Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Divergent Oriented Synthesis (DOS) of *aza*-Heterocyclic Amides through Palladium-catalyzed Ketenimination of 2-Iodo-*N*-(propa-1,2-dien-1-yl)anilines

Xiaoyan Chen,[a] Guanyinsheng Qiu,*[b] Renzhi Liu,[b] Dianpeng Chen,*[c] and Zhiyuan Chen*[a]

[a] Key Laboratory of Functional Small Organic Molecules, Ministry of Education and College of Chemistry & Chemical Engineering, Jiangxi Normal University, Nanchang, Jiangxi 330022, P. R. China. E-mail: zchen@jxnu.edu.cn

[b] College of Biological, Chemical Sciences and Engineering, Jiaxing University, Jiaxing 314001, Zhejiang, China. E-mail: qiuguanyinsheng@mail.zjxu.edu.cn

[c] Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, Shandong, China; Email: chendp@zju.edu.cn

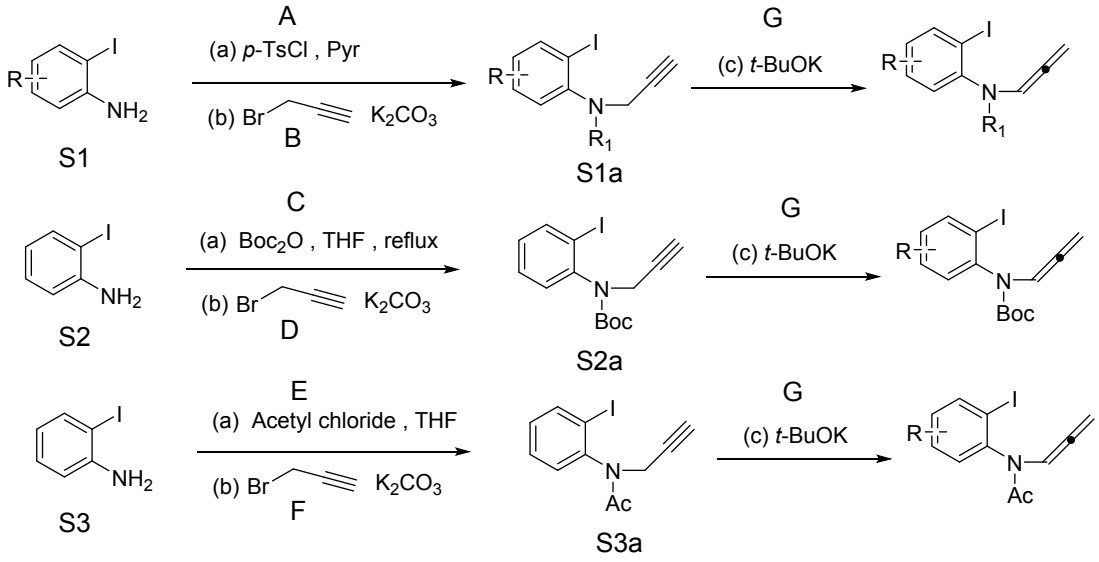
Content

General experimental information.

All reactions were performed in flame-dried glassware under nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased from Aldrich, Acros, Alfa Aesar, or TCI unless otherwise noted. Chromatographic separations were performed using Silicycle 43-60 Å SiO_2. ^{1}H and ^{13}C NMR spectra were obtained on Varian VI-400 and VI-500 spectrometers using $CDCl_3$ with TMS or residual solvent as standard unless otherwise noted. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained on Bruker EQUINOX 55 FTIR. TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV, p-anisoladehyde and phosphomolybdic acid stains. Low-resolution mass spectra were obtained using Waters LCT® (ESI) and Agilent 1100 series LS/MSD (APCI). All spectral data obtained for new compounds are reported here.

General procedure for the preparation of starting materials.

Preparations of allenamides **1a - 1f**. [1]



General procedure A for tosylation:

To a solution of *o*-iodoaniline (1.00 g, 4.56 mmol) in pyridine (4.60 mL) was added *p*-TsCl (0.95 g, 4.83 mmol, 1.05 equiv) at 0°C. The reaction was stirred at rt over night before being quenched with H_2O. The quenched mixture was extracted three times with DCM. The combined organic layers were first washed with 1 M HCl to remove excess pyridine, and then with sat aq $NaHCO_3$, H_2O, sat aq NaCl, and dried over anhyd $MgSO_4$. The filtrate was concentrated under reduced pressure and purified using silica gel flash column chromatography [eluent, PE:EA=10:1] to give the desired product tosylamine (1.58 g, 87% yield).

General procedure B for propargylation:

To a solution of tosylamine (1.58 g, 1.0 equiv.) and potassium carbonate (1.50 equiv.) in DMF (0.4 M) at room temperature, 3-bromopropyne (1.20 equiv., 80% in toluene) was added. The mixture was allowed to stir at 60 ºC overnight. the reaction progress was monitored using TLC analysis. After the reaction was complete, the mixture was filtered through CeliteTM. The filtrate was concentrated under reduced pressure and purified using silica gel flash column chromatography [eluent, PE:EA=10:1] to give the desired propargyl amide **S1a** (1.58 g, 85% yield).

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[1] (a) S. He, R. P. Hsung, W. R. Presser, Z. Ma and B. J. Haugen. *Org. Lett*. 2014, **16**, 2180. (b) G. P. Silva, A. Ali, R. C. Silva, H. Jiang and M. W. Paixão. *Chem. Commun*. 2015, **51**, 15110.

General procedure C:

To a solution of *o*-iodoaniline (2.00 g, 9.14 mmol) in THF (20 mL) was added Boc_2O (2.19 g, 10.05 mmol, 1.10 equiv). The reaction was refluxed for 24 h before being quenched with H_2O. The mixture was extracted three times with DCM. The combined organic layer were washed with sat aq NaCl and dried over anhyd $MgSO_4$. The solution was filtered and concentrated under reduced pressure to give the crude Boc-protected anilide that was used in the next step without further purification.

General procedure D for propargylation:

To a solution of the crude Boc-protected anilide in DMF (45 mL) were added K_2CO_3 (1.90 g, 13.71 mmol, 1.5 eqequiv) and propargyl bromide (0.97 mL, 10.92 mmol, 1.20 equiv) at room. The reaction was stirred at rt for 0.5 h, than at 60°Cstirred overnight, and the reaction progress was monitored using TLC analysis. After the reaction was complete, the reaction was quenched with sat aq NH_4Cl. The quenched mixture was poured into H_2O and extracted three times with DCM. The combined organic layers were washed with equal volume of saturated aqueous NaCl and dried over anhyd. $MgSO_4$. After filtration and concentration under reduced pressure, the crude product was purified using silica gel flash column chromatography [eluent: PE:EA=15:1] to give the desired propargyl amide **S2a** (2.86 g, 88% yield over two steps).

General procedure E:

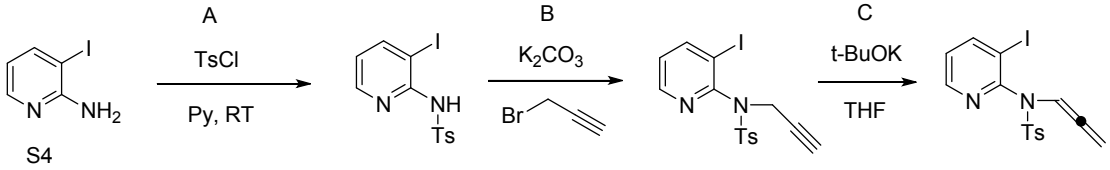
To a solution of *o*-iodoaniline (1.00 g, 4.56 mmol) in CH_2Cl_2 (22 mL) was added pyridine (1.10 mL, 13.70 mmol, 3.00 equiv) and Acetly chloride (1.40 mL, 6.84 mmol, 1.50 equiv). The reaction was stirred at rt overnight before being quenched by H_2O. The quenched mixture was extracted three times with DCM. The combined organic layers were washed with 1.0 M HCl, sat aq $NaHCO_3$, H_2O, and saturated NaCl, and dried over anhydrous $MgSO_4$. The solution was filtered and concentrated under reduced pressure to give the crude carbamate that was used in the next step without further purification.

General procedure F for propargylation:

To a solution of the above crude carbamate in DMF (25 mL) were added K_2CO_3 (1.90 g, 13.71 mmol, 1.5 equiv) and propargyl bromide (0.97 mL, 10.92 mmol, 1.20 equiv)

at room. The reaction was stirred at room temperature for 0.5 h, than stirred at 60°C for overnight. After the reaction was completed as monitored by TLC, the reaction was quenched with sat aq NH_4Cl. The quenched mixture was poured into H_2O and extracted three times with DCM. The combined organic layers were washed with sat aqNaCl and dried over anhyd $MgSO_4$. After filtration and concentration under reduced pressure, the crude product was purified using silica gel column chromatography [gradient eluent: PE:EA=20:1] to give the allenamide 10k directly (0.64 g, 50% yield over two steps).

General procedure for the preparation of pyridine-based allenamide:[2]



S4

General procedure A for tosylation:

Prepared according to General Procedure E using 3-iodopyridin-2-amine (250 mg, 1.14 mmol, 1.0 equiv), 4-methylbenzenesulfonic anhydride (179 mg, 1.14 mmol, 1.0 equiv) and DMAP (13.9 mg, 0.11 mmol, 0.1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 0-30% EtOAc/CH_2Cl_2) to afford the title compound as a white solid (248 mg, 0.66 mmol, 58%).

General procedure B for propargylation:

To a solution of tosylamine (1.00 equiv) and potassium carbonate (1.50 equiv) in DMF (0.4 M) at room temperature, 3-bromopropyne (1.20 equiv, 80% in toluene) was added. The mixture was allowed to stir at 60 ºC overnight. The reaction progress was monitored using TLC analysis. After the reaction was complete, the mixture was filtered through CeliteTM. The filtrate was concentrated under reduced pressure and purified using silica gel flash column chromatography [eluent: PE:EA=10:1] to give the desired propargyl amide (1.58 g, 70% yield).

[2] S. Jalal, K. Paul and U. Jana. *Org. Lett.* 2016, **18**, 6512.

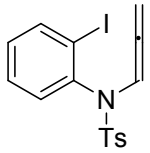
General procedure C for allenation reaction:

To a solution ofamide(1.00 g, 2.43 mmol) in THF (13 mL) was added *t*-BuOK (1.0 M solution in THF, 0.72 mL, 0.72 mmol, 0.30 equiv) at 0°C. The reaction was stirred at rt for 1 h before being concentrated under reduced pressure. Subsequently, the residue was suspended in DCM and then filtered through Celite. The filtrate was concentrated under reduced pressure and the crude residue was purified using silica gel flash column chromatography [eluent: PE:EA=100:1] to give the desired allenamide **10a** (0.80 mg, 55% yield).

General procedure G for allenation reaction:

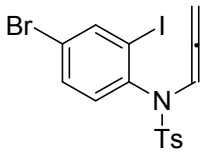
To a solution of allenamide **S1a** (1.00 g, 2.43 mmol) in THF (13 mL) was added t-BuOK (1.0 M solution in THF, 0.72 mL, 0.72 mmol, 0.30 equiv) at 0°C. The reaction was stirred at rt for 1 h before being concentrated under reduced pressure. Subsequently, the residue was first suspended in DCM and then filtered through CeliteTM. The filtrate was concentrated under reduced pressure and the crude residue was purified using silica gel flash column chromatography [eluent:PE:EA=100:1] to give the desired allenamide **1a**.

CHARACTERIZATIONS OF ALLENAMIDES 1a-f.



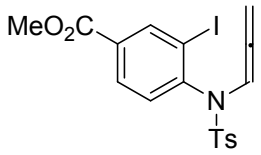
1a: 1.26 g (80% yield); yellow solid, mp 78-79 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 5.00 (m, 2H), 6.76 (m, *J* = 1.6 Hz, 1H), 7.02 (m, 1H), 7.09 (t, *J* = 6.4 Hz,1H), 7.22 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.68 (m, 2H), 7.89 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 21.9, 87.9, 102.2, 128.2, 128.8, 130.0, 130.4, 130.5,136.3, 140.2, 140.5, 144.4, 201.5; **IR (neat) cm^{-1}** 3043m, 2360m, 1434s, 1353s, 1159s, 1018s, 714s, 661s.



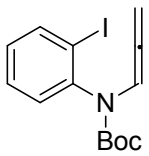
1b: 0.74 g (71% yield); brown solid; mp 154-155 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 5.04 (m, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 7.06 (t, *J* = 6.4 Hz, 1H), 7.34 (m, 3H), 7.66 (m, 2H), 8.03 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 21.9, 88.4, 102.0, 103.0,123.6, 128.2, 130.1, 131.4, 132.1, 136.0, 139.4, 142.7, 144.7, 201.3; **IR (neat) cm^{-1}** 2970m, 2360m,1737s, 1355s, 1161s, 716, 665s; **mass spectrum (ESI):** m/e (% relative intensity) 492.0 $(M+H)^+$.



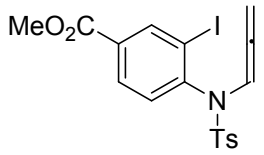
1c: 0.40 g (40% yield); white solid; mp 150-151°C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.77(s, 3H), 4.98 (m, 1H), 5.06 (m, 1H), 6.62 (d, *J* = 8.8 Hz, 1H), 6.73 (m, 1H), 7.09 (t, *J* = 6.0 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 21.9, 55.9, 88.0, 102.5, 102.6, 114.6, 125.2,128.1, 129.9, 130.5, 132.8, 136.3, 144.3, 159.9, 201.5; **IR (neat) cm $^{-1}$** 2925m, 2360m, 1737m, 1485s,1355s, 1227s, 1162s, 837s, 667s; **mass spectrum (ESI):** m/e (% relative intensity) 442.1 (100) $(M+H)^+$.



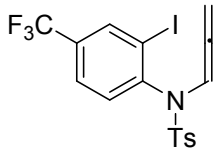
1d: 2.3 g (79% yield); yellow solid; mp 68-69 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38-1.59 (m, 10H), 5.00 (m, 2H), 7.00 (m, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.18-7.36 (m, 3H), 7.85 (d, *J* = 7.2Hz, 1H); **^{13}CNMR (100 MHz, $CDCl_3$)** δ 28.3, 81.7, 87.1, 99.8, 101.3, 124.9, 129.0, 129.3, 129.8, 139.1,139.5, 142.1, 151.6, 201.9; **IR (neat) cm^{-1}**3394w, 2977m, 2359w, 1734s, 1515s, 1365s, 1319s, 1154s, 1016s, 857s, 758s; **mass spectrum (ESI):** m/e (% relative intensity) 375.1 (100) $(M+NH_4)^+$.



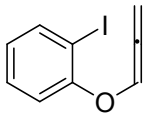
1e: 0.67 g (48% yield); yellow solid; mp 104-105 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.91 (s, 3H), 5.01 (s, 2H), 6.85 (d, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 6.4 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.89 (m, 1H), 8.54 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 21.9, 52.8, 88.3, 101.8, 128.2, 130.0, 130.1, 130.3, 131.9, 136.0, 141.6, 144.3, 144.8, 165.1, 201.4; **IR (neat) cm^{-1}** 3464w, 3360w, 3944m, 2361m, 1718s, 1280s, 1163s, 663s; **mass spectrum (ESI):** m/e (% relative intensity) 470.1 (100) $(M+NH_4)^+$.



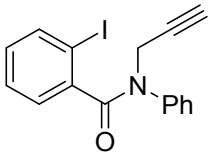
1f:1,o g (55% yield); yellow solid; mp 91-92°C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 2.1 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.55 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 1H), 5.07-5.25 (m, 1H), 4.58 (m, 2H), 4.20-4.22 (m, 2H), 2.45 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 210.09, 145.92, 144.35, 137.46, 136.18, 131.82 (q, ^2J = 33.2Hz), 131.34, 129.63, 128.21, 125.76, 121.63 (q, ^1J = 273.1 Hz), 103.49, 85.41, 76.44, 50.90, 21.80; **IR (neat) cm^{-1}**1955 (w), 1598 (w), 1354 (m), 1163 (s), 1131 (s), 1079 (s), 1026(w), 656 (m); **mass spectrum (ESI):** m/e (% relative intensity) 450.2 (100) $(M+H)^+$.



2-Iodophenyl Propa-dienyl Ether (8):[3] A suspension of 2-iodophenol (2.20 g, 10 mmol), propargyl bromide (1.79 g, 12 mmol), and potassium carbonate (1.66 g, 12 mmol) in THF (25 mL) was boiled under reflux for 16 h. Water (50 mL) and ethyl acetate (20 mL) were then added, the organic layer was separated, dried over Na_2SO_4, and evaporated under reduced pressure, and the residue was dissolved in 3:1 v/v *tert*-butyl alcohol-THF (20 mL). Potassium *tert*-butoxide (1.35 g, 12 mmol) was then added, and the resulting mixture was stirred at room temperature for 16 h. Then the solvent was evaporated under reduced pressure, and dichloromethane (20 mL) was added. The organic layerwas separated, washed with water (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was separated by column chromatography with petroleum ether/ethyl acetate as the eluent on a silica gel column to afford the corresponding product **8** as a colorless oil (1.4 g, 55% yield).

^{1}H NMR (400 MHz,$CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.84-6.76 (m, 2H), 5.43 (d, *J* = 5.9 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 202.3, 156.2, 139.6, 129.8, 124.7, 118.4,116.8, 90.4, 87.2. MS (EI,70eV) m/z 258, 219, 190, 131, 103, 91.



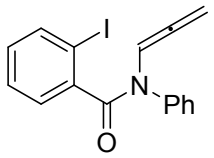
2-Iodo-*N*-phenyl-*N*-(prop-2-yn-1-yl)benzamide [4] **(S5):** Prepared in analogy to a published procedure. To a solution of 2-iodo benzoyl chloride (3.57 g, 13.4 mmol, 1 equiv) in dichloromethane (5 mL) at 0 °C, *N*-(prop-2-yn-1-yl)aniline 21 (1.76 g, 13.4 mmol, 1 equiv), followed by triethylamine (1.63 g, 16.1 mmol, 1.2 equiv) in dichloromethane (12 mL) were added. After stirring at room temperature for 12 h, the reaction mixture was quenched with water (50 mL). The organic layer was separated,

[3] G. Deng, M. Li, K. Yu, C. Liu, Z. Liu, S. Duan, W. Chen, X. Yang, H. Zhang and P. J. Walsh, *Angew. Chem. Int. Ed*. 2019, **58**, 2826.

[4] M. Braun, M. H. Katcher and A. G. Doyle, *Chem. Sci.*, 2013, **4**, 1216.

dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by automated column chromatography PE:EA=20:1 to afford the title compound (3.29 g, 9.11 mmol, 68% yield) as a yellow solid. mp:102-103°C.

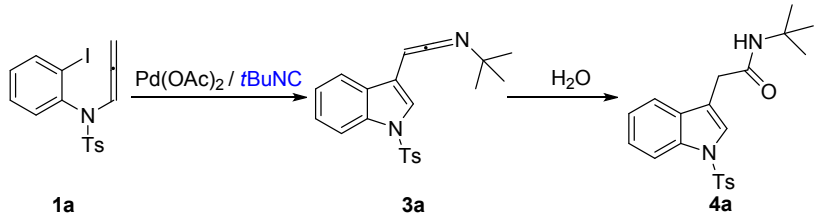
^{1}H NMR (500 MHz, CD_3OD) δ 7.69 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.32–7.47 (m, 2H), 7.05–7.33 (m, 5H), 6.85–7.01 (m, 1H), 4.70 (d, *J* = 2.5 Hz, 2H), 2.72 (t, *J* = 2.5 Hz, 1H); **^{13}C NMR** (125 MHz, CD_3OD) δ 171.84, 142.91, 142.32, 140.37,131.26, 130.06, 129.78, 129.33, 129.25, 128.55, 94.04, 79.20, 74.09, 39.68; **HRMS (ESI+)** calculated for $C_{16}H_{13}INO$ ($[M+H]^+$): 362.0042, found: 362.0028.



2-Iodo-*N*-phenyl-*N*-(propa-1,2-dien-1-yl)benzamide (10). Prepared in analogy to a published procedure. To a solution of 2-iodo-*N*-phenyl-*N*-(prop-2-yn-1-yl)benzamide (2.02 g, 5.6 mmol, 1.0 equiv) in DMF (12.5 mL) at room temperature, sodium hydroxide (269 mg, 6.72 mmol, 1.2 equiv) was added. After stirring at room temperature overnight, dichloromethane (25 mL) was added to the reaction mixture. The organic layer was washed with water (25 mL) and aqueous lithium chloride (10% w/w, 25 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by automated column chromatography (PE:EA=100:1) to afford the title compound (800 mg, 2.22 mmol, 40% yield) as a yellow oil.

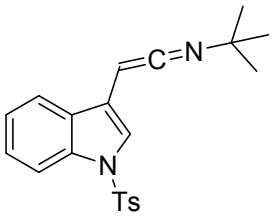
^{1}H NMR (500 MHz, MeOD) δ 7.66–7.76 (m, 2H), 7.29–7.34 (m, 2H), 7.12–7.27 (m, 5H), 6.87–6.97 (m, 1H),5.12 (d, *J* = 6.4 Hz, 2H); **^{13}C NMR (125 MHz, MeOD)** 202.89, 168.75, 141.51, 138.88, 138.70, 129.91, 128.57, 128.52, 128.44, 128.13, 127.13, 100.04, 92.70, 85.92; **HRMS** (ESI^+) calculated for $C_{16}H_{13}INO$ ($[M+H]^+$): 362.0042, found: 362.0029.

3. General procedure for the synthesis of intermediate 3 and compounds 4-11.



1a **3a** **4a**

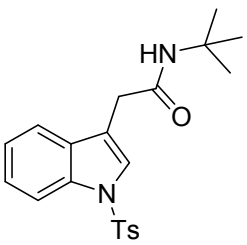
To a test tube equipped with a stir bar was charged with acetamide **1a** (0.30 mmol), *tert*-butyl isocyanide **2** (0.45 mmol), $Pd(OAc)_2$ (0.03 mmol, 10 mol%), Cs_2CO_3 (0.60 mmol, 2.0 equiv.), and dry MeCN (3.0 mL). The reaction was stirred at 60°C with N_2, The reaction was monitored by TLC. Upon completion, the reaction was allowed to cool to room temperature, diluted with ethyl acetate (5.0 mL), then filtered through a short pad of silica. The solid residue was washed with ethyl acetate (~15 mL) unless otherwise noted. Concentration of the filtrate under reduced pressure provided the crude product **3**, which was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1:3) to afford the desired compound **4.**



N-(*tert*-Butyl)-2-(1-tosyl-1*H*-indol-3-yl)ethen-1-imine **(3a)**

Yield 92%, 101 mg; yellow liquid.

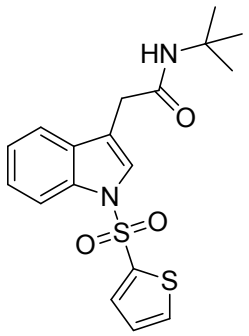
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.33-7.30 (m, 2H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 4.94 (s, 1H), 2.30 (s, 3H), 1.37 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 184.0, 144.8, 135.5, 135.1, 129.8, 129.3, 126.8, 124.8, 122.96, 119.9, 119.4, 114.9, 113.8, 59.7, 49.7, 28.0, 21.5; hydrolyzed into **4a** during HRMS process. **HRMS** (ESI^+) calculated for $C_{21}H_{25}N_2O_3S^+$ ($[M+H]^+$): 385.1580, found: 385.1566.



N-(*tert*-Butyl)-2-(1-tosyl-1*H*-indol-3-yl)acetamid **(4a)**

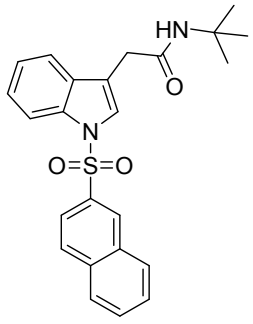
Yield 82%, 94.5 mg; yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 12.0 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 6.3 Hz, 2H), 5.28 (s, 1H), 3.52 (s, 2H), 2.32 (s, 3H), 1.21 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.8, 145.1, 135.2, 135.0, 130.1, 129.9, 126.8, 125.2, 124.70, 123.5, 119.6, 116.7, 113.8, 51.3, 34.4, 28.5, 21.6; **IR (neat)** 3312, 2925, 1651, 1172, 743, 670, 572; **HRMS** (ESI^+) calculated for $C_{21}H_{25}N_2O_3S^+$([M+H]$^+$): 385.1580, found: 385.1580.



N-(tert-butyl)-2-(1-(thiophen-2-ylsulfonyl)-1H-indol-3-yl)acetamide **(4b)**

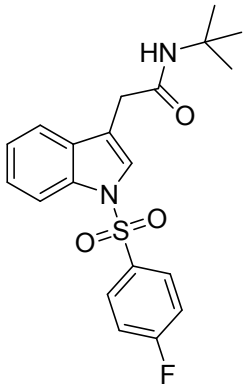
Yield 65%,73.5 mg; yellow solid, **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00 (d, *J* = 8.2 Hz, 1H), 7.66 (t, *J* = 8.2 Hz, 1H), 7.50 (d, *J* = 5.0 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 6.96 (m, 1H), 5.37 (s, 1H), 3.52 (s, 2H), 1.22 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.7, 137.9, 135.1, 133.6, 133.2, 130.3, 127.5, 125.4, 124.5, 123.8, 119.7, 117.6, 113.9, 51.3, 34.3, 28.6;**IR (neat)**3287, 2968, 1648, 1378, 1172, 722, 591; HRMS(ESI+) calculatedfor $C_{18}H_{21}N_2O_3S_2$+ ([M+H]$^+$): 377.0988, found: 377.0984.



N-(*tert*-Butyl)-2-(1-(naphthalen-2-ylsulfonyl)-1*H*-indol-3-yl)acetamide **(4c)**

Yield 70%, 88.3 mg; yellow solid.

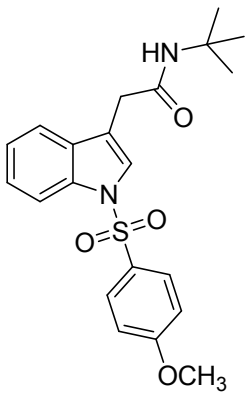
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.80-7.72 (m, 3H), 7.58-7.53 (m, 3H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.25-7.19 (m, 1H), 5.37 (s, 1H), 3.51 (s, 2H), 1.17 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.8, 135.3, 135.2, 134.8, 131.8, 130.2, 129.7, 129.5, 129.4, 128.5, 127.9, 127.8, 125.3, 124.7, 123.6, 121.3, 119.6, 116.9, 113.8, 51.3, 34.3, 28.5; **IR (neat)** 3311, 2960, 1652, 1170, 749, 664, 535; **HRMS** (ESI^+) calculated for $C_{24}H_{25}N_2O_3S+$ ($[M+H]^+$): 421.1580, found: 421.1578.



N-(*tert*-Butyl)-2-(1-((4-fluorophenyl)sulfonyl)-1*H*-indol-3-yl)acetamide **(4d)**

Yield 71%, 83 mg; yellow solid.

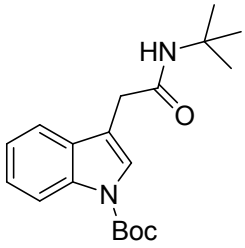
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.2 Hz, 1H), 7.90 – 7.86 (m, 2H), 7.47 (d, *J* = 2.6 Hz, 2H), 7.34 (t, *J* = 7.0 Hz, 1H), 7.27-7.23 (m, 1H), 7.10-7.05 (m, 2H), 5.37 (s, 1H), 3.51 (s, 2H), 1.23 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.7, 164.7 (d, ^1J = 242 Hz), 132.7, 134.0, 129.6 (d, ^2J = 21 Hz), 125.4, 124.5, 123.7, 119.7 (d, ^2J = 24 Hz), 117.3, 116.8, 116.6, 113.7, 51.4, 34.3, 28.6; **IR (neat)**3316, 1651, 1492, 1180, 843, 675, 574; **HRMS** (ESI^+) calculated for $C_{20}H_{22}FN_2O_3S+$ ($[M+H]^+$): 389.1330, found: 389.1350.



N-(*tert*-Butyl)-2-(1-((4-methoxyphenyl)sulfonyl)-1*H*-indol-3-yl)acetamide **(4e)**

Yield 77 %, 92.5 mg; yellow solid.

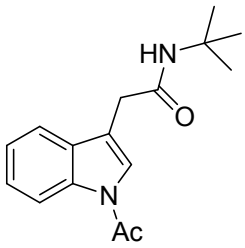
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.2 Hz, 1H), 7.78 (d, *J* = 7.0 Hz, 2H), 7.47 (s, 2H), 7.31-7.22 (m, 2H), 6.82 (d, *J* = 7.4 Hz, 2H), 5.41 (s, 1H), 3.73 (s, 3H), 3.50 (s, 2H), 1.20 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.9, 163.8, 135.2, 130.2, 129.4, 129.0, 125.1, 124.7, 123.4, 119.6, 116.6, 114.5, 113.7, 55.6, 51.3, 34.3, 28.5; **IR (neat)** 3296, 2925, 1654, 1213, 116, 743, 579; **HRMS** (ESI^+) calculated for $C_{21}H_{25}N_2O4S^+$ ($[M+H]^+$): 401.1530, found: 401.1538.



tert-Butyl 3-(2-(*tert*-butylamino)-2-oxoethyl)-1*H*-indole-1-carboxylate **(4f)**

Yield 57 %, 56.5 mg; white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 5.51 (s, 2H), 3.54 (s, 4H), 1.65 (s, 9H), 1.25 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.4, 149.5, 135.6, 129.8, 124.8, 124.5, 122.8, 119.1, 115.3, 114.4, 83.8, 51.3, 34.5, 28.6, 28.2. **IR (neat)** 3288, 2978, 1735, 1639, 1370, 1082, 769; **HRMS**(ESI^+) calculated for $C_{19}H_{27}N_2O_3$+ ($[M+H]^+$): 331.2016, found: 331.2006.

