

Electronic Supplementary Information

Novel isatin-indole derivatives as potential inhibitors of chorismate mutase (CM): their synthesis along with unexpected formation of 2-indolylmethylamino benzoate ester under Pd-Cu catalysis

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Table of contents

S.No.	Content	Page No.
1	Figure S-1S-2
2	Figure S-2S-3
3	Figure S-3S-4
4	Figure S-4S-5
5	Figure S-5S-6
6	Figure S-6S-7
7	Figure S-7S-8
8	Figure S-8S-9
9	Experimental Section, ChemistryS-10
10	Docking studiesS-32
11	Pharmacology, Chorismate mutase enzymatic assayS-33
12	ReferencesS-34

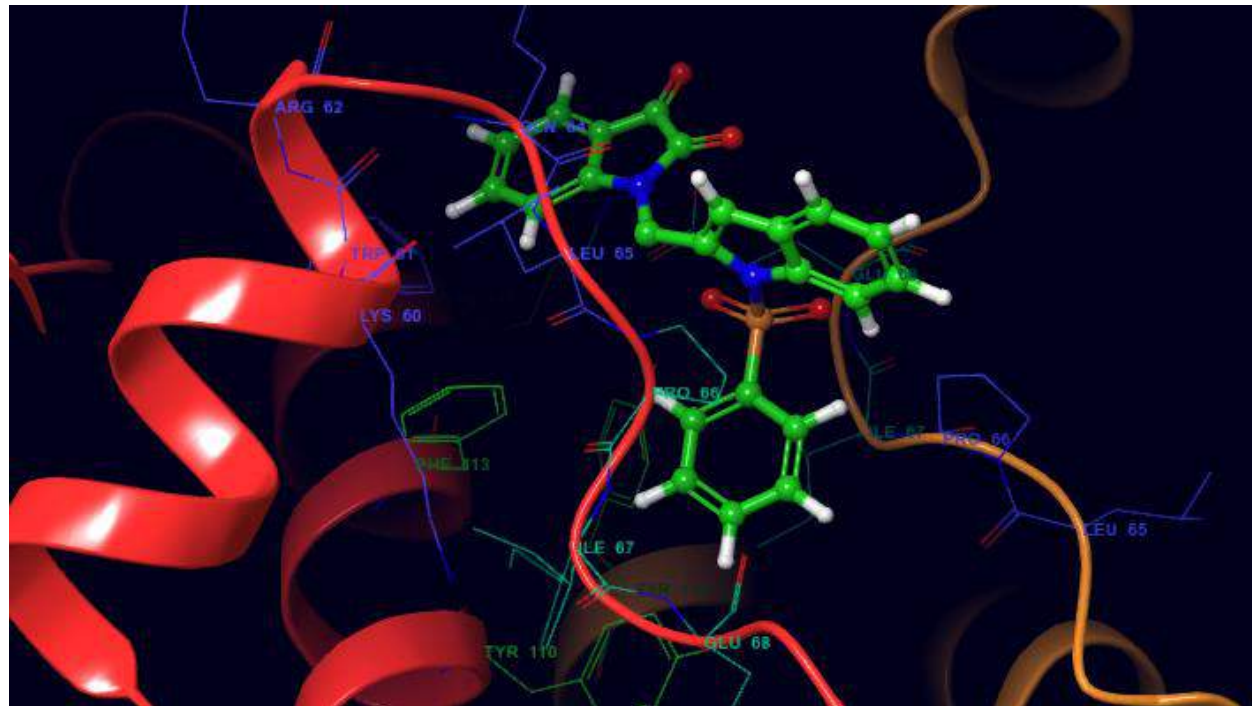
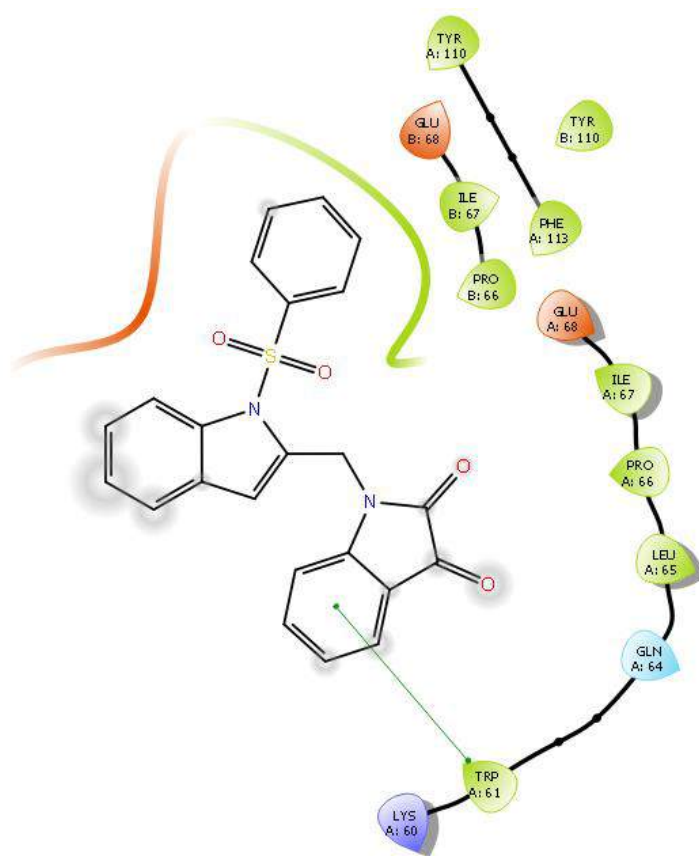


Fig S-1. The 2D followed by 3D interaction diagram of molecule **F-1** with interface residues of chorismate mutase (PDB code: 2FP2).

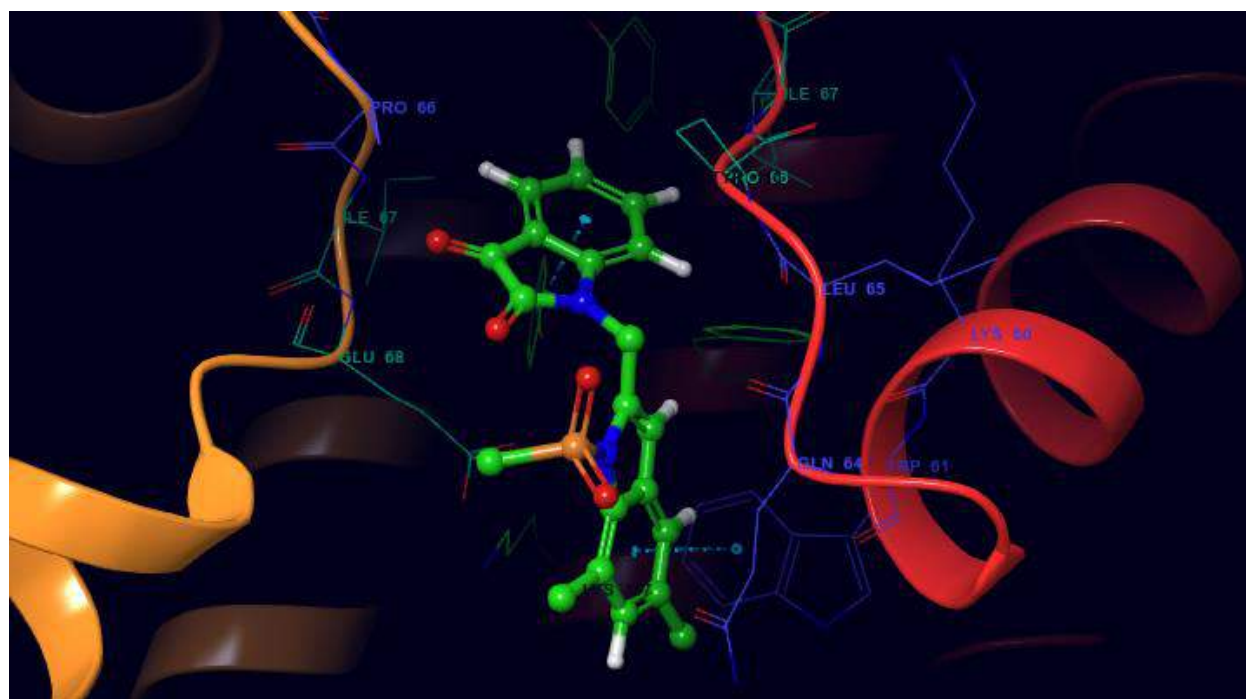
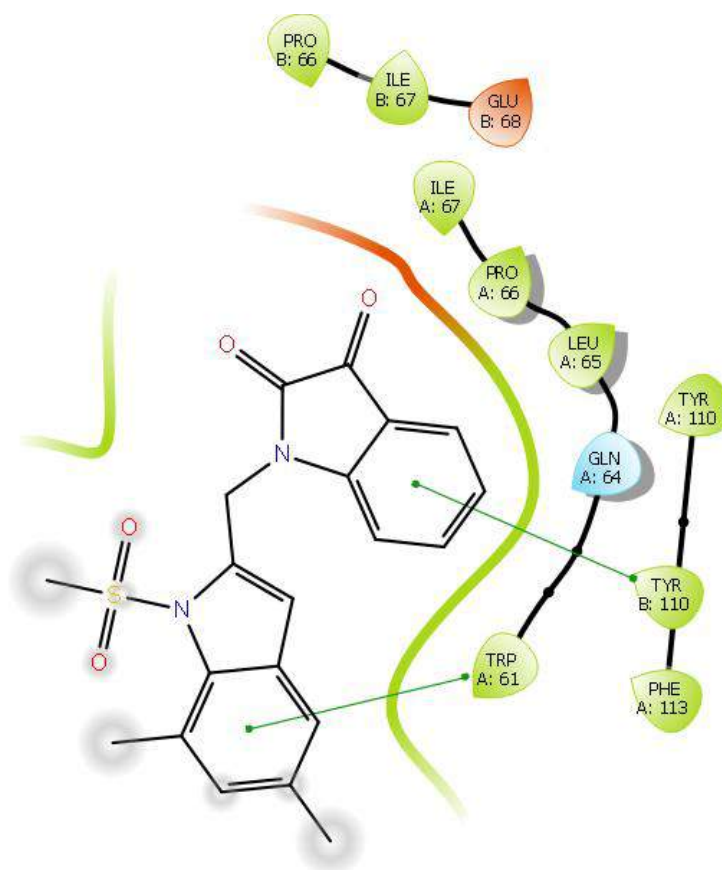


Fig S-2. The 2D followed by 3D interaction diagram of molecule **F-2** with interface residues of chorismate mutase (PDB code: 2FP2). The pi-pi stacking is shown in cyan color.

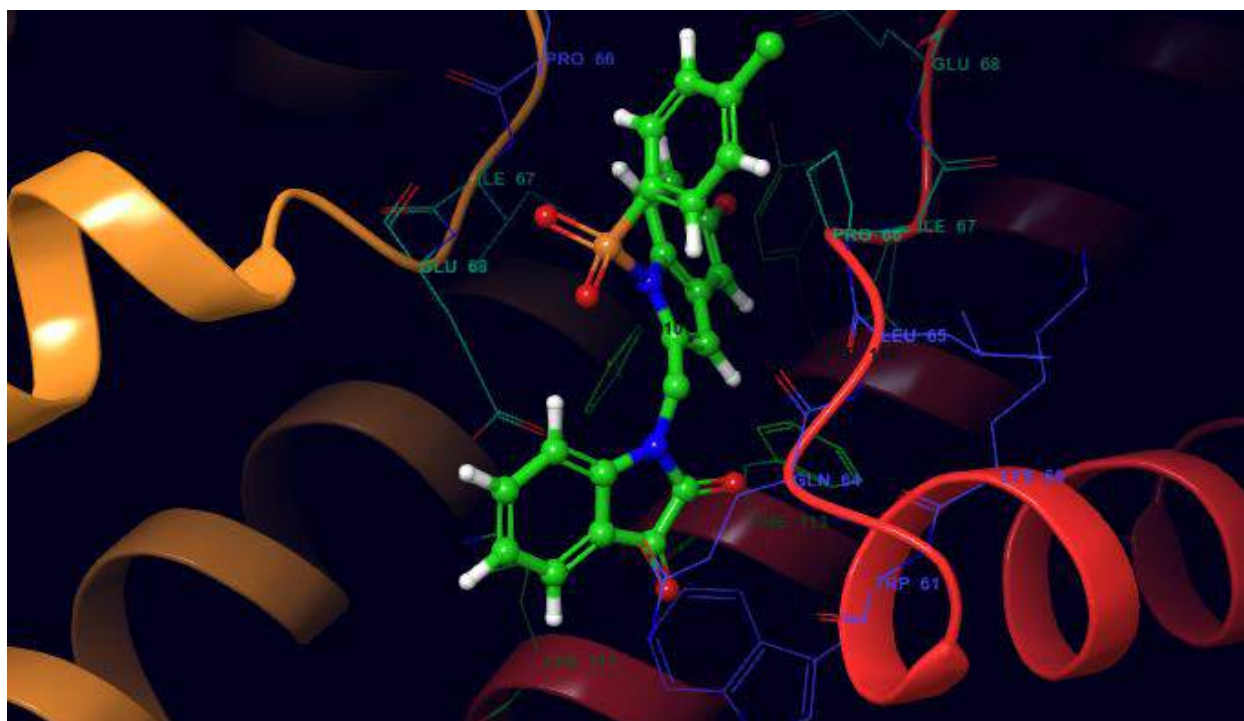
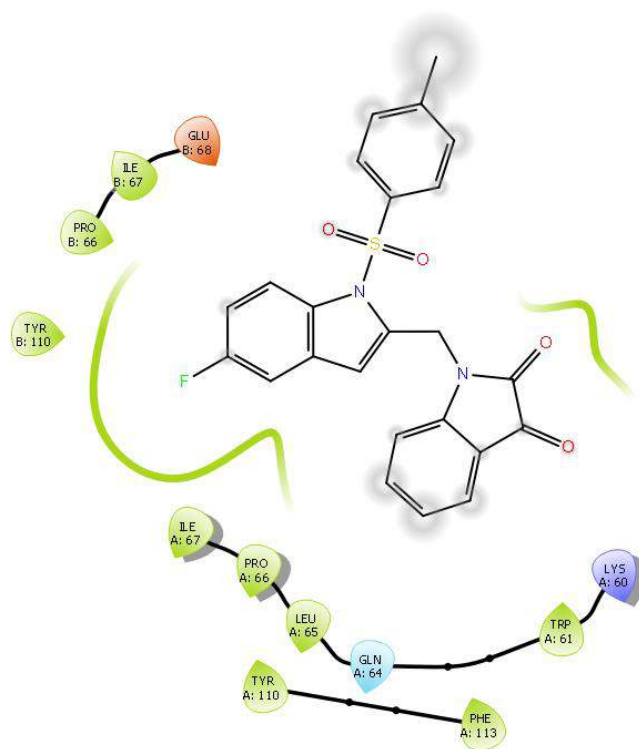


Fig S-3. The 2D followed by 3D interaction diagram of molecule **F-3** with interface residues of chorismate mutase (PDB code: 2FP2).

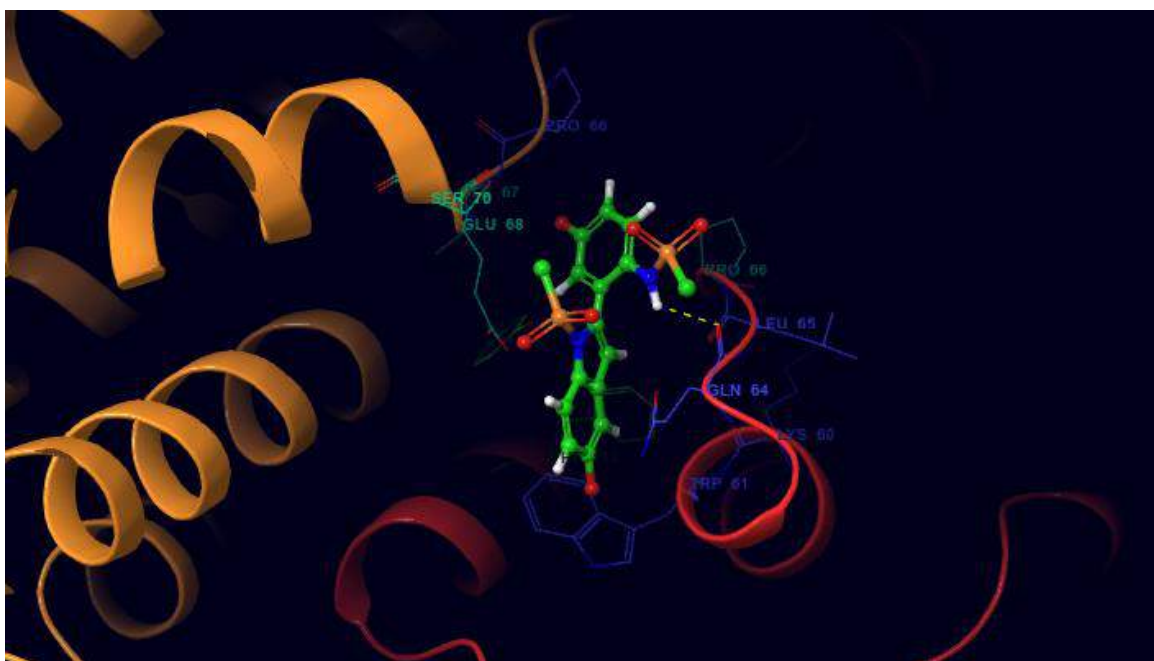
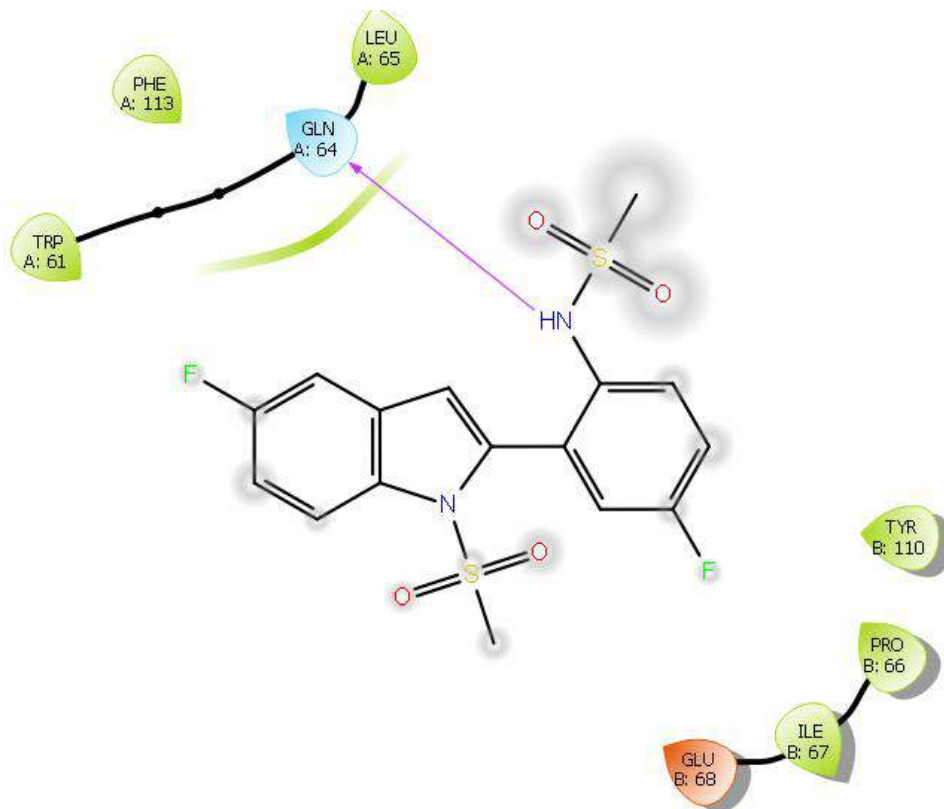


Fig S-4. The 2D followed by 3D interaction diagram of molecule **E** with interface residues of chorismate mutase (PDB code: 2FP2). H-bond is shown in yellow color.

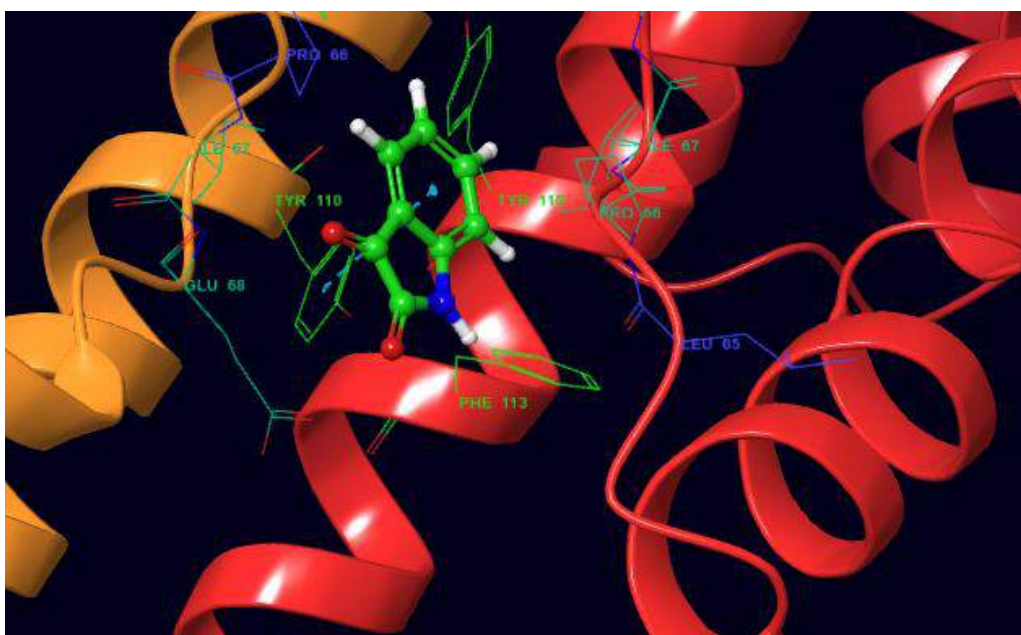
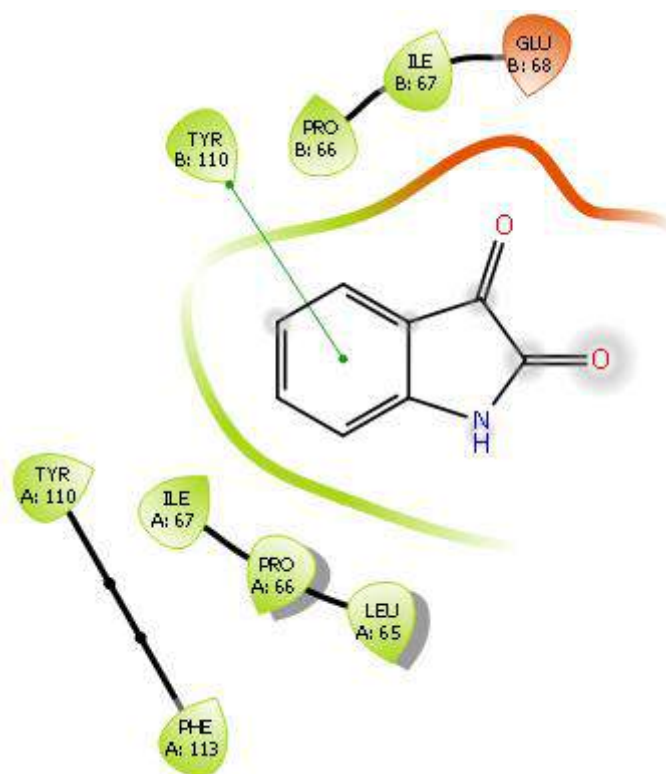


Fig S-5. The 2D followed by 3D interaction diagram of isatin **D** with interface residues of chorismate mutase (PDB code: 2FP2). The pi-pi stacking is shown in cyan color.

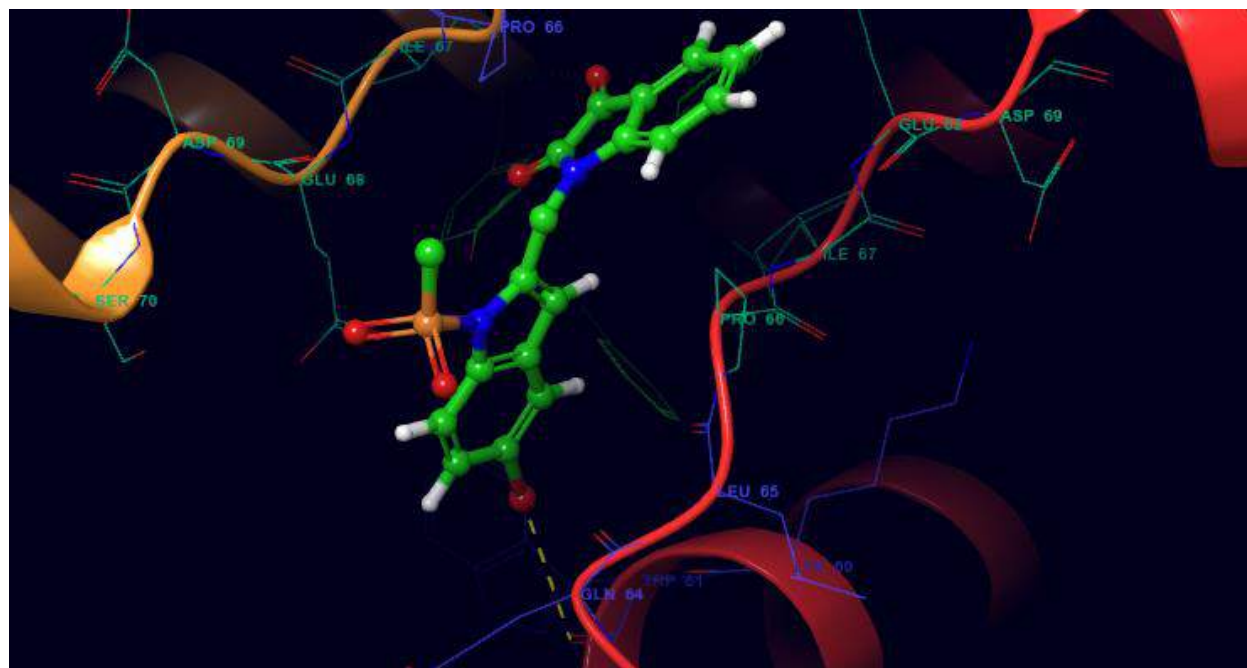
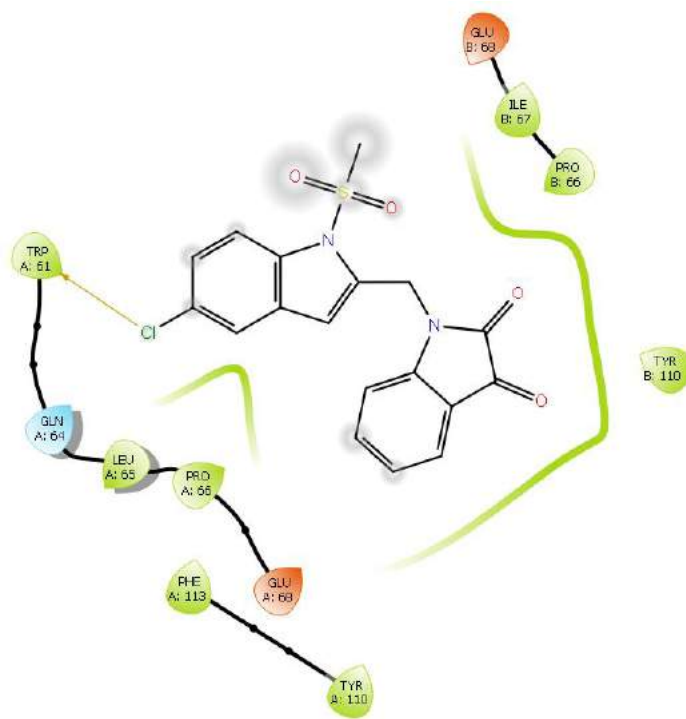


Fig S-6. The 2D followed by 3D interaction diagram of **3e** with interface residues of chorismate mutase (PDB code: 2FP2). The halogen bond is shown in yellow color.

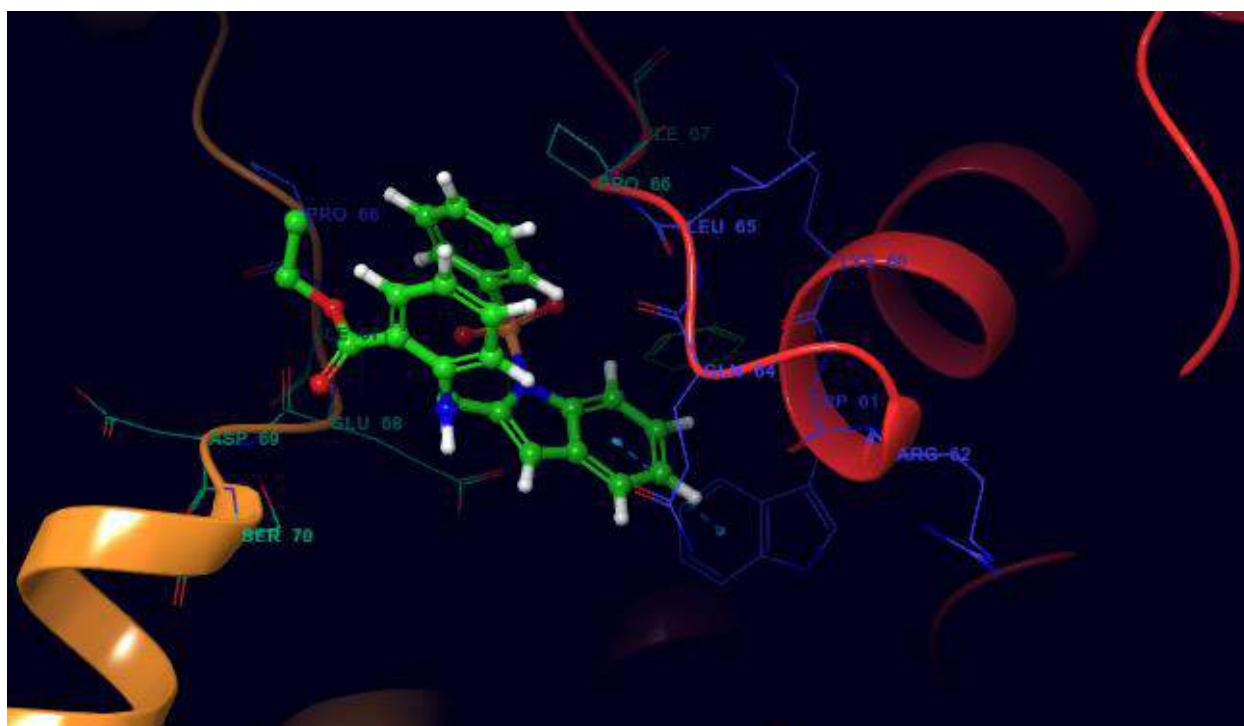
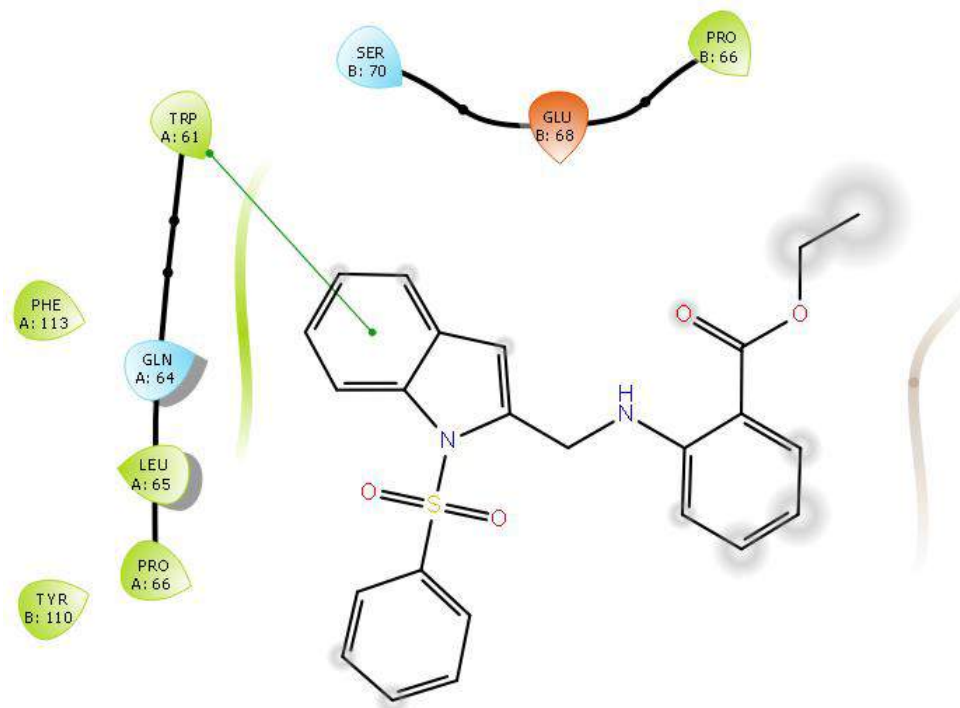


Fig S-7. The 2D followed by 3D interaction diagram of ester **4f** with interface residues of chorismate mutase (PDB code: 2FP2). A relatively lesser number of hydrophobic contacts has been found here and a pi-pi interaction found with TRP61A.

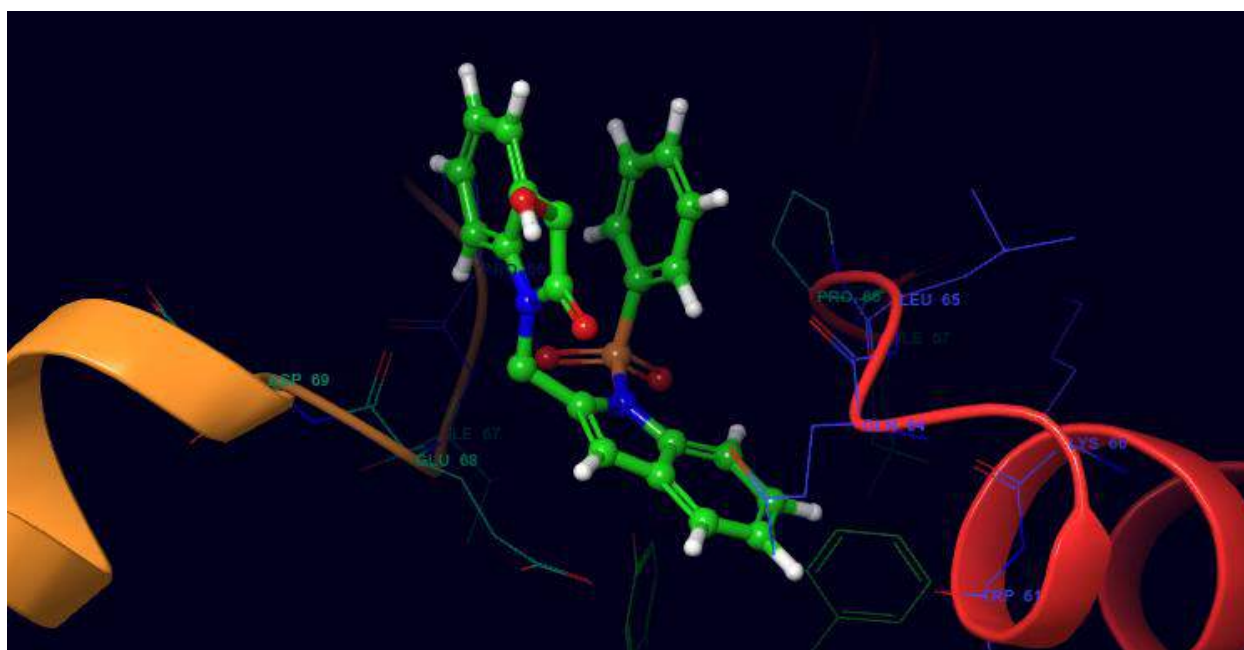
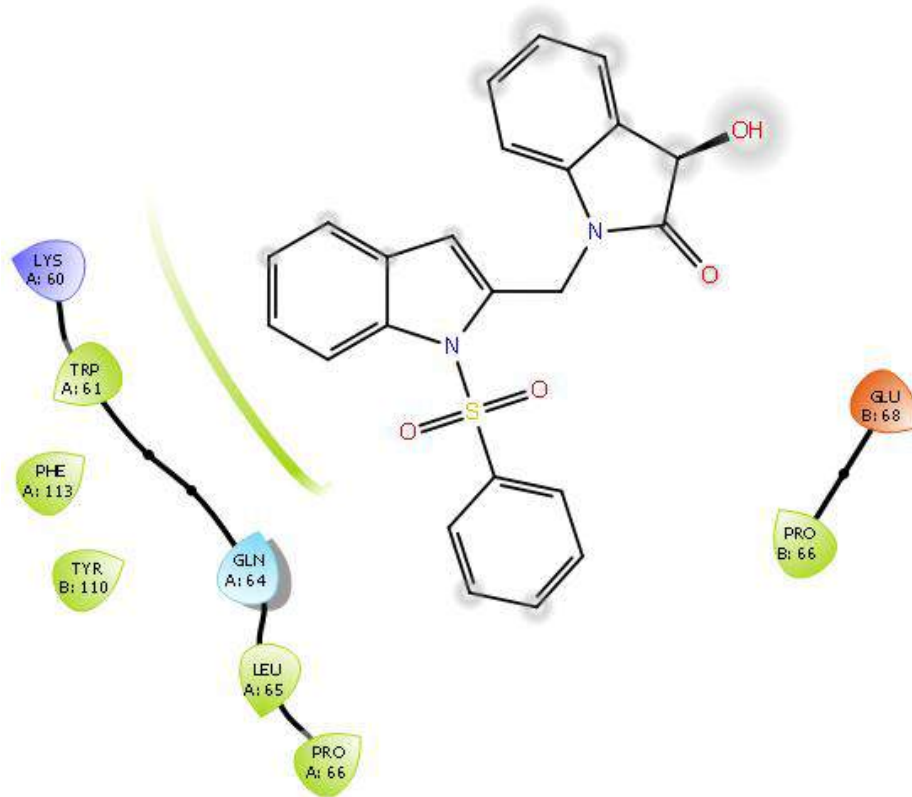


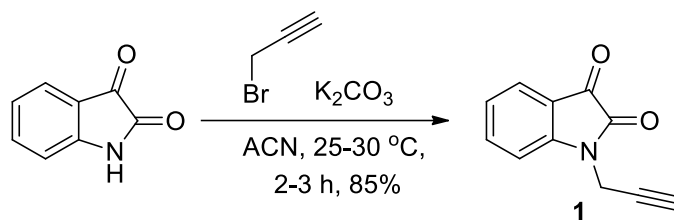
Fig S-8. The 2D followed by 3D interaction diagram of alcohol **5b** with interface residues of chorismate mutase (PDB code: 2FP2). The compound showed lesser number of hydrophobic contacts.

Experimental Section

Chemistry

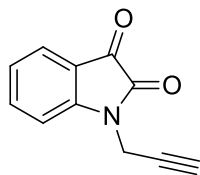
General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane and EtOAc. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 or $\text{DMSO}-d_6$ solution by using a 400 and 100 MHz spectrometer. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublet), td (triplet of doublet), t (triplet), q (quartet) and m (multiplet) as well as bs (broad singlet). Coupling constants (J) are given in hertz. Melting points were determined using melting point apparatus and are uncorrected. MS spectra were obtained on Agilent 6430 series Triple Quad LC-MS / MS spectrometer. Chromatographic purity by HPLC (Agilent 1200 series ChemStation software) was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, diluent, detection wavelength, and retention times. High Resolution Mass Spectra (HRMS) were obtained on a Bruker Compass data analysis 4.0 Spectrometer.

General procedure for the preparation of compound 1



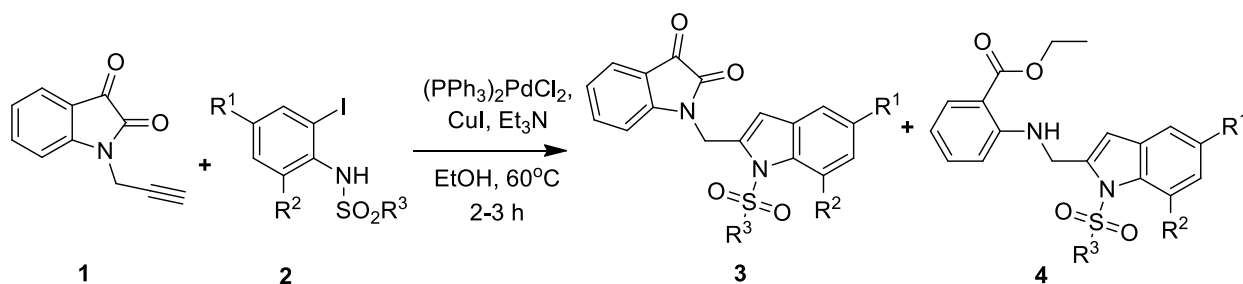
Propargyl bromide (1.2 mmol) was added to a solution of isatin (1.0 mmol) and potassium carbonate (3.0 mmol) in acetonitrile (10 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature (25-30 °C) for 2-3 h. After completion (confirmed by TLC), the mixture was diluted with ice-water (60 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4 , filtered and concentrated under low vacuum. The residue was purified by column chromatography using 5% EtOAc in hexane as eluent to afford the title compound.

1-(Prop-2-yn-1-yl)indoline-2,3-dione



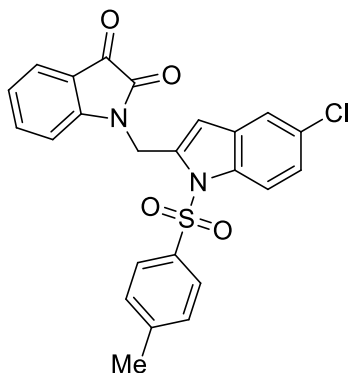
Orange solid (85% yield); mp: 128-130 °C; R_f = 0.5 (20% EtOAc/*n*-hexane); ^1H NMR (400 MHz, DMSO- d_6) δ : 7.75-7.67 (m, 1H, ArH), 7.58 (d, J = 7.6 Hz, 1H, ArH), 7.22 (d, J = 8.0 Hz, 1H, ArH), 7.17 (t, J = 7.6 Hz, 1H, ArH), 4.54 (d, J = 2.4 Hz, 2H, NCH₂), 3.34 (t, J = 2.4 Hz, 1H, HC \equiv C); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 182.9 (C=O), 157.7 (C=O), 149.9, 138.5, 125.0, 124.1, 118.1, 111.6, 77.8 (-C \equiv), 75.4 (HC \equiv), 29.5 (NCH₂); MS (ES mass): m/z 186.0 (M+1, 40%), 146.1 (M-39, 100%).

General procedure for the preparation of compound 3 and 4:



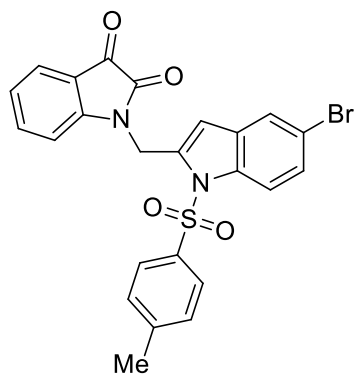
A mixture of compound **1** (1.0 mmol), *o*-iodoanilide **2** (1.2 mmol), (PPh₃)₂PdCl₂ (5 mol%), CuI (5 mol%) and triethylamine (3.0 mmol) in ethanol (methanol is used for compounds **4i** and **4j**) (10 mL) was stirred at 60°C for 2-3 h. After completion of the reaction (indicated by TLC) the reaction mixture is diluted with EtOAc (50 mL) and filtered through celite bed. The organic layer was collected, combined, washed with water (3 × 30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under low vacuum. The crude residue was purified by column chromatography on silica gel using 5% EtOAc in hexane to afford the desired product. All the compounds (**3a-k**, **4a-j**) prepared were characterized by MS, NMR spectra and purity was determined by HPLC method.

1-((5-Chloro-1-tosyl-1H-indol-2-yl)methyl)indoline-2,3-dione (3a)



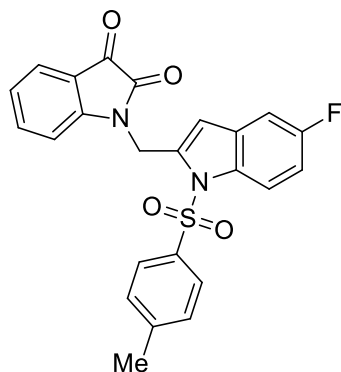
Yellow solid (62% yield); mp: 168-170 °C; R_f = 0.42 (20% EtOAc/*n*-hexane); ^1H NMR (400 MHz, CDCl_3) δ : 8.06 (d, J = 8.8 Hz, 1H, ArH), 7.73 (d, J = 8.4 Hz, 2H, ArH), 7.67 (d, J = 7.2 Hz, 1H, ArH), 7.52 (t, J = 7.6 Hz, 1H, ArH), 7.32-7.24 (m, 4H, ArH), 7.16 (t, J = 7.6 Hz, 1H, ArH), 6.73 (d, J = 8.0 Hz, 1H, ArH), 6.33 (s, 1H, indole (C-3) H), 5.37 (s, 2H, NCH_2), 2.38 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ : 182.5 (C=O), 158.1 (C=O), 150.2, 145.8, 138.6, 135.6, 135.0, 134.8, 130.3 (2C), 130.2, 129.8, 126.4 (2C), 125.6, 125.2, 124.3, 120.4, 117.7, 115.6, 110.8, 109.0, 38.9 (NCH_2), 21.6 (ArMe); HPLC: 97.2%, Column: Symmetry C-18 75*4.6 mm 3.5 μm , mobile phase A: 10 mM Ammonium formate in water, mobile phase B: ACN, (gradient) T/B% : 0/10, 3/10, 15/95, 20/95, 21/10, 25/10; flow rate: 1 mL/min, diluent: ACN:water (80:20), UV: 245.0 nm, retention time 14.5 min; MS (ES mass): m/z 465.0 (M+1, 30%), 318.0 (M-146, 100%).

1-((5-Bromo-1-tosyl-1H-indol-2-yl)methyl)indoline-2,3-dione (3b)



Yellow solid (60% yield); mp: 168-170 °C; R_f = 0.44 (20% EtOAc/*n*-hexane); ^1H NMR (400 MHz, DMSO- d_6) δ : 7.99 (d, J = 8.8 Hz, 1H, ArH), 7.87 (d, J = 8.4 Hz, 2H, ArH), 7.64-7.60 (m, 2H, ArH), 7.55 (dt, J = 8.0, 1.2 Hz, 1H, ArH), 7.50-7.40 (m, 3H, ArH), 7.15 (t, J = 7.6 Hz, 1H, ArH), 6.82 (s, 1H, indole (C-3) H), 6.80 (d, J = 8.0 Hz, 1H, ArH), 5.28 (s, 2H, NCH $_2$), 2.33 (s, 3H, ArCH $_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 183.0 (C=O), 158.8 (C=O), 150.3, 146.6, 138.3, 136.4, 135.8, 134.4, 131.4, 131.0 (2C), 127.8, 126.9 (2C), 125.0, 123.9, 123.8, 118.5, 117.1, 116.4, 111.3, 109.3, 38.2 (NCH $_2$), 21.5 (ArMe); HPLC: 99.4%, Column: Cosmicsil Aura ODS C-18 150*4.6 mm 5 μ m, mobile phase A: 0.1% TFA in water, mobile phase B: ACN, (gradient) T/B% : 0/30, 20/95, 30/95, 31/30, 35/30; flow rate: 1 mL/min, diluent: ACN:water (80:20), UV: 245.0 nm, retention time 16.4 min; MS (ES mass): m/z 508.8 (M $^+$, 90%), 510.9 (M+2, 100%).

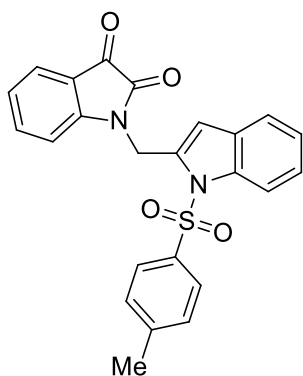
1-((5-Fluoro-1-(4-methylphenyl)sulfonyl-1H-indol-2-yl)methyl)indoline-2,3-dione (3c)



Yellow solid (58% yield); mp: 166-168 °C; R_f = 0.42 (20% EtOAc/*n*-hexane); ^1H NMR (400 MHz, DMSO- d_6) δ : 8.03 (dd, J = 9.2, 4.4 Hz, 1H, ArH), 7.88 (s, 1H, ArH), 7.85 (s, 1H, ArH), 7.62 (d, J = 7.2 Hz, 1H, ArH), 7.55 (dt, J = 7.6, 1.6 Hz, 1H, ArH), 7.43 (d, J = 8.0 Hz, 2H,

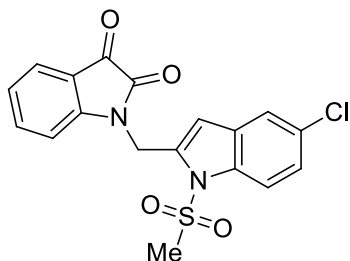
ArH), 7.23 (dd, $J = 8.8, 2.8$ Hz, 1H, ArH), 7.20-7.11 (m, 2H, ArH), 6.84 (s, 1H, indole (C-3) H), 6.81 (d, $J = 7.6$ Hz, 1H, ArH), 5.27 (s, 2H, NCH₂), 2.34 (s, 3H, ArCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 183.0 (C=O), 160.7 (C-F $J = 237.5$ Hz), 158.9 (C=O), 150.3, 146.5, 138.3, 136.8, 134.4, 133.4, 130.9 (2C), 130.8 (C-F $J = 10.6$ Hz), 126.9 (2C), 124.9, 123.9, 118.5, 115.9 (C-F $J = 9.5$ Hz), 113.0 (C-F $J = 24.0$ Hz), 111.2, 110.0 (C-F $J = 4.0$ Hz), 107.1 (C-F $J = 23.8$ Hz), 39.2 (NCH₂), 21.5 (ArMe); HPLC: 98.0%, Column: Cosmiscal Aura ODS C-18 150*4.6 mm 5 μ m, mobile phase A: 0.1% TFA in water, mobile phase B: ACN, (gradient) T/B% : 0/30, 20/95, 30/95, 31/30, 35/30; flow rate: 1 mL/min, diluent: ACN:water (80:20), UV: 240.0 nm, retention time 15.0 min; MS (ES mass): m/z 449.1 (M+1, 100%).

1-[(1-Tosyl-1H-indol-2-yl)methyl]indoline-2,3-dione (3d)



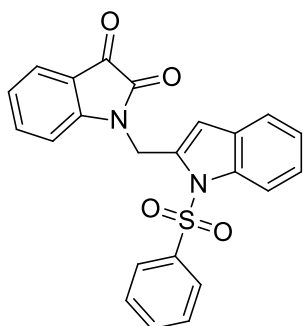
Yellow solid (60% yield); mp: 150-152 °C; $R_f = 0.4$ (20% EtOAc/*n*-hexane); ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.02 (d, $J = 8.4$ Hz, 1H, ArH), 7.88 (d, $J = 7.6$ Hz, 2H, ArH), 7.65-7.60 (m, 1H, ArH), 7.58-7.52 (m, 1H, ArH), 7.45-7.37 (m, 3H, ArH), 7.34-7.26 (m, 1H, ArH), 7.23-7.17 (m, 1H, ArH), 7.17-7.10 (m, 1H, ArH), 6.85 (s, 1H, indole (C-3) H), 6.81 (d, $J = 8.0$ Hz, 1H, ArH), 5.28 (s, 2H, NCH₂), 2.32 (s, 3H, ArCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 183.0 (C=O), 158.8 (C=O), 150.4, 146.3, 138.3, 136.9, 134.7, 134.7, 130.9 (2C), 129.5, 126.8 (2C), 125.2, 124.9, 124.4, 123.9, 121.4, 118.5, 114.4, 111.2, 110.2, 39.2 (NCH₂), 21.5 (ArMe); HPLC: 97.9%, Column: X-Bridge C-18 150*4.6 mm 5 μ m, mobile phase A: 0.1% TFA in water, mobile phase B: ACN, (gradient) T/B% : 0/5, 25/90, 35/90, 36/5, 40/5; flow rate: 1 mL/min, diluent: ACN:water (80:20), UV: 240.0 nm, retention time 21.1 min; MS (ES mass): m/z 431.1 (M+1, 70%), 432.2 (M+2, 100%).

1-[(5-Chloro-1-(methylsulfonyl)-1H-indol-2-yl)methyl]indoline-2,3-dione (3e)



Yellow solid (61% yield); mp: 192-194 °C; $R_f = 0.25$ (20% EtOAc/*n*-hexane); $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ : 7.87 (d, $J = 8.8$ Hz, 1H, ArH), 7.67-7.53 (m, 3H, ArH), 7.36 (dd, $J = 8.8, 2.4$ Hz, 1H, ArH), 7.19-7.07 (m, 2H, ArH), 6.81 (s, 1H, indole (C-3) H), 5.19 (s, 2H, NCH $_2$), 3.61 (s, 3H, SCH $_3$); $^{13}\text{C NMR}$ (100 MHz, DMSO- d_6) δ : 183.1 (C=O), 158.9 (C=O), 150.4, 138.3, 136.7, 135.3, 130.5, 128.4, 124.9, 124.6, 123.9, 120.5, 118.5, 115.4, 111.9, 107.4, 41.7 (SMe), 38.8 (NCH $_2$); HPLC: 98.4%, Column: X-Bridge C-18 150*4.6 mm 5 μm , mobile phase A: 5 mM Ammonium acetate in water, mobile phase B: ACN, (gradient) T/B% : 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1 mL/min, diluent: ACN:water (80:20), UV: 225.0 nm, retention time 16.1 min; MS (ES mass): m/z 389.0 (M+1, 100%); HRMS (ESI) m/z : [M + Na] $^+$ Calculated for C $_{18}$ H $_{13}$ ClN $_2$ NaO $_4$ S: 411.0177, Found: 411.0180.

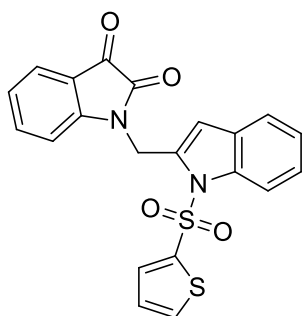
1-[(1-(Phenylsulfonyl)-1H-indol-2-yl)methyl]indoline-2,3-dione (3f)



Yellow solid (60% yield); mp: 172-174 °C; $R_f = 0.31$ (20% EtOAc/*n*-hexane); $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ : 8.05 (d, $J = 8.0$ Hz, 1H, ArH), 8.02-7.89 (m, 2H, ArH), 7.75 (t, $J = 7.2$ Hz, 1H, ArH), 7.70-7.60 (m, 3H, ArH), 7.56 (t, $J = 7.6$ Hz, 1H, ArH), 7.43 (d, $J = 7.6$ Hz, 1H, ArH),

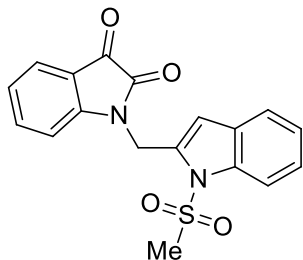
7.34 (t, $J = 7.6$ Hz, 1H, ArH), 7.22 (t, $J = 7.6$ Hz, 1H, ArH), 7.16 (t, $J = 7.6$ Hz, 1H, ArH), 6.89 (s, 1H, indole (C-3) H), 6.82 (d, $J = 8.0$ Hz, 1H, ArH), 5.30 (s, 2H, NCH₂); ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 183.1 (C=O), 158.9 (C=O), 150.4, 138.4, 137.6, 137.0, 135.4, 134.8, 130.5 (2C), 129.5, 126.8 (2C), 125.3, 125.0, 124.6, 123.9, 121.5, 118.6, 114.5, 111.2, 110.3, 39.3 (NCH₂); HPLC: 97.9%, Column: Cosmiscal Aura ODS C-18 150*4.6 mm 5 μ m, mobile phase A: 0.1% TFA in water, mobile phase B: ACN, (gradient) T/B% : 0/10, 20/95, 27/95, 31/10, 35/10; flow rate: 1 mL/min, diluent: ACN:water (80:20), UV: 245.0 nm, retention time 17.3 min; MS (ES mass): m/z 415.2 (M-1, 100%); HRMS (ESI) m/z : [M + Na]⁺ Calculated for C₂₃H₁₆N₂NaO₄S: 439.0723, Found: 439.0728.

1-[[1-(Thiophen-2-ylsulfonyl)-1H-indol-2-yl]methyl]indoline-2,3-dione (3g)



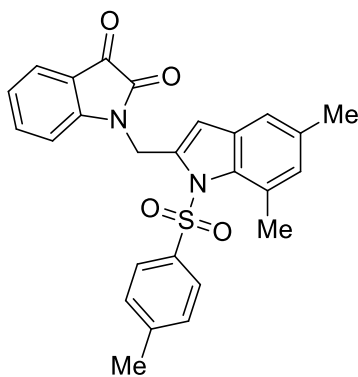
Yellow solid (59% yield); mp: 194-196 °C; $R_f = 0.32$ (20% EtOAc/*n*-hexane); ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.11-7.97 (m, 3H, ArH), 7.64 (d, $J = 7.2$ Hz, 1H, ArH), 7.61-7.53 (m, 1H, ArH), 7.44 (d, $J = 7.6$ Hz, 1H, ArH), 7.38 (t, $J = 7.6$ Hz, 1H, ArH), 7.30-7.20 (m, 2H, ArH), 7.16 (t, $J = 7.6$ Hz, 1H, ArH), 6.91 (s, 1H, indole (C-3) H), 6.86 (d, $J = 8.0$ Hz, 1H, ArH), 5.26 (s, 2H, NCH₂); ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 182.6 (C=O), 158.3 (C=O), 149.9, 137.9, 136.4 (2C), 136.3, 134.2, 134.1, 129.3, 128.3, 124.9, 124.5, 124.3, 123.4, 121.1, 118.1, 114.1, 110.8, 110.4, 38.8 (NCH₂); HPLC: 99.6%, Column: X-Bridge C-18 150*4.6 mm 5 μ m, mobile phase A: 5 mM Ammonium acetate in water, mobile phase B: ACN, (gradient) T/B% : 0/20, 20/90, 30/90, 31/20, 35/20; flow rate: 1 mL/min, diluent: ACN:THF, UV: 245.0 nm, retention time 14.9 min; MS (ES mass): m/z 422.9 (M⁺, 70%), 275.9 (M-146, 100%).

1-[(1-(Methylsulfonyl)-1H-indol-2-yl)methyl]indoline-2,3-dione (3h)



Yellow solid (62% yield); mp: 176-178 °C; R_f = 0.25 (20% EtOAc/*n*-hexane); ^1H NMR (400 MHz, DMSO- d_6) δ : 7.89 (d, J = 8.0 Hz, 1H, ArH), 7.67-7.57 (m, 2H, ArH), 7.50 (d, J = 7.6 Hz, 1H, ArH), 7.38-7.31 (m, 1H, ArH), 7.26 (m, 1H, ArH), 7.17 (t, J = 7.6 Hz, 1H, ArH), 7.12 (d, J = 8.0 Hz, 1H, ArH), 6.83 (s, 1H, indole (C-3) H), 5.20 (s, 2H, NCH $_2$), 3.57 (s, 3H, SCH $_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 182.7 (C=O), 158.4 (C=O), 150.1, 137.9, 136.4, 134.4, 128.7, 124.4, 124.4, 123.5, 123.4, 120.8, 118.1, 113.4, 111.3, 107.7, 41.7 (SMe), 38.4 (NCH $_2$); HPLC: 99.1%, Column: Cosmisil Aura ODS C-18 150*4.6 mm 5 μm , mobile phase A: 0.1% TFA in water, mobile phase B: ACN, (gradient) T/B% : 0/10, 20/95, 37/95, 40/10, 45/10; flow rate: 1 mL/min, diluent: ACN:water (80:20), UV: 245.0 nm, retention time 15.3 min; MS (ES mass): m/z 355.0 (M+1, 30%), 208.0 (M-146, 100%).

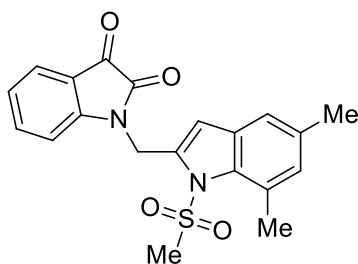
1-((5,7-Dimethyl-1-tosyl-1H-indol-2-yl)methyl)indoline-2,3-dione (3i)



Yellow solid (68% yield); mp: >200 °C; R_f = 0.46 (20% EtOAc/*n*-hexane); ^1H NMR (400 MHz, DMSO- d_6) δ : 7.60 (d, J = 7.6 Hz, 1H, ArH), 7.57-7.50 (m, 1H, ArH), 7.47 (d, J = 7.6 Hz, 2H, ArH), 7.30 (d, J = 8.0 Hz, 2H, ArH), 7.13 (t, J = 7.6 Hz, 1H, ArH), 6.95 (s, 1H, ArH), 6.91 (s,

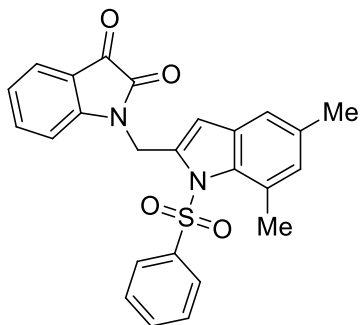
¹H, ArH), 6.81-6.77 (m, 2H, indole (C-3) H, ArH), 5.17 (s, 2H, NCH₂), 2.59 (s, 3H, ArCH₃), 2.31 (s, 3H, ArCH₃), 2.26 (s, 3H, ArCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 182.7 (C=O), 158.4 (C=O), 149.9, 145.1, 137.8, 137.5, 137.0, 135.9, 134.5, 133.0, 130.0, 129.7 (2C), 127.3, 126.2 (2C), 124.4, 123.3, 118.8, 118.0, 115.2, 110.8, 39.8 (NCH₂), 21.5 (ArMe), 21.0 (ArMe), 20.4 (ArMe); HPLC: 98.8%, Column: X-Bridge C-18 150*4.6 mm 5μm, mobile phase A: 5 mM Ammonium acetate in water, mobile phase B: ACN, (gradient) T/B% : 0/10, 23/90, 30/90, 31/10, 35/10; flow rate: 1 mL/min, diluent: DMSO, UV: 245.0 nm, retention time 16.4 min; MS (ES mass): *m/z* 459.1 (M+1, 40%), 312.1 (M-146, 100%).

1-((5,7-Dimethyl-1-(methylsulfonyl)-1*H*-indol-2-yl)methyl)indoline-2,3-dione (3j)



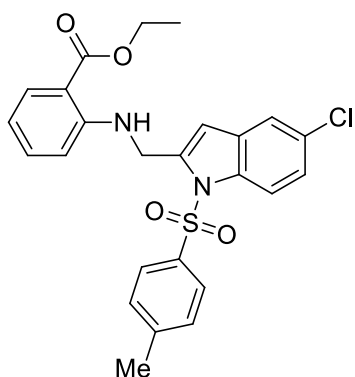
Yellow solid (70% yield); mp: 140-142 °C; *R_f* = 0.29 (20% EtOAc/*n*-hexane); ¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.61 (d, *J* = 7.2 Hz, 1H, ArH), 7.60-7.54 (m, 1H, ArH), 7.14 (t, *J* = 7.2 Hz, 1H, ArH), 7.06 (s, 1H, ArH), 6.98-6.93 (m, 2H, ArH), 6.84 (s, 1H, indole (C-3) H), 5.16 (s, 2H, NCH₂), 3.52 (s, 3H, SCH₃), 2.62 (s, 3H, ArCH₃), 2.29 (s, 3H, ArCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 182.8 (C=O), 158.4 (C=O), 149.9, 137.8, 136.9, 136.1, 133.5, 131.6, 129.7, 125.4, 124.4, 123.4, 118.7, 118.1, 111.4, 111.1, 41.3 (SMe), 39.2 (NCH₂), 21.6 (ArMe), 20.4 (ArMe); HPLC: 97.3%, Column: X-Bridge C-18 150*4.6 mm 3.5μm, mobile phase A: 0.1% TFA in water PH-3 with OPA, mobile phase B: ACN, (gradient) T/B% : 0/10, 3/10, 15/95, 23/95, 25/10, 30/10; flow rate: 1 mL/min, diluent: ACN:water (20:80), UV: 210.0 nm, retention time 13.7 min; MS (ES mass): *m/z* 383.1 (M+1, 20%), 236.1 (M-146, 100%).

1-((5,7-Dimethyl-1-(phenylsulfonyl)-1*H*-indol-2-yl)methyl)indoline-2,3-dione (3k)



Yellow solid (68% yield); mp: >200 °C; R_f =0.47 (20% EtOAc/*n*-hexane); ^1H NMR (400 MHz, DMSO- d_6) δ : 7.65 (t, J = 7.6 Hz, 1H, ArH), 7.62-7.47 (m, 6H, ArH), 7.13 (t, J = 7.6 Hz, 1H, ArH), 6.95 (s, 1H, ArH), 6.91 (s, 1H, ArH), 6.81 (s, 1H, indole (C-3) H), 6.80 (d, J = 8.0 Hz, 1H, ArH), 5.18 (s, 2H, NCH $_2$), 2.59 (s, 3H, ArCH $_3$), 2.26 (s, 3H, ArCH $_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 182.7 (C=O), 158.4 (C=O), 149.8, 137.8, 137.6, 137.0, 135.7, 134.6, 134.4, 132.9, 130.0, 129.3 (2C), 127.2, 126.2 (2C), 124.4, 123.3, 118.9, 118.0, 115.2, 110.8, 39.1 (NCH $_2$), 21.4 (ArMe), 20.4 (ArMe); HPLC: 98.9%, Column: Cosmicsil C-18 150*4.6 mm 5 μm , mobile phase A: 5 mM Ammonium acetate in water, mobile phase B: ACN, (gradient) T/B% : 0/5, 20/90, 25/90, 26/5, 30/5; flow rate: 1 mL/min, diluent: ACN:water (80:20), UV: 240.0 nm, retention time 18.2 min; MS (ES mass): m/z 445.1 (M+1, 30%), 298.0 (M-146, 100%).

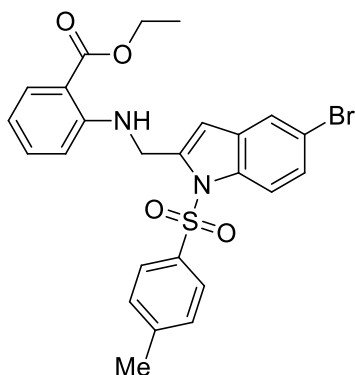
Ethyl 2-[(5-chloro-1-tosyl-1*H*-indol-2-yl)methyl]amino]benzoate (4a)



White solid (28% yield); mp: 126-128 °C; R_f =0.36 (5% EtOAc/*n*-hexane); ^1H NMR (400 MHz, DMSO- d_6) δ : 8.26 (t, J = 6.4 Hz, 1H, NH, D $_2$ O exchangeable), 8.00 (d, J = 8.8 Hz, 1H, ArH), 7.84-7.78 (m, 3H, ArH), 7.60 (d, J = 2.0 Hz, 1H, ArH), 7.37 (d, J = 8.0 Hz, 2H, ArH), 7.31 (dd, J = 8.8, 2.4 Hz, 1H, ArH), 7.29-7.24 (m, 1H, ArH), 6.66 (s, 1H, indole (C-3) H), 6.63-6.58 (m,

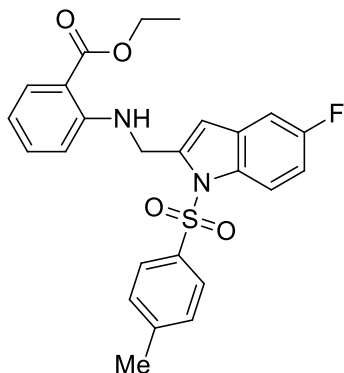
2H, ArH), 4.90 (d, $J = 6.4$ Hz, 2H, NCH₂), 4.28 (q, $J = 7.2$ Hz, 2H, OCH₂), 2.33 (s, 3H, ArCH₃), 1.32 (t, $J = 7.2$ Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 167.6 (C=O), 149.7, 145.8, 140.4, 134.9, 134.6, 134.3, 131.2, 130.5, 130.3 (2C), 128.3, 126.5 (2C), 124.3, 120.4, 115.5, 115.1, 111.7, 110.1, 109.5, 60.2 (OCH₂), 40.5 (NCH₂), 21.0 (ArMe), 14.2 (CH₂Me); HPLC: 97.1%, Column: X-Bridge C-18 150*4.6 mm 5 μ m, mobile phase A: 5 Mm Ammonium acetate in water, mobile phase B: ACN, (gradient) T/B% : 0/20, 20/90, 30/90, 31/20, 35/20; flow rate: 1 mL/min, diluent: THF:ACN:H₂O, UV: 220.0 nm, retention time 22.8 min; MS (ES mass): m/z 482.9 (M⁺, 100%).

