Supporting Information

Asymmetric Mannich reactions of imidazo[2,1-*b*]thiazole-derived nucleophiles with (S_S)-*N*-*tert*-butanesulfinyl (3,3,3)-trifluoroacetaldimine

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1. General information

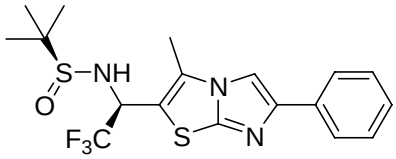
All imine addition reactions were performed in oven-dried vials under N_2 atmosphere. Solvent THF was dried and distilled prior to use. Imidazo[2,1-*b*]thiazoles **2** were synthesized according to literature[1]. Sulfinylimine **1** was obtained from Accela ChemBio Co., Ltd.. LDA (2 M in THF) was from Aldrich. These and other chemicals were used as obtained from commercial sources without further purification. Flash chromatography was performed using silica gel 60 (200-300 mesh). Thin layer chromatography was carried out on silica gel 60 F-254 TLC plates of 20 cm × 20 cm. Melting points are uncorrected. Values of optical rotation were measured on Rudolph Automatic Polarimeter A21101. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AVANCE400M spectrometer. HRMS spectra were carried out at Micromass GCT (TOF MS EI^{+}).

Reference

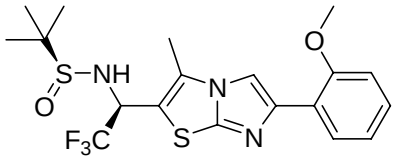
1 G. L. Huang, H. S. Sun, X. J. Qiu, C. Jin, C. Lin, Y. Z. Shen, J. L. Jiang and L. Y. Wang, *Org. Lett.*, 2011, **13**, 5224-5227.

2. Typical procedure for asymmetric addition of sulfinylimine

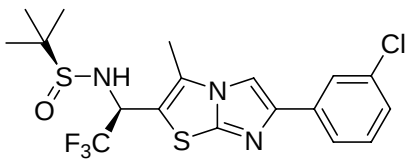
Into an oven-dried reaction vial flushed with N_2 were taken compound **2** (0.85 mmol) and anhydrous THF (3.0 mL). The reaction vial was cooled to -78 ^{o}C and LDA (2 M in THF, 0.39 mL) was added dropwise with stirring. After 1 h at -78 ^{o}C, sulfinylimine **1** (0.5 mmol) dissolved in anhydrous THF (2.0 mL) was added dropwise. Stirring was continued at -78 ^{o}C for 2 h, then the reaction was quenched with saturated NH_4Cl (3.0 mL), followed by H_2O (5.0 mL) and the mixture was brought to room temperature. The organic layer was taken and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was removed to give the crude product, which was purified by TLC plate (hexane/EtOAc, 2:3).



Compound **3a**: white solid, mp 186-188 °C, $[\alpha]_D^{25}$ +157.0 (*c* 0.76, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.82-7.85 (m, 2 H), 7.63 (s, 1 H), 7.41 (t, *J* = 8.0 Hz, 2 H), 7.26-7.31 (m, 1 H), 5.17-5.23 (m, 1 H), 3.90 (s, 1 H), 2.51 (s, 3 H), 1.27 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.7, 147.8, 133.8, 129.8, 128.7, 127.6, 125.3, 122.5 (q, *J* = 280.0 Hz), 114.4, 106.2, 56.8, 54.5 (q, *J* = 33.0 Hz), 22.4, 12.1. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -74.0. HRMS (TOF MS EI^+) *m/z*: calcd for $[C_{18}H_{20}N_3OF_3S_2]$ 415.1000, found 415.1002.

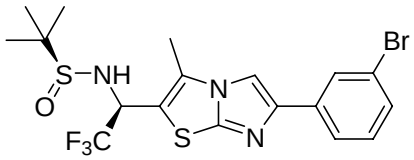


Compound **3b**: yellow solid, mp 76-78 °C, $[\alpha]_D^{25}$ +135.4 (*c* 0.26, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.25 (d, *J* = 8.0 Hz, 1 H), 7.92 (s, 1 H), 7.26 (s, 1 H), 7.07 (t, *J* = 8.0 Hz, 1 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 5.20 (d, *J* = 4.0 Hz, 1 H), 3.99 (s, 3 H), 3.84 (s, 1H), 2.54 (s, 3 H), 1.27 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.1, 147.7, 143.1, 129.9, 128.2, 128.1, 125.3 (d, *J* = 280.0 Hz), 122.4, 121.0, 113.8, 110.8, 110.5, 56.7, 55.4, 54.6 (q, *J* = 32.0 Hz), 22.4, 12.1. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -74.1. HRMS (TOF MS EI^+) *m/z*: calcd for $[C_{19}H_{22}N_3O_2F_3S_2]$ 445.1106, found 445.1101.

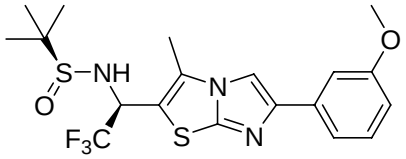


Compound **3c**: white solid, mp 225-227 °C, $[\alpha]_D^{25}$ +144.7 (*c* 0.26, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.84 (t, *J* = 1.6 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.65 (s, 1 H), 7.33 (t, *J* = 8.0 Hz, 1 H), 7.25-7.27 (m, 1 H), 5.17-5.22 (m, 1 H), 3.88 (s, 1 H), 2.53 (s, 3 H), 1.28 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 149.0, 146.4, 135.6, 134.7, 130.0, 129.7, 127.6, 125.4, 125.3 (q, *J* = 280.0 Hz), 123.3, 114.9, 106.7, 56.8,

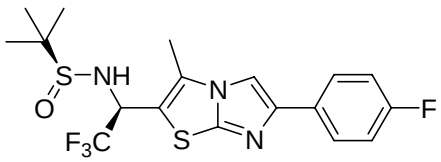
54.5 (q, J = 32.0 Hz), 22.4, 12.2. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -74.0. HRMS (TOF MS EI$^+$) *m/z*: calcd for [$C_{18}H_{19}N_3OF_3S_2Cl$] 449.0610, found 449.0602.



Compound **3d**: white solid, mp 226-227 °C, $[\alpha]_D^{25}$ +125.4 (*c* 0.24, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.00 (t, J = 1.6 Hz, 1 H), 7.77 (d, J = 8.0 Hz, 1 H), 7.64 (s, 1 H), 7.41-7.43 (m, 1 H), 7.25-7.29 (m, 1 H), 5.17-5.22 (m, 1 H), 3.86 (s, 1 H), 2.53 (s, 3 H), 1.28 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.9, 146.3, 135.9, 130.5, 130.2, 129.8, 128.3, 125.3 (q, J = 280.0 Hz), 123.8, 122.9, 114.9, 106.7, 56.8, 54.5 (q, J = 33.0 Hz), 22.4, 12.2. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -74.0. HRMS (TOF MS EI$^+$) *m/z*: calcd for [$C_{18}H_{19}N_3OF_3S_2Br$] 493.0105, found 493.0108.

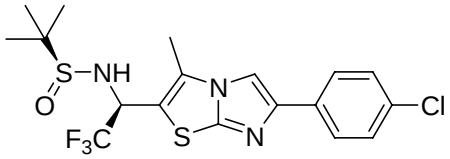


Compound **3e**: yellow solid, mp 165-167 °C, $[\alpha]_D^{25}$ +152.4 (*c* 0.21, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.63 (s, 1 H), 7.38-7.43 (m, 2 H), 7.26-7.33 (m, 1 H), 5.85-5.87 (m, 1 H), 3.88 (s, 3 H), 3.86 (s, 1 H), 2.52 (s, 3 H), 1.28 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.0, 148.6, 147.6, 135.2, 129.8, 129.7, 125.3 (q, J = 280.0 Hz), 117.7, 114.5, 113.8, 110.4, 106.5, 56.8, 55.3, 54.5 (q, J = 32.0 Hz), 22.4, 12.1. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -74.1. HRMS (TOF MS EI$^+$) *m/z*: calcd for [$C_{19}H_{22}N_3O_2F_3S_2$] 445.1106, found 445.1108.

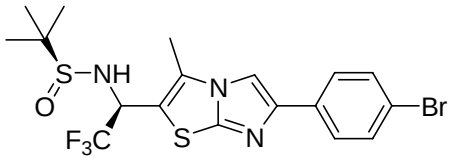


Compound **3f**: white solid, mp 169-170 °C, $[\alpha]_D^{25}$ +152.6 (*c* 0.26, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.78-7.82 (m, 2 H), 7.58 (s, 1 H), 7.10 (t, J = 8.0 Hz, 2 H), 5.17-5.22 (m, 1 H), 3.85 (s, 1 H), 2.52 (s, 3 H), 1.28 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100

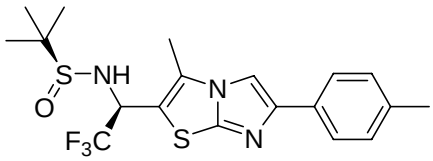
MHz): δ = 163.7, 161.2, 148.8, 147.0, 130.0 (d, *J* = 27.0 Hz), 127.0 (d, *J* = 8.0 Hz), 125.3 (q, *J* = 280.0 Hz), 115.7 (d, *J* = 21.0 Hz), 114.4, 105.9, 56.8, 54.5 (q, *J* = 32.0 Hz), 22.4, 12.1. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -74.1, -114.5. HRMS (TOF MS EI$^+$) *m/z*: calcd for [$C_{18}H_{19}N_3OF_4S_2$] 433.0906, found 433.0897.



Compound **3g**: white solid, mp 190-192 °C, $[\alpha]_D^{25}$ +149.3 (*c* 0.27, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.77 (d, *J* = 8.0 Hz, 2 H), 7.62 (s, 1 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 5.18-5.23 (m, 1 H), 3.94 (s, 1 H), 2.51 (d, *J* = 1.2 Hz, 3 H), 1.27 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.9, 146.7, 133.3, 132.3, 129.7, 128.9, 126.6, 125.3 (q, *J* = 280.0 Hz), 114.7, 106.3, 56.8, 54.5 (q, *J* = 32.0 Hz), 22.4, 12.1. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -74.0. HRMS (TOF MS EI$^+$) *m/z*: calcd for [$C_{18}H_{19}N_3OF_3S_2Cl$] 449.0610, found 449.0600.

