Development of potent *Pf*CLK3 inhibitors based on TCMDC151 as a new class of antimalarials

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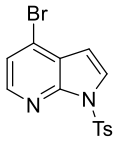
I. General information

Chemicals and solvents were purchased from standard suppliers and used without additional purification. All glassware was dried with a flame under flushing argon gas

or stored in the oven and let cool under an inert atmosphere prior to use. Anhydrous solvents (THF, DCM and Et_2O) were obtained by passage through solvent filtration systems (Pure Solv) and solvents were transferred by syringe. PET ether refers to petroleum (bp. 40-60 °C, reagent grade, Fisher Scientific). All reactions carried out under inert or dry atmosphere were carried out under a blanket of nitrogen. Thin-layer chromatography (TLC) was performed using aluminium plates precoated with silica gel (0.25 mm, 60 A° pore-size) impregnated with a fluorescent indicator (254 nm).Visualization on TLC was achieved by the use of UV light (254 nm). Flash column chromatography was undertaken on silica gel (400-630 mesh). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on AVANCE III 400 Bruker (400 MHz). Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26; CD_3OD, δ 3.31 and DMSO-*d*$_6$, δ 2.50). The following abbreviations were used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quadruplet, sept = septet, m = multiplet. Coupling constants, J, were reported in Hertz unit (Hz). Carbon 13 nuclear magnetic resonance spectroscopy (^{13}C NMR) was recorded on AVANCE III 400 Bruker (101 MHz) and was fully decoupled by broad band decoupling. Chemical shifts were reported in ppm referenced to the centre line of a triplet at 77.0, 49.0, 39.5 ppm of $CDCl_3$, CD_3OD and DMSO-*d*$_6$. Low-resolution mass spectrometry (LRMS) was performed on a Thermo Scientific LCQ Fleet quadrupole mass spectrometer using electrospray ionisation in positive mode (ESI^+), employing a 150 mm x 4 mm C18 column (Dr. Maisch Reprosil Gold). High-resolution mass spectrometry (HRMS) was performed on a Bruker microTOF-Q II (ESI^+). Preparative HPLC was carried out on a Dionex HPLC system equipped with Dionex P680 pumps and a Dionex UVD170U UV-vis detector (monitoring at 214 nm and 280 nm), using a Phenomenex, Gemini, C18, 5 µm, 250 x 21.2 mm column. Gradients were performed using solvents consisting of A (H_2O + 0.1% TFA) and B (CH_3CN + 0.1% TFA) and fractions were lyophilised on a Christ Alpha 2-4 LO plus freeze dryer.

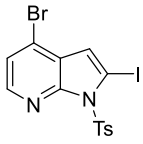
II. Experimental procedures and characterisation data:

4-Bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (3)



To a solution of sodium hydride (1.83 g, 76.1 mmol, 3 equiv.) and tetrabutylammonium bromide (0.25 g, 0.76 mmol, 0.03 equiv.) in dichloromethane (80 mL) at 0 °C was added 4-bromo-1*H*-pyrrolo[2,3-*b*]pyridine, **2** (5 g, 25.4 mmol, 1 equiv.), the mixture was then left to stir at 0 ºC for 15 mins. Toluene sulphonylchloride (5.81 g, 30.5 mmol, 1.2 equiv.) in dichloromethane (20 mL) was slowly added over 5 mins. The mixture was then left to warm up to room temperature and stirred for 1 hour. The reaction was quenched by addition of water and extracted with dichloromethane. The organic layer was washed with brine and dried over magnesium sulphate. The residue was then purified by flash column chromatography (10% ethyl acetate-PET Ether) to give **3** as a colourless solid (8.83 g, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (d, *J* = 5.2 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 4.0 Hz, 1H), 7.35 (d, *J* = 5.3 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.64 (d, *J* = 4.0 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 146.8, 145.5, 145.0, 135.1, 129.7, 128.2, 127.0, 125.7, 124.4, 122.1, 104.9, 21.7; HRMS *m/z calcd for* $C_{14}H_{11}BrN_2NaO_2S$ $[M+Na]^+$ 372.9617 *found* 372.9608 (Δ = 2.3 ppm).

4-Bromo-2-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (4)



n-Butyllithium (2.5 M; 6.30 mL, 15.6 mmol, 1.1 equiv.) was added dropwise to diisopropylamine (2.4 mL, 17.2 mmol, 1.2 equiv) in diethyl ether (30 mL) at -78 °C over a period of 5 mins. The resulting solution was stirred at -78 °C for 60 mins and then slowly added via cannula to a solution of 4-bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine, **3** (5.00 g, 14.2 mmol, 1 equiv.) and tetramethylethylenediamine (2.3 mL, 15.7 mmol, 1.1 equiv.) in diethyl ether (170 mL) over a period of 10 mins at -78 °C. The resulting solution was then stirred at -78 ºC for 90 mins. Iodine (5.40 g, 21.4 mmol, 1,5 equiv.) was added in one portion, and the reaction mixture was stirred at -78 °C for 60 mins. The reaction was quenched with saturated ammonium chloride solution and the organic layer was washed with aqueous sodium thiosulphate and brine before drying over magnesium sulphate. The residue was then purified by column chromatography (20% ethyl acetate-PET ether) to give **4** as a colourless solid (5.59 g, 85 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (d, *J* = 5.2 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 5.2 Hz, 1H), 7.22-7.19 (m, 2H), 6.96 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.1, 145.7, 144.7, 135.4, 129.8, 128.3, 125.3, 123.6, 122.4, 119.4, 21.7; HRMS *m/z calcd for* $C_{14}H_{10}BrIN_2NaO_2S$ $[M+Na]^+$ 498.8583 *found* 498.8602 (Δ = -3.8 ppm).

Method A: General Method of Suzuki Cross-Coupling

To a solution of desired aryl bromide (1.0 equiv) and tetrakis(triphenylphosphine)palladium(0) (0.05 equiv.) in 1,4-dioxane was added boronic acid/ester (1.1 equiv) under a nitrogen atmosphere. Aqueous sodium carbonate (2 M, 7.0 equiv) was then added and the reaction mixture left to stir at 110 ºC for 18 hrs. Solvent was removed under vacuum and the crude was dissolved in ethyl acetate and poured into water and extracted with ethyl acetate. The organic layer was washed with brine before drying over magnesium sulphate and purified by flash column chromatography as indicated.

Method B: Reductive Amination of Aldehydes

To a solution of aryl aldehyde (1.0 equiv) in 1,4-dioxane was added amine (1.5 equiv) and the solution was allowed to stir for 2 mins before the addition of sodium triacetoxyborohydride (2.5 equiv). The reaction mixture was stirred at room temperature for 18 h before quenching with ammonium hydroxide. The reaction mixture was extracted with ethyl acetate and washed with brine. The organic layer was dried over magnesium sulphate and the residue purified by flash column chromatography as indicated.

Method C: Deprotection of azaindole

To a solution of protected 7-azaindole (1 equiv) in methanol was added potassium carbonate (3.5 equiv) and refluxed for 18 h. Poured the reaction into a mixture of EtOAc (10 mL) and H_2O in a separatory funnel. Solvent was then removed under vacuum and the residue was then purified by flash column chromatography as indicated.

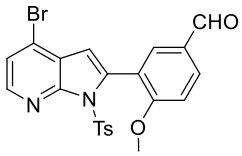
Method D: Suzuki Cross-Coupling with boronate ester

To a 10 mL microwave vial containing the required bromo-7-azaindole (1 equiv) in 1,4- dioxane was added boronic acid/ester (1.1 equiv), Pd(dppf)Cl_2·DCM complex (0.05 equiv.) under a nitrogen atmosphere. The solution was purged with nitrogen for 5 mins and the reaction microwaved at 110 ºC for 0.5 h. The reaction was allowed to cool to room temperature and the mixture was filtered through celite eluting with methanol. The filtrate was evaporated and the resulting residue was purified by preparative HPLC: 10-95% acetonitrile in water + 0.1% TFA to give the desired products.

Method E: Synthesis of boronate ester

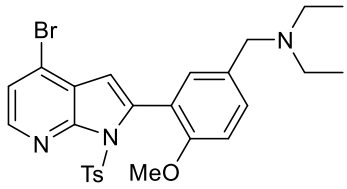
Boronate esters required for Suzuki coupling were prepared according to procedure reported in literature.[1] To a solution of aryl bromide (1 equiv), bis(pinacolato)diboron (1.5 equiv) and potassium acetate (3 equiv) in 1,4-dioxane (20 ml), $PdCl_2$(dppf)-CH_2Cl_2 complex (0.1 equiv) were added under nitrogen and stirred at 100 °C for 3 hour. The reaction mixture was quenched with saturated $NaHCO_3$ and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), filtered and concentrated to dryness. The crude product was purified by chromatography (20% ethyl acetate-PET Ether) to give the desired boronate esters.

3-[4-Bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-4-methoxybenzaldehyde (5)



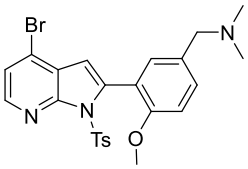
Prepared according to method A. Purification by flash chromatography (50% ethyl acetate-PET ether) afforded **5** as a yellow oil (1.72 g, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.90 (s, 1H), 8.15 (d, *J* = 5.2 Hz, 1H), 7.95 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.84 (d, *J* = 2.1 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 5.3 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.52 (s, 1H), 3.85 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.4, 163.5, 148.7, 145.1, 144.8, 137.6, 135.8, 134.4, 131.4, 129.4, 129.4, 128.1, 125.1, 123.3, 123.1, 122.3, 110.6, 107.9, 56.1, 21.6; HRMS m/z *calcd for* $C_{22}H_{17}BrN_2NaO_4S$ $[M+Na]^+$ 506.9985 *found* 506.9977 (Δ = 1.5 ppm).

***N*-(3-(4-bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-4-methoxybenzyl)-*N*-ethylethanamine (6a)**



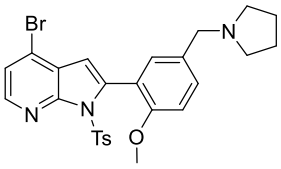
Prepared according to method B. Purification by flash chromatography (5% methanol-dichloromethane) afforded **6a** as a yellow oil (920 mg, 72%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.15 (d, *J* = 5.3 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.65 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.62 (d, *J* = 2.3 Hz, 1H), 7.47 (d, *J* = 5.3 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 1H), 6.65 (s, 1H), 4.45-4.35 (m, 2H), 3.81 (s, 3H), 3.31-3.23 (m, 4H), 2.36 (s, 3H), 1.38 (t, *J* = 7.3 Hz, 7H); ^{13}C NMR (101 MHz, CD_3OD) δ: 159.3, 148.4, 145.7, 144.3, 138.2, 135.5, 133.7, 133.6, 129.1, 127.6, 124.7, 123.3, 122.3, 122.3, 120.8, 111.1, 107.6, 55.2, 54.9, 20.1; HRMS *m/z calcd* for $C_{26}H_{28}BrN_3O_3S$ $[M+H]^+$ 541.1035 *found* 542.1093 (Δ = 2.7 ppm).

1-({3-[4-Bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-4-methoxyphenyl}methyl)-*N*,*N*-dimethylamine (6b)



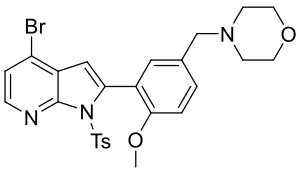
Prepared according to method B. Purification by flash chromatography (5% methanol-dichloromethane) afforded **6b** as a yellow oil (225 mg, 70%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.17 (d, *J* = 5.3 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.65 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.61 (d, *J* = 2.3 Hz, 1H), 7.50 (d, *J* = 5.3 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 1H), 6.66 (s, 1H), 4.27 (d, *J* = 14.4 Hz, 2H), 3.83 (s, 3H), 2.84 (s, 7H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ: 156.2, 147.9, 142.1, 137.0, 131.0, 129.6, 129.5, 124.1, 122.6, 119.3, 118.8, 111.5, 98.8, 62.6, 55.0, 43.6; HRMS m/z *calcd for* $C_{24}H_{25}BrN_3O_3S$ $[M+H]^+$ 514.0795 *found* 514.0790 (Δ = 0.9 ppm).

1-({3-[4-Bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-4 methoxyphenyl}methyl)pyrrolidine (6c)



Prepared according to method B. Purification by flash chromatography (5% methanol-dichloromethane) afforded **6c** as a yellow oil (330 mg, 97%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.13 (d, *J* = 5.2 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.65-7.67 (m`, 2H), 7.42 (d, *J* = 5.3 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 9.1 Hz, 1H), 6.63 (s, 1H), 4.44-4.29 (m, 1H), 3.78 (s, 3H), 2.32 (s, 3H), 2.10-2.06 (p, 4H), 1.95 (s, 4H); ^{13}C NMR (101 MHz, CD_3OD) δ: 176.8, 159.1, 148.4, 145.6, 144.3, 138.6, 135.6, 129.2, 127.6, 124.6, 123.3, 122.8, 122.3, 122.1, 110.9, 107.5, 56.9, 54.9, 52.8, 22.5, 21.5, 20.2; HRMS *m/z calcd for* $C_{26}H_{27}BrN_3O_3S$ $[M+H]^+$ 540.0951 *found* 540.0934 (Δ; = 3.2 ppm).

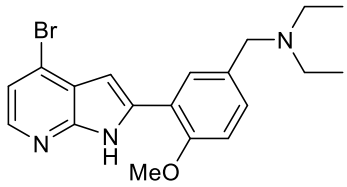
4-({3-[4-Bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-4-methoxyphenyl}methyl)morpholine (6d)



Prepared according to method B. Purification by flash chromatography (5% methanol-dichloromethane) afforded **6d** as a yellow oil (270mg, 80%); ^{1}H NMR (400 MHz, CD3OD) δ: 8.03 (m, 3H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 4.8 Hz, 1H), 7.23-7.18 (m, 3H), 6.96 (s, 1H), 4.36 (s, 2H), 4.04 (s, 3H), 3.34 (t, *J* = 6.2 Hz, 4H), 2.08 (t, *J* = 6.2 Hz, 4H), 1.99 (s, 3H); ^{13}C NMR (101

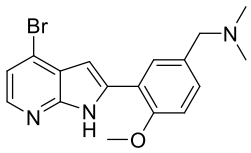
MHz, CD_3OD) δ: 157.5, 147.9, 142.5, 140.4, 136.2, 131.8, 130.4, 128.5, 125.6, 124.3, 123.6, 122.4, 120.1, 118.9, 112.2, 99.4, 62.9, 57.2, 55.2, 53.2, 22.5; HRMS m/z *calcd for* $C_{26}H_{27}BrN_3O_4S$ $[M+H]^+$ 556.0900 *found* 556.0902 (Δ = -0.2 ppm).

_N_-(3-(4-bromo-1_H_-pyrrolo[2,3-_b_]pyridin-2-yl)-4-methoxybenzyl)-_N_-ethylethanamine (7a)



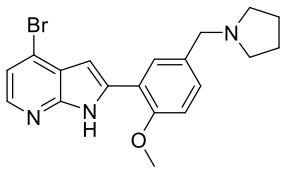
Prepared according to method C. Purification by flash chromatography (10% methanol-dichloromethane) afforded **7a** as a colourless oil (560 mg, 79%); ^1H NMR (400 MHz, CD_3OD) δ: 8.00 (d, *J* = 5.3 Hz, 1H), 7.83 (d, *J* = 2.3 Hz, 1H), 7.36 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.29 (d, *J* = 5.3 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 6.91 (s, 1H), 4.00 (s, 3H), 3.75 (s, 2H), 3.31 (p, *J* = 1.6 Hz, 1H), 2.71 (q, *J* = 7.2 Hz, 4H), 1.15 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ: 156.3, 147.9, 142.1, 136.9, 131.2, 129.7, 124.11, 122.5, 119.4, 118.8, 111.6, 98.8, 56.1, 54.9, 9.4; HRMS *m/z calcd* for $C_{19}H_{22}BrN_3O$ $[M+H]^+$ 387.0946 *found* 388.1008 (Δ = 2.7 ppm).

1-[(3-{4-Bromo-1_H_-pyrrolo[2,3-_b_]pyridin-2-yl}-4-methoxyphenyl)methyl]dimethylamine (7b)



Prepared according to method C. Purification by flash chromatography (10% methanol-dichloromethane) afforded **7b** as a colourless oil (280 mg, 92%); ^1H NMR (400 MHz, CD_3OD) δ: 7.91 (d, *J* = 5.3 Hz, 1H), 7.70 (d, *J* = 2.2 Hz, 1H), 7.23 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.20 (d, *J* = 5.3 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.82 (s, 1H), 3.91 (s, 3H), 3.44 (s, 2H), 2.21 (s, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ: 156.25, 147.90, 142.10, 137.00, 131.01, 129.65, 129.52, 124.12, 122.56, 119.31, 118.78, 111.52, 98.82, 62.59, 54.97, 43.59; HRMS m/z *calcd for* $C_{17}H_{19}BrN_3OS$ $[M+H]^+$ 360.0706 *found* 360.0701 (Δ = 1.4 ppm).

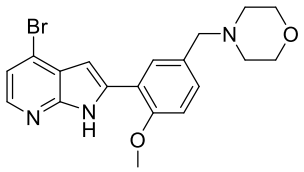
1-[(3-{4-Bromo-1_H_-pyrrolo[2,3-_b_]pyridin-2-yl}-4-methoxyphenyl)methyl]pyrrolidine (7c)



Prepared according to method C. Purification by flash chromatography (10% methanol-dichloromethane) afforded **7c** as a yellow oil (165 mg, 77%); ^1H NMR (400 MHz, CD_3OD) δ: 7.88 (d, *J* = 5.2 Hz, 1H), 7.84 (d, *J* = 2.3 Hz, 1H), 7.36 (dd, *J* =

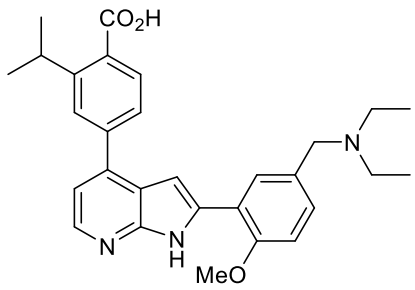
8.5, 2.3 Hz, 1H), 7.16 (dd, *J* = 8.5, 3.4 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.81 (s, 1H), 4.06 (s, 2H), 3.89 (s, 3H), 3.04 (t, *J* = 6.8 Hz, 4H), 1.91 (p, *J* = 3.2 Hz, 4H); ^{13}C NMR (101 MHz, CD_3OD) δ: 157.0, 148.0, 142.4, 136.5, 131.3, 130.0, 126.4, 124.2, 122.4, 119.9, 118.9, 112.0, 99.1, 58.1, 55.1, 53.4, 22.6; HRMS m/z *calcd for* $C_{19}H_{21}BrN_3O$ $[M+H]^+$ 386.0900 *found* 386.0903 (Δ = 0.8 ppm).

4-[(3-{4-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl}-4-methoxyphenyl)methyl]morpholine (7d)



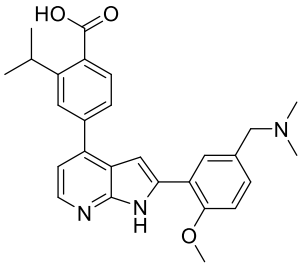
Prepared according to method C. Purification by flash chromatography (10% methanol-dichloromethane) afforded **7d** as a yellow oil (269 mg, 80%); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 12.18 (s, 1H), 8.08 (d, *J* = 5.1 Hz, 1H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.65-7.60 (m, 2H), 7.58-7.55 (m, 1H), 7.33 (d, *J* = 5.1 Hz, 1H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 2.2 Hz, 1H), 3.94 (s, 3H), 3.58 (t, 4H), 3.47 (s, 2H), 2.38 (t, 4H); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ: 156.2, 149.1, 143.5, 136.8, 132.5, 130.9, 129.7, 129.2, 123.4, 122.1, 119.4, 119.1, 112.4, 100.2, 66.7, 62.3, 56.2, 53.6; HRMS m/z *calcd for* $C_{19}H_{21}BrN_3O_2$ $[M+H]^+$ 402.0812 *found* 402.0810 (Δ = 0.5 ppm).

4-(2-(5-((diethylamino)methyl)-2-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-2-isopropylbenzoic acid, 1



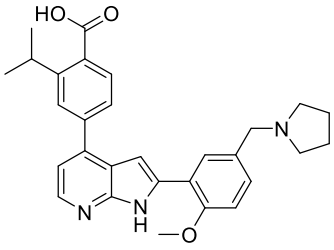
Prepared according to method D. Purification by preparative HPLC 10-95% MeCN/H_2O to give **1** in a (85 mg, 68%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.39 (d, *J* = 5.7 Hz, 1H), 8.01 (d, *J* = 2.2 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 1.8 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.58 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.52 (d, *J* = 5.8 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.31 (s, 1H), 4.37 (s, 2H), 4.07 (s, 3H), 3.94 (p, *J* = 6.9 Hz, 1H), 3.25 (dq, *J* = 14.2, 7.1 Hz, 4H), 1.39-1.34 (m, 12H); ^{13}C NMR (101 MHz, CD_3OD) δ: 169.8, 157.9, 150.1, 145.6, 143.9, 140.0, 137.8, 136.8, 132.9, 131.8, 131.0, 130.3, 126.4, 125.6, 122.1, 121.8, 119.6, 114.9, 112.5, 100.3, 55.3, 55.2, 29.4, 23.0, 7.6; HRMS *m/z calcd* for $C_{29}H_{33}N_3O_3$ $[M+H]^+$ 471.2522 *found* 472.2576 (Δ = 2.1 ppm).

4-(2-{5-[(Dimethylamino)methyl]-2-methoxyphenyl}-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-2-(propan-2-yl)benzoic acid (8a)



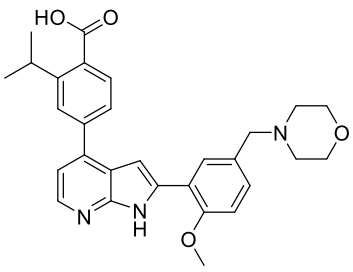
Prepared according to method D. Purification by preparative HPLC 10-95% MeCN/H_2O to give **8a** in a (11 mg, 29%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.27 (d, *J* = 5.4 Hz, 1H), 7.89 (d, *J* = 2.3 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 1.7 Hz, 1H), 7.63 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.44 (dd, *J* = 8.6, 2.3 Hz, 2H), 7.32 (d, *J* = 5.5 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 7.13 (s, 1H), 4.23 (s, 2H), 3.97 (s, 3H), 3.89-3.81 (m, 1H), 2.79 (s, 6H), 1.27 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ: 169.9, 158.1, 150.2, 146.7, 142.6, 139.6, 138.4, 135.1, 133.2, 132.2, 131.1, 130.4, 126.5, 125.7, 122.3, 120.4, 119.2, 115.0, 112.5, 100.5, 60.1, 55.3, 41.4, 29.5, 23.0; HRMS m/z *calcd for* $C_{27}H_{29}N_3O_3$ $[M+H]^+$ 470.2438 *found* 470.2433 (Δ = 1.1 ppm).

4-(2-{2-Methoxy-5-[(pyrrolidin-1-yl)methyl]phenyl}-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-2-(propan-2-yl)benzoic acid (8b)



Prepared according to method D. Purification by preparative HPLC 10-95% MeCN/H_2O to give **8b** in a (27 mg, 37%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.27 (br s, 1H), 7.90 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.36 (s, 1H), 7.21-7.15 (m, 2H), 4.29 (s, 2H), 3.96 (s, 3H), 3.85-3.81 (m, 1H), 3.42 (br s, 2H), 3.14 (br s, 2H), 2.08 (br s, 2H), 1.93 (br s, 2H), 1.26 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ: 169.9, 157.9, 150.1, 144.5, 140.5, 137.4, 132.1, 131.5, 130.4, 130.3, 126.3, 125.5, 123.4, 119.9, 112.4, 100.0, 57.2, 55.2, 53.3, 29.4, 23.0, 22.4; HRMS m/z *calcd for* $C_{29}H_{32}N_3O_3$ $[M+H]^+$ 470.2438 *found* 470.2433 (Δ = 1.1 ppm).

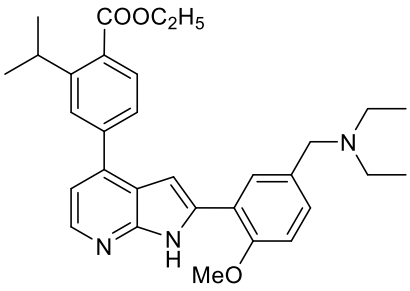
4-(2-{2-Methoxy-5-[(morpholin-4-yl)methyl]phenyl}-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-2-(propan-2-yl)benzoic acid (8c)



Prepared according to method D. Purification by preparative HPLC 10-95% MeCN/H_2O to give **8c** in a (34 mg, 60%); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.43 (d, *J* = 5.8 Hz, 1H), 8.04 (d, *J* = 2.3 Hz, 1H), 8.00 (d, *J* = 8.0 Hz,

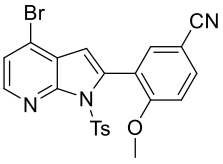
1H), 7.93 (d, *J* = 1.8 Hz, 1H), 7.78 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.61 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.56 (d, *J* = 5.7 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.32 (s, 1H), 4.41 (s, 2H), 4.10 (s, 3H), 4.07 (s, 2H), 3.98-3.93 (m, 1H), 3.76 (s, 2H), 3.44 (s, 2H), 3.26 (s, 2H), 1.39 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz DMSO-d_6) δ: 170.3, 169.7, 149.6, 147.1, 136.0, 133.0, 133.0, 132.2, 132.1, 131.6, 131.3, 130.6, 128.3, 126.5, 125.9, 121.7, 120.6, 112.9, 100.5, 63.8, 59.4, 56.4, 51.2, 49.1, 29.4, 24.4, 24.3; HRMS m/z *calcd for* $C_{29}H_{32}N_3O_4$ $[M+H]^+$ 486.2387 *found* 486.2384 (Δ = 0.8 ppm).

Ethyl 4-(2-(5-((diethylamino)methyl)-2-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-2-isopropylbenzoate (9)



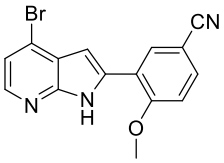
Purification by preparative HPLC 10-95% MeCN/H_2O to give **9** in a (36 mg, 98%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.39 (d, *J* = 5.6 Hz, 1H), 8.01 (d, *J* = 2.2 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.77-7.72 (m, 1H), 7.57 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.49 (d, *J* = 5.7 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.28 (s, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.37 (s, 2H), 4.07 (s, 3H), 3.82 (p, *J* = 6.9 Hz, 1H), 3.25 (p, *J* = 7.4 Hz, 4H), 1.50-1.29 (m, 16H); ^{13}C NMR (101 MHz, CD_3OD) δ: 168.1, 157.9, 149.9, 140.7, 138.8, 137.2, 132.6, 131.1, 130.9, 130.1, 126.4, 125.6, 122.0, 120.1, 114.9, 112.5, 99.9, 60.9, 55.3, 29.6, 22.9, 13.2, 7.7; HRMS *m/z calcd* for $C_{31}H_{37}N_3O_3$ $[M+H]^+$ 499.2835 *found* 500.2913 (Δ = 4.1 ppm)

3-[4-Bromo-1-(4-methylbenzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-4-methoxybenzonitrile (10)



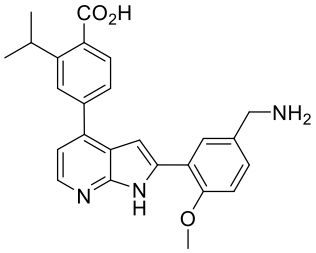
Prepared according to method B. Purification by flash chromatography (50% ethyl acetate-PET ether) afforded **10** as a yellow oil (586 mg, 87%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.23 (d, *J* = 5.2 Hz, 1H), 8.03-7.99 (m, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 5.2 Hz, 1H), 7.41-7.37 (m, 2H), 7.34-7.29 (m, 2H), 6.81 (s, 1H), 3.84 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ: 161.8, 148.3, 145.9, 145.7, 143.5, 137.1, 136.4, 135.5, 134.8, 130.2, 128.2, 125.0, 123.0, 119.3, 112.4, 109.5, 108.3, 103.1, 56.6, 21.6; HRMS m/z *calcd for* $C_{22}H_{16}BrN_3NaO_3S$ $[M+Na]^+$ 503.9988 f*ound* 503.9973 (Δ = 3.0 ppm).

3-{4-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl}-4-methoxybenzonitrile (11)



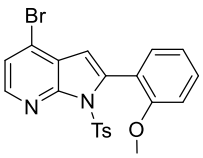
Prepared according to method C. Purification by flash chromatography (10% methanol-dichloromethane) afforded **11** as a yellow oil (327 mg, 59%); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.24 (s, 1H), 8.29 (d, *J* = 2.1 Hz, 1H), 8.06 (d, *J* = 5.1 Hz, 1H), 7.81 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.33 – 7.29 (m, 2H), 6.96 (s, 1H), 3.98 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 207.0, 160.3, 149.1, 144.4, 134.3, 132.5, 124.1, 121.1, 119.4, 119.3, 113.7, 103.8, 101.8, 56.9, 31.2; HRMS m/z *calcd for* $C_{15}H_{11}BrN_3O$ $[M+H]^+$ 328.0080 *found* 328.0076 (Δ = 1.1 ppm).

4-{2-[5-(aminomethyl)-2-methoxyphenyl]-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl}-2-(propan-2-yl)benzoic acid (12)



Prepared according to method D. The filtrate residue was dissolved in methanol (10 mL), $CoCl_2 \cdot 6H_2O$ (3 equiv) was then added before cooling to 0 °C. $NaBH_4$ (10 equiv) was slowly added to the reaction and the mixture was allowed to stir at room temperature for a further 1 hour before filtration through celite and purification by preparative HPLC 10-95% MeCN/H_2O to give **13** (26 mg, 60%); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.01 (s, 1H), 8.30 (d, *J* = 5.0 Hz, 1H), 8.17 (br s, 2H), 7.94 (d, *J* = 2.3 Hz, 1H), 7.82- 7.80 (m, 2H), 7.62 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.41 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.24 (d, *J* = 5.0 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.09 (s, 1H), 3.98 (q, *J* = 5.6 Hz, 2H), 3.89 (s, 3H), 3.83- 3.76 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 6H).; ^{13}C NMR (101 MHz, DMSO-d_6) δ: 169.7, 157.0, 149.6, 149.2, 142.9, 141.4, 140.4, 136.6, 131.4, 130.6, 130.6, 129.7, 126.7, 126.6, 125.9, 120.1, 119.0, 115.2, 112.7, 100.0, 56.3, 42.4, 29.4, 24.3; HRMS m/z *calcd for* $C_{25}H_{26}N_3O_3$ $[M + H]^+$ 416.1969 *found* 416.1968 (Δ = 0.2 ppm).

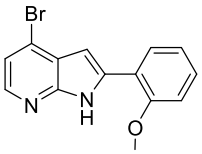
4-Bromo-2-(2-methoxyphenyl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (13)



Prepared according to method A. Purification by flash chromatography (50% ethyl acetate-PET ether) afforded **14** as a colourless oil (960 mg, 32%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, *J* = 5.3 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.41 (td, *J* = 8.2, 1.7 Hz, 1H), 7.29-7.24 (m, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.45

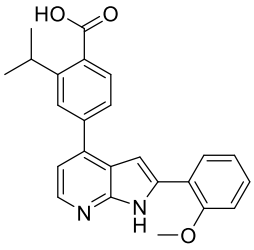
(s, 1H), 3.73 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.3, 148.7, 144.8, 144.4, 139.4, 136.1, 131.1, 130.9, 129.2, 128.2, 124.8, 123.5, 122.1, 121.8, 120.0, 110.4, 107.3, 55.5, 21.6; HRMS m/z *calcd for* $C_{21}H_{17}BrN_2NaO_3S$ $[M+Na]^+$ 479.0035 *found* 479.0035 (Δ = 0.0 ppm).

4-Bromo-2-(2-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (14)



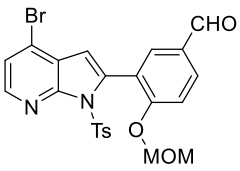
Prepared according to method C. Purification by flash chromatography (10% methanol-dichloromethane) afforded **15** as a colourless oil (300 mg 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.38 (s, 1H), 8.09 (d, *J* = 5.2 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.41-7.34 (m, 1H), 7.30-7.25 (m, 2H), 7.14-7.07 (m, 2H), 6.89 (s, 1H), 4.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.1, 148.1, 143.0, 137.0, 129.9, 128.4, 124.3, 122.2, 121.6, 119.4, 119.3, 112.0, 97.8, 55.9; HRMS m/z *calcd for* $C_{14}H_{12}BrN_2O$ $[M+H]^+$ 303.0128 *found* 303.0122 (Δ = 1.8 ppm).

4-[2-(2-Methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-2-(propan-2-yl)benzoic acid (15)



Prepared according to method D. Purification by preparative HPLC 10-95% MeCN/H_2O to give **16** in a (30 mg, 59%); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 12.05 (s, 1H), 8.32 (d, *J* = 5.0 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.90 (d, *J* = 1.8 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.68 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.38 (ddd, *J* = 8.7, 7.4, 1.7 Hz, 1H), 7.27 (d, *J* = 5.0 Hz, 1H), 7.20-7.18 (m, 2H), 7.08 (td, *J* = 7.6, 1.0 Hz, 1H), 3.92 (s, 3H), 3.90-3.83 (m, 1H), 1.32 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ: 169.7, 157.1, 149.9, 149.6, 141.7, 136.5, 131.1, 130.7, 129.9, 126.5, 125.9, 121.2, 100.3, 45.4, 29.4; HRMS m/z *calcd for* $C_{24}H_{23}N_2O_3$ $[M+H]^+$ 387.17034 *found* 387.1710 (Δ = -1.7 ppm).

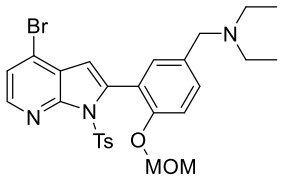
3-(4-Bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-4-(methoxymethoxy)benzaldehyde (16)



Prepared according to method A. Purification by flash chromatography (50% ethyl acetate-PET ether) afforded **17** as a colourless oil (850 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.92 (s, 1H), 8.16 (d, *J* = 5.3 Hz, 1H), 7.92 (dd, *J* = 8.5, 2.1 Hz, 1H),

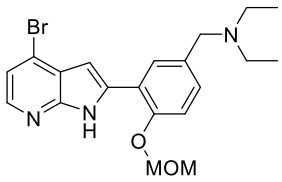
7.84 (d, *J* = 2.1 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.29 (d, *J* = 5.3 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 3H), 6.53 (s, 1H), 5.26-5.22 (m, 2H), 3.46 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.6, 161.7, 148.6, 145.2, 144.9, 137.7, 135.5, 134.4, 131.0, 130.0, 129.4, 128.0, 125.1, 123.6, 122.3, 113.9, 108.0, 95.1, 56.9, 21.6; HRMS m/z *calcd for* $C_{23}H_{19}BrN_2NaO_5S$ $[M+Na]^+$ 537.0090 *found* 537.0098 (Δ = -1.7 ppm).

({3-[4-bromo-1-(4-methylbenzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-4-(methoxymethoxy)phenyl}methyl)diethylamine (17)



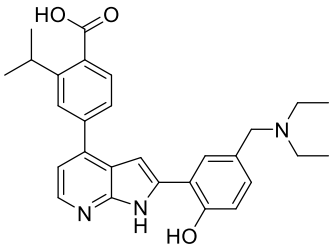
Prepared according to method B. Purification by flash chromatography (5% methanol-dichloromethane) afforded **18** as a colourless oil (672 mg, 87%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.16 (d, *J* = 5.3 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 7.9 Hz, 2H), 7.50 (d, *J* = 5.3 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.68 (s, 1H), 5.18 (br s, 1H), 5.28 (br s, 1H), 4.20 (d, *J* = 5.4 Hz, 2H), 3.43 (s, 3H), 3.10 (q, *J* = 7.1 Hz, 4H), 2.37 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ: 156.7, 148.4, 145.7, 144.3, 138.7, 135.5, 133.1, 132.9, 129.2, 127.6, 124.7, 123.3, 122.8, 122.4, 114.1, 107.5, 94.7, 55.4, 55.4, 46.2, 20.1, 8.4; HRMS m/z *calcd for* $C_{27}H_{31}BrN_3O_4S$ $[M+H]^+$ 572.1213 *found* 572.1208 (Δ = 0.9 ppm).

[(3-{4-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl}-4-(methoxymethoxy)phenyl)methyl]diethylamine (18)



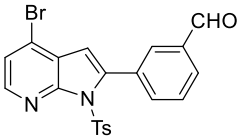
Prepared according to method C. Purification by flash chromatography (10% methanol-dichloromethane) afforded **19** as a yellow oil (420 mg 69%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.03 (d, *J* = 5.2 Hz, 1H), 7.84 (d, *J* = 2.1 Hz, 1H), 7.34 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.31-7.28 (m, 2H), 6.96 (s, 1H), 5.39 (s, 2H), 4.88 (s, 3H), 3.73 (s, 2H), 3.50 (s, 3H), 2.70 (q, *J* = 7.2 Hz, 4H), 1.15 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ: 153.9, 148.0, 142.3, 136.7, 130.9, 130.5, 129.7, 124.2, 122.6, 120.4, 118.9, 115.2, 99.3, 94.7, 56.1, 55.4, 46.1, 9.5; HRMS m/z *calcd for* $C_{21}H_{25}BrN_2O_2$ $[M+H]^+$ 418.1113 *found* 418.1112 (Δ = -0.2 ppm).

4-[2-(2-Methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-2-(propan-2-yl)benzoic acid (19)



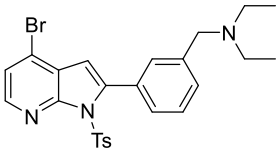
Prepared according to method D. The filter residue was then stirred in a mixture of acetonitrile/HCl (3:1) for 30 mins before filtering through celite and purification by preparative HPLC 10-95% MeCN/H_2O to give **21** in a (72 mg, 70%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.30 (d, *J* = 5.3 Hz, 1H), 7.92 (d, *J* = 2.2 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 1.6 Hz, 1H), 7.68 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.46 (d, *J* = 5.7 Hz, 1H), 7.3-7.31 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 4.24 (s, 2H), 3.85 (sept, *J* = 6.9 Hz, 1H), 3.19-3.12 (m, 4H), 1.30-1.27 (m, 12H); ^{13}C NMR (101 MHz, CD_3OD) δ: 169.8, 156.5, 150.2, 139.7, 138.9, 135.4, 132.7, 132.1, 130.8, 130.4, 126.6, 125.7, 121.0, 117.4, 117.1, 115.0, 99.7, 55.4, 46.4, 29.5, 23.0; HRMS m/z *calcd for* $C_{28}H_{32}N_3O_3$ $[M + H]^+$ 458.2438 *found* 458.2430 (Δ = 1.8 ppm).

3-(4-bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)benzaldehyde (20)



Prepared according to method A. Purification by flash chromatography (50% ethyl acetate-PET ether) afforded **22** as a colourless oil (500 mg, 76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.04 (s, 1H), 8.23 (d, *J* = 5.2 Hz, 1H), 7.96 (t, *J* = 1.8 Hz, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 5.3 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 6.56 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 191.8, 149.5, 145.5, 145.2, 141.0, 136.0, 135.9, 135.2, 133.3, 130.6, 130.3, 129.6, 128.5, 127.9, 125.3, 123.6, 122.9, 109.1, 21.7; HRMS m/z *calcd for* $C_{21}H_{15}BrN_2NaO_3S$ $[M+Na]^+$ 476.9879 *found* 476.9884 (Δ = -1.0 ppm).

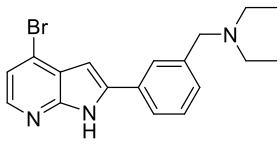
({3-[4-Bromo-1-(4-methylbenzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-4-(methoxymethoxy)phenyl}methyl)diethylamine (21)



Prepared according to method B. Purification by flash chromatography (5% methanol-dichloromethane) afforded **23** as a colourless oil (154 mg, 83%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.22 (d, *J* = 5.3 Hz, 1H), 7.87 (d, *J* = 1.9 Hz, 1H), 7.75-7.70 (m, 2H), 7.68 (d, *J* = 7.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 5.3 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.79 (s, 1H), 4.50 (s, 2H), 3.35-3.30 (m, 4H), 2.35 (s, 3H), 1.42 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ: 156.7, 148.4, 145.7, 144.3, 138.7, 135.5, 133.1, 132.9, 129.2, 127.6, 124.7, 123.3, 122.8, 122.4, 114.1, 107.5, 94.7, 55.4, 55.4, 46.2,

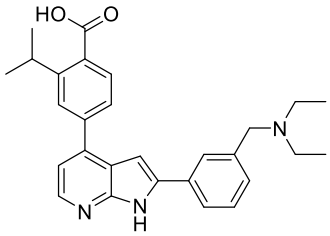
20.1, 8.4; HRMS m/z *calcd for* $C_{25}H_{27}BrN_3O_2S$ $[M+H]^+$ 512.1002 *found* 512.1013 (Δ = -2.3 ppm).

[(3-{4-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl}phenyl)methyl]diethylamine (22)



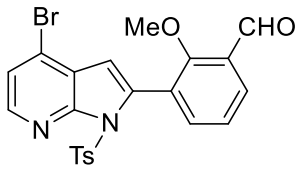
Prepared according to method C. Purification by flash chromatography (10% methanol-dichloromethane) afforded **24** as a colourless oil (95 mg, 89%); ^{1}H NMR (400 MHz, CD_3OD) δ: 7.92 (d, *J* = 5.3 Hz, 1H), 7.78 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 5.3 Hz, 1H), 6.76 (s, 1H), 3.70 (s, 2H), 2.62 (q, *J* = 7.2 Hz, 4H), 1.06 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ: 148.9, 142.4, 139.7, 131.5, 129.7, 128.9, 126.8, 124.7, 124.2, 123.2, 118.9, 96.9, 56.8, 46.3, 9.6; HRMS m/z *calcd for* $C_{18}H_{21}BrN_3$ $[M+H]^+$ 358.0913 *found* 358.0907 (Δ = 1.7 ppm).

4-(2-{3-[(Diethylamino)methyl]phenyl}-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-2-(propan-2-yl)benzoic acid (23)



Prepared according to method D. Purification by preparative HPLC 10-95% MeCN/H_2O to give **25** in a (30 mg, 70%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.25 (s, 1H), 7.94 (s, 1H), 7.91 (d, *J* = 6.9 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.73 (s, 1H), 7.62 (s, 2H), 7.53 (s, 2H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 5.2 Hz, 1H), 7.04 (s, 1H), 4.32 (s, 2H), 3.83 (sept, *J* = 13.9, 6.9 Hz, 1H), 3.16 (br s, 4H), 1.27 (q, *J* = 7.2 Hz, 12H); ^{13}C NMR (101 MHz, CD_3OD) δ: 170.0, 150.1, 132.3, 130.8, 130.6, 130.3, 129.9, 128.1, 127.0, 126.2, 125.5, 115.1, 111.9, 97.8, 55.7, 46.7, 29.4, 23.0, 7.6; HRMS m/z *calcd for* $C_{28}H_{32}N_3O_2$ $[M + H]^+$ 442.2489 *found* 442.2476 (Δ = 3.0 ppm).

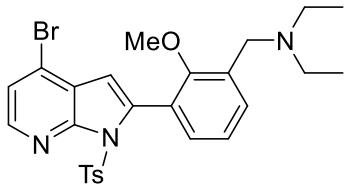
3-(4-bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-2-methoxybenzaldehyde (24)



Prepared according to method A. Purification by flash chromatography (50% ethyl acetate-PET ether) afforded **26** as a colourless oil (990 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.49 (s, 1H), 8.28 (d, *J* = 5.3 Hz, 1H), 8.07-7.90 (m, 3H), 7.59 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.41 (d, *J* = 5.3 Hz, 1H), 7.37-7.30 (m, 1H), 7.25 (d, *J* = 6.7 Hz, 2H), 6.66 (s,

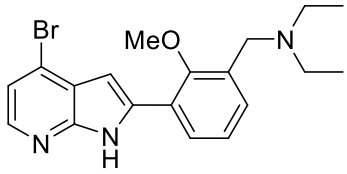
1H), 3.75 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 189.6, 162.0, 148.7, 145.4, 145.0, 137.1, 137.1, 135.6, 130.2, 129.4, 129.0, 128.6, 127.3, 125.2, 123.7, 123.1, 122.5, 108.1, 63.6, 21.7; HRMS *m/z calcd* for $C_{22}H_{17}BrN_2O_4SNa$ $[M+Na]^+$ 507.9990 *found* 508.0068 (Δ = 0.2 ppm).

_N_-(3-(4-bromo-1-tosyl-1_H_-pyrrolo[2,3-_b_]pyridin-2-yl)-2-methoxybenzyl)-_N_-ethylethanamine (25)



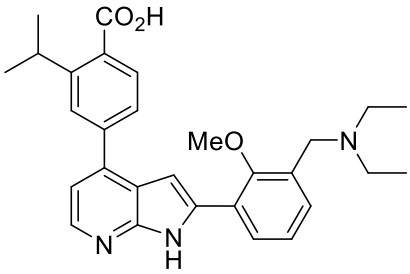
Prepared according to method B. Purification by flash chromatography (50% ethyl acetate-PET ether) afforded **27** as a yellow oil (765 mg, 81%; ^{1}H NMR (400 MHz, CD_3OD) δ: 8.18 (d, *J* = 5.3 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.69 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.63 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.51 (d, *J* = 5.3 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.33-7.27 (m, 2H), 6.85 (s, 1H), 4.56 (d, *J* = 13.3 Hz, 1H), 4.28 (d, *J* = 13.3 Hz, 1H), 3.58 (s, 3H), 2.35 (s, 3H), 1.39 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ: 178.1, 158.6, 148.6, 145.9, 144.8, 138.4, 135.2, 133.7, 132.8, 129.2, 127.8, 126.4, 124.9, 124.2, 124.1, 123.2, 122.6, 108.0, 60.3, 50.2, 22.4, 20.2, 8.1; HRMS *m/z calcd* for $C_{26}H_{28}BrN_3O_3S$ $[M+H]^+$ 541.1035 *found* 542.1095 (Δ = 3.6 ppm).

_N_-(3-(4-bromo-1_H_-pyrrolo[2,3-_b_]pyridin-2-yl)-2-methoxybenzyl)-_N_-ethylethanamine (26)



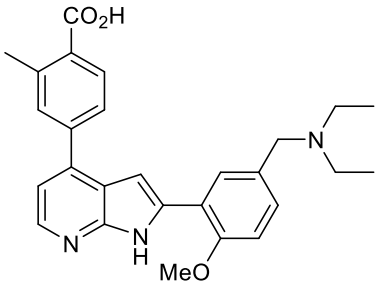
Prepared according to method C. Purification by flash chromatography (5% methanol-dichloromethane) afforded **28** as a yellow oil (630 mg, 85%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.12 (d, *J* = 5.4 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.59 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.46-7.37 (m, 2H), 7.03 (s, 1H), 4.43 (s, 2H), 3.69 (s, 3H), 3.32-3.28 (m, 4H), 1.43 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ: 157.0, 147.6, 142.1, 135.7, 132.8, 131.9, 125.6, 125.4, 125.3, 124.5, 123.2, 119.2, 100.5, 60.6, 50.9, 7.7; HRMS *m/z calcd* for $C_{19}H_{22}BrN_3O$ $[M+H]^+$ 387.0946 *found* 388.1008 (Δ = 2.7 ppm).

4-(2-(3-((diethylamino)methyl)-2-methoxyphenyl)-1_H_-pyrrolo[2,3-_b_]pyridin-4-yl)-2-isopropylbenzoic acid (27)



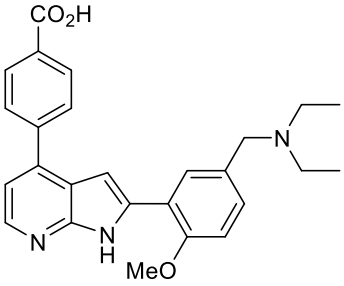
Prepared according to method D. Purification by preparative HPLC 10-95% MeCN/H_2O to give **29** in a (30 mg, 74%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.41 (s, 1H), 7.98-7.92 (m, 2H), 7.89 (d, *J* = 1.7 Hz, 1H), 7.73 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.58 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.47-7.43 (m, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.23 (s, 1H), 4.43 (s, 2H), 3.94 (p, *J* = 6.8 Hz, 1H), 3.72 (s, 3H), 3.31-3.25 (m, 5H), 1.42 (t, *J* = 7.3 Hz, 6H), 1.36 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ: 169.9, 157.1, 150.1, 140.6, 136.3, 132.8, 131.9, 131.4, 130.3, 126.3, 125.5, 125.4, 124.6, 100.5, 60.7, 50.8, 29.4, 23.0, 7.7; HRMS *m/z calcd* for $C_{29}H_{33}N_3O_3$ $[M+H]^+$ 471.2522 *found* 472.2579 (Δ = 3.4 ppm).