Ethyl 2-[[5-bromo-1-tosyl-1*H*-indol-2-yl)methyl]amino]benzoate (4b)



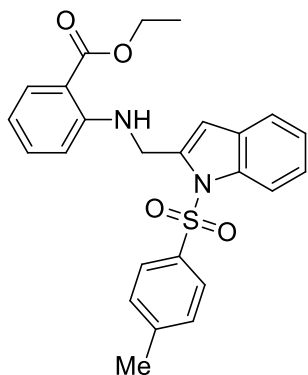
White solid (30% yield); mp: 117-119 °C; $R_f = 0.39$ (5% EtOAc/*n*-hexane); ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.25 (t, $J = 6.4$ Hz, 1H, NH, D₂O exchangeable), 7.94 (d, $J = 8.8$ Hz, 1H, ArH), 7.85-7.77 (m, 3H, ArH), 7.72 (d, $J = 1.6$ Hz, 1H, ArH), 7.42 (dd, $J = 8.8, 2.0$ Hz, 1H, ArH), 7.37 (d, $J = 8.0$ Hz, 2H, ArH), 7.29-7.22 (m, 1H, ArH), 6.64 (s, 1H, indole (C-3) H), 6.59 (t, $J = 7.6$ Hz, 2H, ArH), 4.89 (d, $J = 6.4$ Hz, 2H, NCH₂), 4.27 (q, $J = 7.2$ Hz, 2H, OCH₂), 2.32 (s, 3H, ArCH₃), 1.31 (t, $J = 7.2$ Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 168.0 (C=O), 150.2, 146.3, 140.7, 135.7, 135.0, 134.7, 131.7, 131.5, 130.8 (2C), 127.4, 126.9 (2C), 123.9, 116.9, 116.3, 115.5, 112.2, 110.5, 110.0, 60.6 (OCH₂), 41.0 (NCH₂), 21.5 (ArMe), 14.6 (CH₂Me); HPLC: 97.1%, Column: X-Bridge C-18 150*4.6 mm 5 μ m, mobile phase A: 5 mM Ammonium acetate in water, mobile phase B: ACN, (gradient) T/B% : 0/20, 20/90, 30/90, 31/20, 35/20; flow rate: 1 mL/min, diluent: ACN:H₂O (80:20), UV: 220.0 nm, retention time 22.5 min; MS (ES mass): m/z 526.0 (M⁺, 90%), 528.9 (M⁺², 100%).

Ethyl 2-[(5-fluoro-1-tosyl-1H-indol-2-yl)methyl]amino]benzoate (4c)



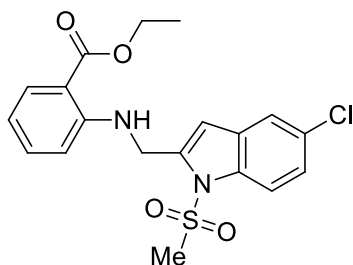
White solid (31% yield); mp: 131-133 °C; R_f =0.32 (5% EtOAc/*n*-hexane); ^1H NMR (400 MHz, DMSO- d_6) δ : 8.25 (t, J = 6.0 Hz, 1H, NH, D₂O exchangeable), 8.00 (dd, J = 9.2, 4.4 Hz, 1H, ArH), 7.87-7.75 (m, 3H, ArH), 7.41-7.31 (m, 3H, ArH), 7.31-7.24 (m, 1H, ArH), 7.17-7.08 (m, 1H, ArH), 6.67 (s, 1H, indole (C-3) H), 6.65-6.56 (m, 2H, ArH), 4.90 (d, J = 6.0 Hz, 2H, NCH₂), 4.28 (q, J = 7.2 Hz, 2H, OCH₂), 2.33 (s, 3H, ArCH₃), 1.32 (t, J = 7.2 Hz, 3H, CH₂CH₃); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 167.5 (C=O), 160.2 (d, C-F J = 236.9 Hz), 149.7, 147.8, 145.7, 140.6, 134.5 (d, C-F J = 21.2 Hz), 132.9, 131.8, 131.2, 130.3 (2C), 130.2, 126.4 (2C), 115.4 (d, C-F J = 9.7 Hz), 115.1, 112.2 (C-F J = 25.2 Hz), 111.7, 110.1 (d, C-F J = 5.6 Hz), 106.7 (d, C-F J = 23.8 Hz), 60.1 (OCH₂), 40.5 (NCH₂), 21.0 (ArMe), 14.1 (CH₂Me); HPLC: 97.0%, Column: Eclipse plus C-18 250*4.6 mm 5 μ m, mobile phase A: 5 mM Ammonium acetate in water, mobile phase B: ACN, (gradient) T/B% : 0/30, 30/90, 40/90, 41/30, 45/30; flow rate: 1 mL/min, diluent: ACN:THF, UV: 220.0 nm, retention time 31.3 min; MS (ES mass): m/z 467.0 (M+1, 100%).

Ethyl 2-[(1-tosyl-1H-indol-2-yl)methyl]amino]benzoate (4d)



White solid (25% yield); mp: 93-95 °C; R_f = 0.35 (5% EtOAc/*n*-hexane); ^1H NMR (400 MHz, CDCl_3) δ : 8.15 (d, J = 8.4 Hz, 1H, ArH), 7.95 (dd, J = 8.0, 1.6 Hz, 1H, ArH), 7.67 (d, J = 8.4 Hz, 2H, ArH), 7.39 (d, J = 7.6 Hz, 1H, ArH), 7.33-7.26 (m, 2H, ArH), 7.26-7.16 (m, 4H, ArH), 6.65 (m, 2H, ArH, NH (D_2O exchangeable)), 6.55 (s, 1H, indole (C-3) H), 4.85 (s, 2H, NCH_2), 4.32 (q, J = 7.2 Hz, 2H, OCH_2), 2.35 (s, 3H, ArCH_3), 1.38 (t, J = 7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ : 168.4 (C=O), 149.0, 145.0, 137.5, 135.9, 134.5, 131.6, 129.9 (2C), 129.2, 126.4 (2C), 124.5, 123.6, 120.8, 116.6, 114.4, 112.9, 112.8, 110.5, 110.3, 60.6 (OCH_2), 42.5 (NCH_2), 21.6 (ArMe), 14.3 (CH_2Me); HPLC: 99.9%, Column: X-Bridge C-18 150*4.6 mm 5 μm , mobile phase A: 0.1% TFA in water, mobile phase B: ACN, (gradient) T/B% : 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1 mL/min, diluent: ACN:H₂O (80:20), UV: 220.0 nm, retention time 21.3 min; MS (ES mass): m/z 449.0 (M+1, 100%).

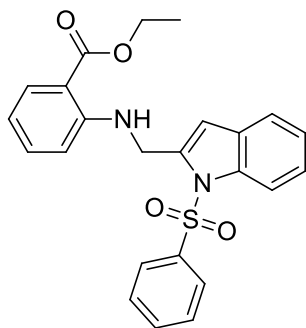
Ethyl 2-[[5-chloro-1-(methylsulfonyl)-1H-indol-2-yl]methyl]amino]benzoate (4e)



White solid (28% yield); mp: 94-96 °C; R_f = 0.35 (5% EtOAc/*n*-hexane); ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ : 8.21 (t, J = 6.4 Hz, 1H, NH, D_2O exchangeable), 7.88-7.79 (m, 2H, ArH), 7.67 (d, J = 2.0 Hz, 1H, ArH), 7.38-7.30 (m, 2H, ArH), 6.88 (d, J = 8.8 Hz, 1H, ArH), 6.68 (s, 1H, indole (C-3) H), 6.61 (t, J = 7.6 Hz, 1H, ArH), 4.81 (d, J = 6.4 Hz, 2H, NCH_2), 4.27 (q, J = 7.2

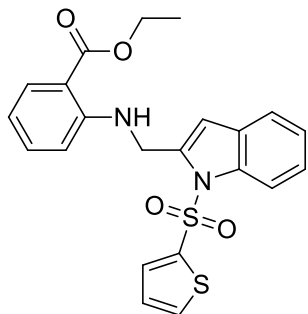
Hz, 2H, OCH₂), 3.44 (s, 3H, SCH₃), 1.31 (t, $J = 7.2$ Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 168.1 (C=O), 150.3, 140.7, 135.2, 135.7, 131.7, 130.6, 128.3, 124.5, 120.7, 115.6, 115.5, 112.4, 110.4, 108.5, 60.7 (OCH₂), 41.5 (SMe), 40.5 (NCH₂), 14.6 (CH₂Me); HPLC: 99.5%, Column: X-Bridge C-18 150*4.6 mm 5μm, mobile phase A: 0.1% TFA in water, mobile phase B: ACN, (gradient) T/B% : 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1 mL/min, diluent: ACN:H₂O (80:20), UV: 225.0 nm, retention time 20.2 min; MS (ES mass): m/z 407.1 (M+1, 30%), 242.0 (M-164, 100%).

Ethyl 2-[[1-(phenylsulfonyl)-1H-indol-2-yl]methyl]amino]benzoate (4f)



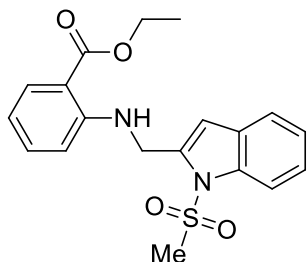
White solid (30% yield); mp: 102-104 °C; $R_f = 0.40$ (5% EtOAc/*n*-hexane); ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.28 (t, $J = 6.4$ Hz, 1H, NH, D₂O exchangeable), 8.01 (d, $J = 8.4$ Hz, 1H, ArH), 7.94-7.88 (m, 2H, ArH), 7.83 (dd, $J = 8.0, 1.6$ Hz, 1H, ArH), 7.72-7.67 (m, 1H, ArH), 7.55 (m, 2H, ArH), 7.50 (d, $J = 7.6$ Hz, 1H, ArH), 7.30 (m, 2H, ArH), 7.24-7.19 (m, 1H, ArH), 6.73 (s, 1H, indole (C-3) H), 6.68 (d, $J = 8.4$ Hz, 1H, ArH), 6.64-6.58 (m, 1H, ArH), 4.92 (d, $J = 6.4$ Hz, 2H, NCH₂), 4.28 (q, $J = 7.2$ Hz, 2H, OCH₂), 1.32 (t, $J = 7.2$ Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 168.0 (C=O), 150.3, 139.0, 137.9, 136.9, 135.1, 135.1, 131.7, 130.3 (2C), 129.5, 126.8 (2C), 125.1, 124.3, 121.5, 115.5, 114.5, 112.2, 111.0, 110.6, 60.6 (OCH₂), 40.9 (NCH₂), 14.6 (CH₂Me); HPLC: 95.1%, Column: Eclipse XDB C-18 150*4.6 mm 5μm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in ACN, (gradient) T/B% : 0/10, 5/10, 25/90, 30/90, 31/10, 35/10; flow rate: 1 mL/min, diluent: ACN:H₂O (80:20), UV: 218.0 nm, retention time 26.5 min; MS (ES mass): m/z 435.0 (M+1, 100%).

Ethyl 2-[(1-(thiophen-2-ylsulfonyl)-1H-indol-2-yl)methyl]amino]benzoate (4g)



White solid (30% yield); mp: 92-94 °C; R_f = 0.35 (5% EtOAc/*n*-hexane); ^1H NMR (400 MHz, DMSO- d_6) δ : 8.27 (t, J = 6.4 Hz, 1H, NH, D₂O exchangeable), 8.06-7.97 (m, 2H, ArH), 7.93 (dd, J = 4.0, 1.6 Hz, 1H, ArH), 7.84 (dd, J = 8.0, 2.0 Hz, 1H, ArH), 7.52 (d, J = 7.6 Hz, 1H, ArH), 7.38-7.28 (m, 2H, ArH), 7.27-7.22 (m, 1H, ArH), 7.16 (dd, J = 4.85, 4.0 Hz, 1H, ArH), 6.73 (2s, 2H, indole (C-3) H, ArH), 6.64-6.58 (m, 1H, ArH), 4.88 (d, J = 6.4 Hz, 2H, NCH₂), 4.29 (q, J = 7.2 Hz, 2H, OCH₂), 1.32 (t, J = 7.2 Hz, 3H, CH₂CH₃); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 167.6 (C=O), 149.8, 138.3, 136.6, 136.2, 135.9, 134.6, 134.1, 131.2, 129.2, 128.1, 124.7, 124.1, 121.1, 115.0, 114.2, 111.7, 111.1, 110.1, 60.2 (OCH₂), 40.5 (NCH₂), 14.6 (CH₂Me); HPLC: 99.2%, Column: X-Bridge C-18 150*4.6 mm 5 μ m, mobile phase A: 5 mM Ammonium acetate in water, mobile phase B: ACN, (gradient) T/B% : 0/20, 20/90, 30/90, 31/20, 35/20; flow rate: 1 mL/min, diluent: ACN:H₂O (80:20), UV: 220.0 nm, retention time 19.6 min; MS (ES mass): m/z 440.9 (M⁺, 80%), 275.9 (M-164, 100%).

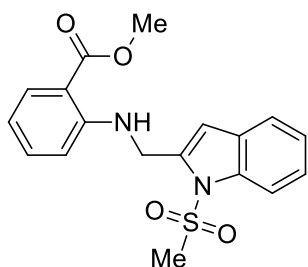
Ethyl 2-[(1-(methylsulfonyl)-1H-indol-2-yl)methyl]amino]benzoate (4h)



White solid (30% yield); mp: 82-84 °C; R_f = 0.32 (5% EtOAc/*n*-hexane); ^1H NMR (400 MHz, DMSO- d_6) δ : 8.22 (t, J = 6.4 Hz, 1H, NH, D₂O exchangeable), 7.92-7.80 (m, 2H, ArH), 7.58 (d,

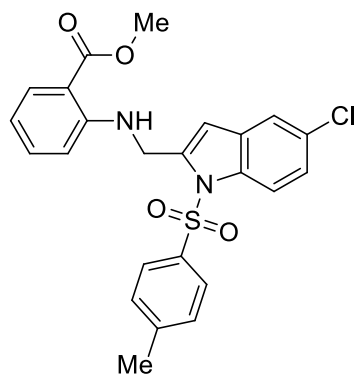
$J = 7.6$ Hz, 1H, ArH), 7.39-7.29 (m, 2H, ArH), 7.28-7.22 (m, 1H, ArH), 6.93 (d, $J = 8.8$ Hz, 1H, ArH), 6.74 (s, 1H, indole (C-3) H), 6.65-6.58 (m, 1H, ArH), 4.82 (d, $J = 6.4$ Hz, 2H, NCH₂), 4.29 (q, $J = 7.2$ Hz, 2H, OCH₂), 3.40 (s, 3H, SCH₃), 1.32 (t, $J = 7.2$ Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ : 167.7 (C=O), 149.9, 138.4, 136.3, 134.7, 131.2, 128.6, 124.2, 123.4, 120.9, 115.0, 113.5, 111.9, 109.9, 109.0, 60.2 (OCH₂), 40.8 (NCH₂), 40.1 (SMe), 14.6 (CH₂Me); HPLC: 99.8%, Column: X-Bridge C-18 150*4.6 mm 5 μ m, mobile phase A: 5 mM Ammonium acetate in water, mobile phase B: ACN, (gradient) T/B% : 0/30, 30/90, 40/90, 41/5, 45/5; flow rate: 1 mL/min, diluent: ACN:THF, UV: 220.0 nm, retention time 22.0 min; MS (ES mass): m/z 373.0 (M+1, 40%), 207.9 (M-164, 100%).

Methyl 2-[(1-(methylsulfonyl)-1H-indol-2-yl)methyl]amino]benzoate (4i)



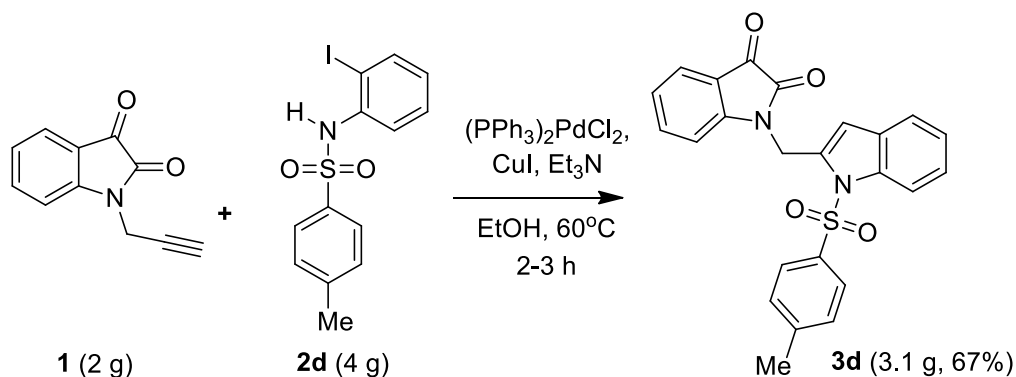
White solid (25% yield); mp: 130-132 °C; $R_f = 0.34$ (10% EtOAc/*n*-hexane); ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.21 (t, $J = 6.4$ Hz, 1H, NH, D₂O exchangeable), 7.88 (d, $J = 8.4$ Hz, 1H, ArH), 7.83 (dd, $J = 8.0, 1.6$ Hz, 1H, ArH), 7.58 (d, $J = 7.6$ Hz, 1H, ArH), 7.40-7.22 (m, 3H, ArH), 6.94 (d, $J = 8.4$ Hz, 1H, ArH), 6.74 (s, 1H, indole (C-3) H), 6.66-6.58 (m, 1H, ArH), 4.82 (d, $J = 6.4$ Hz, 2H, NCH₂), 3.82 (s, 3H, OCH₃), 3.40 (s, 3H, SCH₃); ¹³C NMR (100 MHz, CDCl₃) δ : 168.9 (C=O), 139.5, 137.7, 137.0, 134.8, 131.8, 129.9, 129.0, 127.3, 124.9, 123.8, 122.4, 121.1, 113.8, 110.7, 51.8 (OMe), 41.0 (NCH₂), 40.2 (SMe); HPLC: 99.4%, Column: Eclipse plus C-18 250*4.6 mm 5 μ m, mobile phase A: 5 mM Ammonium acetate in water, mobile phase B: ACN, (gradient) T/B% : 0/30, 20/90, 30/90, 31/30, 35/30; flow rate: 1 mL/min, diluent: ACN:H₂O (80:20), UV: 215.0 nm, retention time 18.1 min; MS (ES mass): m/z 359.0 (M+1, 30%), 208.0 (M-150, 100%).

Methyl 2-[(5-chloro-1-tosyl-1H-indol-2-yl)methyl]amino]benzoate (4j)



White solid (26% yield); mp: 84-86 °C; R_f =0.40 (10% EtOAc/*n*-hexane); ^1H NMR (400 MHz, DMSO- d_6) δ : 8.24 (t, J = 6.4 Hz, 1H, NH, D $_2$ O exchangeable), 8.01 (d, J = 9.2 Hz, 1H, ArH), 7.78-7.85 (m, 3H, ArH), 7.59 (d, J = 2.0 Hz, 1H, ArH), 7.37 (d, J = 8.4 Hz, 2H, ArH), 7.34-7.24 (m, 2H, ArH), 6.65 (s, 1H, indole (C-3) H), 6.64-6.57 (m, 2H, ArH), 4.90 (d, J = 6.4 Hz, 2H, NCH $_2$), 3.80 (s, 3H, OCH $_3$), 2.33 (s, 3H, ArCH $_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 167.9 (C=O), 149.7, 145.8, 140.4, 134.9, 134.6, 134.3, 131.2, 130.5, 130.3 (2C), 128.3, 126.4 (2C), 124.3, 120.4, 115.5, 115.1, 111.7, 109.9, 109.5, 51.6 (OMe), 40.5 (NCH $_2$), 21.0 (ArMe; HPLC: 98.5%, Column: Eclipse plus C-18 250*4.6 mm 5 μ m, mobile phase A: 5 mM Ammonium acetate in water, mobile phase B: ACN, (gradient) T/B% : 0/30, 20/90, 30/90, 31/30, 35/30; flow rate: 1 mL/min, diluent: ACN:H $_2$ O (80:20), UV: 215.0 nm, retention time 23.7 min; MS (ES mass): m/z 468.9 (M $^+$, 100%).

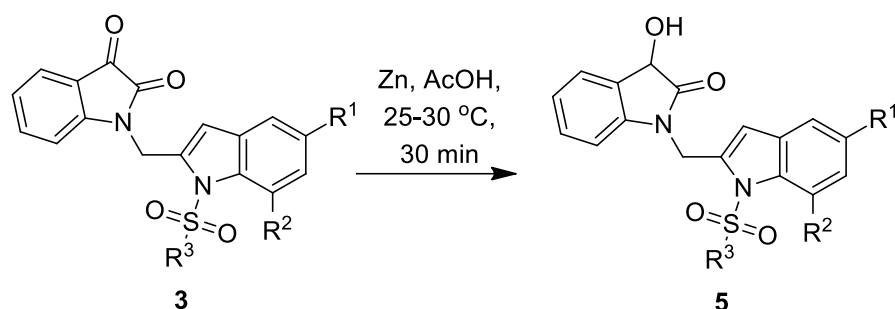
Preparation of compound 3d in gram scale



A mixture of 1-(prop-2-yn-1-yl)indoline-2,3-dione **1** (2.0 g, 10.8 mmol), *N*-(2-iodophenyl)-4-methylbenzenesulfonamide **2d** (4.0 g, 10.8 mmol), (PPh $_3$) $_2$ PdCl $_2$ (379.0 mg, 0.5 mmol), CuI (102.7 mg, 0.5 mmol) and triethylamine (3.0 mL, 21.6 mmol) in ethanol (30 mL) was stirred at

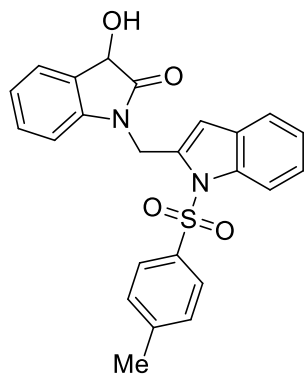
60°C for 2 h. After completion of the reaction (indicated by TLC) the reaction mixture is diluted with EtOAc (150 mL) and filtered through celite bed. The organic layer was collected, combined, washed with water (3 × 100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under low vacuum. The crude residue was purified by column chromatography on silica gel using 10% EtOAc in hexane to afford 1-{(1-tosyl-1*H*-indol-2-yl)methyl}indoline-2,3-dione (**3d**, 67% yield).

General procedure for the preparation of compound 5



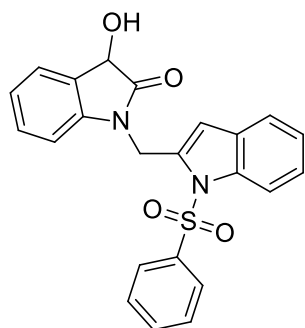
Zinc powder (100 mesh) (5 mmol) was added to a solution of compound **3** (1.0 mmol) in acetic acid (10 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature (25-30 °C) for 30 min. After completion (confirmed by TLC), the mixture was filtered by Whatman filter paper to remove Zn. The filtrate was added to crush ice and stirred with glass rod till solid persists. Filter by Whatman filter paper and the solid was purified by column chromatography using 10% EtOAc in hexane as eluent to afford the title compound.

3-Hydroxy-1-{(1-tosyl-1*H*-indol-2-yl)methyl}indolin-2-one (**5a**)



White solid (90% yield); mp: 195-197 °C; R_f = 0.21 (30% EtOAc/*n*-hexane); ^1H NMR (400 MHz, DMSO- d_6) δ : 8.04 (d, J = 8.4 Hz, 1H, ArH), 7.90 (d, J = 8.4 Hz, 2H, ArH), 7.47-7.38 (m, 4H, ArH), 7.35-7.28 (m, 1H, ArH), 7.21 (q, J = 6.8 Hz, 2H, ArH), 7.07 (t, J = 7.2 Hz, 1H, ArH), 6.67 (d, J = 8.0 Hz, 1H, ArH), 6.39 (2s, 2H, indole (C-3) H, OH (D₂O exchangeable)), 5.25 (m, 2H, NCH₂), 5.12 (d, J = 7.6 Hz, 1H, CH-OH), 2.35 (s, 3H, ArCH₃); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 176.2 (C=O), 145.8, 142.3, 136.4, 135.2, 134.3, 130.4 (2C), 129.1, 128.9, 128.7, 126.5 (2C), 124.8, 124.7, 124.0, 122.6, 120.8, 114.0, 108.9, 108.8, 68.8 (CH-OH), 38.2 (NCH₂), 21.0 (ArMe); HPLC: 97.9%, Column: Eclipse XDB C-18 150*4.6 mm 5 μ m, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in ACN, (gradient) T/B% : 0/30, 20/90, 30/90, 31/30, 35/30; flow rate: 1 mL/min, diluent: ACN:water (80:20), UV: 250.0 nm, retention time 14.7 min; MS (ES mass): m/z 433.1 (M+1, 20%), 284.0 (M-148, 100%).

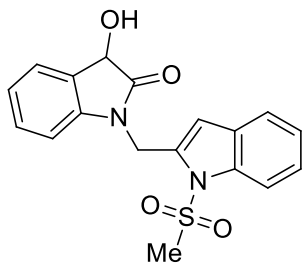
3-Hydroxy-1-[[1-(phenylsulfonyl)-1H-indol-2-yl]methyl]indolin-2-one (5b)



White solid (89% yield); mp: 187-189 °C; R_f = 0.21 (30% EtOAc/*n*-hexane); ^1H NMR (400 MHz, DMSO- d_6) δ : 8.09-7.96 (m, 3H, ArH), 7.75 (t, J = 7.6 Hz, 1H, ArH), 7.64 (t, J = 8.0 Hz, 2H, ArH), 7.46-7.38 (m, 2H, ArH), 7.36-7.29 (m, 1H, ArH), 7.21 (t, J = 7.6 Hz, 2H, ArH), 7.07

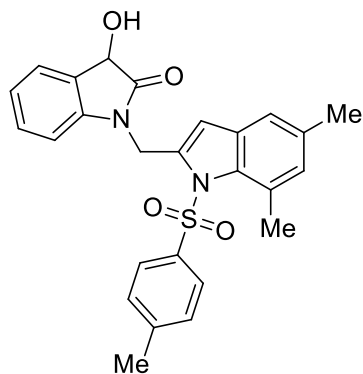
(t, $J = 7.6$ Hz, 1H, ArH), 6.67 (d, $J = 8.0$ Hz, 1H, ArH), 6.39 (2s, 2H, indole (C-3) H, OH (D₂O exchangeable)), 5.34-5.19 (m, 2H, NCH₂), 5.12 (d, $J = 8.0$ Hz, 1H, CH-OH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 176.2 (C=O), 142.3, 137.2, 136.4, 135.2, 134.9, 130.0 (2C), 129.1, 128.9, 128.7, 126.4 (2C), 124.8, 124.7, 124.1, 122.6, 120.9, 114.0, 109.0, 108.8, 68.8 (CH-OH), 38.2 (NCH₂); HPLC: 99.3%, Column: Cosmiscil C-18 150*4.6 mm 5 μ m, mobile phase A: 5 mM Ammonium acetate in water, mobile phase B: ACN, (gradient) T/B% : 0/5, 20/90, 25/90, 26/5, 30/5; flow rate: 1 mL/min, diluent: ACN:water (80:20), UV: 210.0 nm, retention time 15.6 min; MS (ES mass): m/z 419.1 (M+1, 20%), 270.0 (M-148, 100%).

3-Hydroxy-1-[[1-(methylsulfonyl)-1H-indol-2-yl]methyl]indolin-2-one (5c)



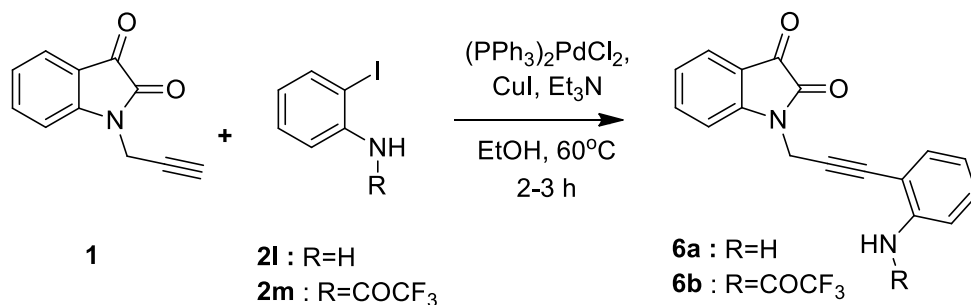
White solid (90% yield); mp: 155-157 °C; $R_f = 0.18$ (30% EtOAc/*n*-hexane); ¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.90 (d, $J = 8.4$ Hz, 1H, ArH), 7.50 (d, $J = 7.6$ Hz, 1H, ArH), 7.43 (d, $J = 7.2$ Hz, 1H, ArH), 7.37-7.30 (m, 1H, ArH), 7.29-7.21 (m, 2H, ArH), 7.08 (t, $J = 7.6$ Hz, 1H, ArH), 6.99 (d, $J = 7.6$ Hz, 1H, ArH), 6.38 (2s, 2H, indole (C-3) H, OH (D₂O exchangeable)), 5.26-5.06 (m, 3H, NCH₂, CH-OH), 3.57 (s, 3H, SCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 176.2 (C=O), 142.4, 136.3, 135.3, 129.1, 128.7, 128.5, 124.7, 124.3, 123.5, 122.6, 120.7, 113.4, 109.3, 107.0, 68.9 (CH-OH), 41.1 (SMe), 37.8 (NCH₂); HPLC: 99.4%, Column: Eclipse XDB C-18 150*4.6 mm 5 μ m, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in ACN, (gradient) T/B% : 0/5, 20/90, 25/90, 26/5, 30/5; flow rate: 1 mL/min, diluent: ACN:water (80:20), UV: 210.0 nm, retention time 14.3 min; MS (ES mass): m/z 357.0 (M+1, 20%), 208.0 (M-148, 100%).

1-[(5,7-dimethyl-1-tosyl-1H-indol-2-yl)methyl]-3-hydroxyindolin-2-one (5d)



White solid (87% yield); mp: >200 °C; R_f = 0.3 (30% EtOAc/*n*-hexane); ^1H NMR (400 MHz, DMSO- d_6) δ : 7.48 (d, J = 8.0 Hz, 2H, ArH), 7.39 (d, J = 7.2 Hz, 1H, ArH), 7.30 (d, J = 8.0 Hz, 2H, ArH), 7.20 (t, J = 8.0 Hz, 1H, ArH), 7.05 (t, J = 7.6 Hz, 1H, ArH), 6.92 (2s, 2H, ArH), 6.67 (d, J = 8.0 Hz, 1H, ArH), 6.34 (2s, 2H, indole (C-3) H, OH (D₂O exchangeable)), 5.23-5.02 (m, 3H, NCH₂, CH-OH), 2.59 (s, 3H, ArCH₃), 2.23 (s, 3H, ArCH₃), 2.32 (s, 3H, ArCH₃); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 176.2 (C=O), 145.0, 142.2, 138.5, 136.9, 134.5, 133.0, 132.8, 129.9, 129.7 (2C), 129.1, 128.7, 127.3, 126.3 (2C), 124.7, 122.5, 118.8, 114.4, 108.9, 68.8 (CH-OH), 38.2 (NCH₂), 21.6 (ArMe), 21.0 (ArMe), 20.5 (ArMe); HPLC: 90.5%, Column: X-Bridge phenyl C-18 150*4.6 mm 5 μm , mobile phase A: 0.05% TFA in water, mobile phase B: ACN:Water (90:10), (gradient) T/B% : 0/2, 5/2, 20/90, 25/90, 26/2, 30/2; flow rate: 1 mL/min, diluent: ACN:water (80:20), UV: 215.0 nm, retention time 16.3 min; MS (ES mass): m/z 461.1 (M+1, 20%), 312.1 (M-148, 100%).

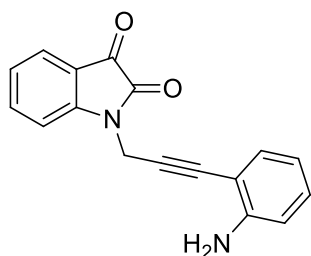
General procedure for the preparation of compound 6:



A mixture of compound **1** (1.0 mmol), Compound **2l** or **2m** (1.2 mmol), (PPh₃)₂PdCl₂ (5 mol%), CuI (5 mol%) and triethylamine (3.0 mmol) in ethanol (10 mL) was stirred at 60°C for 2-3 h. After completion of the reaction (indicated by TLC) the reaction mixture is diluted with EtOAc

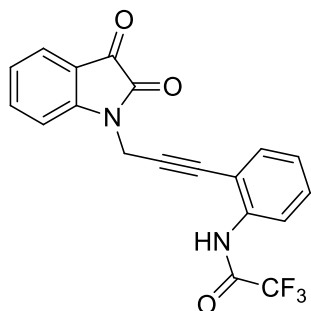
(50 mL) and filtered through celite bed. The organic layer was collected, combined, washed with water (3×30 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under low vacuum. The crude residue was purified by column chromatography on silica gel using 10% EtOAc in hexane to afford the desired product. Compounds (**6a** and **6b**) prepared, characterized by MS, NMR spectra and purity was determined by HPLC method.

1-{3-(2-Aminophenyl)prop-2-yn-1-yl}indoline-2,3-dione (**6a**)



Orange solid (82% yield); mp: 84-86 °C; $R_f=0.36$ (20% EtOAc/*n*-hexane); ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ : 7.74-7.66 (m, 1H, ArH), 7.58 (d, $J = 7.2$ Hz, 1H, ArH), 7.38 (d, $J = 8.0$ Hz, 1H, ArH), 7.16 (t, $J = 7.6$ Hz, 1H, ArH), 7.08 (dd, $J = 7.6, 1.2$ Hz, 1H, ArH), 7.05-6.99 (m, 1H, ArH), 6.64 (d, $J = 8.0$ Hz, 1H, ArH), 6.44 (t, $J = 7.6$ Hz, 1H, ArH), 5.41 (bs, 2H, NH_2 , D_2O exchangeable), 4.81 (s, 2H, NCH_2); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ : 183.2 (C=O), 157.9 (C=O), 150.6, 150.1, 138.4, 132.1, 130.3, 124.9, 123.9, 118.2, 116.0, 114.2, 111.8, 105.1, 87.8 ($-\text{C}\equiv$), 81.2 ($-\text{C}\equiv$), 30.6 (NCH_2); MS (ES mass): m/z 277.1 ($\text{M}+1$, 30%), 249.1 ($\text{M}-28$, 100%).

N-[2-{3-(2,3-dioxindolin-1-yl)prop-1-yn-1-yl}phenyl]-2,2,2-trifluoroacetamide (**6b**)



Yellow solid (92% yield); mp: 92-94 °C; $R_f=0.55$ (20% EtOAc/*n*-hexane); ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ : 11.06 (bs, H, NH, D_2O exchangeable), 7.69 (dt, $J = 8.0, 1.2$ Hz, 1H, ArH), 7.61 (d, $J = 7.2$ Hz, 1H, ArH), 7.55 (dd, $J = 7.6, 1.2$ Hz, 1H, ArH), 7.50-7.44 (m, 1H, ArH), 7.40 (d, $J =$

7.0 Hz, 1H, ArH), 7.35 (dt, $J = 7.6, 1.2$ Hz, 1H, ArH), 7.26 (d, $J = 8.0$ Hz, 1H, ArH), 7.19 (t, $J = 7.2$ Hz, 1H, ArH), 4.81 (s, 2H, NCH₂); ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 182.7 (C=O), 157.2 (C=O), 155.2 (C-F $J = 36.7$ Hz), 149.6, 138.2, 136.1, 132.7, 129.7, 127.6, 126.7, 124.5, 123.6, 119.0, 117.6, 117.2 (C-F $J = 287.0$ Hz), 111.1, 88.2 (-C \equiv), 79.1 (-C \equiv), 29.7 (NCH₂); HPLC: 99.2%, Column: X-Bridge ODS C-18 150*4.6 mm 5 μ m, mobile phase A: 5 mM Ammonium acetate in water, mobile phase B: ACN, (gradient) T/B% : 0/30, 30/90, 40/90, 41/5, 45/5; flow rate: 1 mL/min, diluent: ACN:THF, UV: 240.0 nm, retention time 13.3 min; MS (ES mass): m/z 372.9 (M⁺, 100%).

Docking study

All ligand structures were built in MarvinSketch.¹ Protein (2FP2) as well as all ligands were prepared (means optimization, charge calculation, deletion of co-crystal ligand, and addition of hydrogen etc.) using AtuDock tool.² All ligands were docked at interface site of *Mtb*CM (which is homodimer) using reliable open-source tool AutoDock Vina.³ The grid map was made up of 20X20X20 points using AutoGrid with 0.54, 3.92, and 42.25 as center_X, center_Y, and center_Z respectively. To search all possible conformation of ligands thoroughly, exhaustiveness value of 20 were used, which made the process little more time consuming, but accurately identified the best pose of individual ligand.

To check the reproducibility of docking result, we have performed docking of each individual ligand at least ten times and maximum difference found ± 0.2 . The validation of docking protocol was done by re-docking the co-crystal ligand (TSA) and calculating RMSD difference between co-crystal one and docked one in PyMOL,⁴ maximum RMSD was 1.713 (<2) that indicated accuracy of our docking protocol.

Pharmacology

In vitro assay for CM inhibition

Enzyme and Reagents

Mycobacterium tuberculosis chorismate mutase (*Mtb*CM) gene was PCR amplified and cloned into expression vector pET22b. *Mtb*CM was purified from over expressed culture of BL21 (DE3) harboring pET22b/ *Mtb*CM by Ni-NTA affinity chromatography. The substrate chorismic acid was obtained from Sigma (SIGMA cat # 1701).

The CM enzymatic assay

Activity of chorismate mutase enzyme was based on the direct observation of conversion of chorismate to prephenate spectrophotometrically at OD₂₇₄. The reaction volume of the assay was maintained at 100 µl. The substrate chorismic acid (2 mM) was pre incubated at 37 °C for 5 min in the buffer containing 50 mM Tris-HCl (pH 7.5), 0.5 mM EDTA, 0.1 mg/ml bovine serum albumin, and 10 mM β-Mercaptoethanol. The reaction was started by adding 180 pmol of CM enzyme to the pre-warmed chorismic acid solution. Inhibitory screening of the test compounds against CM activity was measured at 30 µM (10 nM to 30 µM for concentration dependent study) concentration of the effectors. The reaction was allowed to proceed at 37 °C and was terminated after 5 min with 100 µl of 1 N HCl and absorbance was read at 274 nm. Alternatively, the reaction was allowed to proceed for further 10 min and was then terminated with 180 µM of 2.5N NaOH and absorbance was measured at 320 nm. A blank with no enzyme for every reaction was kept as a control to account for the non enzymatic conversion of chorismate to prephenate. The % of enzyme inhibition caused by the test compound was calculated by the following formula:

% inhibition = 100 – residual activity of CM

Residual activity of CM = $[A_{274} \{S + (E' + C)\} - A_{274} (S + C)] / [A_{274} (S + E) - A_{274} (S)]$

S = absorbance of the substrate (chorismic acid) at 274 nm; E' = absorbance of the enzyme (CM) at 274 nm with compound; E = absorbance of the enzyme (CM) at 274 nm without compound; C = test compound; A₂₇₄ indicates absorbance at 274 nm (this is replaced by A₃₂₀ for absorbance at 320 nm).

Computational ADME prediction

Software and methods

The ADME predictions were performed by using the SwissADME web-tool [15], where the molecules were drawn using Marvin JS (version 16.4.18, 2016) and converted into SMILES by JChem Web Services (version 14.9.29, 2013). Then the 3D conformations were generated through the StringMolExport function. All descriptors and important molecular parameters of physicochemical properties were computed by OpenBable API (version 2.3.0, 2012). The

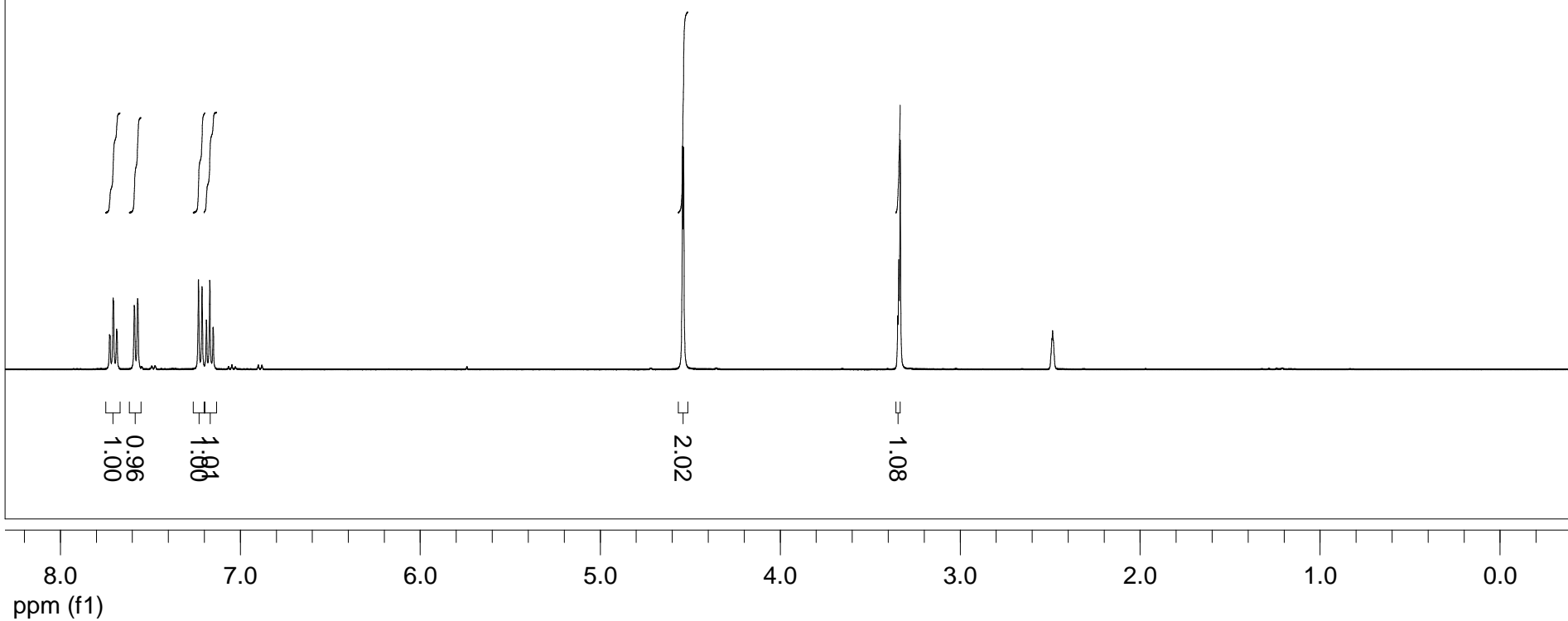
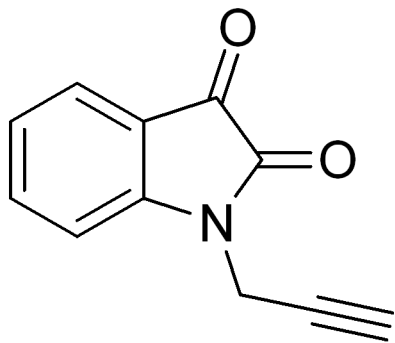
predictive models were mostly generated by Quantitative Structure-Property Relationship (QSPR) methods along with some other robust models. As the SwissADME is a web-based tool, all these process are done in an automated manner.

References

1. Huey, R., and G. M. Morris. "AutoDock tools." *La Jolla, CA, USA: The Scripps Research Institute* (2003).
2. Trott, Oleg, and Arthur J. Olson. "AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading." *Journal of computational chemistry* 31, no. 2 (2010): 455-461.
3. DeLano, W.L., 2002. Pymol: An open-source molecular graphics tool. *CCP4 Newsletter On Protein Crystallography*, 40(1), pp.82-92.

Copies of spectra

^1H NMR (Varian, 400 MHz) spectrum of compound **1** in $\text{DMSO-}d_6$



182.949

157.750

149.857

138.546

125.000

124.059

118.096

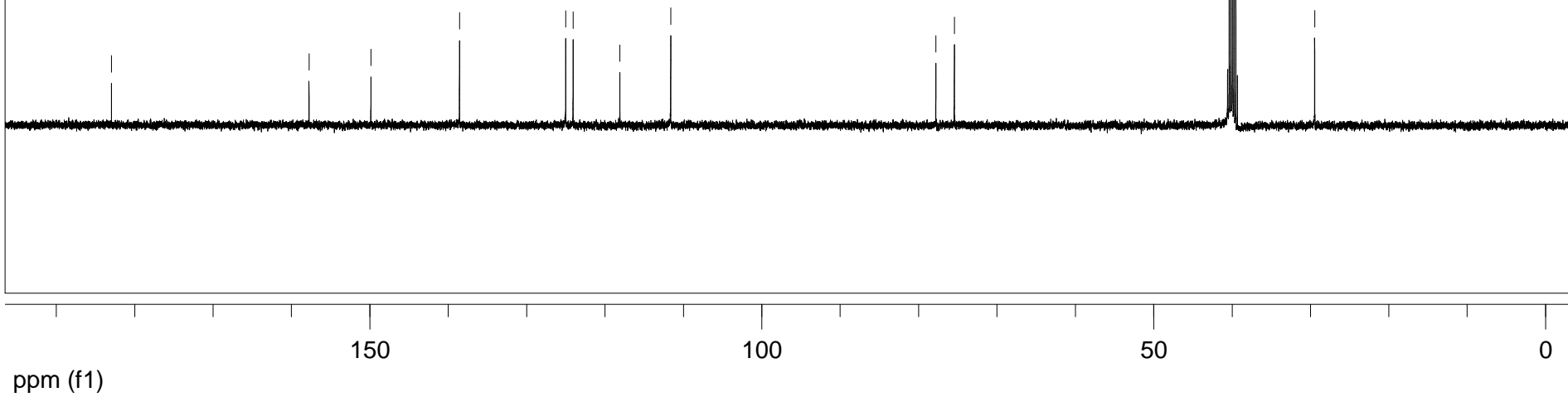
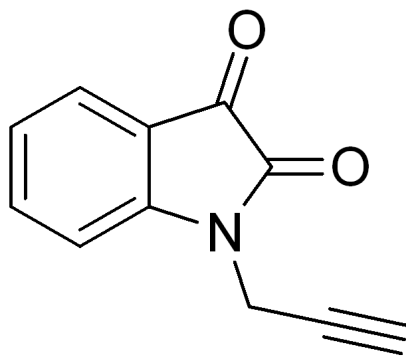
111.611

77.790

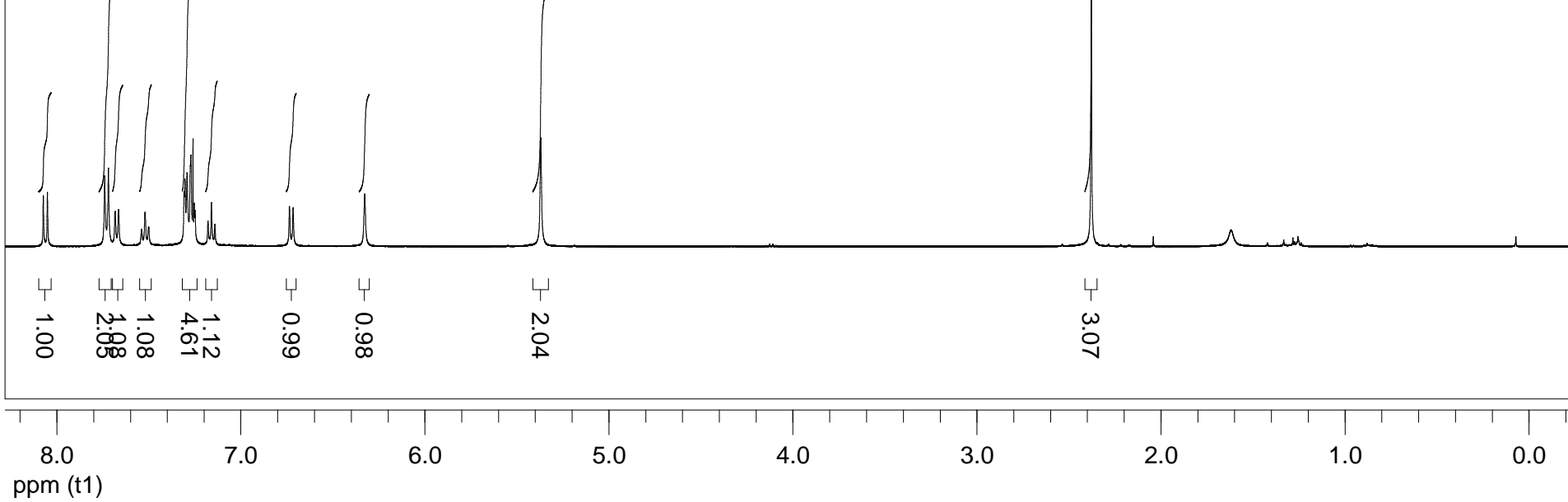
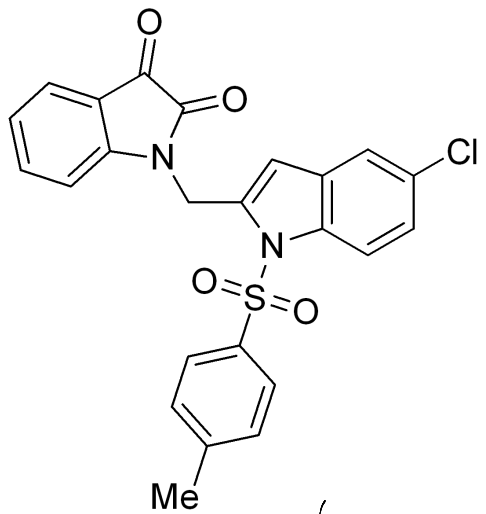
75.422

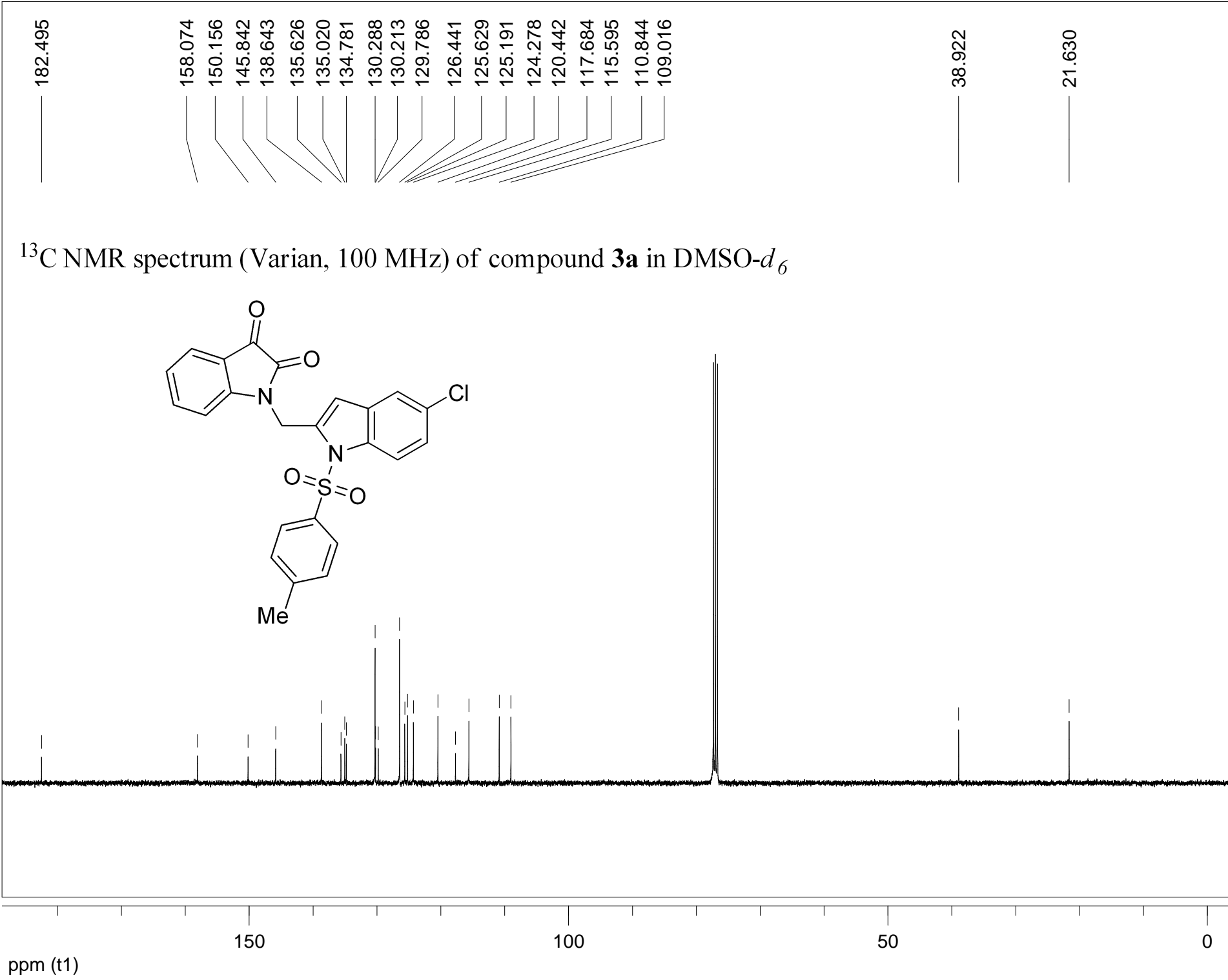
29.452

^{13}C NMR spectrum (Varian, 100 MHz) of compound **1** in $\text{DMSO-}d_6$

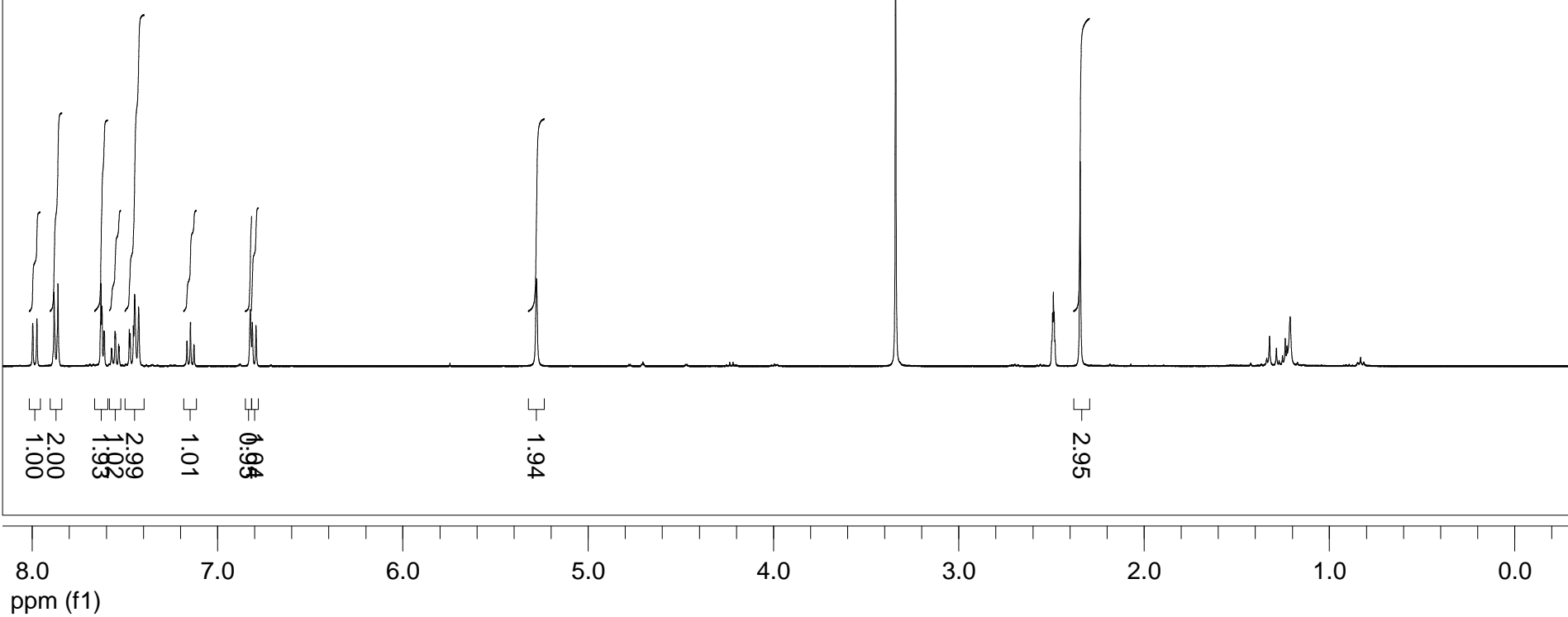
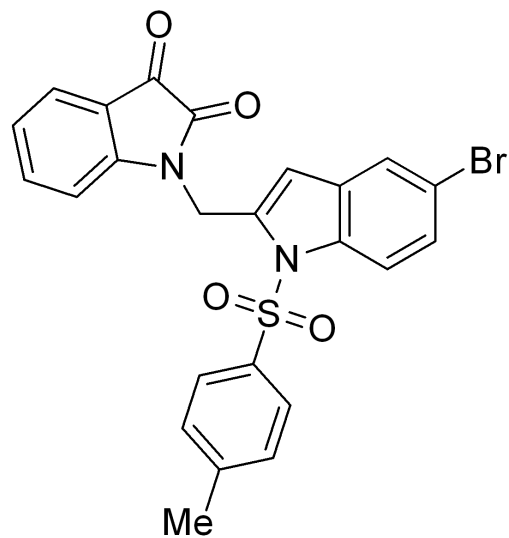
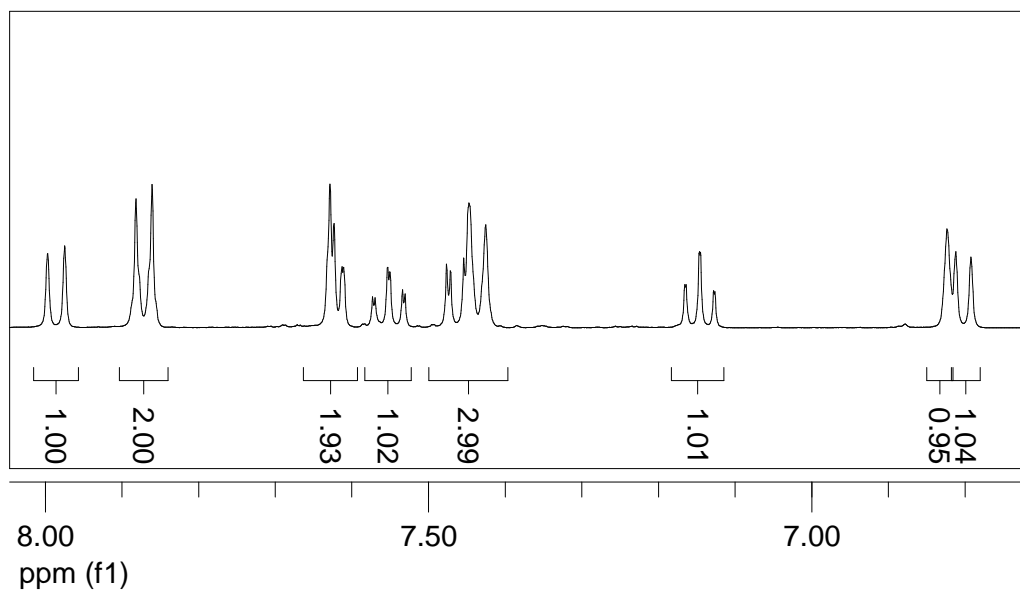


^1H NMR (Varian, 400 MHz) spectrum of compound **3a** in $\text{DMSO-}d_6$

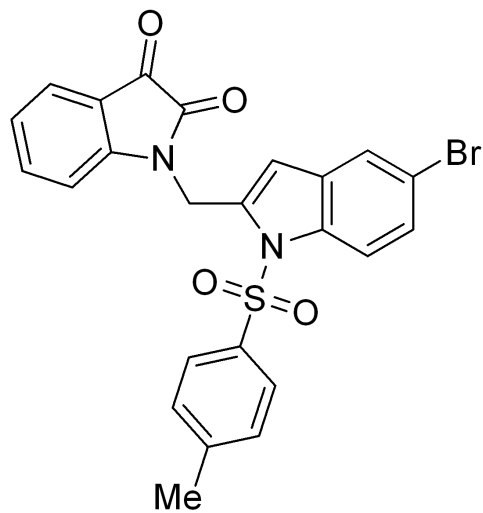




^1H NMR (Varian, 400 MHz) spectrum of compound **3b** in $\text{DMSO-}d_6$



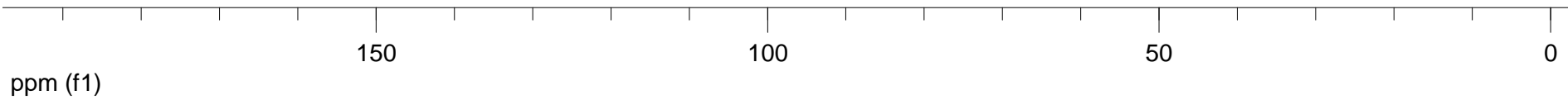
^{13}C NMR spectrum (Varian, 100 MHz) of compound **3b** in $\text{DMSO-}d_6$



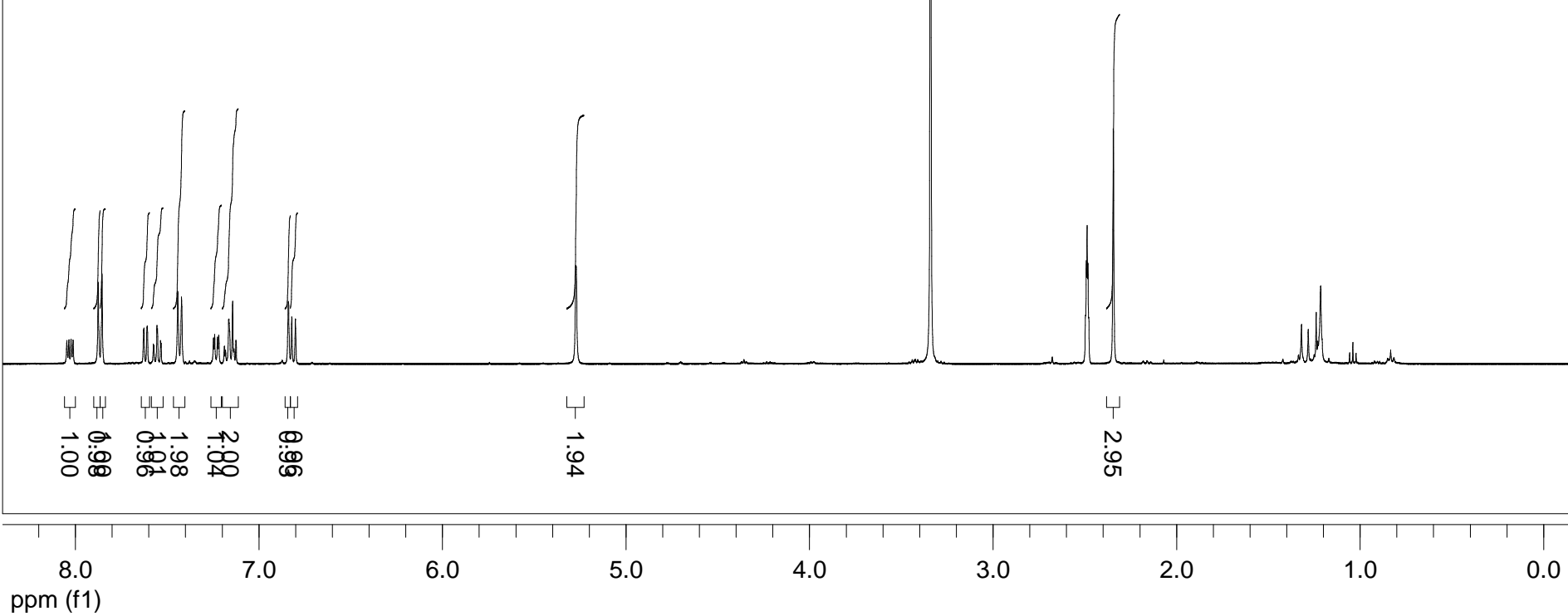
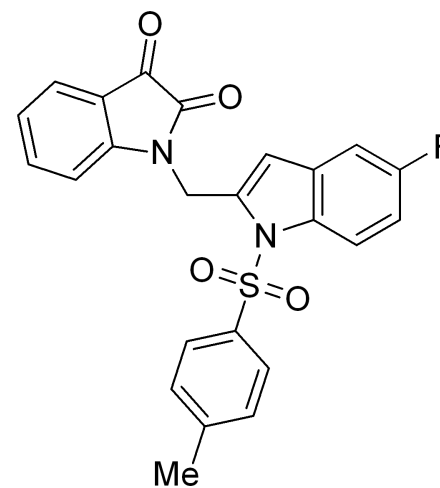
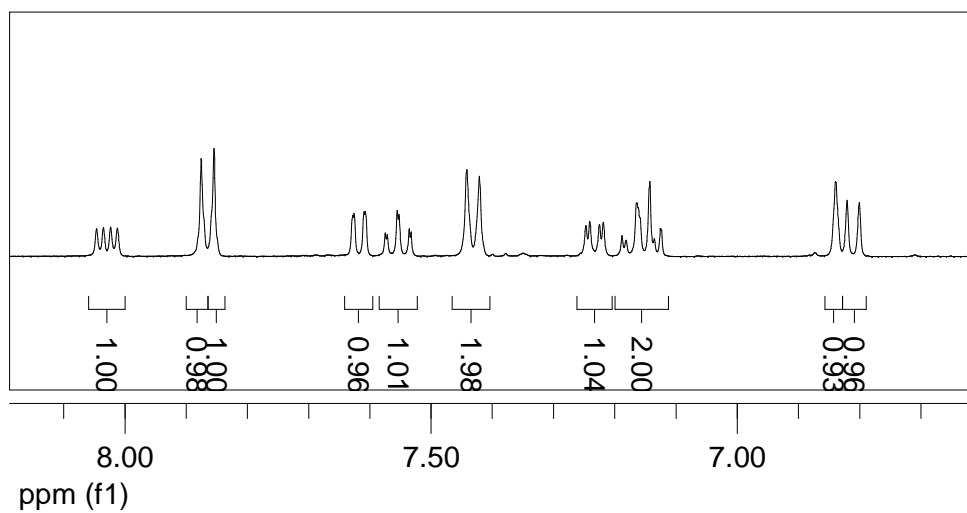
182.953
158.847
150.272
146.615
138.339
136.413
135.781
134.399
131.443
130.993
127.768
126.894
124.956
123.936
123.767
118.532
117.073
116.355
111.237
109.331