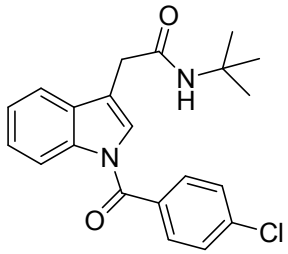


2-(1-Acetyl-1*H*-indol-3-yl)-*N*-(*tert*-butyl)acetamide **(4g)**

Yield 50 %, 41 mg; white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.38-7.34 (m, 2H), 7.31-7.25 (m, 1H), 5.46 (s, 1H), 3.55 (s, 2H), 2.61 (s, 3H), 1.29 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.0, 168.4, 135.9, 129.9, 125.6, 123.9, 123.8, 118.8, 116.7, 116.2, 51.4, 34.3, 28.6, 24.0; **IR (neat)** 3298, 2961, 1696, 1640, 1453,

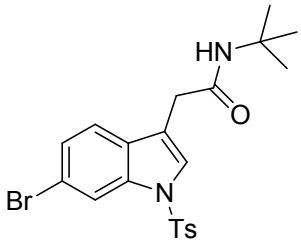
1224, 746; **HRMS** (ESI$^+$) calculated for $C_{16}H_{21}N_2O_2^+$ ([M+H]$^+$): 273.1598, found: 273.1584.



N-(*tert*-Butyl)-2-(1-(4-chlorobenzoyl)-1*H*-indol-3-yl)acetamide **(4h)**

Yield 37%, 41 mg; white solid.

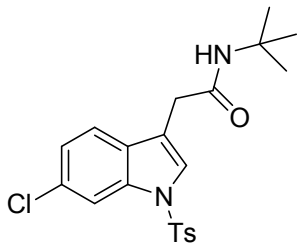
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.53 (q, *J* =8.0 Hz, 3H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 10.8 Hz, 1H), 5.42 (s, 1H), 3.53 (s, 2H), 1.27 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.8, 167.3, 138.4, 136.3, 132.7, 130.6, 130.2, 129.0, 125.7, 125.6, 124.3, 119.1, 116.6, 116.2, 51.4, 34.3, 28.6; **IR (neat)** 3280, 1692, 1641, 1357, 1147, 874, 755; **HRMS**(ESI+) calculated for $C_{21}H_{22}ClN_2O_2$+ ([M+H]$^+$): 369.1364, found: 369.1366.



2-(6-Bromo-1-tosyl-1*H*-indol-3-yl)-*N*-(*tert*-butyl)acetamide **(4i)**

Yield 76%, 106 mg; yellow solid;

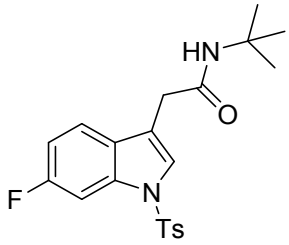
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.44 (s, 1H), 7.32 (s, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 5.42 (s, 1H), 3.46 (s, 2H), 2.31 (s, 3H), 1.22 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.6, 145.4, 135.8, 134.8, 130.1, 129.1, 126.8, 126.7, 125.0, 120.9, 118.8, 116.7, 116.6, 51.4, 34.1, 28.5, 21.6; **IR (neat)** 3374, 2897, 1632, 1172, 854, 665,554; **HRMS** (ESI$^+$) calculated for $C_{21}H_{24}BrN_2O_3S$+ ([M+H]$^+$): 463.0686, found: 463.0682.



N-(*tert*-Butyl)-2-(6-chloro-1-tosyl-1*H*-indol-3-yl)acetamide **(4j)**

Yield 71%, 89 mg; yellow solid.

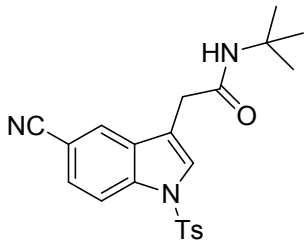
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.4 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.46 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.22 (s, 1H), 7.20-7.16 (m, 2H), 5.42 (s, 1H), 3.46 (s, 2H), 2.31 (s, 3H), 1.22 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.6, 145.4, 135.5, 134.8, 131.1, 130.1, 128.8, 126.7, 125.1, 124.1, 120.5, 116.6, 113.9, 51.4, 34.2, 28.5, 21.6; **IR (neat)** 3406, 2963, 1648, 1365, 1172, 670, 579; **HRMS** (ESI^+) calculated for $C_{21}H_{24}ClN_2O_3S^+$ ($[M+H]^+$): 419.1191, found: 419.1189.



N-(*tert*-Butyl)-2-(6-fluoro-1-tosyl-1*H*-indol-3-yl)acetamide **(4k)**

Yield 53%, 64 mg; yellow solid.

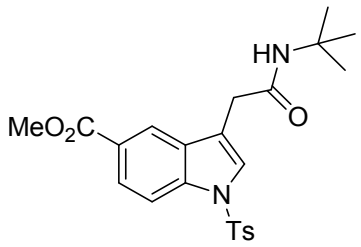
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.88 (m, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.51 (s, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.13-7.10 (m, 1H), 7.03-6.99 (m, 1H), 5.55 (s, 1H), 3.44 (s, 2H), 2.29 (s, 3H), 1.23 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.6, 159.6 (d, ^1J = 241.2 Hz), 145.3, 134.8, 131.85, 130.80, 130.0, 126.7,126.5, 126.3, 116.8, 114.8, 113.1 (d, ^2J = 25.6 Hz), 105.4 (d, ^2J = 24.2 Hz), 51.4, 34.1, 28.5, 21.5. **IR (neat)** 3313, 2924, 1651, 1174, 809, 670, 584; HRMS(ESI+) calculatedfor $C_{21}H_{24}FN_2O_3S$+ ($[M+H]^+$): 403.1486, found: 403.1478.



N-(*tert*-Butyl)-2-(5-cyano-1-tosyl-1*H*-indol-3-yl)acetamide **(4l)**

Yield 54%, 66 mg; yellow solid.

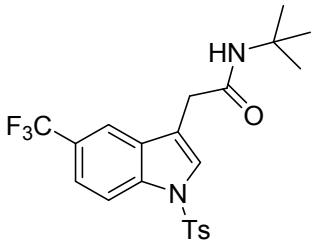
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.6 Hz, 1H), 7.85 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.63 (s, 1H), 7.54-7.52 (m, 1H), 7.25-7.23 (m, 2H), 5.50 (s, 1H), 3.49 (s, 2H), 2.34 (s, 3H), 1.29 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.1, 145.8, 136.7, 134.6, 130.5, 130.2, 127.9, 126.9, 126.5, 124.9, 119.2, 116.3, 114.4, 106.8, 51.6, 33.8, 28.6, 21.6;**IR (neat)** 3316, 2922, 1365, 1176, 743, 586, 569; **HRMS** (ESI^+) calculated for $C_{22}H_{24}N_3O_3S+$ ($[M+H]^+$): 410.1533, found: 410.1537.



Methyl 3-(2-(*tert*-butylamino)-2-oxoethyl)-1-tosyl-1*H*-indole-5-carboxylate **(4m)**

Yield 55%, 73 mg; yellow solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.01 (s, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.57 (s, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 5.41 (s, 1H), 3.90 (s, 3H), 3.54 (s, 2H), 2.32 (s, 3H), 1.26 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.5, 167.0, 145.4, 137.7, 134.9, 130.1, 130.0, 126.8, 126.2, 125.9, 125.5, 121.9, 117.0, 113.5, 52.1, 51.5, 34.0, 28.6, 21.6; **IR (neat)** 3329, 2957, 1720, 1652, 1171, 670, 588; **HRMS** (ESI^+) calculated for $C_{23}H_{27}N_2O_5S+$ ($[M+H]^+$): 443.1635, found: 443.1631.

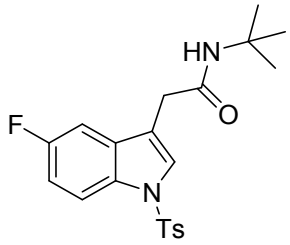


N-(*tert*-Butyl)-2-(1-tosyl-5-(trifluoromethyl)-1*H*-indol-3-yl)acetamide **(4n)**

Yield 65%,88 mg; yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 3H), 7.61 (s, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.52 (s, 1H), 3.52 (s, 2H), 2.32 (s, 3H), 1.26 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.4, 145.6, 136.6, 132.4 (q, *J* = 272 Hz), 130.1, 126.8, 126.2, 125.7 (d, *J* = 32 Hz), 125.3, 124.4 (d, *J* =

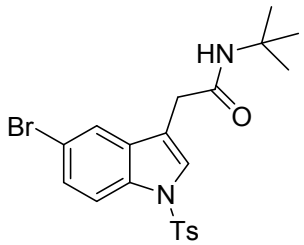
271Hz), 121.7 (d, *J* = 3.0 Hz), 117.3 (d, *J* = 4.0 Hz), 116.7, 114.0, 51.5, 34.0, 28.5, 21.5; **IR (neat)** 3322, 2968, 1649, 1316, 1172, 671, 594; **HRMS**(ESI$^+$) calculated for $C_{22}H_{24}F_3N_2O_3S$+ ([M+H]$^+$): 362.0042, found: 362.0029.



N-(*tert*-Butyl)-2-(5-fluoro-1-tosyl-1*H*-indol-3-yl)acetamide **(4o)**

Yield 73%, 88 mg; yellow solid.

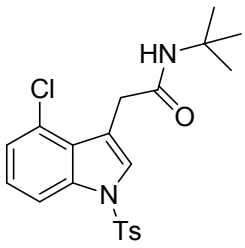
^{1}H NMR (400 MHz,$CDCl_3$) δ 7.9-7.88 (m, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.51 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.13-7.10 (m, 1H), 7.03-6.99 (m,1H), 5.55 (s, 1H), 3.44 (s, 2H), 2.29 (s, 3H), 1.23 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.6, 159.6 (d, *J* = 241.1 Hz), 145.3, 134.8, 131.5 (d, *J* = 3.8 Hz), 131.4, 130.0, 126.7, 126.3, 116.8 (d, *J* = 4.1 Hz), 114.8 (d, *J* = 9.4 Hz), 113.1 (d, *J* = 25.6 Hz), 105.4 (d, *J* = 24.2 Hz), 51.4, 34.1, 28.5, 21.5; **IR (neat)** 3326, 2966, 1648, 1370, 1140, 893, 592; **HRMS**(ESI$^+$) calculated for $C_{21}H_{24}FN_2O_3S^+$ ([M+H]$^+$): 403.1486, found: 403.1484.



2-(5-Bromo-1-tosyl-1*H*-indol-3-yl)-*N*-(*tert*-butyl)acetamide **(4p)**

Yield 68%, 95 mg; yellow solid.

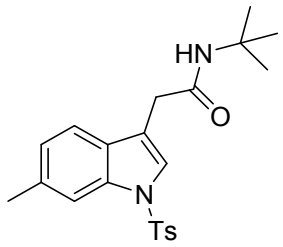
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 1.6 Hz, 1H), 7.48 (s, 1H), 7.41-7.38 (m,1H), 7.20 (d, *J* = 8.2 Hz, 2H), 5.39 (s, 1H), 3.45 (s, 2H), 2.31 (s, 3H), 1.25 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.4, 145.4, 134.8, 133.9, 132.0, 130.0, 128.0, 126.7, 125.8, 122.4, 117.0, 116.1, 115.2, 51.4, 34.1, 28.6, 21.6. **IR (neat)** 3301, 2964, 1647, 1371, 1172, 671, 575; **HRMS** (ESI$^+$) calculated for $C_{21}H_{24}BrN_2O_3S$+ ([M+H]$^+$): 463.0686, found: 463.0686.



N-(*tert*-Butyl)-2-(4-chloro-1-tosyl-1*H*-indol-3-yl)acetamideb **(4q)**

Yield 60%, 75.5 mg; yellow solid.

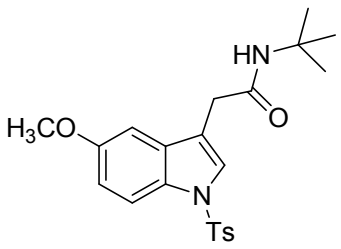
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.88 (m, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.52 (s, 1H), 7.20 (t, *J* = 8.0 Hz, 3H), 7.17-7.15 (m, 1H), 5.34 (s, 1H), 3.71 (s, 2H), 2.31 (s, 3H), 1.24 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.2, 145.4, 136.5, 134.7, 130.0, 126.9, 126.8, 126.6, 125.6, 124.4, 116.1, 112.4, 51.2, 35.3, 28.6, 21.6; **IR (neat)** 3326, 2924, 1655, 1365, 1171, 671, 579; **HRMS** (ESI^+) calculated for $C_{21}H_{24}ClN_2O_3S+$ ($[M+H]^+$): 419.1191, found: 419.1197.



N-(*tert*-Butyl)-2-(6-methyl-1-tosyl-1*H*-indol-3-yl)acetamide **(4r)**

Yield 73%,87.2 mg, white solid.

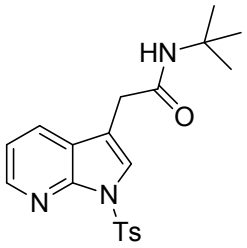
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.39 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 5.38 (s, 1H), 3.47 (s, 2H), 2.45 (s, 3H), 2.29 (s, 3H), 1.19 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.9, 144.9, 135.7, 135.4, 135.2, 129.9, 127.9, 126.7, 125.03, 124.0, 119.2, 116.7, 113.8, 51.2, 34.4, 28.5, 21.9, 21.5; **IR (neat)** 3405, 2964, 1651, 1364, 1173, 1110, 665, 581; **HRMS** (ESI^+) calculated for $C_{22}H_{27}N_2O_3S+$ ($[M+H]^+$): 399.1737, found: 399.1717.



N-(*tert*-Butyl)-2-(5-methoxy-1-tosyl-1*H*-indol-3-yl)acetamide **(4s)**

Yield 65%, 80.8 mg; white solid.

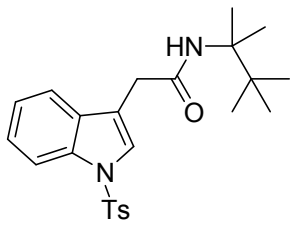
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.71 (dd, *J* = 8.2, 2.0 Hz, 2H), 7.42 (d, *J* = 1.6 Hz, 1H), 7.19 (d, *J* = 6.5 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 1H), 6.86 (s, 1H), 5.25 (s, 1H), 3.78 (s, 3H), 3.49 (s, 2H), 2.31 (s, 3H), 1.20 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.7, 156.6, 144.9, 135.0, 131.1, 129.9, 129.8, 126.7, 125.4, 116.8, 114.8, 114.6, 101.6, 101.6, 55.6, 51.2, 34.5, 28.5, 21.5; **IR (neat)** 3405, 2961, 1652, 1225, 1170, 670, 596; **HRMS** (ESI^+) calculated for $C_{22}H_{27}N_2O_4S^+$ ($[M+H]^+$): 415.1686, found: 415.1646.



N-(*tert*-Butyl)-2-(1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetamide **(4t)**

Yield 60%, 69.4 mg; yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 4.2 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 2H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.60 (s, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.16-7.12 (m, 1H), 5.55 (s, 1H), 3.48 (s, 2H), 2.32 (s, 3H), 1.25 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.7, 147.4, 145.2, 145.2, 135.3, 129.6, 128.5, 127.9, 124.42 (s), 122.7, 118.9, 113.3, 51.5, 34.5, 28.6, 21.6; **IR (neat)** 3396, 2962, 1648, 1363, 1175, 669, 581; **HRMS** (ESI^+) calculated for $C_{20}H_{24}N_3O_3S^+$ ($[M+H]^+$): 386.1533, found: 386.1512.

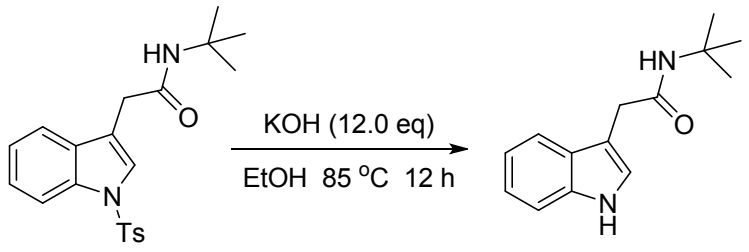


2-(1-Tosyl-1*H*-indol-3-yl)-*N*-(2,3,3-trimethylbutan-2-yl)acetamide **(4u)**

Yield 70%, 89.6 mg; yellow solid.

^{1}H NMR (400MHz,$CDCl_3$) δ 8.00 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 4.5 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 3.8 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.32 (s, 1H), 3.53 (s, 3H), 2.32 (s, 3H), 1.26 (s, 6H), 0.71 (s,9H); **^{13}C NMR**

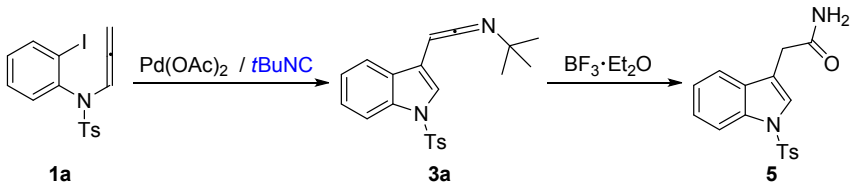
(100 MHz, $CDCl_3$) δ 168.4, 145.1, 135.3, 135.2, 130.1, 129.9, 126.8, 125.2, 124.7, 123.5, 119.7, 116.4, 113.7, 55.2, 52.0, 34.5, 31.1, 28.7, 21.5;**IR (neat)**3303, 2924, 1645, 1172, 743, 670, 537; **HRMS** (ESI^+) calculated for $C_{25}H_{33}N_2O_3S^+$ ($[M+H]^+$): 441.2206, found: 441.2200.



4a **4v**

***N*-(*tert*-Butyl)-2-(1*H*-indol-3-yl)acetamide (4v):** To a solution of KOH (3.6 mmol, 12.0 equiv., 201.6 mg) in EtOH (3.0 mL) were added acetamide **4a** (115.4 mg, 0.3 mmol, 1.5 equiv) at room temperature. The reaction was stirred at 85°C overnight. After the reaction was monitored as completed, the solution was concentrated under reduced pressure. The mixture was diluted with DCM (2.0 mL), and then poured into H_2O, extracted three times with DCM. The combined organic layer was washed with sat NaCl, dried over anhyd. $MgSO_4$. Concentration under reduced pressure of the crude product followed by purification using silica gel column chromatography [gradient eluent: PE:MeOH=2:1] to give the product **4v** (70%, 48.4 mg) as a white solid.

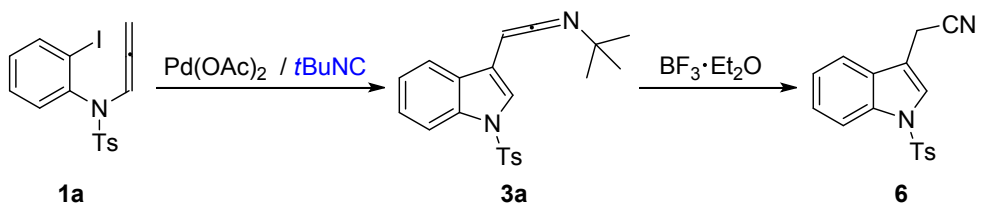
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 1.8 Hz, 1H), 5.62 (s, 2H), 3.66 (s, 2H), 1.25 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 171.1, 136.5, 126.9, 123.8, 122.3, 119.8, 118.6, 111.5, 109.2, 51.1, 34.7, 28.6; **IR (neat)** 3406, 2924, 1638, 1543, 1326, 747, 427; **HRMS** (ESI^+) calculated for $C_{14}H_{19}N_2O^+$ ($[M+H]^+$): 231.1492, found: 231.1492.



1a **3a** **5**

2-(1-Tosyl-1*H*-indol-3-yl)acetamide (5): To a test tube equipped with a stir bar was charged with acetamide **1a** (0.20 mmol), *tert*-butyl isocyanide **2** (0.30 mmol), $Pd(OAc)_2$ (0.02mmol, 10 mol%), Cs_2CO_3 (0.40 mmol, 2.0 equiv.), and dry MeCN (2.0 mL). The reaction was stirred at 60 °C for 14-22 h under N_2 until complete consumption of the acetamide **1a** and allowed to cool to room temperature. The reaction mixture was filtered through a short pad of Celite and concentrated. The crude product was dissolved in dichloroethane (2.0 mL) at 0°C, $BF_3{\cdot}Et_2O$ (248 μL, 2.0 mmol, 10.0 equiv) was added. The reaction mixture was then stirred at 50 °C for 10 h. Water was added at room temperature, the crude product was extracted in the aqueous layer at pH=0 and the organic layer was discarded. The combined aqueous layer was then basified with sat. aqueous $NaHCO_3$ and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 andconcentrated under reduced pressure. The crude product was purified by column chromatography with DCM/MeOH=5:1 as eluent to afford the desired **5** as a yellow solid (36mg, 55% yield over two steps).

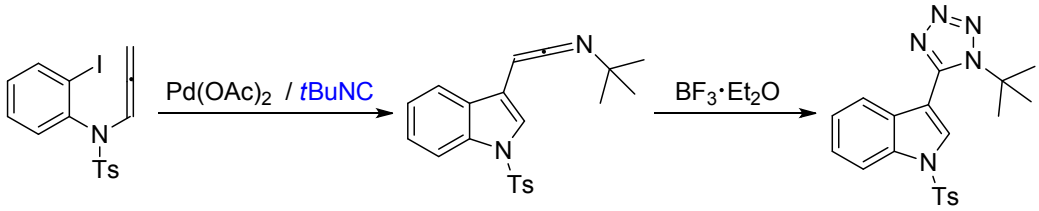
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.53 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 7.0 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 5.86 (s, 1H), 5.60 (s, 1H), 3.61 (s, 2H), 2.32 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 172.4, 145.2, 135.2, 135.0, 130.1, 130.0, 126.8, 125.2, 124.89 (s), 123.5, 119.5, 115.8, 113.7, 32.7, 21.6; **IR (neat)** 3386, 1654, 1374, 1169, 744, 579, 536; **HRMS** (ESI$^+$) calculatedfor $C_{17}H_{17}N_2O_3S^+$ ([M+H]$^+$): 329.0954, found: 329.0982



1a **3a** **6**

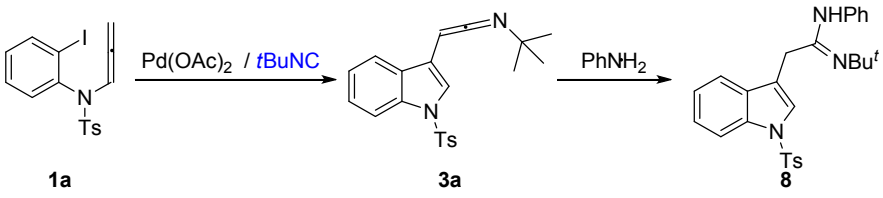
2-(1-Tosyl-1*H*-indol-3-yl)acetonitrile (6): To a test tube equipped with a stir bar was charged with acetamide **1a** (0.20 mmol), tert-butyl isocyanide **2** (0.30 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol%), Cs_2CO_3 (0.40 mmol, 2.0 equiv.), and dry MeCN (2.0 mL). The reaction was stirred at 60 ^oC for 14-22 h under N_2 until complete consumption of theacetamide **1a**. The reaction was allowed to cool to room temperature. The reaction mixture was filtered through a short pad of Celite and concentrated under reduced pressure. The crude product was dissolved in dichloroethane (2 mL) and $BF_3{\cdot}Et_2O$ (27 μL, 0.22 mmol, 1.1equiv) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred until complete consumption of the acetamide. The reaction mixture was quenched with sat. aqueous $NaHCO_3$, extracted with DCM and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc = 4:1 as eluent to afford **6** as a yellow solid (33.0 mg, 53% yield over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.61 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.25-7.23 (m, 2H), 3.74 (s, 2H), 2.34 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 145.3, 135.1, 134.9, 130.0, 128.7, 126.9, 125.5, 124.4, 123.6, 118.8, 116.7, 113.9, 111.4, 21.6, 14.4; **IR (neat)** 3417, 1363, 1174, 979, 671, 585, 532; **HRMS** (ESI^+) calculated for $C_{17}H_{15}N_2O_2S^+$ ($[M+H]^+$): 311.0849, found: 311.0853.



3-(1-(Tert-butyl)-1*H*-tetrazol-5-yl)-1-tosyl-1*H*-indole (7): To a test tube equipped with a stir bar was charged with acetamide**1a** (0.20 mmol), *tert*-butyl isocyanide **2** (0.30 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol%), Cs_2CO_3 (0.40 mmol, 2.0 equiv.), and dry MeCN (2.0 mL). The reaction was stirred at 60 °C for 14-22 h under N_2 until complete consumption of the acetamide **1a**. The reaction was allowed to cool to room temperature, filtered through a short pad of Celite and concentrated under reduced pressure. A solution of $TMSN_3$ (1.1 eq) in *t*BuOH (2.0 mL), prepared according to a reported procedure, was then added at 0 °C and the reaction mixture was warmed to room temperature and stirred until complete consumption of the **3a**. The reaction mixture was concentrated under reduced pressure, then partitioned between sat. aqueous $NaHCO_3$ and EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc=10:1 as eluent to afford **7** as a white solid (47.5 mg, 60 % yield over two steps).

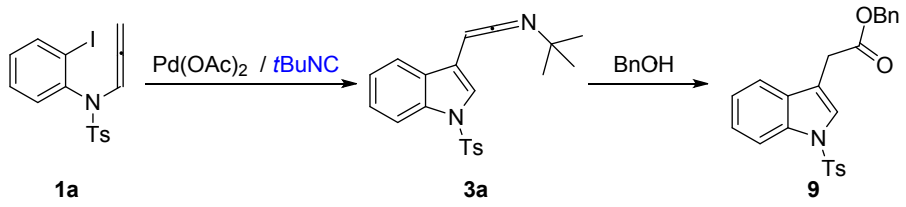
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.34-7.28 (m 2H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.18 (t, *J* = 6.6 Hz, 2H), 4.43 (s, 2H), 2.29 (s, 3H), 1.62 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 151.7, 145.2, 135.1, 135.0, 129.9, 129.6, 126.8, 125.3, 124.4, 123.5, 119.4, 116.6, 113.8, 61.3, 29.7, 22.3, 21.5; **IR (neat)** 3112, 2921, 1364, 1176, 743, 586, 569; **HRMS** (ESI^+) calculated for $C_{21}H_{24}N_5O_2S^+$ ($[M+H]^+$): 410.1645, found: 410.1625.



***N'*-(*tert*-Butyl)-*N*-phenyl-2-(1-tosyl-1*H*-indol-3-yl)acetimidamide (8).** To a test tube equipped with a stir bar was charged with acetamide **1a** (0.20 mmol), *tert*-butyl isocyanide **2a** (0.30 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol%), Cs_2CO_3 (0.40 mmol,

2.0 equiv.), and dry MeCN (2.0 mL). The reaction was stirred at 60 °C for 14-22 h under N_2 until complete consumption of the acetamide **1a**. Upon completion, aniline (1.2 equiv) was added., and the reaction mixture was stirred at 90 °C until complete consumption of the α–oxo-ketenimine. The reaction mixture was partitioned between sat. aqueous NH_4Cl and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under recuced pressure. The crude product was purified by column chromatography with PE/EtOAc as eluent to afford the desired **8** as a yellow solid (38.0 mg , yield: 49%).

^{1}H NMR (400 MHz,$CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.29-7.23 (m, 3H), 7.17-7.09 (m, 5H), 6.84 (t, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 7.4 Hz, 2H), 3.91 (s, 1H), 3.37 (s, 2H), 2.23 (s, 3H), 1.21 (s, 9H). **^{13}C NMR (100 MHz,$CDCl_3$)** δ 152.3, 151.5, 145.0, 135.4, 135.1, 130.2, 129.9, 128.9, 126.7, 125.2, 124.6, 123.5, 121.8, 121.5, 119.5, 118.5, 113.9, 51.3, 28.5, 27.6, 21.5. **HRMS** (ESI^+) calculated for $C_{27}H_{30}N_3O_2S^+$ ($[M+H]^+$): 460.2053, found: 460.2058.

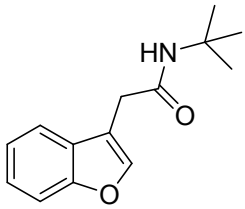


1a **3a** **9**

Benzyl 2-(1-tosyl-1*H*-indol-3-yl)acetate (9). To a test tube equipped with a stir bar was charged with acetamide **1a** (0.20mmol), tert-butyl isocyanide **2a** (0.30 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol%), Cs_2CO_3 (0.40 mmol, 2.0 equiv.), and dry MeCN (2.0 mL). The reaction was stirred at 60 °C for 14 h until complete consumption of the acetamide **1a**, then benzyl alcohol (1.2 equiv) was added and the reaction mixture was stirred at 90 °C until complete reaction. The reaction mixture was partitioned between sat. aqueous NH_4Cl and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under recuced pressure. The crude product was purified by column chromatography with PE/EtOAc as eluent to afford the desired **9** as a yellow solid (42.0 mg, yield: 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 8.2Hz, 2H), 7.49 (s, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.26-7.20 (m, 6H), 7.18-7.14 (m, 1H), 7.10 (d, *J* =

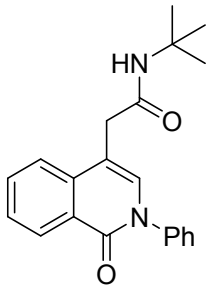
8.2 Hz, 2H), 5.07 (s, 2H), 3.66 (s, 2H), 2.24 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.4, 144.9, 135.6, 135.3, 135.0, 130.4, 129.9, 128.6, 128.4, 128.3, 126.8, 124.9, 124.8, 123.2, 119.6, 115.0, 113.7, 66.9, 31.1, 21.6. **HRMS** (ESI^+) calculated for $C_{24}H_{22}NO_4S^+$ ($[M+H]^+$): 420.1264, found: 420.1269.



2-(Benzofuran-3-yl)-*N*-(*tert*-butyl)acetamide **(11)**

Yield 60%, 41.6 mg; colorless oil.

