Supporting Information

Identification of 2-arylquinazolines with alkyl-polyamine motifs as potent antileishmanial agents: Synthesis and biological evaluation studies

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Experimental Section

General Information. All starting materials of AR/GR grades and solvents of LR quality were purchased from Sigma-Aldrich, Avra synthesis Pvt. Ltd., Merck life sciences, and Thermofischer scientific and were utilized as received without further purification. The aluminium pre-coated TLC (silica gel 60 F_{254}, 0.2 mm) and aluminium pre-coated TLC (Aluminium oxide 60 F_{254}, neutral) plates, supplied by Merck Life Sciences Private limited were utilized with UV-identification and iodine visualization reagent for monitoring the progress of the reactions. All the intermediates and final products were purified from the respective reaction mixtures by column chromatography using silica gel (silica gel 100−200 mesh, neutral, spherical) or alumina oxide neutral eluting with hexane, ethyl acetate and methanol solvents. Evaporation of solvents was performed at reduced pressure, using a Bűchi rotary evaporator.

Melting point: The melting point of synthesized compounds were obtained on digital melting point apparatus (PERFIT INDIA).

Proton and Carbon-NMR: ^{1}H NMR spectra were measured on a Bruker Avance III-400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm using tetramethylsilane as an internal standard in $CDCl_3$/CD_3OD/DMSO-d_6/D_2O with integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dt = doublet of triplet, dd = doublet of doublet, br. = broad), and J = coupling constants (Hz). $^{13}C\{^{1}H\}$-NMR spectra were measured on a Bruker Avance III-400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm.

IR Spectroscopy: Infrared (IR) spectra were taken on a PerkinElmer FTIR with an ATR and IR Microscope spectrometer.

Mass spectrometry: Mass spectra were recorded on Bruker maxis Q-TOF with ESI mode or Thermo Scientific LTQ-XL with ESI mode.

General procedure for synthesis of 2-aryl substituted quinazolin-4-one (Scheme 1, 13a-h)

The various derivatives of 2-aryl-quinazolin-4-one were synthesized by known procedure.[1]

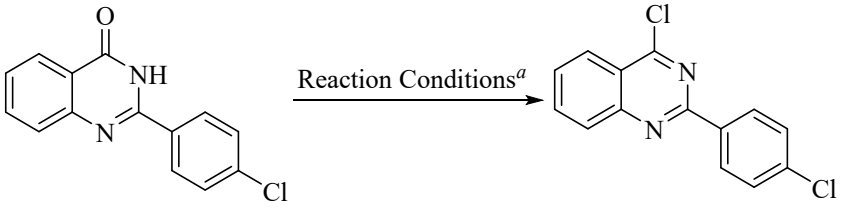
General procedure for synthesis of 2-aryl-4-chloro-substituted quinazoline (Scheme 1, 14a-d)

The 2-Aryl-4-chloro-quinazolines were prepared by known procedure.[2] The only variation in the procedure is heating the reaction mass at 60 °C instead of 120 °C (Table S1 for optimization study to improve the yield)

General procedure for synthesis of 2-aryl-4-alkypolyaminoquinazolines (Scheme 1, 15-26) : 2-Aryl-4-alkypolyaminoquinazolines were synthesized by reported procedure.[2]

General procedure for synthesis of 2-aryl-4-alkypolyaminoquinazolines (Scheme 1, 27-40): 2-aryl-4-alkypolyaminoquinazolines were prepared by known procedure.[3]

Table S1: Optimization Study

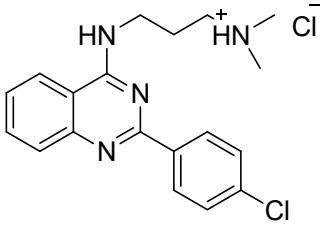


#	Reaction Conditions	Yield (%)[b]
1	$POCl_3$ (2 mL), 120 °C, 4 h	35
2	$POCl_3$ (2 mL), 60 °C, 4 h	55
3	$POCl_3$ (2 mL), 30 °C, 24 h	10
4	$POCl_3$ (1 mL), 60 °C, 8 h	40

[a]Reaction was done at 1 mmol scale. [b]Isolated yield

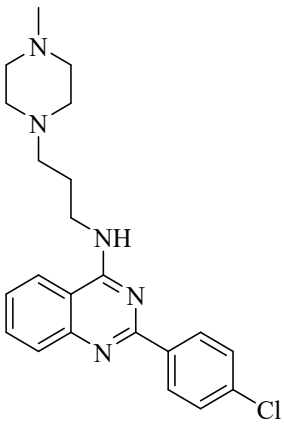
Characterization data of 2-aryl-4-alkypolyaminoquinazolines (Scheme 1, 15-40):

[2-(4-Chloro-phenyl)-quinazolin-4-yl]- (3-dimethylamino-propyl)-ammonium; chioride (15):



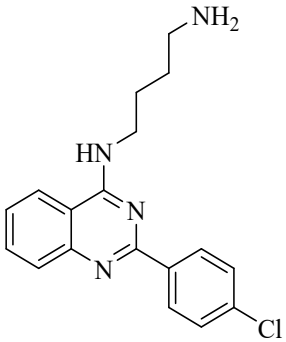
White solid, 90 mg, 95 % R*f* = 0.33 (50% EtOAc in Methanol); m.p. 210 °C; ^{1}H NMR (400 MHz, D_2O): δ 7.96 (d, *J* = 8.68 Hz, 2H), 7.92 (d, *J* = 8.28 Hz, 1H), 7.88-7.84 (m, 1H), 7.67 (d, *J* = 8.24 Hz, 1H), 7.60-7.56 (m, 1H), 7.47 (d, *J* = 8.64 Hz, 2H), 3.75 (t, *J* = 6.72 Hz, 2H), 3.16-3.12 (m, 2H), 2.72 (s, 6H), 2.07 (m, 2H) ppm; IR (ATR): υ_{max} 3236, 3060, 2943, 2822, 1615, 762 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{19}H_{22}ClN_4$ $[M]^+$ 341.1528, found: 341.1520.

[2-(4-Chloro-phenyl)-quinazolin-4-yl]-[3-(4-methyl-piperazin-1-yl)-propyl]-amine (16):



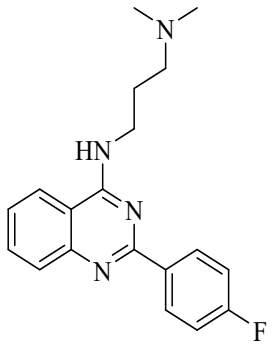
Light brown solid, 60 mg, 60%, R*f* = 0.33 (50 % EtOAc in Methanol); m.p. 163-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (d, *J* = 8.52 Hz, 2H), 8.15 (s, 1H), 7.93 (d, *J* = 8.12, 1H), 7.87 (d, *J* = 8.36, 1H), 7.72 (t, *J* = 7.2 Hz, 1H), 7.44-7.40 (m, 2H, NH), 3.91-3.78 (m, 2H), 2.74-2.64 (m, 6H), 2.40 (s, 3H), 1.99-1.85 (m, 6H) ppm; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.8, 159.7, 150.2, 137.7, 135.9, 132.3, 130.5, 129.7, 128.6, 128.3, 125.0, 121.6, 114.04, 58.6, 55.0, 53.3, 46.1, 42.2, 23.8 ppm; IR: υ_{max} 3177, 2962, 2932, 2828, 1925, 1584, 759 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{22}H_{27}ClN_5$ $[M+H]^+$ 396.1955, found: 396.1949.

N^{1}-[2-(4-Chloro-phenyl)-quinazolin-4-yl]-butane-1, 4-diamine (17):



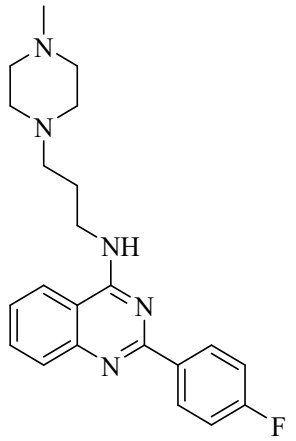
White solid, 62 mg, 75%, R*f* = 0.33 (50 % EtOAc in Methanol); m.p. 117-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$+MeOD): δ 8.39 (d, *J* = 8.56 Hz, 2H), 8.09 (d, *J* = 8.16 Hz, 1H), 7.82 (d, *J* = 8.12 Hz, 1H), 7.75 (t, *J* = 7.16 Hz, 1H), 7.69 (s, 1H), 7.50-7.46 (m, 2H, NH), 3.85 (t, *J* = 6.64 Hz, 2H), 2.98 (t, *J* = 7.6 Hz, 2H), 1.96 (s, 2H), 1.90 (q, *J* = 7.72 Hz, 2H), 1.85-1.78 (m, 2H) ppm; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$+MeOD): δ 156.1, 155.8, 145.8, 133.4, 132.1, 128.7, 125.7, 124.4, 123.5, 121.6, 117.8, 109.9, 36.1, 35.3, 21.5, 21.1 ppm; IR: υ_{max} 3306, 2933, 1615, 1583, 763 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{19}ClN_4Na$ $[M+Na]^+$ 349.1196, found: 349.1189.

N'-[2-(4-Fluoro-phenyl)-quinazolin-4-yl]-N, N-dimethyl-propane-1, 3-diamine (18):



Light orange solid, 70 mg, 85%, R*f* = 0.33 (50 % EtOAc in Methanol); m.p. 110-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.58 (dd, J = 5.76, 2.12 Hz, 2H), 7.87 (d, J = 8.24 Hz, 1H), 7.70 (dt, J = 7.02, 1.28, Hz, 1H), 7.62 (d, J = 8.12 Hz, 1H), 7.40 (dt, J = 7.54, 1.0 Hz, 1H), 7.16 (t, J = 8.76 Hz, 2H), 3.90 (t, J = 5.72 Hz, 2H), 2.62 (t, J = 5.52 Hz, 2H), 2.41 (s, 6H), 1.93 (quint, J = 5.88, 2H) ppm; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.5, 163.0 (d, $J_{C\text{-}F}$ = 247 Hz), 159.9, 159.8 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 7 Hz), 150.3, 135.4, 135.4 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3 Hz), 132.2, 130.4, 130.3 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 9 Hz), 128.5, 125.1, 121.0, 115.0, 114.8 (d, $J_{C\text{-}C\text{-}F}$ = 22 Hz), 114.1,59.8, 45.5, 42.4, 24.7 ppm; IR: υ_{max} 3215, 2952, 2817, 1533, 1598, 763 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{19}H_{22}FN_4$ $[M+H]^+$ 325.1828, found: 325.1832.

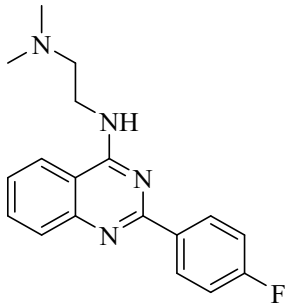
[2-(4-Fluoro-phenyl)-quinazolin-4-yl]- [3-(4-methyl-piperazin-1-yl)-propyl]-amine (19):



White solid, 80 mg, 85%, R*f* = 0.33 (50 % EtOAc in Methanol); m.p. 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (t, J = 5.88 Hz, 2H), 8.18 (s, 1H), 7.89 (t, J = 8.52 Hz, 2H), 7.71 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 7.4 Hz, 1H), 7.14 (t, J = 8.68 Hz, 2H), 3.88 (q, J = 5.28 Hz, 2H), 2.70-2.58 (m, 8H), 2.39 (s, 3H), 2.04-1.93 (m, 4H) ppm; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.5, 163.0 (d, $J_{C\text{-}F}$ = 247 Hz), 159.9, 159.8 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 7 Hz), 150.3, 135.4, 135.3 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3 Hz), 132.3, 130.4, 130.3 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 9 Hz) , 128.5, 124.8, 121.6, 115.1, 114.9 (d, $J_{C\text{-}C\text{-}F}$ = 22 Hz), 113.9, 58.9, 55.2, 53.5, 46.2, 42.5, 23.8 ppm; IR: υ_{max} 3194,

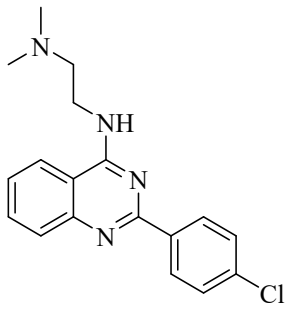
2933, 2796, 1598 cm[1]; HRMS (ESI) *m/z*: calcd. for $C_{22}H_{27}FN_5$ $[M+H]^+$ 380.225, found: 380.2245.

N'-[2-(4-Fluoro-phenyl)-quinazolin-4-yl]-N, N-dimethyl-ethane-1, 2-diamine (20):



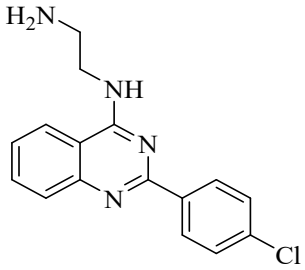
White solid, 70 mg, 87%, R*f* = 0.33 (50 % EtOAc in Methanol); m.p. 117-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (dd, *J* = 5.84, *J* = 8.52 Hz, 2H), 7.90 (d, *J* = 8.32 Hz 1H), 7.80 (d, *J* = 8.08 Hz, 1H), 7.73 (t, *J* = 7.72 Hz, 1H), 7.43 (t, *J* = 7.52 Hz, 1H), 7.17 (t, *J* = 8.68 Hz, 2H), 6.63 (s, 1H), 3.84 (q, *J* = 5.36, 2H), 2.70 (t, *J* = 5.84 Hz, 2H), 2.36 (s, 6H) ppm; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.5, 163.1 (d, $J_{C\text{-}F}$ = 248 Hz), 159.6, 159.5 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 9 Hz), 150.3, 135.2, 135.2 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3 Hz), 132.5, 130.4, 130.3 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 8 Hz) , 128.6, 125.3, 120.9, 115.1, 114.9 (d, $J_{C\text{-}C\text{-}F}$ = 22 Hz), 113.7, 57.5, 45.2, 38.2 ppm; IR: υ_{max} 3324, 2948, 1572, 1357, 1218 cm[1]; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{19}FN_4Na$ $[M+Na]^+$ 333.1491, found: 333.1486.

N'-[2-(4-Chloro-phenyl)-quinazolin-4-yl]-N, N-dimethyl-ethane-1, 2-diamine (21):



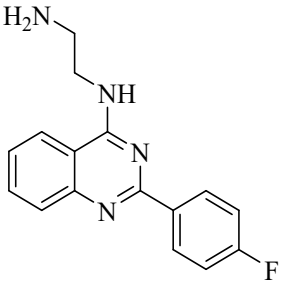
Light brown solid, 69 mg, 84%, R*f* = 0.33 (50 % EtOAc in Methanol); m.p. 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, *J* = 8.24, Hz, 2H), 7.88 (d, *J* = 8.2, Hz, 2H), 7.82 (d, *J* = 7.96, Hz, 2H), 7.72 (t, *J* = 7.32 Hz, 1H), 7.43 (d, *J* = 8.04 Hz, 3H), 6.76 (s, 1H), 3.87-3.86 (m, 2H), 2.77-2.76 (m, 2H), 2.40 (s, 6H) ppm; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.6, 159.5, 150.3, 137.6, 136.0, 132.5, 129.7, 128.6, 128.3, 125.5, 121.1, 113.9, 57.6, 45.1, 38.0 ppm; IR: υ_{max} 3408, 2859, 1571, 1359, 756 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{19}ClN_4Na$ $[M+Na]^+$ 349.1196, found: 349.1190.

N'-[2-(4-Chloro-phenyl)-quinazolin-4-yl]-ethane-1, 2-diamine (22):



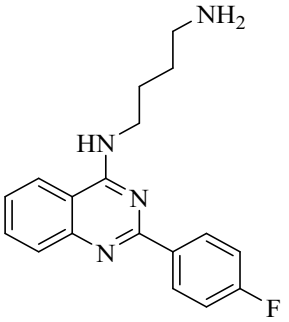
White solid, 57 mg, 77%, R*f* = 0.33 (50 % EtOAc in Methanol); m.p. >200 °C; ^{1}H NMR (400 MHz, $CDCl_3$+MeOD): δ 8.39 (d, J = 8.48 Hz, 2H), 8.18 (d, J = 8.2 Hz 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.79 (t, J = 7.36 Hz, 1H), 7.53 (t, J = 7.72 Hz, 1H), 7.48 (d, J = 8.48 Hz 2H), 4.08 (t, J = 5.76 Hz, 2H), 3.40-3.38 (m, 2H) ppm; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$+MeOD): δ 160.6, 159.6, 149.7, 137.0, 136.3, 133.1, 129.6, 128.3, 127.2, 126.0, 122.3, 113.8, 39.3, 38.6 ppm; IR: υ_{max} 3335, 2933, 1564, 1353, 760 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{15}ClN_4Na$ $[M+Na]^+$ 321.0883, found: 321.0875.

N'-[2-(4-Fluoro-phenyl)-quinazolin-4-yl]-ethane-1, 2-diamine (23):



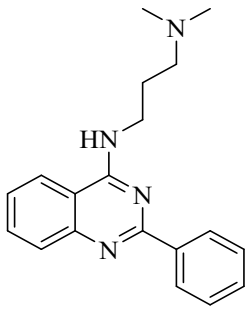
Light brown solid, 57 mg, 80%, R*f* = 0.33 (50 % EtOAc in Methanol); m.p. 143-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$+MeOD): δ 8.56-8.52 (m, 2H), 7.87-7.81 (m, 2H), 7.70 (t, J = 7.04 Hz, 1H), 7.40 (s, 1H), 7.14 (t, J = 8.28 Hz, 2H), 6.68 (s, 1H), 3.97-3.66 (m, 2H), 3.51-3.40 (m, 2H), 2.93-2.49 (m, 2H) ppm; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$+MeOD): δ 165.5, 163.0 (d, $J_{C\text{-}F}$ = 248 Hz), 160.3, 159.9 (d, $J_{C\text{-}C\text{-}F}$ = 47 Hz), 149.8, 134.9, 134.8, 132.9, 131.4, 131.3 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 9 Hz), 130.4, 130.3 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 8 Hz), 127.3, 125.6, 121.8, 115.1, 114.9 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 21 Hz), 114.6, 113.8, 41.8, 40.0 ppm; IR: υ_{max} 3329, 2853, 1573, 1221 cm^{1}; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{15}FN_4Na$ $[M+Na]^+$ 305.1179, found: 305.1165.

N'-[2-(4-Fluoro-phenyl)-quinazolin-4-yl]-butane-1, 4-diamine (24):



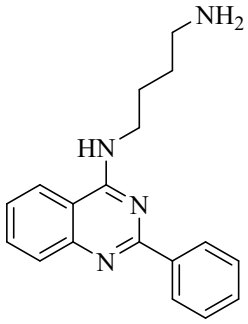
Light brown solid, 65 mg, 82%, R*f* = 0.33 (50 % EtOAc in Methanol); m.p. 122-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$+MeOD): δ 8.47 (dd, *J* = 8.68, 5.68 Hz, 2H), 8.06 (d, *J* = 8.16 Hz, 1H), 7.84 (d, *J* = 8.36 Hz, 1H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.48 Hz, 1H), 7.15 (t, *J* = 8.68 Hz, 2H), 3.80 (t, *J* = 5.96 Hz, 2H), 2.98 (m, 2H), 1.86 (quin, *J* = 6.72 Hz, 4H) ppm; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$+ MeOD): δ 165.5, 163.0 (d, $J_{C\text{-}F}$ = 248 Hz), 160.2, 160.0 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 18 Hz), 149.6, 135.0, 135.0, 132.7, 130.4, 130.3 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 8 Hz), 126.9, 125.5, 122.0, 115.0, 114.8 (d, $J_{C\text{-}C\text{-}F}$ = 22 Hz), 113.8, 40.03, 39.4, 25.7, 25.0 ppm; IR: υ_{max} 3343, 2940, 1580, 1221 cm^{1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{19}FN_4Na$ $[M+Na]^+$ 333.1492, found: 333.1485.

N, N-Dimethyl-N'- (2-phenyl-quinazolin-4-yl]-propane-1, 3-diamine (25):



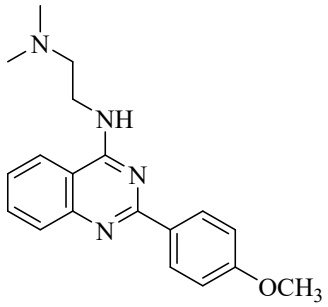
Semi-solid, 68 mg, 88%, R*f* = 0.33 (50 % EtOAc in Methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (dd, *J* = 1.84, *J* = 8.16 Hz, 2H), 8.39 (s, 1H), 7.88 (d, *J* = 7.92 Hz, 1H), 7.79 (d, *J* = 8.04 Hz, 1H), 7.71 (dt, *J* = 7.12, 1.12 Hz, 1H), 7.50-7.39 (m, 4H), 3.92-3.91 (m, 2H), 2.74 (t, *J* = 5.8 Hz, 2H), 2.47 (s, 6H), 2.03 (quin, *J* = 6 Hz, 2H) ppm; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.6, 159.9, 150.4, 139.2, 132.2, 129.8, 128.5, 128.3, 128.1, 125.3, 121.3, 114.2, 58.4, 44.7, 40.9, 24.5 ppm; IR: υ_{max} 3271, 2948, 1573, 1362 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{19}H_{22}N_4Na$ $[M+Na]^+$ 329.1742, found: 329.1731.

N'- (2-phenyl-quinazolin-4-yl]-butane-1, 4-diamine (26):



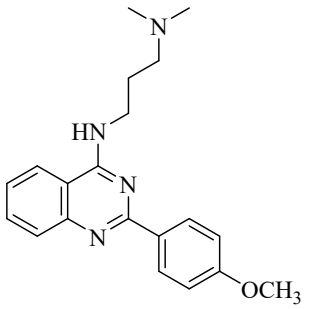
Semi-solid, 75 mg, 76% R*f* = 0.33 (20% EtOAc in Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, *J* = 6.72 Hz, 2H), 7.89 (d, *J* = 8.28 Hz, 1H), 7.80 (d, *J* = 7.32 Hz, 1H), 7.69 (t, *J* = 7.36 Hz, 1H), 7.49-7.36 (m, 4H), 6.80 (s, 1H), 3.81-3.80 (m, 2H), 2.85 (m, 2H), 2.32 (m, 2H), 1.86 (m, 2H), 1.68 (m, 2H) ppm; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.6, 159.7, 150.5, 139.1, 132.3, 129.9, 128.7, 128.3, 128.2, 125.1, 120.9, 113.9, 41.1, 30.3, 29.7, 26.6 ppm; IR: υ_{max} 3287, 2855, 1572, 1362 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{21}N_4$ $[M+H]^+$ 293.1766, found: 293.1783.

N^1-(2-(4-Methoxyphenyl)quinazolin-4-yl)-N^2, N^2-dimethylethane-1, 2-diamine (27):



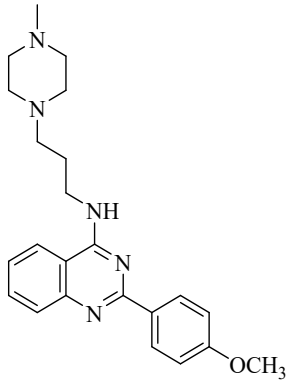
White semisolid,13%, R_f = 0.3 (10% Methanol in EtOAc); m.p. 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.48 Hz, 2H), 7.89 (d, *J* = 8.36 Hz, 1H), 7.77 (d, *J* = 8.16 Hz, 1H), 7.72 (dd, *J* = 7.84, 7.52 Hz 1H), 7.41 (dd, *J* = 7.56, 7.48 Hz, 1H), 7.02 (d, *J* = 8.52 Hz, 2H), 6.54 (s, NH), 3.91 (s, 3H), 3.83-3.87 (m, 2H), 2.69 (t, *J* = 5.82 Hz, 2H), 2.36 (s, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.3, 160.3, 159.5, 150.5, 132.3, 131.8, 129.9, 128.5, 124.8, 121.0, 113.7, 113.5, 57.6, 55.3, 45.2, 38.2, 38.1. IR: υ_{max} 3257, 2939, 1576, 1246, 843 cm^{-1}. LTQ (ESI) m/z: calculated for $C_{19}H_{23}N_4O$ $[M+H]^+$ 323.41, found: 323.48.