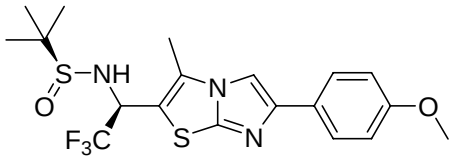


Compound **3h**: white solid, mp 193-194 °C, $[\alpha]_D^{25}$ +134.9 (*c* 0.22, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.72 (d, *J* = 8.0 Hz, 2 H), 7.63 (s, 1 H), 7.54 (d, *J* = 8.0 Hz, 2 H), 5.17-5.21 (m, 1 H), 3.88 (s, 1 H), 2.52 (s, 3 H), 1.28 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.9, 146.7, 132.8, 131.8, 129.7, 126.8, 125.3 (q, *J* = 280.0 Hz), 121.4, 114.7, 106.4, 56.8, 54.5 (q, *J* = 33.0 Hz), 22.4, 12.1. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -74.0. HRMS (TOF MS EI$^+$) *m/z*: calcd for [$C_{18}H_{19}N_3OF_3S_2Br$] 493.0105, found 493.0108.

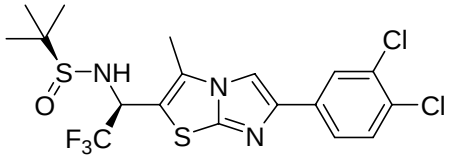


Compound **3i**: white solid, mp 200-202 °C, $[\alpha]_D^{25}$ +159.7 (*c* 0.23, $CHCl_3$). ^{1}H NMR

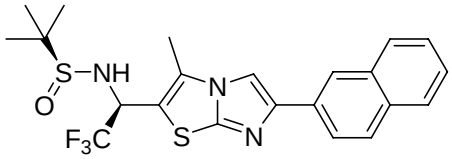
($CDCl_3$, 400 MHz): δ = 7.74 (d, *J* = 8.0 Hz, 2 H), 7.59 (s, 1 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 5.16-5.22 (m, 1 H), 3.86 (s, 1 H), 2.52 (s, 3 H), 2.38 (s, 3 H), 1.27 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.6, 147.9, 137.4, 131.0, 129.8, 129.4, 125.2, 122.5 (q, *J* = 281.0 Hz), 114.2, 105.8, 56.8, 54.5 (q, *J* = 32.0 Hz), 22.4, 21.2, 12.1. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -74.1. HRMS (TOF MS EI^+) *m/z*: calcd for $[C_{19}H_{22}N_3OF_3S_2]$ 429.1156, found 429.1157.



Compound **3j**: yellow solid, mp 141-142 °C, $[\alpha]_D^{25}$ +147.6 (*c* 0.21, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.77 (d, *J* = 8.0 Hz, 2 H), 7.54 (s, 1 H), 6.96 (d, *J* = 8.0 Hz, 2 H), 5.17-5.21 (m, 1 H), 3.91 (s, 1 H), 3.84 (s, 3 H), 2.50 (s, 3 H), 1.27 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.3, 148.6, 147.8, 129.8, 126.6, 122.5 (q, *J* = 280.0 Hz), 114.2, 113.9, 105.2, 56.7, 55.3, 54.5 (q, *J* = 32.0 Hz), 22.4, 12.1. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -74.1. HRMS (TOF MS EI^+) *m/z*: calcd for $[C_{19}H_{22}N_3O_2F_3S_2]$ 445.1106, found 445.1107.



Compound **3k**: yellow solid, mp 146-148 °C, $[\alpha]_D^{25}$ +146.7 (*c* 0.21, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.95 (d, *J* = 4.0 Hz, 1 H), 7.66 (dd, *J* = 4.0, 8.0 Hz, 1 H), 7.64 (s, 1 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 5.17-5.22 (m, 1 H), 3.86 (s, 1 H), 2.53 (s, 3 H), 1.28 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 149.0, 145.4, 133.9, 132.9, 131.2, 130.6, 129.7, 127.0, 124.4, 122.4 (q, *J* = 280.0 Hz), 115.1, 106.8, 56.8, 54.5 (q, *J* = 32.0 Hz), 22.4, 12.1. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -74.0. HRMS (TOF MS EI^+) *m/z*: calcd for $[C_{18}H_{18}N_3OF_3S_2Cl_2]$ 483.0220, found 483.0226.



Compound **3l**: white solid, mp 199-201 °C, $[\alpha]_D^{25}$ +164.1 (*c* 0.28, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.38 (s, 1 H), 7.86-7.90 (m, 3 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.75 (s, 1 H), 7.44-7.50 (m, 2 H), 5.19-5.23 (m, 1 H), 3.88 (s, 1 H), 2.55 (s, 3 H), 1.29 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 149.0, 147.8, 133.7, 133.0, 131.0, 129.8, 128.4, 128.2, 127.7, 126.3, 125.9, 123.9, 123.6, 122.5 (q, *J* = 280.0 Hz), 114.5, 106.6, 56.8, 54.5 (q, *J* = 33.0 Hz), 22.4, 12.2. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -74.0. HRMS (TOF MS EI^+) *m/z*: calcd for $[C_{22}H_{22}N_3OF_3S_2]$ 465.1156, found 465.1151.

3. Reaction of large scale application study

Into an oven-dried round-bottom flask flushed with N_2 were taken compound **2a** (8.5 mmol) and anhydrous THF (20.0 mL). The reaction flask was cooled to -78 °C and LDA (2 M in THF, 3.9 mL) was added dropwise with stirring. After 1 h at -78 °C, sulfinylimine **1** (5 mmol) dissolved in anhydrous THF (10.0 mL) was added dropwise. Stirring was continued at -78 °C for 2.5 h, then the reaction was quenched with saturated NH_4Cl (10.0 mL), followed by H_2O (15.0 mL) and the mixture was brought to room temperature. The organic layer was taken and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was removed to give the crude product, which was purified by column chromatography (hexane/EtOAc, 1:1).

4. X-ray crystallography for 3c

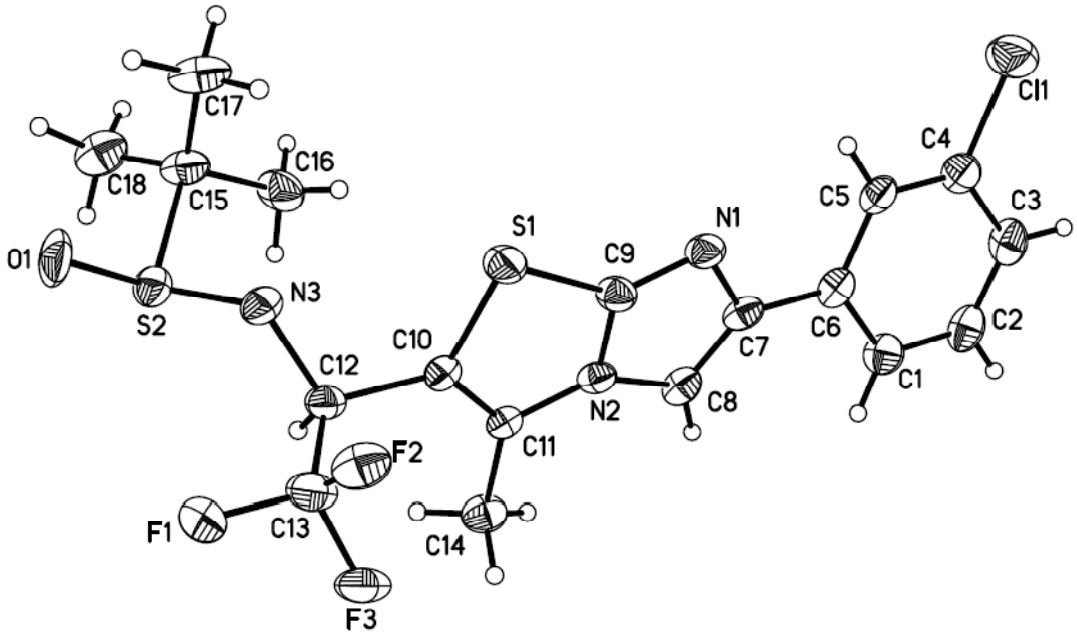
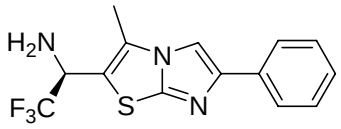


Fig. 1 ORTEP structure of compound **3c**. (CCDC number 941569).

5. Conversion of 3a affording free chiral primary amine 4

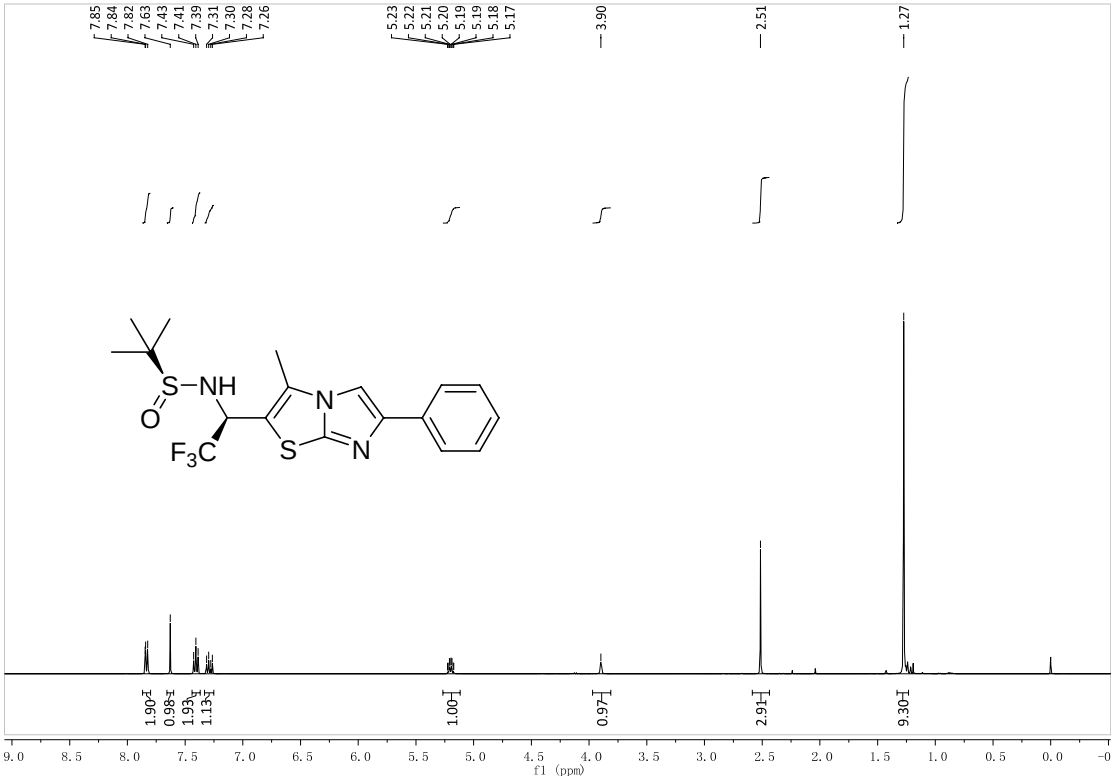
3a (0.5 mmol) and MeOH (5.0 mL) were placed in a 25 mL round-bottom flask and aq HCl (36%, 1 mL) was added. The reaction was stirred at r.t. for 8 h, during which time the cleavage was monitored by TLC. Volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10.0 mL) and Et_3N (15 mmol) was added. The reaction was stirred at r.t. for 1 h then H_2O (10.0 mL) was added. The organic layer was taken, washed with H_2O (2 × 10 mL), dried with anhydrous Na_2SO_4, filtered and the solvent was removed to give the crude product, which was purified by TLC plate (hexane/EtOAc, 2:3).

