Antibiofilm Activity of Quinazoline Derivatives against *Mycobacterium smegmatis*

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Biological assay protocols and data

Biofilm inhibition assay. *M. smegmatis* was grown in 7H9 (ADC, 0.5% Tween 80) for 48 h and this culture was used to inoculate Difco M9 minimal salts media (OD600=0.01) supplemented with glucose (20% Sigma-Aldrich, 2 mL per 100 mL), $MgSO_4$ (1 M, 200 µL per 100 mL), and $CaCl_2$ (1 M, 10 µL per 100 mL). 100 µL per well of the subculture was aliquoted into the center two columns of a 96-well PVC microtiter plate. Columns 1 and 12 served as negative control wells. Then compound from DMSO stock solutions was added to aliquots of the subculture to give the desired concentration to be tested and aliquoted (100 µL per well) into the remaining wells of the 96-well PVC microtiter plate. Sample plates were then wrapped in GLAD Press n'Seal and were incubated under stationary conditions for 48 h at 37 °C. After incubation, the media was discarded, and the plates were washed thoroughly with water. The wells were stained with 110 µL of a 0.1% solution of crystal violet and then left at ambient temperature for 30 min. Crystal violet solution was discarded and plates washed thoroughly with water. 200 µL of 95% ethanol was added to each well, and the plates left covered at ambient temperature for 10 min. 125 µL of the ethanol solution was transferred to a polystyrene microtiter plate. Biofilm inhibition was quantified by measuring the OD_{540} of each well. The values obtained from the two negative control lanes were subtracted from the OD_{540} of the other columns.

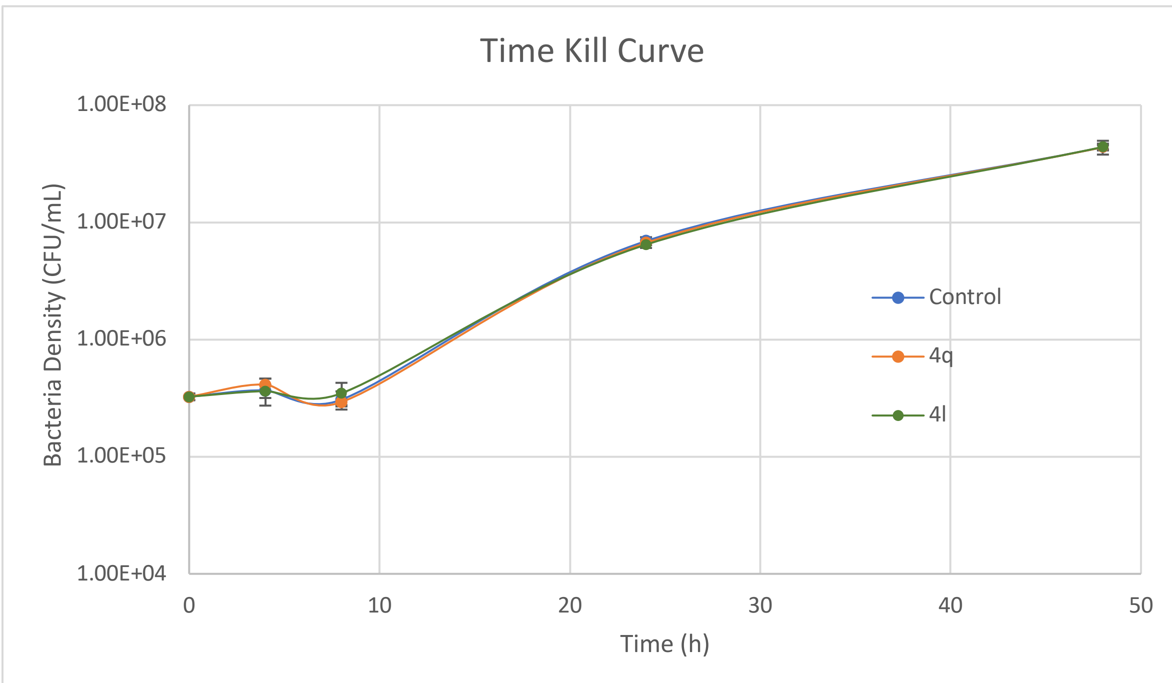
Hemolysis Assay. Was performed on mechanically difibrinated sheep blood (Hemostat Laboratories: DSB100). Difibrinated blood (1.5 mL) was placed into an Eppendorf tube and centrifuged for 10 min at 10,000 rpm. The supernatant was removed and then the cells were resuspended in 1 mL of phosphate-buffered saline (PBS). The suspension was centrifuged as before, the supernatant removed, and the cells were resuspended two more times. The final cell suspension was diluted 10-fold. Compound was added from a DMSO stock solution to aliquots of the 10-fold suspension dilution of blood to give the desired concentrations to be tested. Triton X (1%) was used as a positive control (100% lysis). PBS was used as a negative control (zero hemolysis). Samples were placed in an incubator at 37 °C with shaking at 200 rpm for 1 h. After 1 h, the samples were centrifuged for 10 min at 10,000 rpm. The resulting supernatant was diluted by a factor of 40 in distilled water. The absorbance of the supernatant was then measured with a UV spectrometer at 540 nm.

Time kill curves. *M. smegmatis* was grown in 7H9 (ADC, 0.5% Tween80) for 48 h, and this culture was used to inoculate Difco M9 minimal salts media (OD600=0.01). Aliquots (3mL) were placed in culture tubes and dosed with compound from stock solutions in DMSO. Untreated inoculated media served as the control. Tubes were incubated at 37 °C with shaking. Samples were taken at 4, 8, 24, and 48 h time points, serially diluted in fresh M9, and plated on 7H10 plates. Plates were incubated at 37 °C for 48 h, and the number of colonies were counted.

Bacterial strains. The *Mycobacterium smegmatis* strain (ATCC 700084, mc_2155) was obtained from ATCC (Manassas, VA). Stock cultures were stored in glycerol stock media (25% v/v glycerol and 7H9, ADC, Tween 80) and maintained at -80 °C. The strain was maintained and cultured in

7H9 or on 7H10 agar (OADC, glycerol) until utilized in the assays outlined above. All assays were run in duplicate and repeated at least two separate times. All compounds were dissolved as their HCl salts in molecular biology grade DMSO as 10 or 100 mM stock solutions and stored at -20 °C.

Figure S1. Time kill curve for compounds **4l** and **4q** against *M. smegmatis*. Both compounds were tested at 60 µM.



Chemistry experimental and characterization

General remarks. All reagents used for chemical synthesis were purchased from commercially available sources without further purification. Flash chromatography was performed using 60 Å mesh standard grade silica gel from Sorbetch. NMR solvents were obtained from Cambridge Isotope Labs and used as is. All ^{1}H NMR (300 or 500 MHz) were recorded at 25°C on Varian Mercury spectrometers or a (700 MHz) Bruker Avance spectrometer. All ^{13}C NMR (101, 126, or 151 MHz) spectra were recorded at 25°C on Varian Mercury spectrometers or a (175 MHz) Bruker Avance spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to the respective NMR solvent; coupling constants (J) are in hertz (Hz). Abbreviations used are s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; p, pentet; h, hextet; m, multiplet. All high-resolution mass spectrometry measurements were made in the Molecular Education, Technology, and Research Innovation Center (METRIC) at NC State University. Infrared spectra were obtained on a FT/IR-4100 spectrophotometer (νmax in cm^{-1}). UV absorbance was recorded on a Genesys 10 scanning UV/visible spectrophotometer (λmax in nm).

Procedure for 2-amino-6-nitroquinazoline formation (**2**). Commercially available guanidine carbonate (1g, 8.28 mmol, 1.4 eq) and 2-fluoro-5-nitrobenzaldehyde (1 g, 5.91 mmol, 1 eq) were dissolved in acetonitrile (100 mL) over molecular sieves. K_2CO_3 (1.14 g, 8.28 mmol, 1.4 eq) was added and the reaction was heated to 72 °C for 16 h. The molecular sieves were removed, and the reaction mixture was concentrated and then dissolved in ethyl acetate. The mixture was filtered, then the filtrate was washed with sat. $NaHCO_3$ (20 mL x 2) and brine (20 mL x 2) and dried over Na_2SO_4. The product was purified by flash chromatography (0.5-3% MeOH/NH_3: DCM). Following concentration, this afforded 2-amino-6-nitroquinazoline (**2**) as an orange solid. Yield 40% (450 mg, 2.37 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.82 (d, J = 2.6 Hz, 1H), 8.35 (dd, J = 9.3, 2.7 Hz, 1H), 7.62 (s, 2H), 7.51 – 7.41 (m, 1H) ppm; ^{13}C NMR (176 MHz, DMSO) δ 165.31, 162.92, 155.64, 141.21, 127.91, 126.17, 126.12, 117.94 ppm.; IR ν_{max} (cm^{-1}): 3455, 3313, 3081, 1649, 1618, 1471, 1384; UV/Vis (λ_{max} nm): 310; HRMS (ESI) calcd for $C_8H_6N_4O_2$ $[M+H]^+$: 191.0564, found 191.0565.

Procedure for 2,6-diaminoquinazoline formation (**3**). 2-amino-6-nitroquinazoline (1 g, 5.26 mmol, 1eq), Pd/C (0.06 g, 0.53 mmol, 0.1 eq), and ethanol (20 mL) were combined over nitrogen gas. The reaction was put under hydrogen gas and allowed to stir at room temperature for 8 h. The reaction was filtered over celite and washed with ethyl acetate (20 mL x 2). The orange solid was isolated without further purification to yield, 2,6-diaminoquinazoline (**3**). Yield 93% (780 mg, 4.87 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.35 (s, 1H), 7.79 – 7.67 (m, 2H), 7.29 – 7.27 (m, 1H) , 6.80 (s, 2H), 5.74 (s, 2H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.97, 161.16, 147.77, 146.12, 128.54, 127.71, 123.25, 107.93 ppm; IR ν_{max} (cm^{-1}): 3438, 3425, 3400, 3300, 3161, 1617, 1586; UV/Vis (λ_{max} nm): 290; HRMS (ESI) calcd for $C_8H_8N_4$ $[M+H]^+$: 161.0822, found 161.0825.

Amide containing derivatives (4a-x)

N-(2-aminoquinazolin-6-yl)acetamide (**4a**): Compound **3** (87 mg, 0.54 mmol, 1 eq) was dissolved in anhydrous THF (2 mL) under nitrogen gas and cooled to 0 °C. K_3PO_4 (0.14 g, 0.68 mmol, 1.25 eq) was added and the reaction was stirred for 20 minutes. Acetyl chloride (0.04 mL, 0.54 mmol, 1 eq) was then added dropwise and the reaction stirred for 10 h at room temperature. The reaction was quenched with water/ethyl acetate. The organic material was extracted with ethyl acetate (20 mL x 3). The organic fractions were combined and dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by flash chromatography (0.5-3% MeOH/NH_3:DCM) to afford compound **4a** as a yellow solid. Yield 33% (37 mg, 0.18 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.07 (s, 1H), 9.03 (s, 1H), 8.16 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 9.1, 2.1 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 6.69 (s, 2H), 2.05 (s, 3H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 168.79, 162.22, 160.80, 149.00, 133.84, 128.22, 125.47, 119.74, 115.69, 24.40 ppm; IR ν_{max} (cm^{-1}): 3253, 3063, 1659, 1505; UV/Vis (λ_{max} nm): 286; HRMS (ESI) calcd for $C_{10}H_{10}N_4O$ [M+H]$^+$: 203.0927, found 203.0931.

The remaining amide derivatives (**4b-x**) followed the same general procedure outlined for the synthesis of **4a** with substitution of the appropriate acid chloride:

N-(2-aminoquinazolin-6-yl)propanamide (**4b**): Propionyl chloride (0.05 mL, 0.52 mmol, 1 eq). Afforded compound **4b** as a yellow solid. Yield 46% (51 mg, 0.24 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.00 (s, 1H), 9.02 (s, 1H), 8.18 (d, J = 2.4 Hz, 1H), 7.69 (dd, J = 9.0, 2.4 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.68 (s, 2H), 2.32 (q, J = 7.6 Hz, 2H), 1.08 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 172.48, 162.18, 160.79, 148.97, 133.88, 128.28, 125.44, 119.75, 115.73, 29.94, 10.20 ppm; IR ν_{max} (cm^{-1}): 3250, 3053, 1660, 1541; UV/Vis (λ_{max} nm): 290; HRMS (ESI) calcd for $C_{11}H_{12}N_4O$ [M+H]$^+$: 217.1084, found 217.1087.

N-(2-aminoquinazolin-6-yl)butanamide (**4c**): Butanoyl chloride (0.06 mL, 0.53 mmol, 1 eq). Afforded compound **4c** as a light yellow solid. Yield 58% (71 mg, 0.31 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.00 (s, 1H), 9.03 (s, 1H), 8.20 (d, J = 2.4 Hz, 1H), 7.69 (dd, J = 9.1, 2.5 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 6.71 (s, 2H), 2.29 (t, J = 7.4 Hz, 2H), 1.61 (h, J = 7.4 Hz, 2H), 0.90 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 171.66, 162.19, 160.79, 148.98, 133.83, 128.31, 125.43, 119.74, 115.79, 31.15, 19.09, 14.11 ppm; IR ν_{max} (cm^{-1}): 3233, 3106, 1653, 1543; UV/Vis (λ_{max} nm): 286; HRMS (ESI) calcd for $C_{12}H_{14}N_4O$ [M+H]$^+$: 231.1240, found 231.1245.

N-(2-aminoquinazolin-6-yl)pentanamide (**4d**): Pentanoyl chloride (0.06 mL, 0.53 mmol, 1 eq). Afforded compound **4d** as a yellow solid. Yield 61% (80 mg, 0.33 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.00 (s, 1H), 9.02 (s, 1H), 8.19 (d, J = 2.3 Hz, 1H), 7.68 (dd, J = 9.1, 2.3 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.69 (s, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.57 (p, J = 7.5 Hz, 2H), 1.32-1.24 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 171.81, 162.20, 160.78, 148.98, 133.85, 128.32, 125.42, 119.75, 115.79, 36.55, 27.78, 22.32, 14.22 ppm; IR ν_{max}

(cm^{-1}): 3250, 3083, 1655, 1509; UV/Vis (λ_{max} nm): 290; HRMS (ESI) calcd for $C_{13}H_{16}N_4O$ $[M+H]^+$: 245.1397, found 245.1402.

N-(2-aminoquinazolin-6-yl)hexanamide (**4e**): Hexanoyl chloride (0.17 mL, 1.25 mmol, 1eq). Afforded compound **4e** as a yellow solid. Yield 48% (156 mg, 0.60 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.00 (s, 1H), 9.01 (s, 1H), 8.18 (d, J = 2.4 Hz, 1H), 7.72 – 7.64 (m, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.67 (s, 2H), 2.30 (t, J = 7.4 Hz, 2H), 1.60 (p, J = 7.3 Hz, 2H), 1.32 – 1.26 (m, 4H), 0.86 (t, 3H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.41, 169.74, 155.09, 137.12, 135.57, 130.55, 118.77, 117.93, 117.19, 36.76, 31.72, 25.53, 22.55, 14.42 ppm; IR ν_{max} (cm^{-1}): 3208, 3038, 1662, 1539; UV/Vis (λ_{max} nm): 292; HRMS (ESI) calcd for $C_{14}H_{18}N_4O$ $[M+H]^+$: 259.1553, found 259.1552.

N-(2-aminoquinazolin-6-yl)heptanamide (**4f**): Heptanoyl chloride (0.11 mL, 0.69 mmol, 1 eq). Afforded compound **4f** as a yellow solid. Yield 44% (83 mg, 0.31 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.99 (s, 1H), 9.02 (s, 1H), 8.19 (d, J = 2.4 Hz, 1H), 7.68 (dd, J = 9.1, 2.4 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.69 (s, 2H), 2.29 (t, J = 7.4 Hz, 2H), 1.57 (p, J = 7.2 Hz, 2H), 1.27 – 1.21 (m, 6H), 0.83 (t, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.75, 162.17, 160.76, 148.94, 133.82, 128.24, 125.40, 119.71, 115.70, 36.80, 31.51, 28.81, 25.58, 22.46, 14.39 ppm; IR ν_{max} (cm^{-1}): 3268, 3105, 1670, 1515; UV/Vis (λ_{max} nm): 290; HRMS (ESI) calcd for $C_{15}H_{20}N_4O$ $[M+H]^+$: 273.1710, found 273.1710.

N-(2-aminoquinazolin-6-yl)octanamide (**4g**): Octanoyl chloride (0.13 mL, 0.75 mmol, 1 eq). Afforded compound **4g** as a yellow solid. Yield 42% (90 mg, 0.31 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.00 (s, 1H), 9.02 (s, 1H), 8.19 (d, J = 2.3 Hz, 1H), 7.68 (dd, J = 9.1, 2.4 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.69 (s, 2H), 2.29 (t, J = 7.4 Hz, 2H), 1.58 (p, J = 6.9 Hz, 2H), 1.25 – 1.18 (m, 8H), 0.82 (t, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.75, 162.16, 160.76, 148.94, 133.83, 128.24, 125.38, 119.71, 115.70, 36.80, 31.64, 29.11, 28.96, 25.63, 22.53, 14.38 ppm; IR ν_{max} (cm^{-1}): 3323, 3253, 3148, 3063, 1666, 1598, 1541; UV/Vis (λ_{max} nm): 290; HRMS (ESI) calcd for $C_{16}H_{22}N_4O$ $[M+H]^+$: 287.1866, found 287.1867.

N-(2-aminoquinazolin-6-yl)nonanamide (**4h**): Nonanoyl chloride (0.26 mL, 1.44 mmol, 1eq). Afforded compound **4h** as an orange solid. Yield 11% (47 mg, 0.16 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.99 (s, 1H), 9.01 (s, 1H), 8.18 (d, J = 2.4 Hz, 1H), 7.68 (dd, J = 9.1, 2.5 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.66 (s, 2H), 2.30 (t, J = 7.4 Hz, 2H), 1.64 – 1.52 (m, 2H), 1.31 – 1.22 (m, 10H), 0.83 (t, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.41, 169.74, 155.09, 137.12, 135.57, 130.55, 118.77, 117.93, 117.19, 36.76, 31.72, 29.25, 29.12, 29.07, 25.53, 22.55, 14.42 ppm; IR ν_{max} (cm^{-1}): 3255, 3125, 3050, 1666, 1541; UV/Vis (λ_{max} nm): 292; HRMS (ESI) calcd for $C_{17}H_{24}N_4O$ $[M+H]^+$: 301.2023, found 301.2020.

N-(2-aminoquinazolin-6-yl)benzamide (**4i**): Benzoyl chloride (0.07 mL, 0.62 mmol, 1 eq). Afforded compound **4i** as a yellow solid. Yield 40% (66 mg, 0.25 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 9.08 (s, 1H), 8.34 (d, J = 2.4 Hz, 1H), 7.97 (d, J = 6.6 Hz, 2H), 7.93 (d, J = 2.4 Hz, 1H), 7.56 – 7.51 (m, 3H), 7.43 (d, J = 9.1 Hz, 1H), 6.77 (s, 2H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.01, 162.36, 160.95, 149.36, 135.25, 133.61, 132.07, 129.36, 128.88, 128.09, 125.32, 119.63, 117.36, ppm; IR ν_{max} (cm^{-1}): 3320, 3161, 1655, 1541; UV/Vis (λ_{max} nm): 292; HRMS (ESI) calcd for $C_{15}H_{12}N_4O$ $[M+H]^+$: 265.1084, found 265.1084.

N-(2-aminoquinazolin-6-yl)-4-methylbenzamide (**4j**): 4-tolyoyl chloride (0.08 mL, 0.59 mmol, 1 eq). Afforded compound **4j** as a light yellow solid. Yield 36% (59 mg, 0.21 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.09 (s, 1H), 8.35 (d, J = 2.4 Hz, 1H), 7.96 (dd, J = 9.1, 2.5 Hz, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 9.1 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 6.79 (s 2H), 2.37 (s, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.87, 162.35, 160.89, 149.27, 142.12, 133.68, 132.30, 129.46, 129.41, 128.11, 125.26, 119.64, 117.38, 21.46 ppm; IR ν_{max} (cm^{-1}): 3275, 3108, 1660, 1542; UV/Vis (λ_{max} nm): 290; HRMS (ESI) calcd for $C_{16}H_{14}N_4O$ $[M+H]^+$: 279.1240, found 279.1240.

N-(2-aminoquinazolin-6-yl)-4-ethylbenzamide (**4k**): 4-ethyl benzoyl chloride (0.09 mL, 0.59 mmol, 1 eq). Afforded compound **4k** as a light yellow solid. Yield 53% (91 mg, 0.31 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.09 (s, 1H), 8.35 (s, 1H), 8.03 – 7.90 (m, 3H), 7.44 (d, J = 9.1 Hz, 1H), 7.36 (d, J = 6.4 Hz, 2H), 6.78 (s, 2H), 2.66 (q, J = 8.1 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.90, 162.33, 160.93, 149.30, 148.23, 133.71, 132.68, 129.37, 128.23, 128.21, 125.28, 119.65, 117.28, 28.54, 15.86 ppm; IR ν_{max} (cm^{-1}): 3300, 3120, 1671, 1593, 1515; UV/Vis (λ_{max} nm): 292; HRMS (ESI) calcd for $C_{17}H_{16}N_4O$ $[M+H]^+$: 293.1397, found 293.1397.

N-(2-aminoquinazolin-6-yl)-4-propylbenzamide (**4l**): 4-propyl benzoyl chloride (0.21 mL, 1.25 mmol, 1eq). Afforded compound **4l** as an orange solid. Yield 8% (29 mg, 0.09 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.31 (s, 1H), 9.07 (s, 1H), 8.32 (d, J = 2.4 Hz, 1H), 7.94 – 7.87 (m, 3H), 7.41 (d, J = 9.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 6.72 (s, 2H), 2.62 (t, J = 7.6 Hz, 2H), 1.61 (h, J = 7.4 Hz, 2H), 0.89 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 169.83, 166.26, 155.19, 147.04, 137.02, 132.17, 131.75, 129.80, 128.89, 128.34, 118.72, 118.70, 117.83, 37.54, 24.35, 14.07 ppm; IR ν_{max} (cm^{-1}): 3288, 3080, 2930, 1671, 1594, 1516; UV/Vis (λ_{max} nm): 296; HRMS (ESI) calcd for $C_{18}H_{18}N_4O$ $[M+H]^+$: 307.1553, found 307.1553.

N-(2-aminoquinazolin-6-yl)-4-butylbenzamide (**4m**): 4-butyl benzoyl chloride (0.24 mL, 1.25 mmol, 1eq). Afforded compound **4m** as a yellow solid. Yield 50% (200 mg, 0.62 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.30 (s, 1H), 9.07 (s, 1H), 8.32 (d, J = 2.4 Hz, 1H), 7.98 – 7.88 (m, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 9.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 6.72 (s, 2H), 2.65 (t, J = 7.6 Hz, 2H), 1.57 (p, J = 7.6 Hz, 2H), 1.30 (h, J = 7.4 Hz, 2H), 0.89 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.89, 162.30, 160.91, 149.29, 146.84, 133.71, 132.67, 129.33, 128.74, 128.13, 125.27, 119.64, 117.22, 35.44, 31.53, 22.51, 14.40 ppm; IR ν_{max} (cm^{-1}): 3315, 3113, 2920, 1673, 1595, 1517; UV/Vis (λ_{max} nm): 294; HRMS (ESI) calcd for $C_{19}H_{20}N_4O$ [M+H]$^+$: 321.1710, found 321.1709.

N-(2-aminoquinazolin-6-yl)-4-pentylbenzamide (**4n**): 4-pentyl benzoyl chloride (0.38 mL, 1.87 mmol, 1eq). Afforded compound **4n** as an orange solid. Yield 8% (48 mg, 0.14 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.30 (s, 1H), 9.07 (s, 1H), 8.32 (d, *J* = 2.4 Hz, 1H), 7.93 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 9.1 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 6.71 (s, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 1.63 – 1.55 (m, 2H), 1.30 – 1.25 (m, 4H), 0.85 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 169.76, 166.25, 155.24, 147.28, 136.99, 132.13, 131.73, 128.83, 128.35, 118.71, 117.91, 35.43, 31.31, 30.86, 22.41, 14.40 ppm; IR ν_{max} (cm^{-1}): 3308, 3120, 2926, 1671, 1593, 1515; UV/Vis (λ_{max} nm): 294; HRMS (ESI) calcd for $C_{20}H_{22}N_4O$ [M+H]$^+$: 335.1866, found 335.1867.

N-(2-aminoquinazolin-6-yl)-4-hexylbenzamide (**4o**): 4-hexyl benzoyl chloride (0.27 mL, 1.25 mmol, 1eq). Afforded compound **4o** as a yellow solid. Yield 12% (50 mg, 0.14 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.30 (s, 1H), 9.07 (s, 1H), 8.33 (d, *J* = 2.3 Hz, 1H), 7.91 (dd, *J* = 15.7, 8.5 Hz, 3H), 7.42 (d, *J* = 9.0 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 2H), 6.73 (s, 2H), 2.62 (t, *J* = 7.7 Hz, 2H), 1.57 (p, *J* = 7.0 Hz, 2H), 1.30 – 1.22 (m, 6H), 0.84 (t, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.86, 162.28, 160.89, 149.27, 146.82, 133.69, 132.65, 129.31, 128.72, 128.12, 125.25, 119.62, 117.21, 35.43, 31.53, 31.15, 28.73, 22.51, 14.39 ppm; IR ν_{max} (cm^{-1}): 3295, 3125, 2924, 1671, 1591, 1514; UV/Vis (λ_{max} nm): 294; HRMS (ESI) calcd for $C_{21}H_{24}N_4O$ [M+H]$^+$: 349.2023, found 349.2021.