4-(2-(5-((diethylamino)methyl)-2-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-2-methylbenzoic acid (28)



Prepared according to method D. Purification by preparative HPLC 10-95% MeCN/H_2O to give **30** in a (50 mg, 75%); ^{1}H NMR (101 MHz, CD_3OD) δ: 8.27 (d, *J* = 5.6 Hz, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 7.94 (d, *J* = 2.3 Hz, 1H), 7.70 – 7.61 (m, 2H), 7.46 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.36 (d, *J* = 5.6 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 7.16 (s, 1H), 4.27 (s, 2H), 3.99 (s, 3H), 3.15 (p, *J* = 7.2 Hz, 4H), 2.63 (s, 3H), 1.27 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (400 MHz, CD_3OD) δ: 168.9, 157.8, 140.9, 140.3, 136.5, 133.0, 131.5, 131.3, 131.2, 125.9, 122.2, 119.6, 115.1, 112.5, 99.7, 55.3, 20.6, 7.6; HRMS *m/z calcd* for $C_{27}H_{29}N_3O_3$ $[M+H]^+$ 443.2209 *found* 444.2214 (Δ = 1.4 ppm).

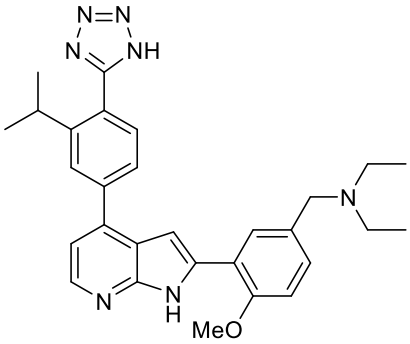
4-(2-(5-((diethylamino)methyl)-2-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzoic acid (29)



Prepared according to method D. Purification by preparative HPLC 10-95% MeCN/H_2O to give **31** in a (100 mg, 85%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.28 (d, *J* = 5.5 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 2H), 7.95 (d, *J* = 2.3 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 2H), 7.46 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.38 (d, *J* = 5.6 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 7.17 (s, 1H), 4.27 (s, 2H), 3.99 (s, 3H), 3.15 (p, *J* = 7.3 Hz, 4H), 1.27 (t, *J* = 7.3 Hz, 6H); ^{13}C

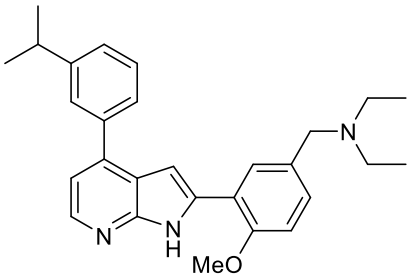
NMR (101 MHz, CD_3OD) δ: 168.0, 157.6, 148.6, 143.1, 142.4, 140.9, 136.3, 132.0, 130.9, 130.6, 129.9, 129.3, 128.3, 122.1, 120.8, 114.9, 112.4, 98.6, 55.5, 55.2, 7.6; HRMS *m/z calcd* for $C_{26}H_{27}N_3O_3$ $[M+H]^+$ 429.2052 *found* 430.2056 (Δ = 1.1 ppm).

_N_-ethyl-N-(3-(4-(3-isopropyl-4-(1H-tetrazol-5-yl)phenyl)-1_H_-pyrrolo[2,3-_b_]pyridin-2-yl)-4-methoxybenzyl)ethanamine (30)



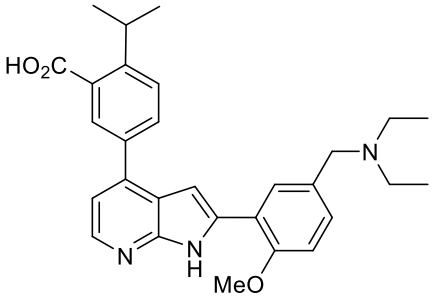
Prepared according to method D. Purification by preparative HPLC 10-95% MeCN/H_2O to give **32** in a (27 mg, 62%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.39 (d, *J* = 5.8 Hz, 1H), 8.01 (d, *J* = 2.3 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 1.8 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.58 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.52 (d, *J* = 5.8 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.31 (s, 1H), 4.37 (s, 2H), 4.07 (s, 3H), 3.94 (p, *J* = 6.9 Hz, 1H), 3.25 (dd, *J* = 12.2, 7.0 Hz, 4H), 1.42-1.33 (m, 12H); ^{13}C NMR (101 MHz, CD_3OD) δ: 169.8, 157.9, 150.1, 145.6, 143.9, 140.0, 137.8, 136.8, 132.9, 131.8, 131.0, 130.3, 126.4, 125.6, 122.1, 121.8, 119.6, 114.9, 112.5, 100.3, 55.3, 55.2, 29.4, 23.0, 7.6; HRMS *m/z calcd* for $C_{29}H_{33}N_7O$ $[M+H]^+$ 495.2747 *found* 496.2829 (Δ = 0.6 ppm).

_N_-ethyl-_N_-(3-(4-(3-isopropylphenyl)-1_H_-pyrrolo[2,3-_b_]pyridin-2-yl)-4-methoxybenzyl)ethanamine (31)



Prepared according to method D. Purification by preparative HPLC 10-95% MeCN/H_2O to give **33** in a (67 mg, 82%); ^{1}H NMR (101 MHz, CD_3OD) δ: 8.37 (d, *J* = 5.9 Hz, 1H), 8.03 (d, *J* = 2.2 Hz, 1H), 7.75 -7.68 (m, 2H), 7.61-7.54 (m, 2H), 7.50 (dd, *J* = 16.9, 6.8 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.37 (s, 2H), 4.08 (s, 3H), 3.25 (p, *J* = 7.5 Hz, 4H), 3.08 (p, *J* = 6.9 Hz, 1H), 1.43-1.31 (m, 12H); ^{13}C NMR (400 MHz, CD_3OD) δ: 157.9, 149.9, 137.2, 132.8, 131.1, 128.9, 127.7, 126.5, 126.1, 122.1, 119.8, 114.9, 112.5, 100.3, 55.3, 34.1, 23.1, 7.6; HRMS *m/z calcd* for $C_{28}H_{33}N_3O$ $[M+H]^+$ 427.2624 *found* 428.2624 (Δ = 3.8 ppm).

5-(2-(5-((diethylamino)methyl)-2-methoxyphenyl)-1_H_-pyrrolo[2,3-_b_]pyridin-4-yl)-2-isopropylbenzoic acid (32)



Prepared according to method D. Purification by preparative HPLC 10-95% MeCN/H_2O to give **34** in a (55 mg, 78%); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.41 (d, *J* = 5.7 Hz, 1H), 8.26 (d, *J* = 2.0 Hz, 1H), 7.99 (ddd, *J* = 9.3, 8.0, 1.9 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.60 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.53 (d, *J* = 5.7 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.36 (s, 1H), 4.43 (s, 2H), 3.92 (p, *J* = 6.9 Hz, 1H), 3.73 (s, 3H), 3.31-3.25 (m, 4H), 1.42 (t, *J* = 7.3 Hz, 6H), 1.34 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ: 169.8, 157.0, 151.0, 145.4, 144.8, 137.8, 136.9, 134.4, 133.1, 131.9, 131.6, 131.3, 129.8, 127.2, 125.4, 124.9, 124.7, 121.6, 114.9, 100.8, 60.7, 50.9, 29.4, 22.8, 7.7; HRMS *m/z calcd* for $C_{29}H_{33}N_3O_3$ $[M+H]^+$ 471.2522 *found* 472.2579 (Δ = 3.4 ppm).

III. Assay

P. falciparum culture and synchronisation

P. falciparum cultures were maintained in RPMI-1640 media (Invitrogen) supplemented with 0.2% sodium bicarbonate, 0.5% Albumax II, 2.0 mM L-glutamine (Sigma) and 10 mg/L gentamycin. For continuous culture, the parasites were kept at 4% haematocrit in human erythrocytes from 0+ blood donors and between 0.5 - 3% parasitaemia maintained in an incubator at 37 °C, 5% carbon dioxide (CO_2), 5% oxygen (O_2) and 90% nitrogen (N_2). To obtain highly synchronous ring stage parasites for the drug assays, cultures were double synchronised using Percoll and Sorbitol synchronisation as previously described.[2-3] First, highly segmented schizonts were enriched by centrifugation on a 70% Percoll (GE Healthcare) cushion gradient. The Schizont pellet was collected and washed before fresh erythrocytes were added to a final haematocrit of 4%. The schizonts were incubated for about 1-2 hours shaking continuously to allow egress and re-invasion of new erythrocytes. Residual schizonts were then removed by treating the pellet with sorbitol to generate highly synchronous 1-2 hours old ring-stage parasites.

Determining the IC_{50} of compound inhibitors and drugs-*ex vivo*

To determine the IC_{50} of the molecules in parasites (*P. falciparum* 3D7) *ex vivo*, the molecules were diluted 1 in 3 from a starting concentration of 100 µM for 12 dilution

points. Fifty microliters of freshly diluted drugs, at twice the required final concentrations were aliquoted into black 96-well plates. To the drug plates, 50 µl of parasites prepared at 8% haematocrit at a parasitaemia (0.3 - 0.5%) were added and mixed by pipetting up and down several times giving a final culture volume of 100 µl at the required drug concentration (top concentration of 100 µM) and 4% haematocrit. To the 'no drug' control, growth media was added and uninfected erythrocytes were included on the plate as blank. The outer wells were filled with media to reduce evaporation from the experimental wells and the plates incubated for 50 hours (±2 hours) to allow the parasites sufficient time to re-invade before they are collected and frozen. To quantify growth inhibition, the plates were thawed at room temperature for at least 1 hour and 100 µl of lysis buffer (20 mM Tris-HCl; 5 mM EDTA; 0.004% saponin and triton X-100) in PBS containing Sybr Green I (1µl in 5 ml) was added to each well and mixed by pipetting up and down several times and incubated for 1 hour in the dark shaking. Using a Fluroskan/ClarioStar plate reader at excitation of 485 nm and emission of 538 nm, plate absorbances were acquired. The data was normalised against the controls and graphs were generated using Graph Pad Prism 8 to determine the IC_{50} values using the non-linear regression log (inhibitor) versus response (three parameter) curve.

Time Resolve Florescence Energy Transfer (TR-FRET) to determine the IC_{50} of the inhibitors with full-length *Pf*CLK3 recombinant protein

The TR-FRET assays, a high-throughput inhibition assay, as described previously[4] was used to determine the potency of the small molecules generated against full-length *Pf*CLK3 recombinant protein in a kinase buffer (containing 50 mM HEPES, 10 mM $MgCl_2$, 2 mM DTT, 0.01% Tween 20, and 1 mM EGTA), U*Light*-labeled peptide substrate (MBP peptide (sequence: CFFKNIVTPRTPPPSQGK). First, in a 10µL reaction volume, 5µl of twice the required enzyme concentration (50 nM) and 2.5µl of 4 times the required substrate concentration mix containing cold ATP, and the serially diluted drugs were mixed in a black 384-plate well plate and incubated at 37 ˚C for 1 hour. The reaction was stopped after incubation by adding the stopping/detection solution (containing 30 mM EDTA in 1X Lance detection buffer and 3 nM Europium-labeled anti-phospho specific antibody) and incubated for

another hour at RT before phosphorylation signals were measured using the ClarioStar.

For each test compound, percent inhibition (response) which was calculated using the formula: $\text{Percentage inhibition (response)} = \left[\frac{(Kinase\ activy\ -blank)}{(Maximum\ kinase\ activity-blank)}\right] * 100$

was plotted against log molar concentration of compound to calculate the IC_{50} (potency) of each inhibitor molecule and plotted using GraphPad prism software. All experiments were done in triplicates and the data presented is the S.E.M of three independent experiments run in triplicates.

*Pf*CLK3 phosphorylation of substrate results in the Europium-labeled anti-phospho specific antibody recognizing the phosphorylated site on the substrate. The Europium donor fluorophore is excited at 320- or 340 nm and energy is transferred to the U*Light* acceptor dye on the substrate, which finally results in the emission of light at 665nm. The level of *ULight* peptide phosphorylation correlates with the intensity of the emission. For normalization, a no kinase and a no inhibitor reaction wells were included and all experiments conducted in triplicates. Drug dilutions, protein concentrations and incubation times were the same for easy comparison of results.

IV. Microsomal stability

Compounds were incubated at 37 ºC at a concentration of 1 µM with CD1 mouse liver microsomes (GIBCO™, Thermo Fisher Scientific) in a suspension of 50 mM potassium phosphate buffer (pH 7.4) with a final protein concentration of 0.5 mg/mL. The reaction was started by the addition of excess NADPH and then quenched at several time points starting from time zero then at 3, 6, 9, 15 and 30 min addition of acetonitrile to an aliquot of the sample. Internal standard was added to each sample before centrifugation to remove any precipitates before monitoring loss of parent compound by HPLC analysis using Shimadzu LC-20A (Shimadzu, UK). Prism (Graphpad, USA) was used to fit an exponential decay for substrate depletion and subsequently rate constant (k) from the peak area of the parent compound to internal standard at each time point. Rate of intrinsic clearance (CL_{int}) was then calculated according to the methods of Obach using the equation:[5]

CL_{int} (mL/min/g liver) = k x v x microsomal protein yield

Where V is the incubation volume (volume/mg protein) and microsomal protein yield is assumed to be 52.5 mg protein/ g liver. With verapamil used as a positive control.

V. Distribution coefficient ($LogD_{7.4}$)

Distribution coefficient ($LogD_{7.4}$) was estimated by correlation of the compounds chromatographic retention properties to those of 10 standard compounds with known distribution coefficients ranging from -0.5 to 5.5 at pH 7.4. A fast gradient HPLC methodology was used based on the method developed by Valkó *et al*.[6]

VI. Kinase Screen Method and Data:

Each enzyme is assayed in its linear range with 0.3 µM substrate in 50 mM Tris pH 7. 5, 0.1 mM EGTA, 0.01 mM DTT, relevant Mg/ATP (5, 20 or 50 µM) for 30 min at room temp. Assays are stopped by the addition of 3% orthophosphoric acid and harvester onto p81 filter paper using the Perkin elmer unifilter harvester. Once dried, they are read on a Perkin elmer Topcount NXT scintillation counter for 30 sec/well.[7]

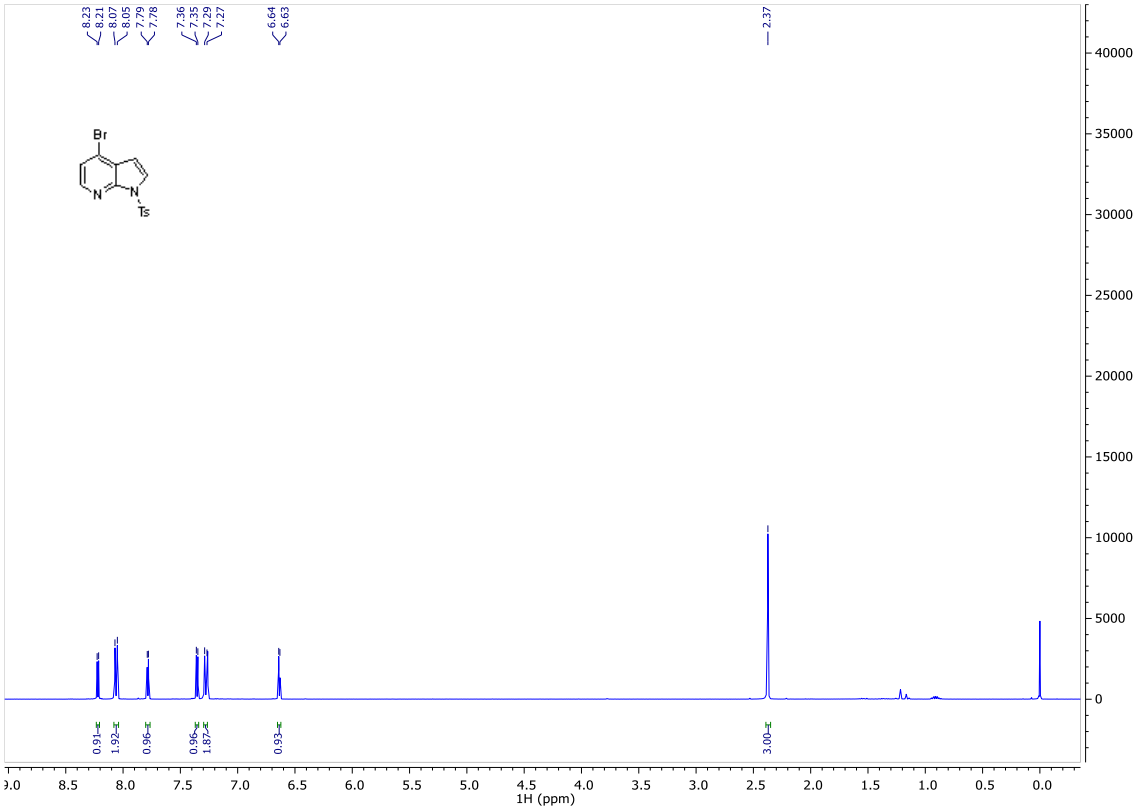
Kinase Concentration (1 µM)	% Activity
IKKb	144
PDGFRA	133
EPH-B1	124
PKCz	121
TIE2	120
BTK	119
p38d MAPK	117
ERK2	115
LKB1	115
PKBa	115
PKCγ	114
TTBK2	114
EF2K	113
HER4	112
p38b MAPK	112
MEKK1	112
MLK1	111
PDK1	111
MAPKAP-K3	110
EPH-B3	108
MLK3	107
PIM1	107
TLK1	106
RSK1	106
PINK	106
p38g MAPK	105
WNK1	105
PAK4	105

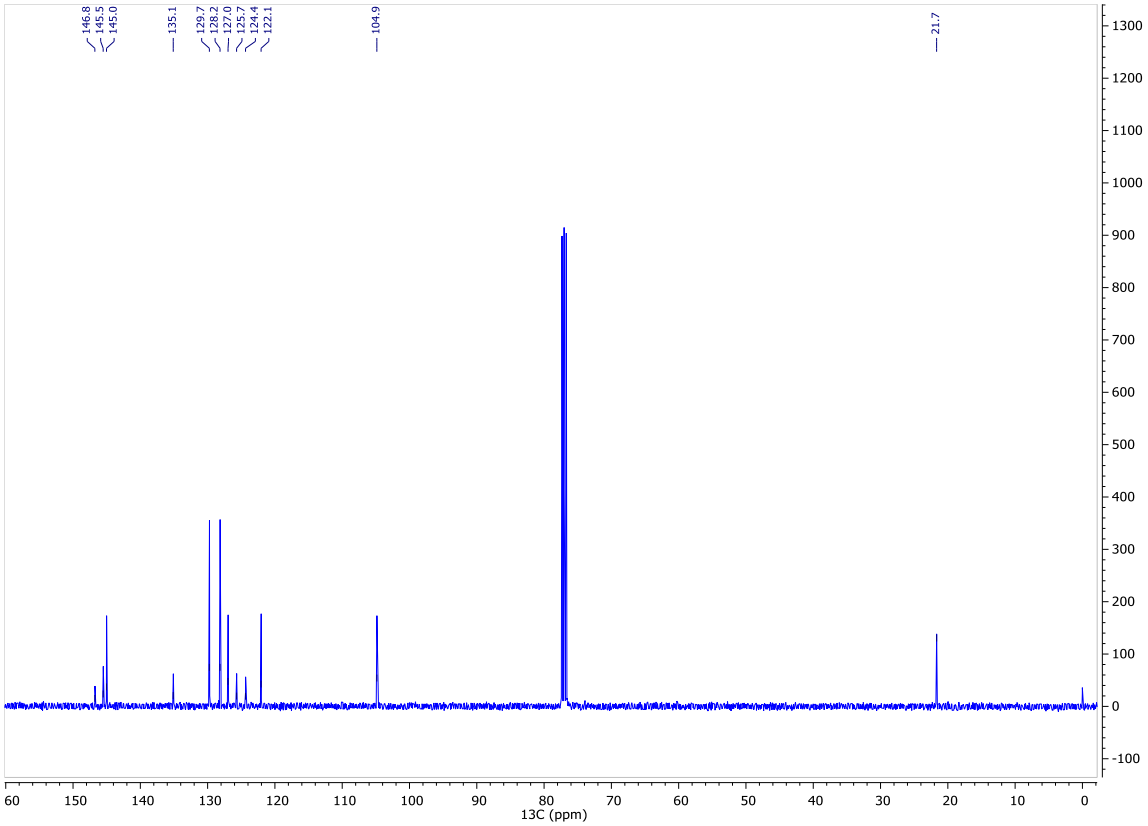
DAPK1	**105**
PLK1	**104**
MPSK1	**104**
PKA	**103**
MAPKAP-K2	**102**
TTBK1	**102**
DYRK3	**101**
IRR	**101**
ERK1	**100**
EIF2AK3	**100**
MKK6	**100**
EPH-B2	**100**
MSK1	**99**
DYRK2	**99**
NEK6	**96**
ULK2	**96**
PKBb	**96**
CK1γ2	**93**
HIPK3	**93**
PIM2	**93**
PAK6	**92**
SRPK1	**92**
ROCK 2	**92**
CK1δ	**91**
ASK1	**91**
CK2	**90**
SYK	**89**
p38a MAPK	**89**
PRAK	**88**
NEK2a	**87**
RSK2	**87**
TrkA	**87**
S6K1	**87**
CAMK1	**86**
TTK	**86**
MELK	**85**
JNK1	**85**
PKD1	**85**
PAK2	**84**
EPH-A4	**83**
HIPK1	**83**
EPH-B4	**82**
VEG-FR	**80**
PIM3	**80**
ULK1	**80**
SmMLCK	**80**
MKK1	**79**
CHK1	**78**
TESK1	**78**
IR	**77**
CHK2	**77**
PAK5	**75**
BRSK2	**74**
CSK	**74**
SIK3	**71**
DYRK1A	**71**
MST2	**68**
YES1	**67**

TBK1	**66**
BRSK1	**66**
EPH-A2	**64**
PKCa	**64**
JNK2	**62**
MST3	**62**
Aurora B	**59**
MST4	**59**
ZAP70	**59**
MARK4	**59**
ABL	**59**
HIPK2	**56**
ERK8	**55**
TSSK1	**55**
ERK5	**54**
MARK1	**52**
JNK3	**52**
IKKe	**52**
IGF-1R	**51**
GSK3b	**51**
FGF-R1	**50**
PRK2	**48**
STK33	**44**
MINK1	**44**
Src	**42**
SIK2	**41**
Lck	**39**
TAO1	**39**
OSR1	**38**
SGK1	**38**
MARK2	**34**
MARK3	**34**
BRK	**33**
GCK	**31**
AMPK (hum)	**30**
MNK2	**29**
TAK1	**25**
IRAK4	**24**
JAK3	**22**
DDR2	**21**
NUAK1	**18**
CLK2	**17**
Aurora A	**17**
MKK2	**17**
RIPK2	**16**
MAP4K5	**14**
CDK2-Cyclin A	**12**
PHK	**10**
TGFBR1	**6**
IRAK1	**6**
CDK9-Cyclin T1	**2**
CAMKKb	**2**
MAP4K3	**1**
MNK1	**0**

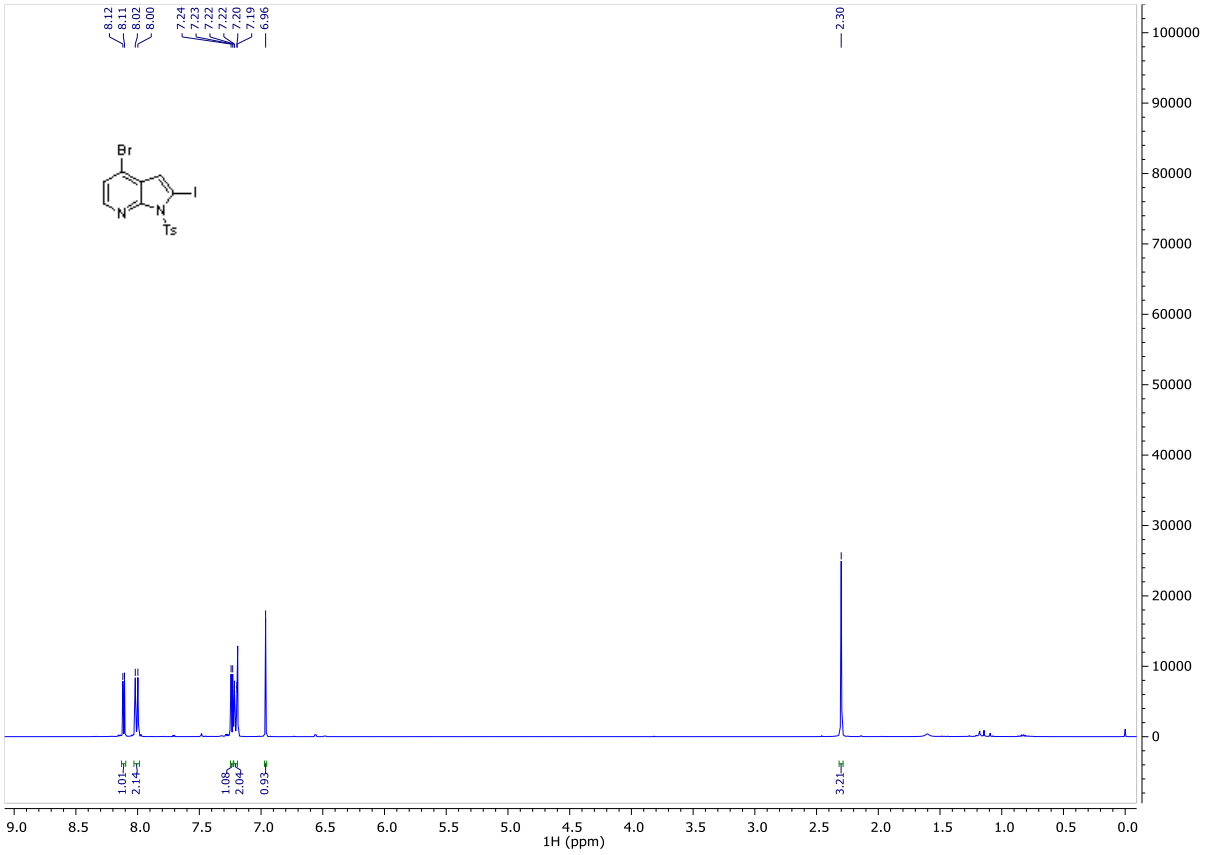
VII. NMR Spectra

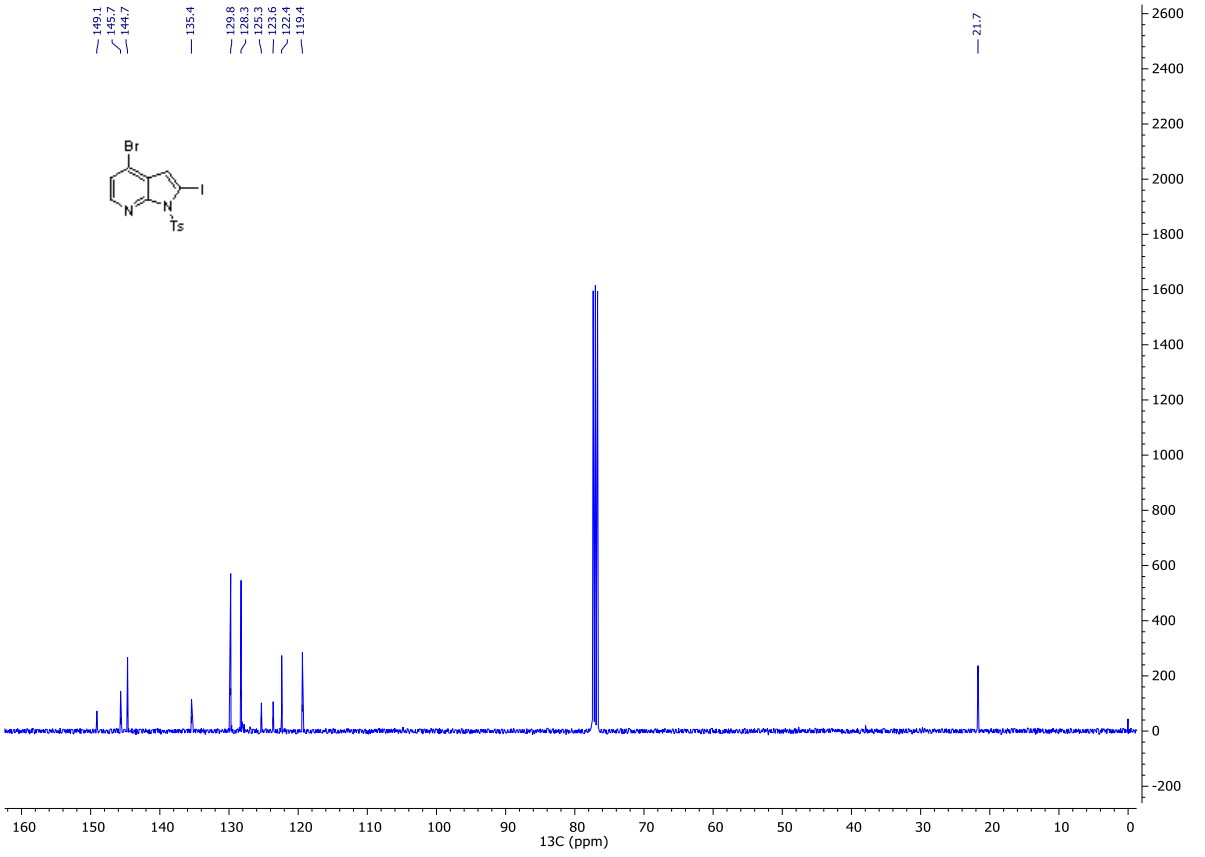
^{1}H and ^{13}C NMR spectra for compound 3



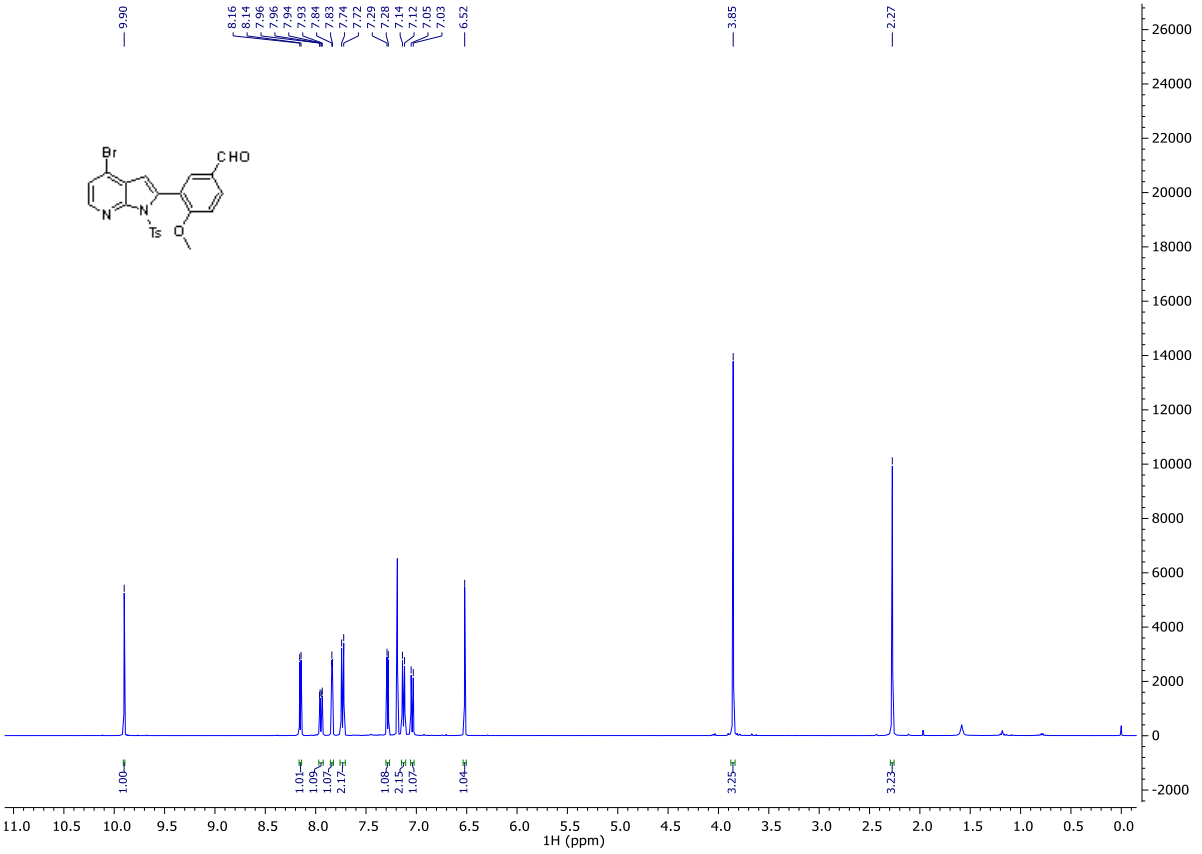


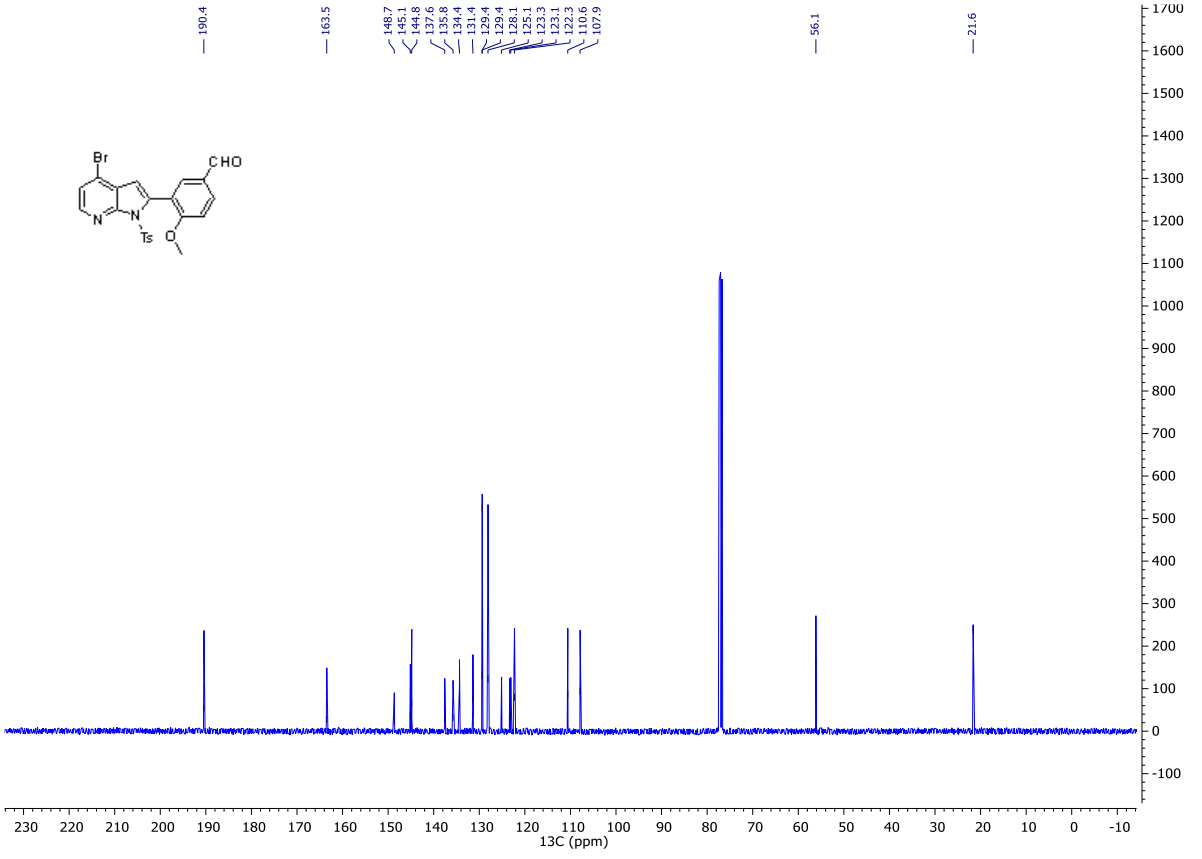
^{1}H and ^{13}C NMR spectra for compound 4



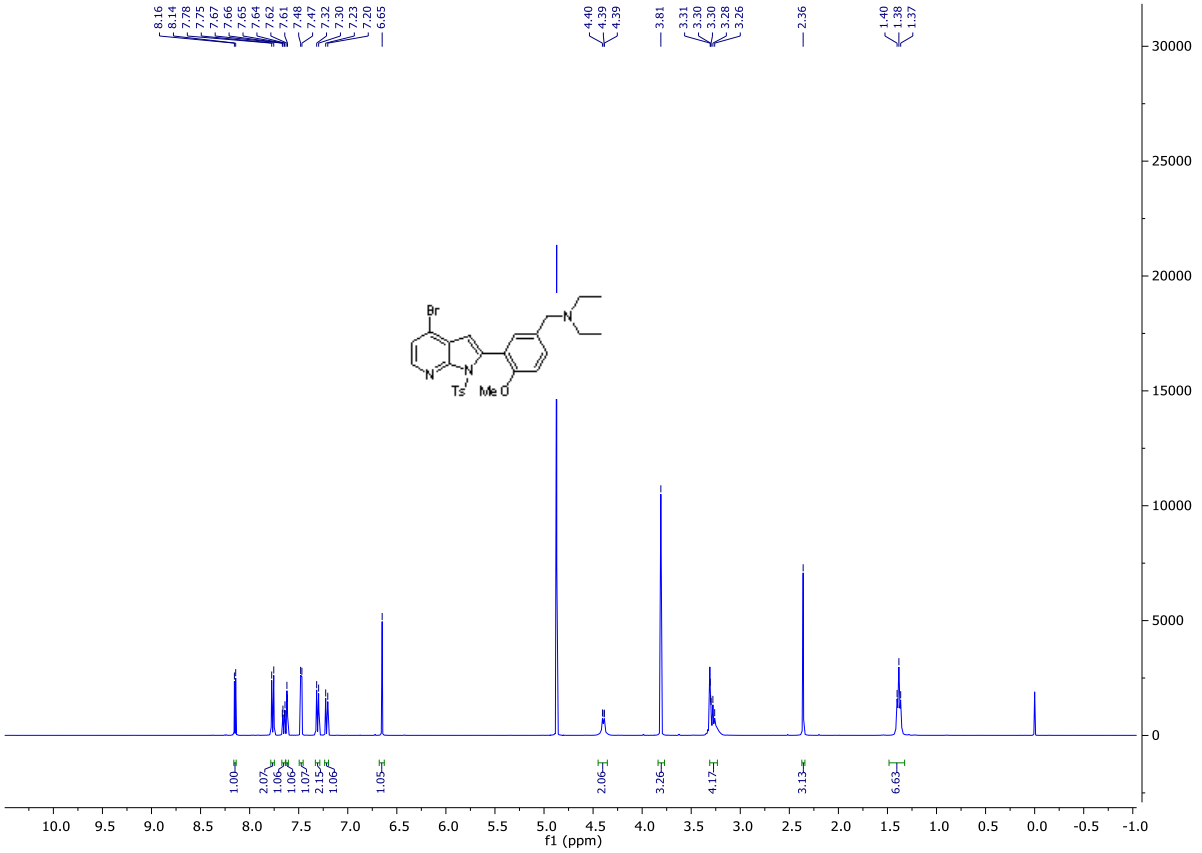


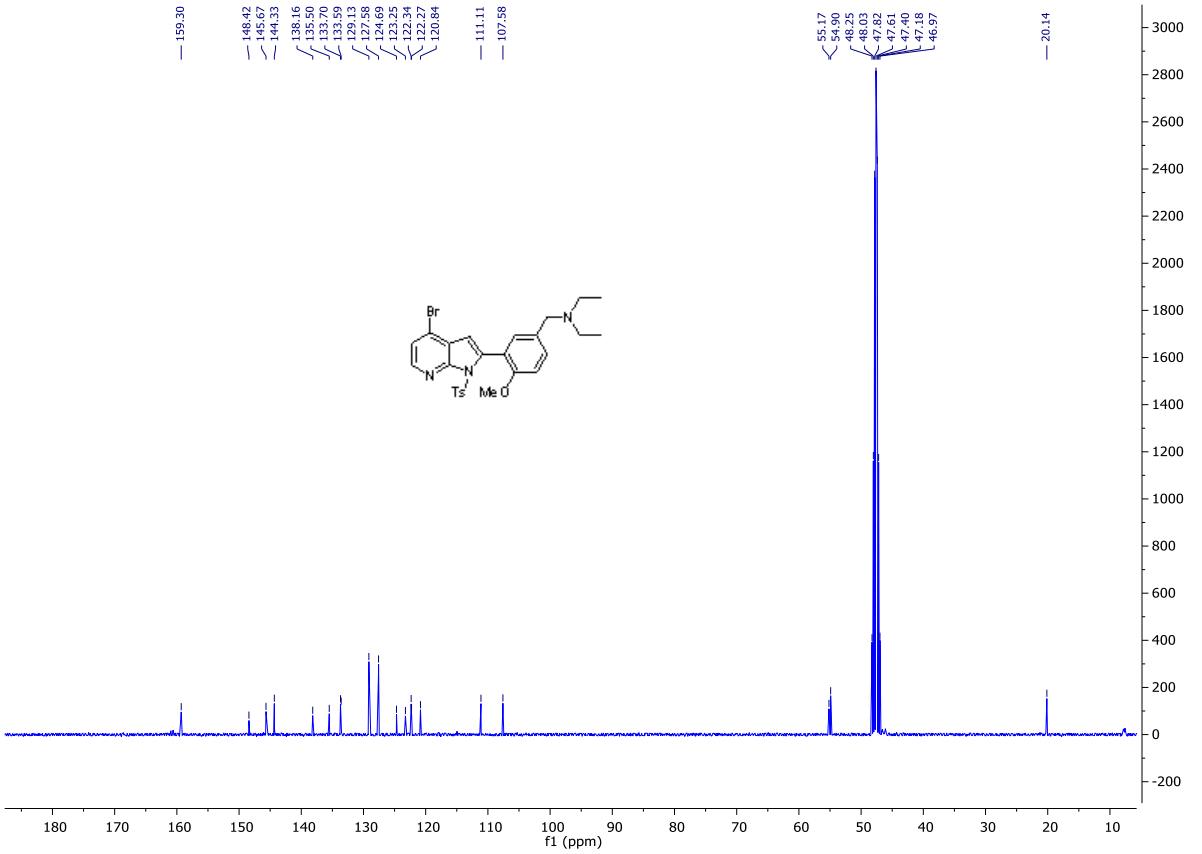
^{1}H and ^{13}C NMR spectra for compound 5



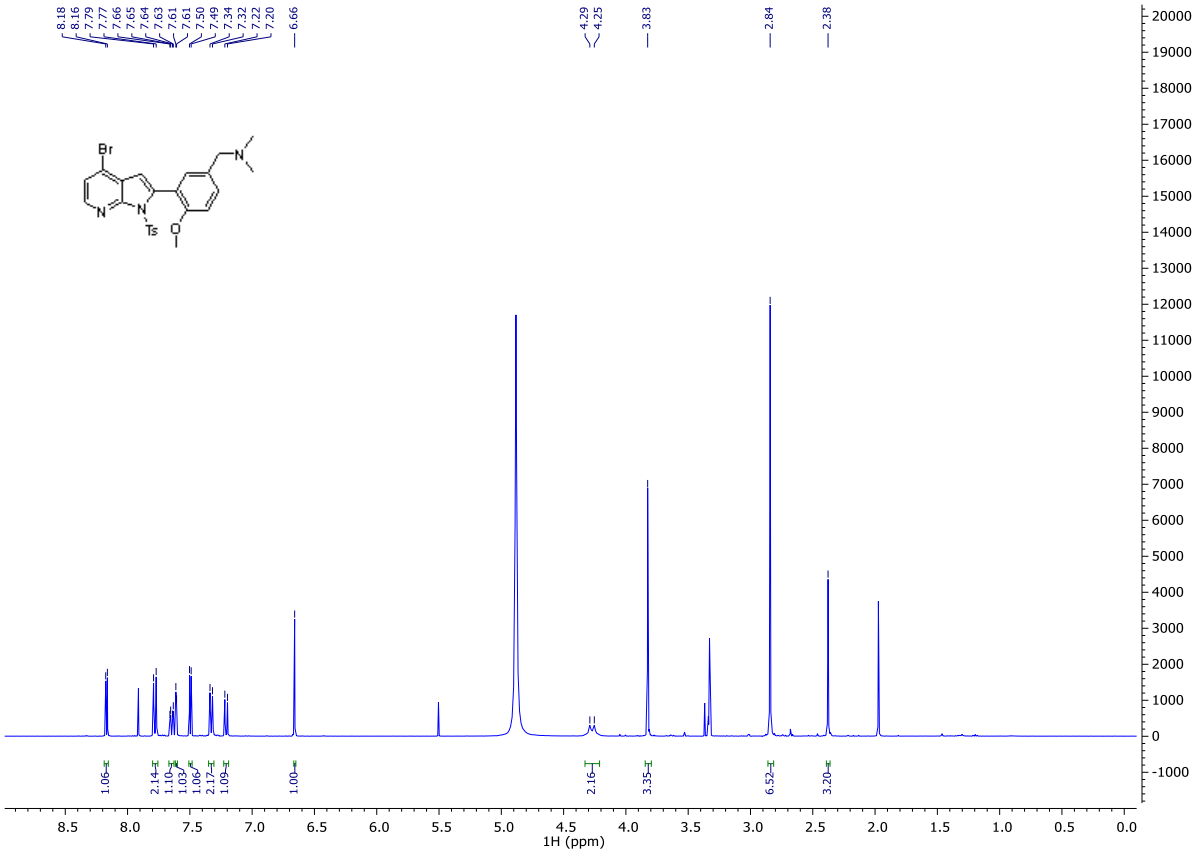


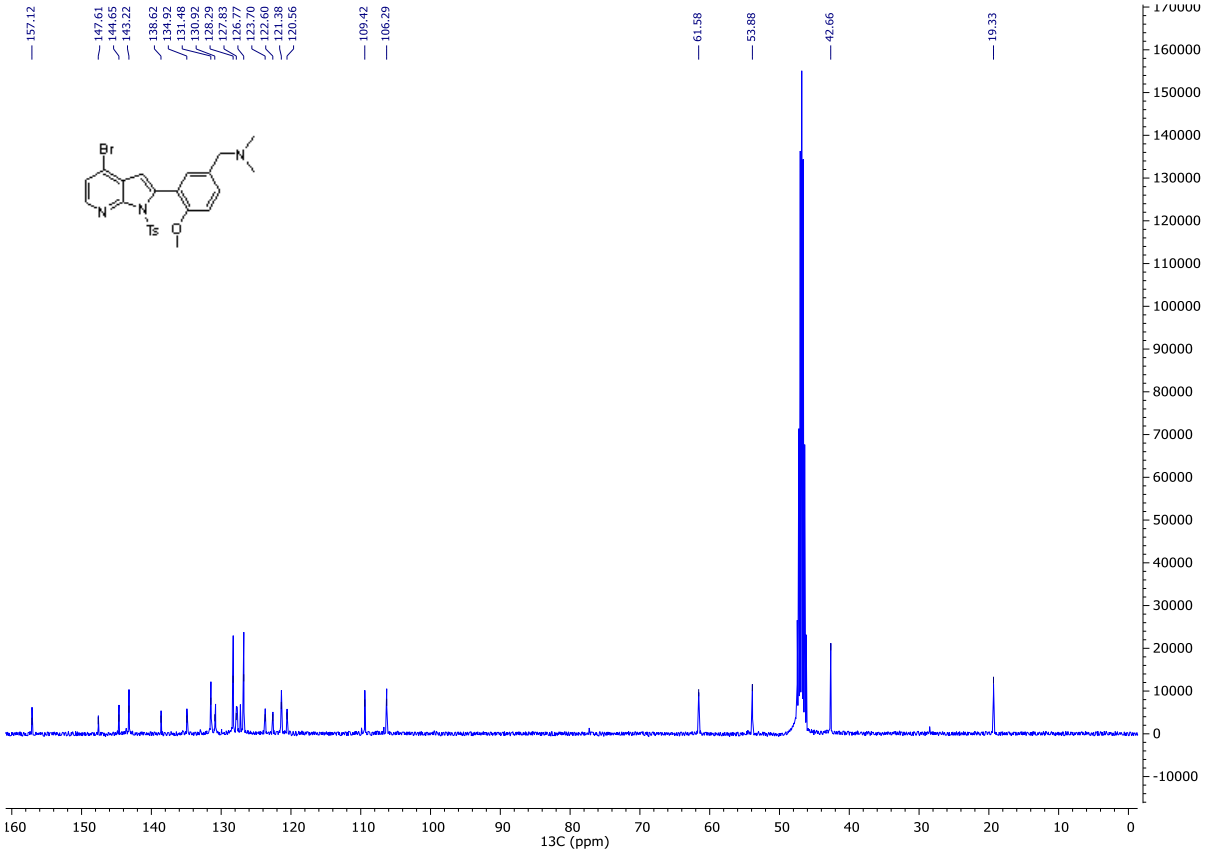
^{1}H and ^{13}C NMR spectra for compound 6a