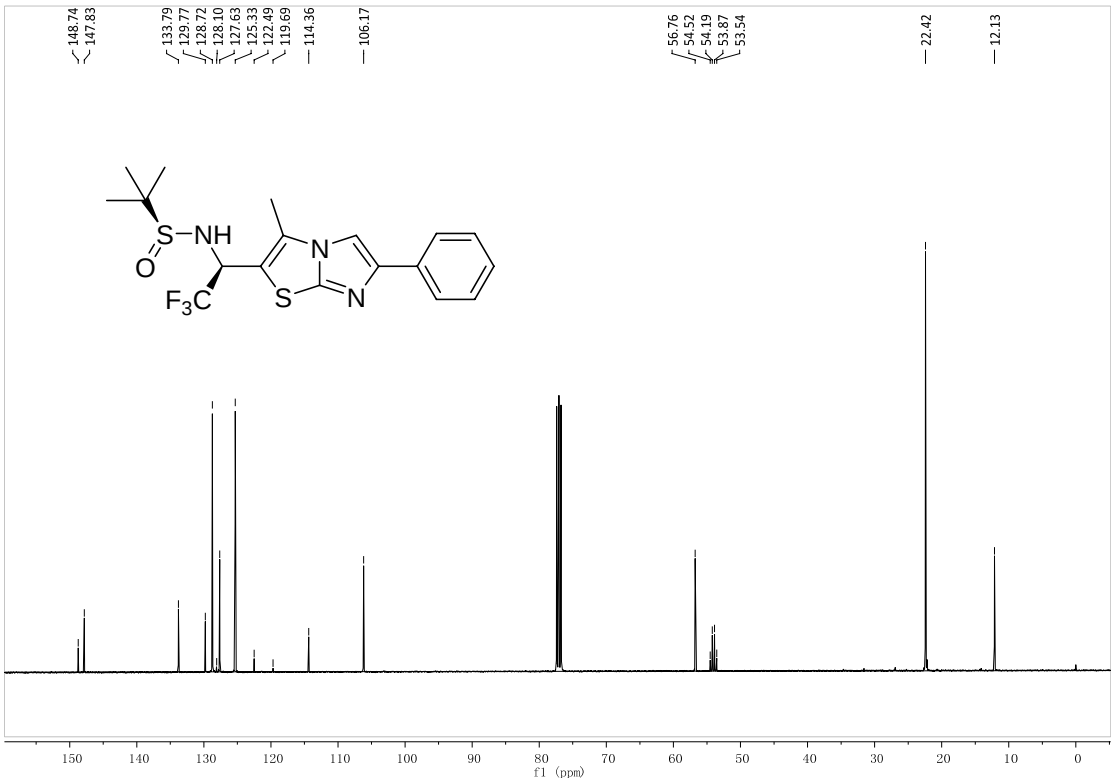


Compound **4**: white solid, mp 119-121 °C, $[\alpha]_D^{25}$ +33.3 (*c* 0.20, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.83 (d, *J* = 8.0 Hz, 2 H), 7.56 (s, 1 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 7.28 (t, *J* = 8.0 Hz, 1 H), 4.72 (q, *J* = 8.0 Hz, 1 H), 2.41 (s, 3 H), 1.90 (s, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.3, 147.2, 133.9, 128.7, 127.5, 126.7, 125.1, 123.5 (q, *J* = 280.0 Hz), 118.9, 105.8, 52.6 (q, *J* = 32.0 Hz), 12.0. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -76.8. HRMS (TOF MS EI$^+$) *m/z*: calcd for [$C_{14}H_{12}N_3F_3S$] 311.0704, found 311.0696.

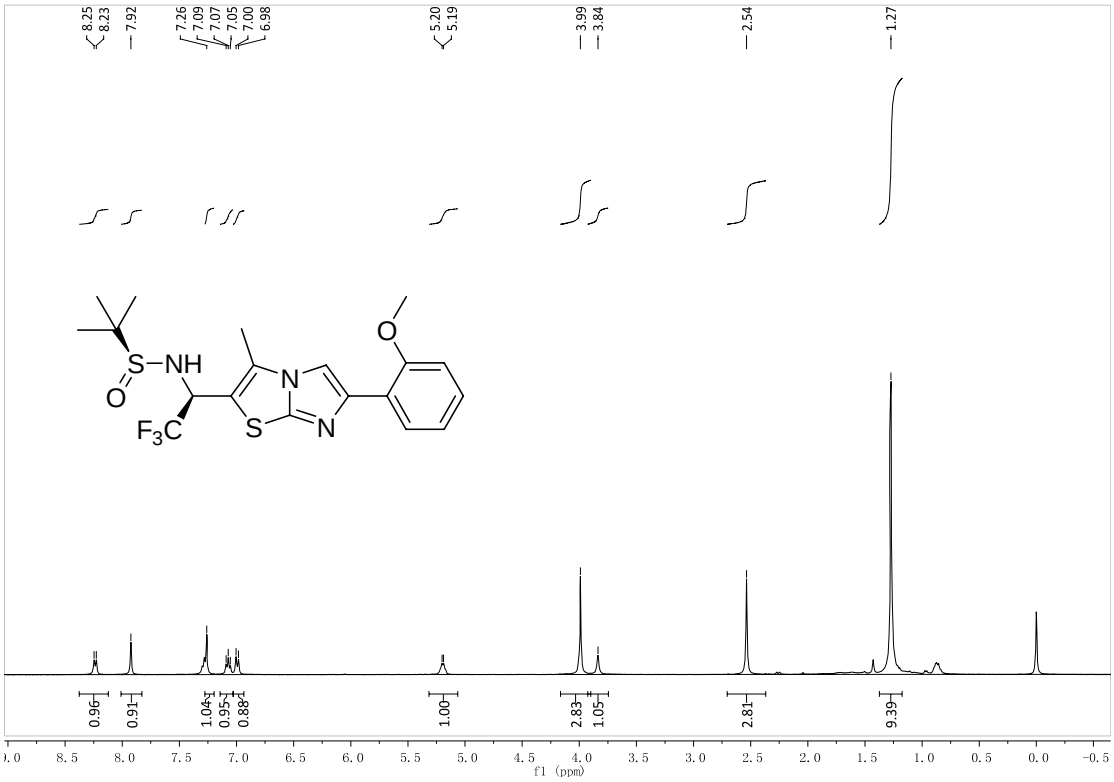
6. ^{1}H and ^{13}C NMR spectra for compound 3 and 4

