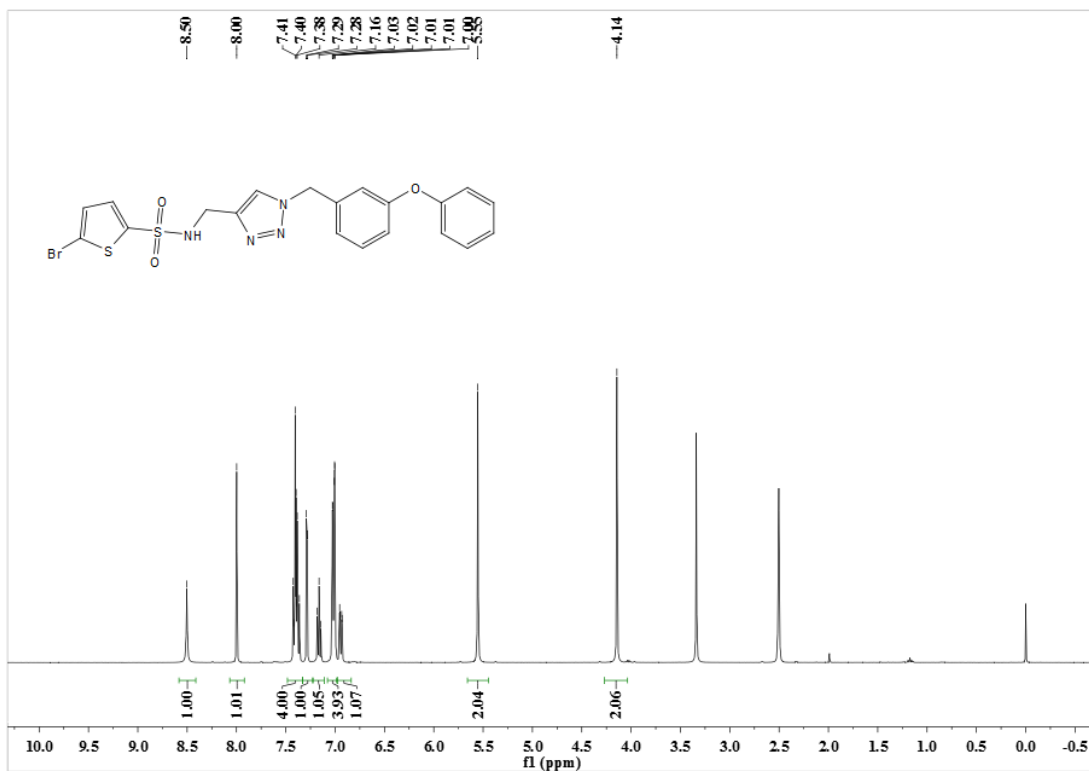




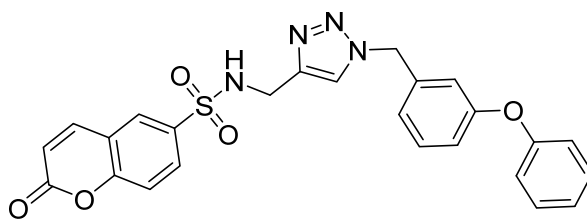
5-bromo-N-((1-(3-phenoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)thiophene-2-sulfonamide (11c)



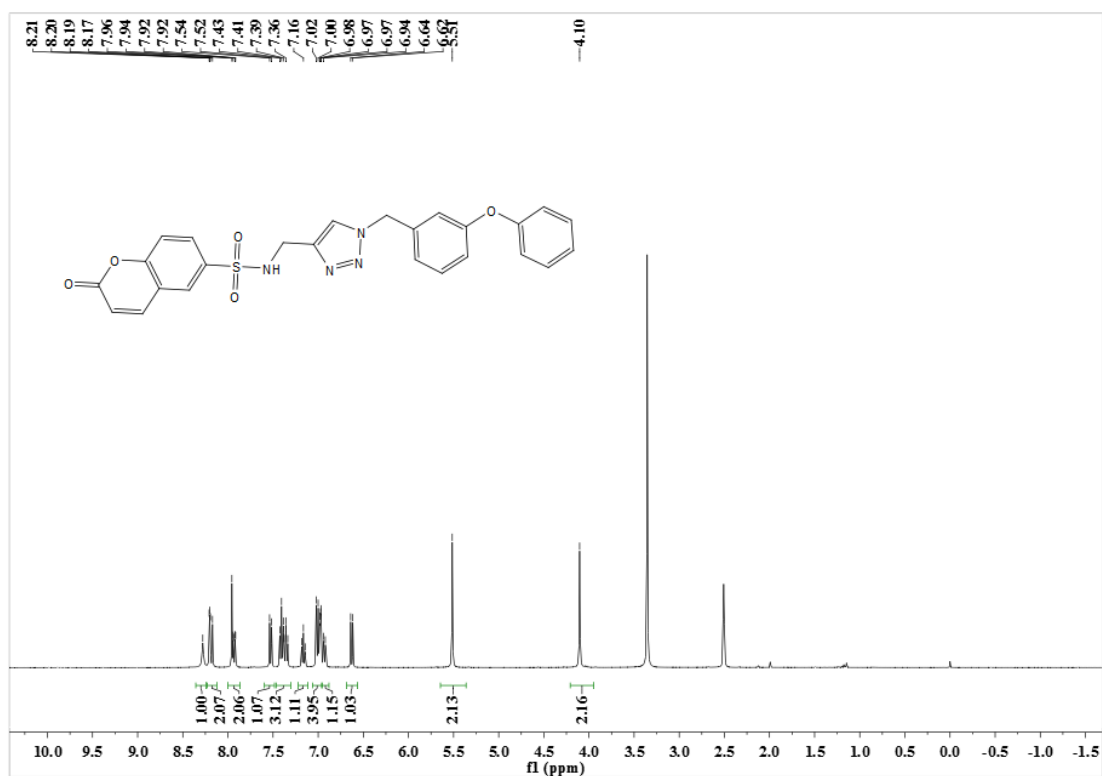
White solid, yield: 59.1%, mp: 111-112°C. <sup>1</sup>H NMR (400 MHz, DMSO) δ 8.50 (s, 1H, NH), 8.00 (s, 1H, Ar), 7.48 – 7.33 (m, 4H, Ar), 7.29 (d, *J* = 4.0 Hz, 1H, Ar), 7.16 (t, *J* = 7.4 Hz, 1H, Ar), 7.08 – 6.98 (m, 4H, Ar), 6.94 (dd, *J* = 8.1, 1.8 Hz, 1H, Ar), 5.55 (s, 2H, PhCH<sub>2</sub>), 4.14 (s, 2H, NHCH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO) δ 157.39, 156.68, 143.79, 142.76, 138.60, 132.79, 131.69, 130.91, 130.61, 124.21, 124.09, 123.28, 119.28, 118.70, 118.52, 118.43 (Ar), 52.78 (PhCH<sub>2</sub>), 38.67 (NHCH<sub>2</sub>). HRMS (ESI) calcd for C<sub>20</sub>H<sub>18</sub>BrN<sub>4</sub>O<sub>3</sub>S<sub>2</sub> [M+H]<sup>+</sup>: 505.0007, found: 505.0004. IR: 3118, 1489, 1403, 1328, 1253, 1158, 1086, 819, 786, 749, 605, 522 cm<sup>-1</sup>.