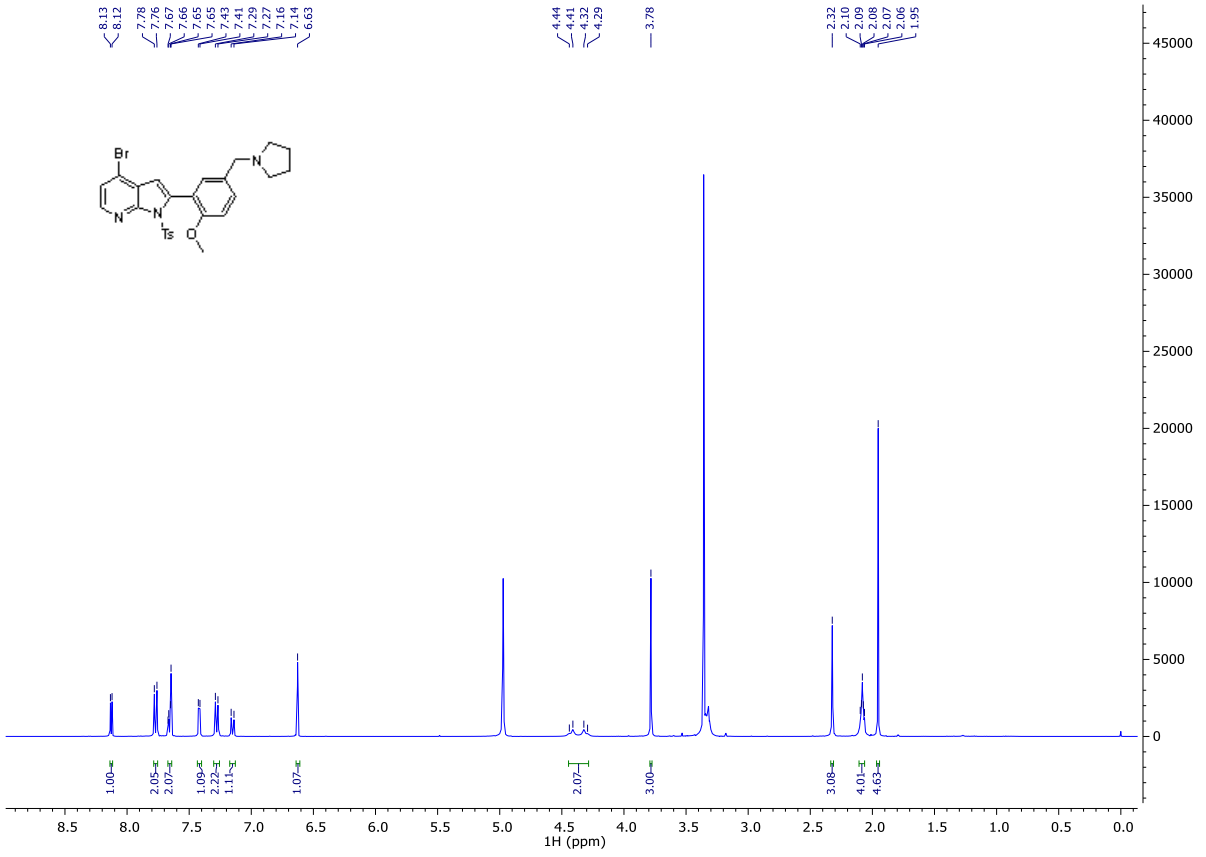


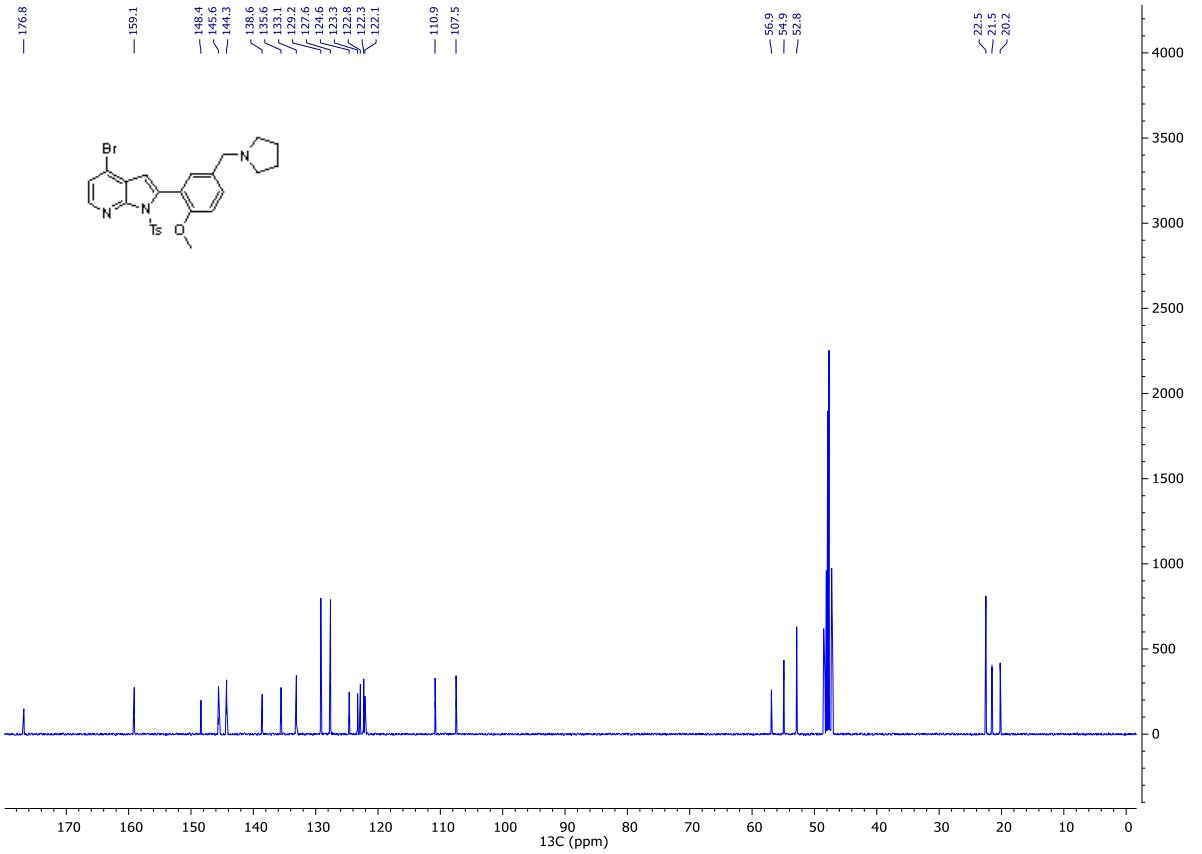
^{1}H and ^{13}C NMR spectra for compound 6b



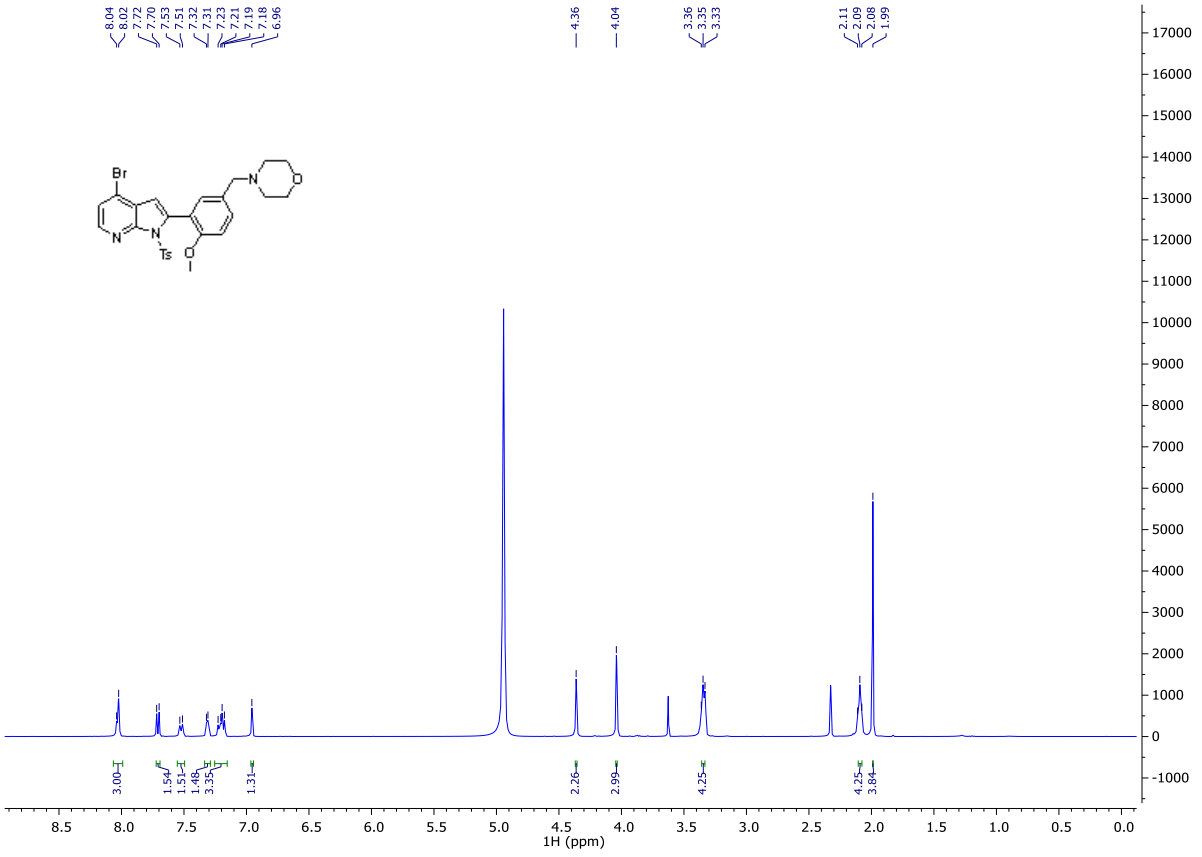


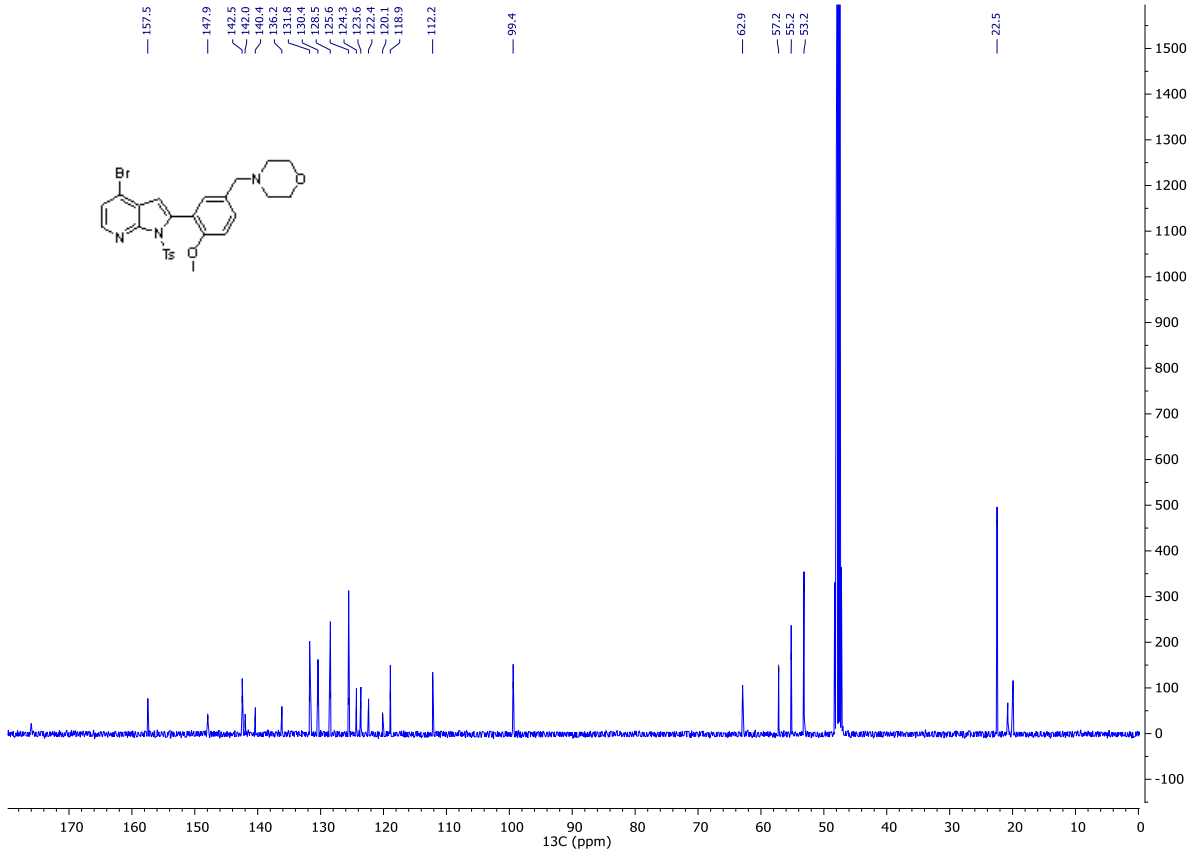
^{1}H and ^{13}C NMR spectra for compound 6c



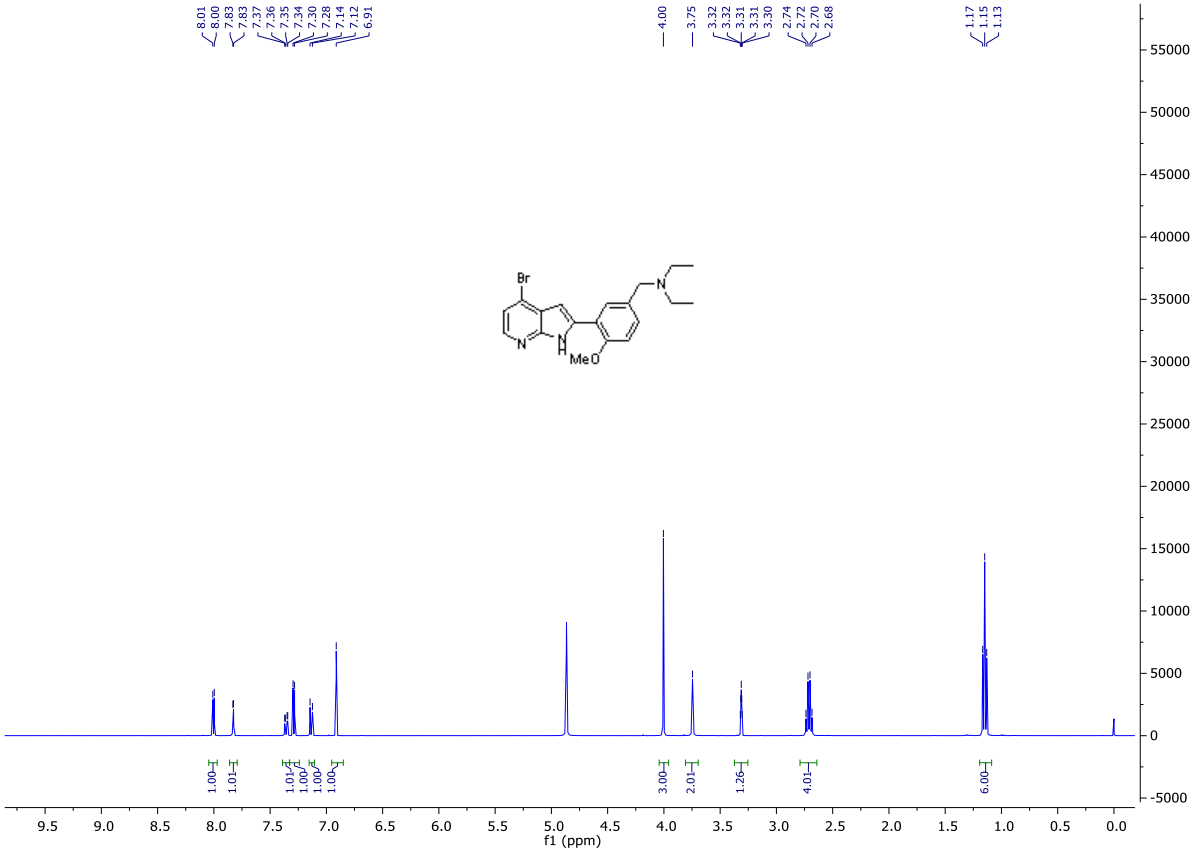


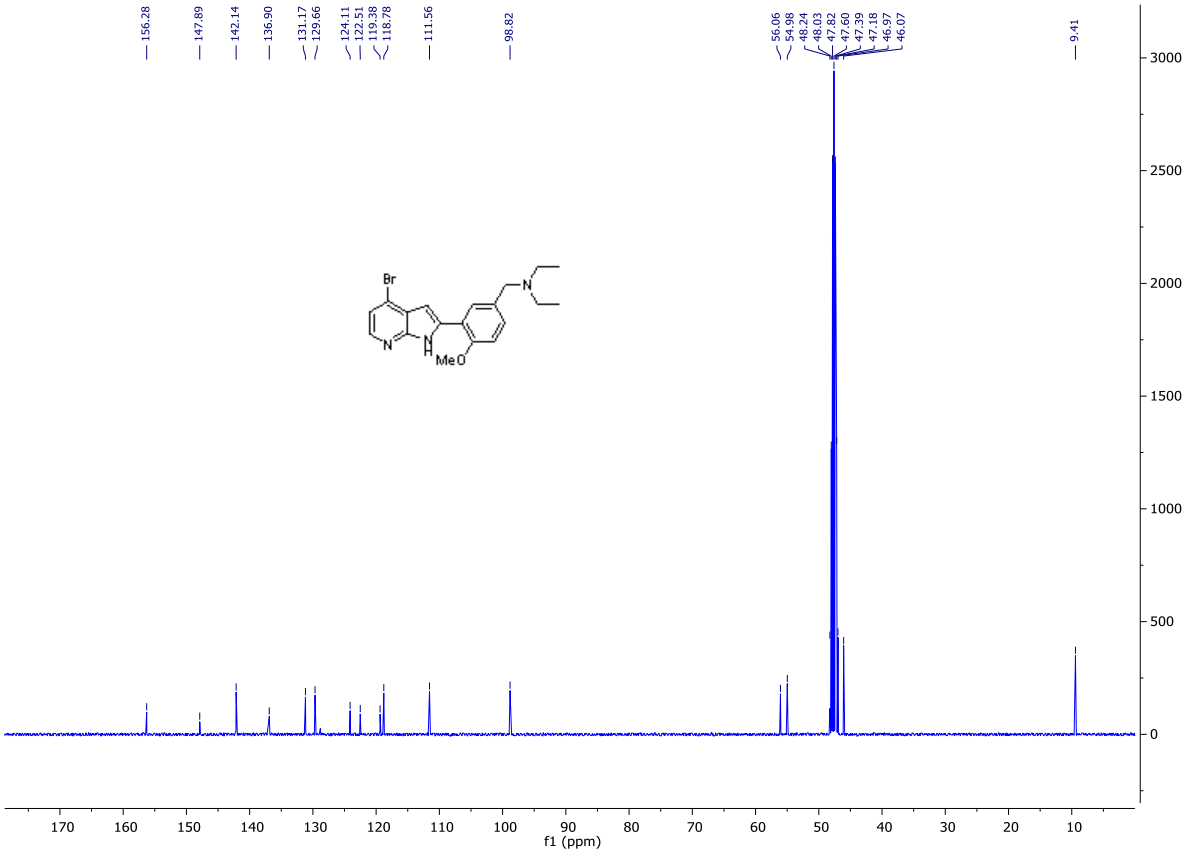
^{1}H and ^{13}C NMR spectra for compound 6d



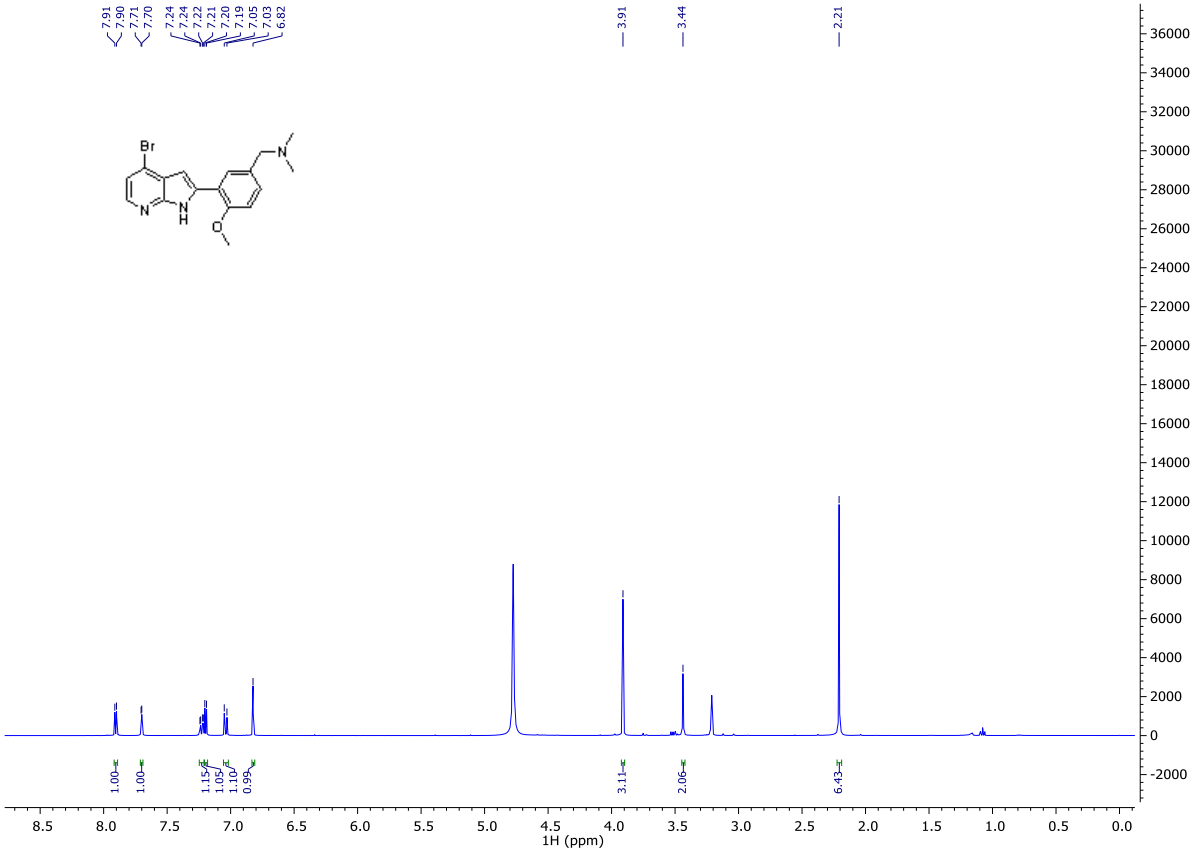

157.5
147.9
142.5
142.0
140.4
136.2
131.8
130.4
128.5
125.6
124.3
123.6
122.4
120.1
118.9
112.2
99.4
62.9
57.2
55.2
53.2
22.5
Br
N
O
N
Ts
O
13C (ppm)

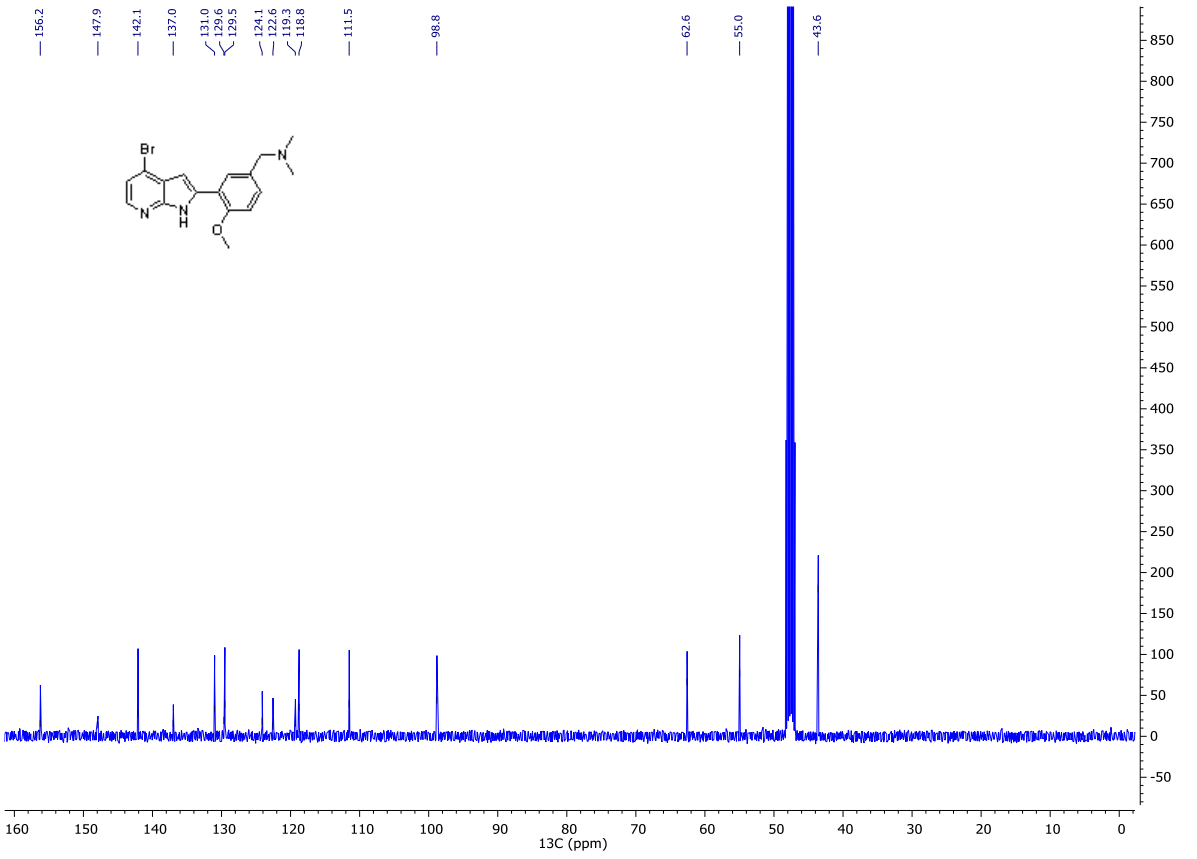
^{1}H and ^{13}C NMR spectra for compound 7a



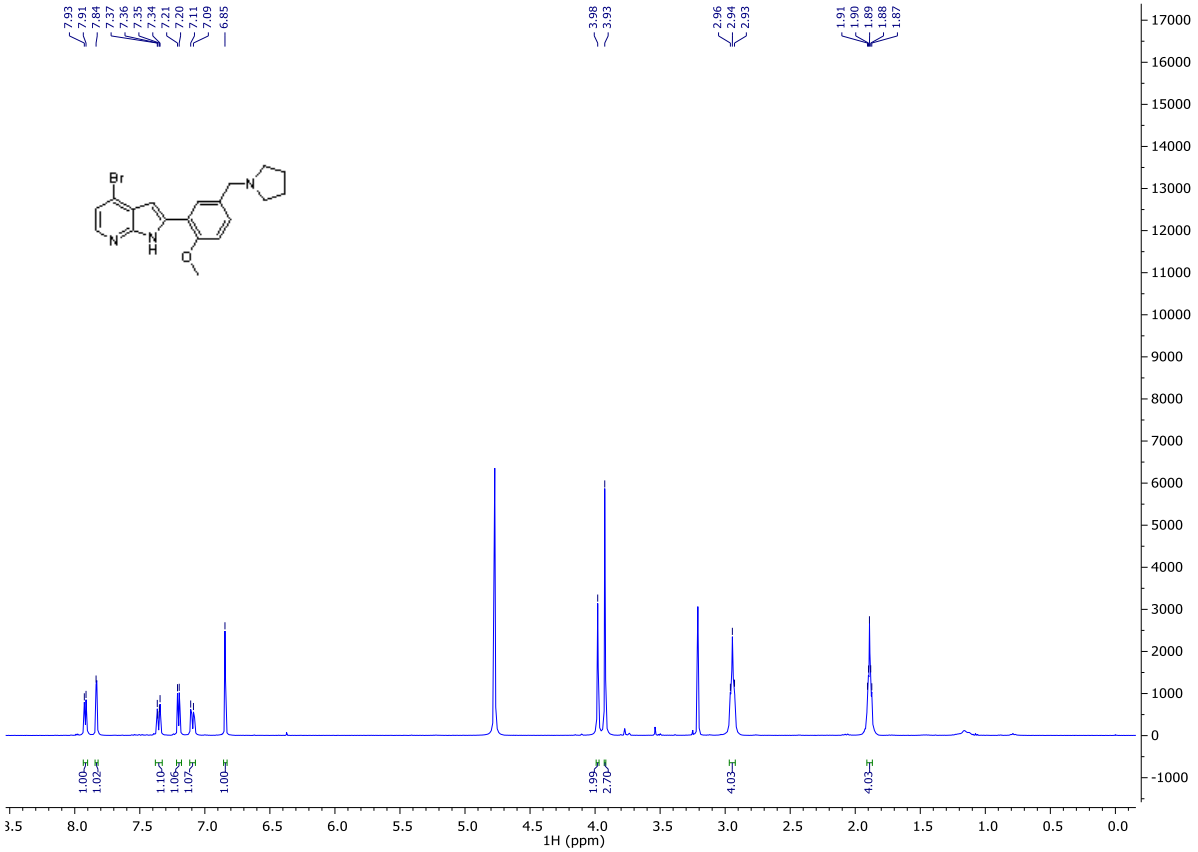


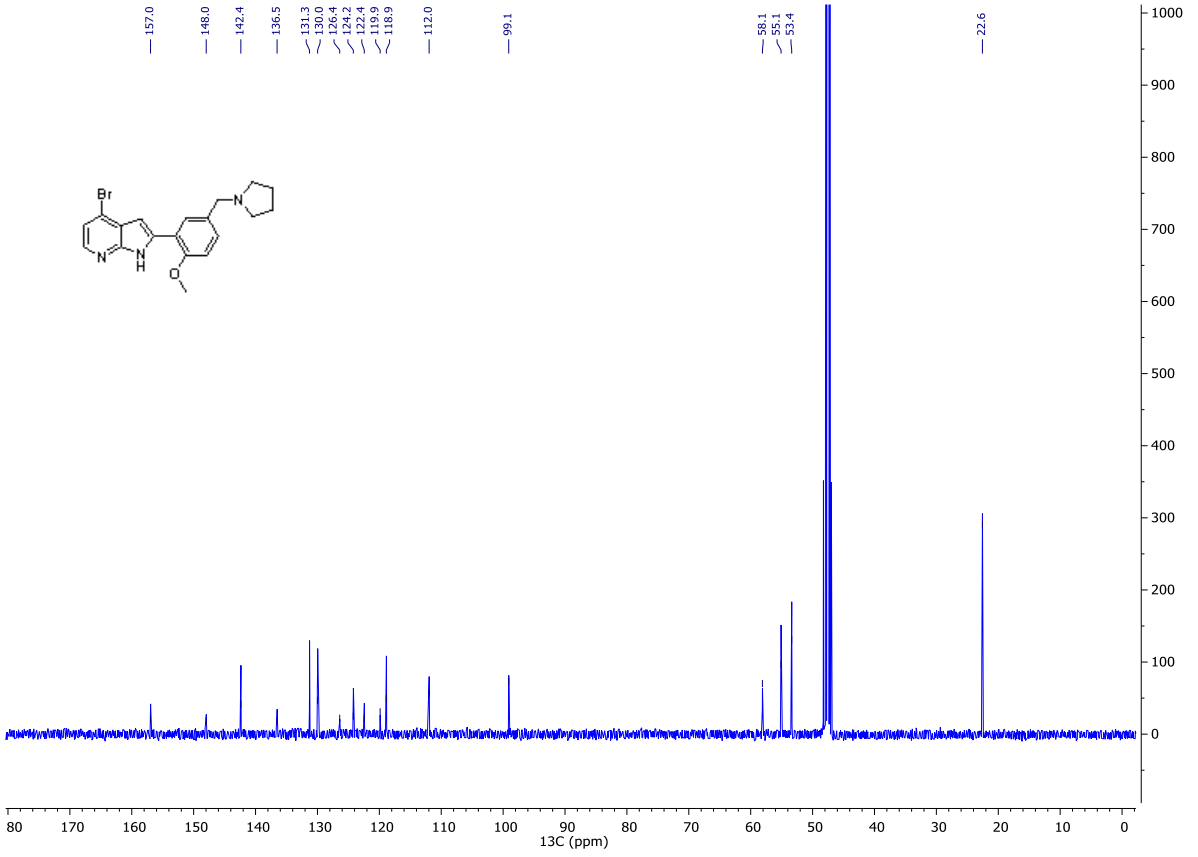
^{1}H and ^{13}C NMR spectra for compound 7b



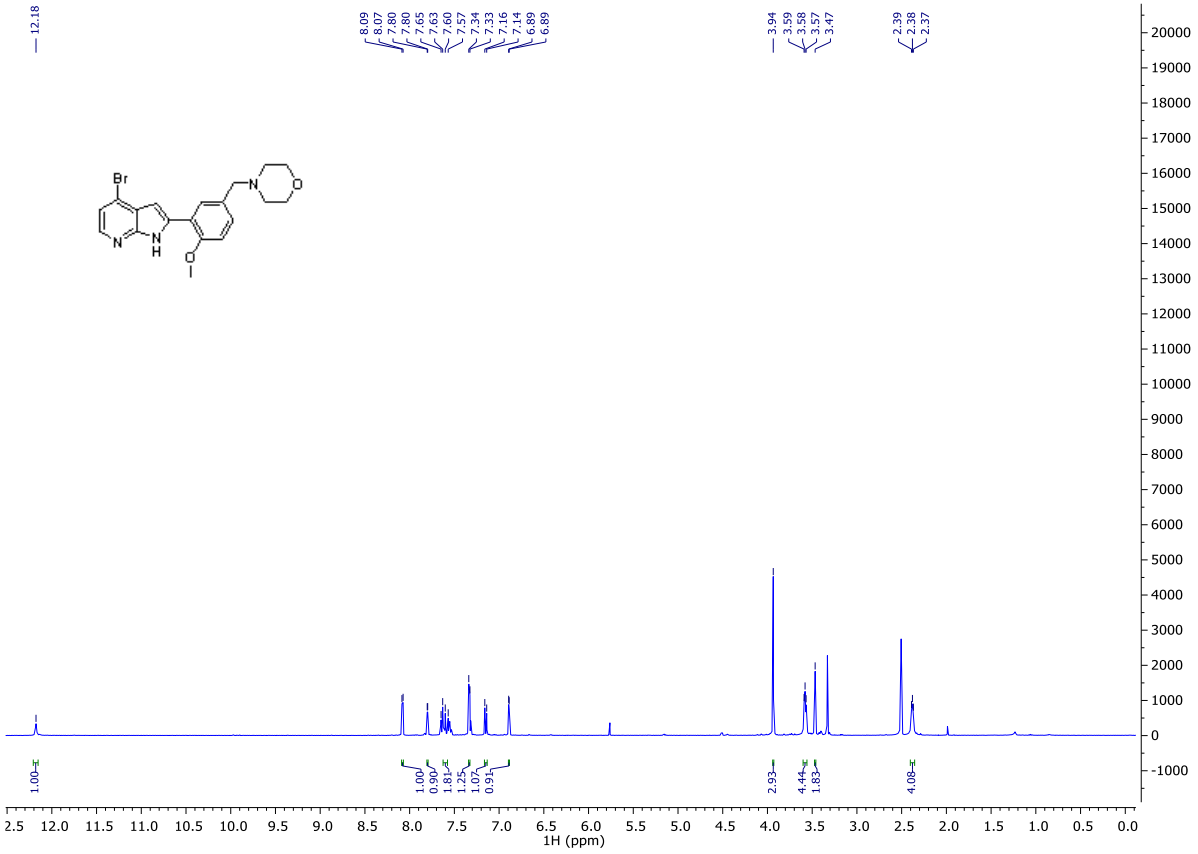


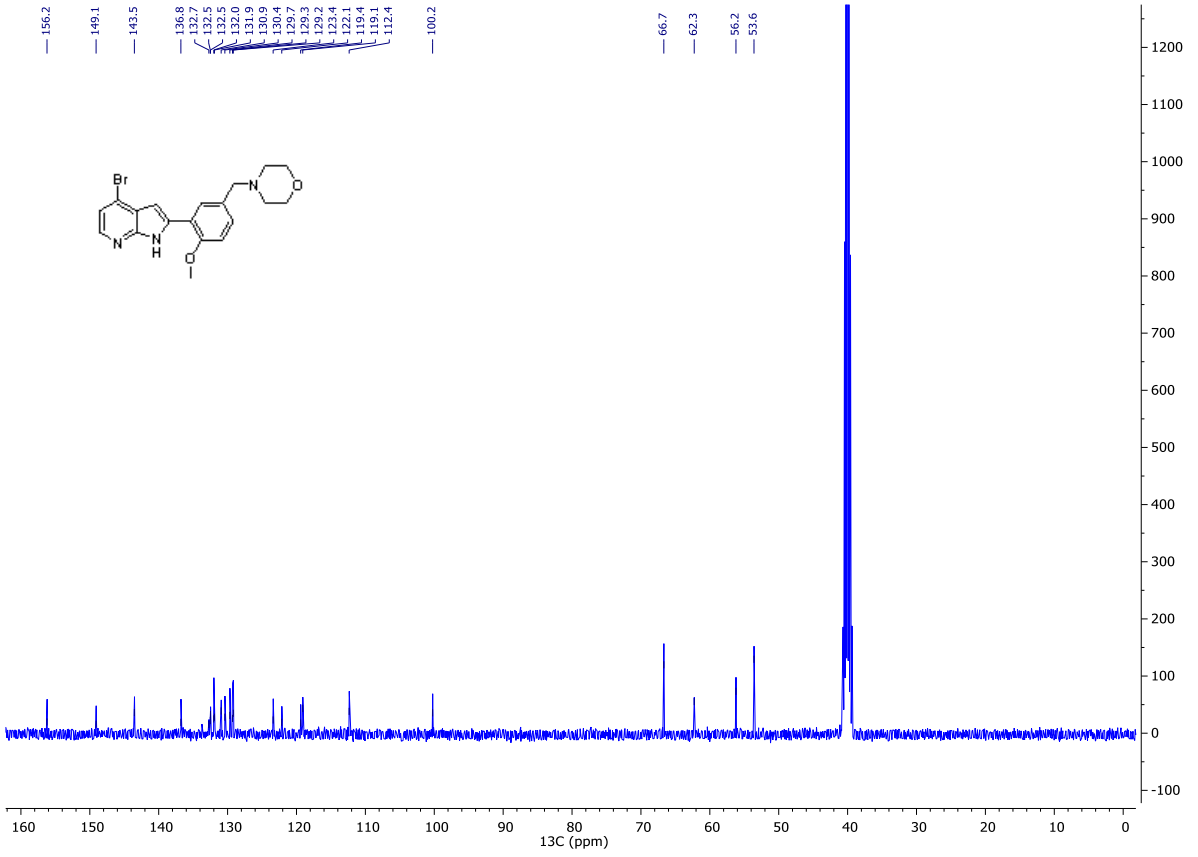
^{1}H and ^{13}C NMR spectra for compound 7c



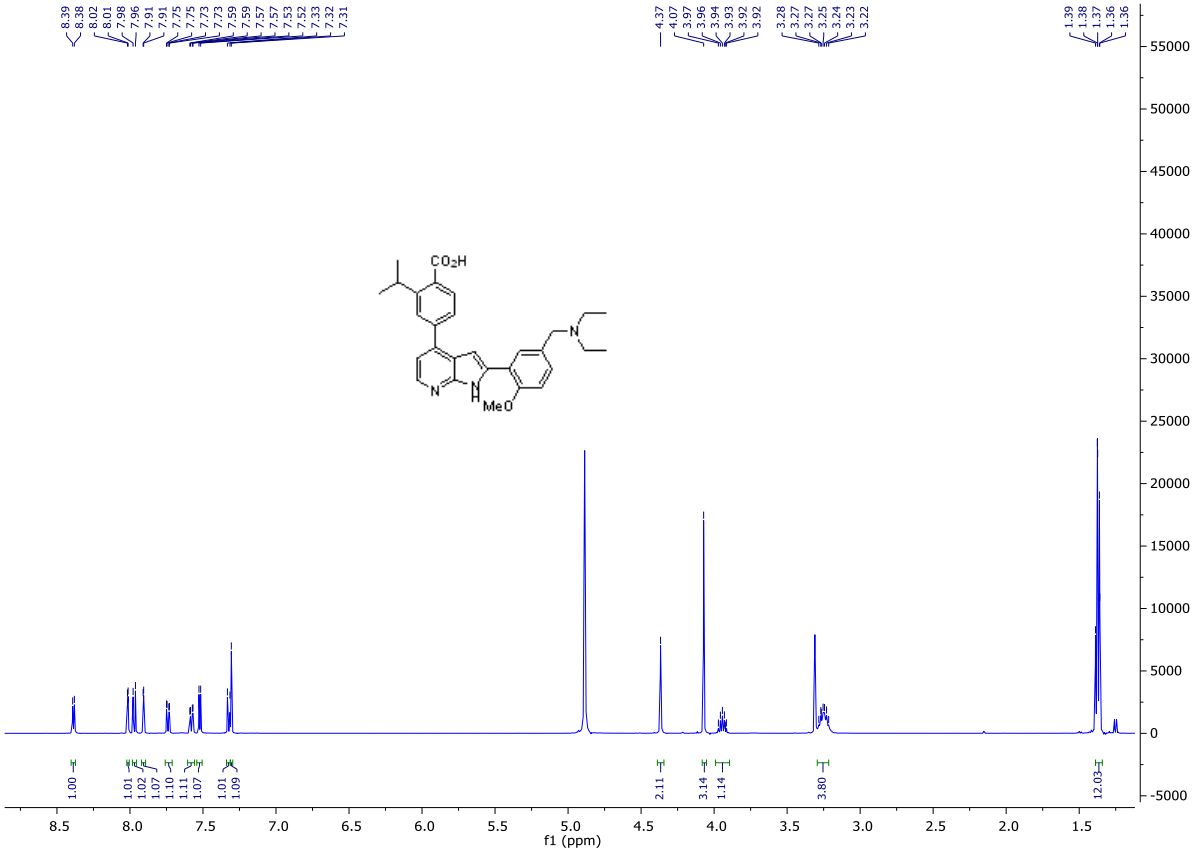


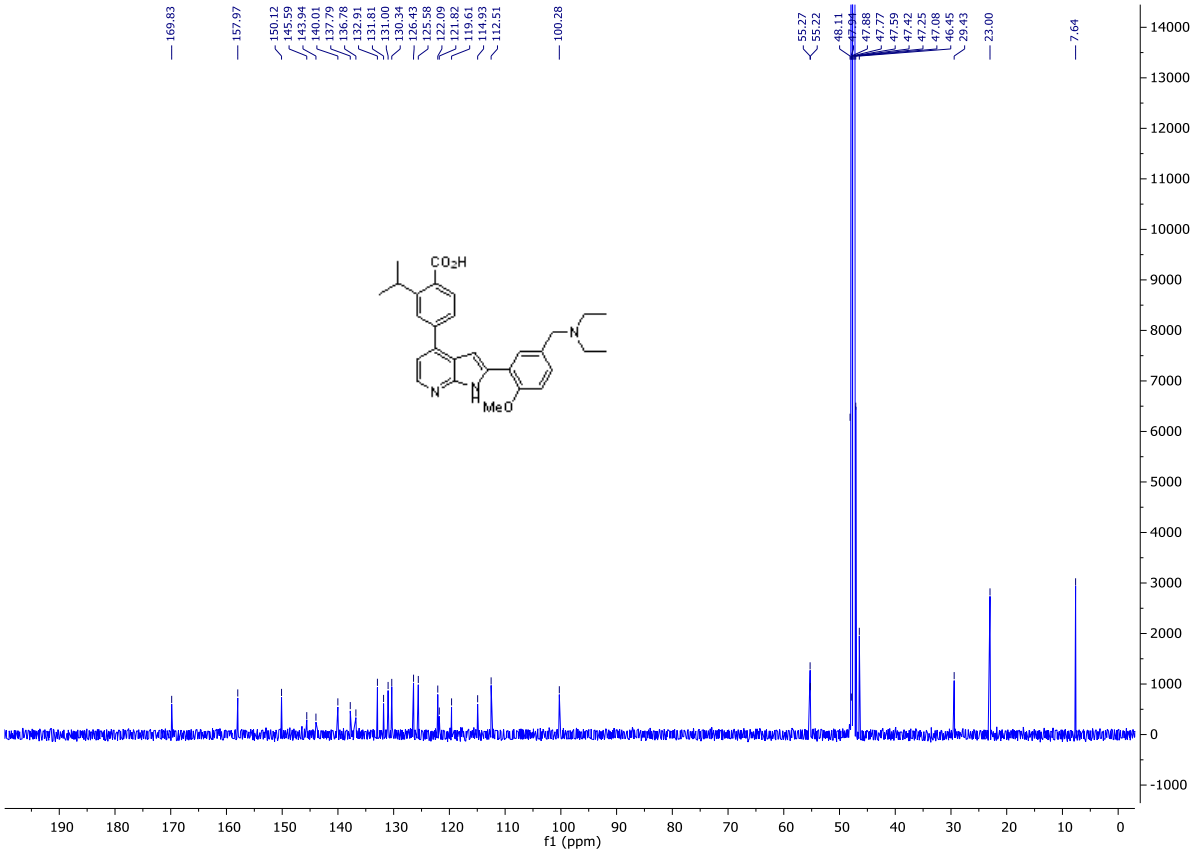
^{1}H and ^{13}C NMR spectra for compound 7d