N^1-(2-(4-Methoxyphenyl)quinazolin-4-yl)-N^3, N^3-dimethylpropane-1, 3-diamine (28):



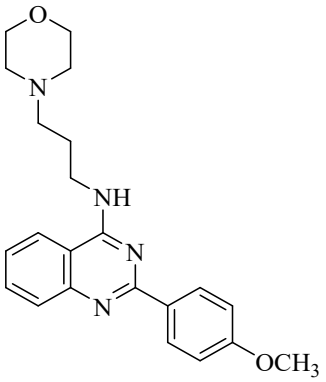
White solid, 12%, R_f = 0.3 (5% Methanol in EtOAc); m.p. 100-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60–8.49 (m, 3H), 7.87 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.37 (dd, J = 8.1, 1.1 Hz 1H), 7.69 (dd, J = 8.32, 1.28 Hz, 1H), 7.07–6.97 (m, 2H), 3.96–3.87 (m, 5H), 2.63 (t, J = 5.66 Hz, 2H), 2.40 (s, 6H), 1.91–1.95 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO–d_6) δ 160.9, 159.4, 159.0, 149.9, 132.4, 131.2, 129.4, 127.5, 124.7, 122.5, 113.6, 113.4, 56.9, 55.1, 44.9, 40.1, 39.8, 39.6, 39.4, 39.2 39.0, 38.8, 26.2. IR: υ_{max} 2941, 1573, 1360, 1248, 766 cm^{-1}. LTQ (ESI) m/z: calculated for $C_{20}H_{25}N_4O$ $[M+H]^+$ 337.40, found: 337.55.

2-(4-Methoxyphenyl)-N-(3-(4-methylpiperazin-1-yl)propyl)quinazolin-4-amine (29):



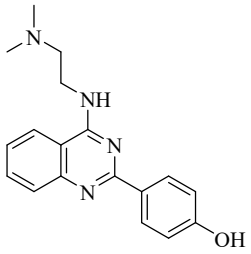
Creamish white solid, 14%, R_f = 0.3 (15% Methanol in EtOAc); m.p. 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 8.8 Hz, 2H), 8.06 (s, 1H, NH), 7.87–7.90 (m, 2H), 7.72 (dd, J = 7.52, 7.24 Hz, 1H), 7.39 (dd, J = 7.76, 7.24 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 3.95–3.87 (m, 5H), 2.68 (m, 10H), 2.41 (s, 3H), 1.95–1.99 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1, 159.3, 158.5, 149.3, 130.9, 130.7, 128.7, 127.2, 123.1, 120.3, 112.6, 112.2, 57.6, 54.1, 54.0, 52.3, 45.0, 41.2, 22.7. IR: υ_{max} 3262, 2937, 1574, 1161, 765 cm^{-1}. LTQ (ESI) m/z: calculated for $C_{23}H_{30}N_5O$ $[M+H]^+$ 392.50, found: 392.46.

2-(4-Methoxyphenyl)-N-(3-morpholinopropyl)quinazolin-4-amine (30):



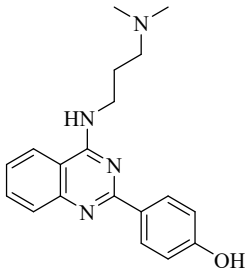
White solid, 18%, R_f = 0.3 (15% Methanol in EtOAc); m.p. 159-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 8.8 Hz, 2H), 7.89 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.76–7.65 (m, 2H), 7.41 (dd, J = 7.8, 7.24 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 3.95– 3.88 (m, 5H), 3.86 (t, J = 4.54 Hz, 4H), 2.66 (t, J = 5.72 Hz, 2H), 2.59 (s, 4H), 2.01–1.91 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.3, 160.5, 159.6, 150.5, 132.2, 131.9, 129.9, 128.6, 124.6, 121.0, 113.7, 113.5, 67.0, 59.1, 55.3, 54.0, 42.0, 23.9. IR: υ_{max} 2953, 1573, 1359, 1117, 765 cm^{-1}. LTQ (ESI) m/z: calculated for $C_{22}H_{27}N_5O_2$ $[M+H]^+$ 379.2, found: 379.36.

4-(4-((2-(Dimethylamino)ethyl)amino)quinazolin-2-yl)phenol (31):



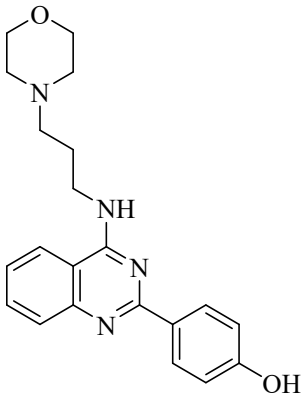
Creamish white solid, 17%, R_f = 0.3 (15% Methanol in EtOAc); m.p. 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.16 Hz, 1H), 7.74 (dd, J = 7.68, 7.52 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.46 (dd, J = 7.56, 7.48 Hz, 1H), 6.62 (s, NH), 3.87–3.82 (m, 2H), 2.71 (t, J = 5.8 Hz, 2H), 2.37 (s, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.6, 159.5, 150.3, 138.0, 132.5, 131.3, 130.0, 128.6, 125.4, 124.5, 121.0, 113.9, 57.5, 45.2, 38.2. IR: υ_{max} 3403, 2945, 1577, 1168, 764 cm^{-1}; LTQ (ESI) m/z: calcd. for $C_{18}H_{21}N_4O$ $[M+H]^+$ 309.17, found: 309.30.

4-(4-((3-(Dimethylamino)propyl)amino)quinazolin-2-yl)phenol (32):



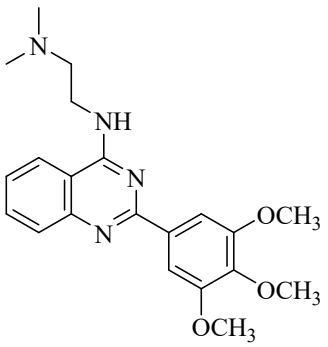
White solid, 20%, R_f = 0.3 (20% Methanol in EtOAc); m.p. 122-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.47 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.3 Hz, 1H), 7.72 (dd, J = 7.8, 7.4 Hz, 1H), 7.61 (d, J = 8.5 Hz, 3H), 7.42 (dd, J = 7.68, 7.36 Hz, 1H), 3.92–3.88 (m, 2H), 2.63 (t, J = 4.6 Hz, 2H), 2.40 (s, 6H), 1.96–1.89 (m, 2H)**;** ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.82, 158.8, 149.2, 137.2, 131.2, 130.2, 129.0, 127.5, 124.3, 123.4, 119.9, 113.2, 58.9, 44.5, 41.4, 23.7. IR: υ_{max} 3240, 2944, 1579, 1360, 765 cm^{-1}; LTQ (ESI) m/z: calcd. for $C_{19}H_{23}N_4O$ $[M+H]^+$ 323.18, found: 323.35.

4-(4-((3-Morpholinopropyl)amino)quinazolin-2-yl)phenol (33):



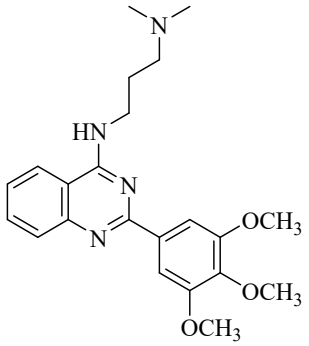
Creamish white solid, 32%, R_f = 0.3 (5% Methanol in EtOAc); m.p. 158-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.75 (dd, J = 7.76, 7.52 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 7.52 Hz, 1H), 3.96–3.83 (m, 6H), 2.75 – 2.67 (m, 2H), 2.62 (s, 4H), 2.04–1.94 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.9, 159.8, 149.7, 137.8, 132.7, 131.3, 129.9, 127.8, 125.5, 124.6, 121.3, 113.8, 66.7, 57.8, 53.6, 40.6, 24.2. IR: υ_{max} 3244, 2958, 1580, 1359, 763 cm^{-1}; LTQ (ESI) m/z: calcd. for $C_{21}H_{25}N_4O_2$ $[M+H]^+$ 365.19, found: 365.28.

N^1, N^1-Dimethyl-N^2-(2-(3, 4, 5-trimethoxyphenyl)quinazolin-4-yl)ethane-1, 2-diamine (34):



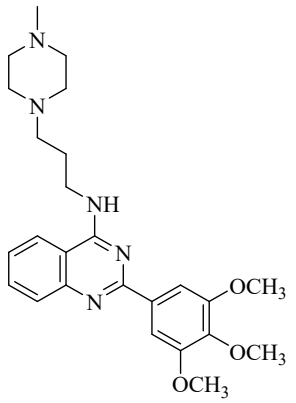
Brown solid, 27%, R_f = 0.3 (10% Methanol in EtOAc); m.p. 143-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.36 Hz, 1H), 7.93 (d, J = 8.32 Hz, 1H), 7.73 (dd, J = 7.44 Hz, J = 7.60 Hz, 1H), 7.69 (s, 2H), 7.43 (dd, J = 7.68 Hz, J = 7.52 Hz 1H), 4.84 (s, NH), 4.11 (t, J = 5.44 Hz, 2H), 4.01 (s, 6H), 3.92 (s, 3H), 3.47 (s, 3H), 3.36 (t, J = 5.50 Hz, 2H), 2.58 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.8, 158.5, 153.3, 152.8, 140.2, 133.9, 132.8, 128.6, 125.6, 124.9, 114.8, 105.5, 60.9, 56.3, 49.5, 47.7, 42.09, 34.03. IR: υ_{max} 2942, 2835, 1530, 1003, 845 cm^{-1}. LTQ (ESI) m/z: calcd. for $C_{21}H_{27}N_4O_3$ $[M+H]^+$ 382.20, found: 381.53.

N^1, N^1-Dimethyl-N^3-(2-(3, 4, 5-trimethoxyphenyl)quinazolin-4-yl)propane-1, 3-diamine (35):



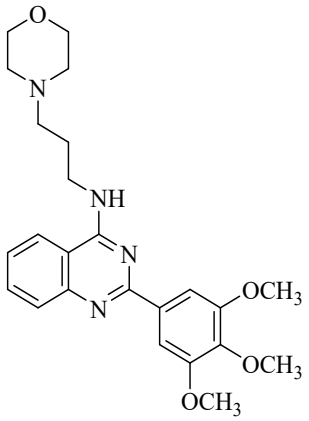
Greyish white solid, 25%, R_f = 0.3 (15% Methanol in EtOAc); m.p. 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, NH), 7.89 (s, 3H), 7.72 (dd, J = 7.40, 7.12 Hz, 1H), 7.63 (d, J = 7.80 Hz, 1H), 7.41 (dd, J = 7.16, 7.12 Hz,1H), 4.03 (s, 6H), 3.94 (s, 5H), 2.65 (s, 2H), 2.41 (s, 6H), 1.95 (s, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.3, 159.7, 153.0, 150.3, 139.8, 134.9, 132.2, 128.5, 125.2, 121.0, 114.2, 105.5, 60.9, 59.8, 56.2, 49.5, 45.5, 42.3, 24.7. IR: υ_{max} 3385, 2941, 1534, 1004, 838 cm^{-1}; LTQ (ESI) m/z: calculated for $C_{22}H_{29}N_4O_3$ $[M+H]^+$ 397.22, found: 397.34.

N-(3-(4-Methylpiperazin-1-yl)propyl)-2-(3, 4, 5-trimethoxyphenyl)quinazolin-4-amine (36):



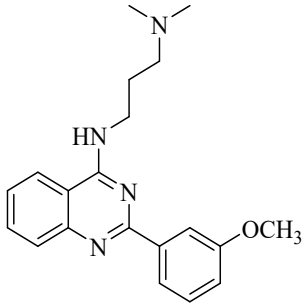
Creamish white solid, 16%, R_f = 0.3 (30% Methanol in EtOAc); m.p. 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, NH), 7.96 – 7.87 (m, 4H), 7.74 (dd, J = 8.24, 1.24 Hz, 1H), 7.43 (dd, J = 8.2, 1.2 Hz,1H), 4.04 (s, 6H), 3.95–3.88 (m, 5H), 2.85-2.55 (m, 10H), 2.41 (s, 3H), 2.02–1.94 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.3, 159.7, 153.0, 150.3, 139.9, 134.8, 132.3, 128.5, 124.7, 121.6, 113.9, 105.5, 60.9, 58.9, 56.1, 55.2, 53.5, 46.2, 42.4, 23.8. IR: υ_{max} 3278, 2939, 1126, 1006, 769 cm^{-1}; LTQ (ESI) m/z: calculated for $C_{25}H_{34}N_5O_3$ $[M+H]^+$ 452.57, found: 452.39.

N-(3-Morpholinopropyl)-2-(3, 4, 5-trimethoxyphenyl)quinazolin-4-amine (37):



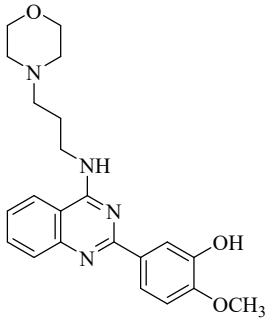
Light brown solid, 23%, R_f = 0.3 (5% Methanol in EtOAc); m.p. 71-73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, NH), 7.94 (d, J = 8.04 Hz, 2H), 7.88 (d, J = 5.4 Hz, 3H), 7.76 (ddd, J = 1.2 Hz, J = 8.28 Hz, J = 8.28 Hz, 1H), 7.46 (dd, J = 8.1, 1.0 Hz,1H), 4.03 (s, 6H), 3.95 (s, 5H), 3.87 (t, J = 4.6 Hz, 4H), 2.77–2.69 (m, 2H), 2.64 (s, 4H), 1.98-2.04 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1, 159.7, 152.8, 149.2, 139.9, 133.9, 132.8, 127.2, 125.4, 121.3, 113.5, 105.6, 66.5, 60.8, 57.7, 56.0, 53.6, 40.6, 24.1. IR: υ_{max} 3391, 2941, 1574, 1124, 845 cm^{-1}. LTQ (ESI) m/z: calculated for $C_{24}H_{31}N_4O_4$ $[M+H]^+$ 439.26, found: 439.46.

N^1-(2-(3-Methoxyphenyl)quinazolin-4-yl)-N^3, N^3-dimethylpropane-1, 3-diamine (38):



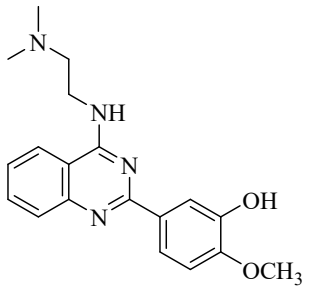
White semisolid, 26%, R_f = 0.3 (40% EtOAc in Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, NH), 8.24–8.11 (m, 2H), 7.91 (d, J = 8.3 Hz, 1H), 7.71 (d, J =7.6 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 7.8 Hz, 2H), 7.04 (dd, J = 7.02, 1.8 Hz, 1H), 3.95 (s, 3H), 3.92–3.87 (m, 2H), 2.65–2.60 (m, 2H), 2.40 (s, 6H), 1.95–1.89 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.5, 159.8, 159.6, 150.3, 140.8, 132.1, 129.1, 128.6, 125.2, 121.0, 116.0, 114.3, 113.2, 59.8, 55.3, 45.5, 42.3, 29.7, 24.8; IR: υ_{max} 3390, 2945, 1550, 1020, 845 cm^{-1}; LTQ (ESI) m/z: calculated for $C_{20}H_{25}N_4O[M+H]^+$ 337.45, found: 3372.

2-Methoxy-5-(4-((3-morpholinopropyl)amino)quinazolin-2-yl)phenol (39):



Creamish white solid, 21%, R_f = 0.3 (15% Methanol in EtOAc); m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.25 (s, NH), 8.19 (d, J = 8.2 Hz, 1H), 8.01–7.90 (m, 2H), 7.79 – 7.65 (m, 2H), 7.43 (dd, J = 7.12, 6.92 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 3.84 (s, 3H), 3.70 (d, J = 5.8 Hz, 2H), 3.59 (s, 4H), 2.43 (dd, J = 12.6, 5.6 Hz, 2H), 2.39 (s, 4H), 1.93–1.86 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.4, 159.2, 149.9, 149.5, 146.0, 132.4, 131.6, 127.5, 124.6, 122.5, 119.6, 115.0, 113.6, 111.3, 66.1, 56.2, 55.5, 53.3, 36.4, 36.3, 25.4. IR: υ_{max} 3411, 2944, 1576, 1360, 764 cm^{-1}; LTQ (ESI) m/z: calculated for $C_{22}H_{27}N_4O_3$ $[M+H]^+$ 395.4, found: 395.56.

*5-(4-((2-(Dimethylamino)ethyl)amino)quinazolin-2-yl)-2-methoxyphenol (40)**:***



Light yellow solid, 12%, R_f = 0.3 (20% Methanol in EtOAc); m.p. 141-143 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.23 (s, NH), 8.19 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 11.1 Hz, 2H), 7.79–7.66 (m, 2H), 7.44 (dd, J = 7.12, 7.04 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 3.83 (s, 5H), 2.79 (s, 2H), 2.39 (s, 6H); ^{13}C { NMR (100 MHz, DMSO-d_6) δ 159.9, 159.6, 150.4, 150.1, 146.5, 133.0, 131.9, 128.0, 125.2, 123.2, 120.1, 115.6, 114.1, 111.9, 57.3, 56.0, 44.8, 40.5, 37.9, 21.6; IR: υ_{max} 3420, 2954, 1566, 1372, 738 cm^{-1}. LTQ (ESI) m/z: calculated for $C_{19}H_{23}N_4O_2$ $[M+H]^+$ 339.41, found: 339.59.

Bio-evaluation studies:

Culture condition of *Leishmania* promastigotes

Leishmania donovani wild-type (WT, MHOM/80/IN/Dd8) were cultured at 24 °C in RPMI-1640 HEPES-modified medium supplemented with 0.2% sodium bicarbonate, 100 µg/mL penicillin, 100 µg/mL streptomycin, 100 µg/mL gentamycin, and 10 % heat-inactivated Fetal Bovine Serum (FBS). The medium was maintained at pH 7.2.

In vitro antileishmanial activity

In vitro antileishmanial activity of *L. donovani* promastigotes was assayed colorimetrically by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay as described earlier (Mosmann,1983). Briefly, 2×10^5 log phase promastigotes of *L. donovani* were incubated for 48 h in 96 well plates and treated with increasing concentrations of antileishmanial compounds (10–100 µM) at 24 °C for 48 h. The Stock solutions (10 mM) of investigated compounds were prepared in DMSO and stored at -80 degree C. For treatment, the working concentration was prepared to obtain the desired final concentration and added to the cell culture. For treatment, the solution was diluted with culture medium to obtain the desired final concentration. MTT was added at a final concentration of 400 µg/mL and further incubated at 37 °C for 4 h. The cells were centrifuged at 3000*g* for 10 min and the supernatant was discarded. The resultant purple formazan formed was dissolved in 100 µL DMSO and finally absorbance was recorded at 540 nm on a Tecan microplate reader. The

percentage viability of promastigotes was calculated relatively by considering 100 % viability in untreated promastigotes and the results were expressed as the inhibitor concentration at which there was 50% inhibition of the parasite growth. Miltefosine was used as the control drug. The results were expressed as mean ± SD of three independent experiments.

Cytotoxicity

To check the cytotoxic effect of compounds on the host macrophages, the viability was assessed using MTT assay.[4] Approximately 2×10^5 THP-1 monocytes were seeded in 96-well microplate, differentiated into macrophages with 20 ng/mL of phorbol 12-myristate 13-acetate (PMA) and grown at 37 °C for 48 h. The unadhered cells were removed by washing with serum-free medium and adhered macrophages were treated with increasing concentrations of compounds from a range of 10 to 100 μM (10, 20, 50, and 100 μM). After drug treatment, the cells were further grown at 37 °C for 48 h in a humidified atmosphere of 5 % CO_2. Miltefosine was used as the standard. Selectivity index was calculated.

Methodology

Expression and purification of *Leishmania donovani* trypanothione reductase (*Ld*-TryR)

Cloning of *L. donovani* trypanothione reductase (*Ld*-TryR) gene having size of 1476 bp in recombinant pET30a vector was previously reported by our group.[5] pET30a*Ld*-TryR clone was transformed in *E. coli* BL21 (DE3) for the expression of recombinant enzyme. Expression of recombinant *Ld*-TryR enzyme was done in LB media containing kanamycin as selection marker antibiotic (50 μg/mL) and 0.1 mM IPTG as inducer at 25 °C for 14 h. Cell pellets were prepared using centrifugation at 6000g 4 °C for 5 min. Further, cell pellets were resuspended in Tris-HCl (20 mM; pH 7.8) containing lysozyme (100 μg/mL) and Triton X-100 (0.1 %). Cell lysis was done by sonication and centrifugation was done at 12000g for 30 min to collect the soluble protein fractions of cell lysate. Recombinant *Ld*-TryR enzyme was purified using HIS-Select HF nickel affinity chromatography. Cell lysate was loaded into a pre-equilibrated (20 mM Tris-HCl (pH 7.8), 10 mM imidazole (pH 7), 150 mM NaCl and 0.1 % Triton X-100) nickel affinity resin column and allowed to pass. Column was washed with wash buffer containing 20 mM Tris-HCl, 300 mM sodium chloride and 0.1 % Triton X-100 and gradient concentration of imidazole (10 mM imidazole, 20 mM imidazole). Finally, His-

tagged *Ld*-TryR protein was eluted using elution buffer containing 20 mM Tris-Cl, 150 mM imidazole and 300 mM sodium chloride. The protein concentration was estimated by bicinchoninic acid (BCA) method by using Bovine serum albumin (BSA) as standard and purified protein samples were run on 12.5 % sodium dodecyl sulfate polyacrylamide gel to check the purity.

Enzyme inhibition study of recombinant *Ld*-TryR

Assessment of *Ld*-TryR enzyme inhibition was carried out using colorimetric method as described by Bogerrt *et al*.[6] Inhibition study of recombinant *Ld*TryR enzyme was performed using compound **27** and compound **28** with increasing concentrations (5-100 µM) in 20 % DMSO. The final concentration of DMSO in the reaction was 0.2 %. 4-chloromercuricbenzoic acid (10 µM) was used as standard inhibitor of *Ld*-TryR enzyme.[7] The reaction volume for assay was 200 µl containing sterile filtered water, recombinant *Ld*-TryR (250 ng) and master mix of 40 mM HEPES, 1 mM EDTA, 150 µM NADPH, 50 µM DTNB and 100 µM $T[S]_2$. The kinetic interval for this reaction was 30 sec with the duration of 4 min. The reaction components along with the inhibitor were incubated at 25°C for 5 minutes. After incubation, trypanothione disulfide (substrate) was added and absorbance was measured at 412 nm. CMB was taken as the positive control. Two independent experiments were performed with recombinant *Ld*-TryR enzyme. Activity of recombinant enzyme was taken as 100 % and relative activity was calculated for enzyme in presence of inhibitors.

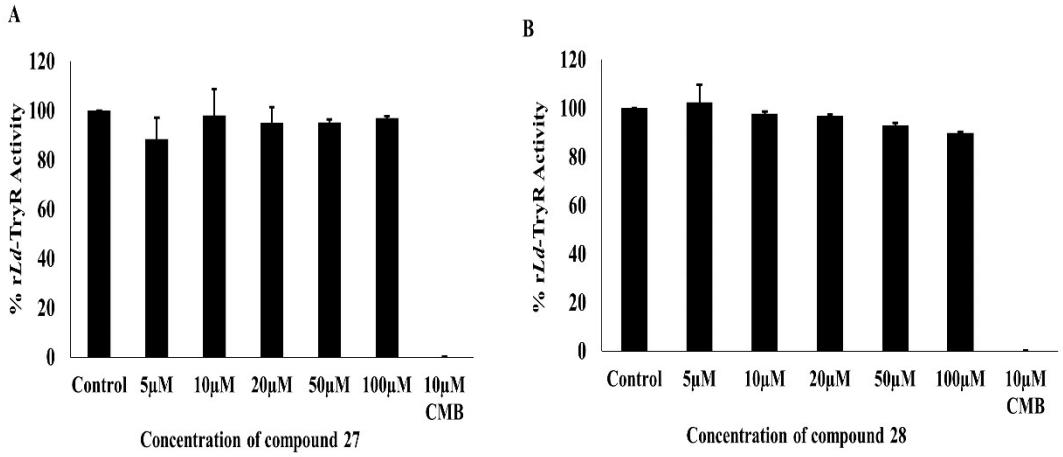


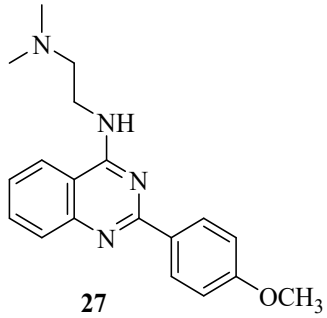
Figure S-1: Recombinant *Ld*-TryR inhibition study. (A) Percentage r*Ld*-TryR activity in presence and absence of **compound 27** with concentrations ranging from 5-100 µM was calculated. (B) Percentage r*Ld*-TryR activity in presence and absence of **compound 28** with

concentrations ranging from 5-100 μM was calculated. Results shown correspond to mean ± standard deviation (S.D.) of two independent experiments.