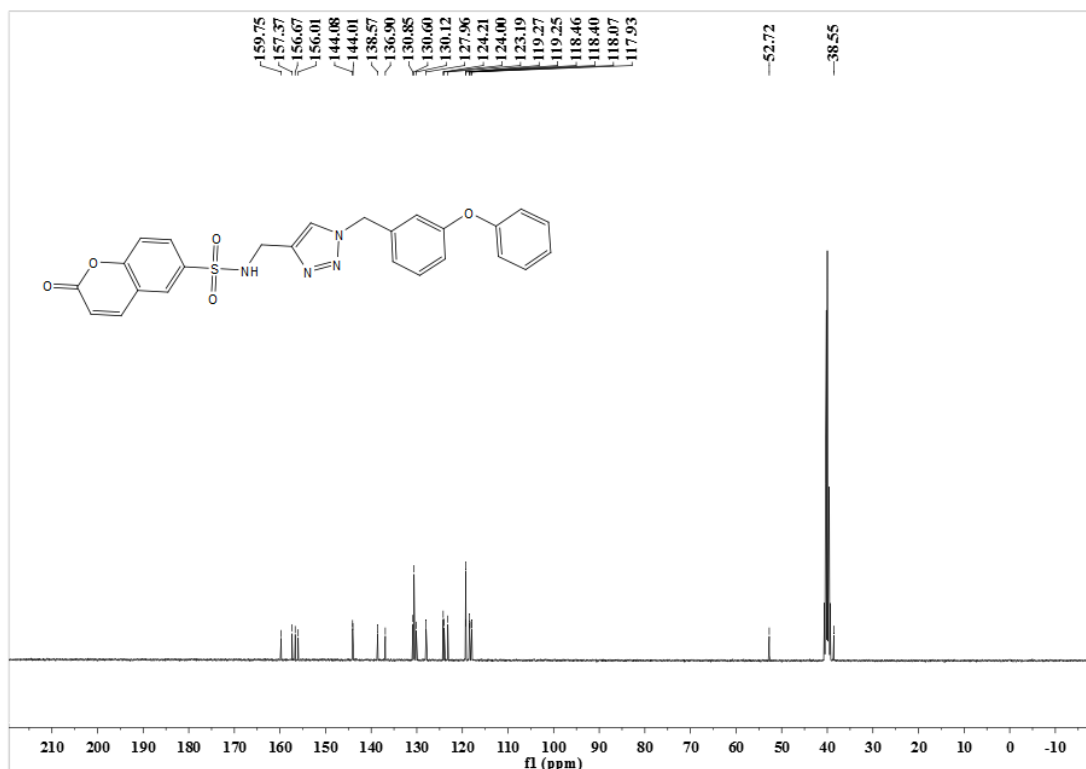


2-oxo-N-((1-(3-phenoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-chromene-6-sulfonamide (11d)

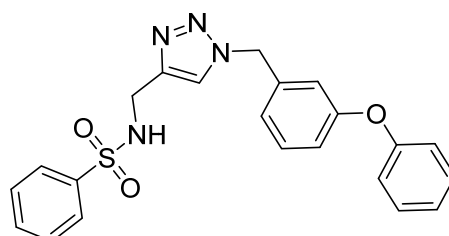


White solid, yield: 61.9%, mp: 144-146°C.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.28 (s, 1H, NH), 8.19 (dd,  $J = 9.1, 5.9$  Hz, 2H, Ar), 8.00 – 7.87 (m, 2H, Ar), 7.53 (d,  $J = 8.7$  Hz, 1H, Ar), 7.38 (dt,  $J = 16.3, 7.9$  Hz, 3H, Ar), 7.16 (t,  $J = 7.4$  Hz, 1H, Ar), 7.06 – 6.96 (m, 4H, Ar), 6.93 (d,  $J = 8.2$  Hz, 1H, Ar), 6.63 (d,  $J = 9.6$  Hz, 1H, Ar), 5.51 (s, 2H,  $\text{PhCH}_2$ ), 4.10 (s, 2H,  $\text{NHCH}_2$ ).  $^{13}\text{C}$  NMR (100 MHz, DMSO)  $\delta$  159.75, 157.37, 156.67, 156.01, 144.08, 144.01, 138.57, 136.90, 130.85, 130.60, 130.12, 127.96, 124.21, 124.00, 123.19, 119.27, 119.25, 118.46, 118.40, 118.07, 117.93 (Ar), 52.72 ( $\text{PhCH}_2$ ), 38.55 ( $\text{NHCH}_2$ ). HRMS (ESI) calcd for  $\text{C}_{25}\text{H}_{21}\text{N}_4\text{O}_5\text{S}$   $[\text{M}+\text{H}]^+$ : 489.1237, found: 489.1233. IR: 3256, 3137, 1744, 1488, 1321, 1252, 1157, 1107, 834, 751, 601  $\text{cm}^{-1}$ .

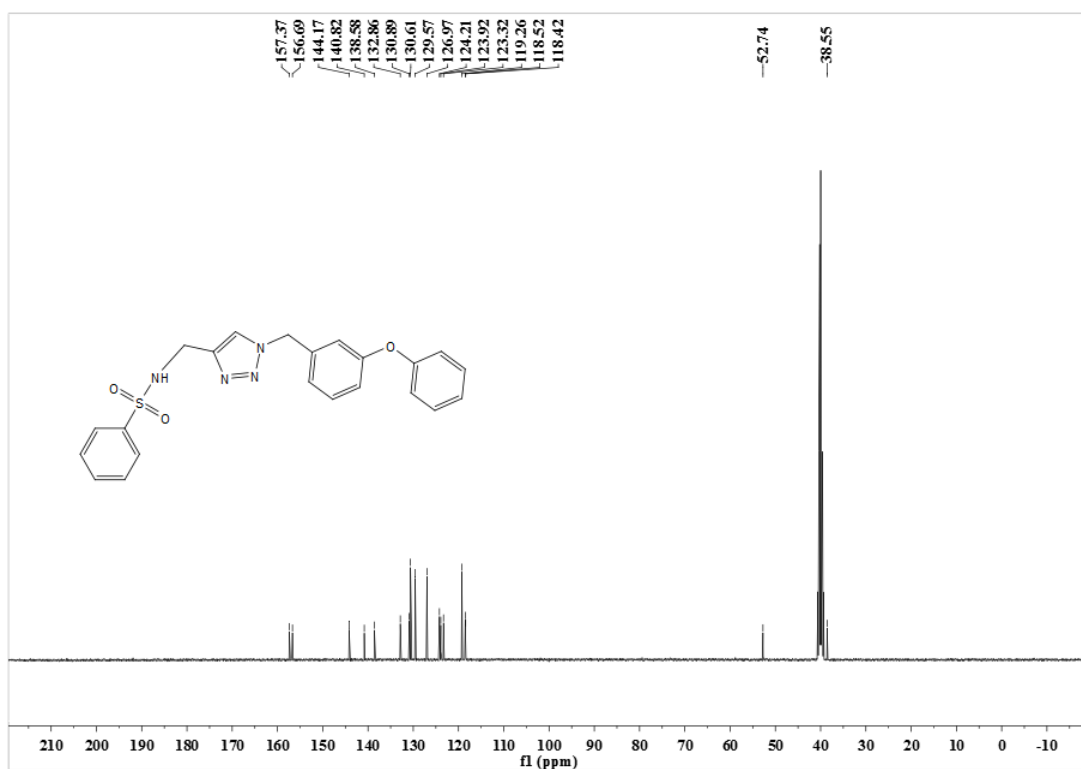
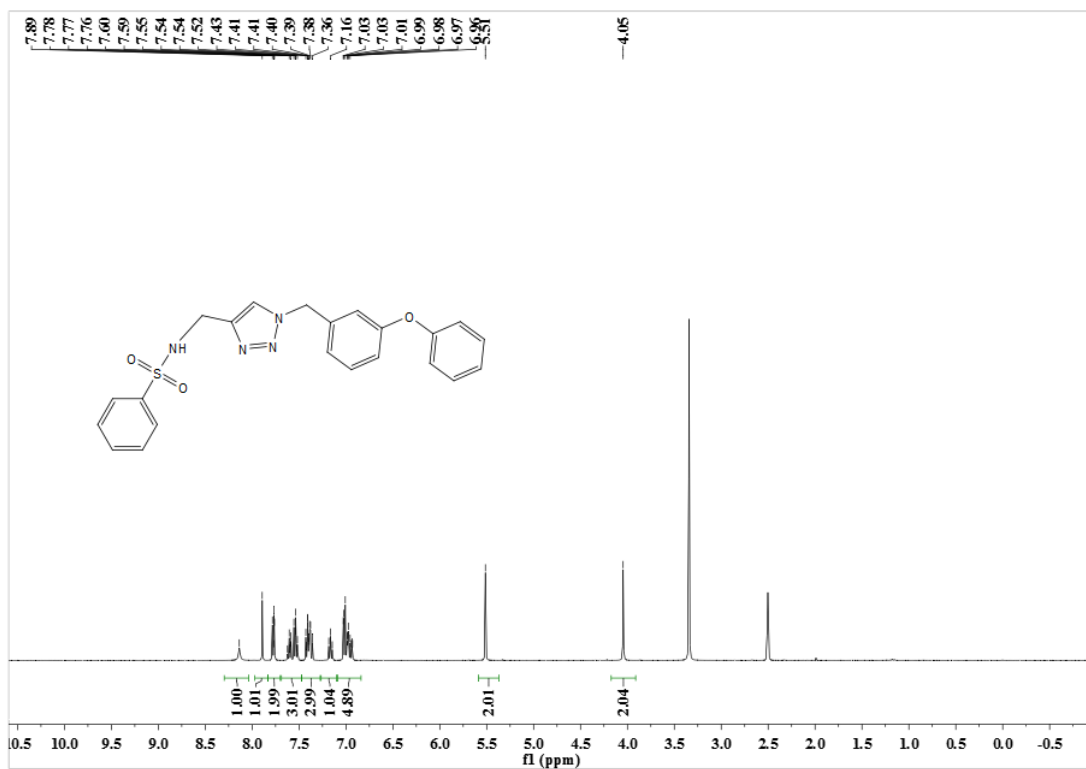