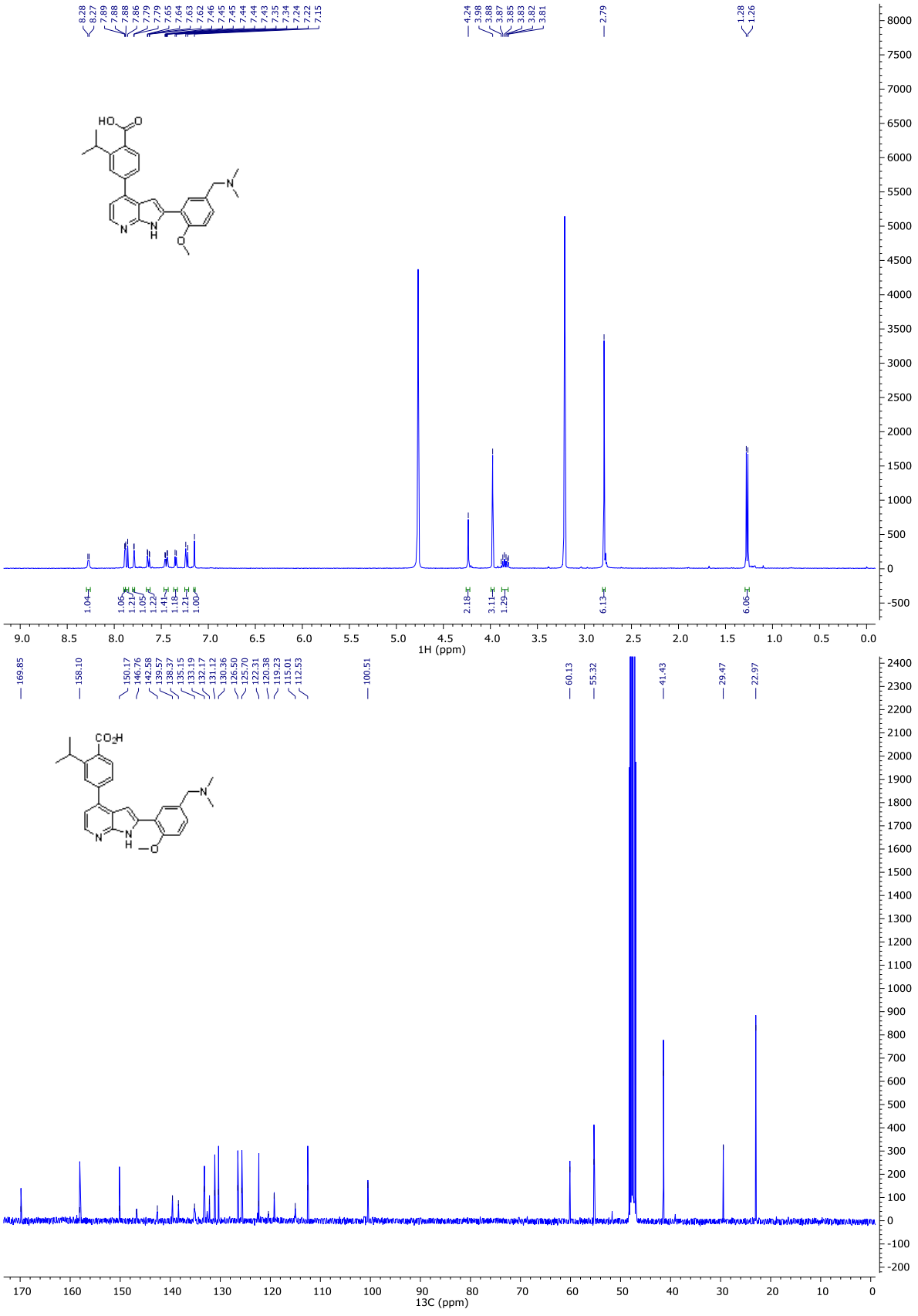


^{1}H and ^{13}C NMR spectra for compound 1

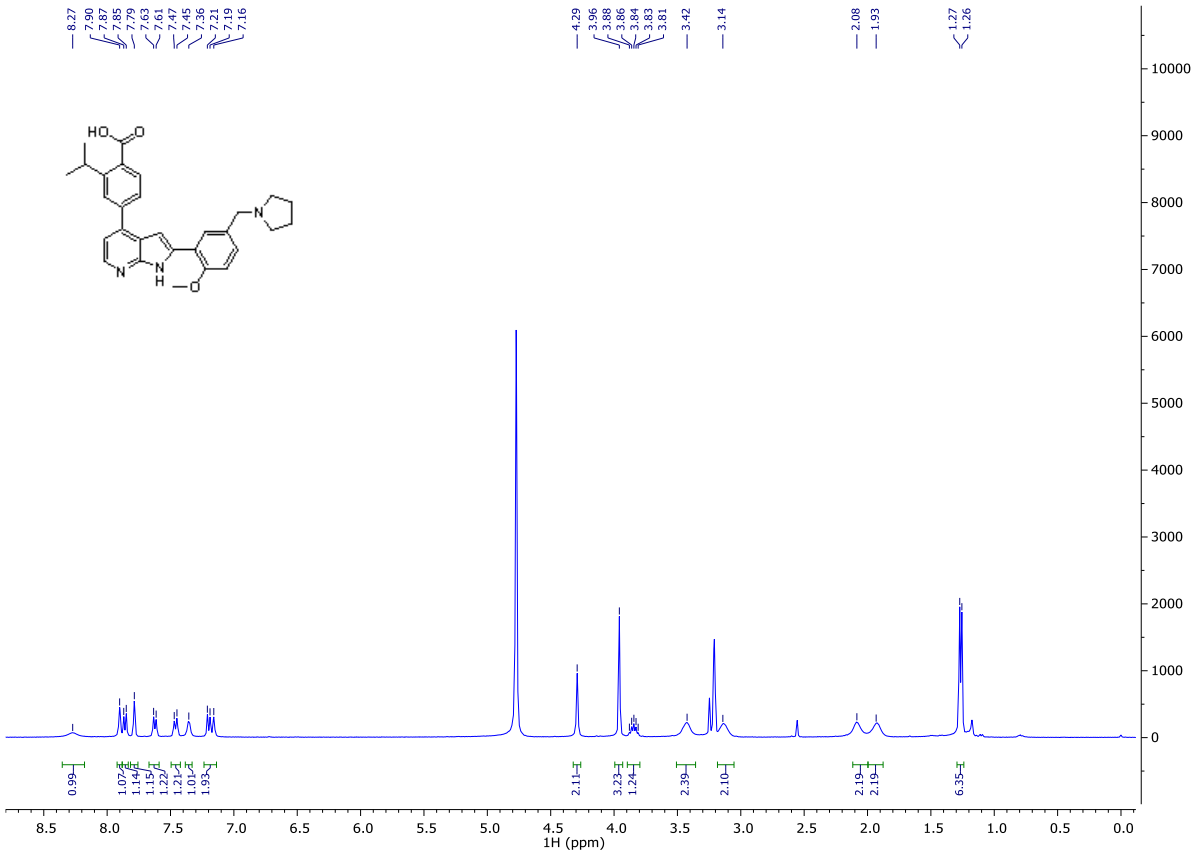


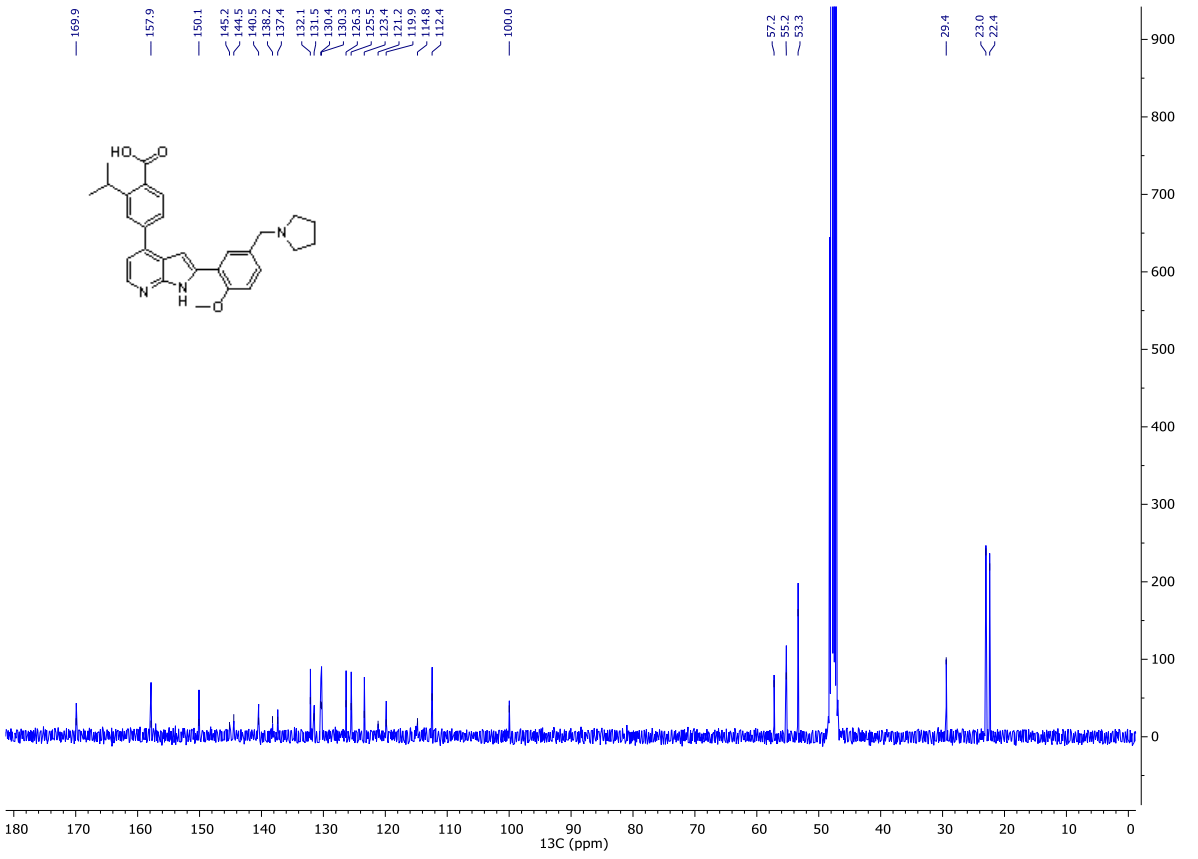


^{1}H and ^{13}C NMR spectra for compound 8a

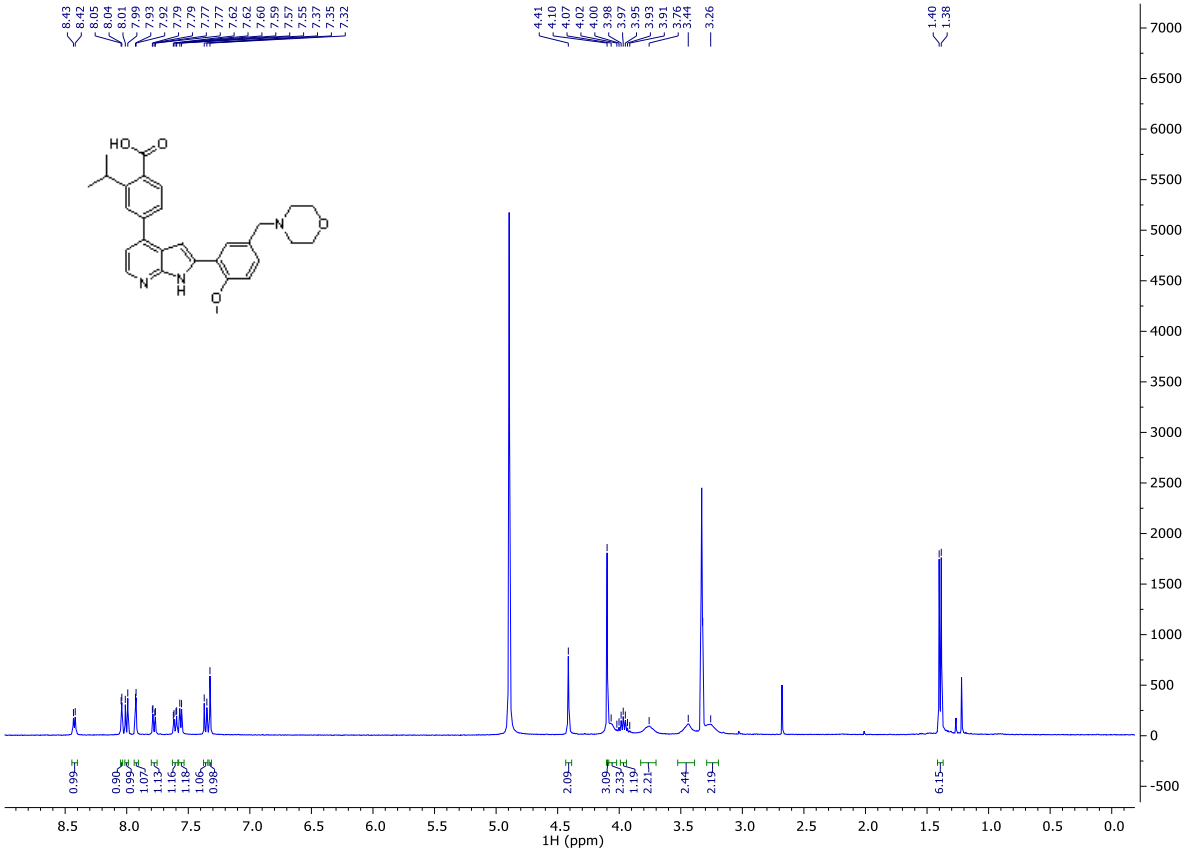


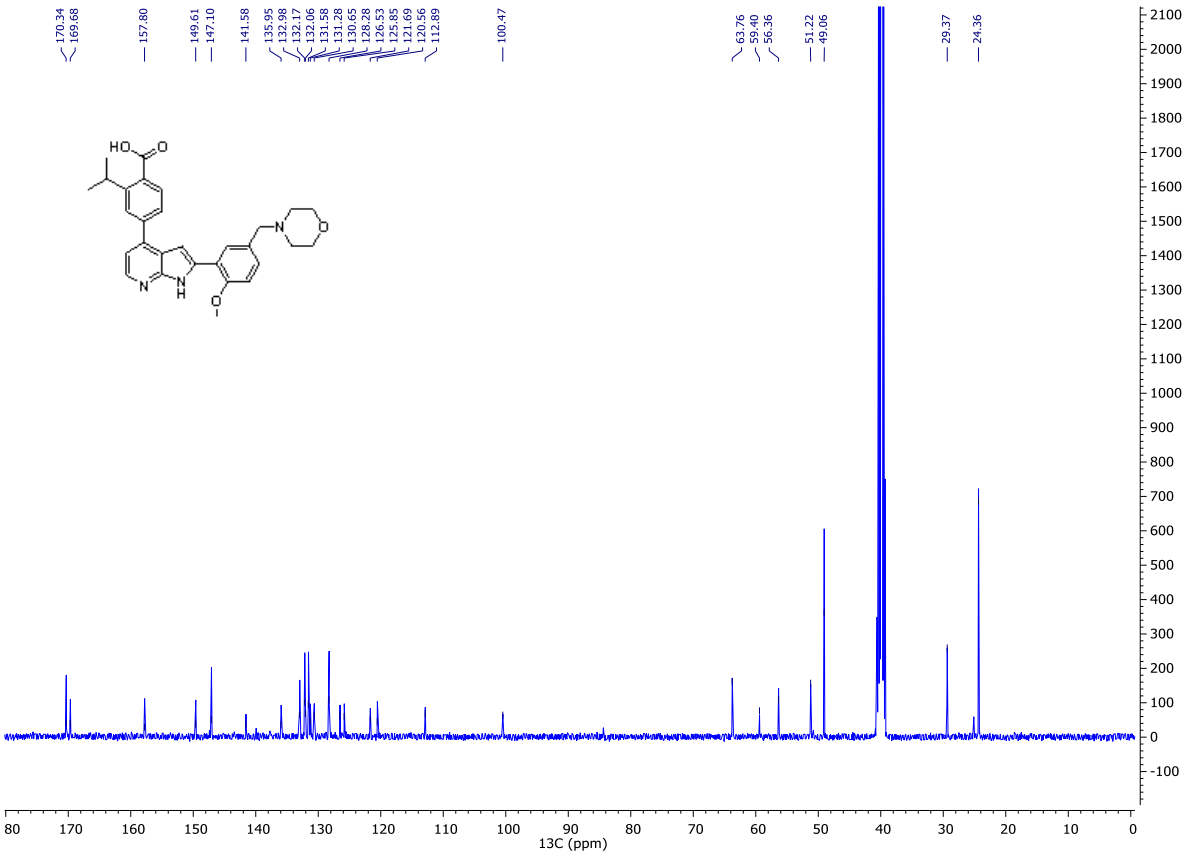
^{1}H and ^{13}C NMR spectra for compound 8b



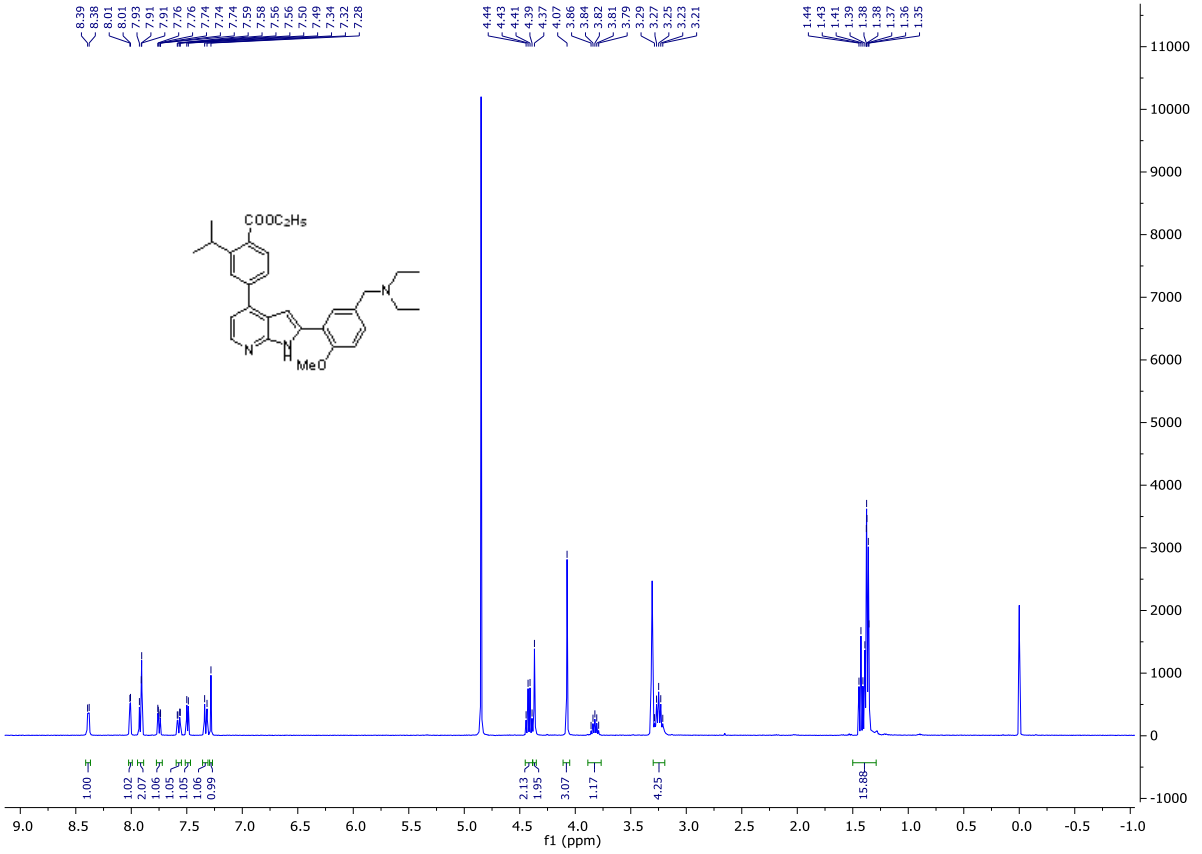


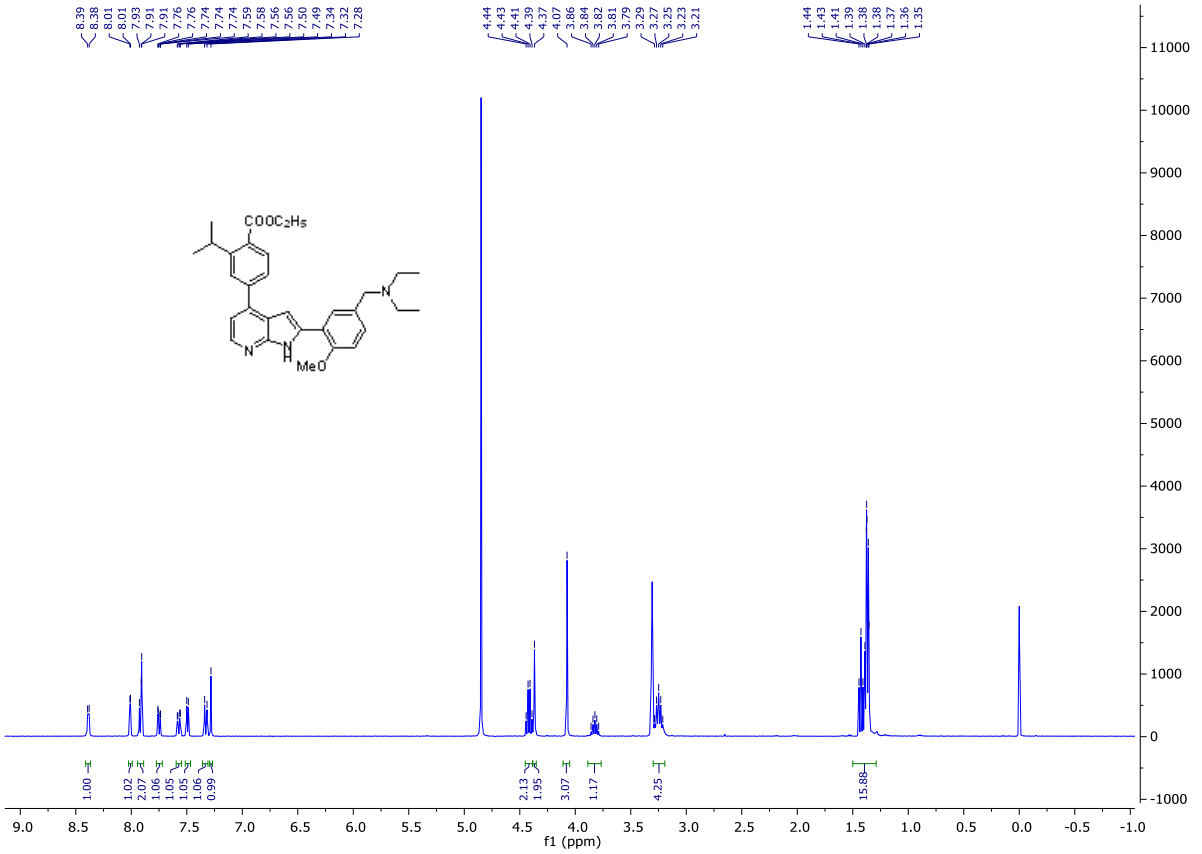
^{1}H and ^{13}C NMR spectra for compound 8c



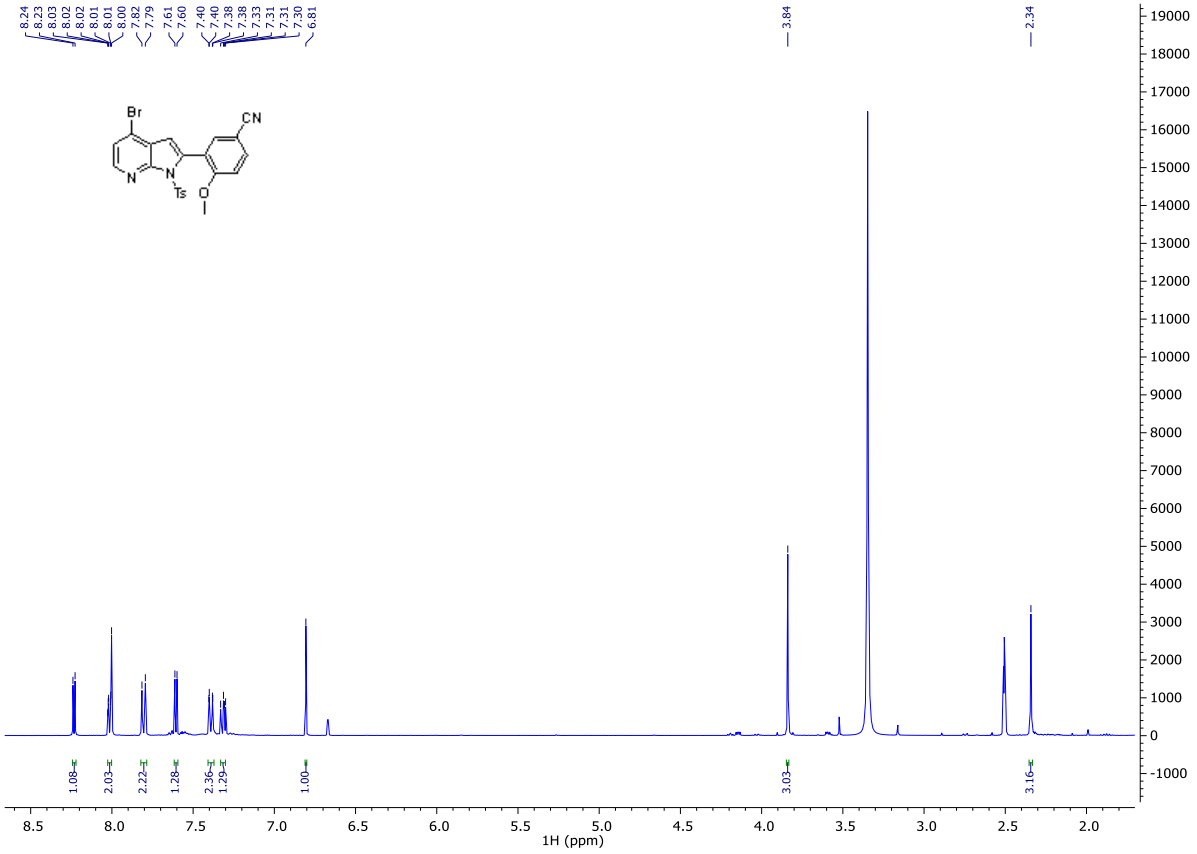


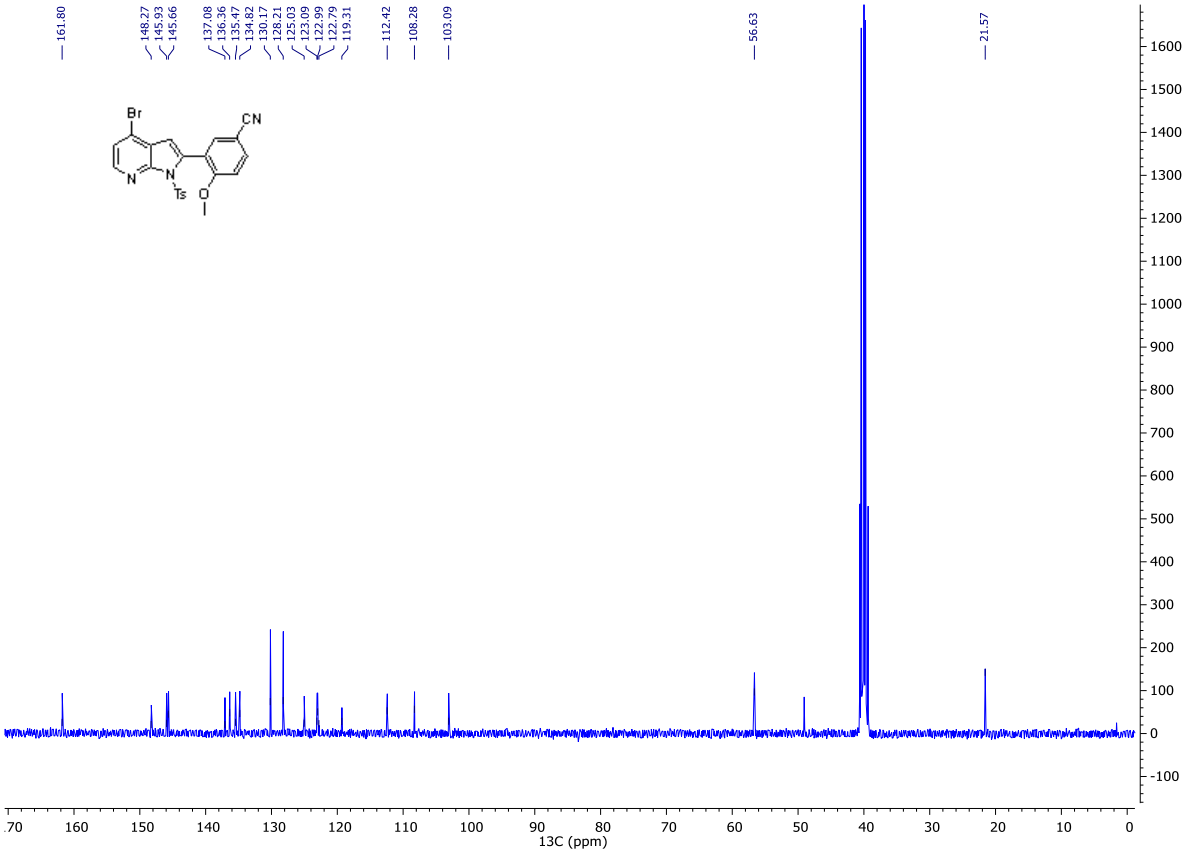
^{1}H and ^{13}C NMR spectra for compound 9



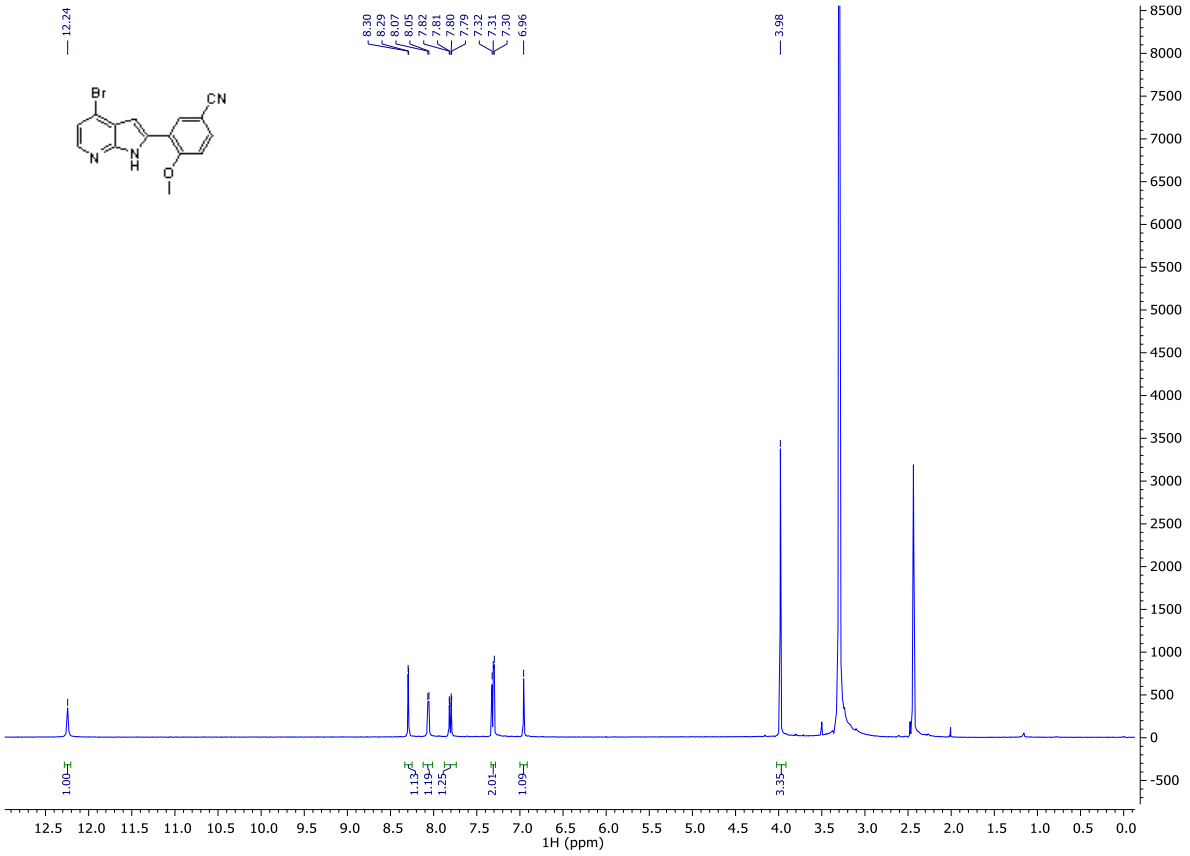


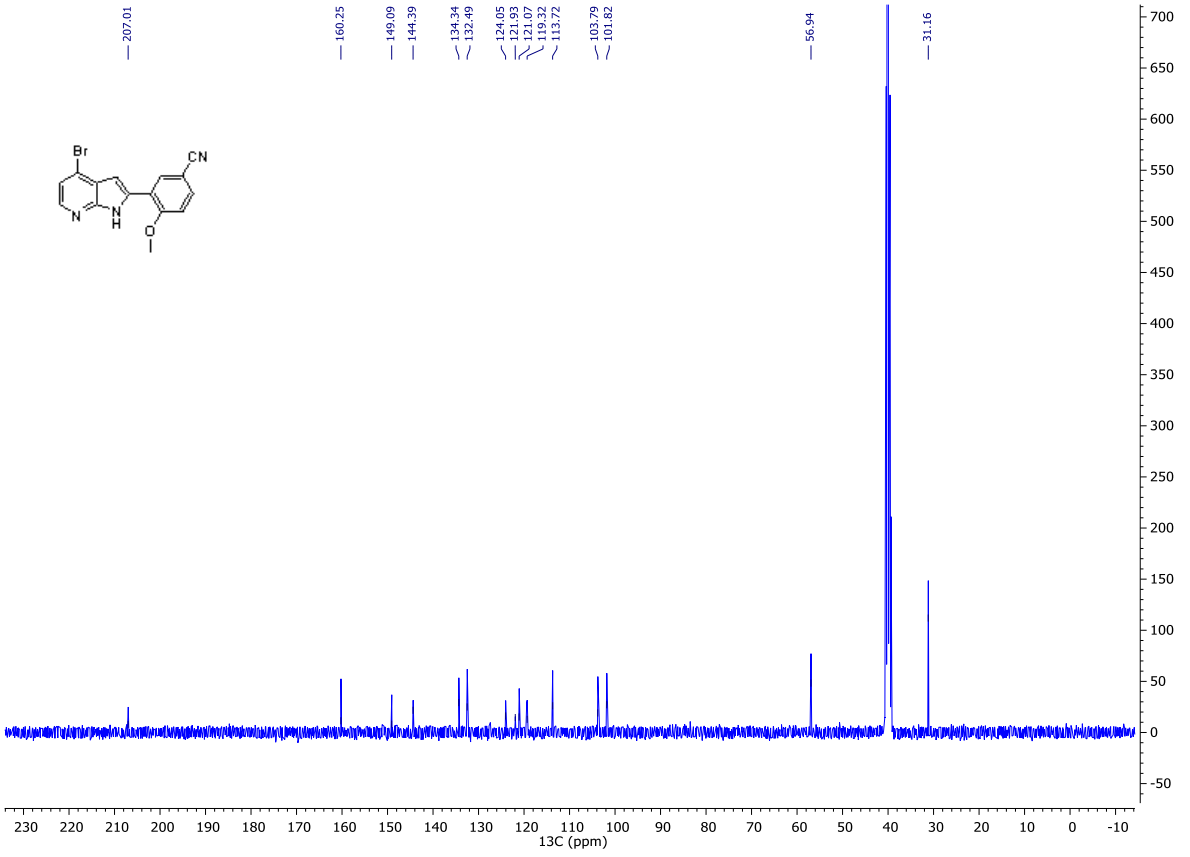
^{1}H and ^{13}C NMR spectra for compound 10



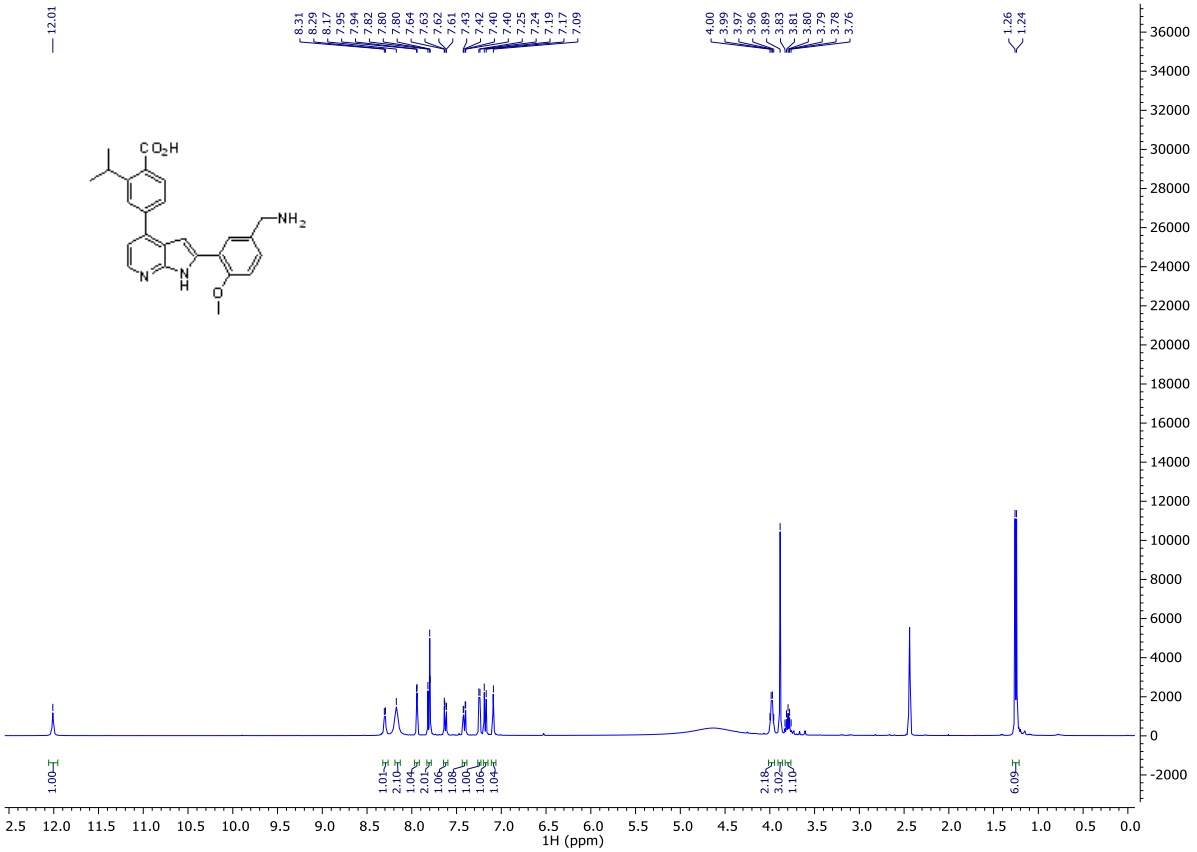


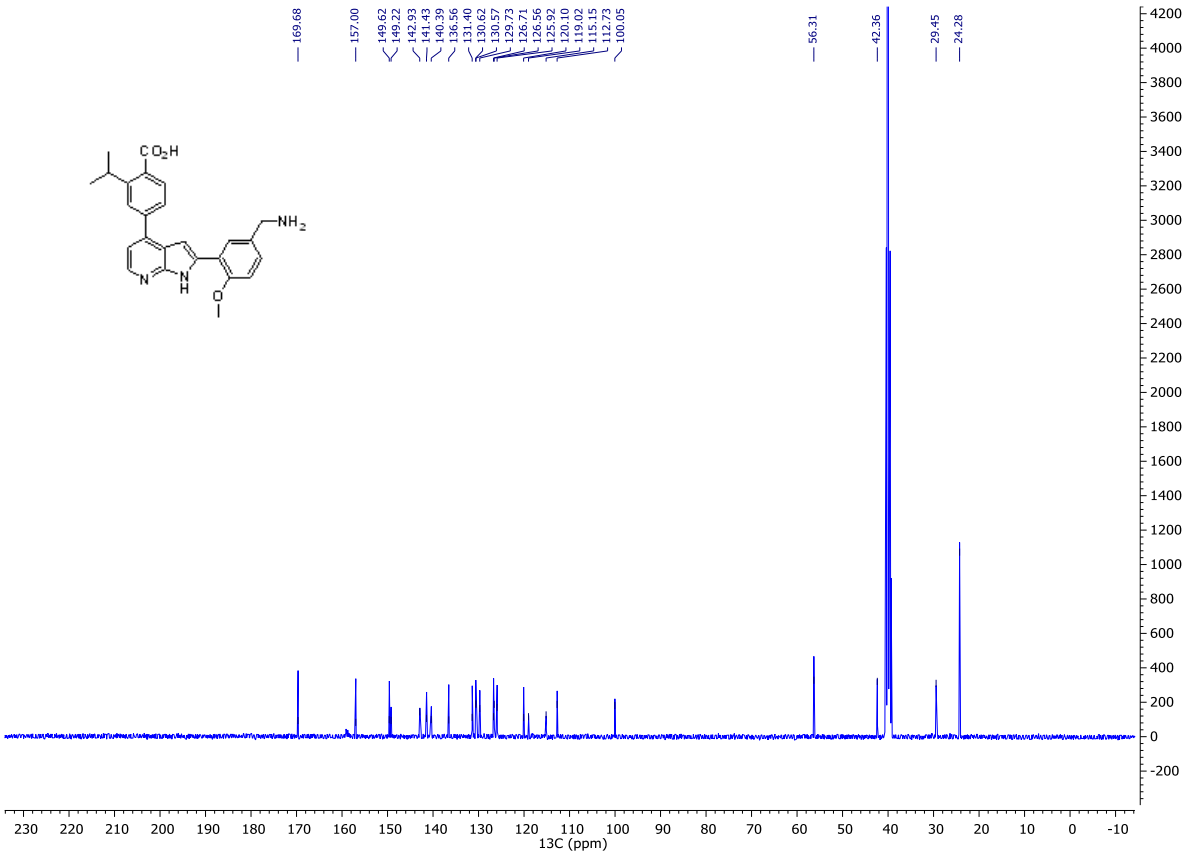
^{1}H and ^{13}C NMR spectra for compound 11



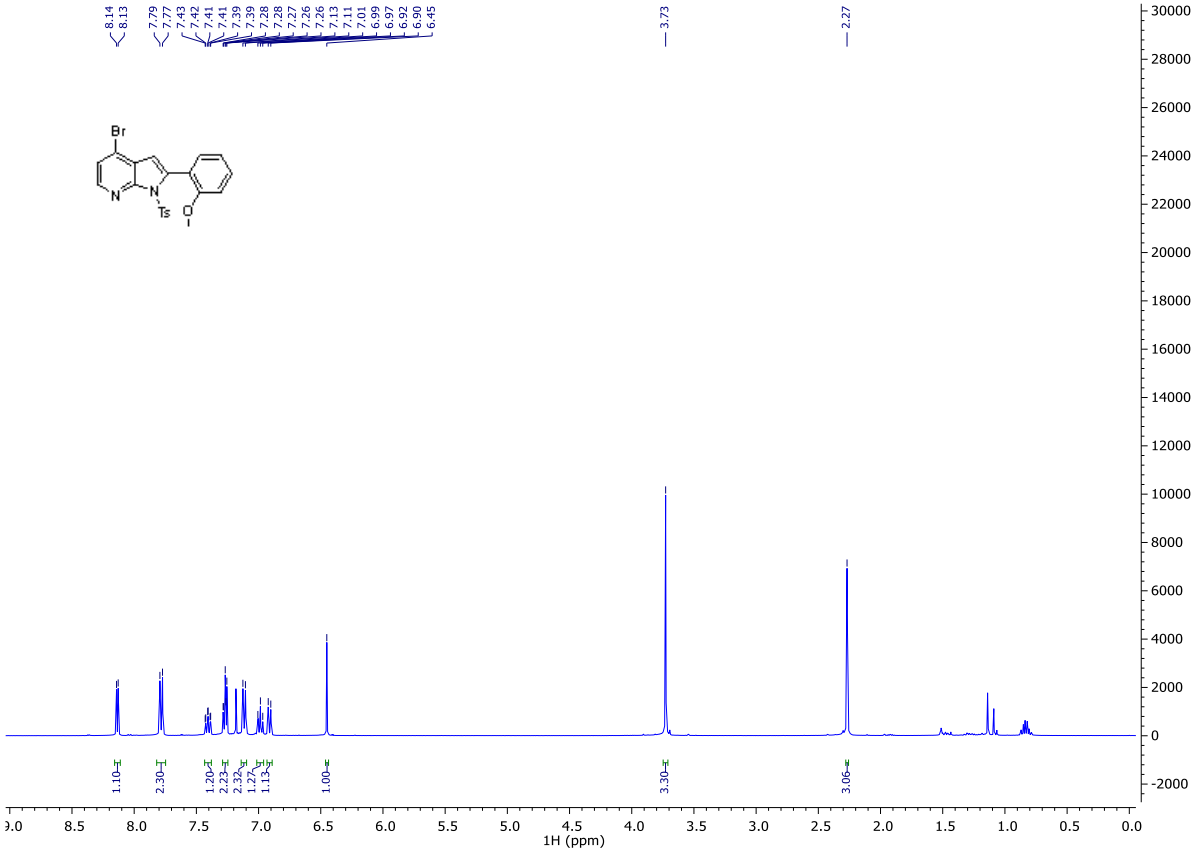


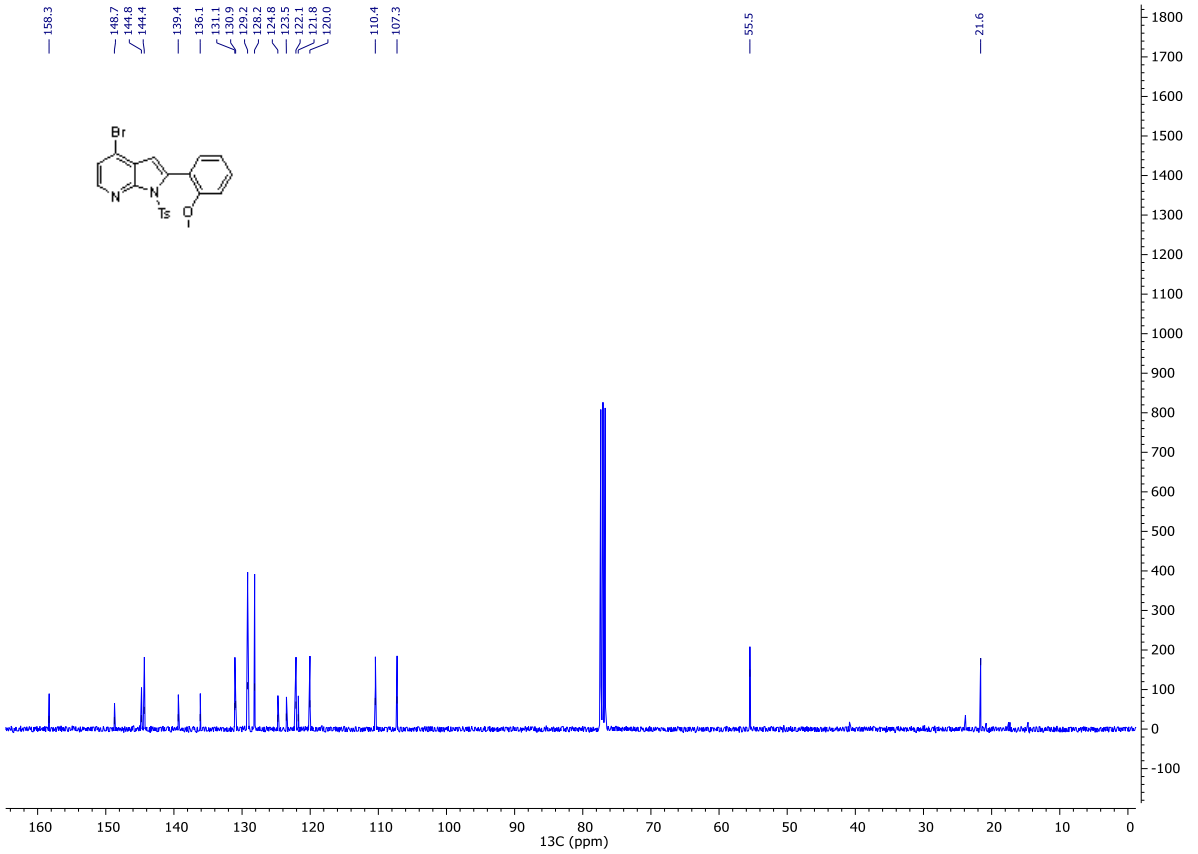
^{1}H and ^{13}C NMR spectra for compound 12