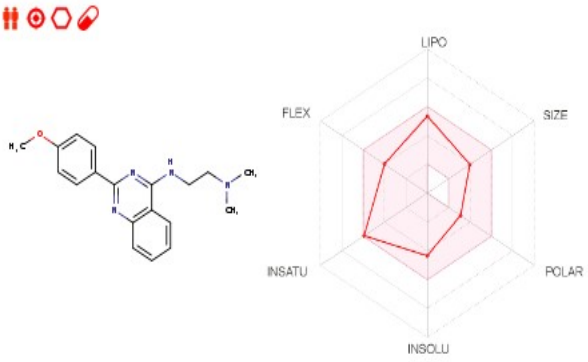
Measurement of mitochondrial ROS generation

MitoSOX (Invitrogen) is a probe which is selectively oxidized by superoxide radical and preferentially targeted to living cell's mitochondria. Assay was performed using the protocol by Rahat *et al*.[8] with slight modification. Approximately 1×10^6 parasites/ml were treated with IC_{50} (~5 μM) and $2 \times IC_{50}$ (~10 μM) doses of **compound 27** and **compound 28** for 3 h, 6 h, 24 h and 48 h. *L. donovani* promastigotes maintained in culture medium were used as negative control and cells treated with antimycin A (10 μM) were used as a positive control and 0.2 % DMSO was taken as vehicle control. Parasites were then collected, washed in 1X HBSS twice, and incubated for 20 minutes at 25°C with 1X HBSS containing 5 μM freshly prepared MitoSOX red dye. Fluorescence for each time point was measured using Tecan M Pro 200 Fluorescence spectrophotometer at 510/580 nm of excitation and emission, respectively. Two independent set of experiments were performed.

SwissADME® Evalution Report:



27



SMILES COc1ccc(cc1)c1nc(NCCN(C)C)c2c(n1)cccc2

Physicochemical Properties	
Formula	C19H22N4O
Molecular weight	322.40 g/mol
Num. heavy atoms	24
Num. arom. heavy atoms	16
Fraction Csp3	0.26
Num. rotatable bonds	6
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	98.09
TPSA	50.28 Å²

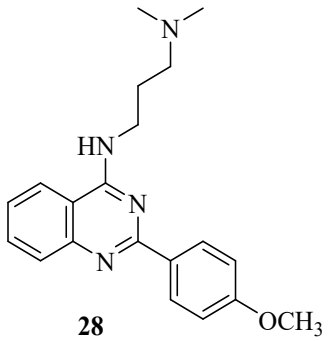
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.57
Log $P_{o/w}$ (XLOGP3)	3.84
Log $P_{o/w}$ (WLOGP)	3.09
Log $P_{o/w}$ (MLOGP)	2.64
Log $P_{o/w}$ (SILICOS-IT)	3.06
Consensus Log $P_{o/w}$	3.24

Water Solubility	
Log *S* (ESOL)	-4.36
Solubility	1.42e-02 mg/ml ; 4.41e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.59
Solubility	8.25e-03 mg/ml ; 2.56e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-6.92
Solubility	3.85e-05 mg/ml ; 1.19e-07 mol/l
Class	Poorly soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.54 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	2.59



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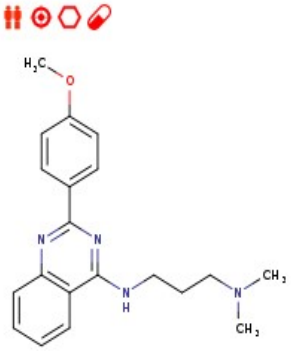
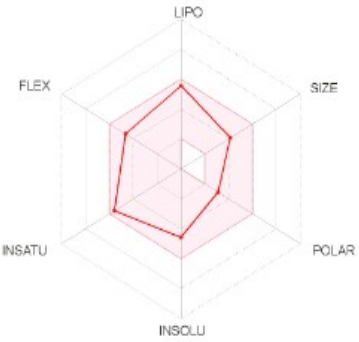




SMILES COc1ccc(cc1)c1nc(NCCCN(C)C)c2c(n1)cccc2

Physicochemical Properties	
Formula	C20H24N4O
Molecular weight	336.43 g/mol
Num. heavy atoms	25
Num. arom. heavy atoms	16
Fraction Csp3	0.30
Num. rotatable bonds	7
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	102.90
TPSA	50.28 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.88
Log $P_{o/w}$ (XLOGP3)	4.19
Log $P_{o/w}$ (WLOGP)	3.48
Log $P_{o/w}$ (MLOGP)	2.86
Log $P_{o/w}$ (SILICOS-IT)	3.45
Consensus Log $P_{o/w}$	3.57

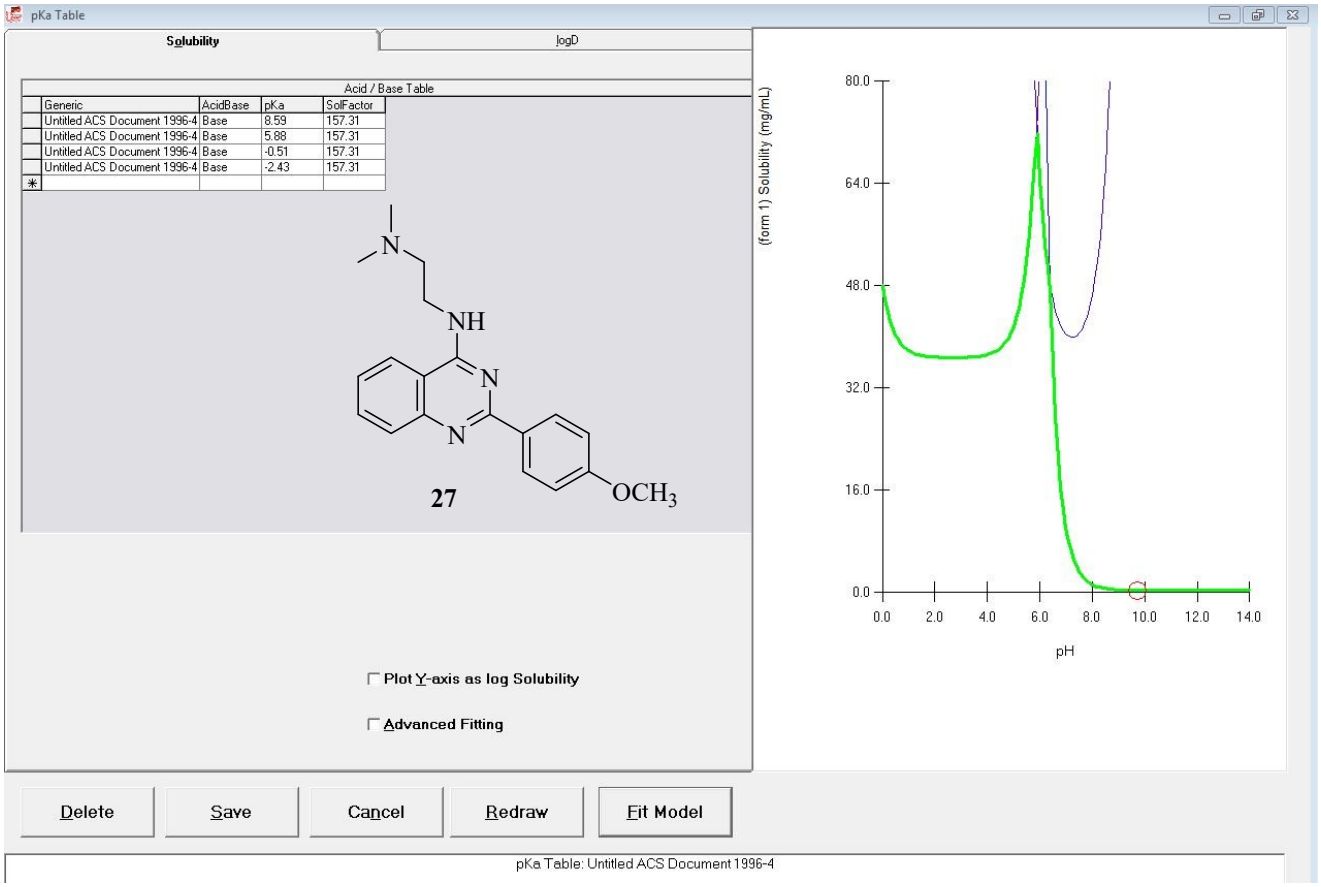
Water Solubility	
Log *S* (ESOL)	-4.58
Solubility	8.91e-03 mg/ml ; 2.65e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.96
Solubility	3.73e-03 mg/ml ; 1.11e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.32
Solubility	1.61e-05 mg/ml ; 4.80e-08 mol/l
Class	Poorly soluble

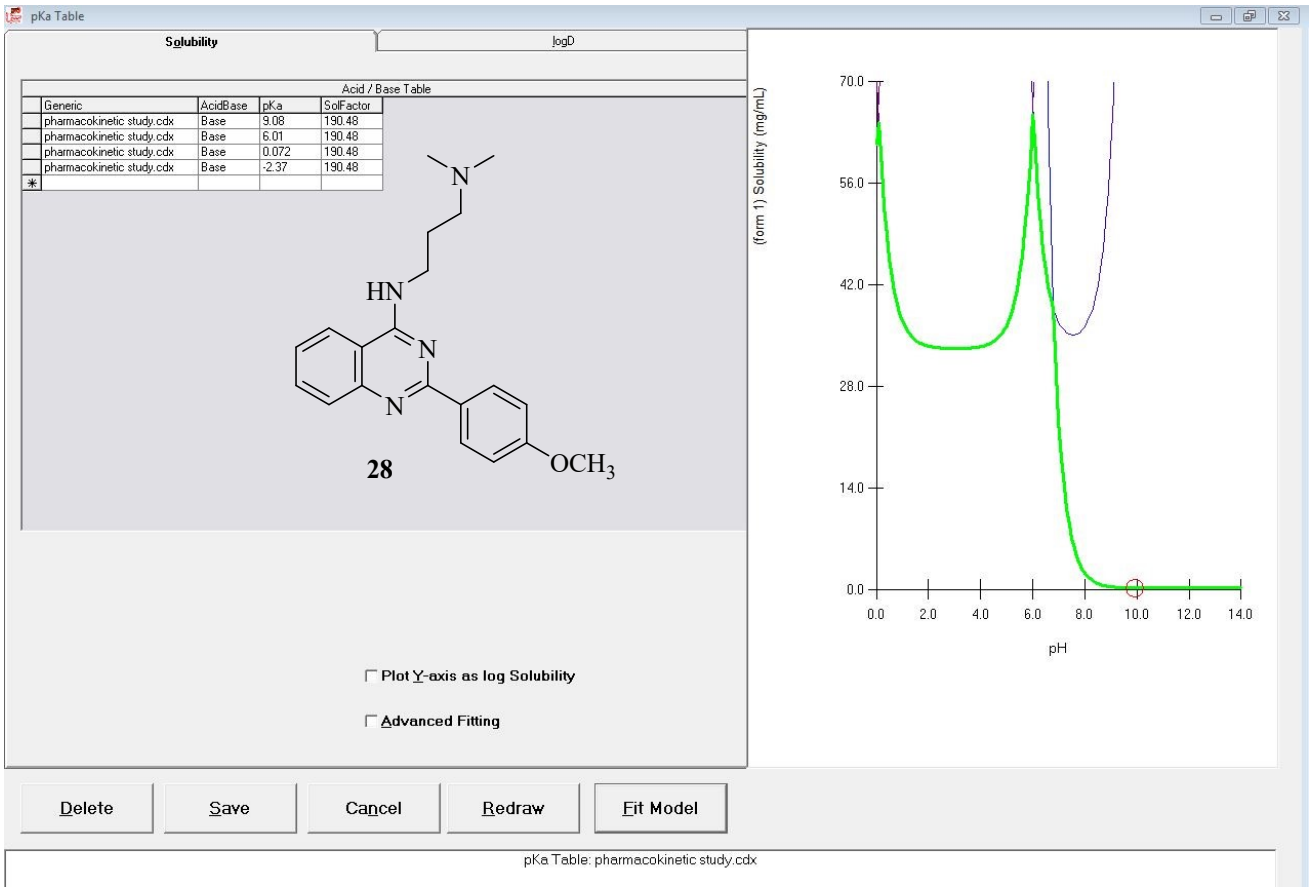
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.38 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	2.66

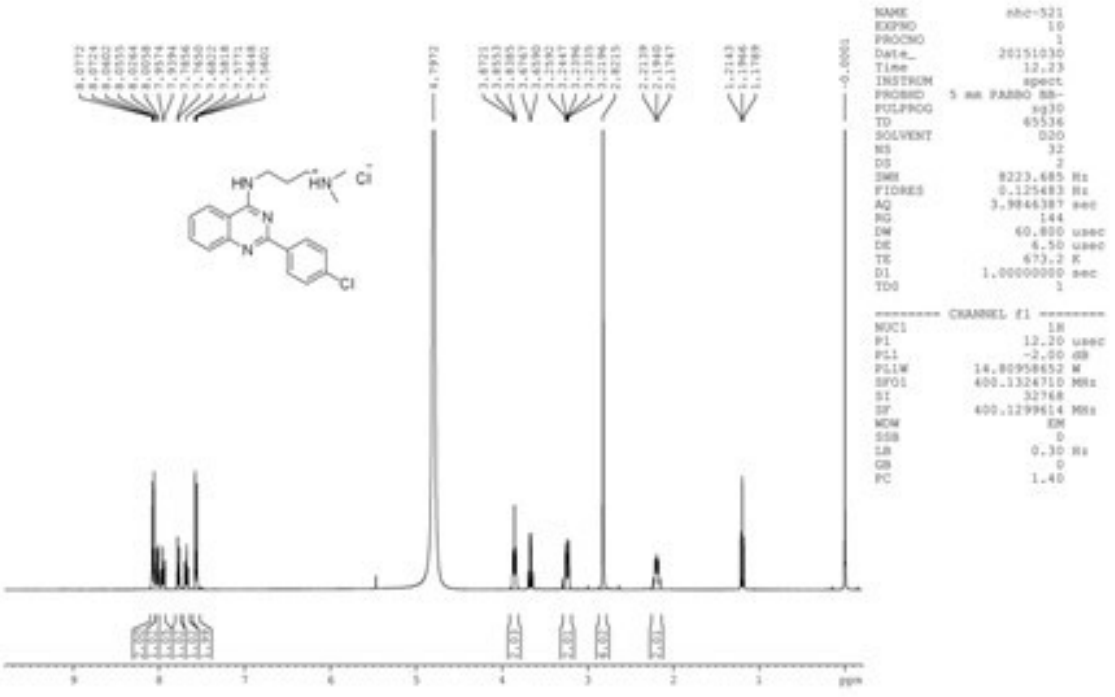
SimulationPlus® Evalution Report:



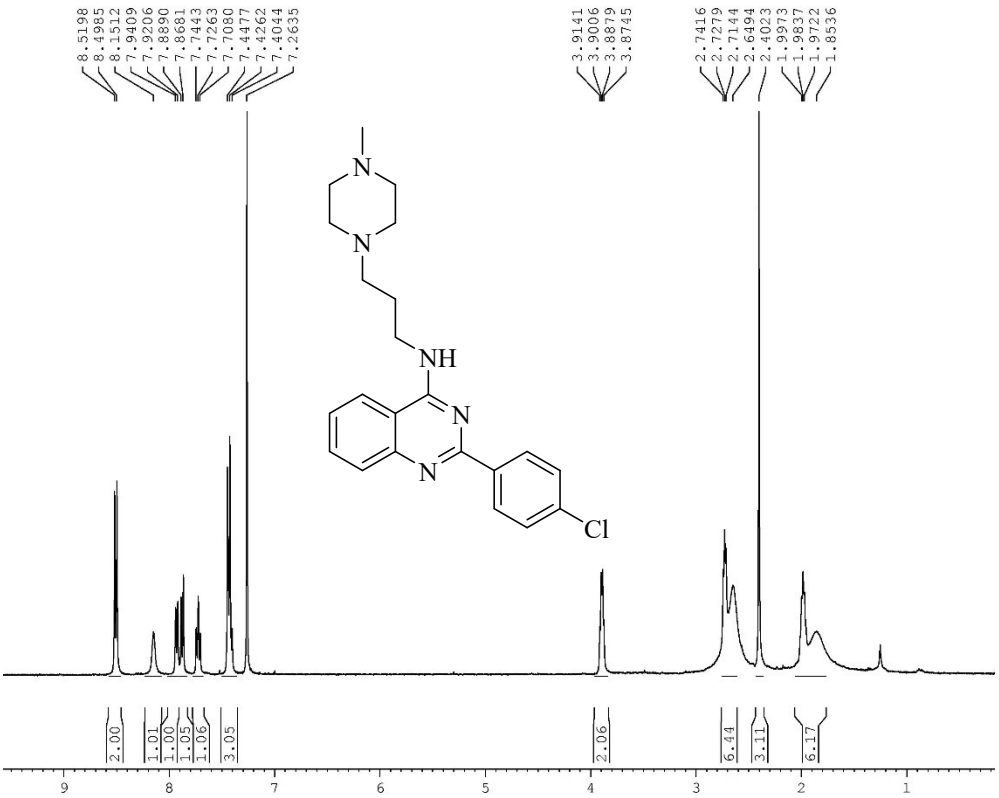


^{1}H and ^{13}C{^{1}H}-NMR spectra of 2-aryl-4-alkypolyaminoquinazolines:

^{1}H NMR, 15



^{1}H NMR, 16



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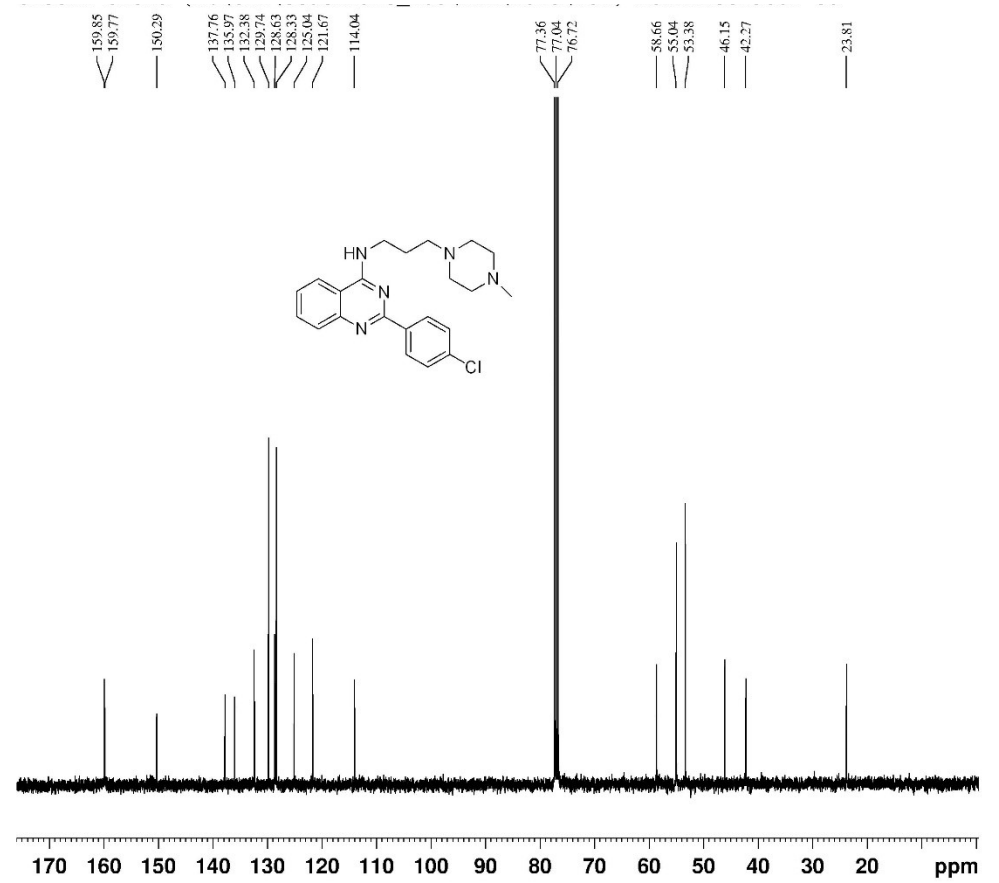

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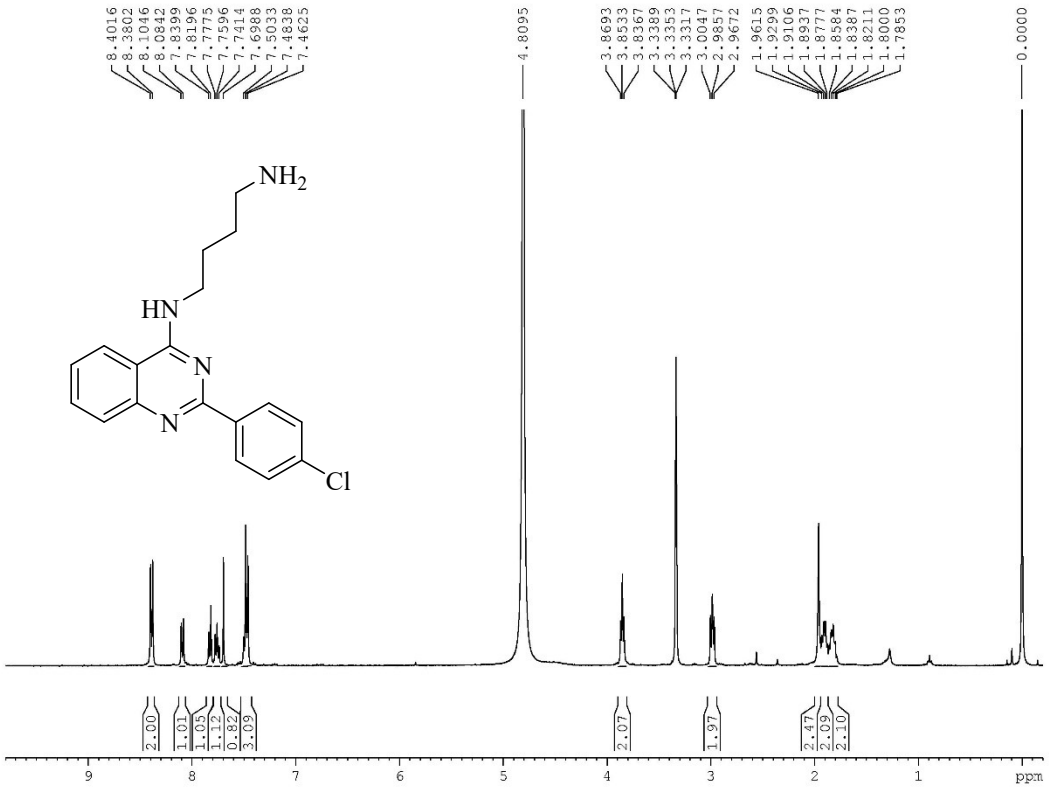