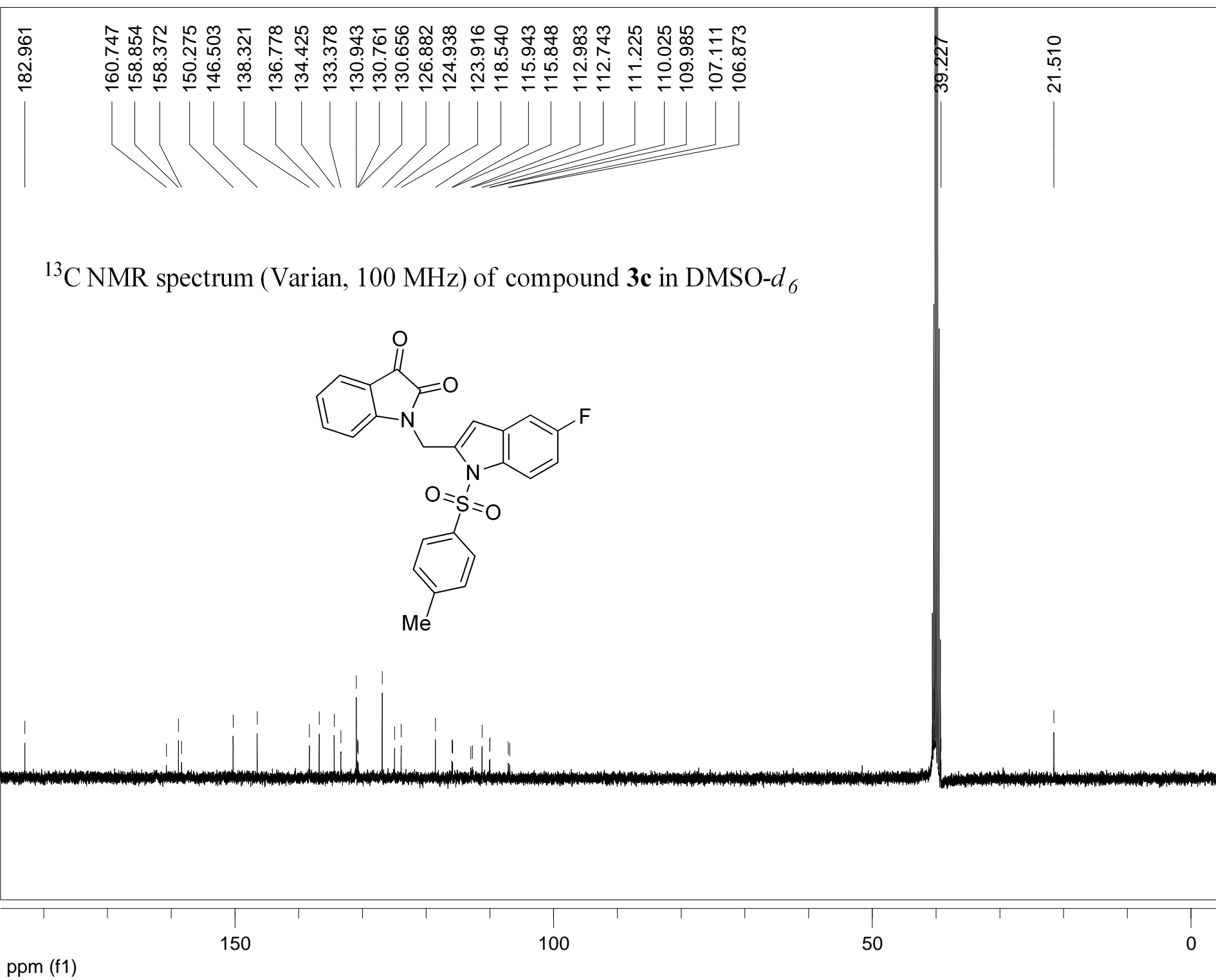
39.167

21.525

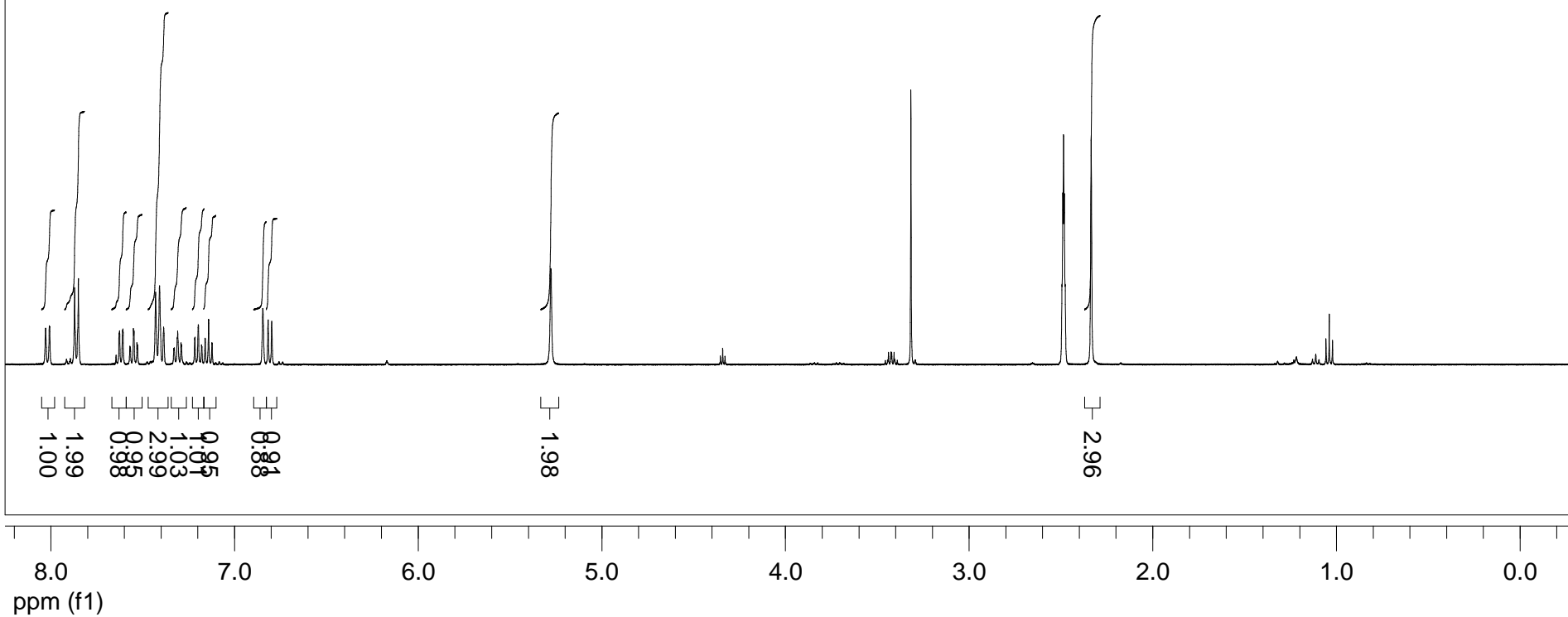
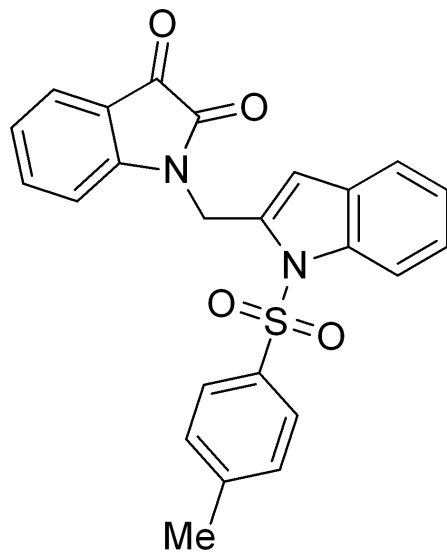


^1H NMR (Varian, 400 MHz) spectrum of compound **3c** in $\text{DMSO-}d_6$



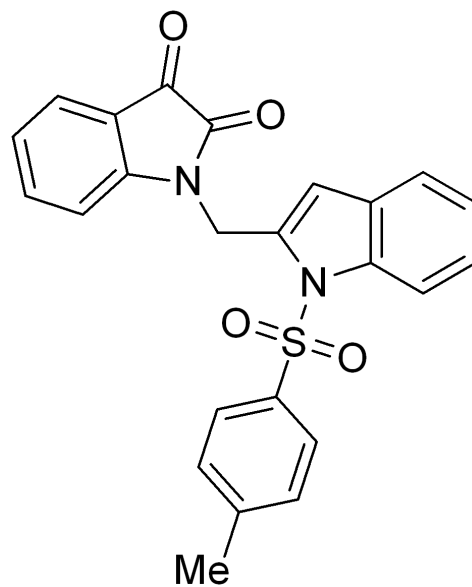


^1H NMR (Varian, 400 MHz) spectrum of compound **3d** in $\text{DMSO-}d_6$



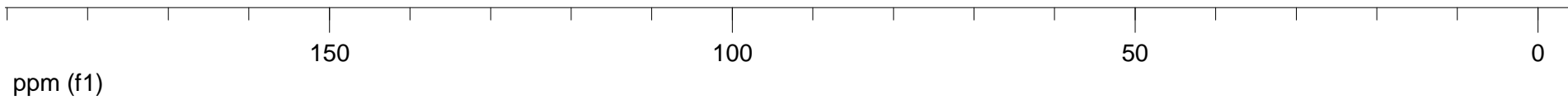
183.048
158.837
150.372
146.298
138.308
136.932
134.730
134.671
130.872
129.499
126.847
125.171
124.924
124.426
123.873
121.373
118.542
114.449
111.244
110.166

^{13}C NMR spectrum (Varian, 100 MHz) of compound **3d** in $\text{DMSO-}d_6$

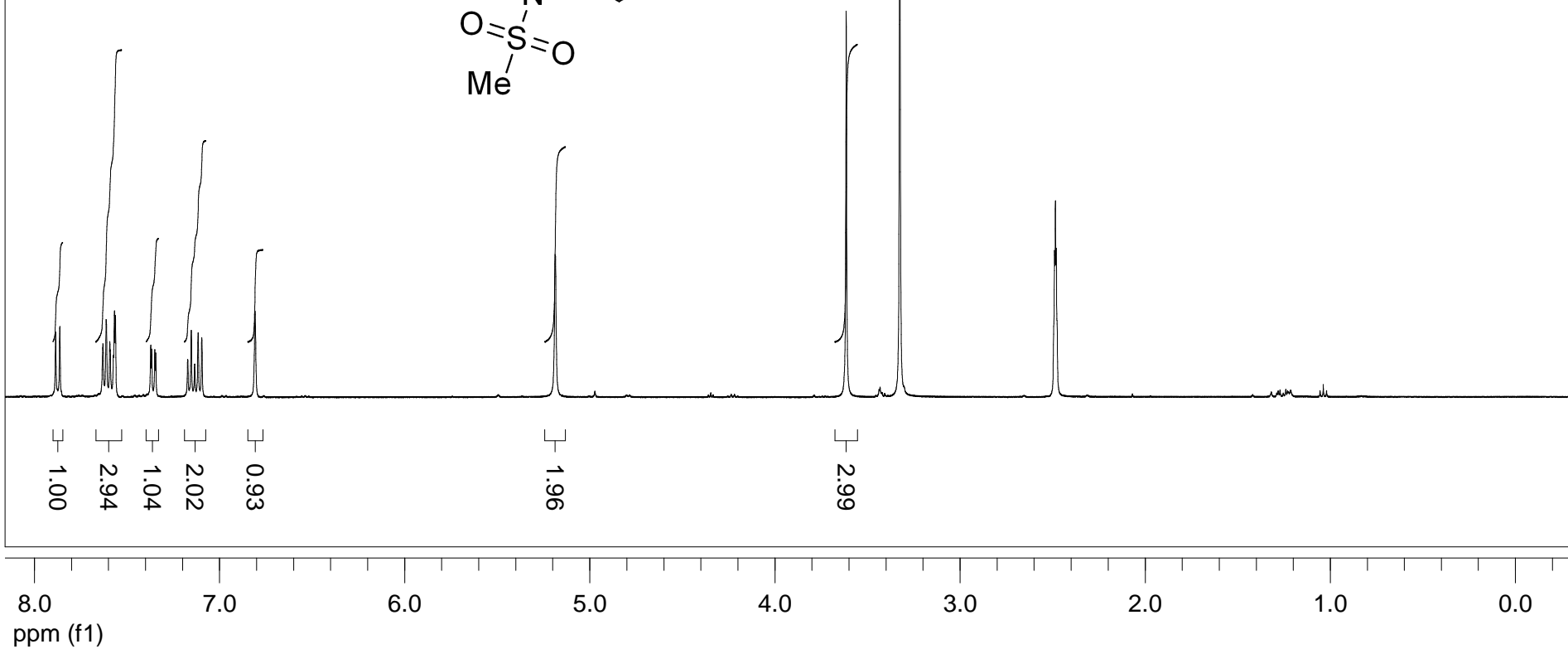
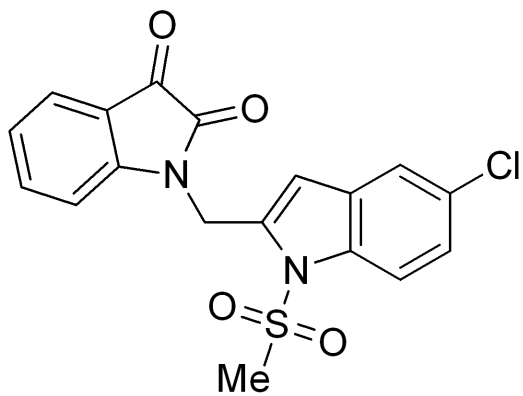


39.230

21.495



^1H NMR (Varian, 400 MHz) spectrum of compound **3e** in $\text{DMSO-}d_6$



183.076

158.851

150.441

138.290

136.666

135.316

130.501

128.434

124.857

124.644

123.900

120.528

118.514

115.432

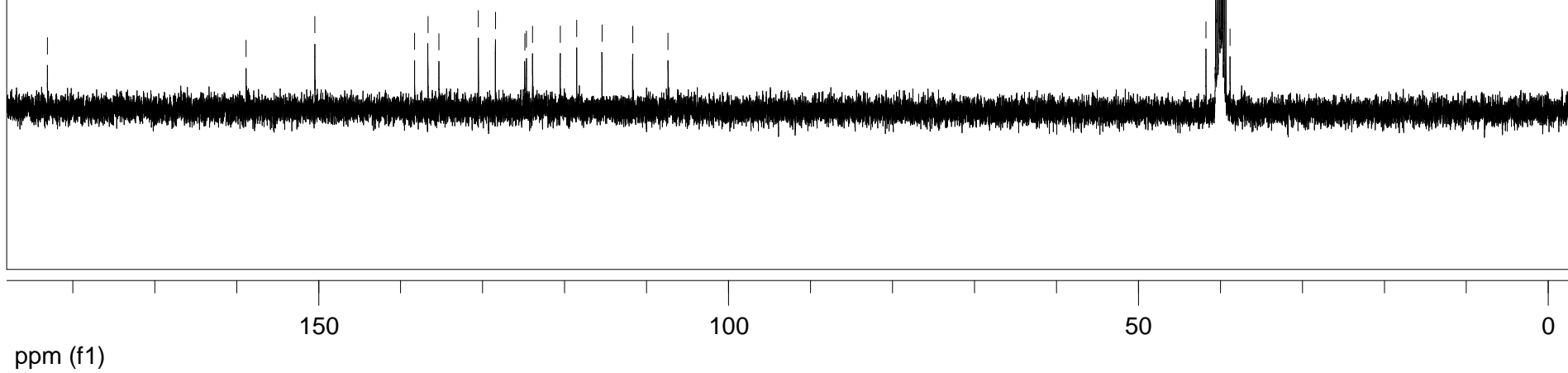
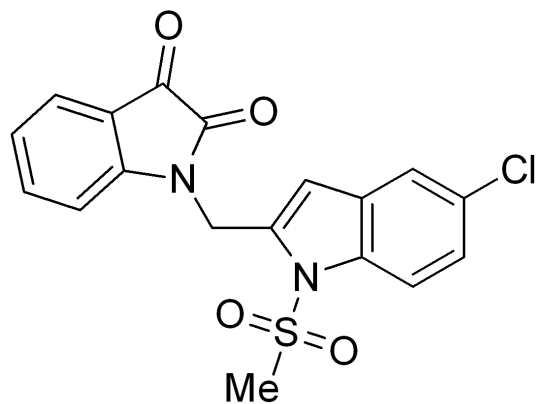
111.683

107.372

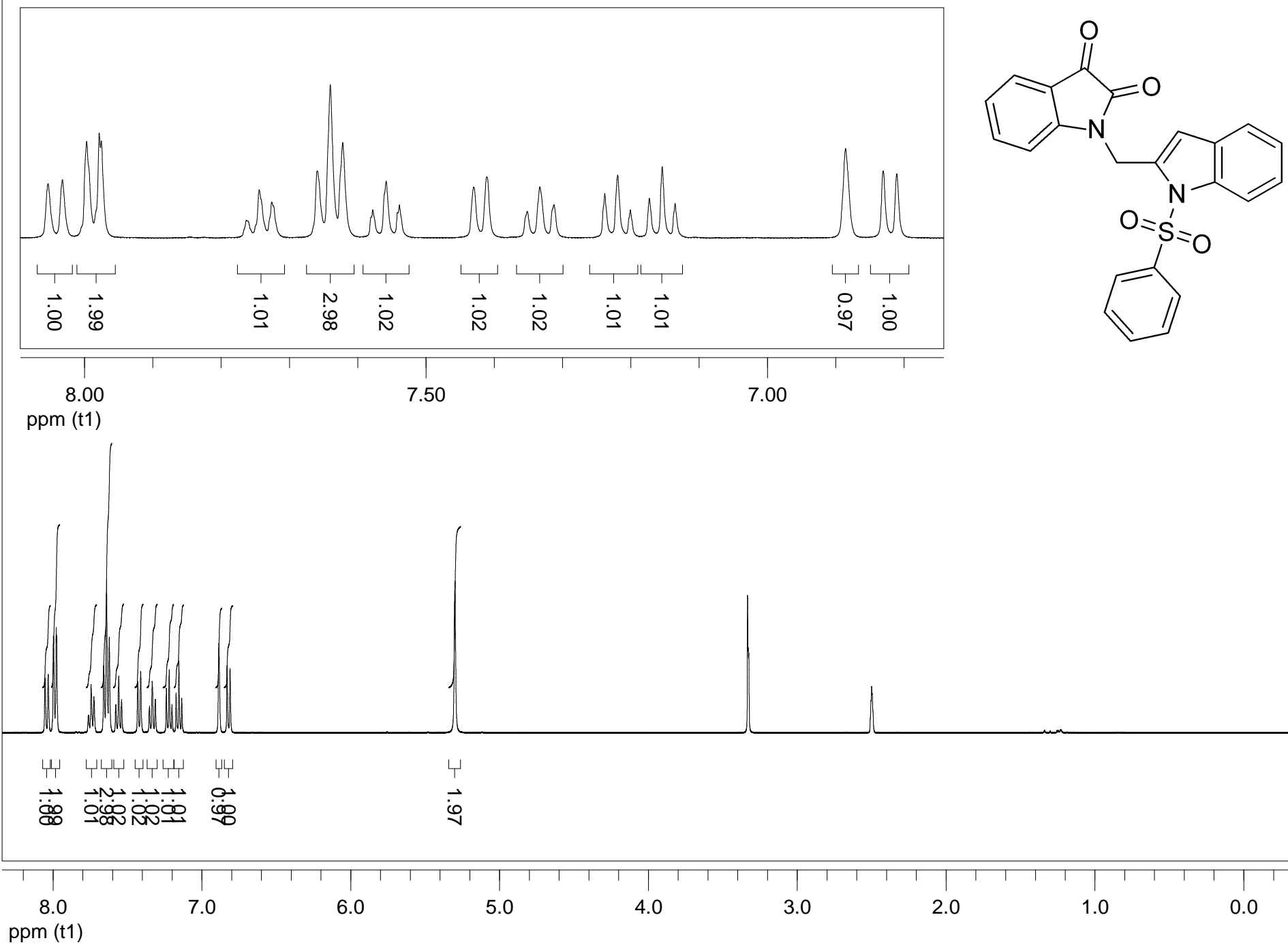
41.748

38.809

^{13}C NMR spectrum (Varian, 100 MHz) of compound **3e** in $\text{DMSO-}d_6$

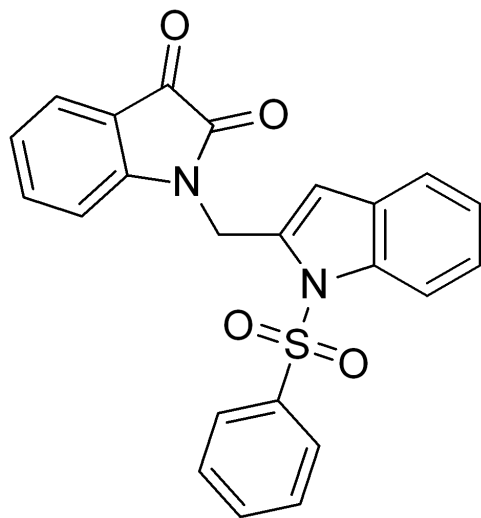


^1H NMR (Varian, 400 MHz) spectrum of compound **3f** in $\text{DMSO-}d_6$

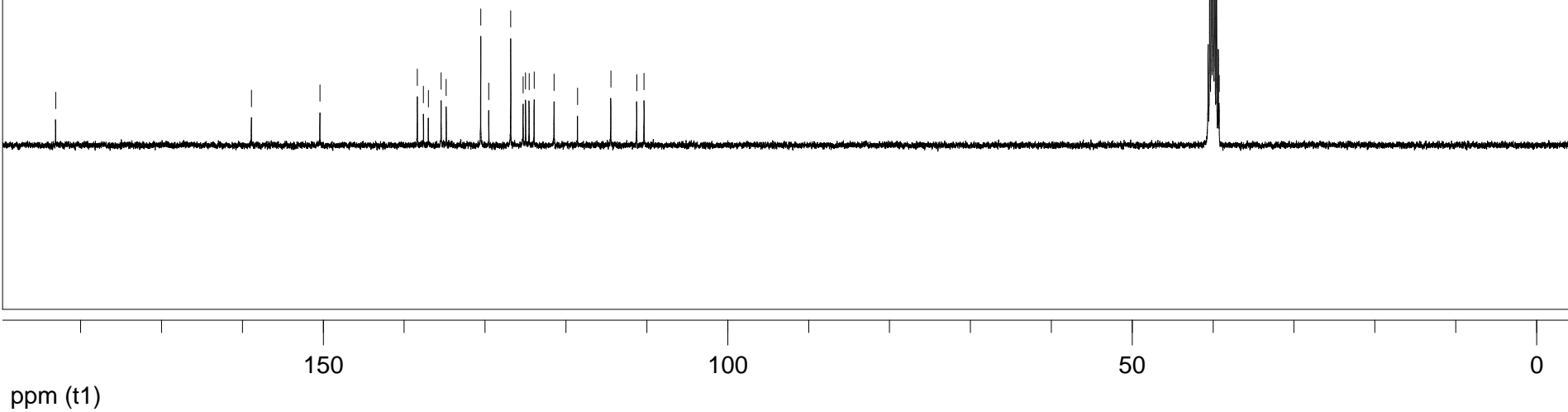


183.076
158.879
150.406
138.363
137.600
137.000
135.417
134.786
130.527
129.524
126.819
125.287
124.976
124.550
123.928
121.463
118.571
114.455
111.246
110.336

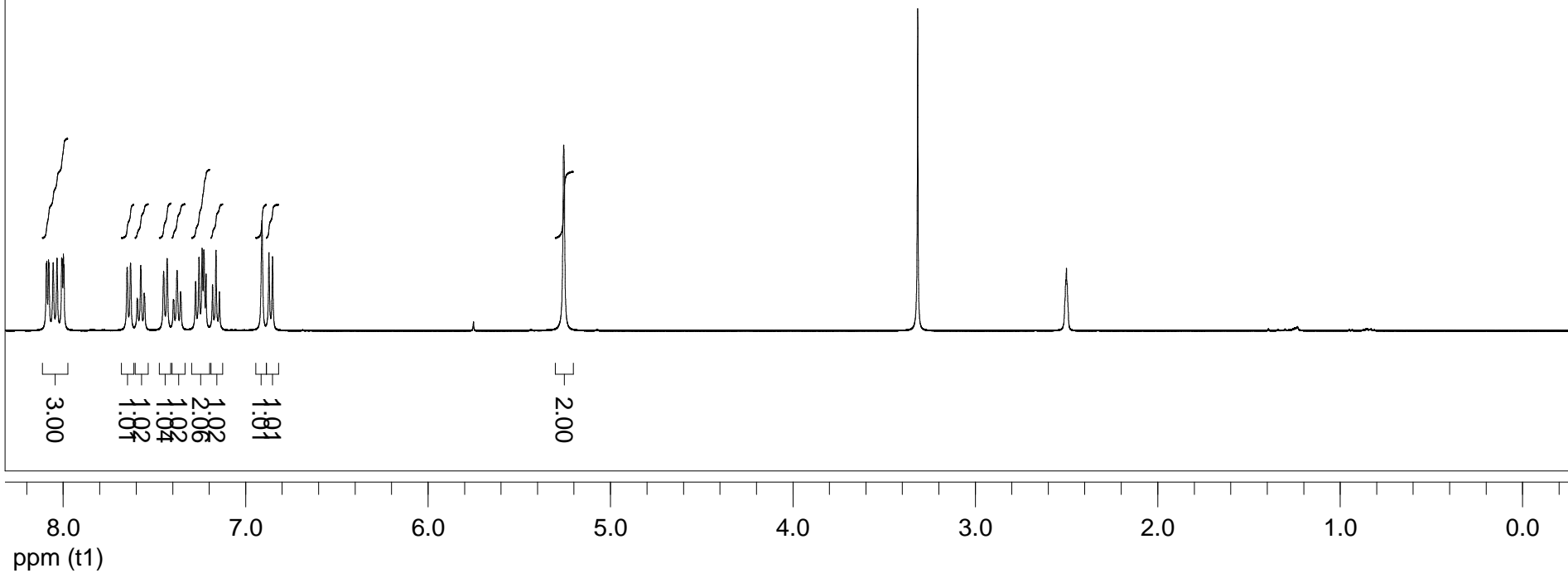
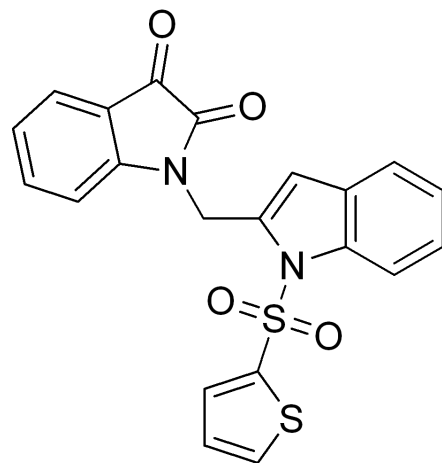
^{13}C NMR spectrum (Varian, 100 MHz) of compound **3f** in $\text{DMSO-}d_6$

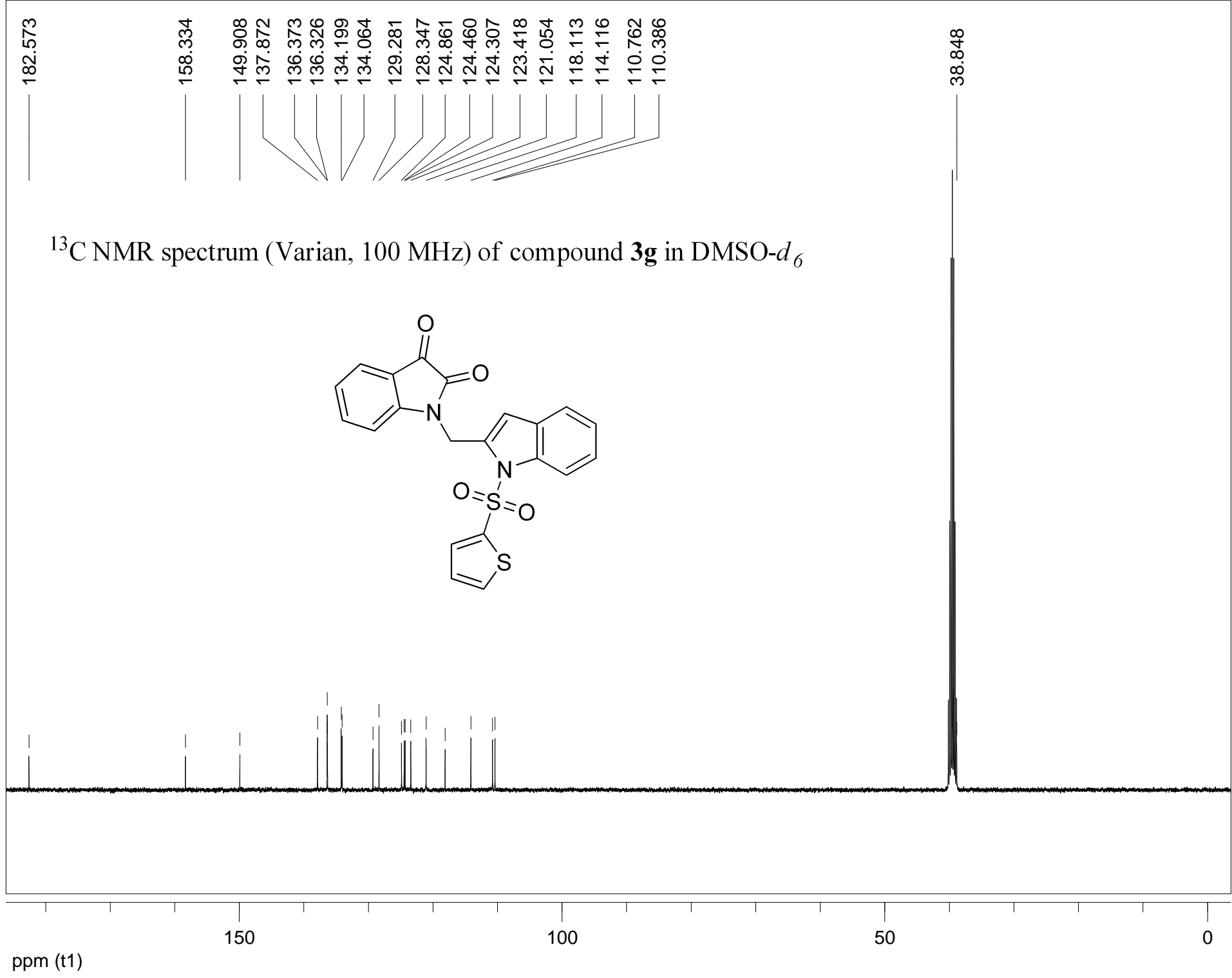


39.251

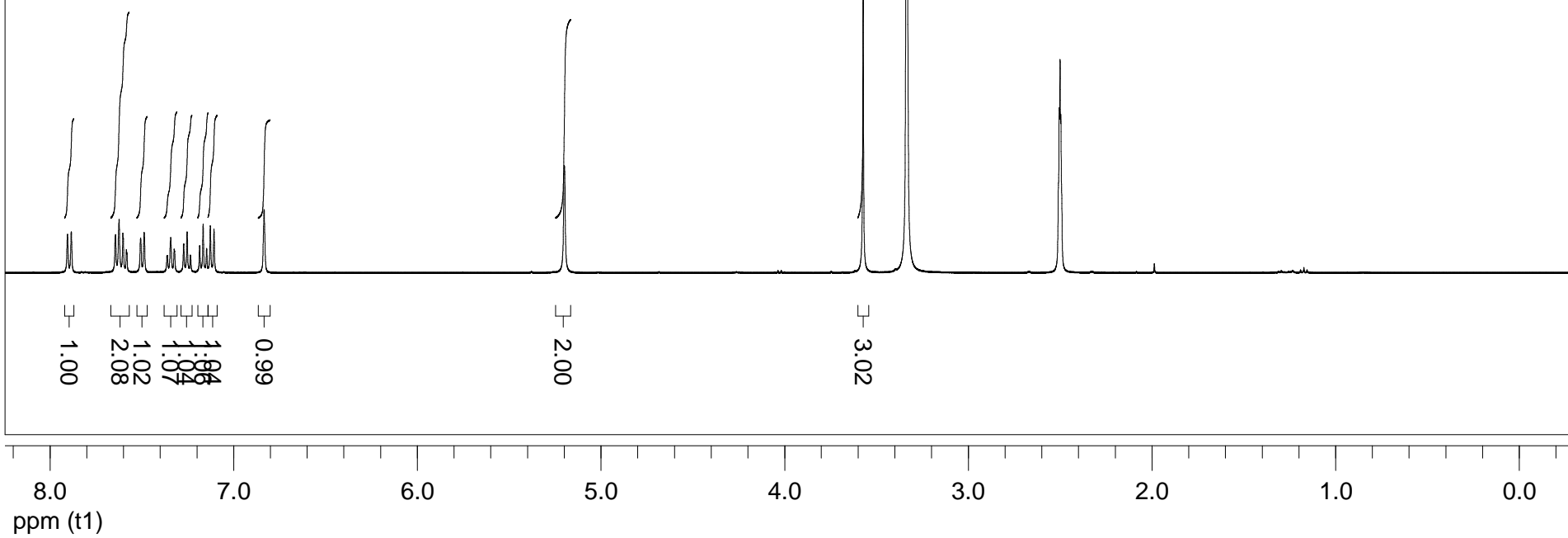
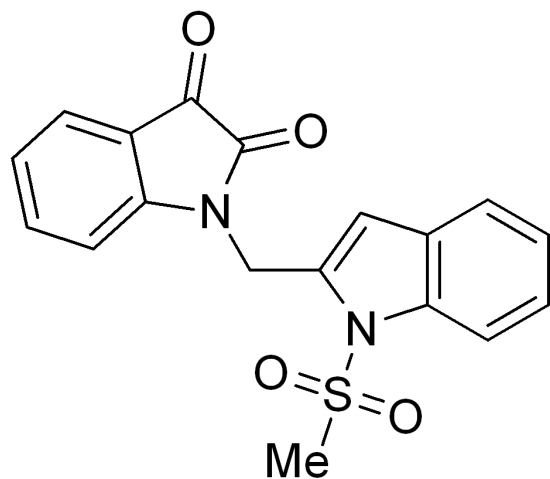


^1H NMR (Varian, 400 MHz) spectrum of compound **3g** in $\text{DMSO-}d_6$





^1H NMR (Varian, 400 MHz) spectrum of compound **3h** in $\text{DMSO-}d_6$



182.750

158.406

150.133

137.863

136.393

134.392

128.675

124.411

124.354

123.485

123.435

120.807

118.074

113.415

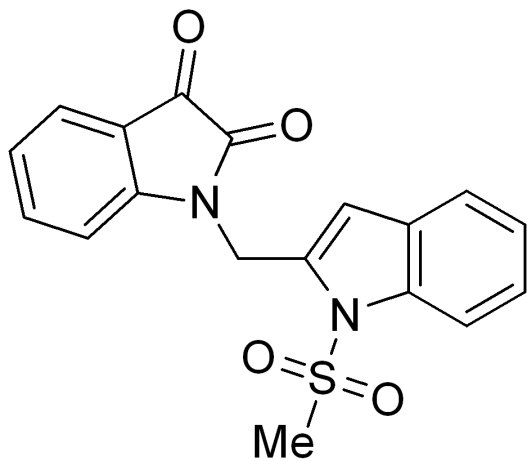
111.260

107.666

41.067

38.432

^{13}C NMR spectrum (Varian, 100 MHz) of compound **3h** in $\text{DMSO-}d_6$



ppm (t1)

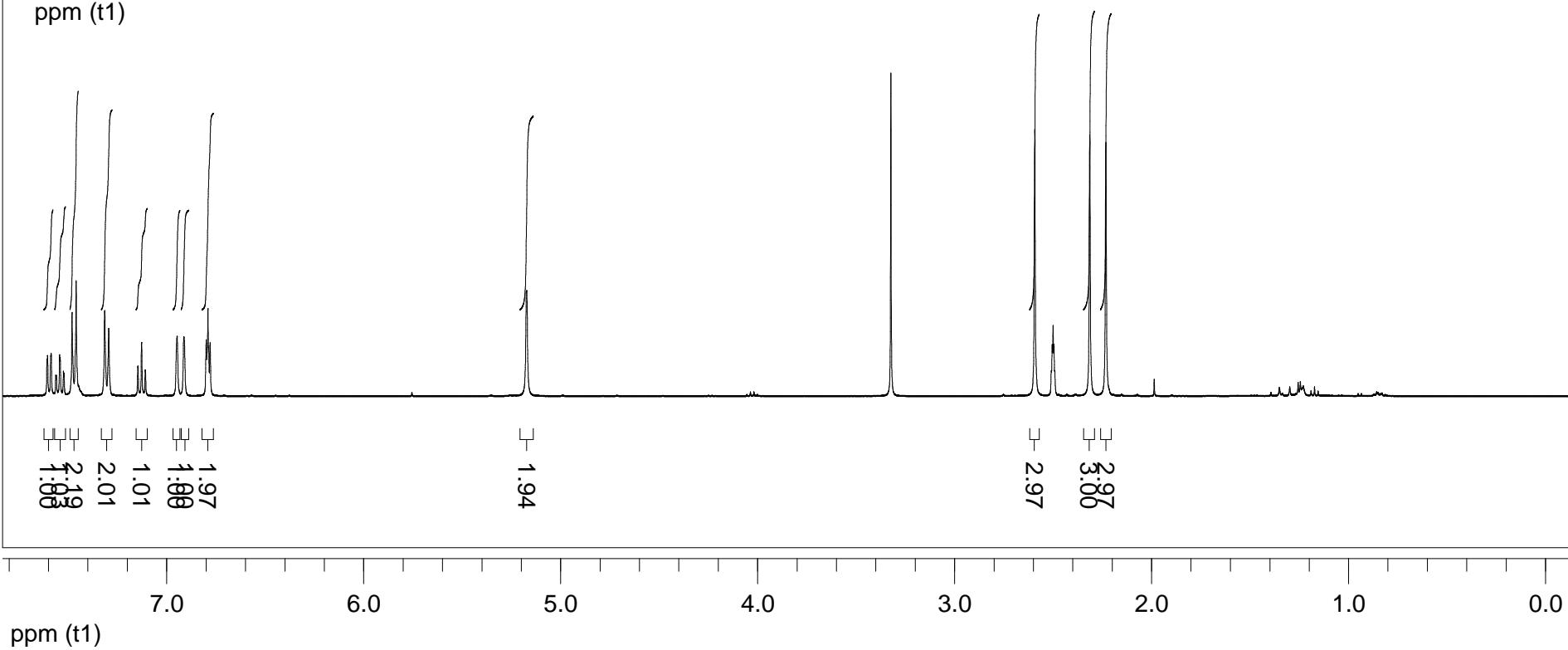
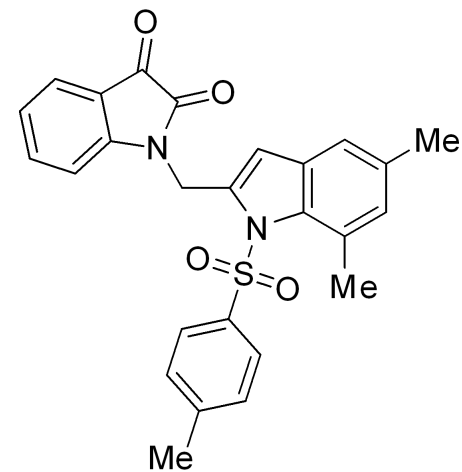
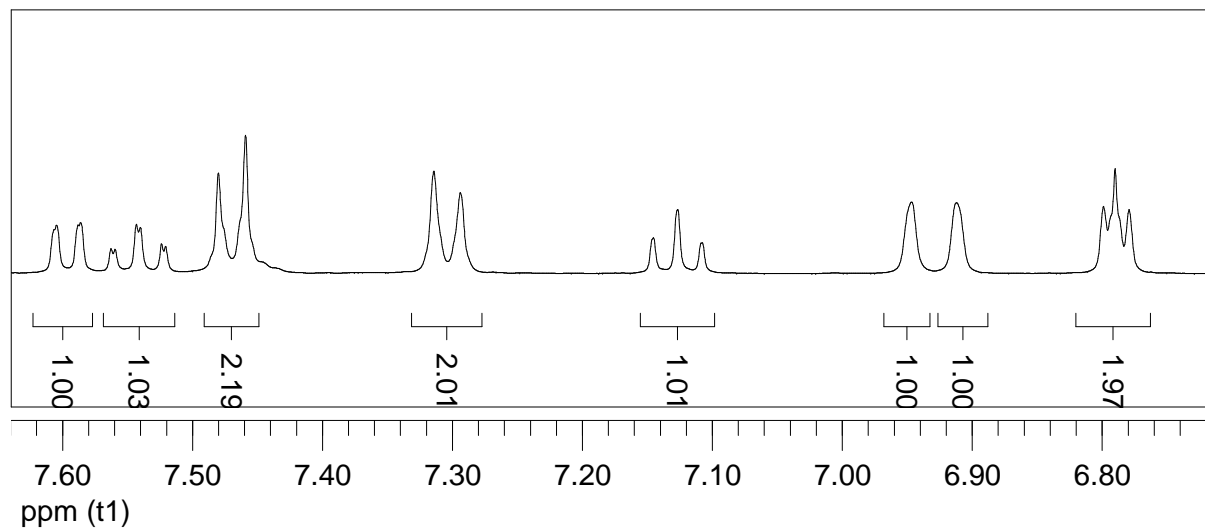
150

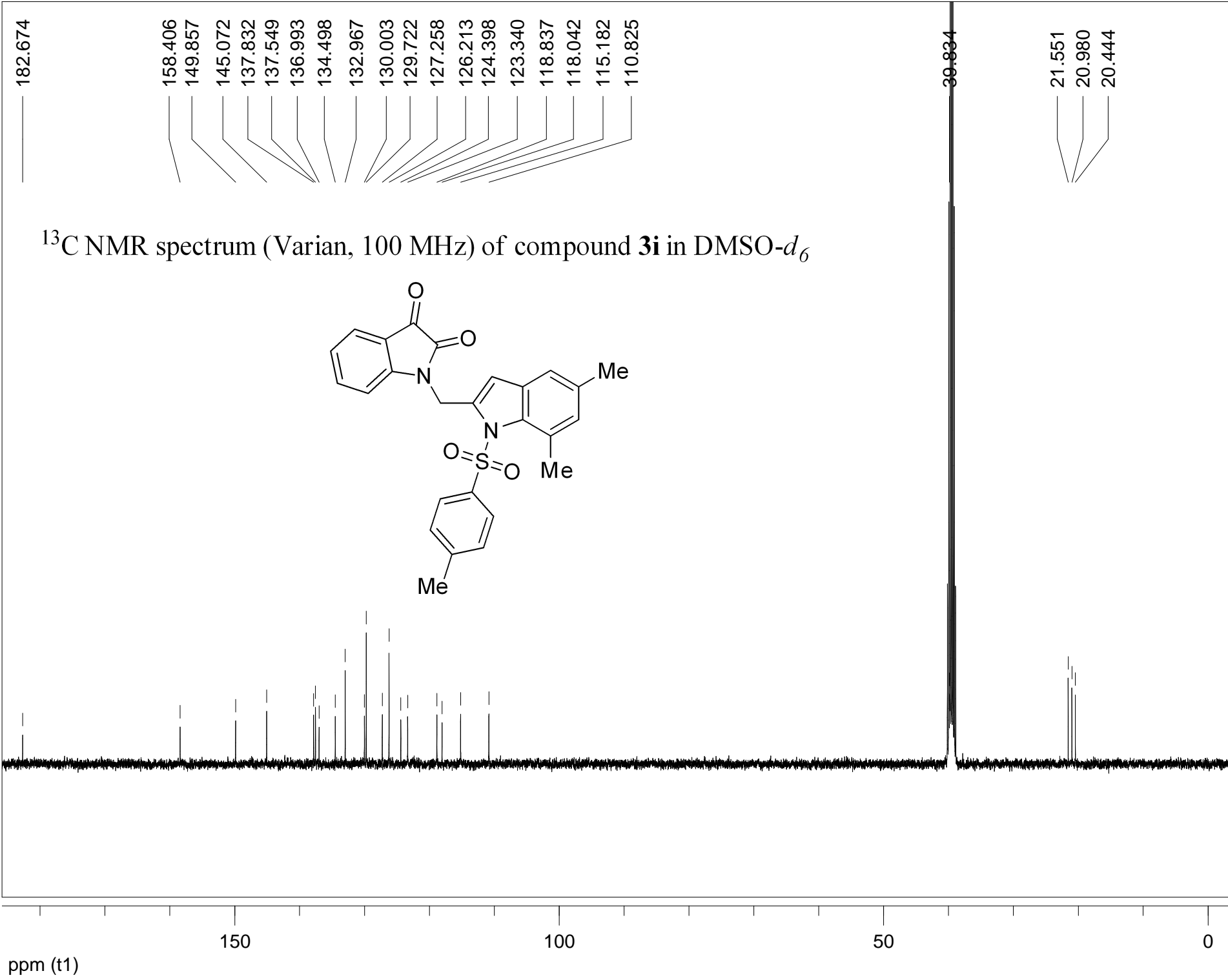
100

50

0

^1H NMR (Varian, 400 MHz) spectrum of compound **3i** in $\text{DMSO-}d_6$



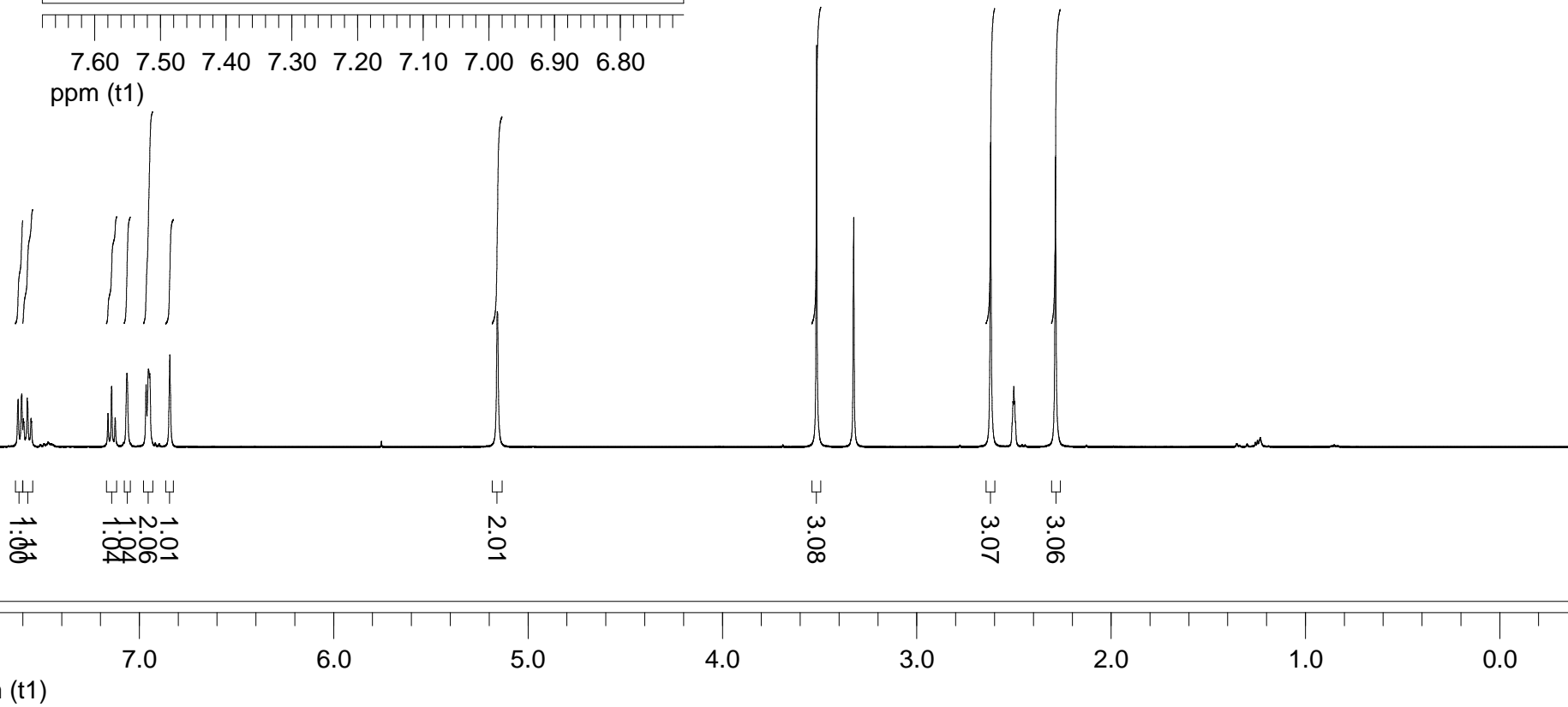
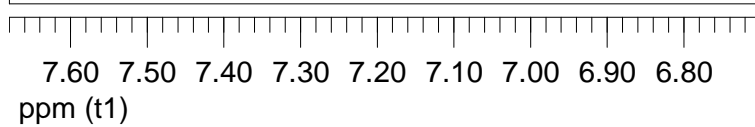
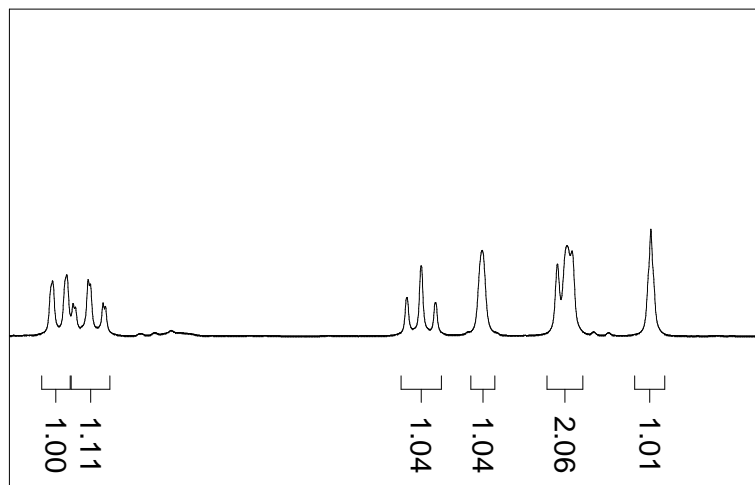
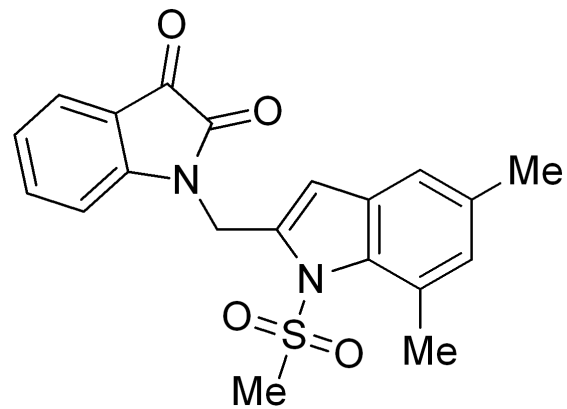


182.674
158.406
149.857
145.072
137.832
137.549
136.993
134.498
132.967
130.003
129.722
127.258
126.213
124.398
123.340
118.837
118.042
115.182
110.825

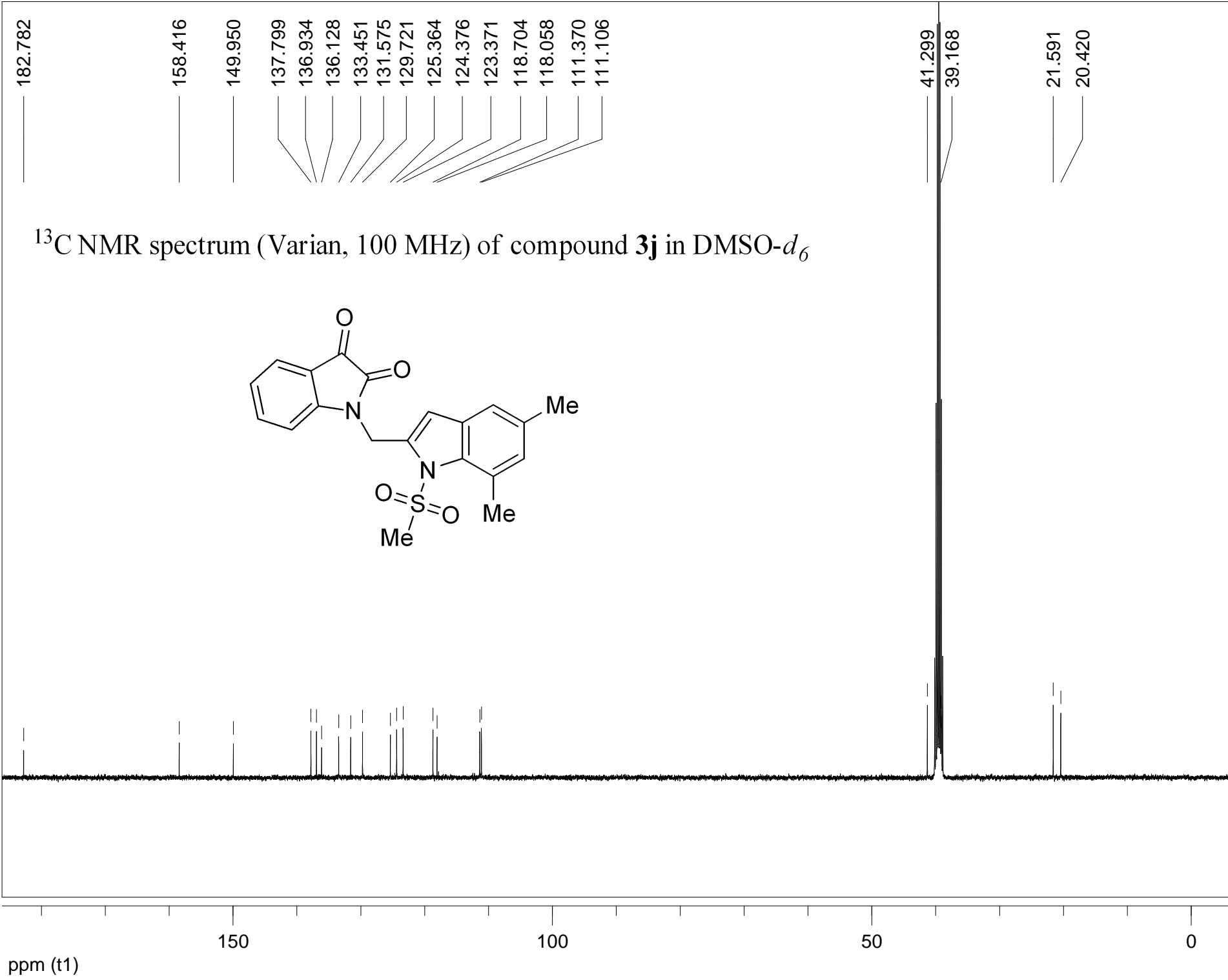
39.834
21.551
20.980
20.444

ppm (t1) 150 100 50 0

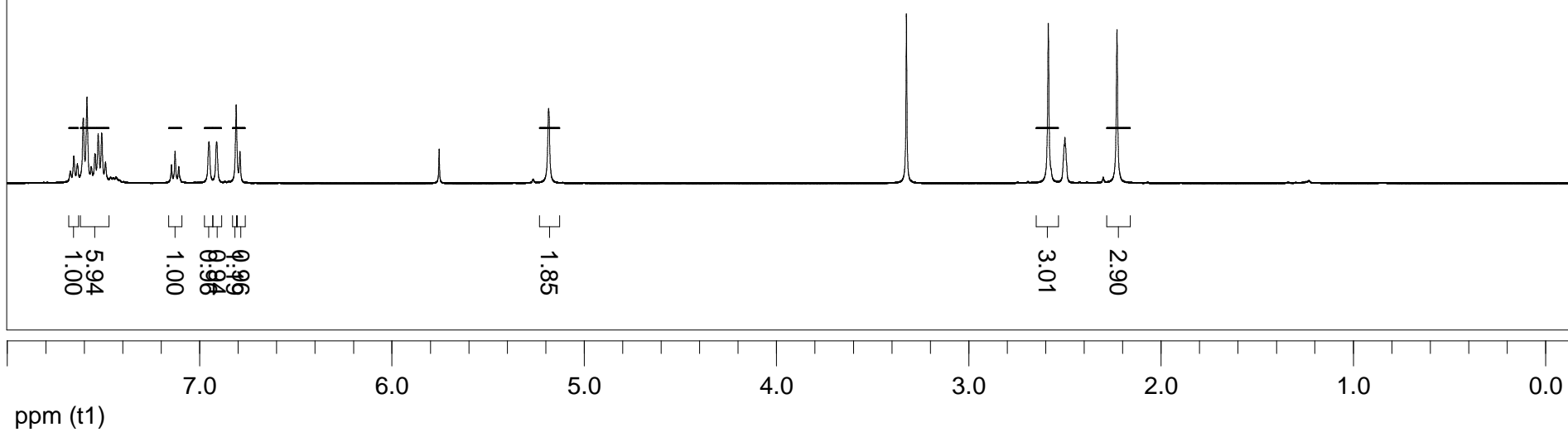
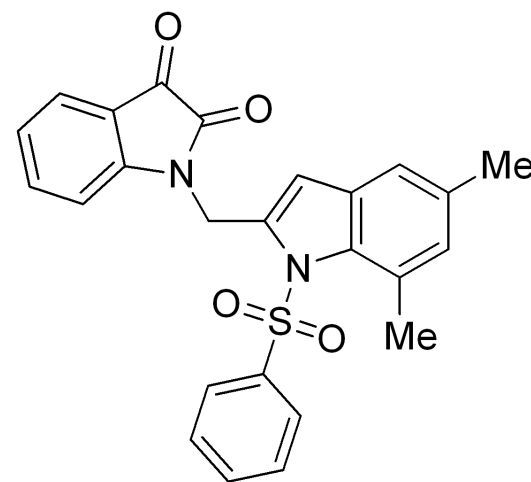
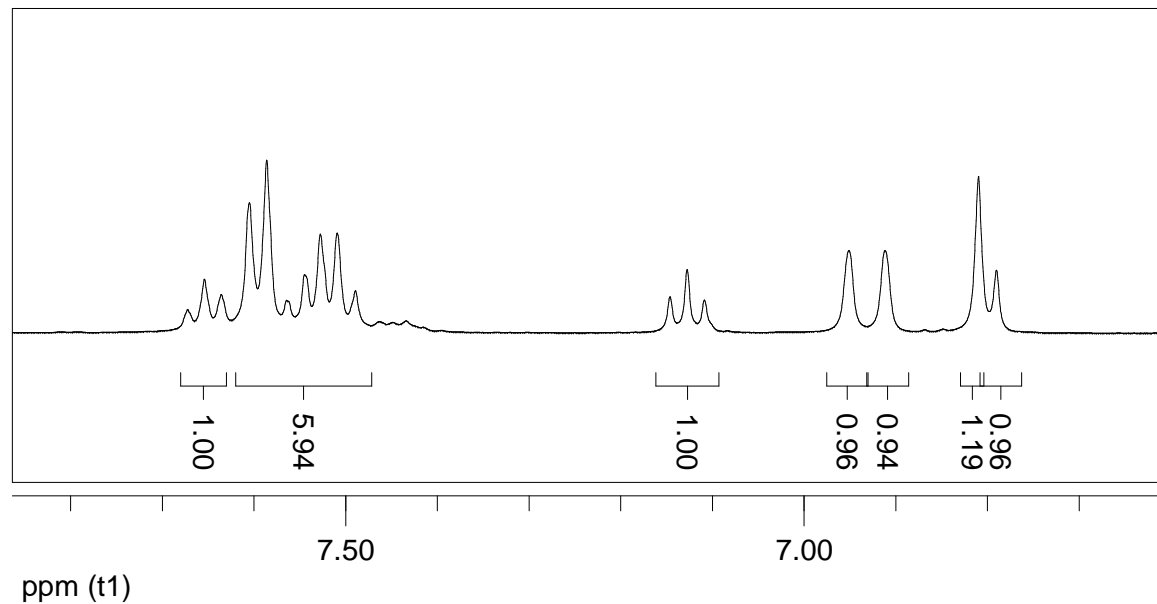
^1H NMR (Varian, 400 MHz) spectrum of compound **3j** in $\text{DMSO-}d_6$



ppm (t1)

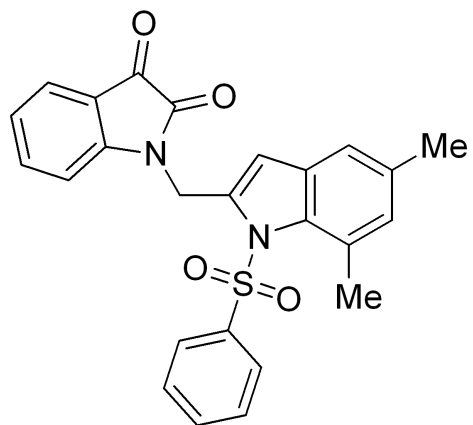


^1H NMR (Varian, 400 MHz) spectrum of compound **3k** in $\text{DMSO-}d_6$

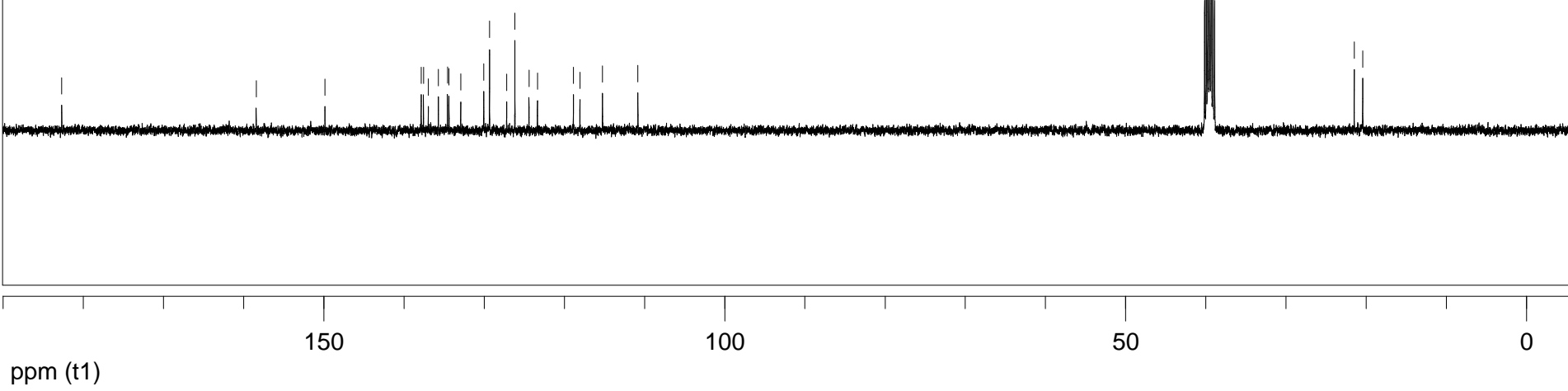


182.660
158.416
149.842
137.834
137.562
136.963
135.696
134.567
134.375
132.909
130.031
129.319
127.181
126.155
124.400
123.342
118.858
118.048
115.238
110.812

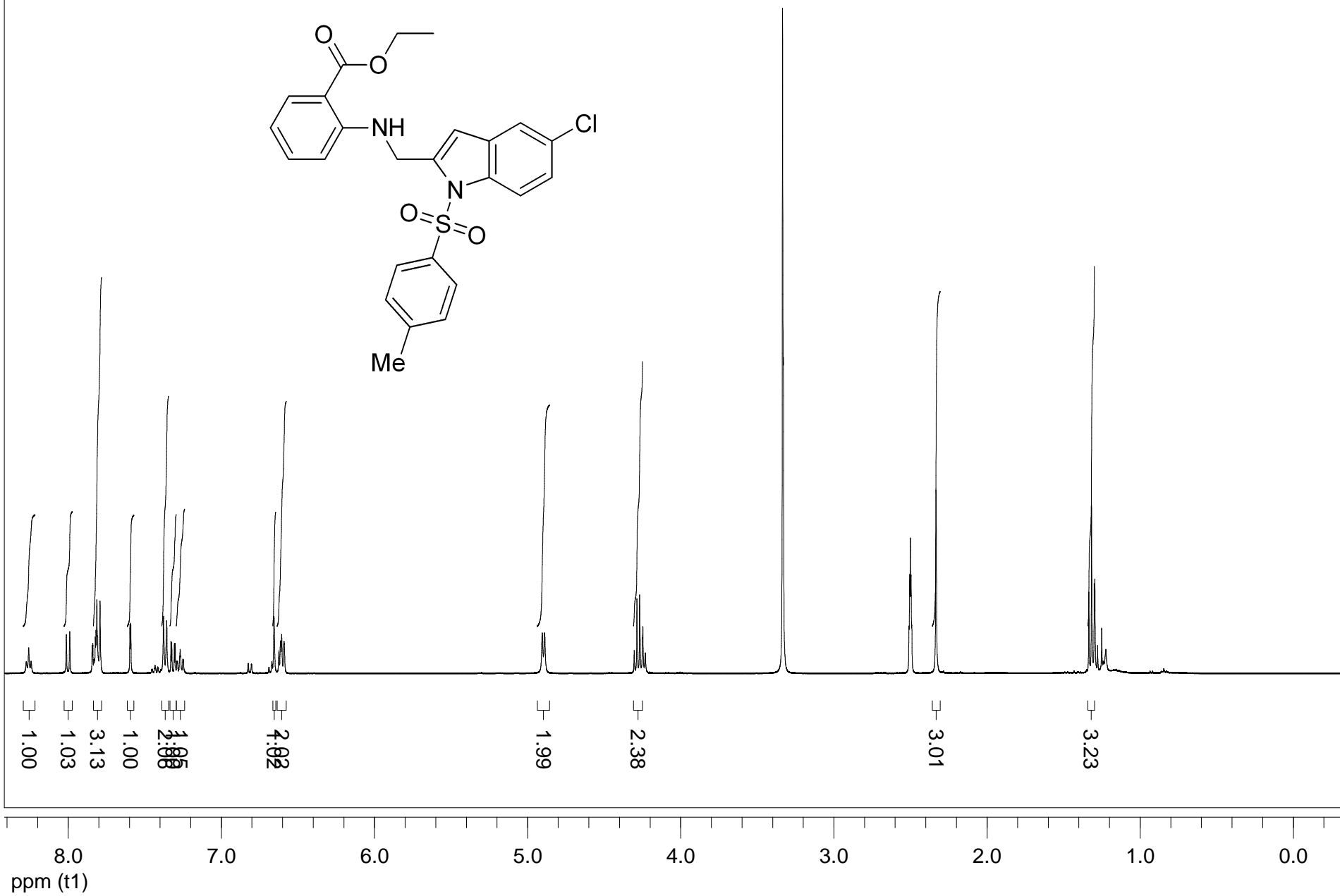
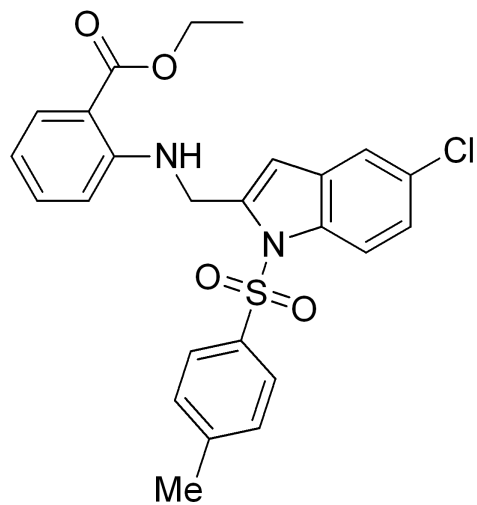
^{13}C NMR spectrum (Varian, 100 MHz) of compound **3k** in $\text{DMSO-}d_6$



39.101
21.490
20.428



^1H NMR (Varian, 400 MHz) spectrum of compound **4a** in $\text{DMSO-}d_6$



167.558
149.720
145.806
140.398
134.934
134.573
134.291
131.237
130.510
130.332
128.312
126.472
124.348
120.438
115.511
115.109
111.700
110.131
109.538

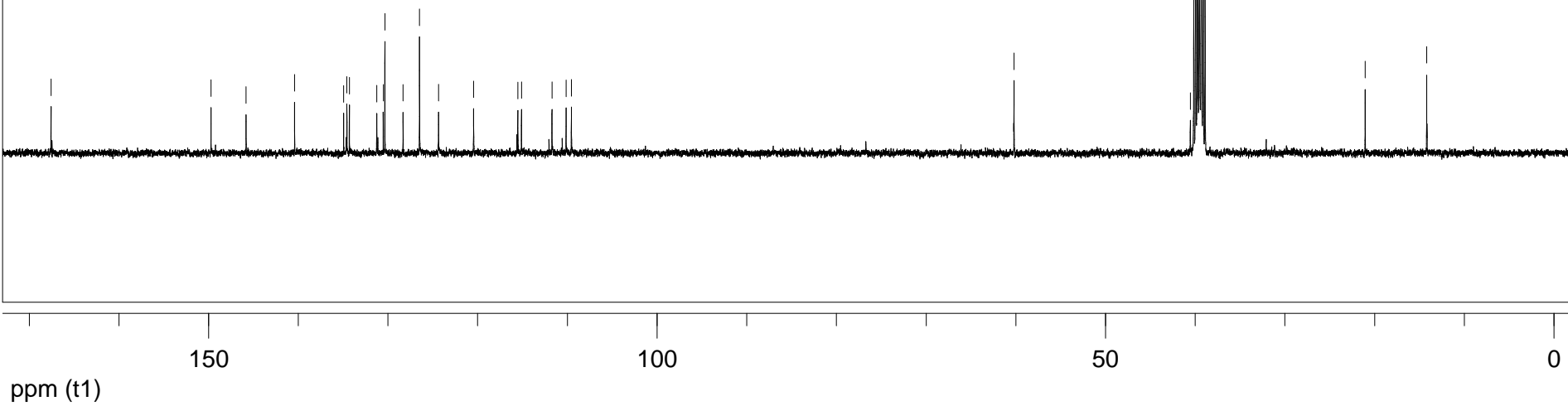
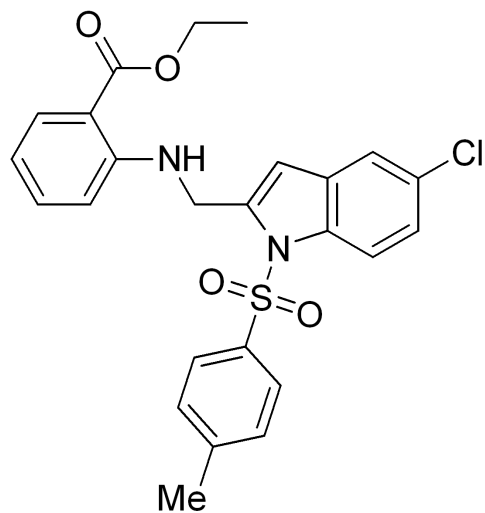
60.183