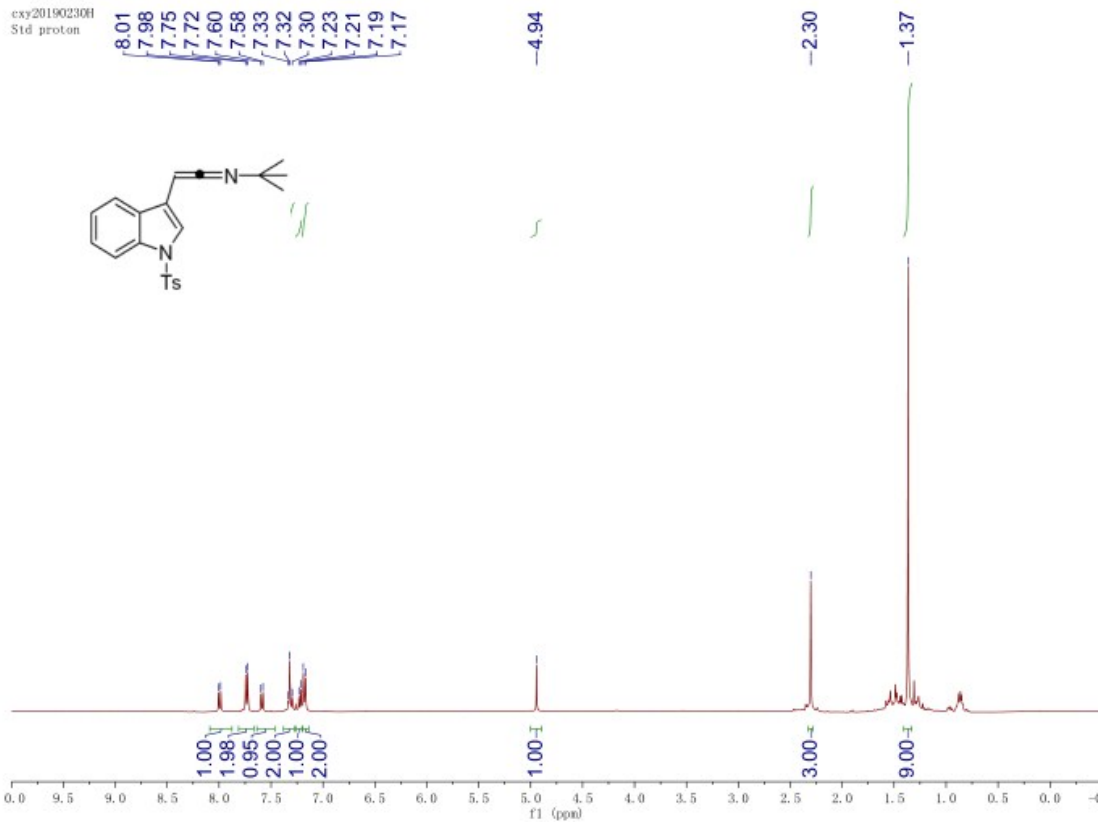
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.4 Hz, 1H), 5.48 (s, 1H), 3.54 (s, 2H), 1.27 (s, 9H). **^{13}C NMR (100MHz, $CDCl_3$)** δ 168.9, 155.4, 142.9, 127.3, 124.7, 122.8, 119.6, 114.4, 111.6, 51.3, 32.9, 28.6; **IR (neat)** 3267, 2924, 1640, 1453, 1363, 1088, 756; **HRMS** (ESI^+) calculated for $C_{14}H_{18}NO_2^+$ ($[M+H]^+$): 232.1332, found: 232.1318.



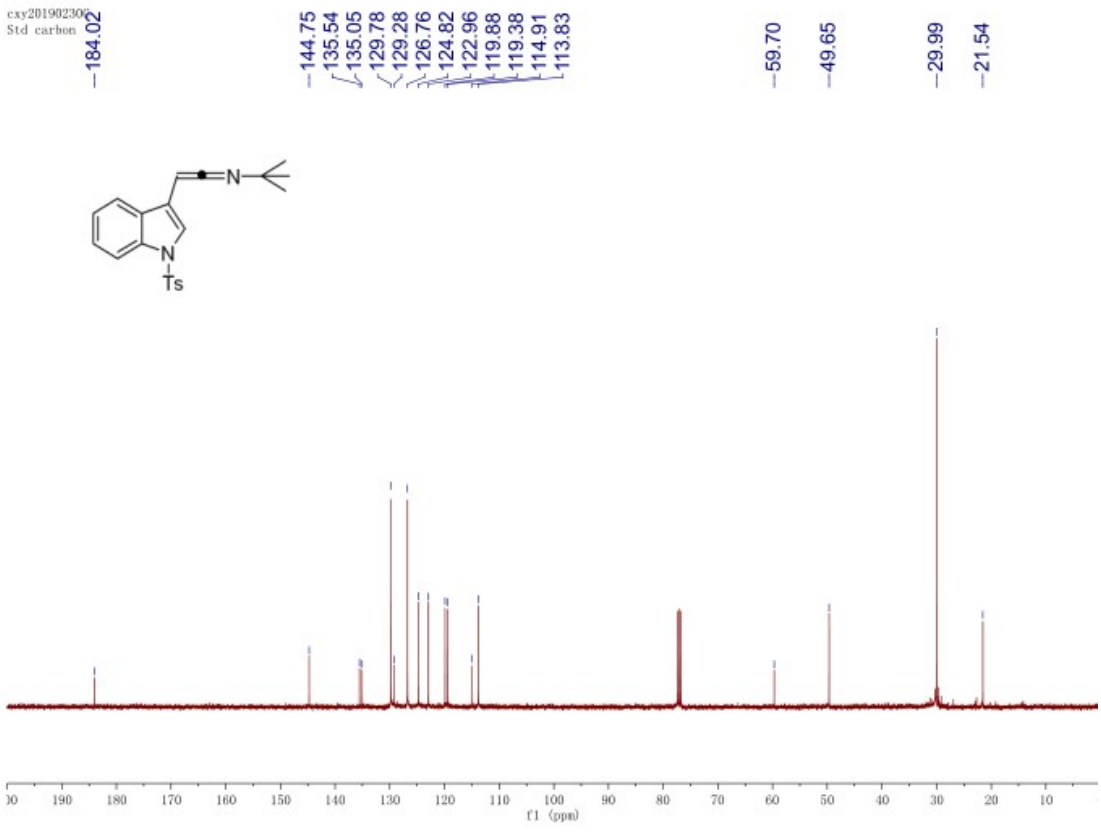
N-(*tert*-Butyl)-2-(1-oxo-2-phenyl-1,2-dihydroisoquinolin-4-yl)acetamide **(13)**

Yield 50%, 50.2 mg; yellow solid..**^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.51 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.49(t, *J* = 7.6 Hz ,2H), 7.44-7.39 (m, 3H), 7.15 (s, 1H), 5.53 (s, 1H), 3.50 (s, 2H), 1.27 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.3, 161.7, 141.0, 136.3, 132.8, 132.3, 129.3, 128.8, 128.2, 127.5, 126.8, 126.6, 123.1, 110.7, 51.5, 39.0, 28.6; **IR (neat)** 3324, 2963, 1656, 1545, 1490, 1273, 762, 694; **HRMS** (ESI^+) calculated for $C_{21}H_{23}N_2O_2$+ ($[M+H]^+$): 335.1754, found: 335.1756.

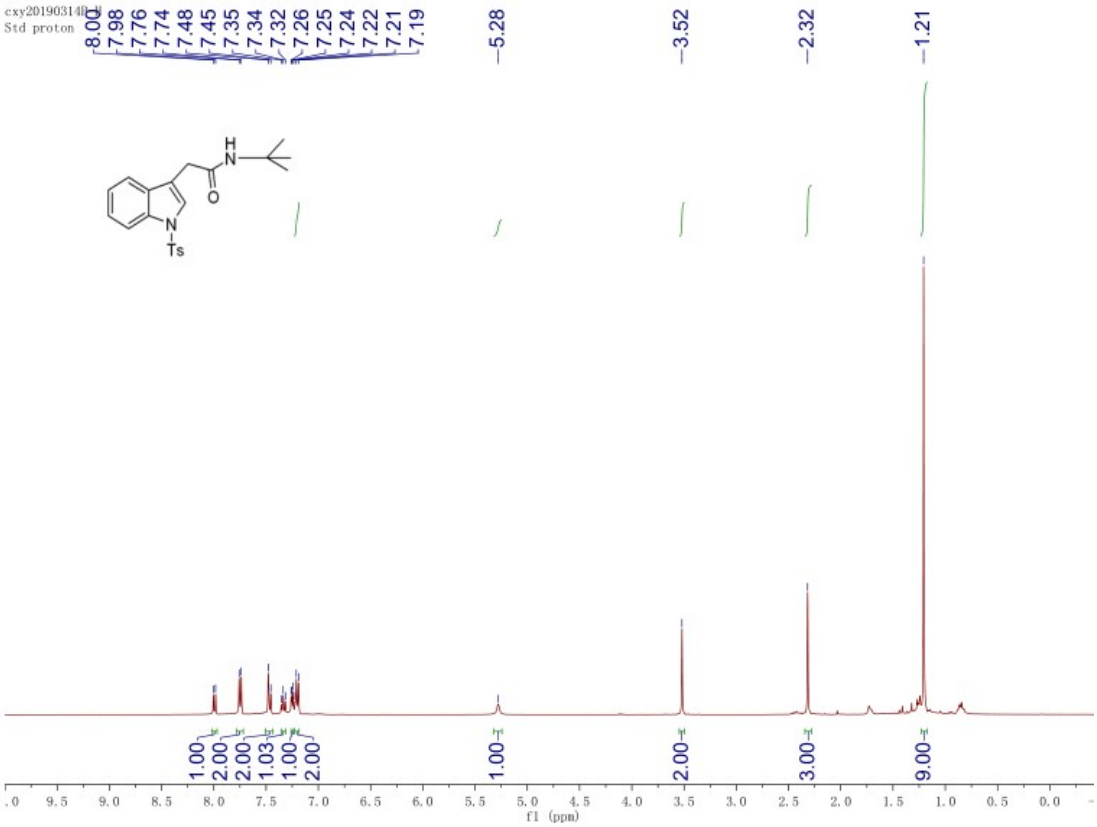
Crude ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of intermediate 3a



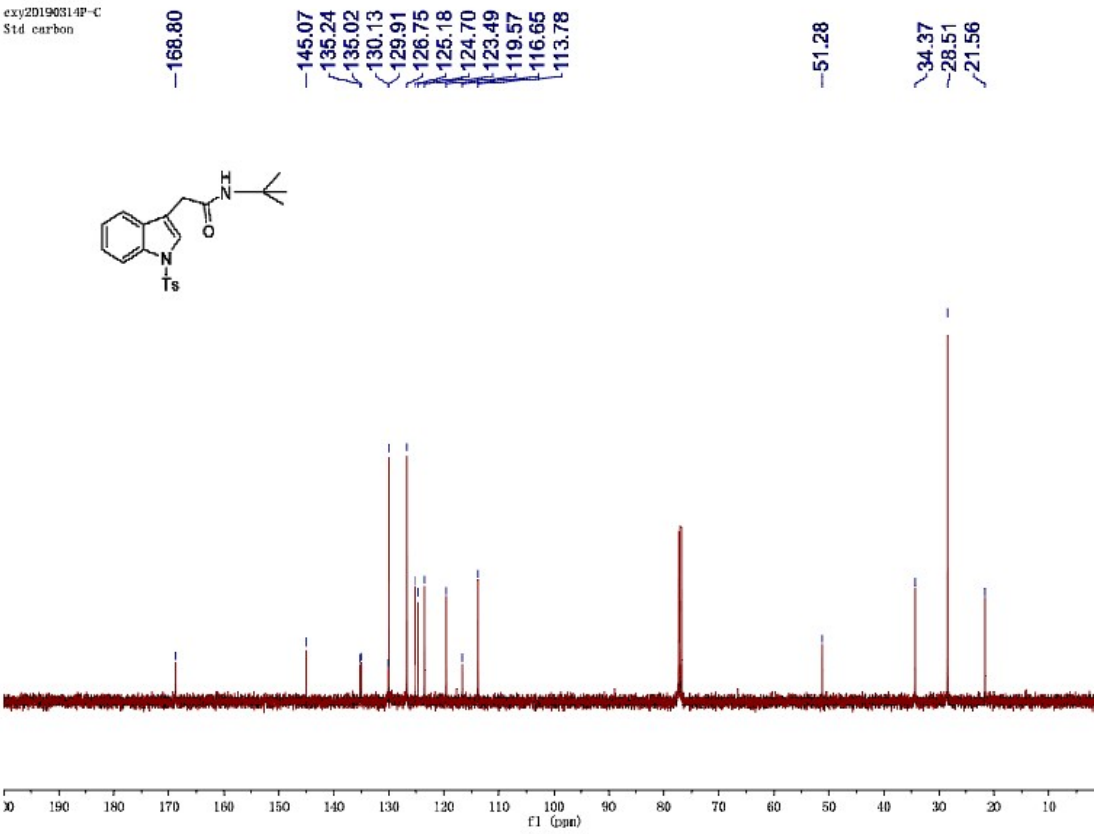
Crude^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 3a



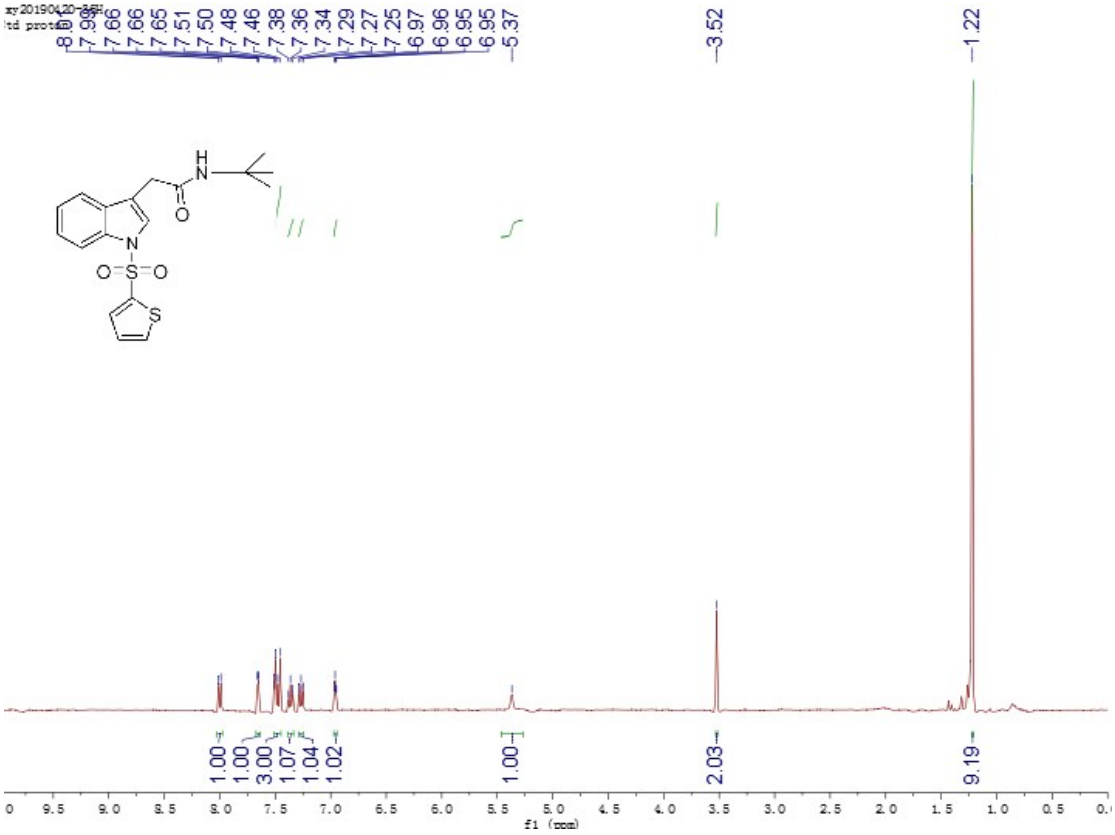
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4a



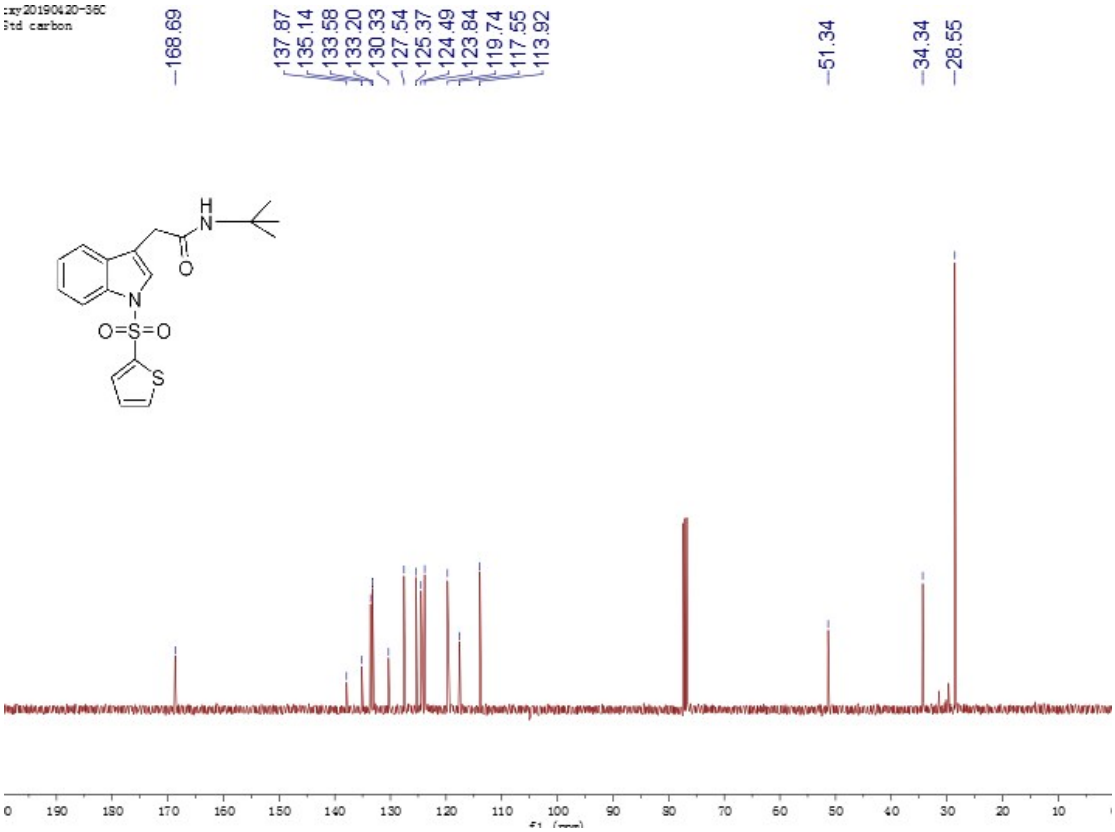
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4a



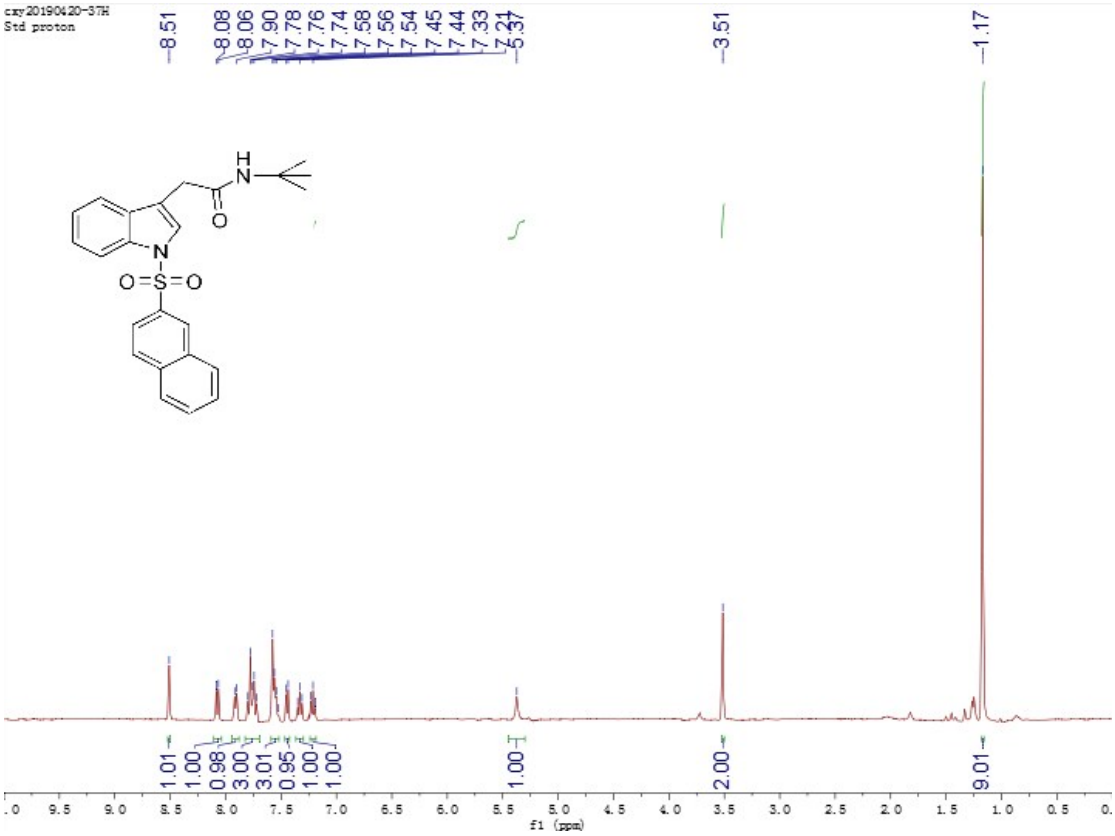
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4b



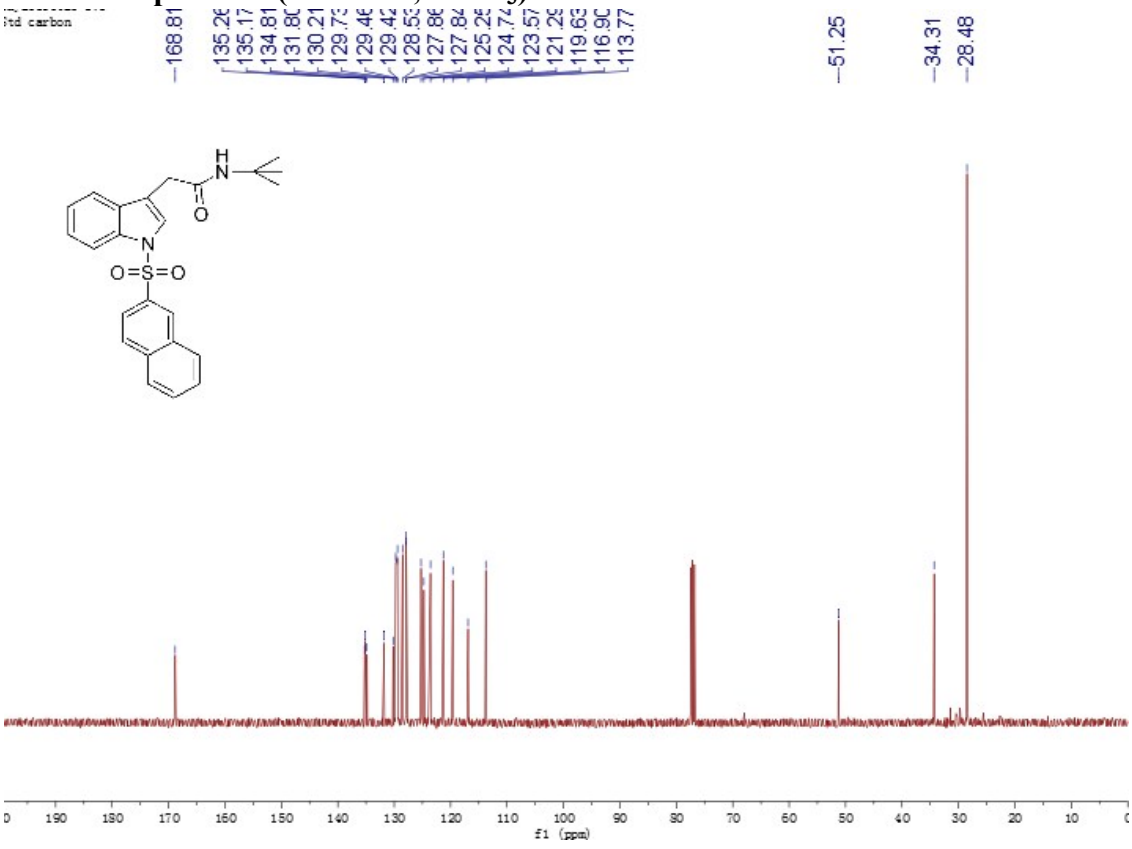
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4b



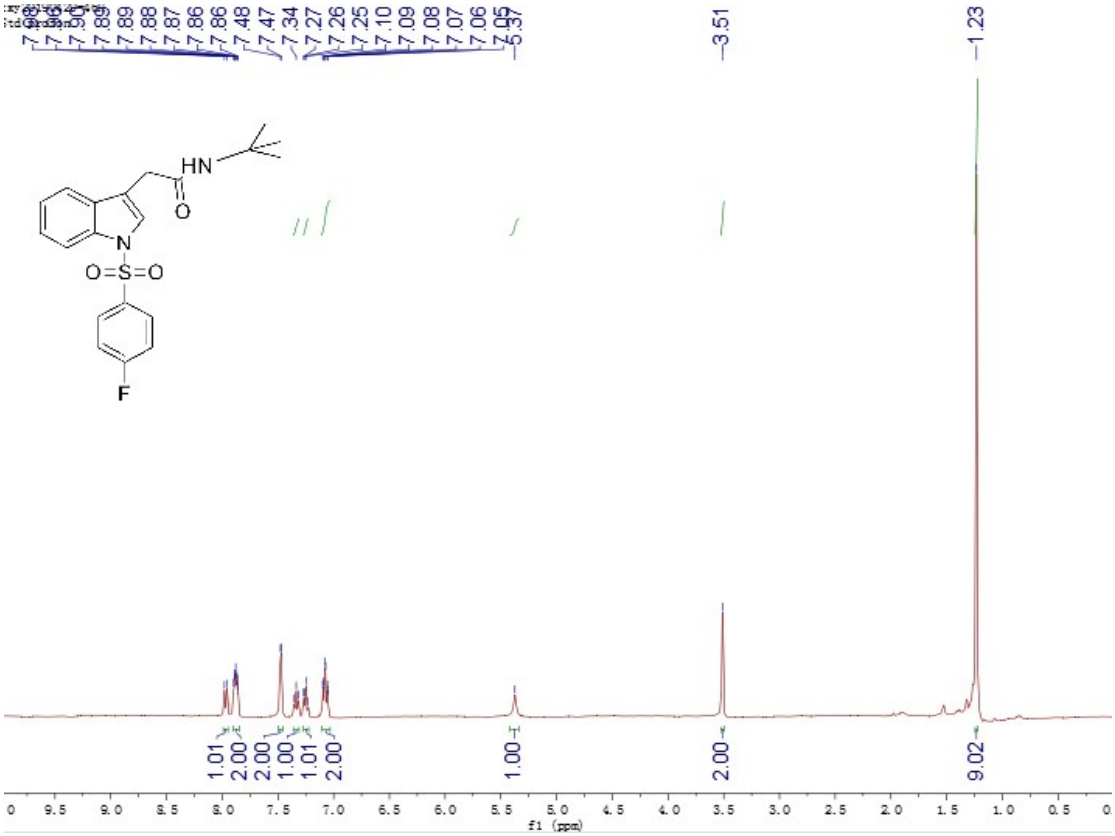
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4c



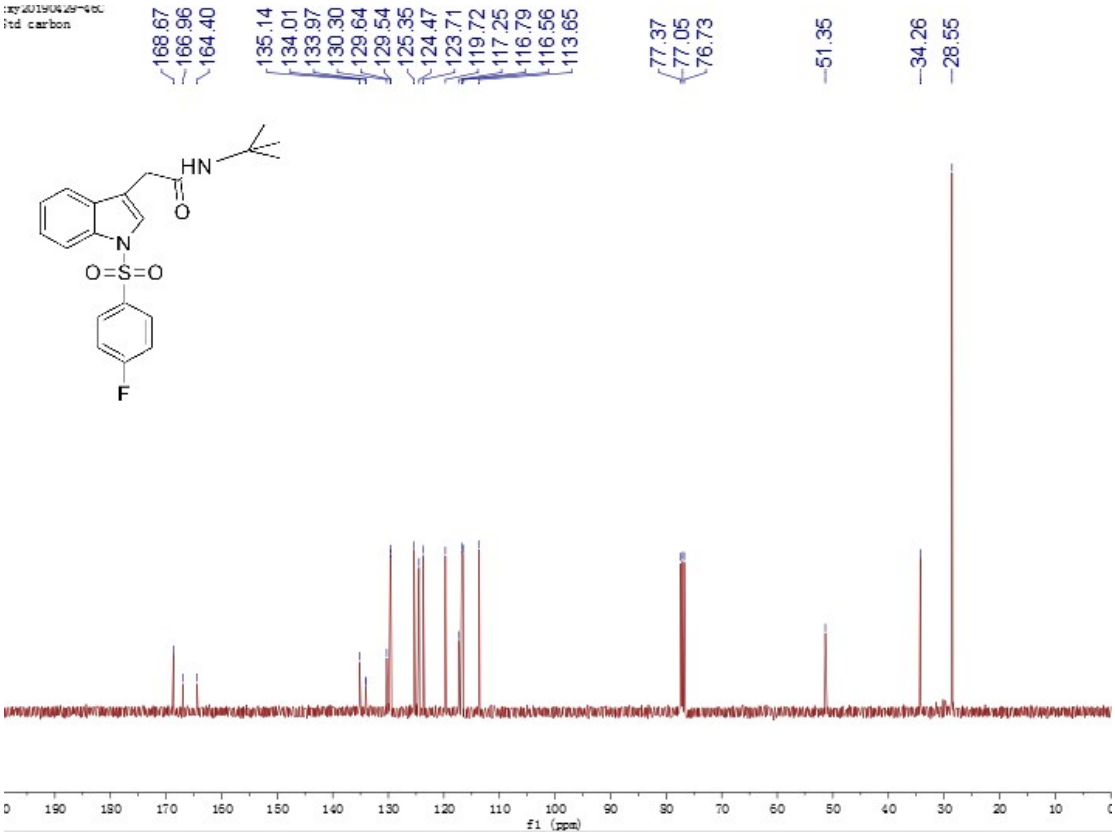
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4c