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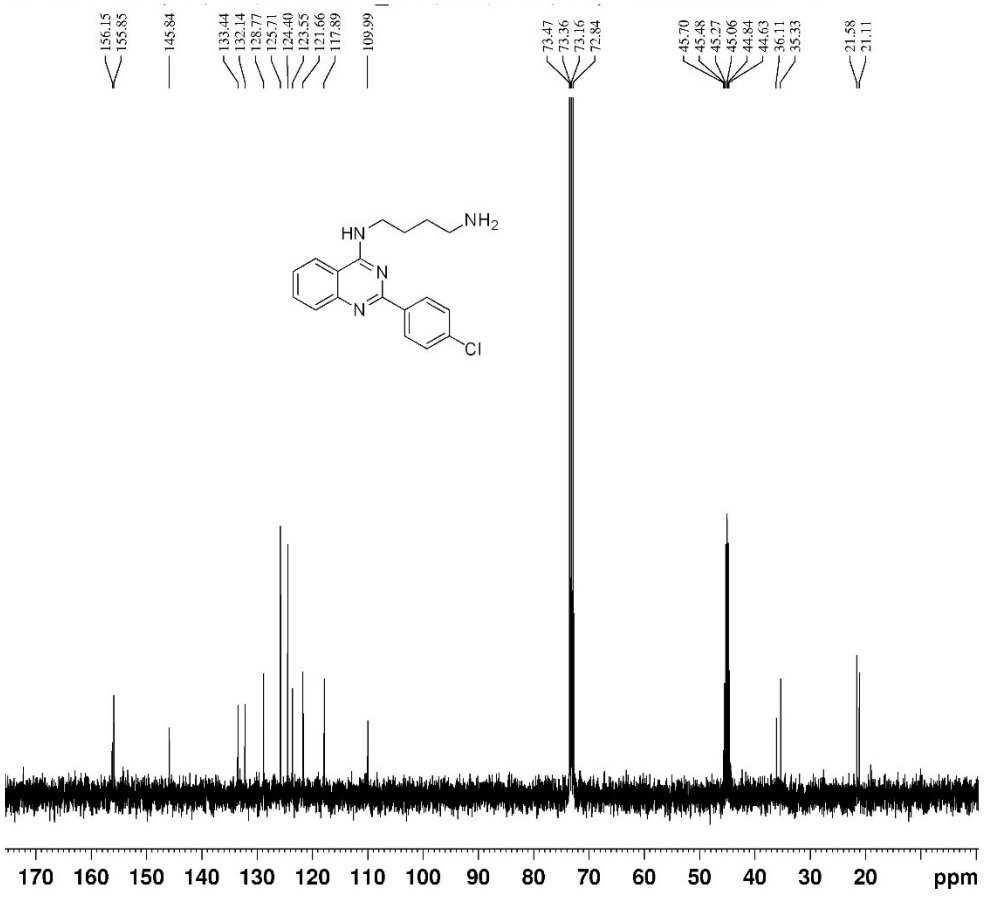
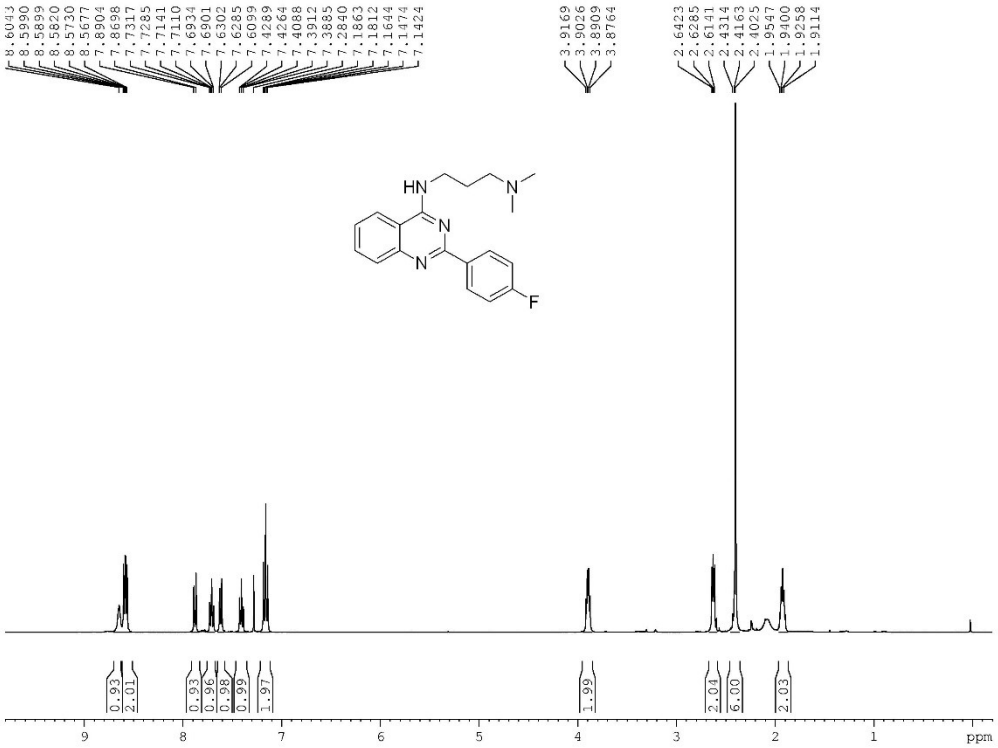


^{1}H NMR, 18



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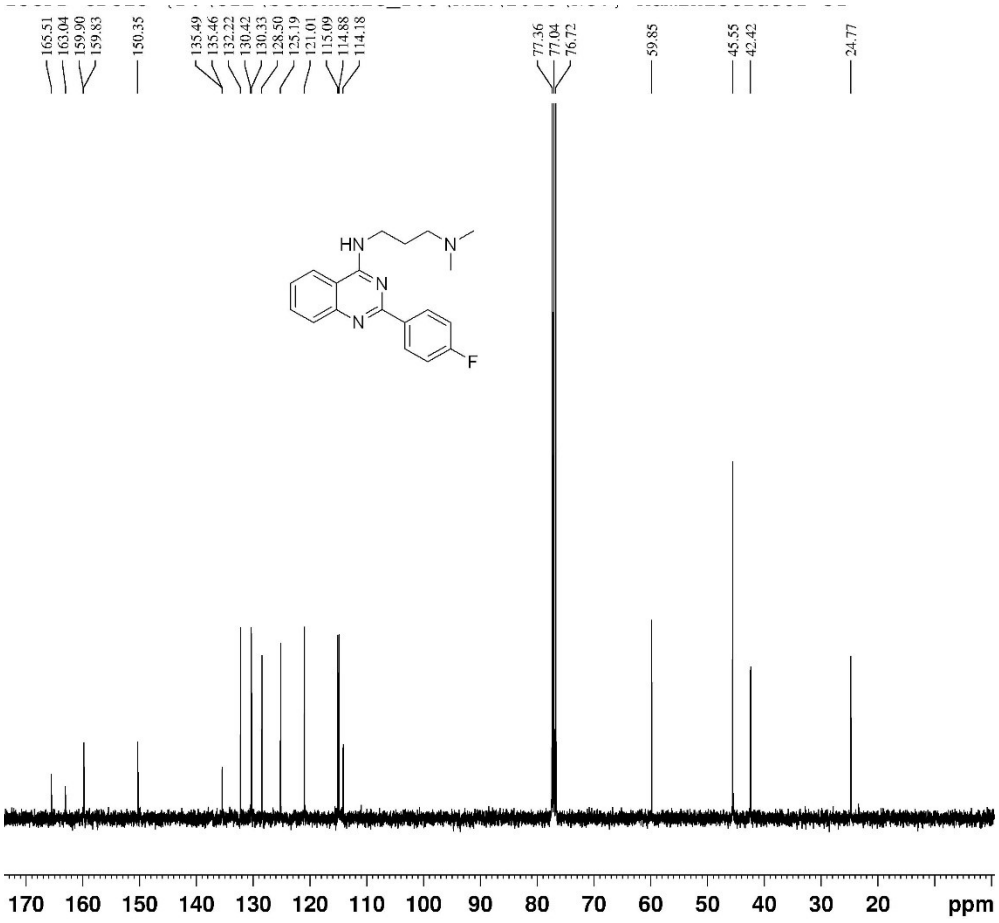
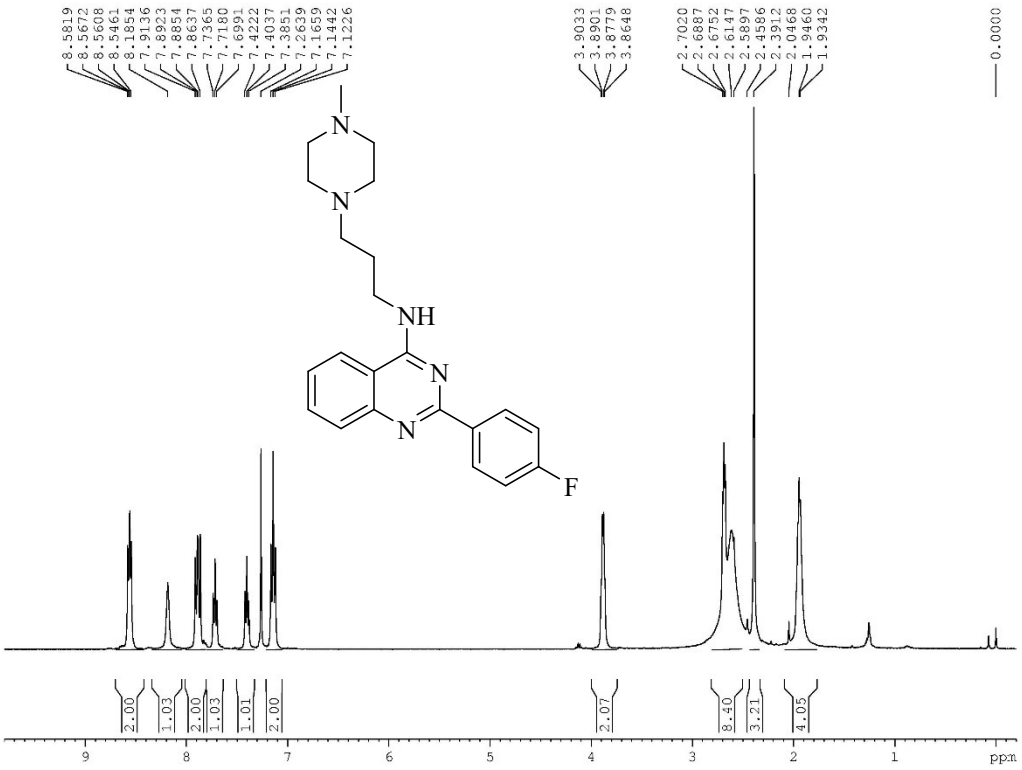


^{1}H NMR, 19



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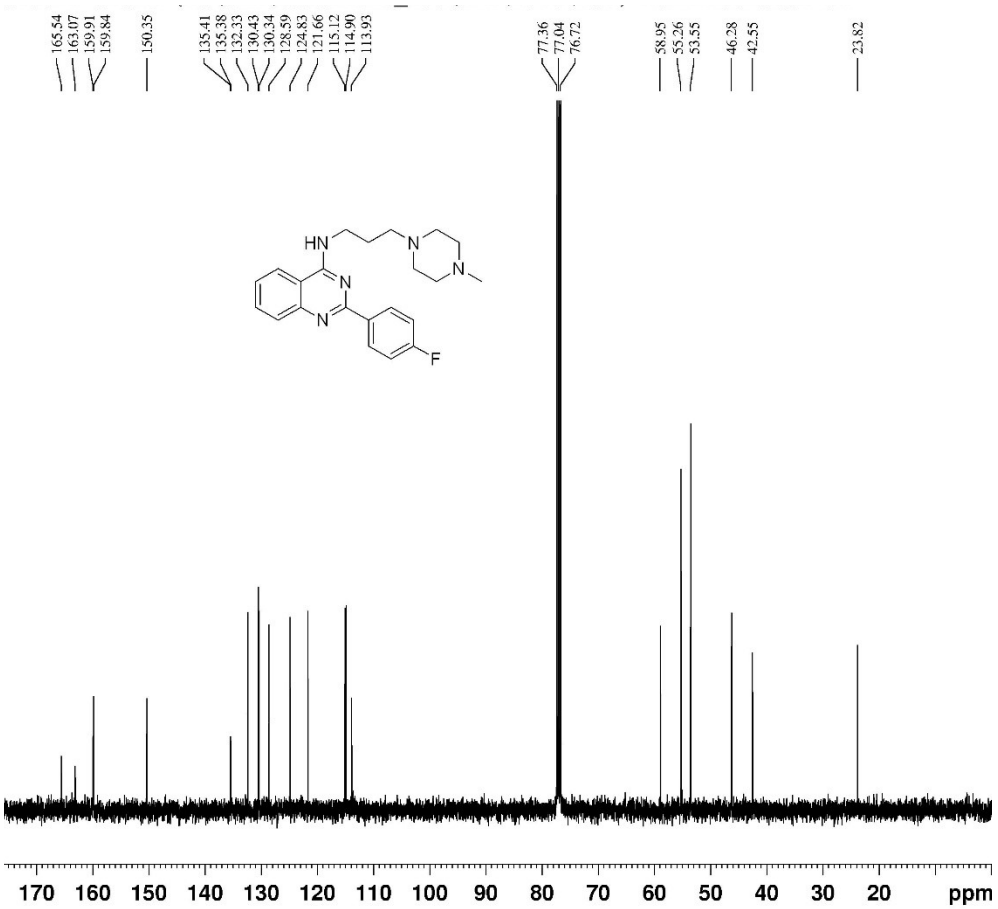
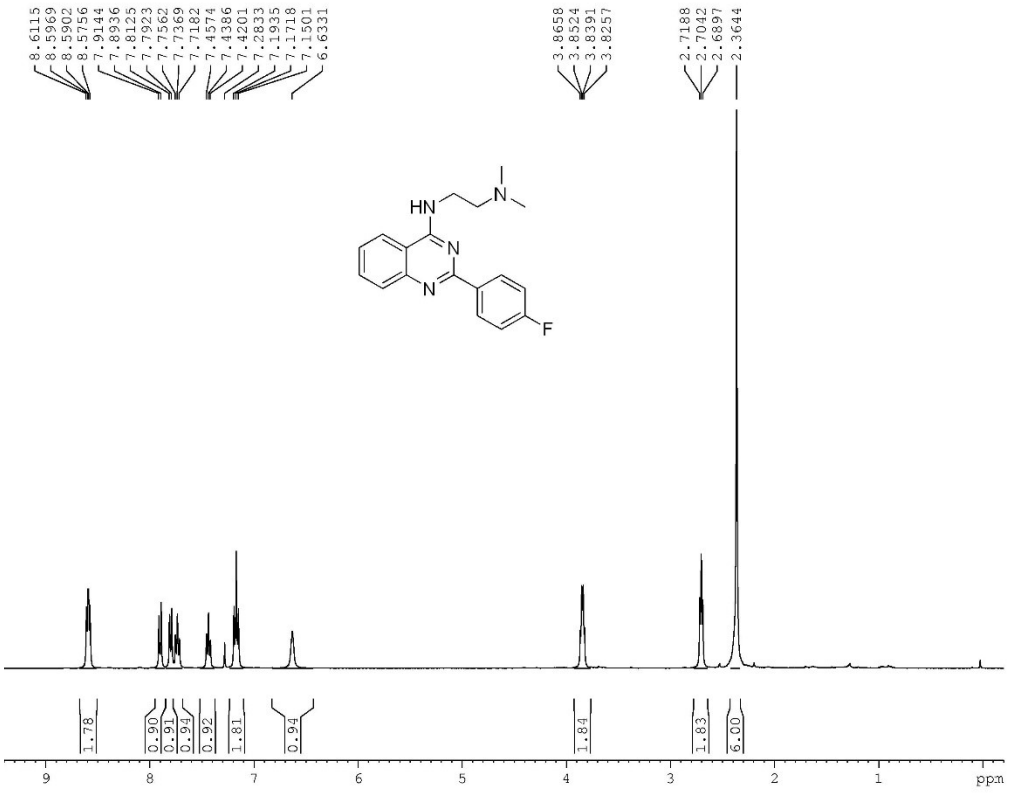
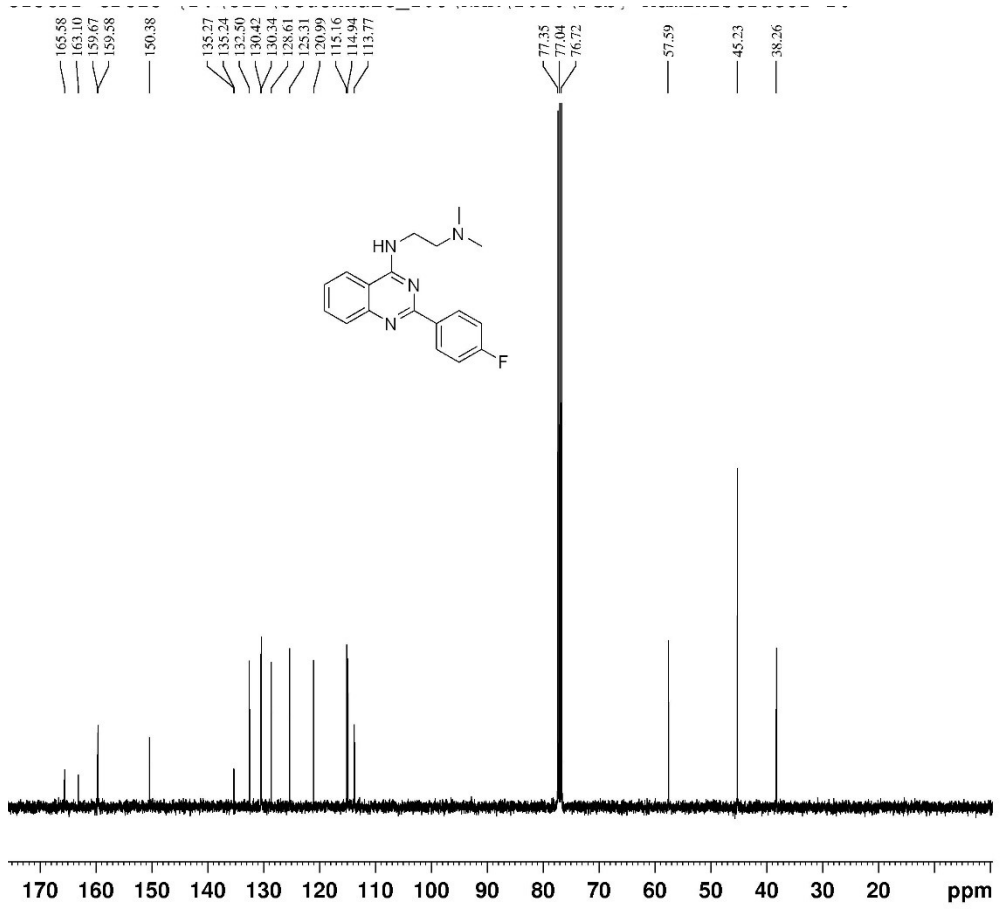