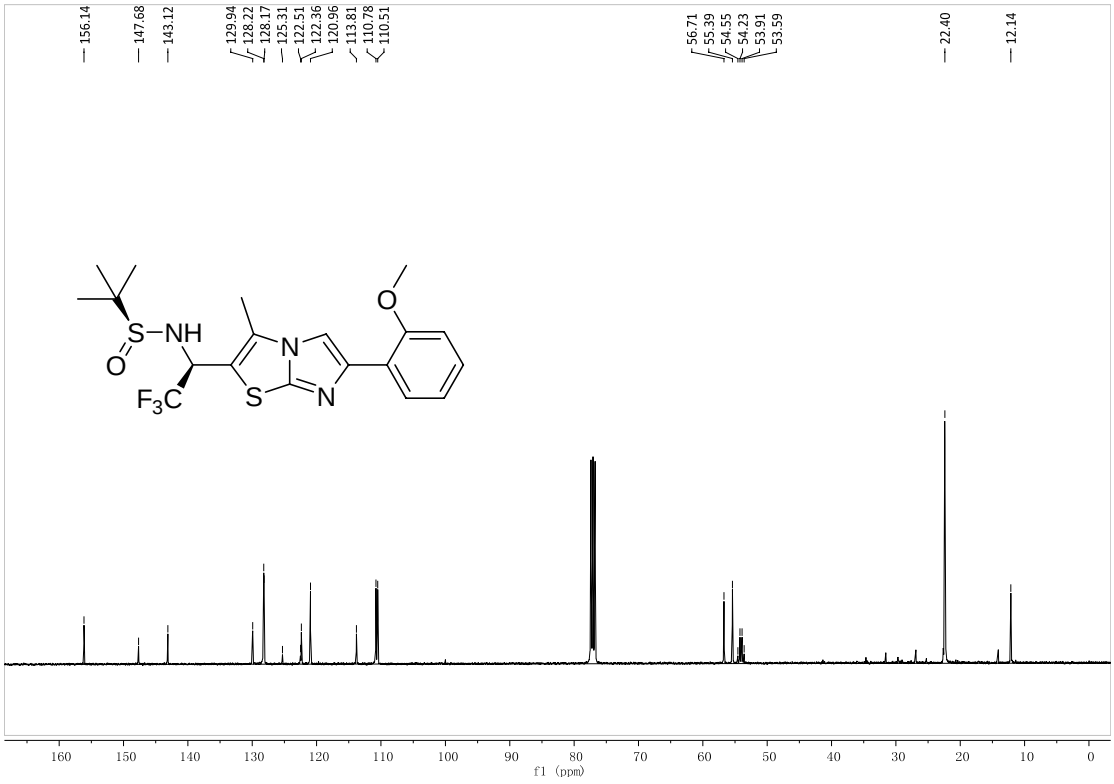
^{1}H and ^{13}C NMR of 3a



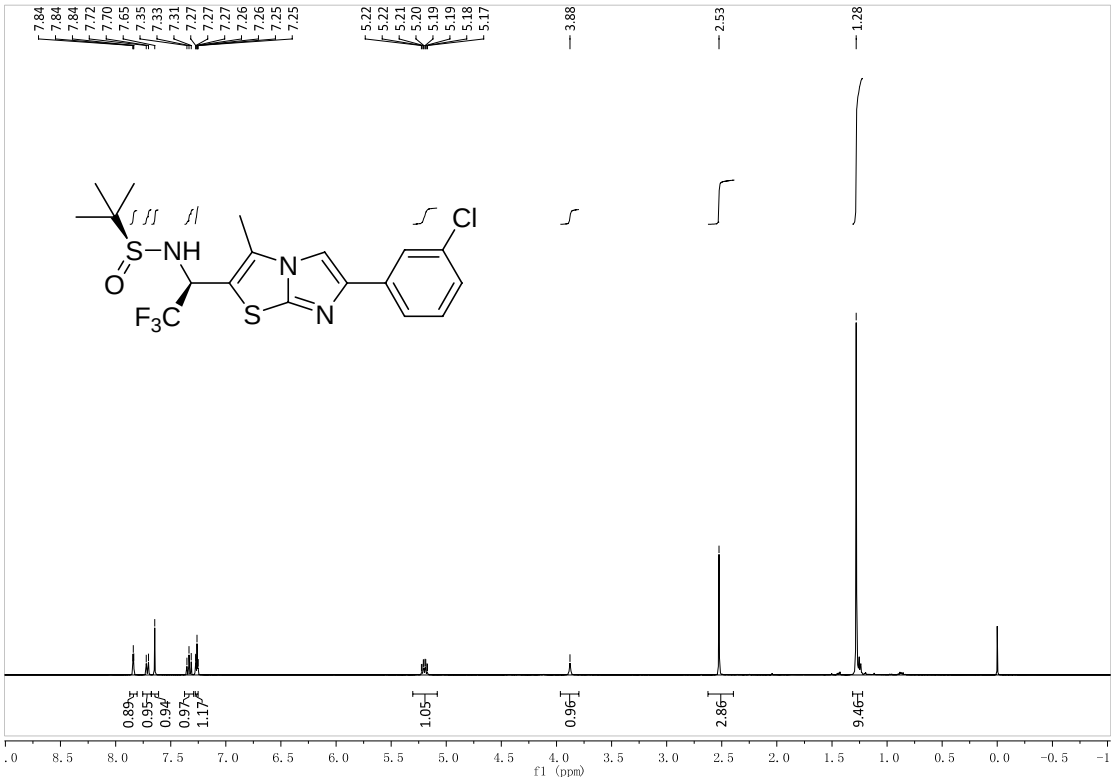


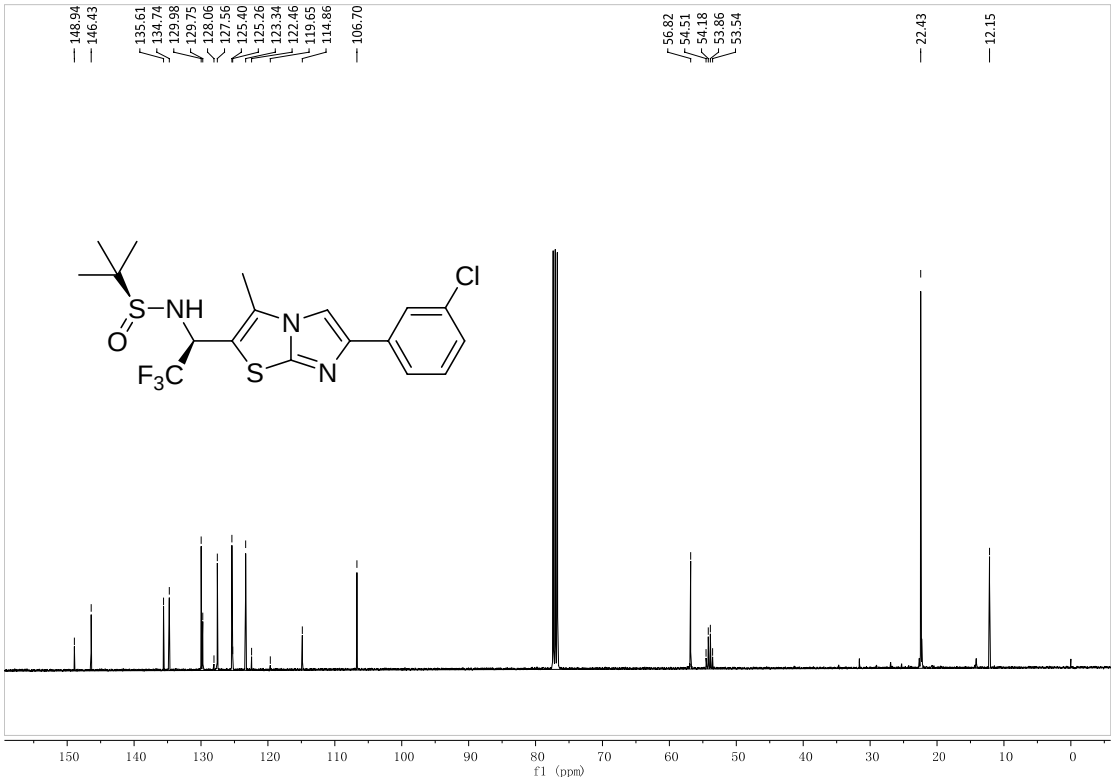
^{1}H and ^{13}C NMR of 3b



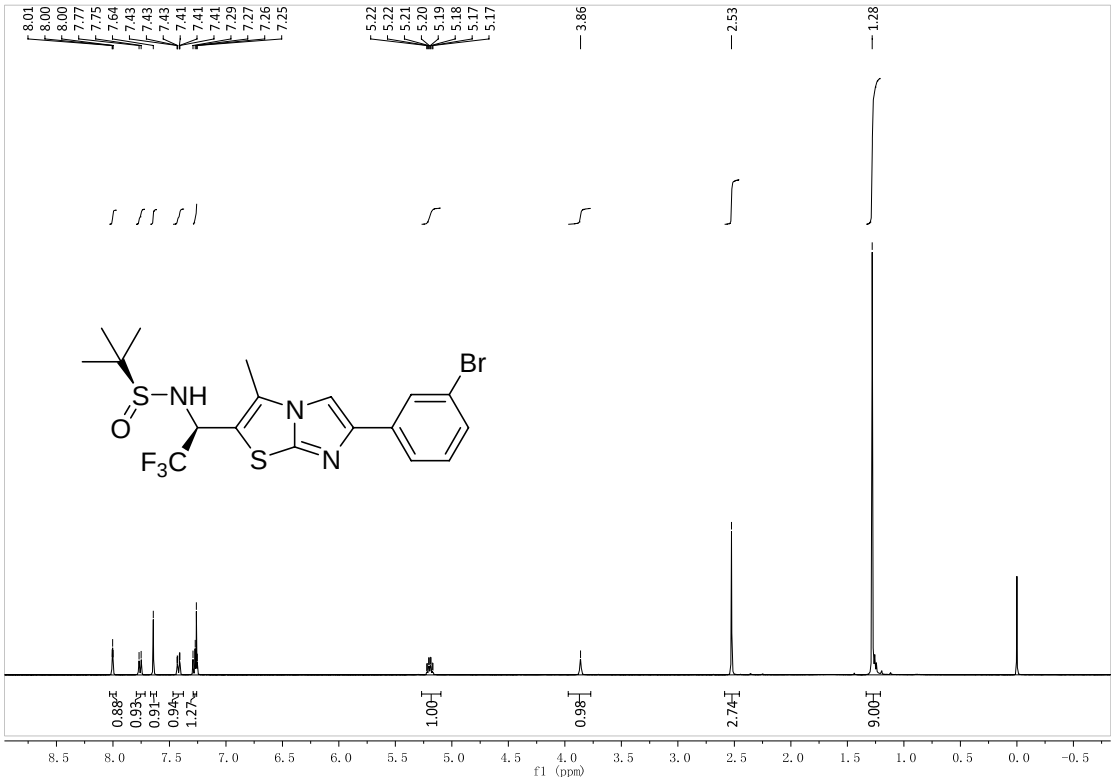


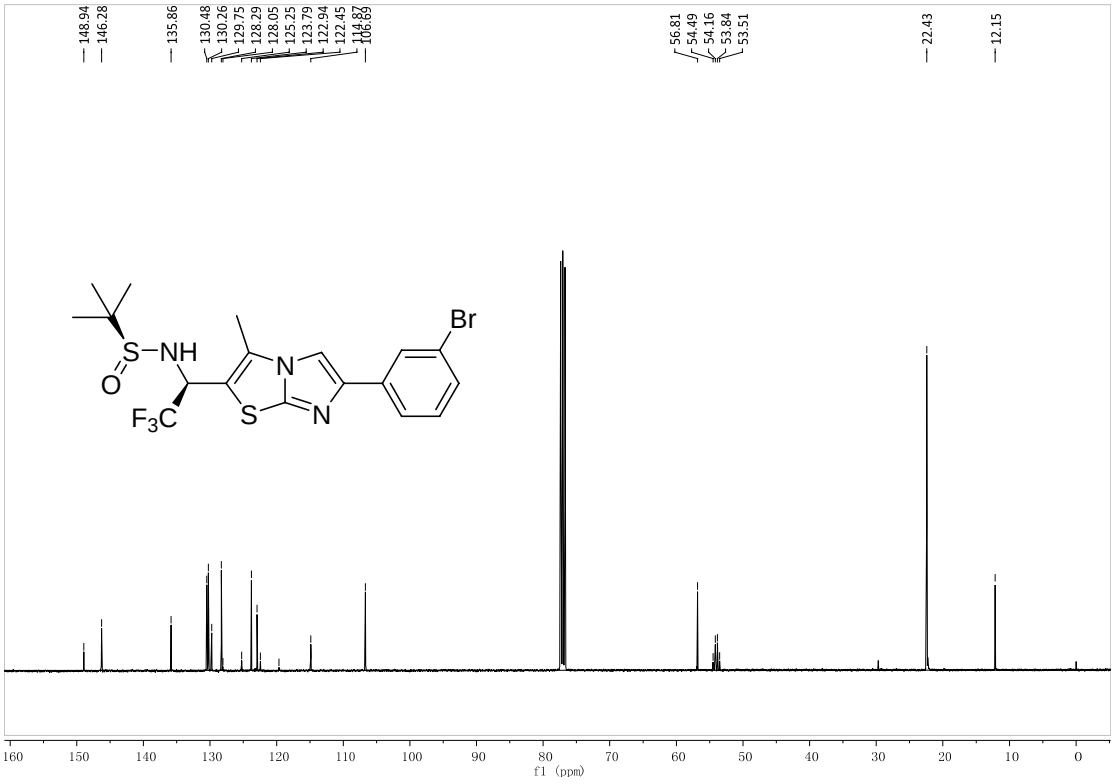