40.533

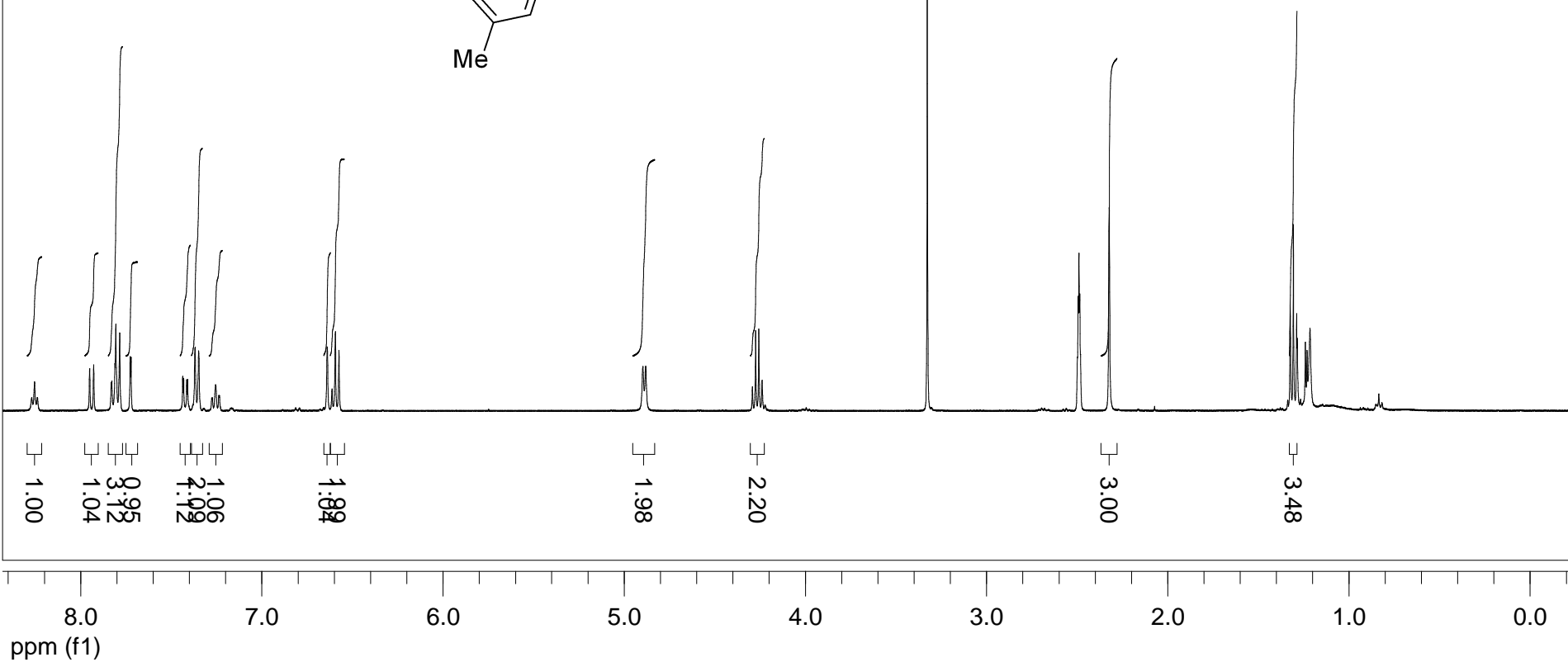
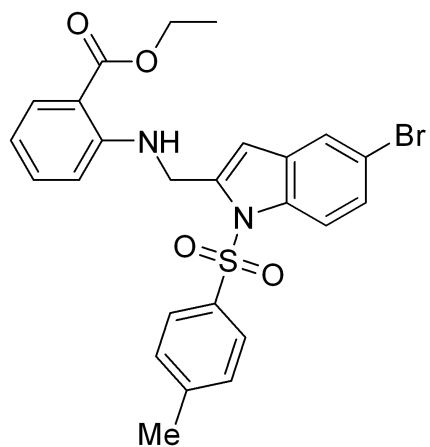
21.034

14.179

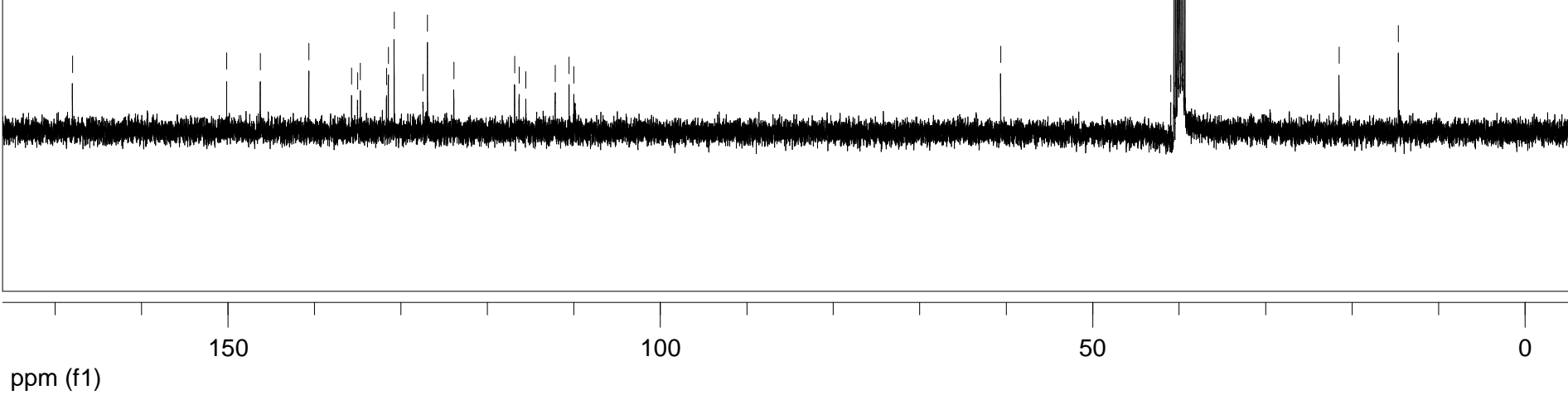
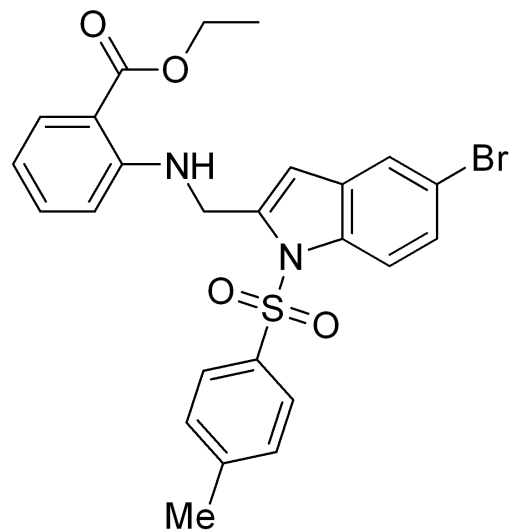
^{13}C NMR spectrum (Varian, 100 MHz) of compound **4a** in $\text{DMSO-}d_6$



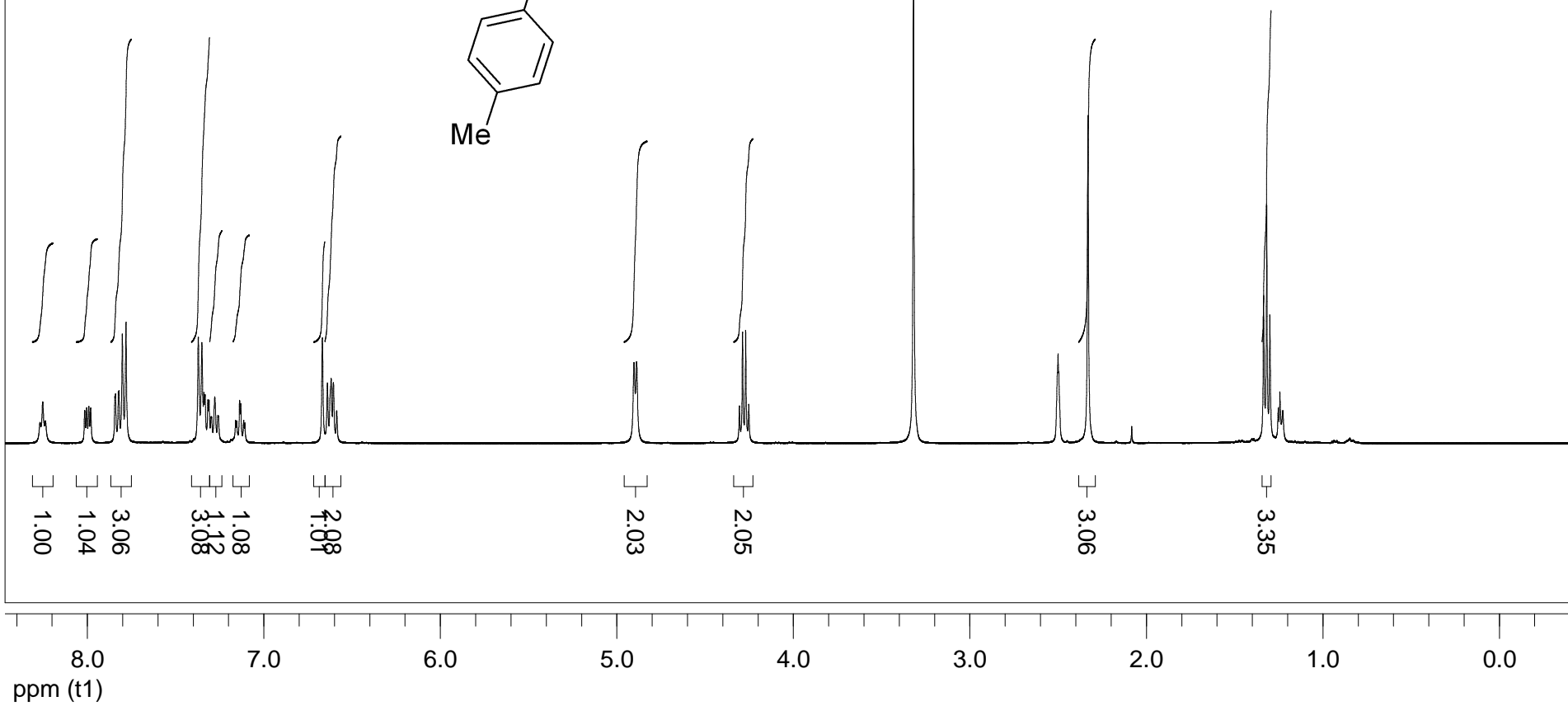
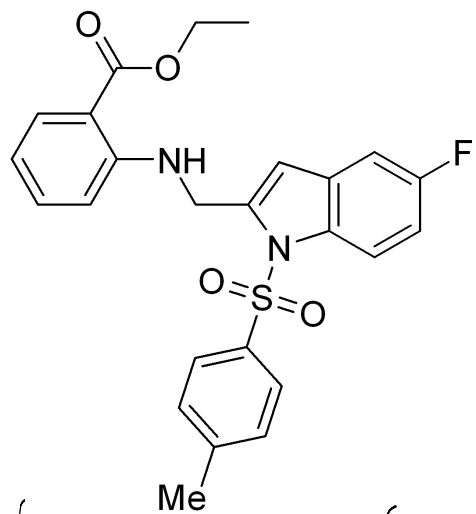
^1H NMR (Varian, 400 MHz) spectrum of compound **4b** in $\text{DMSO-}d_6$



^{13}C NMR spectrum (Varian, 100 MHz) of compound **4b** in $\text{DMSO-}d_6$



^1H NMR (Varian, 400 MHz) spectrum of compound **4c** in $\text{DMSO-}d_6$



167.538
160.197
157.829
149.718
147.880
145.662
140.583
134.547
134.335
132.859
131.800
131.215
130.259
130.167
126.415
115.437
115.341
115.064
112.221
111.968
111.680
110.118
110.063
106.660
106.421

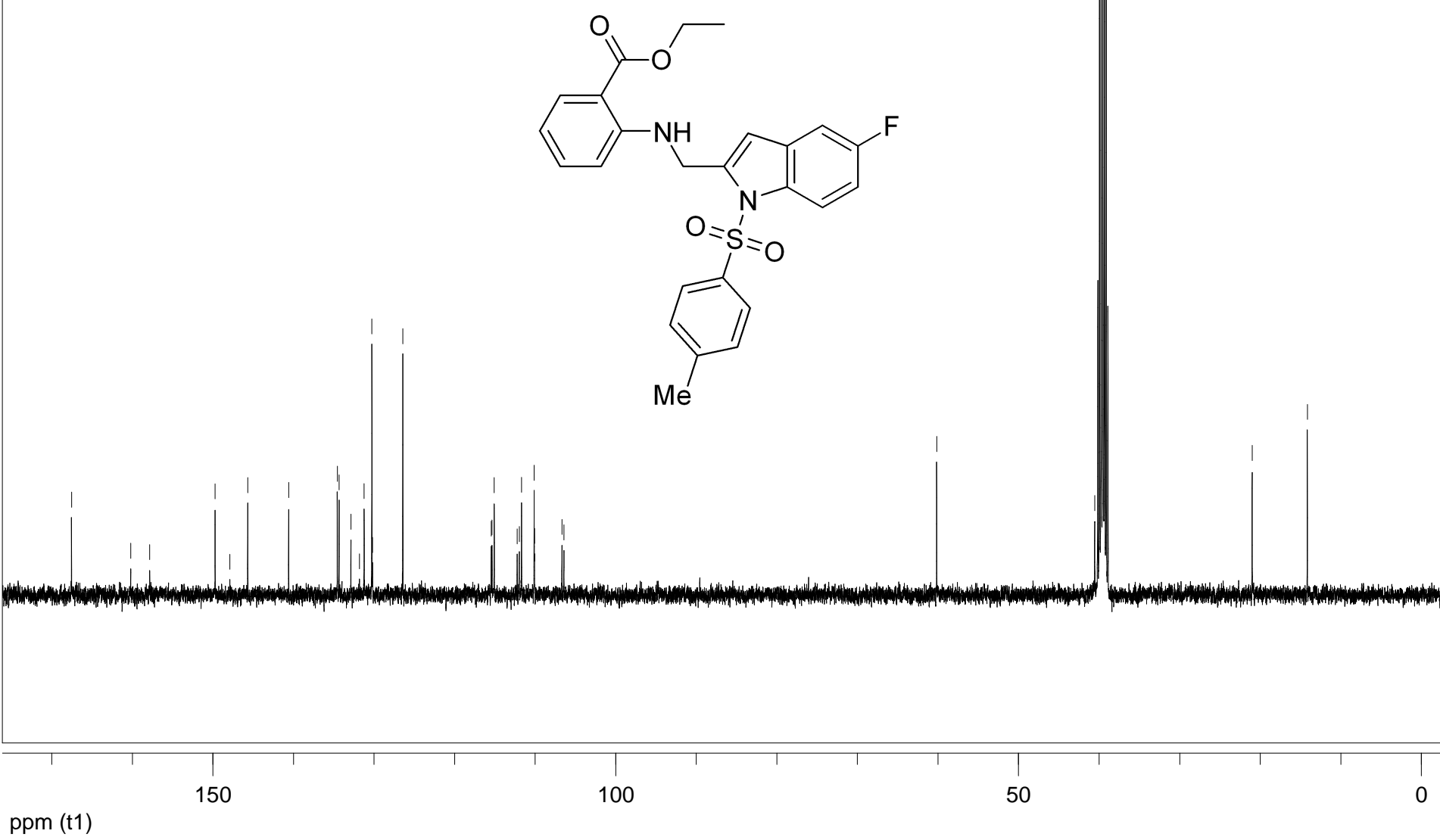
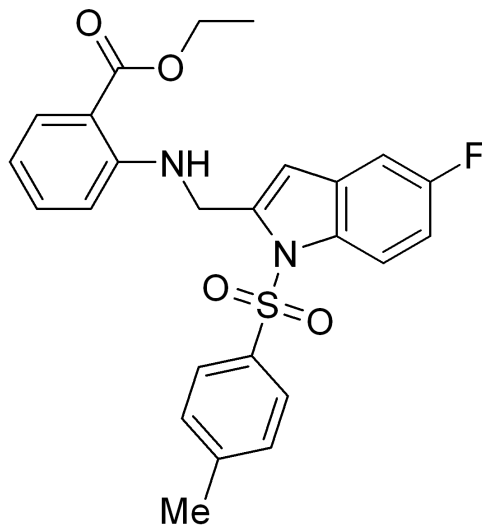
60.147

40.537

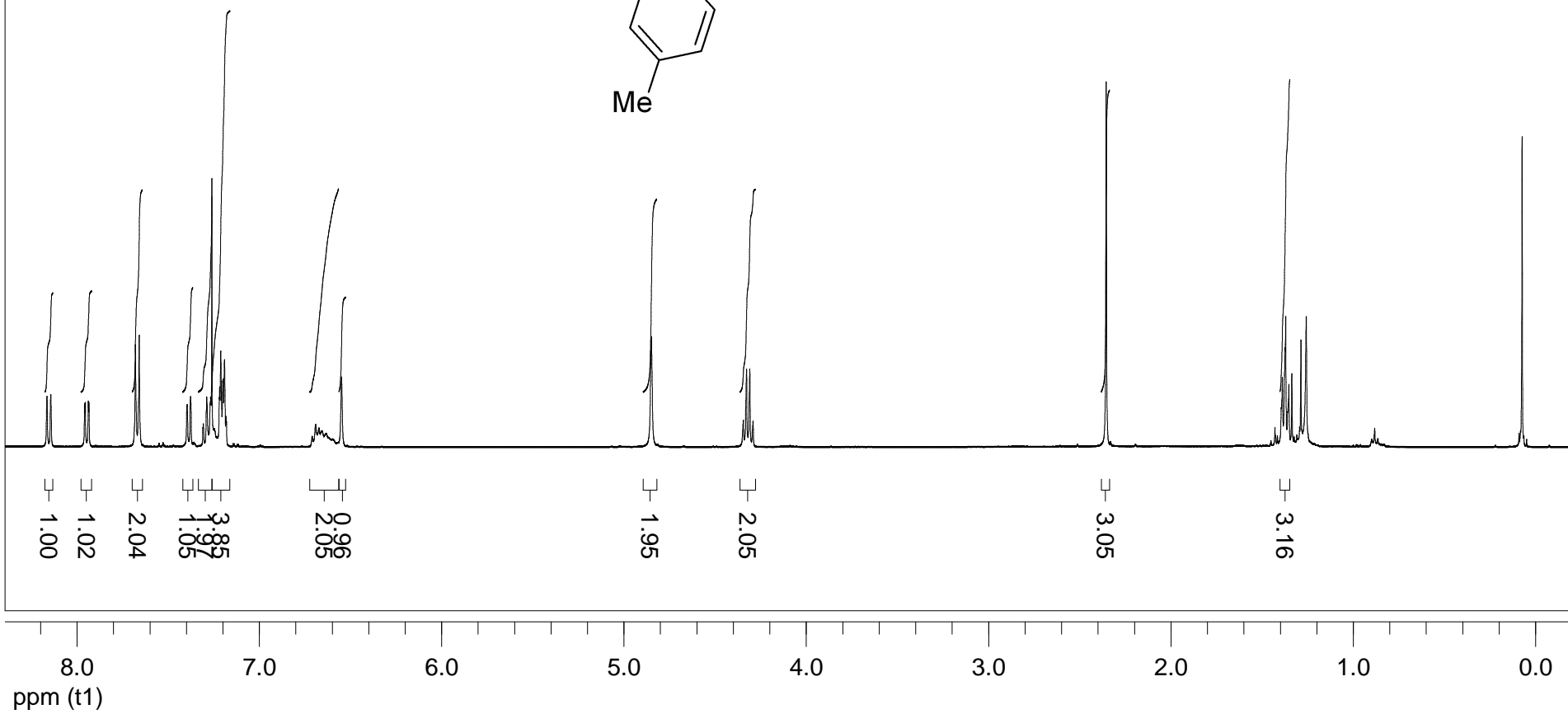
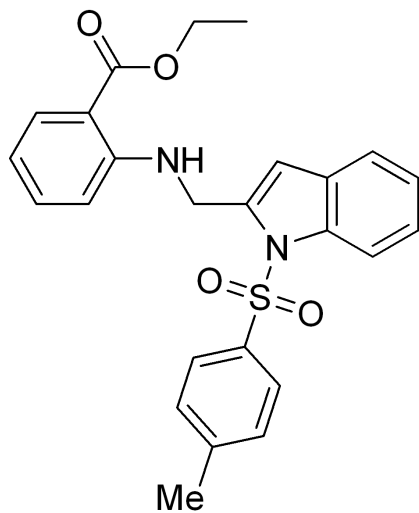
20.993

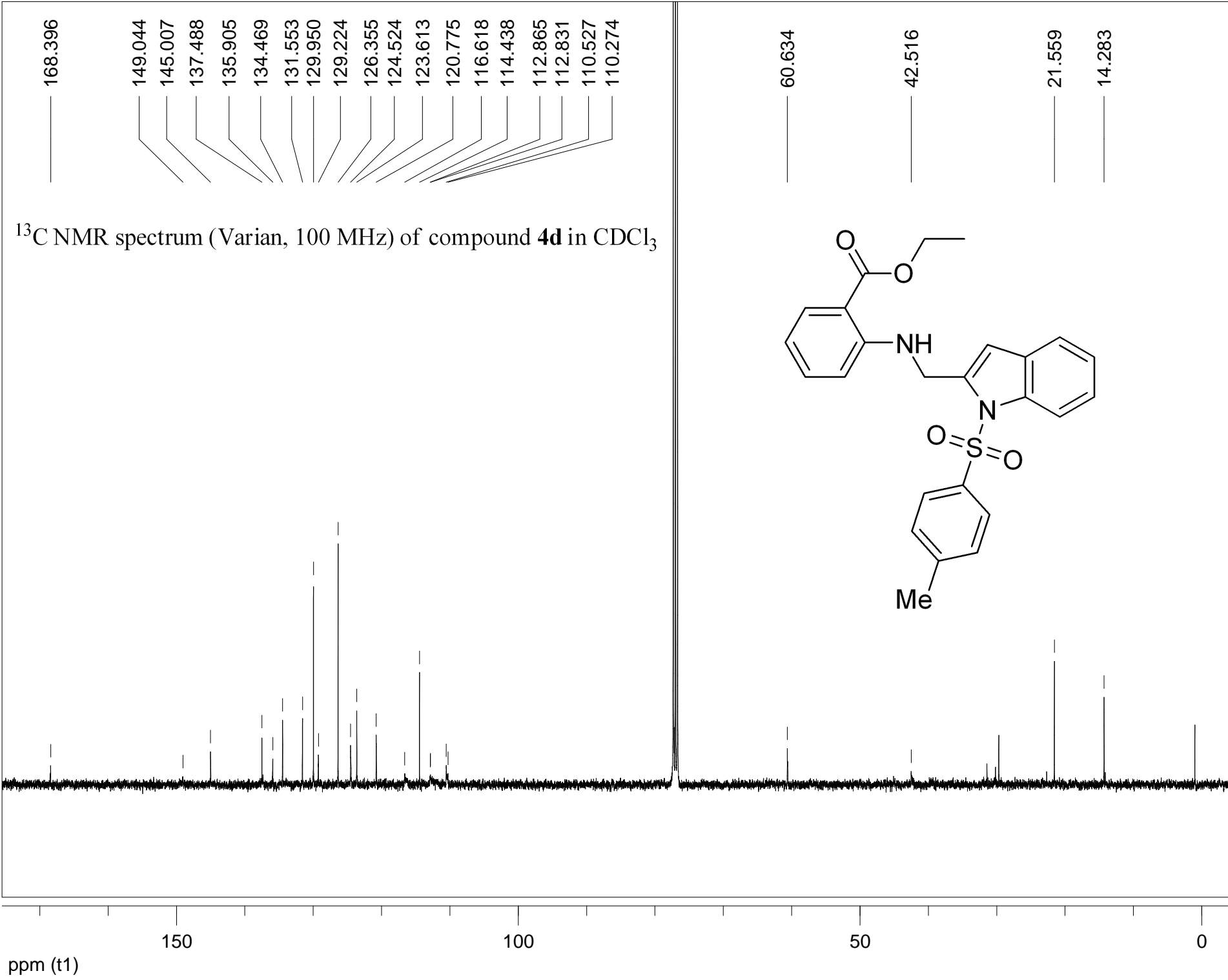
14.147

^{13}C NMR spectrum (Varian, 100 MHz) of compound **4c** in $\text{DMSO-}d_6$

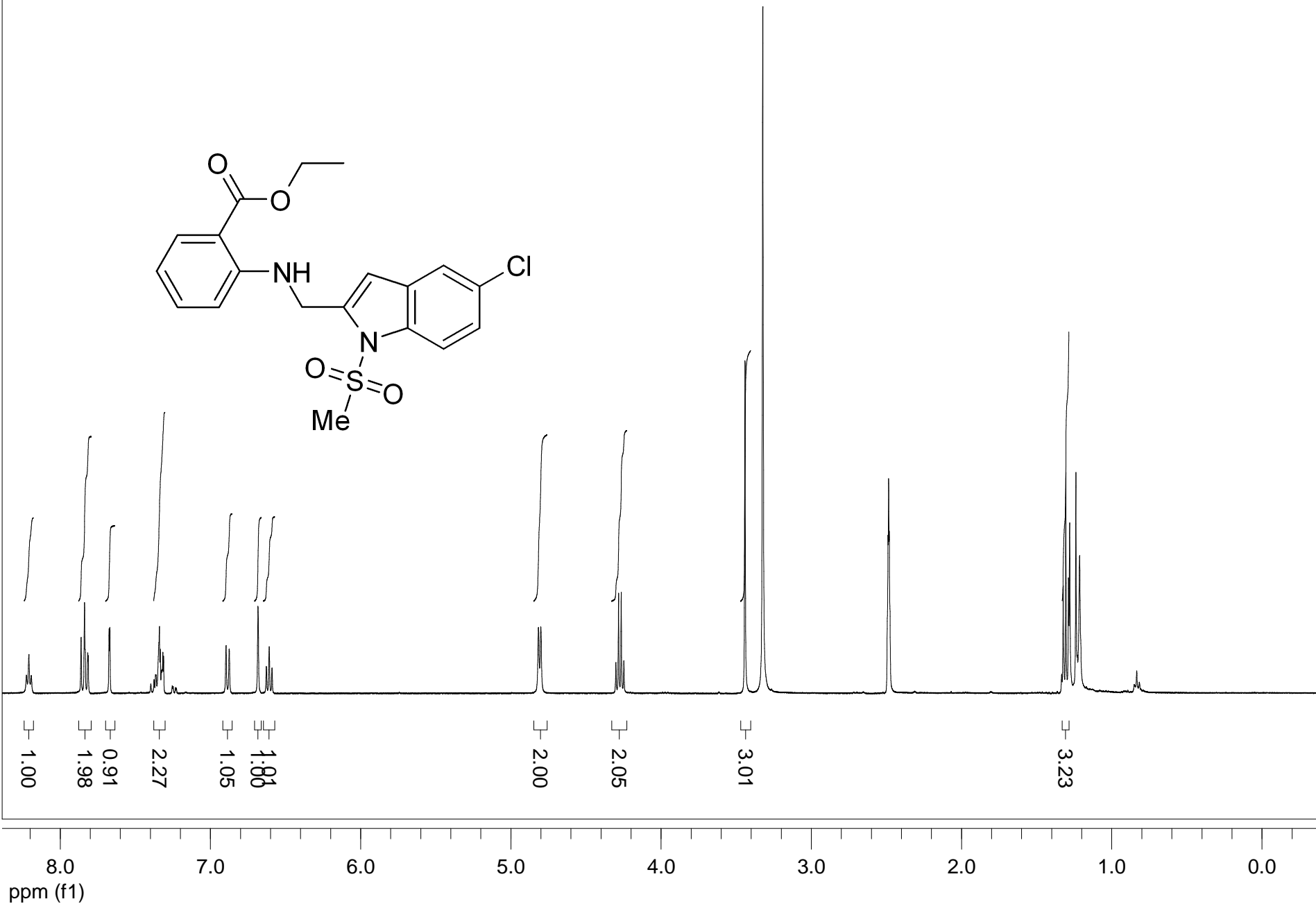
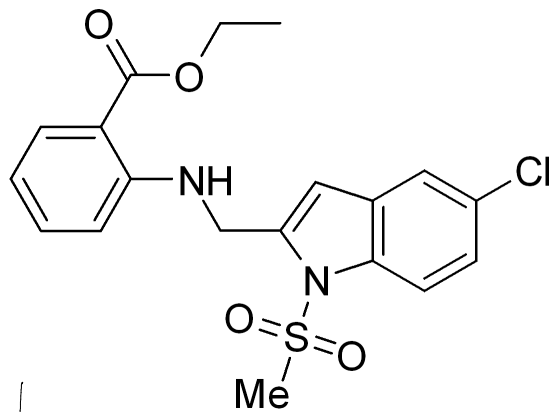


^1H NMR (Varian, 400 MHz) spectrum of compound **4d** in CDCl_3





^1H NMR (Varian, 400 MHz) spectrum of compound **4e** in $\text{DMSO-}d_6$



168.125
150.306
140.728
135.246
135.169
131.670
130.578
128.336
124.482
120.693
115.572
115.492
112.390
110.393
108.547

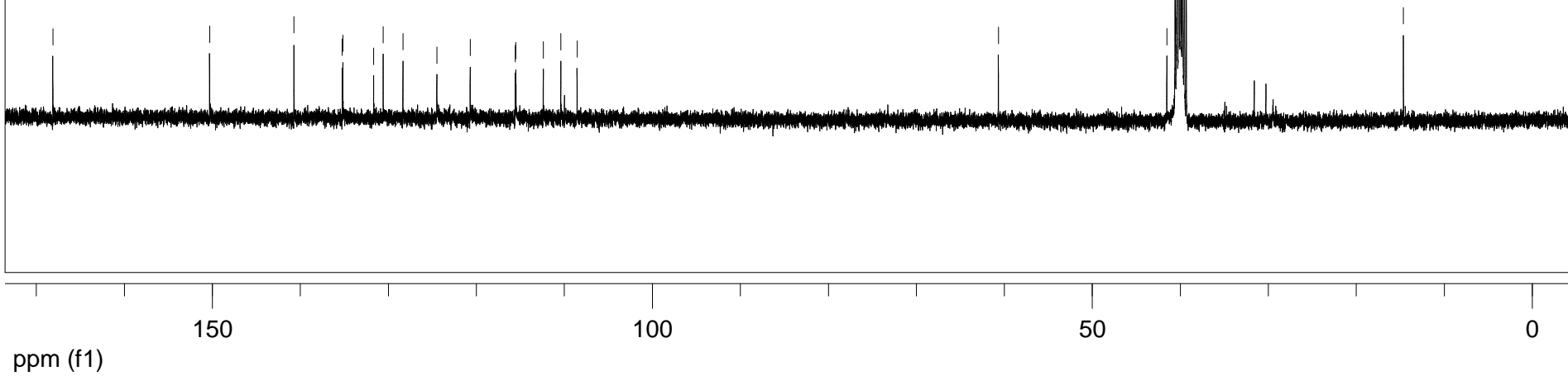
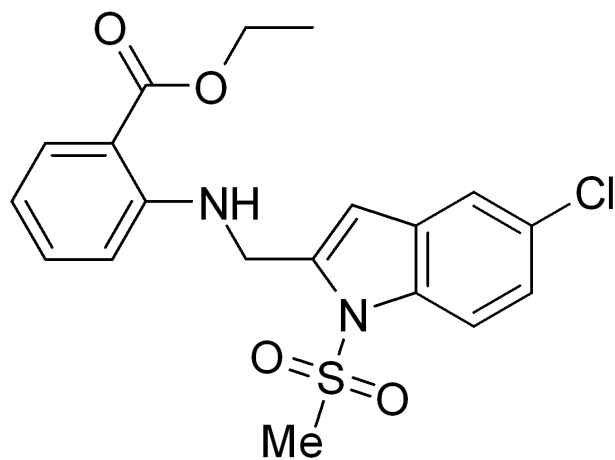
60.671

41.528

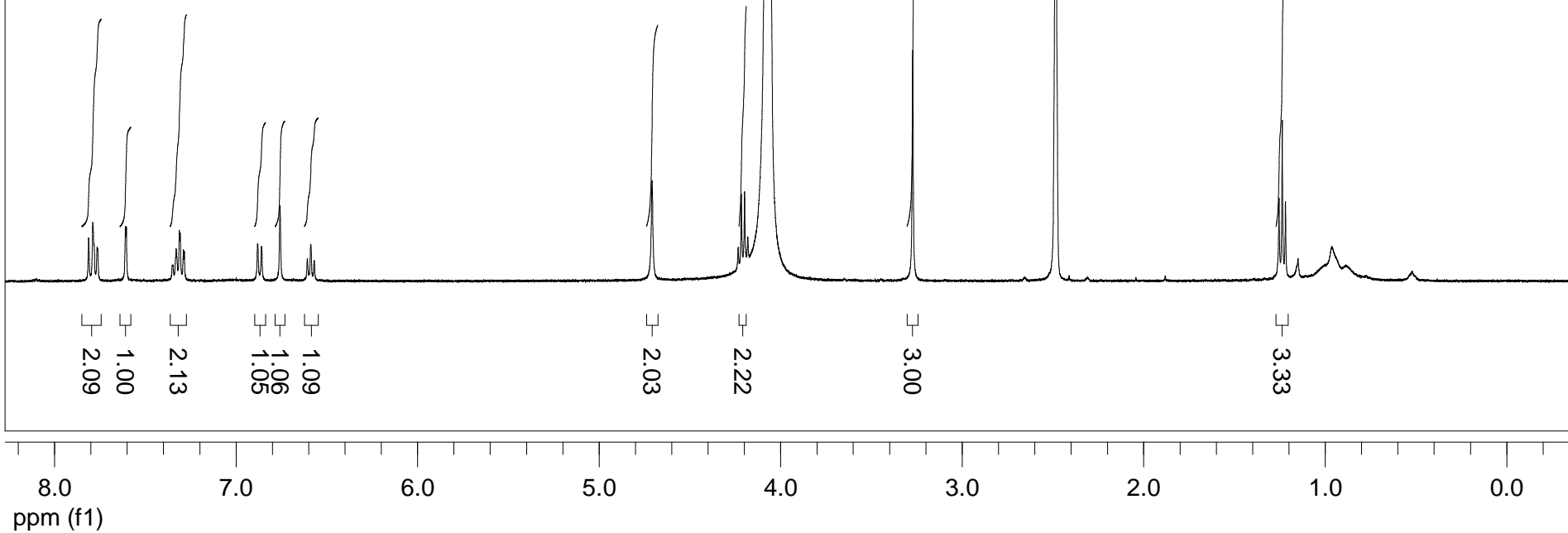
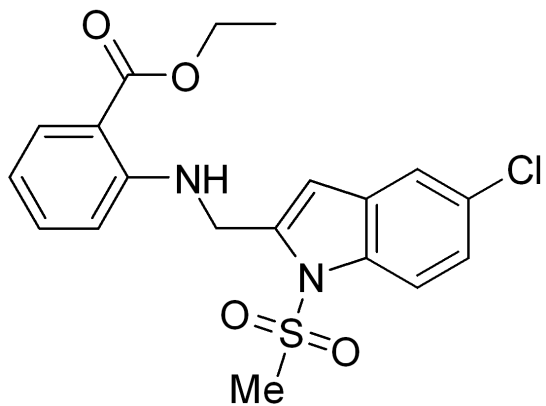
40.451

14.636

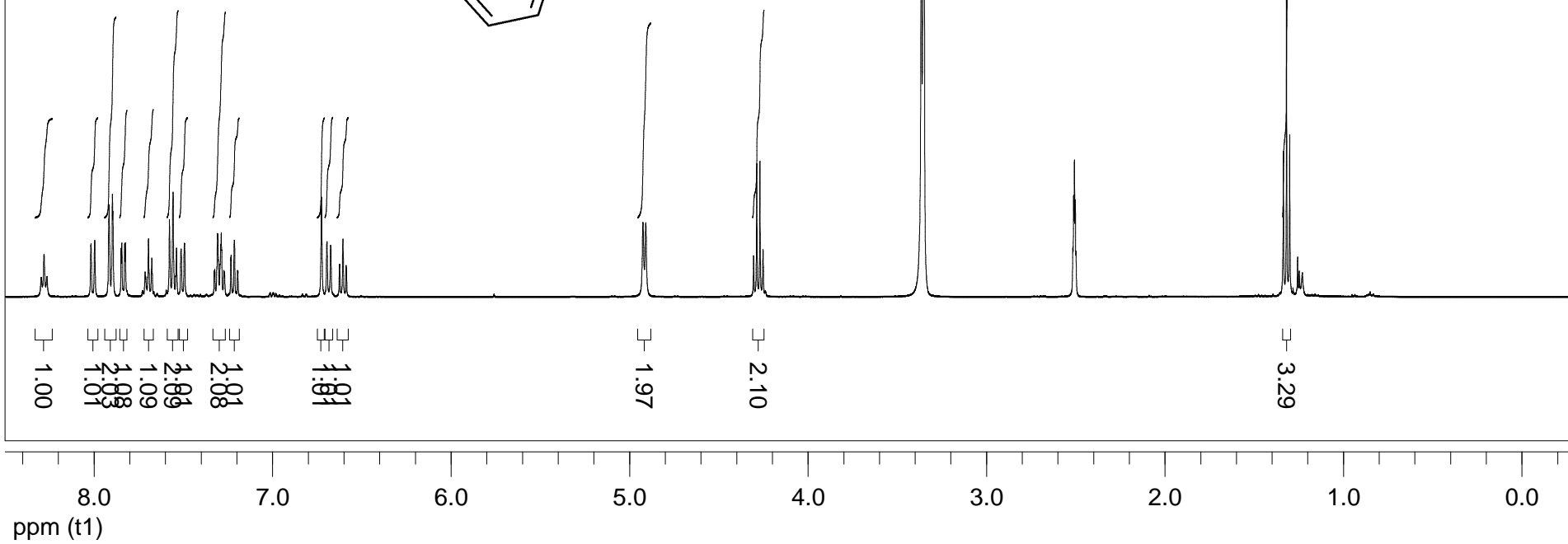
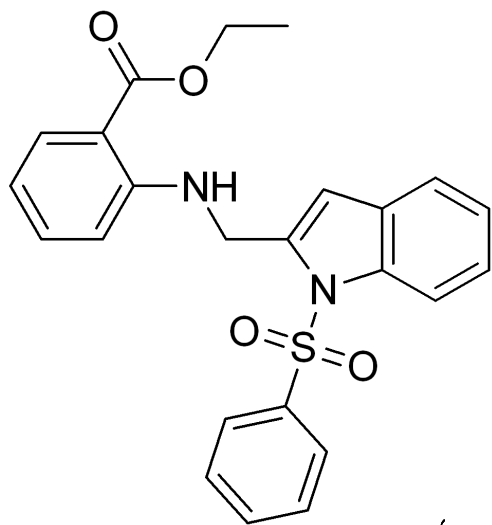
^{13}C NMR spectrum (Varian, 100 MHz) of compound **4e** in $\text{DMSO-}d_6$



D₂O exchange spectrum of compound **4e** in DMSO-*d*₆



^1H NMR (Varian, 400 MHz) spectrum of compound **4f** in $\text{DMSO-}d_6$



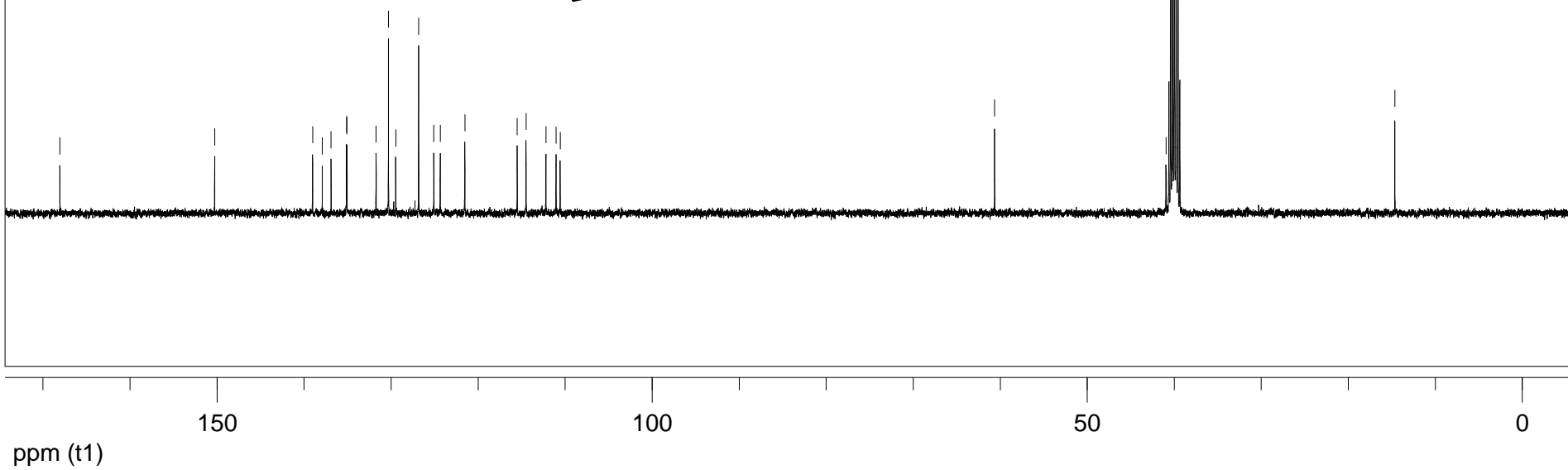
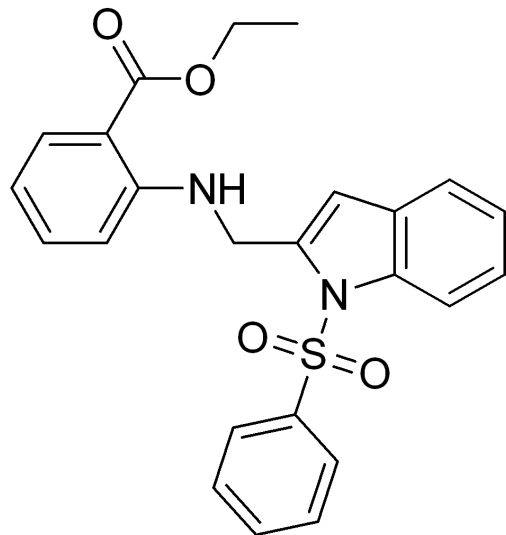
168.043
150.264
139.011
137.895
136.881
135.115
135.054
131.714
130.290
129.451
126.821
125.073
124.337
121.516
115.495
114.483
112.202
111.029
110.562

60.636

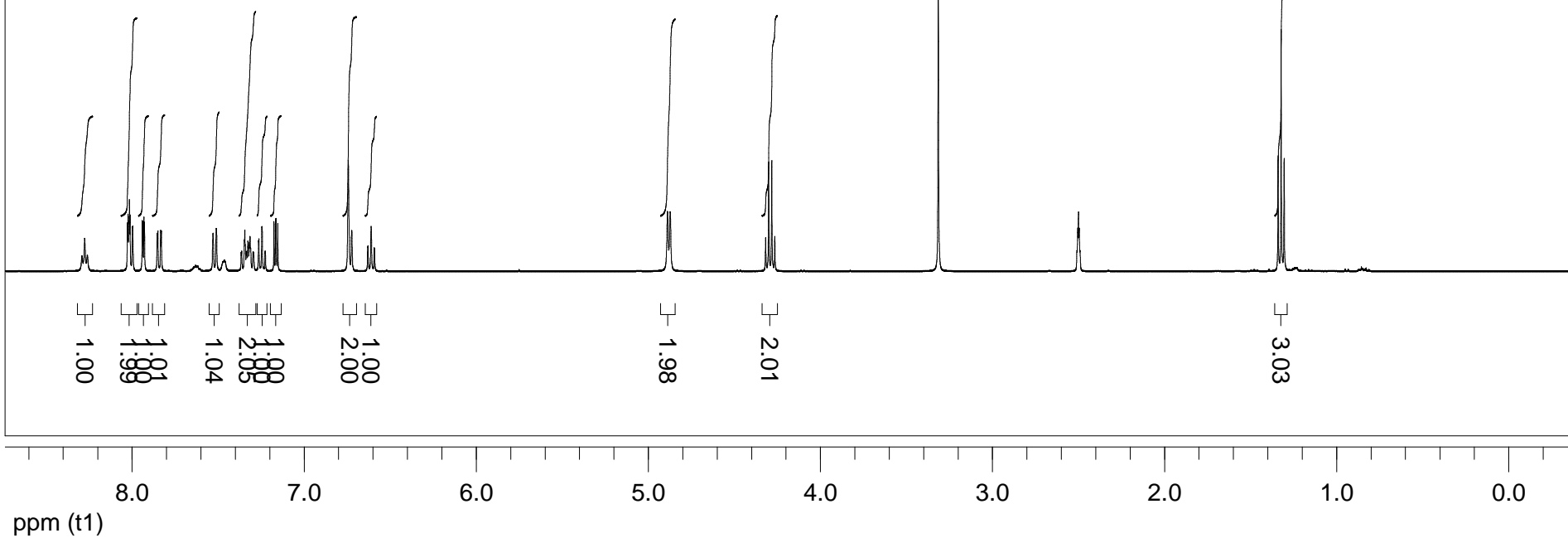
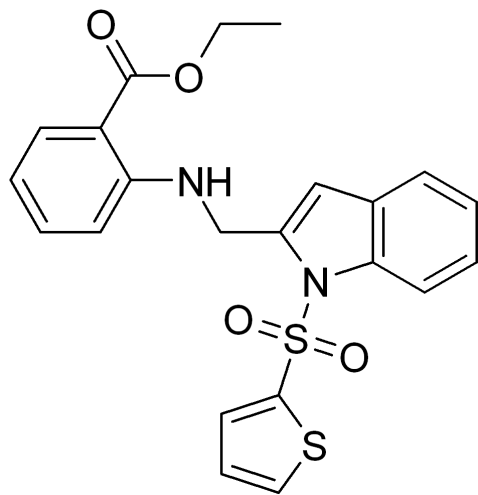
40.946

14.650

^{13}C NMR spectrum (Varian, 100 MHz) of compound **4f** in $\text{DMSO-}d_6$



^1H NMR (Varian, 400 MHz) spectrum of compound **4g** in $\text{DMSO-}d_6$



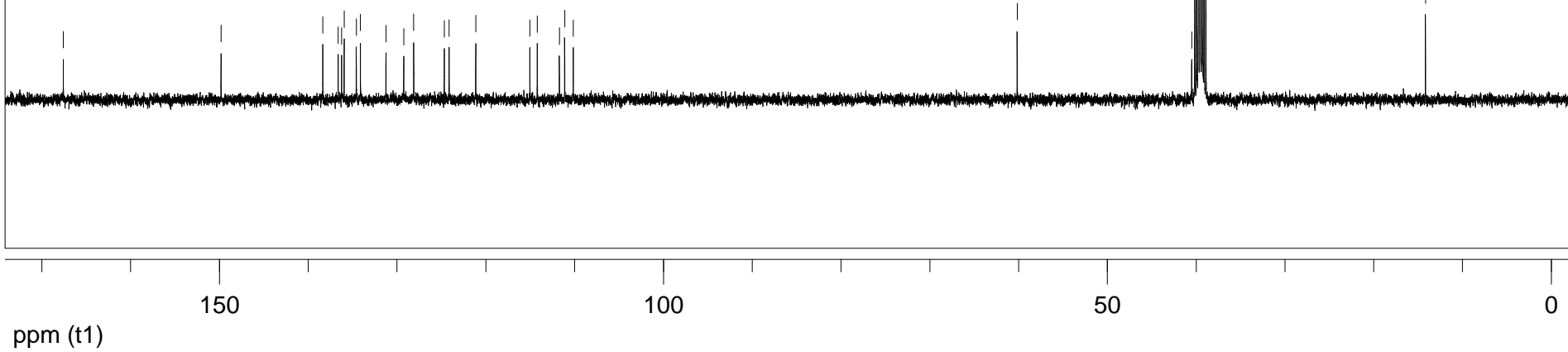
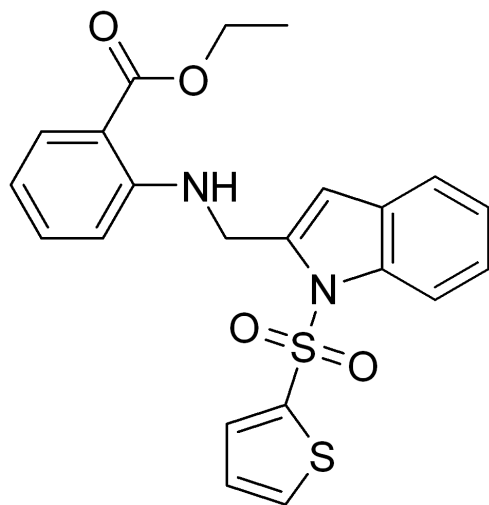
167.573
149.806
138.342
136.621
136.231
135.947
134.578
134.117
131.237
129.240
128.112
124.665
124.125
121.121
115.028
114.195
111.706
111.109
110.147

60.152

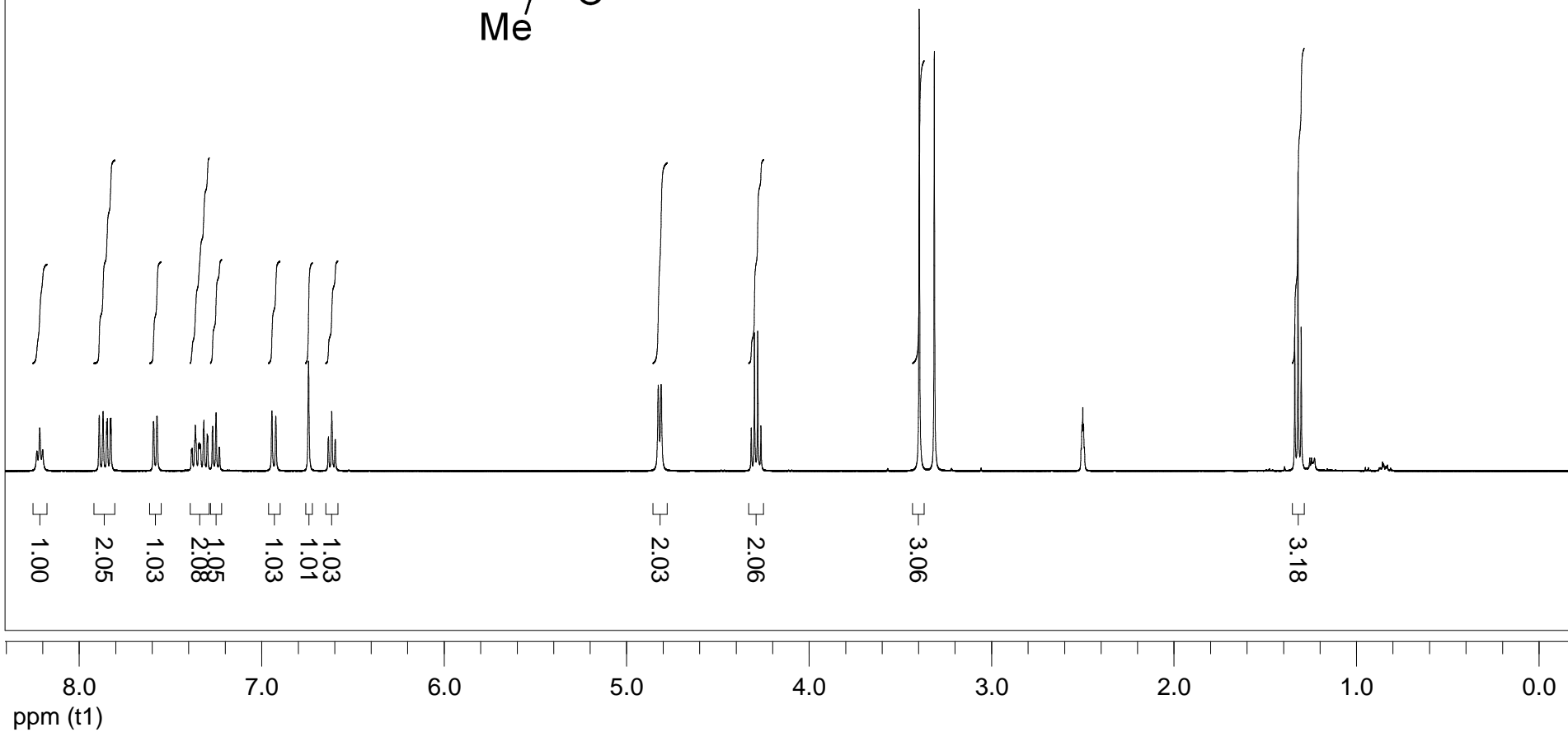
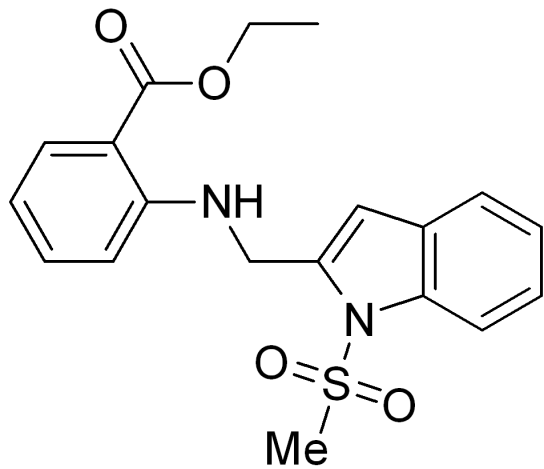
40.486

14.156

^{13}C NMR spectrum (Varian, 100 MHz) of compound **4g** in $\text{DMSO-}d_6$



^1H NMR (Varian, 400 MHz) spectrum of compound **4h** in $\text{DMSO-}d_6$



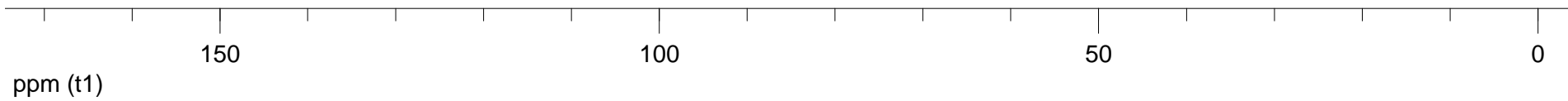
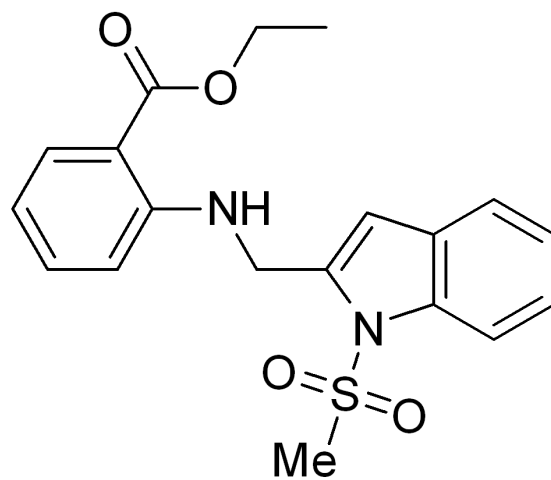
167.681
149.909
138.381
136.282
134.665
131.213
128.638
124.246
123.364
120.870
115.015
113.496
111.930
109.950
108.997

60.170

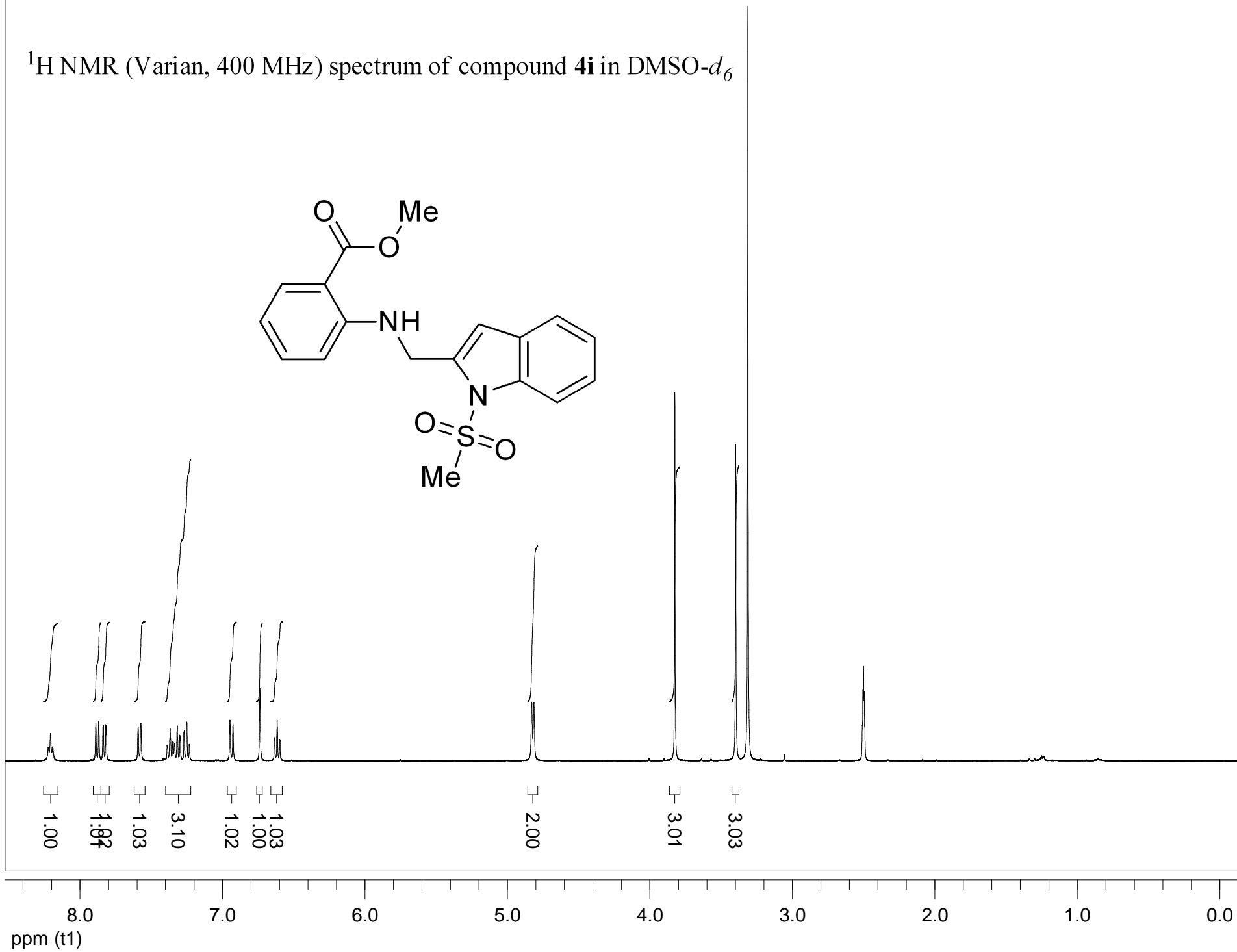
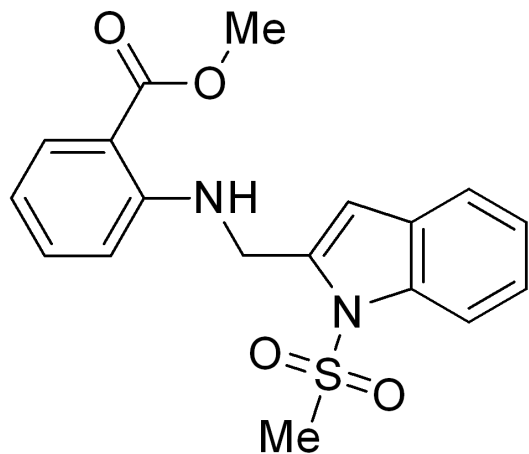
40.840
40.148

14.150

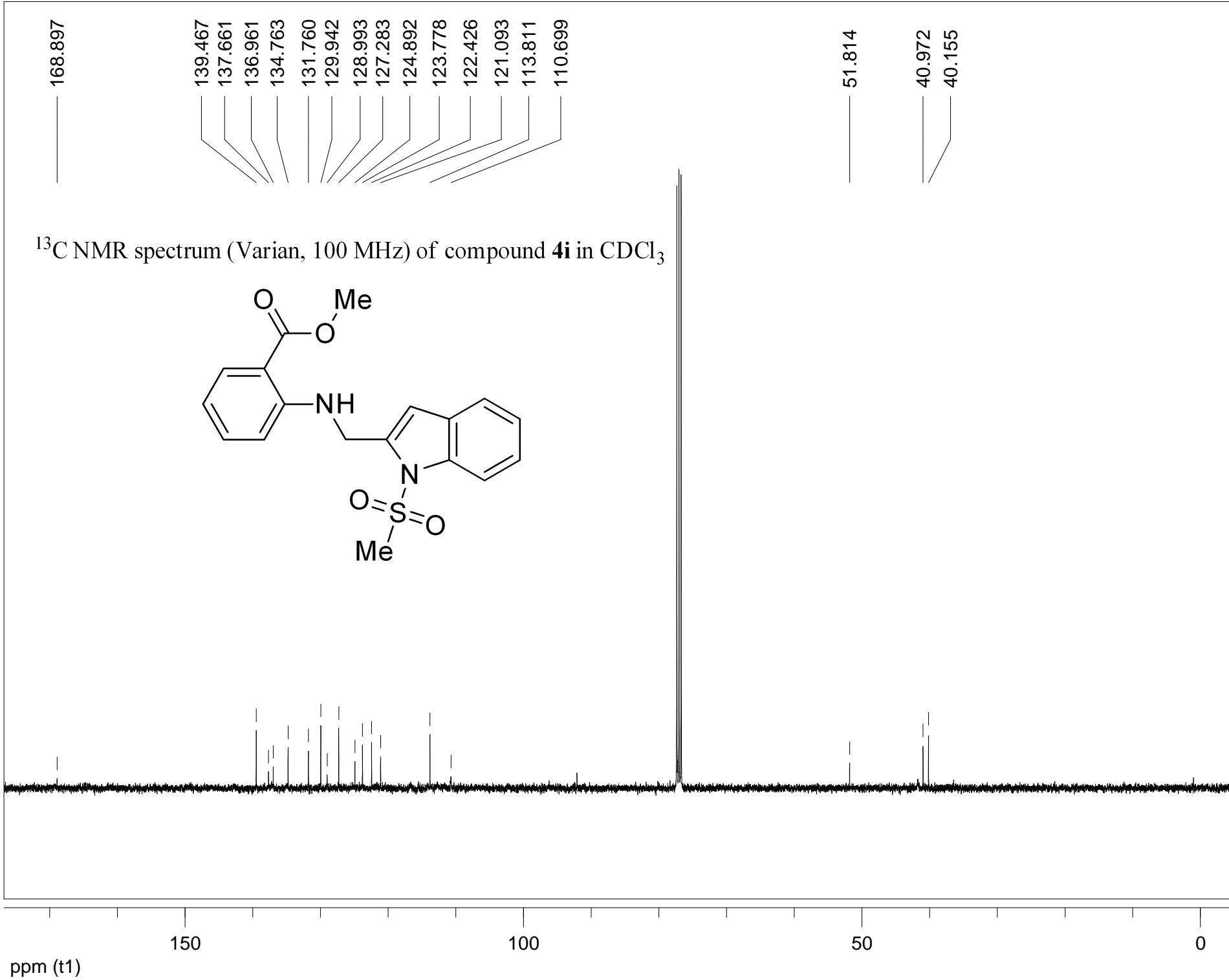
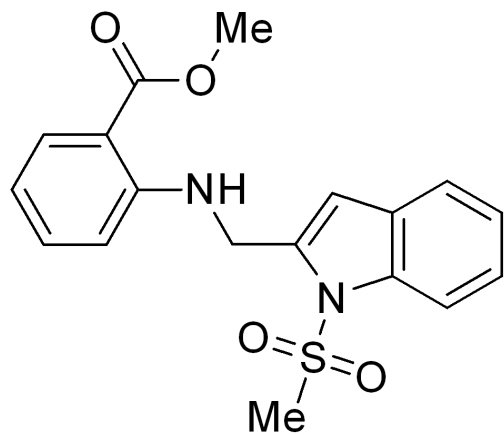
^{13}C NMR spectrum (Varian, 100 MHz) of compound **4h** in $\text{DMSO-}d_6$



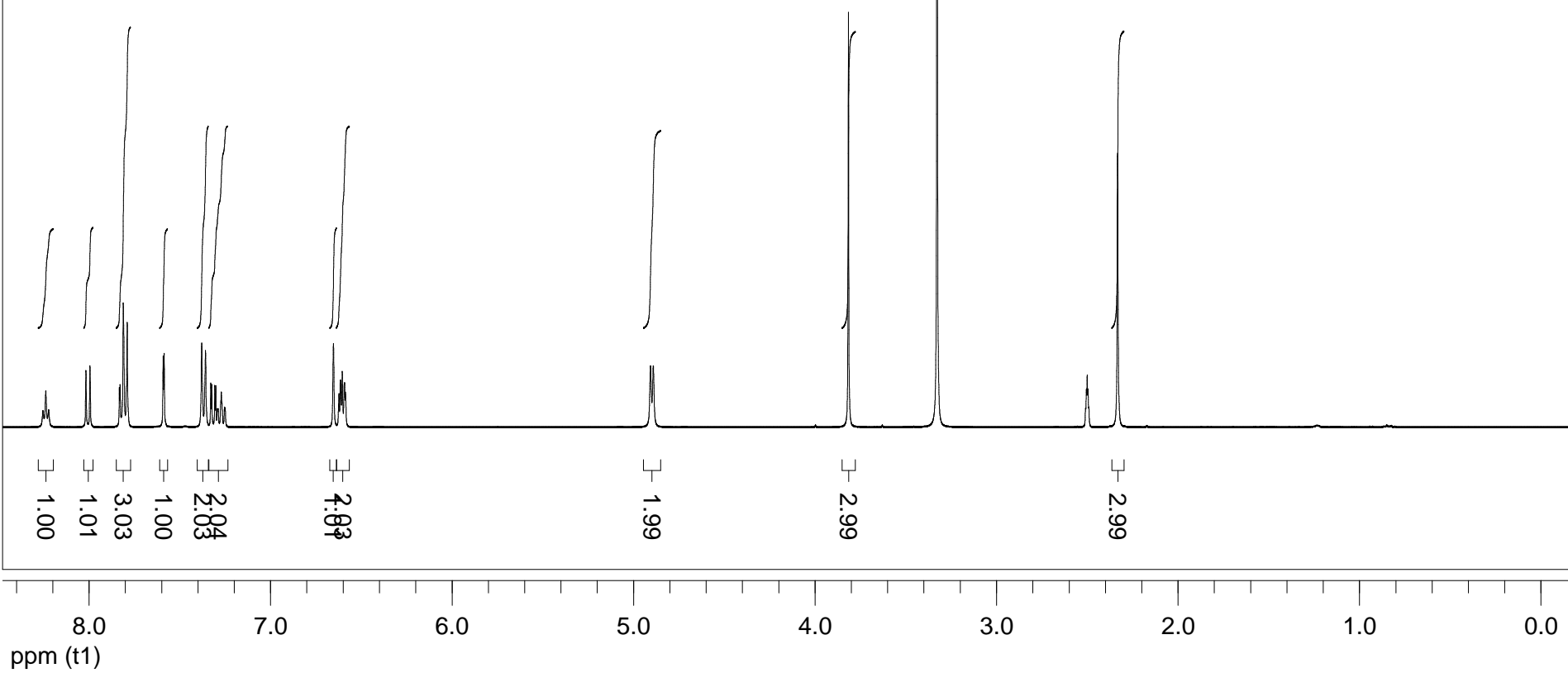
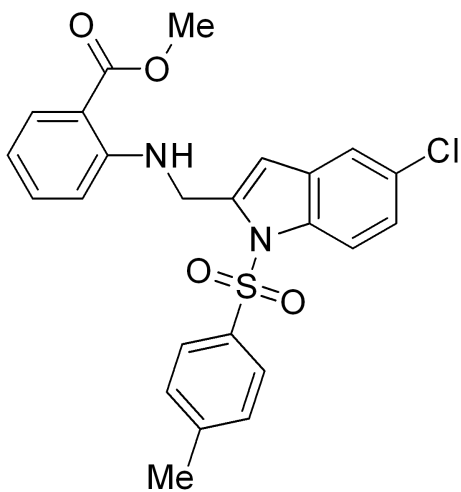
^1H NMR (Varian, 400 MHz) spectrum of compound **4i** in $\text{DMSO-}d_6$