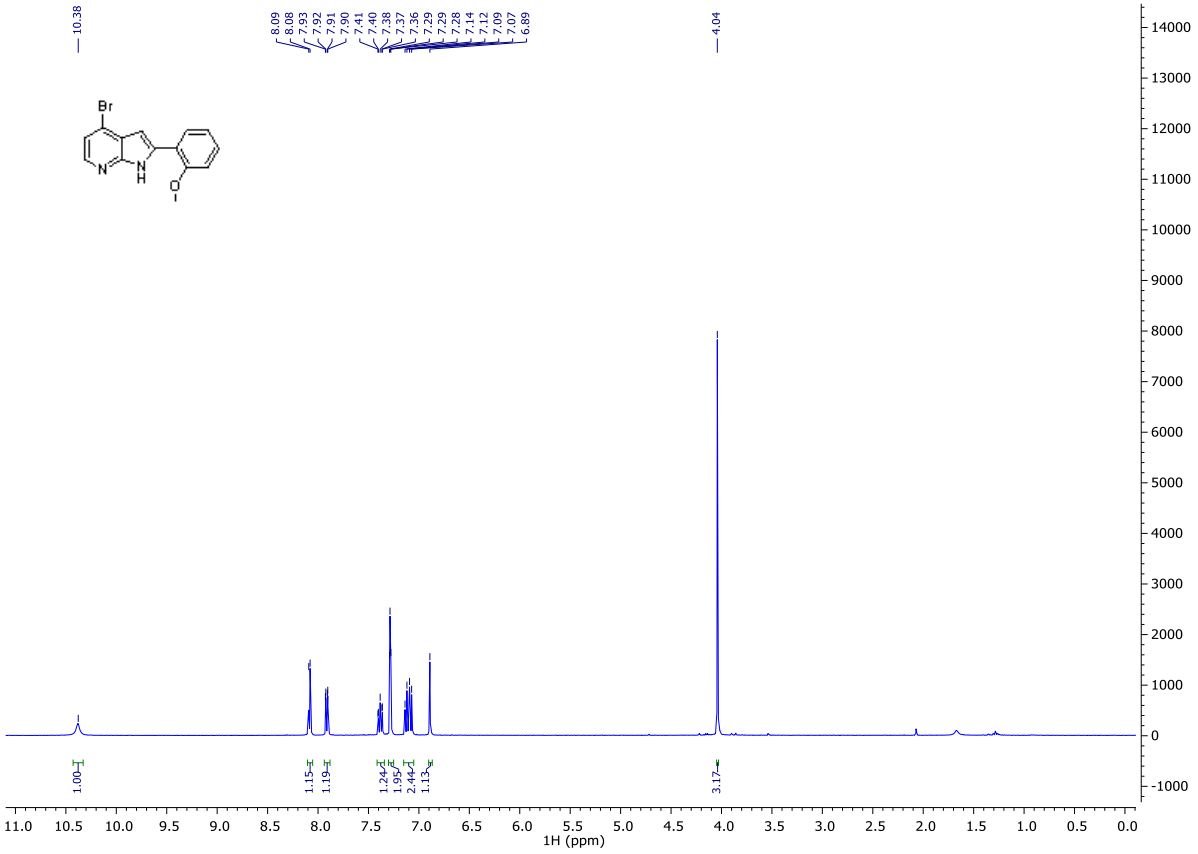


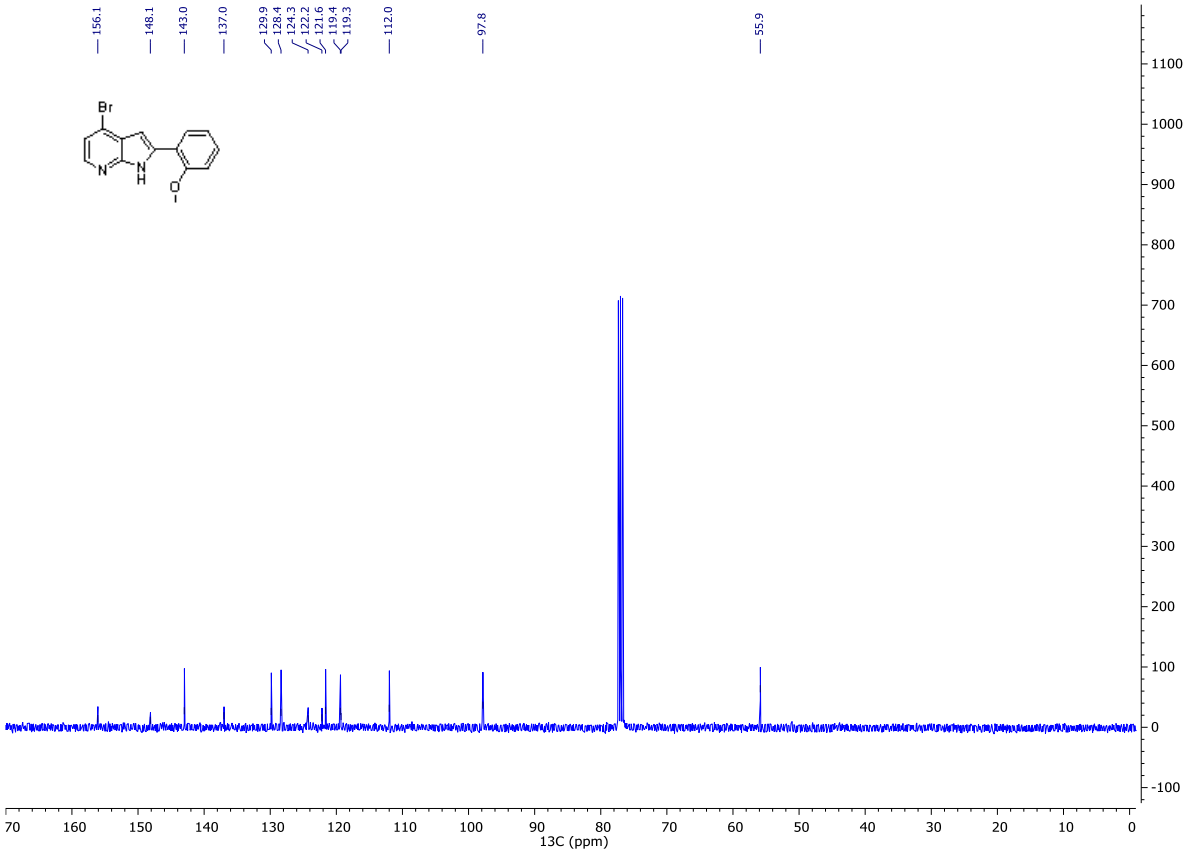
^{1}H and ^{13}C NMR spectra for compound 13



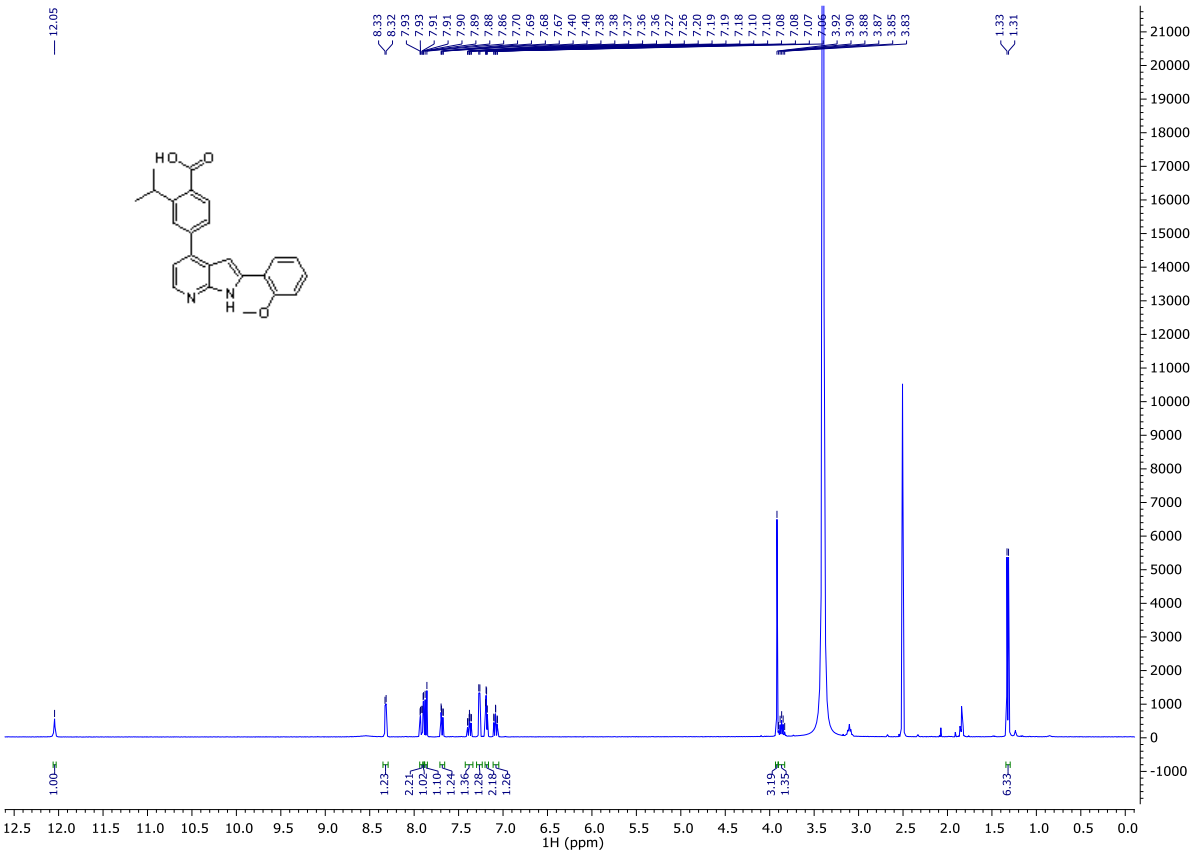


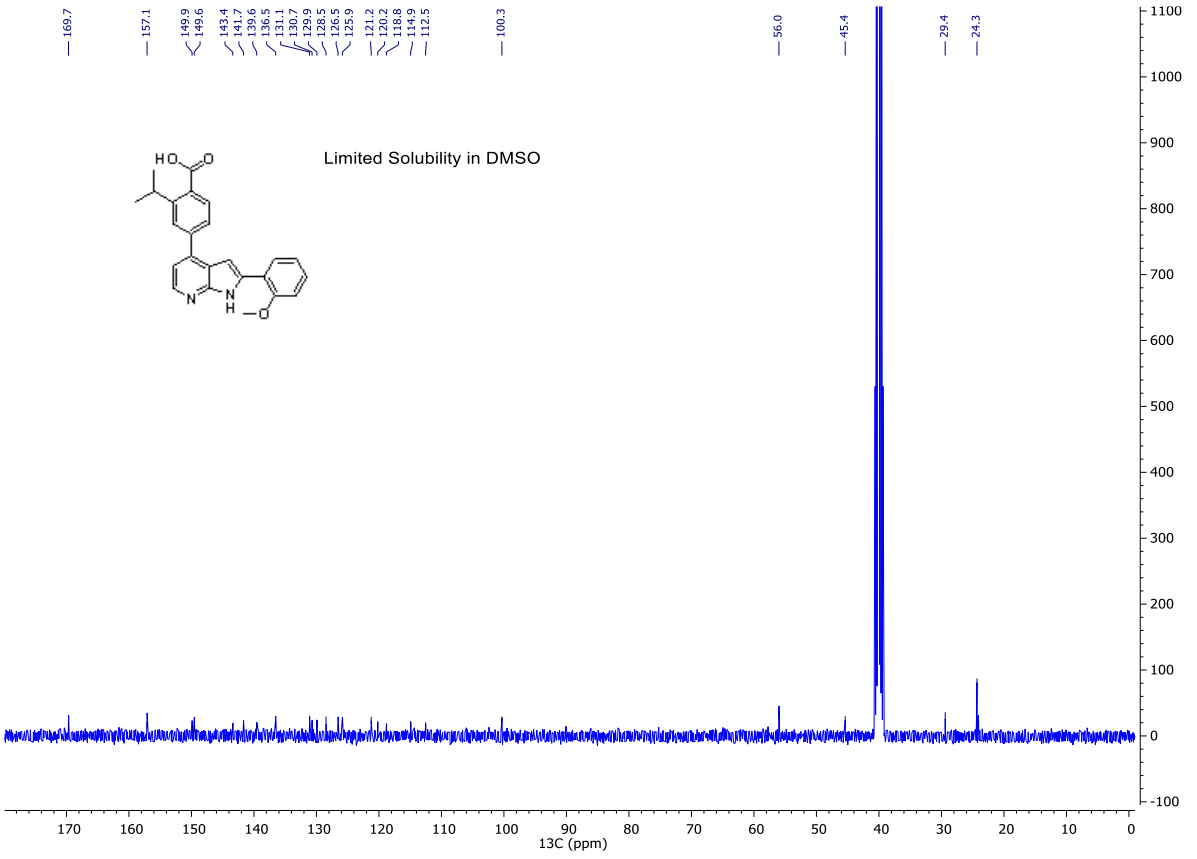
^{1}H and ^{13}C NMR spectra for compound 14



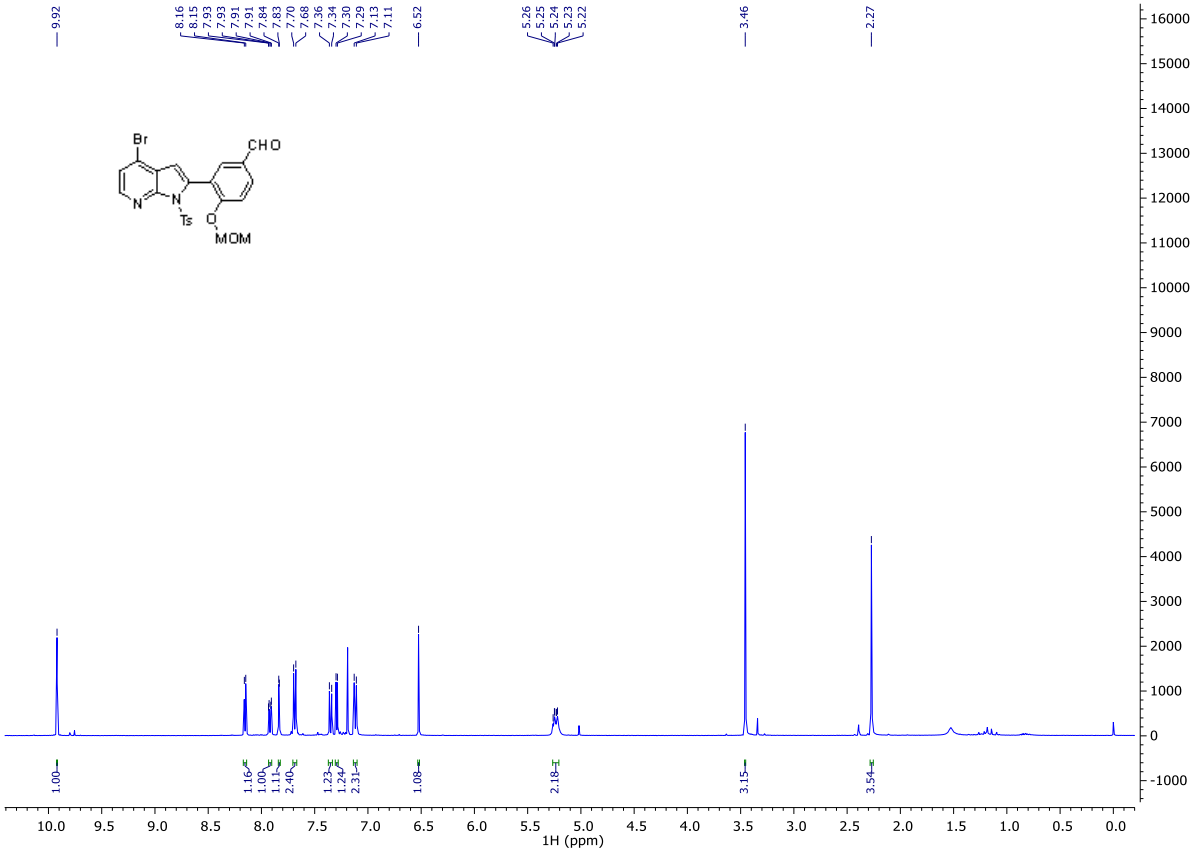


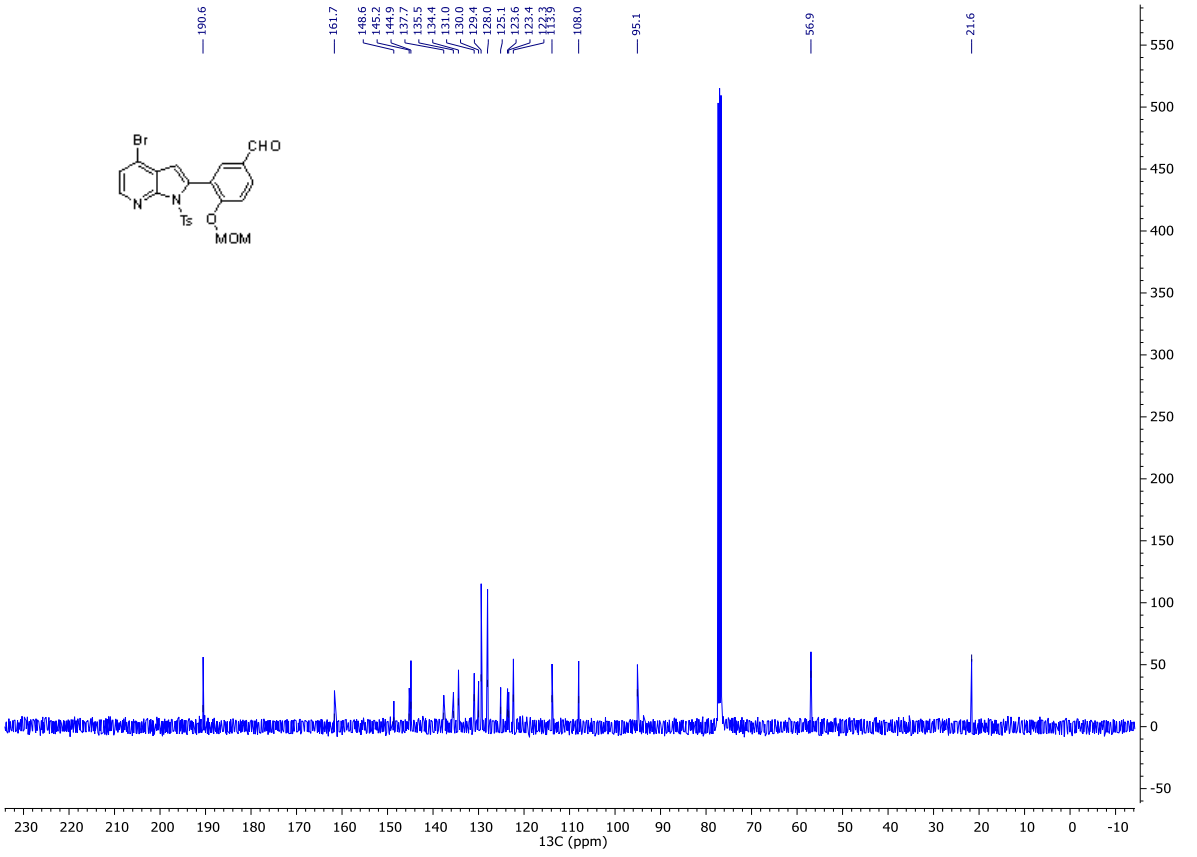
^{1}H and ^{13}C NMR spectra for compound 15



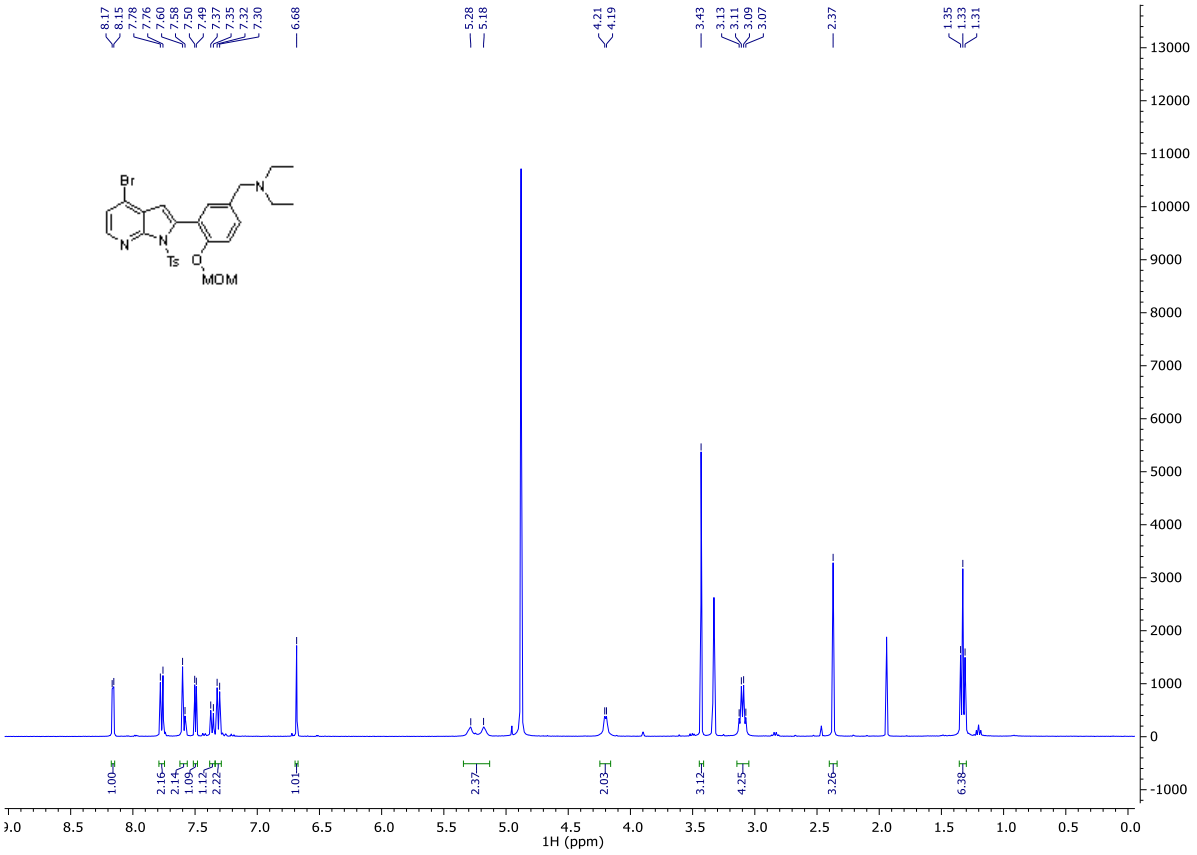


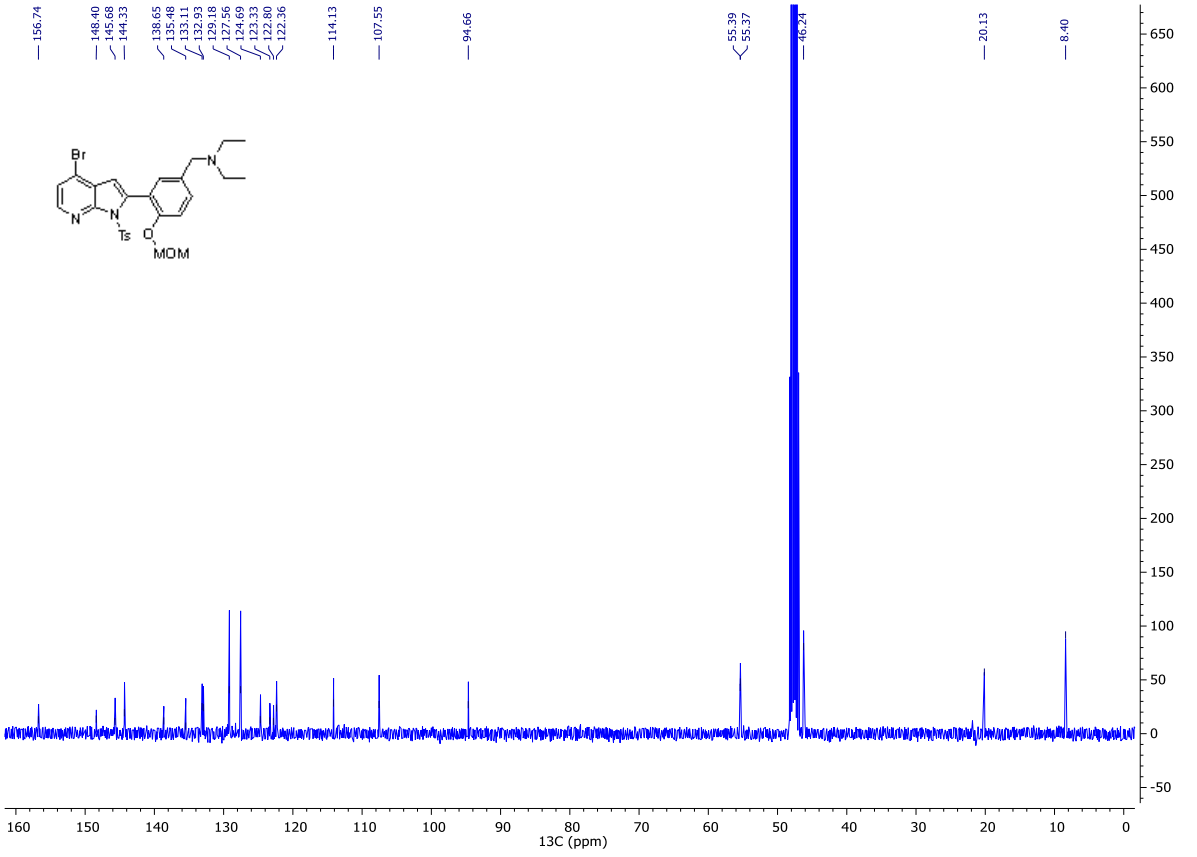
^{1}H and ^{13}C NMR spectra for compound 16



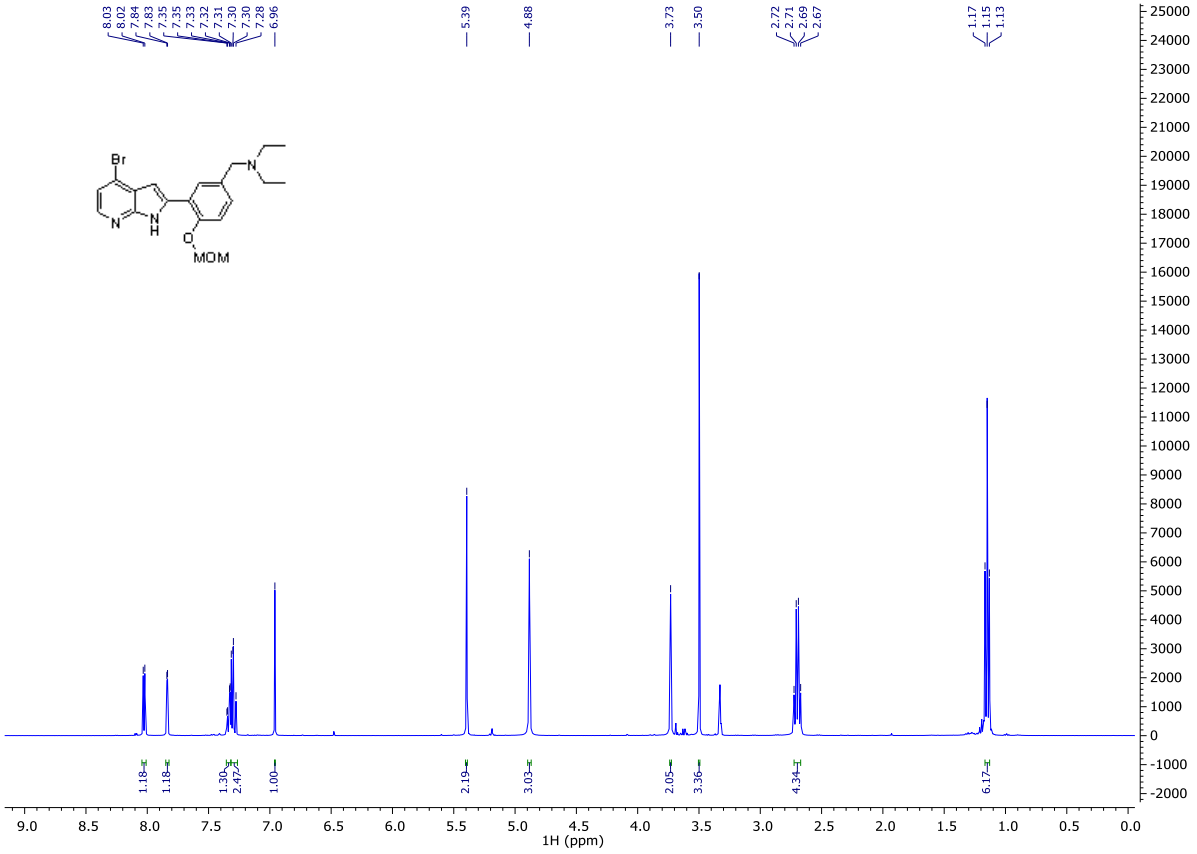


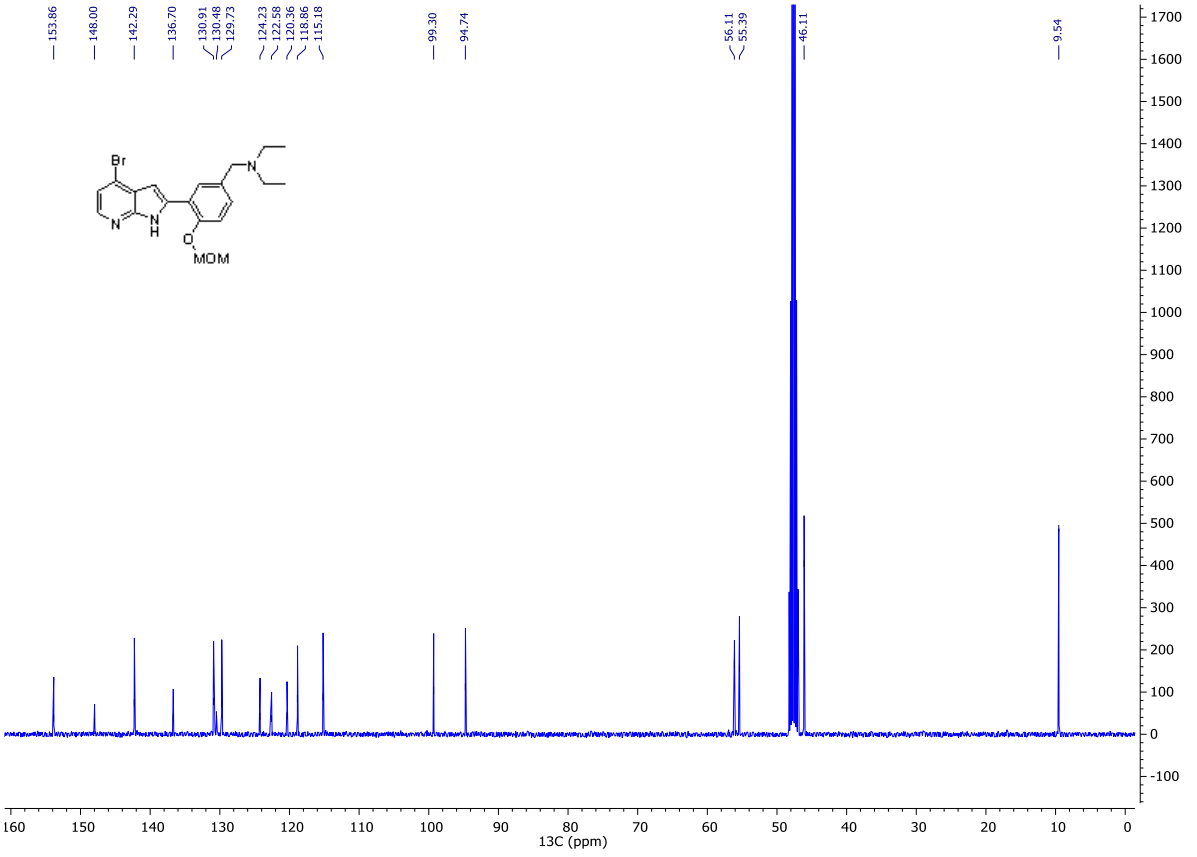
^{1}H and ^{13}C NMR spectra for compound 17



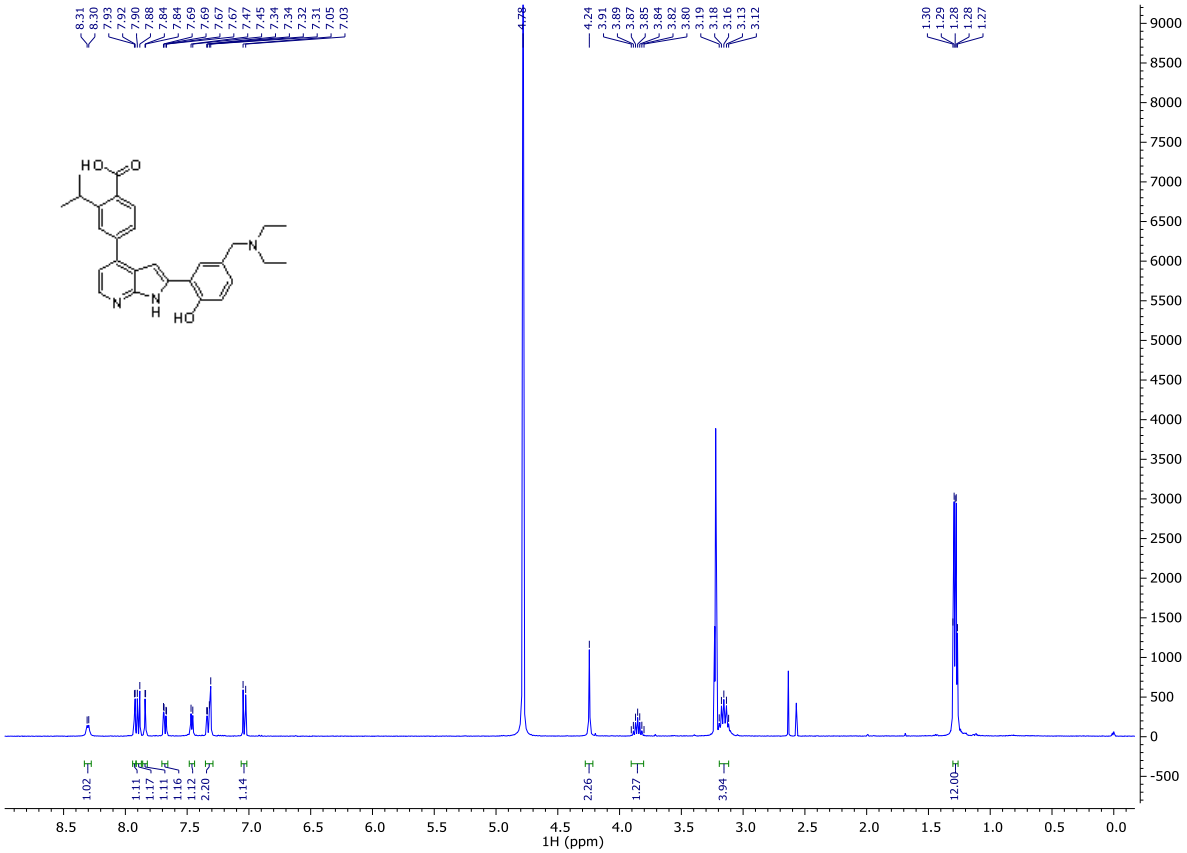


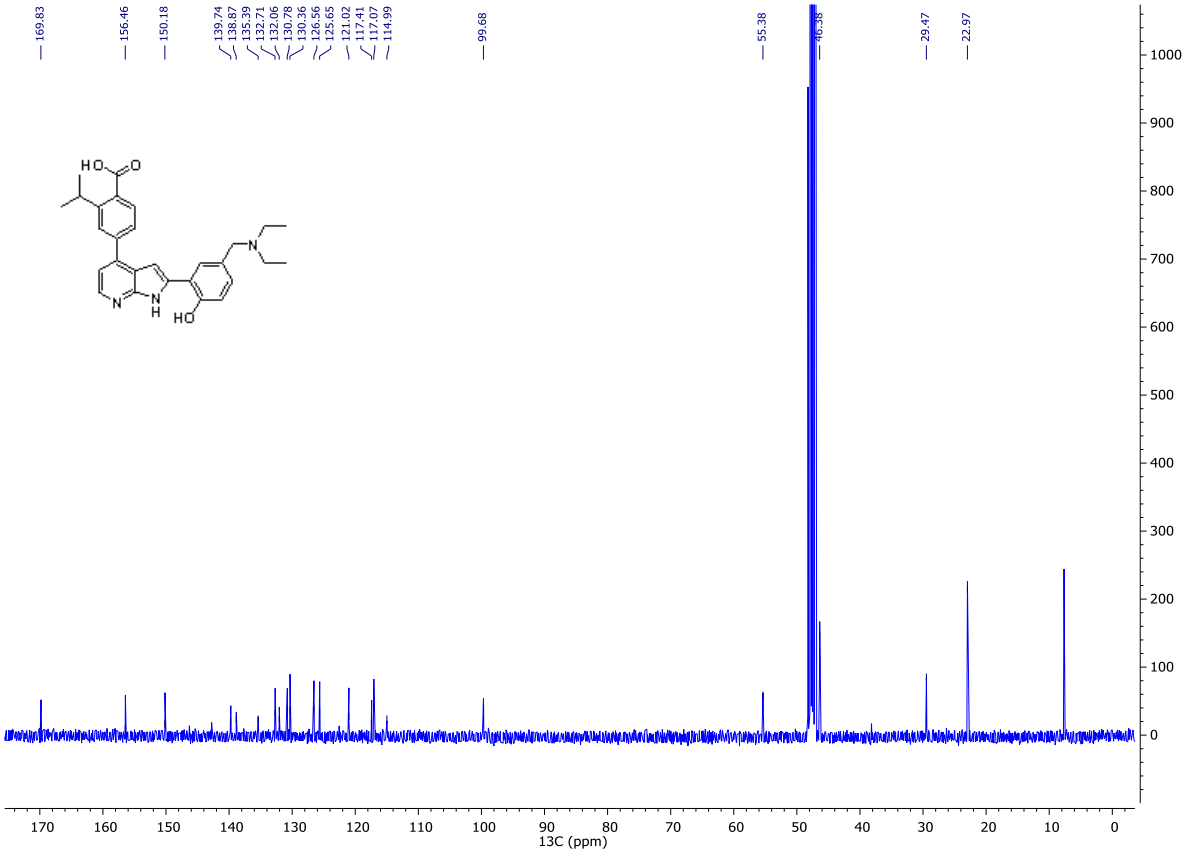
^{1}H and ^{13}C NMR spectra for compound 18



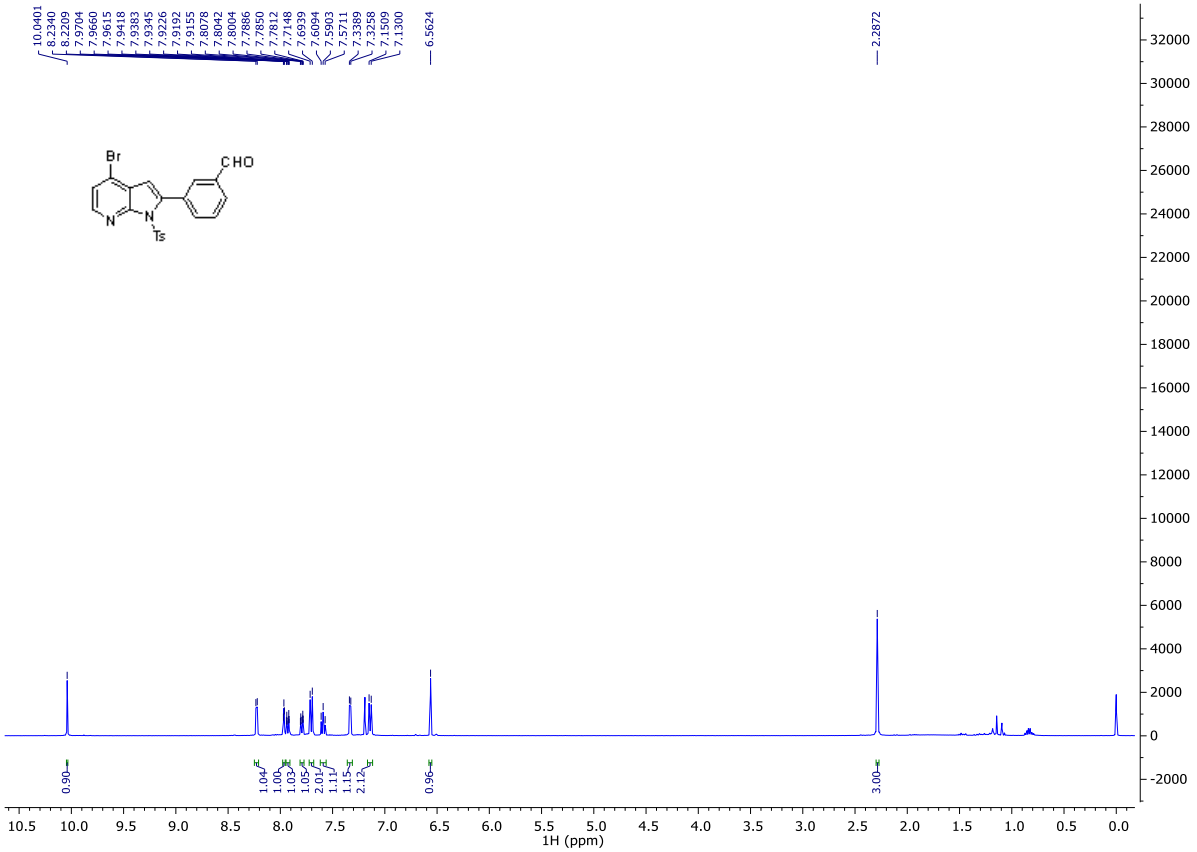


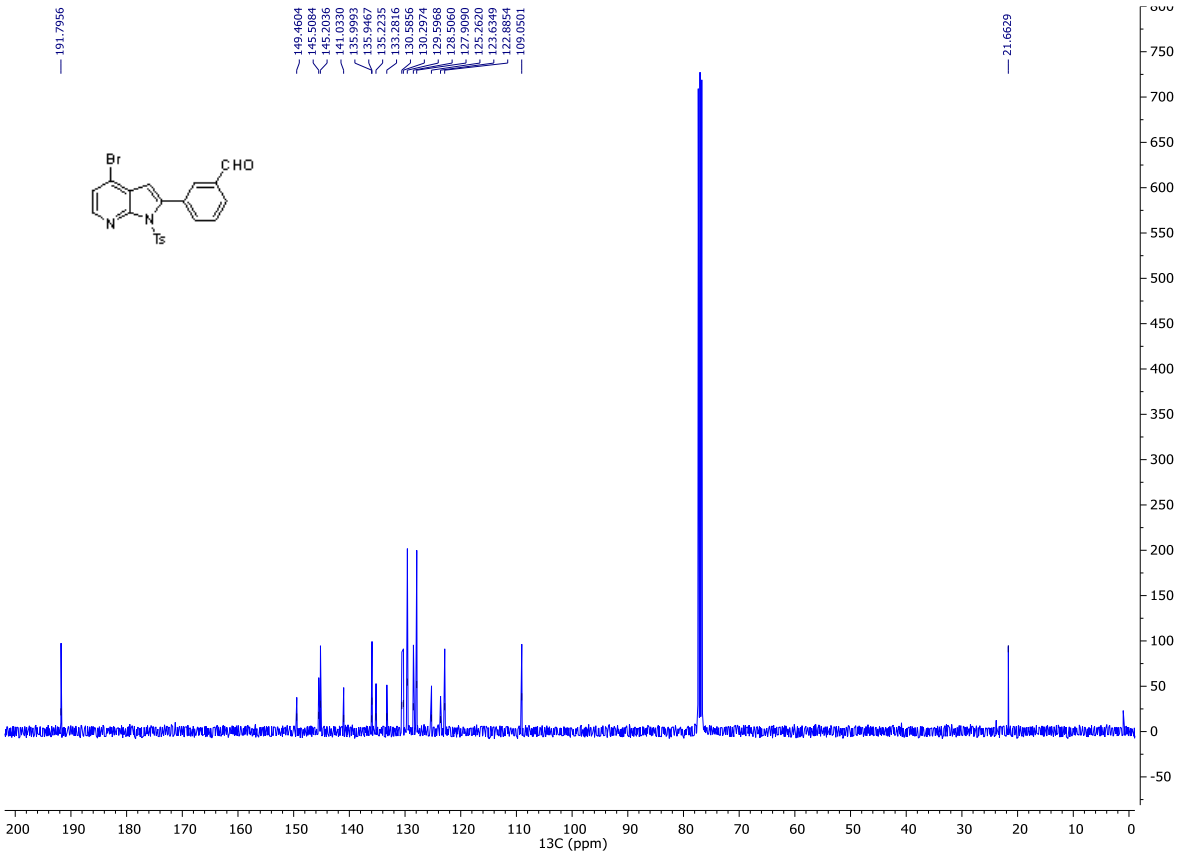
^{1}H and ^{13}C NMR spectra for compound 19



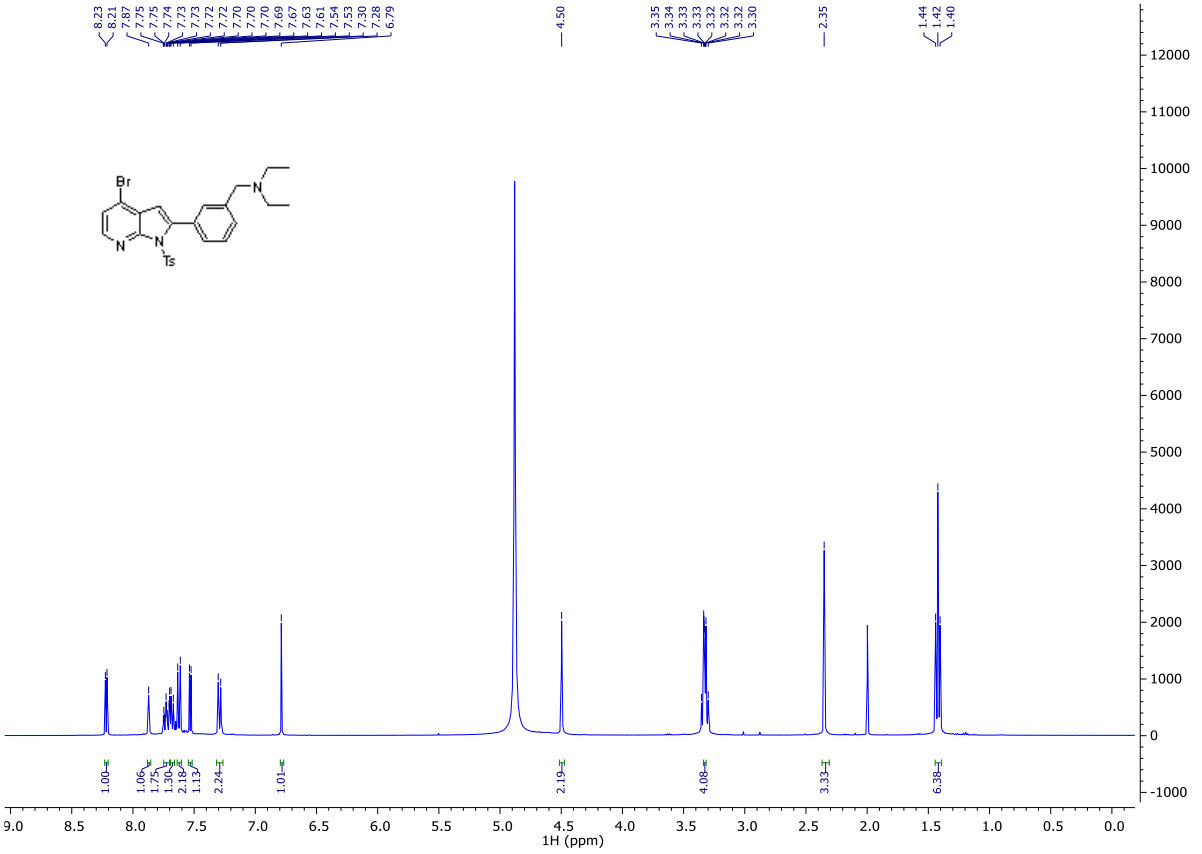


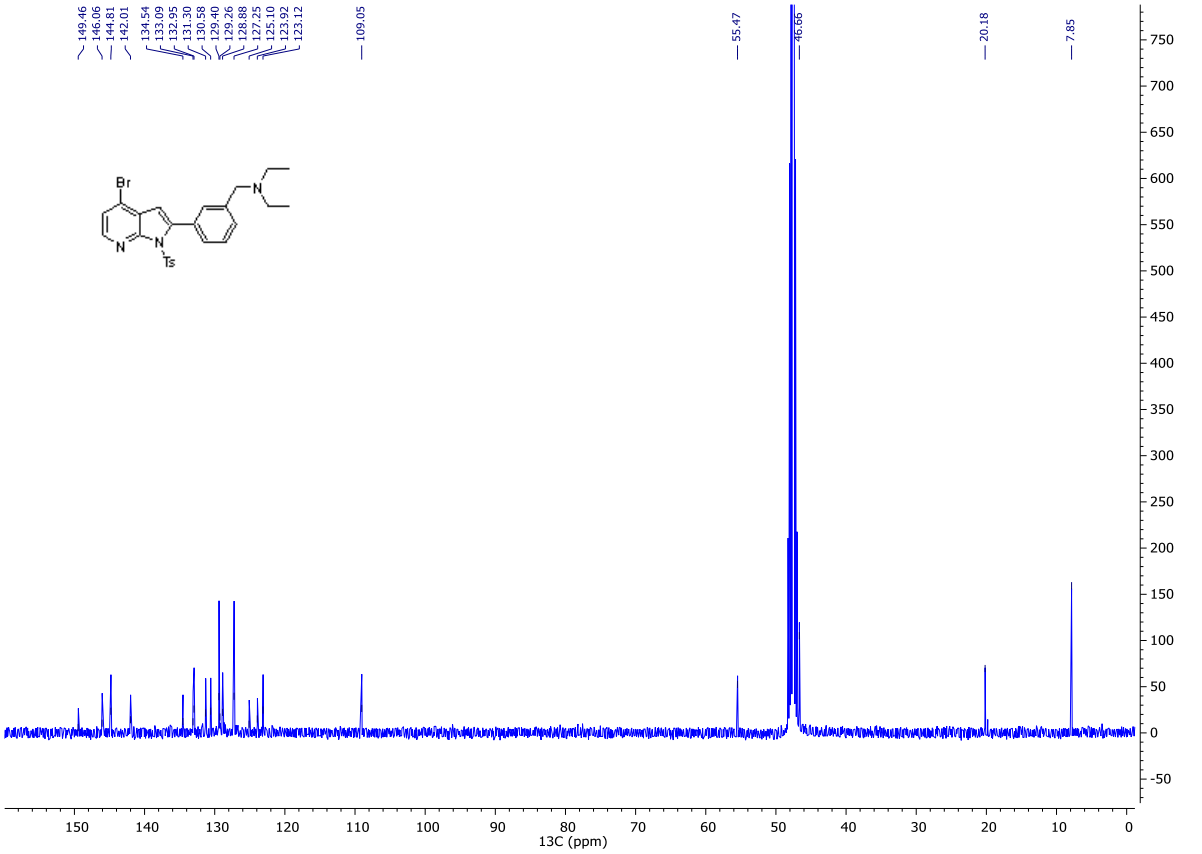
^{1}H and ^{13}C NMR spectra for compound 20