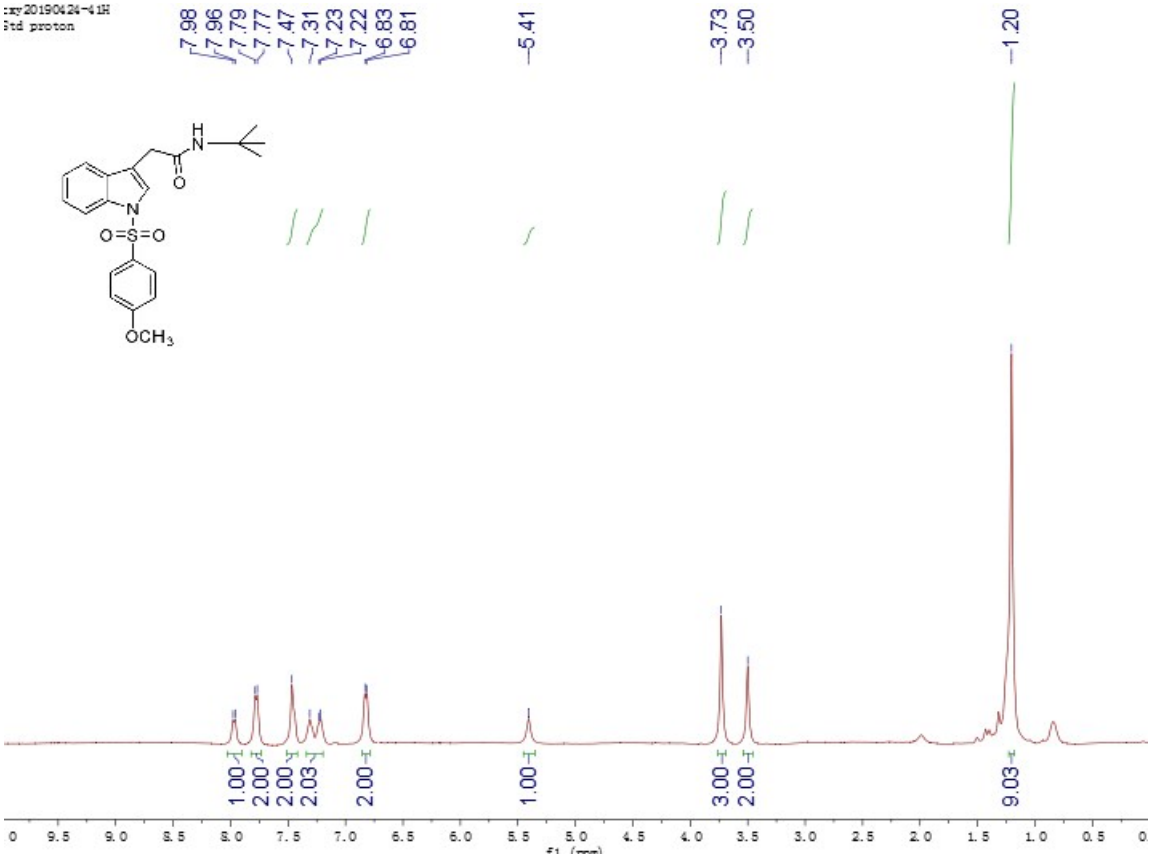
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4d



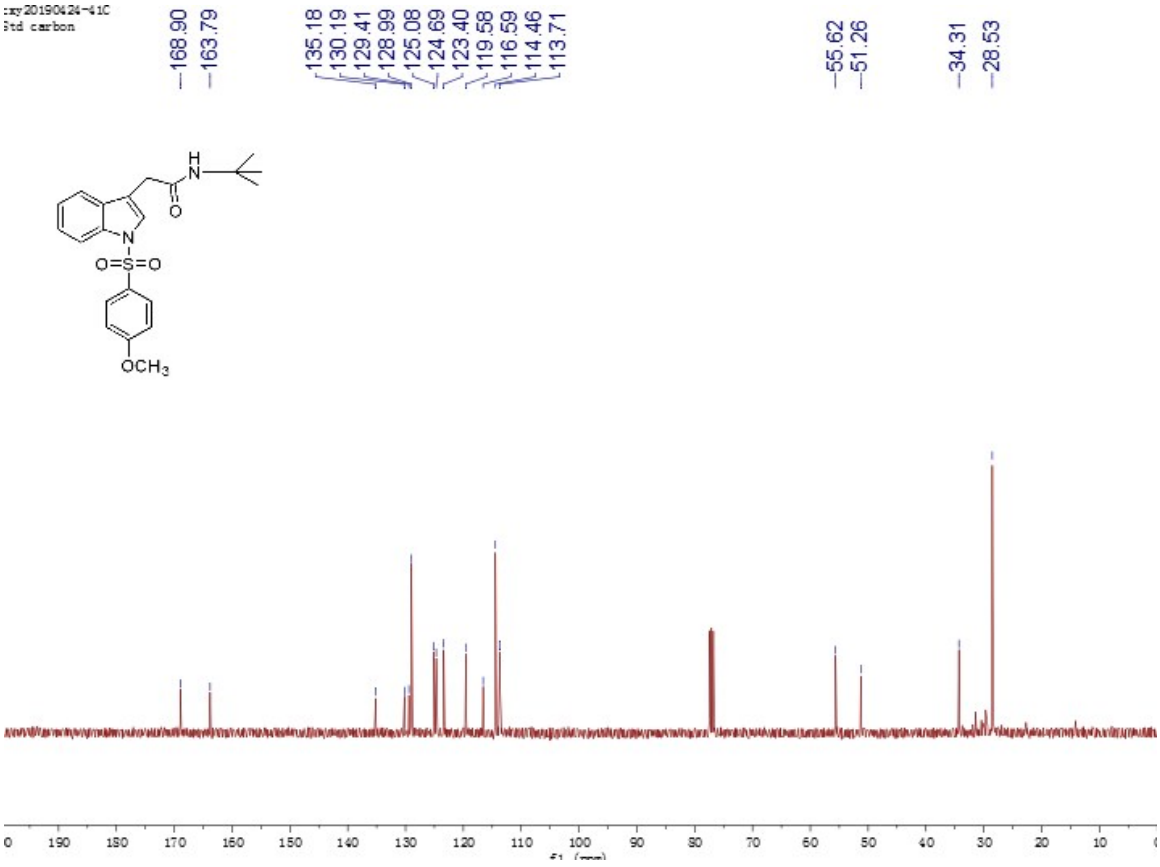
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4d



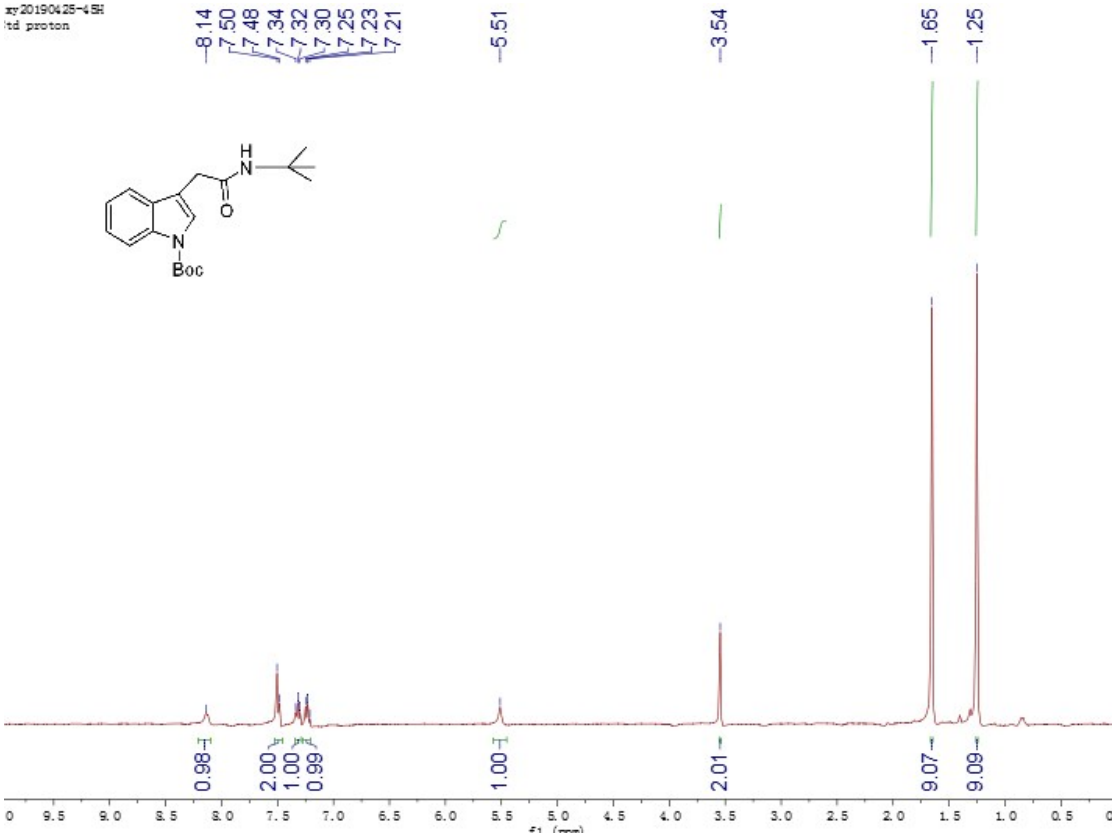
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4e



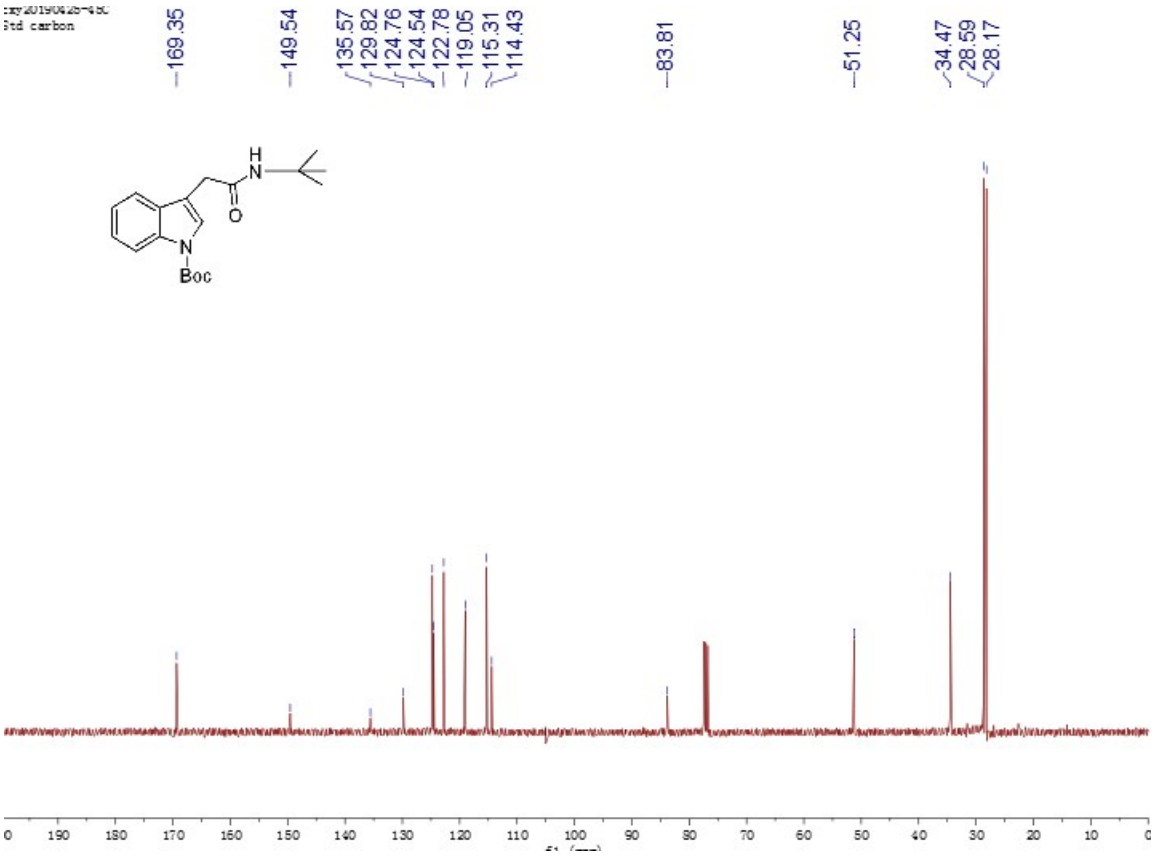
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4e



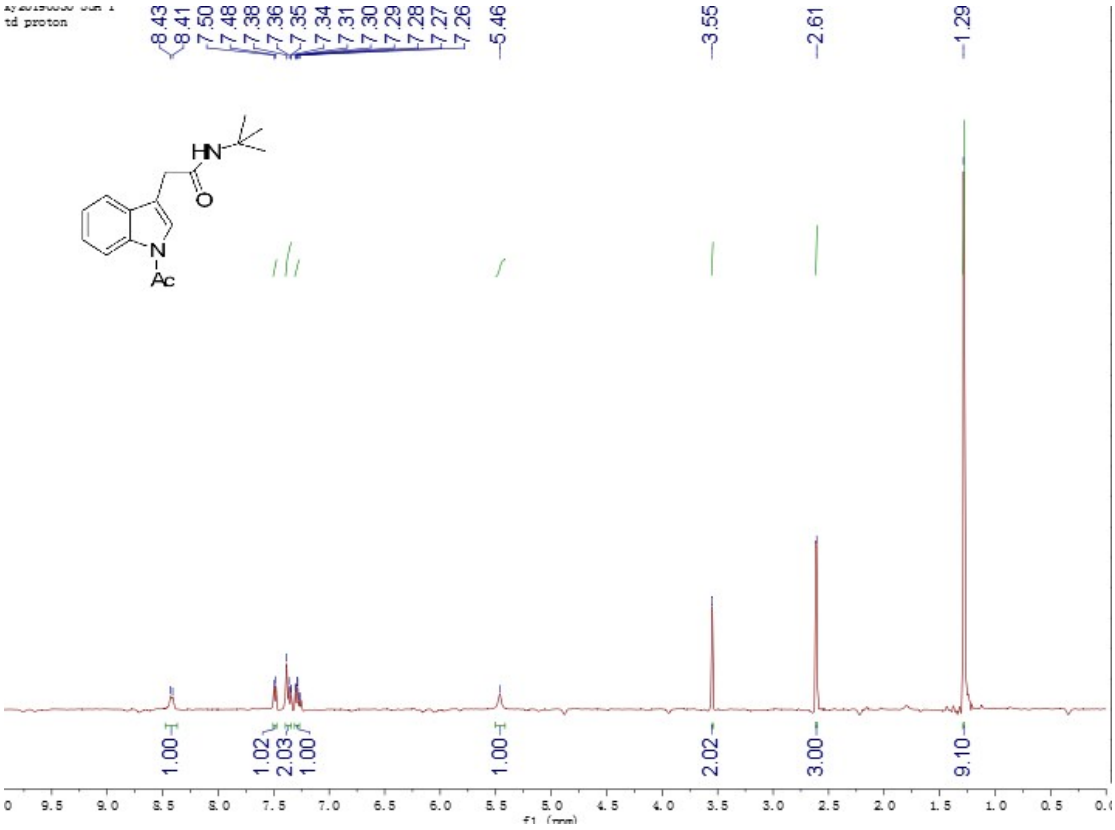
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4f



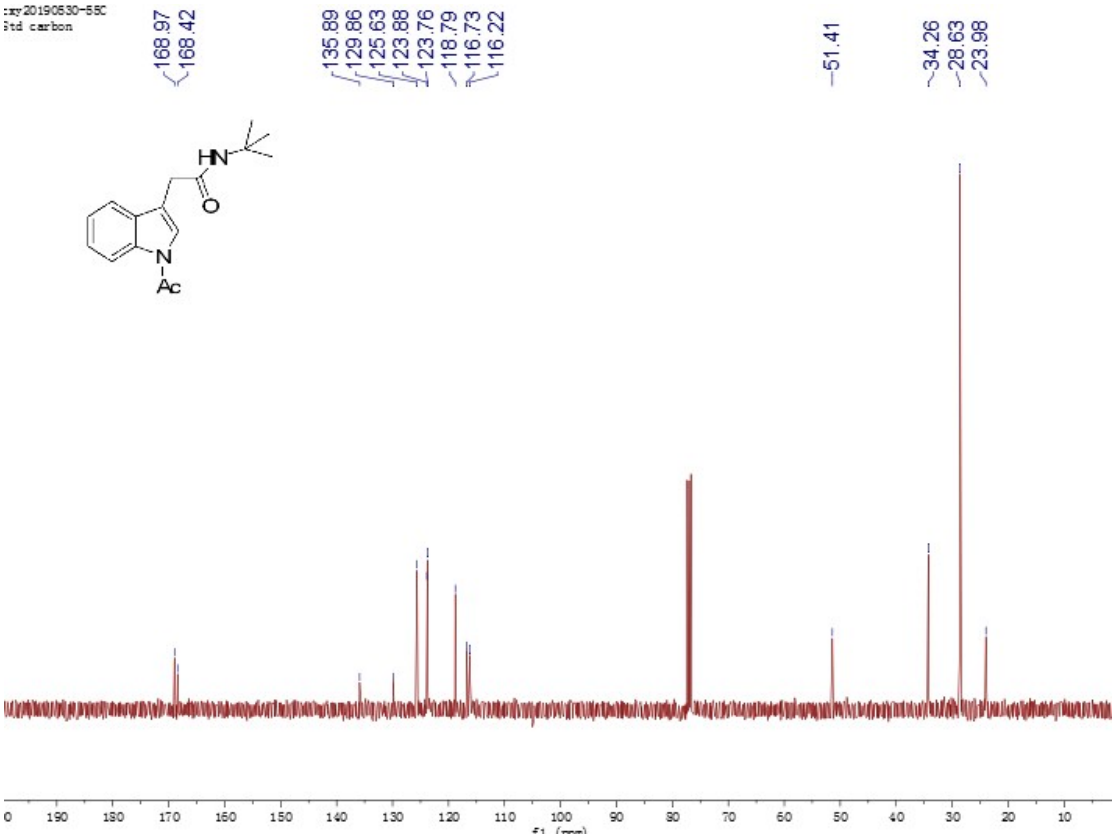
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4f



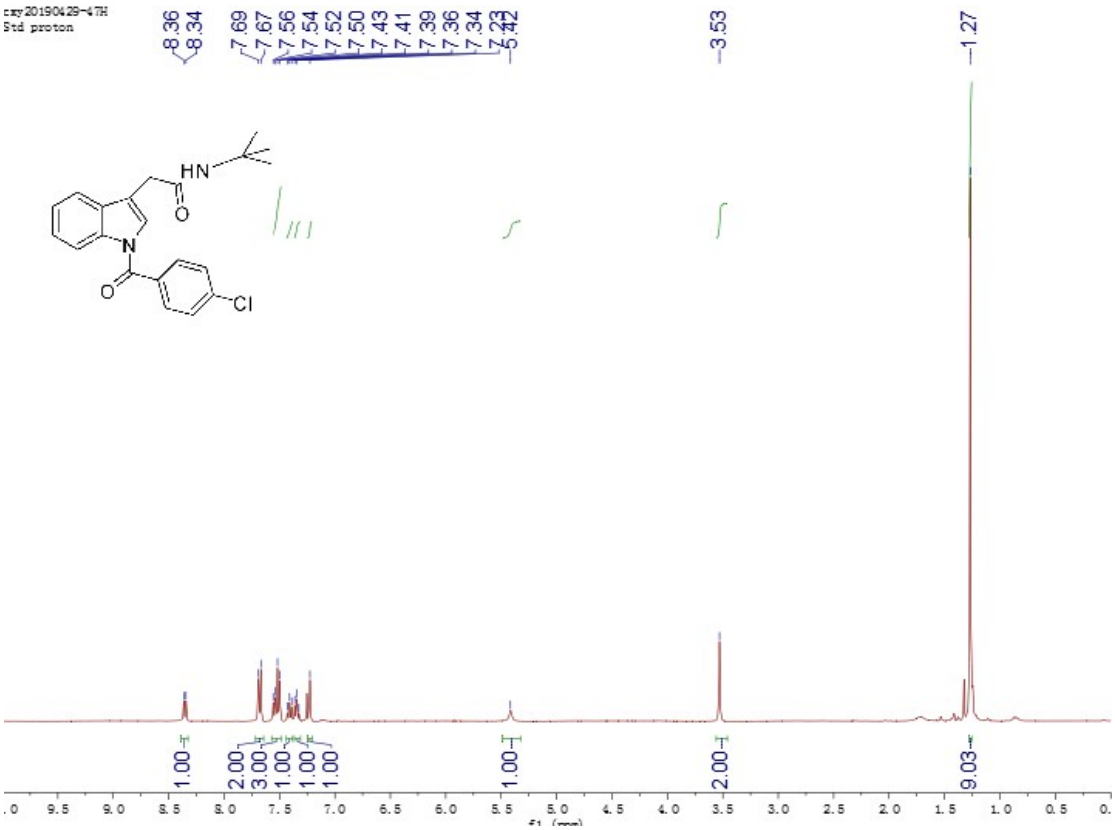
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4g



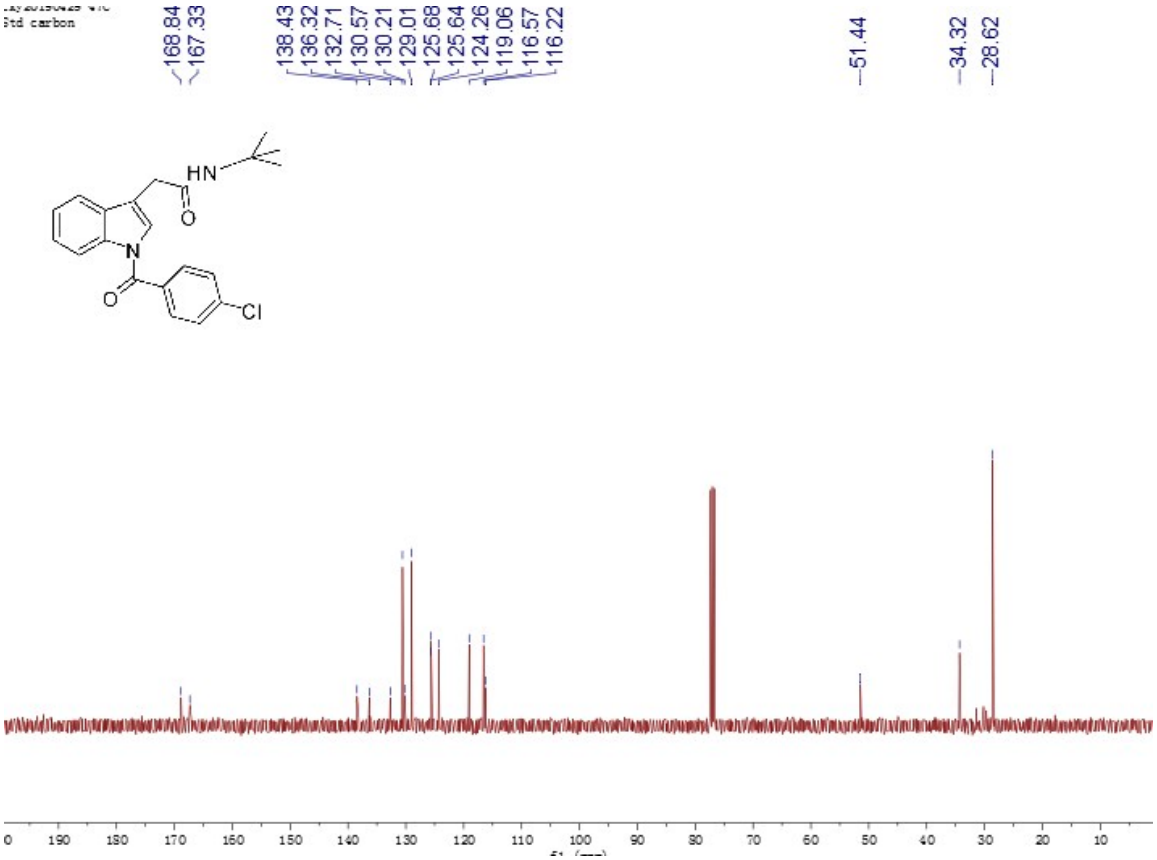
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4g



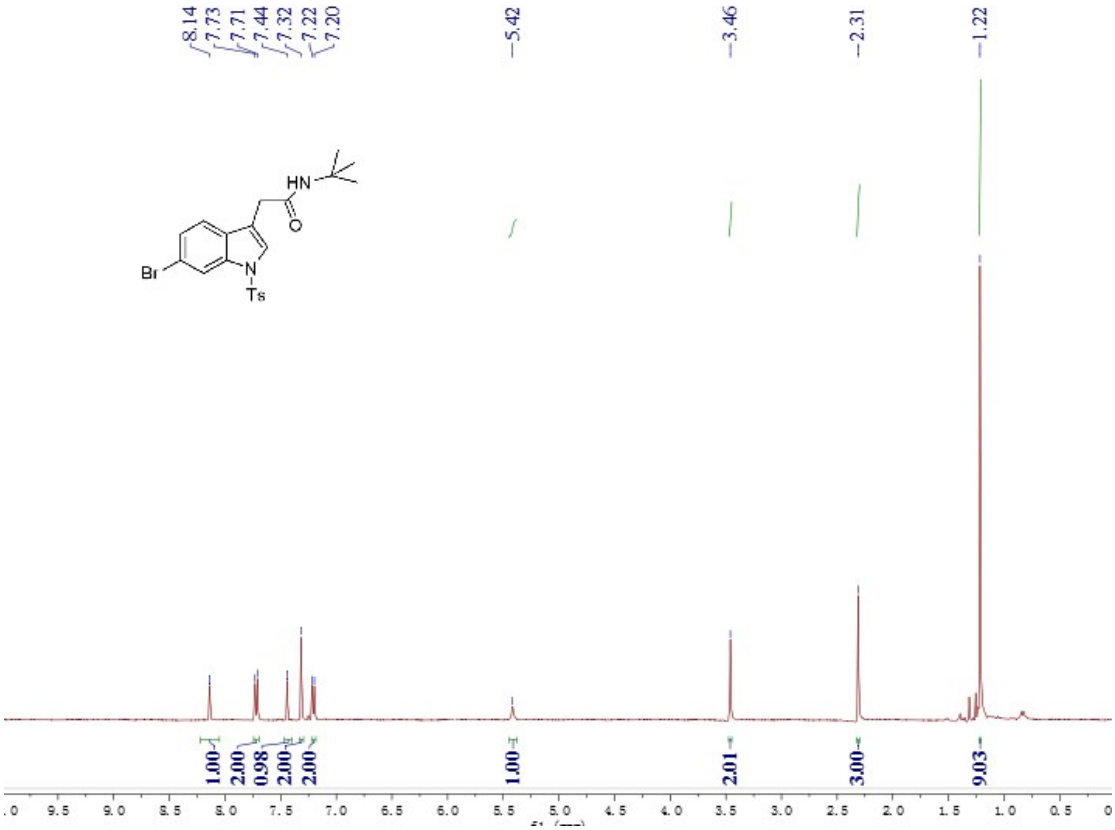
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4h



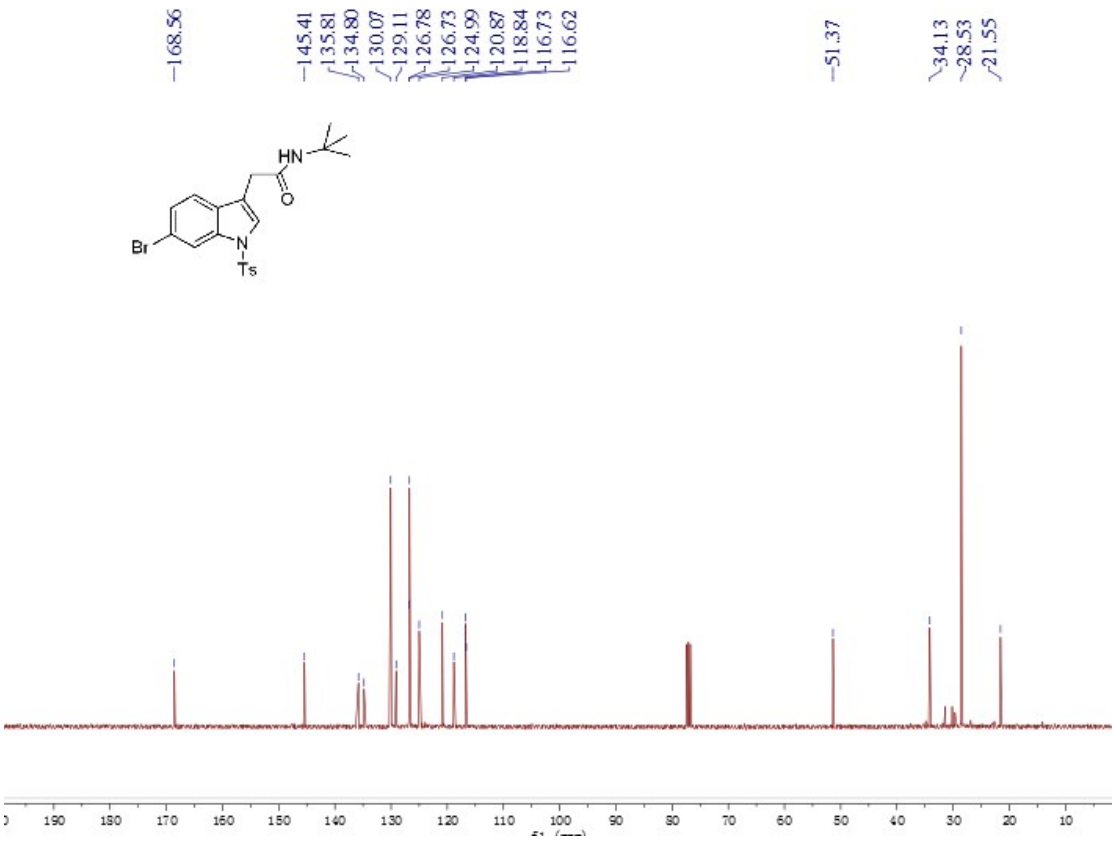
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4h