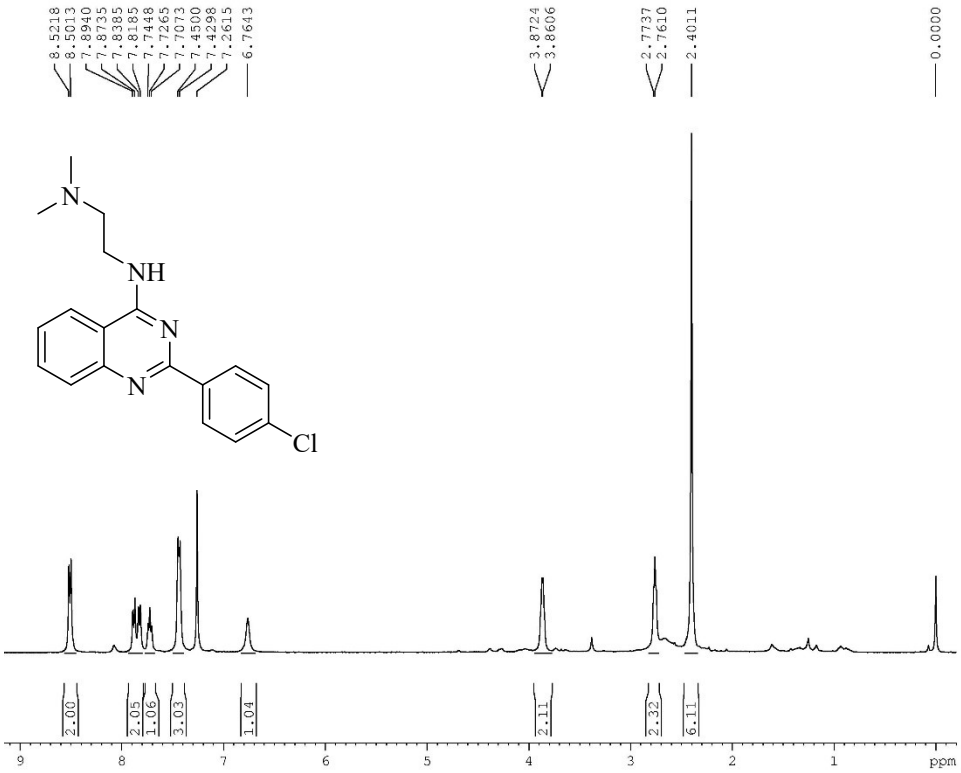
^{1}H NMR, 20



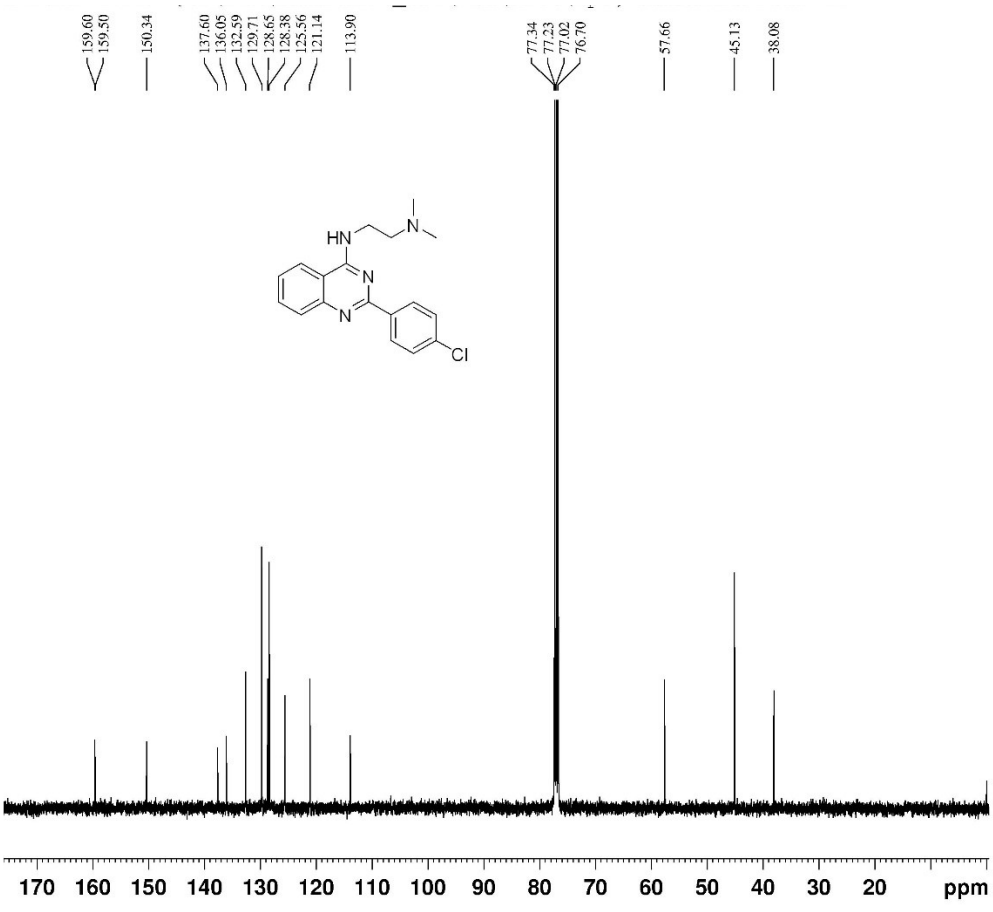
^{13}C NMR, 20



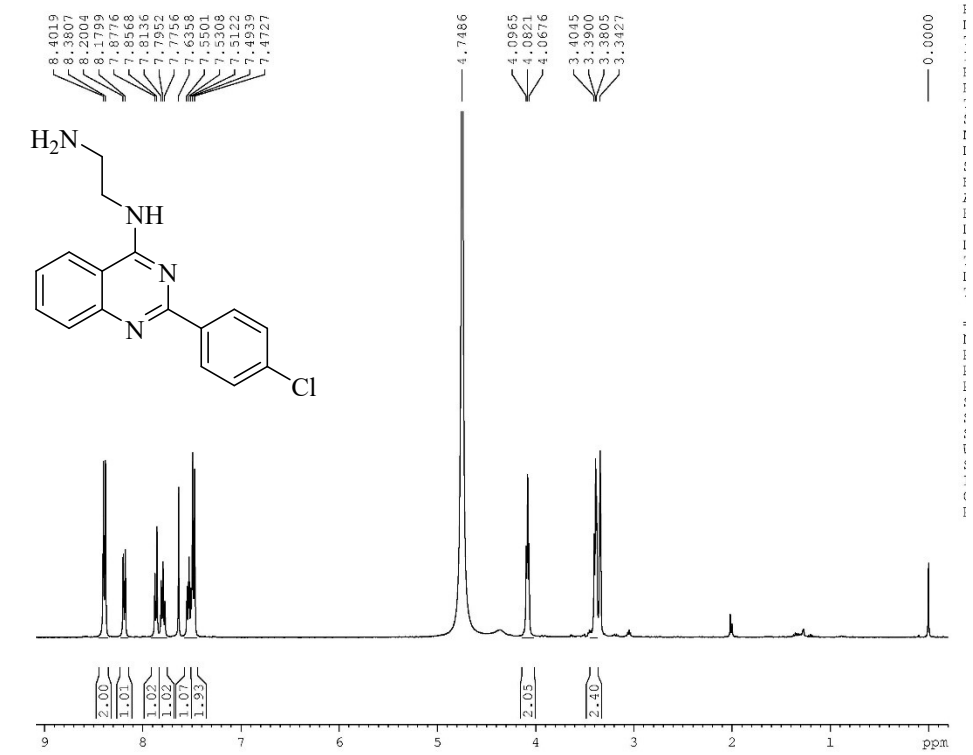
^{1}H NMR, 21



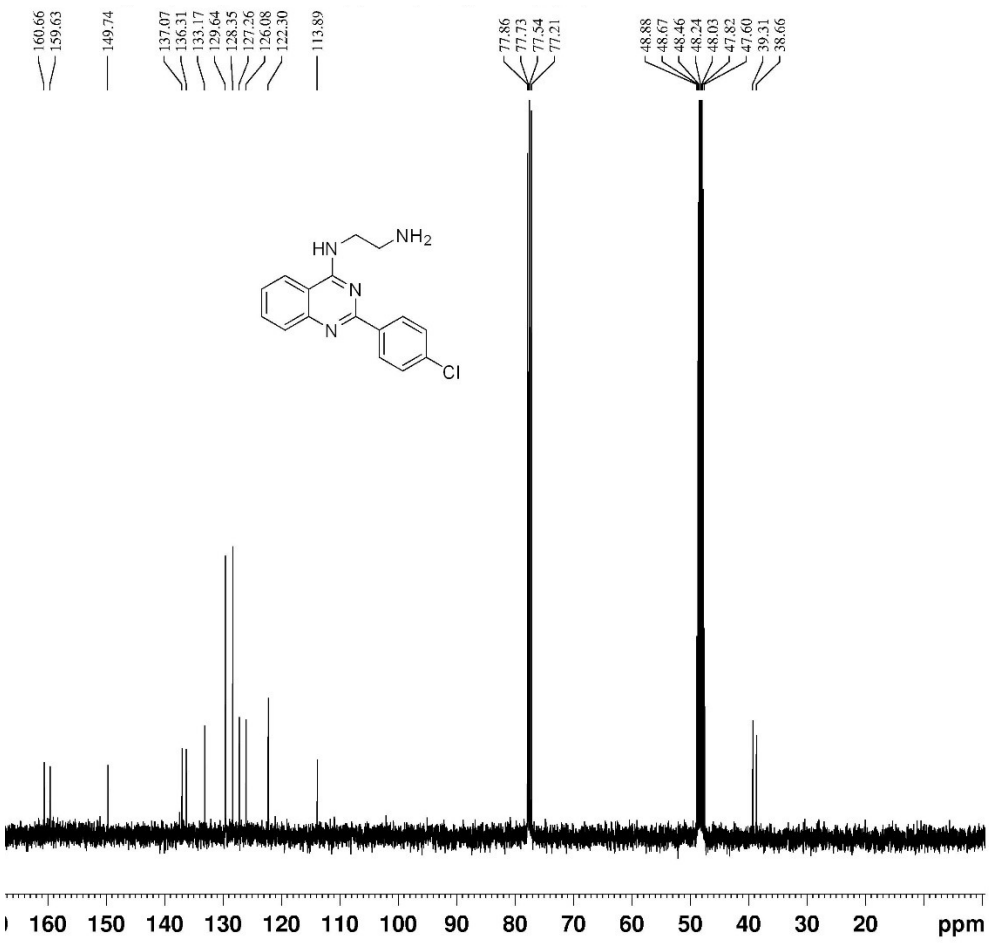
^{13}C NMR, 21



^{1}H NMR, 22



^{13}C NMR, 22



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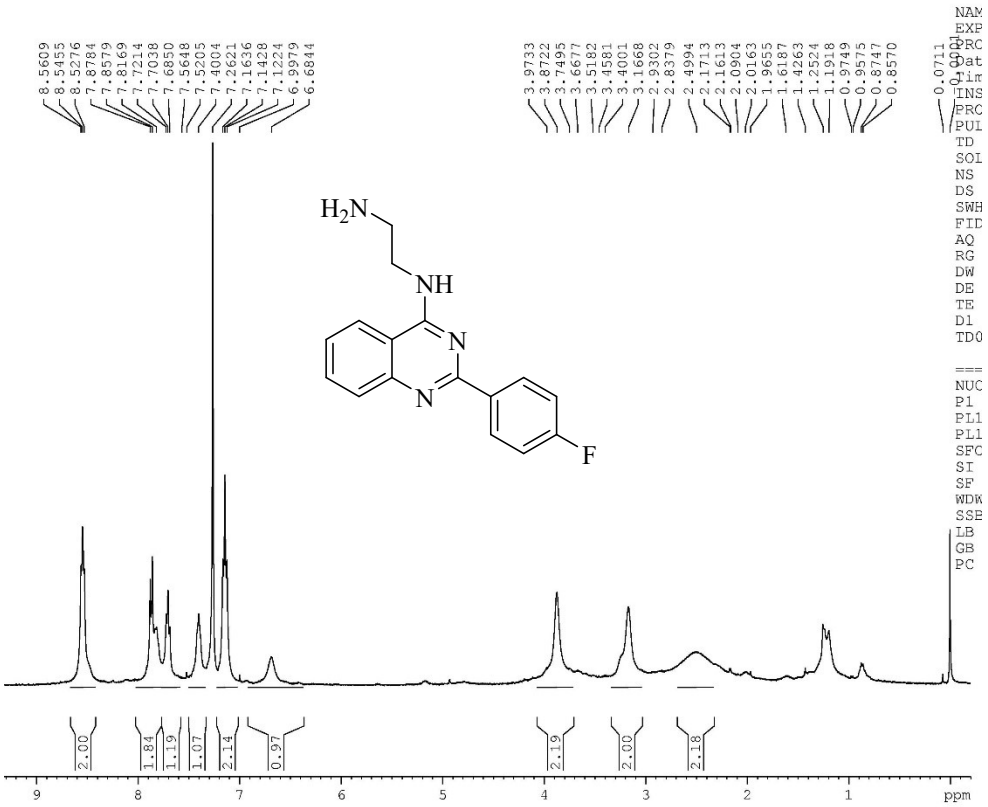
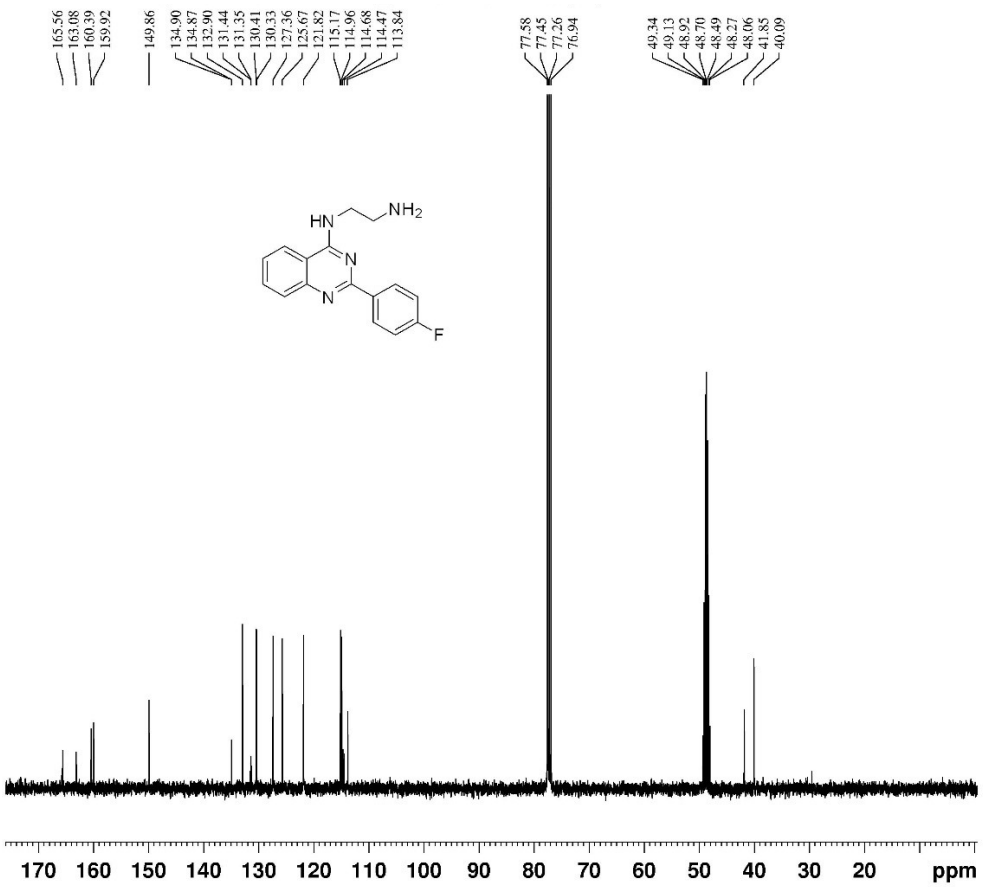
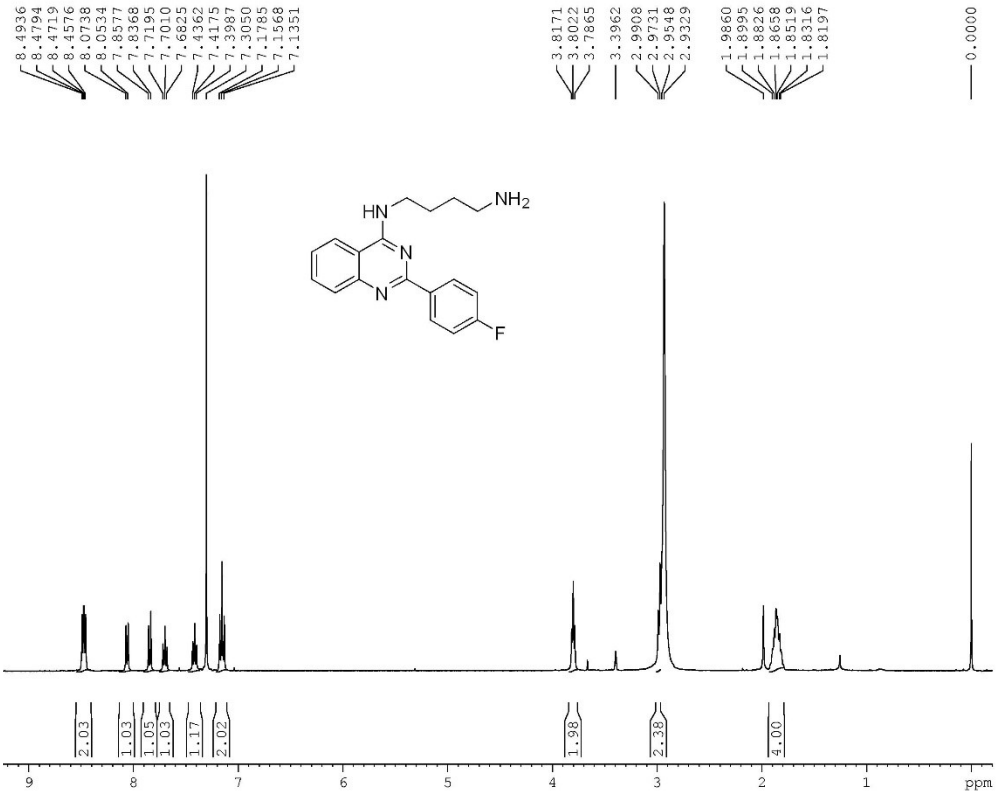


^{13}C NMR, 23



^{1}H NMR, 24



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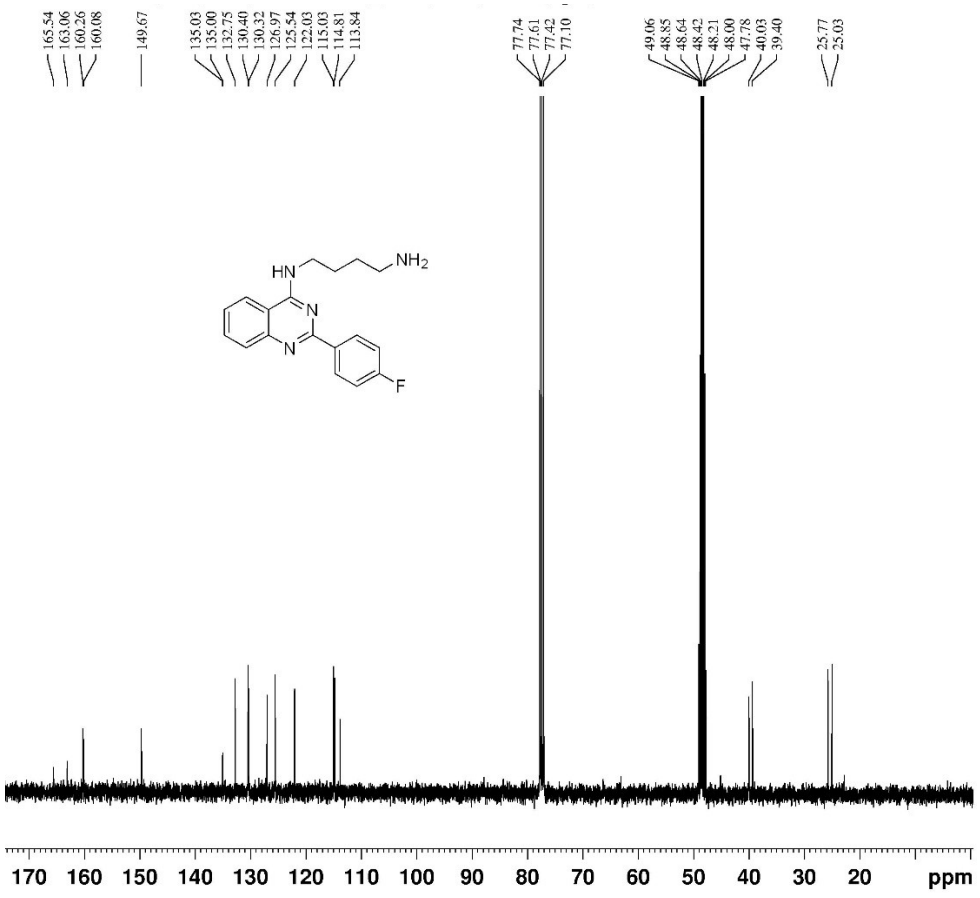
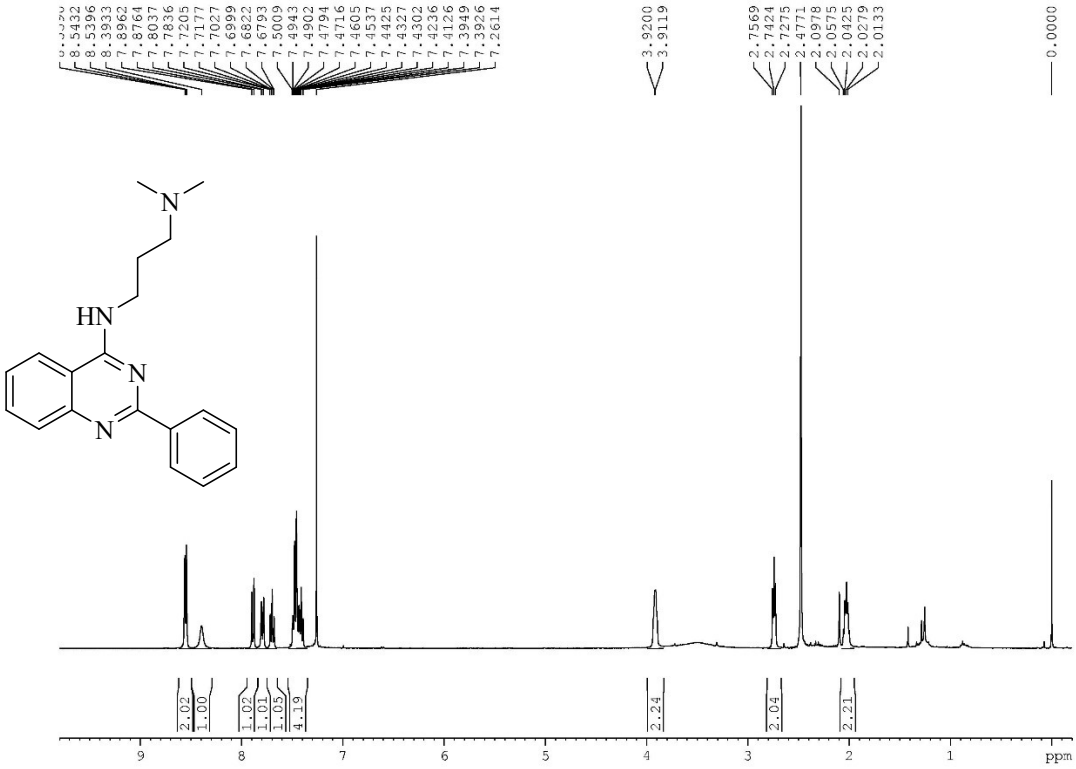


^{1}H NMR, 25



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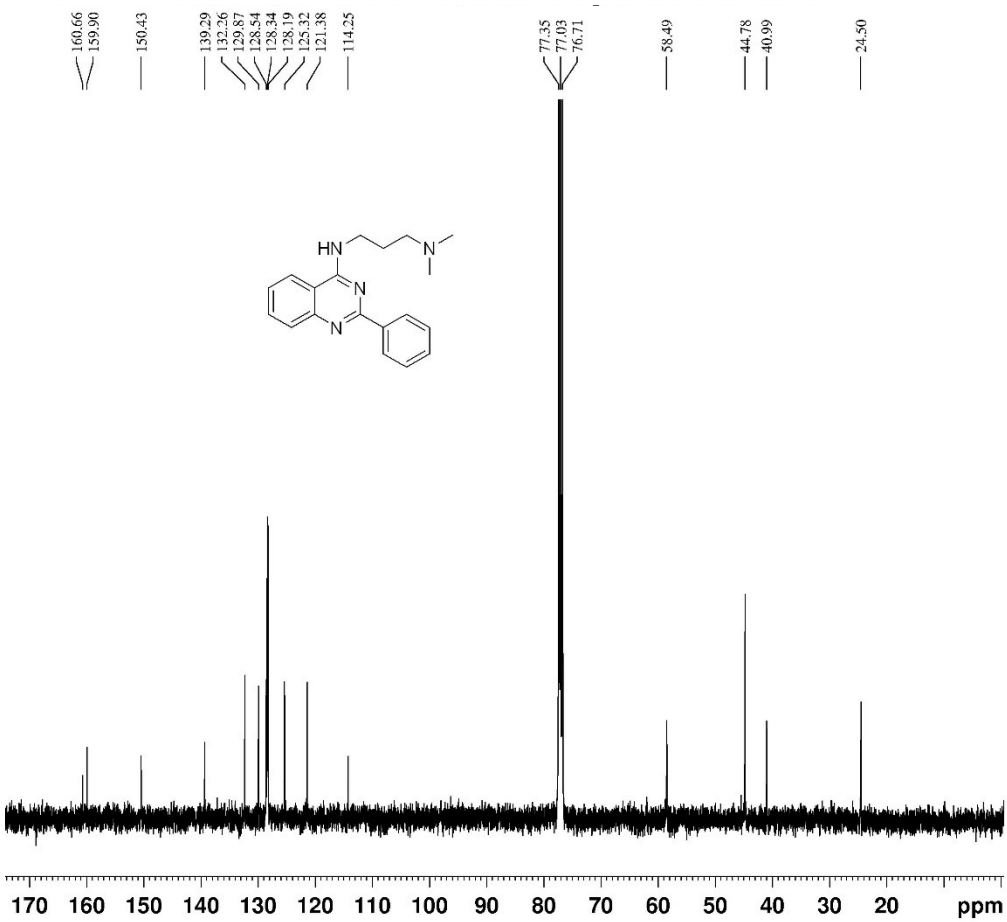
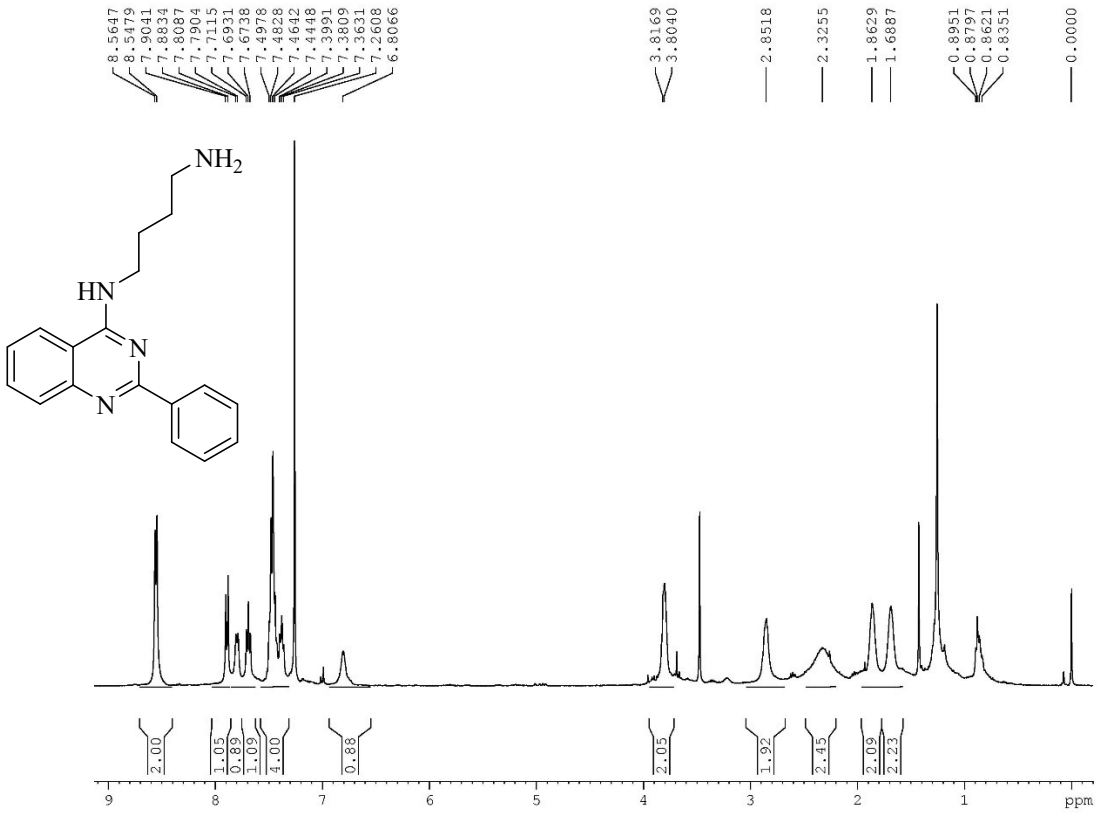