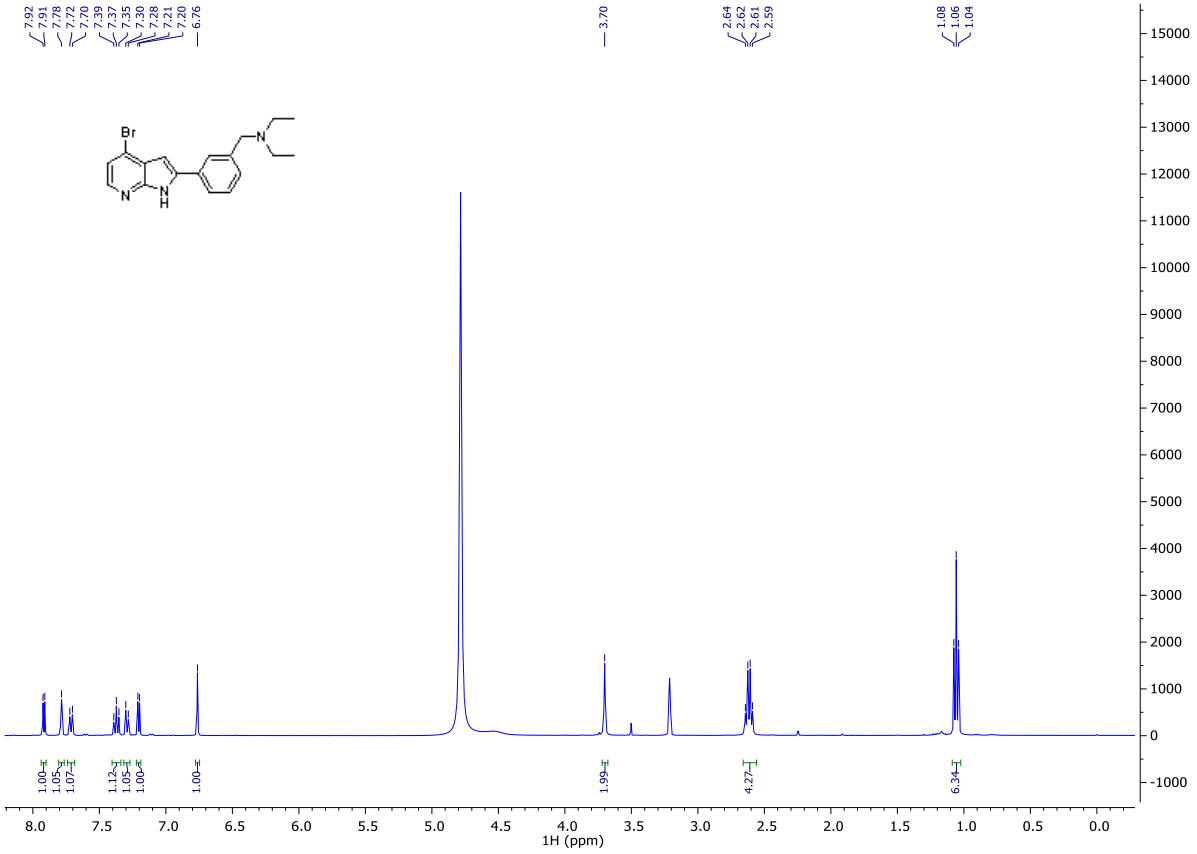


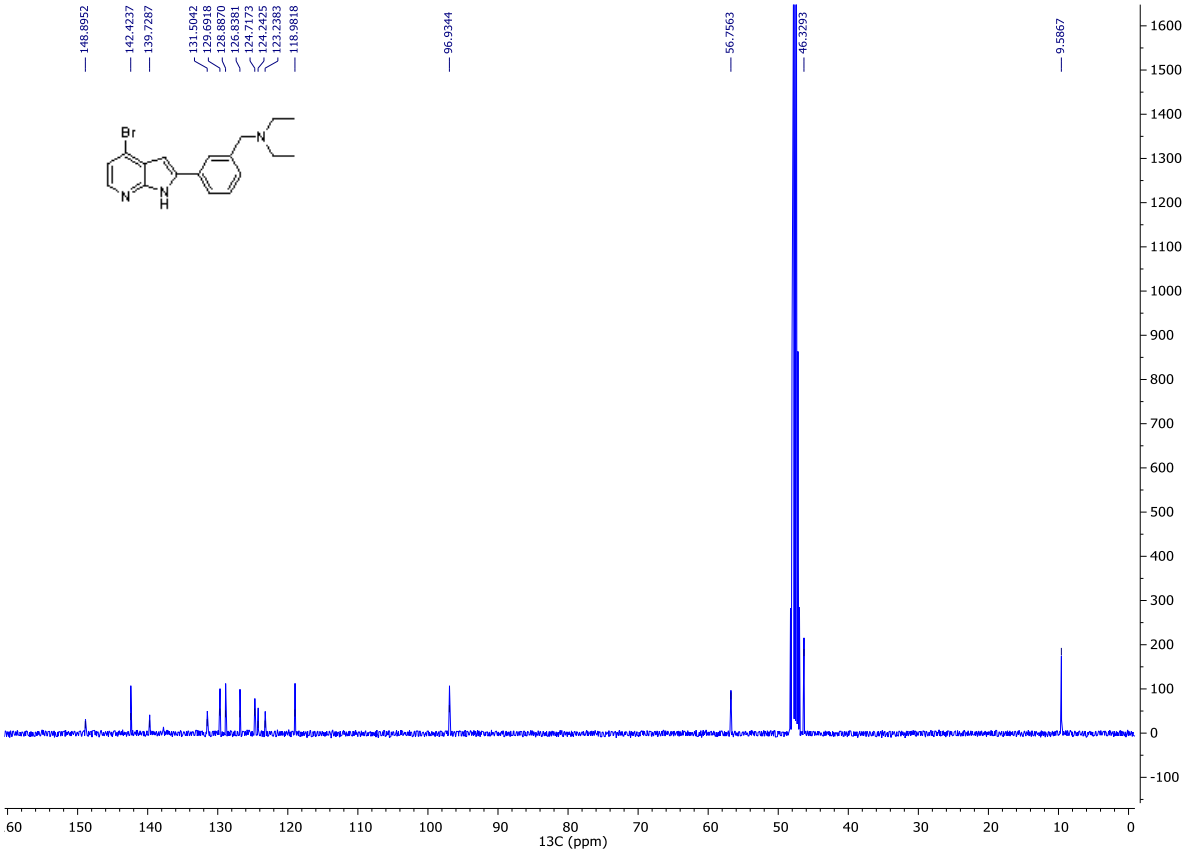
^{1}H and ^{13}C NMR spectra for compound 21



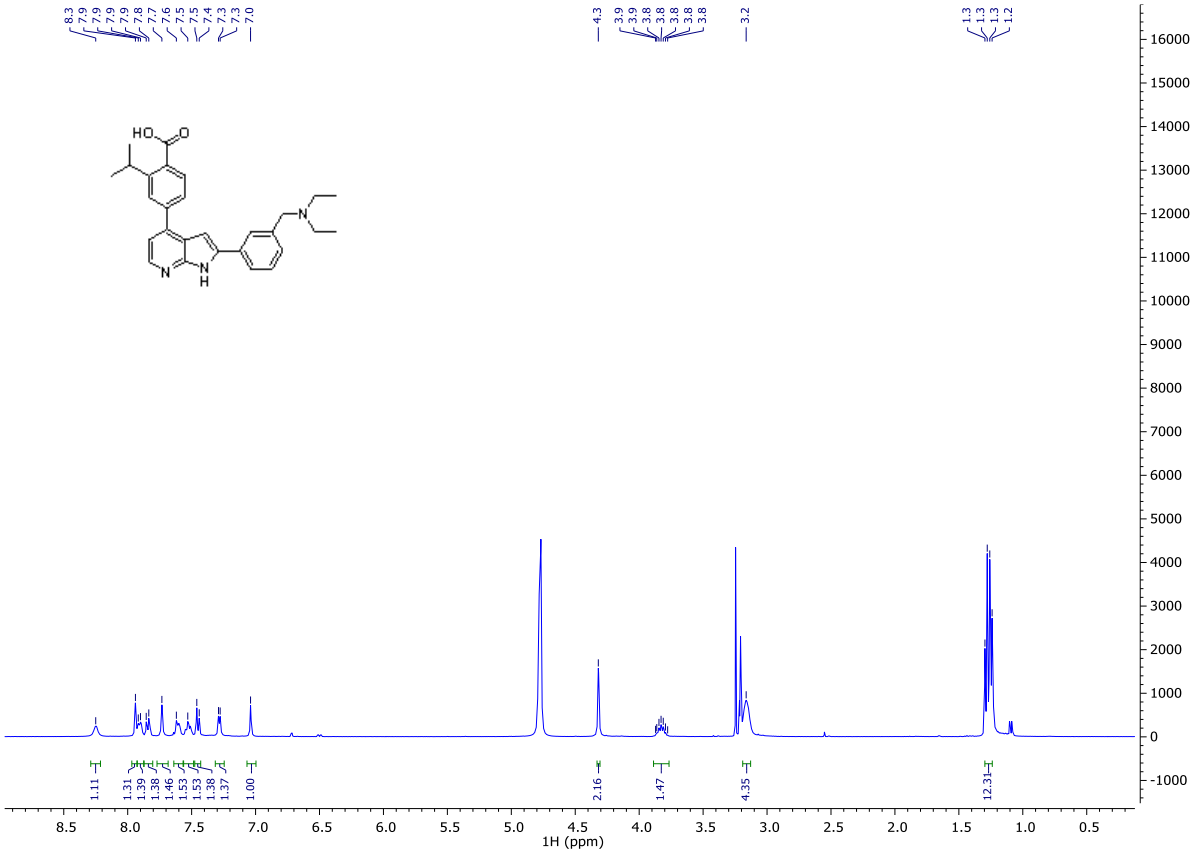


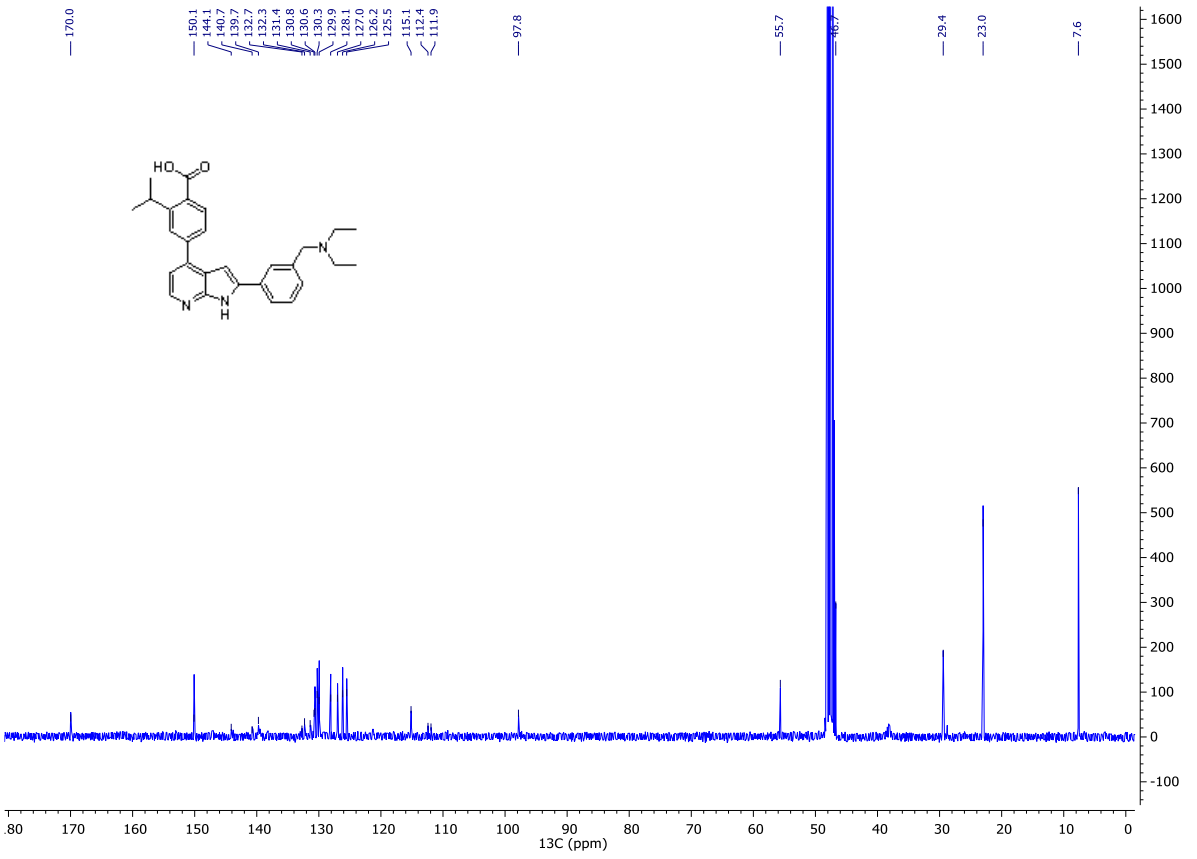
^{1}H and ^{13}C NMR spectra for compound 22



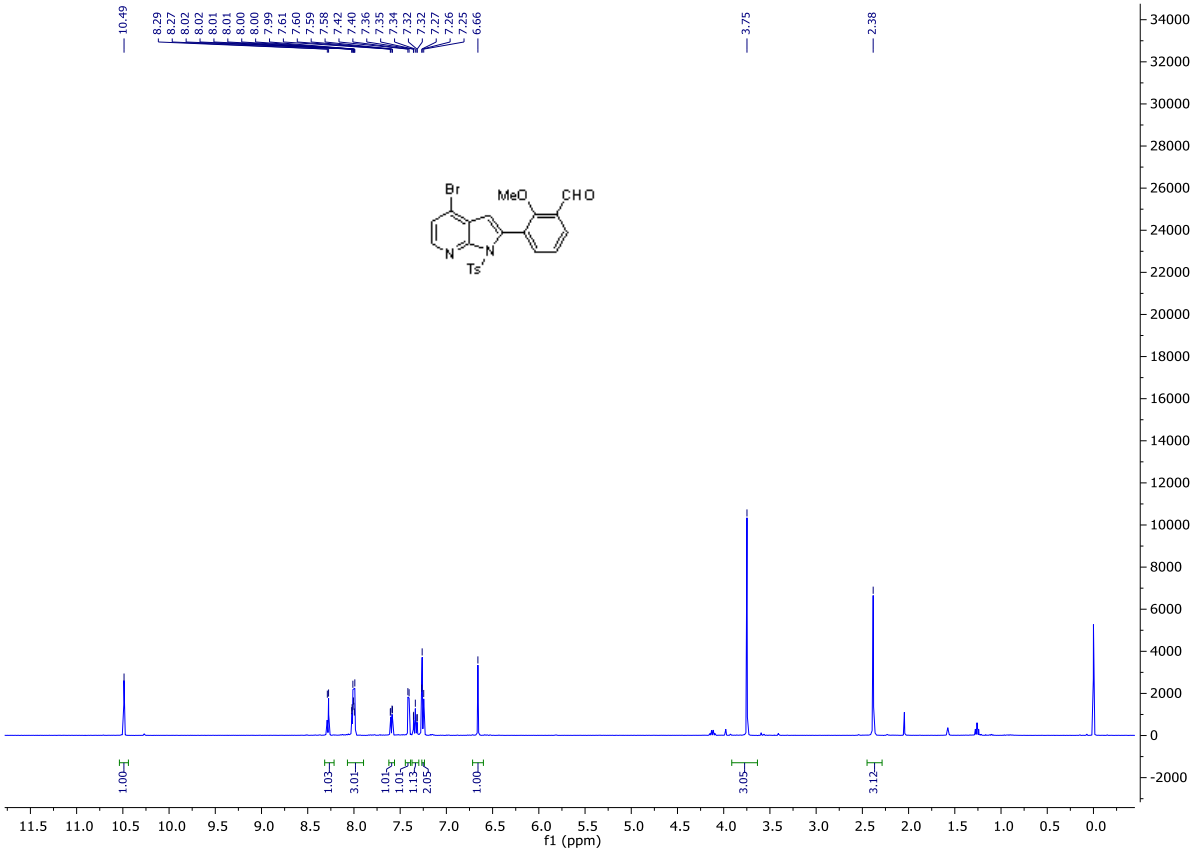


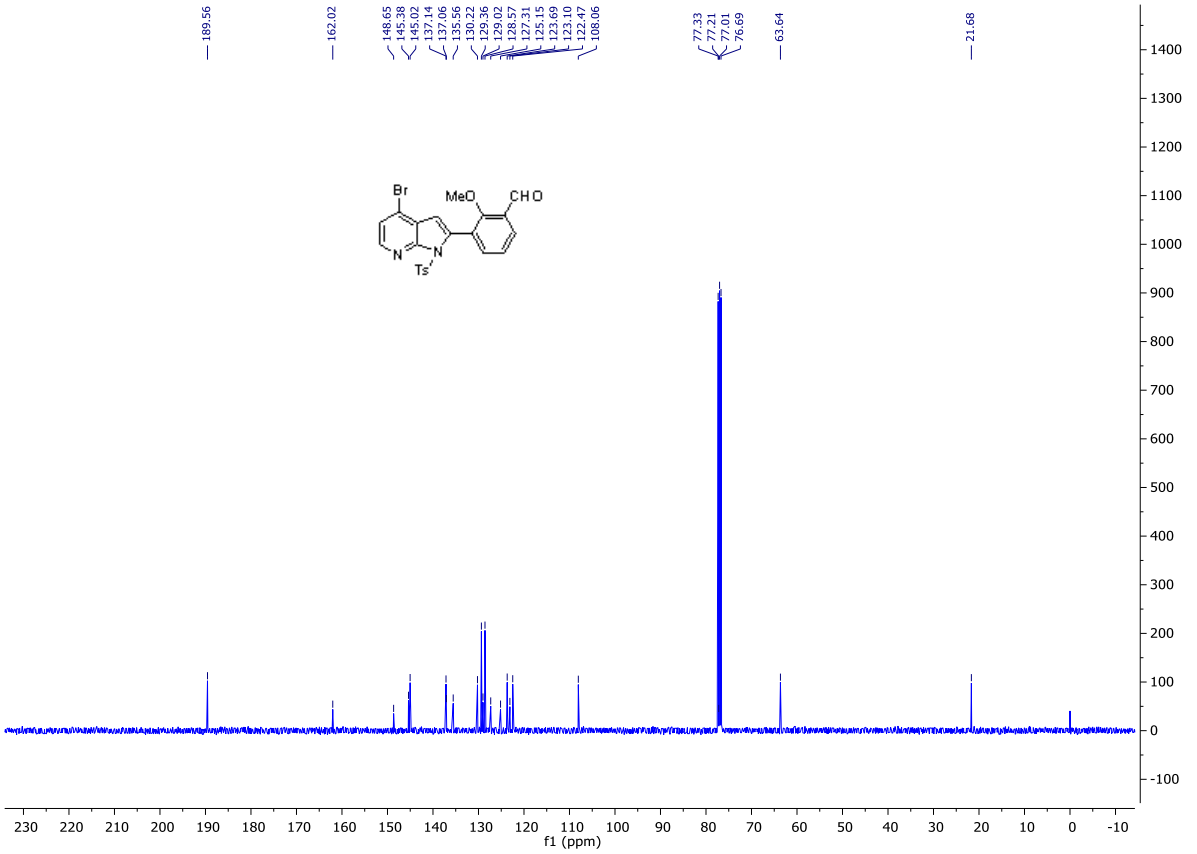
^{1}H and ^{13}C NMR spectra for compound 23



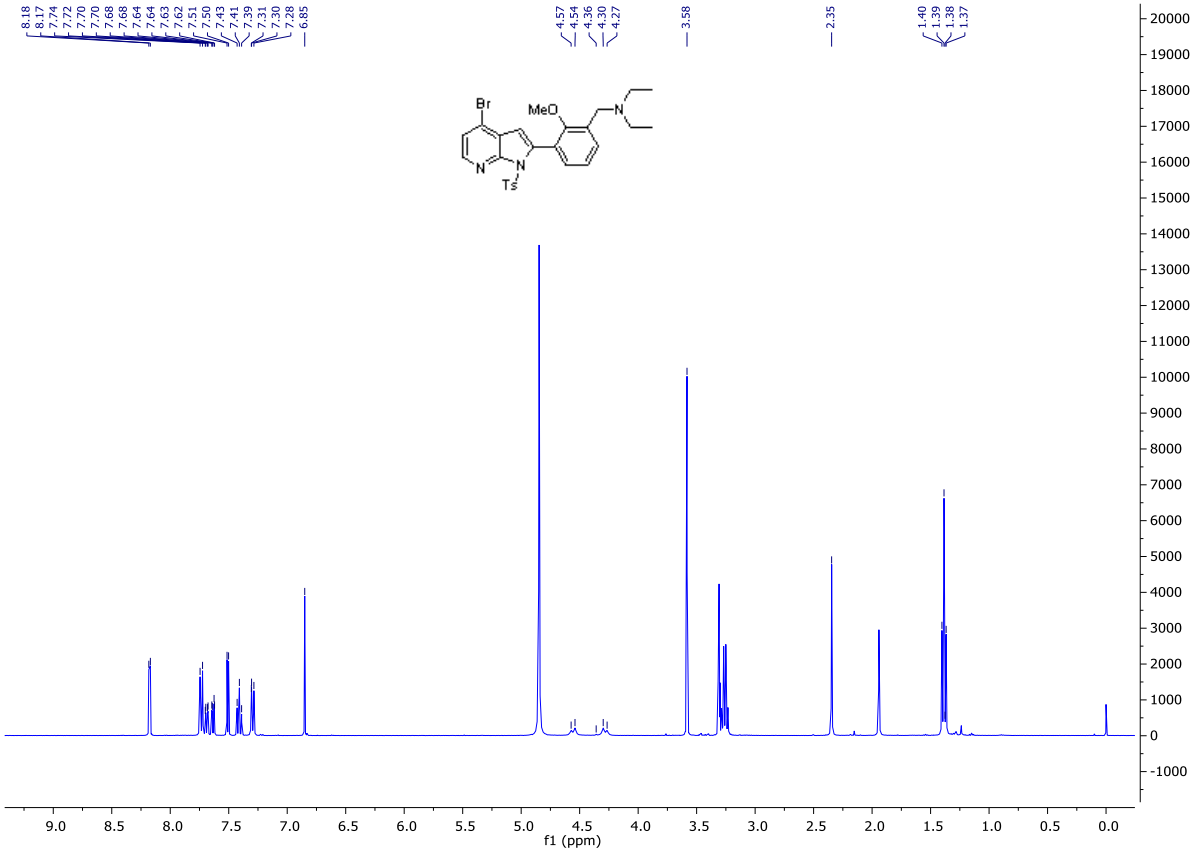


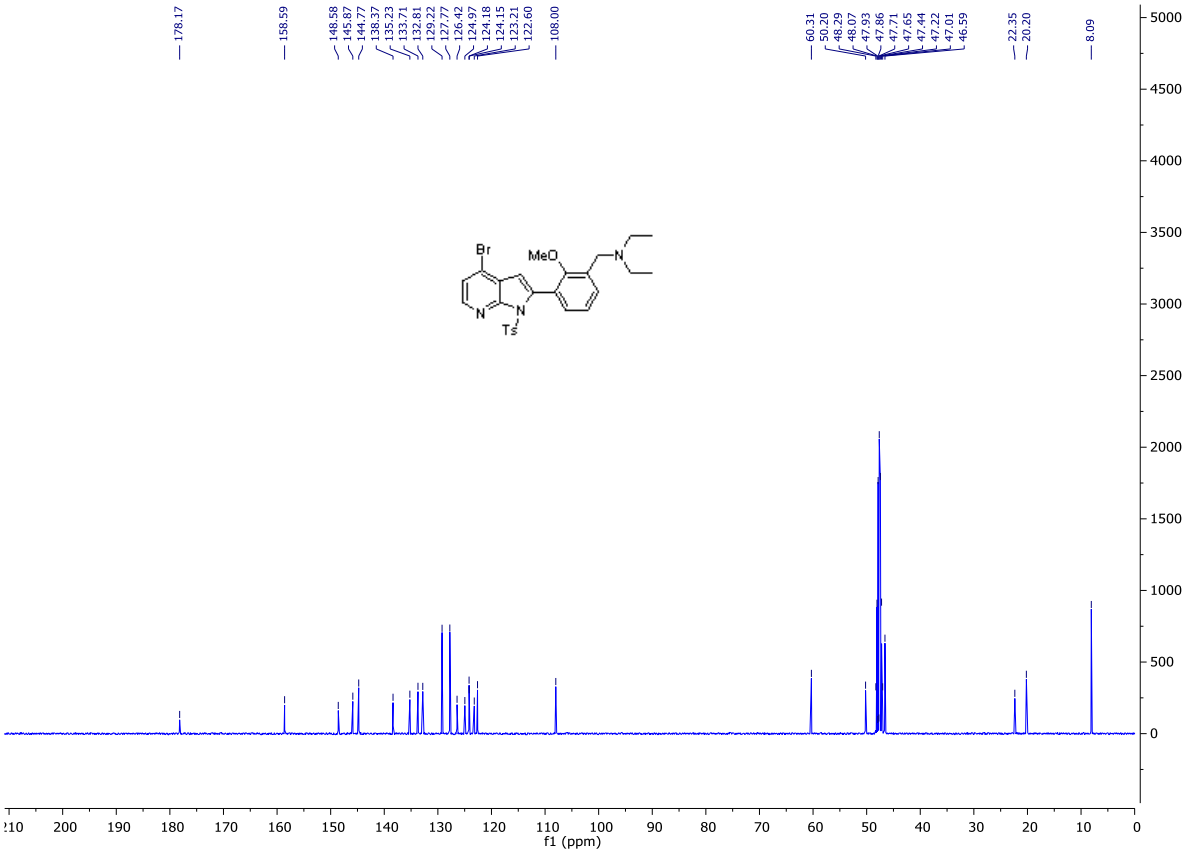
^{1}H and ^{13}C NMR spectra for compound 24



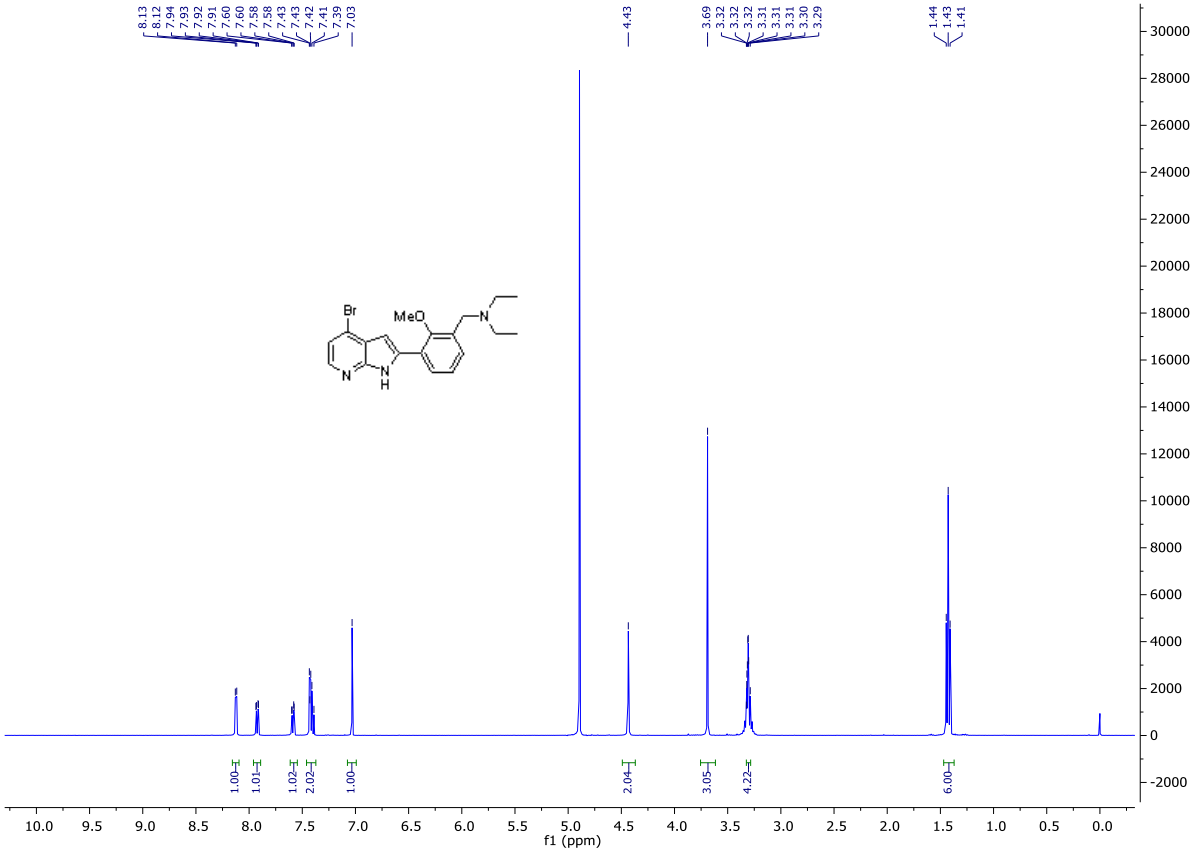


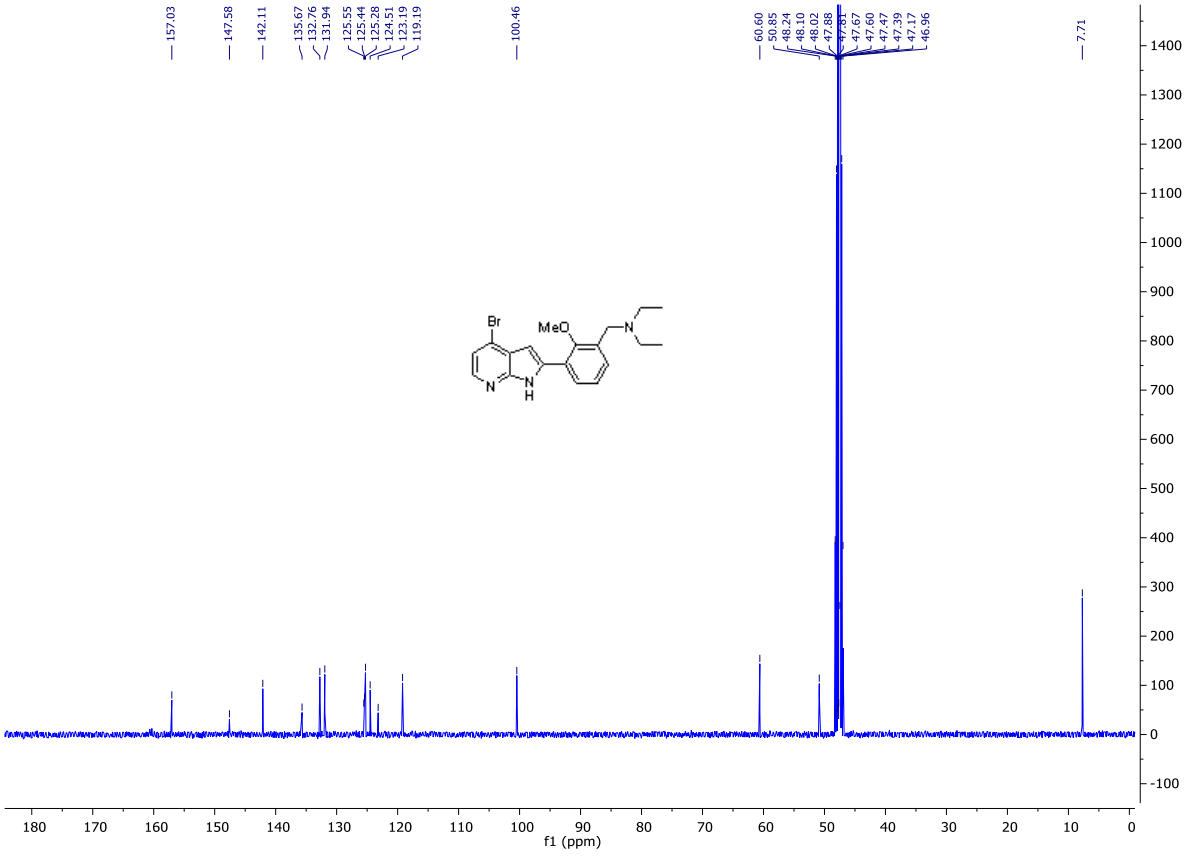
^{1}H and ^{13}C NMR spectra for compound 25



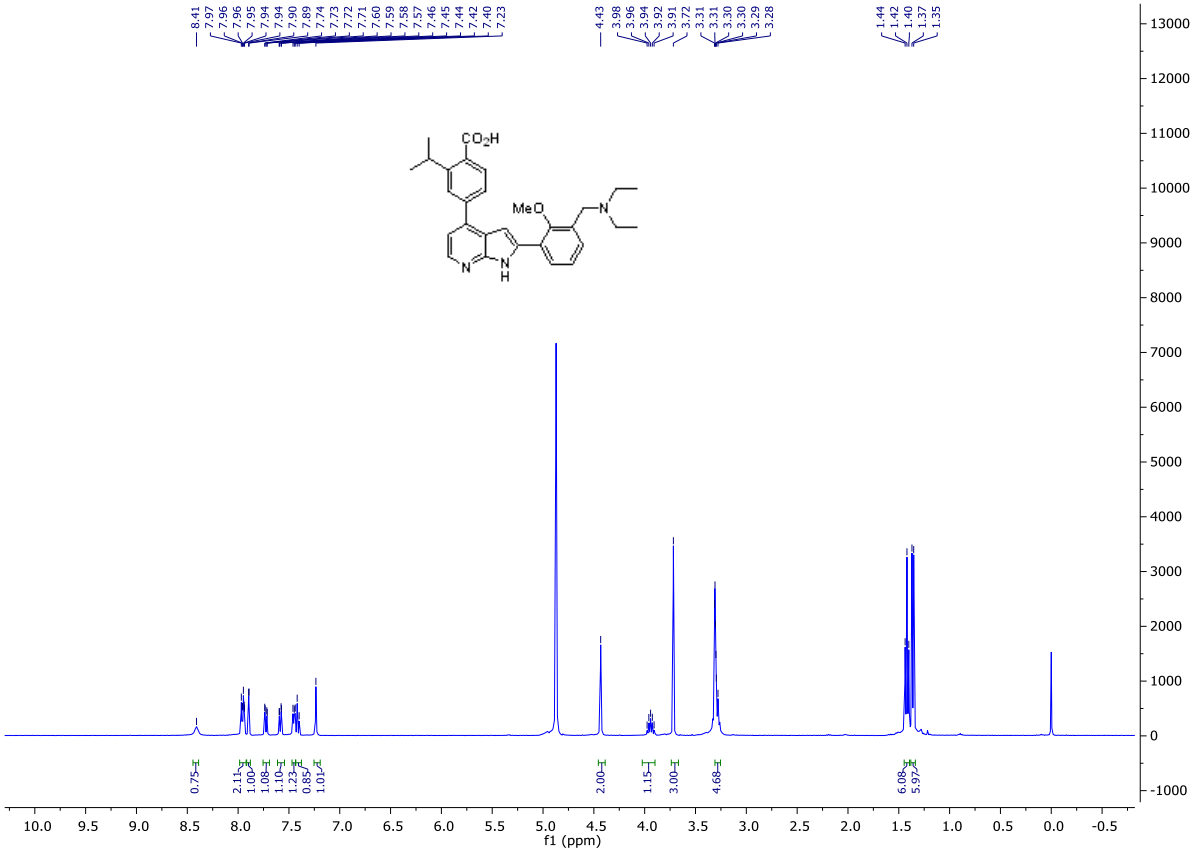


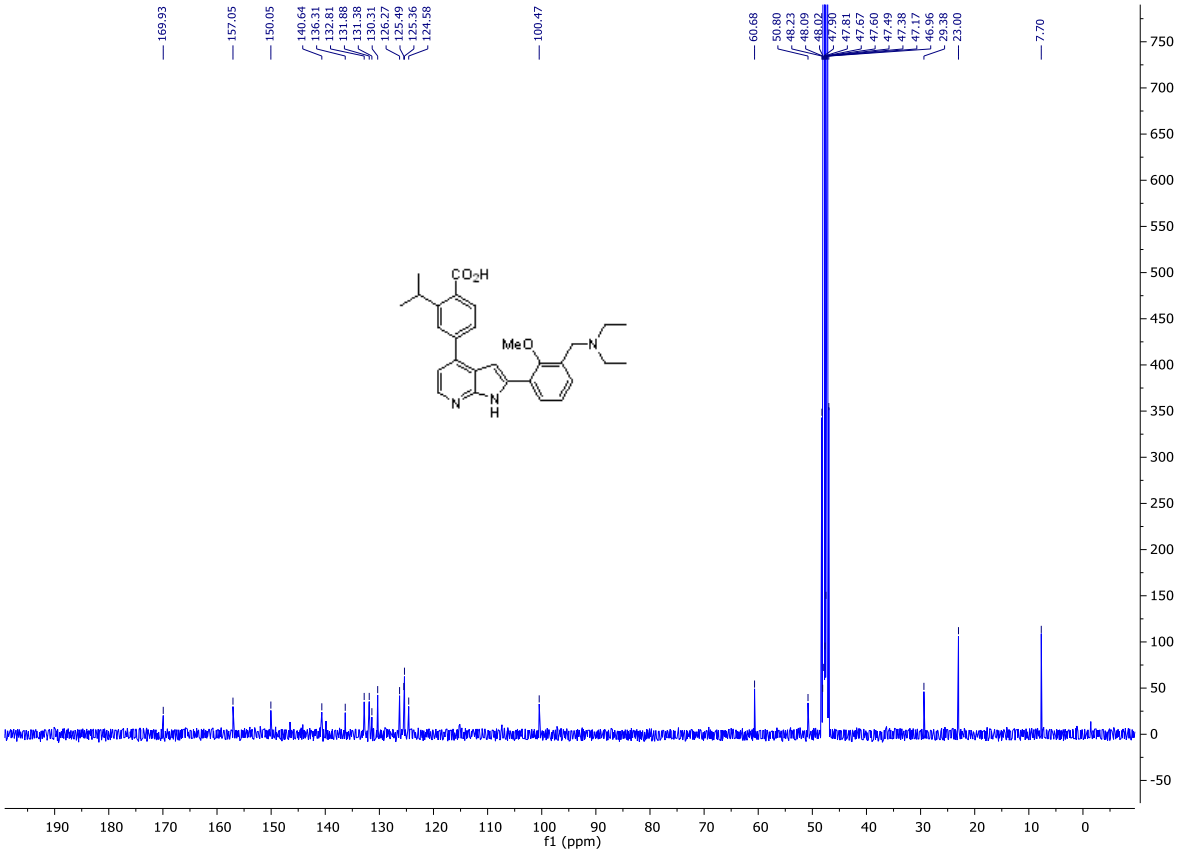
^{1}H and ^{13}C NMR spectra for compound 26



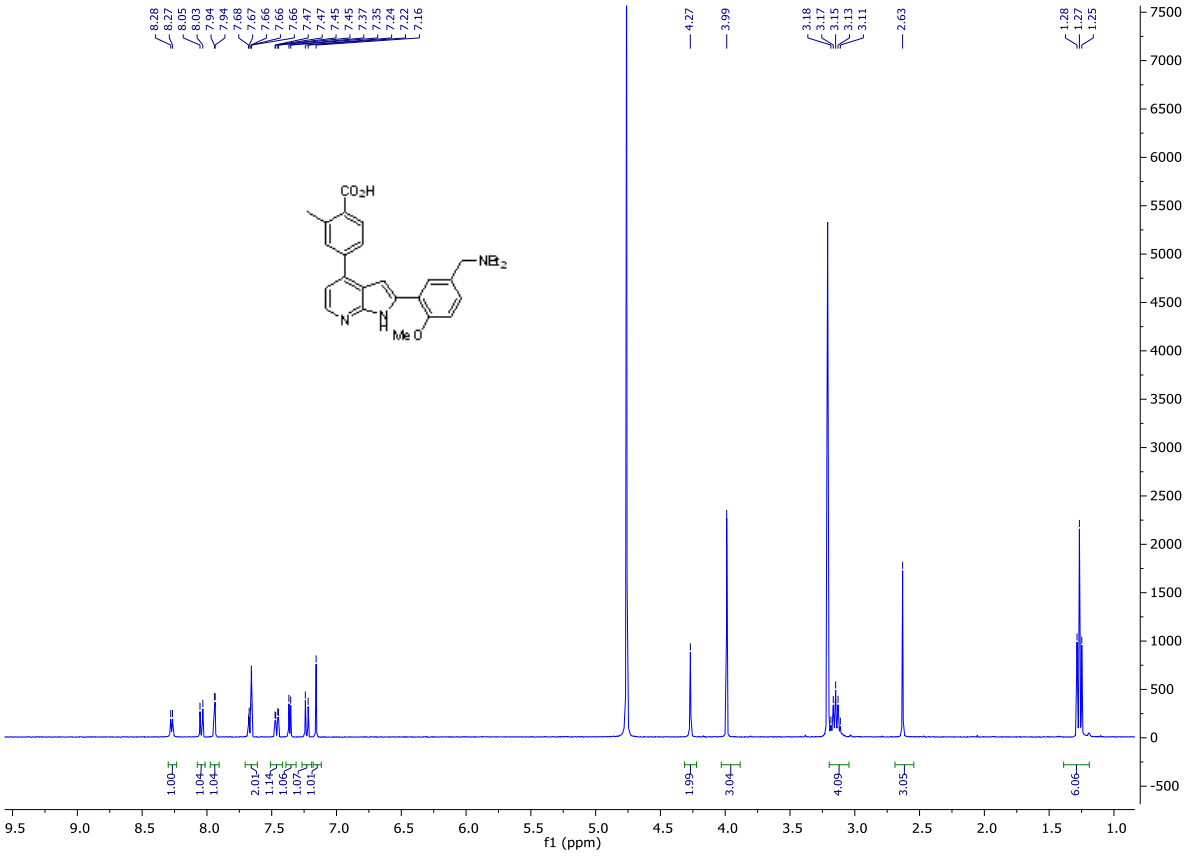


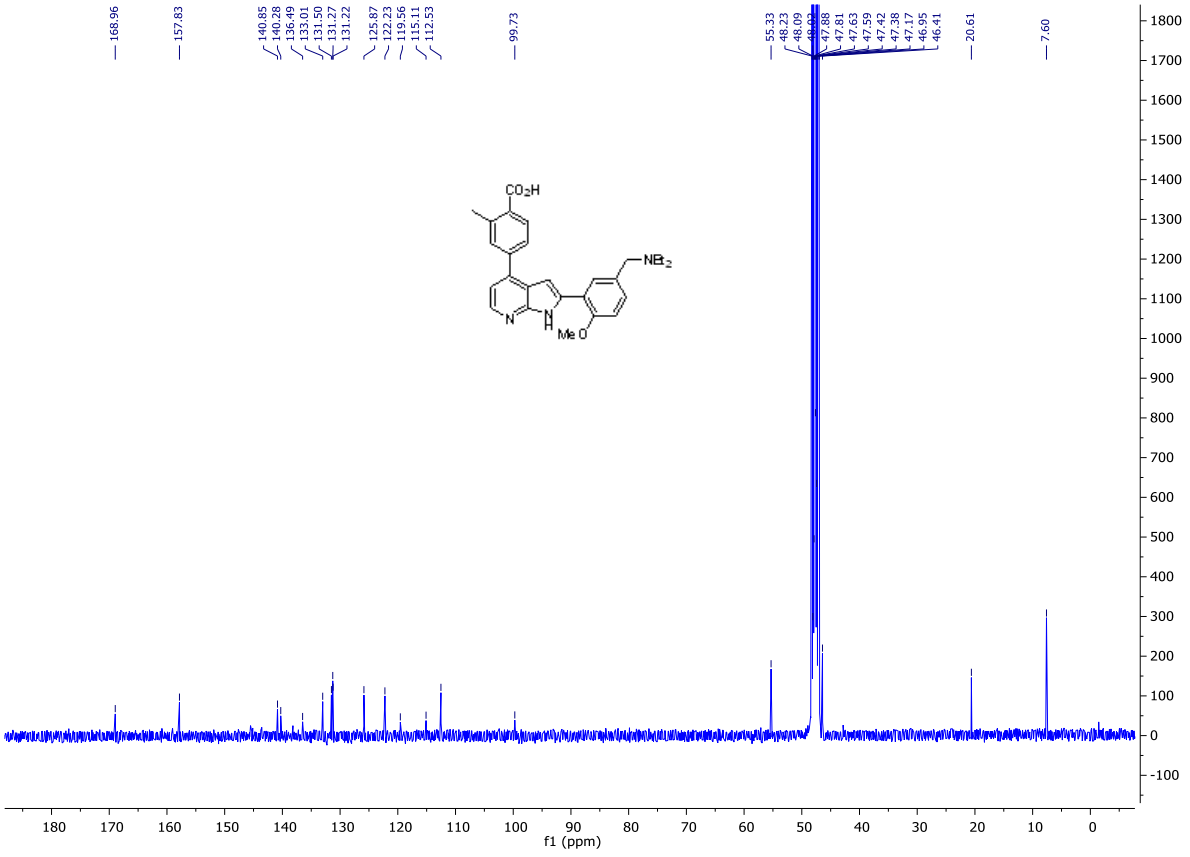
^{1}H and ^{13}C NMR spectra for compound 27