^{13}C NMR spectrum (Varian, 100 MHz) of compound **4i** in CDCl_3



^1H NMR (Varian, 400 MHz) spectrum of compound **4j** in $\text{DMSO-}d_6$



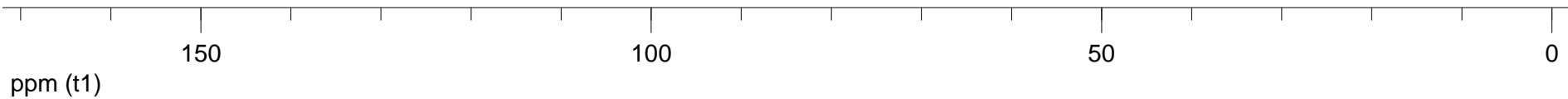
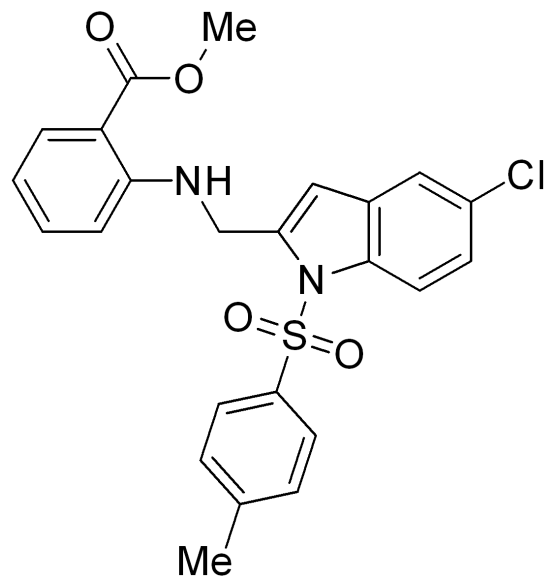
167.953
149.662
145.784
140.374
134.941
134.615
134.305
131.232
130.488
130.315
128.300
126.435
124.330
120.409
115.492
115.140
111.702
109.942
109.494

51.611

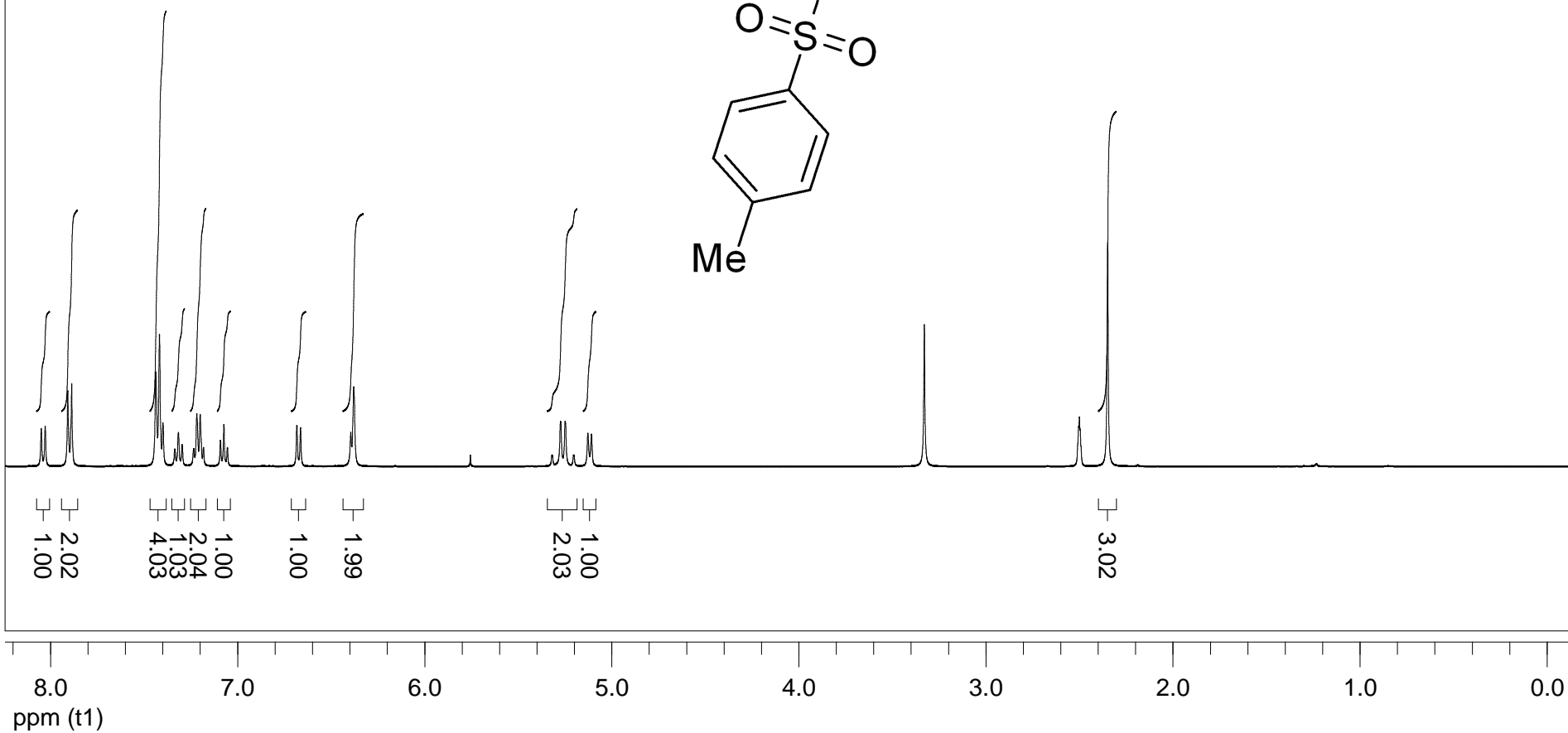
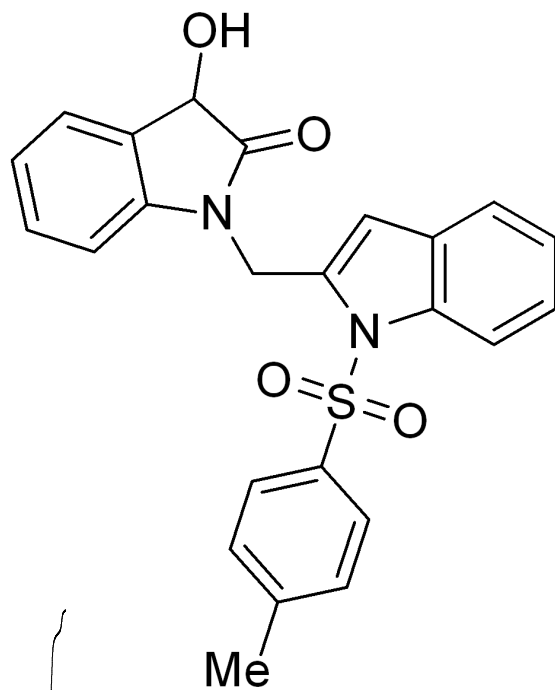
40.532

21.010

^{13}C NMR spectrum (Varian, 100 MHz) of compound **4j** in $\text{DMSO-}d_6$



^1H NMR (Varian, 400 MHz) spectrum of compound **5a** in $\text{DMSO-}d_6$



176.186

145.828

142.277

136.394

135.163

134.270

130.397

129.083

128.916

128.717

126.457

124.773

124.664

123.955

122.569

120.841

113.985

108.888

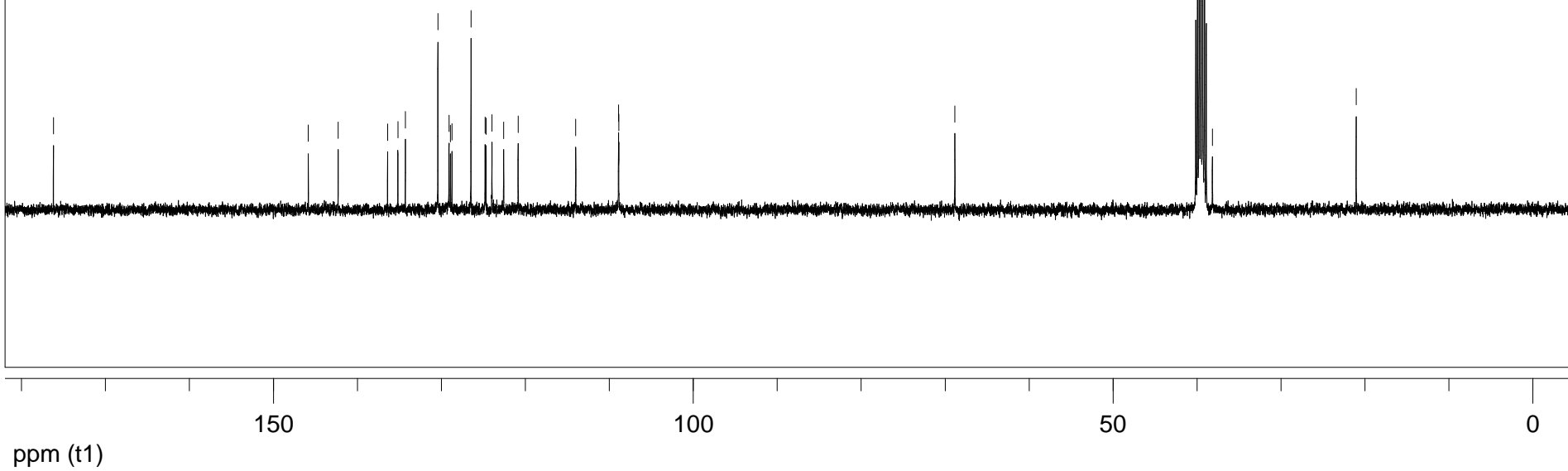
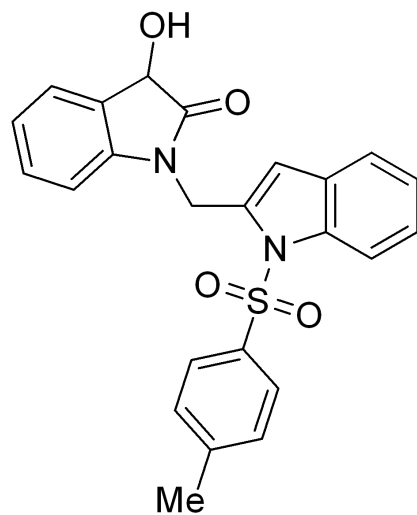
108.855

68.826

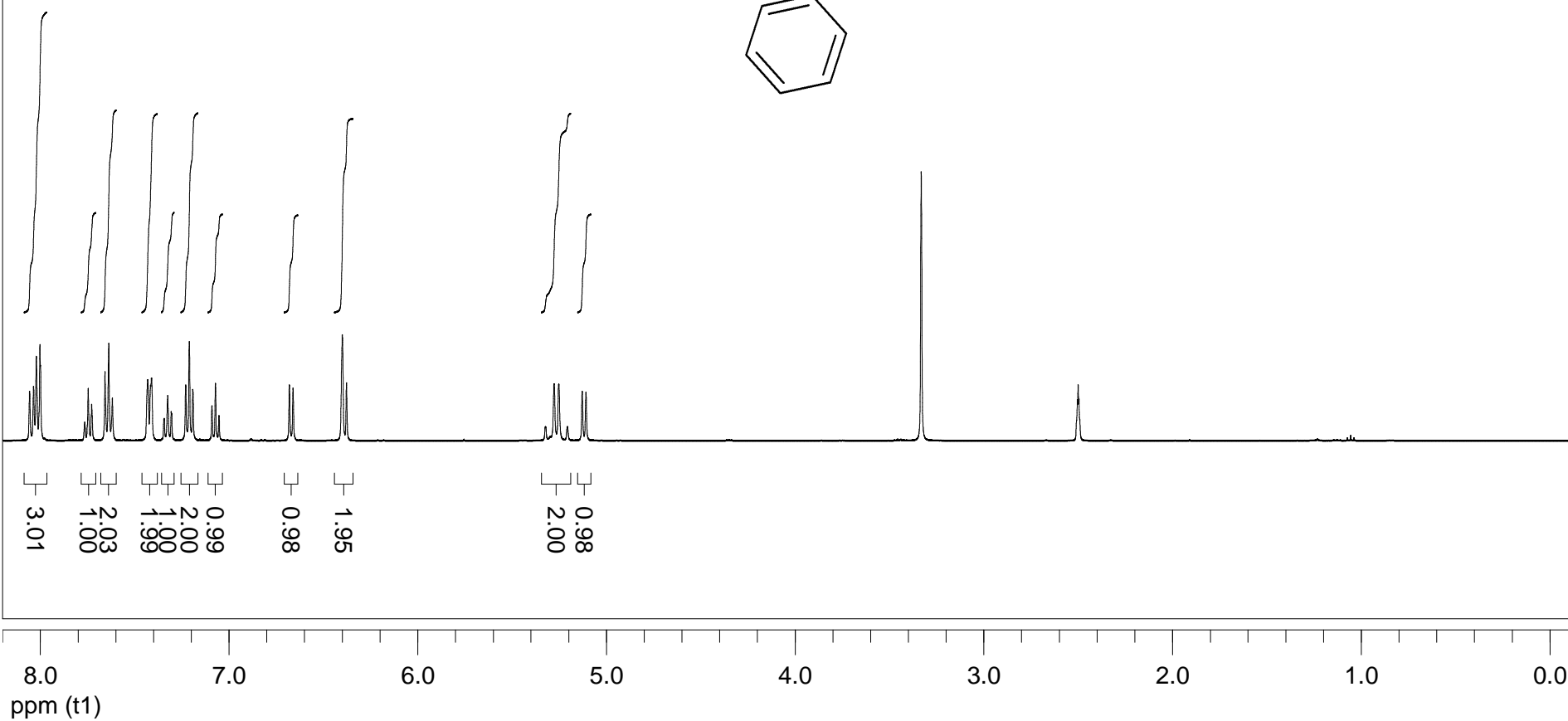
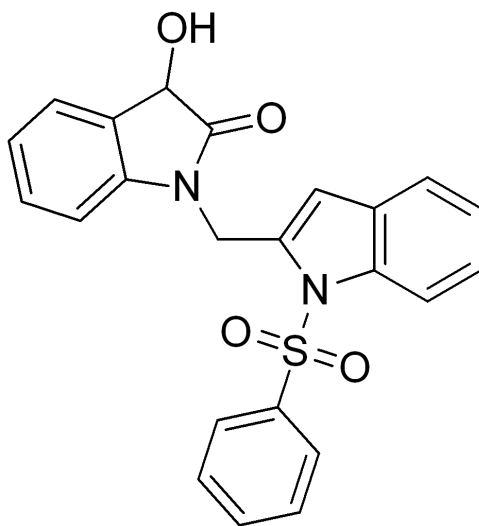
38.166

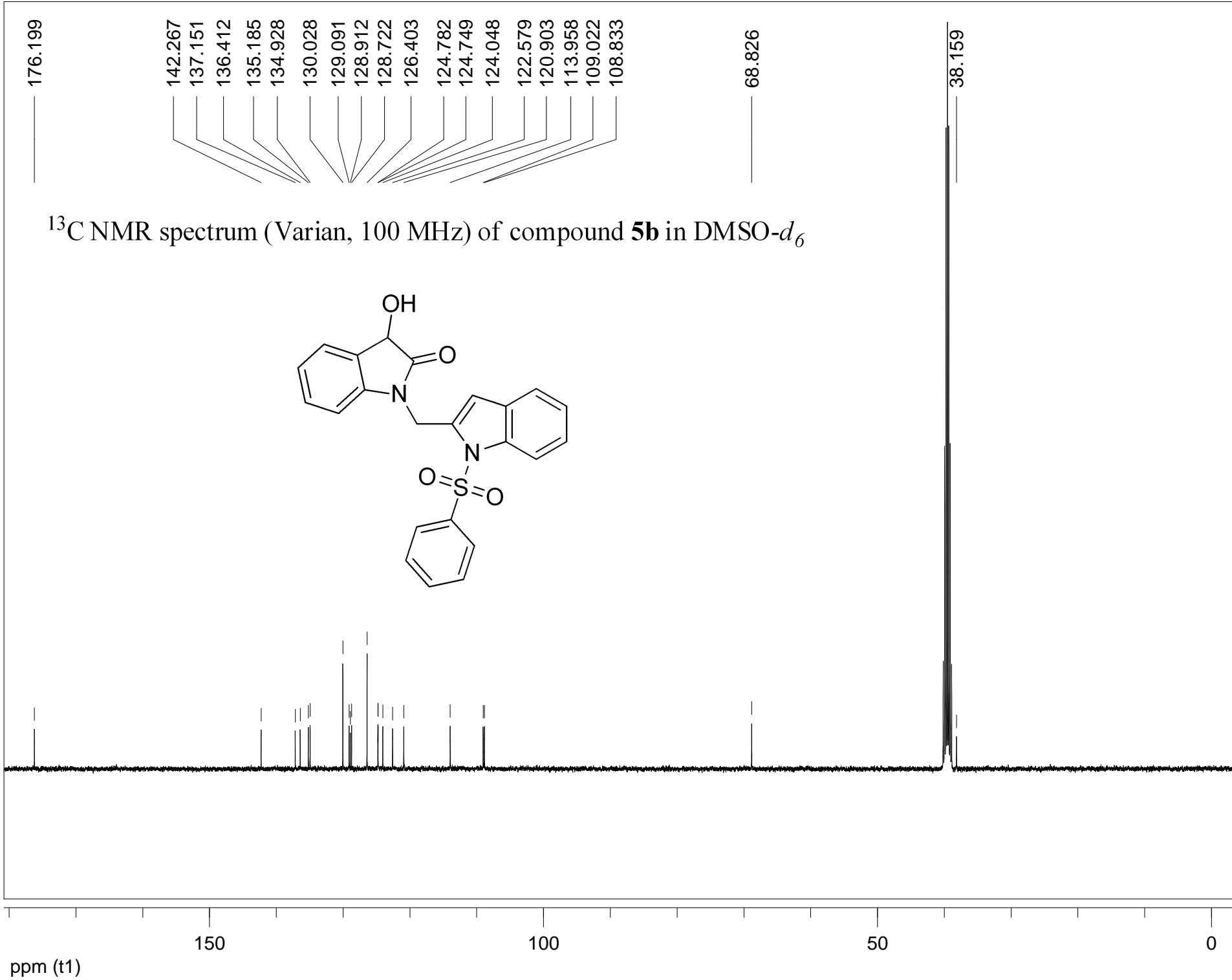
21.038

^{13}C NMR spectrum (Varian, 100 MHz) of compound **5a** in $\text{DMSO-}d_6$

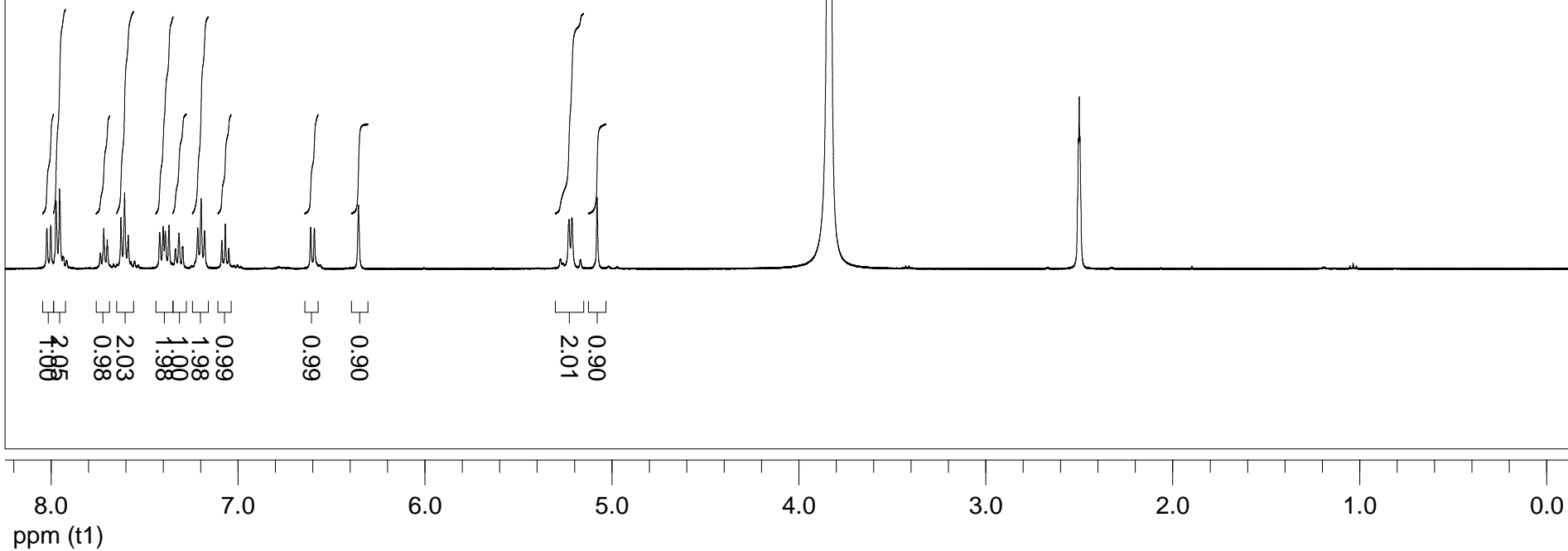
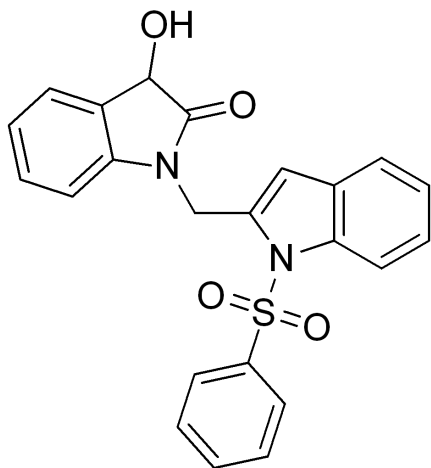


^1H NMR (Varian, 400 MHz) spectrum of compound **5b** in $\text{DMSO-}d_6$

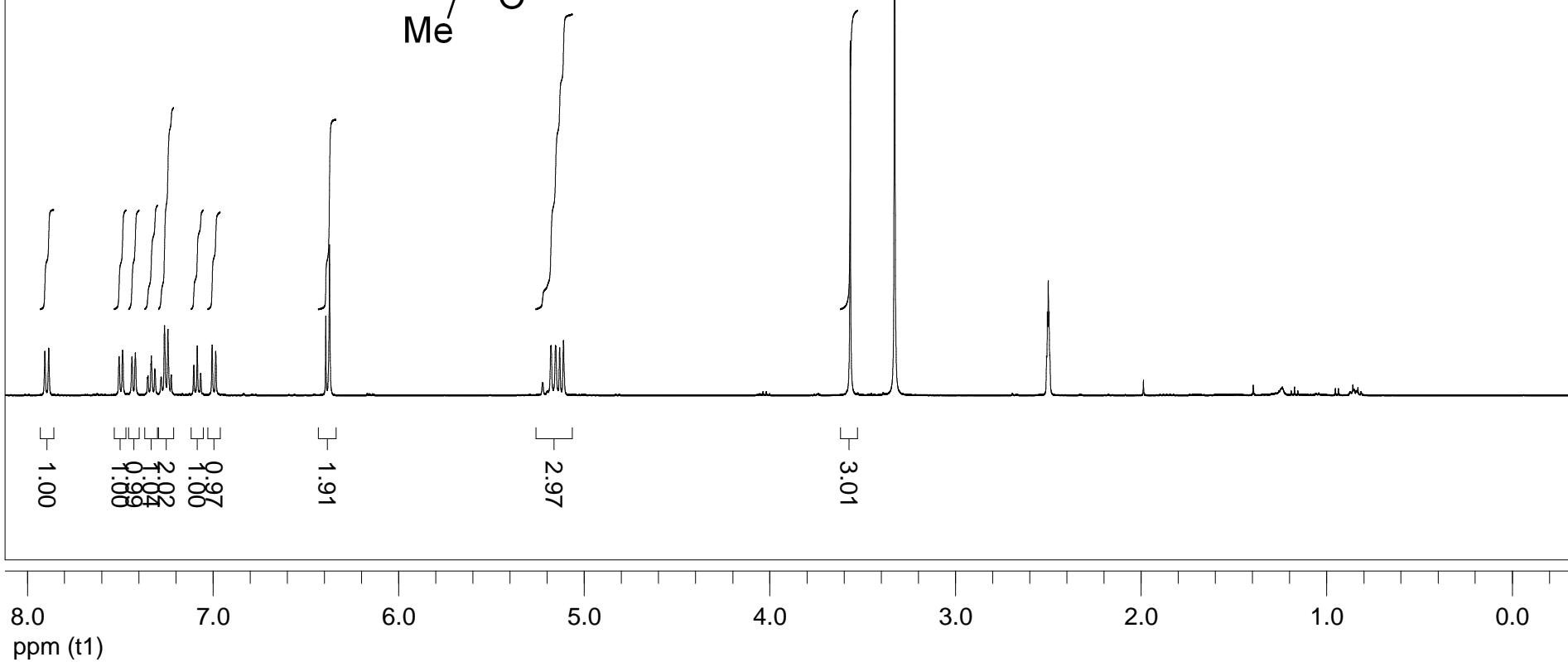
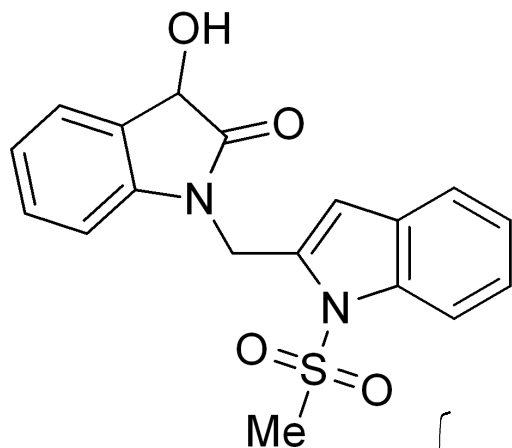




D₂O exchange spectrum of compound **5b** in DMSO-*d*₆



^1H NMR (Varian, 400 MHz) spectrum of compound **5c** in $\text{DMSO-}d_6$



176.227

142.436

136.312

135.254

129.086

128.686

128.546

124.712

124.310

123.491

122.581

120.729

113.436

109.318

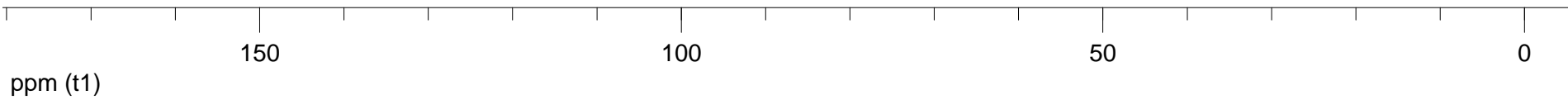
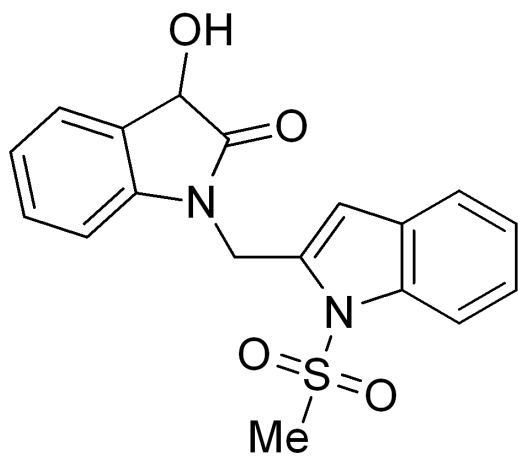
107.004

68.865

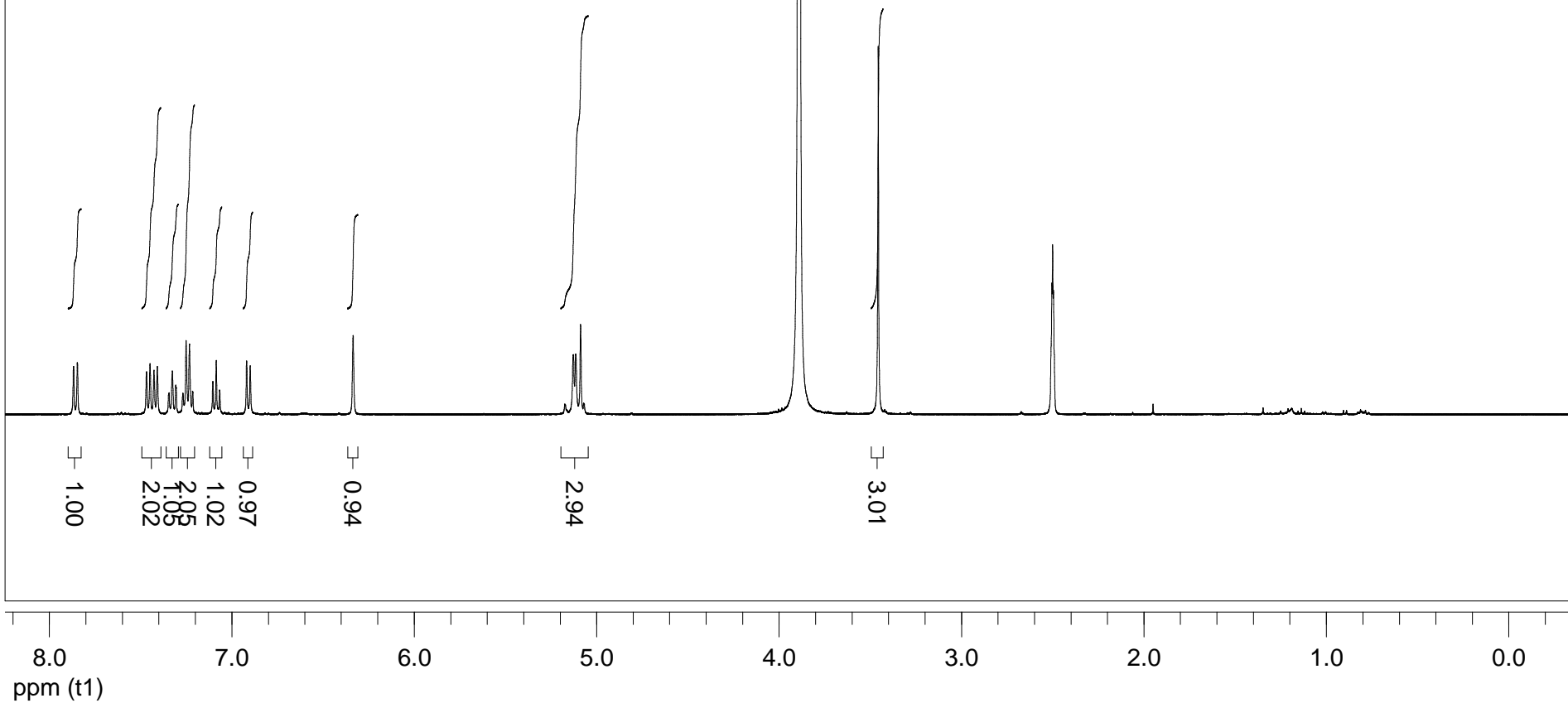
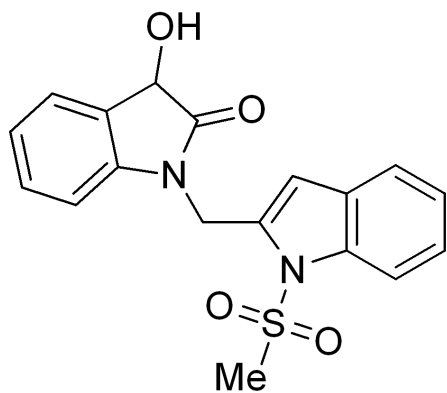
41.088

37.784

^{13}C NMR spectrum (Varian, 100 MHz) of compound **5c** in $\text{DMSO-}d_6$



D₂O exchange spectrum of compound **5c** in DMSO-*d*₆

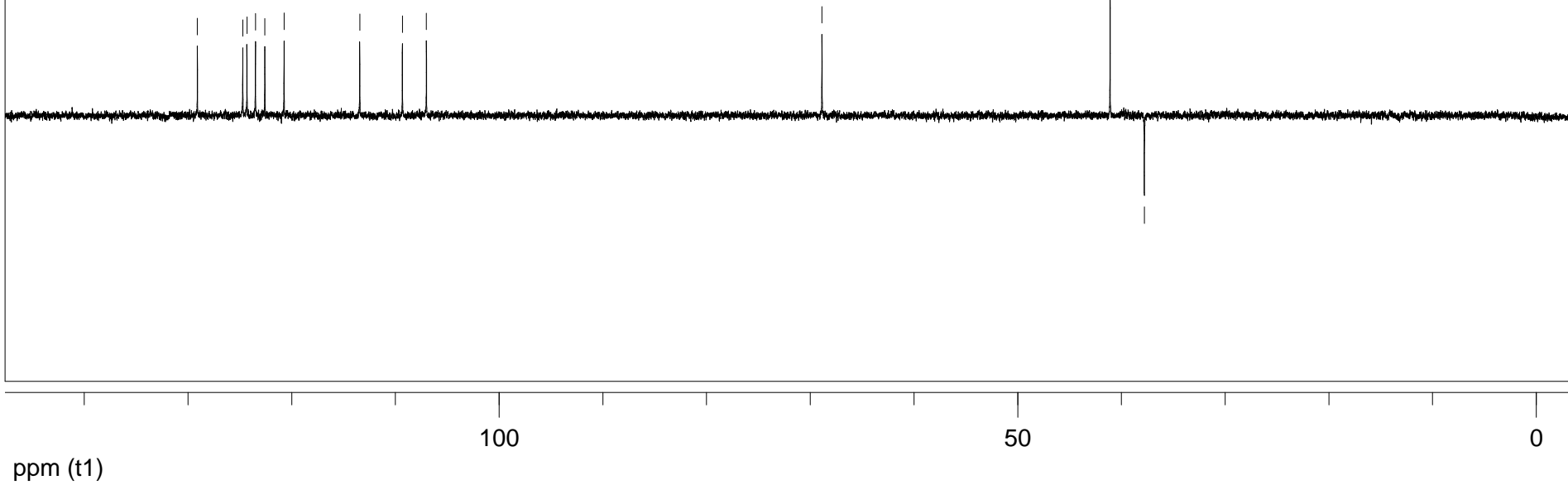
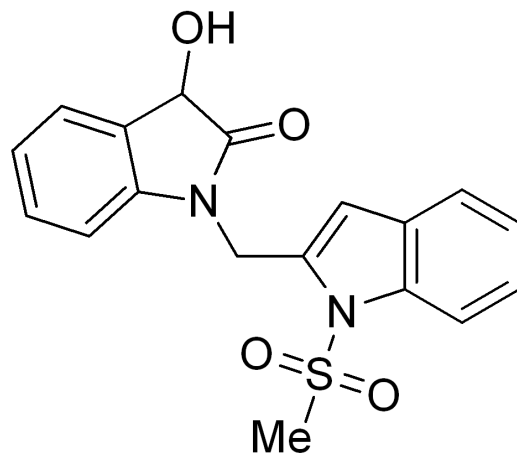


129.083
124.709
124.307
123.487
122.578
120.726
113.432
109.314
106.999

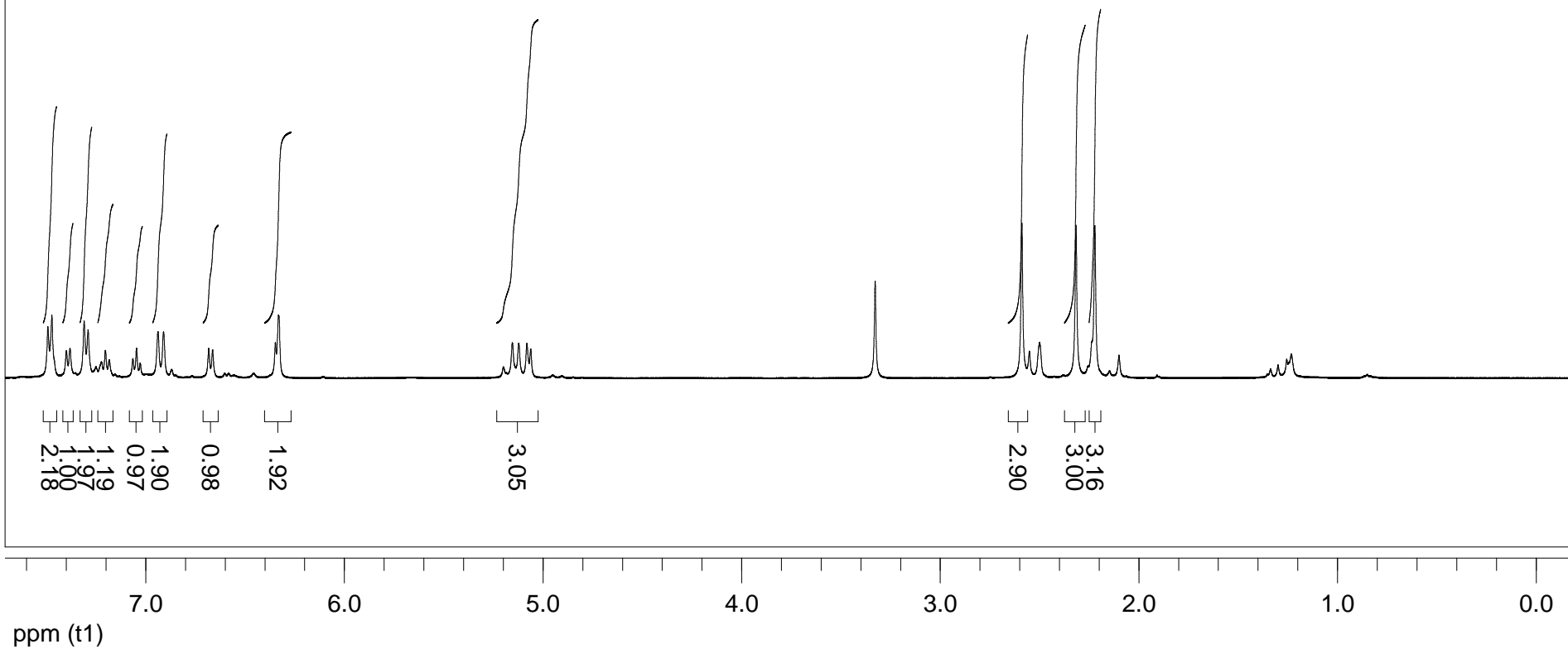
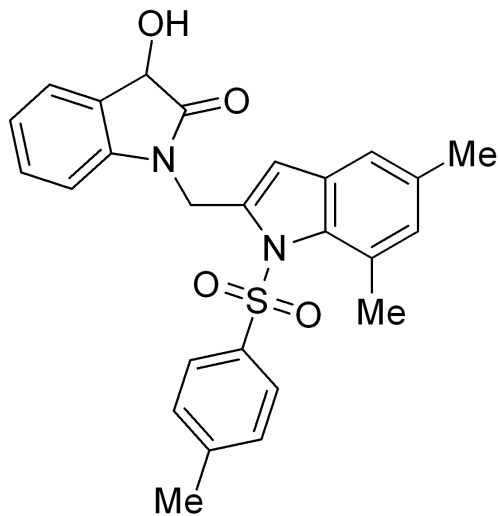
68.861

41.085
37.780

DEPT spectrum of compound **5c** in DMSO-*d*₆



^1H NMR (Varian, 400 MHz) spectrum of compound **5d** in $\text{DMSO-}d_6$

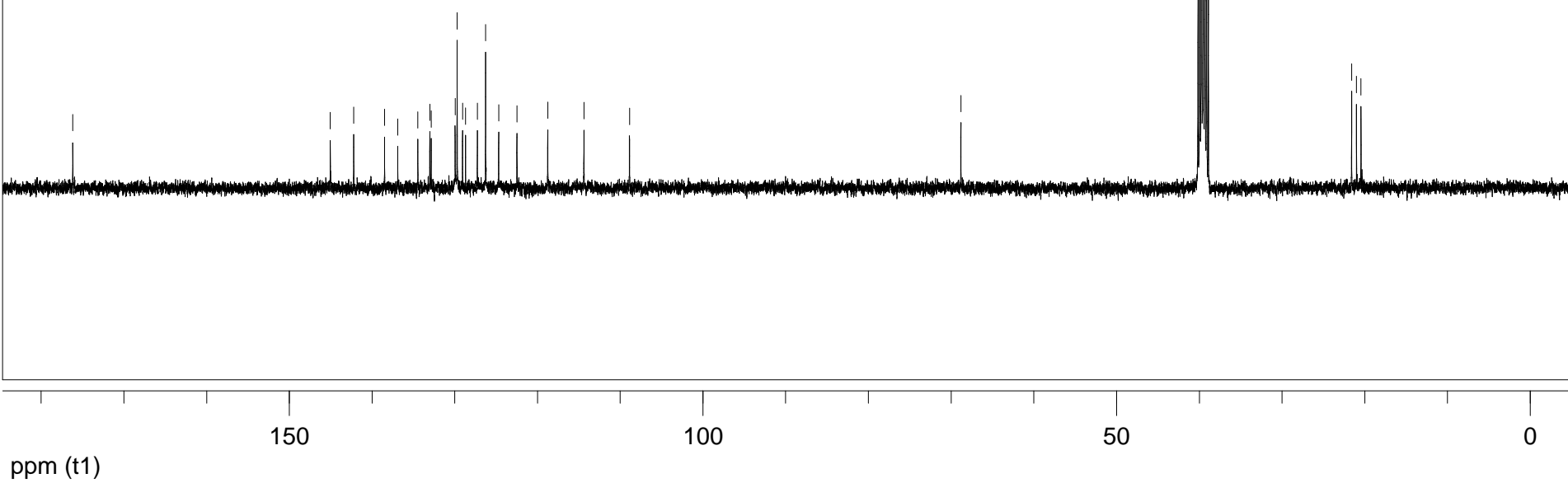
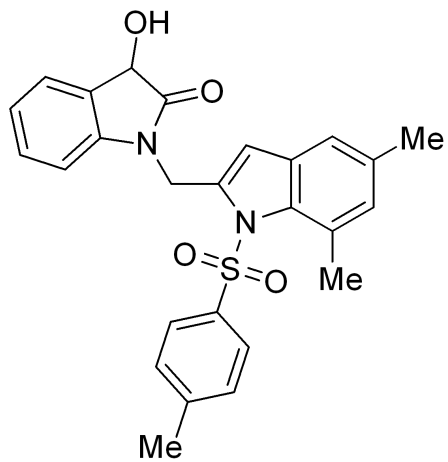


176.170
145.043
142.214
138.480
136.880
134.459
133.005
132.837
129.949
129.703
129.052
128.683
127.260
126.268
124.685
122.472
118.750
114.376
108.871

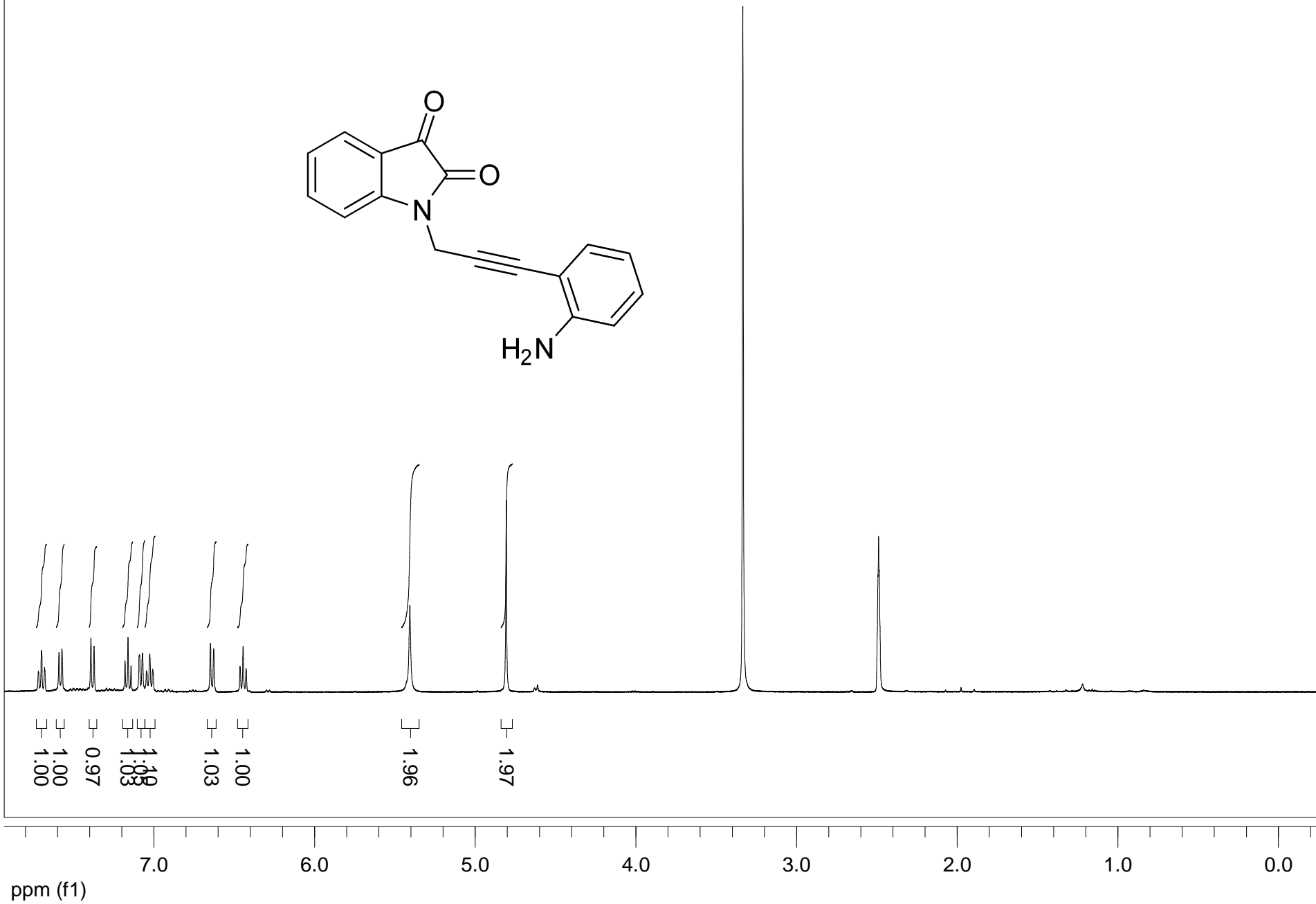
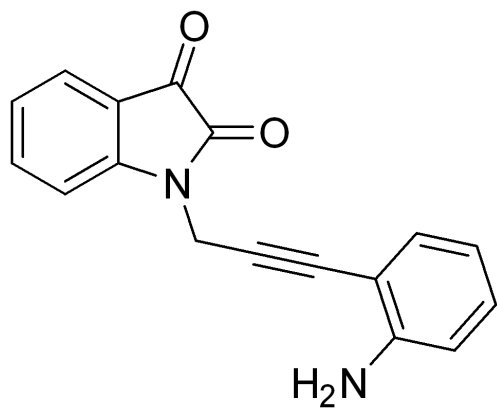
68.812

21.575
20.985
20.449

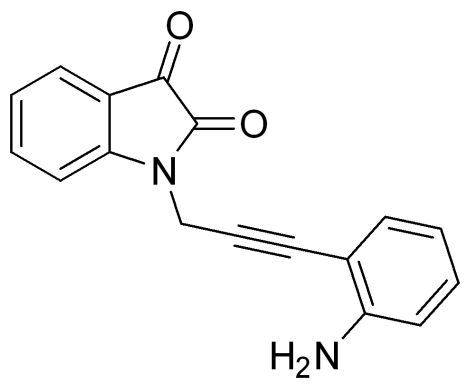
^{13}C NMR spectrum (Varian, 100 MHz) of compound **5d** in $\text{DMSO-}d_6$



^1H NMR (Varian, 400 MHz) spectrum of compound **6a** in $\text{DMSO-}d_6$

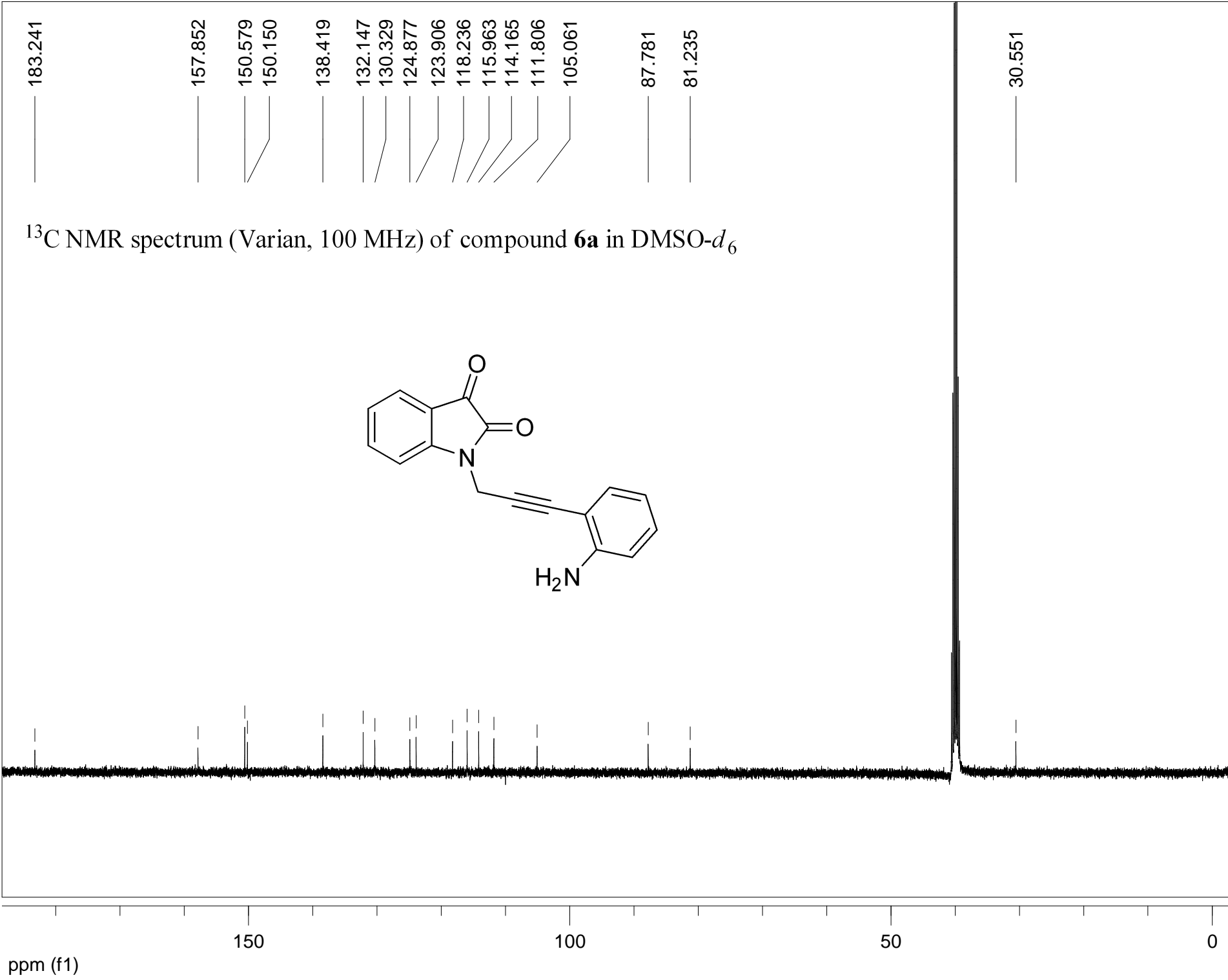


¹³C NMR spectrum (Varian, 100 MHz) of compound **6a** in DMSO-*d*₆

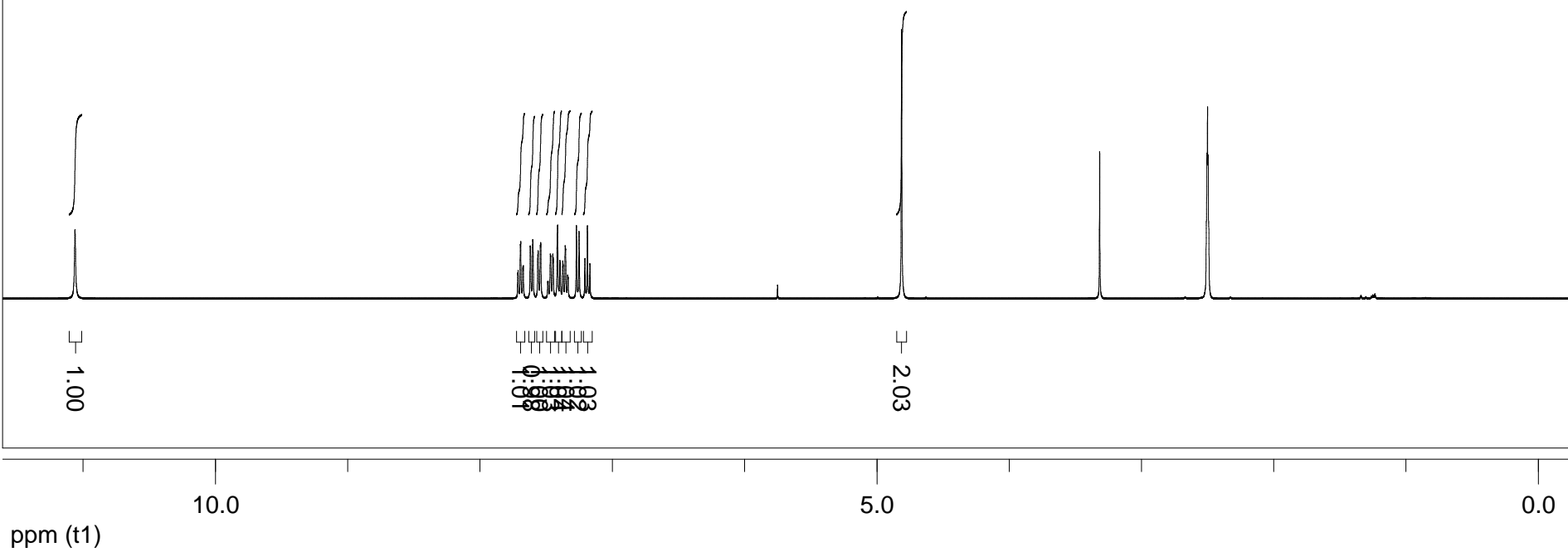
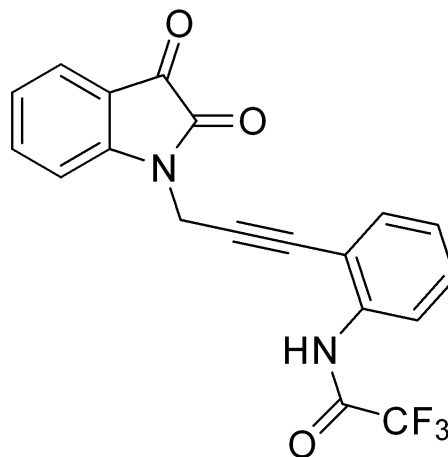
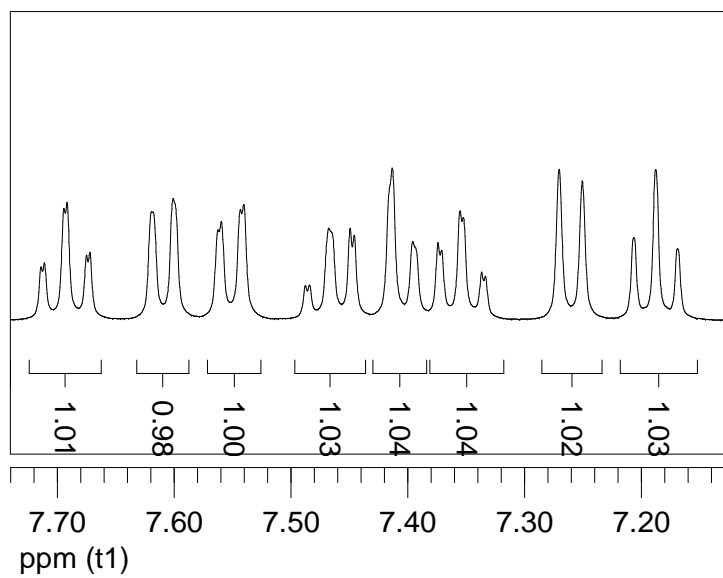


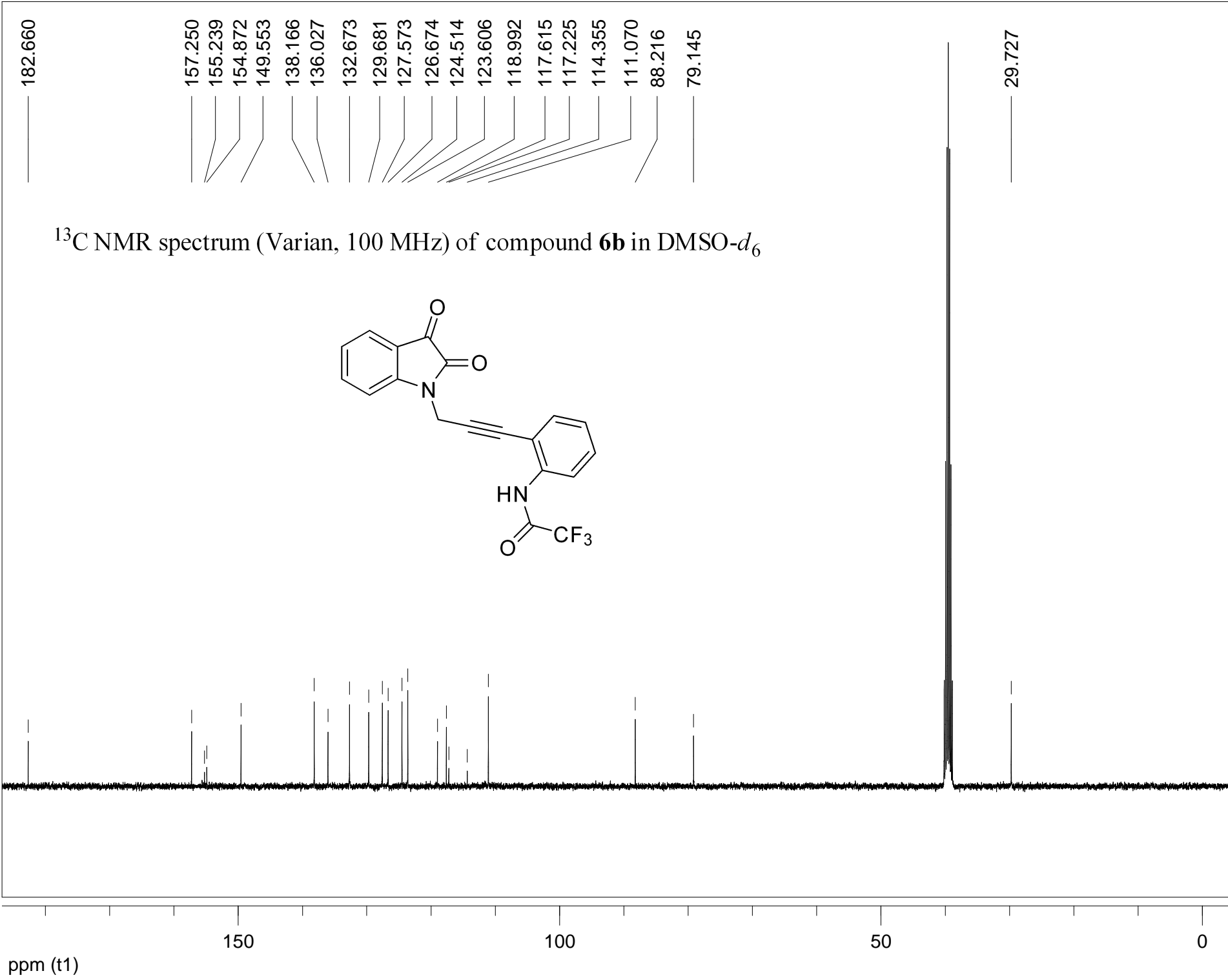
- 183.241
- 157.852
- 150.579
- 150.150
- 138.419
- 132.147
- 130.329
- 124.877
- 123.906
- 118.236
- 115.963
- 114.165
- 111.806
- 105.061
- 87.781
- 81.235

- 30.551



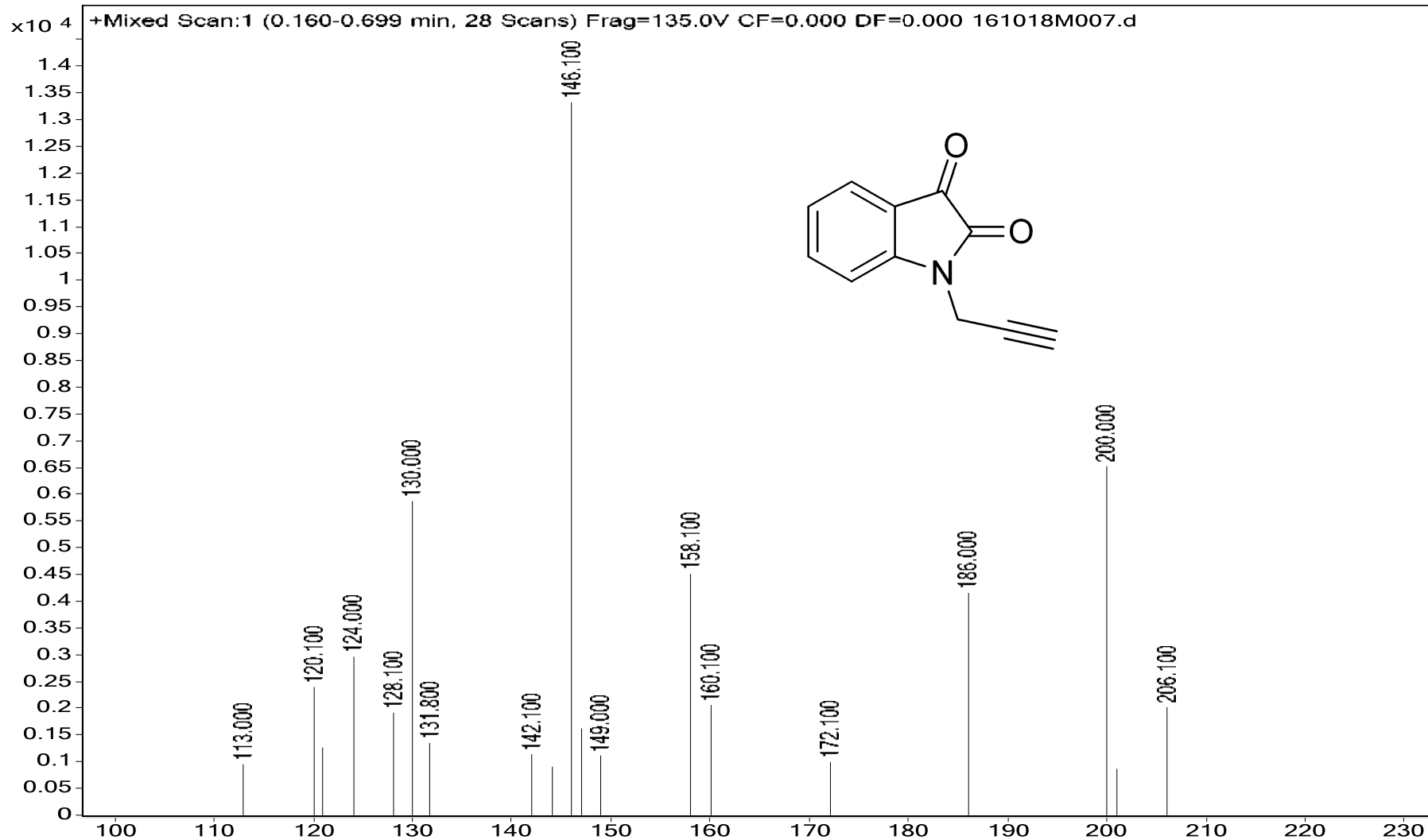
^1H NMR (Varian, 400 MHz) spectrum of compound **6b** in $\text{DMSO-}d_6$





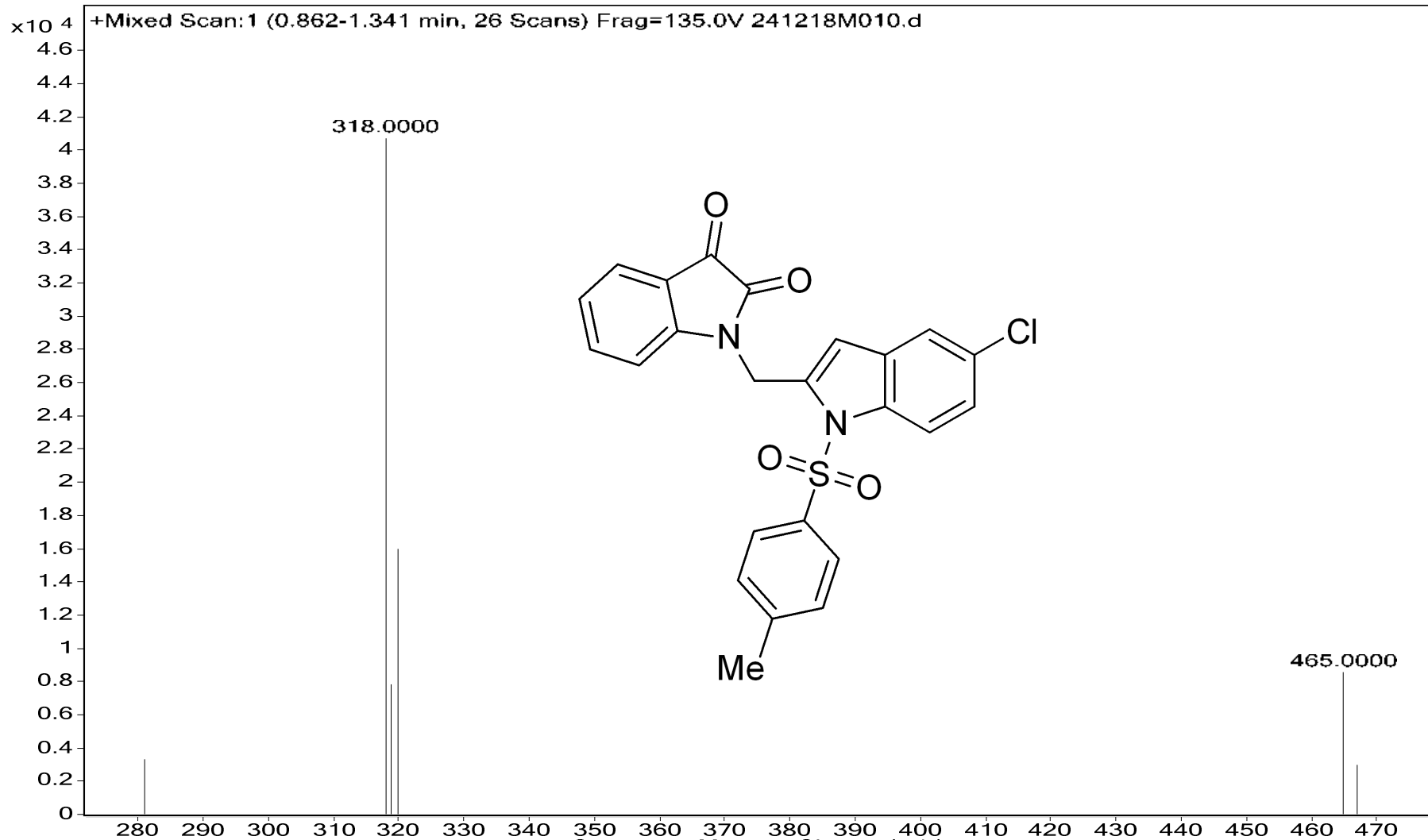
Mass spectrum of compound 1

Sample Name	ILS-GSR-I2-alk	Position	Vial 6	Instrument Name	LCMS	User Name	
Inj Vol	2	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	161018M007.d	ACQ Method	MMI-SM.m	Comment	MM18J020	Acquired Time	10/16/2018 12:27:41 PM