N-(2-aminoquinazolin-6-yl)-4-heptylbenzamide (**4p**): 4-heptyl benzoyl chloride (0.30 mL, 1.25 mmol, 1eq). Afforded compound **4p** as a yellow solid. Yield 22% (100 mg, 0.28 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.31 (s, 1H), 9.07 (s, 1H), 8.33 (d, *J* = 2.4 Hz, 1H), 7.95 – 7.87 (m, 3H), 7.41 (d, *J* = 9.1 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 6.73 (s, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 1.61 – 1.55 (m, 2H), 1.31 – 1.22 (m, 8H), 0.88 – 0.78 (m, 3H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 169.66, 166.23, 155.31, 147.27, 136.95, 132.13, 131.69, 128.82, 128.69, 128.35, 118.73, 118.68, 118.01, 35.47, 31.73, 31.20, 29.07, 28.99, 22.56, 14.43 ppm; IR ν_{max} (cm^{-1}): 3420, 3380, 3275, 3100, 1671, 1591, 1515; UV/Vis (λ_{max} nm): 294; HRMS (ESI) calcd for $C_{22}H_{26}N_4O$ [M+H]$^+$: 363.2179, found 363.2173.

N-(2-aminoquinazolin-6-yl)-4-chlorobenzamide (**4q**): 4-chlorobenzoyl chloride (0.16 mL, 1.25 mmol, 1eq). Afforded compound **4q** as an orange solid. Yield 50% (184 mg, 0.62 mmol). ^{1}H NMR (300 MHz,) δ 10.45 (s, 1H), 9.08 (s 1H), 8.31 (d, *J* = 2.4 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.92 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 9.1 Hz, 1H), 6.75 (s, 2H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 169.81, 165.23, 155.25, 137.27, 136.70, 133.37, 131.76, 131.61, 130.29, 129.02, 118.94, 118.67, 117.91 ppm; IR ν_{max} (cm^{-1}): 3250, 3105, 1666, 1540, 777; UV/Vis (λ_{max} nm): 292; HRMS (ESI) calcd for $C_{15}H_{11}ClN_4O$ $[M+H]^+$: 299.0694, found 299.0694.

N-(2-aminoquinazolin-6-yl)-4-bromobenzamide (**4r**): 4-bromobenzoyl chloride (0.12 mL, 0.56 mmol, 1 eq). Afforded compound **4r** as a yellow solid. Yield 63% (122 mg, 0.35 mmol). ^1H NMR (300 MHz, DMSO-d_6) δ 10.45 (s, 1H), 9.09 (s, 1H), 8.32 (s, 1H), 7.92 (d, J = 8.8 Hz, 3H), 7.73 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.9 Hz, 1H), 6.77 (s, 2H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.99, 162.37, 160.98, 149.44, 134.29, 133.40, 131.88, 130.22, 129.33, 125.84, 125.35, 119.63, 117.54 ppm; IR ν_{max} (cm^{-1}): 3263, 3105, 1665, 1539, 750, 578; UV/Vis (λ_{max} nm): 296; HRMS (ESI) calcd for $C_{15}H_{11}BrN_4O$ $[M+H]^+$: 343.0189, found 343.0190.

N-(2-aminoquinazolin-6-yl)-4-fluorobenzamide (**4s**): 4-fluorobenzoyl chloride (0.07 mL, 0.56 mmol, 1 eq). Afforded compound **4s** as a pastel yellow solid. Yield 65% (103 mg, 0.36 mmol). ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 9.09 (s, 1H), 8.32 (s, 1H), 8.05 (d, J = 2.1 Hz, 2H), 7.93 (d, J = 9.1 1H), 7.43 (d, J = 9.1 Hz, 1H), 7.35 (dd, J = 8.9, 2.1 Hz, 2H), 6.77 (s, 2H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.79, 164.90, 163.31, 162.35, 160.97, 149.40, 133.52, 131.68, 131.65, 130.86, 130.77, 129.38, 125.33, 119.64, 117.49, 115.91, 115.69 ppm; IR ν_{max} (cm^{-1}): 3350, 3145, 1654, 1593, 1507, 1351, 1276; UV/Vis (λ_{max} nm): 298; HRMS (ESI) calcd for $C_{15}H_{11}FN_4O$ $[M+H]^+$: 283.0990, found 283.0988.

N-(2-aminoquinazolin-6-yl)-4-iodobenzamide (**4t**): 4-iodobenzoyl chloride (0.15 g, 0.56 mmol, 1 eq). Afforded compound **4t** as a yellow solid. Yield 63% (138 mg, 0.35 mmol). ^1H NMR (300 MHz, DMSO-d_6) δ 10.44 (s, 1H), 9.09 (s, 1H), 8.33 (d, J = 2.4 Hz, 1H), 7.96 – 7.89 (m, 3H), 7.76 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 9.1 Hz, 1H), 6.79 (s, 2H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.26, 162.37, 160.97, 149.42, 137.75, 134.59, 133.41, 130.04, 129.34, 125.35, 119.63, 117.53, 99.76 ppm; IR ν_{max} (cm^{-1}): 3278, 1664, 1584, 1539, 500; UV/Vis (λ_{max} nm): 296; HRMS (ESI) calcd for $C_{15}H_{11}N_4OI$ $[M+H]^+$: 391.0050, found 391.0046.

N-(2-aminoquinazolin-6-yl)-3,5-dichlorobenzamide (**4u**): 3,5-dichlorobenzoyl chloride (0.11 g, 0.52 mmol, 1 eq). Afforded compound **4u** as a yellow solid. Yield 68% (118 mg, 0.35 mmol). ^1H NMR (300 MHz, DMSO-d_6) δ 10.54 (s, 1H), 9.08 (s, 1H), 8.29 (s, 1H), 7.98 (s, 2H), 7.90 (d, J = 7.8 Hz, 1H), 7.82 (s, 1H), 7.43 (d, J = 9.1 Hz, 1H), 6.79 (s, 2H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 163.10, 162.47, 161.07, 149.59, 138.40, 134.81, 133.05, 131.41, 129.20, 126.95, 125.45, 119.58, 117.71 ppm; IR ν_{max} (cm^{-1}): 3320, 3225, 3088, 1657, 1540, 749, 617; UV/Vis (λ_{max} nm): 292; HRMS (ESI) calcd for $C_{15}H_{10}Cl_2N_4O$ $[M+H]^+$: 333.0304, found 333.0308.

N-(2-aminoquinazolin-6-yl)-3,5-difluorbenzamide (**4v**): 3,5-difluorobenzoyl chloride (0.06 mL, 0.52 mmol, 1 eq). Afforded compound **4v** as a pale yellow solid. Yield 34% (53 mg, 0.18 mmol). ^1H NMR (300 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.09 (s, 1H), 8.30 (s, 1H), 7.91 (d, J = 9.2 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 9.2 Hz, 1H), 7.43 (d, J = 9.2 Hz, 1H), 6.78 (s, 2H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 163.44, 163.37, 163.34, 163.32, 163.30, 162.48, 162.04, 161.97, 161.08, 149.60, 138.73, 138.68, 138.63, 133.02, 129.26, 125.46, 119.58, 117.75, 111.66, 111.64, 111.54, 111.51, 107.71, 107.56, 107.41 ppm; IR ν_{max} (cm^{-1}): 3363, 3313, 3114, 1664, 1548, 1359, 1316; UV/Vis (λ_{max} nm): 292; HRMS (ESI) calcd for $C_{15}H_{10}F_2N_4O$ [M+H]$^+$: 301.0895, found 301.0900.

N-(2-aminoquinazolin-6-yl)-2-chloroacetamide (**4w**): Chloroacetyl chloride (0.05 mL, 0.62 mmol, 1eq). Afforded compound **4w** as a pastel yellow solid. Yield 59% (87 mg, 0.37 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.46 (s, 1H), 9.07 (s, 1H), 8.16 (d, *J* = 1.8 Hz, 1H), 7.70 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.40 (d, *J* = 9.0 Hz, 1H), 6.76 (s, 2H), 4.27 (s, 2H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 165.17, 162.50, 160.90, 149.23, 132.94, 128.30, 125.59, 119.63, 116.59, 43.98 ppm; IR ν_{max} (cm^{-1}): 3328, 3225, 3200, 3113, 3080, 1668, 1598, 794; UV/Vis (λ_{max} nm): 290; HRMS (ESI) calcd for $C_{10}H_9ClN_4O$ [M+H]$^+$: 237.0538, found 237.0539.

N-(2-aminoquinazolin-6-yl)-2,2,2-trichloroacetamide (**4x**): Trichloroacetyl chloride (0.07 mL, 0.62 mmol, 1eq). Afforded compound **4x** as a yellow solid. Yield 15% (29 mg, 0.09 mmol). ^{1}H NMR (700 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.13 (s, 1H), 8.14 (d, *J* = 2.3 Hz, 1H), 7.88 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.45 (d, *J* = 8.9 Hz, 1H), 6.85 (s, 2H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.67, 161.31, 160.42, 150.10, 131.56, 129.84, 125.59, 119.53, 119.43, 79.67 ppm; IR ν_{max} (cm^{-1}): 3320, 3085, 1665, 1509, 818; UV/Vis (λ_{max} nm): 292; HRMS (ESI) calcd for $C_{10}H_7Cl_3N_4O$ [M+H]$^+$: 304.9758, found 304.9761.

Sulfonamide containing derivatives (5a-f)

N-(2-aminoquinazolin-6-yl)methane sulfonamide (**5a**): Compound **3** (0.18 g, 1.15 mmol, 1 eq) was dissolved in anhydrous DCM (2 mL) under nitrogen gas. Pyridine (0.14 mL, 1.72 mmol, 1.5 eq) was added and the reaction cooled to 0 °C. After 20 minutes, methane sulfonyl chloride (0.10 mL, 1.27 mmol, 1.1 eq) was added dropwise and the reaction stirred for 12 h at room temperature. The reaction was quenched with water. The organic material was extracted with DCM (20 mL x 3). The organic fractions were combined and dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by flash chromatography (0.5-3.5% MeOH/NH_3:DCM) to afford compound **5a** as a brown solid. Yield 10% (24 mg, 0.10 mmol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.81 (s, 1H), 9.10 (s, 1H), 7.60 (d, *J* = 2.1 Hz, 1H), 7.55 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.43 (d, *J* = 8.9 Hz, 1H), 6.81 (s, 2H), 3.01 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.12, 161.27, 149.96, 132.80, 129.96, 126.51, 120.09, 117.92, 39.73 ppm; IR ν_{max} (cm^{-1}): 3380, 3273, 3050, 1663, 1519; UV/Vis (λ_{max} nm): 290; HRMS (ESI) calcd for $C_9H_{10}N_4O_2S$ [M+H]$^+$: 239.0597, found 239.0593.

The remaining sulfonamide derivatives (**5b-f**) followed the same general procedure outlined for the synthesis of **5a** with substitution of the appropriate sulfonyl chloride:

N-(2-aminoquinazolin-6-yl) ethane sulfonamide (**5b**): Ethane sulfonyl chloride (0.10 mL, 1.03 mmol, 1.1 eq). Afforded compound **5b** as a brown solid. Yield 15% (34 mg, 0.14 mmol). ^{1}H NMR (700 MHz, DMSO-d_6) δ 9.84 (s, 1H), 9.08 (s, 1H), 7.59 (d, *J* = 2.5 Hz, 1H), 7.56 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.42 (d, *J* = 8.9 Hz, 1H), 6.75 (s, 2H), 3.11 (q, *J* = 7.3 Hz, 2H), 1.21 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.29, 160.98, 149.58, 132.56, 129.33, 126.29, 119.86, 117.17, 45.41, 8.56 ppm; IR ν_{max} (cm^{-1}): 3353, 3070, 1665, 1507; UV/Vis (λ_{max} nm): 294; HRMS (ESI) calcd for $C_{10}H_{12}N_4O_2S$ [M+H]$^+$: 253.0754, found 253.0753.

N-(2-aminoquinazolin-6-yl)propane-1- sulfonamide (**5c**): 1-propane sulfonyl chloride (0.08 mL, 0.69 mmol, 1.1 eq). Afforded compound **5c** as a yellow solid. Yield 12% (20 mg, 0.07 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.54 (s, 1H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.80 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 6.75 (s, 2H), 3.20 – 3.09 (m, 2H), 1.68 (h, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 169.44, 155.41, 136.01, 131.01, 130.88, 119.02, 117.69, 117.54, 53.11, 17.31, 13.04 ppm; IR ν_{max} (cm^{-1}): 3288, 3117, 1661, 1604, 1520; UV/Vis (λ_{max} nm): 290; HRMS (ESI) calcd for $C_{11}H_{14}N_4O_2S$ [M+H]$^+$: 267.0910, found 267.0912.

N-(2-aminoquinazolin-6-yl)butane-1- sulfonamide (**5d**): 1-butane sulfonyl chloride (0.12 mL, 0.96 mmol, 1.1 eq). Afforded compound **5d** as a yellow solid. Yield 19% (48 mg, 0.17 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.54 (s, 1H), 7.87 (d, *J* = 2.3 Hz, 1H), 7.79 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 6.75 (s, 2H), 3.22 – 3.11 (m, 2H), 1.63 (p, *J* = 7.5 Hz, 2H), 1.32 (h, *J* = 7.6 Hz, 2H), 0.81 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 169.35, 155.41, 136.00, 130.99, 130.89, 119.02, 117.68, 117.56, 51.12, 25.57, 21.13, 13.95 ppm; IR ν_{max} (cm^{-1}): 3303, 3124, 1662, 1603, 1521; UV/Vis (λ_{max} nm): 290; HRMS (ESI) calcd for $C_{12}H_{16}N_4O_2S$ [M+H]$^+$: 281.1067, found 281.1067.

N-(2-aminoquinazolin-6-yl)hexane-1- sulfonamide (**5e**): 1-hexane sulfonyl chloride (0.18 mL, 1.1 mmol, 1.1 eq). Afforded compound **5e** as a yellow solid. Yield 52% (161 mg, 0.52 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.83 (s, 1H), 9.06 (s, 1H), 7.56 – 7.52 (m, 1H), 7.50 (d, *J* = 2.5 Hz, 1H), 7.39 (d, *J* = 8.9 Hz, 1H), 6.75 (s, 2H), 3.11 – 3.00 (m, 2H), 1.63 (p, *J* = 7.5 Hz, 2H), 1.34 – 1.12 (m, 6H), 0.82 – 0.73 (m, 3H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 169.35, 155.41, 136.00, 130.99, 130.89, 119.02, 117.68, 117.56, 51.12, 25.57, 21.13, 21.03, 13.95, 13.89 ppm; IR ν_{max} (cm^{-1}): 3508, 3363, 3258, 3091, 1661, 1603, 1522; UV/Vis (λ_{max} nm): 290; HRMS (ESI) calcd for $C_{14}H_{20}N_4O_2S$ [M+H]$^+$: 309.1380, found 309.1381.

N-(2-aminoquinazolin-6-yl)thiophene-2-sulfonamide (**5f**): 2-thiophene sulfonyl chloride (0.21 g, 1.17 mmol, 1.1 eq). Afforded compound **5f** as a yellow solid. Yield 5% (16 mg, 0.05 mmol). ^{1}H NMR (700 MHz, DMSO-d_6) δ 10.44 (s, 1H), 9.07 (s, 1H), 7.88 (d, *J* = 2.5 Hz, 1H), 7.53-7.44 (m, 2H), 7.43 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.35 (d, *J* = 9.0 Hz, 1H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.80 (s, 2H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.43, 161.12, 149.97, 140.13, 133.88, 132.95, 131.51, 129.84, 128.10, 126.16, 119.65, 118.87 ppm; IR ν_{max} (cm^{-1}): 3350, 3060, 1663, 1505; UV/Vis (λ_{max} nm): 290; HRMS (ESI) calcd for $C_{12}H_{10}N_4O_2S_2$ $[M+H]^+$: 307.0318, found 307.0319.

[1]H and [13]C Nuclear Magnetic Resonance Spectra

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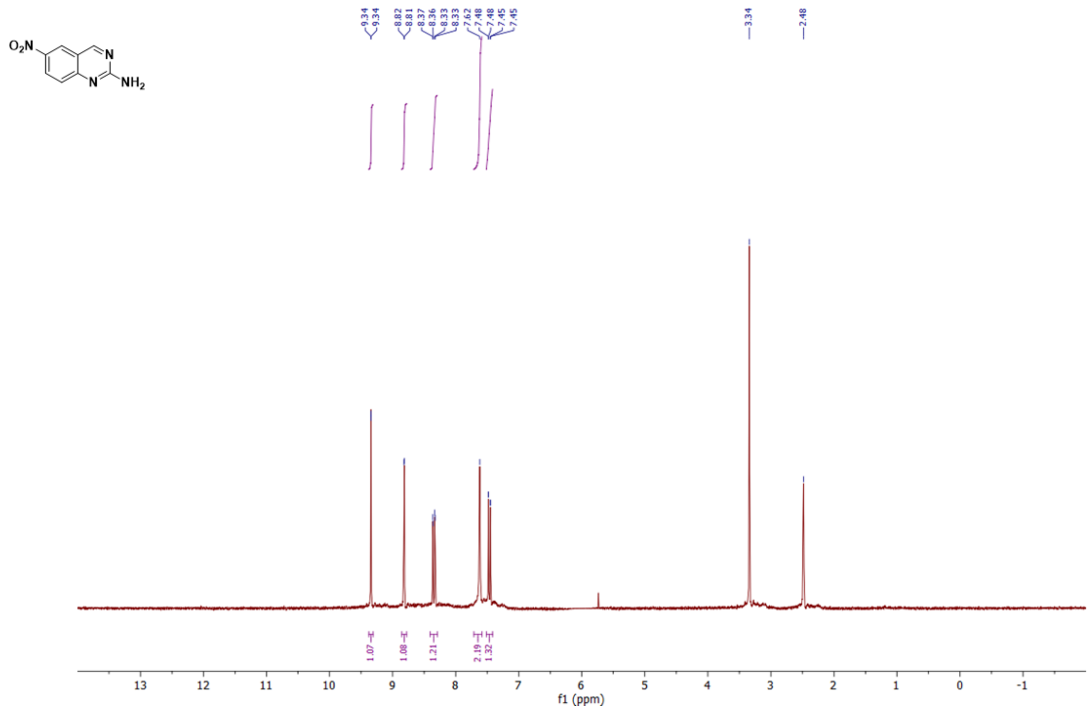
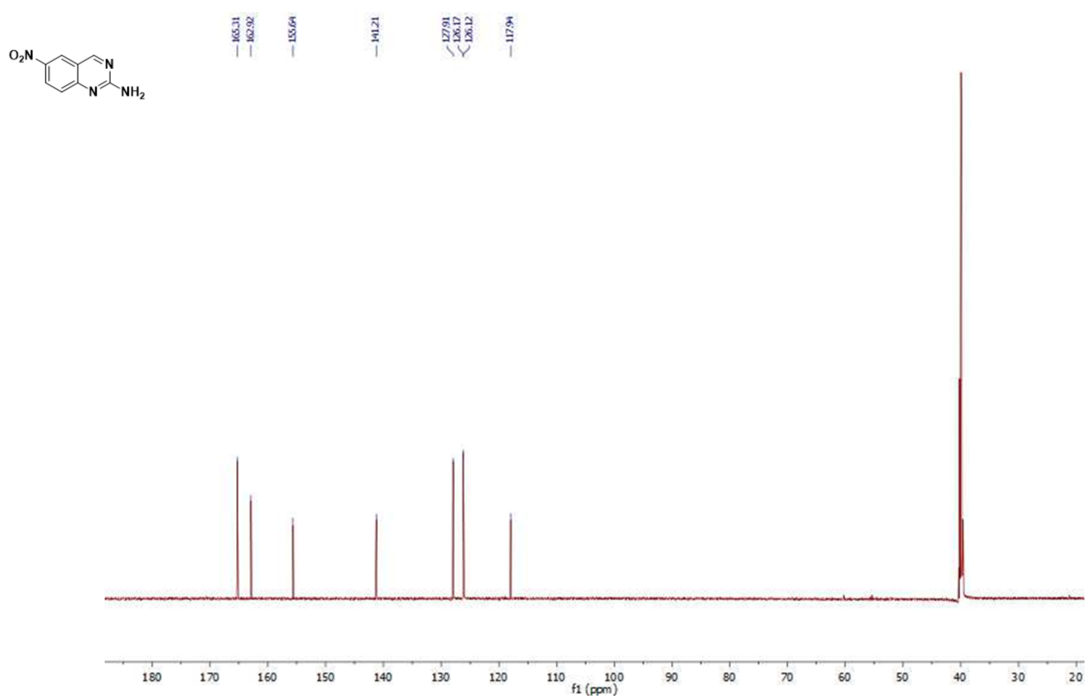
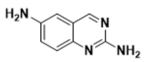