^{1}H and ^{13}C NMR of 3c



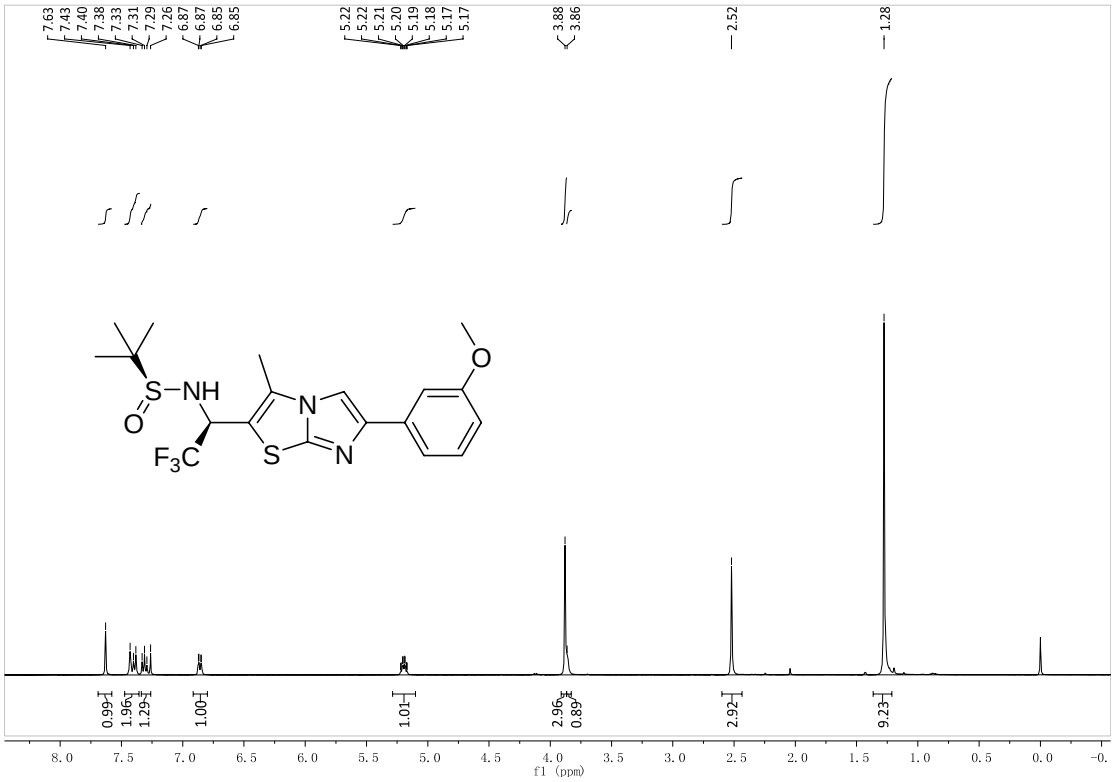


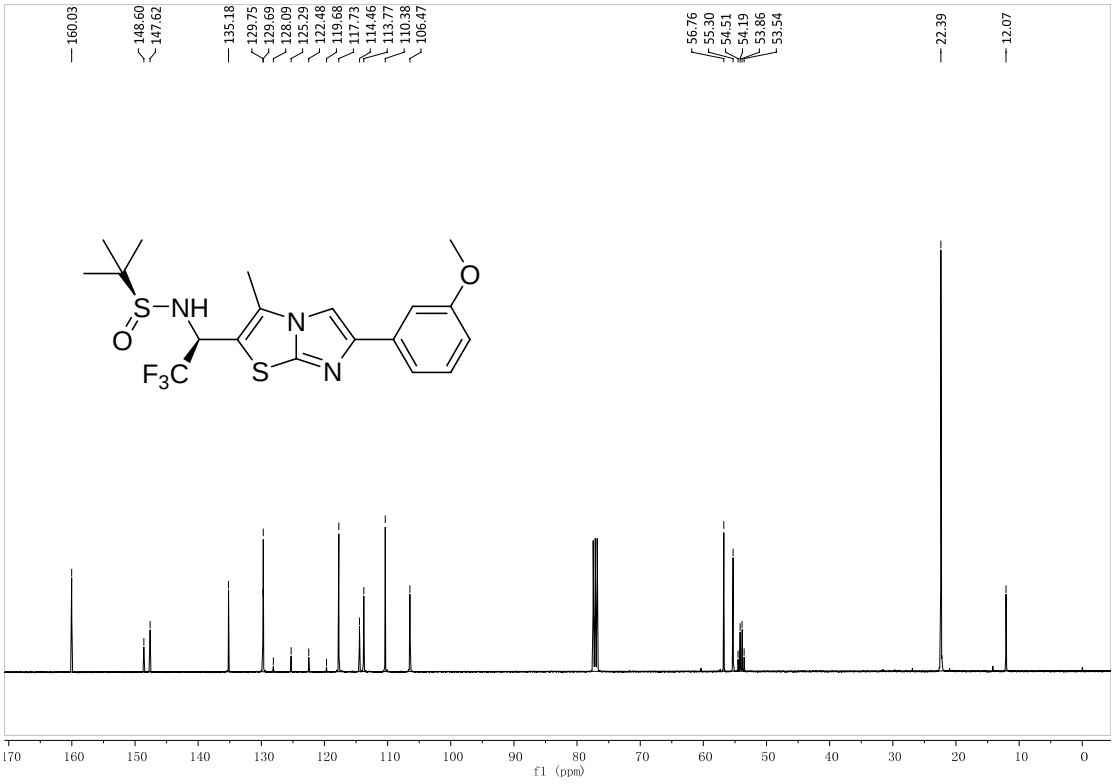
^{1}H and ^{13}C NMR of 3d



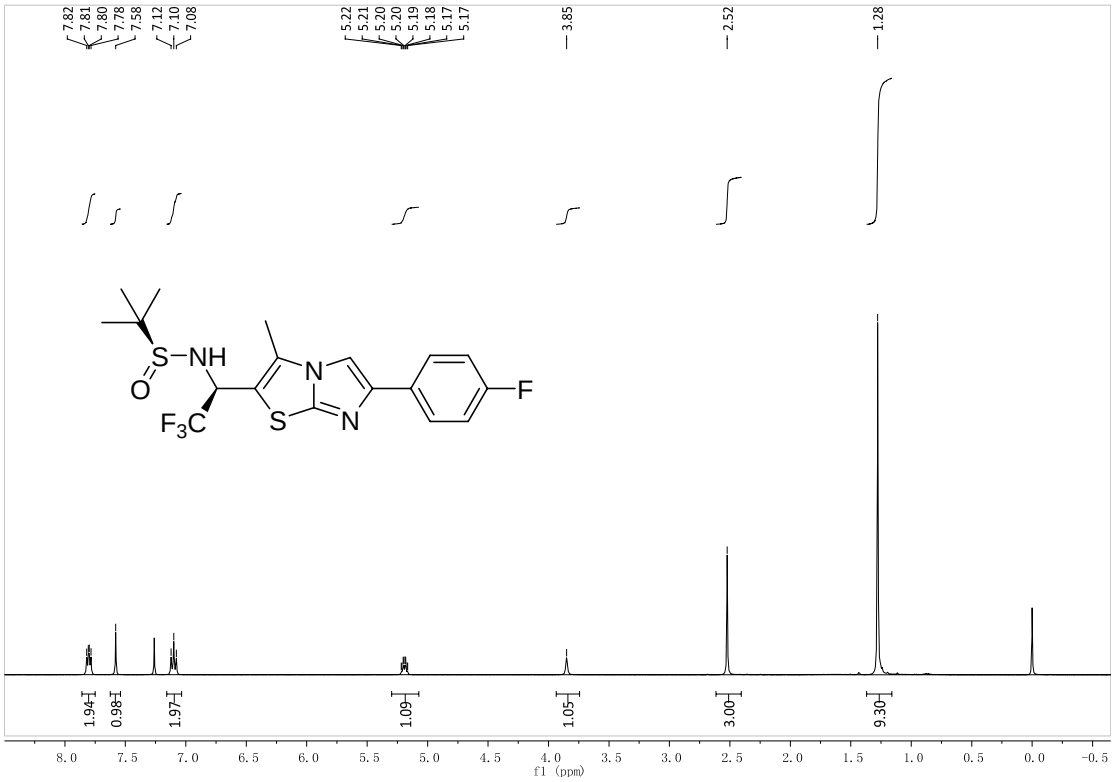


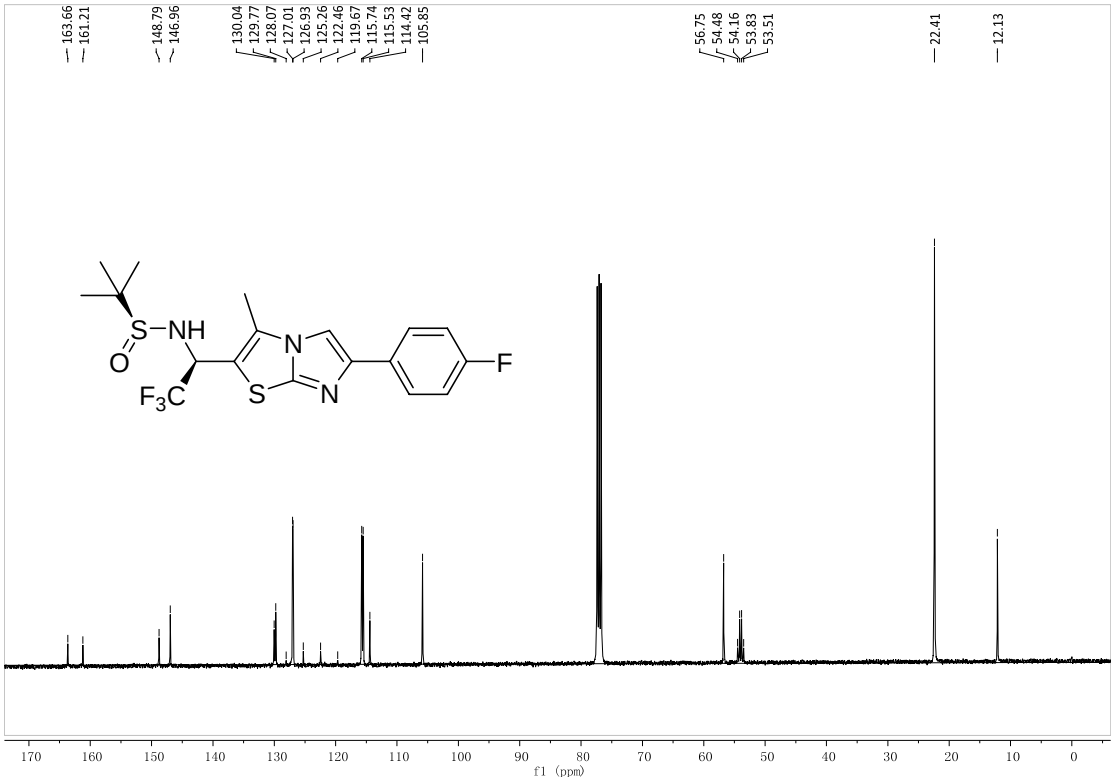