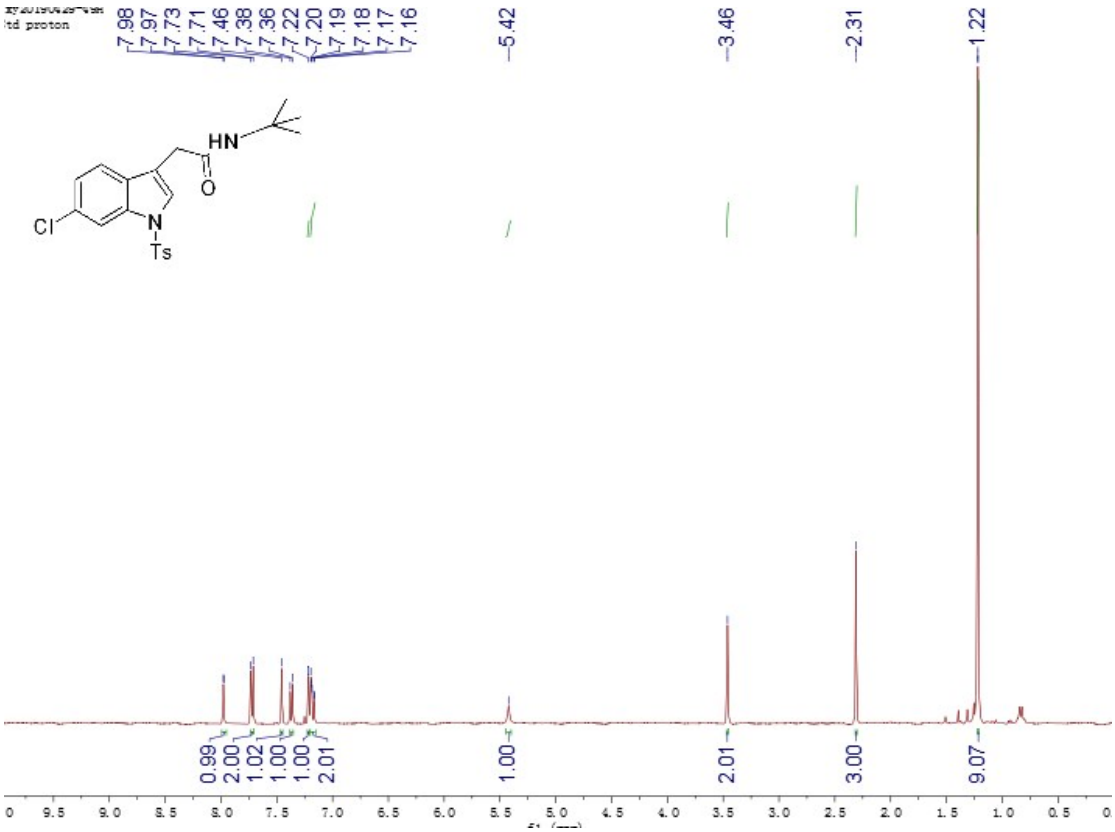
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4i



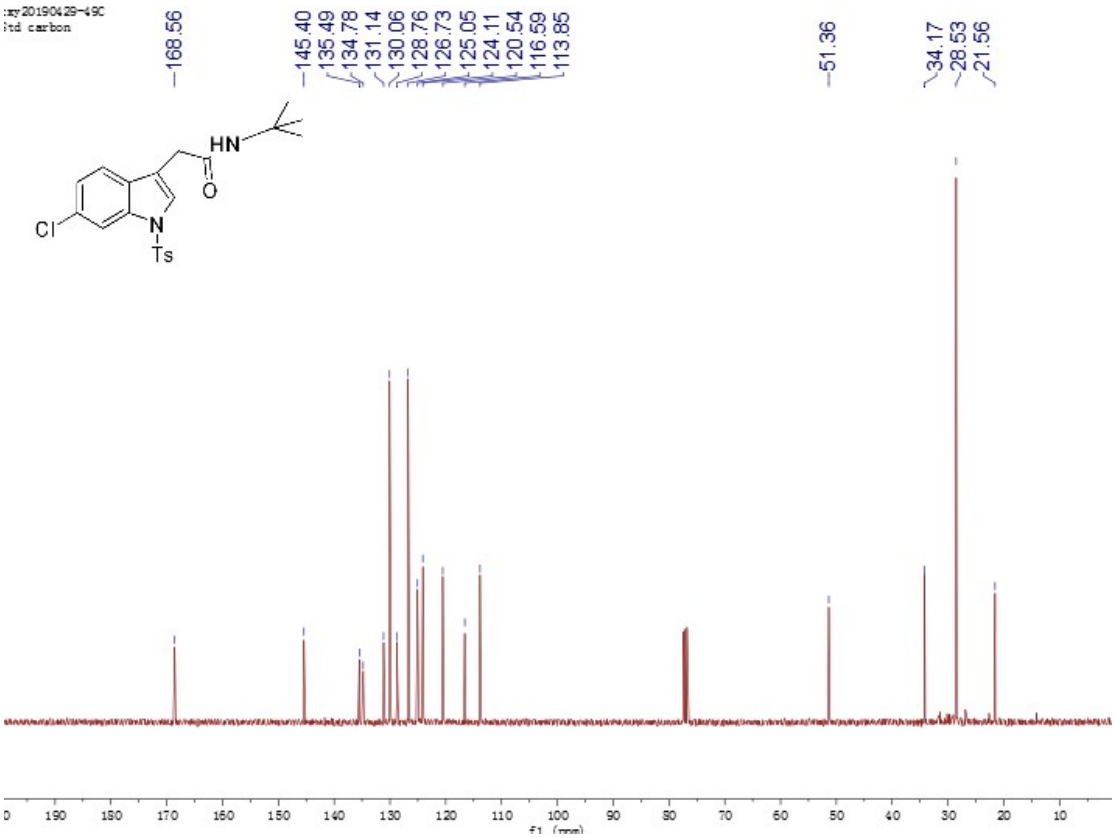
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4i



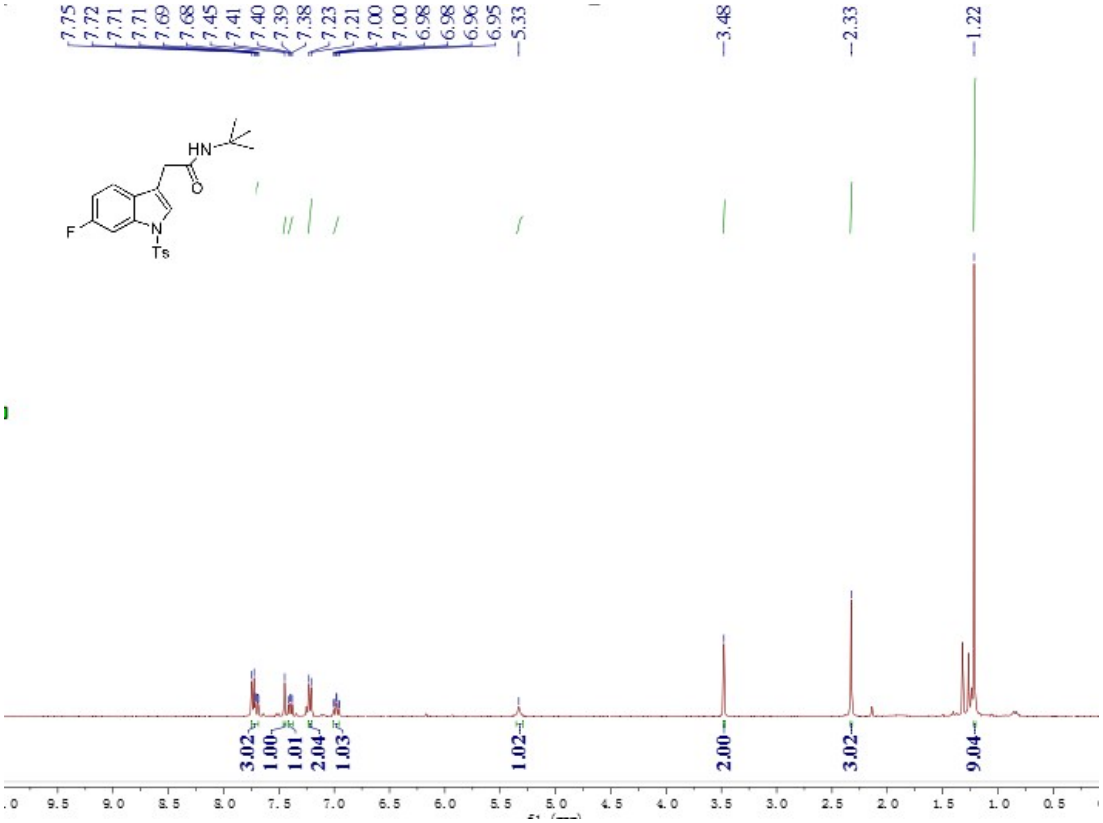
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4j



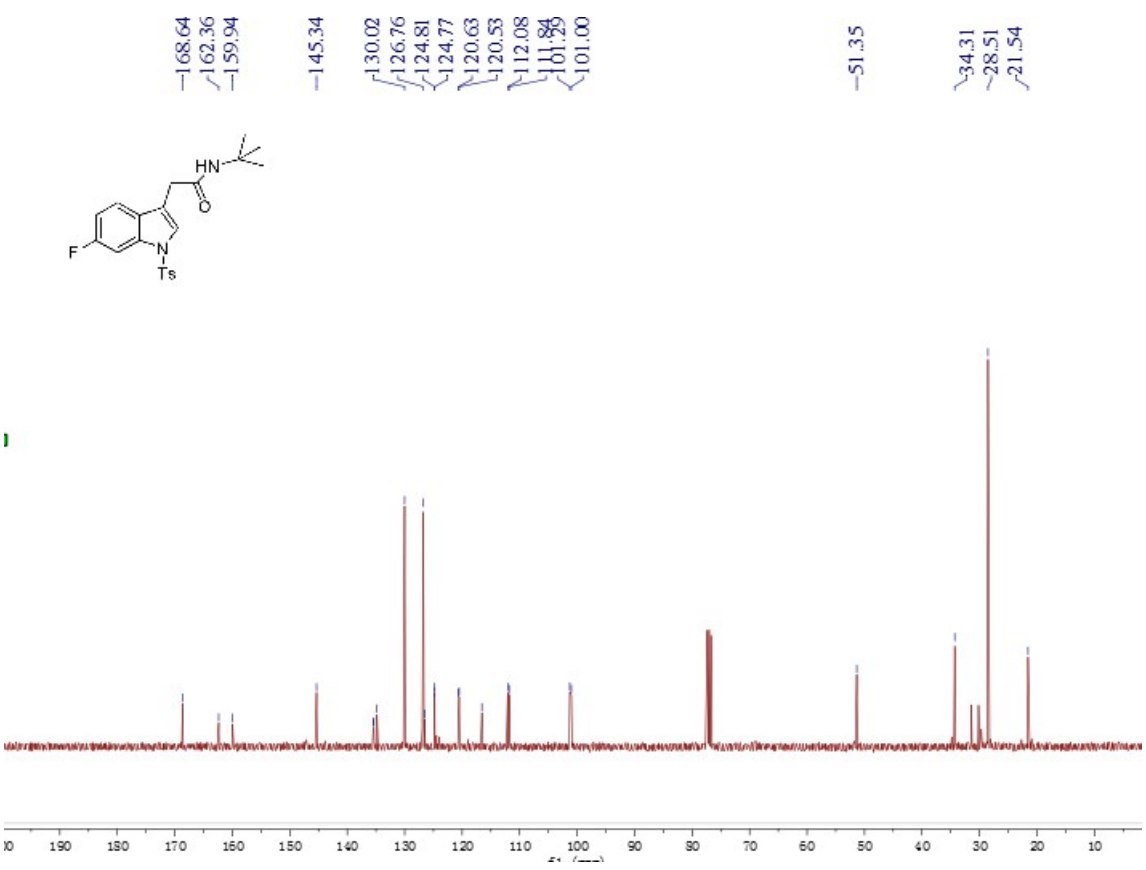
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4j



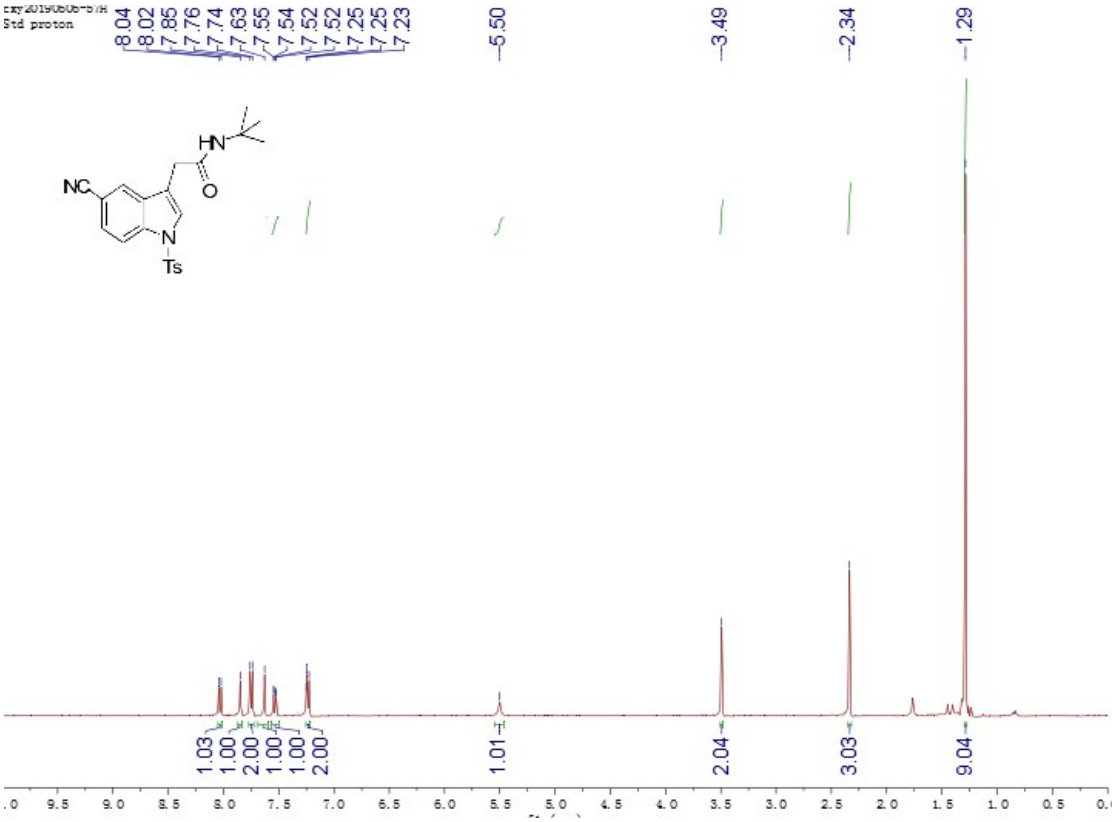
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4k



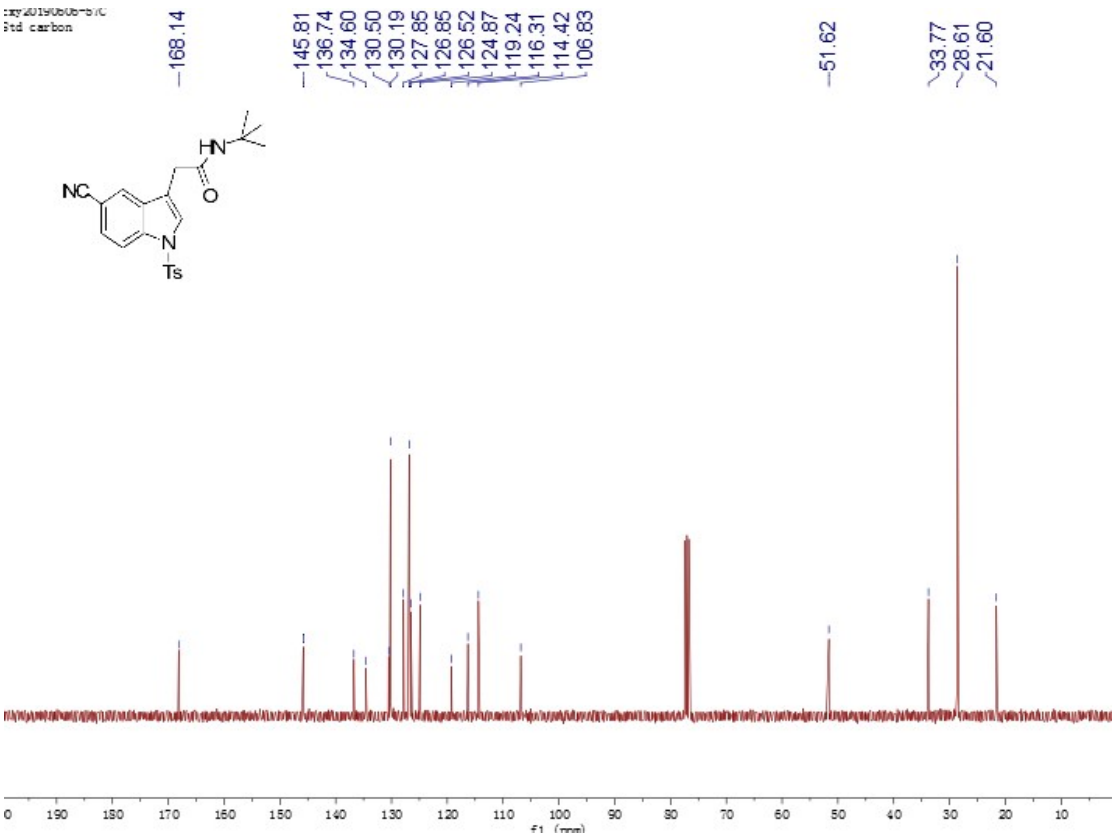
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4k



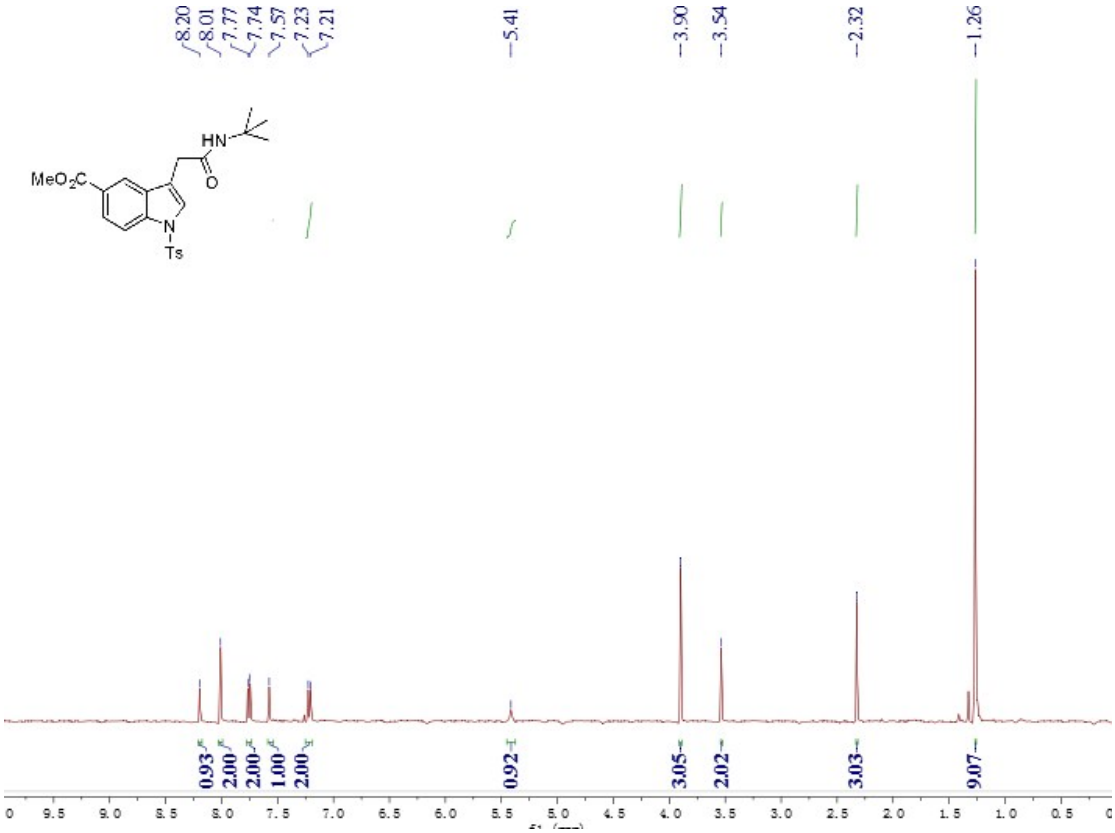
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4l



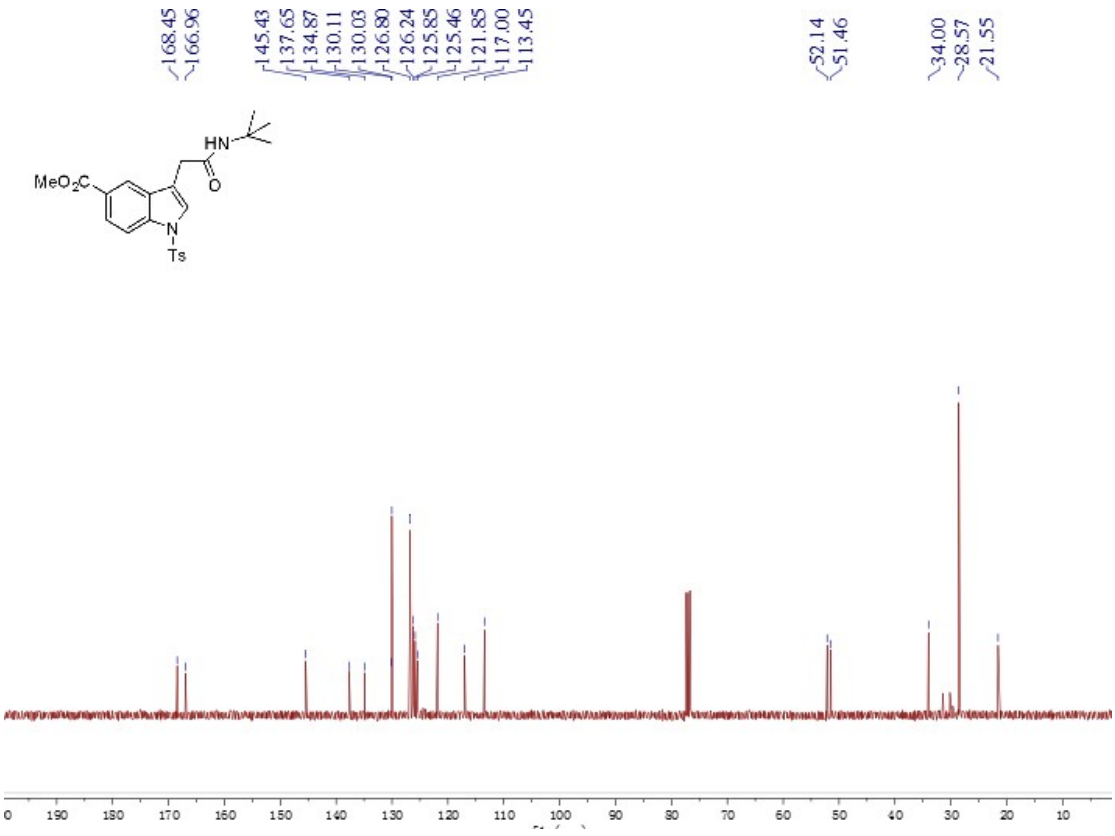
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4l



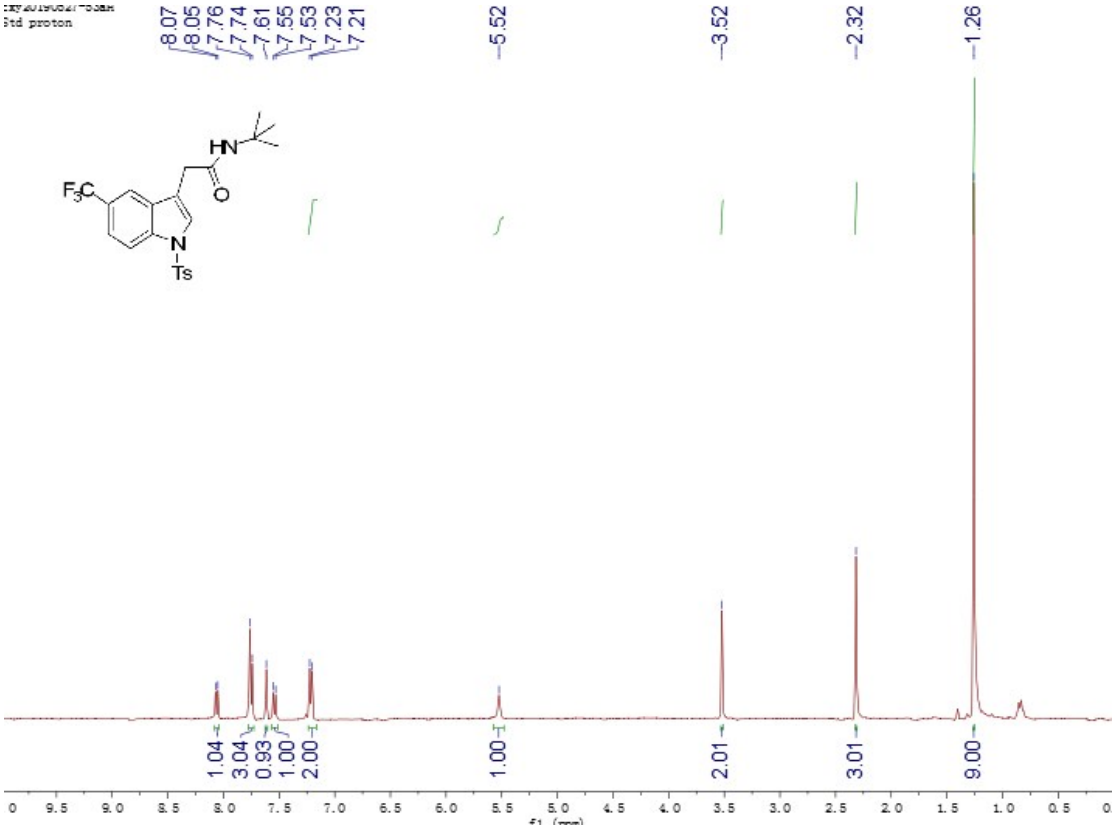
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4m



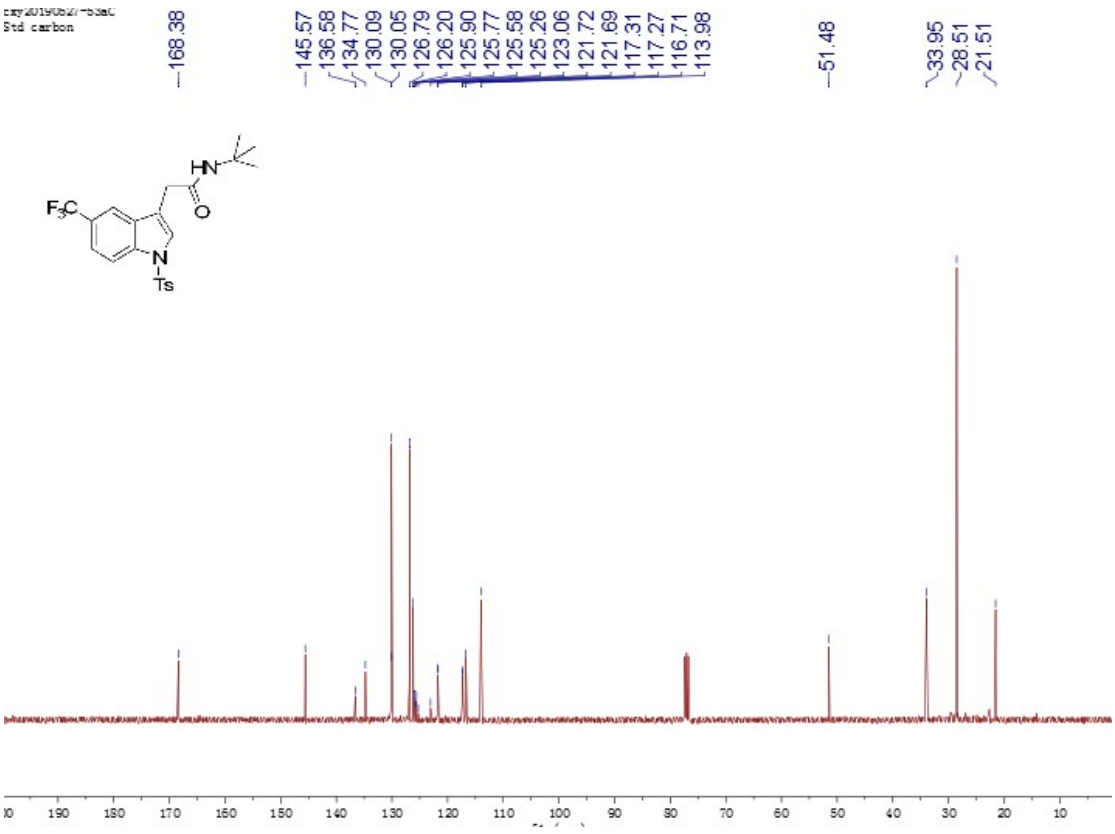
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4m