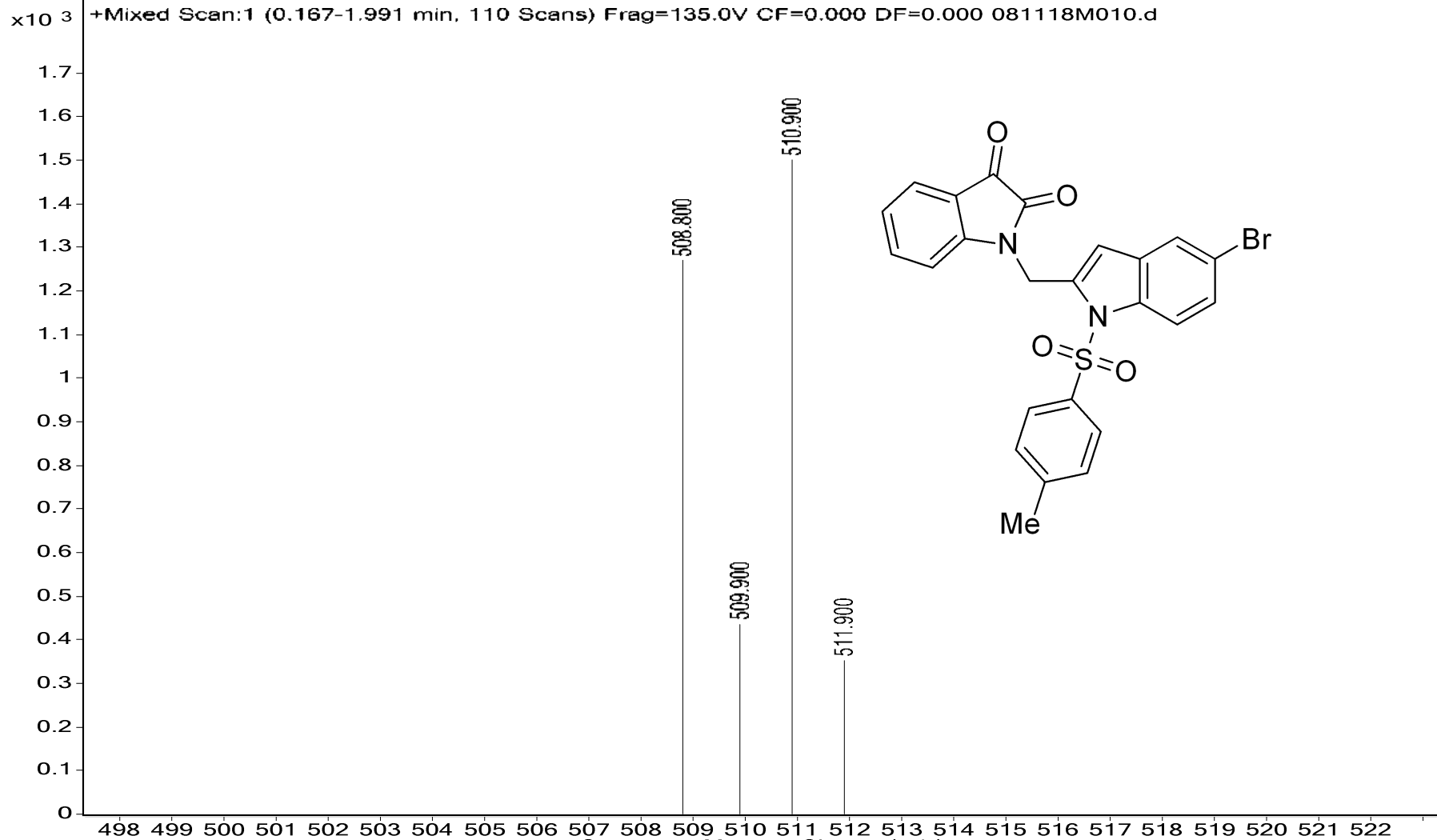
Mass spectrum of compound 3a

Sample Name	ILS-GSR-I2-Cl-Ts	Position	Vial 10	Instrument Name	LCMS	User Name	
Inj Vol	2	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	241218M010.d	ACQ Method	MMI-SM.m	Comment	MM18L033	Acquired Time	12/24/2018 2:00:20 PM



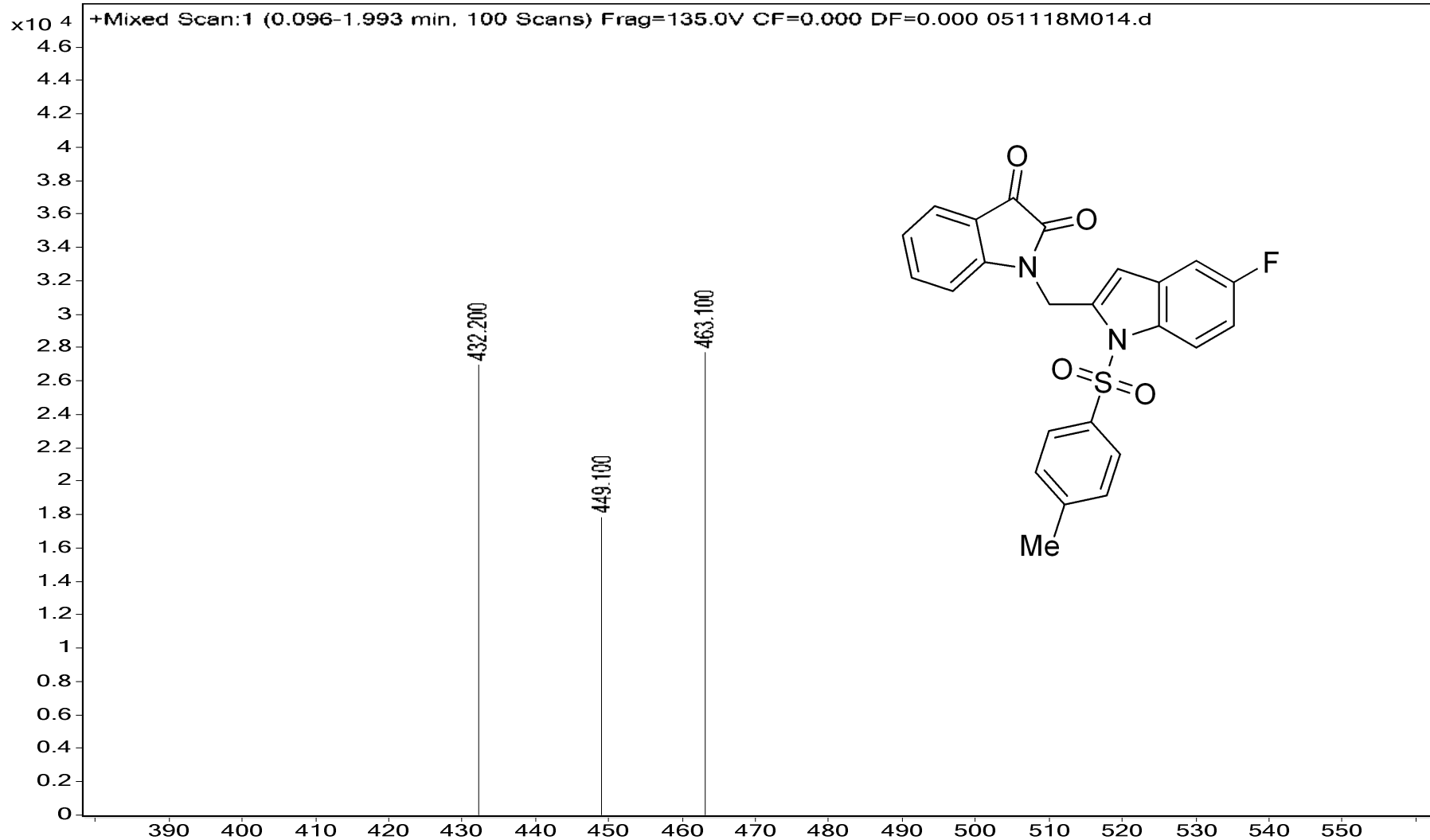
Mass spectrum of compound **3b**

Sample Name	ILS/GSR/I2/BrTS	Position	Vial 60	Instrument Name	LCMS	User Name	
Inj Vol	5	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	081118M010.d	ACQ Method	MMI-SM.m	Comment	MM18K008	Acquired Time	11/8/2018 2:37:06 PM



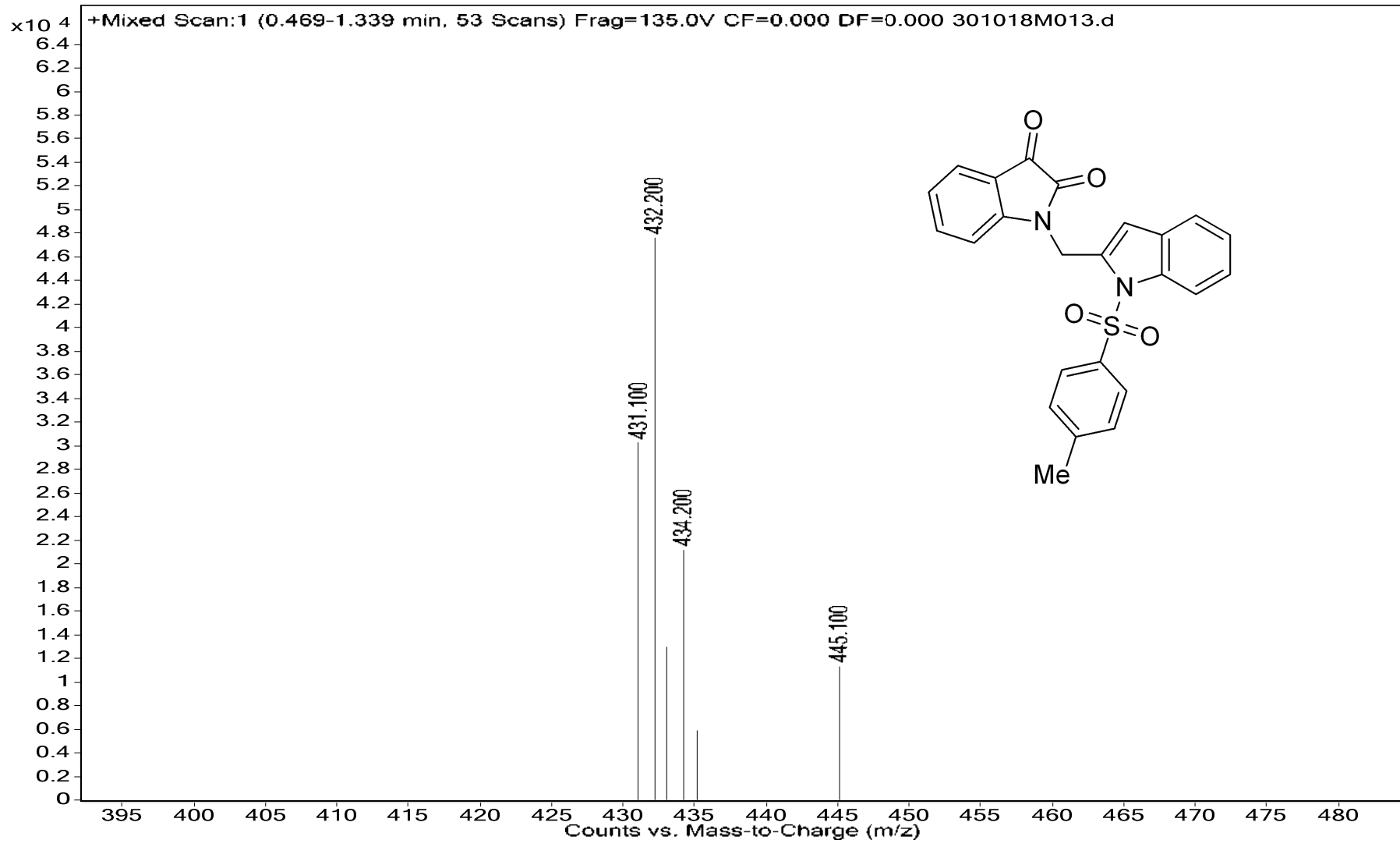
Mass spectrum of compound 3c

Sample Name	ILS-GSR-I2-FTS	Position	Vial 6	Instrument Name	LCMS	User Name	
Inj Vol	5	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	051118M014.d	ACQ Method	MMI-SM.m	Comment	MM18K005	Acquired Time	11/5/2018 12:28:53 PM



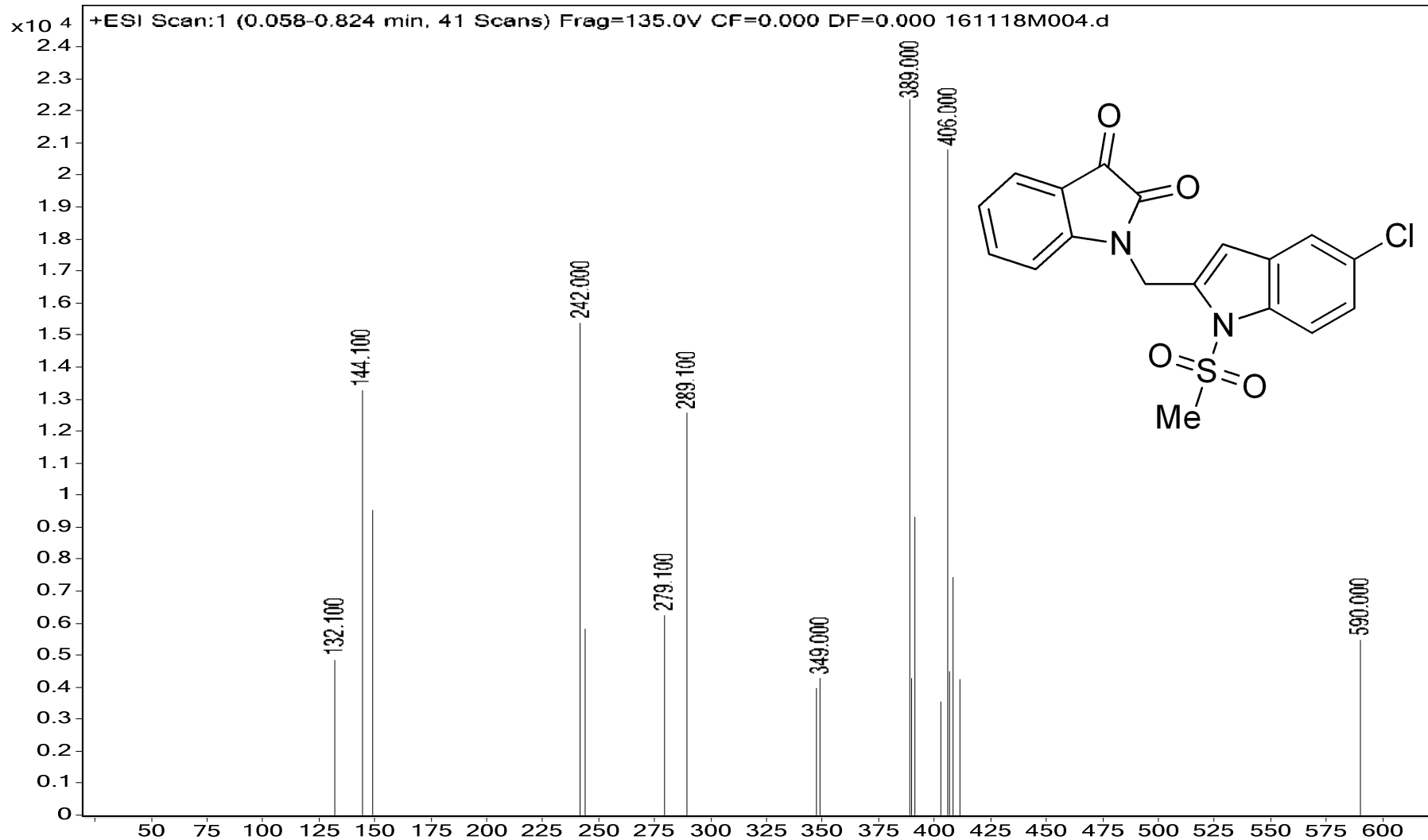
Mass spectrum of compound 3d

Sample Name	ILS-GSR-I2-Ts	Position	Vial 26	Instrument Name	LCMS	User Name	
Inj Vol	2	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	301018M013.d	ACQ Method	MMI-SM.m	Comment	MM18J040	Acquired Time	10/30/2018 2:36:42 PM



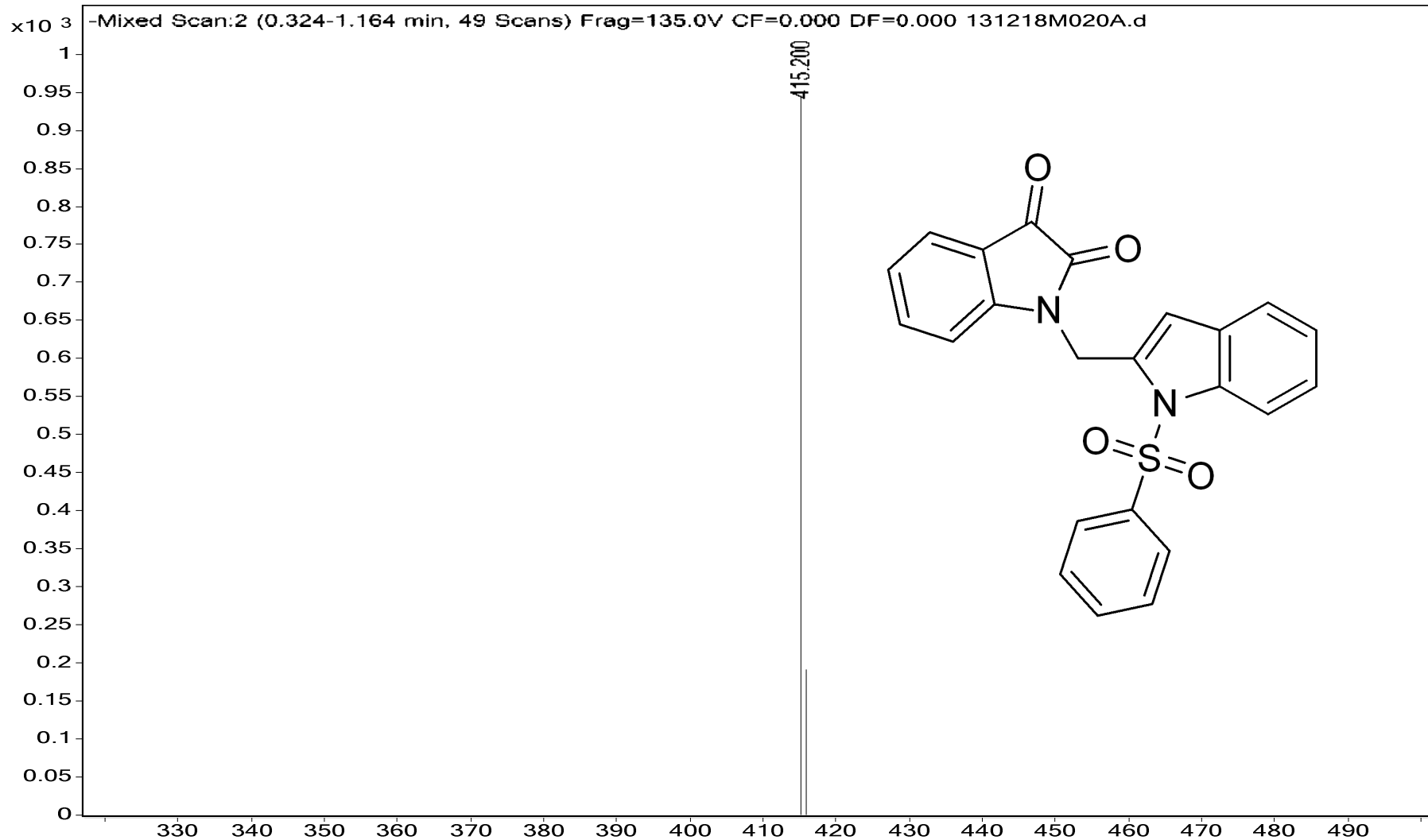
Mass spectrum of compound 3e

Sample Name	ILS-GSR-I2-CL-MS	Position	Vial 8	Instrument Name	LCMS	User Name	
Inj Vol	5	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	161118M004.d	ACQ Method	ESI-SM.m	Comment	MM18K017	Acquired Time	11/16/2018 1:05:54 PM



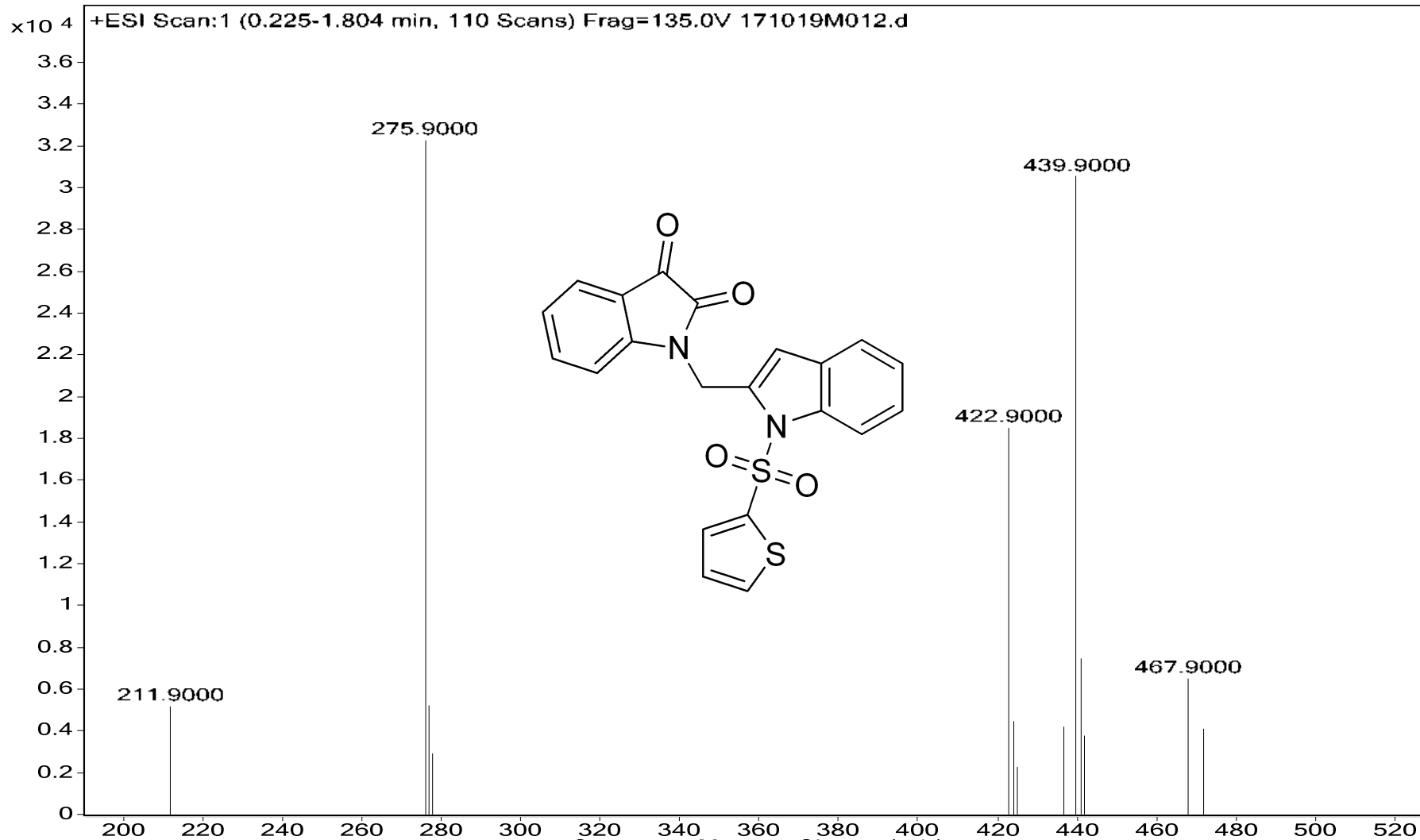
Mass spectrum of compound 3f

Sample Name	ILS-GSR-I2-Ben	Position	Vial 17	Instrument Name	LCMS	User Name	
Inj Vol	8	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	131218M020A.d	ACQ Method	MMI-SM.m	Comment	MM18L014	Acquired Time	12/13/2018 3:14:04 PM



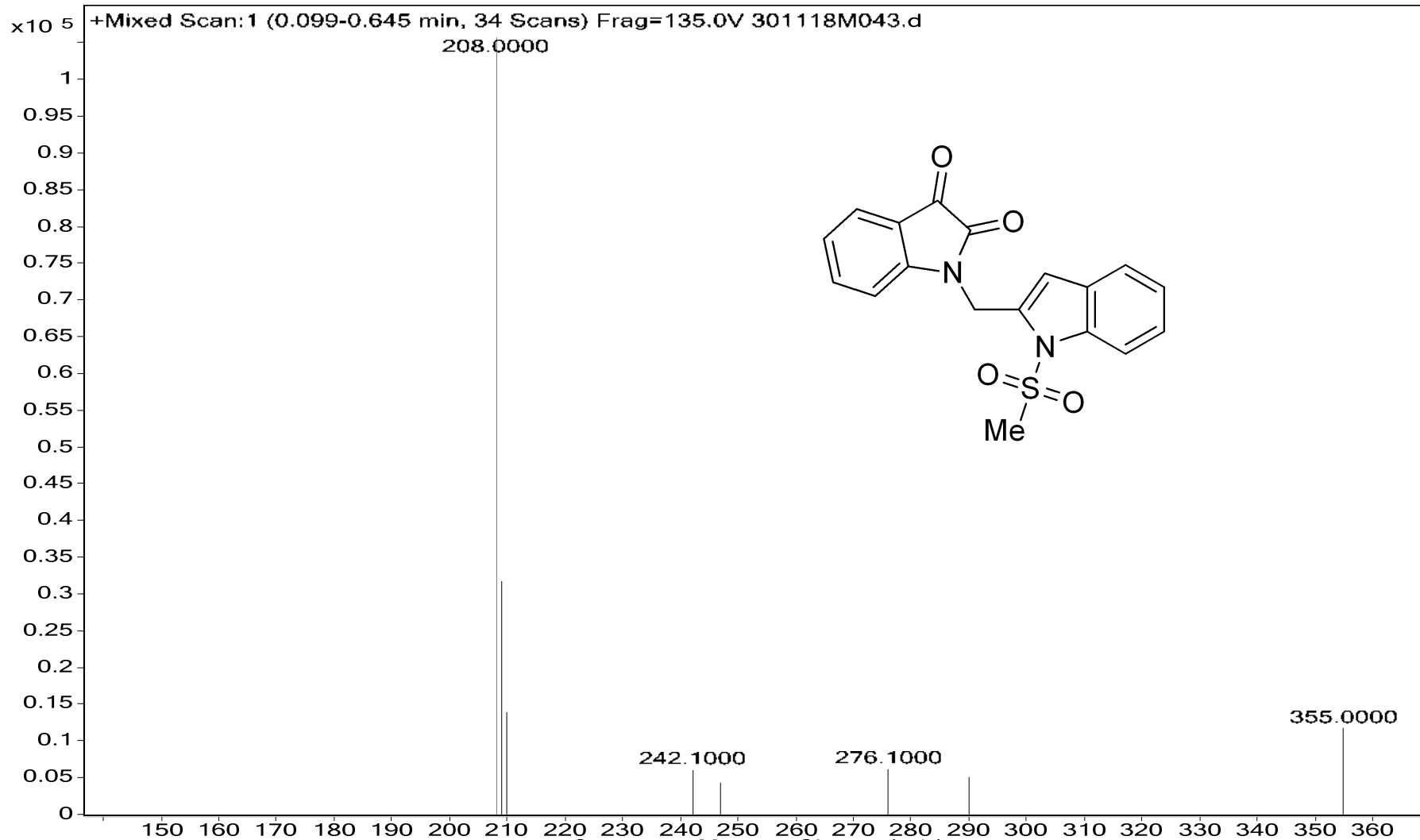
Mass spectrum of compound 3g

Sample Name	ILS-GSR-I2-Th	Position	Vial 11	Instrument Name	LCMS	User Name	
Inj Vol	3	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	171019M012.d	ACQ Method	MMI-SM.m	Comment	MM19J033	Acquired Time	10/17/2019 1:47:26 PM



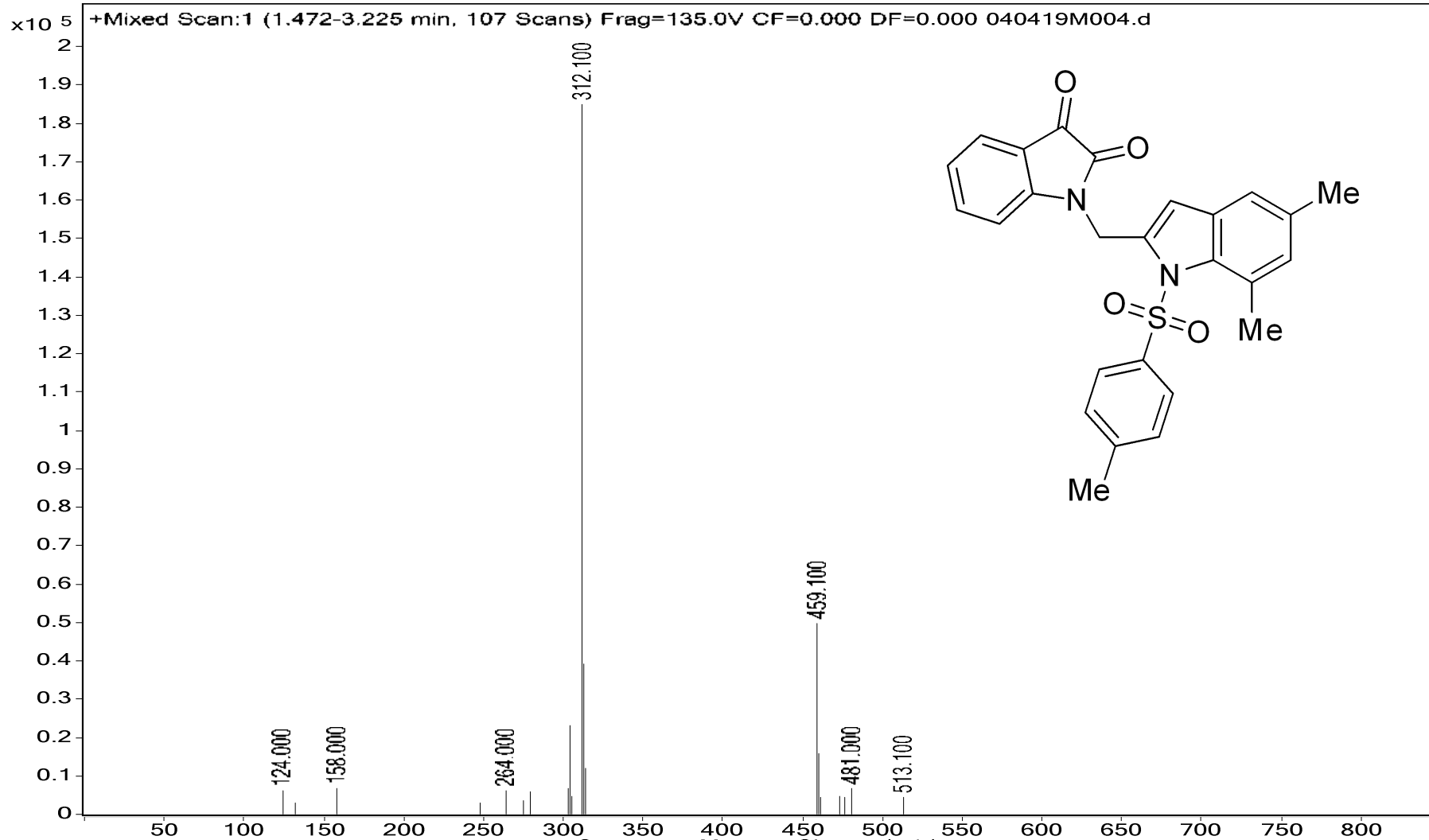
Mass spectrum of compound 3h

Sample Name	ILS-GSR-I2-MS	Position	Vial 30	Instrument Name	LCMS	User Name	
Inj Vol	10	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	301118M043.d	ACQ Method	MMI-SM.m	Comment	MM18K034	Acquired Time	11/30/2018 4:07:45 PM



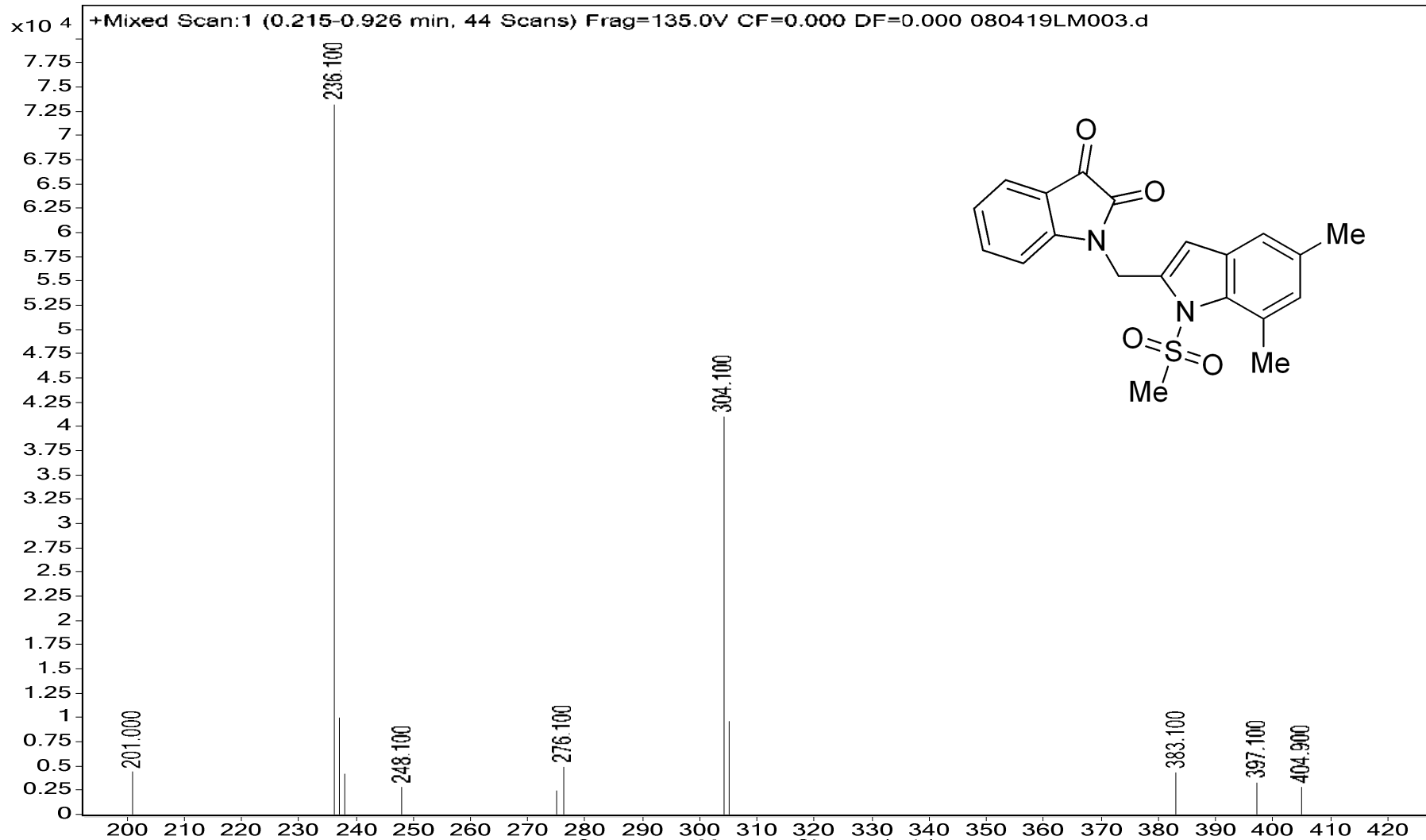
Mass spectrum of compound 3i

Sample Name	ILS-GSR-I2-DTS	Position	Vial 14	Instrument Name	LCMS	User Name	
Inj Vol	8	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	040419M004.d	ACQ Method	MMI-SM.m	Comment	MM19D003	Acquired Time	4/4/2019 12:32:56 PM



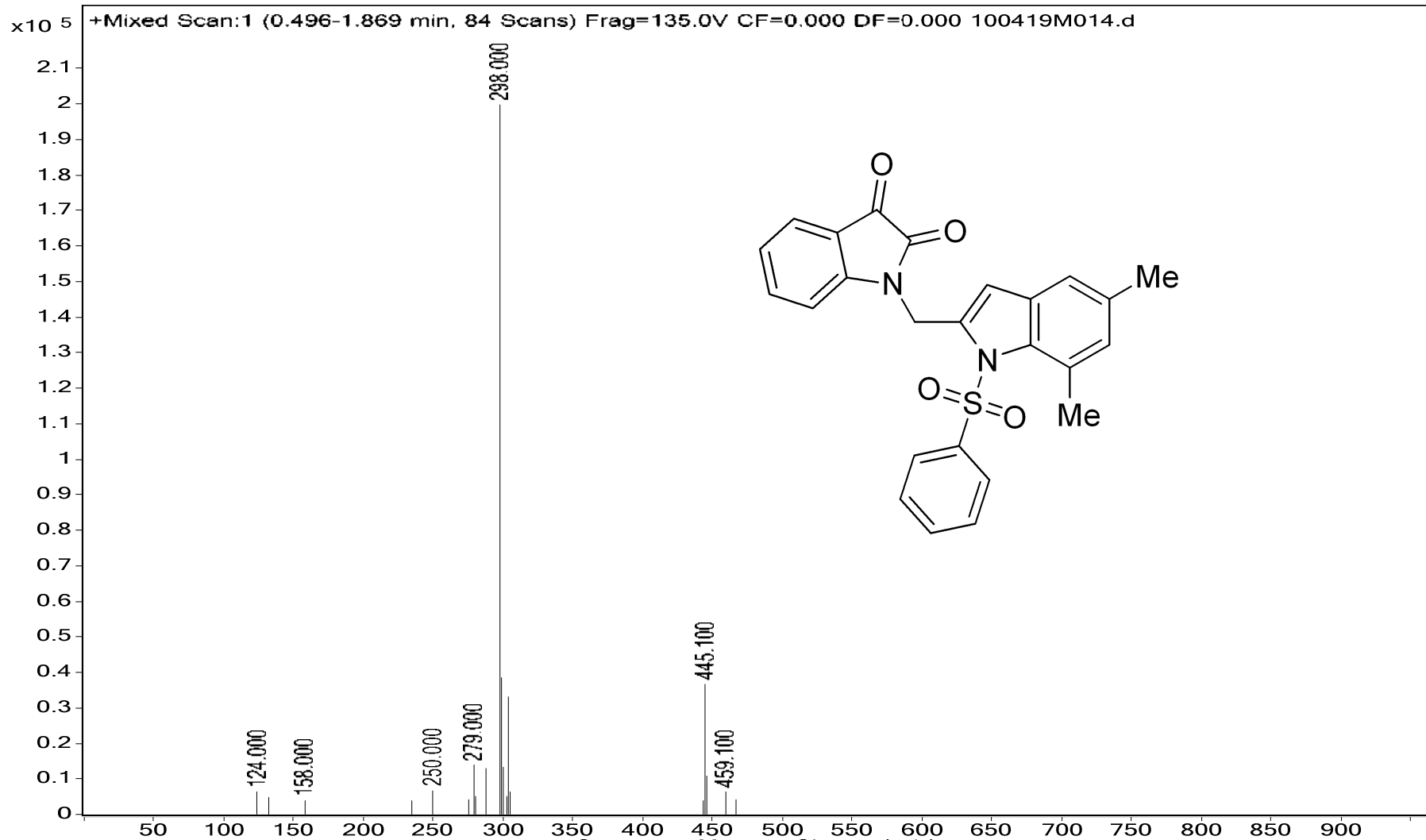
Mass spectrum of compound 3j

Sample Name	ILS-GSR-I2-DMS	Position	Vial 3	Instrument Name	LCMS	User Name	
Inj Vol	2	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	080419LM003.d	ACQ Method	MMI-SM.m	Comment	MM19D008	Acquired Time	4/8/2019 1:21:22 PM



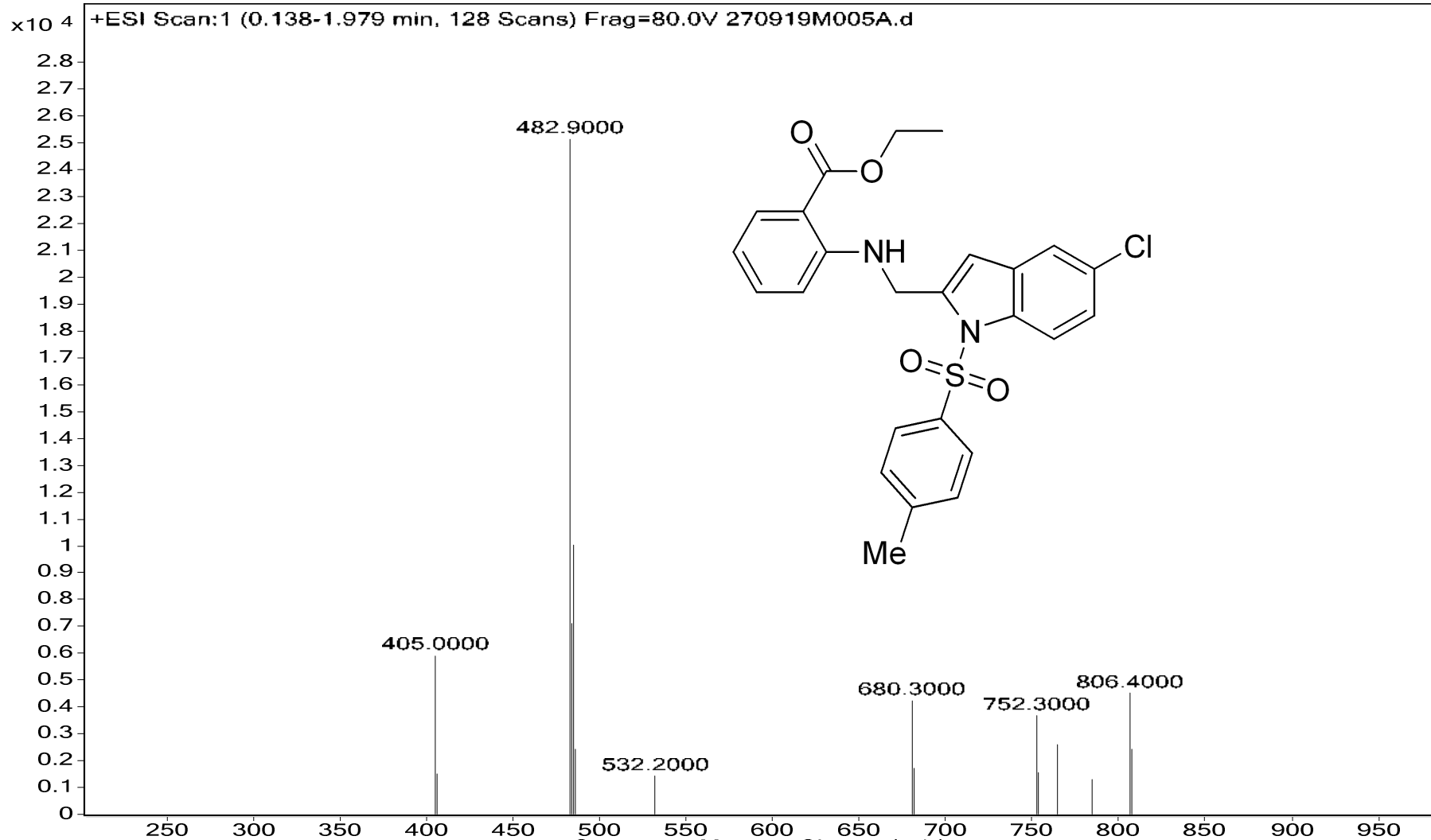
Mass spectrum of compound 3k

Sample Name	ILS-GSR-I2-DB	Position	Vial 30	Instrument Name	LCMS	User Name	
Inj Vol	4	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	100419M014.d	ACQ Method	MMI-SM.m	Comment	MA19D011	Acquired Time	4/10/2019 1:15:39 PM



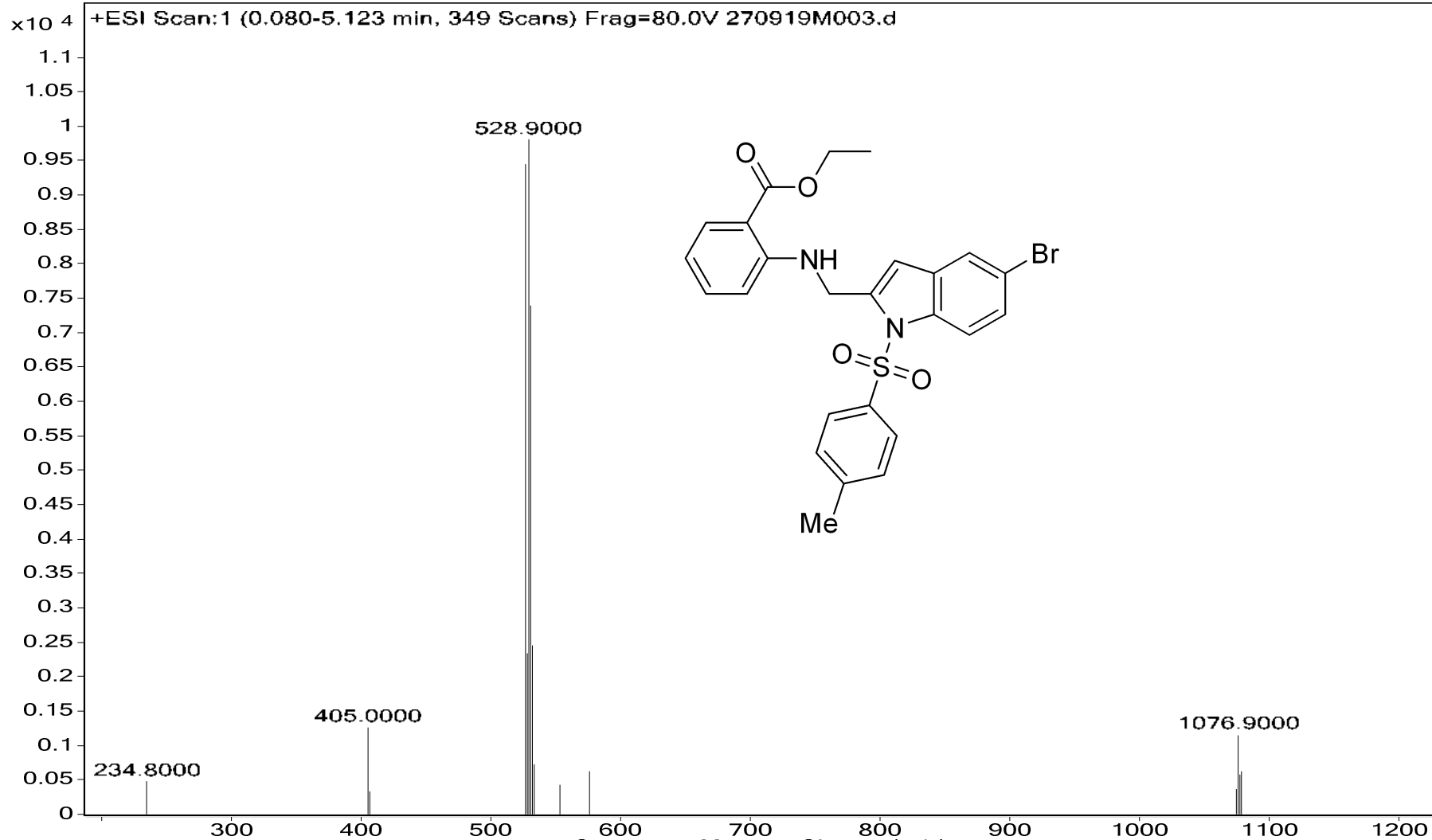
Mass spectrum of compound 4a

Sample Name	ILS-GSR-CI-Ts2	Position	Vial 45	Instrument Name	LCMS	User Name	
Inj Vol	5	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	270919M005A.d	ACQ Method	MMI-SM.m	Comment	MM19I065	Acquired Time	9/27/2019 11:17:01 AM



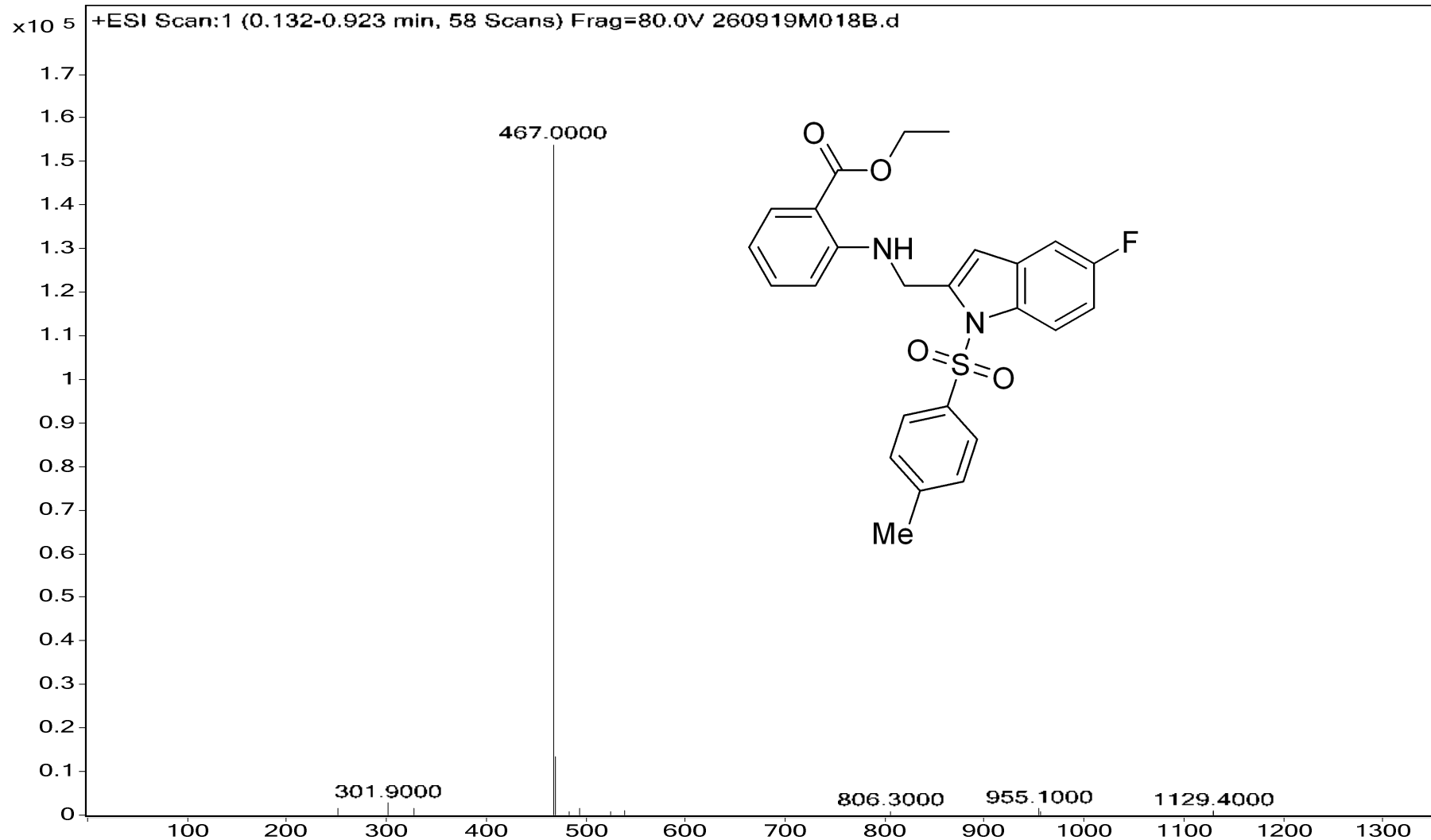
Mass spectrum of compound 4b

Sample Name	ILS-GSR-Br2	Position	Vial 43	Instrument Name	LCMS	User Name	
Inj Vol	10	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	270919M003.d	ACQ Method	MMI-SM.m	Comment	MM19I063	Acquired Time	9/27/2019 11:07:54 AM



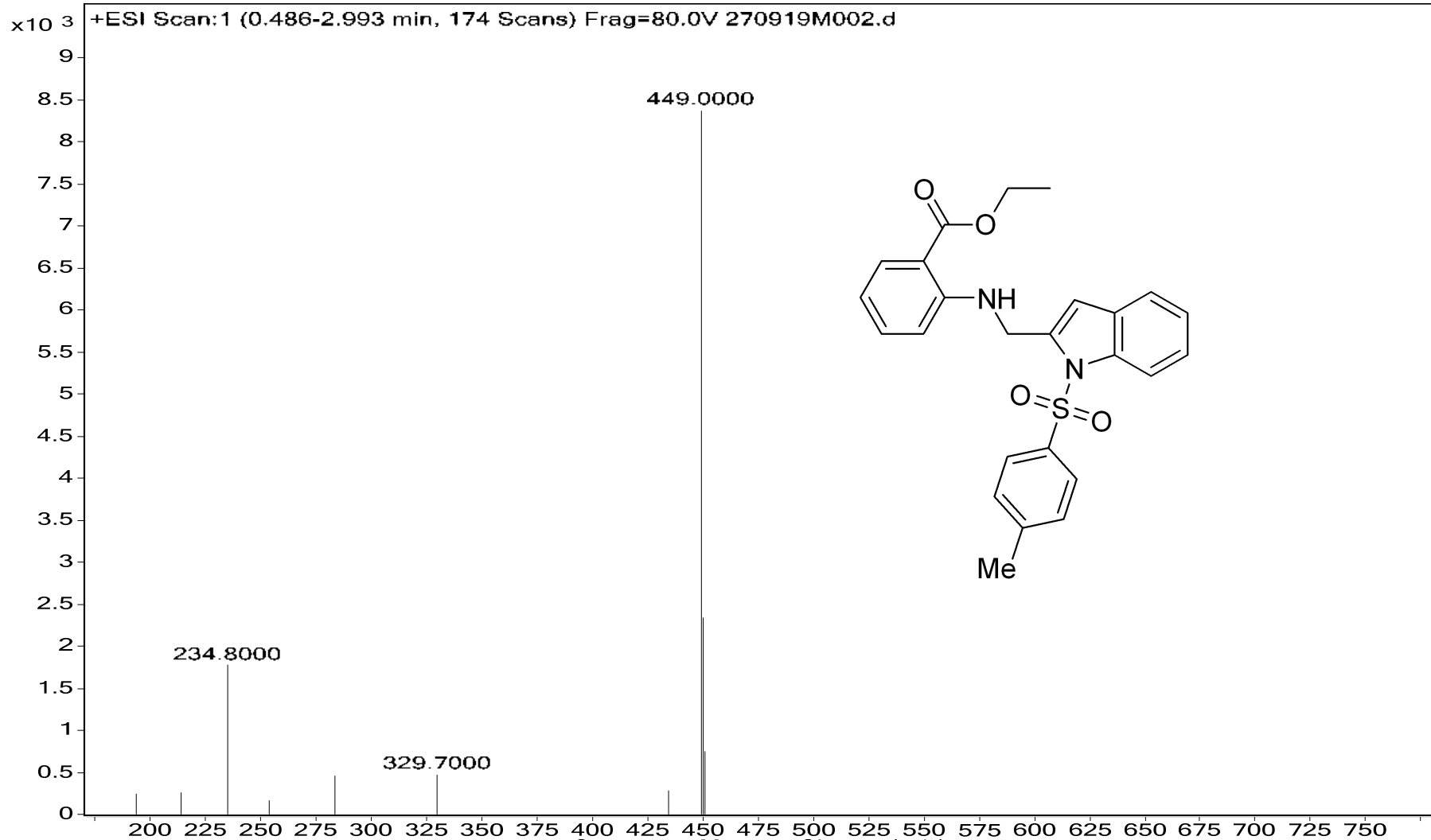
Mass spectrum of compound 4c

Sample Name	ILS-GSR-I2-F2	Position	Vial 33	Instrument Name	LCMS	User Name	
Inj Vol	5	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	260919M018B.d	ACQ Method	MMI-SM.m	Comment	MM19I059	Acquired Time	9/26/2019 4:10:50 PM



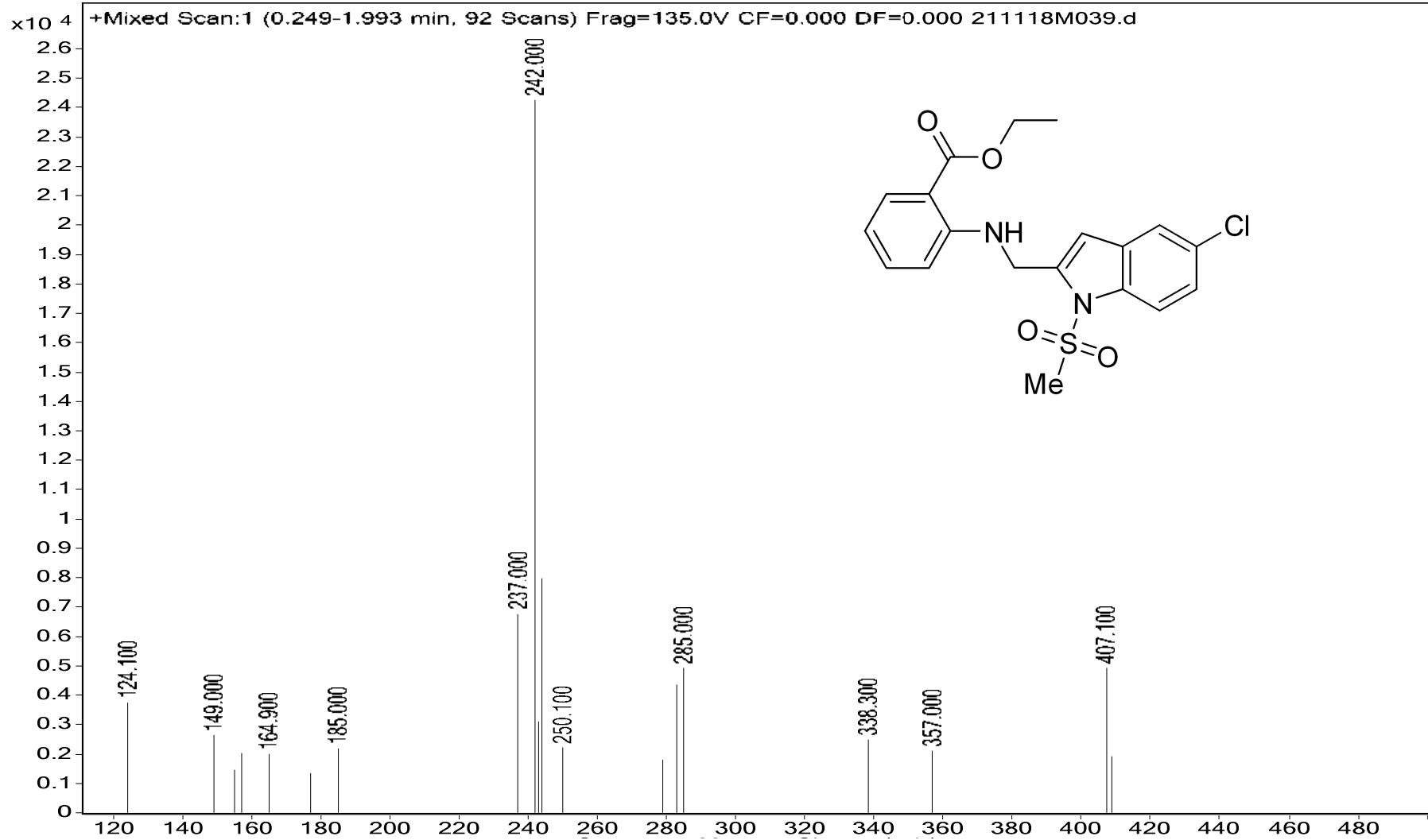
Mass spectrum of compound 4d

Sample Name	ILS-GSR-TS2	Position	Vial 42	Instrument Name	LCMS	User Name	
Inj Vol	5	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	270919M002.d	ACQ Method	MMI-SM.m	Comment	MM19I062	Acquired Time	9/27/2019 10:46:13 AM



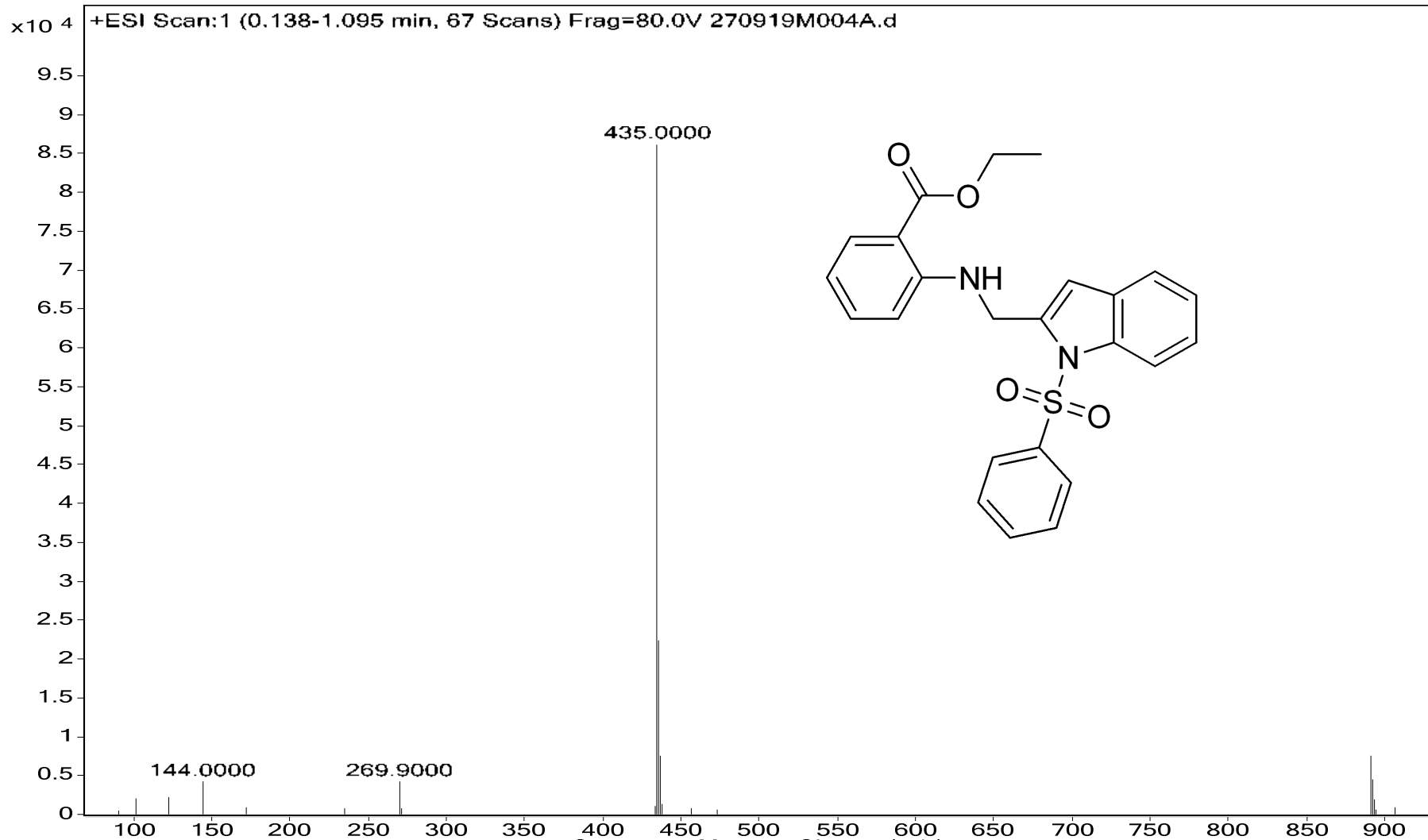
Mass spectrum of compound 4e

Sample Name	ILS-GSR-I2-CL2	Position	Vial 27	Instrument Name	LCMS	User Name	
Inj Vol	2	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	211118M039.d	ACQ Method	MMI-SM.m	Comment	MM18K021	Acquired Time	11/21/2018 4:11:41 PM



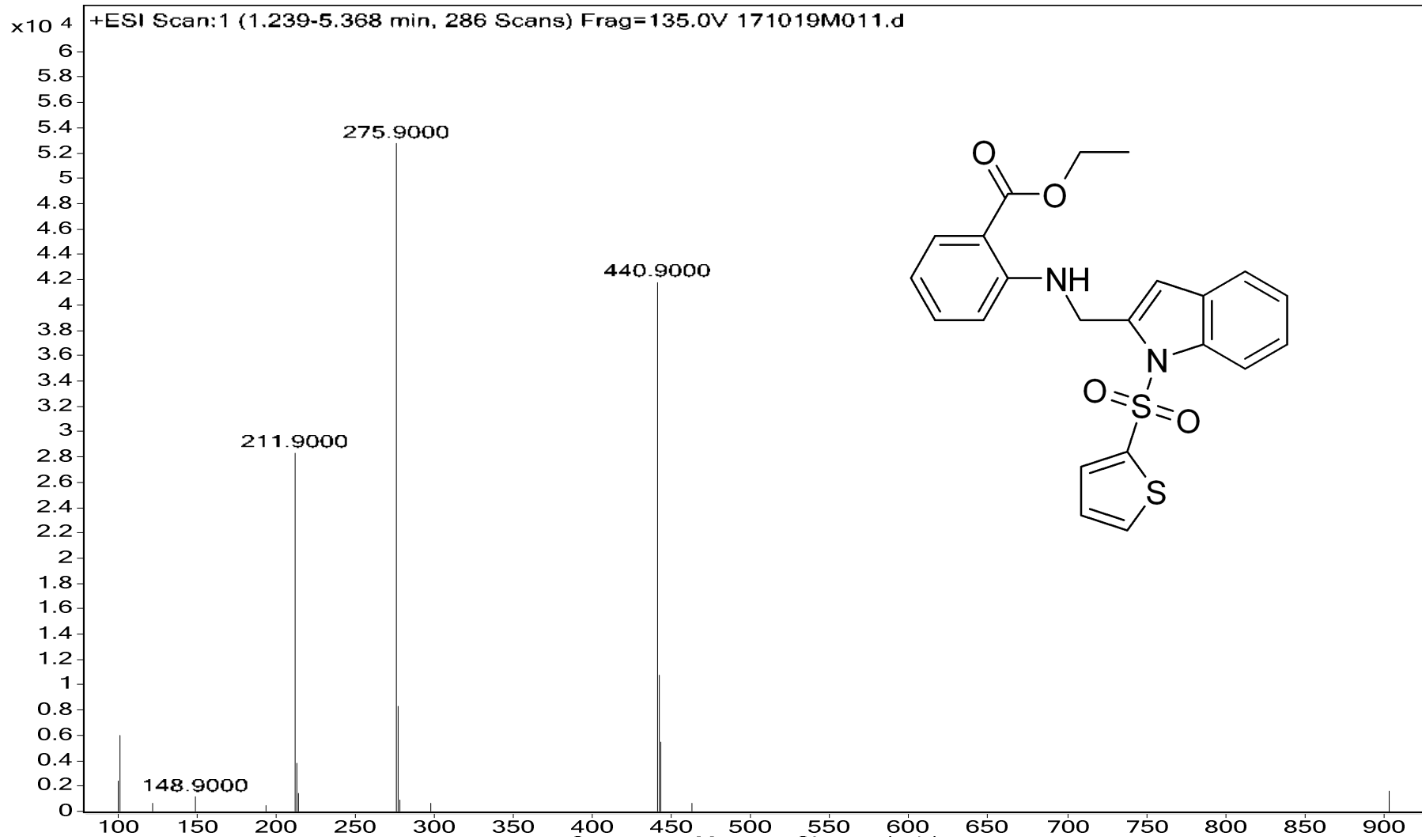
Mass spectrum of compound 4f

Sample Name	ILS-GSR-Ben2	Position	Vial 44	Instrument Name	LCMS	User Name	
Inj Vol	5	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	270919M004A.d	ACQ Method	MMI-SM.m	Comment	MM19I064	Acquired Time	9/27/2019 11:10:00 AM