^{1}H and ^{13}C NMR of 3e



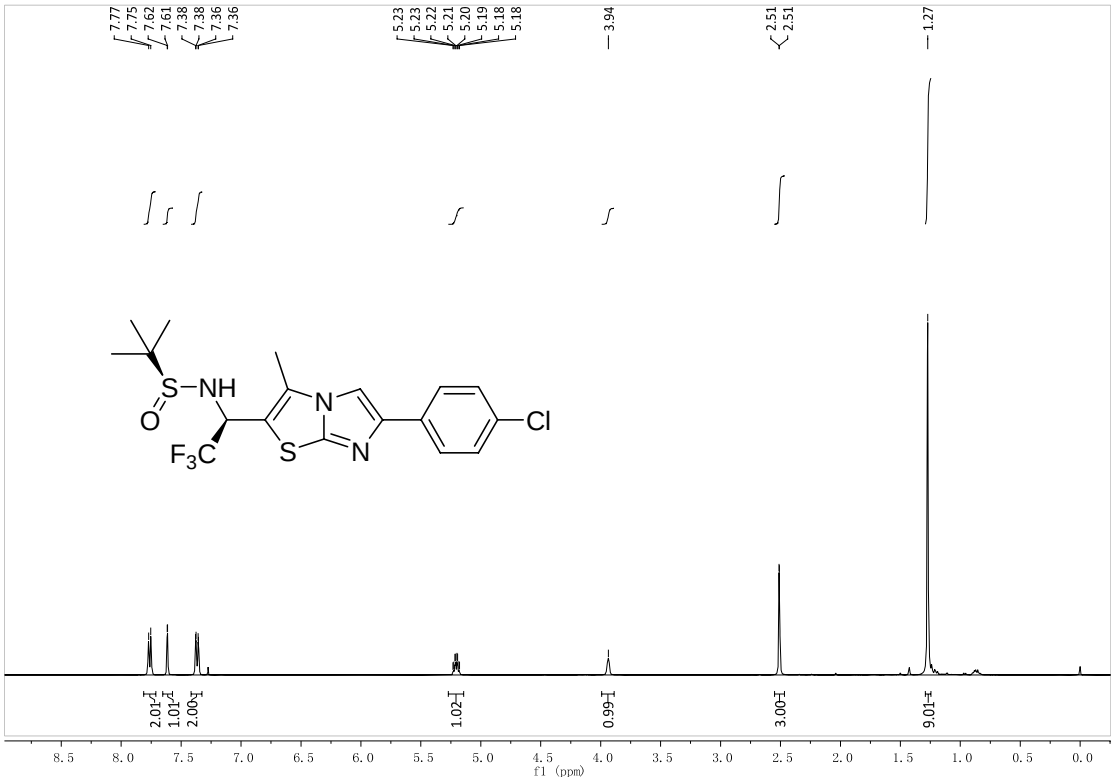


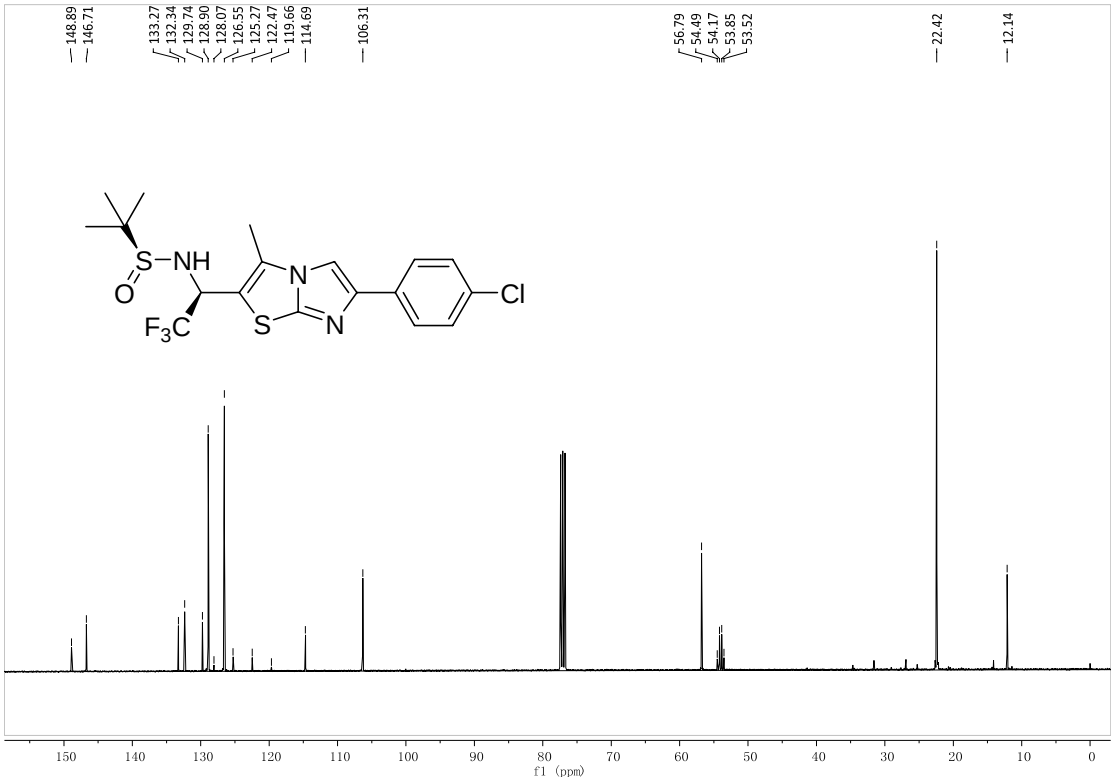
^{1}H and ^{13}C NMR of 3f



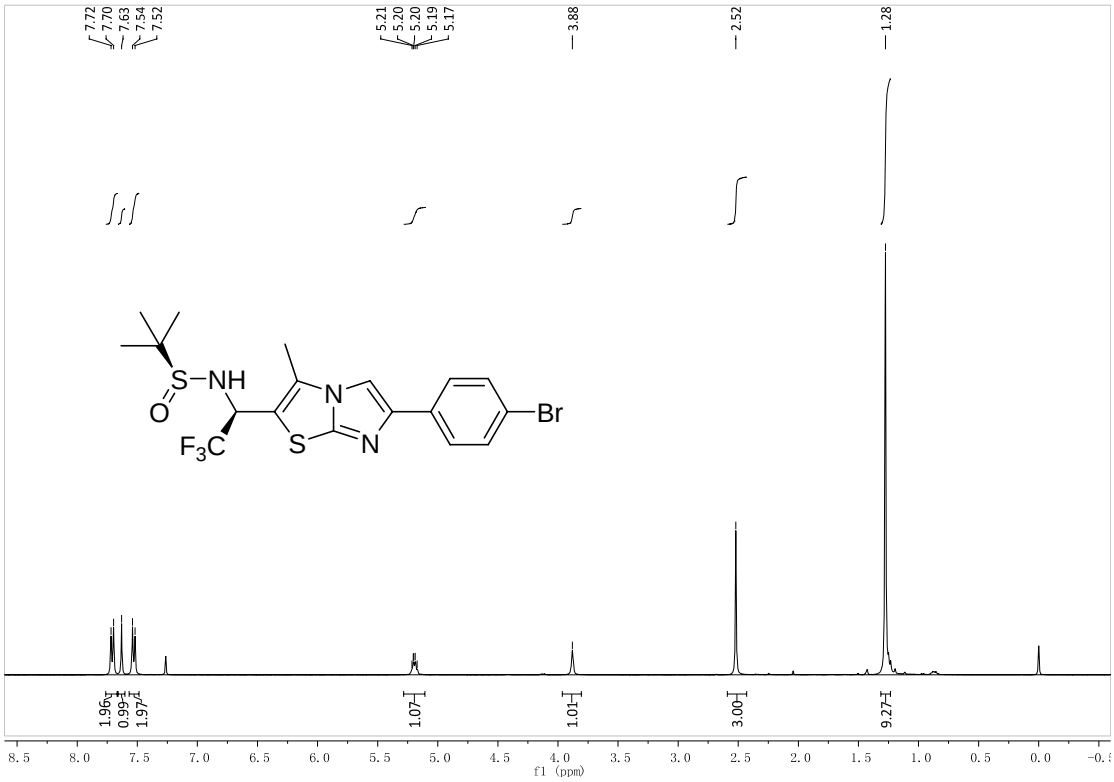


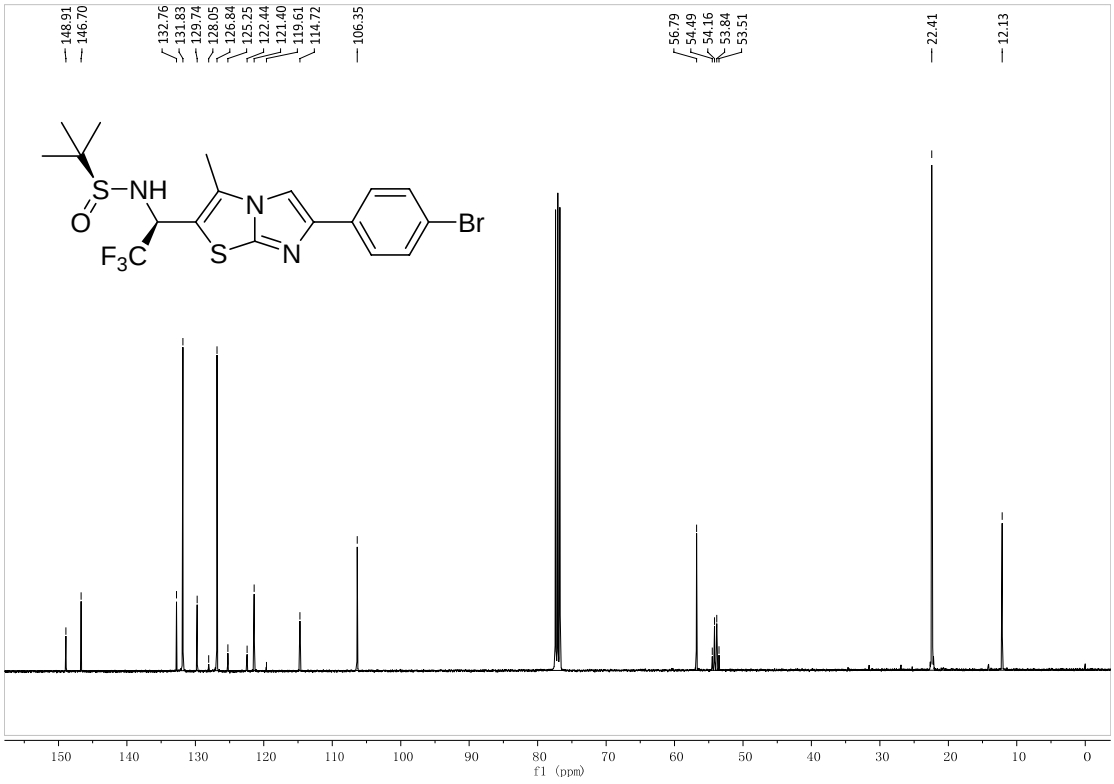
^{1}H and ^{13}C NMR of 3g