Compound 3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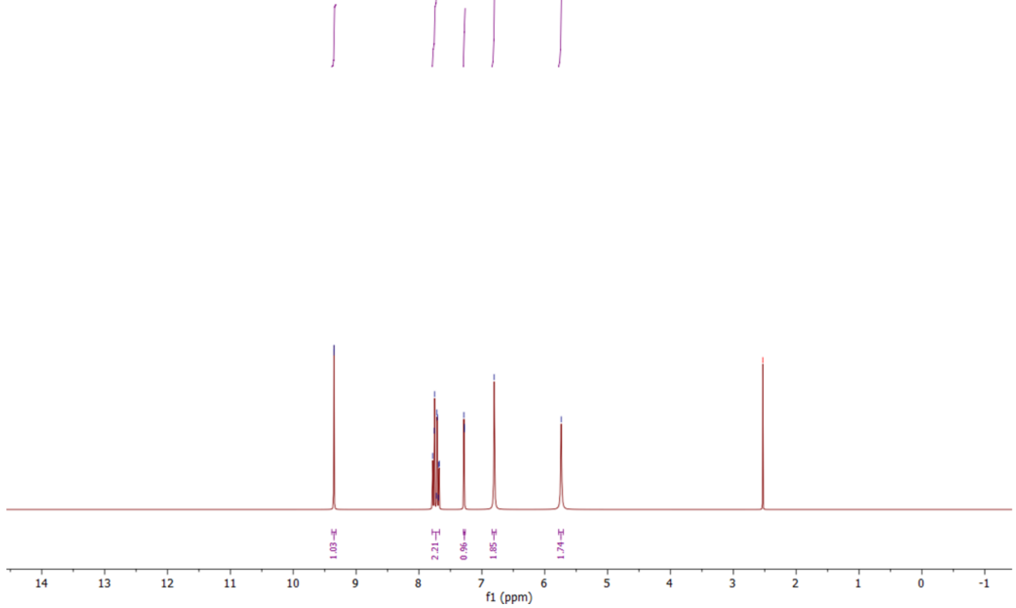
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7.27
6.80
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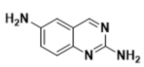
f1 (ppm)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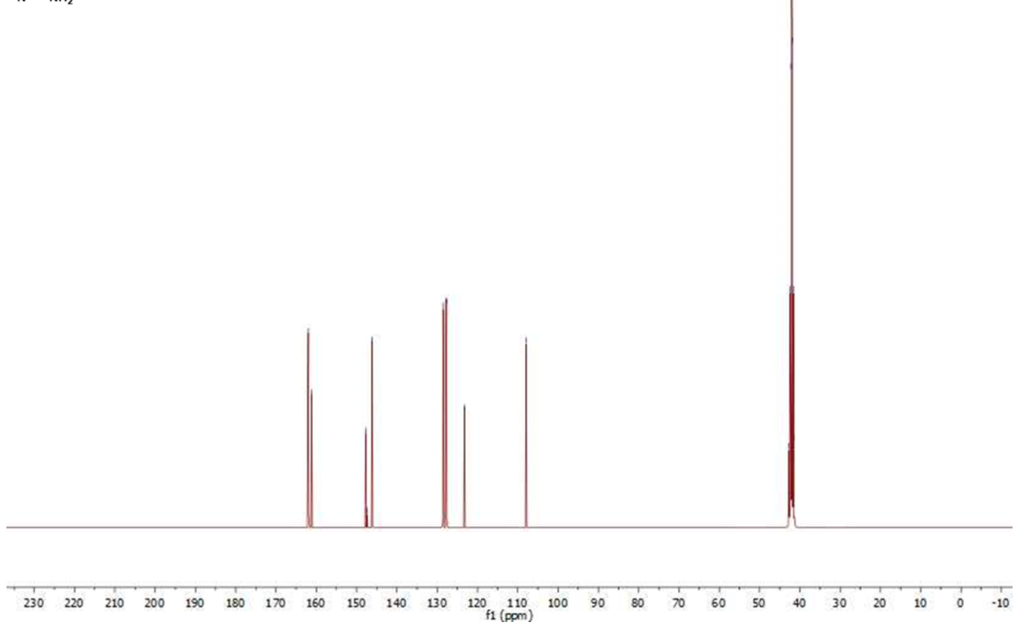
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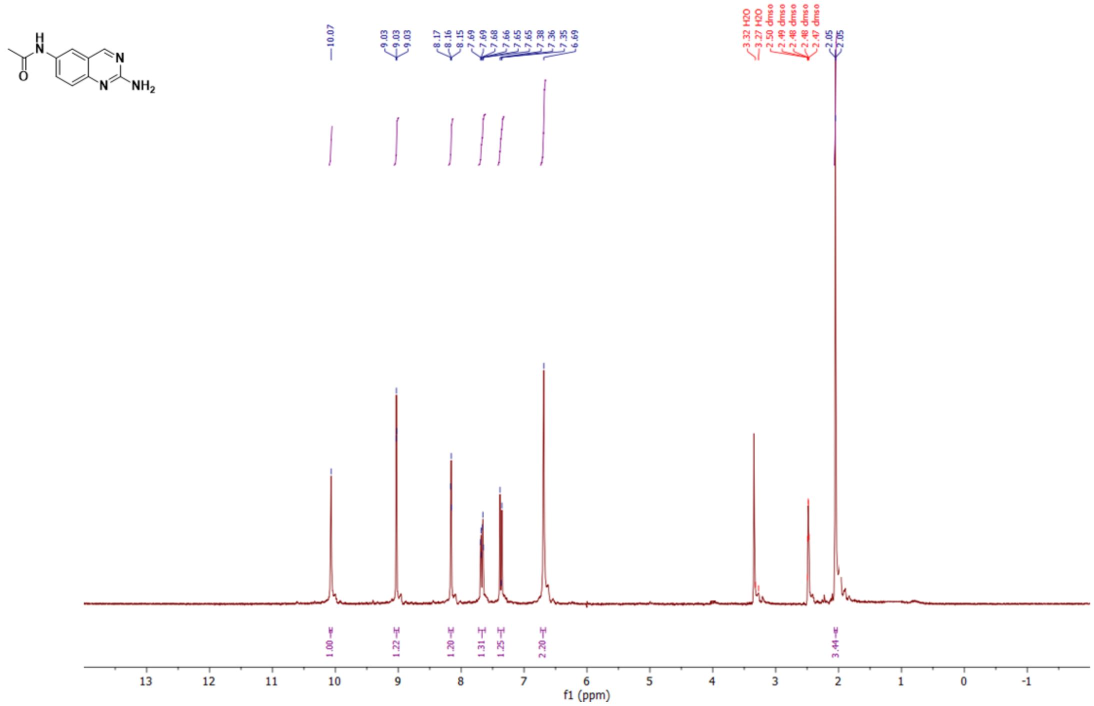
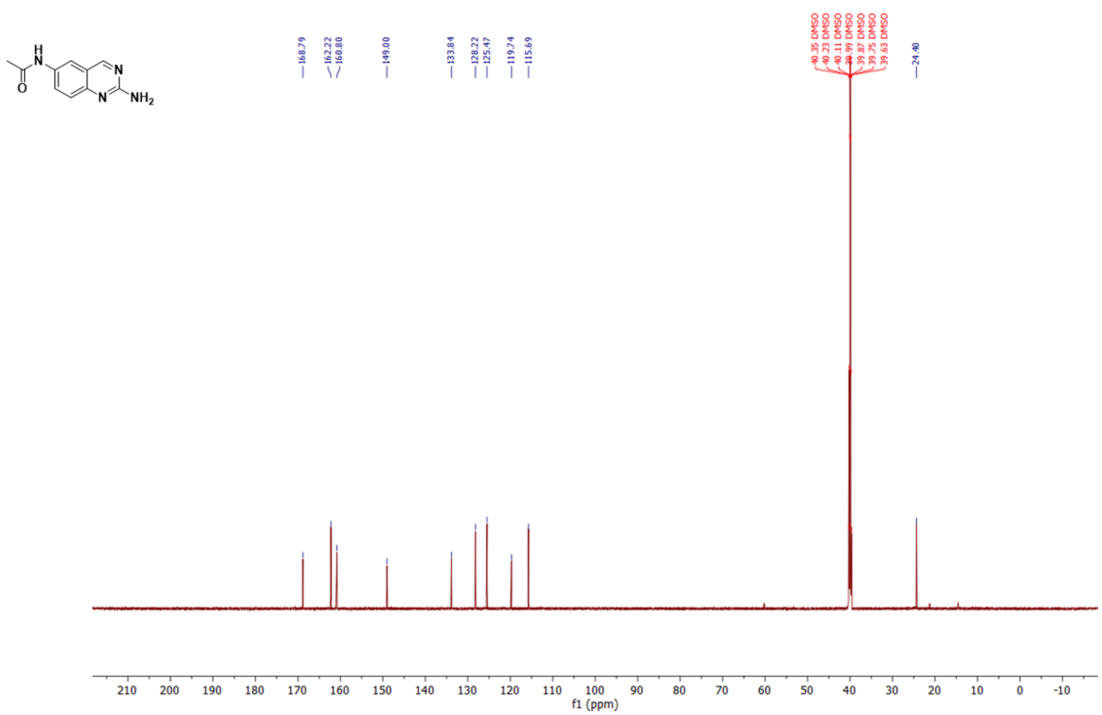
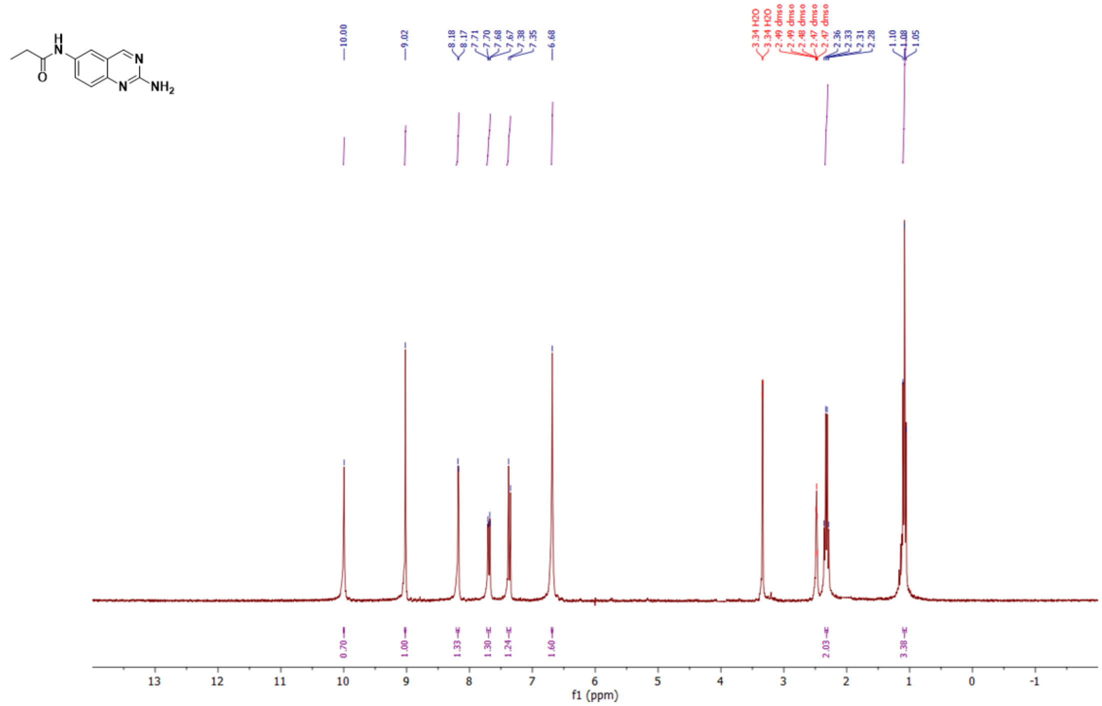
f1 (ppm)

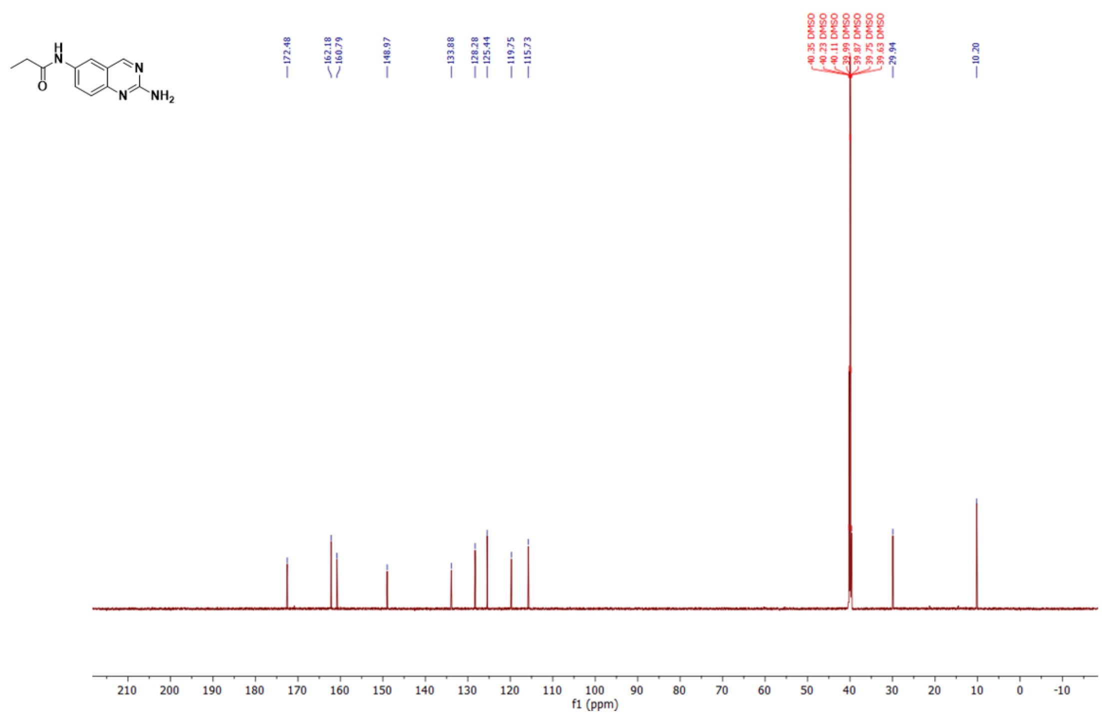
Compound 4a



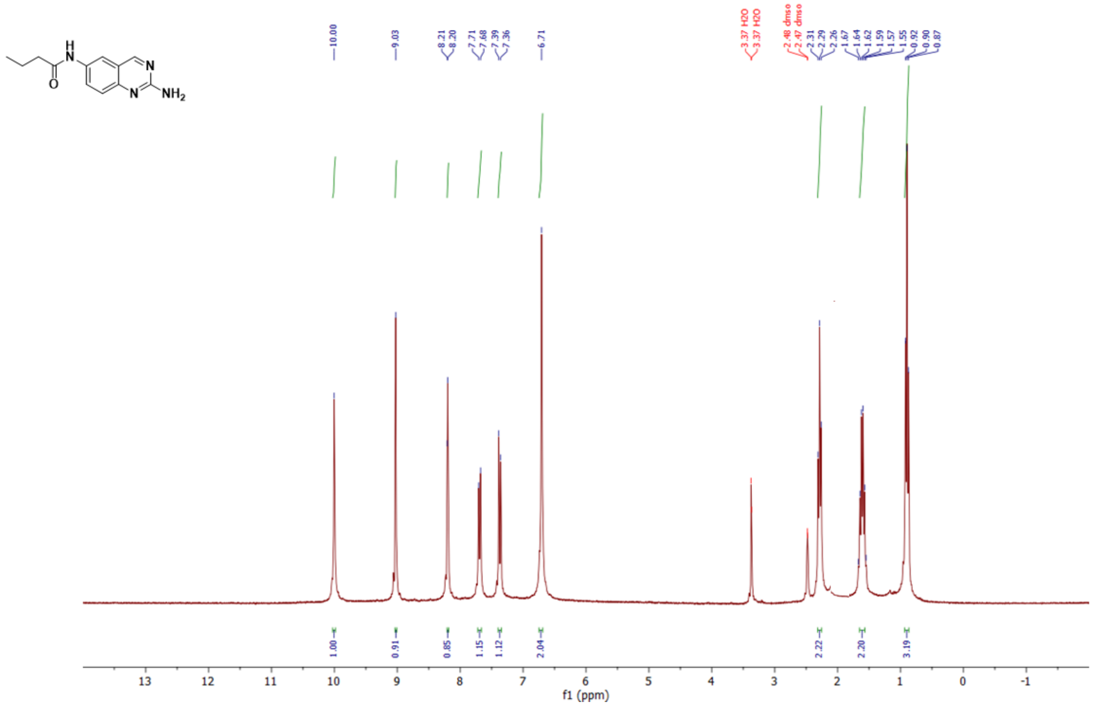


Compound 4b





Compound 4c



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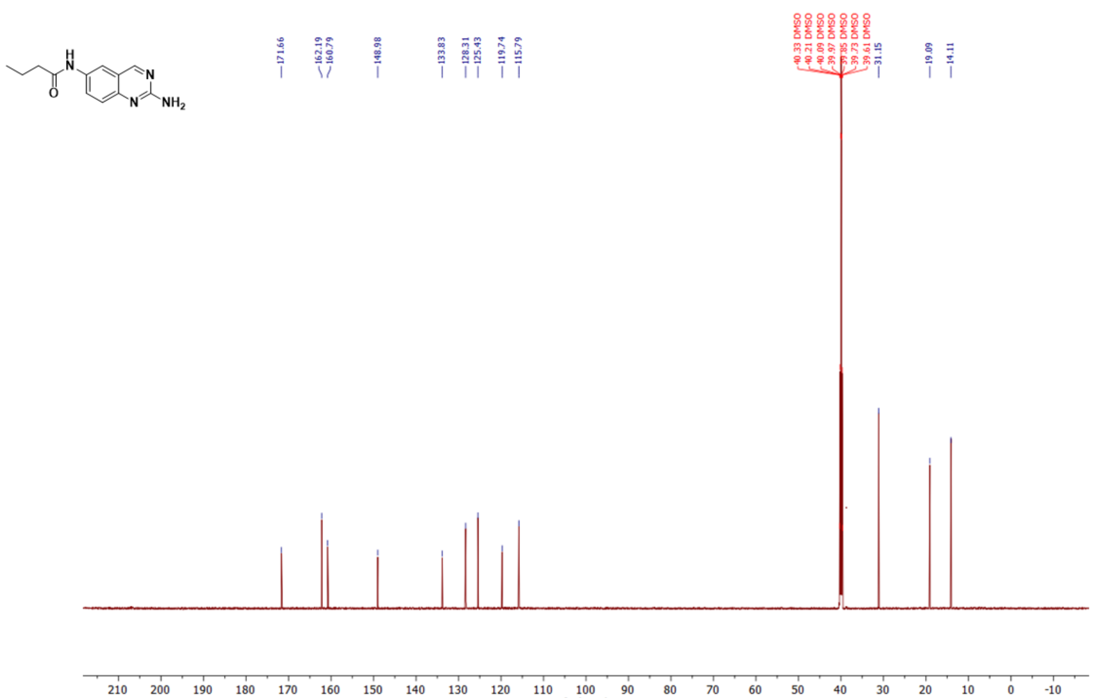

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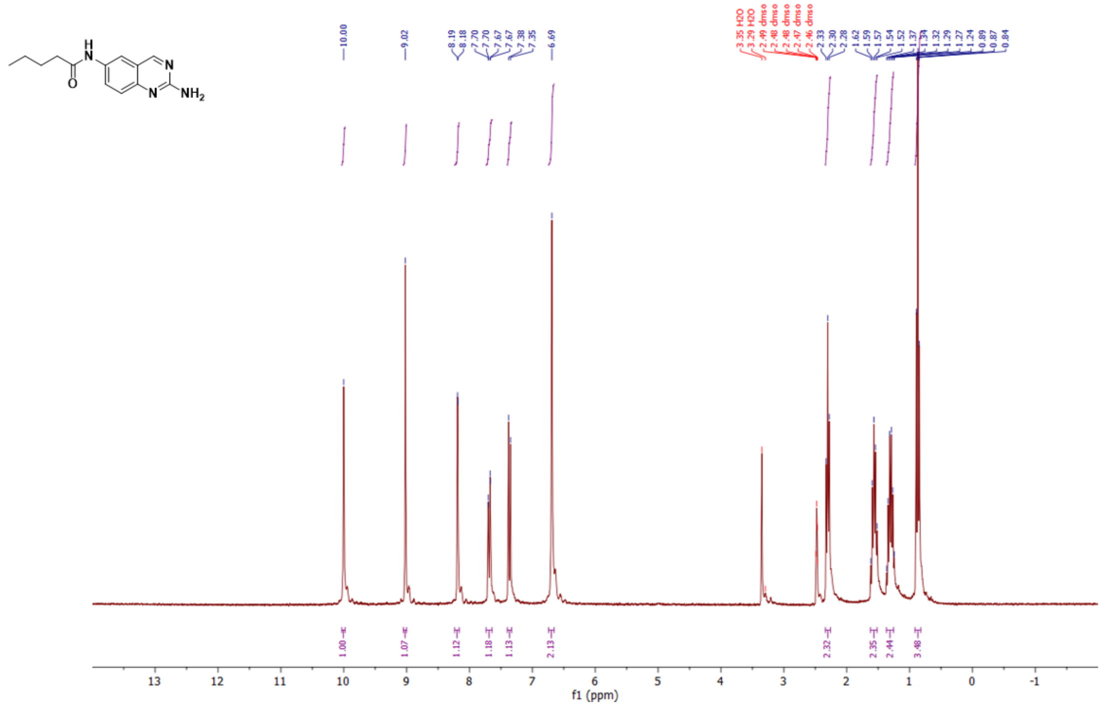
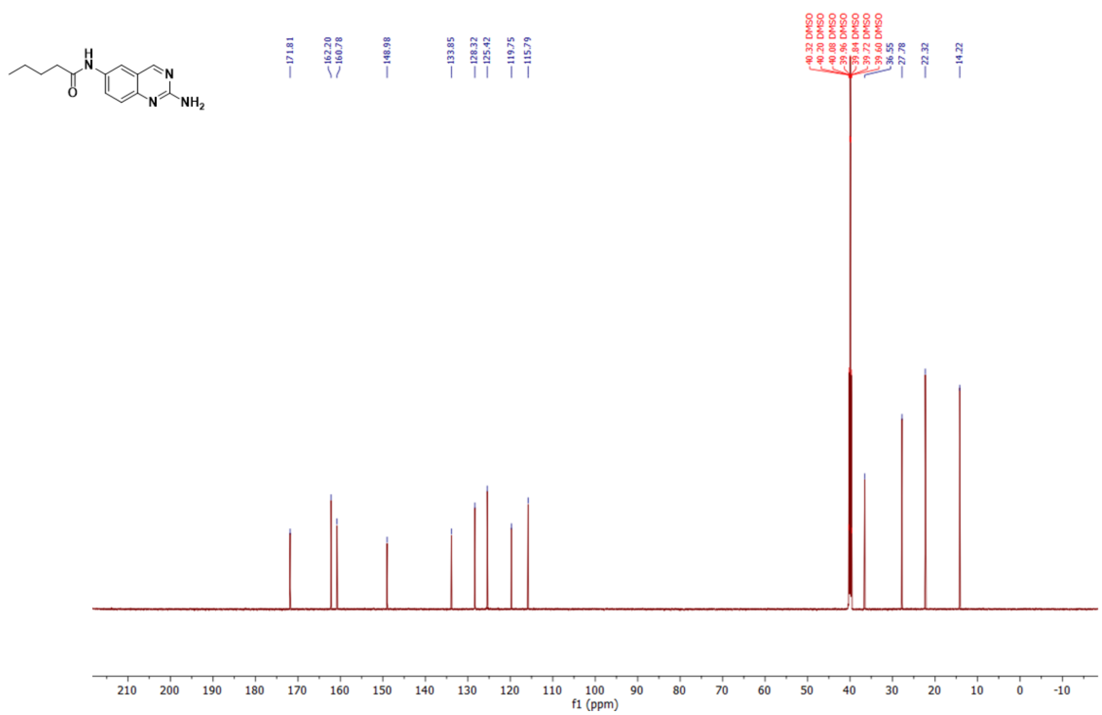
162.19
160.79
148.98
133.83
128.31
125.43
119.74
115.79
40.33 DMSO
40.21 DMSO
40.09 DMSO
39.97 DMSO
39.85 DMSO
39.73 DMSO
39.61 DMSO
31.15
19.09
14.11
f1 (ppm)

Compound 4d

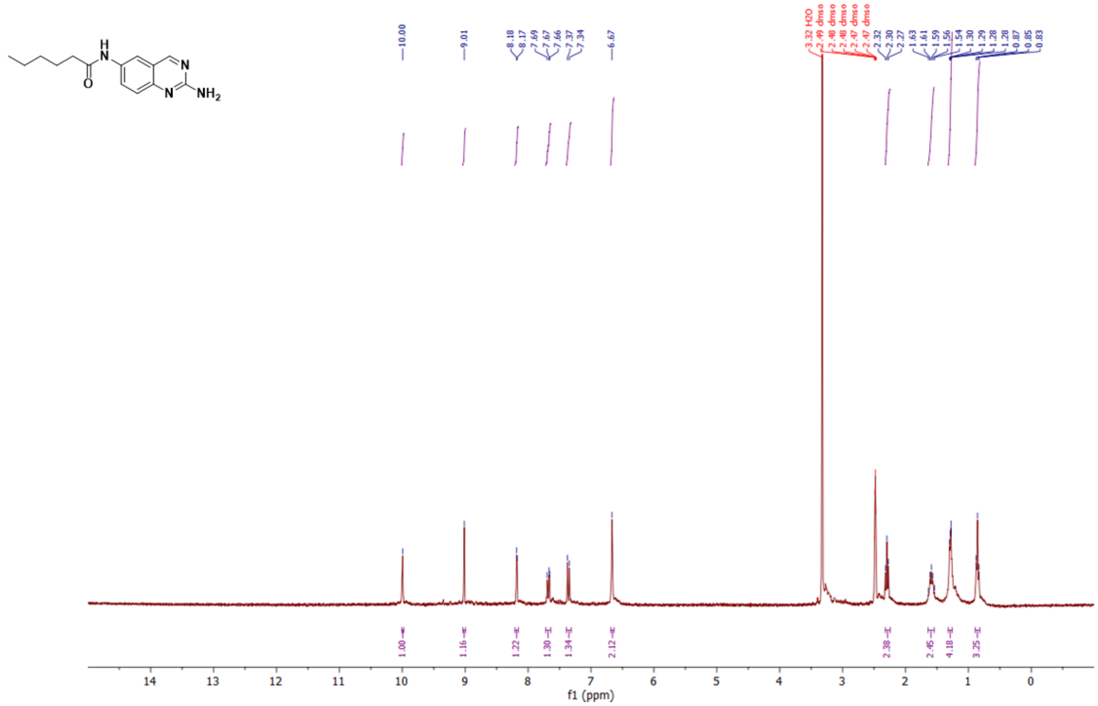


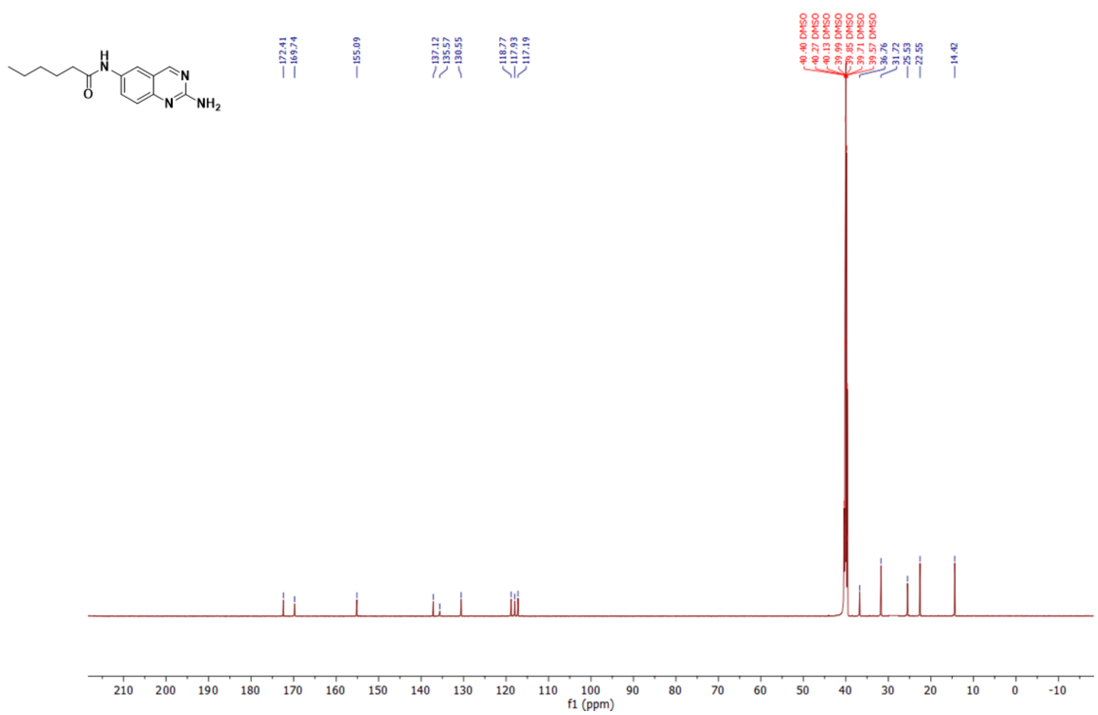
H
N
NH2
O
10.00
9.02
8.19
8.18
7.70
7.70
7.67
7.67
7.38
7.35
6.69
3.35 H2O
3.29 H2O
2.49 dmso
2.48 dmso
2.48 dmso
2.47 dmso
2.46 dmso
2.33
2.30
2.28
1.62
1.59
1.57
1.54
1.52
1.37
1.34
1.32
1.29
1.27
1.24
0.89
0.87
0.84
1.00
1.07
1.12
1.18
1.13
2.13
2.32
2.35
2.44
3.48
f1 (ppm)