N-((1-(3-phenoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (11e)

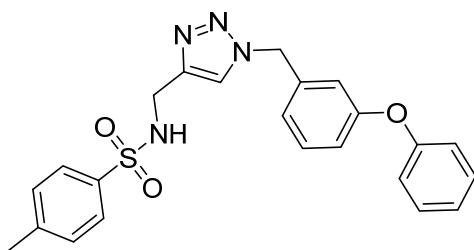


White solid, yield : 56.8%, mp: 127-130°C. <sup>1</sup>H NMR (400 MHz, DMSO) δ 8.14 (s, 1H, NH), 7.89 (s, 1H, Ar), 7.77 (dd, *J* = 5.3, 3.4 Hz, 2H, Ar), 7.69 – 7.47 (m, 3H, Ar), 7.47 – 7.27 (m, 3H, Ar), 7.16 (t, *J* = 7.4 Hz, 1H, Ar), 7.09 – 6.84 (m, 5H, Ar), 5.51 (s, 2H, PhCH<sub>2</sub>), 4.05 (s, 2H, NHCH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO) δ 157.37, 156.69, 144.17, 140.82, 138.58, 132.86, 130.89, 130.61, 129.57, 126.97, 124.21, 123.92, 123.32, 119.26, 118.52, 118.42 (Ar), 52.74 (PhCH<sub>2</sub>), 38.55 (NHCH<sub>2</sub>). HRMS (ESI) calcd for C<sub>22</sub>H<sub>21</sub>N<sub>4</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: 421.1338, found: 421.1334. IR: 3269, 3123, 1587, 1495, 1322, 1253, 1215, 1157, 690, 587 cm<sup>-1</sup>.

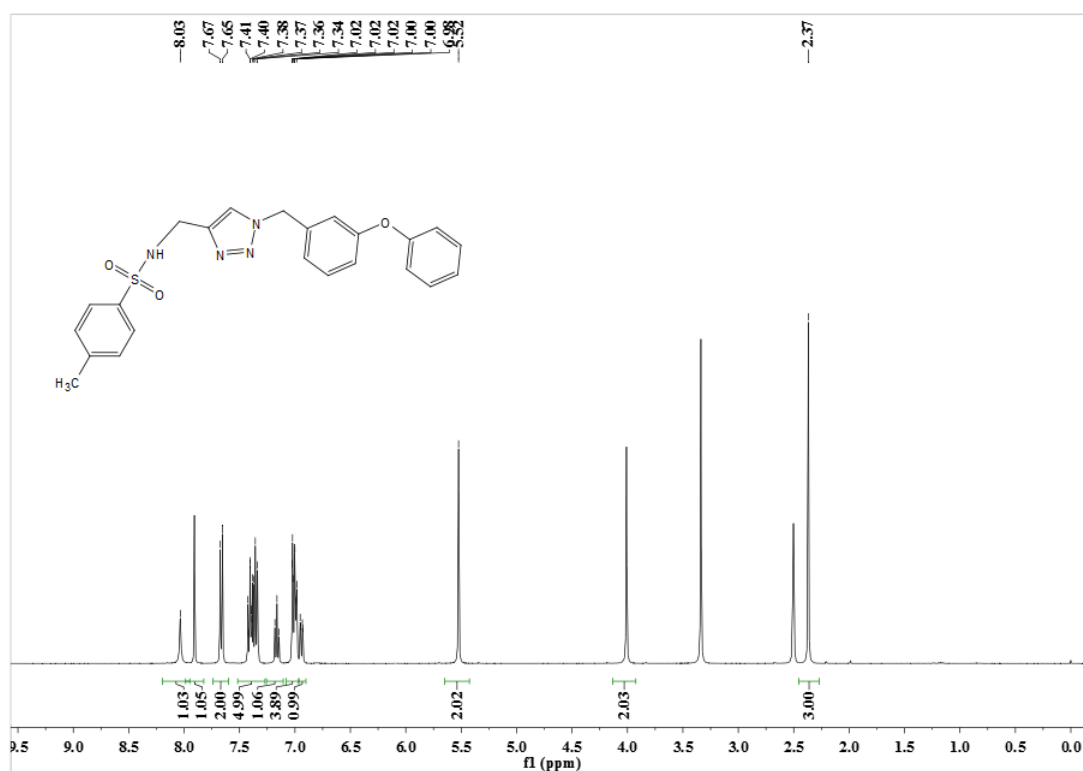


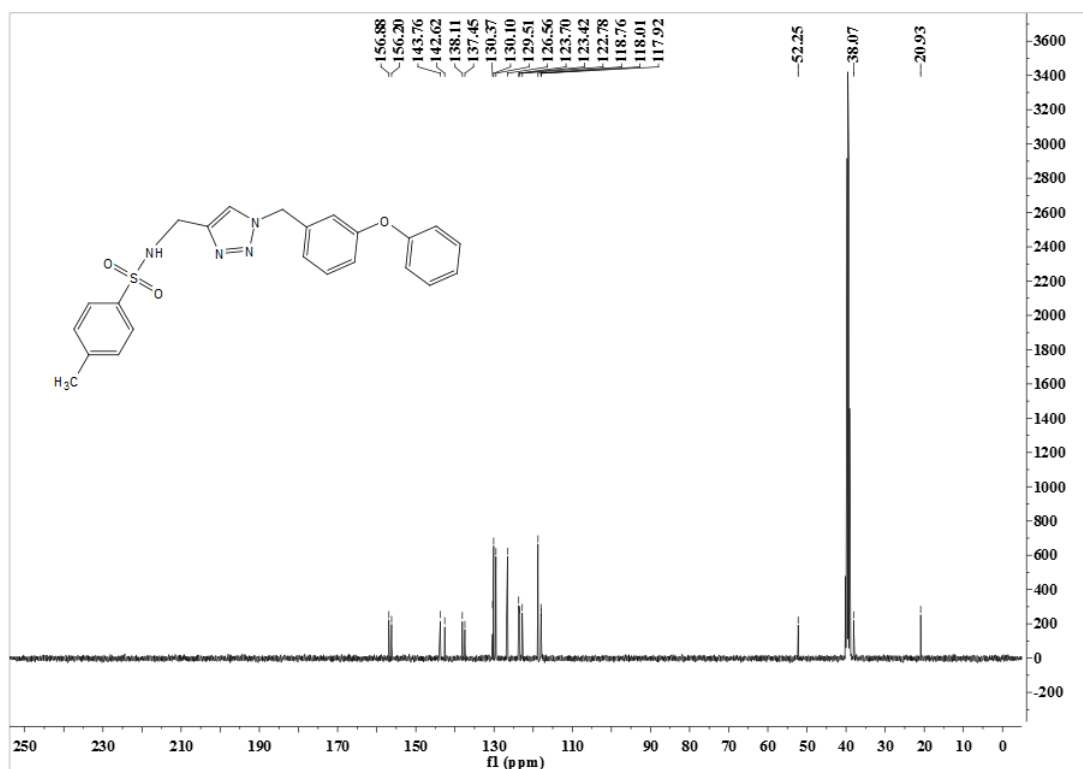
4-methyl-N-((1-(3-phenoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (11 f)