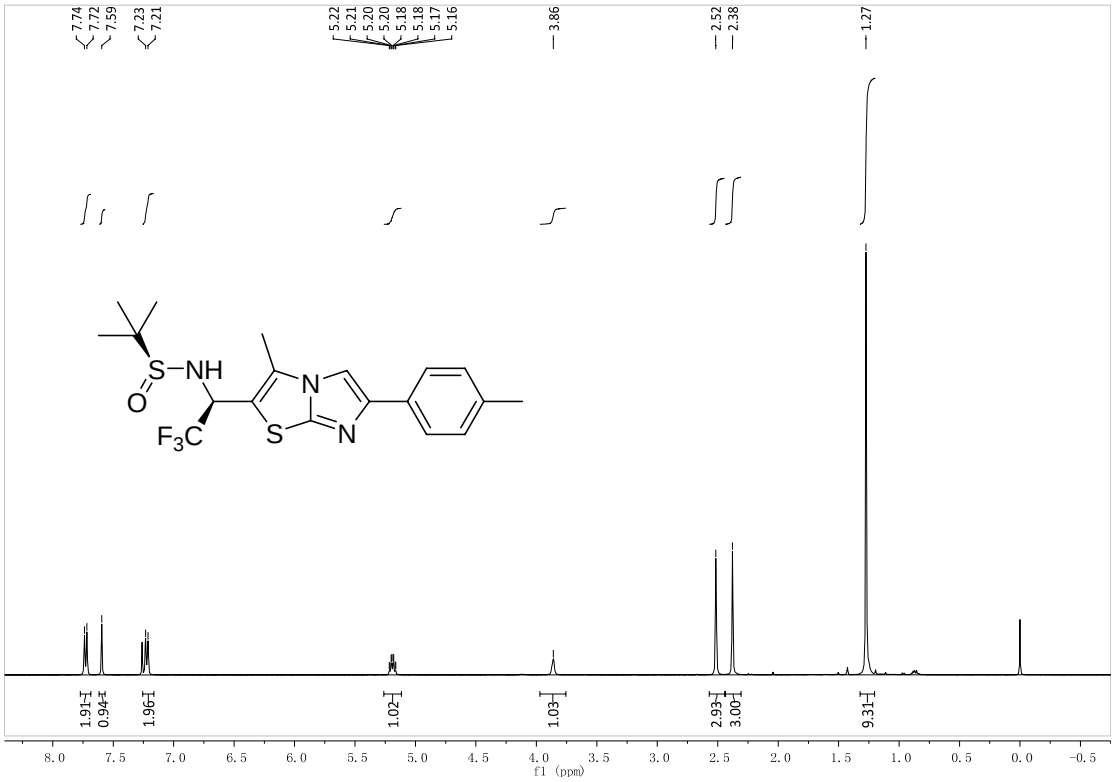


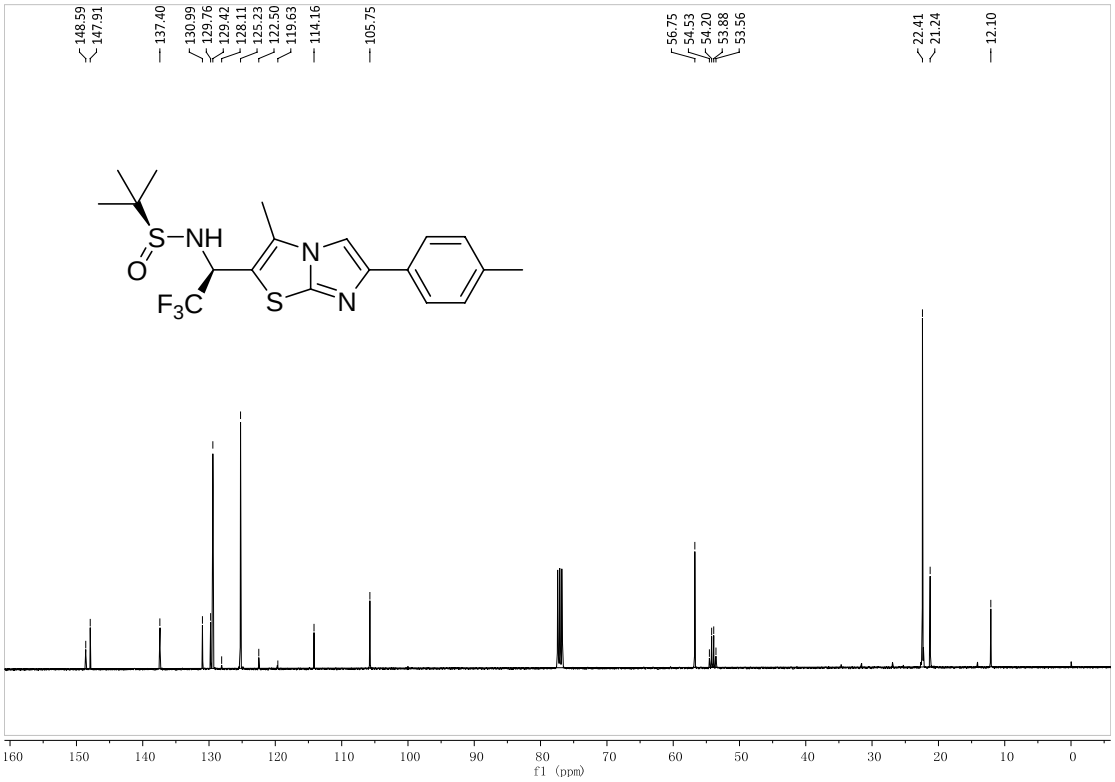
^{1}H and ^{13}C NMR of 3h



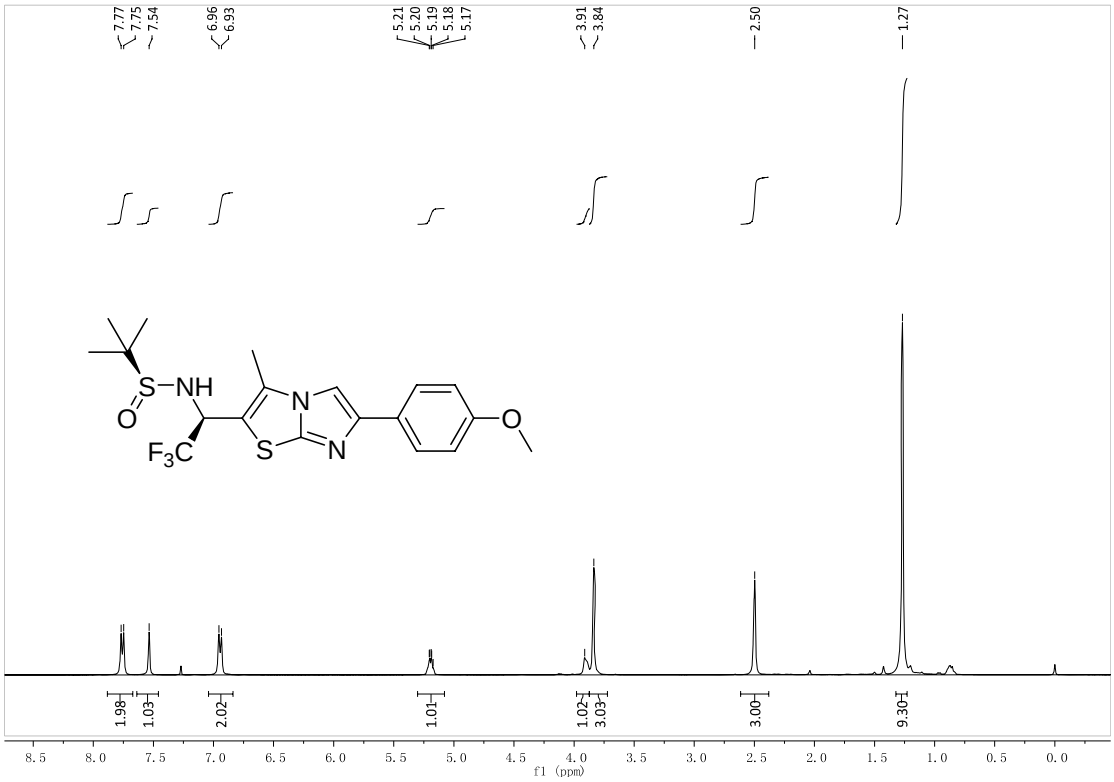


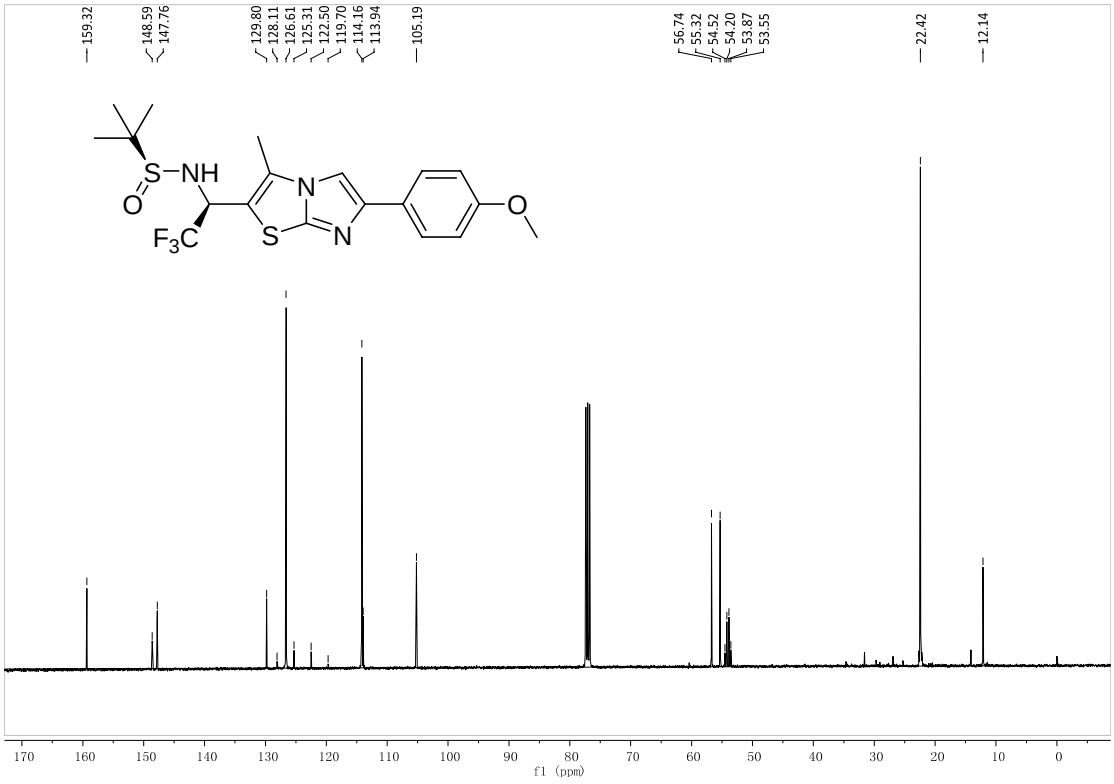
^{1}H and ^{13}C NMR of 3i



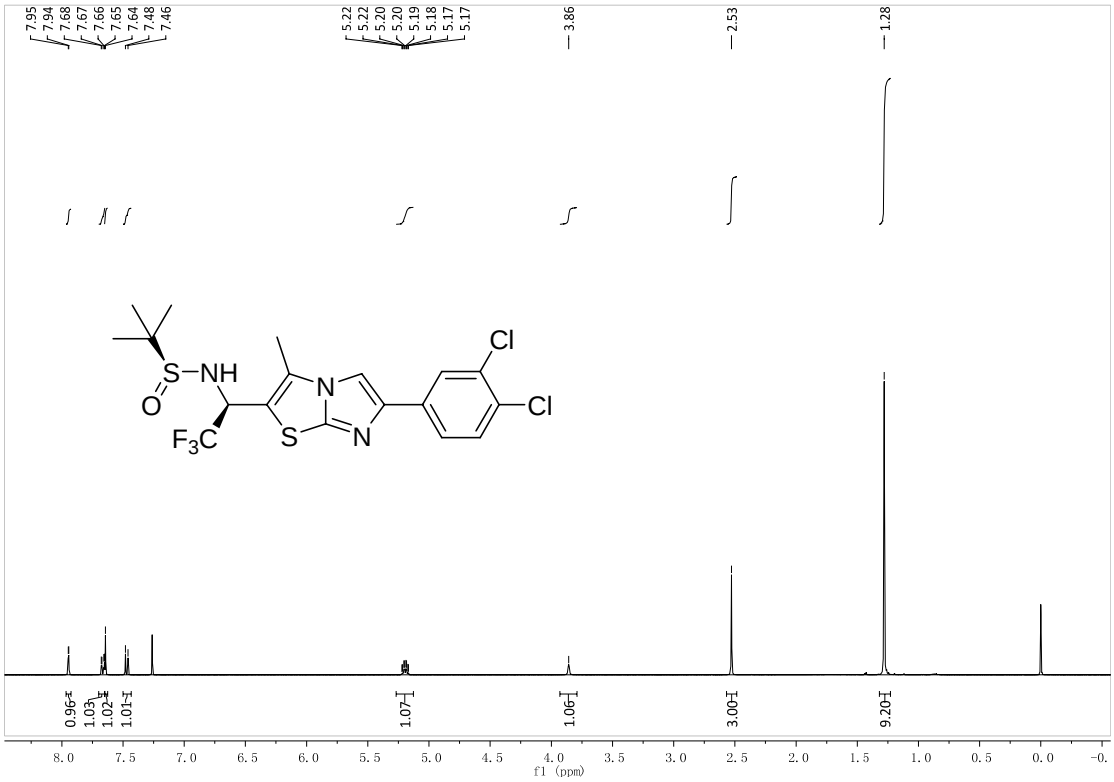