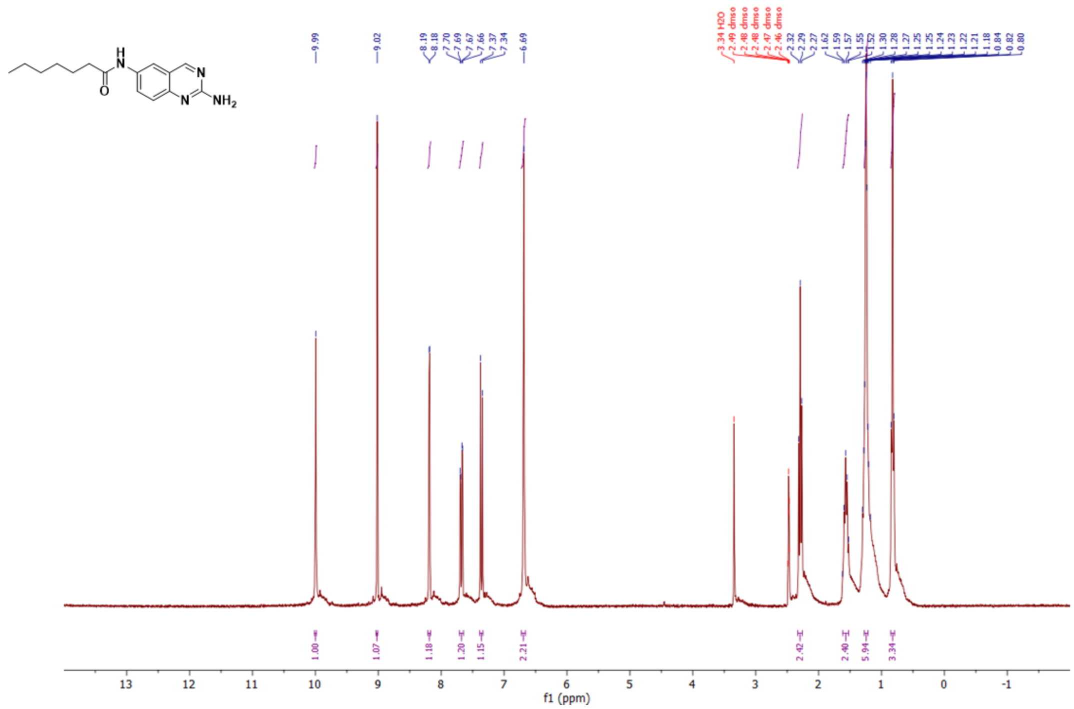
H
N
NH2
O
171.81
162.20
160.78
148.98
133.85
128.32
125.42
119.75
115.79
40.32 DMSO
40.20 DMSO
40.08 DMSO
39.96 DMSO
39.84 DMSO
39.72 DMSO
39.60 DMSO
36.55
27.78
22.32
14.22
f1 (ppm)

Compound 4e

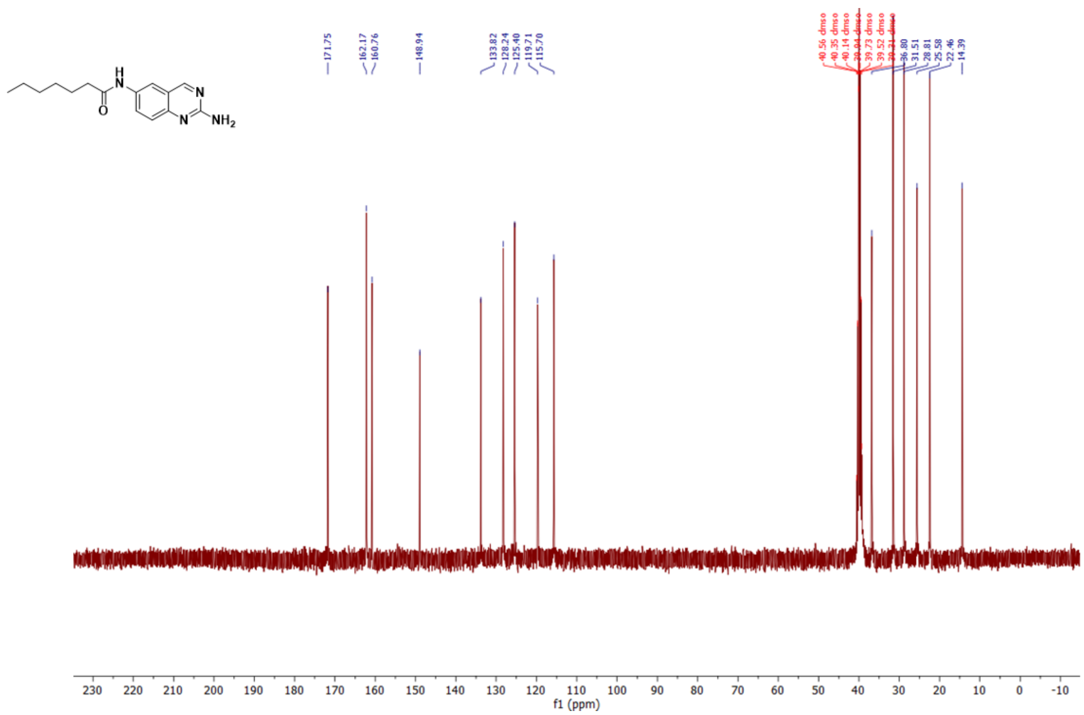




Compound 4f

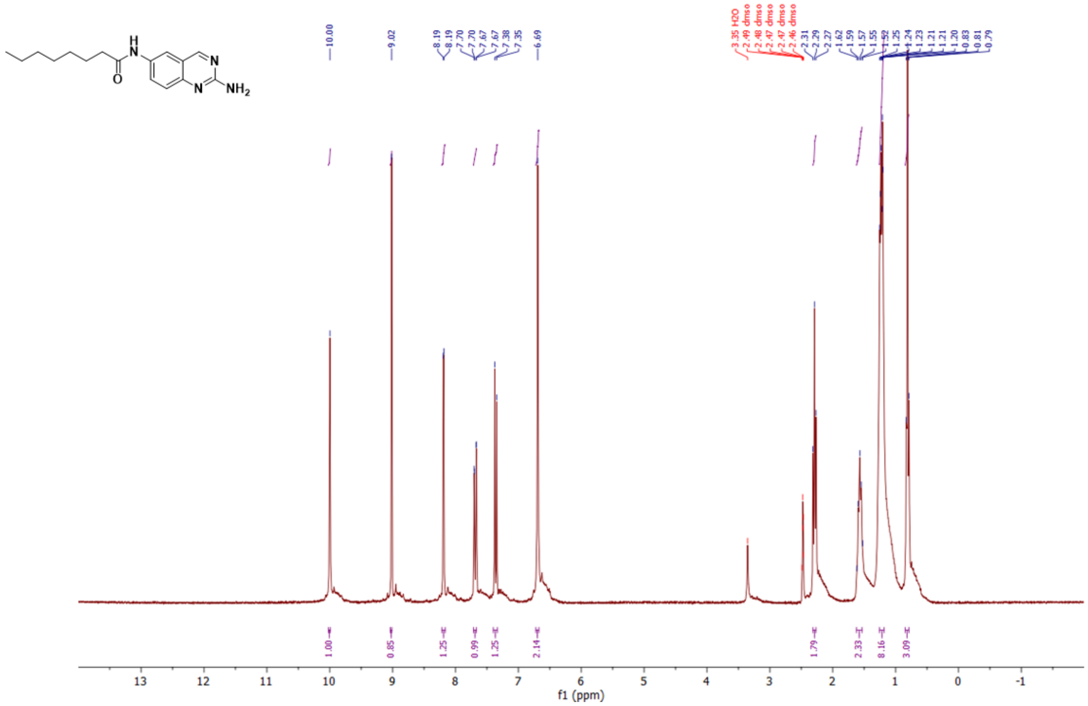


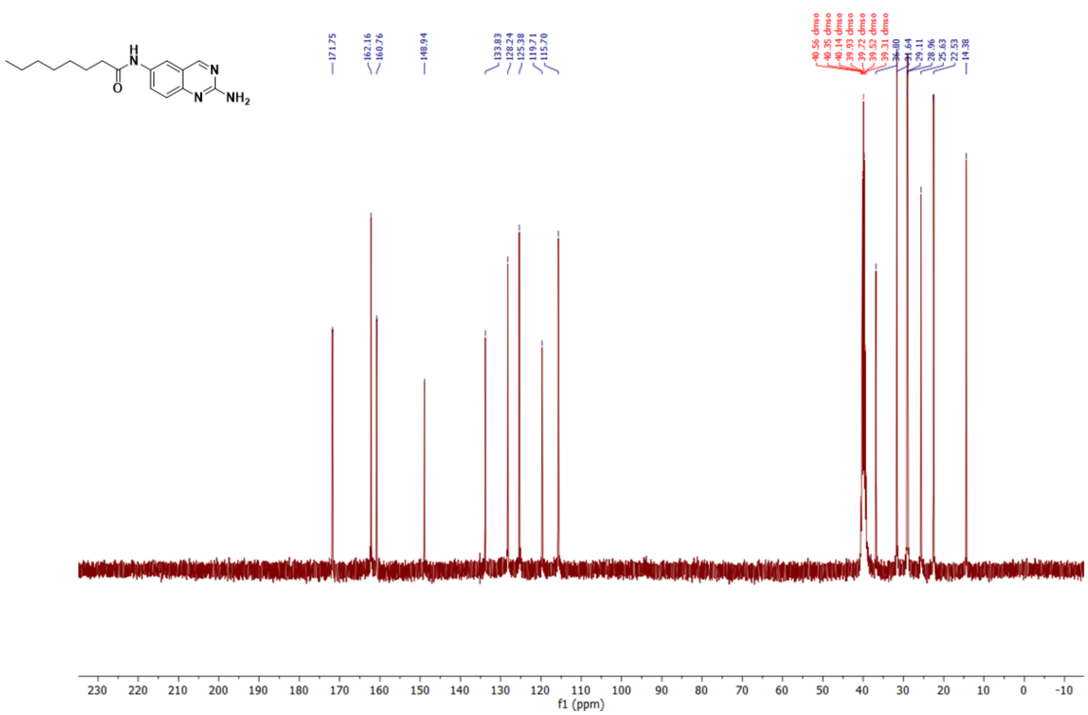
9.99
9.02
8.19
8.18
7.70
7.69
7.67
7.66
7.37
7.34
6.69
3.34 H2O
2.49 dmso
2.48 dmso
2.48 dmso
2.47 dmso
2.46 dmso
2.32
2.29
2.27
1.62
1.59
1.57
1.55
1.52
1.30
1.28
1.27
1.25
1.25
1.24
1.23
1.22
1.21
1.18
0.84
0.82
0.80
1.00
1.07
1.18
1.20
1.15
2.21
2.42
2.40
5.94
3.34
f1 (ppm)



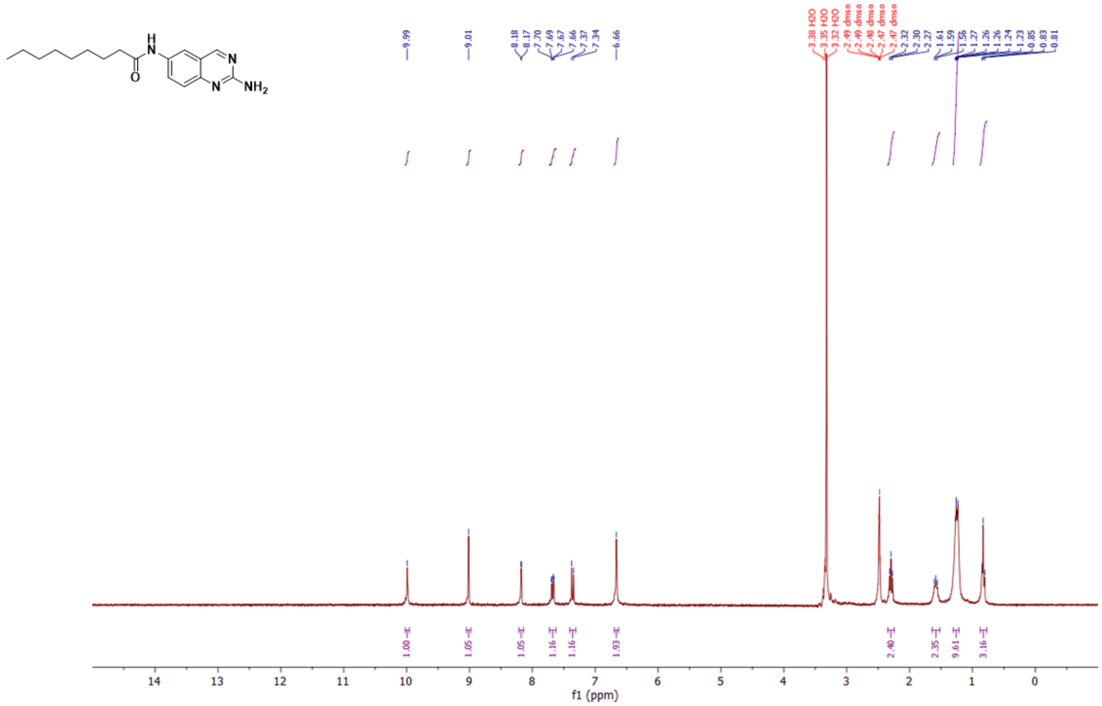
171.75
162.17
160.76
148.94
133.82
128.24
125.40
119.71
115.70
40.56 dmso
40.35 dmso
40.14 dmso
39.94 dmso
39.73 dmso
39.52 dmso
39.31 dmso
36.80
31.51
28.81
25.58
22.46
14.39
f1 (ppm)

Compound 4g

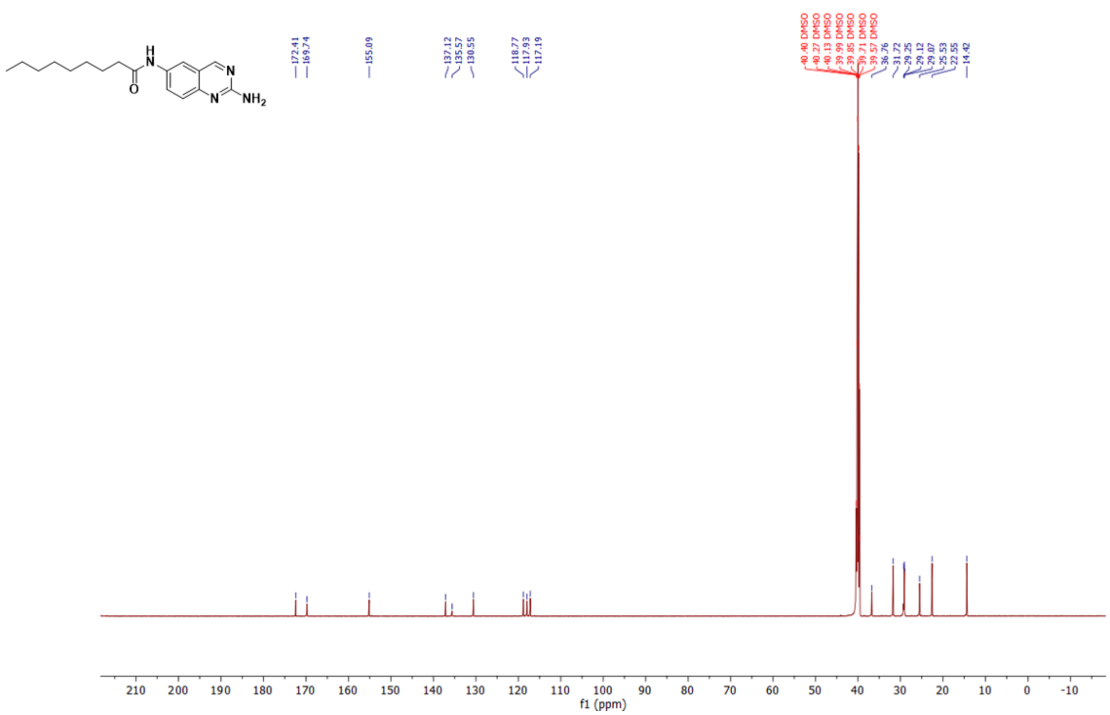




Compound 4h

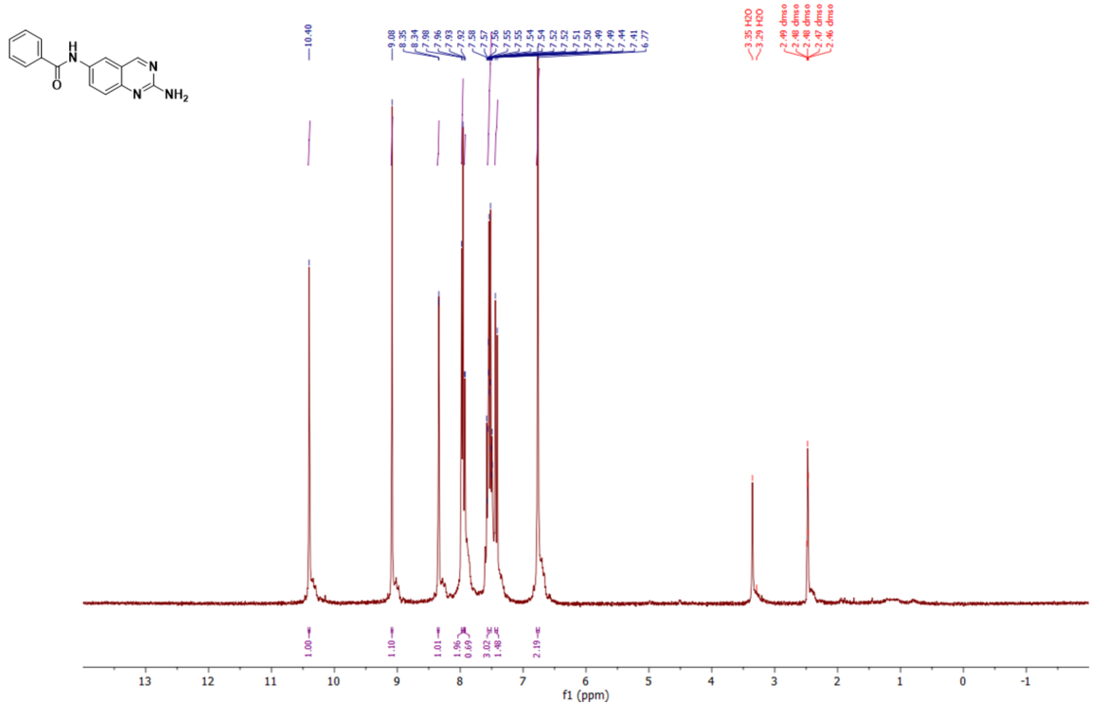


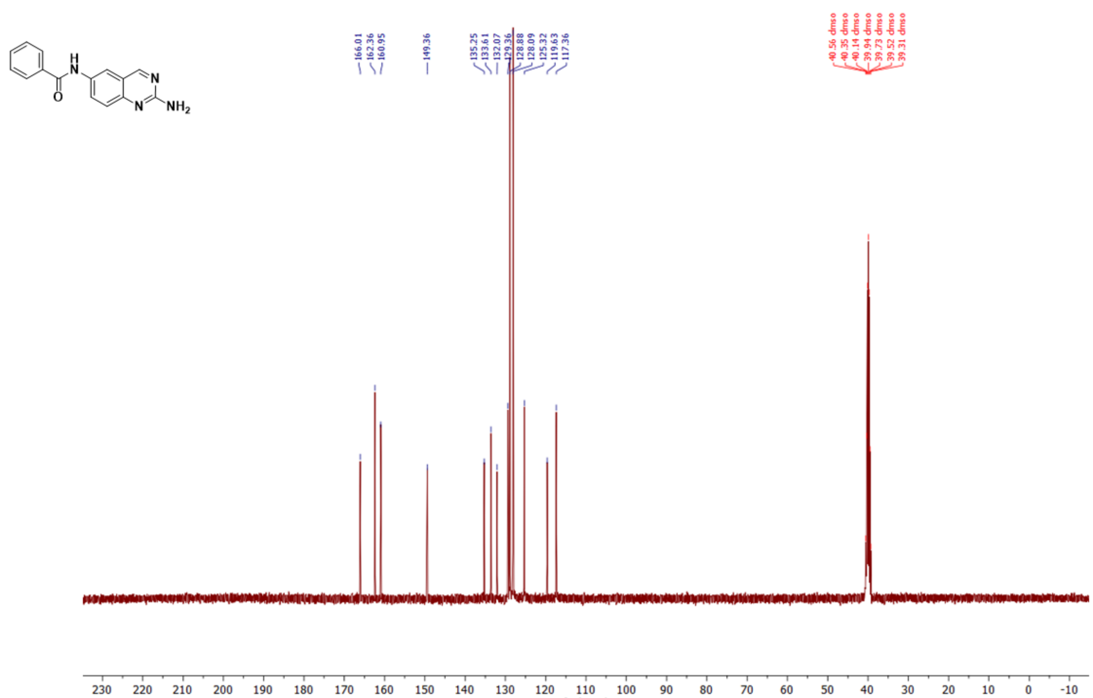
H
N
N
O
NH2
9.99
9.01
8.18
8.17
7.70
7.69
7.67
7.66
7.37
7.34
6.66
3.38 H2O
3.35 H2O
3.32 H2O
2.32
2.30
2.27
1.61
1.59
1.27
1.26
1.24
1.23
0.85
0.83
0.81
1.00
1.05
1.05
1.16
1.16
1.93
2.40
2.35
9.61
3.16
f1 (ppm)



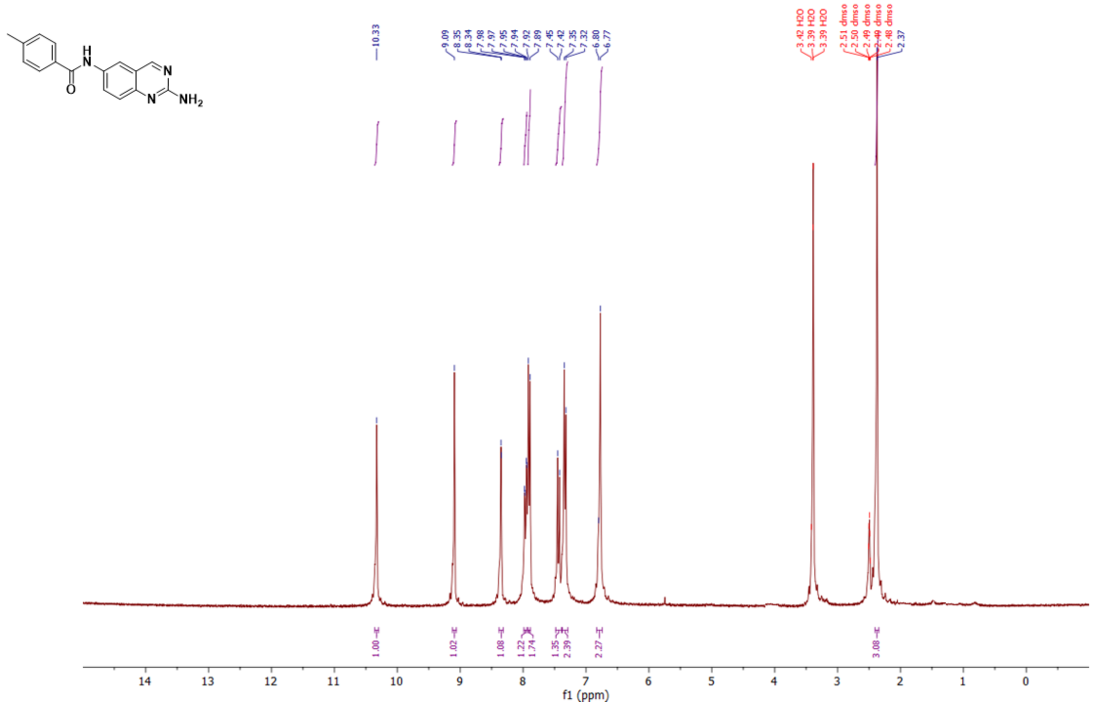
H
N
N
O
NH2
172.41
169.74
155.09
137.12
135.57
130.55
118.77
117.93
117.19
36.76
31.72
29.25
29.12
29.07
25.53
22.55
14.42
f1 (ppm)