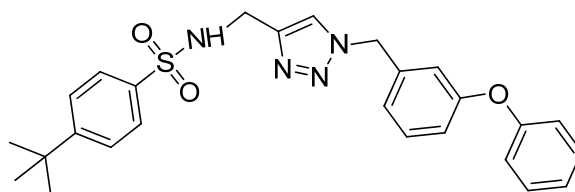


White solid, yield : 66.5%, mp: 118-121°C.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.03 (s, 1H, NH), 7.91 (s, 1H, Ar), 7.66 (d,  $J = 8.2$  Hz, 2H, Ar), 7.52 – 7.27 (m, 5H, Ar), 7.16 (t,  $J = 7.4$  Hz, 1H, Ar), 7.08 – 6.97 (m, 4H, Ar), 6.94 (dd,  $J = 8.0, 2.1$  Hz, 1H, Ar), 5.52 (s, 2H,  $\text{PhCH}_2$ ), 4.01 (s, 2H,  $\text{NHCH}_2$ ), 2.37 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (100MHz, DMSO)  $\delta$  156.88, 156.20, 143.76, 142.62, 138.11, 137.45, 130.37, 130.10, 129.51, 126.56, 123.70, 123.42, 122.78, 118.76, 118.01, 117.92 (Ar), 52.25 ( $\text{PhCH}_2$ ), 38.07 ( $\text{NHCH}_2$ ), 20.93 ( $\text{CH}_3$ ). HRMS (ESI) calcd for  $\text{C}_{23}\text{H}_{23}\text{N}_4\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 435.1497, found: 435.1491. IR: 3294, 3251, 1590, 1491, 1328, 1265, 1160, 819, 755, 687, 557  $\text{cm}^{-1}$ .

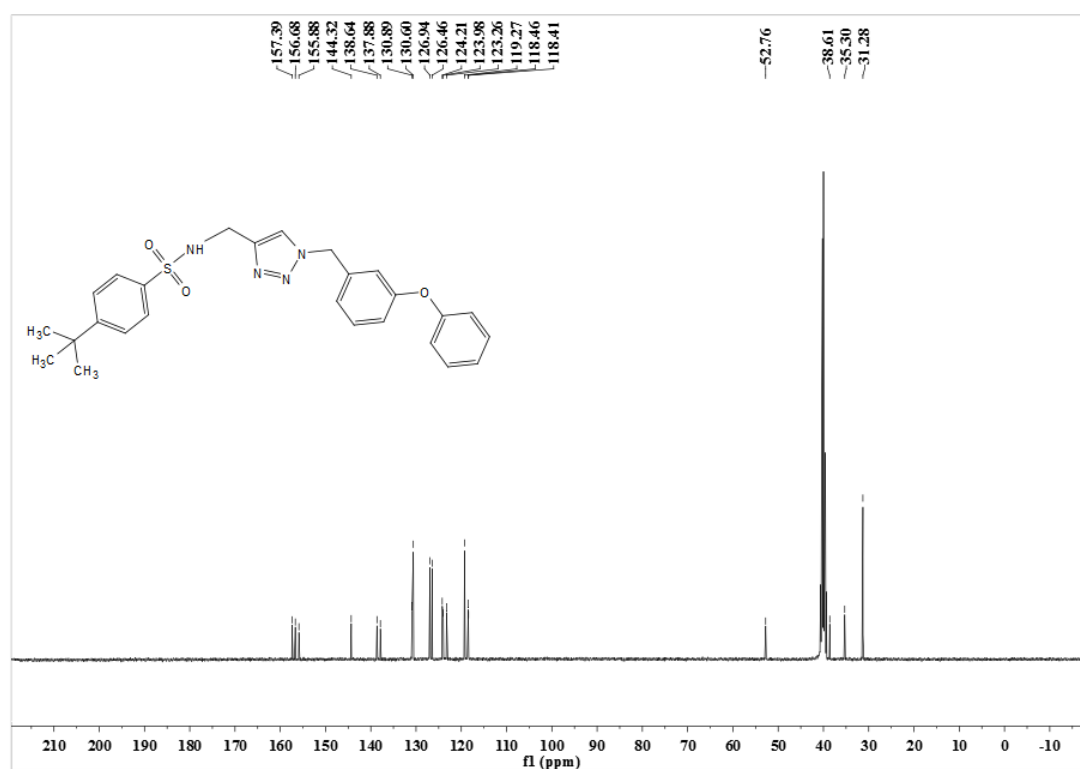
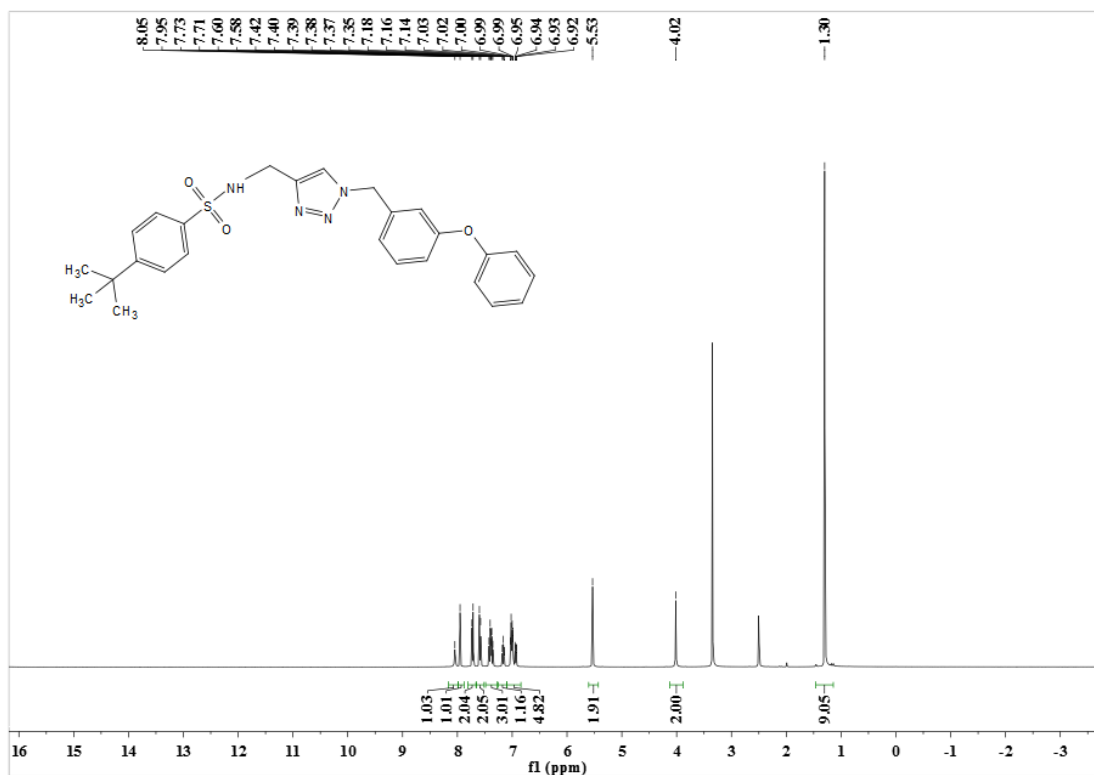