^{1}H NMR, 26



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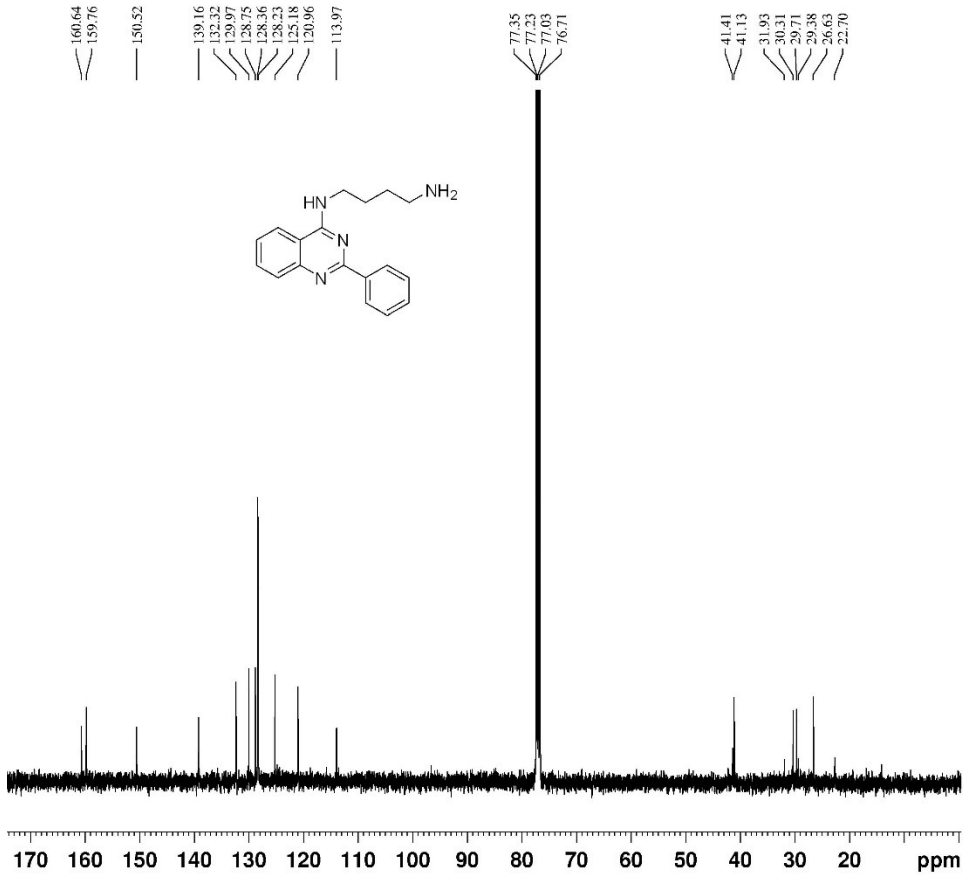
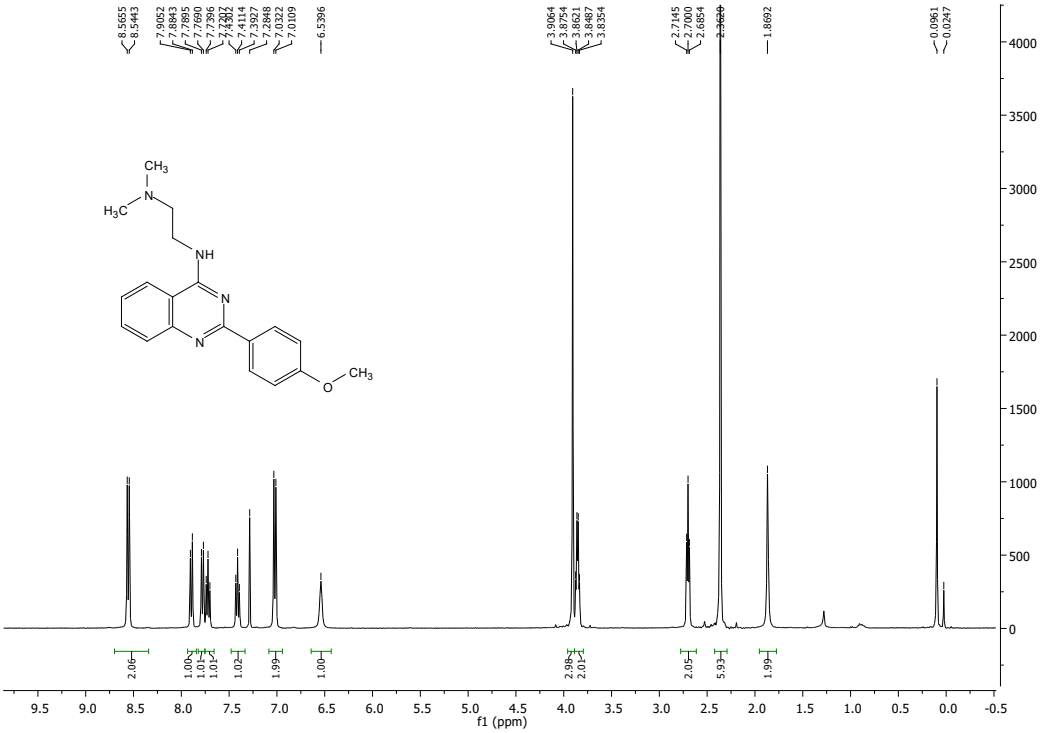


^{1}H NMR, 27



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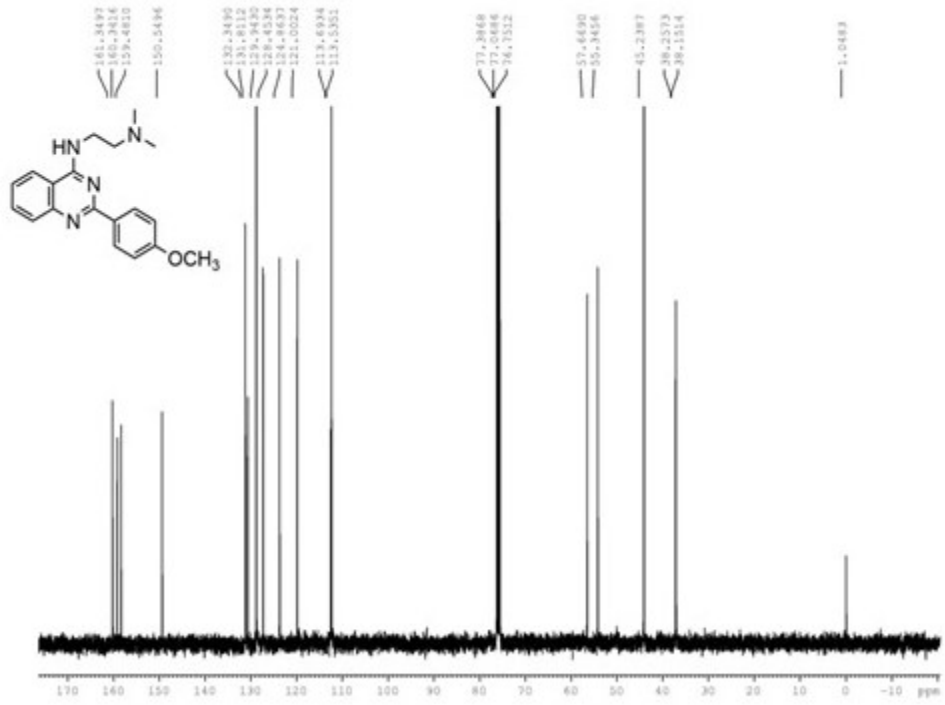
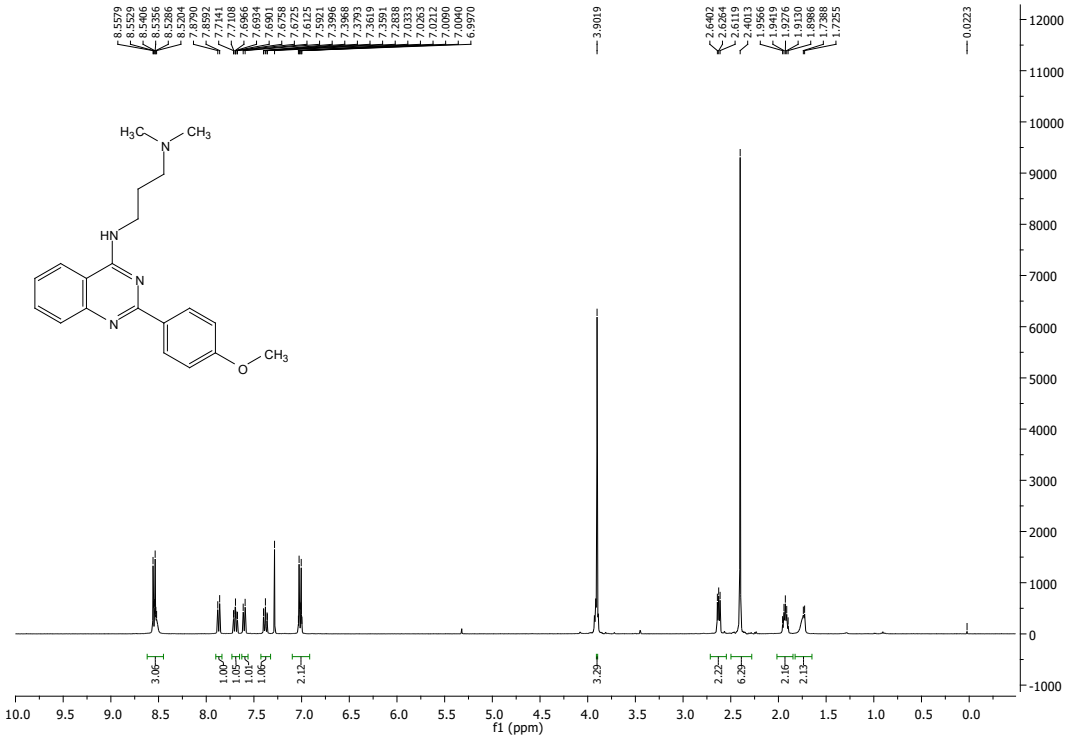


^{1}H NMR, 28



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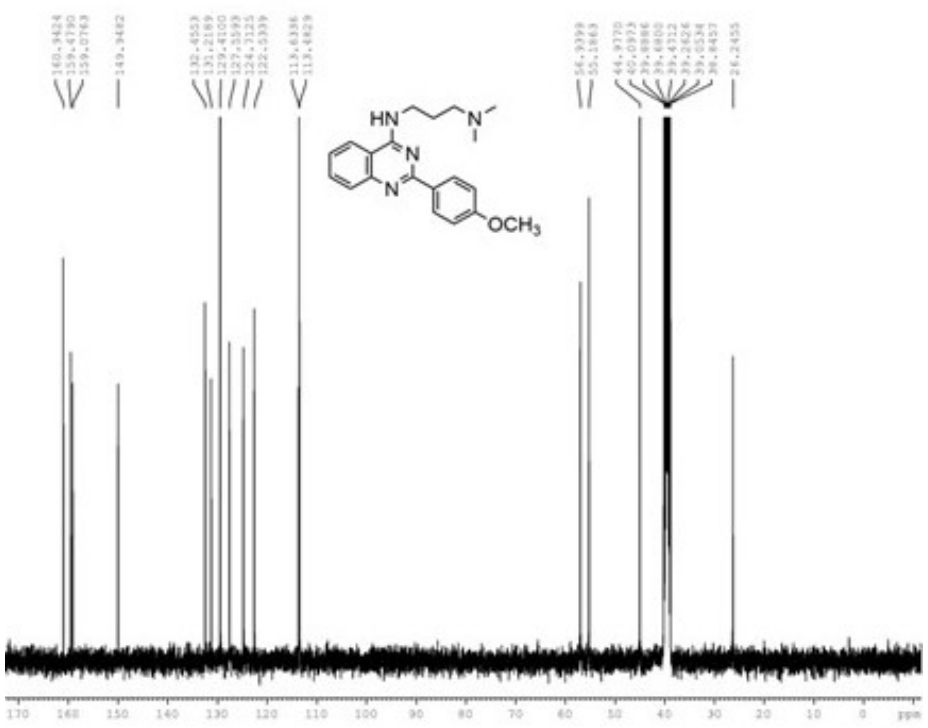

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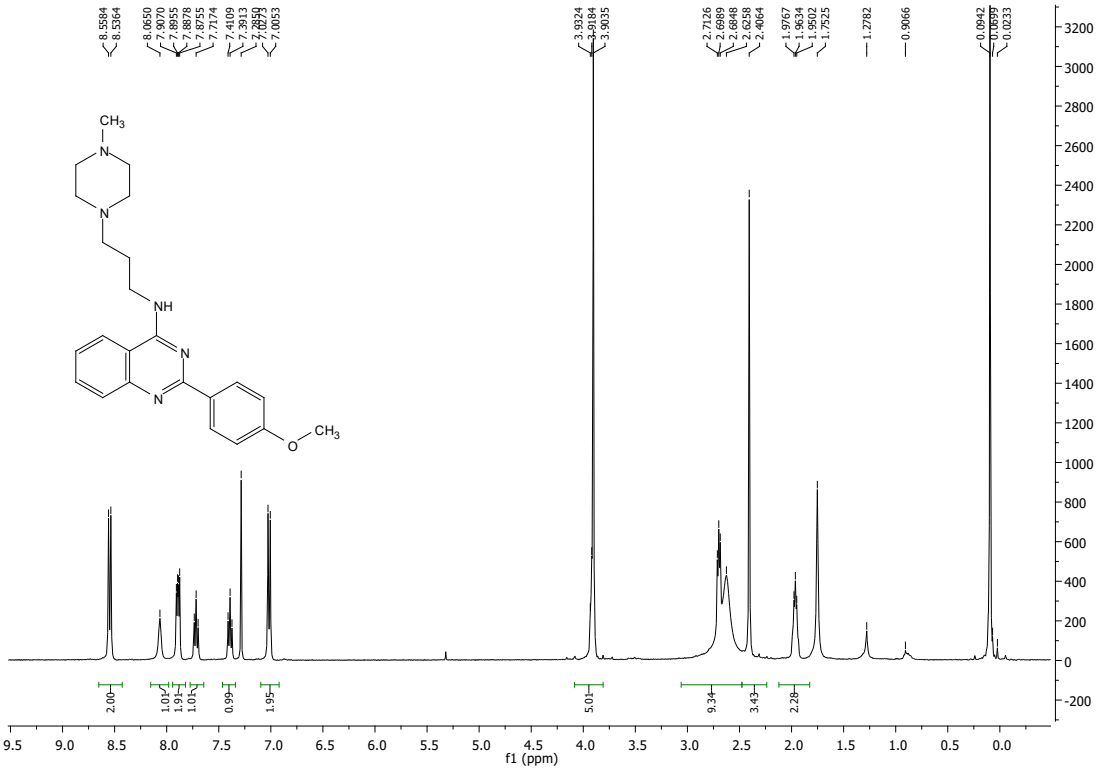

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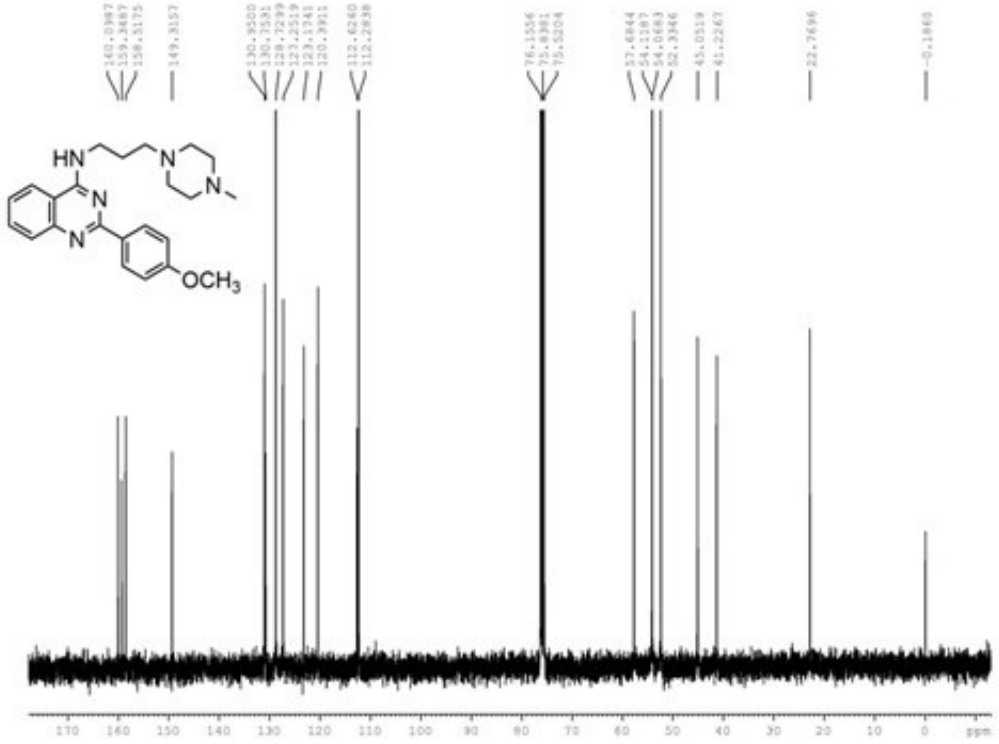
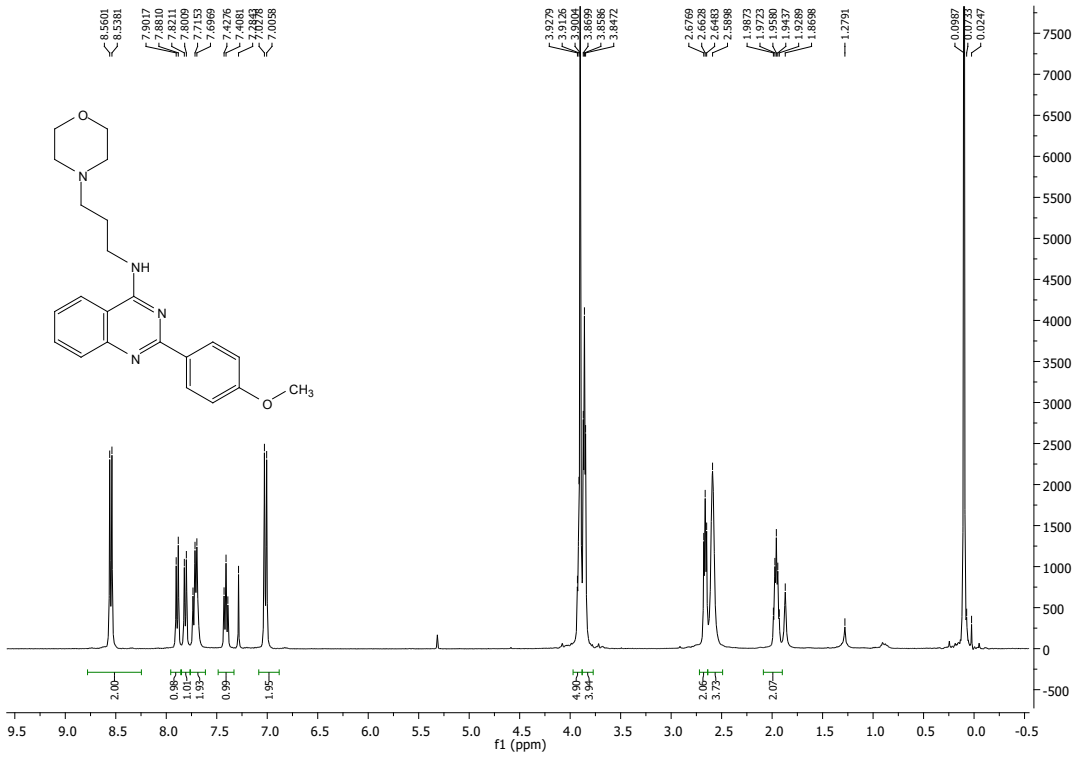
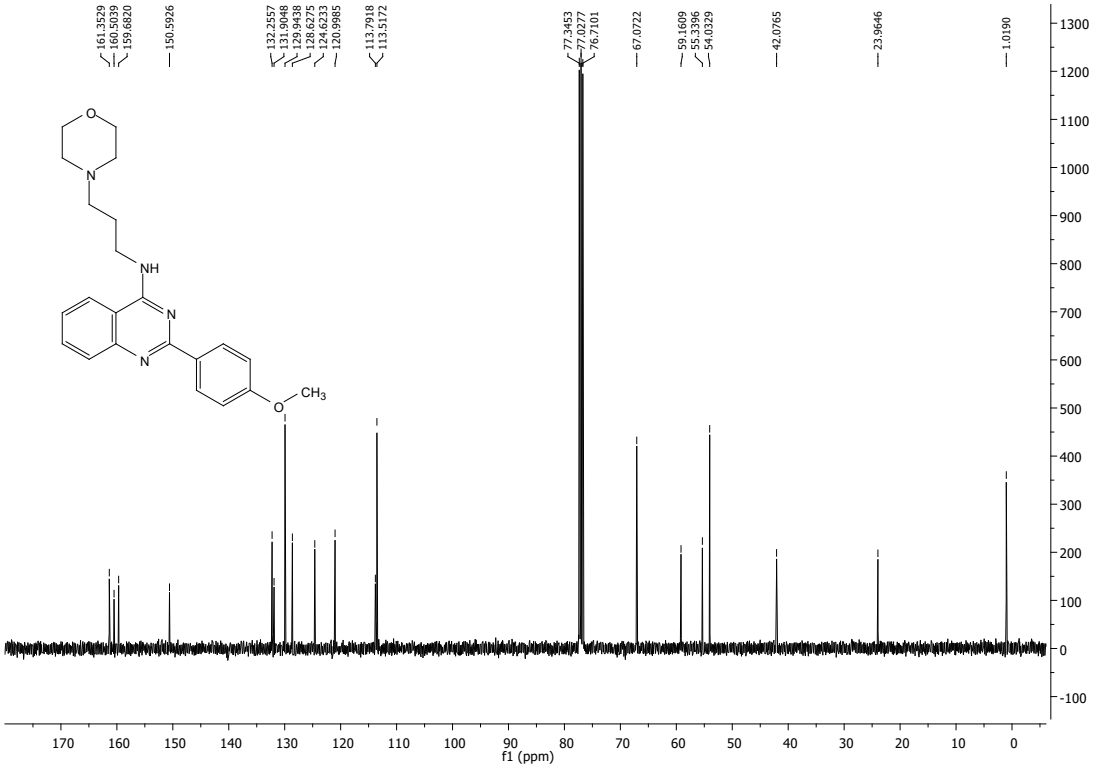