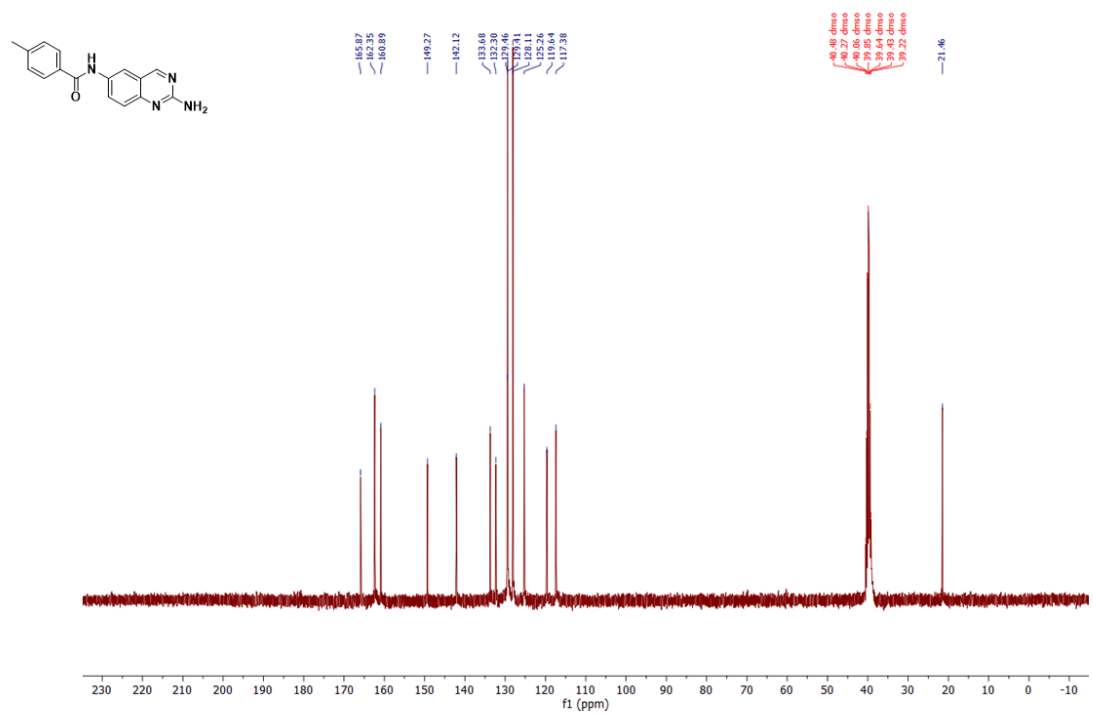
Compound 4i



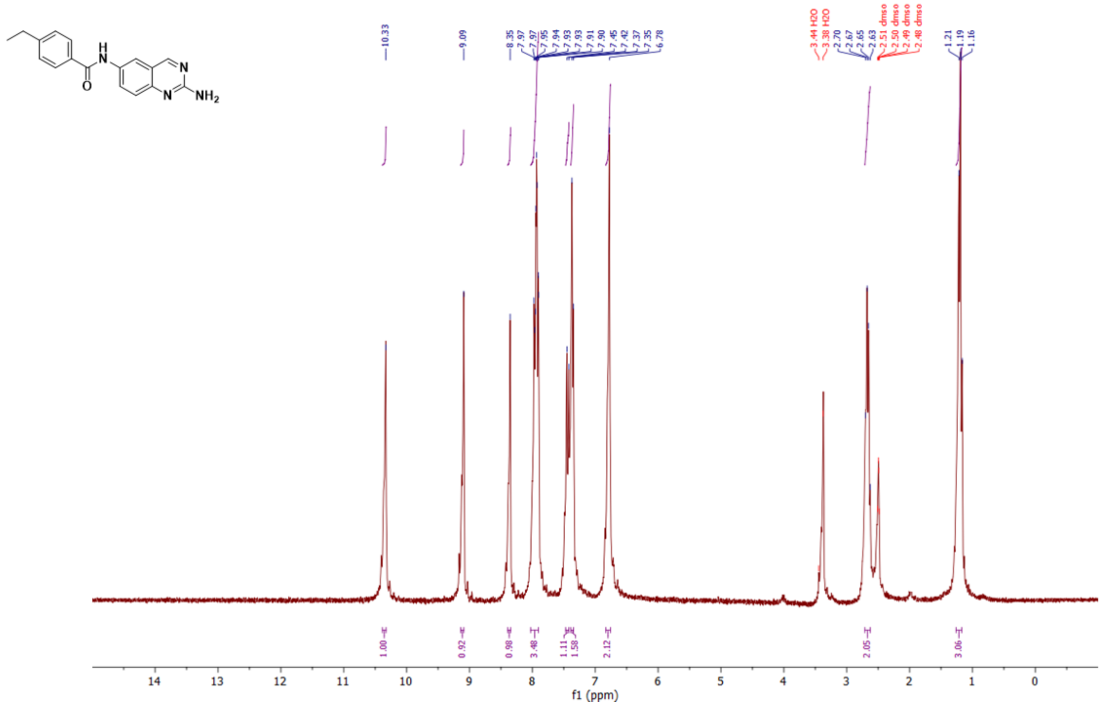


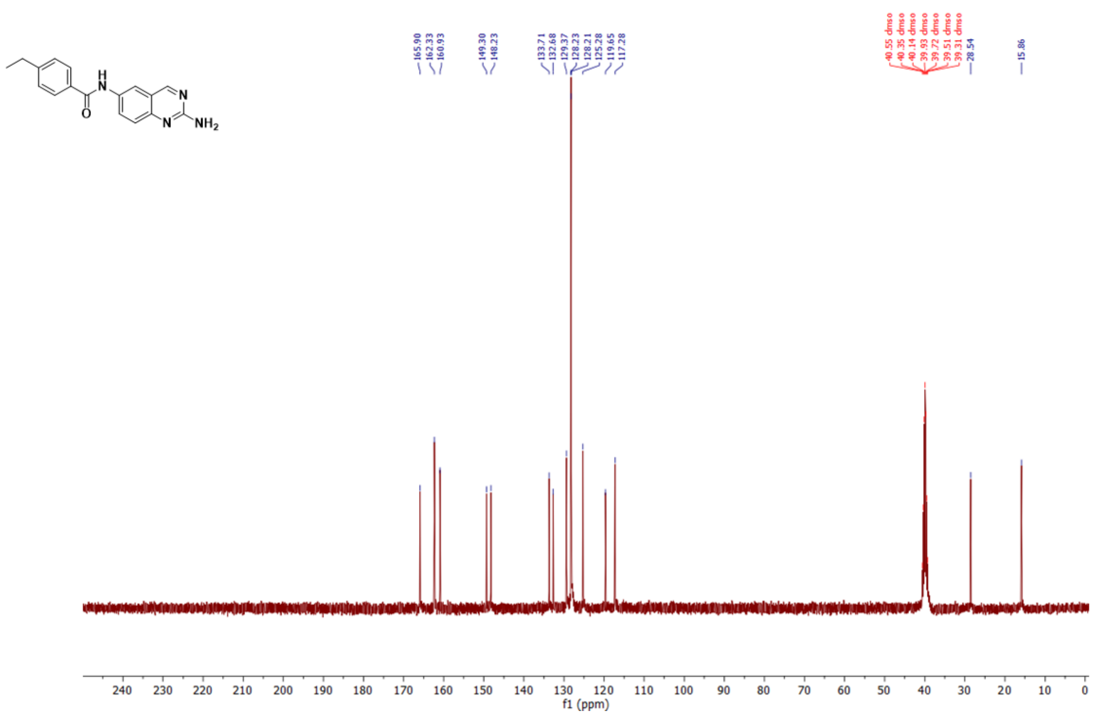
Compound 4j



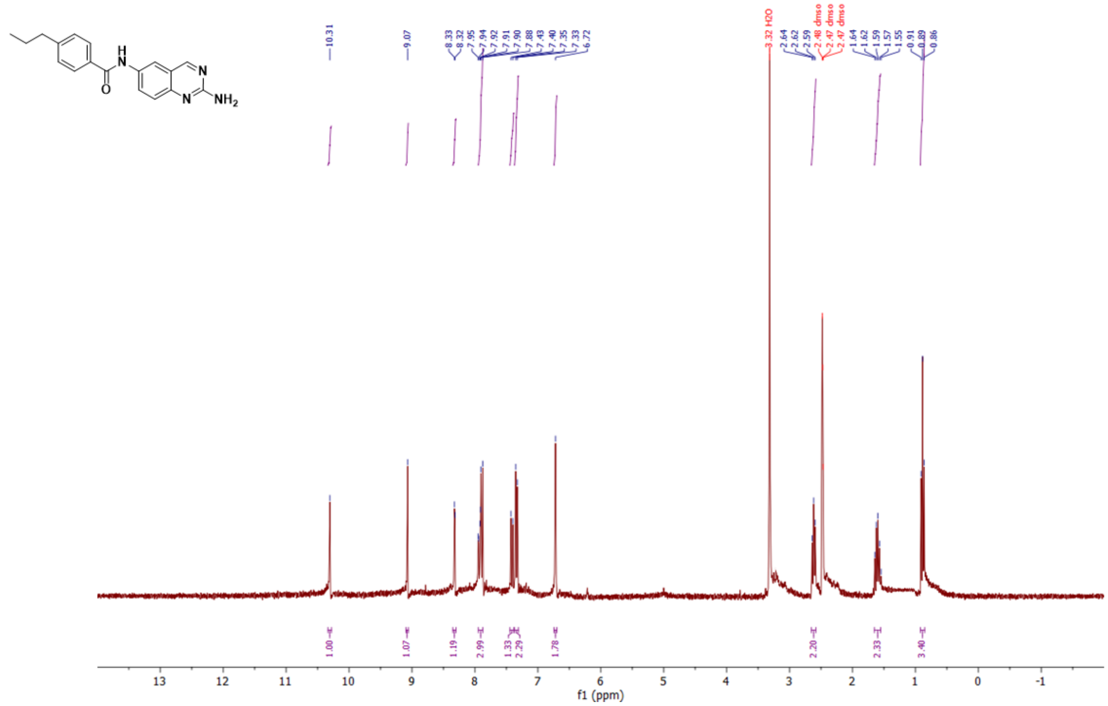


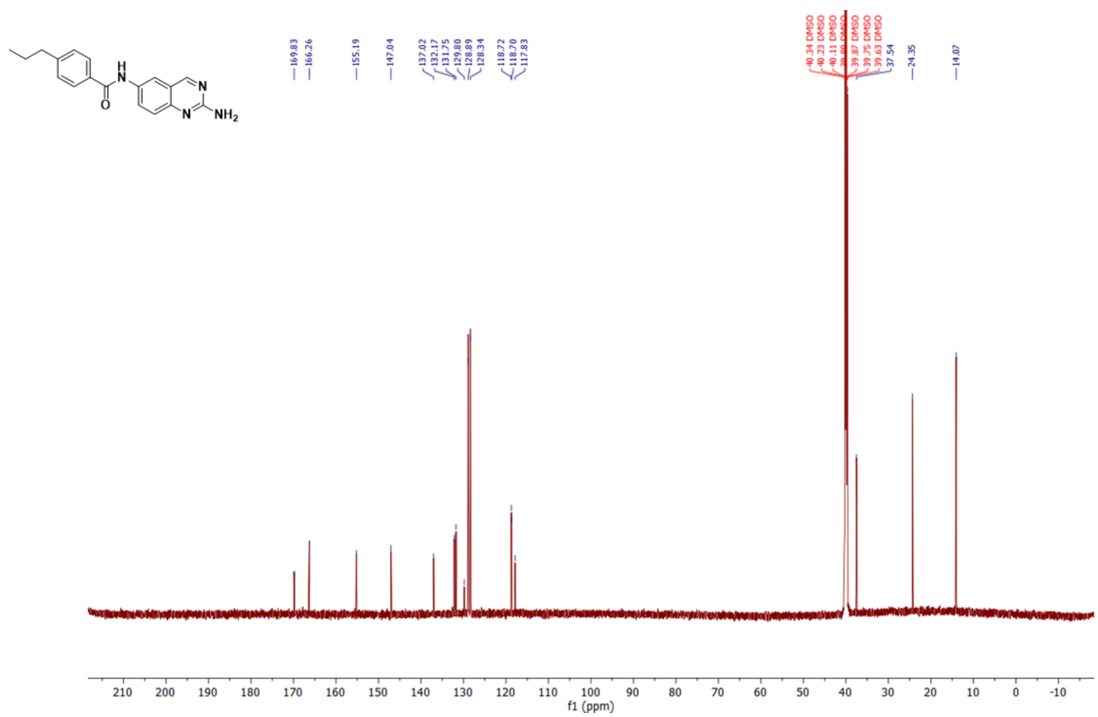
Compound 4k



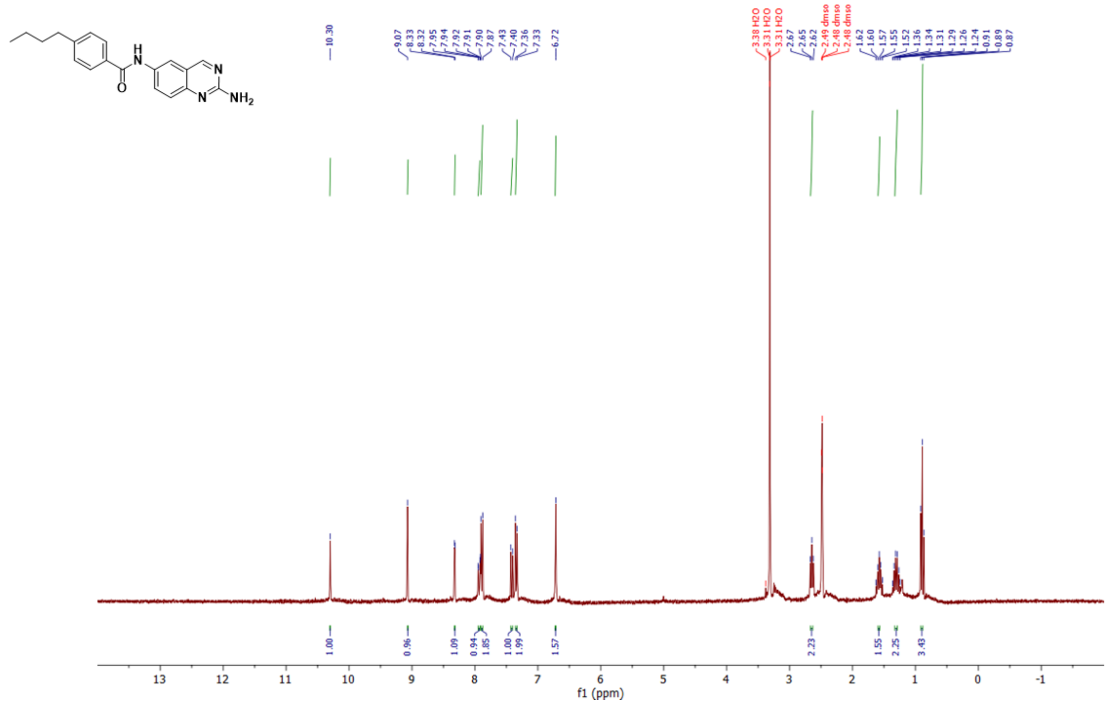


Compound 4l

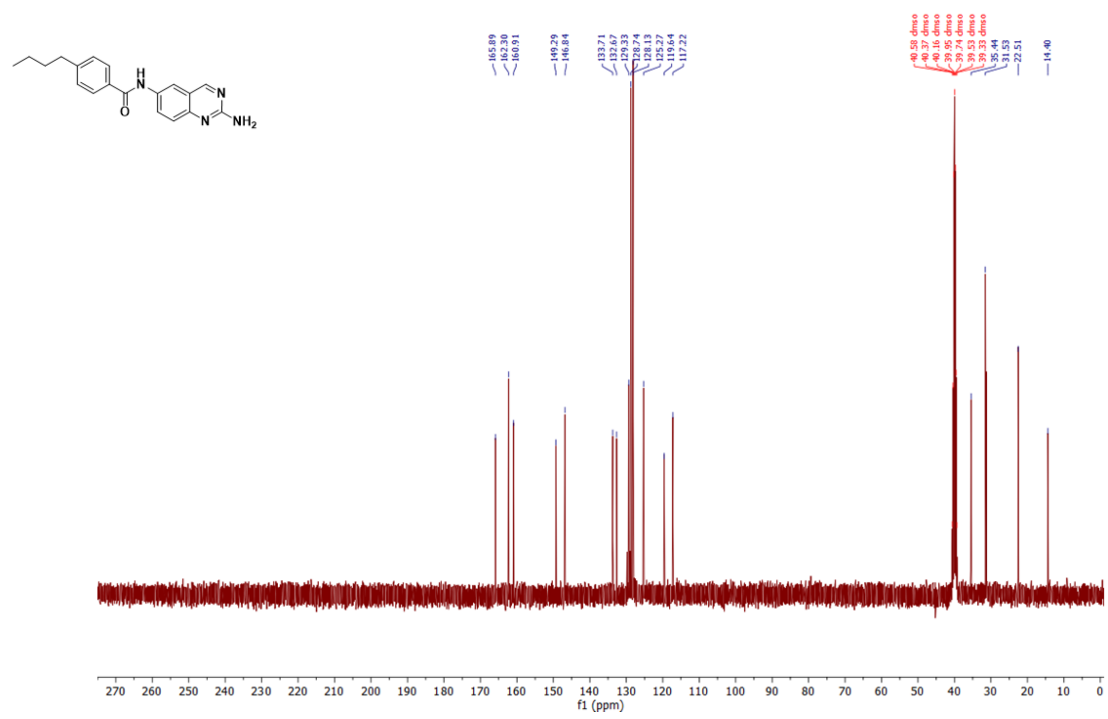




Compound 4m

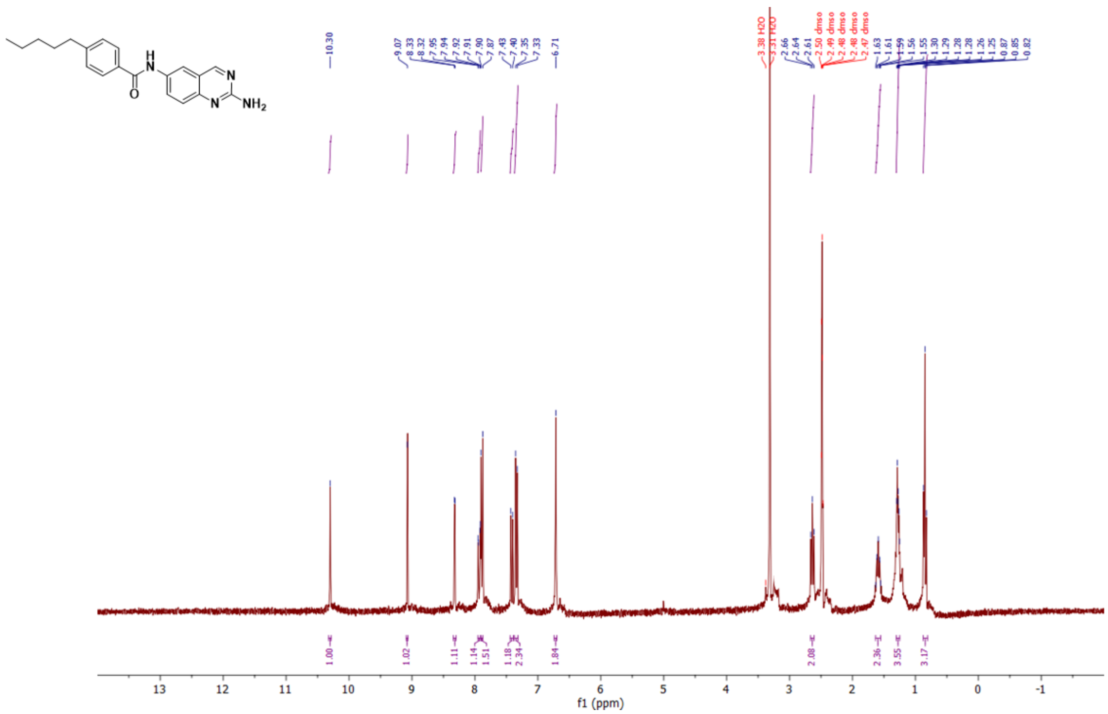


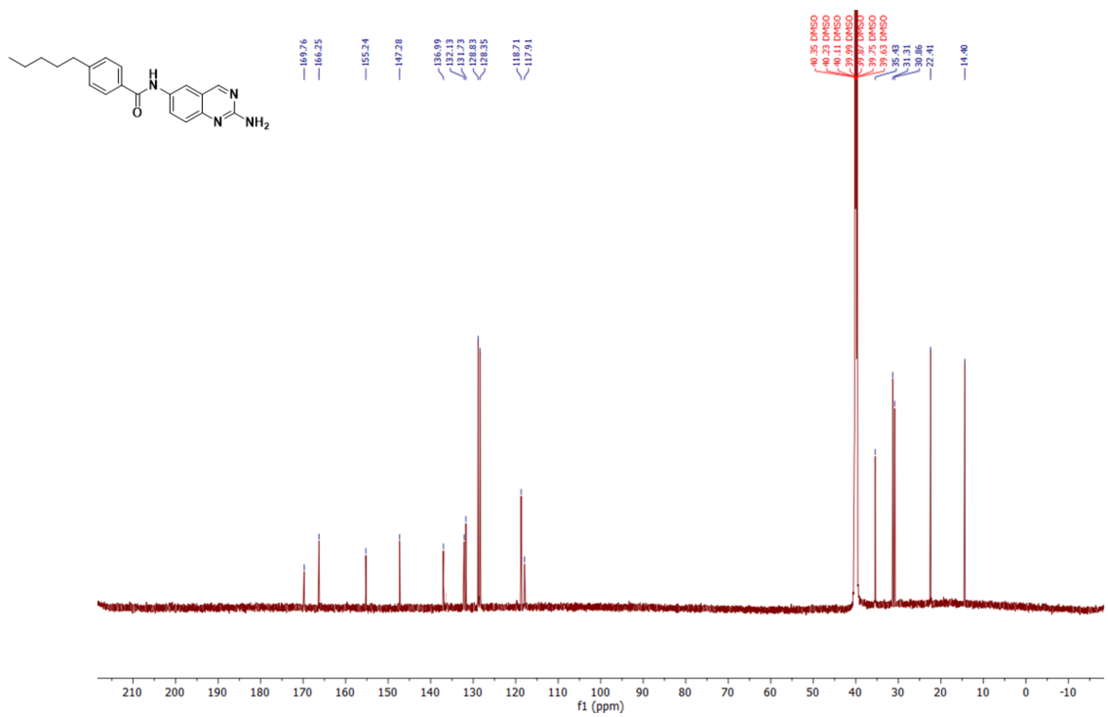
10.30
9.07
8.33
8.32
7.95
7.94
7.92
7.91
7.90
7.87
7.43
7.40
7.36
7.33
6.72
3.38 H2O
3.31 H2O
3.31 H2O
2.67
2.65
2.62
2.49 dmso
2.48 dmso
2.48 dmso
1.62
1.60
1.57
1.55
1.52
1.36
1.34
1.31
1.29
1.26
1.24
0.91
0.89
0.87
1.00
0.96
1.09
0.94
1.85
1.00
1.99
1.57
2.23
1.55
2.25
3.43
f1 (ppm)



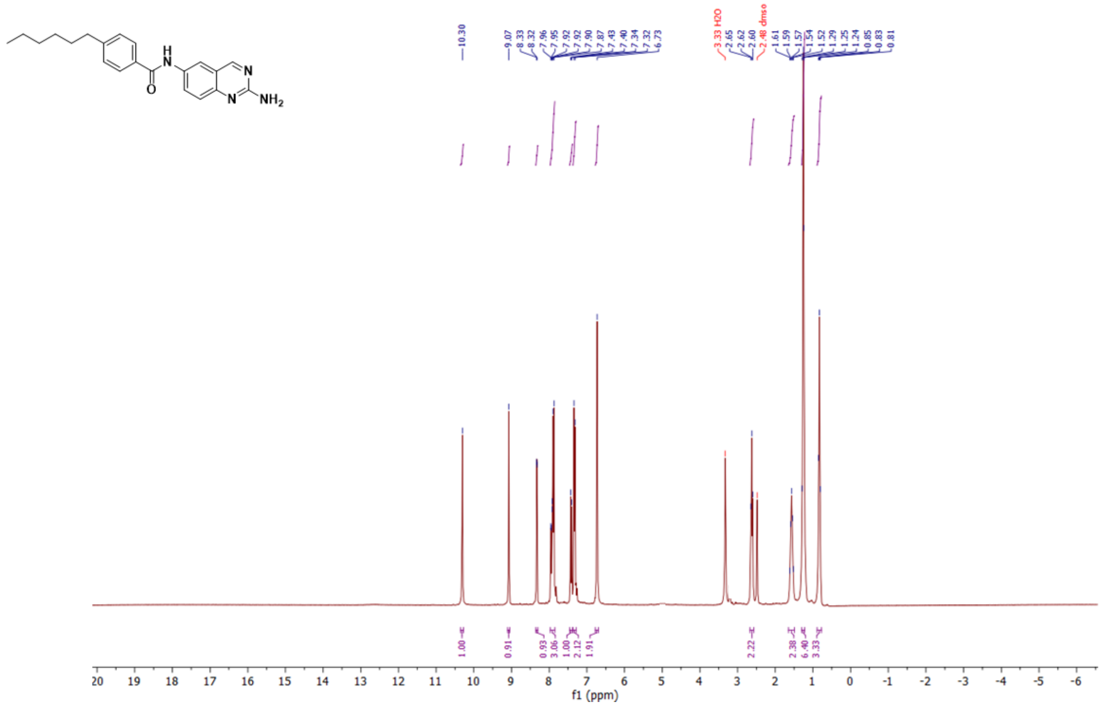
165.89
162.30
160.91
149.29
146.84
133.71
132.67
129.33
128.74
128.13
125.27
119.64
117.22
40.58 dmso
40.37 dmso
40.16 dmso
39.95 dmso
39.74 dmso
39.53 dmso
39.33 dmso
35.44
31.53
22.51
14.40
f1 (ppm)