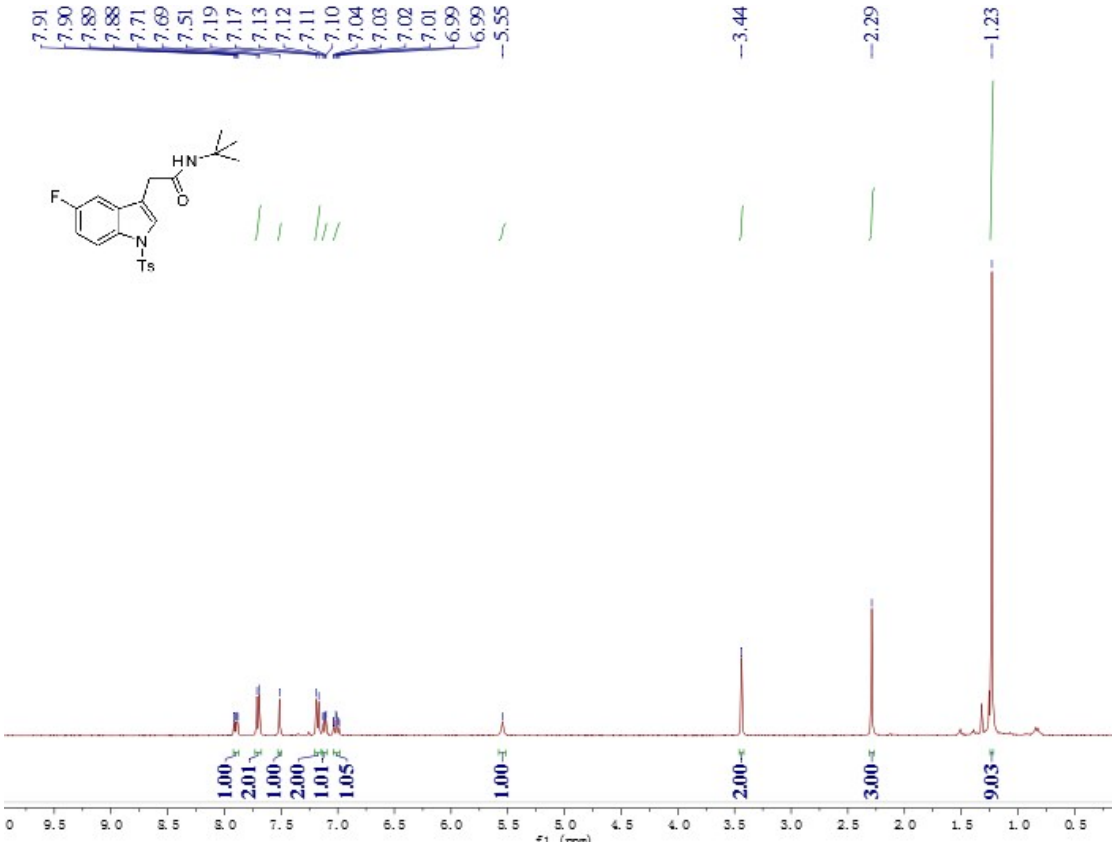
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4n



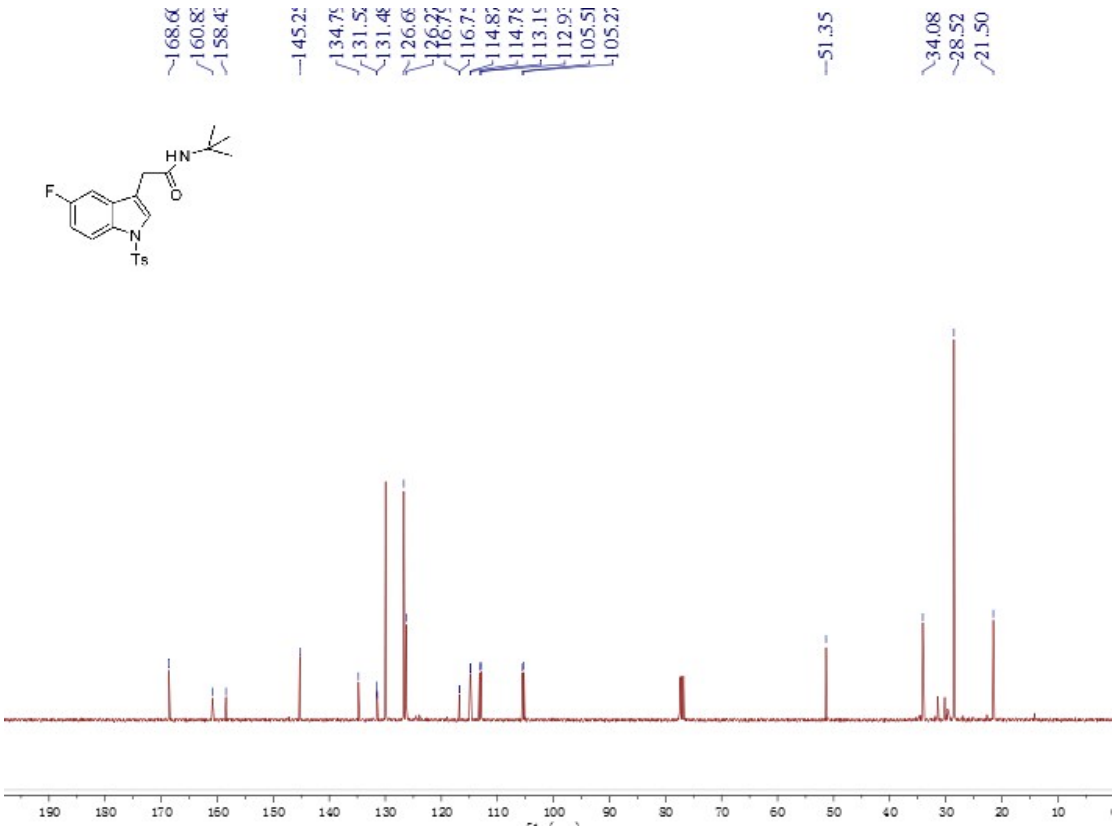
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4m



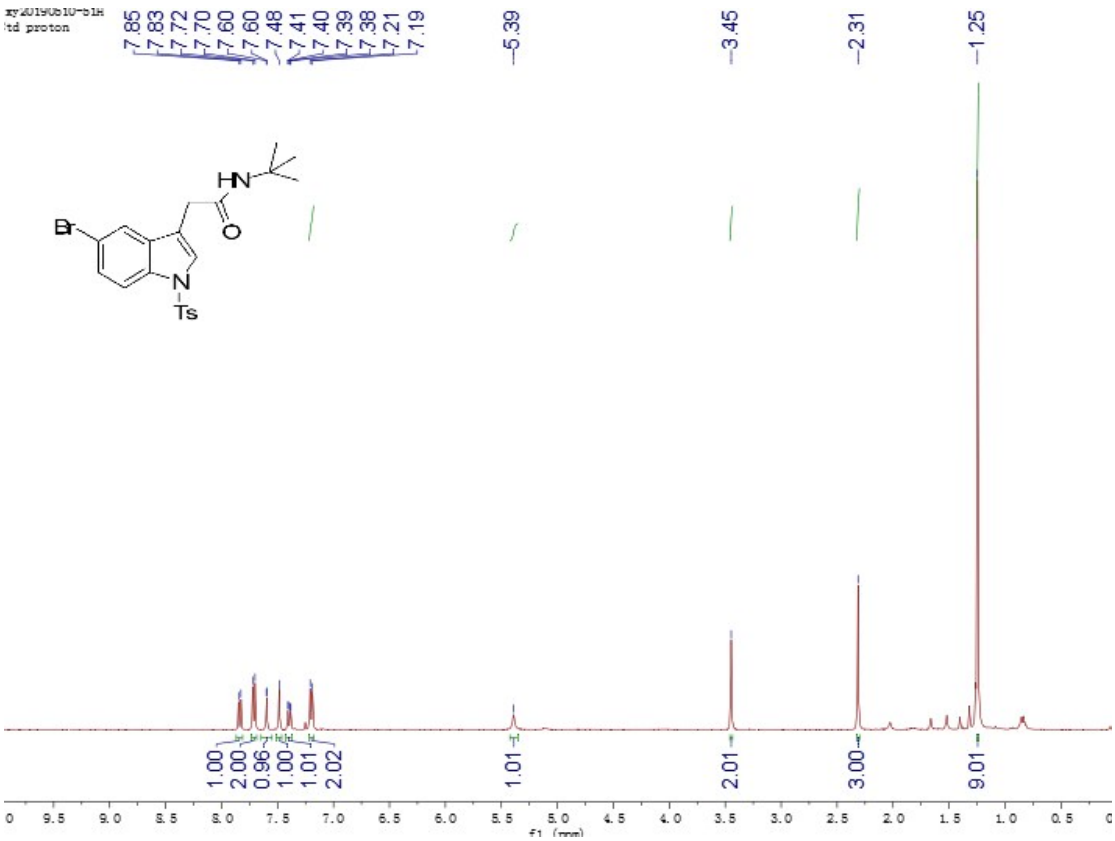
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4o



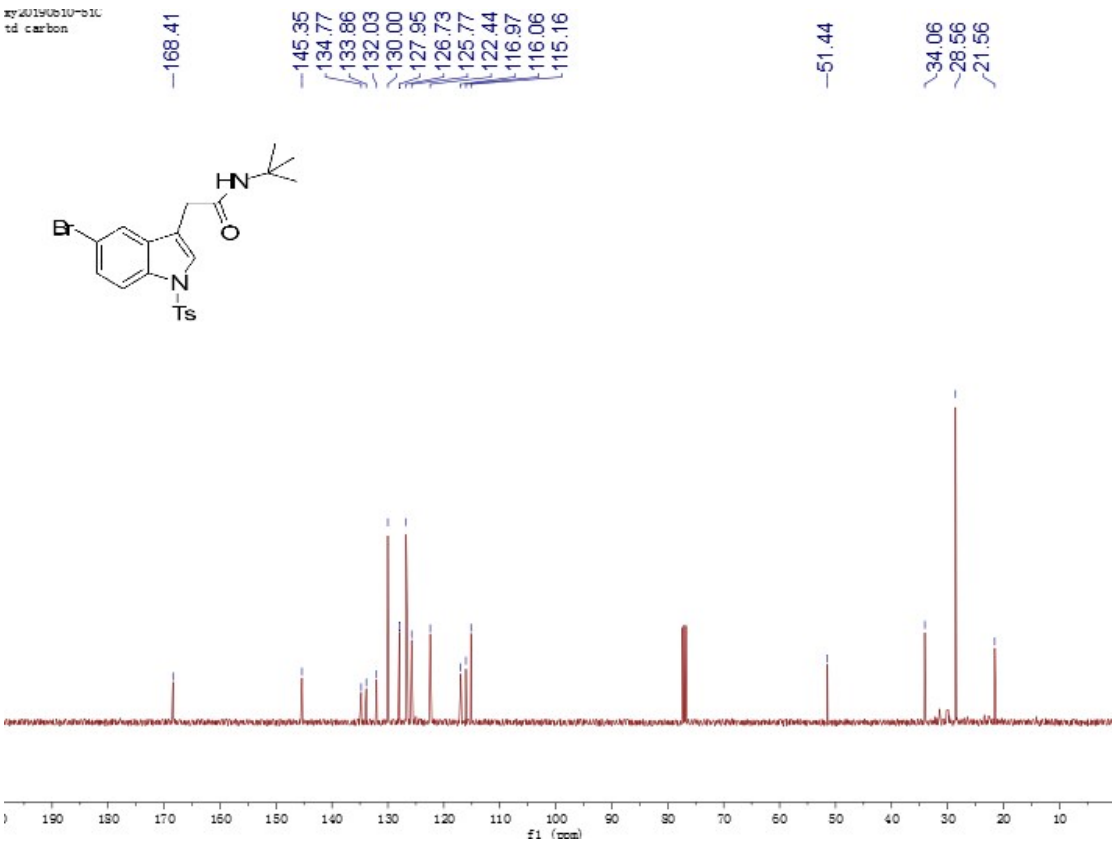
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4o



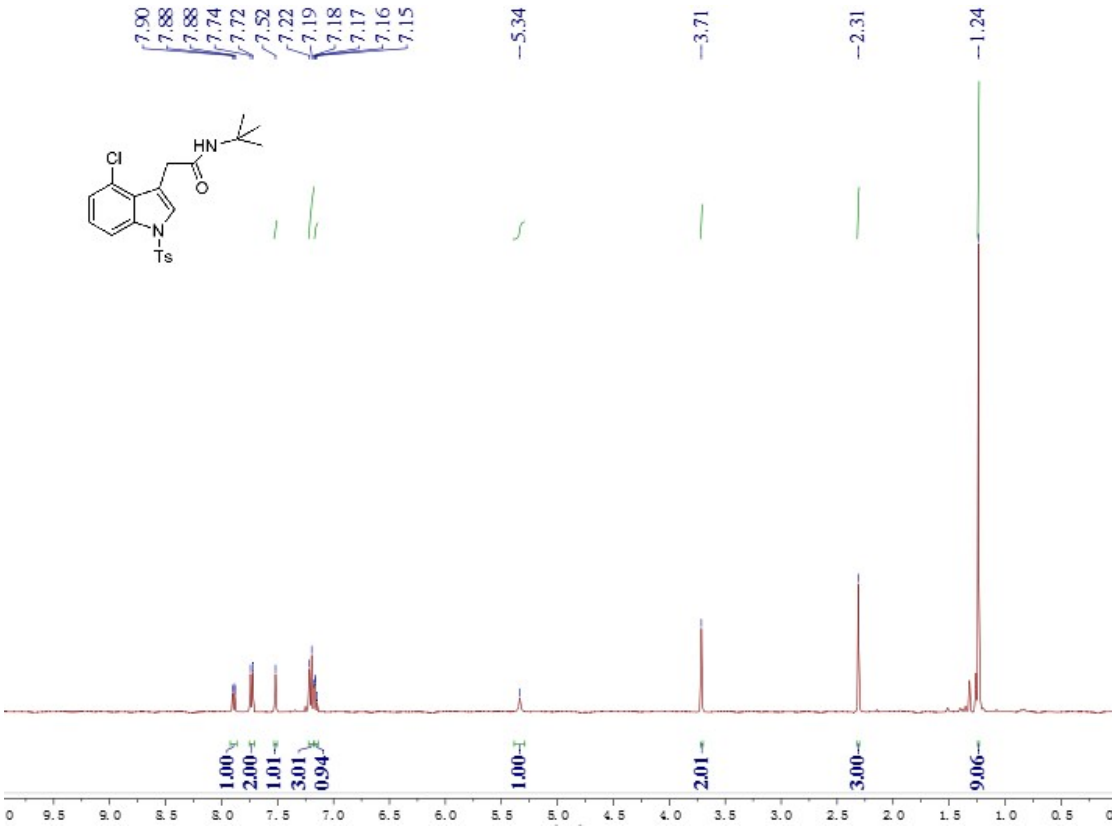
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4p



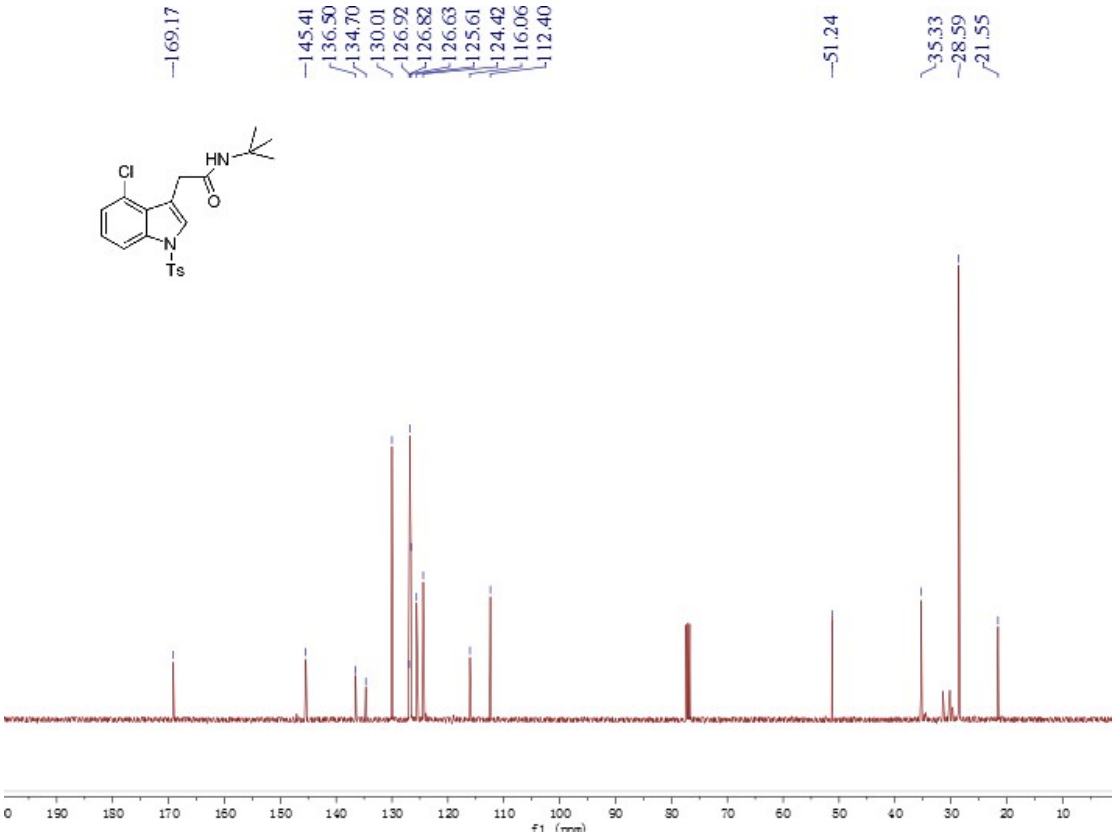
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4p



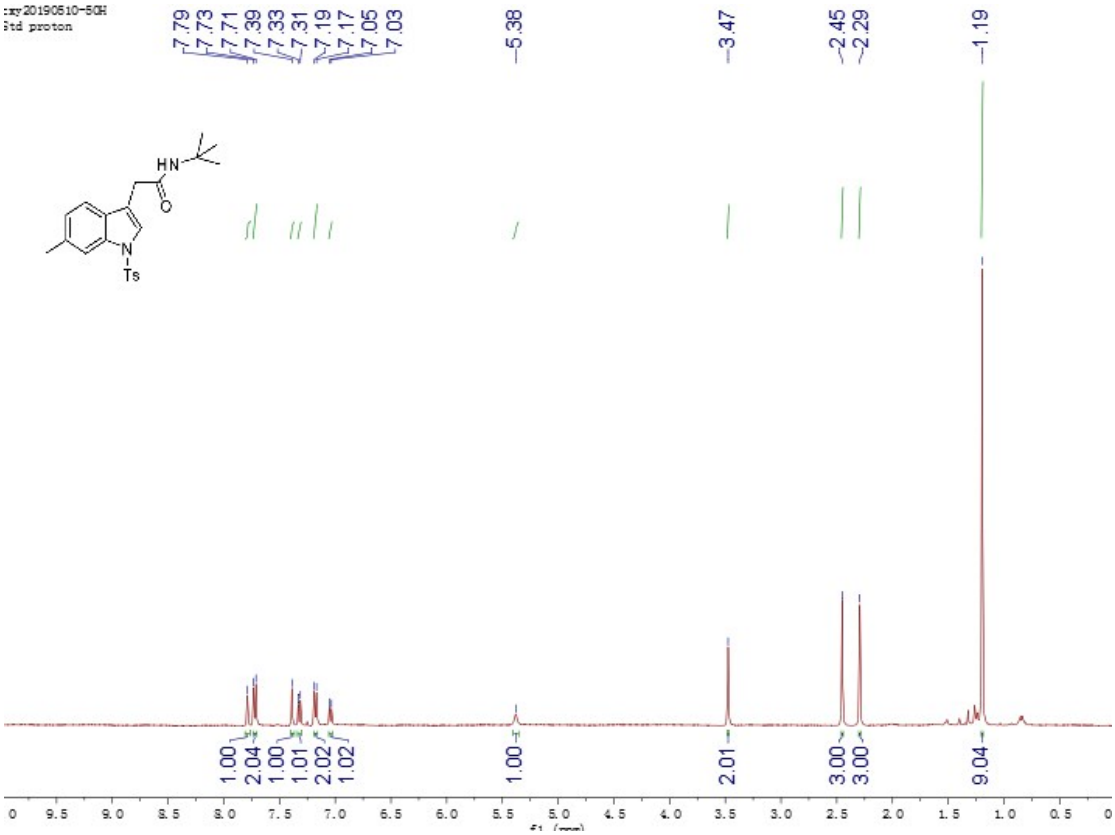
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4q



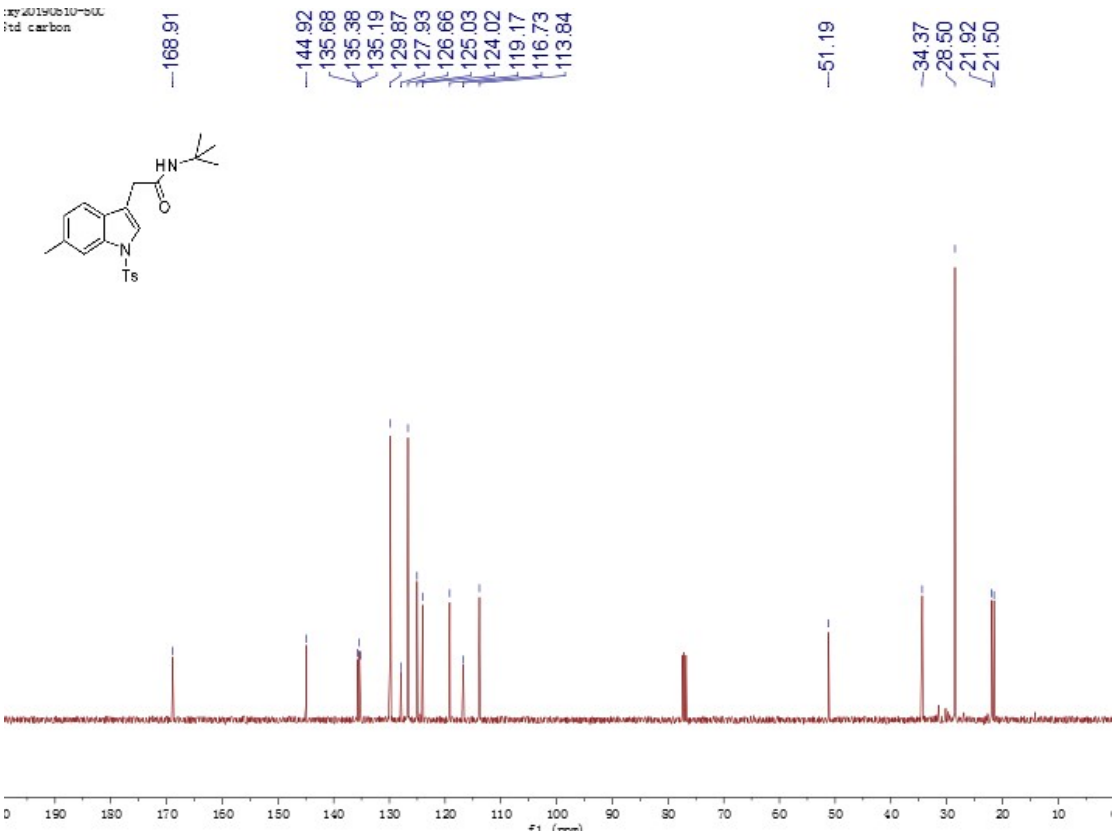
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4q



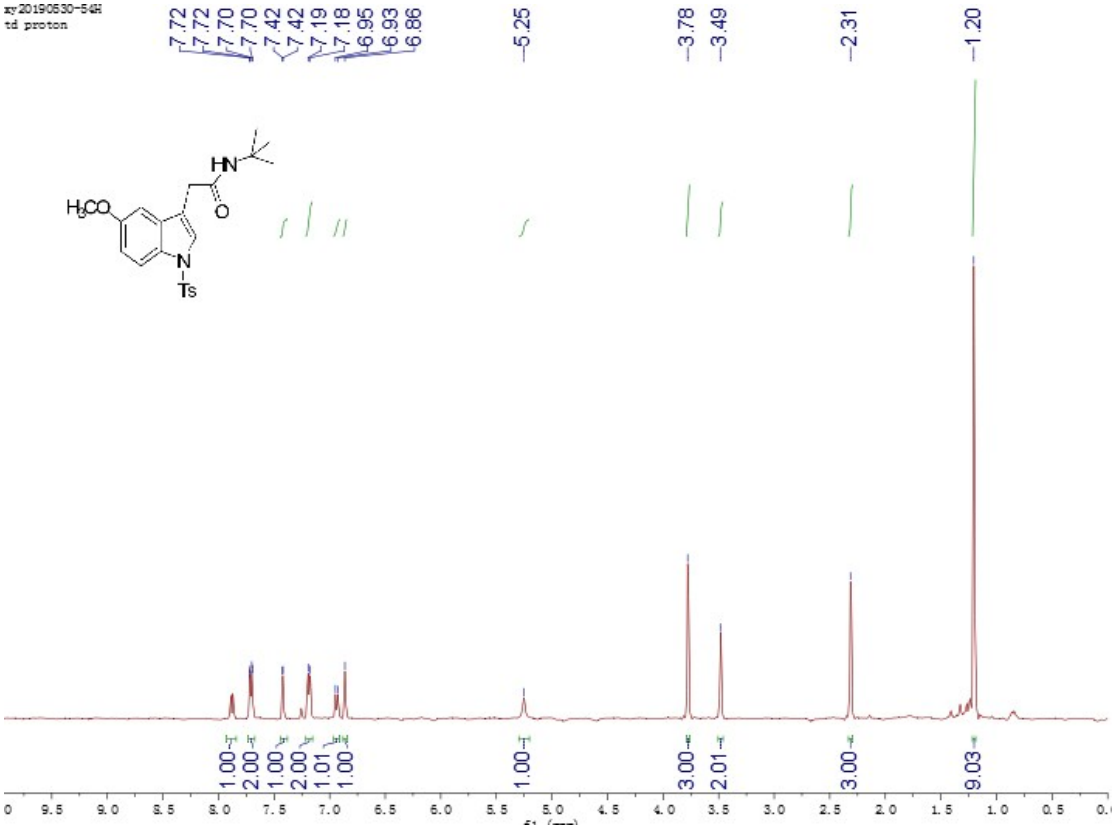
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4r



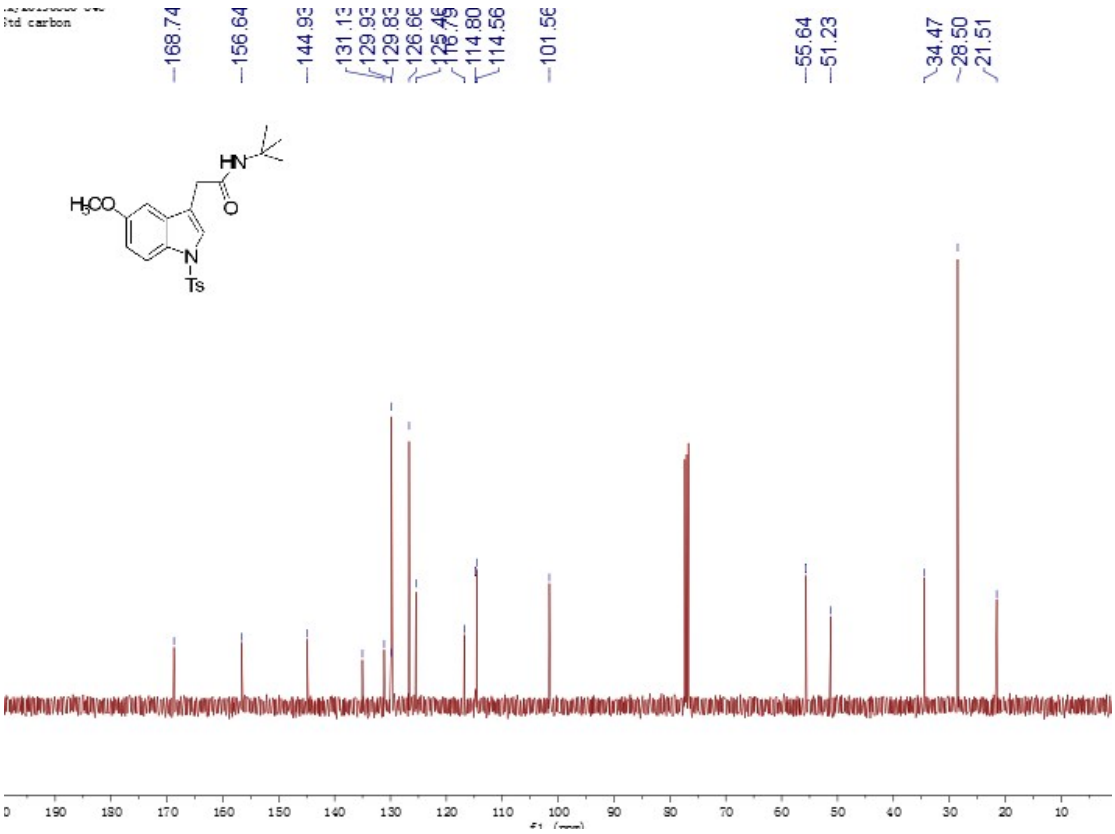
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4r