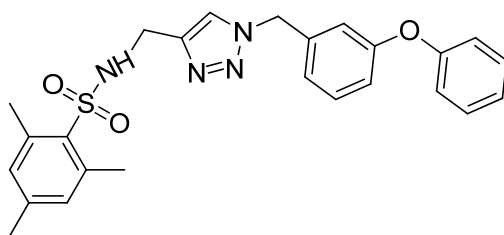
4-(tert-butyl)-N-((1-(3-phenoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (11g)



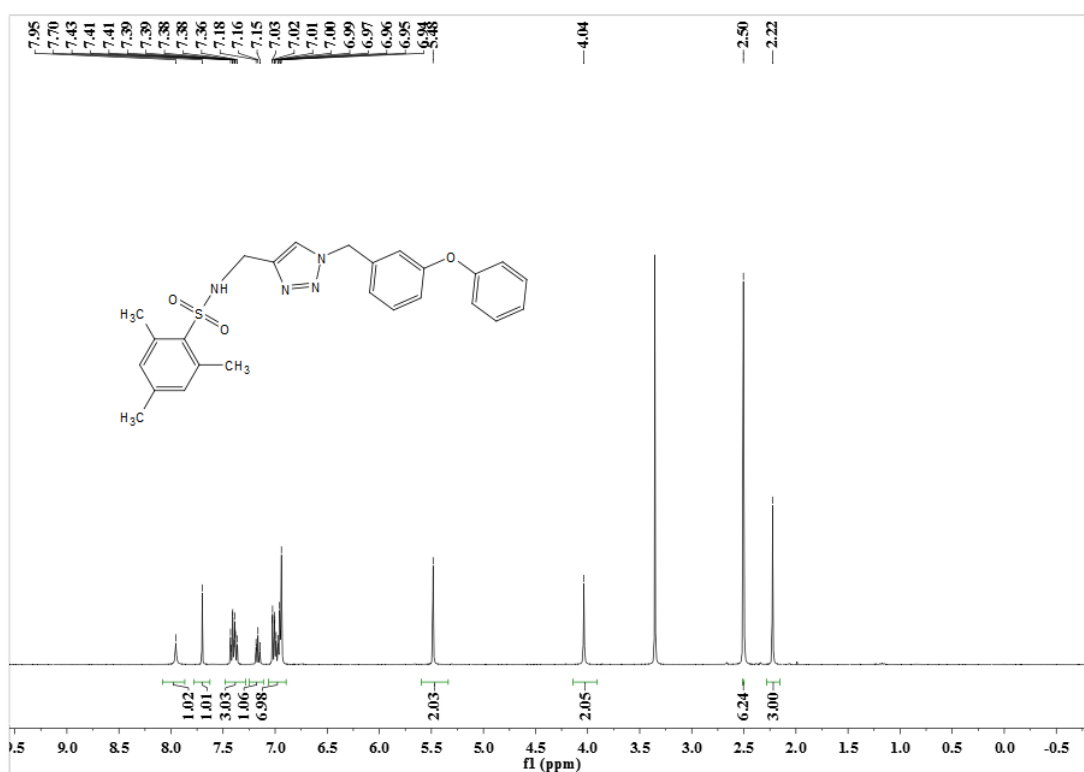
White solid, yield : 49.3%, mp: 137-139°C. <sup>1</sup>H NMR (400 MHz, DMSO) δ 8.05 (s, 1H, NH), 7.95 (s, 1H, Ar), 7.72 (d, *J* = 8.5 Hz, 2H, Ar), 7.59 (d, *J* = 8.6 Hz, 2H, Ar), 7.39 (dt, *J* = 11.7, 8.1 Hz, 3H, Ar), 7.16 (t, *J* = 7.4 Hz, 1H, Ar), 7.10 – 6.84 (m, 5H, Ar), 5.53 (s, 2H, PhCH<sub>2</sub>), 4.02 (s, 2H, NHCH<sub>2</sub>), 1.30 (s, 9H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO) δ 157.39, 156.68, 155.88, 144.32, 138.64, 137.88, 130.89, 130.60, 126.94, 126.46, 124.21, 123.98, 123.26, 119.27, 118.46, 118.41 (Ar), 52.76 (PhCH<sub>2</sub>), 38.61 (NHCH<sub>2</sub>), 35.30 (C(CH<sub>3</sub>)<sub>3</sub>), 31.28 (C(CH<sub>3</sub>)<sub>3</sub>). HRMS (ESI) calcd for C<sub>26</sub>H<sub>29</sub>N<sub>4</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: 477.1967, found: 477.1960. IR: 3268, 1593, 1488, 1322, 1242, 1163, 1047, 754, 570 cm<sup>-1</sup>.

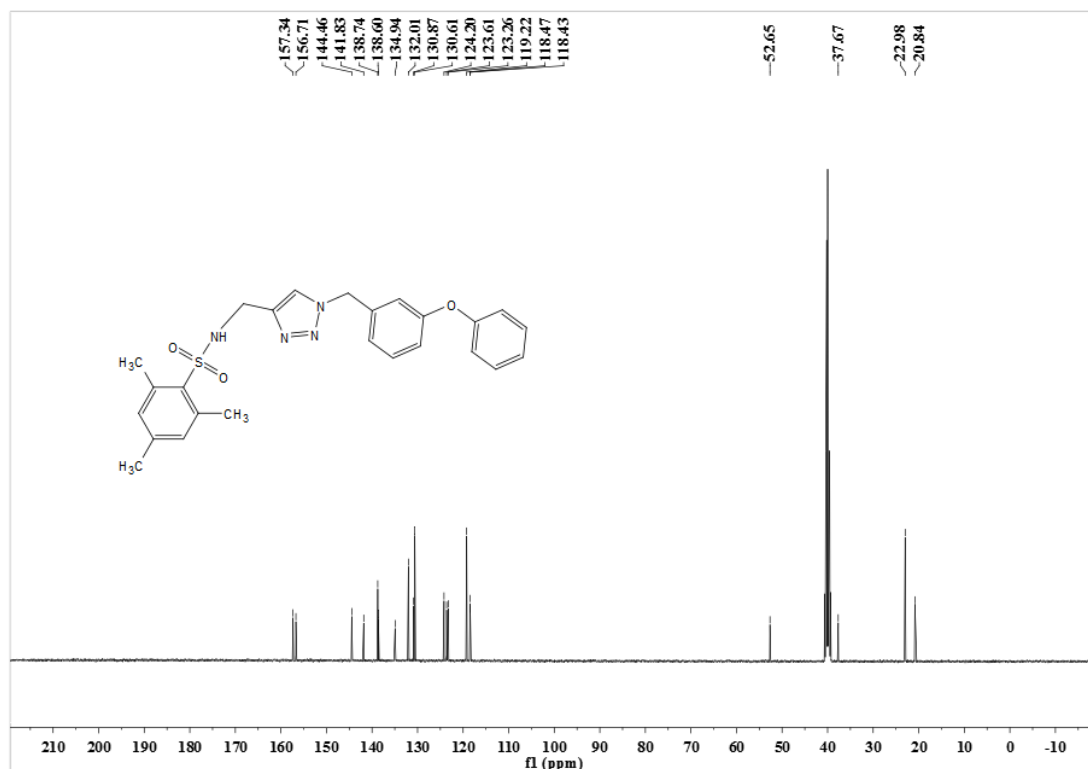


2,4,6-trimethyl-N-((1-(3-phenoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (11h)

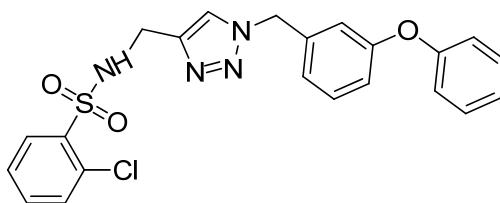


White solid, yield : 78.7%, mp: 111-113°C.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  7.95 (s, 1H, NH), 7.70 (s, 1H, Ar), 7.48 – 7.28 (m, 3H, Ar), 7.17 (dd,  $J$  = 10.6, 4.2 Hz, 1H, Ar), 7.06 – 6.89 (m, 7H, Ar), 5.48 (s, 2H,  $\text{PhCH}_2$ ), 4.04 (s, 2H,  $\text{NHCH}_2$ ), 2.50 (s, 6H,  $\text{CH}_3$ ), 2.22 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz, DMSO)  $\delta$  157.34, 156.71, 144.46, 141.83, 138.74, 138.60, 134.94, 132.01, 130.87, 130.61, 124.20, 123.61, 123.26, 119.22, 118.47, 118.43 (Ar), 52.65 ( $\text{PhCH}_2$ ), 37.67 ( $\text{NHCH}_2$ ), 22.98 ( $\text{CH}_3$ ), 20.84 ( $\text{CH}_3$ ). HRMS (ESI) calcd for  $\text{C}_{25}\text{H}_{27}\text{N}_4\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 463.1807, found: 463.1804. IR: 3307, 3269, 1587, 1488, 1326, 1257, 1243, 1154, 736, 657  $\text{cm}^{-1}$ .