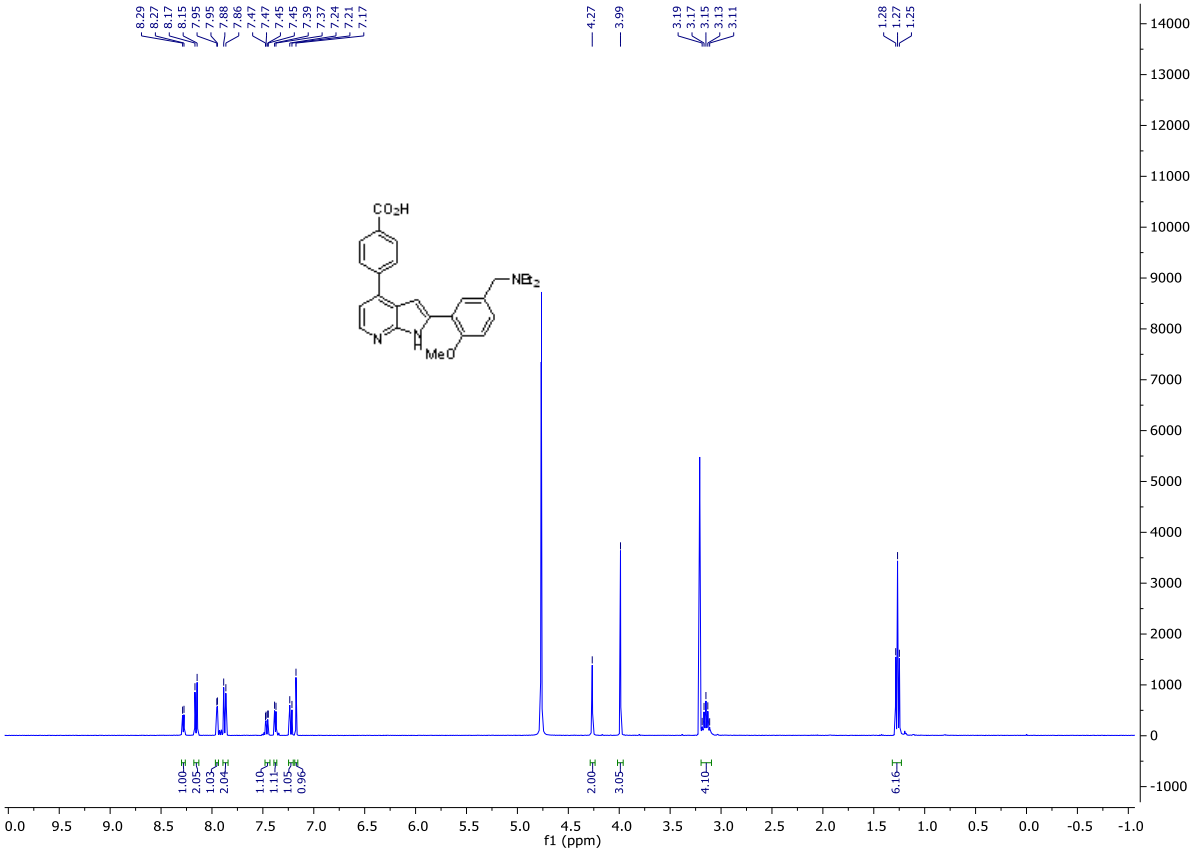


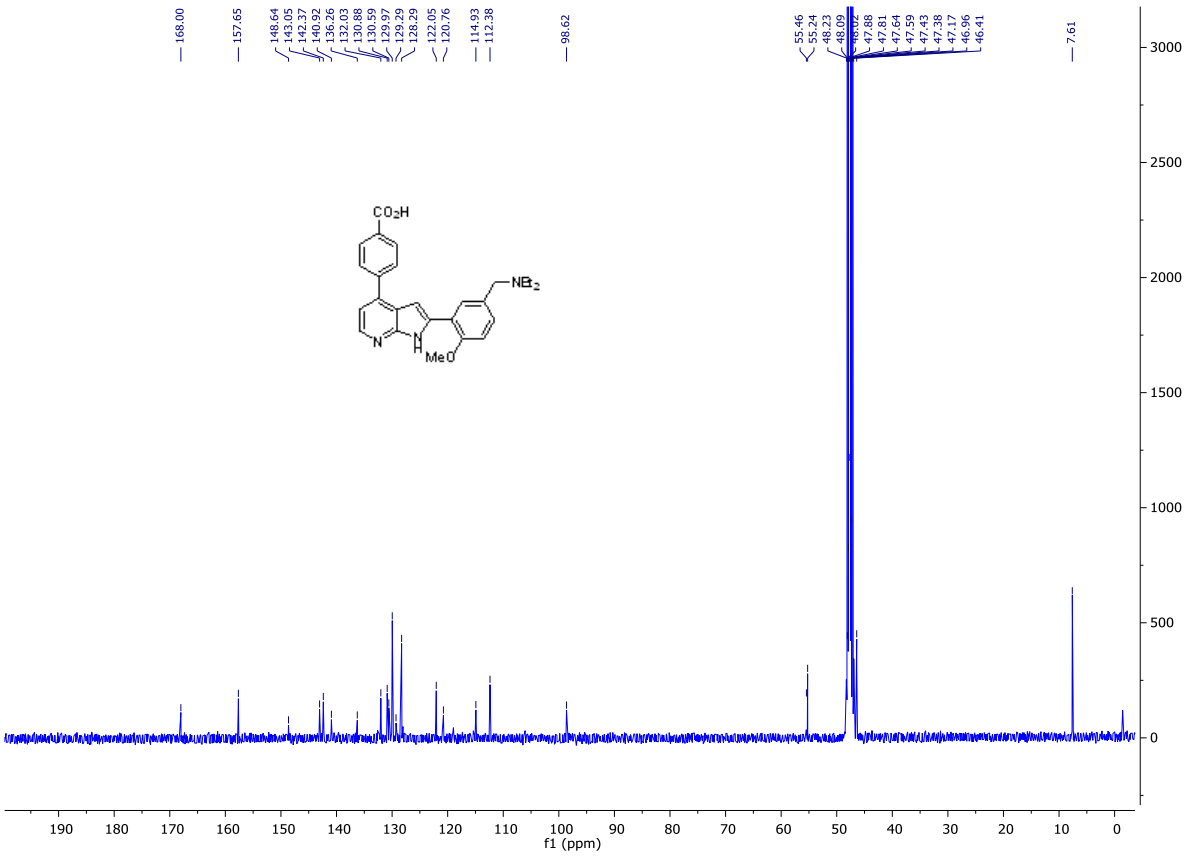
^{1}H and ^{13}C NMR spectra for compound 28



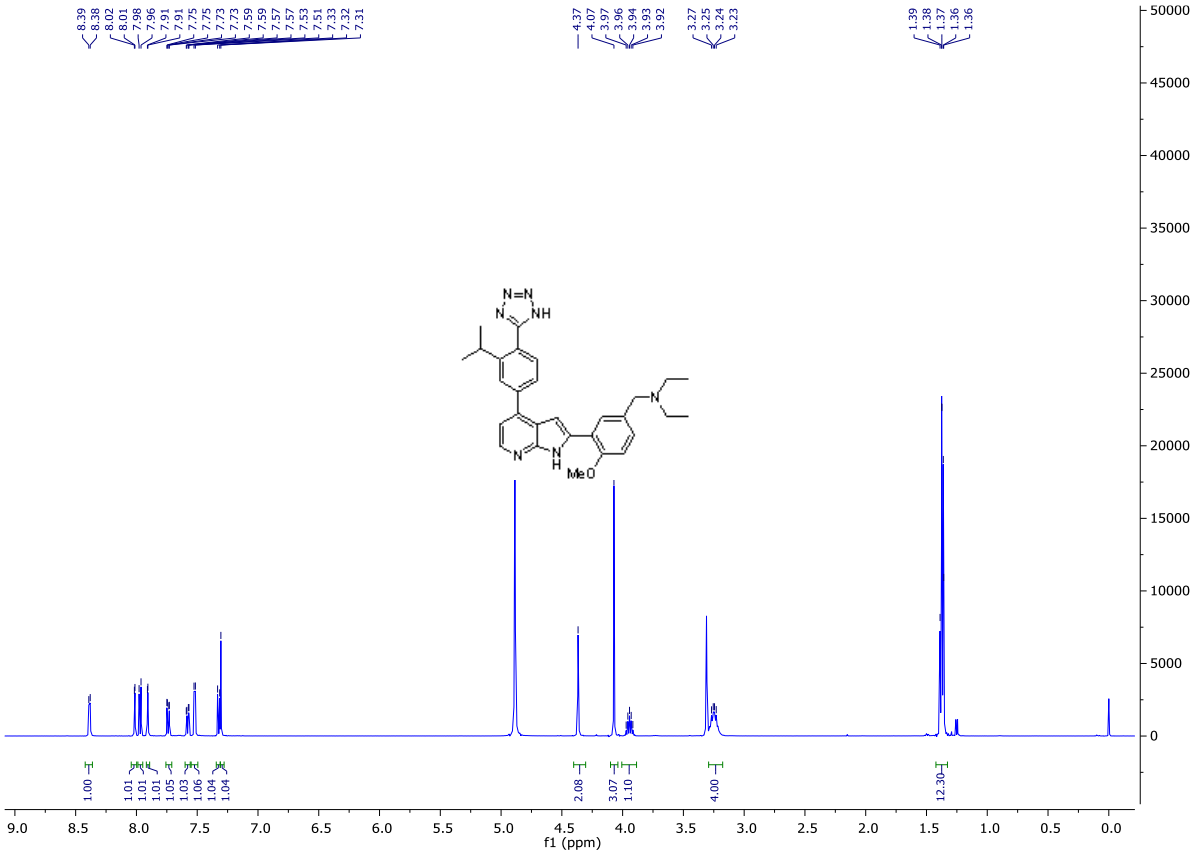


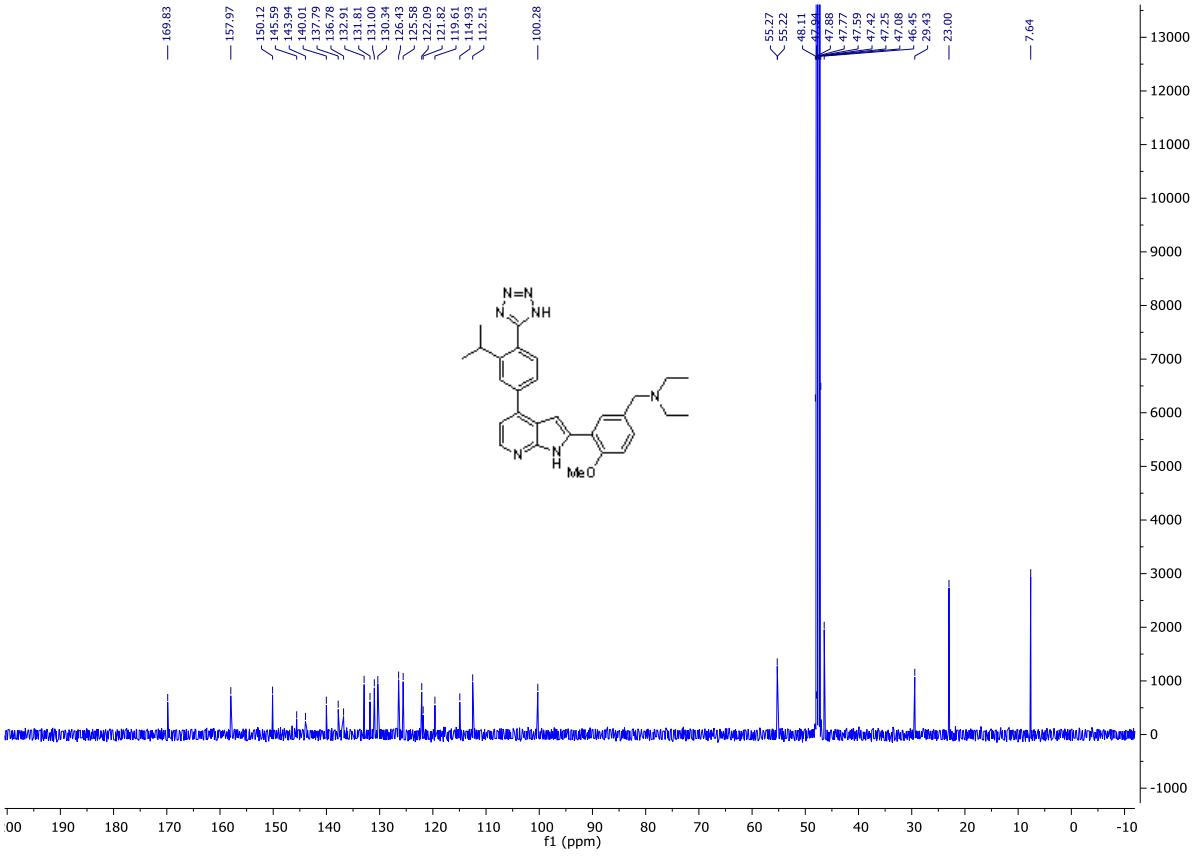
^{1}H and ^{13}C NMR spectra for compound 29



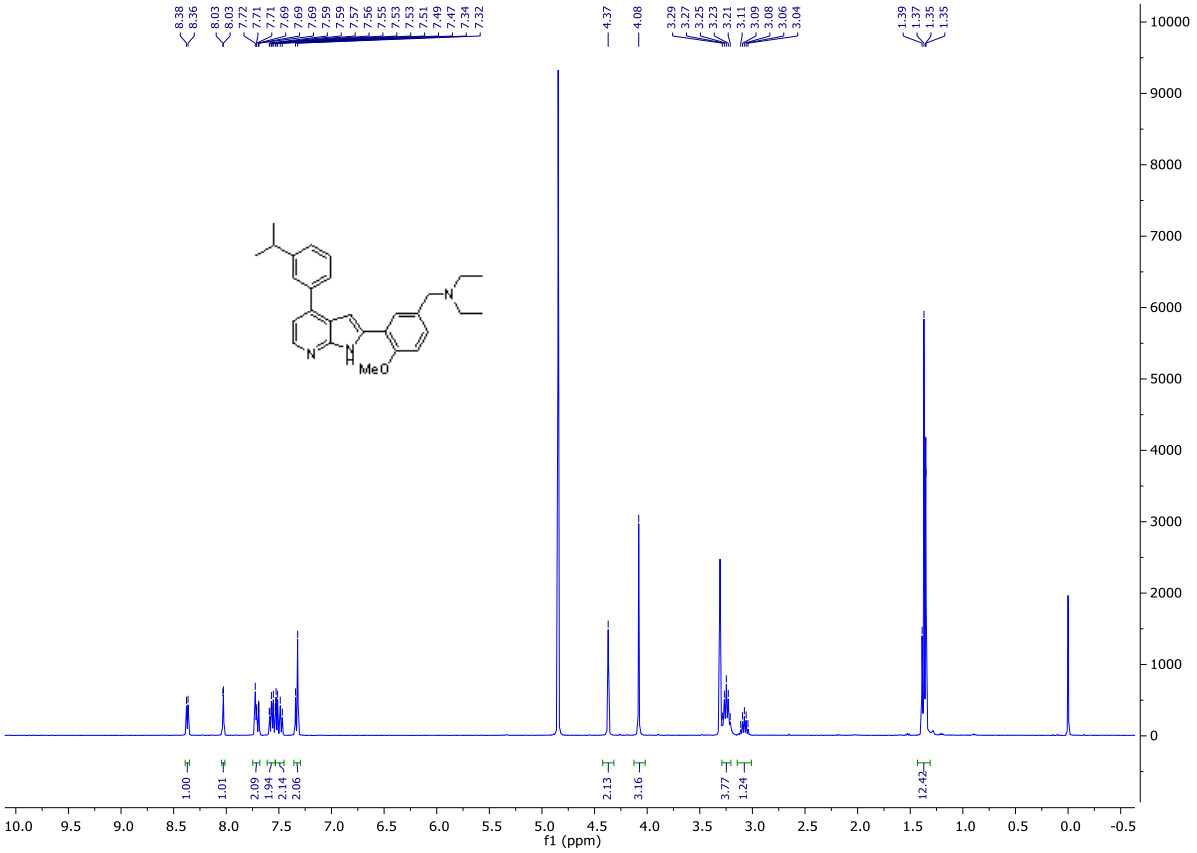


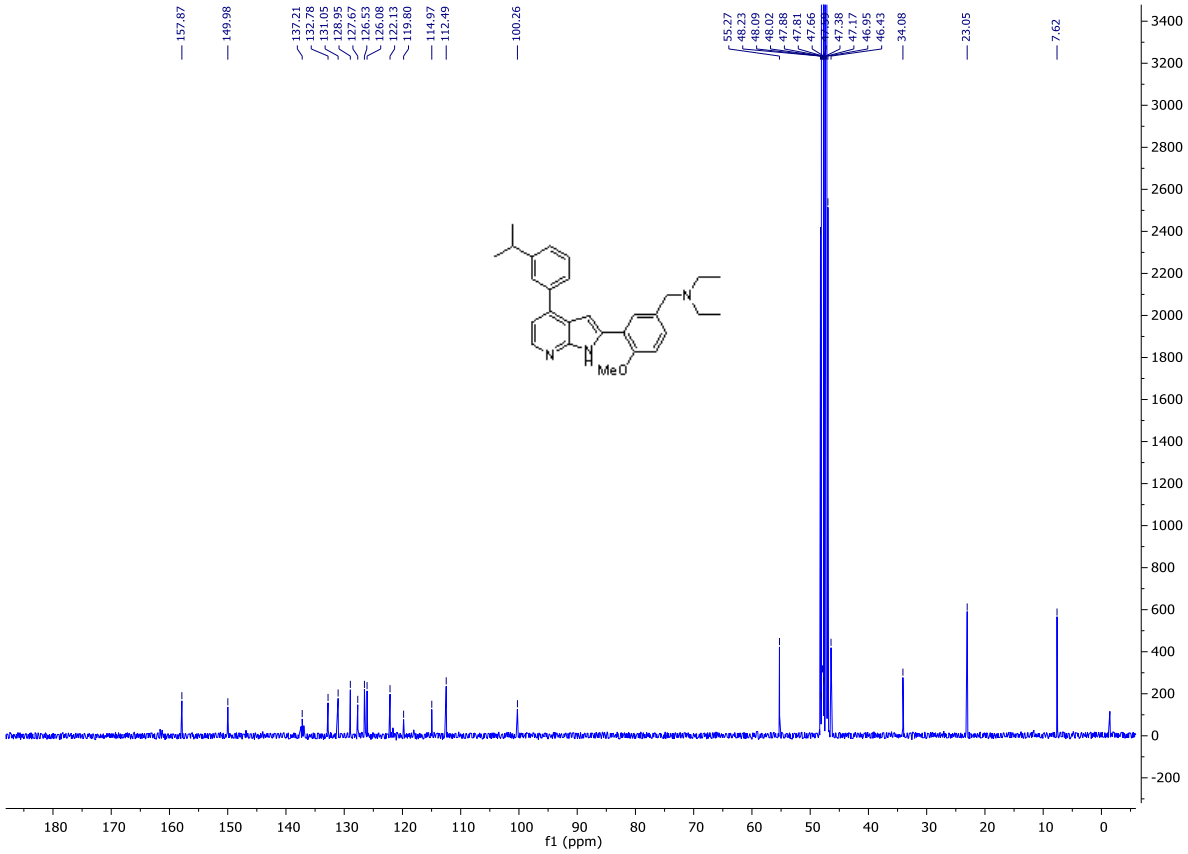
^{1}H and ^{13}C NMR spectra for compound 30



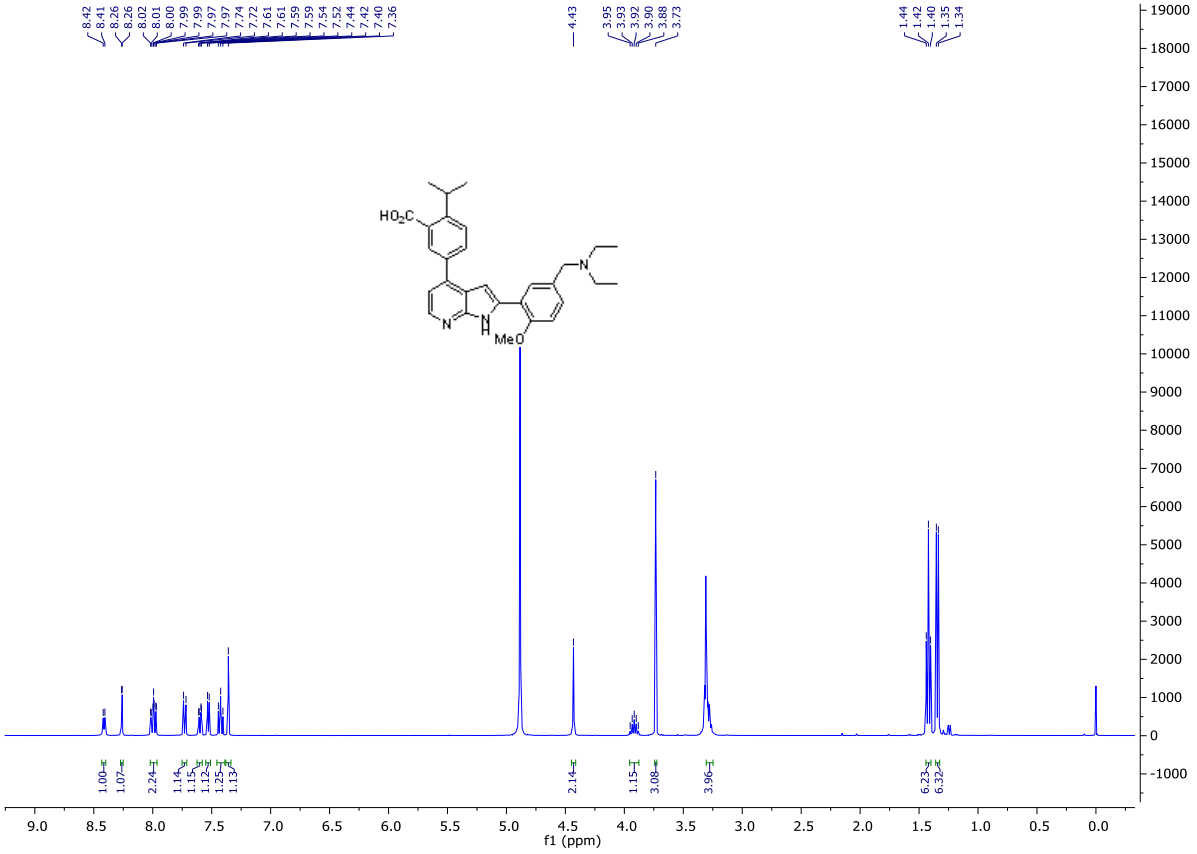


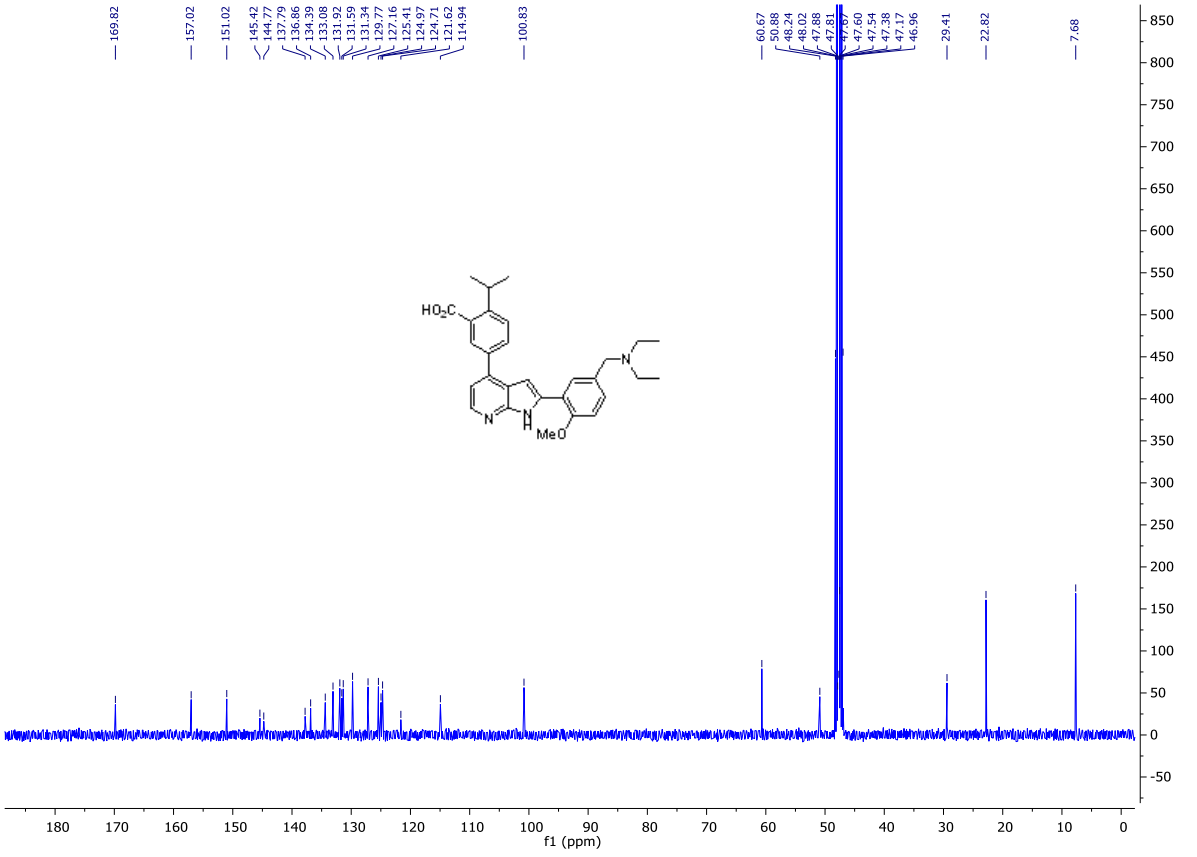
^{1}H and ^{13}C NMR spectra for compound 31




157.87
149.98
137.21
132.78
131.05
128.95
127.67
126.53
126.08
122.13
119.80
114.97
112.49
100.26
55.27
48.23
48.09
48.02
47.88
47.81
47.66
47.38
47.17
46.95
46.43
34.08
23.05
7.62
MeO
f1 (ppm)

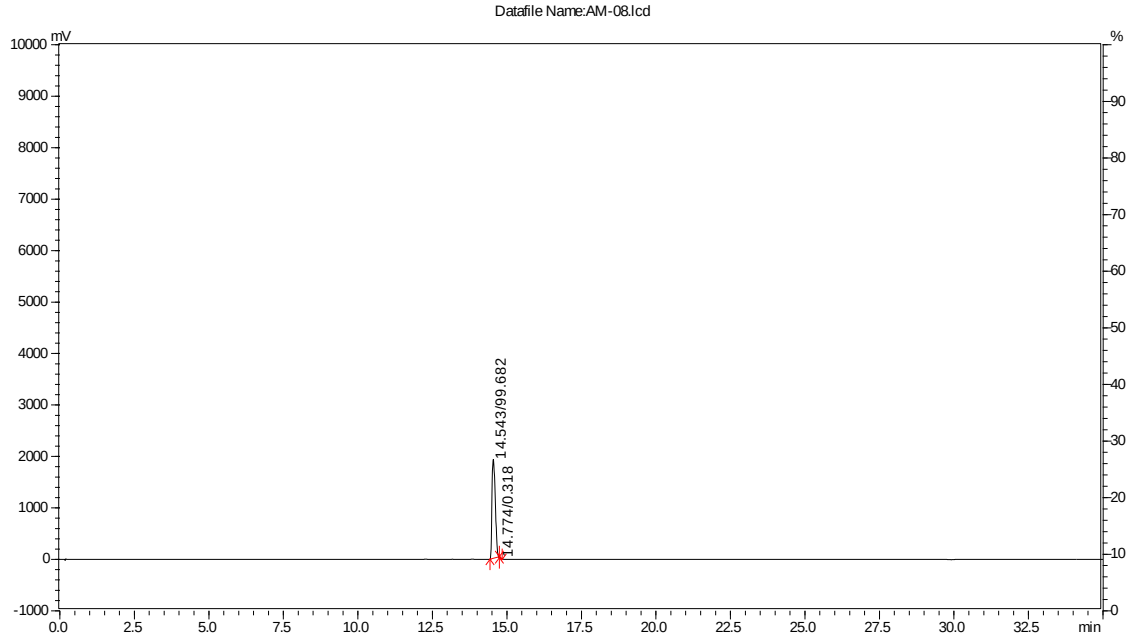
^{1}H and ^{13}C NMR spectra for compound 32