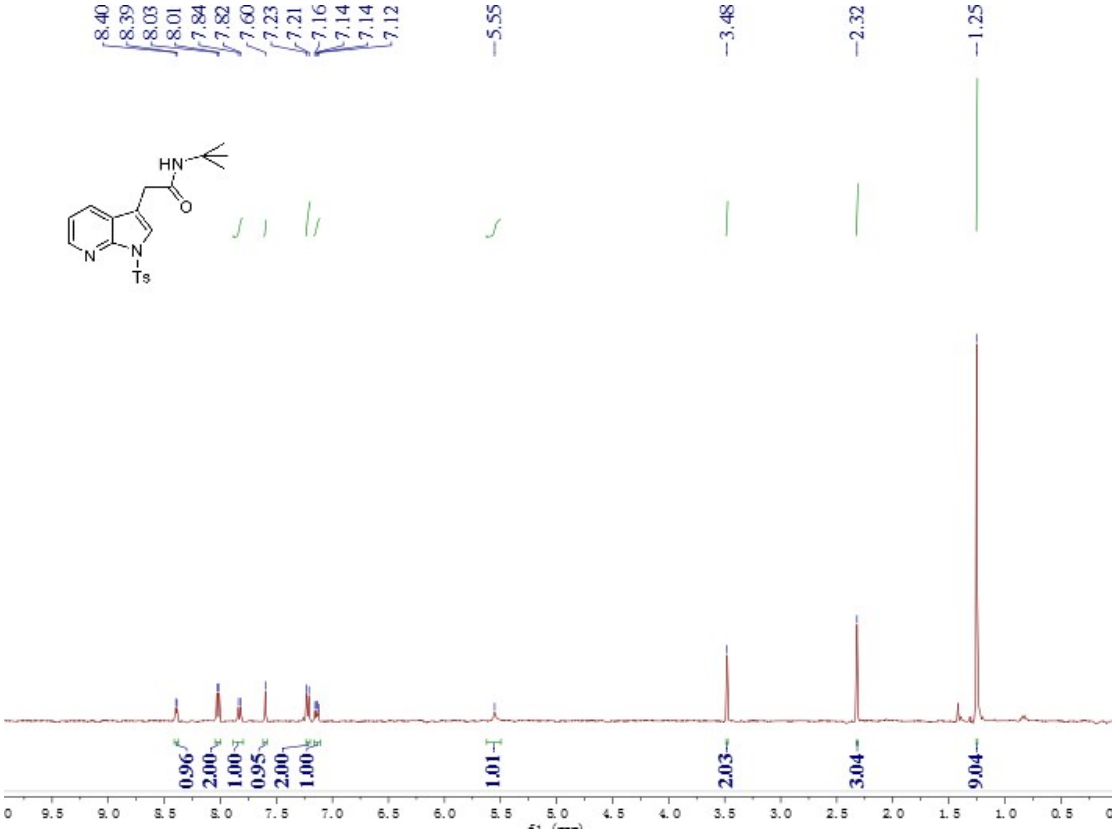
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4s



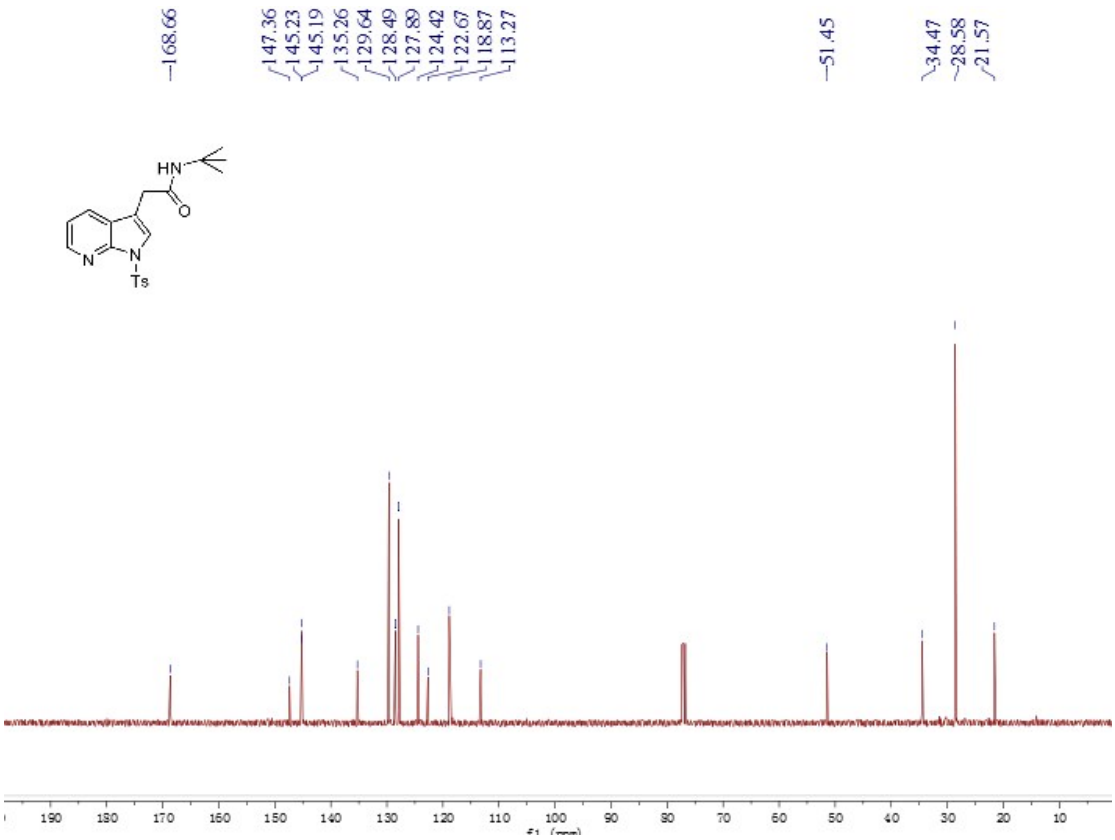
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4s



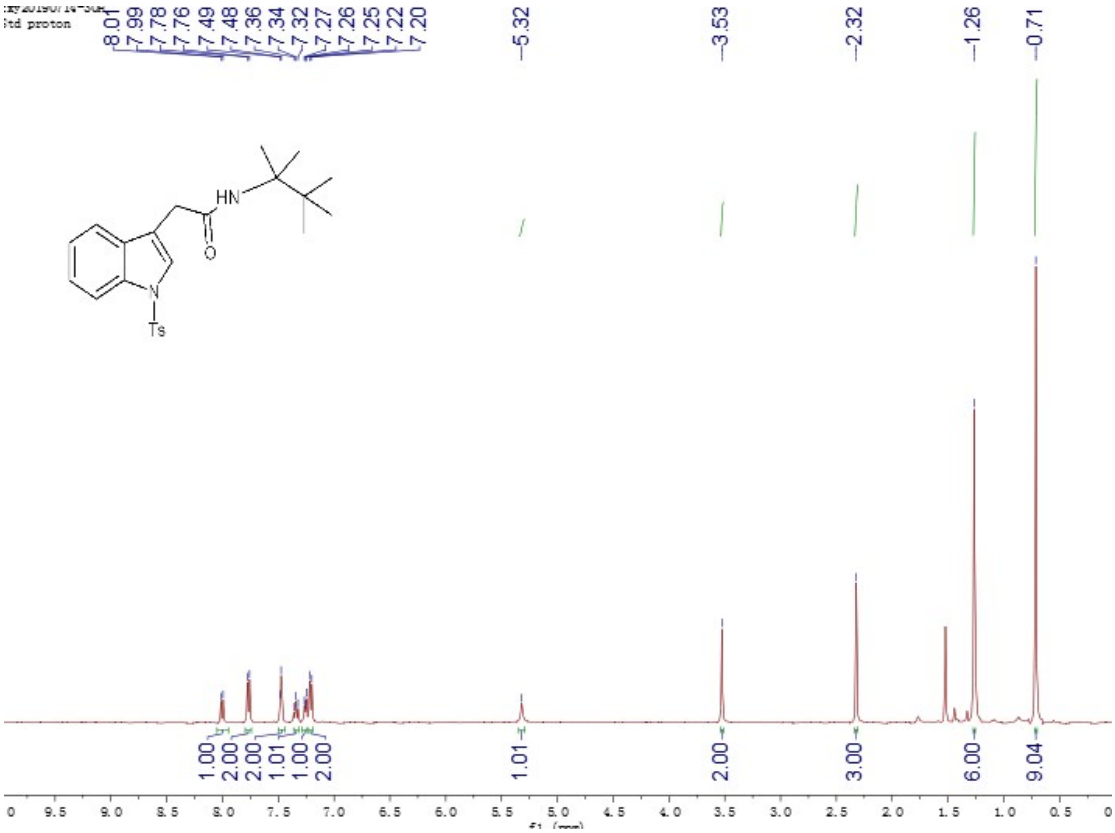
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4t



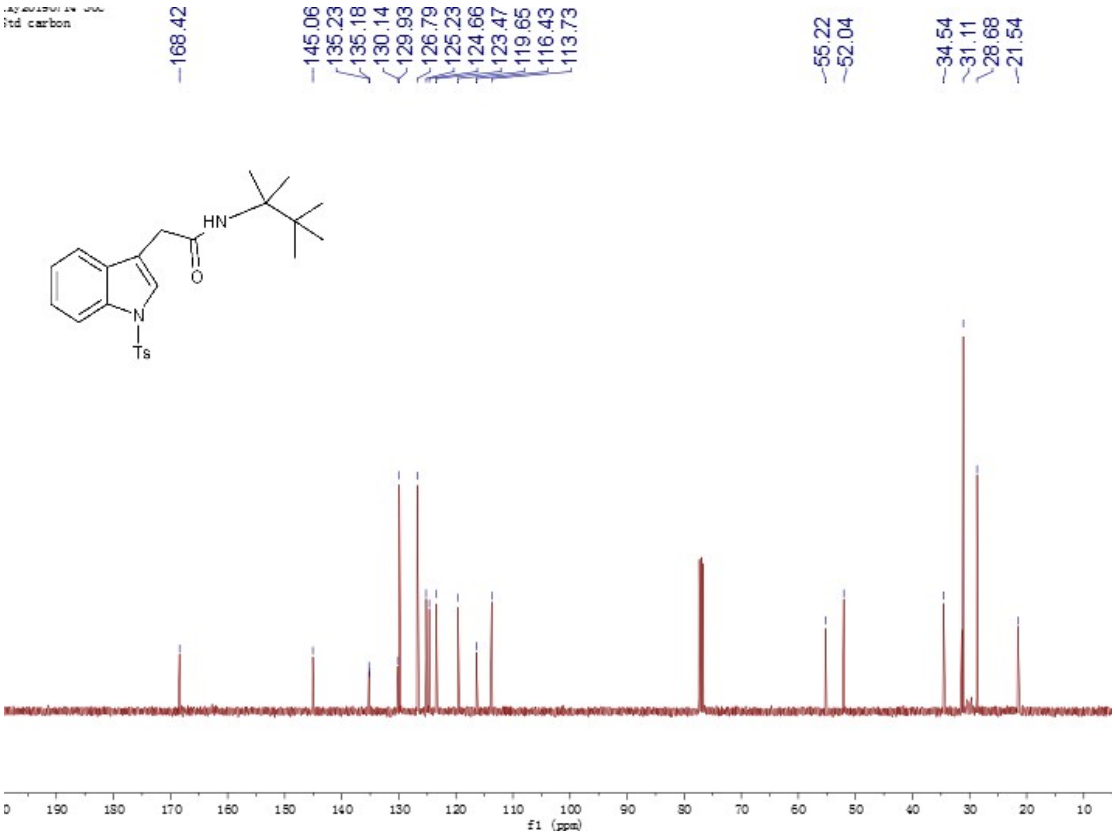
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4t



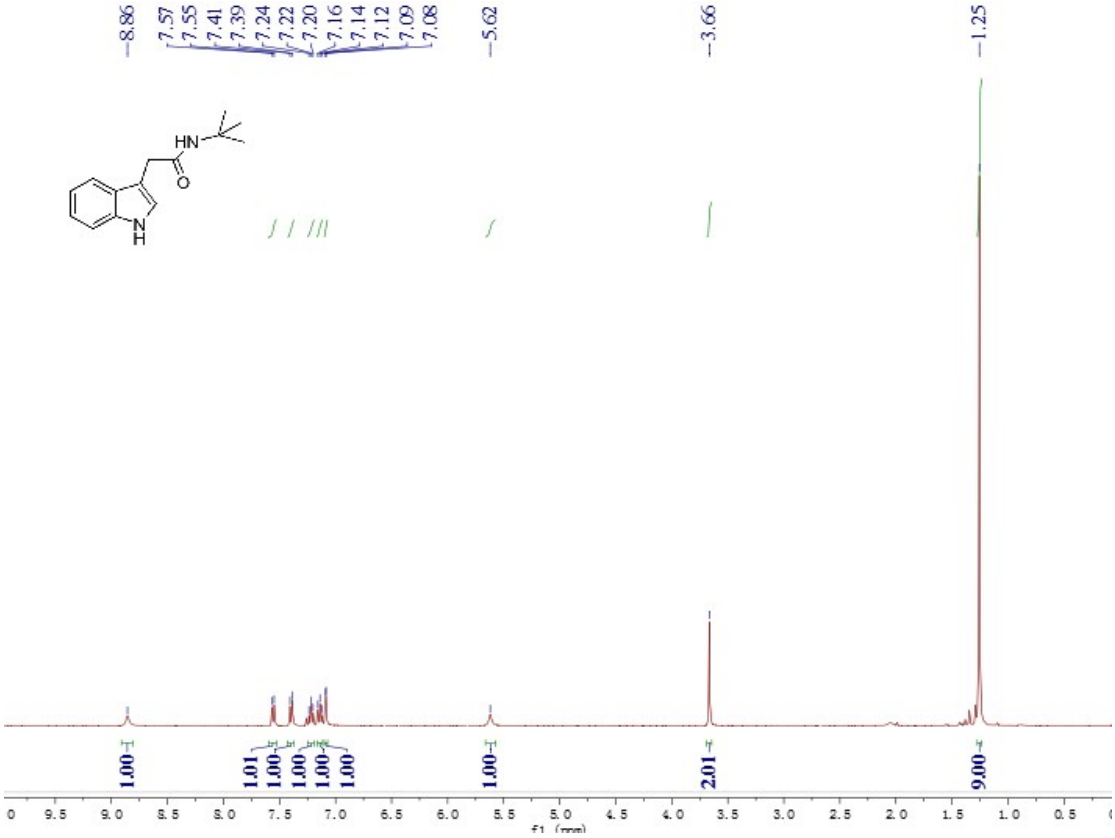
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4u



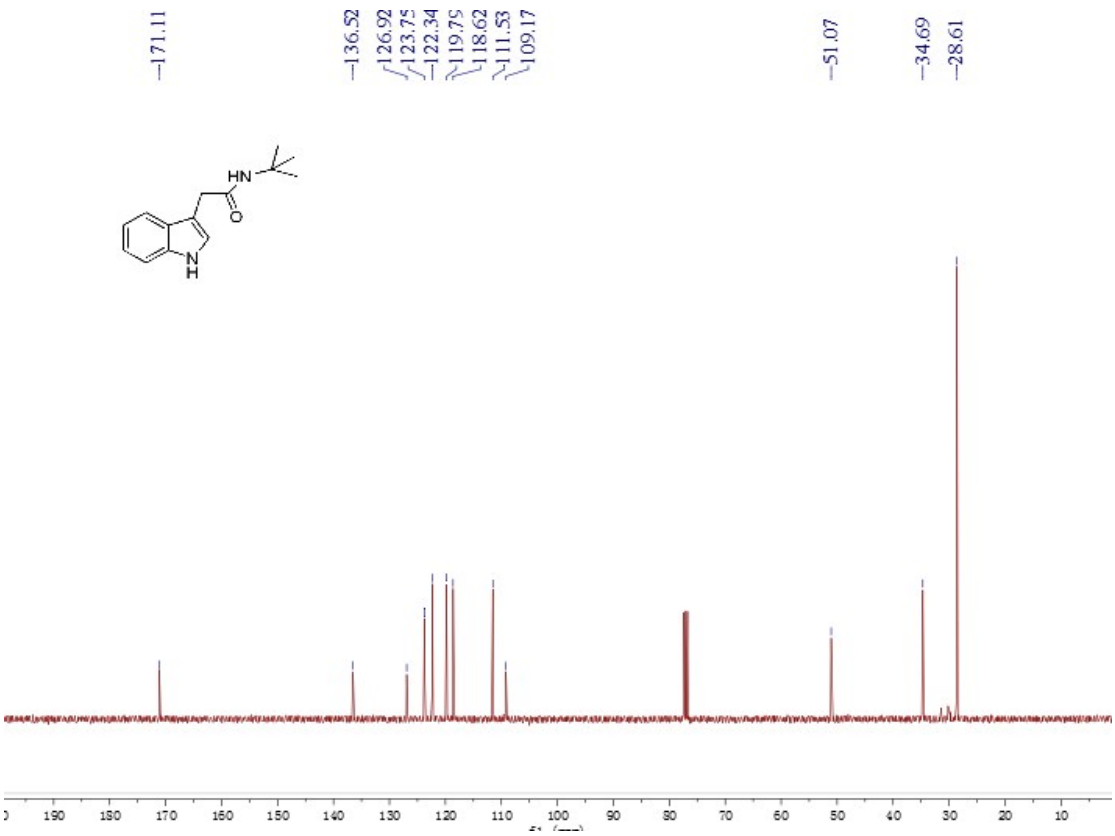
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4u



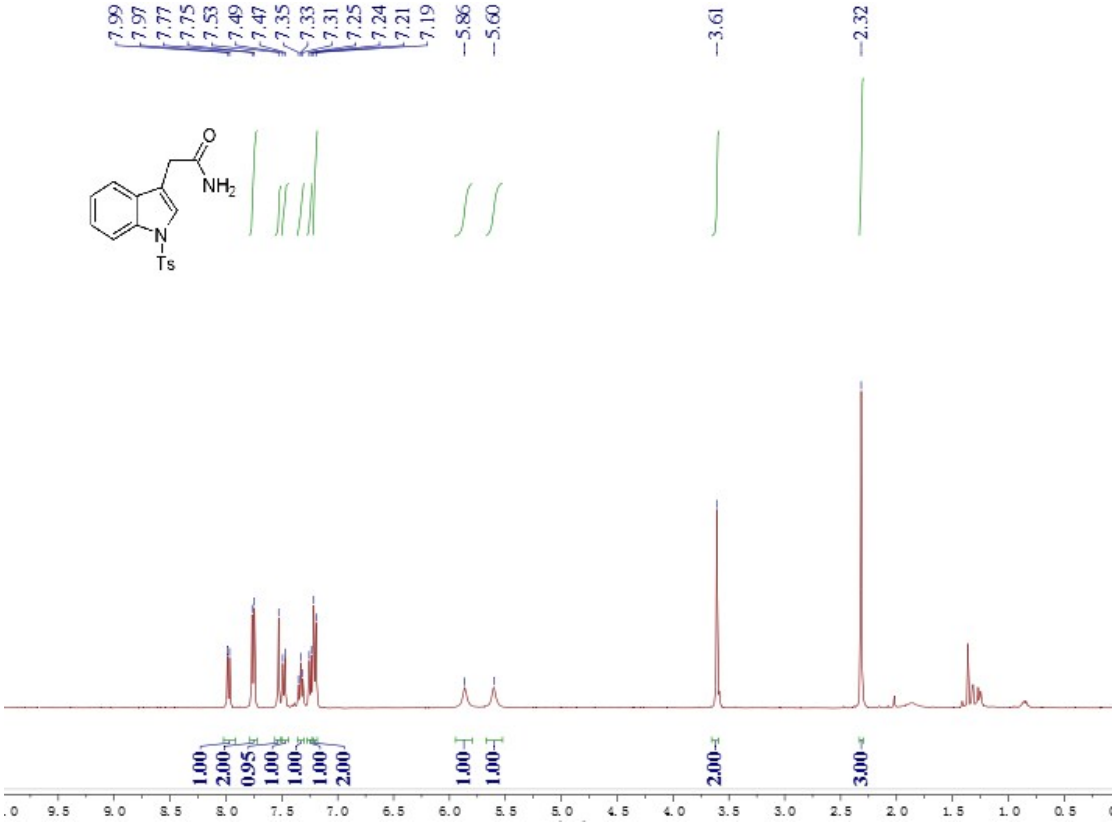
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4v



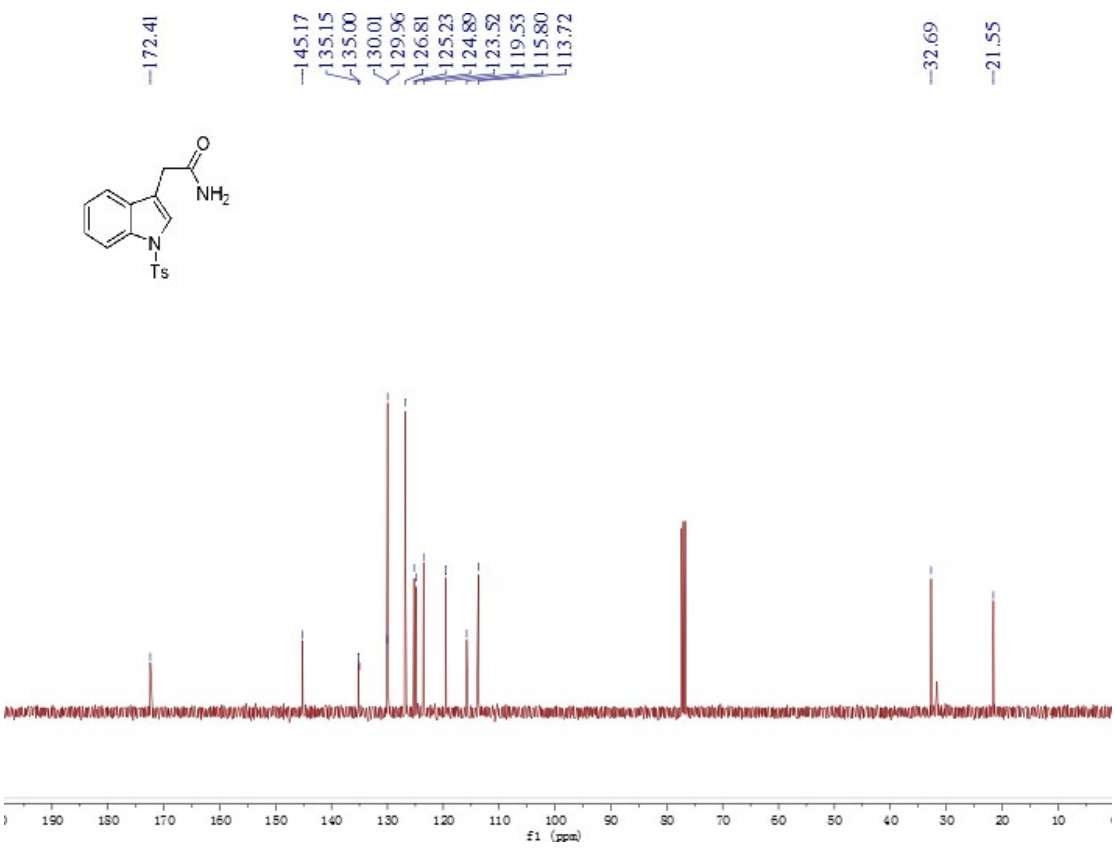
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4v



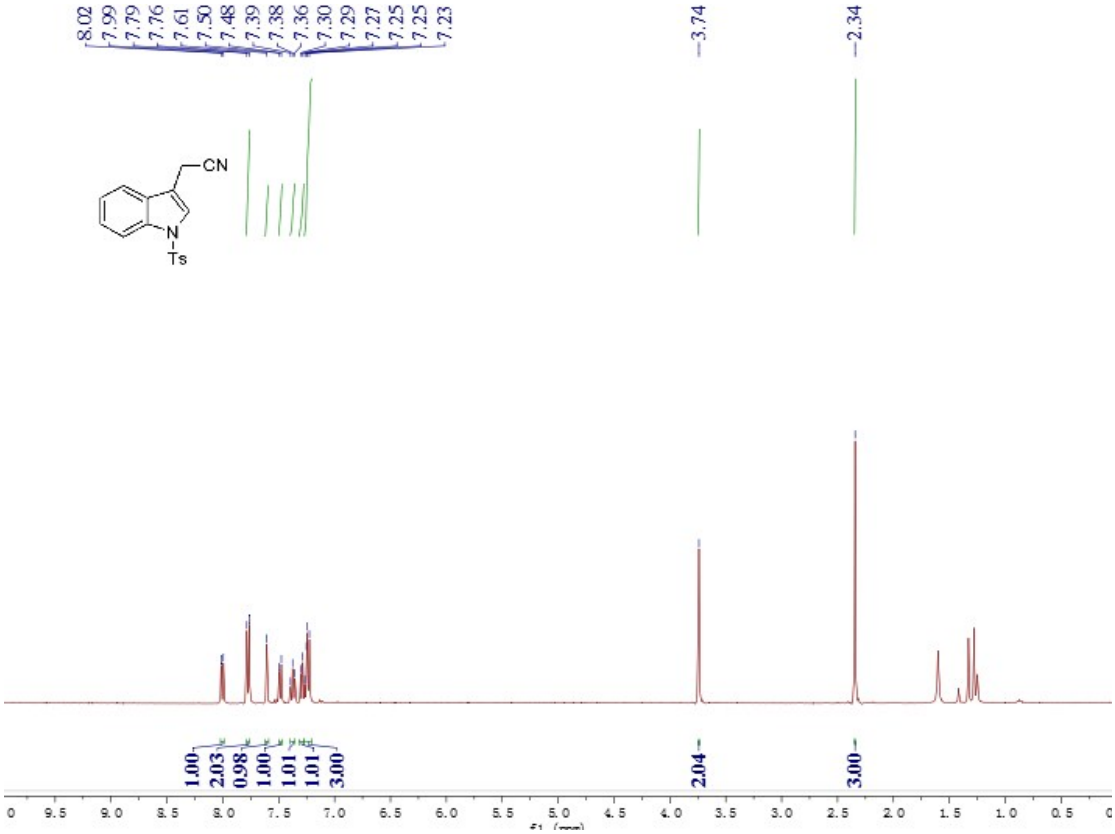
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 5



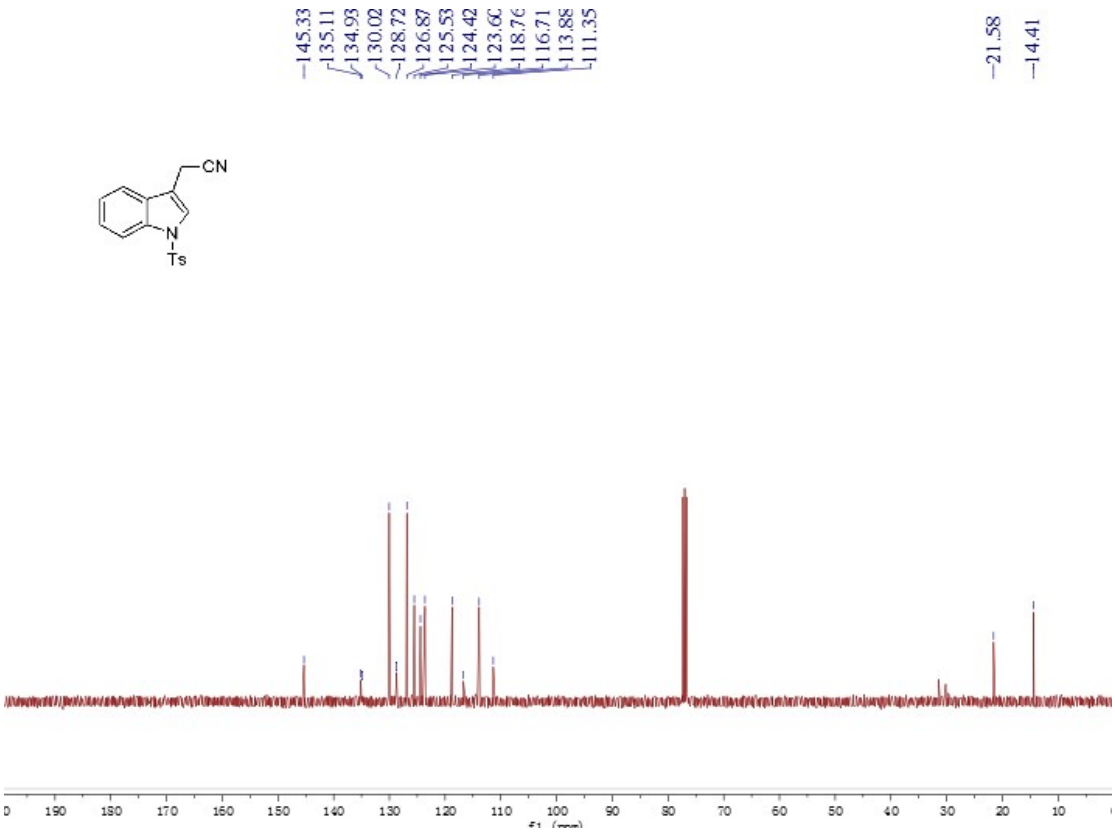
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 5



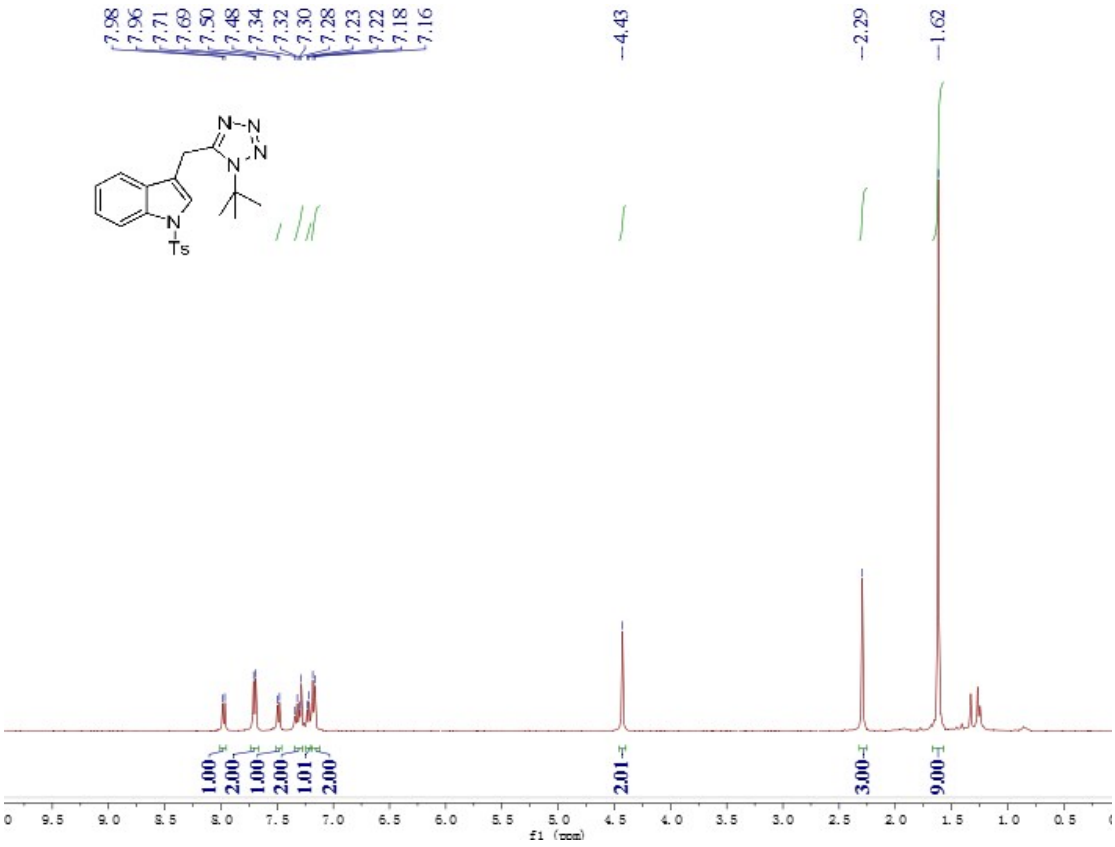
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 6