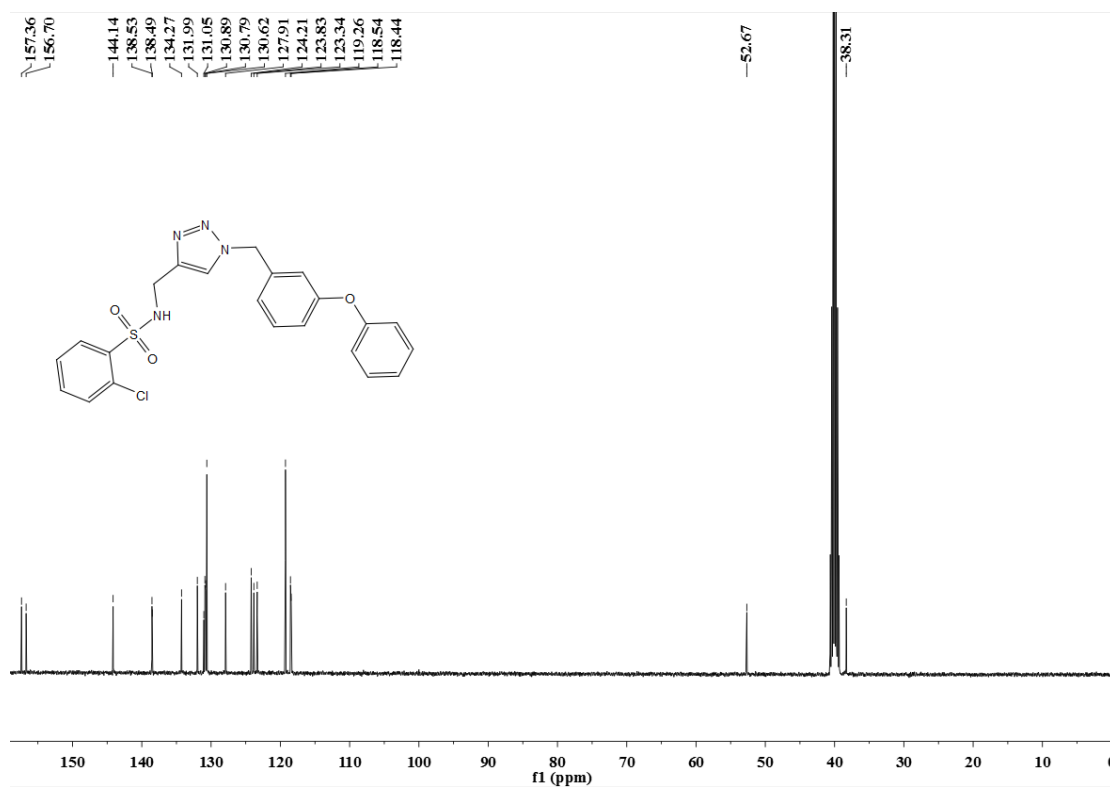
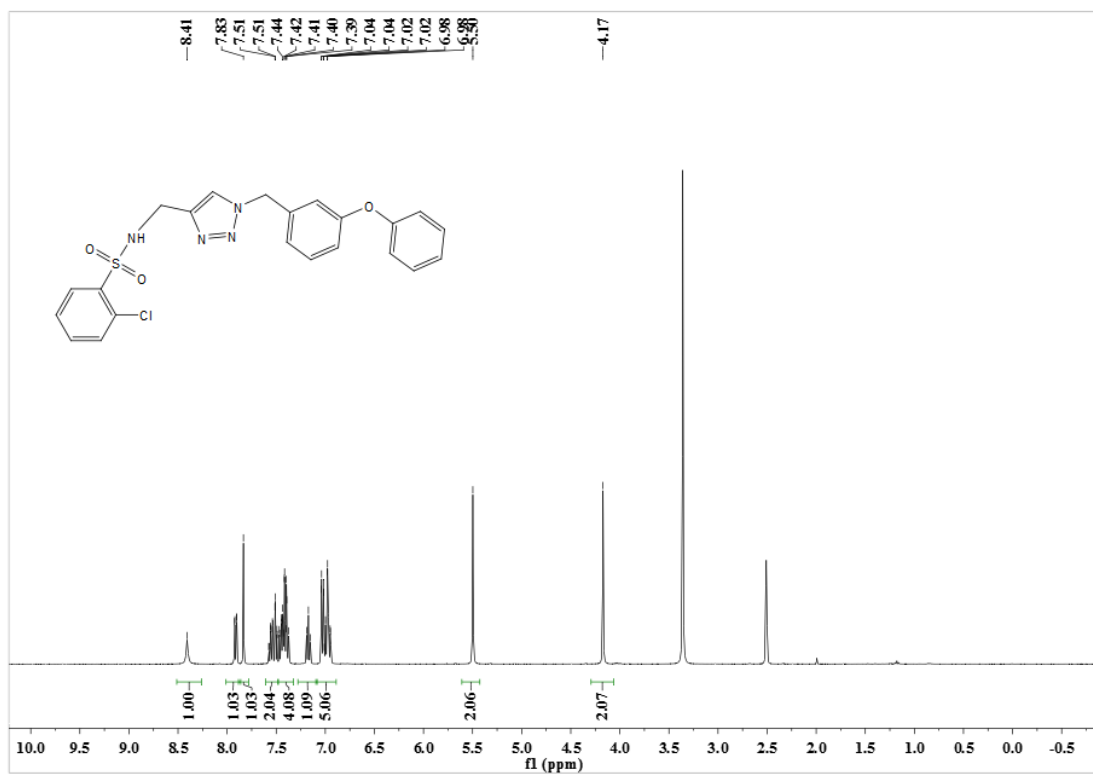




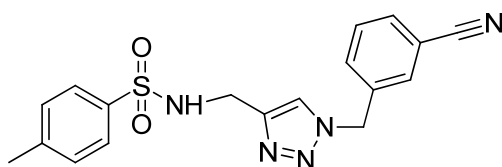
2-chloro-N-((1-(3-phenoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide (11i)