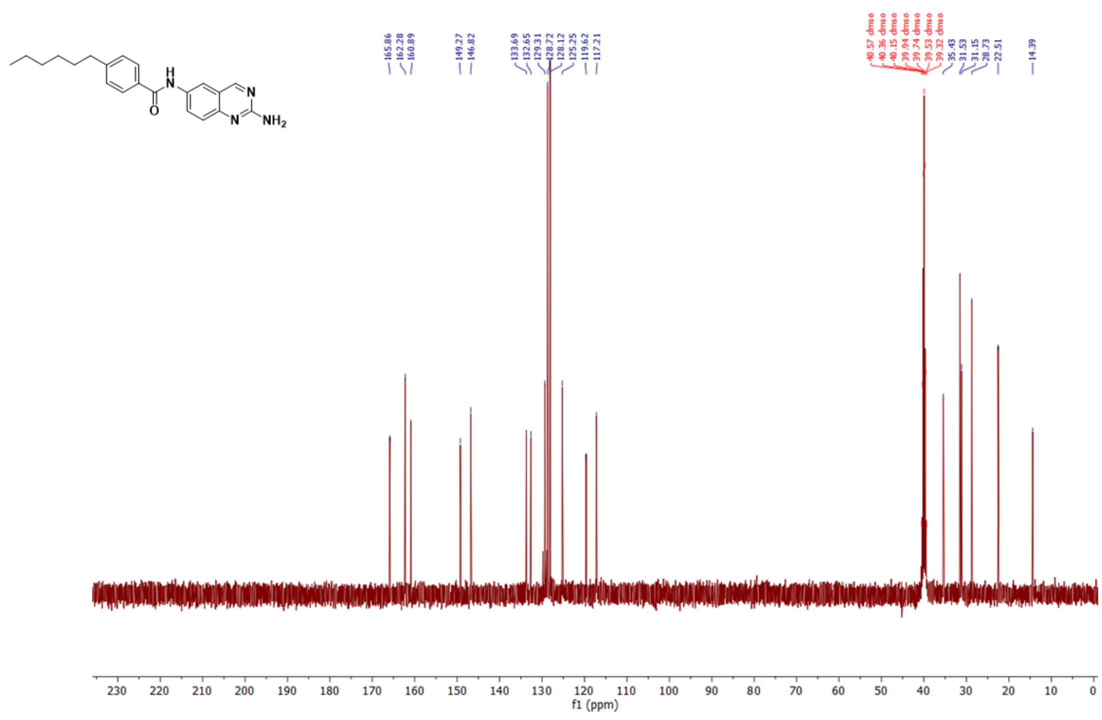
Compound 4n



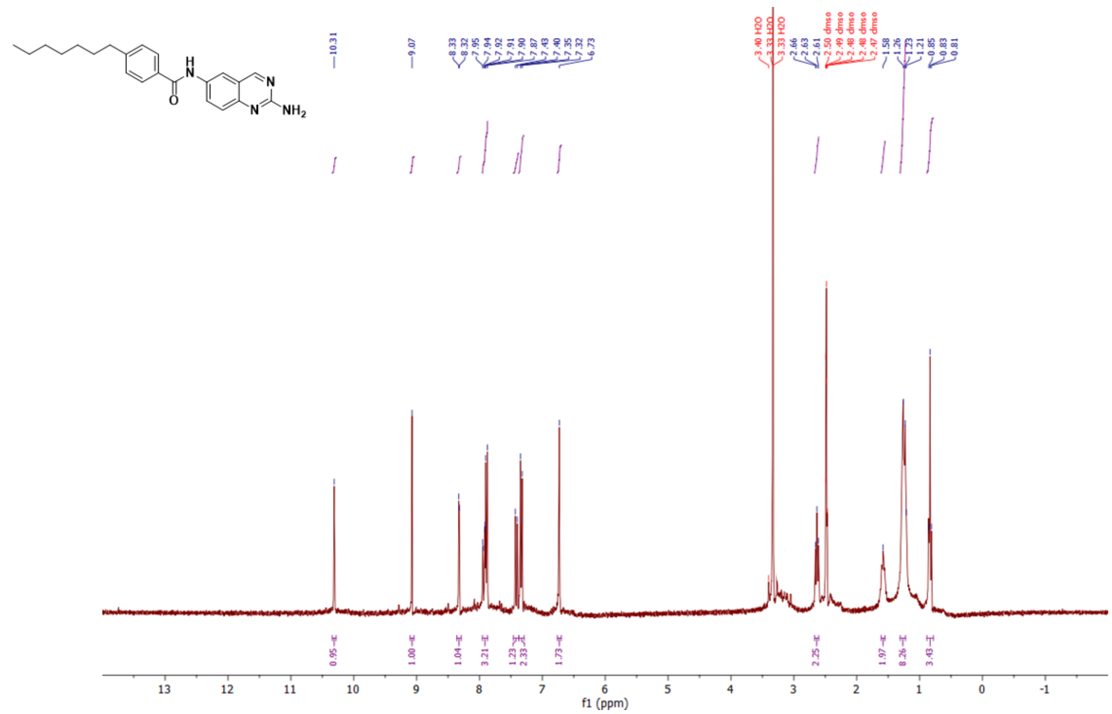


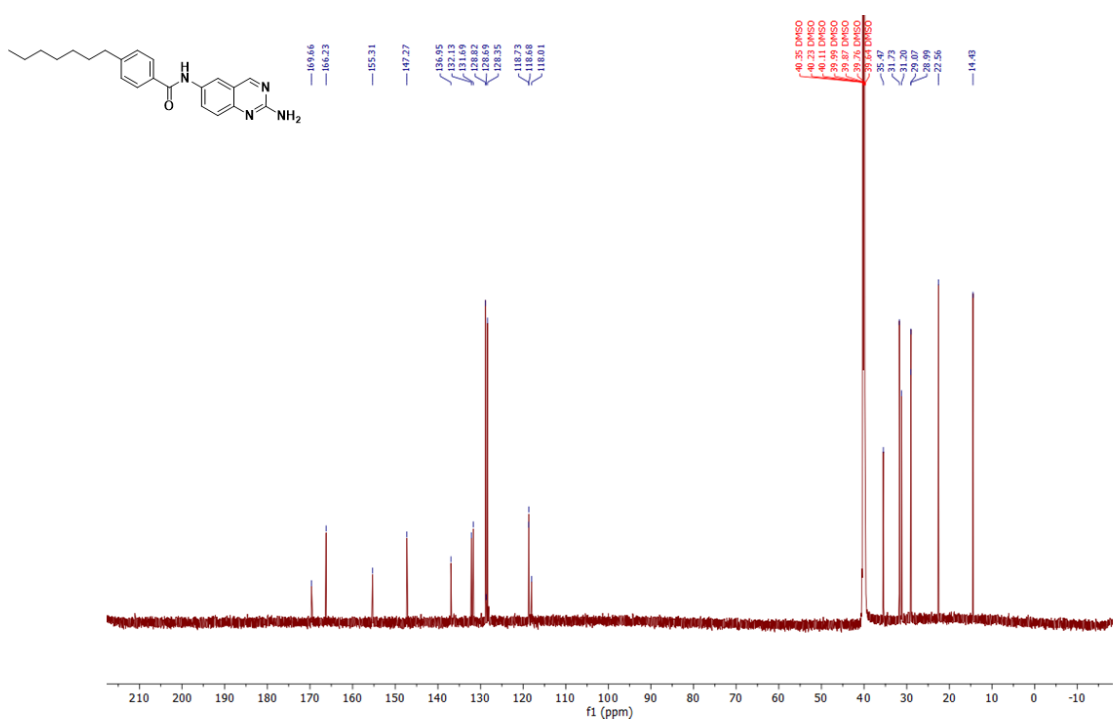
Compound 4o



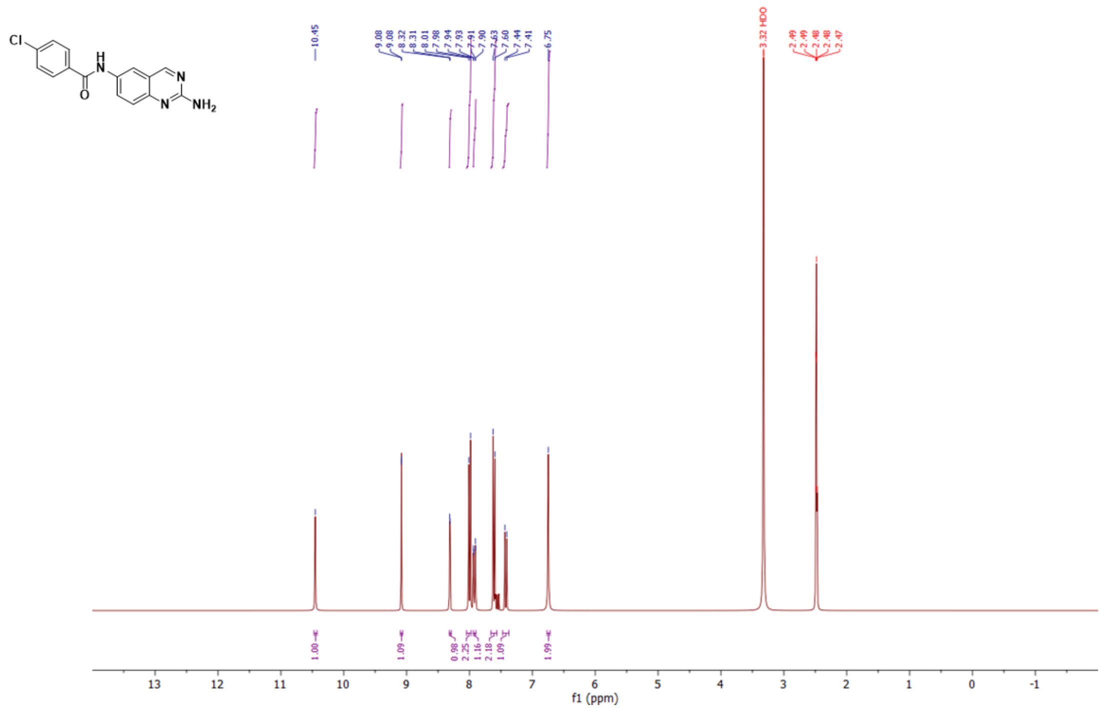


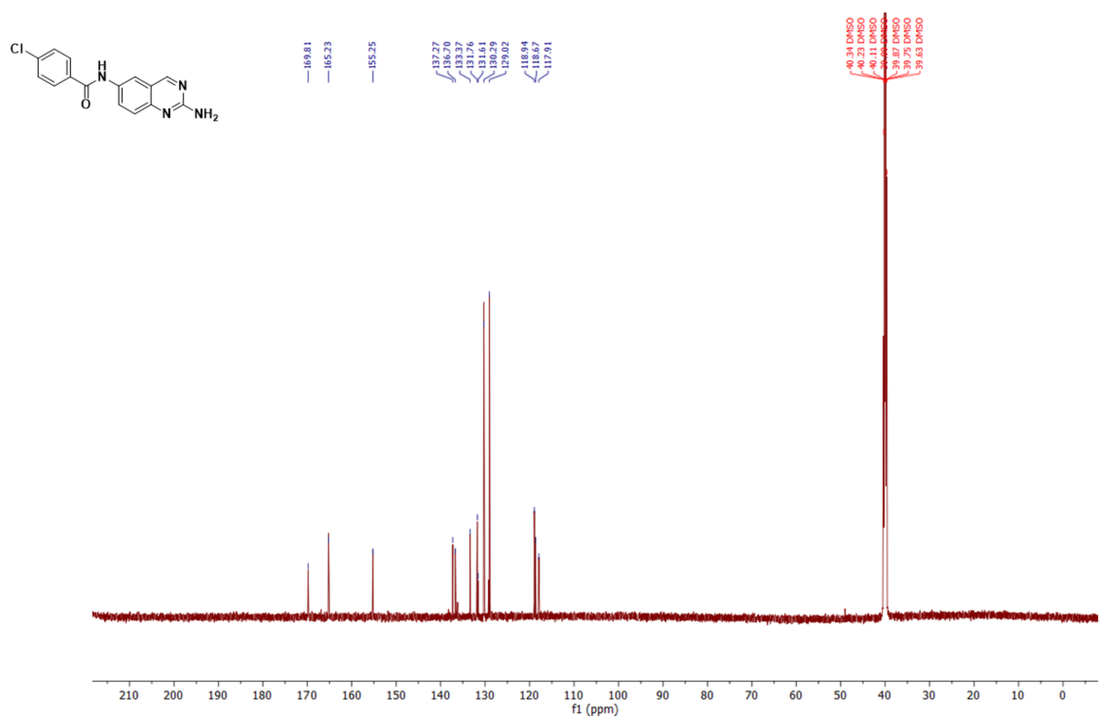
Compound 4p



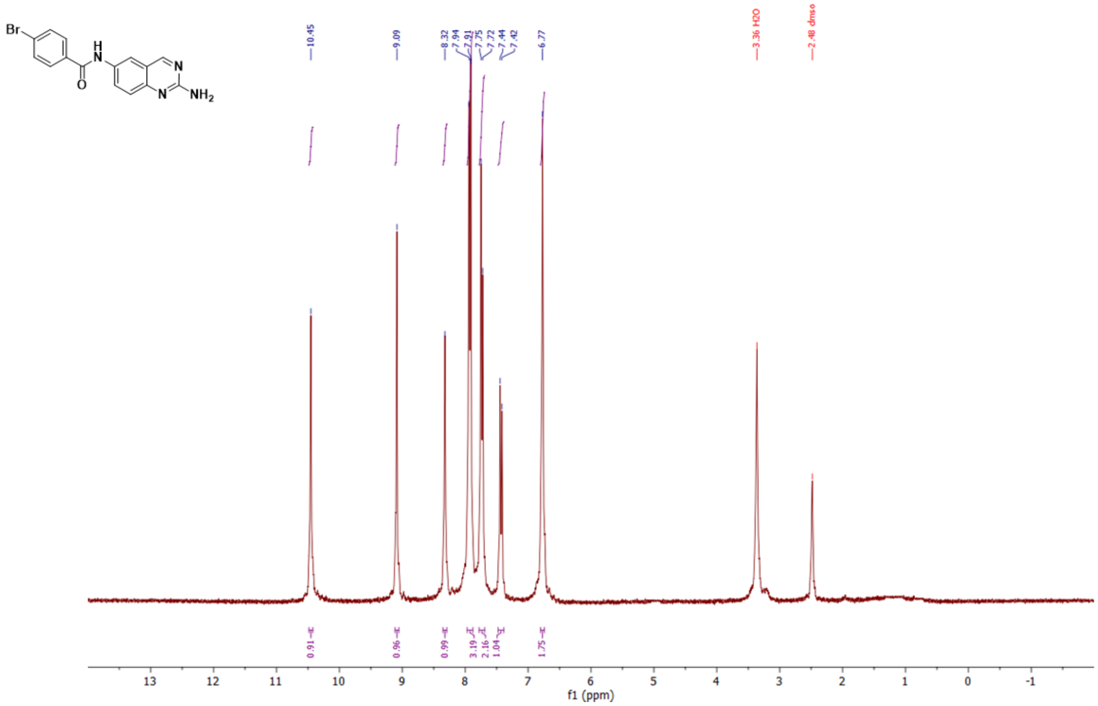


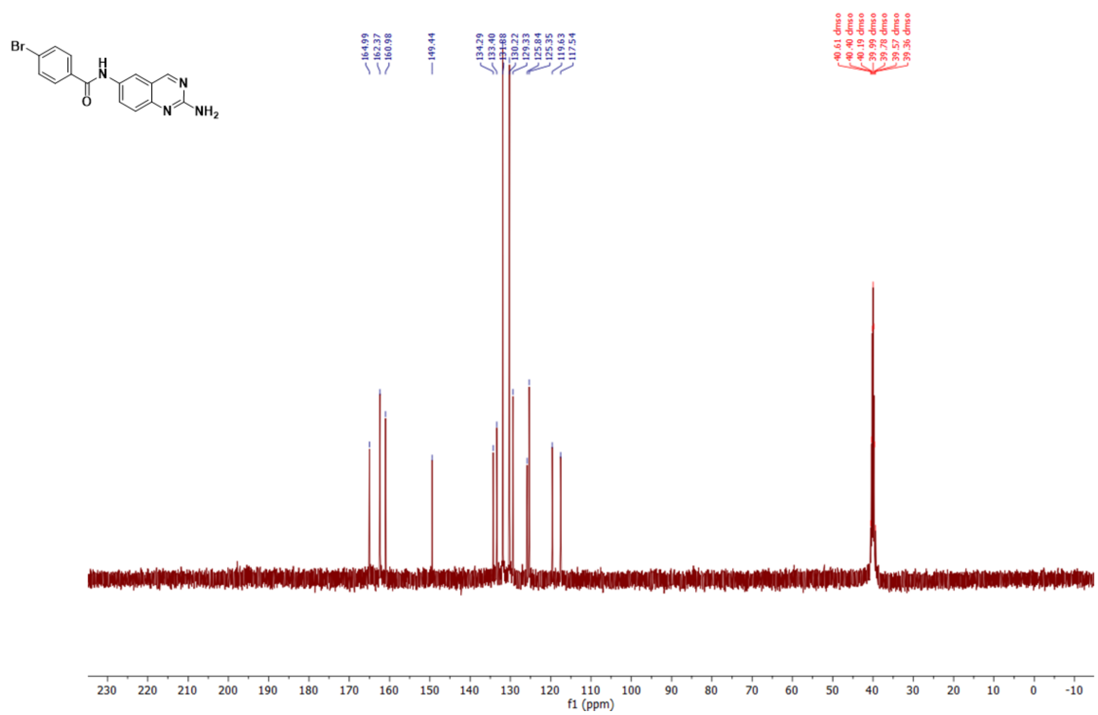
Compound 4q



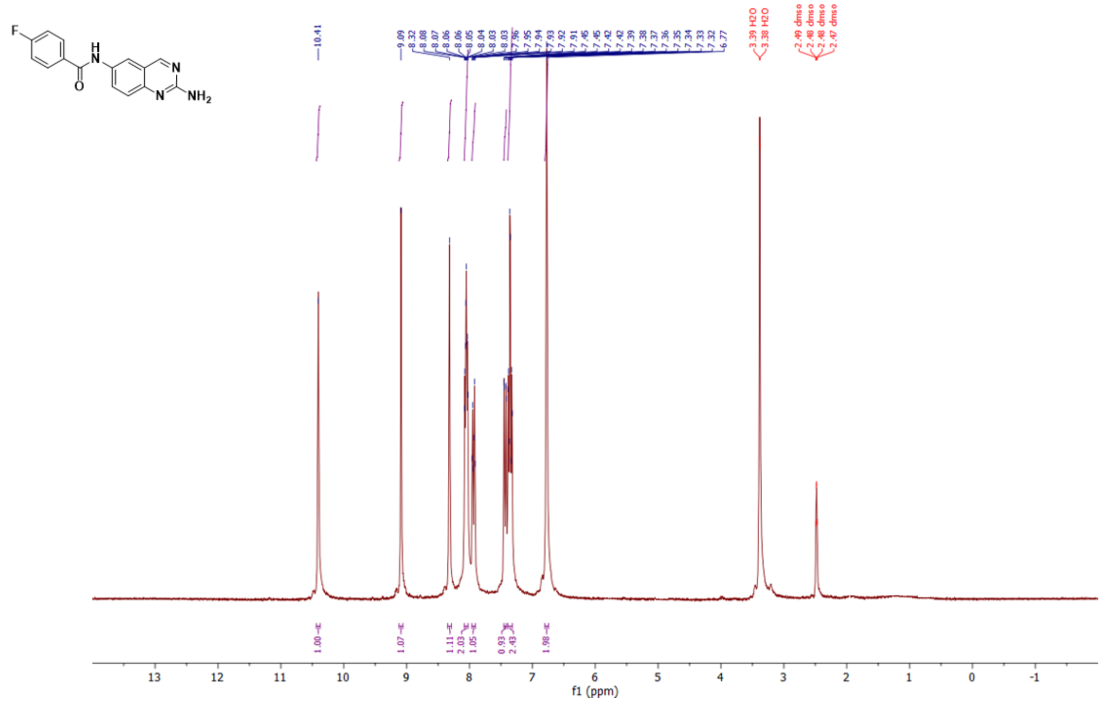


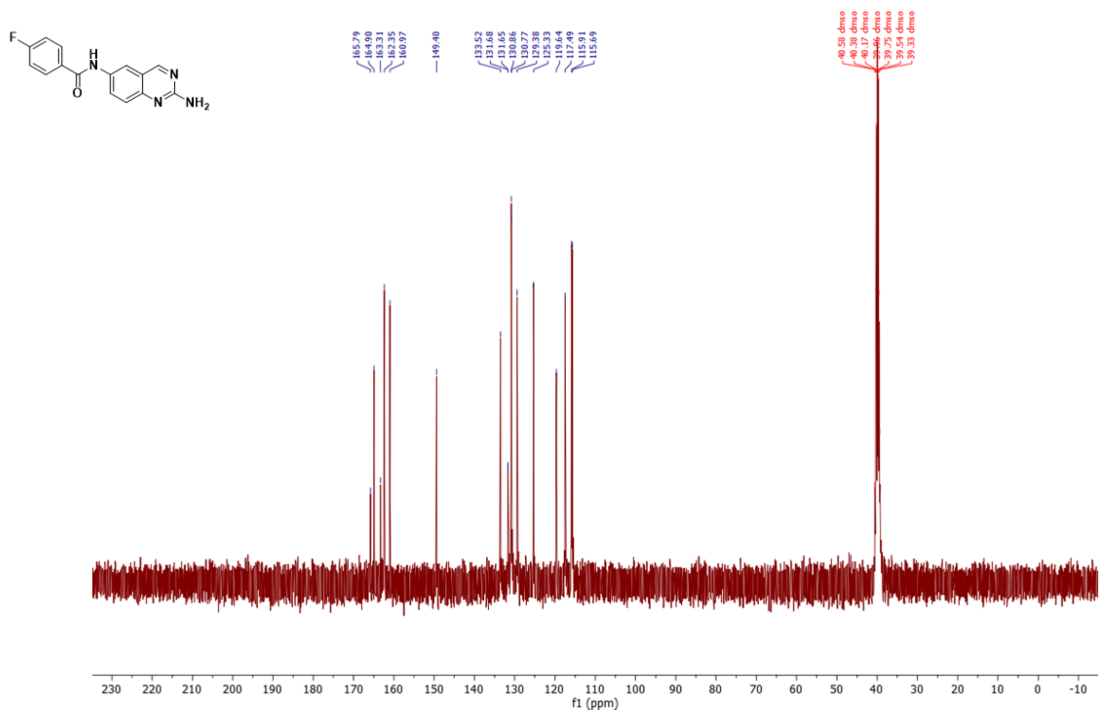
Compound 4r


Br
H
N
O
N
N
NH2
10.45
9.09
8.32
7.94
7.91
7.75
7.72
7.44
7.42
6.77
3.36 H2O
2.48 dmso
0.91
0.96
0.99
3.19
2.16
1.04
1.75
f1 (ppm)

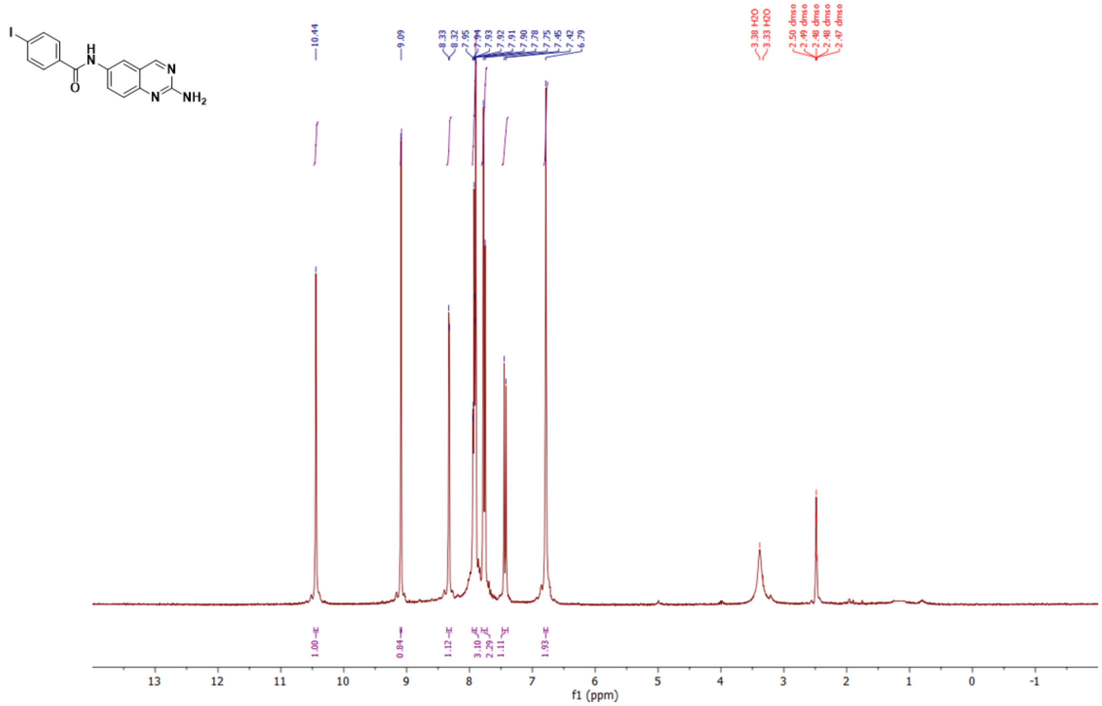

Br
H
N
O
N
N
NH2
164.99
162.37
160.98
149.44
134.29
133.40
131.88
130.22
129.33
125.84
125.35
119.63
117.54
40.61 dmso
40.40 dmso
40.19 dmso
39.99 dmso
39.78 dmso
39.57 dmso
39.36 dmso
f1 (ppm)