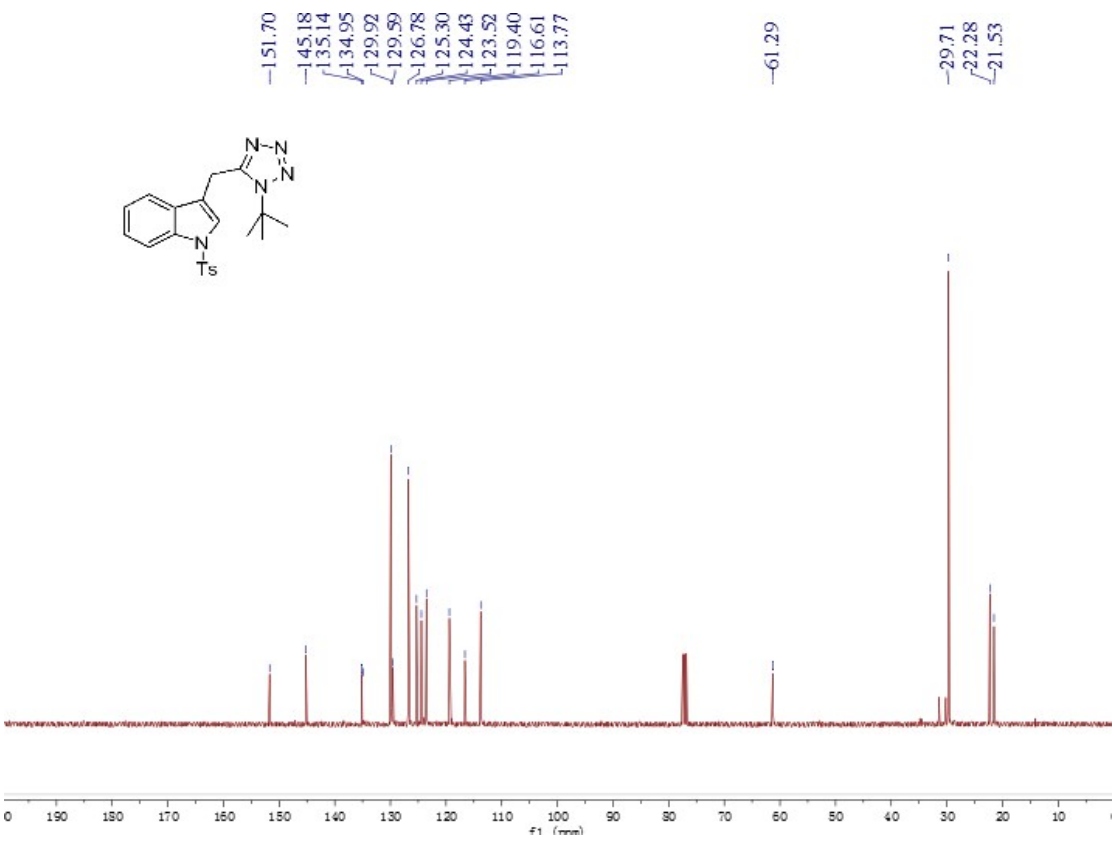
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 6



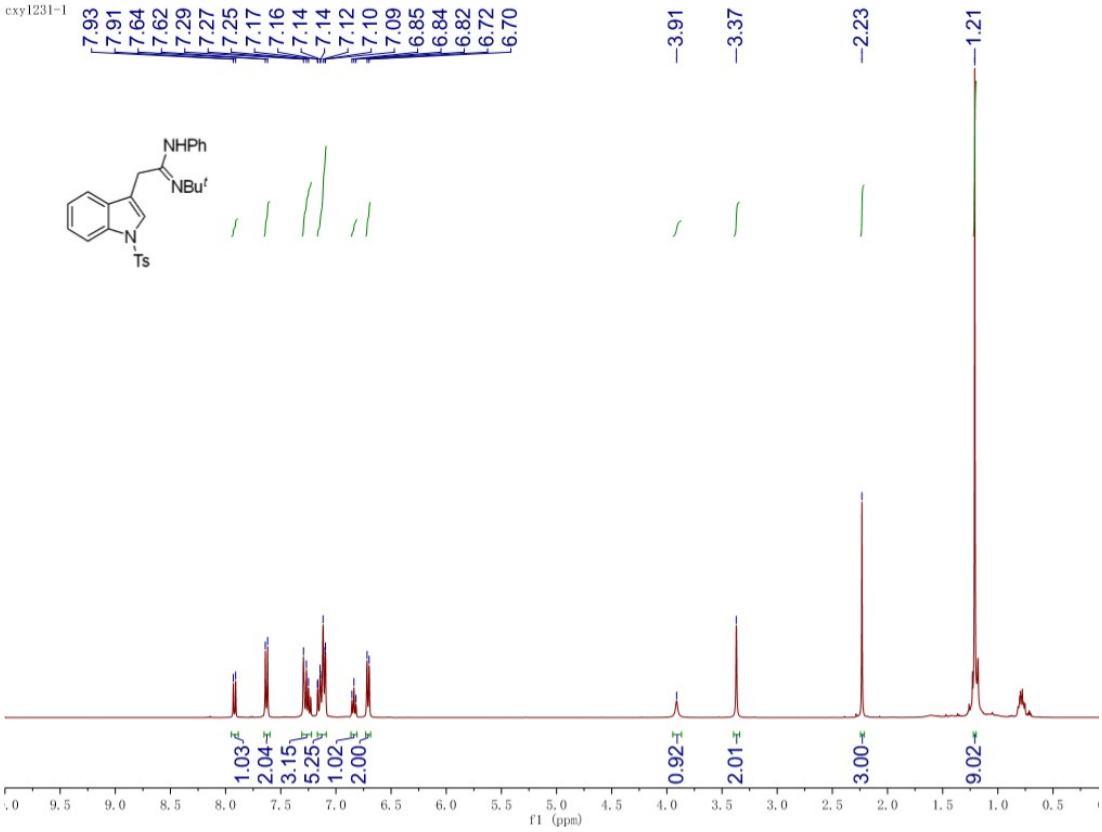
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 7



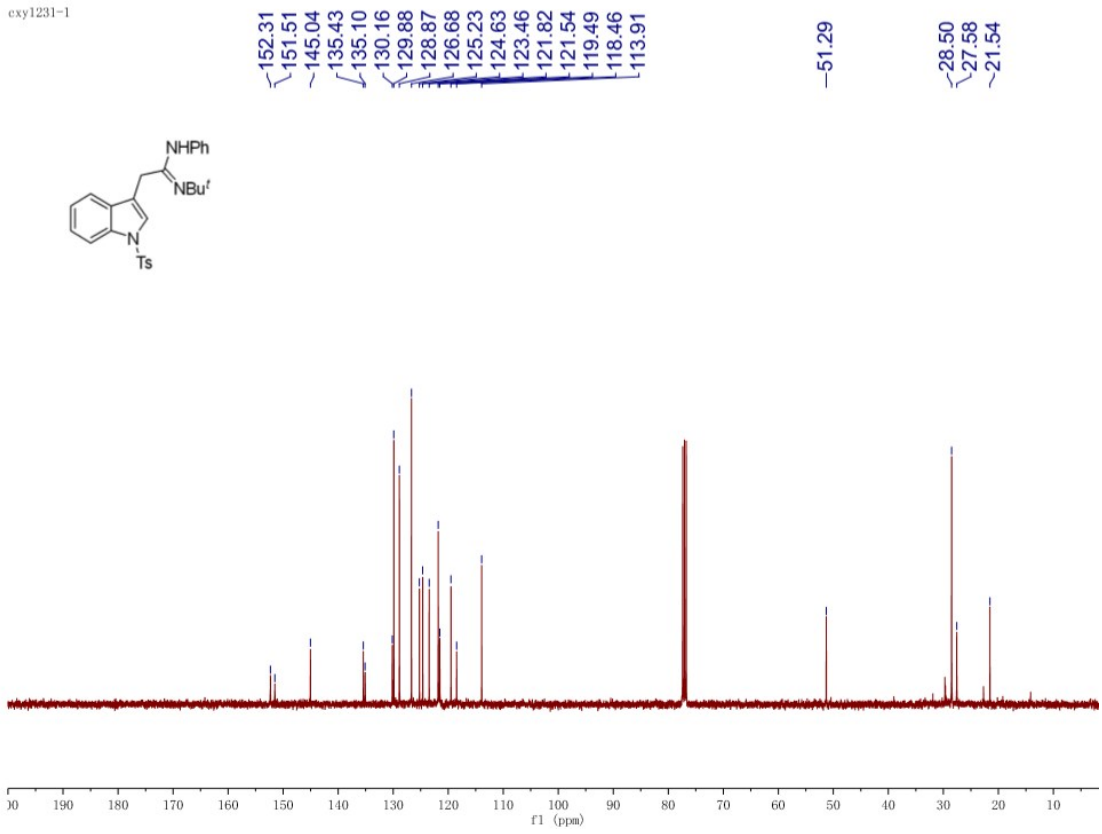
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 7



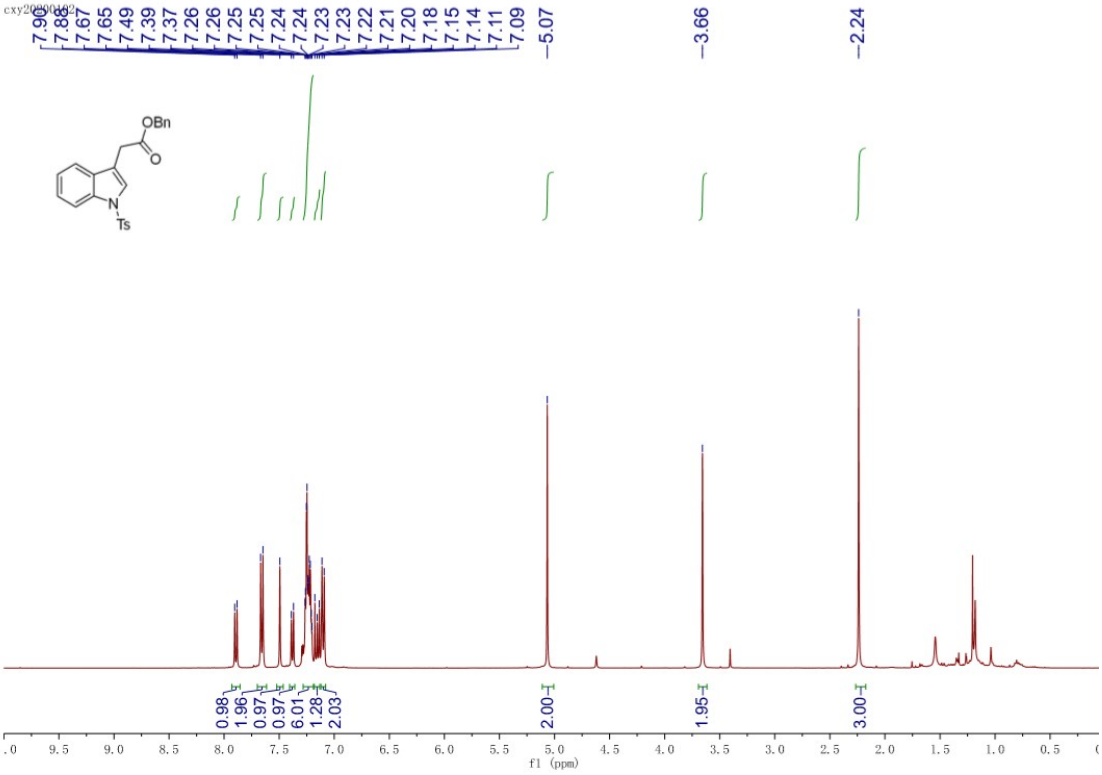
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 8



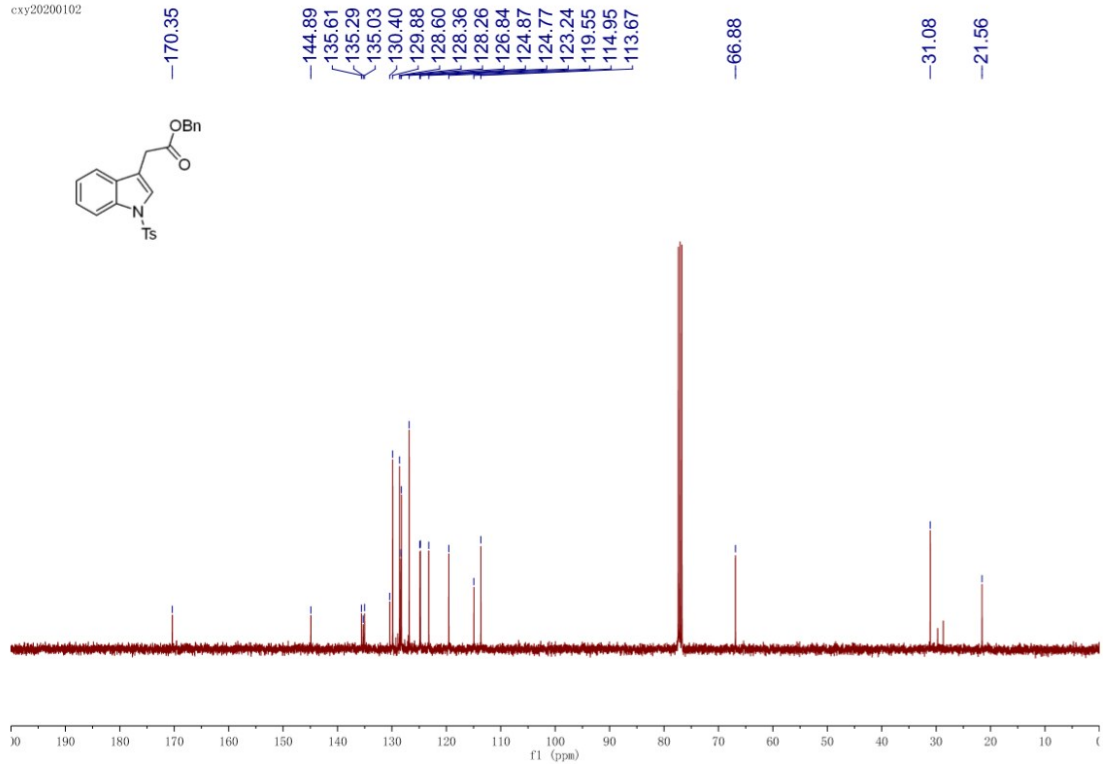
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 8



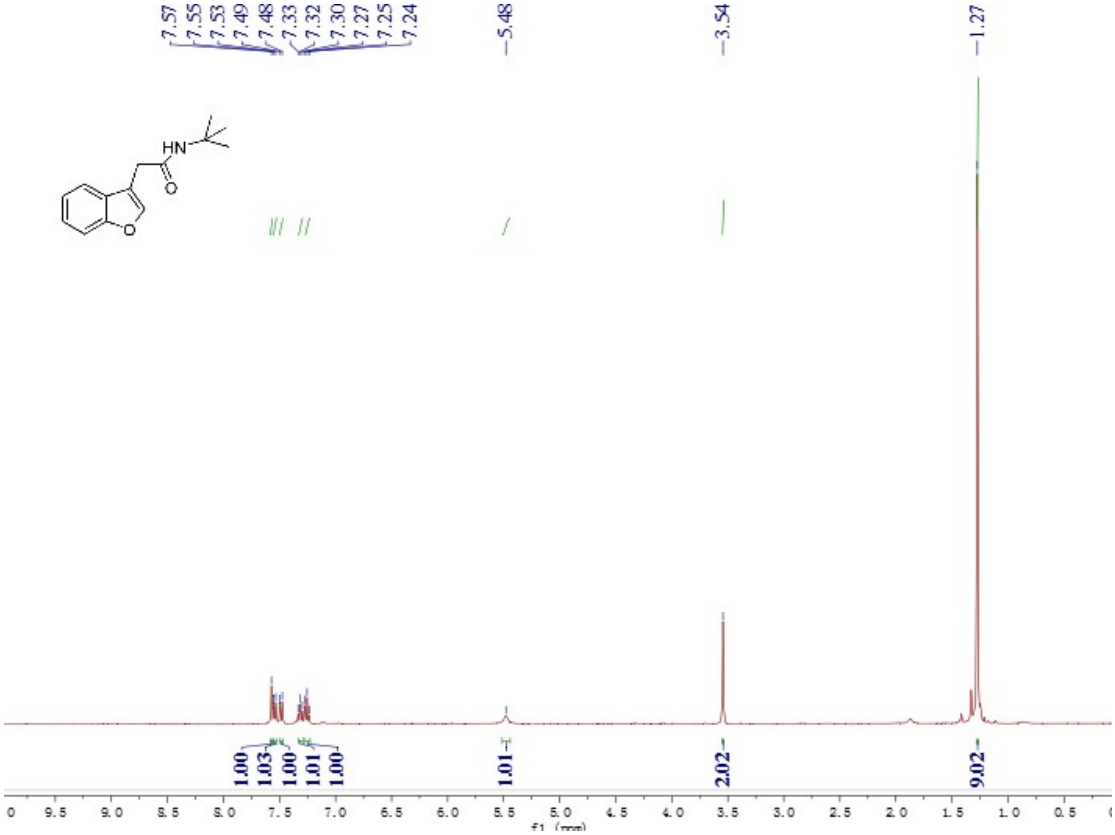
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 9



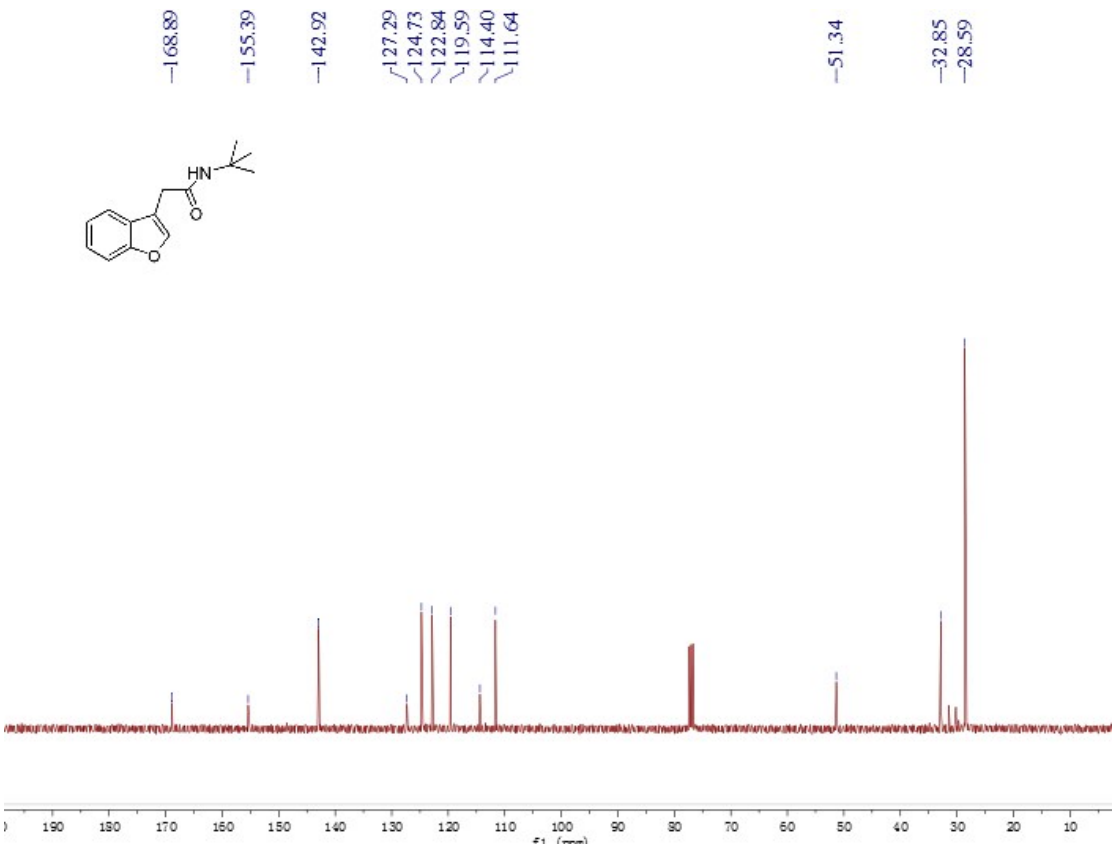
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 9



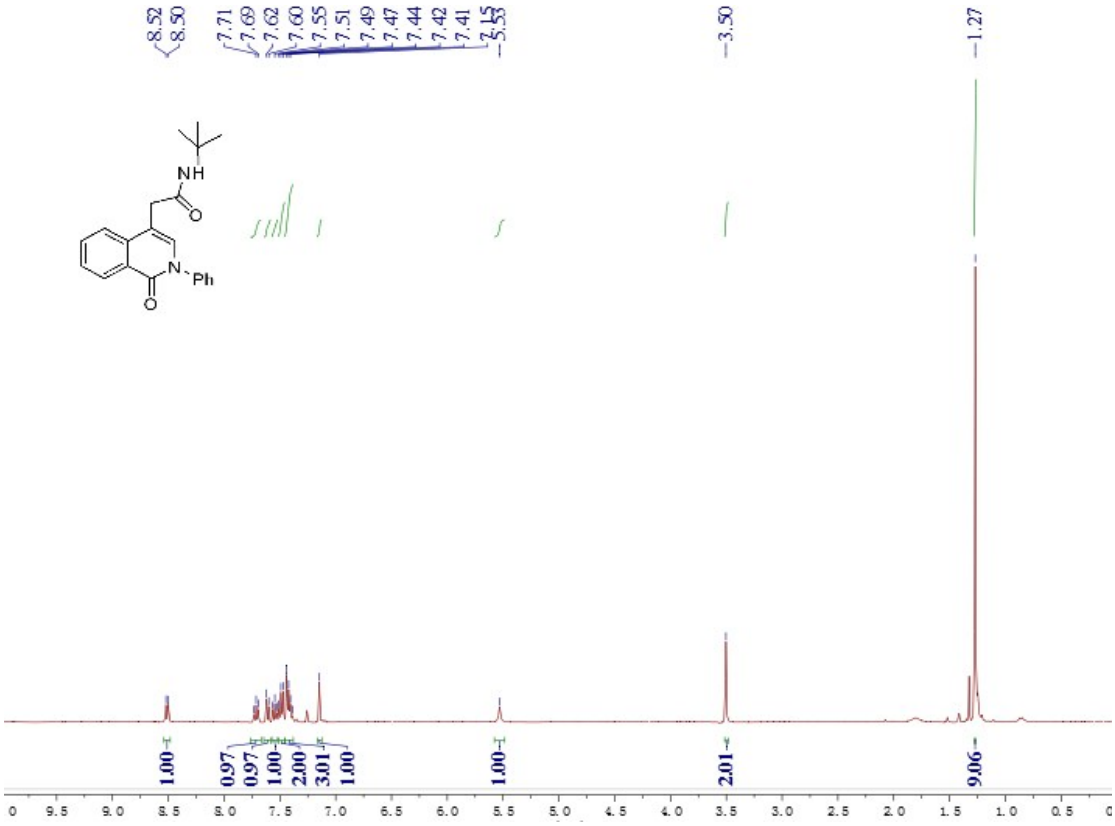
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 11



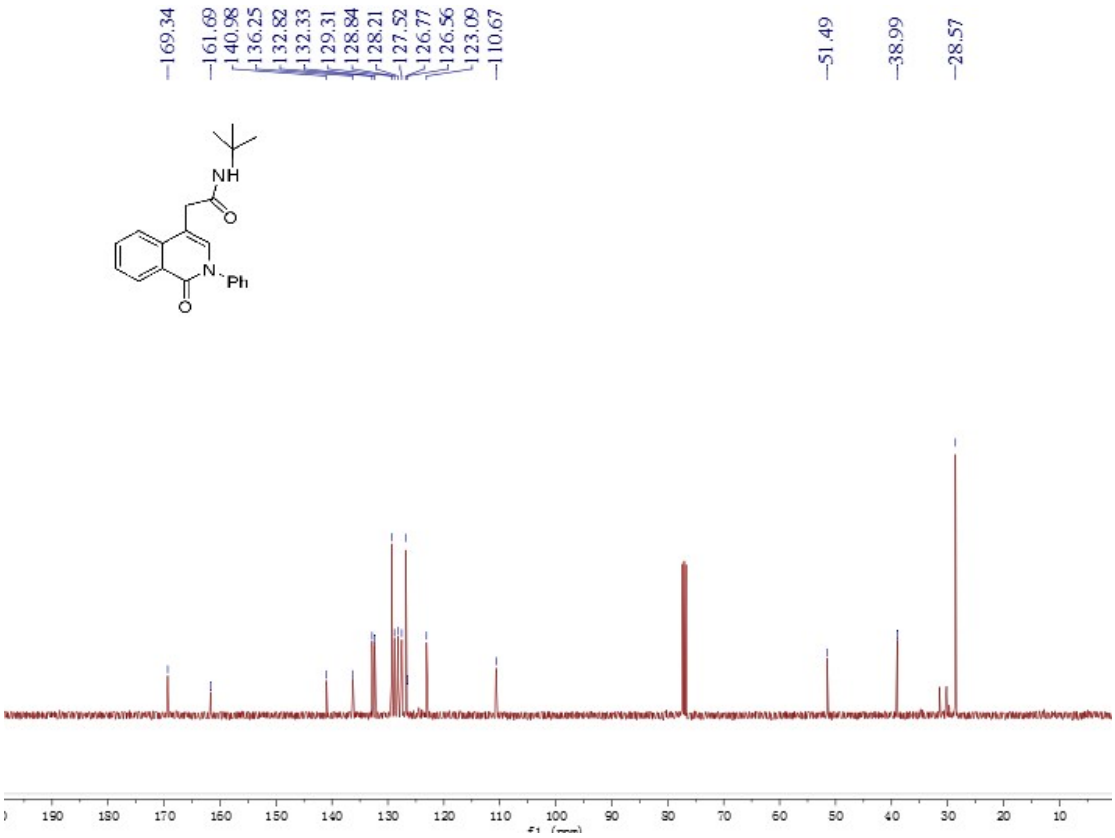
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 11



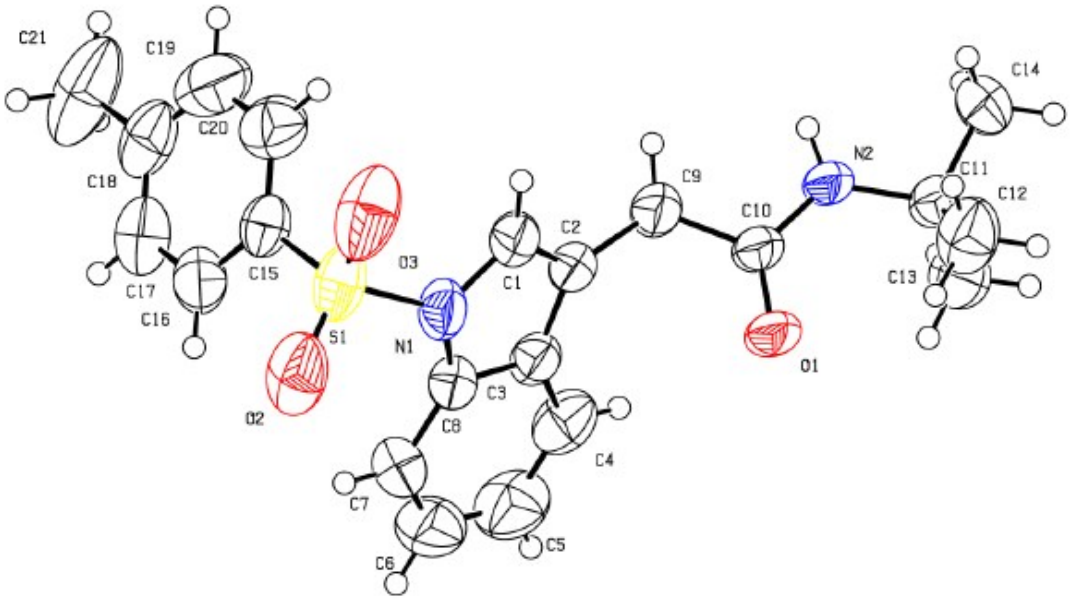
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 13

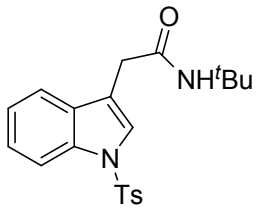


^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 13



5. X-ray crystal structure of 4a.





4a

Datablock: ga_90422a_a

Bond precision: C-C = 0.0036 A Wavelength=1.34138

Cell: a=9.6428(9) b=13.1230(18) c=33.188(5)
alpha=90 beta=90 gamma=90
Temperature: 298 K

	Calculated	Reported
Volume	4199.7(9)	4199.7(9)
Space group	P b c a	P b c a
Hall group	-P 2ac 2ab	-P 2ac 2ab
Moiety formula	C21 H24 N2 O3 S	?
Sum formula	C21 H24 N2 O3 S	C21 H24 N2 O3 S
Mr	384.48	384.48
Dx,g cm-3	1.216	1.216
Z	8	8
Mu (mm-1)	1.011	1.011
F000	1632.0	1632.0
F000'	1637.72	
h,k,lmax	12,16,41	12,16,41
Nref	4297	4295
Tmin,Tmax	0.865,0.922	0.646,0.751
Tmin'	0.769	