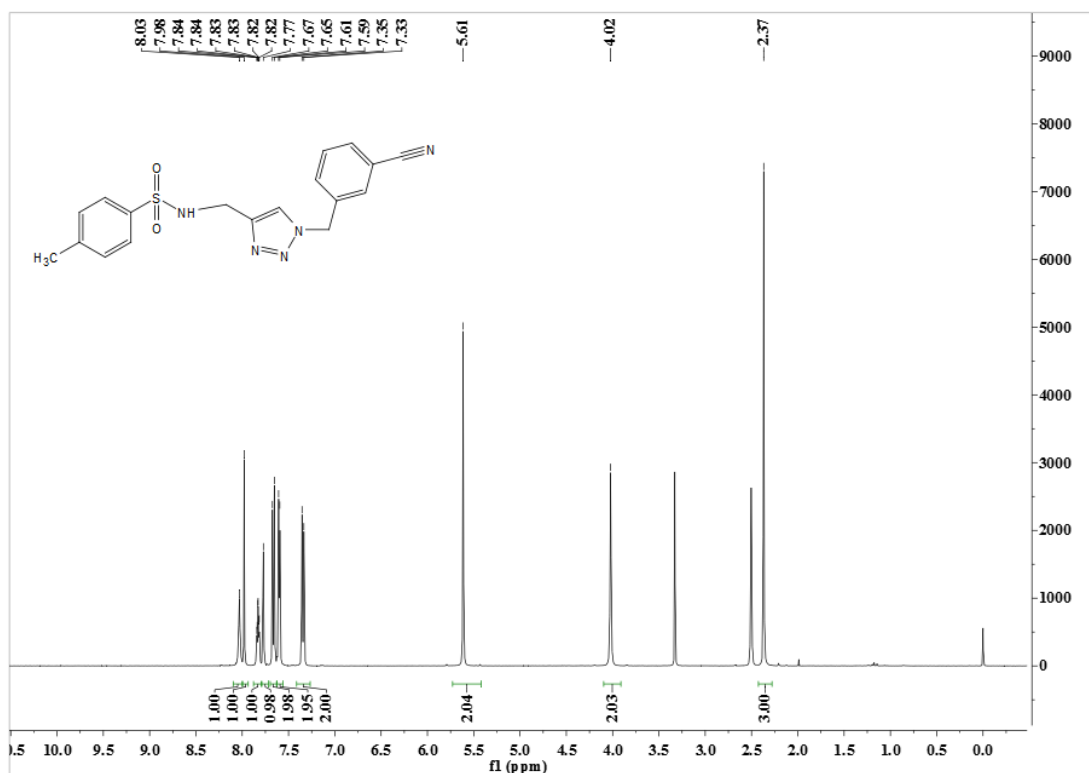
White solid, yield : 80.8%, mp: 97-99°C. <sup>1</sup>H NMR (400 MHz, DMSO) δ 8.41 (s, 1H, NH), 7.91 (dd, *J* = 7.8, 1.5 Hz, 1H, Ar), 7.83 (s, 1H, Ar), 7.61 – 7.48 (m, 2H, Ar), 7.48 – 7.32 (m, 4H, Ar), 7.17 (t, *J* = 7.4 Hz, 1H, Ar), 7.10 – 6.89 (m, 5H, Ar), 5.50 (s, 2H, PhCH<sub>2</sub>), 4.17 (s, 2H, NHCH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO) δ 157.36, 156.70, 144.14, 138.53, 138.49, 134.27, 131.99, 131.05, 130.89, 130.79, 130.62, 127.91, 124.21, 123.83, 123.34, 119.26, 118.54, 118.44 (Ar), 52.67 (PhCH<sub>2</sub>), 38.31 (NHCH<sub>2</sub>). HRMS (ESI) calcd for C<sub>22</sub>H<sub>20</sub>ClN<sub>4</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: 455.0948, found: 455.0945. IR: 3137, 1593, 1489, 1451, 1332, 1253, 1212, 1157, 758, 688, 585 cm<sup>-1</sup>.

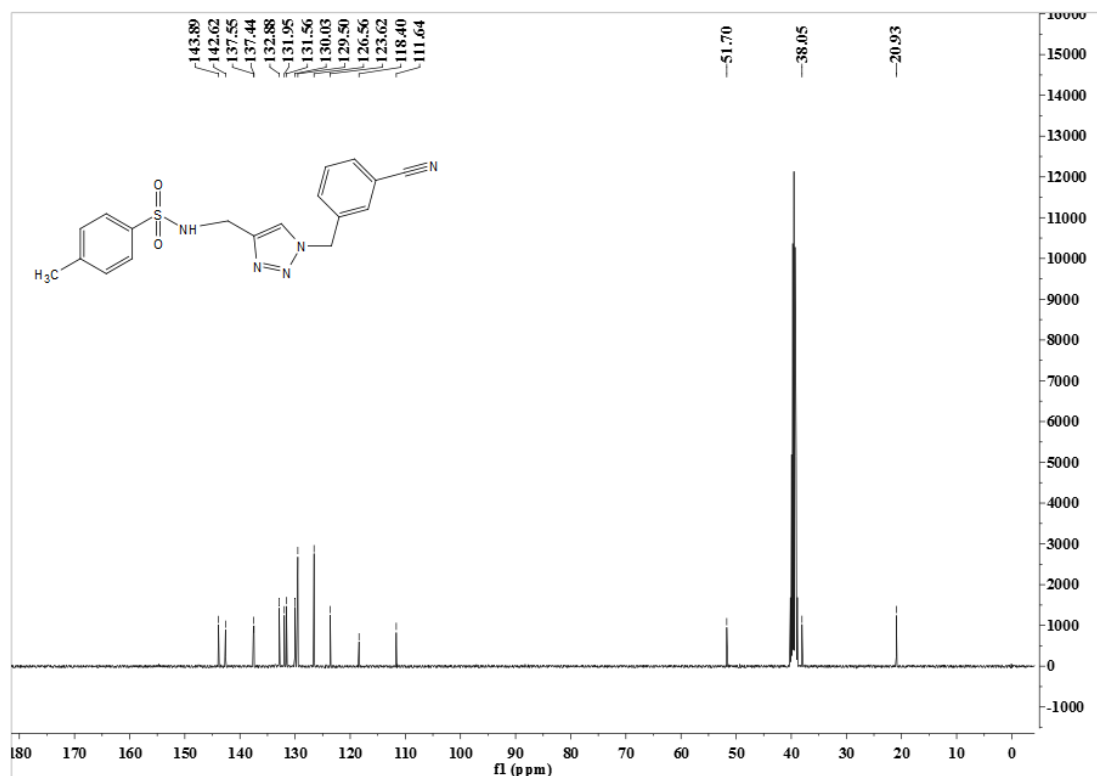


N-((1-(3-cyanobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methylbenzene sulfonamide (11j)

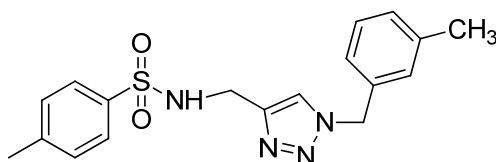


White solid, yield : 58.1%, mp: 145-147 °C.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.03 (s, 1H, NH), 7.98 (s, 1H, Ar), 7.83 (td,  $J = 4.6, 1.4$  Hz, 1H, Ar), 7.77 (s, 1H, Ar), 7.66 (d,  $J = 8.2$  Hz, 2H, Ar), 7.60 (d,  $J = 5.0$  Hz, 2H, Ar), 7.34 (d,  $J = 8.0$  Hz, 2H, Ar), 5.61 (s, 2H,  $\text{PhCH}_2$ ), 4.02 (s, 2H,  $\text{NHCH}_2$ ), 2.37 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz, DMSO)  $\delta$  143.89, 142.62, 137.55, 137.44, 132.88, 131.95, 131.56, 130.03, 129.50, 126.56, 123.62, 118.40, 111.64 (Ar), 51.70 ( $\text{PhCH}_2$ ), 38.05 ( $\text{NHCH}_2$ ), 20.93 ( $\text{CH}_3$ ). HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_5\text{O}_2\text{S}$   $[\text{M}+\text{H}]^+$ : 368.1181, found: 368.1181. IR: 3265, 2217, 1430, 1323, 1160, 1049, 889, 709, 546  $\text{cm}^{-1}$ .