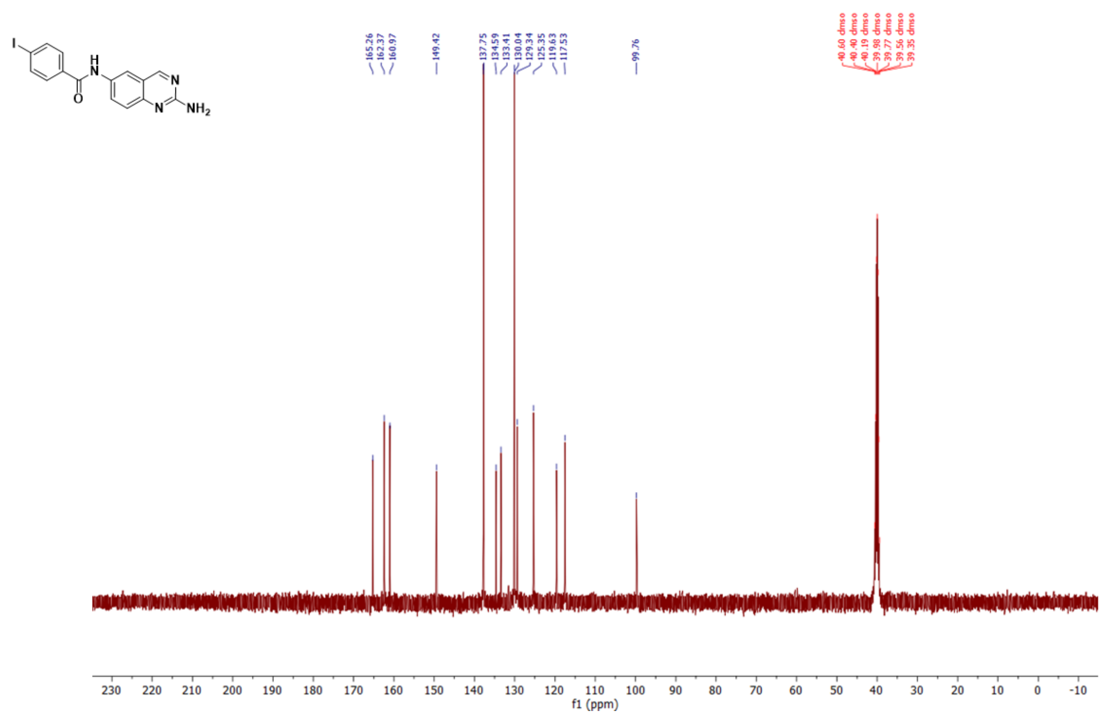
Compound 4s


F
H
N
O
N
N
NH2
10.41
9.09
8.32
8.08
8.07
8.06
8.06
8.05
8.04
8.03
8.03
8.03
7.96
7.95
7.94
7.93
7.92
7.91
7.45
7.45
7.42
7.42
7.39
7.38
7.37
7.36
7.35
7.34
7.33
7.32
6.77
3.39 H2O
3.38 H2O
2.49 dmso
2.48 dmso
2.48 dmso
2.47 dmso
1.00
1.07
1.11
2.03
1.05
0.93
2.43
1.98
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

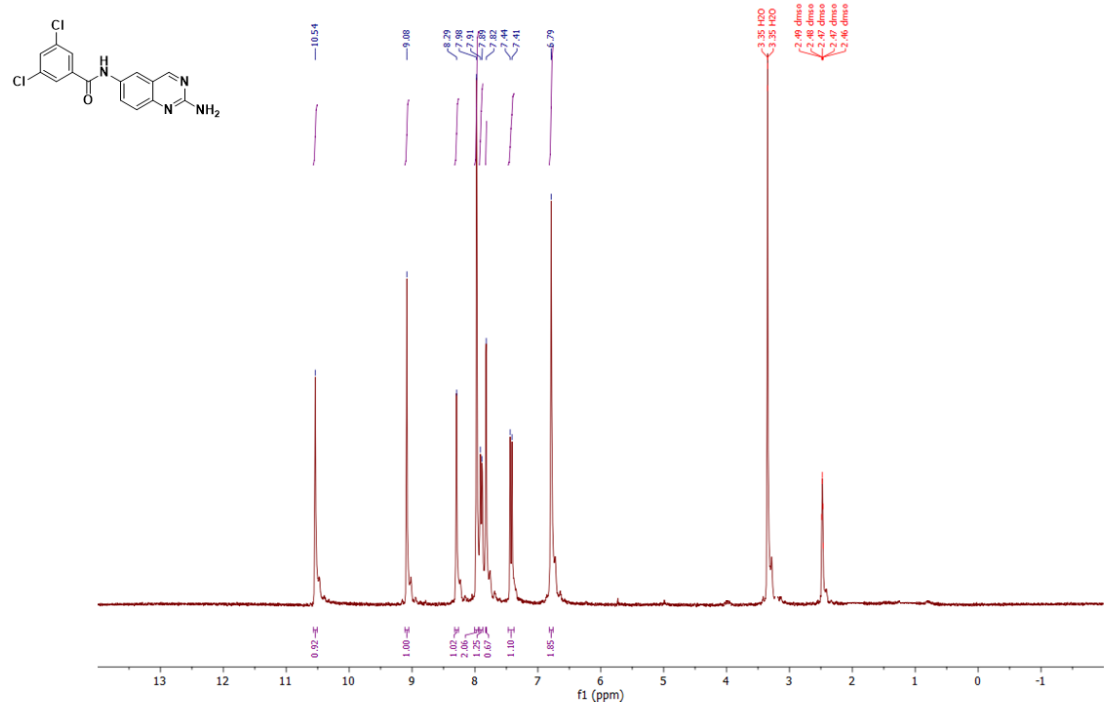

F
H
N
O
N
N
NH2
165.79
164.90
163.31
162.35
160.97
149.40
133.52
131.68
131.65
130.86
130.77
129.38
125.33
119.64
117.49
115.91
115.69
40.58 dmso
40.38 dmso
40.17 dmso
39.96 dmso
39.75 dmso
39.54 dmso
39.33 dmso
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 4t

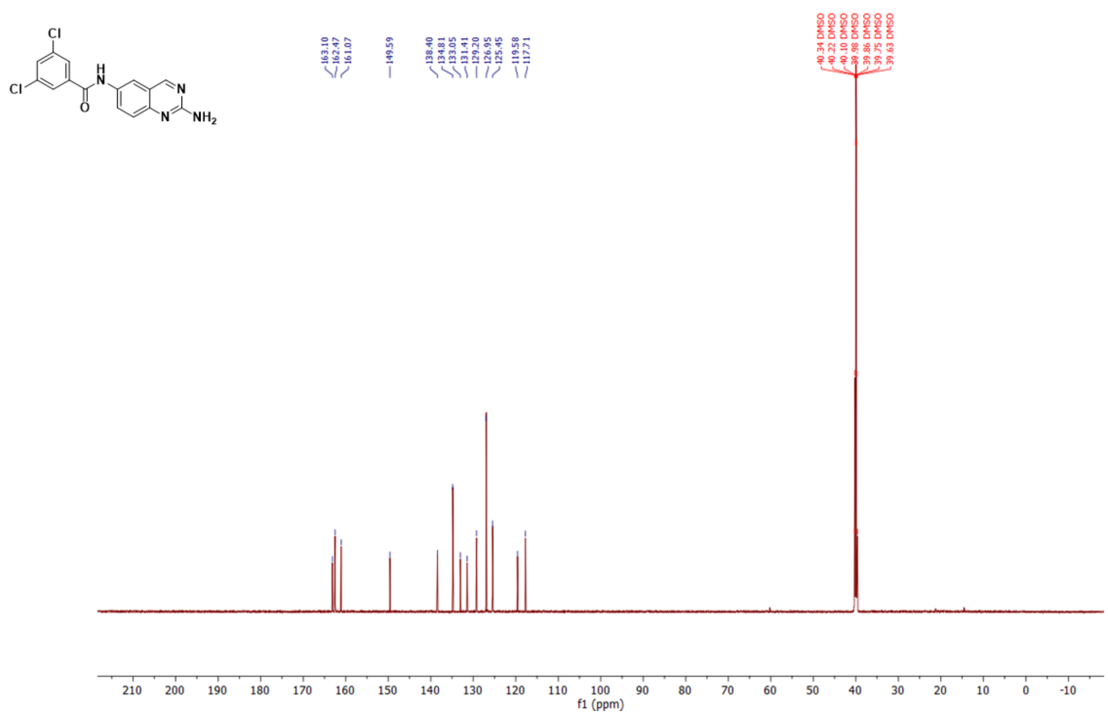




Compound 4u

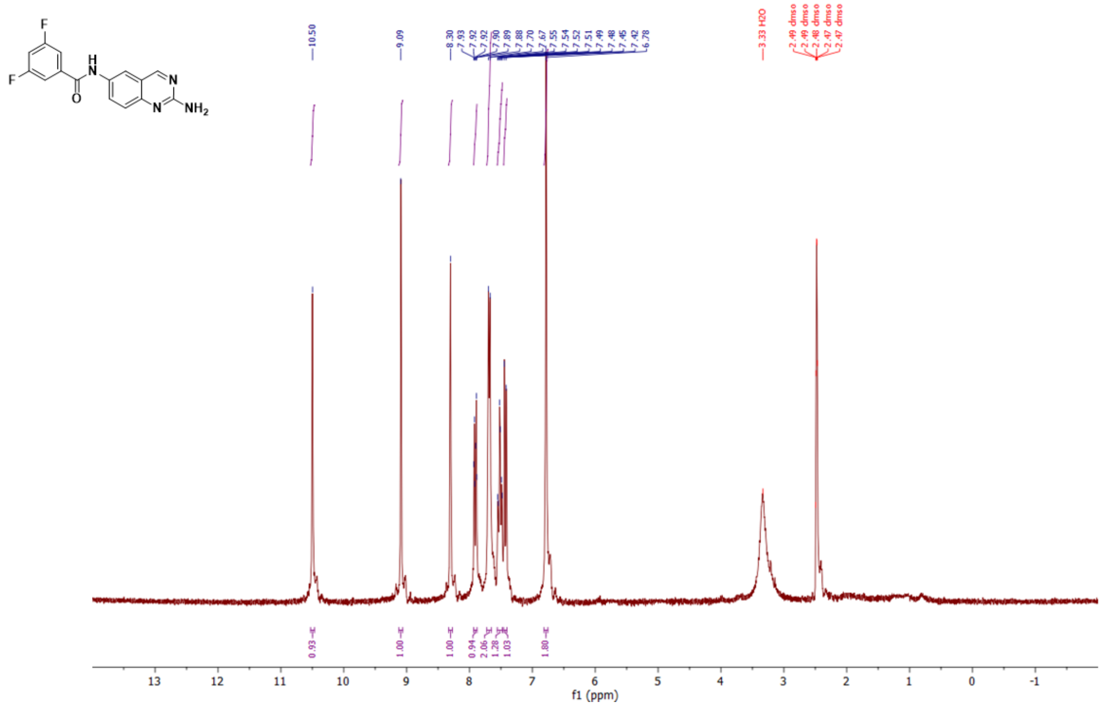


Cl
Cl
H
N
O
N
N
NH2
10.54
9.08
8.29
7.98
7.91
7.89
7.82
7.44
7.41
6.79
3.35 H2O
3.35 H2O
2.49 dmso
2.48 dmso
2.47 dmso
2.47 dmso
2.46 dmso
0.92
1.00
1.02
2.06
1.25
0.67
1.10
1.85
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

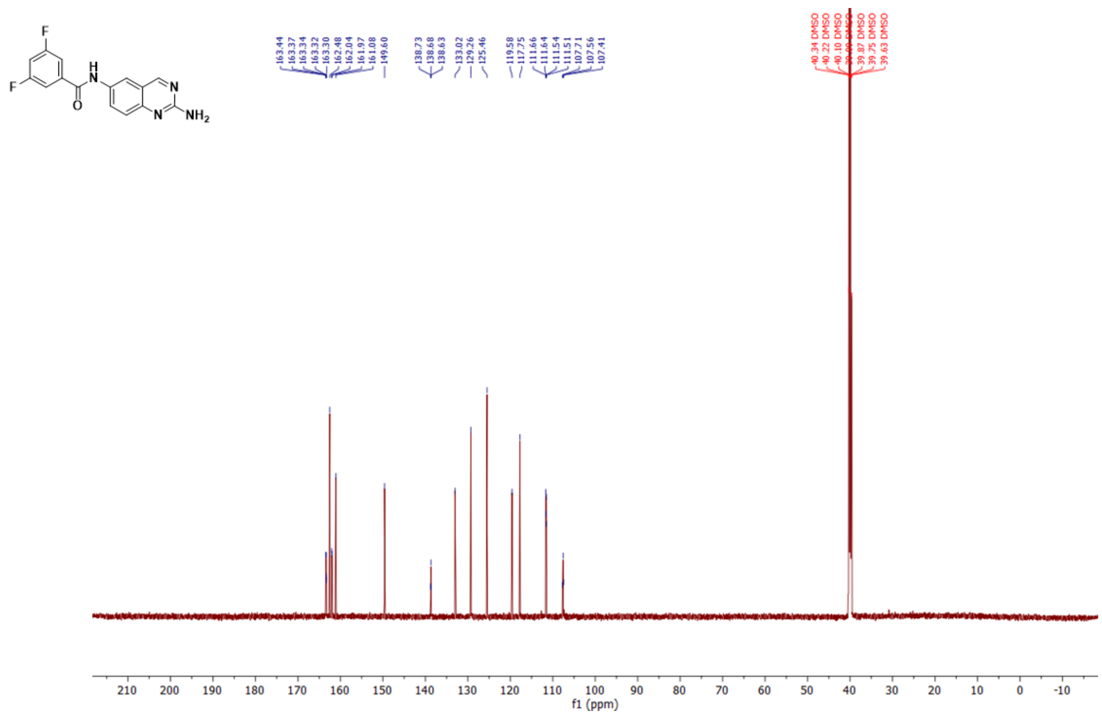


Cl
Cl
H
N
O
N
N
NH2
163.10
162.47
161.07
149.59
138.40
134.81
133.05
131.41
129.20
126.95
125.45
119.58
117.71
40.34 DMSO
40.22 DMSO
40.10 DMSO
39.98 DMSO
39.86 DMSO
39.75 DMSO
39.63 DMSO
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 4v

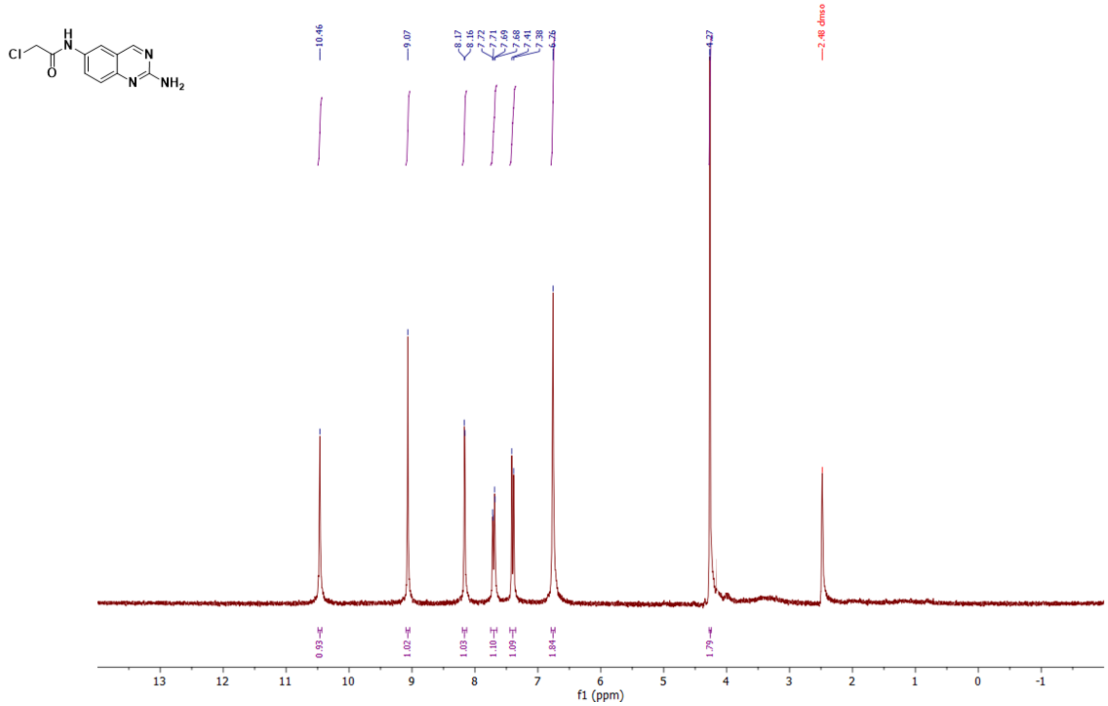


F
F
H
N
O
N
N
NH2
10.50
9.09
8.30
7.93
7.92
7.92
7.90
7.89
7.88
7.70
7.67
7.55
7.54
7.52
7.51
7.49
7.48
7.45
7.42
6.78
3.33 H2O
2.49 dmso
2.49 dmso
2.48 dmso
2.47 dmso
2.47 dmso
0.93
1.00
1.00
0.94
2.06
1.28
1.03
1.80
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

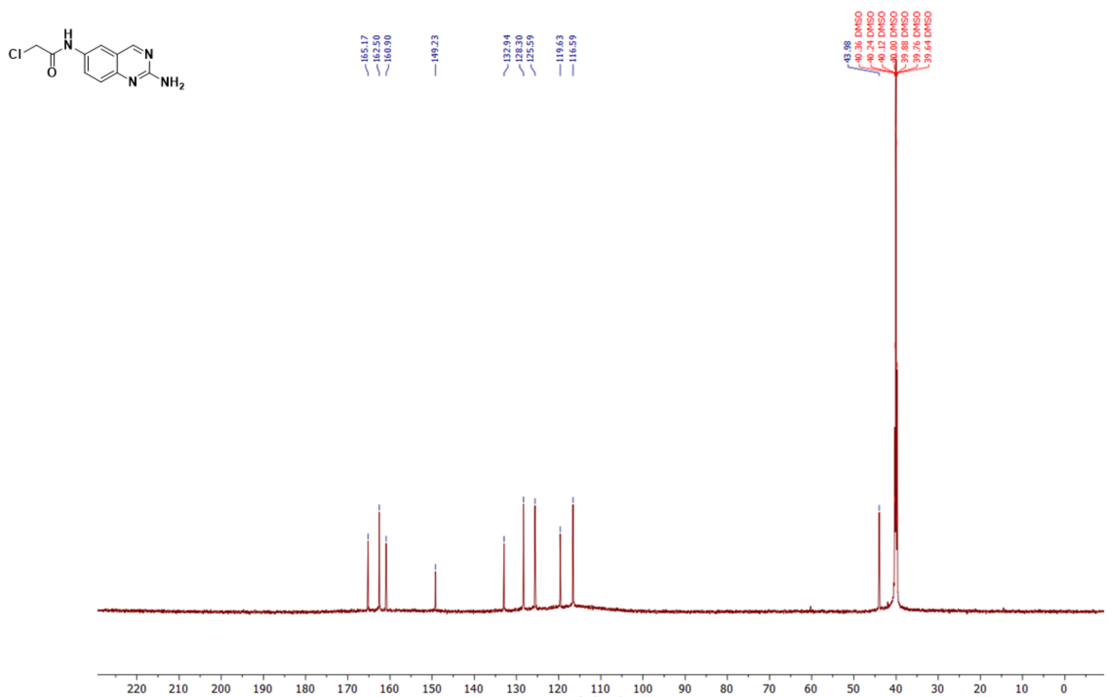


F
F
H
N
O
N
N
NH2
163.44
163.37
163.34
163.32
163.30
162.48
162.04
161.97
161.08
149.60
138.73
138.68
138.63
133.02
129.26
125.46
119.58
117.75
111.66
111.64
111.54
111.51
107.71
107.56
107.41
40.34 DMSO
40.22 DMSO
40.10 DMSO
39.87 DMSO
39.75 DMSO
39.63 DMSO
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 4w

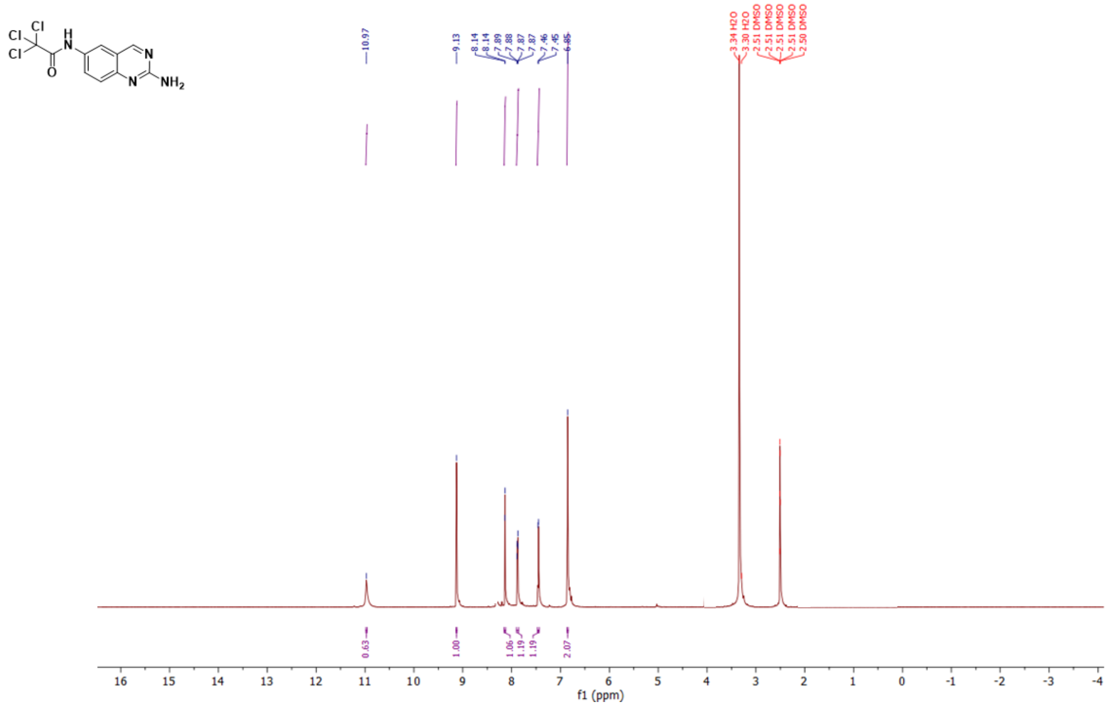


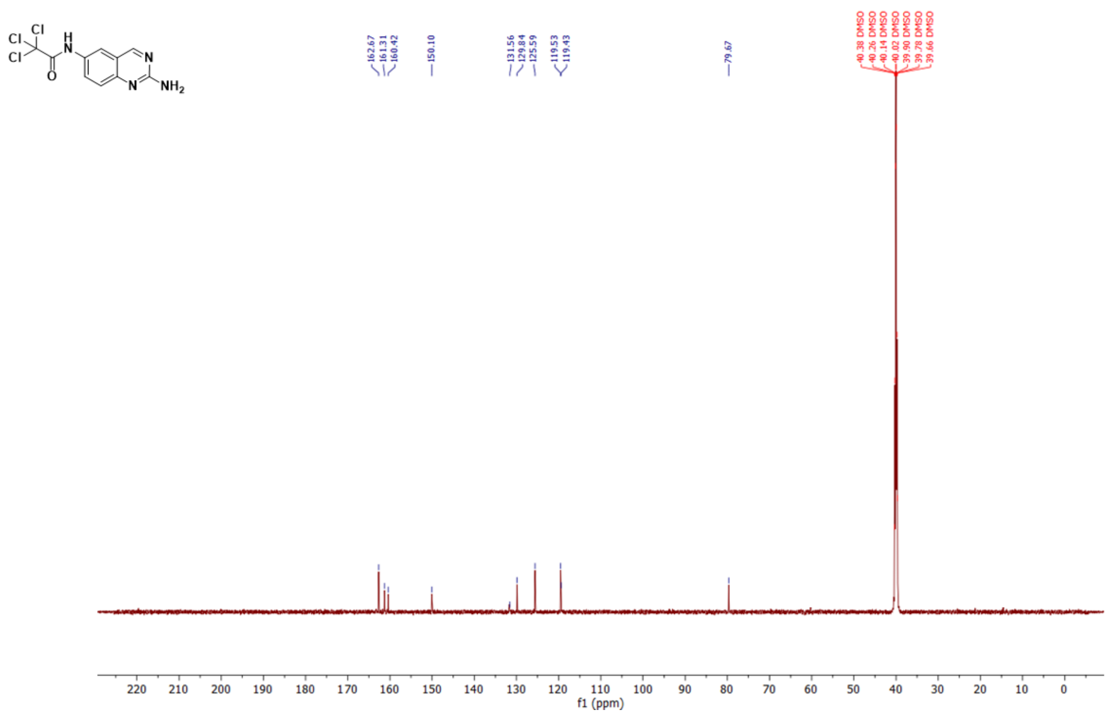
Cl
H
N
O
N
N
NH2
10.46
9.07
8.17
8.16
7.72
7.71
7.69
7.68
7.41
7.38
6.76
4.27
2.48 dmso
0.93
1.02
1.03
1.10
1.09
1.84
1.79
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)



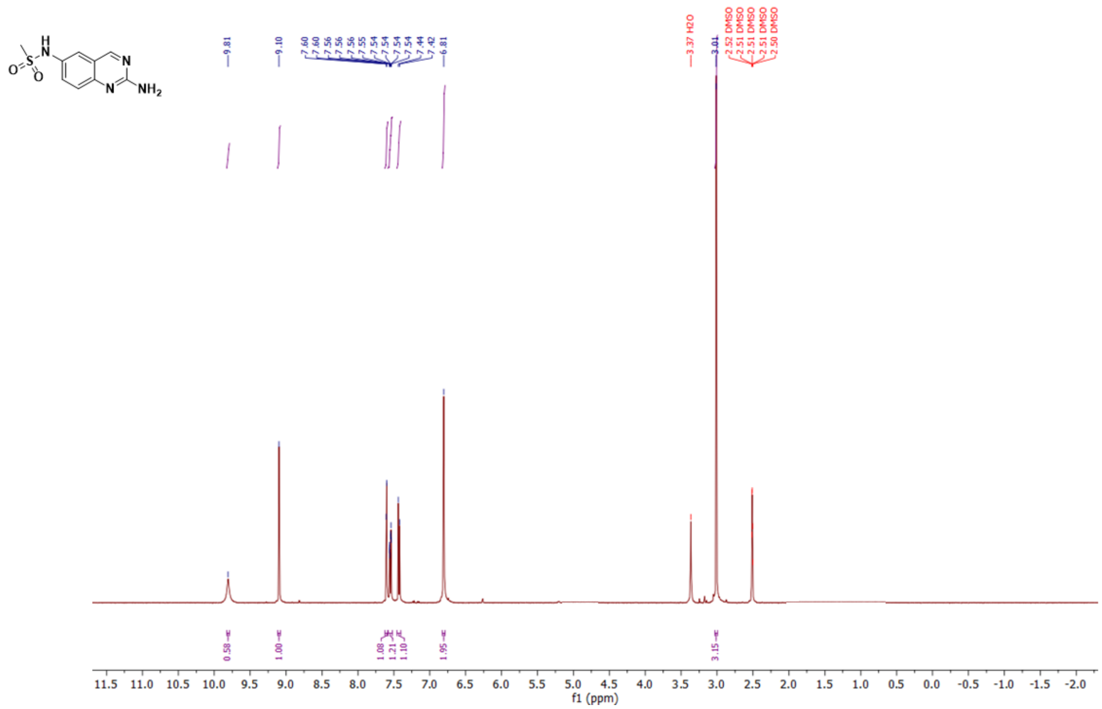
Cl
H
N
O
N
N
NH2
165.17
162.50
160.90
149.23
132.94
128.30
125.59
119.63
116.59
43.98
40.36 DMSO
40.24 DMSO
40.12 DMSO
40.00 DMSO
39.88 DMSO
39.76 DMSO
39.64 DMSO
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Compound 4x