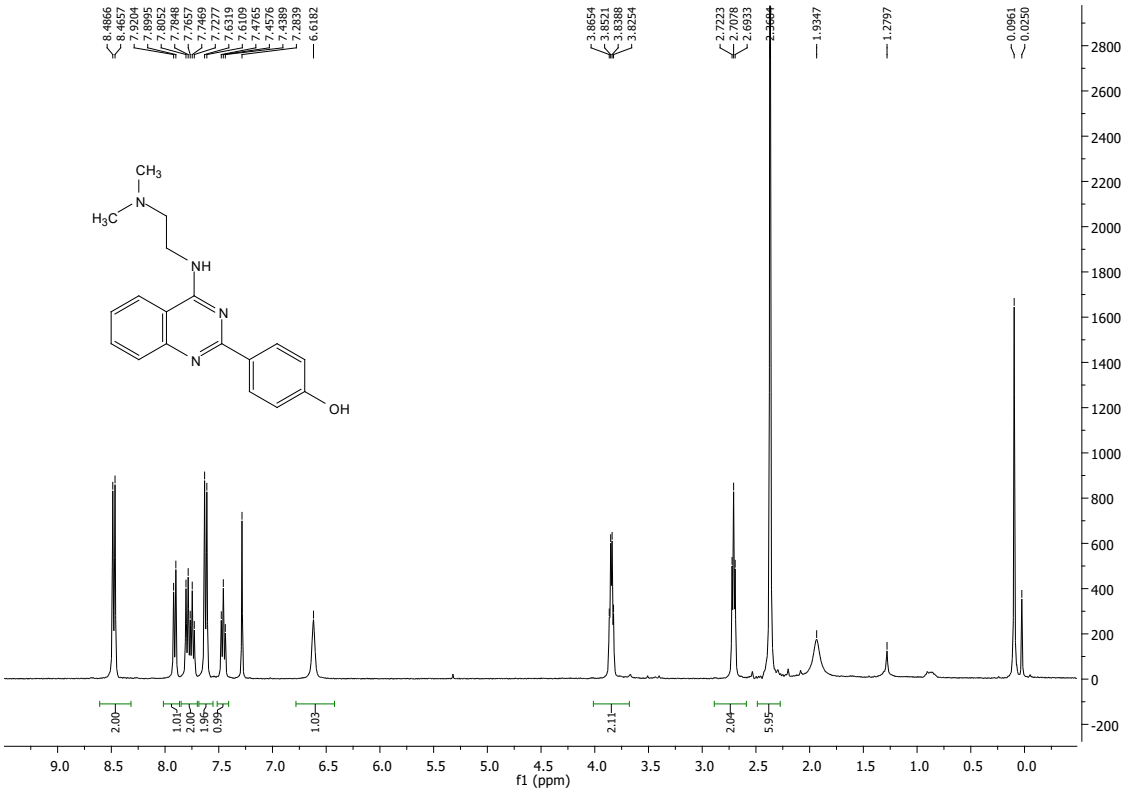
^{1}H NMR, 30



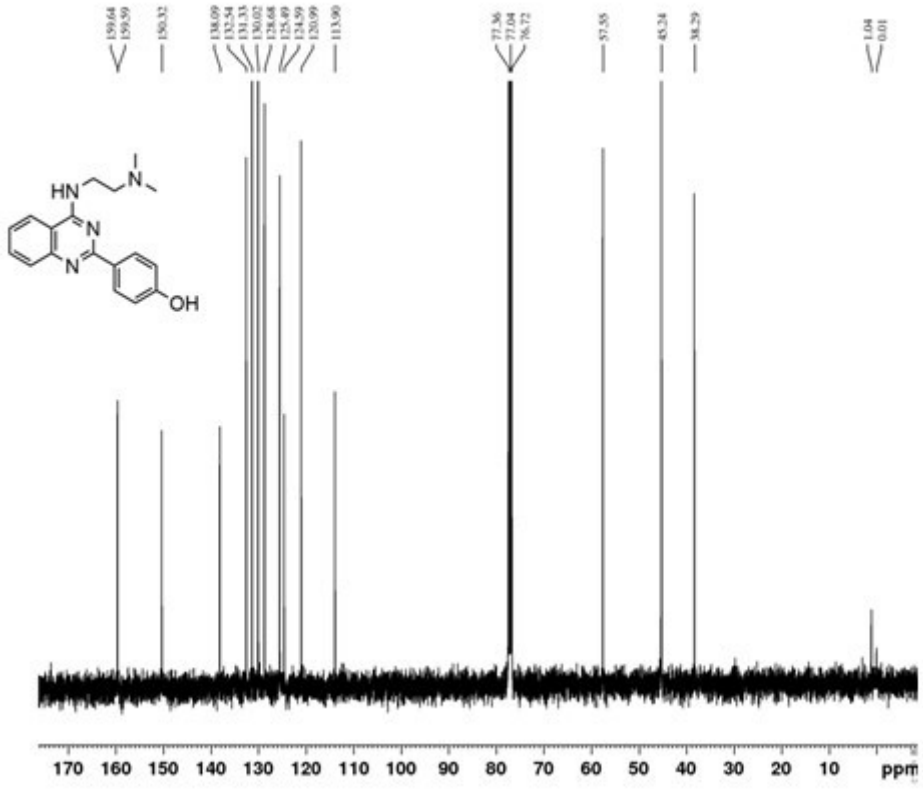
^{13}C NMR, 30



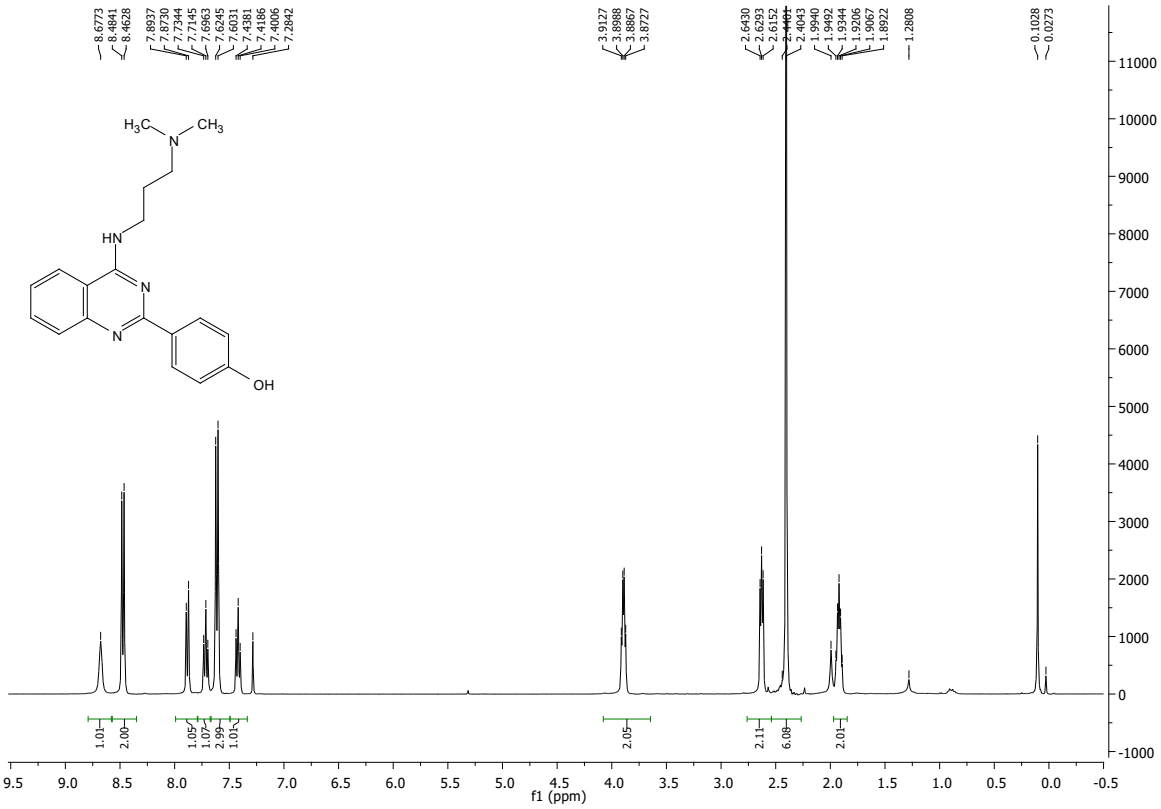
^{1}H NMR, 31



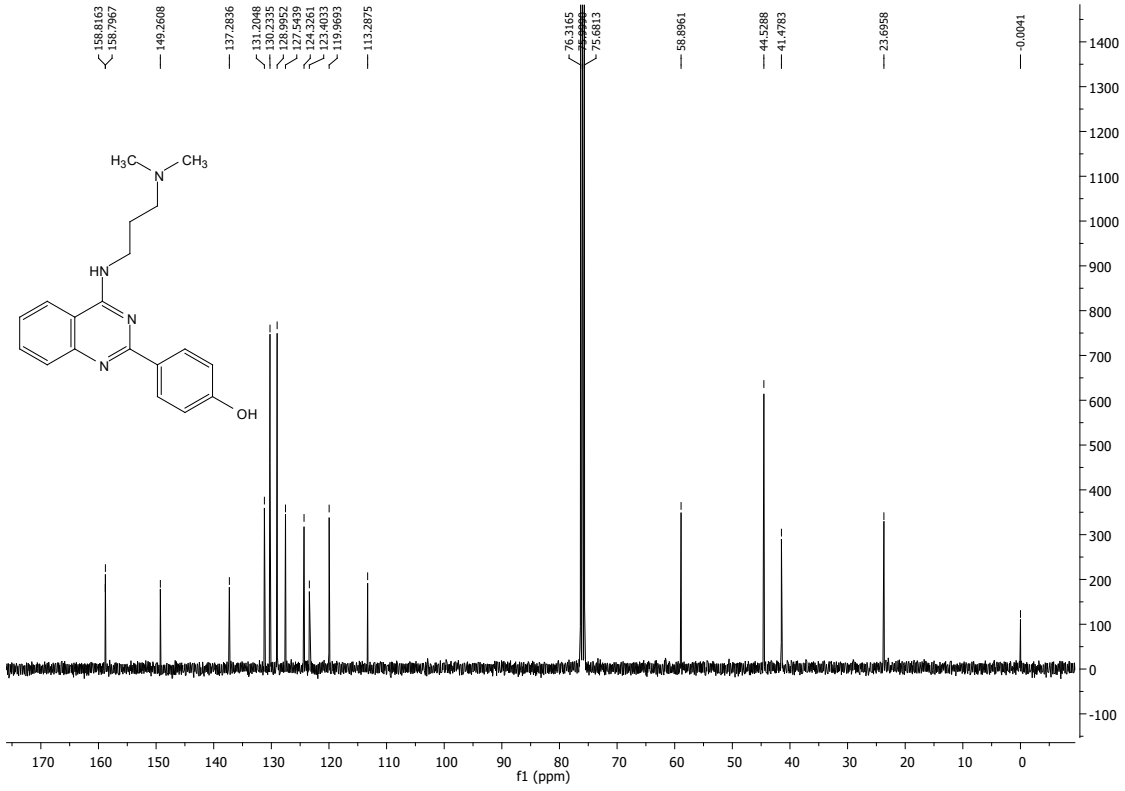
^{13}C NMR, 31



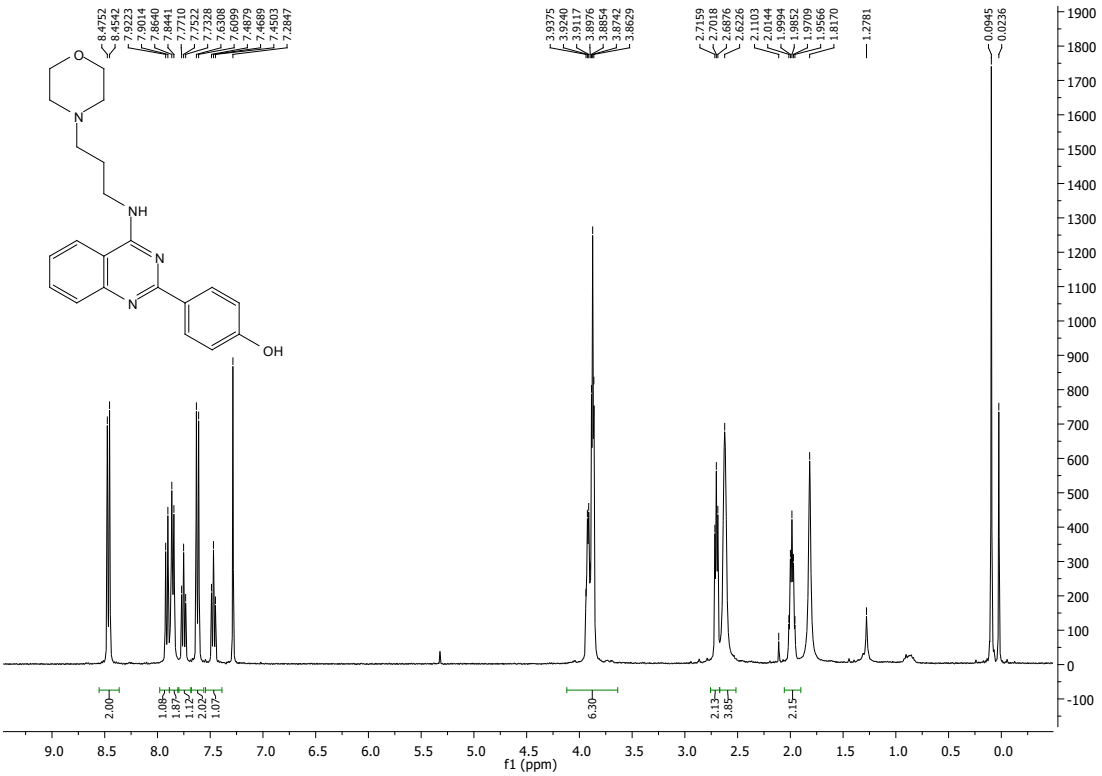
^{1}H NMR, 32



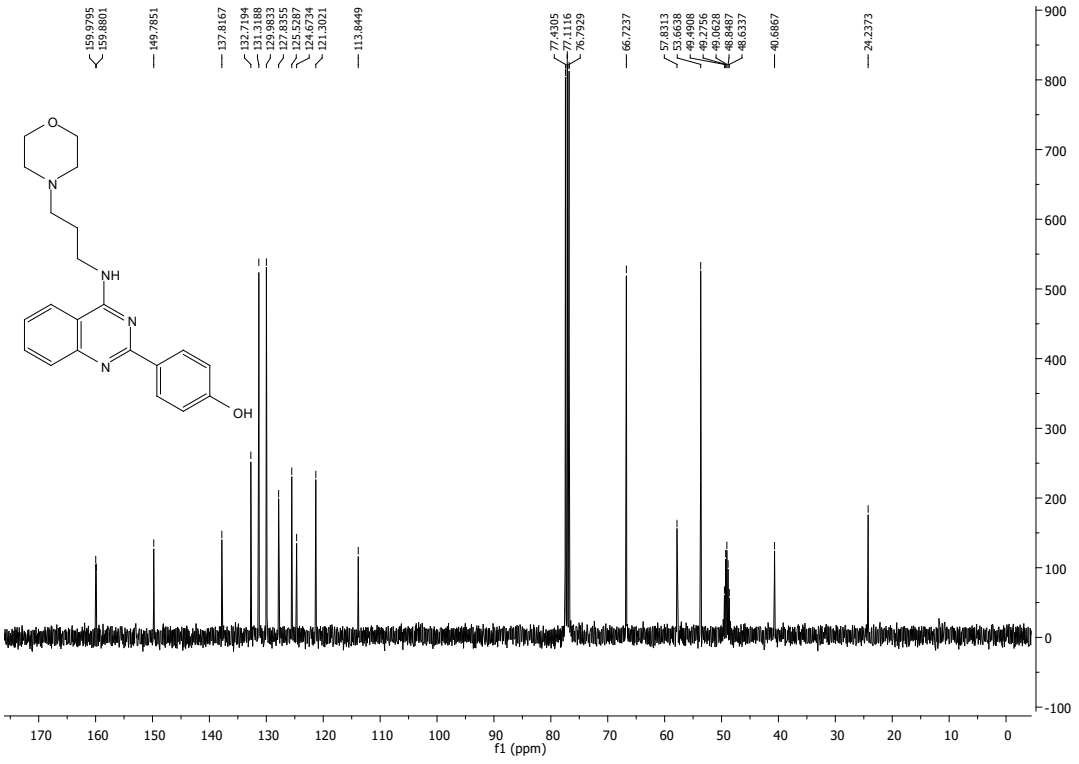
^{13}C NMR, 32



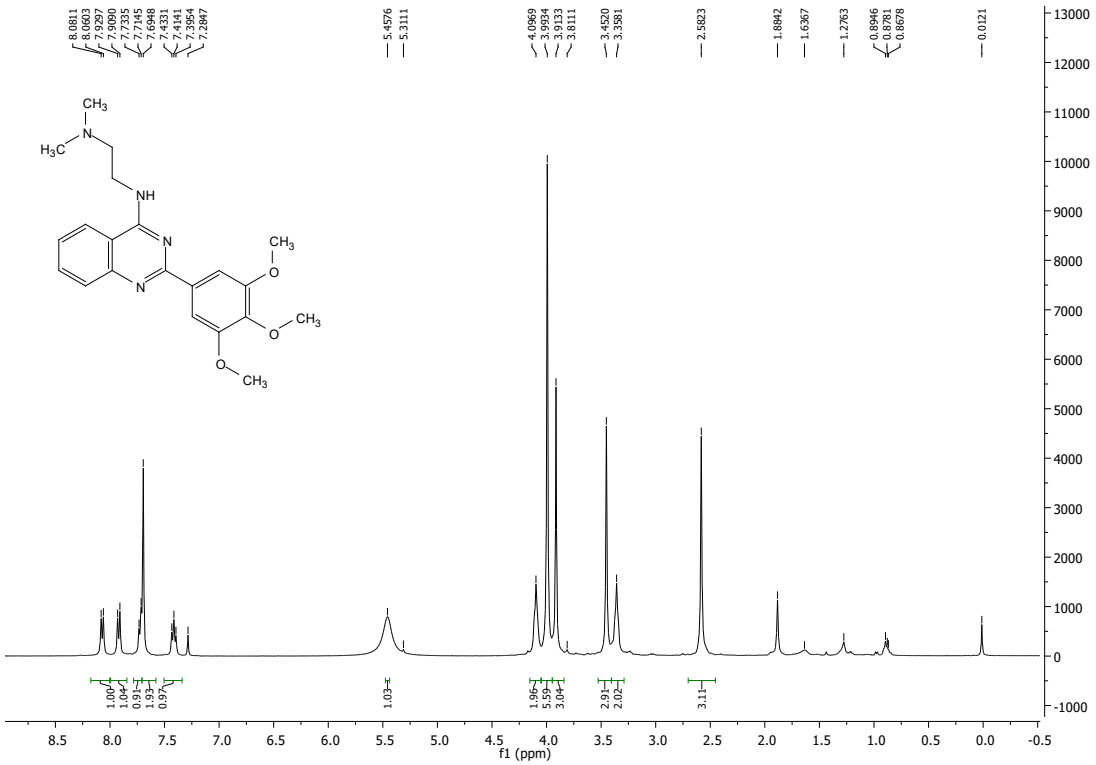
^{1}H NMR, 33



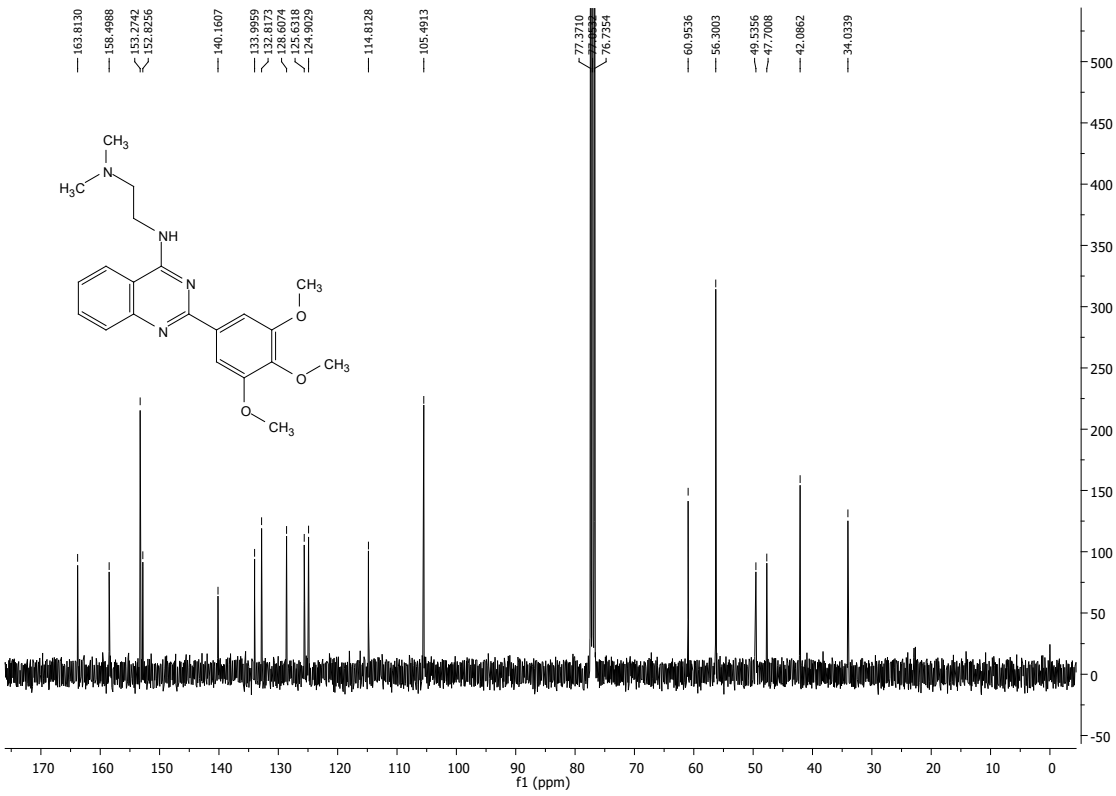
^{13}C NMR, 33



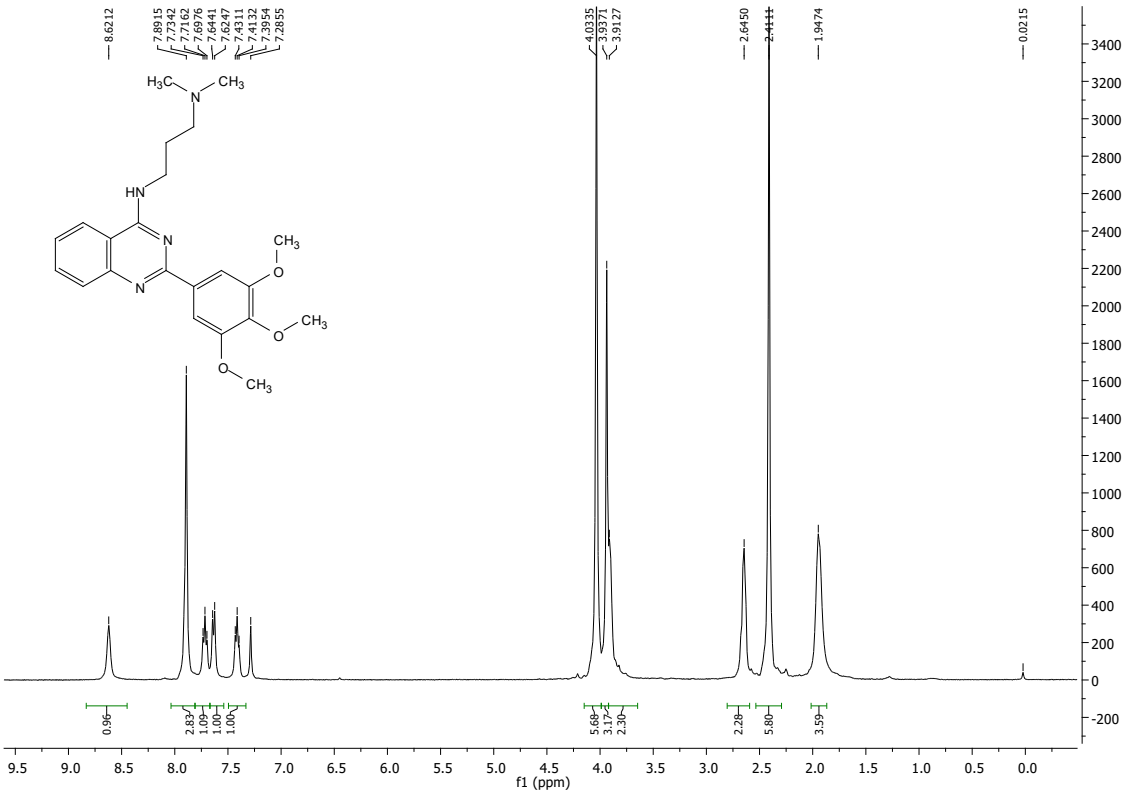
^{1}H NMR, 34



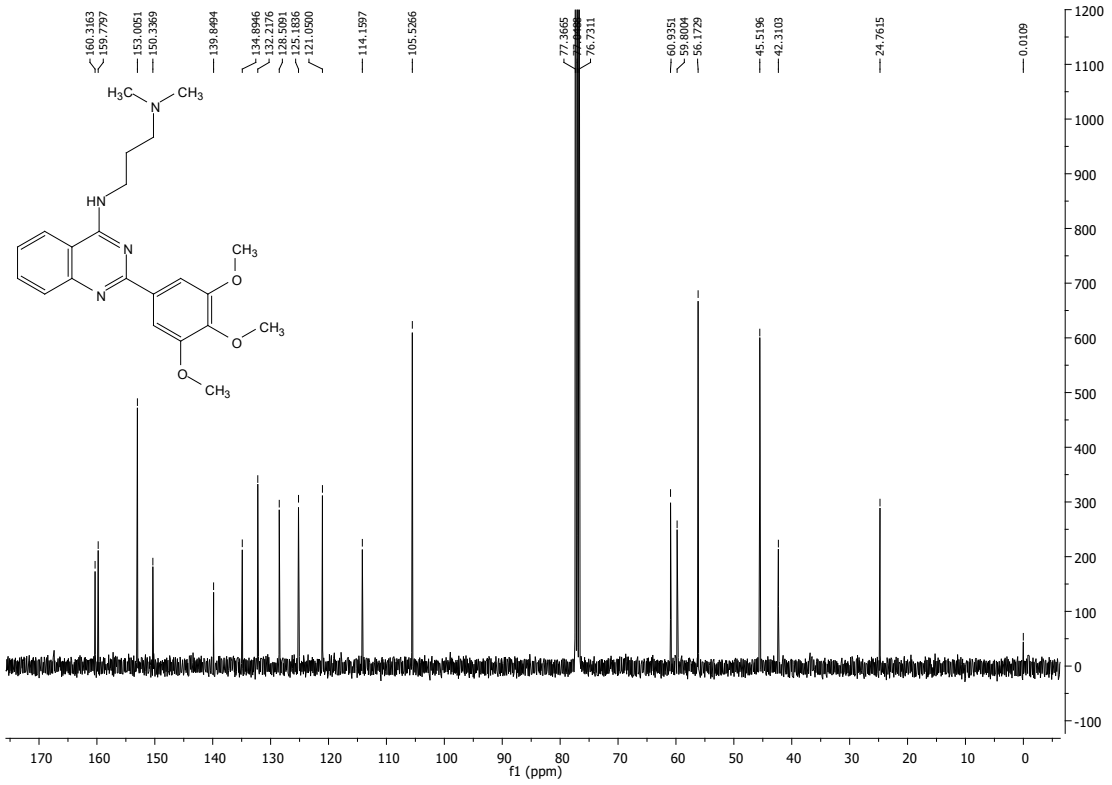
^{13}C NMR, 34



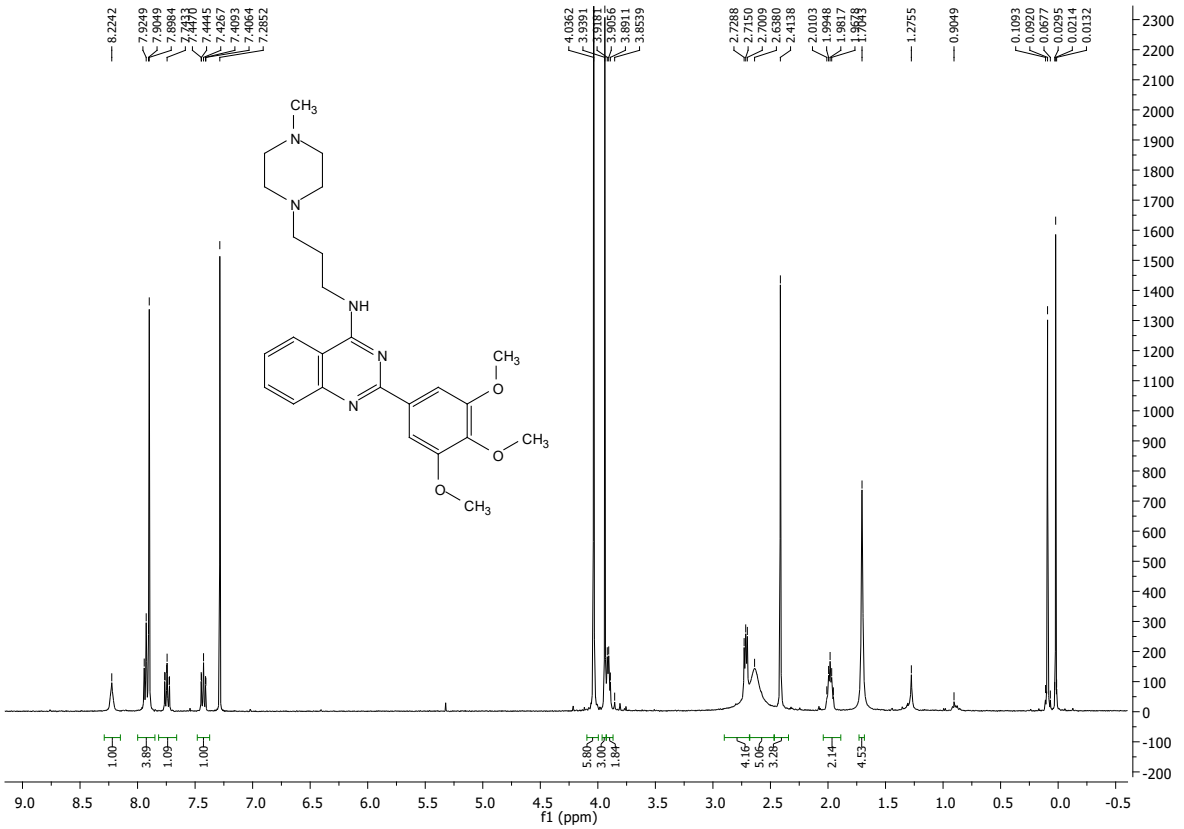