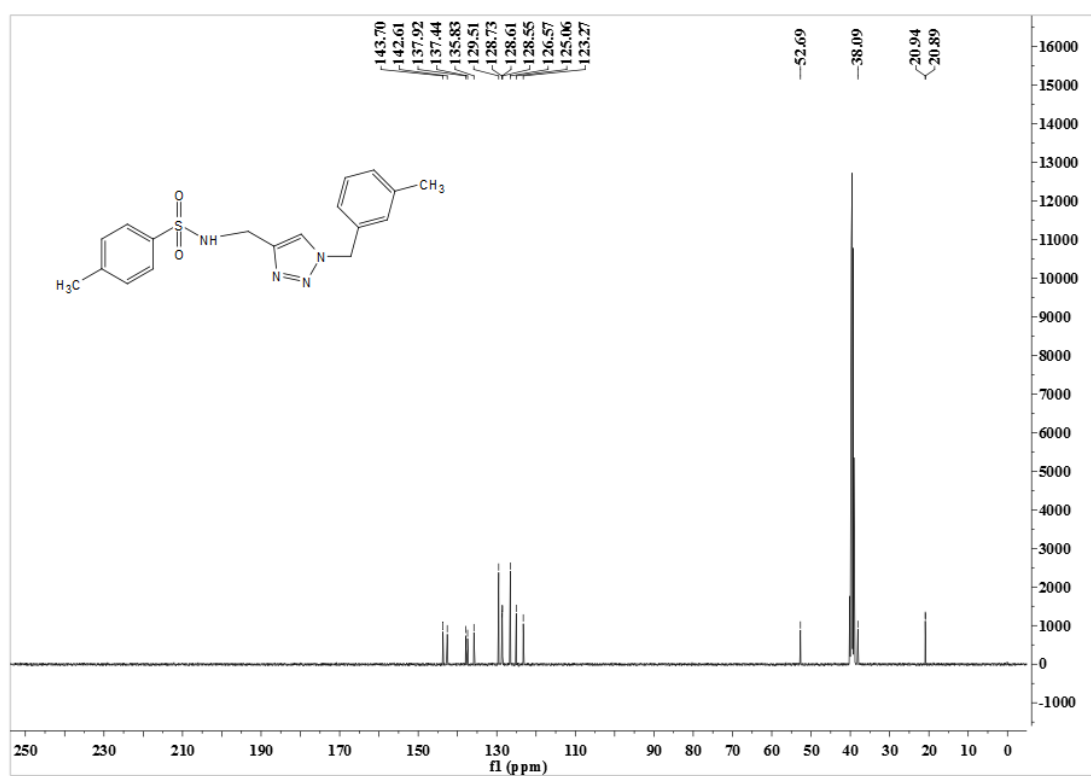
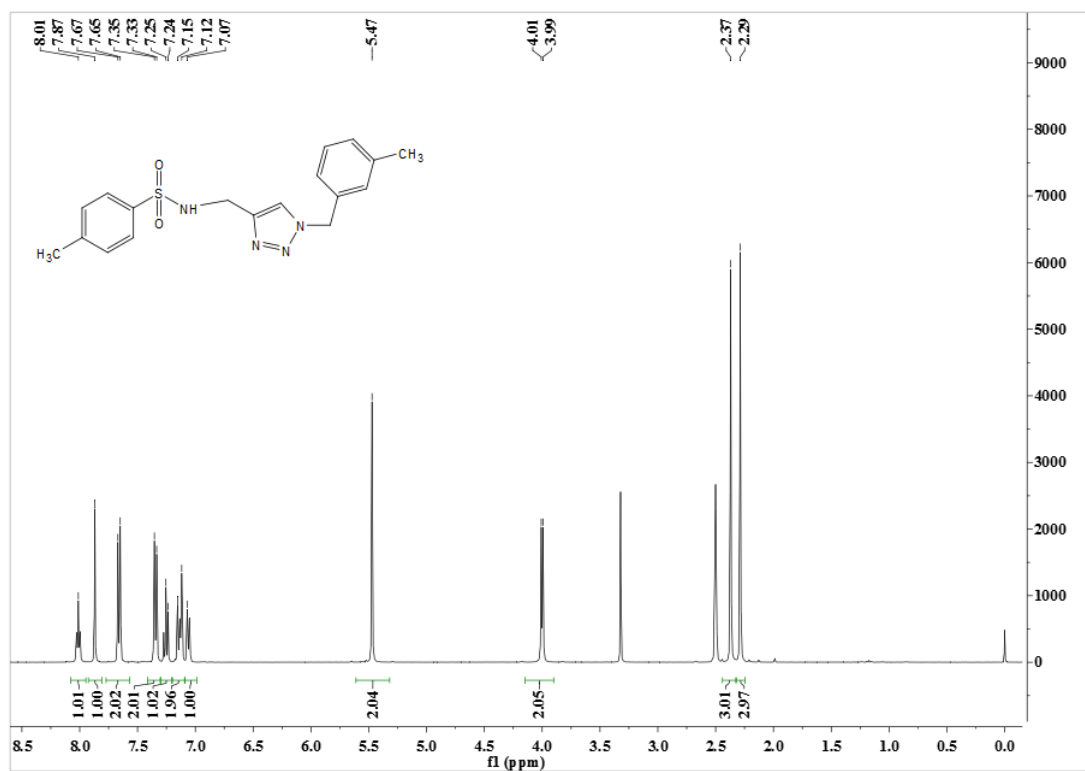


4-methyl-N-((1-(3-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (11k)

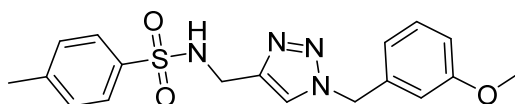


White solid, yield : 67.7%, mp: 145-148 °C.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.01 (t,  $J = 6.0$  Hz, 1H, NH), 7.87 (s, 1H, Ar), 7.66 (d,  $J = 8.1$  Hz, 2H, Ar), 7.34 (d,  $J = 8.0$  Hz, 2H, Ar), 7.25 (t,  $J = 7.5$  Hz, 1H, Ar), 7.14 (dd,  $J = 15.2, 7.5$  Hz, 2H, Ar), 7.06 (d,  $J = 7.6$  Hz, 1H, Ar), 5.47 (s, 2H, PhCH<sub>2</sub>), 4.00 (d,  $J = 6.0$  Hz, 2H, NHCH<sub>2</sub>), 2.37 (s, 3H, CH<sub>3</sub>), 2.29 (s, 3H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO)  $\delta$  143.70, 142.61, 137.92, 137.44, 135.83, 129.51, 128.73, 128.61, 128.55, 126.57, 125.06, 123.27 (Ar), 52.69 (PhCH<sub>2</sub>), 38.09 (NHCH<sub>2</sub>), 20.94 (CH<sub>3</sub>), 20.89 (CH<sub>3</sub>). HRMS (ESI) calcd for C<sub>18</sub>H<sub>21</sub>N<sub>4</sub>O<sub>2</sub>S [M+H]<sup>+</sup>: 357.1388, found: 357.1385. IR: 3258, 3121, 1452, 1325, 1160, 1098, 772, 669, 558 cm<sup>-1</sup>.





N-((1-(3-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methylbenzenesulfonamide (11l)



White solid, yield : 82.8%, mp: 112-114 °C.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.02 (s, 1H, NH), 7.89 (s, 1H, Ar), 7.66 (d,  $J = 8.2$  Hz, 2H, Ar), 7.34 (d,  $J = 8.1$  Hz, 2H, Ar), 7.28 (t,  $J = 7.9$  Hz, 1H, Ar), 6.99 – 6.85 (m, 2H, Ar), 6.82 (d,  $J = 7.6$  Hz, 1H, Ar), 5.49 (s, 2H,  $\text{PhCH}_2$ ), 4.01 (s, 2H,  $\text{NHCH}_2$ ), 3.74 (s, 3H,  $\text{OCH}_3$ ), 2.37 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz, DMSO)  $\delta$  159.40, 143.72, 142.62, 137.45, 137.38, 129.84, 129.51, 126.56, 123.34, 120.00, 113.79, 113.37 (Ar), 55.08 ( $\text{OCH}_3$ ), 52.60 ( $\text{PhCH}_2$ ), 38.08 ( $\text{NHCH}_2$ ), 20.92 ( $\text{CH}_3$ ). HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{21}\text{N}_4\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 373.1339, found: 373.1334. IR: 3294, 3247, 1600, 1322, 1286, 1265, 1091, 1040, 775, 668, 557  $\text{cm}^{-1}$ .