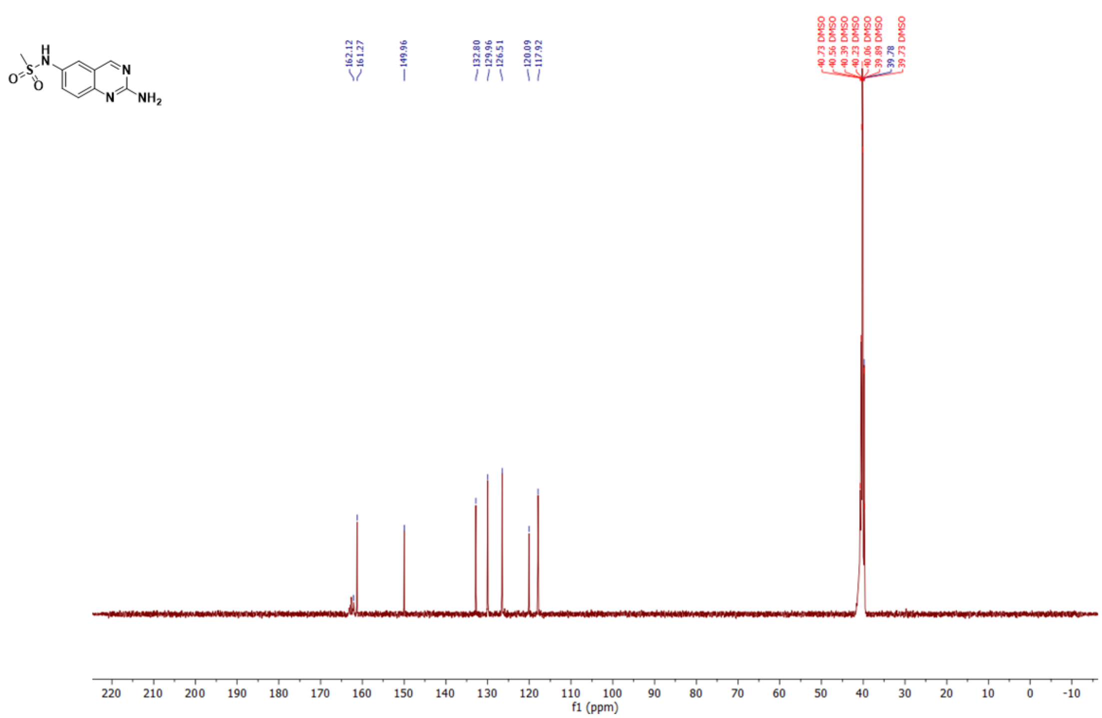




Compound 5a

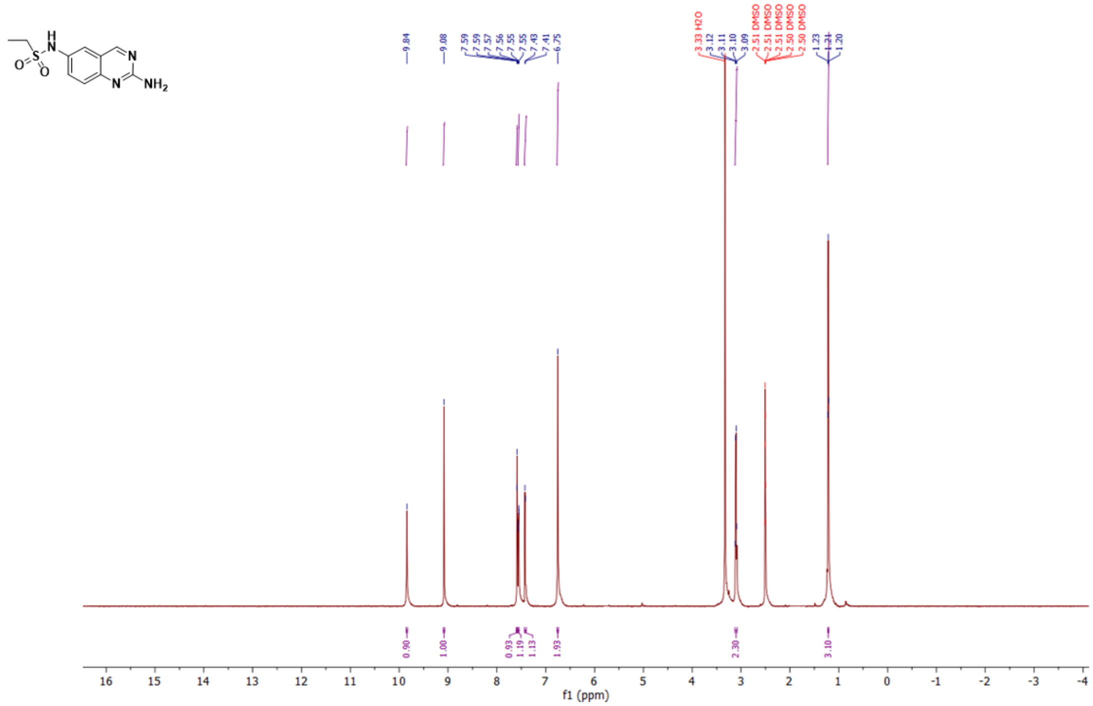


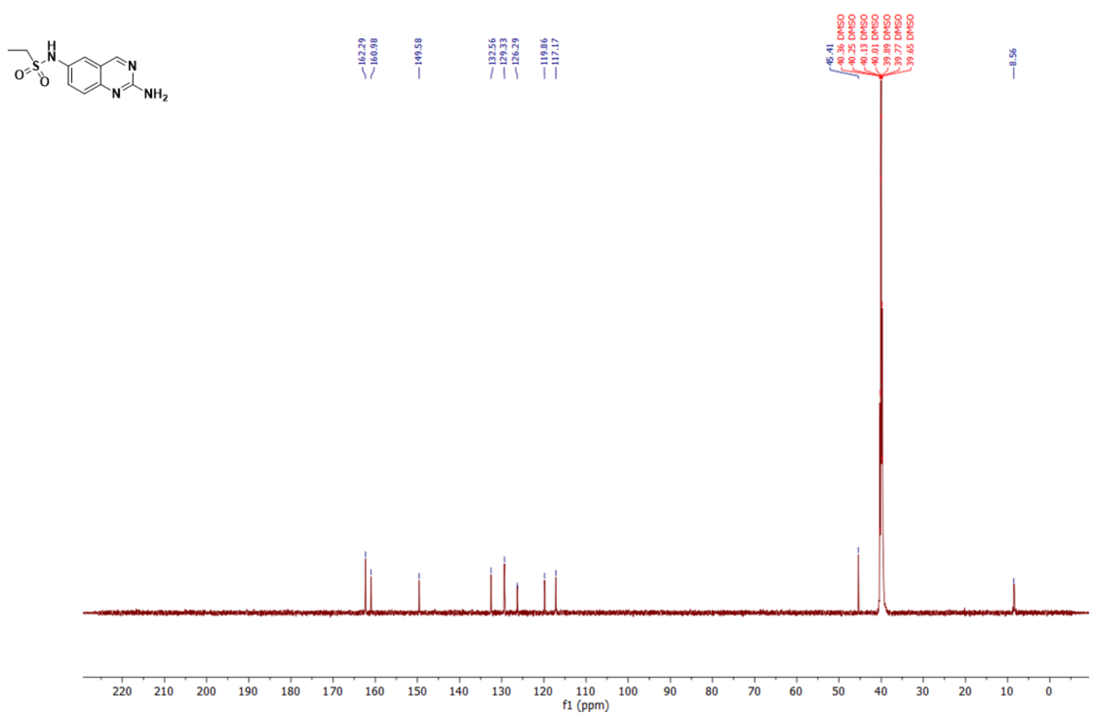
NH2
9.81
9.10
7.60 7.60 7.56 7.56 7.56 7.55 7.54 7.54 7.54 7.54 7.44 7.42
6.81
3.37 H2O
3.01
2.52 DMSO 2.51 DMSO 2.51 DMSO 2.51 DMSO 2.50 DMSO
0.58
1.00
1.08 1.21 1.10
1.95
3.15
f1 (ppm)



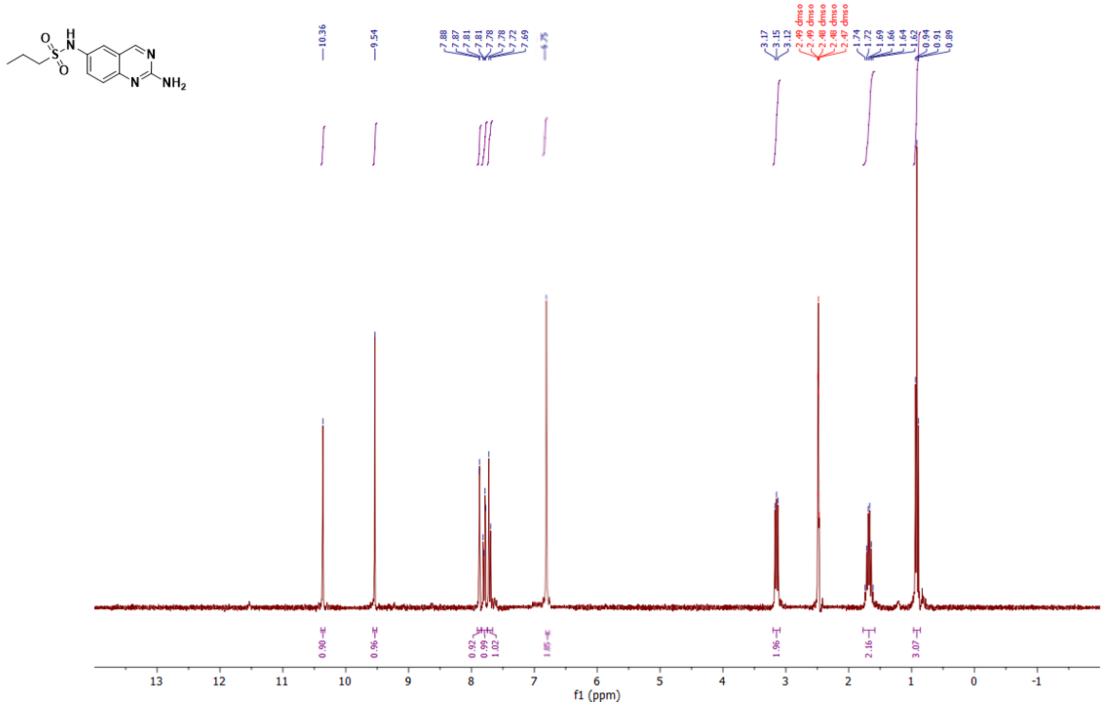
NH2
162.12 161.27
149.96
132.80 129.96 126.51
120.09 117.92
40.73 DMSO 40.56 DMSO 40.39 DMSO 40.23 DMSO 40.06 DMSO 39.89 DMSO 39.78 39.73 DMSO
f1 (ppm)

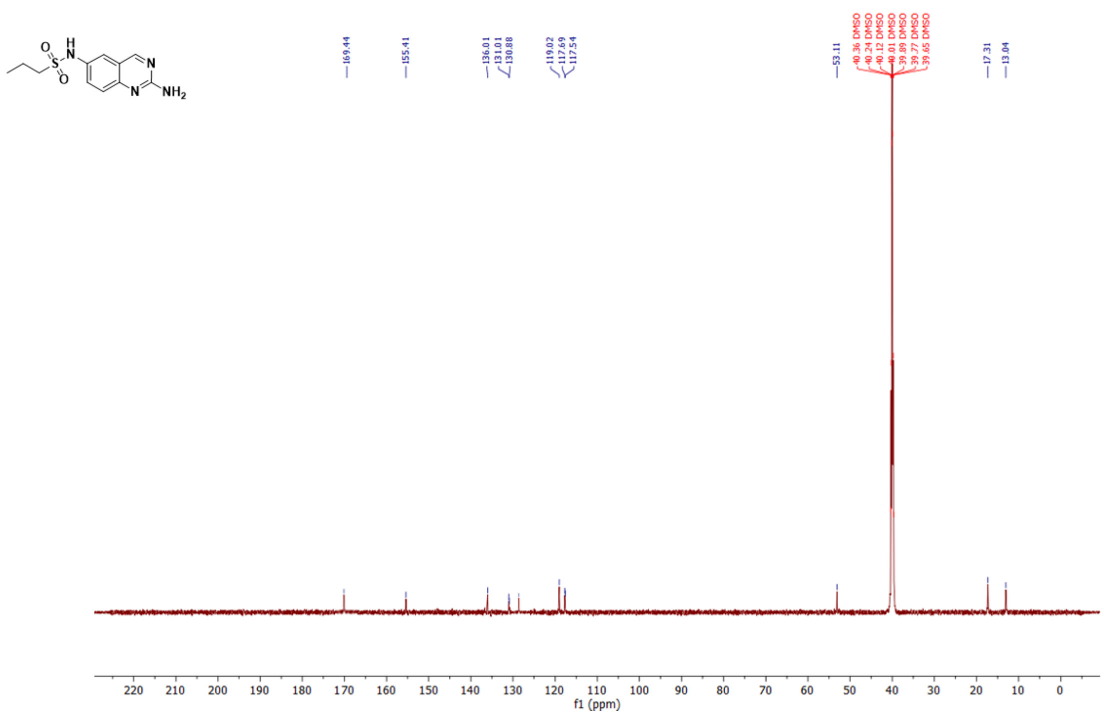
Compound 5b


9.84
9.08
7.59
7.59
7.57
7.56
7.55
7.55
7.43
7.41
6.75
3.33 H2O
3.12
3.11
3.10
3.09
2.51 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
2.50 DMSO
1.23
1.21
1.20
0.90
1.00
0.93
1.19
1.13
1.93
2.30
3.10
f1 (ppm)

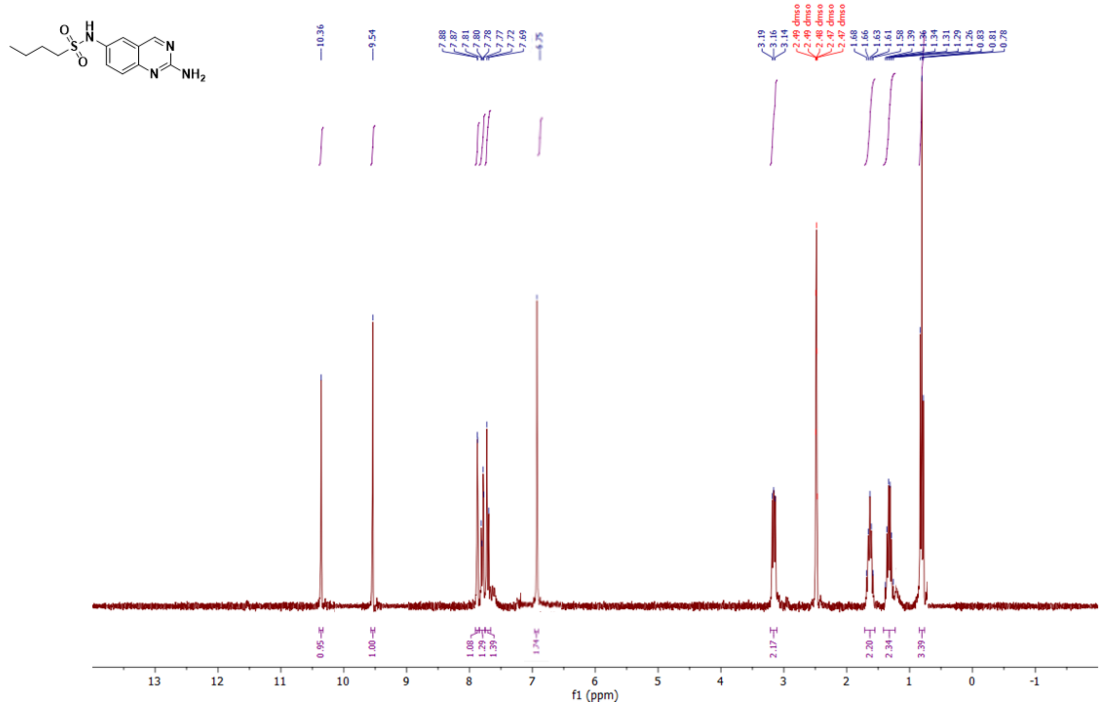

162.29
160.98
149.58
132.56
129.33
126.29
119.86
117.17
45.41
40.36 DMSO
40.25 DMSO
40.13 DMSO
40.01 DMSO
39.89 DMSO
39.77 DMSO
39.65 DMSO
8.56
f1 (ppm)

Compound 5c

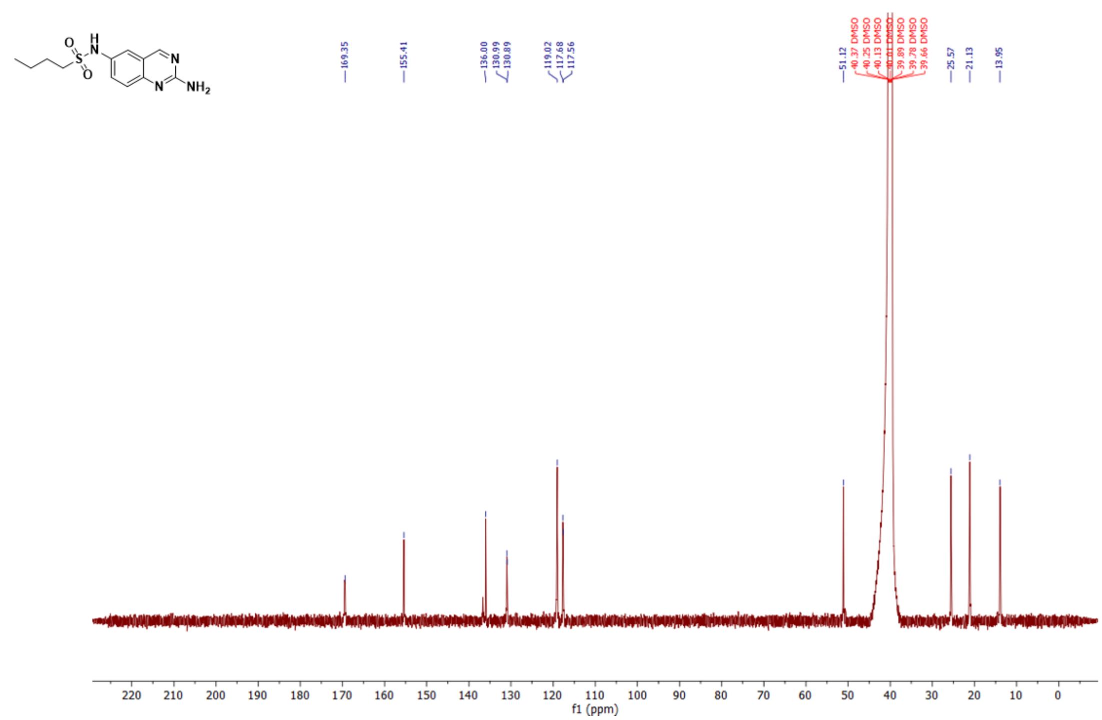




Compound 5d

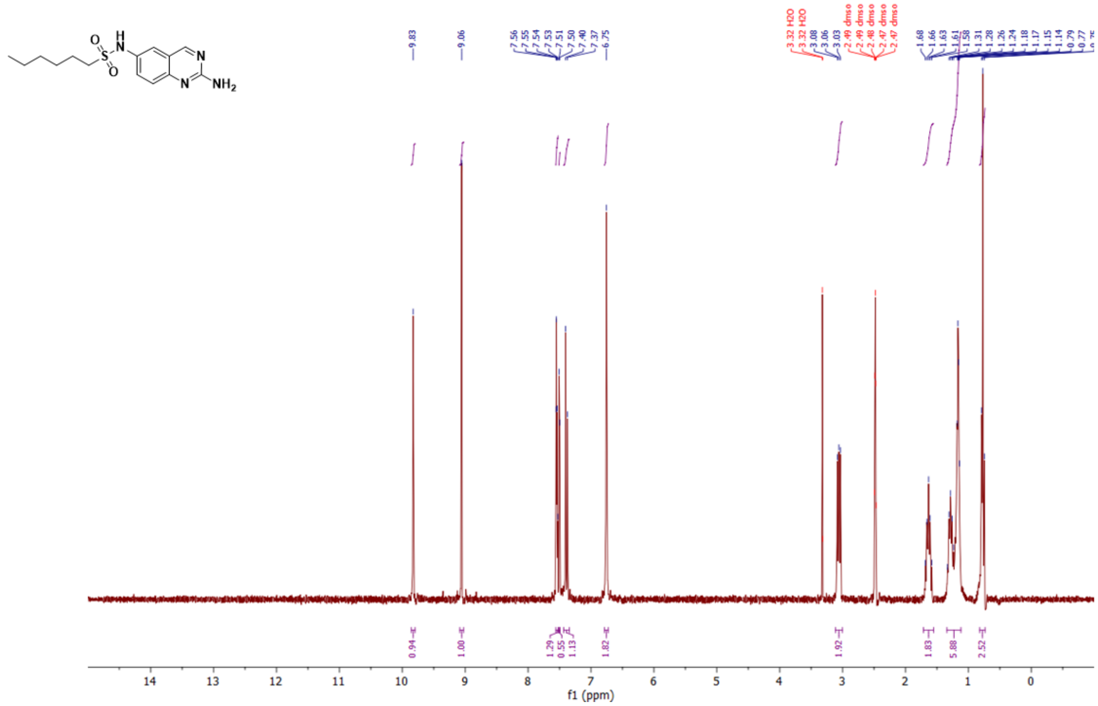


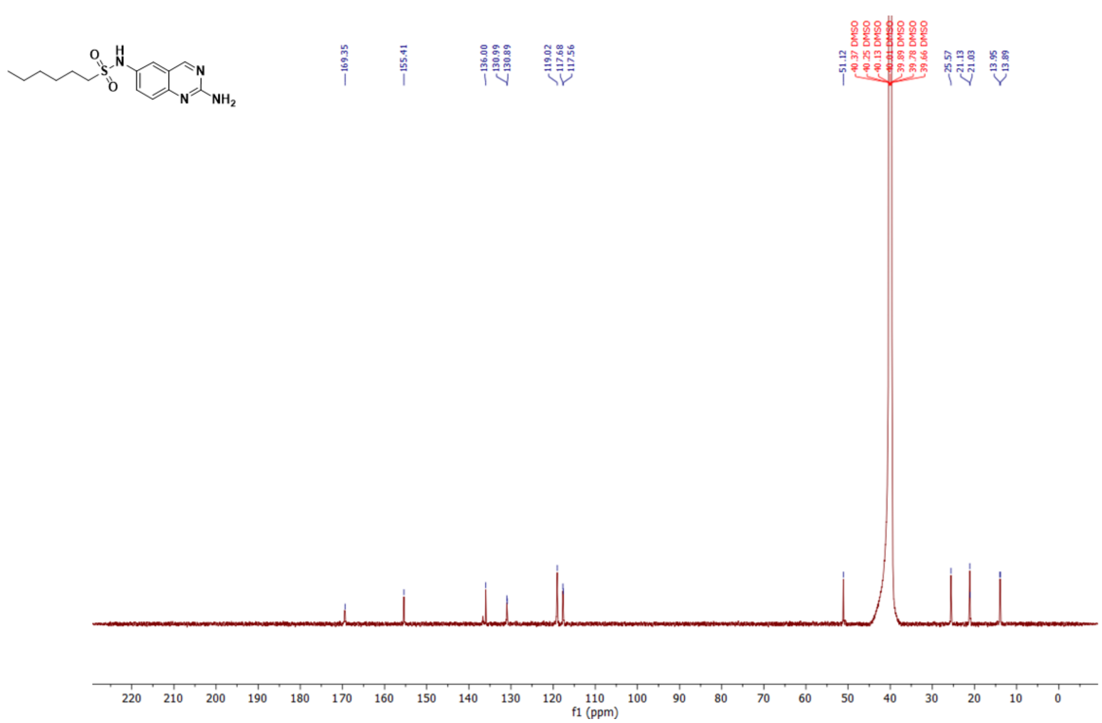
10.36
9.54
7.88
7.87
7.81
7.80
7.78
7.77
7.72
7.69
6.75
3.19
3.16
3.14
2.49 dmso
2.49 dmso
2.48 dmso
2.47 dmso
2.47 dmso
1.68
1.66
1.63
1.61
1.58
1.39
1.36
1.34
1.31
1.29
1.26
0.83
0.81
0.78
0.95
1.00
1.08
1.29
1.39
1.74
2.17
2.20
2.34
3.39
f1 (ppm)



169.35
155.41
136.00
130.99
130.89
119.02
117.68
117.56
51.12
40.37 DMSO
40.25 DMSO
40.13 DMSO
39.89 DMSO
39.78 DMSO
39.66 DMSO
25.57
21.13
13.95
f1 (ppm)

Compound 5e





Compound 5f