^{1}H NMR, 35



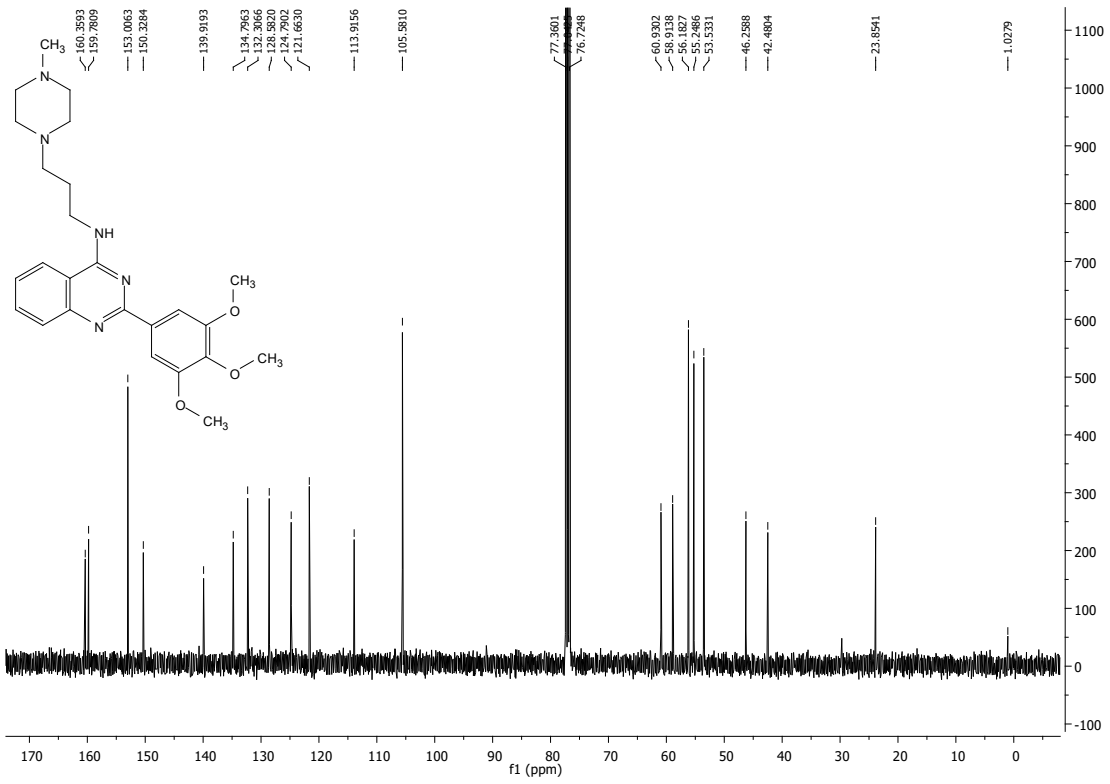
^{13}C NMR, 35



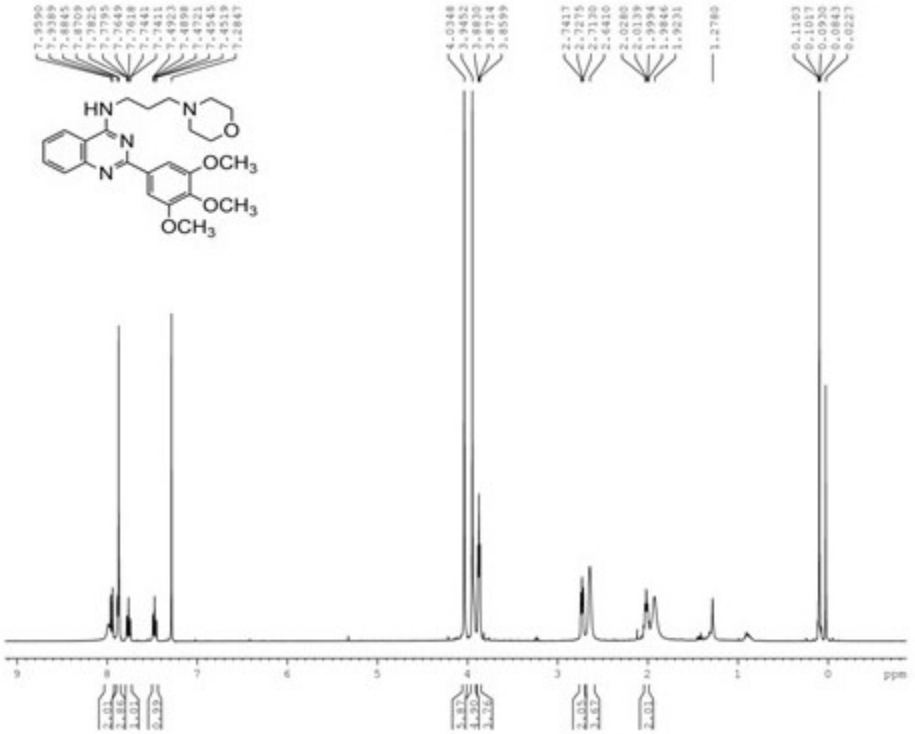
^{1}H NMR, 36



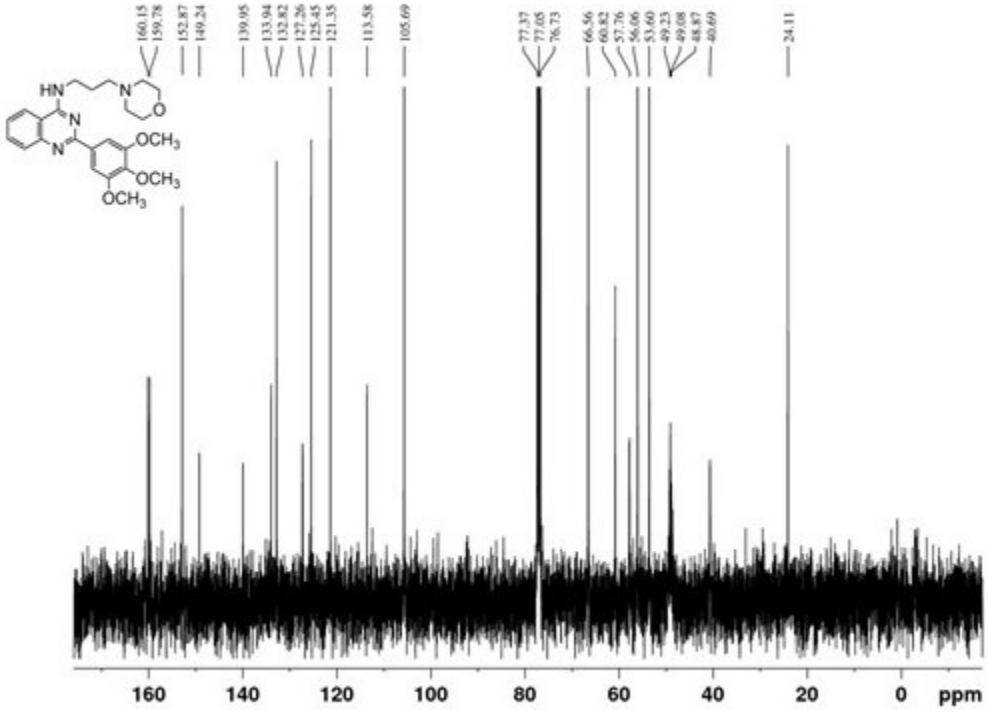
^{13}C NMR, 36



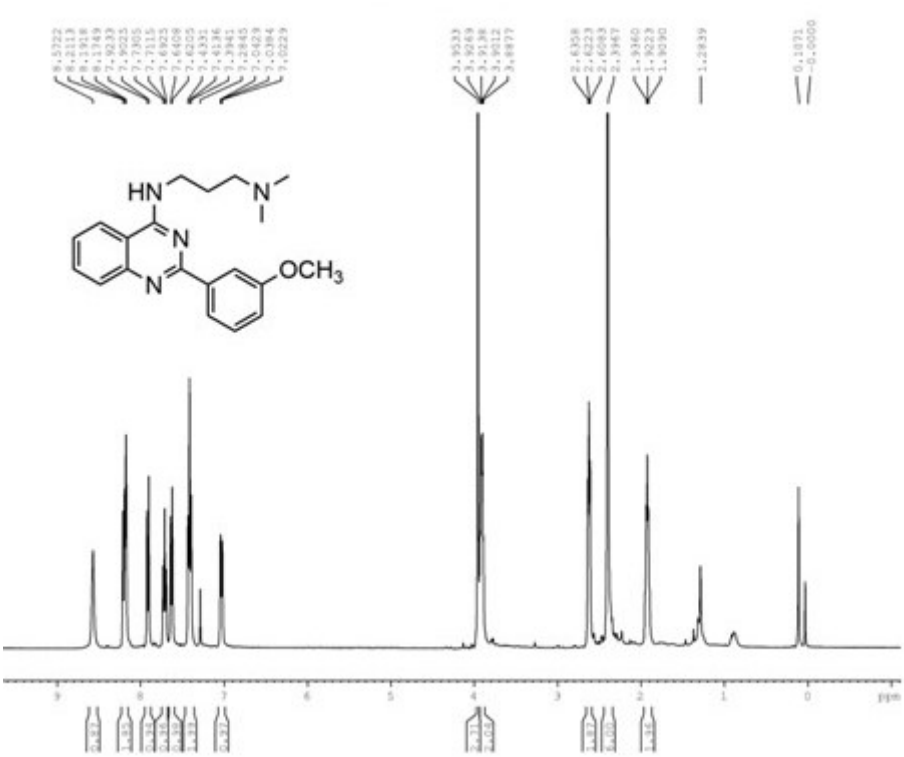
^{1}H NMR, 37



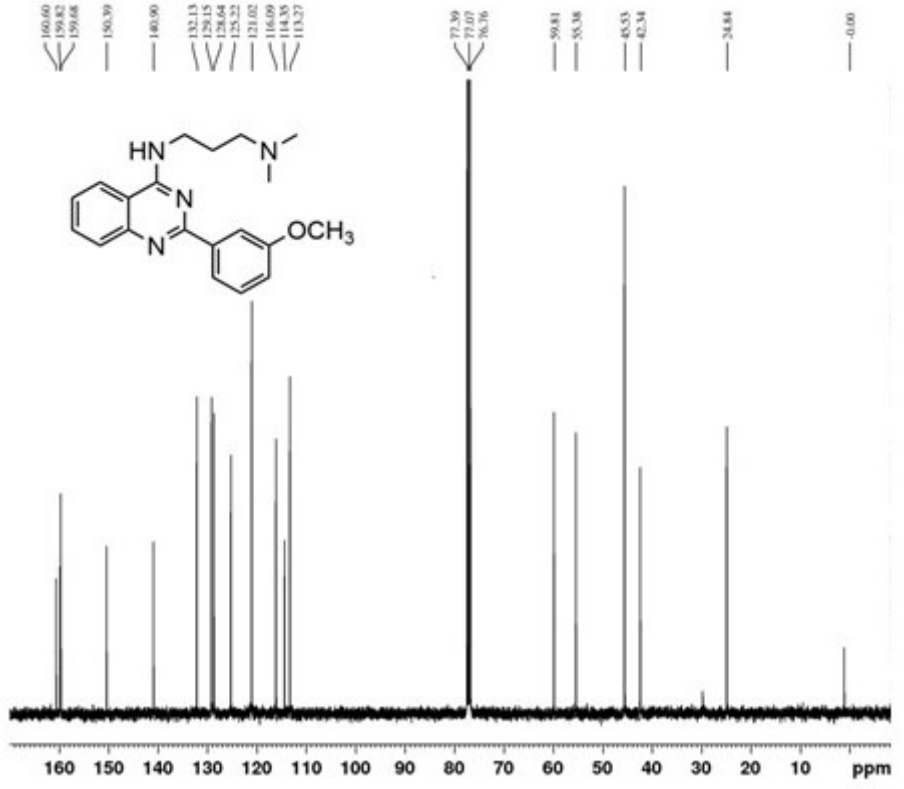
^{13}C NMR, 37



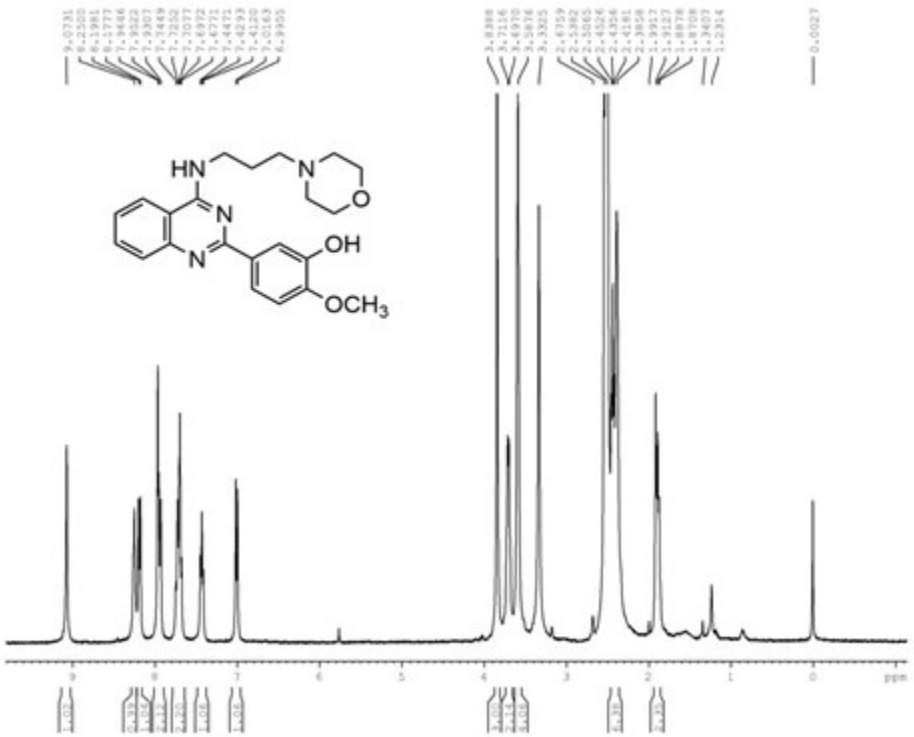
^{1}H NMR, 38



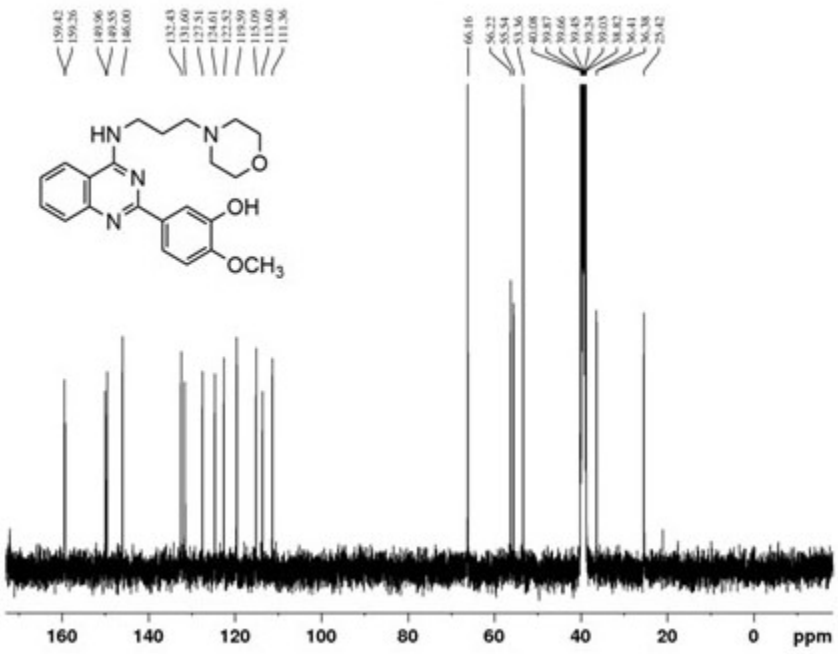
^{13}C NMR, 38



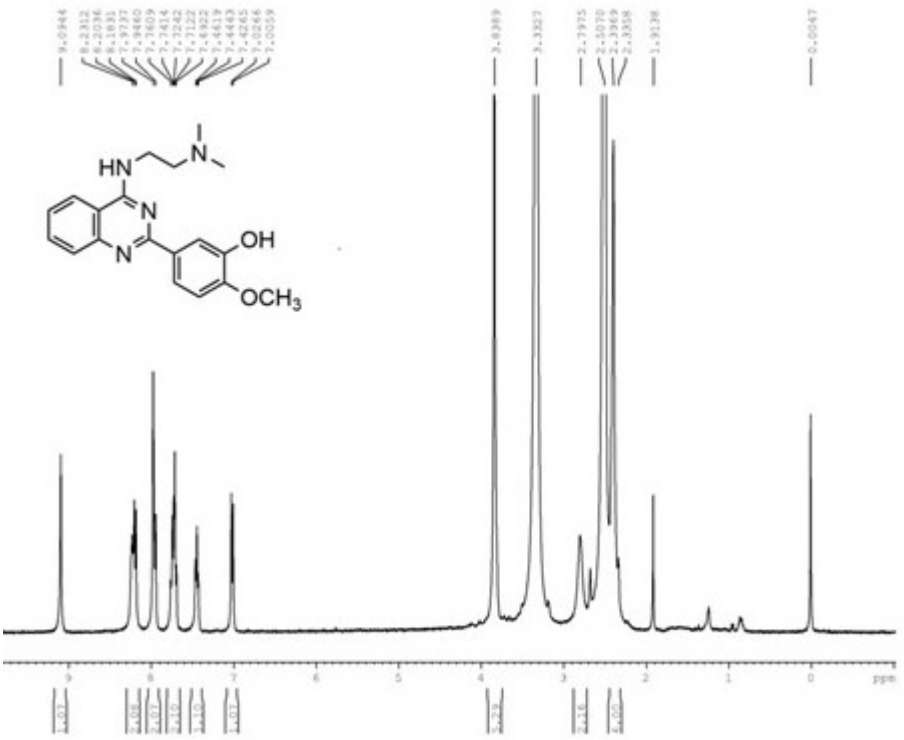
^{1}H NMR, 39



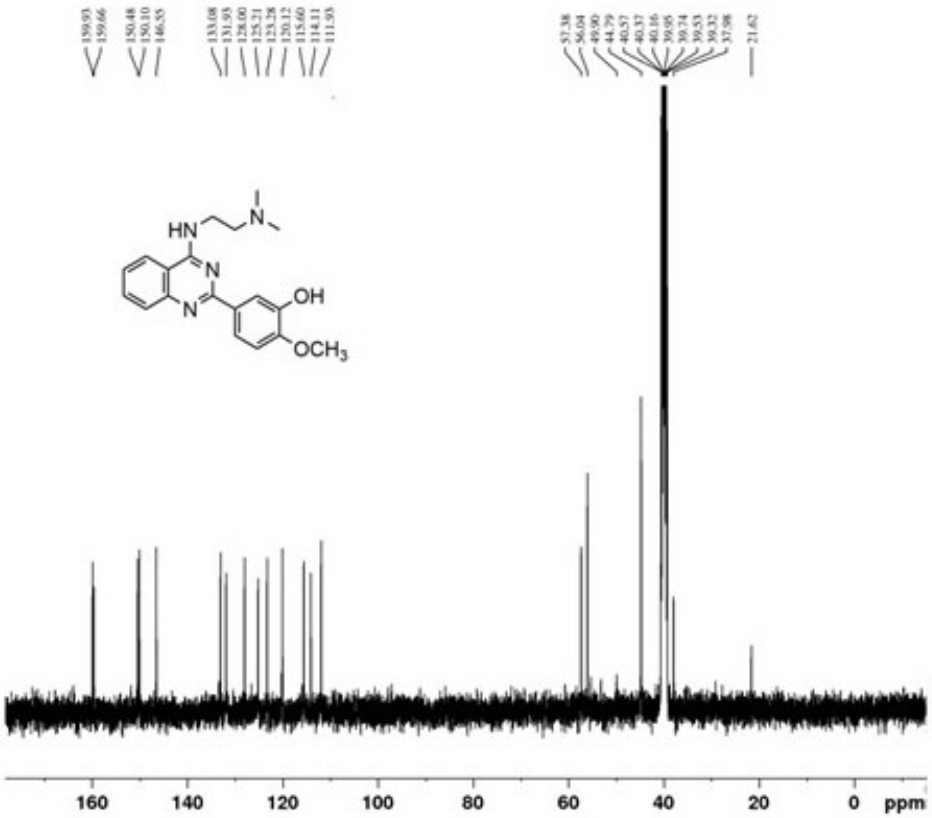
^{13}C NMR, 39



^{1}H NMR, 40



^{13}C NMR, 40



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