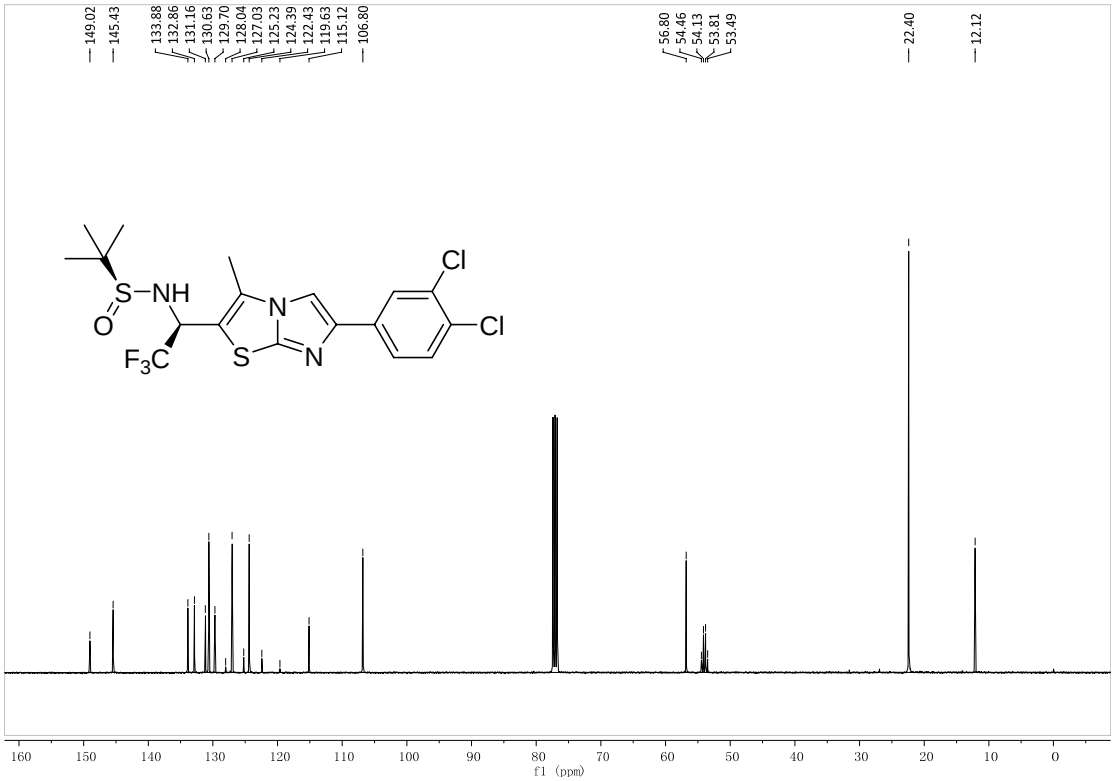
^{1}H and ^{13}C NMR of 3j



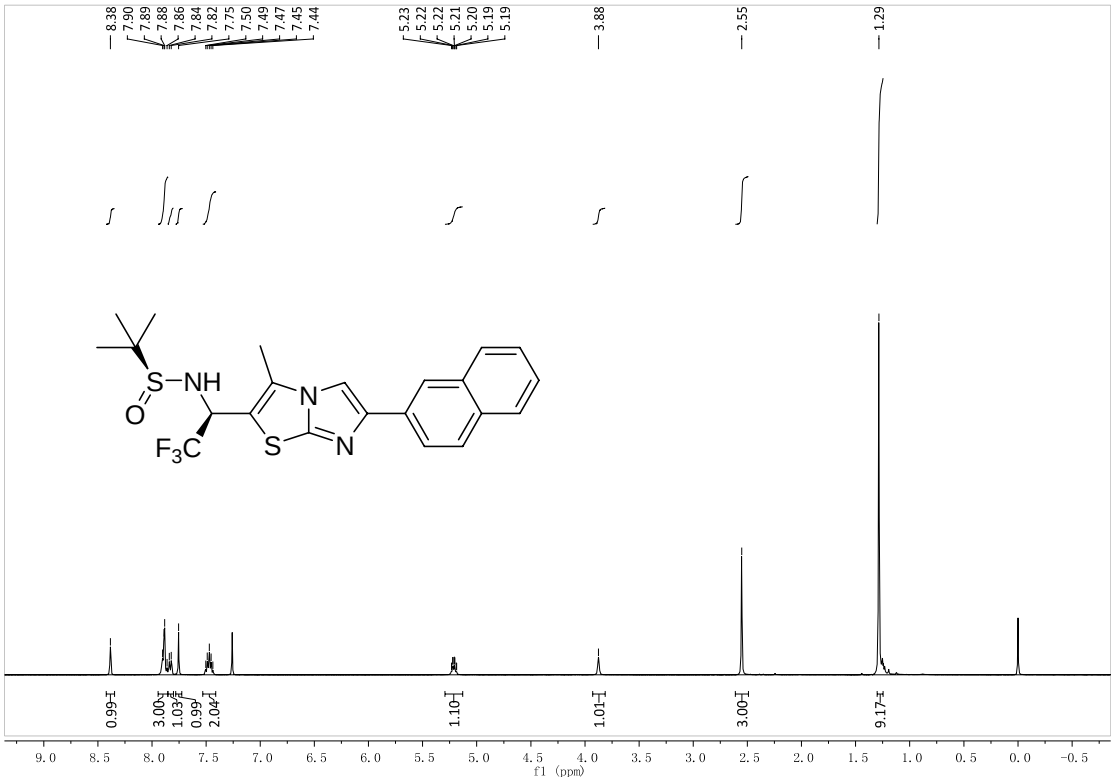


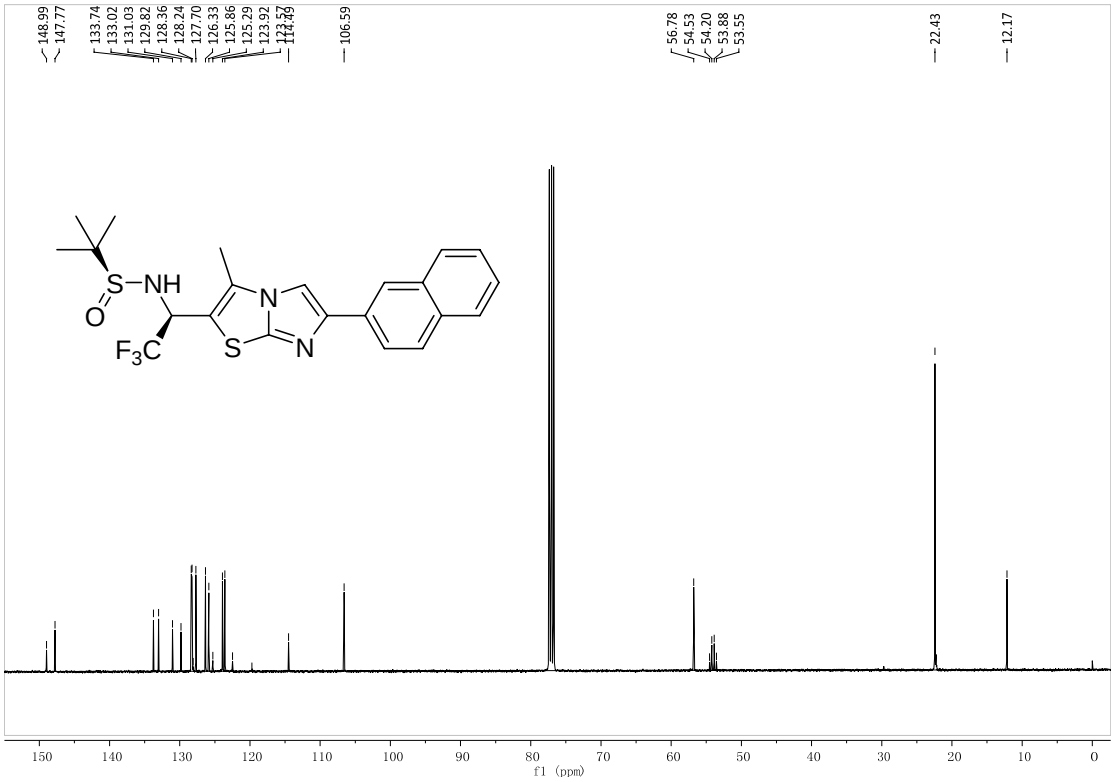
^{1}H and ^{13}C NMR of 3k





^{1}H and ^{13}C NMR of 3l





^{1}H and ^{13}C NMR of 4