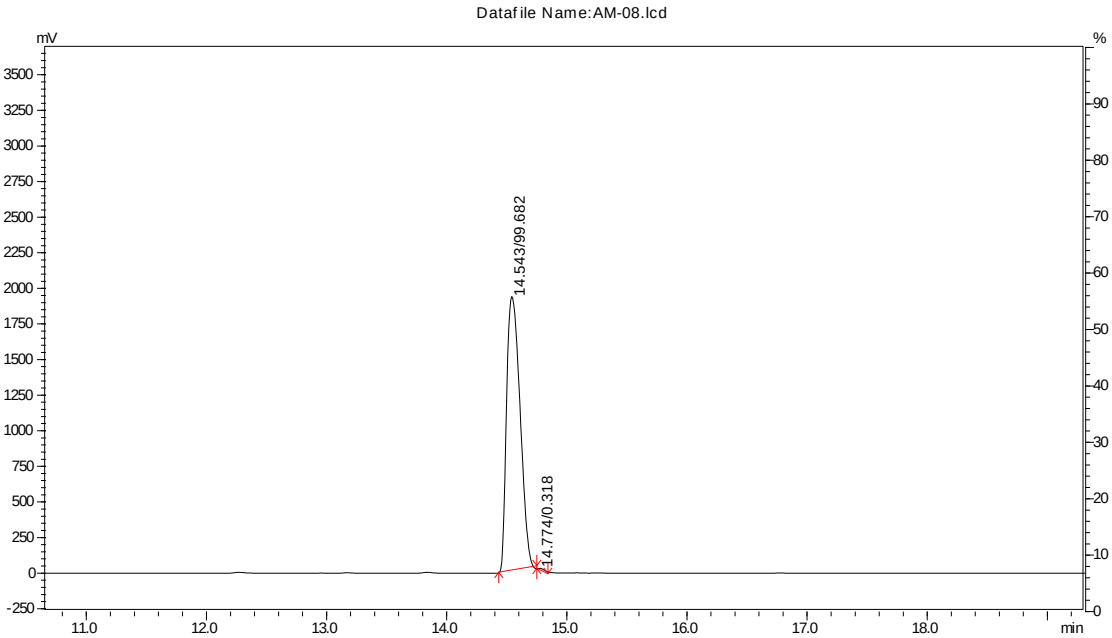


VIII. HPLC:

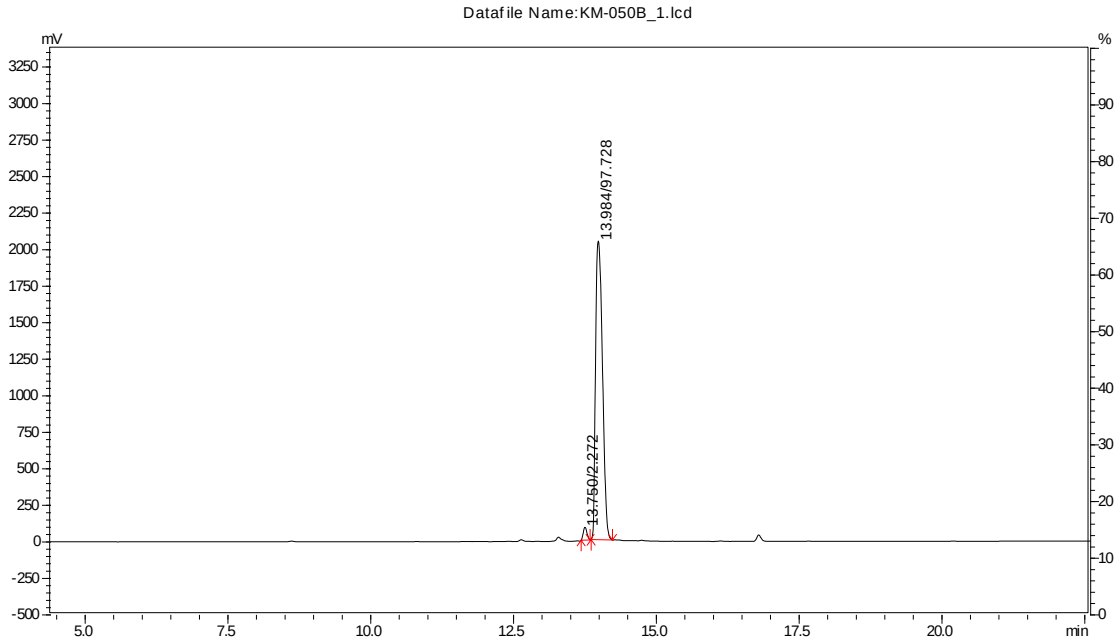
HPLC chromatogram of 1



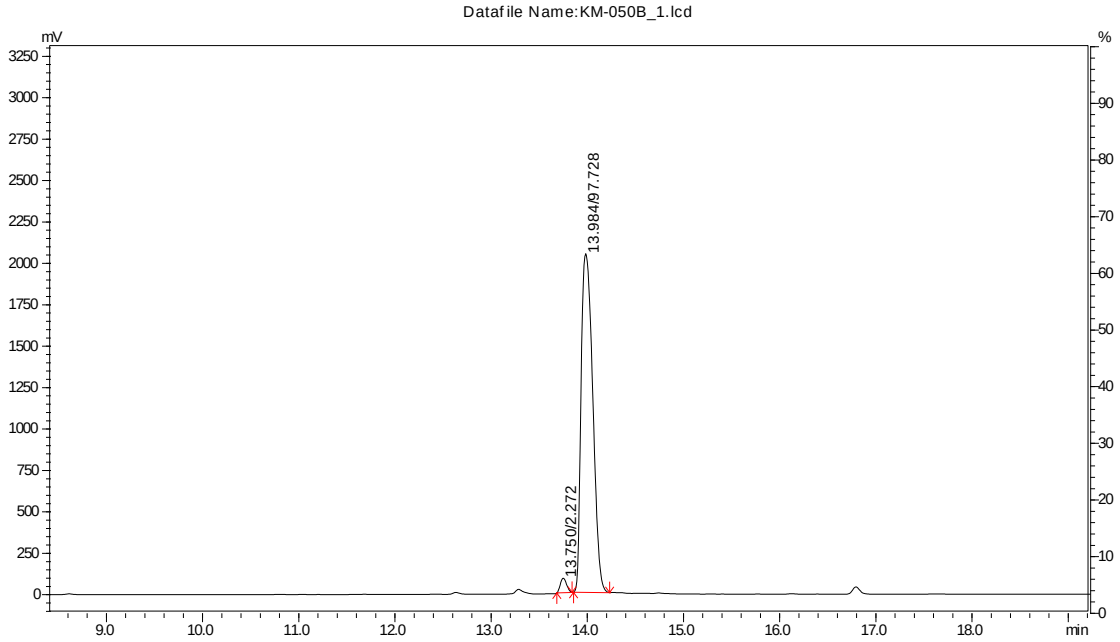
HPLC chromatogram of 1, gradient zoom



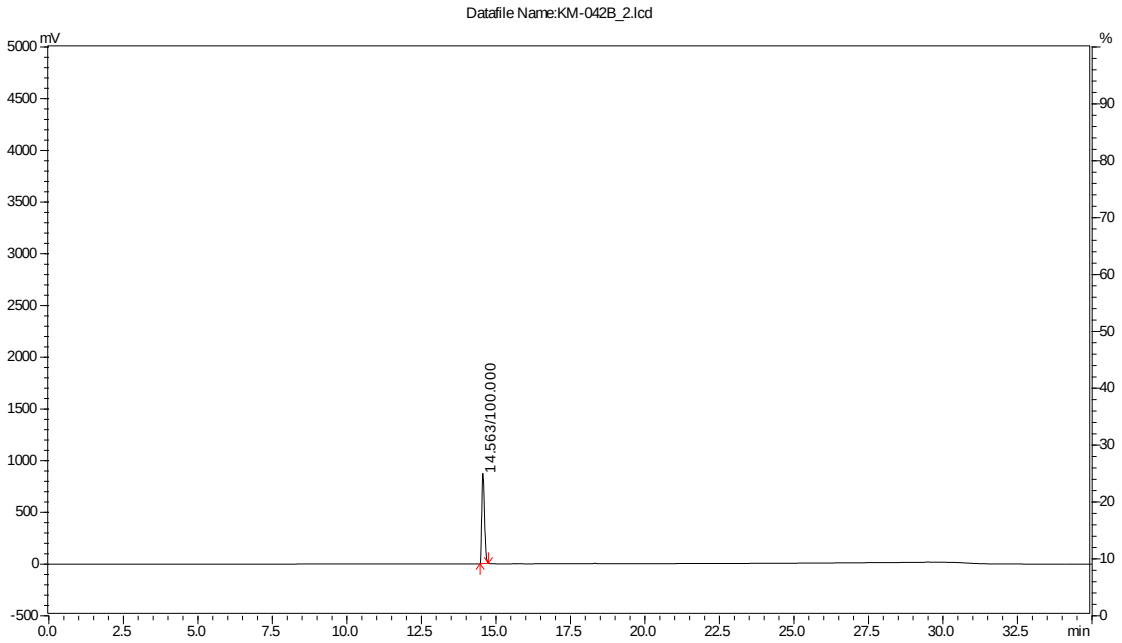
HPLC chromatogram of 8a



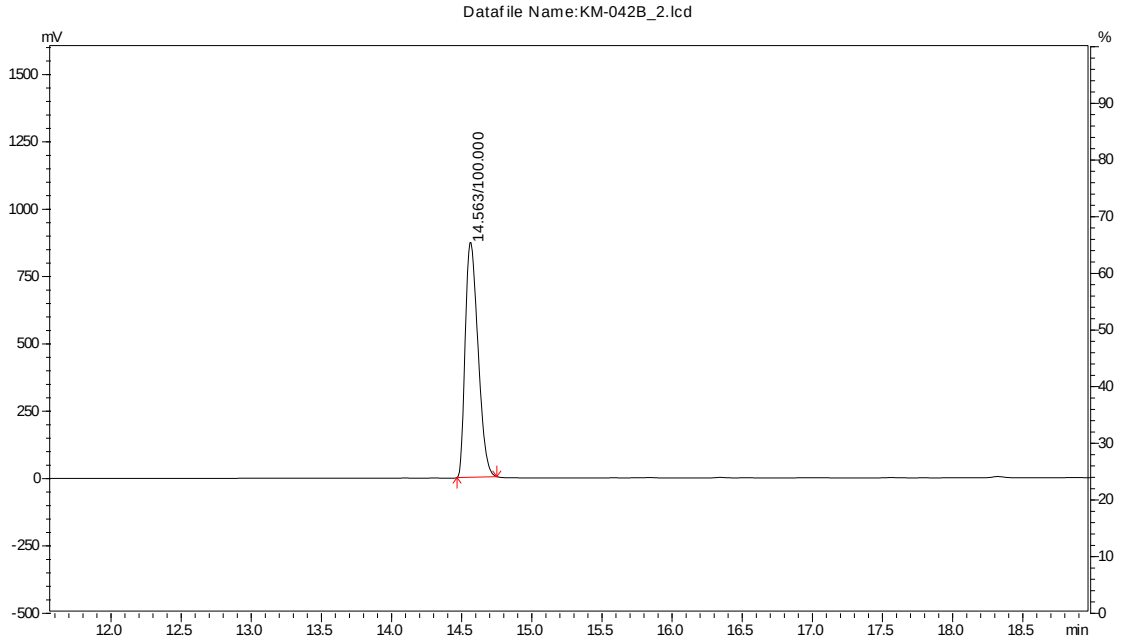
HPLC chromatogram of 8a, gradient zoom



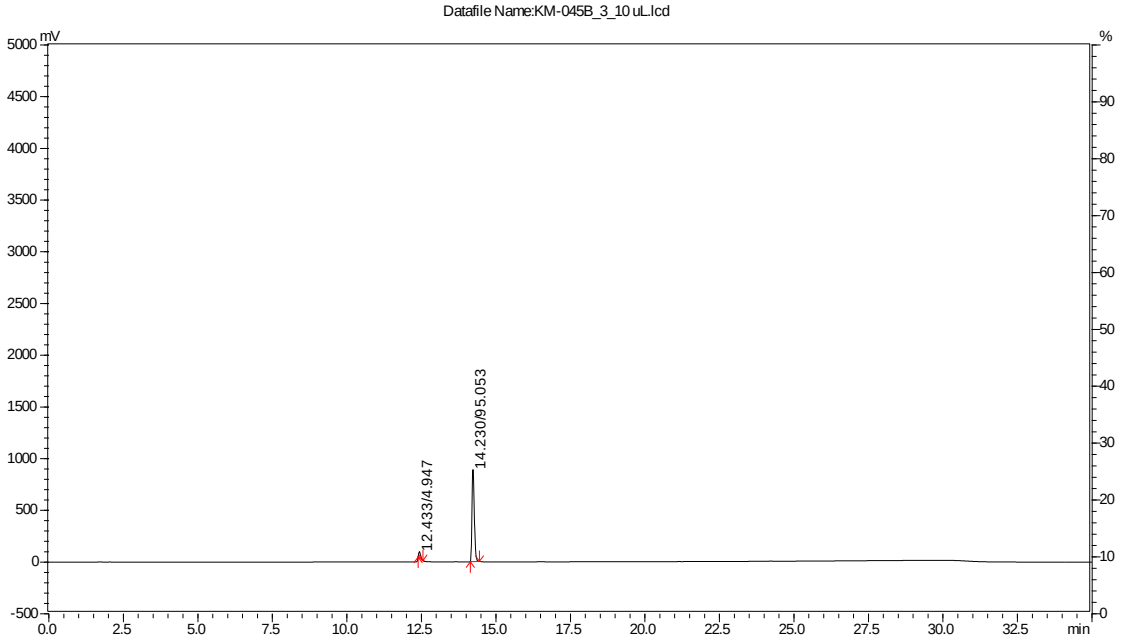
HPLC chromatogram of 8b



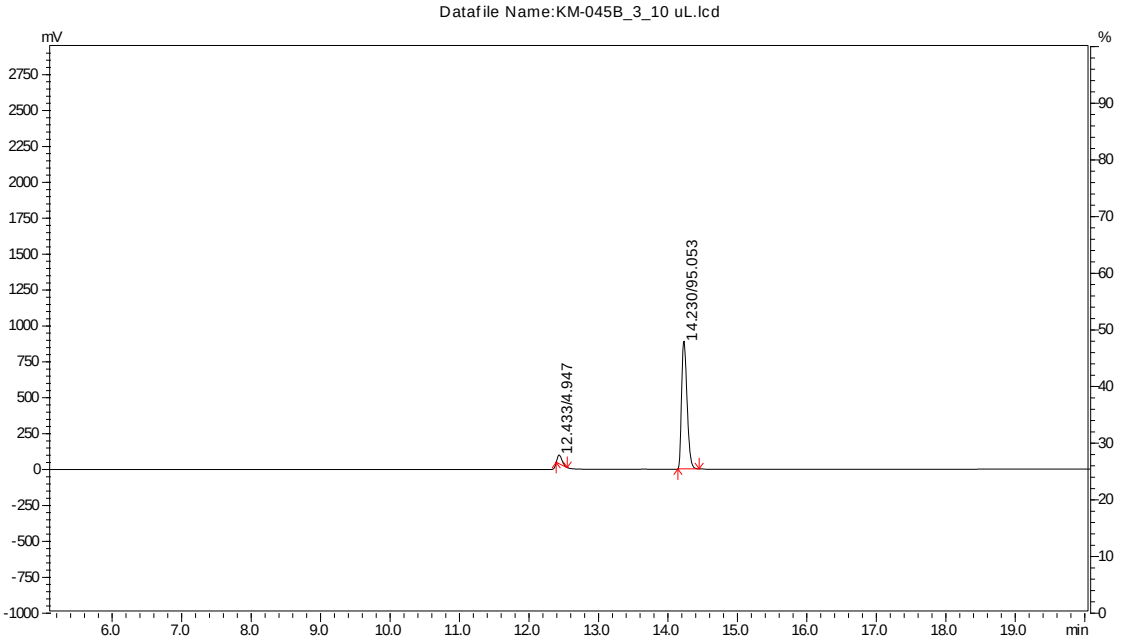
HPLC chromatogram of 8b, gradient zoom



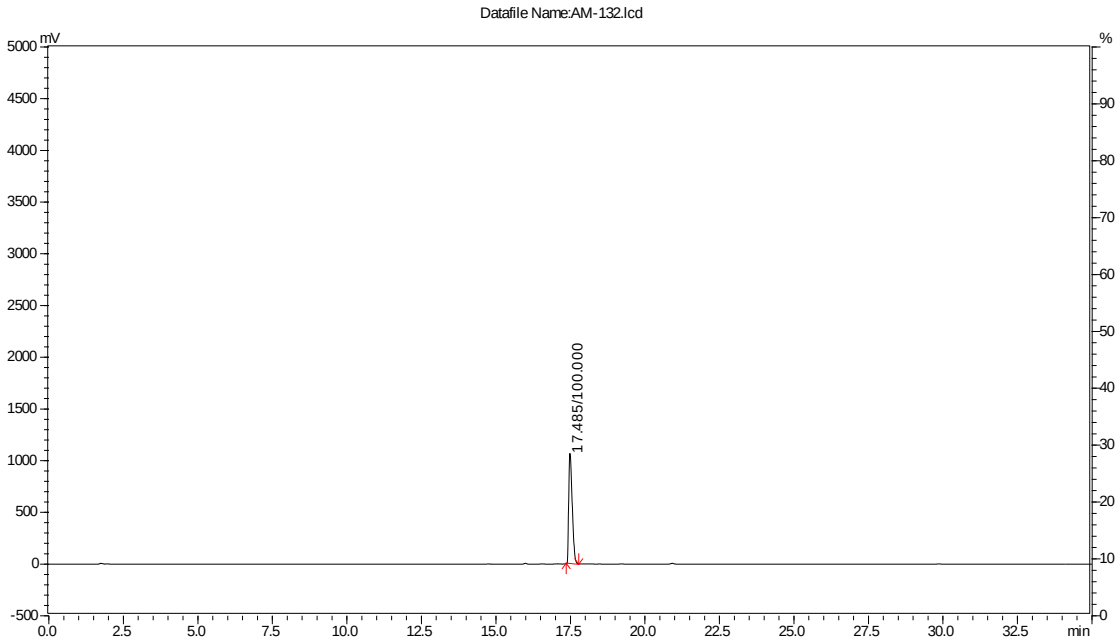
HPLC chromatogram of 8c



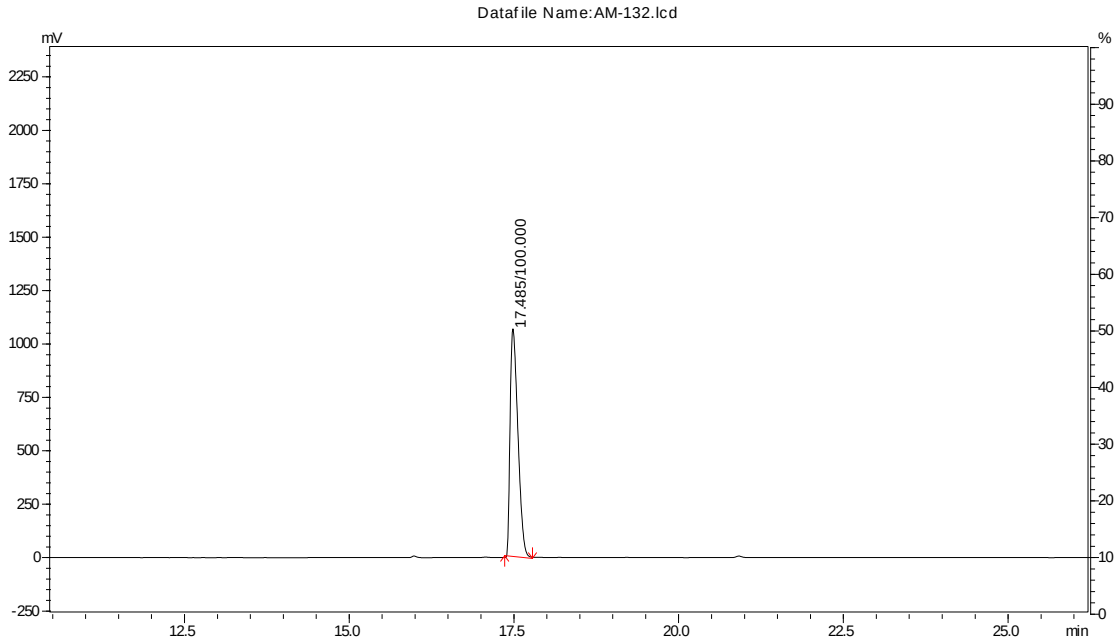
HPLC chromatogram of 8c, gradient zoom



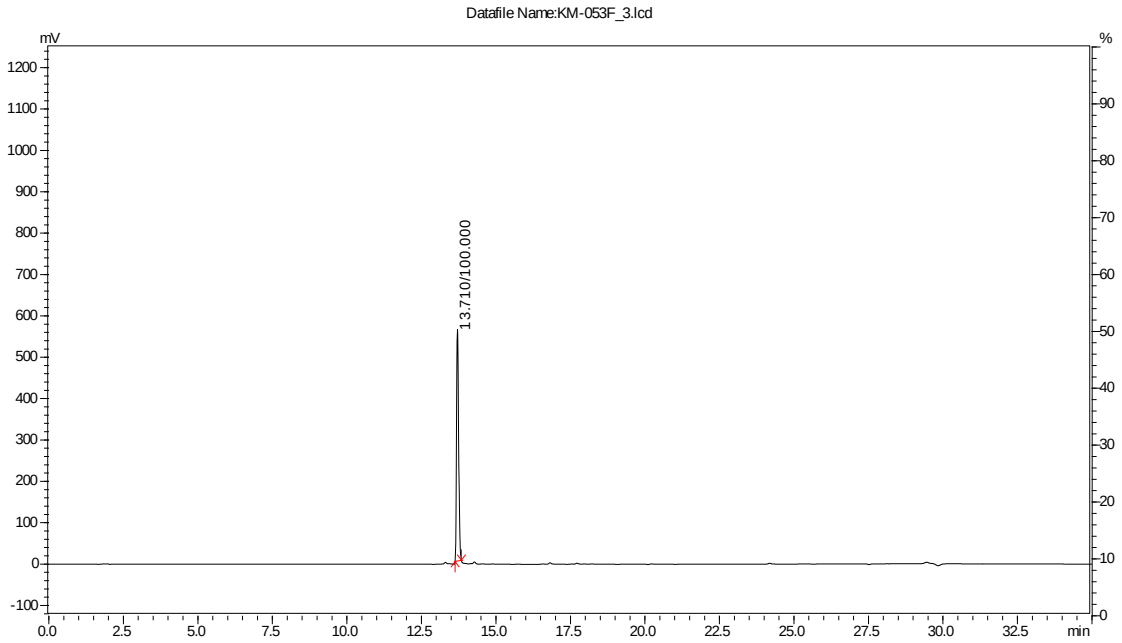
HPLC chromatogram of 9



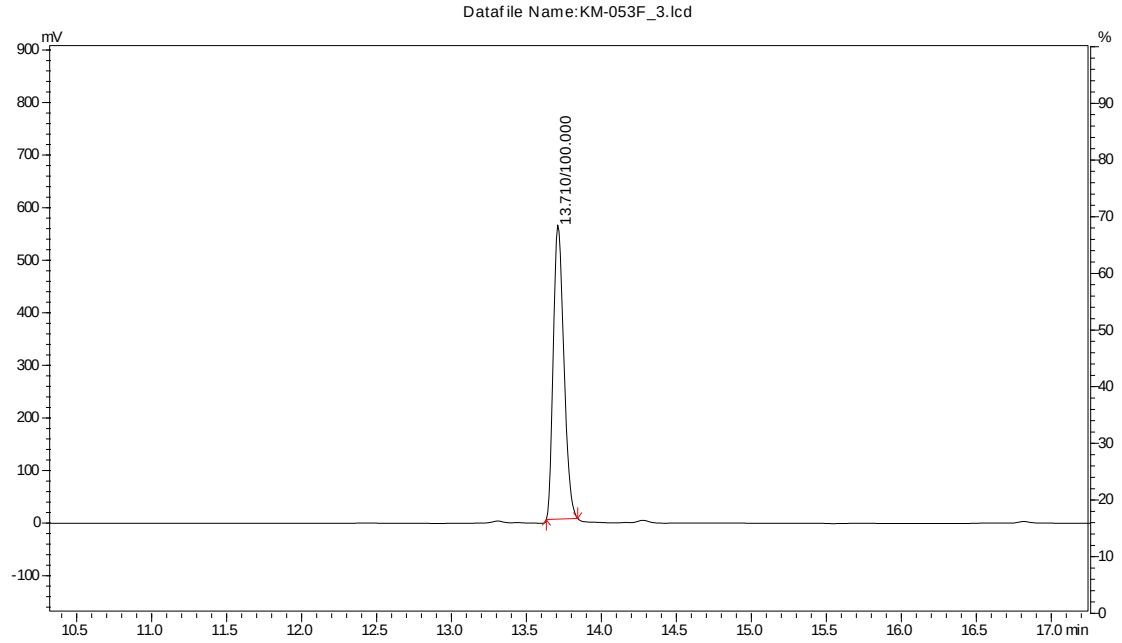
HPLC chromatogram of 9, gradient zoom



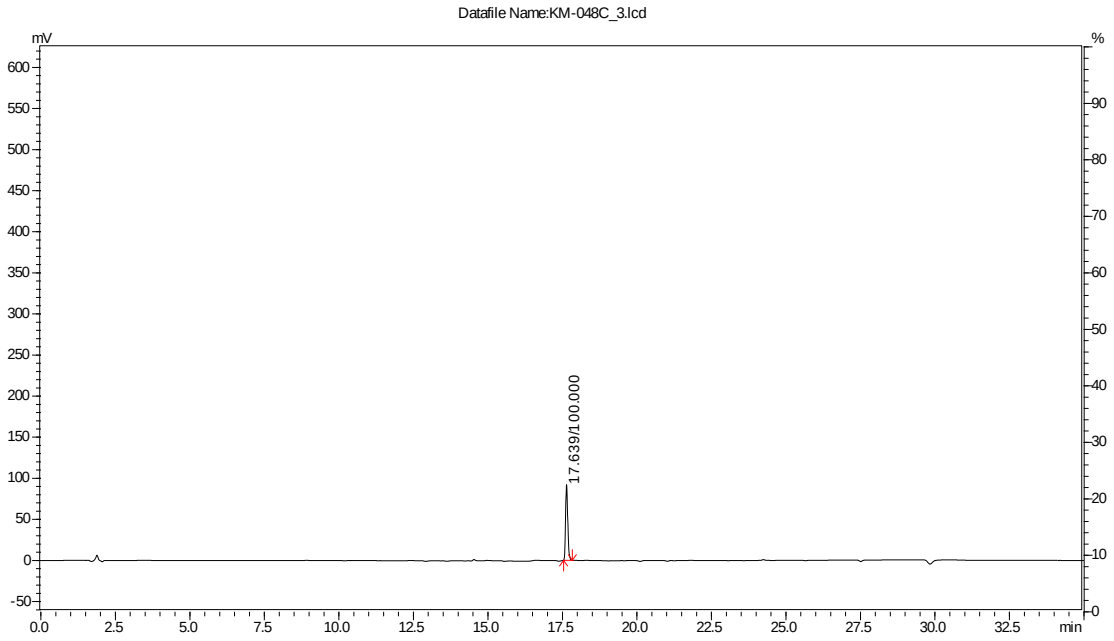
HPLC chromatogram of 12



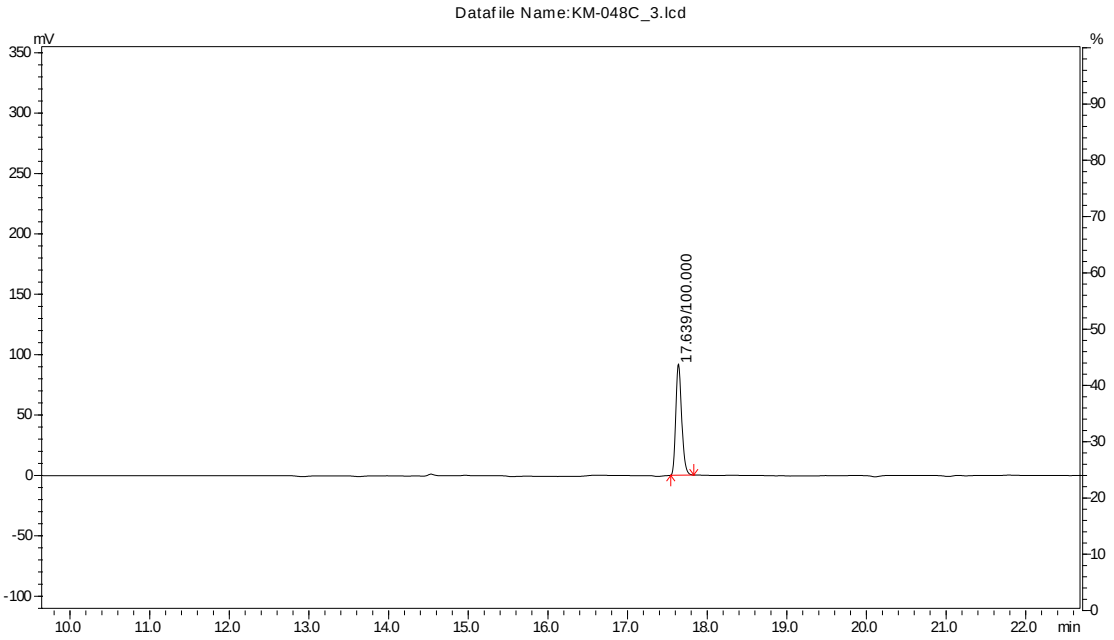
HPLC chromatogram of 12, gradient zoom



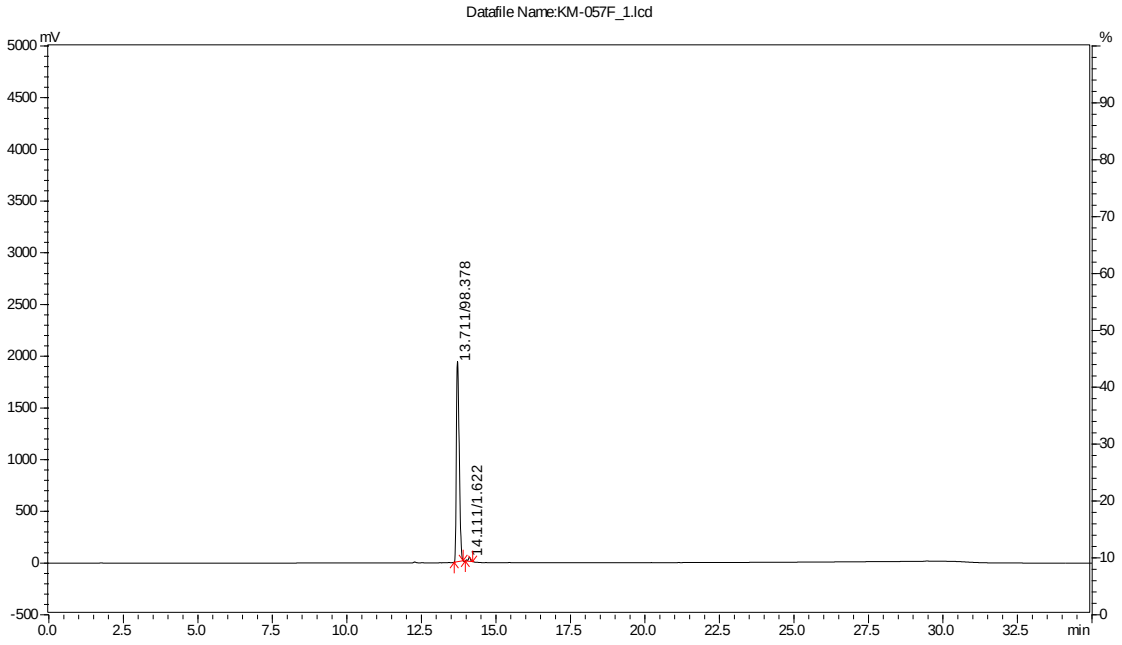
HPLC chromatogram of 15



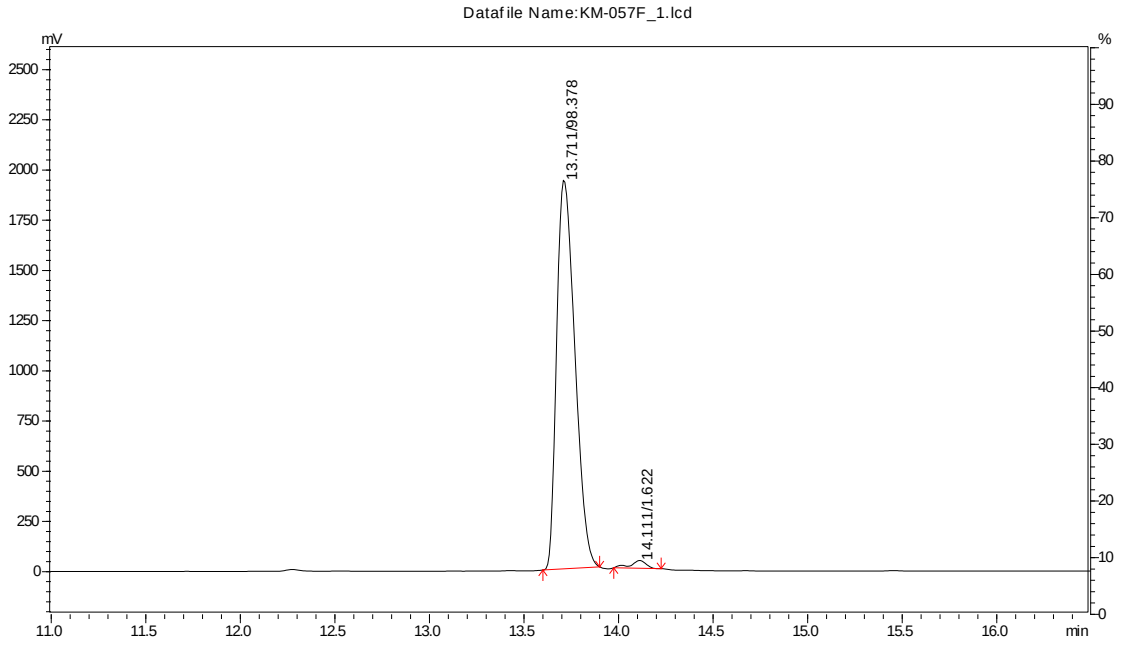
HPLC chromatogram of 15, gradient zoom



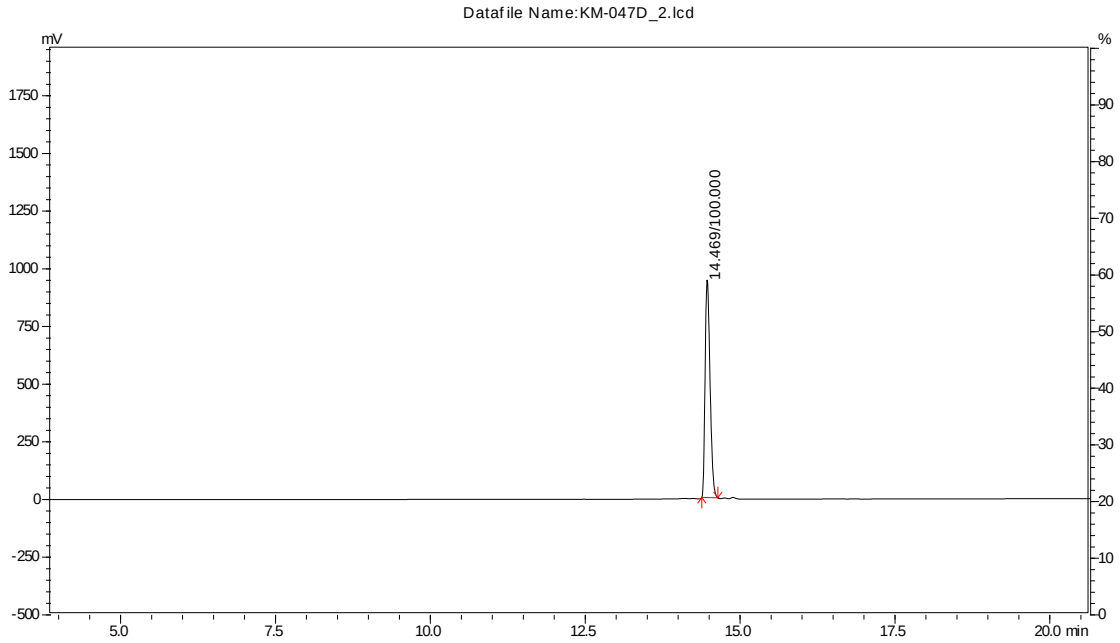
HPLC chromatogram of 19



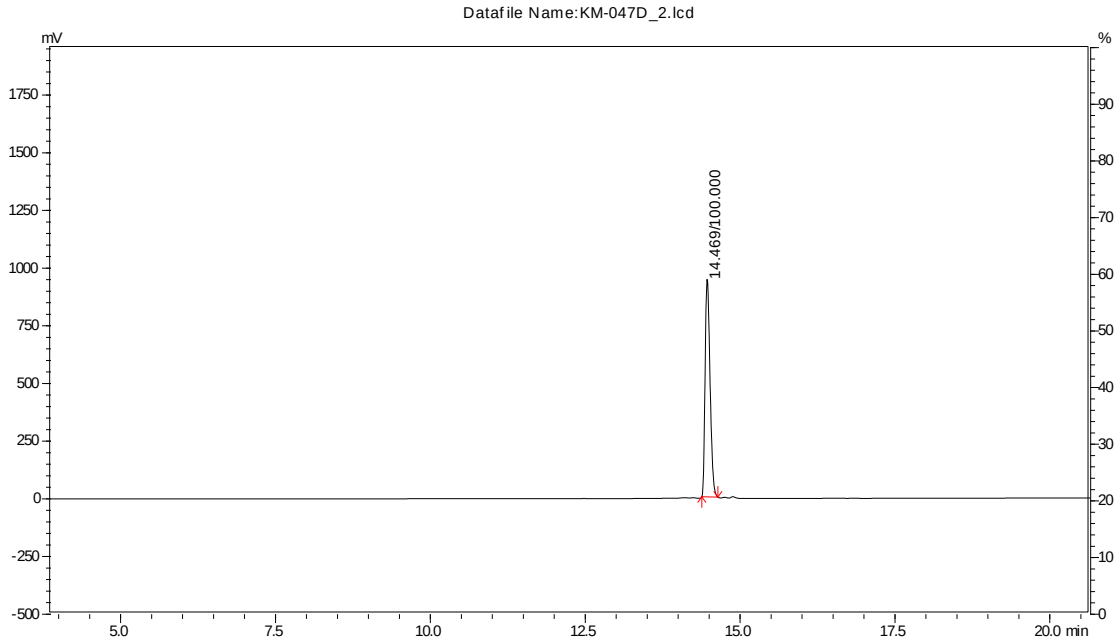
HPLC chromatogram of 19, gradient zoom



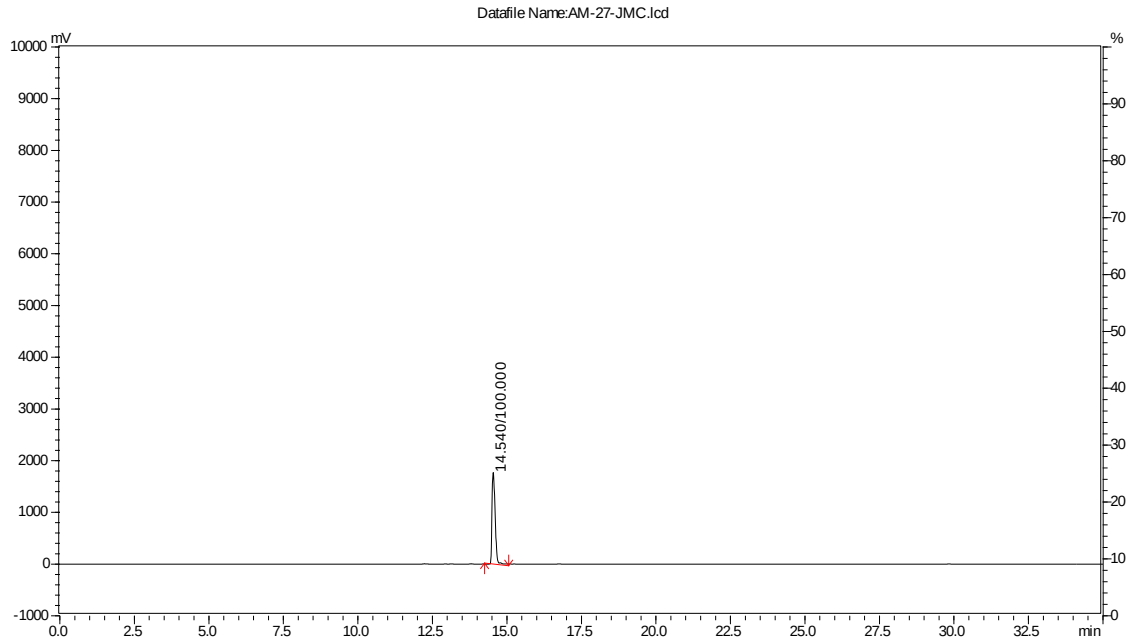
HPLC chromatogram of 23



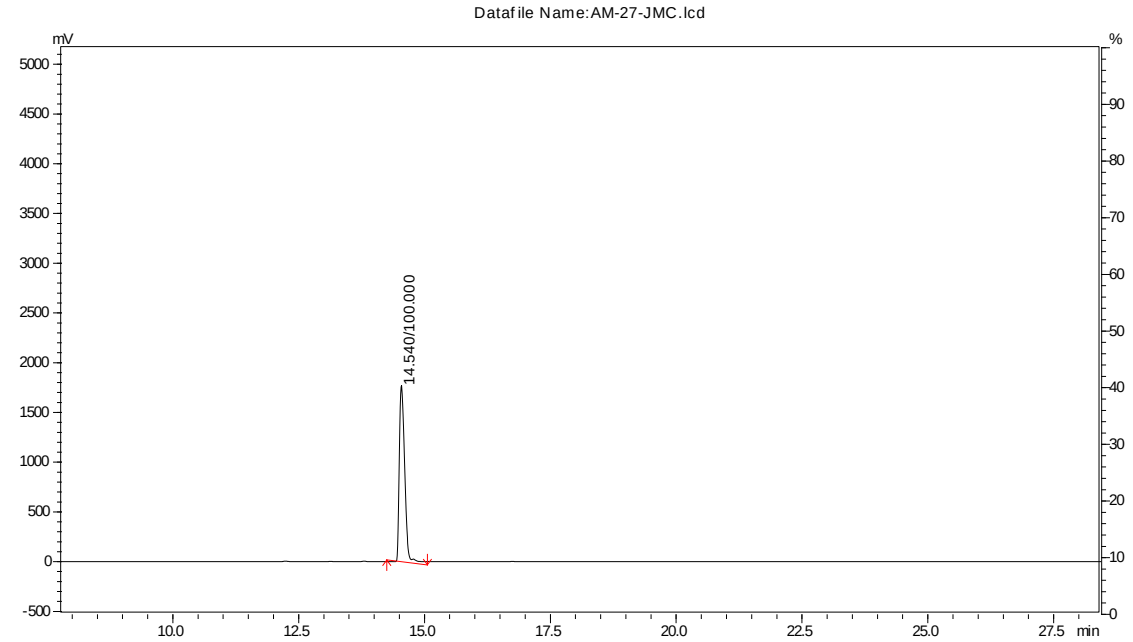
HPLC chromatogram of 23, gradient zoom



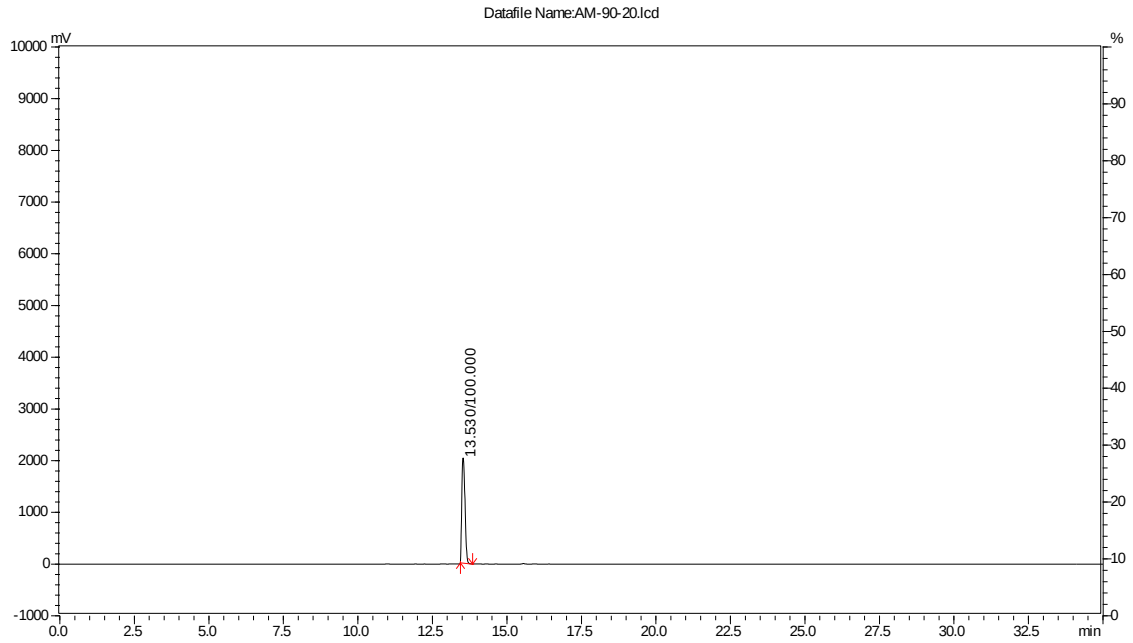
HPLC chromatogram of 27



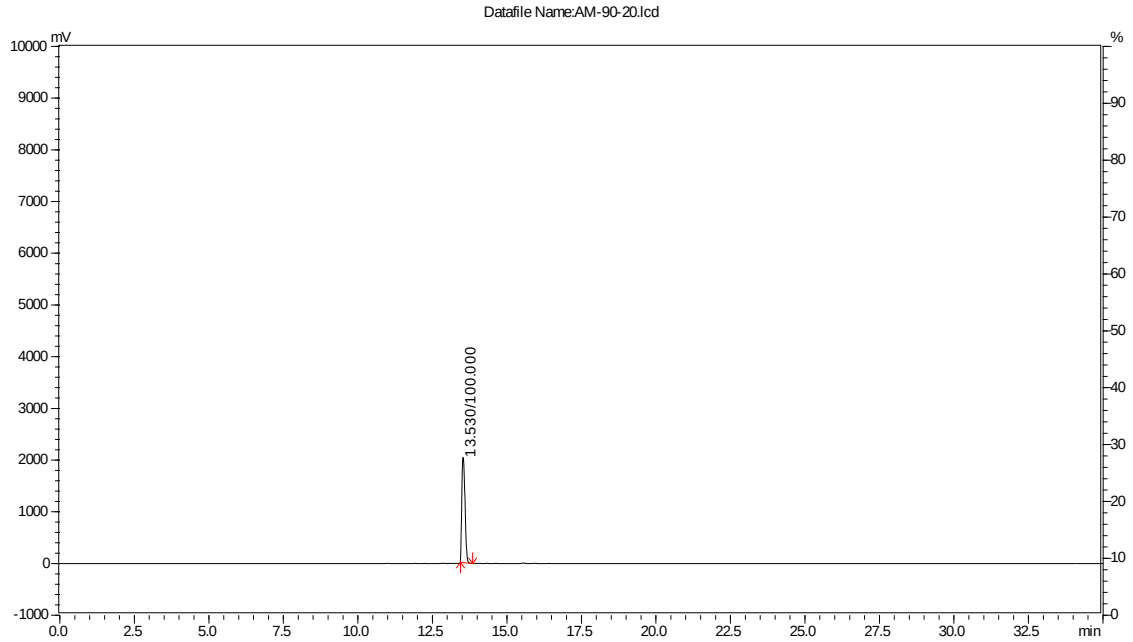
HPLC chromatogram of 27, gradient zoom



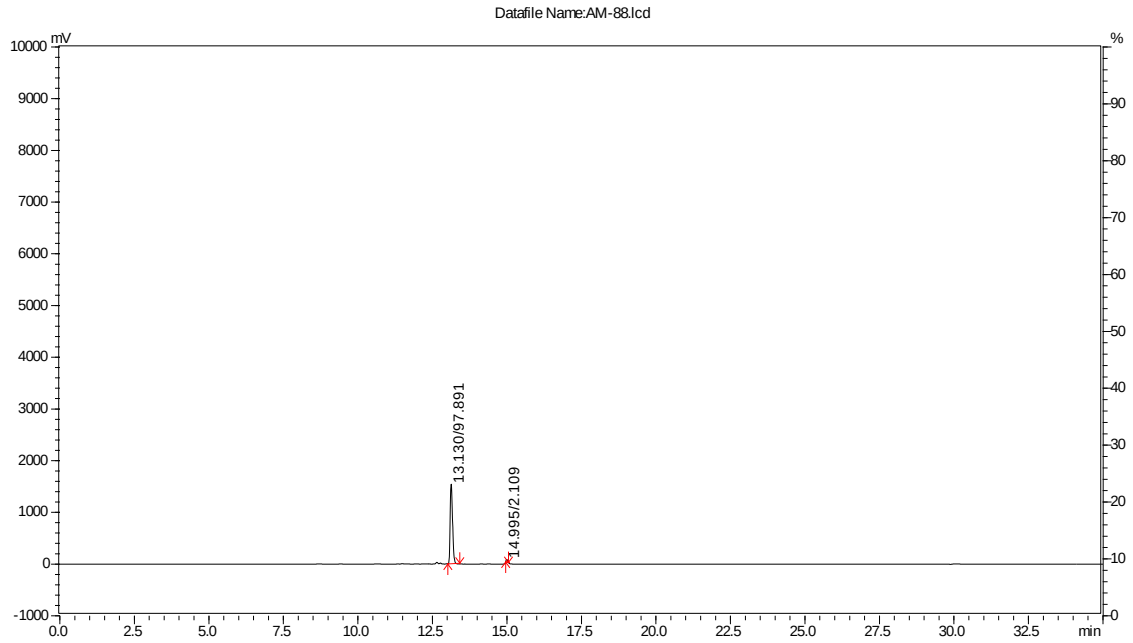
HPLC chromatogram of 28



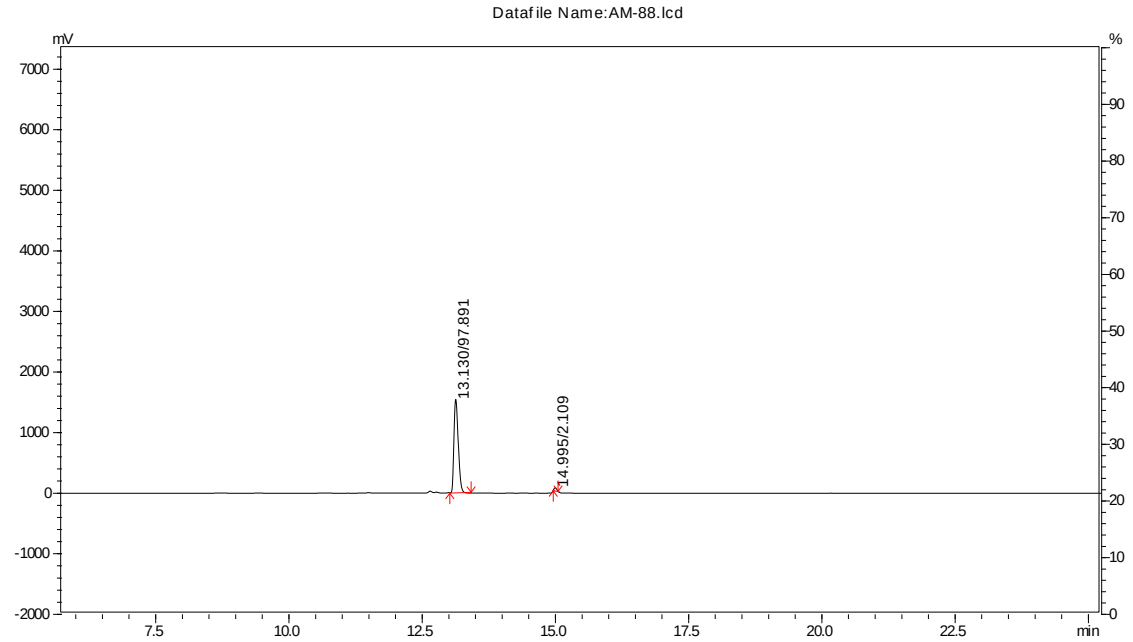
HPLC chromatogram of 28, gradient zoom



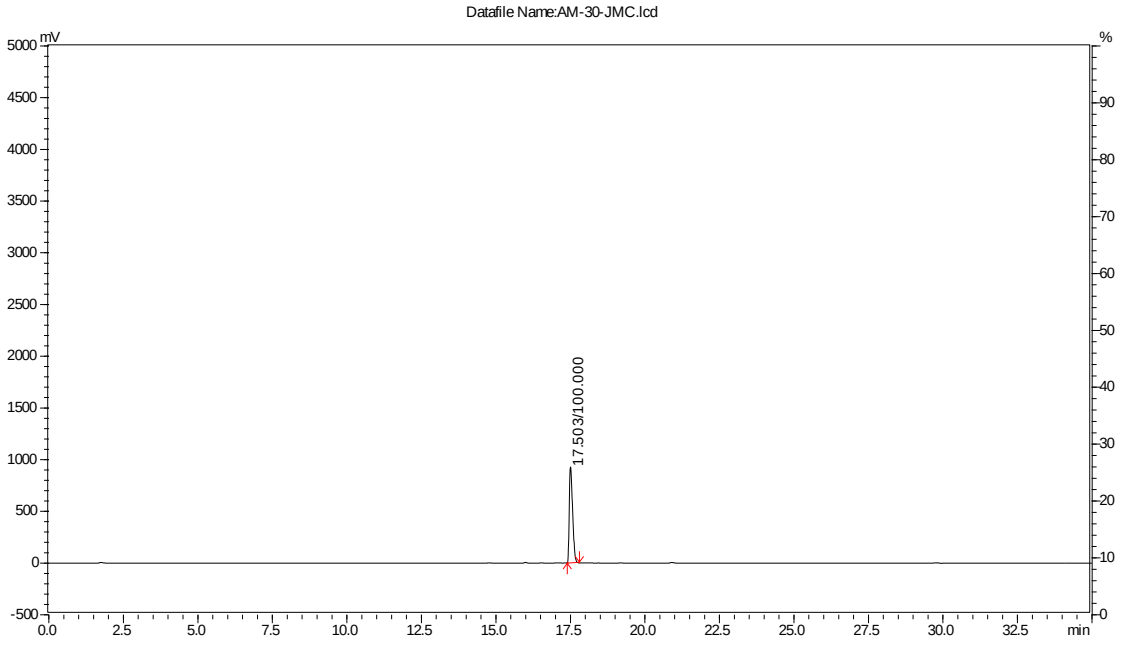
HPLC chromatogram of 29



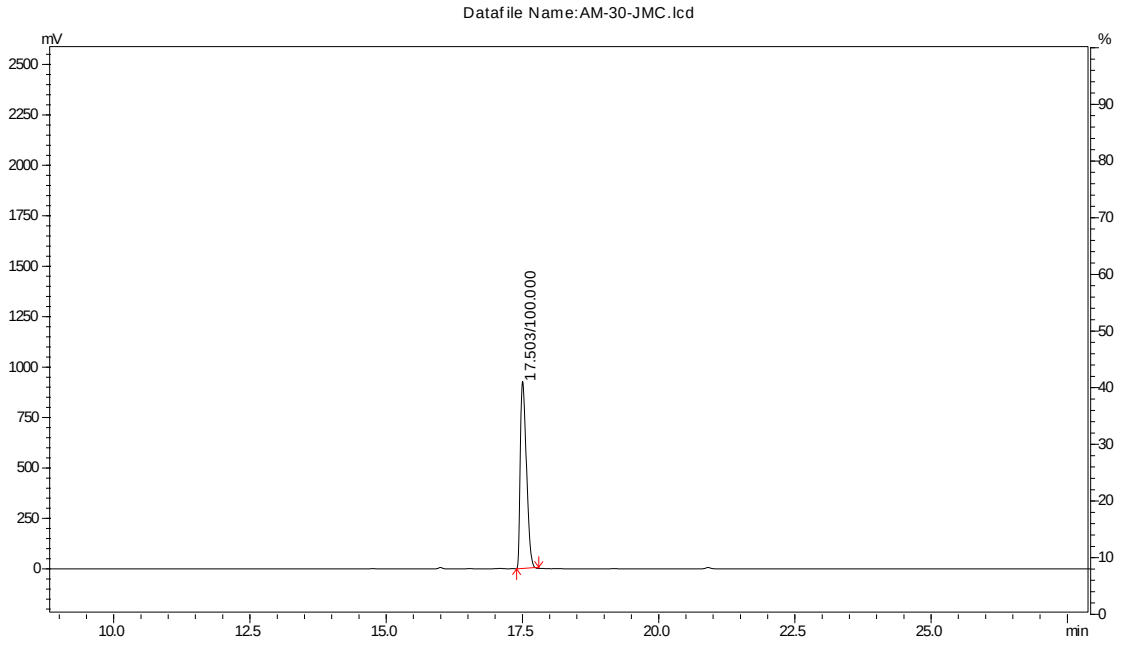
HPLC of chromatogram 29, gradient zoom



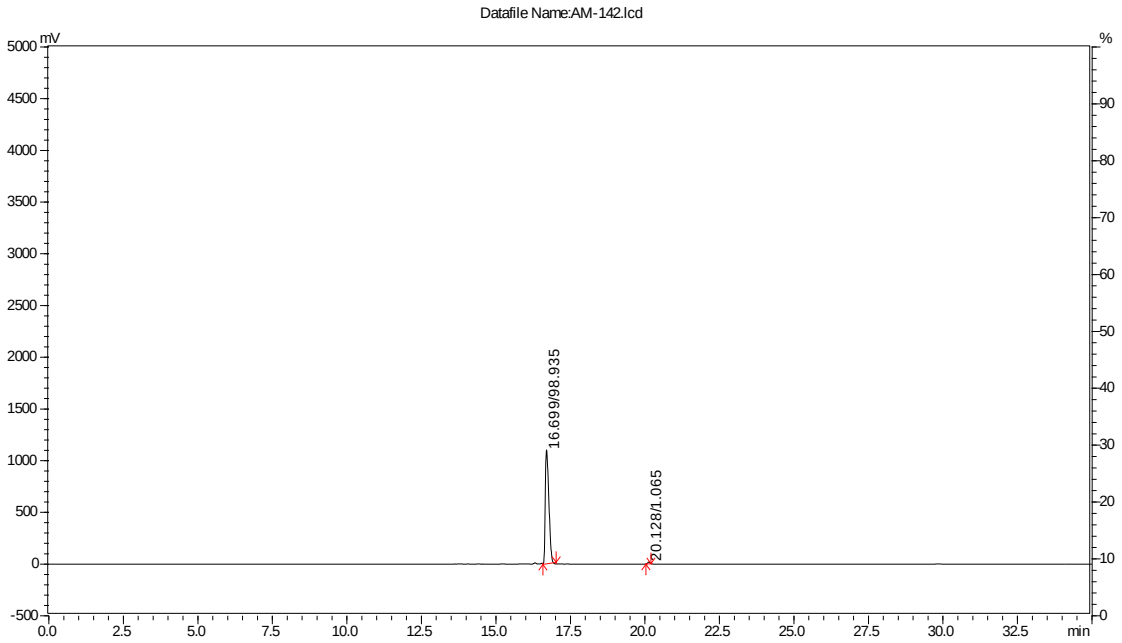
HPLC chromatogram of 30



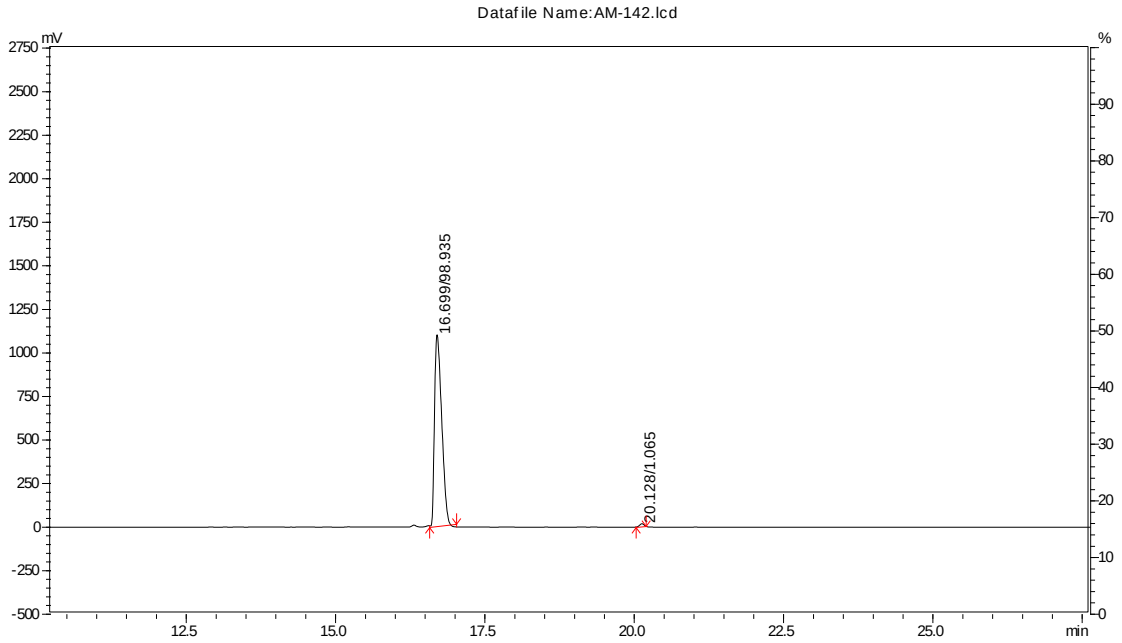
HPLC Chromatogram of 30, gradient zoom



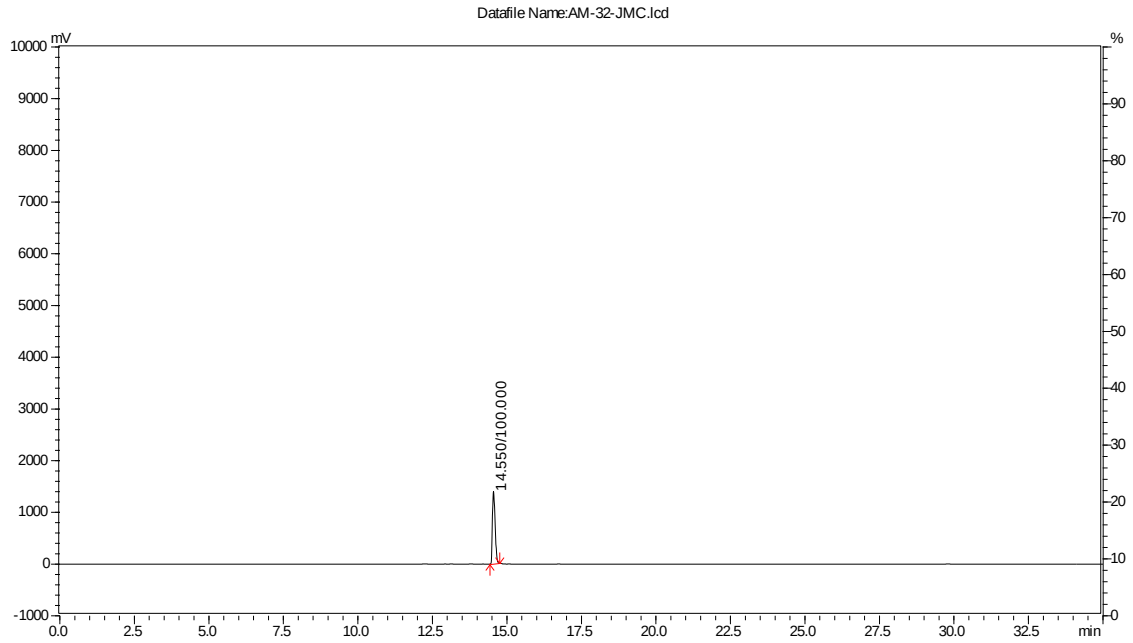
HPLC chromatogram of 31



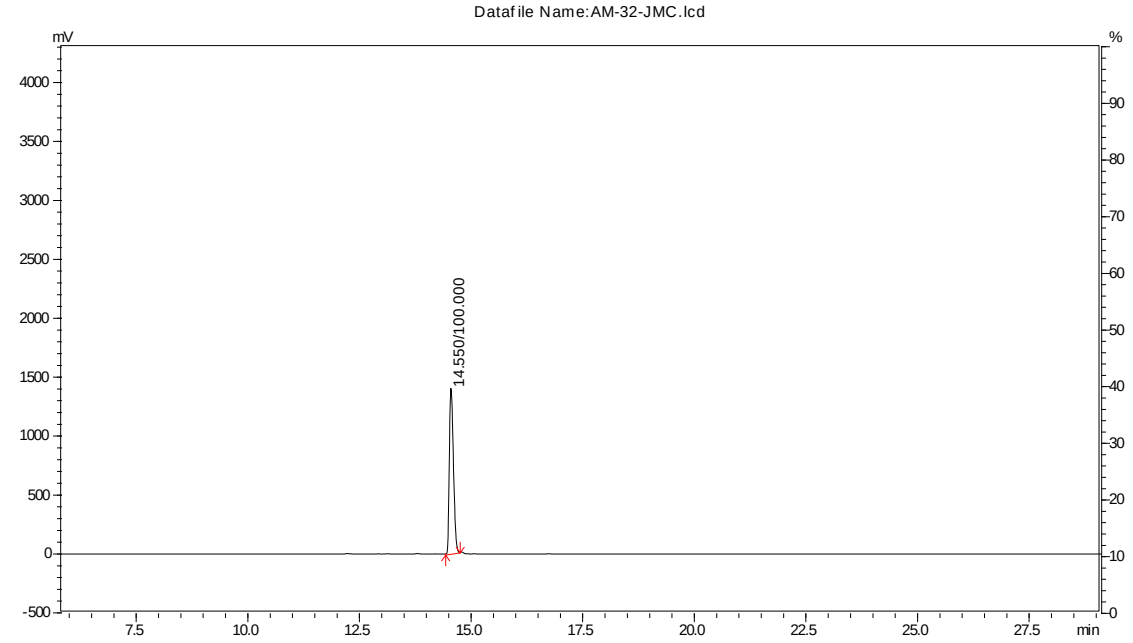
HPLC chromatogram of 31, gradient zoom



HPLC Chromatogram of 32



HPLC chromatogram of 32, gradient zoom



HPLC Purity and Smiles:

Analogue	HPLC Purity (%)	Smiles
1	99.7	[O-]C(=O)c1ccc(-c2ccnc3c2cc([nH]3)-c4c(OC)ccc(C[NH+](CC)CC)c4)cc1C(C)C
8a	97.7	[O-]C(=O)c1ccc(-c2ccnc3c2cc([nH]3)-c4c(OC)ccc(C[NH+](C)C)c4)cc1C(C)C
8b	100	[O-]C(=O)c1ccc(-c2ccnc3c2cc([nH]3)-c4c(OC)ccc(C[NH+]5CCCC5)c4)cc1C(C)C
8c	95	[O-]C(=O)c1ccc(-c2ccnc3c2cc([nH]3)-c4c(OC)ccc(C[NH+]5CCOCC5)c4)cc1C(C)C
9	100	CC(C)C1=CC(C2=C3C(NC(C4=C(OC)C=CC(CN(CC)CC)=C4)=C3)=NC=C2)=CC=C1C(OCC)=O
12	100	[O-]C(=O)c1ccc(-c2ccnc3c2cc([nH]3)-c4cc(C[NH3+])ccc4OC)cc1C(C)C
15	100	[O-]C(=O)c1ccc(-c2ccnc3c2cc([nH]3)-c4ccccc4OC)cc1C(C)C
19	98.4	Oc1ccc(C[NH+](CC)CC)cc1-c2cc3c([nH]2)nccc3-c4ccc(c(C(C)C)c4)C([O-])=O
23	100	[O-]C(=O)c1ccc(-c2ccnc3c2cc([nH]3)-c4cccc(C[NH+](CC)CC)c4)cc1C(C)C
27	100	CC(C)C1=CC(C2=C3C(NC(C4=CC=CC(CN(CC)CC)=C4OC)=C3)=NC=C2)=CC=C1C(O)=O
28	100	CC1=CC(C2=C3C(NC(C4=C(OC)C=CC(CN(CC)CC)=C4)=C3)=NC=C2)=CC=C1C(O)=O
29	97.9	CCN(CC)CC1=CC(C2=CC3=C(C4=CC=C(C(O)=O)C=C4)C=CN=C3N2)=C(OC)C=C1
30	100	CC(C)C1=CC(C2=C3C(NC(C4=C(OC)C=CC(CN(CC)CC)=C4)=C3)=NC=C2)=CC=C1C5=NN=NN5
31	98.9	CC(C)C1=CC(C2=C3C(NC(C4=C(OC)C=CC(CN(CC)CC)=C4)=C3)=NC=C2)=CC=C1
32	100	CC(C)C(C(C(O)=O)=C1)=CC=C1C2=C3C(NC(C4=C(OC)C=CC(CN(CC)CC)=C4)=C3)=NC=C2

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