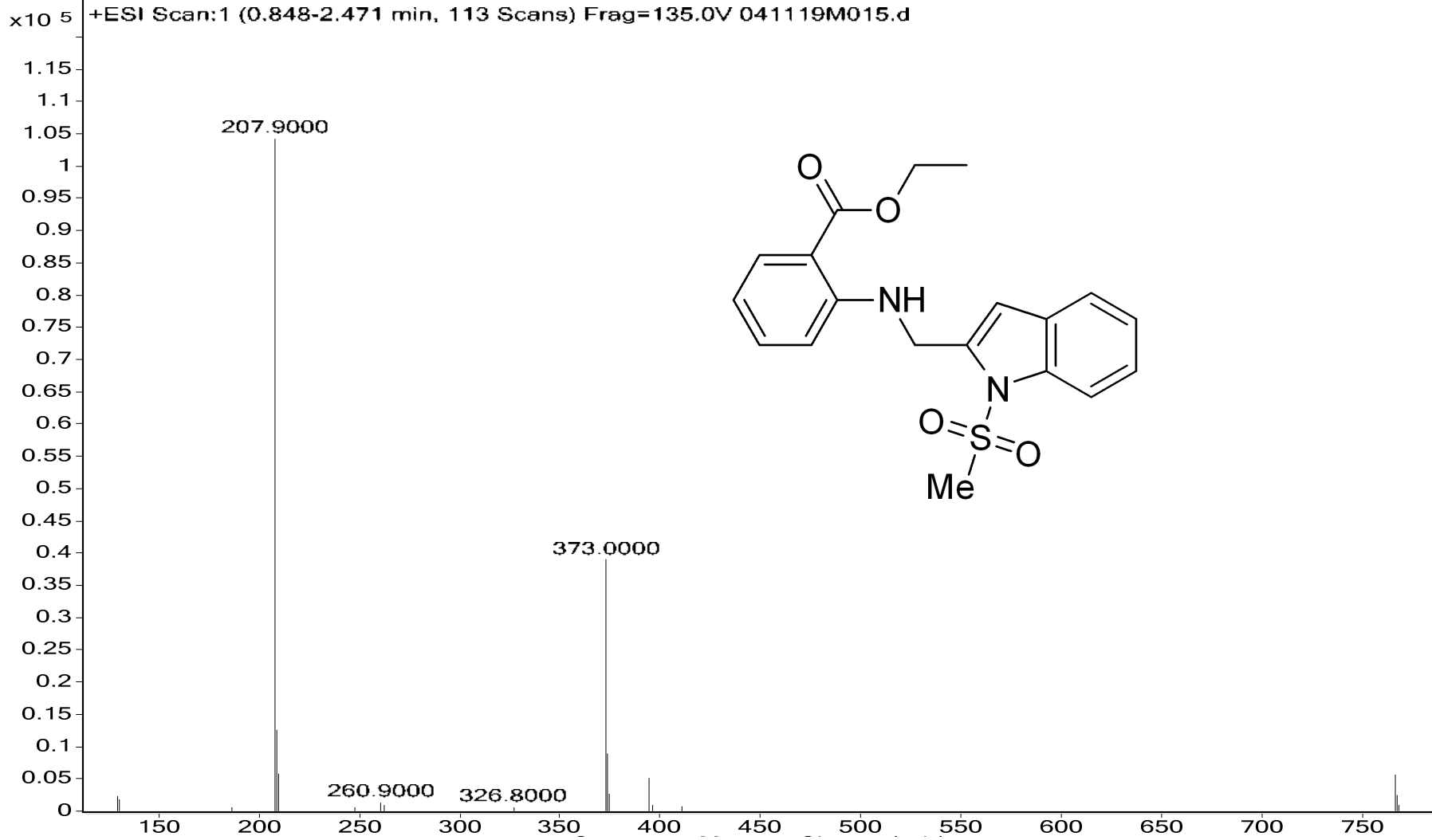
Mass spectrum of compound 4g

Sample Name	ILS-GSR-I2-Th2	Position	Vial 10	Instrument Name	LCMS	User Name	
Inj Vol	3	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	171019M011.d	ACQ Method	MMI-SM.m	Comment	MM19J032	Acquired Time	10/17/2019 1:36:25 PM



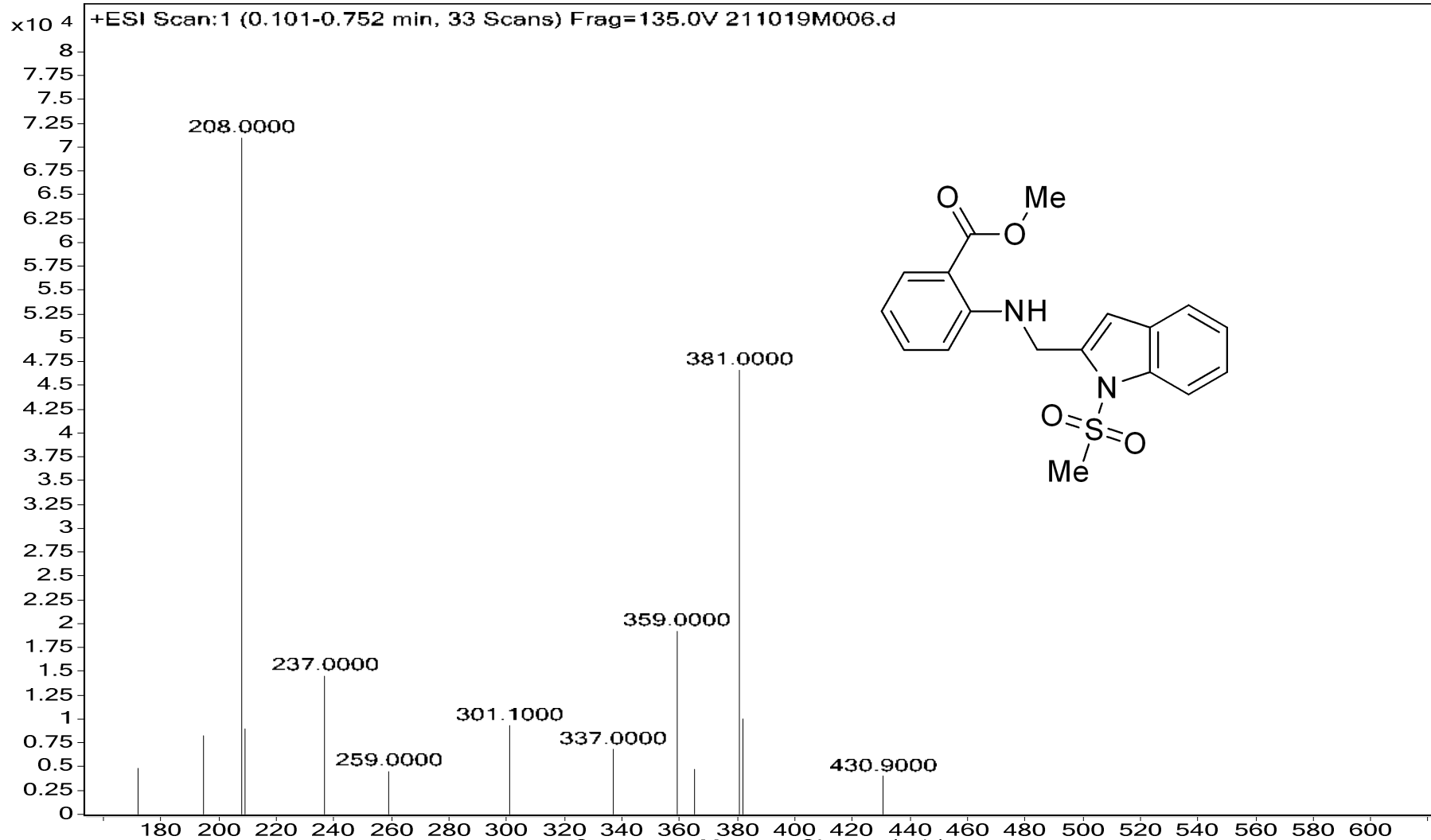
Mass spectrum of compound 4h

Sample Name	ILS-GSR-I2-MS2	Position	Vial 39	Instrument Name	LCMS	User Name	
Inj Vol	3	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	041119M015.d	ACQ Method	MMI-SM.m	Comment	MM19K007	Acquired Time	11/4/2019 4:11:01 PM



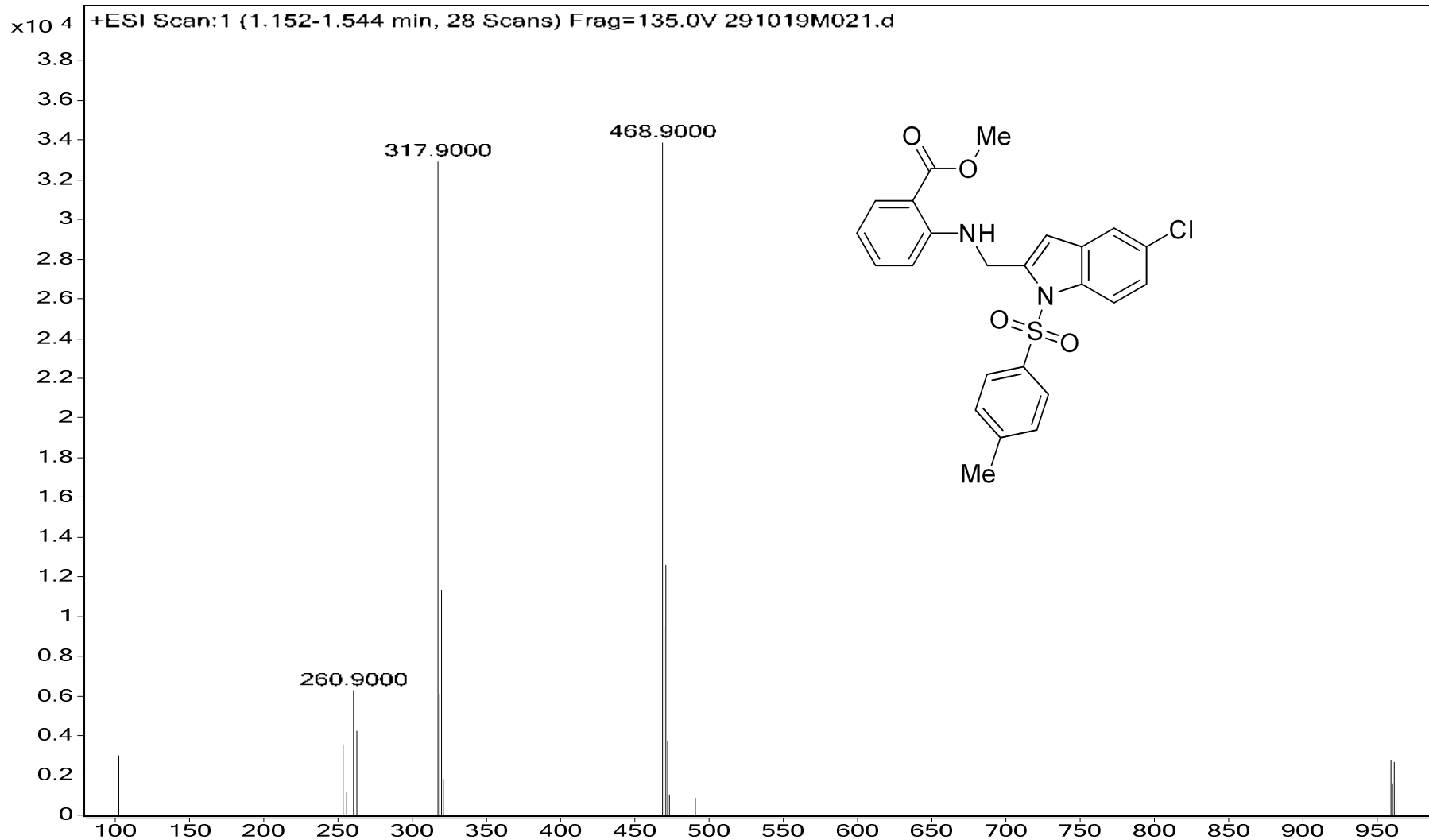
Mass spectrum of compound 4i

Sample Name	ILS-GSR-I2-MS-Me	Position	Vial 9	Instrument Name	LCMS	User Name	
Inj Vol	3	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	211019M006.d	ACQ Method	MMI-SM.m	Comment	MM19J037	Acquired Time	10/21/2019 12:40:12 PM



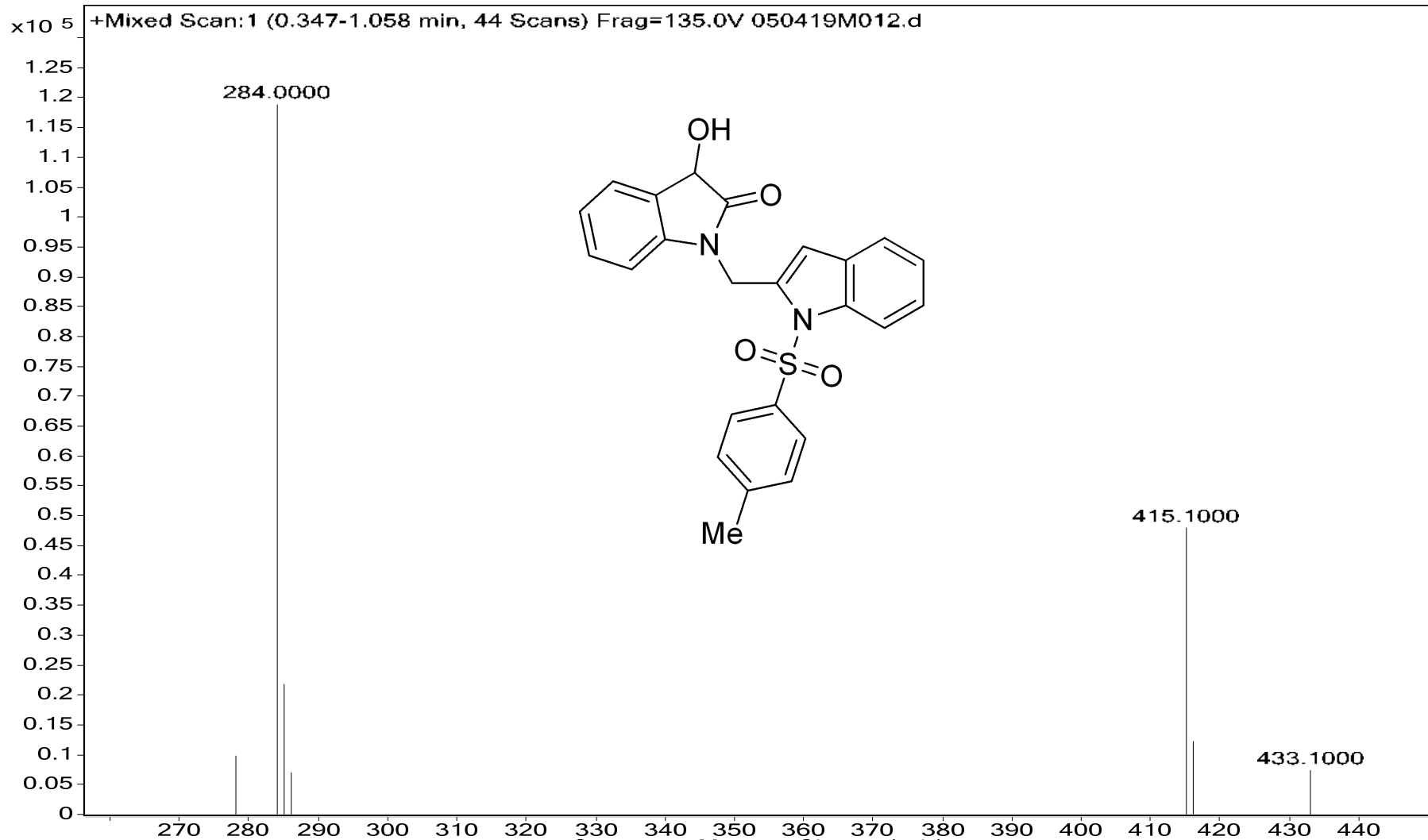
Mass spectrum of compound 4j

Sample Name	ILS-GSR-I2-Cl-Me	Position	Vial 59	Instrument Name	LCMS	User Name	
Inj Vol	3	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	291019M021.d	ACQ Method	MMI-SM.m	Comment	MM19J058	Acquired Time	10/29/2019 4:03:21 PM



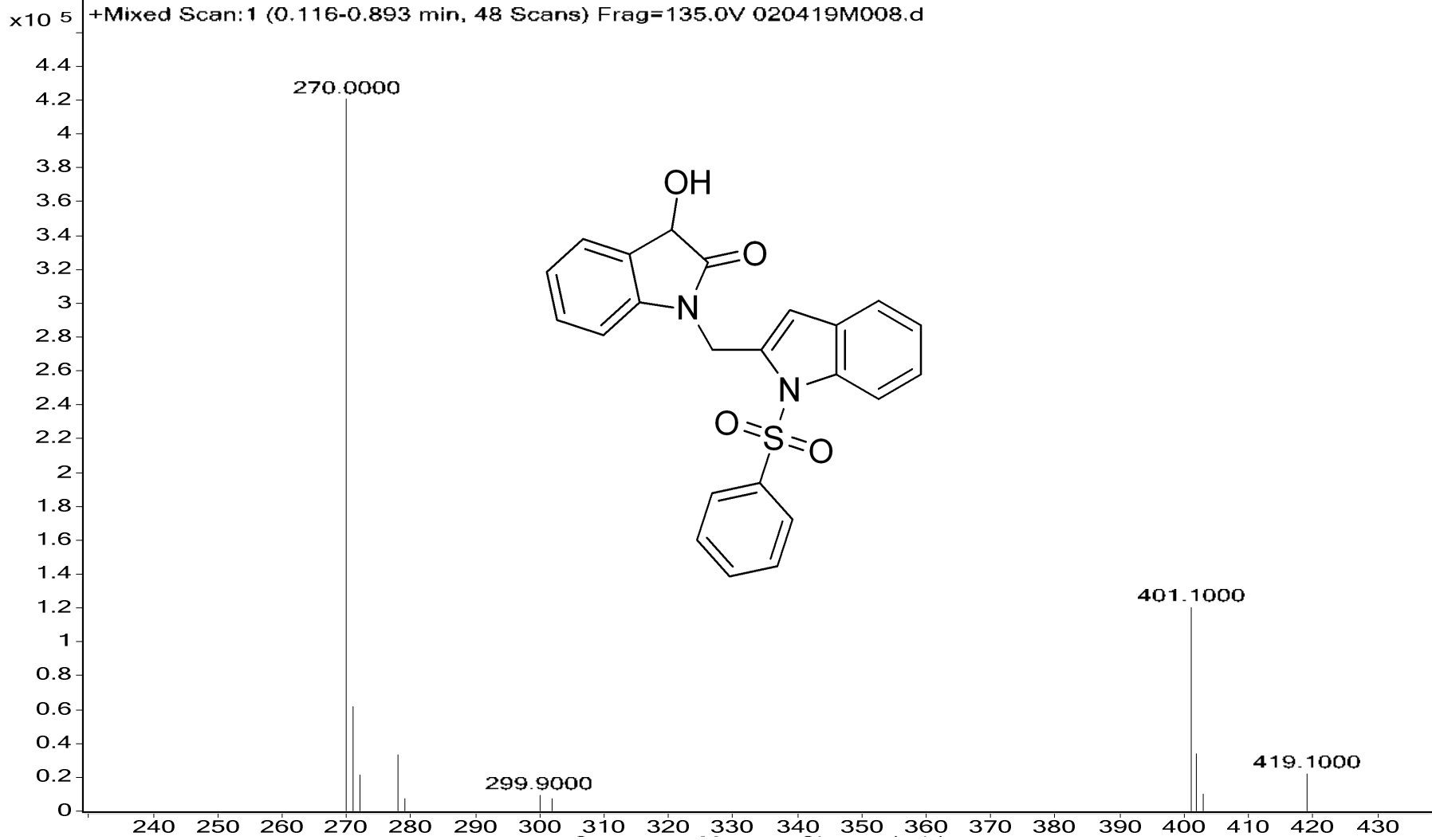
Mass spectrum of compound 5a

Sample Name	ILS-GSR-Z-TS	Position	Vial 30	Instrument Name	LCMS	User Name	
Inj Vol	3	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	050419M012.d	ACQ Method	MMI-SM.m	Comment	MM19D006	Acquired Time	4/5/2019 3:57:09 PM



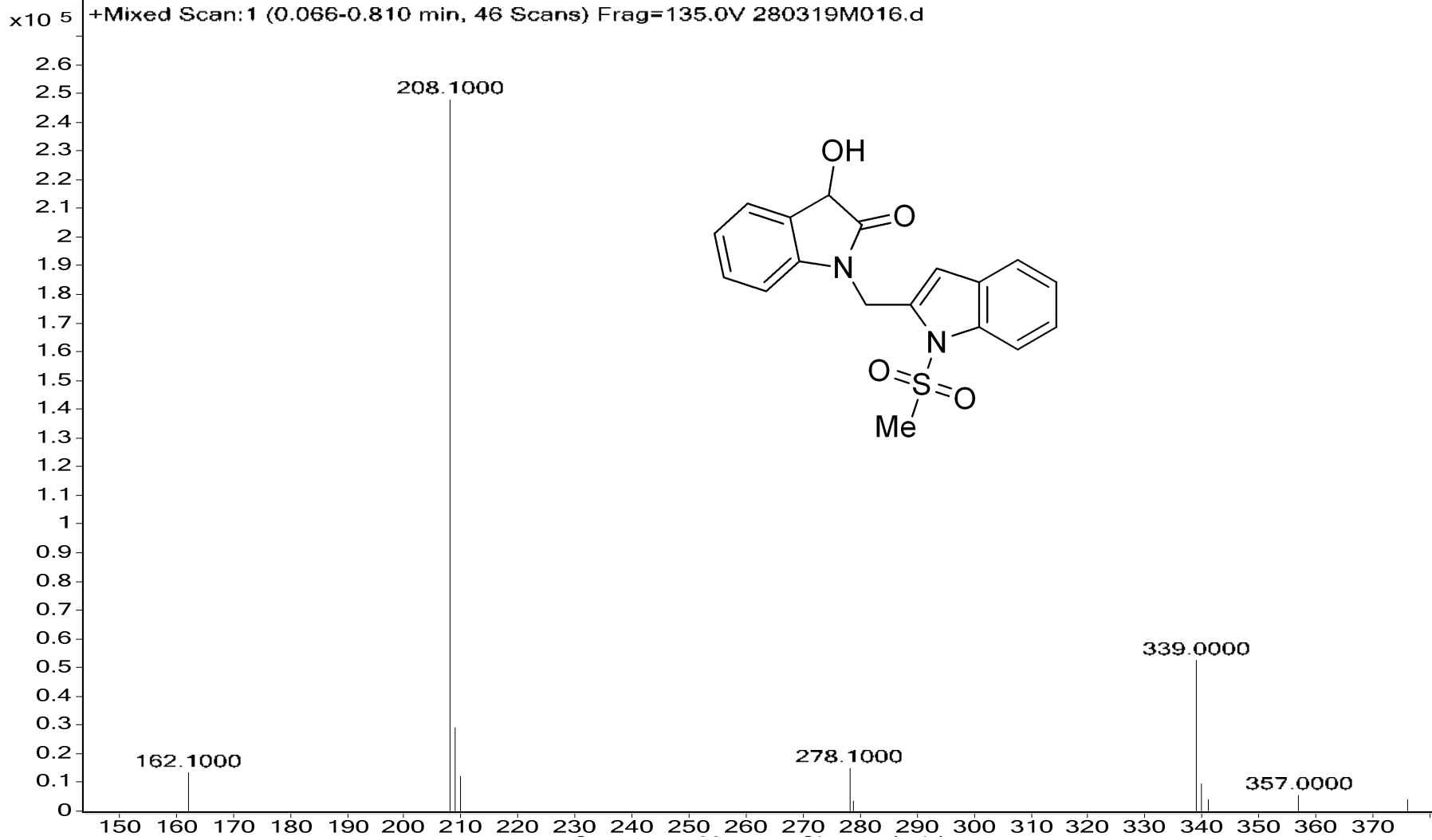
Mass spectrum of compound 5b

Sample Name	ILS-GSR-Z-Ben	Position	Vial 25	Instrument Name	LCMS	User Name	
Inj Vol	4	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	020419M008.d	ACQ Method	MMI-SM.m	Comment	MM19D001	Acquired Time	4/2/2019 1:05:12 PM



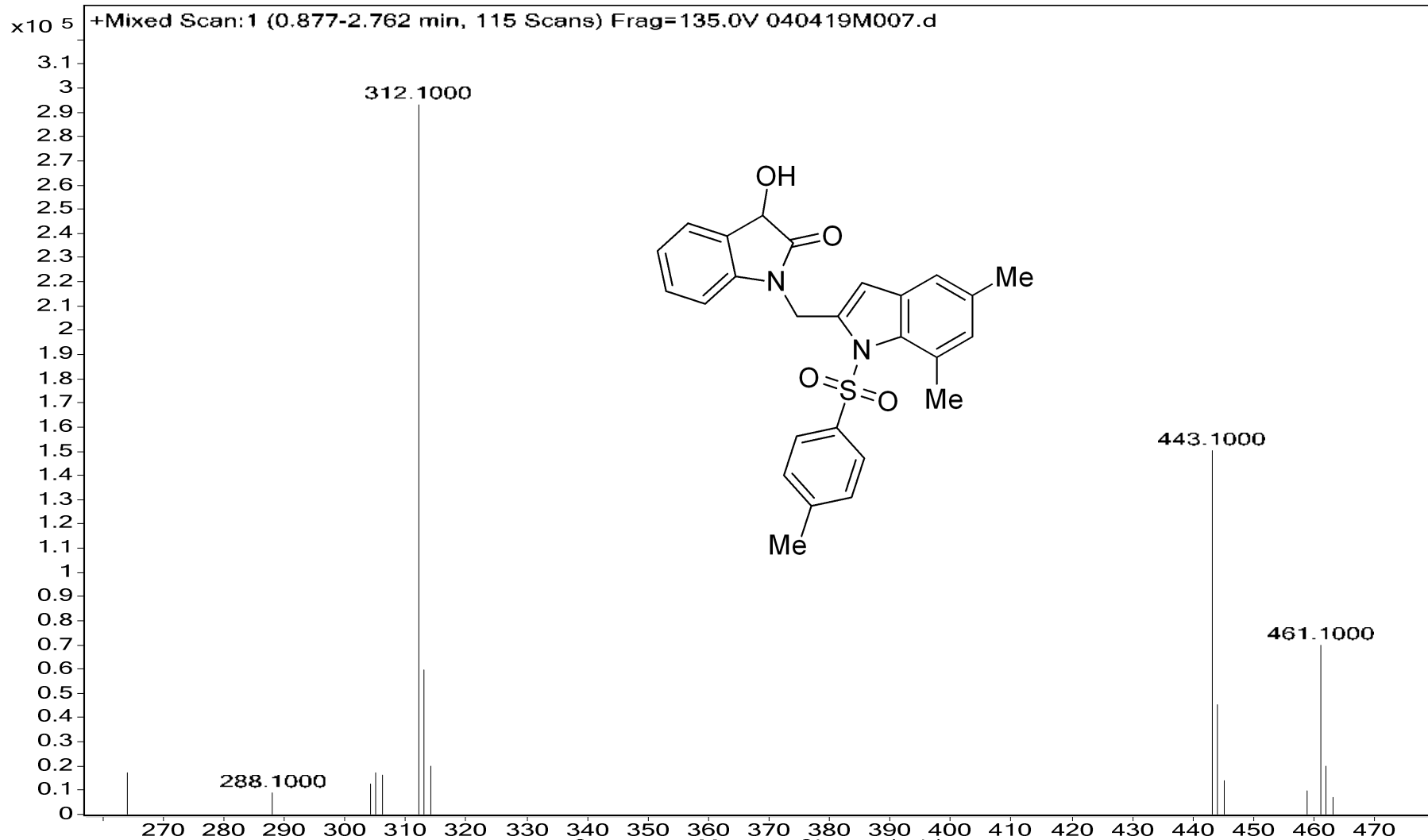
Mass spectrum of compound 5c

Sample Name	ILS-GSR-Z-MS	Position	Vial 49	Instrument Name	LCMS	User Name	
Inj Vol	10	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	280319M016.d	ACQ Method	MMI-SM.m	Comment	MM19C036	Acquired Time	3/28/2019 6:19:58 PM



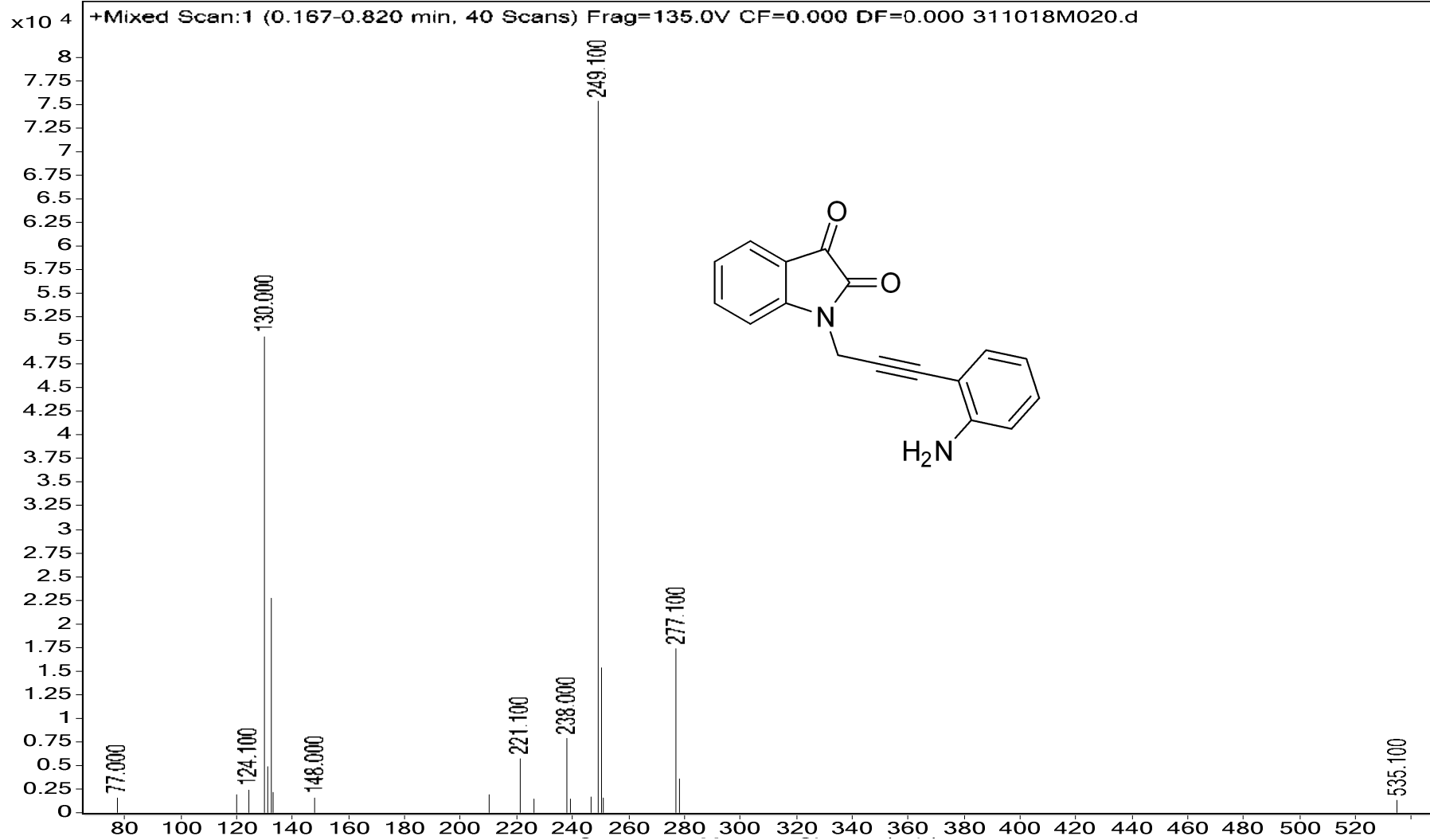
Mass spectrum of compound 5d

Sample Name	ILS-GSR-Z-DTS	Position	Vial 17	Instrument Name	LCMS	User Name	
Inj Vol	4	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	040419M007.d	ACQ Method	MMI-SM.m	Comment	MA19D004	Acquired Time	4/4/2019 3:52:49 PM



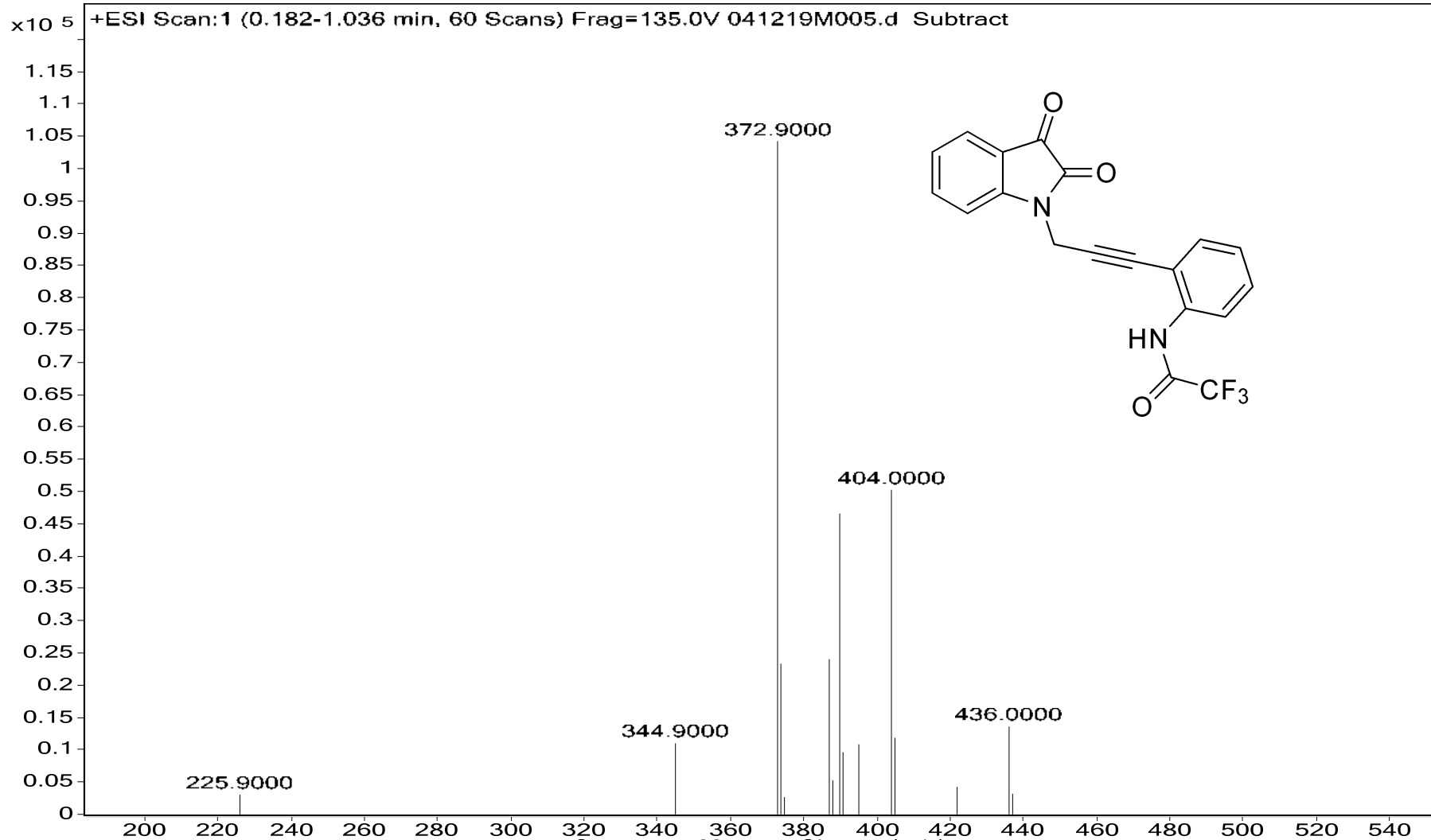
Mass spectrum of compound 6a

Sample Name	ILS-GSR-I2-An	Position	Vial 14	Instrument Name	LCMS	User Name	
Inj Vol	2	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	311018M020.d	ACQ Method	MMI-SM.m	Comment	MM18J042	Acquired Time	10/31/2018 4:15:43 PM



Mass spectrum of compound **6b**

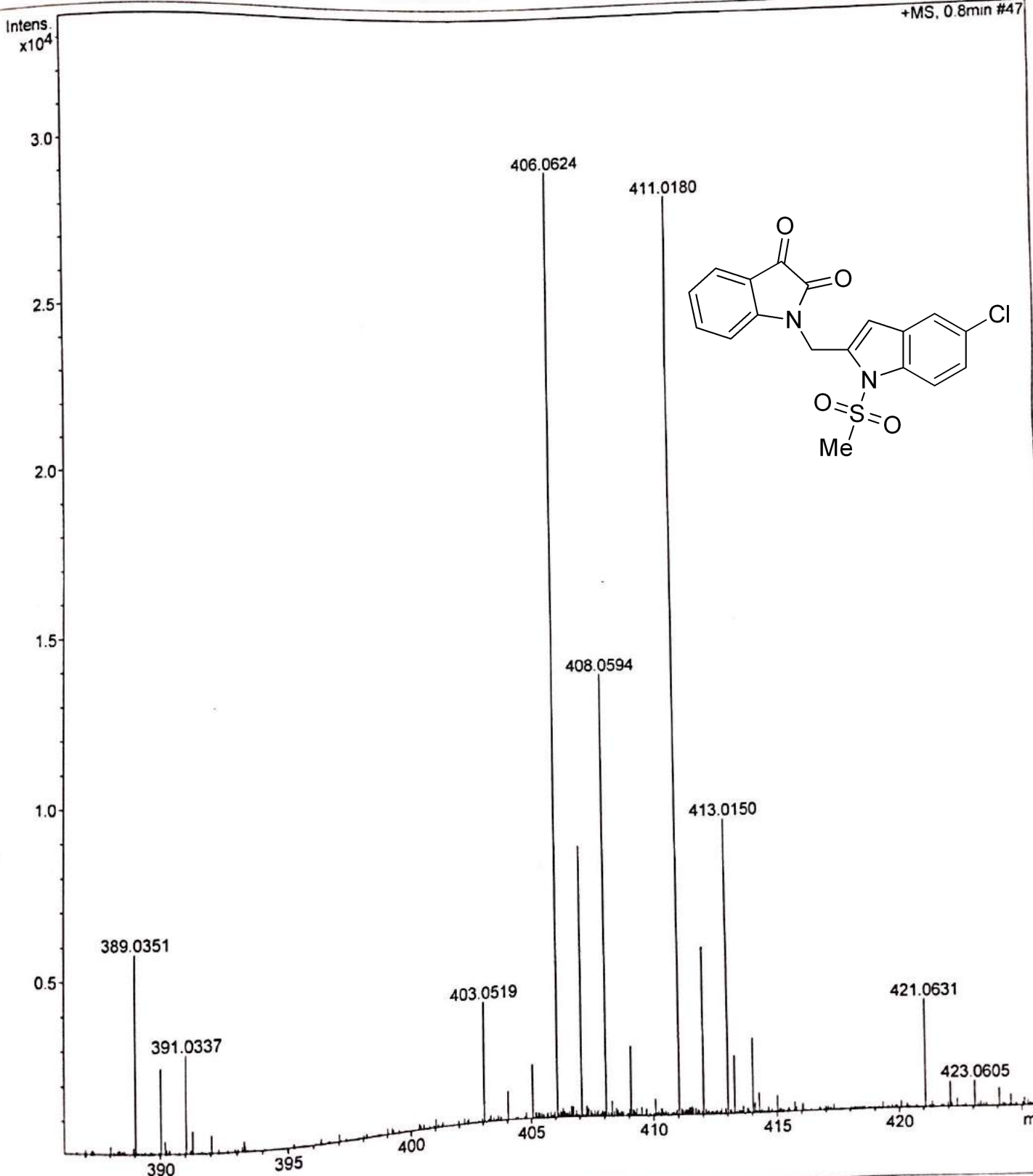
Sample Name	ILS-GSR-I2-CO	Position	Vial 26	Instrument Name	LCMS	User Name	
Inj Vol	3	InjPosition		SampleType	Sample	IRM Calibration Status	Not Applicable
Data Filename	041219M005.d	ACQ Method	MMI-SM.m	Comment	MM19L005	Acquired Time	12/4/2019 12:57:29 PM



HRMS spectrum of compound 3e

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	3800 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	6.0 l/min
Scan End	1800 m/z	Set Collision Cell RF	350.0 Vpp	Set Divert Valve	Waste



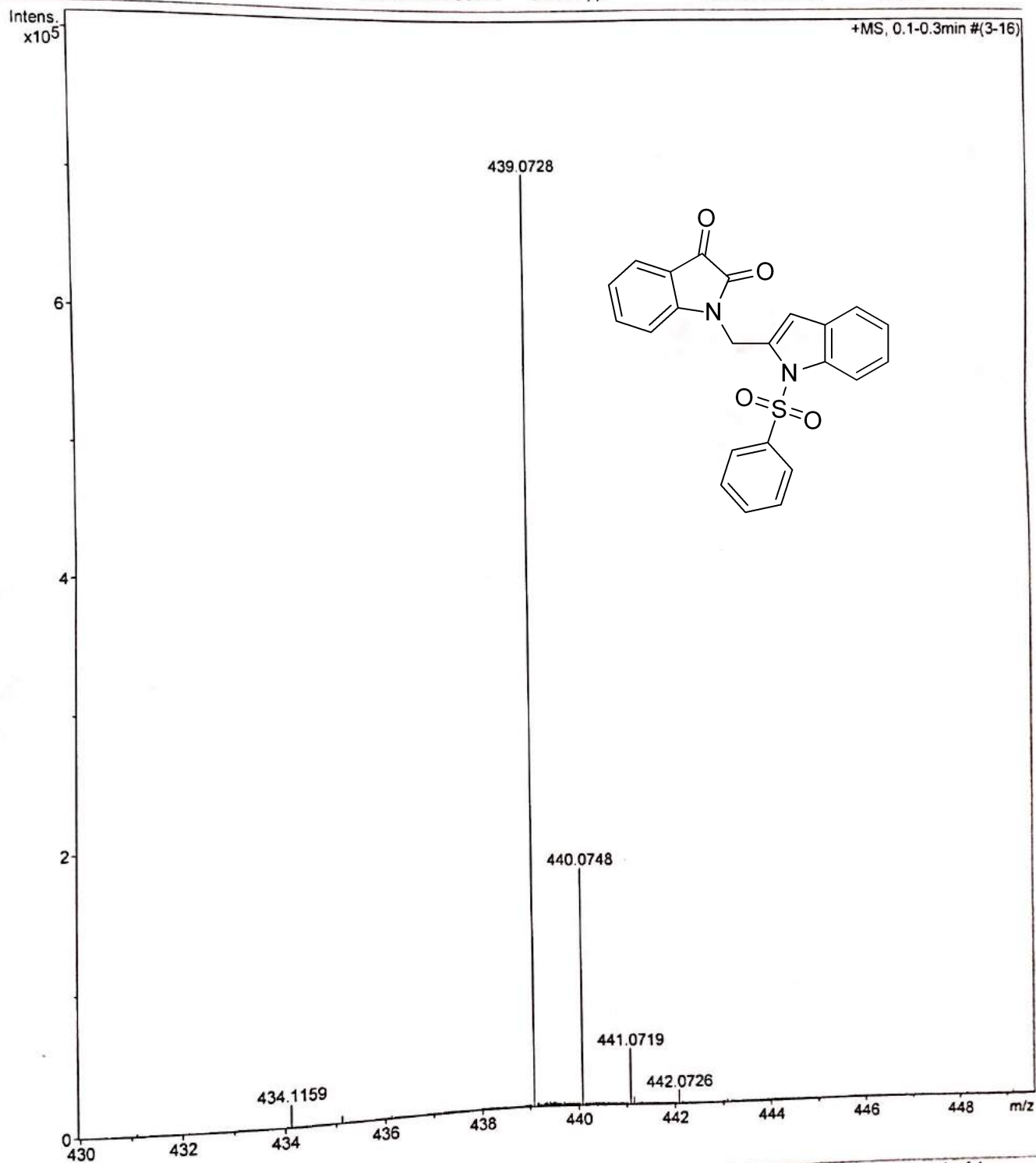
printed: 12/5/2019 3:25:33 AM

Page 1 of 1

HRMS spectrum of compound 3f

Acquisition Parameter

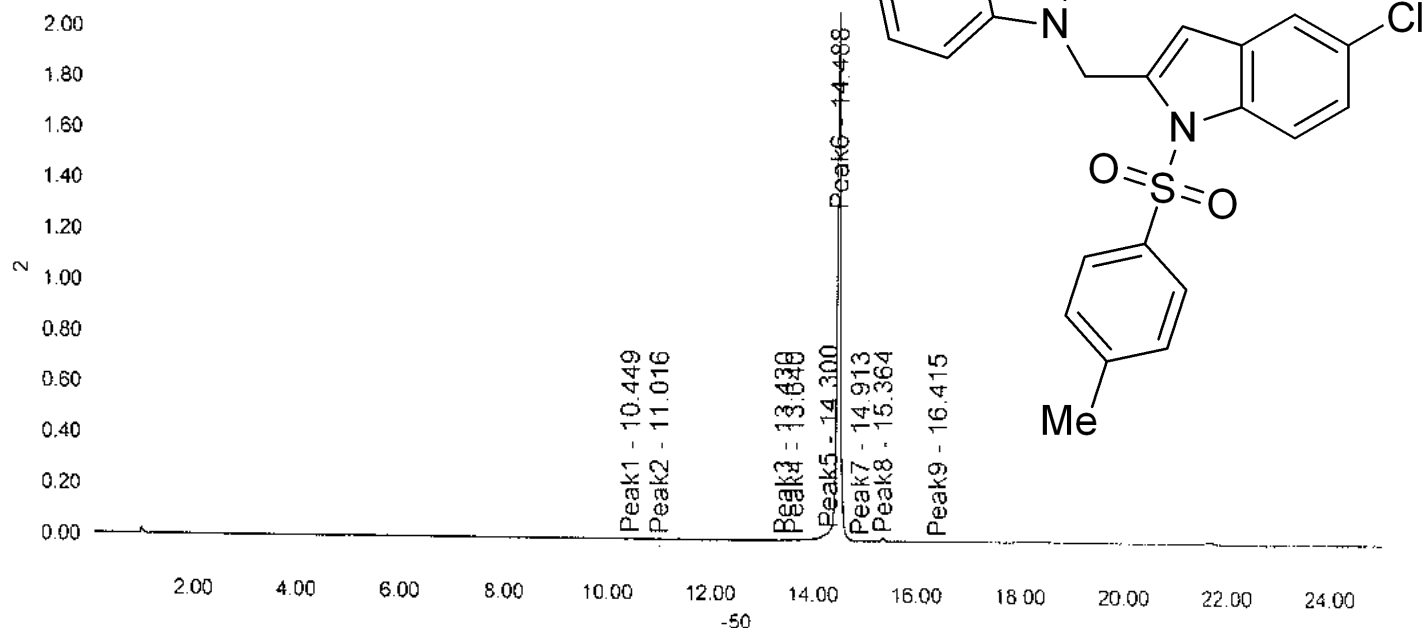
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	3800 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	6.0 l/min
Scan End	1800 m/z	Set Collision Cell RF	350.0 Vpp	Set Divert Valve	Waste



SAMPLE INFORMATION

Sample Name:	ILS-GSR-I2-CI-Ts	Acquired By:	System
AR Number :	CM18L011	Sample Set Name:	26122018_005
Vial:	70	Acq. Method Set:	API LVO_M
Injection #:	1	Processing Method:	ILS PROC
Injection Volume:	10.00 ul	Channel Name:	245.0nm
Run Time:	25.0 Minutes	Proc. Chnl. Descr.:	PDA 245.0 nm
Date Acquired: 12/26/2018 10:52:41 AM IST			
Date Processed: 12/26/2018 12:42:50 PM IST			

Column : Symmetry C18 4.6*75mm 3.5um
 Mobile phase : A) 10mM Ammonium Formate in water B) ACN
 T/B: 0/10, 3/10, 15/95, 20/95, 21/10, 25/10
 Flow: 1.0ml/min, Diluent: ACN:water(80:20)



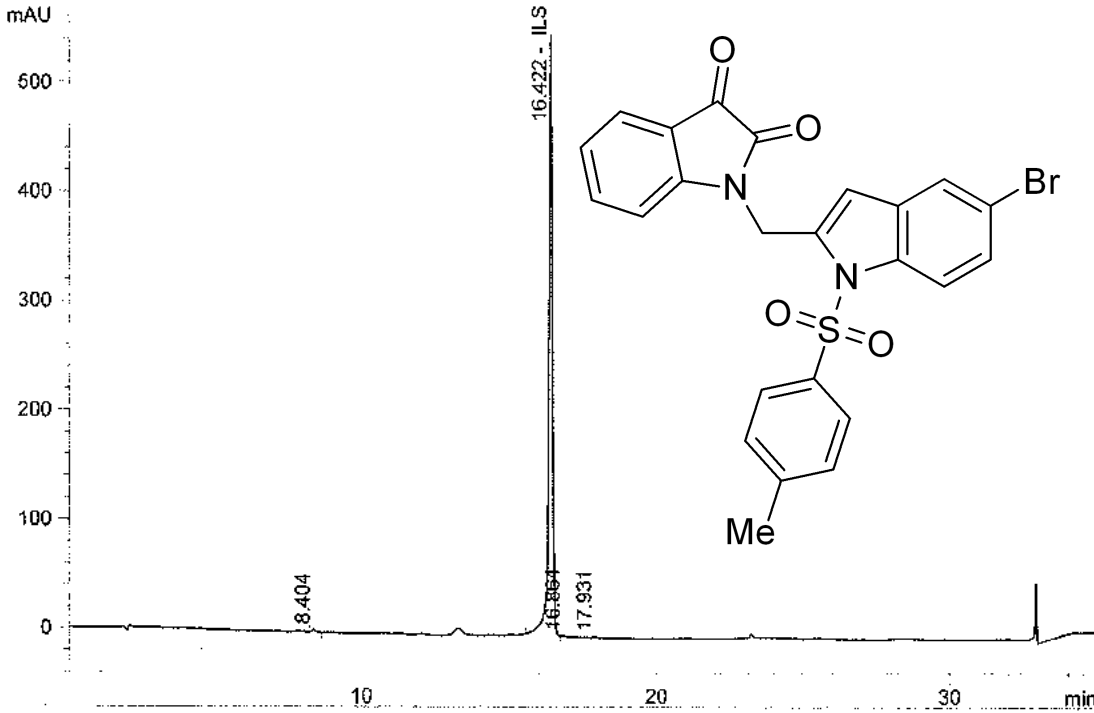
Peak Name	RT	Area	% Area
1 Peak1	10.449	7731	0.08
2 Peak2	11.016	2411	0.02
3 Peak3	13.430	7498	0.07
4 Peak4	13.640	6863	0.07
5 Peak5	14.300	197026	1.95
6 Peak6	14.488	9803070	97.15
7 Peak7	14.913	10534	0.10
8 Peak8	15.364	52651	0.52

Peak Name	RT	Area	% Area
9 Peak9	16.415	3233	0.03

Injection Date : Tue, 6. Nov. 2018 Seq Line : 1
 Sample Name : ILS-GSR-I2-BrTs Sample Name : 2
 Acq Operator : RAMESH G Inj. No. : 1
 A R Number : CM18K003 -> Inj. Vol. : 5 µl
 Acq. Method : D:\DATA\2018\NOV-2018\06112018-002 2018-11-06 14-37-->
 Analysis Method : D:\CHEM32\1\METHODS\LVO IMP_M2.M
 Last Changed : Tue, 6. Nov. 2018, 03:37:23 pm

Column : Cosmicsil Aura ODS 150*4.6mm 5µm
 Mobile phase: A) 0.1% TFA in water , B) ACN
 T/B%: 0/30,20/95,30/95,31/30,35/30.
 Flow:1.0ml/min, Diluent: ACN:Water (80:20).

*DAD1, Sig=245.00, 1.00 Ref=off, EXT of 06112018-006.D



Customized Report: test2

Sorted By Signal
 Calib. Data Modified : Tue, 6. Nov. 2018, 03:37:23 pm

#	Compound Name	RT	RelRT	Area	Area%	Symmetry	Plates	Resolution
1		8.404	0.51	22.799	0.451	0.865	22010.08	
2	ILS	16.422	1.00	5019.009	99.353	1.248	89939.64	35.929
3		16.864	1.03	3.938	0.078	0.640	70025.63	1.861
4		17.931	1.09	5.940	0.118	0.907	100192.05	4.424

Analyzed By

Checked By *Rep*

*** End of Report ***

06/11/18

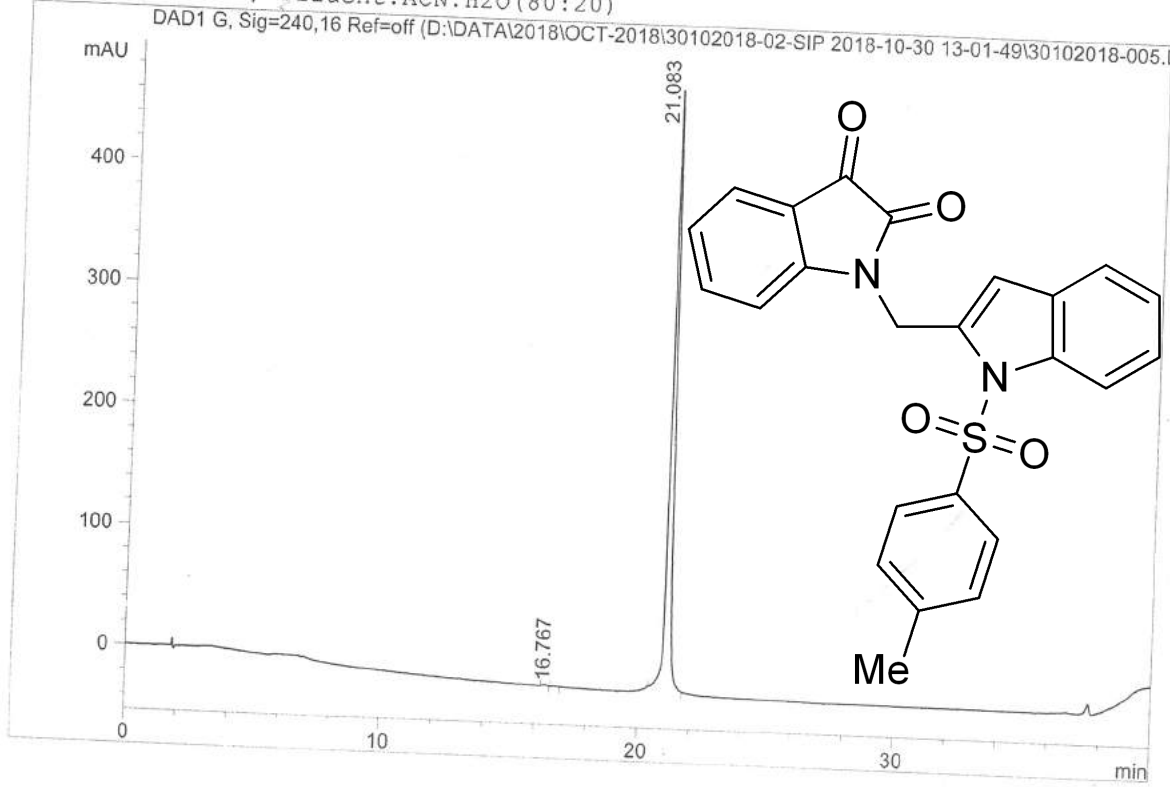
06/11/2018

Injection Date : Tue, 30. Oct. 2018
 Sample Name : ILS-GSR-I2-TS
 Acq Operator : RamaDevi
 A R Number : CM18J022
 Acq. Method : D:\DATA\2018\OCT-2018\30102018-02-SIP 2018-10-30 13-->
 Analysis Method : D:\CHEM32\1\METHODS\API SIP_M2.M
 Last Changed : Tue, 30. Oct. 2018, 03:54:27 pm

Seq Line : 3
 Sample Name : 12
 Inj. No. : 1
 Inj. Vol. : 5 µl

Column : X- Bridge C18 150*4.6mm 5µm
 Mobile phase: A) 0.1% TFA in water , B) ACN
 T/B%: 0/5, 25/90, 35/90, 36/5, 40/5
 Flow: 1.0ml/min, Diluent: ACN:H2O (80:20)

DAD1 G, Sig=240,16 Ref=off (D:\DATA\2018\OCT-2018\30102018-02-SIP 2018-10-30 13-01-49\30102018-005.



Customized Report: test2

Sorted By Signal
 Calib. Data Modified : Tue, 30. Oct. 2018, 03:54:27 pm

#	Compound Name	RT	RelRT	Area	Area%	Symmetry	Plates	Resolution
1		16.376	0.78	10.325	0.209	0.686	69067.33	
2		16.767	0.80	3.978	0.081	0.581	36463.84	1.299
3		21.083	1.00	4923.281	99.710	0.711	134012.57	14.820

Analyzed By: *[Signature]* 30/10/2018
 Checked By: *[Signature]* 30/10/2018

*** End of Report ***

HPLC of compound 3e

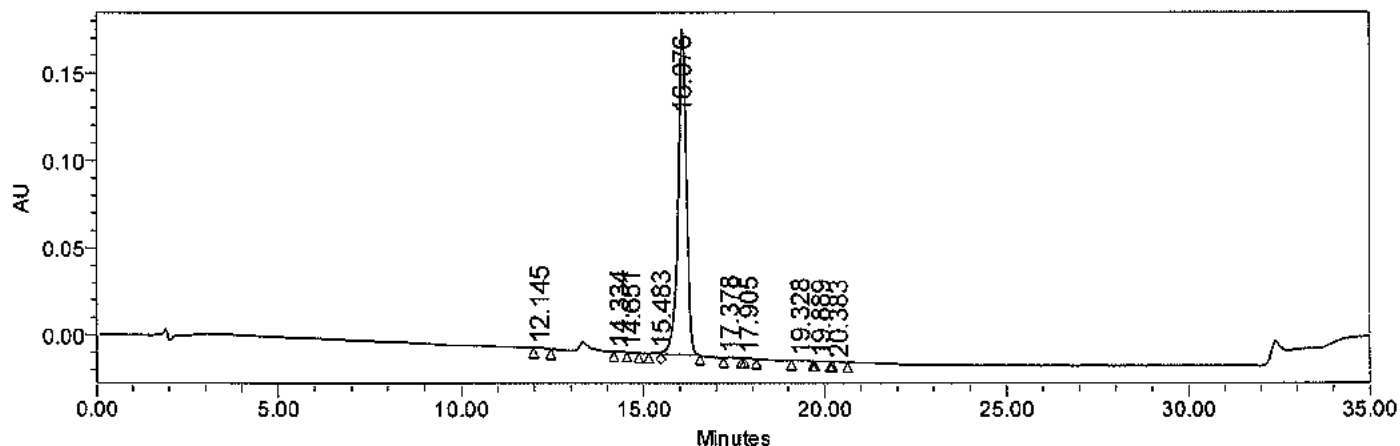


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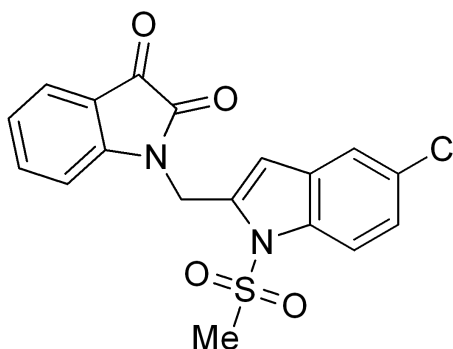
SAMPLE INFORMATION

Sample Name:	ILS-GSR-I2-CL-MS	Acquired By:	System
A.R.Number:	CM19L001	Sample Set Name:	02122019002
Vial:	67	Acq. Method Set:	API ABT_M
Injection #:	1	Processing Method:	ILS PRO
Injection Volume:	5.00 ul	Channel Name:	225.0nm
Run Time:	35.0 Minutes	Proc. Chnl. Descr.:	PDA 225.0 nm
Date Acquired:	12/2/2019 11:42:45 PM IST		
Date Processed:	12/3/2019 9:48:45 AM IST		

Column: X-Bridge C-18 150*4.6mm 5µm
 Mobile phase: A) 5mMNH4OAC in water B) ACN
 T/%B: 0/5, 20/90,30/90, 31/5, 35/5
 Flow: 1.0ml/min, Diluent: ACN:H2O (80:20)



	RT	Height	Area	% Area
1	12.145	564	7860	0.26
2	14.334	190	2461	0.08
3	14.651	179	2122	0.07
4	15.483	1008	13426	0.45
5	16.076	186642	2955091	98.40
6	17.378	407	5722	0.19
7	17.905	255	2908	0.10
8	19.328	505	9265	0.31
9	19.889	133	1852	0.06
10	20.383	180	2413	0.08

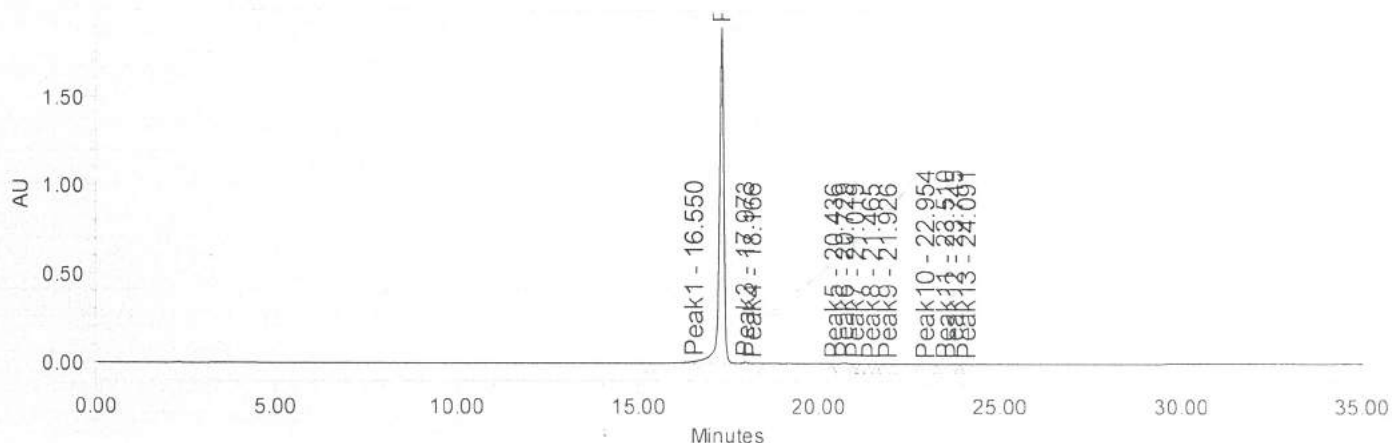


SAMPLE INFORMATION

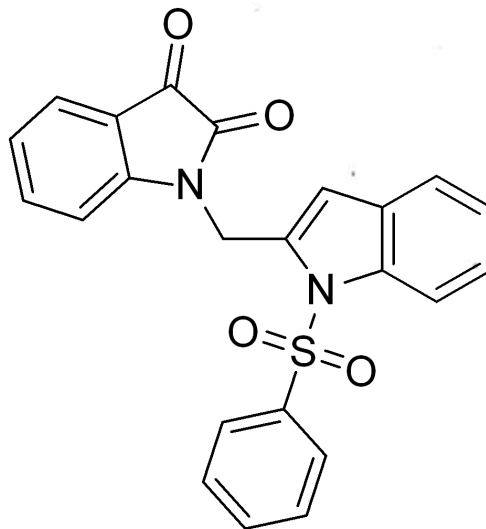
Sample Name:	ILS-GSR-I2-Ben	Acquired By:	System
A.R.Number:	CM18L006	Sample Set Name:	17122018_004
Vial:	27	Acq. Method Set:	API CRI_M
Injection #:	1	Processing Method:	ILS PROC
Injection Volume:	10.00 ul	Channel Name:	245.0nm
Run Time:	35.0 Minutes	Proc. Chnl. Descr.:	PDA 245.0 nm

Date Acquired: 12/17/2018 8:58:35 PM IST
Date Processed: 12/18/2018 10:55:03 AM IST

Column: Cosmicsil Aura ODS C-18 150*4.6mm 5um
Mobile phase: A) 0.1% TFA in water B) ACN
T/%B: 0/10,20/95,27/95,31/10,35/10
Flow: 1.0ml/min, Diluent: ACN :H2O (80:20)



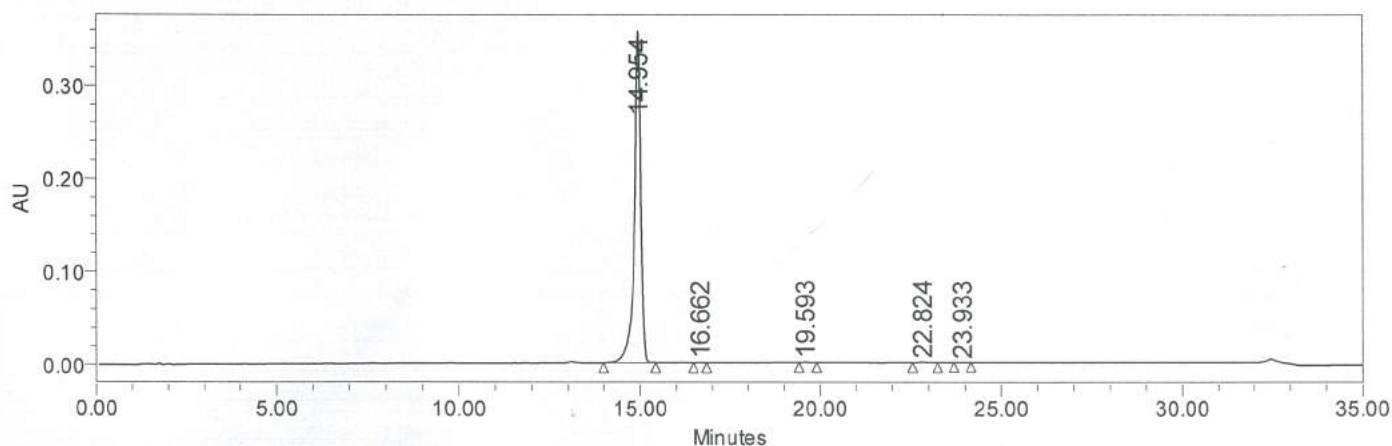
Peak Name	RT	Height	Area	% Area
1 Peak1	16.550	10876	207920	1.24
2 Peak2	17.316	1895676	16387912	97.92
3 Peak3	17.973	9328	79452	0.47
4 Peak4	18.166	553	5933	0.04
5 Peak5	20.436	98	591	0.00
6 Peak6	20.729	4210	33049	0.20
7 Peak7	21.019	68	415	0.00
8 Peak8	21.465	98	701	0.00
9 Peak9	21.926	1450	11162	0.07
10 Peak10	22.954	183	1996	0.01
11 Peak11	23.510	95	1024	0.01



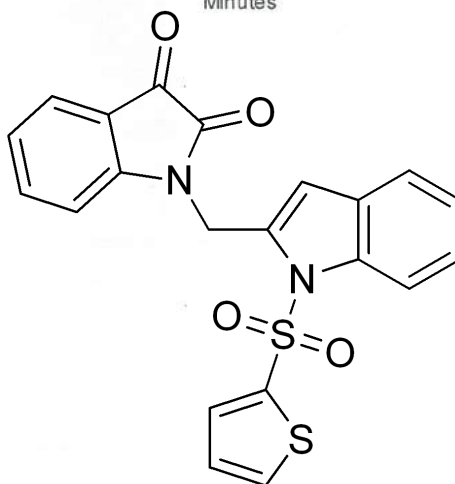
SAMPLE INFORMATION

Sample Name:	ILS-GSR-I2-TH	Acquired By:	System
A.R.Number:	CA19J031	Sample Set Name:	18102019_02
Vial:	56	Acq. Method Set:	ILS_RS_MET
Injection #:	1	Processing Method:	ILS PRO
Injection Volume:	5.00 ul	Channel Name:	245.0nm
Run Time:	35.0 Minutes	Proc. Chnl. Descr.:	PDA 245.0 nm
Date Acquired:	10/18/2019 10:51:25 PM IST		
Date Processed:	10/21/2019 5:05:36 PM IST		

Column: X-BRIDGE C-18 150*4.6mm 5µm
 Mobile phase: A) 5mMNH4OAC in water B) ACN
 T/%B: 0/20, 20/90,30/90, 31/20, 35/20
 Flow: 1.0ml/min, Diluent: ACN:THF



	RT	Height	Area	% Area
1	14.954	356962	4363138	99.57
2	16.662	196	1789	0.04
3	19.593	589	5894	0.13
4	22.824	732	8833	0.20
5	23.933	131	2227	0.05



Analysed by

Amey
21/10/19

Checked by

lp
21/10/19



HPLC of compound 3i

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SAMPLE INFORMATION

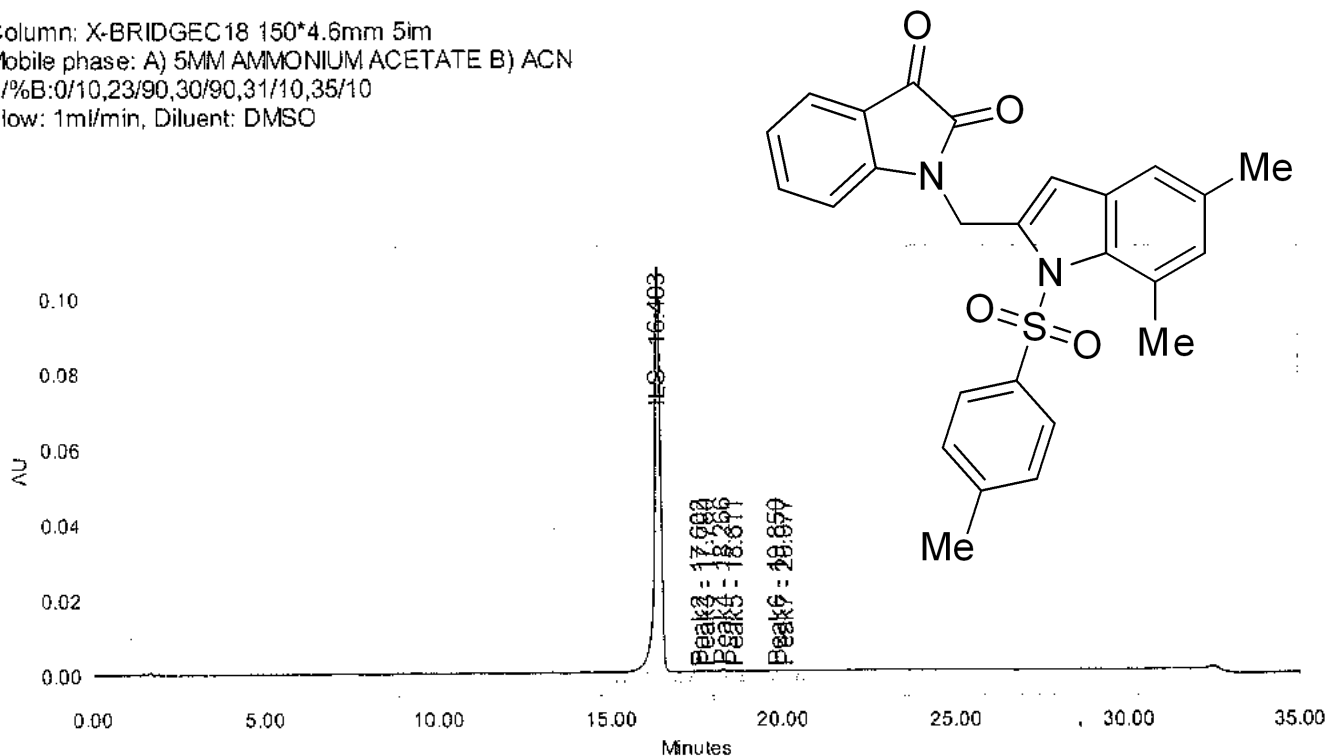
Sample Name: ILS-GSR-I2-DTS
A.R.Number:
Vial: 95
Injection #: 1
Injection Volume: 5.00 ul
Run Time: 35.0 Minutes

Acquired By: System
Sample Set Name: FF
Acq. Method Set: ILS_MET
Processing Method: ILS_PRO
Channel Name: 245.0nm
Proc. Chnl. Descr.: PDA 245.0 nm

Date Acquired: 4/4/2019 8:59:06 PM IST

Date Processed: 4/5/2019 9:49:40 AM IST

Column: X-BRIDGEC18 150*4.6mm 5m
Mobile phase: A) 5MM AMMONIUM ACETATE B) ACN
T/%B:0/10,23/90,30/90,31/10,35/10
Flow: 1ml/min, Diluent: DMSO



Peak Name	RT	Height	Area	% Area	RT Ratio
1 ILS	16.403	107752	1271511	98.77	
2 Peak2	17.602	144	1306	0.10	1.07
3 Peak3	17.780	282	3666	0.28	1.08
4 Peak4	18.266	499	5133	0.40	1.11
5 Peak5	18.611	212	2261	0.18	1.13
6 Peak6	19.850	40	382	0.03	1.21

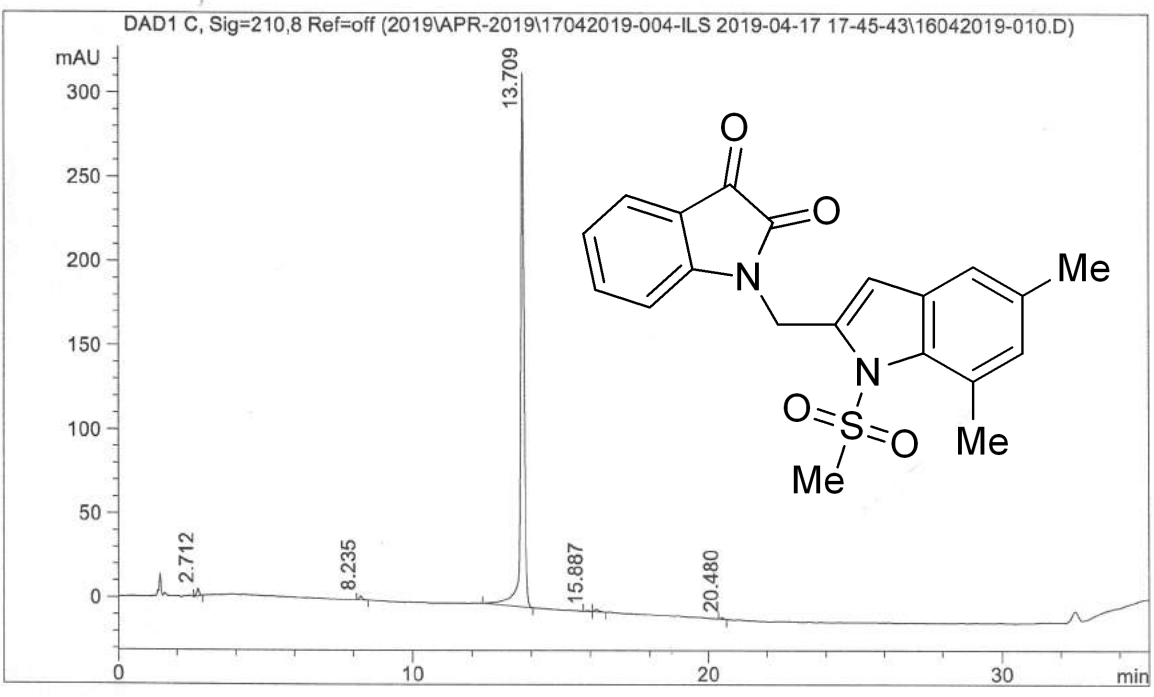
Injection Date : Wed, 17. Apr. 2019 Seq Line : 2
 Location : Vial 42
 Sample Name : ILS-GSR-I2-DMS Inj. No. : 1
 AR Number : CA19D008 -> Inj. Vol. : 5 µl

Acq. Method : C:\Chem32\1\DATA\2019\APR-2019\17042019-004-ILS 2019->
 Analysis Method : C:\CHEM32\1\METHODS\API ILS.M
 Last Changed : Mon, 22. Apr. 2019, 05:13:52 pm
 (modified after loading)

COLUMN: X-BRIDGE C18, 150*4.6mm 3.5µm
 A) 0.1% TEA IN WATER (pH 3) B) ACN
 T/%B: 0/10, 3/10, 15/95, 23/95, 25/10, 30/10
 Flow rate: 1.0mL/min DILUENT: ACN: H2O (20:80)

A) 0.1% TEA in WATER pH-3 with OPA.

HPLC of compound 3j



Customized Report: Short

Sorted By Signal
 Calib. Data Modified : Mon, 22. Apr. 2019, 05:13:51 pm
 Multiplier : 1.000000
 Dilution : 1.000000
 Uncalibrated Peaks : not reported

Signal 1: DAD1 C, Sig=210,8 Ref=off

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	2.712	MM	0.106	28.207	1.025	
2	8.235	MM	0.135	18.232	0.662	
3	13.709	MM	0.141	2677.587	97.284	ILS
4	15.887	MF	0.166	5.870	0.213	
5	16.193	FM	0.178	15.830	0.575	
6	20.480	MM	0.111	6.624	0.241	

M. Renuka.
22/04/2019.

Handwritten signature and date: 22/04/2019



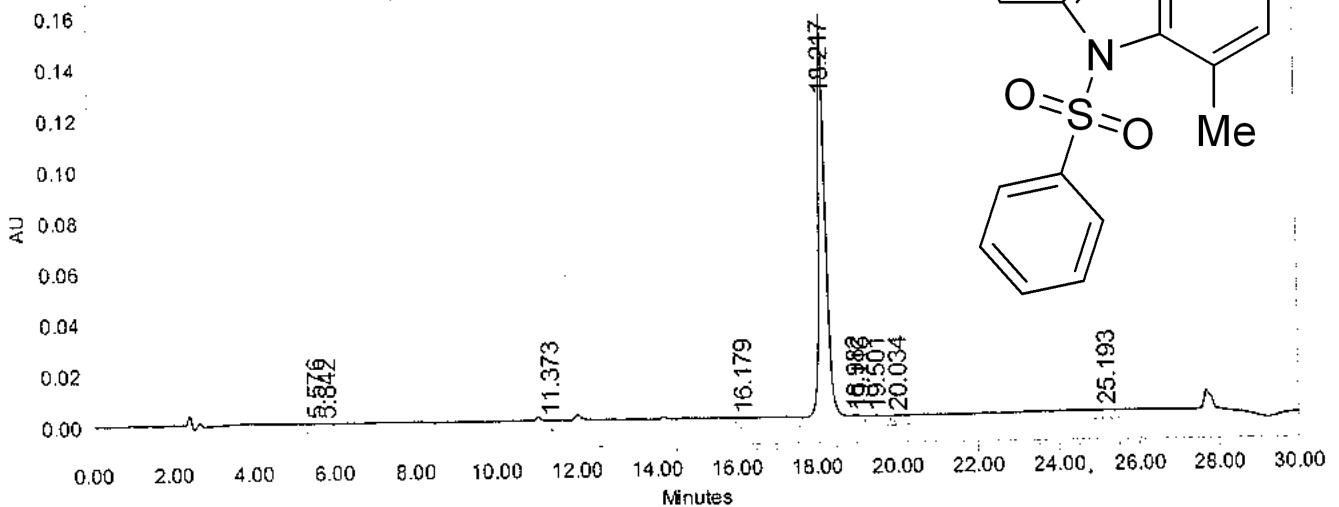
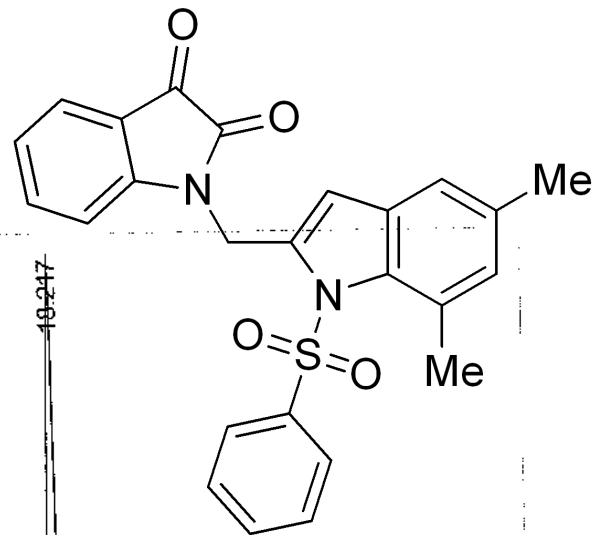
HPLC of compound 3k

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SAMPLE INFORMATION

Sample Name:	ILS-GSR-I2-DB	Acquired By:	System
A.R.Number:	CA19D013	Sample Set Name:	22042019_002
Vial:	103	Acq. Method Set:	API BDM IMP01 B4_M
Injection #:	1	Processing Method:	BDM PRO
Injection Volume:	5.00 ul	Channel Name:	240.0nm
Run Time:	30.0 Minutes	Proc. Chnl. Descr.:	PDA 240.0 nm
Date Acquired:	4/22/2019 7:10:08 PM IST		
Date Processed:	4/23/2019 11:25:52 AM IST		

Column: COSMOSIL C-18 150*4.6mm 5µm
Mobile phase: A) 5MM AMMONIUM ACETATE in water B) ACN
T/%B: 0/5,20/90,25/90,26/5,30/5
Flow: 1.0ml/min, Diluent: ACN:H2O (80:20)



	RT	Height	Area	% Area
1	5.576	103	1247	0.07
2	5.842	52	479	0.03
3	11.373	95	567	0.03
4	16.179	94	864	0.05
5	18.217	157152	1853508	98.95
6	18.982	601	7746	0.41

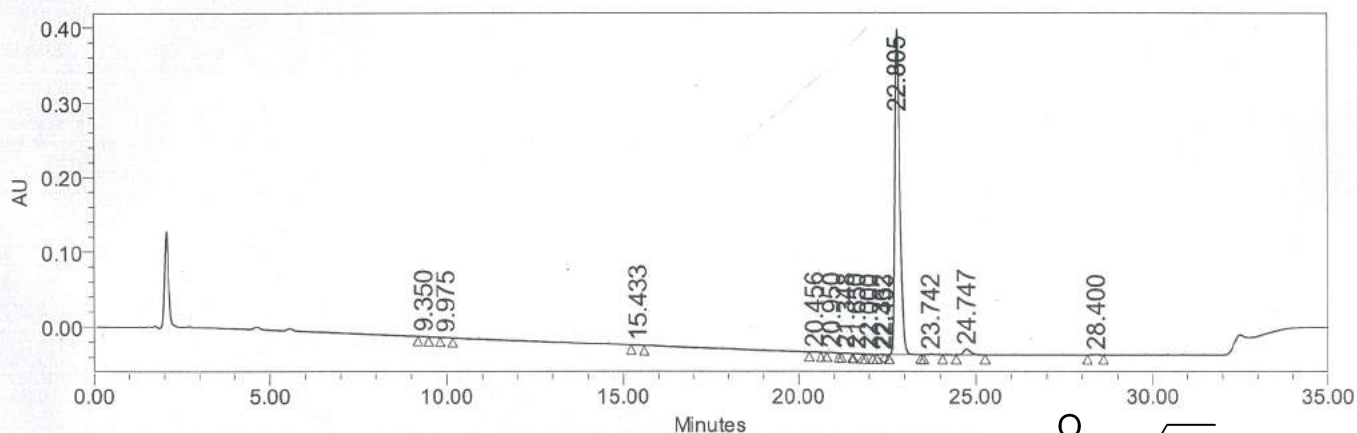
	RT	Height	Area	% Area
7	19.116	271	2359	0.13
8	19.501	227	3892	0.21
9	20.034	122	1155	0.06
10	25.193	124	1316	0.07

HPLC of compound 4a

SAMPLE INFORMATION

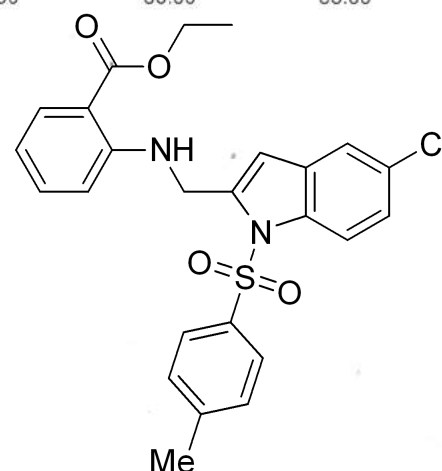
Sample Name:	ILS-GSR-I-CL-TS	Acquired By:	System
A.R.Number:	CM19J023	Sample Set Name:	14102019_03
Vial:	108	Acq. Method Set:	ILS_RS_MET
Injection #:	1	Processing Method:	ILS_PRO
Injection Volume:	5.00 ul	Channel Name:	220.0nm
Run Time:	35.0 Minutes	Proc. Chnl. Descr.:	PDA 220.0 nm
Date Acquired:	10/14/2019 11:22:15 PM IST		
Date Processed:	10/15/2019 10:31:16 AM IST		

Column: X-Bridge C-18 150*4.6mm 5um
 Mobile phase: A) 5mMNH4OAC in water B) ACN
 T/%B: 0/20, 20/90,30/90, 31/20, 35/20
 Flow: 1.0ml/min, Diluent: THF:ACN:H2O (80:20)



	RT	Height	Area	% Area
1	9.350	194	1781	0.04
2	9.975	377	3955	0.09
3	15.433	339	3722	0.08
4	20.456	192	1956	0.04
5	20.950	212	2267	0.05
6	21.348	278	2771	0.06
7	21.650	154	1159	0.03
8	22.000	89	648	0.01
9	22.362	96	723	0.02
10	22.433	71	333	0.01
11	22.805	434335	4380168	97.13

	RT	Height	Area	% Area
12	23.742	634	9127	0.20
13	24.747	7271	96556	2.14
14	28.400	343	4532	0.10



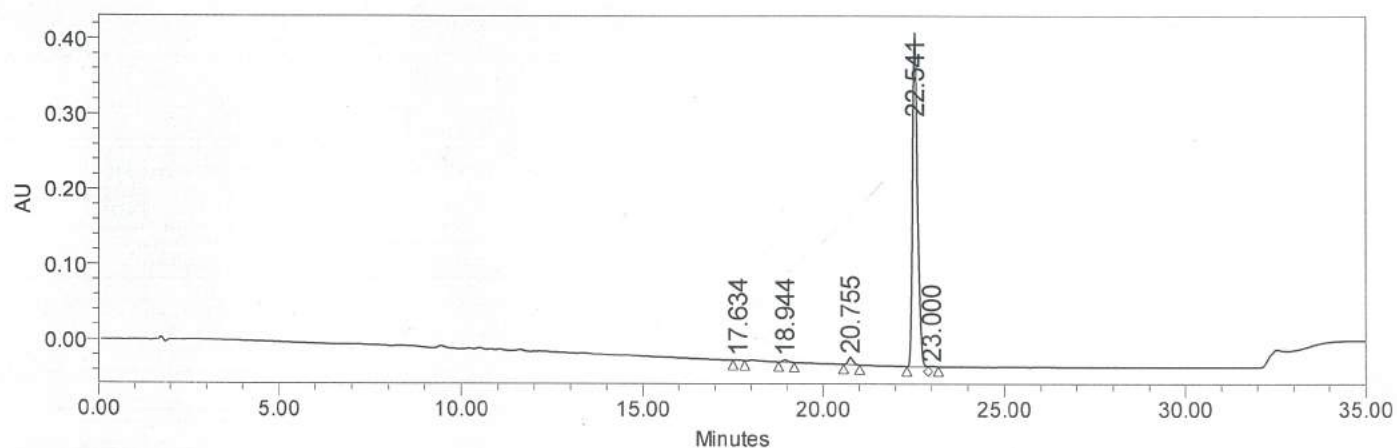
M. Kenuka
15/10/19

Ref
15/10/19

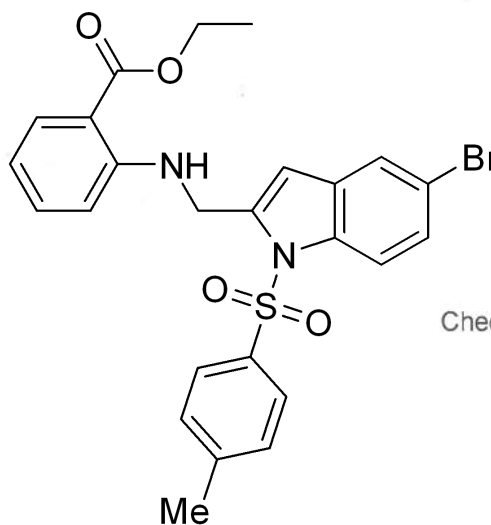
SAMPLE INFORMATION

Sample Name:	ILS-GSR/I2-Br2	Acquired By:	System
A.R.Number:	MC19I043	Sample Set Name:	28092019_02
Vial:	12	Acq. Method Set:	ILS_RS_MET
Injection #:	1	Processing Method:	ILS PRO
Injection Volume:	5.00 ul	Channel Name:	220.0nm
Run Time:	35.0 Minutes	Proc. Chnl. Descr.:	PDA 220.0 nm
Date Acquired: 9/28/2019 10:13:20 PM IST			
Date Processed: 9/30/2019 3:45:08 PM IST			

Column: X-BRIDGE C-18 150*4.6mm 5µm
 Mobile phase: A) 5mMNH4OAC in water B) ACN
 T/%B: 0/20, 20/90,30/90, 31/20, 35/20
 Flow: 1.0ml/min, Diluent: ACN:H2O (80:20)



	RT	Height	Area	% Area
1	17.634	617	5296	0.11
2	18.944	2874	28824	0.62
3	20.755	9333	93273	2.01
4	22.541	445850	4497948	97.12
5	23.000	622	6171	0.13



Analysed by

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30/09/19

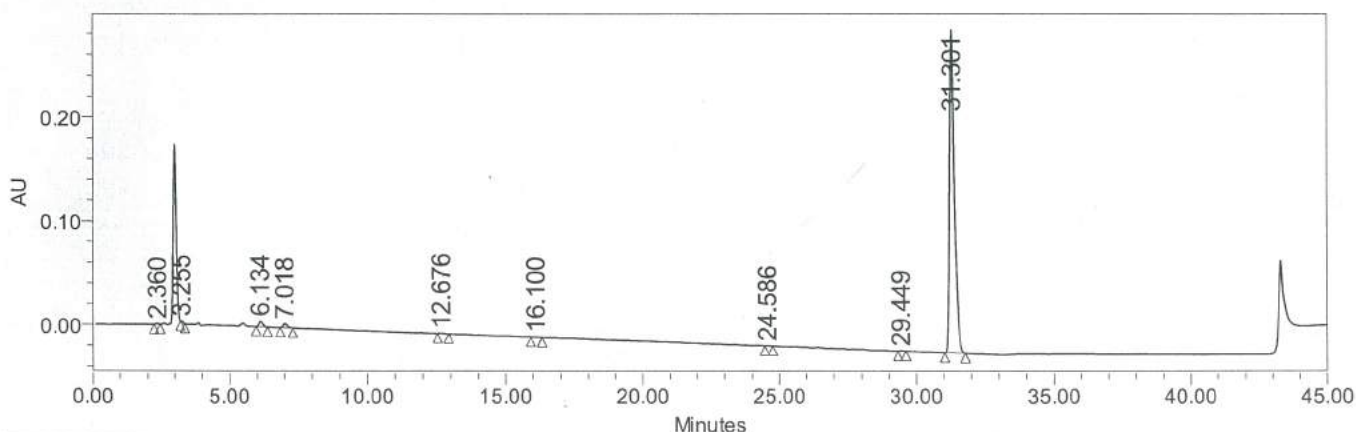
Checked by

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30/09/19

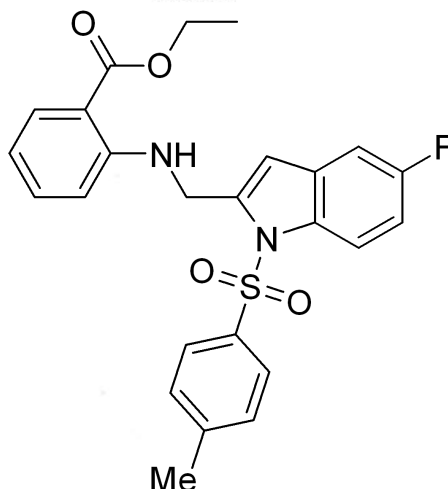
SAMPLE INFORMATION

Sample Name:	ILS-GSR-I2-F2	Acquired By:	System
A.R.Number:	CM19I042	Sample Set Name:	21102019_03
Vial:	56	Acq. Method Set:	ILS_RS_MET2
Injection #:	1	Processing Method:	ILS PRO
Injection Volume:	5.00 ul	Channel Name:	220.0nm
Run Time:	45.0 Minutes	Proc. Chnl. Descr.:	PDA 220.0 nm
Date Acquired: 10/22/2019 1:14:28 AM IST			
Date Processed: 10/22/2019 11:46:13 AM IST			

Column: Eclipse plus C18 250*4.6mm 5µm
 Mobile phase: A) 5mMNH4OAC in water B) ACN
 T/%B: 0/30,30/90,40/90,41/30,45/30
 Flow: 1.0ml/min, Diluent: ACN:THF



	RT	Height	Area	% Area
1	2.360	778	4810	0.13
2	3.255	942	5128	0.13
3	6.134	5528	54547	1.43
4	7.018	3771	39405	1.03
5	12.676	471	5115	0.13
6	16.100	183	2404	0.06
7	24.586	231	2389	0.06
8	29.449	309	2759	0.07
9	31.301	310569	3702334	96.95



Analysed by

M. Renuka 22/10/2019

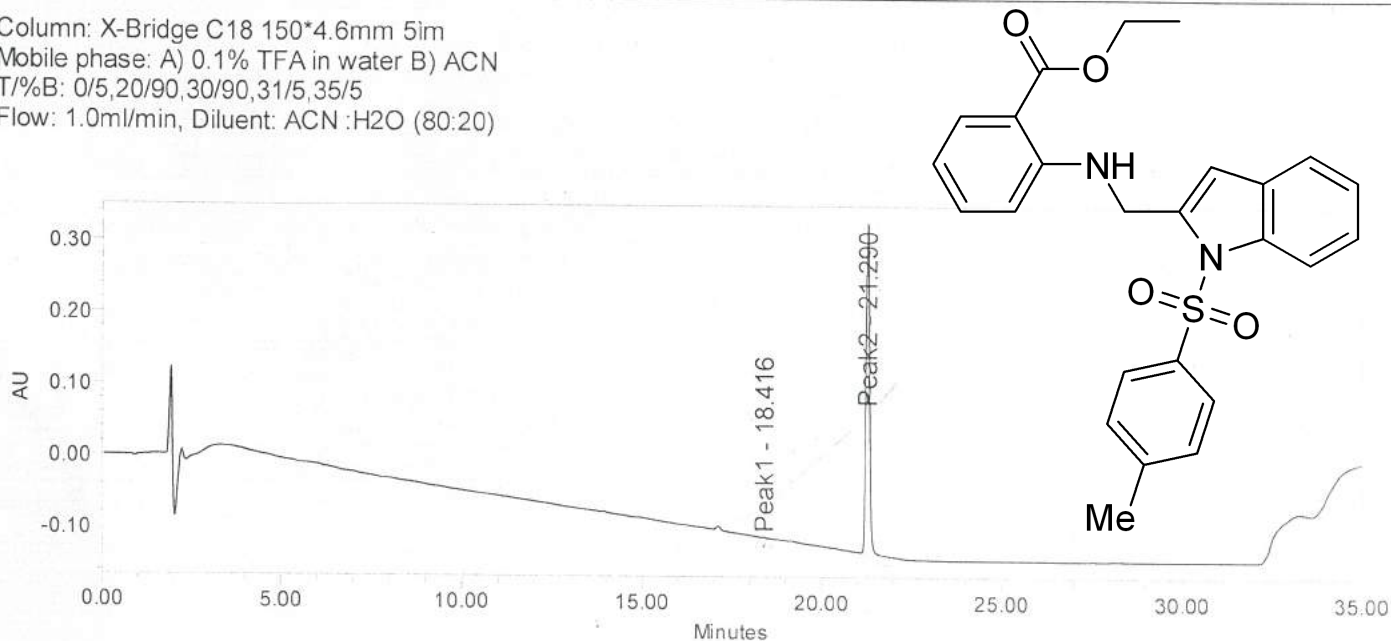
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22/10/19

SAMPLE INFORMATION

Sample Name:	ILS-GSR-I2-TS2	Acquired By:	System
A.R.Number:	CM18L016	Sample Set Name:	10122018_001
Vial:	3	Acq. Method Set:	EST IMP_M
Injection #:	1	Processing Method:	ILS PROC
Injection Volume:	10.00 ul	Channel Name:	220.0nm
Run Time:	35.0 Minutes	Proc. Chnl. Descr.:	PDA 220.0 nm
Date Acquired:	12/10/2018 1:14:50 PM IST		
Date Processed:	12/10/2018 2:03:15 PM IST		

Column: X-Bridge C18 150*4.6mm 5µm
 Mobile phase: A) 0.1% TFA in water B) ACN
 T/%B: 0/5,20/90,30/90,31/5,35/5
 Flow: 1.0ml/min, Diluent: ACN :H2O (80:20)



Peak Name	RT	Height	Area	% Area
1 Peak1	18.416	344	1969	0.06
2 Peak2	21.290	462214	3331685	99.94

Analysed by

MO
10/12/18

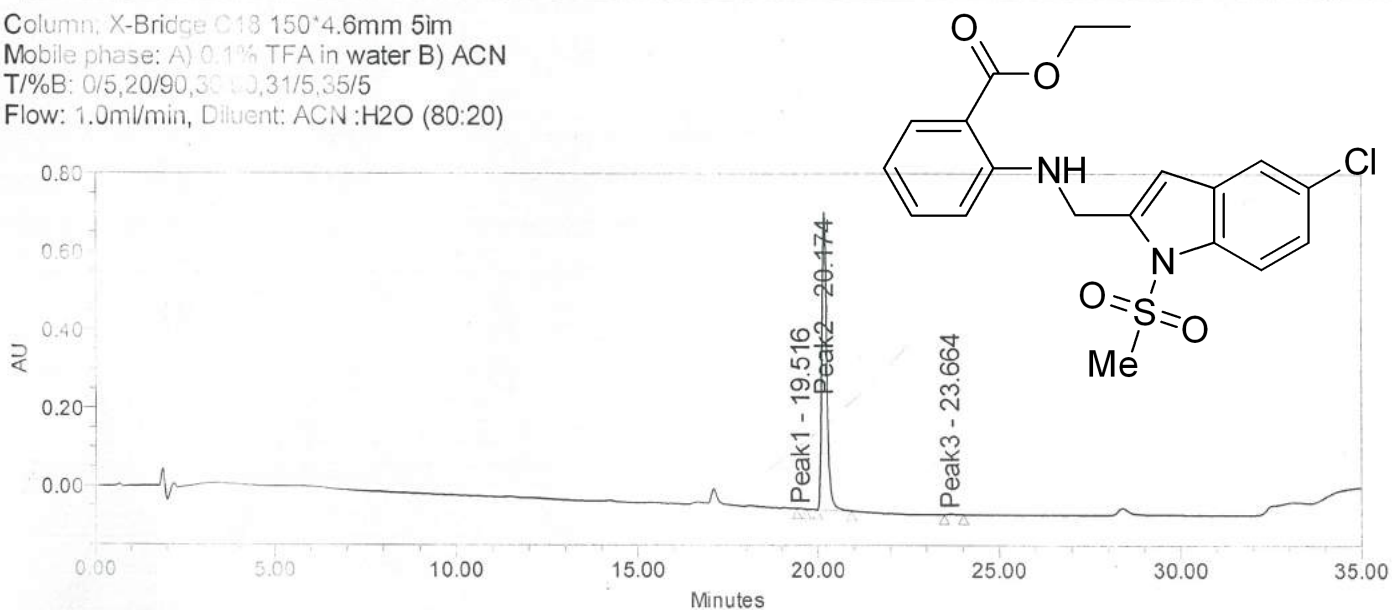
Checked by

dep
10/12/2018

SAMPLE INFORMATION

Sample Name:	ILS-GSR-I2-Cl2	Acquired By:	System
A.R.Number:	CM18K004	Sample Set Name:	14112018_003
Vial:	28	Acq. Method Set:	EST IMP_M
Injection #:	1	Processing Method:	ILS PROC
Injection Volume:	10.00 ul	Channel Name:	225.0nm
Run Time:	35.0 Minutes	Proc. Chnl. Descr.:	PDA 225.0 nm
Date Acquired:	11/14/2018 10:00:55 PM IST		
Date Processed:	11/15/2018 10:03:33 AM IST		

Column: X-Bridge C18 150*4.6mm 5µm
 Mobile phase: A) 0.1% TFA in water B) ACN
 T%B: 0/5,20/90,30/70,31/5,35/5
 Flow: 1.0ml/min, Diluent: ACN :H2O (80:20)



Peak Name	RT	Height	Area	% Area
1 Peak1	19.516	1336	9956	0.14
2 Peak2	20.174	765836	7319701	99.53
3 Peak3	23.664	2360	24250	0.33

Analysed by

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15/11/18

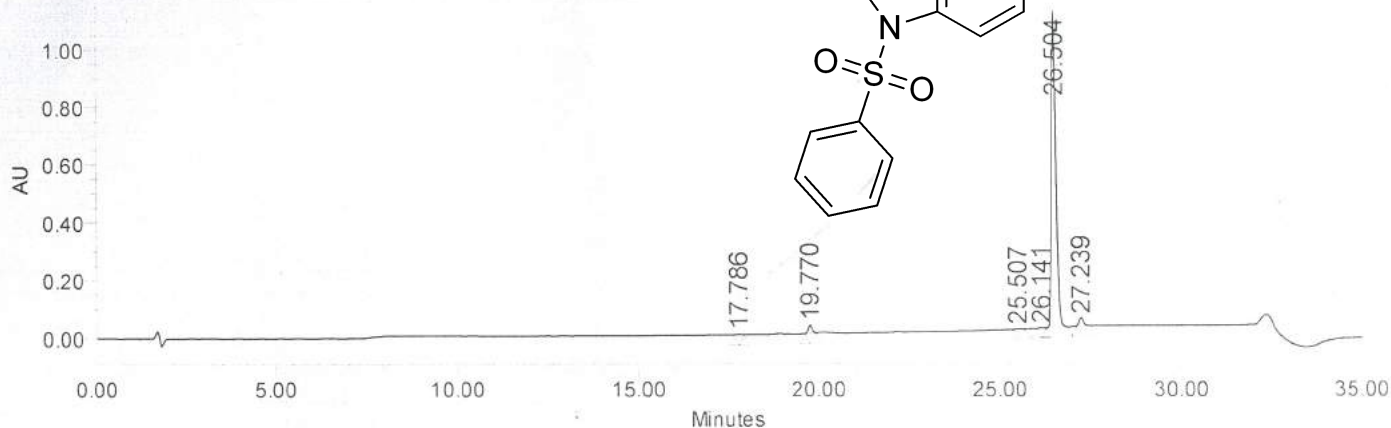
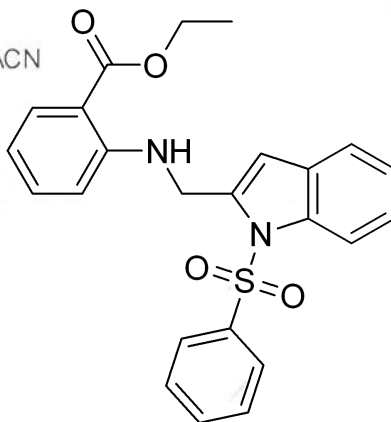
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15/11/18

SAMPLE INFORMATION

Sample Name:	ILS-GSR-I2-BEN2	Acquired By:	System
A.R.Number:	CM18L003	Sample Set Name:	12122018_004
Vial:	13	Acq. Method Set:	API HMA1
Injection #:	1	Processing Method:	ILS PROC
Injection Volume:	10.00 ul	Channel Name:	218.0nm@1
Run Time:	35.0 Minutes	Proc. Chnl. Descr.:	PDA 218.0 nm
Date Acquired:	12/12/2018 8:44:30 PM IST		
Date Processed:	12/13/2018 11:06:21 AM IST		

Column: Eclipse XDB C18 150*4.6mm 5µm
 Mobile phase: A) 0.05% TFA in water B) 0.05% TFA in ACN
 T/%B: 0/10,5/10,25/90,30/90,31/10,35/10
 Flow: 1.0ml/min, Diluent: ACN :H2O (80:20)



	RT	Height	Area	% Area
1	17.786	1100	8575	0.09
2	19.770	28638	217966	2.21
3	25.507	1311	11876	0.12
4	26.141	1378	10114	0.10
5	26.504	1095421	9384780	95.11
6	27.239	27376	234215	2.37

Analysed by

[Signature]
13/12/2018

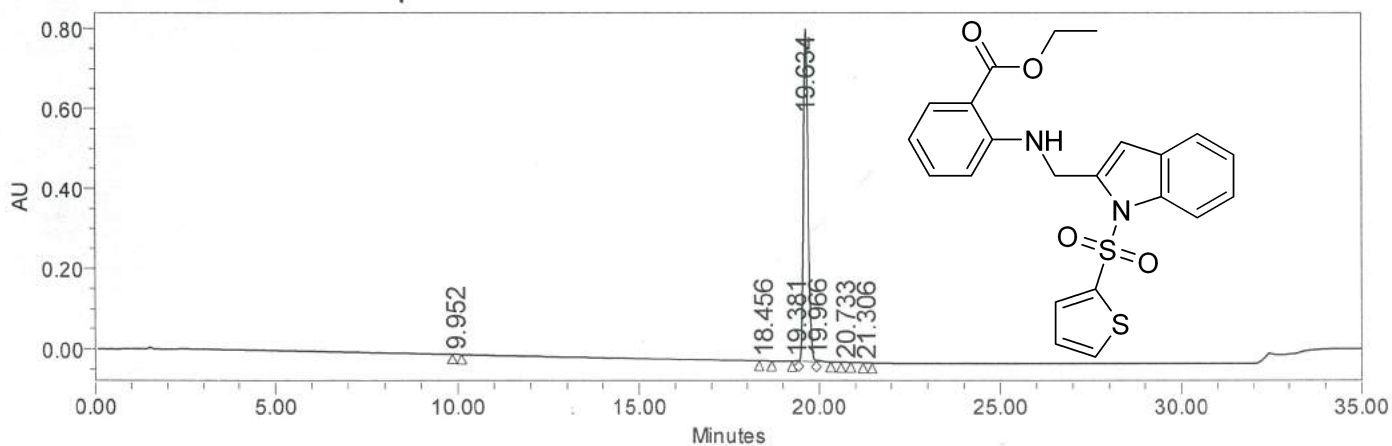
Checked by

[Signature]
13/12/2018

SAMPLE INFORMATION

Sample Name:	ILS-GSR-I2-TH2	Acquired By:	System
A.R.Number:	CA19J030	Sample Set Name:	18102019_02
Vial:	55	Acq. Method Set:	ILS_RS_MET
Injection #:	1	Processing Method:	ILS PRO
Injection Volume:	5.00 ul	Channel Name:	220.0nm
Run Time:	35.0 Minutes	Proc. Chnl. Descr.:	PDA 220.0 nm
Date Acquired: 10/18/2019 10:12:56 PM IST			
Date Processed: 10/21/2019 5:04:11 PM IST			

Column: X-BRIDGE C-18 150*4.6mm 5µm
 Mobile phase: A) 5mMNH4OAC in water B) ACN
 T/%B: 0/20, 20/90,30/90, 31/20, 35/20
 Flow: 1.0ml/min, Diluent: ACN:THF:H₂O (80:20)



	RT	Height	Area	% Area
1	9.952	689	5648	0.07
2	18.456	696	6437	0.08
3	19.381	1519	9517	0.13
4	19.634	827522	7547546	99.20
5	19.966	4102	37224	0.49
6	20.733	181	1401	0.02
7	21.306	99	874	0.01

Analysed by *Lomy*
21/10/19

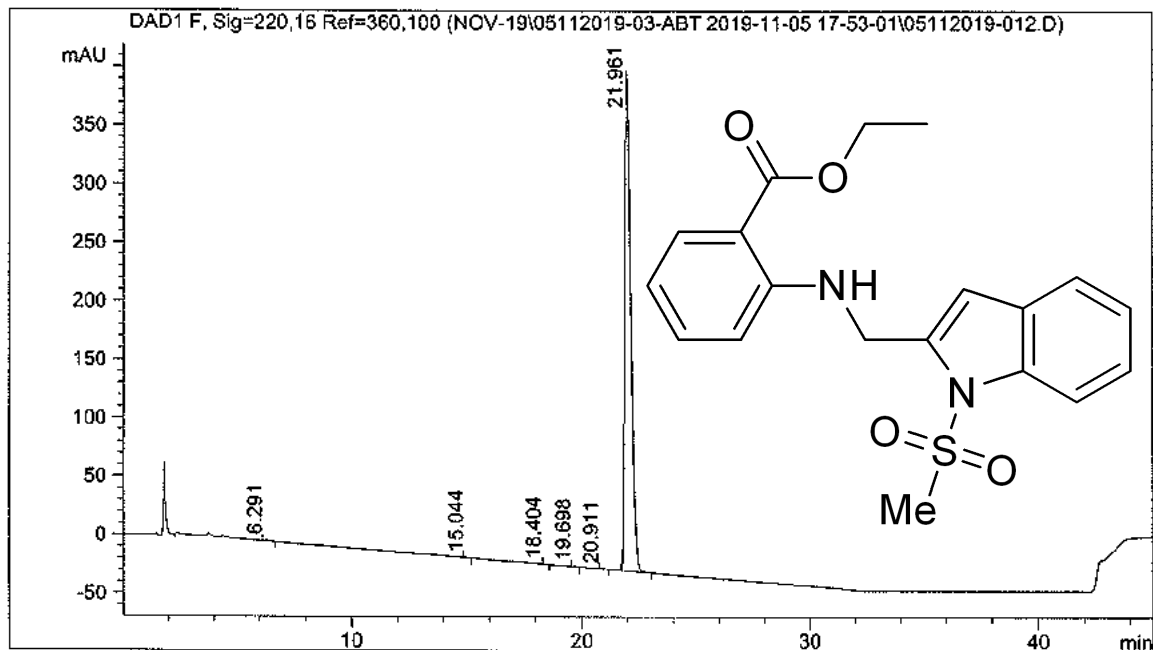
Checked by *del*
21/10/19

Injection Date : Tue, 5. Nov. 2019 Seq Line : 5
Sample Name : ILS-GSR-I2-MS2 Location : Vial 4
CM19K002 -> CM19K002 -> Inj. No. : 1
Inj. Vol. : 5 µl

Acq. Method : C:\Chem32\1\DATA\NOV-19\05112019-03-ABT 2019-11-05 1->
Analysis Method : C:\CHEM32\1\METHODS\ILS NP_M.M
Last Changed : Wed, 6. Nov. 2019, 09:50:20 am
(modified after loading)

Column : X-Bridge C18 150*4.6mm 5µm
Mobile phase: A) 5mM NH4OAC in H2O B) ACN
T/B% : 0/30,30/90,40/90,41/5,45/5
Flow:1.0mL/min ,Diluent: ACN :THF

HPLC of compound 4h



Customized Report: Short

Sorted By Signal

Calib. Data Modified : Wed, 6. Nov. 2019, 09:50:20 am
Multiplier : 1.000000
Dilution : 1.000000
Uncalibrated Peaks : not reported

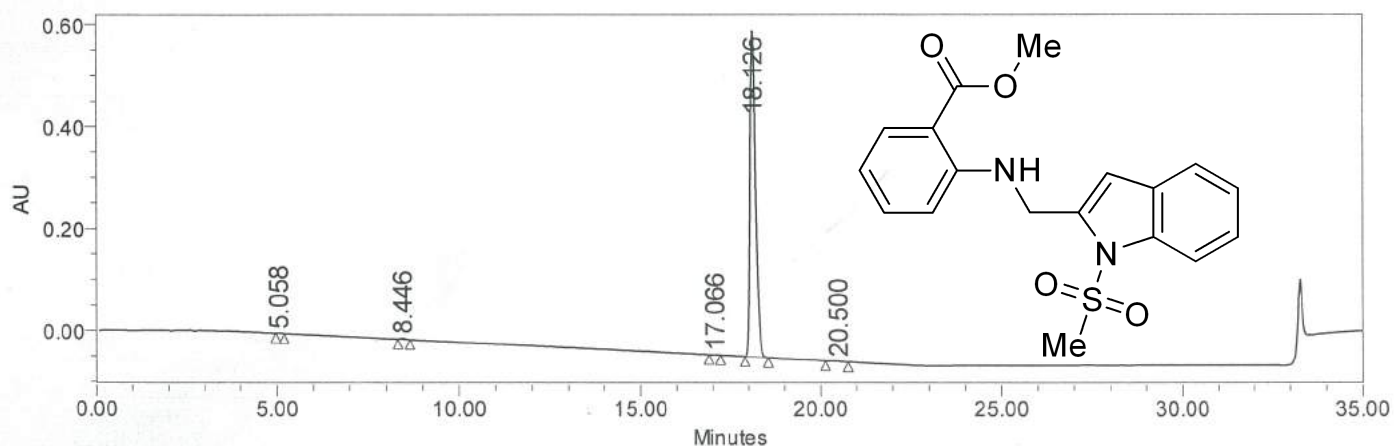
Signal 1: DAD1 F, Sig=220,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	6.291	MM	0.226	9.488	0.121	
2	15.044	MM	0.249	2.003	0.026	
3	18.404	MM	0.159	1.235	0.016	
4	19.698	MM	0.158	2.227	0.028	
5	20.911	MM	0.221	2.751	0.035	
6	21.961	MM	0.304	7799.881	99.774	

SAMPLE INFORMATION

Sample Name:	ILS-GSR-I2-MS-Me	Acquired By:	System
A.R.Number:	CM19J033	Sample Set Name:	30102019_03
Vial:	12	Acq. Method Set:	ILS_RS_MET3
Injection #:	1	Processing Method:	ILS PRO
Injection Volume:	5.00 ul	Channel Name:	215.0nm
Run Time:	35.0 Minutes	Proc. Chnl. Descr.:	PDA 215.0 nm
Date Acquired: 10/30/2019 11:19:44 PM IST			
Date Processed: 10/31/2019 9:23:58 AM IST			

Column: ECLIPSE PLUS C-18 250*4.6mm 5µm
 Mobile phase: A) 5mMNH4OAC in water B) ACN
 T/%B: 0/30, 20/90,30/90, 31/30, 35/30
 Flow: 1.0ml/min, Diluent: ACN:H2O (80:20)



	RT	Height	Area	% Area
1	5.058	285	2422	0.04
2	8.446	2199	20270	0.30
3	17.066	492	5327	0.08
4	18.126	640850	6677323	99.42
5	20.500	646	10690	0.16

Analysed by

M. Renuka
31/10/2019

Checked by

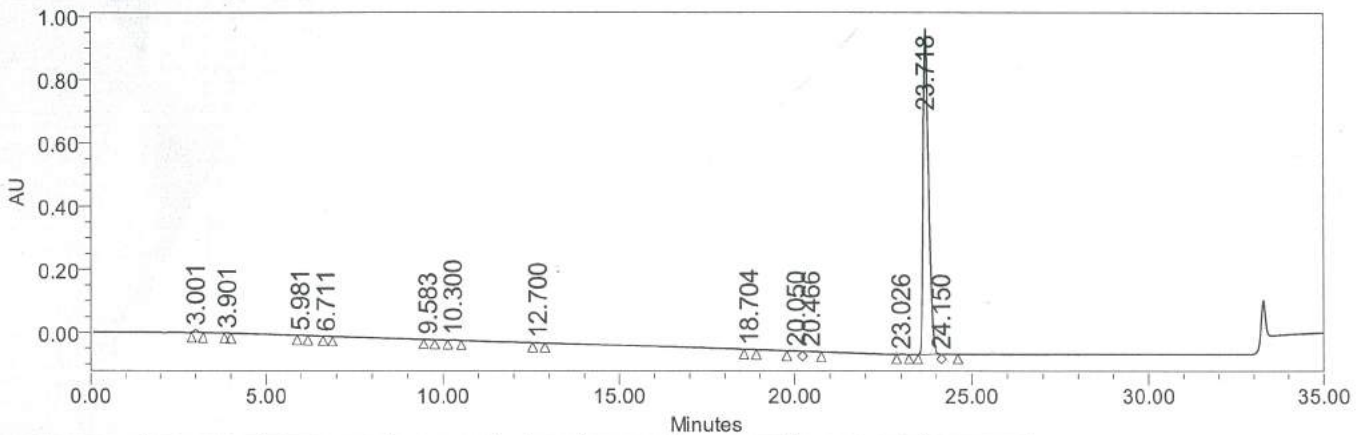
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31/10/19

HPLC of compound 4j

SAMPLE INFORMATION

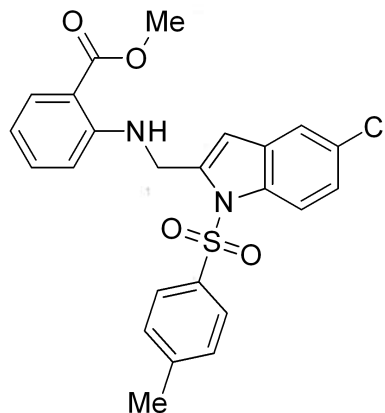
Sample Name:	ILS-GSR-l2-CI-Me	Acquired By:	System
A.R.Number:	CM19J053	Sample Set Name:	30102019_03
Vial:	13	Acq. Method Set:	ILS_RS_MET3
Injection #:	1	Processing Method:	ILS PRO
Injection Volume:	5.00 ul	Channel Name:	215.0nm
Run Time:	35.0 Minutes	Proc. Chnl. Descr.:	PDA 215.0 nm
Date Acquired:	10/30/2019 11:58:10 PM IST		
Date Processed:	10/31/2019 9:26:29 AM IST		

Column: ECLIPSE PLUS C-18 250*4.6mm 5µm
 Mobile phase: A) 5mMNH4OAC in water B) ACN
 T/%B: 0/30, 20/90,30/90, 31/30, 35/30
 Flow: 1.0ml/min, Diluent: ACN:H2O (80:20)



	RT	Height	Area	% Area
1	3.001	8505	62206	0.57
2	3.901	1781	10421	0.10
3	5.981	850	7560	0.07
4	6.711	349	3319	0.03
5	9.583	214	2108	0.02
6	10.300	1469	14176	0.13
7	12.700	272	3042	0.03
8	18.704	673	8046	0.07
9	20.050	811	12156	0.11
10	20.466	808	14765	0.14
11	23.026	1661	14792	0.14

	RT	Height	Area	% Area
12	23.718	1028493	10659619	98.51
13	24.150	670	8390	0.08

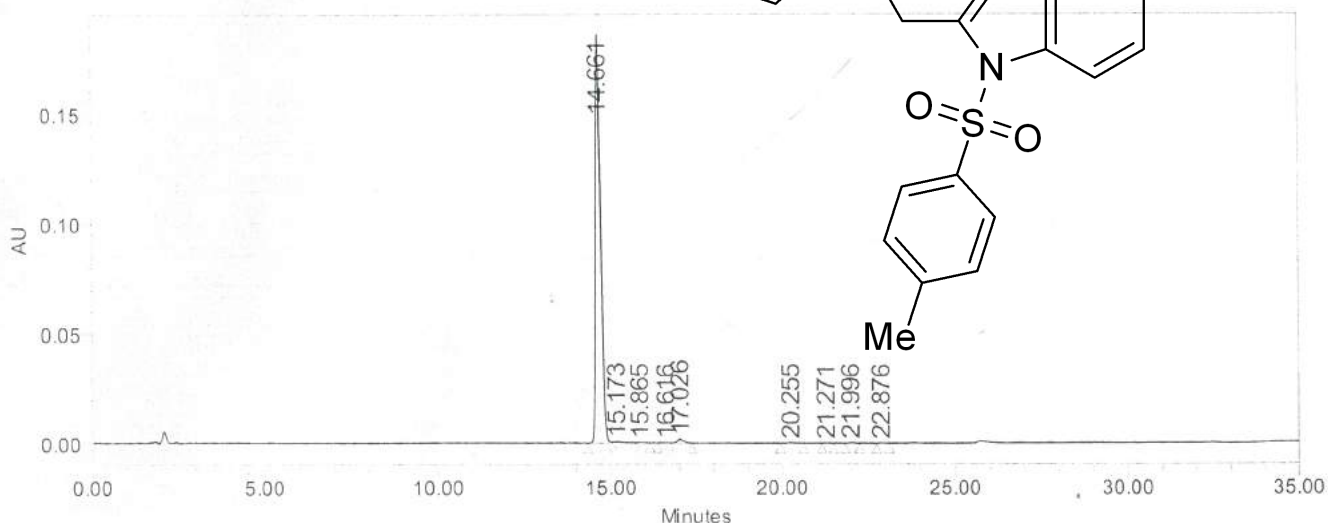
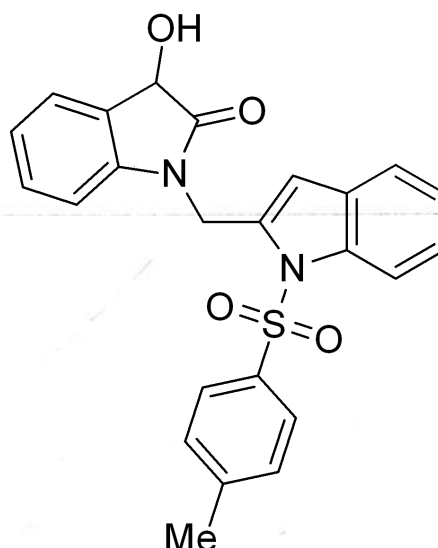


M. Renuka
 31/10/2019

SAMPLE INFORMATION

Sample Name:	ILS-GSR-Z-TS	Acquired By:	System
A.R.Number:	CA19D006	Sample Set Name:	05042019_003
Vial:	30	Acq. Method Set:	ILS_MET
Injection #:	2	Processing Method:	ILS_PRO
Injection Volume:	5.00 ul	Channel Name:	250.0nm
Run Time:	35.0 Minutes	Proc. Chnl. Descr.:	PDA 250.0 nm
Date Acquired:	4/6/2019 12:13:09 AM IST		
Date Processed:	4/9/2019 10:43:39 AM IST		

Column: Eclips XDB C18 150*4.6mm 5µm
 Mobile phase: A) 0.05% TFA in water B) 0.05% TFA in ACN
 T/%B: 0/30,20/90,30/90,31/30,35/30
 Flow: 1.0ml/min, Diluent: ACN:WATER (80:20)



	RT	Height	Area	% Area
1	14.661	186475	2026338	97.90
2	15.173	560	10821	0.52
3	15.865	179	2426	0.12
4	16.616	60	873	0.04
5	17.026	1833	22617	1.09
6	20.255	123	2077	0.10

	RT	Height	Area	% Area
7	21.271	62	686	0.03
8	21.996	284	3288	0.16
9	22.876	63	741	0.04

M. Benyka
09/04/2019

dep
09/04/19



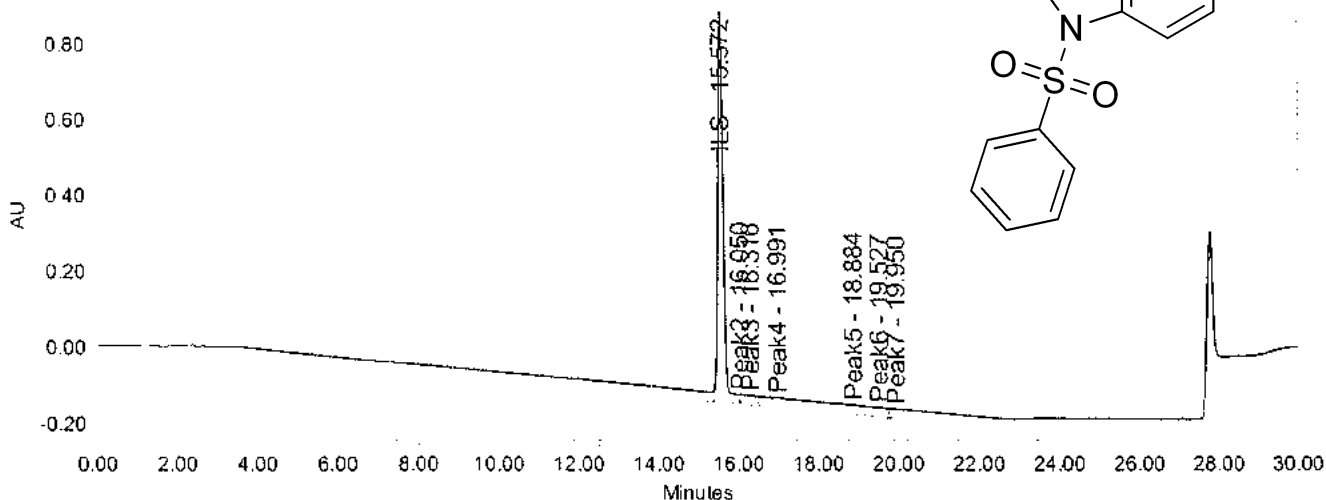
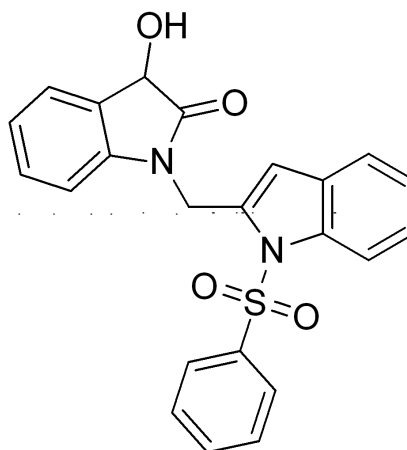
HPLC of compound 5b

CPRI@DRILS

SAMPLE INFORMATION

Sample Name:	ILS-GSR-Z-BEN	Acquired By:	System
A.R.Number:	CA19D014	Sample Set Name:	22042019_002
Vial:	104	Acq. Method Set:	API BDM IMP01 B4_M
Injection #:	1	Processing Method:	BDM PRO
Injection Volume:	5.00 ul	Channel Name:	210.0nm
Run Time:	30.0 Minutes	Proc. Chnl. Descr.:	PDA 210.0 nm
Date Acquired:	4/22/2019 7:41:42 PM IST		
Date Processed:	4/23/2019 11:33:57 AM IST		

Column: COSMICSIL C-18 150*4.6mm 5um
Mobile phase: A) 5MM AMMONIUM ACETATE in water B) ACN
T/%B: 0/5,20/90,25/90,26/5,30/5
Flow: 1.0ml/min, Diluent: ACN:H2O (80:20)



Peak Name	RT	Height	Area	% Area
1 ILS	15.572	1005543	8302178	99.26
2 Peak2	16.050	491	3855	0.05
3 Peak3	16.316	328	3500	0.04
4 Peak4	16.991	2285	22383	0.27
5 Peak5	18.884	1499	12097	0.14
6 Peak6	19.527	1898	15178	0.18

Peak Name	RT	Height	Area	% Area
7 Peak7	19.950	528	4608	0.06

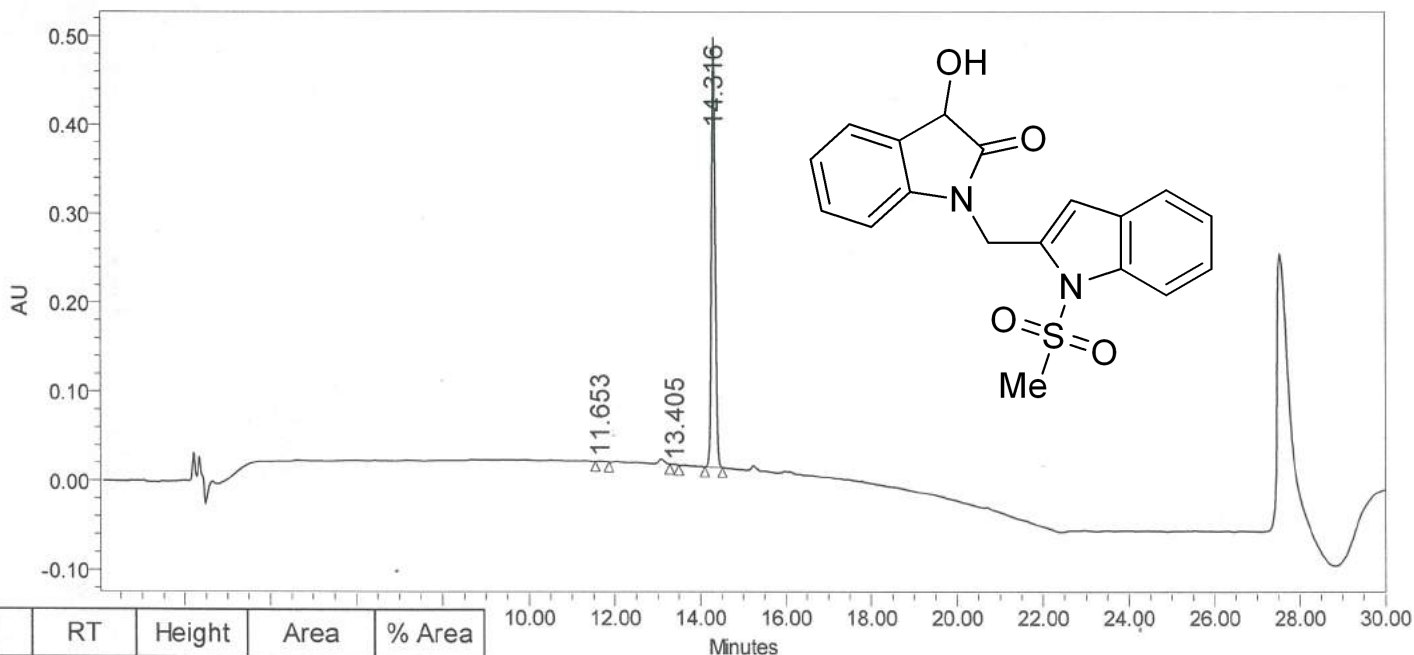
Reported by User: System
Report Method: CPRI@DRILS_RRT
Report Method ID: 4191
Page: 1 of 2

Project Name: 2019\APR-2019
Date Printed:
4/23/2019
11:34:17 AM Asia/Calcutta

SAMPLE INFORMATION

Sample Name:	ILS/GSR/Z/MS	Acquired By:	System
AR Number :	CM19D012	Sample Set Name:	12042019_004
Vial:	105	Acq. Method Set:	API LEC
Injection #:	1	Processing Method:	ILS PRO
Injection Volume:	5.00 ul	Channel Name:	210.0nm@1
Run Time:	30.0 Minutes	Proc. Chnl. Descr.:	PDA 210.0 nm
Date Acquired: 4/12/2019 9:05:00 PM IST			
Date Processed: 4/13/2019 3:46:49 PM IST			

Column : COSMICSIL C18 150*4.6mm 5µm
 Mobile phase : A) 0.05%TFA in water B) 0.05%TFA in ACN
 T/%B: 0/5,20/90,25/90,26/5,30/5
 Flow:1.0ml/min,Diluent: ACN:H2O(80:20)



	RT	Height	Area	% Area
1	11.653	957	10455	0.38
2	13.405	829	4947	0.18
3	14.316	477224	2750816	99.44

Analysed By:

[Signature]
13/04/2019

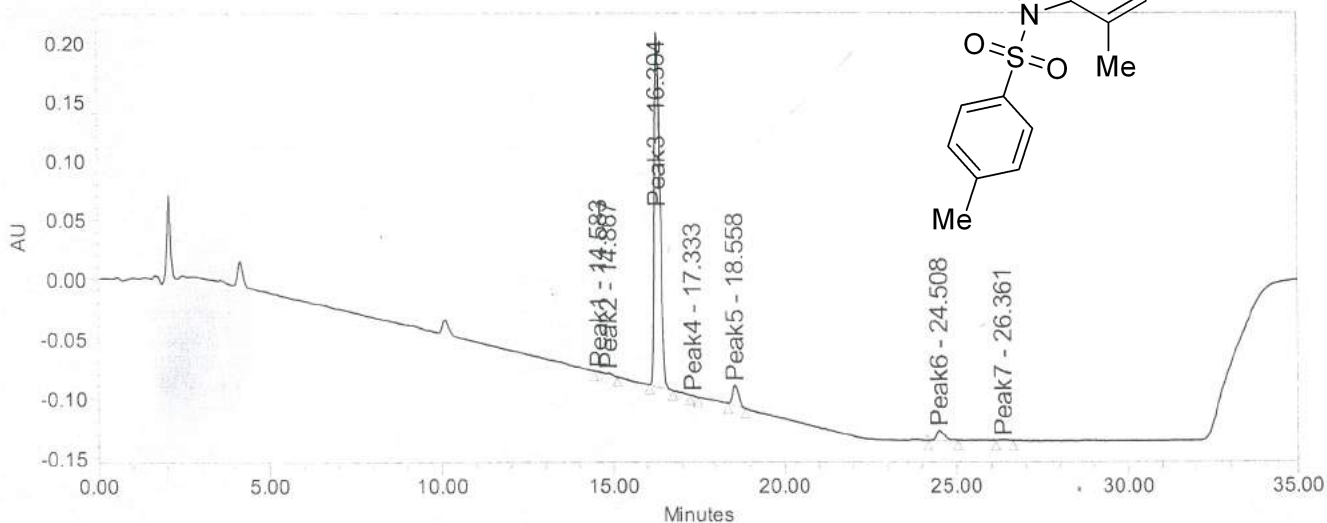
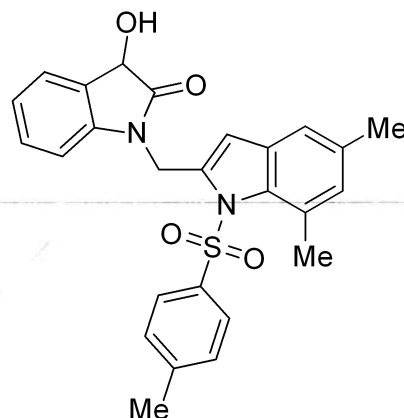
Checked By:

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15/04/2019

SAMPLE INFORMATION

Sample Name:	ILS-GSR-Z-DTS	Acquired By:	System
A.R.Number:	CA19D005	Sample Set Name:	05042019_003
Vial:	29	Acq. Method Set:	ILS_MET
Injection #:	1	Processing Method:	ILS_PRO
Injection Volume:	5.00 ul	Channel Name:	215.0nm
Run Time:	35.0 Minutes	Proc. Chnl. Descr.:	PDA 215.0 nm
Date Acquired:	4/5/2019 10:23:35 PM IST		
Date Processed:	4/8/2019 11:36:06 AM IST		

Column: X BRIDGE PHENYL C18 150*4.6mm 5µm
 Mobile phase: A) 0.05%TFA IN WATER B) ACN:WATER(90:10)
 T/%B: 0/2,5/2,20/90,25/90,26/2,30/2
 Flow: 1.0ml/min, Diluent: THF:ACN:WATER (80:20)



	Peak Name	RT	Height	Area	% Area
1	Peak1	14.583	453	6116	0.16
2	Peak2	14.867	1146	15057	0.40
3	Peak3	16.304	298825	3407381	90.54
4	Peak4	17.333	292	2318	0.06
5	Peak5	18.558	16753	203625	5.41
6	Peak6	24.508	8123	123701	3.29

	Peak Name	RT	Height	Area	% Area
7	Peak7	26.361	311	5044	0.13

M. Lenika.
08/04/2019

lp
08/04/2019

