

Supporting Information
for DOI: 10.1055/s-0040-1707080

© 2020. Thieme. All rights reserved.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

SUPPORTING INFORMATION

2-Aminoquinazolines by Chan-Evans-Lam coupling of guanidines with 2-formylphenylboronic acids

Vitalii V. Solomin,^{a,b} Alberts Seins,^{a,b} Aigars Jirgensons^{a,b*}

^a Latvian Institute of Organic Synthesis, Aizkraukles 21, Riga, LV-1006, Latvia.

^b Faculty of Materials Science and Applied Chemistry, Riga Technical University, P. Valdena Str. 3, Riga LV-1048, Latvia.

Email: aigars@osi.lv

Contents

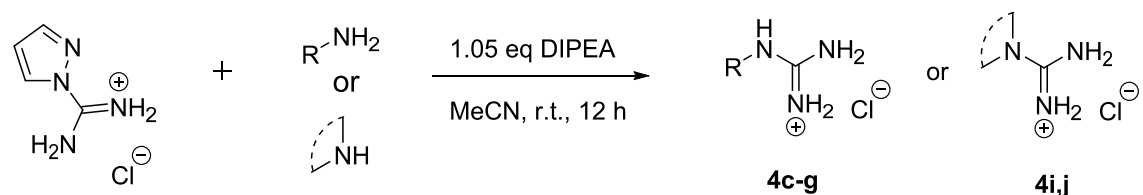
1. General information	1
2. Synthesis of substituted guanidine hydrochlorides 4c-g, 4i,j	1
3. Synthesis of 2-aminoquinazolines (3, 5a-j, 7a-f, 8a-f)	3
4. Characterization data of 2-aminoquinazolines 3, 5a-j, 7a-f, 8a-f.	5
5. Copies of NMR spectra	12

1. General information

All reagents were purchased from commercial source and used without further purification. Melting points were determined using a digital melting point apparatus and uncorrected. ¹H NMR spectra were recorded at 400 MHz using TMS as internal standard, ¹³C NMR spectra were recorded at 101 MHz using TMS as internal standard. All chemical shifts were reported as δ values (ppm) relative to TMS and observed coupling constants (J) are given in Hertz (Hz). High resolution molecular masses (HRMS) were determined on a hybrid quadrupole time-of-flight (TOF) mass spectrometer Waters Synapt G2-Si equipped with an electron spray ion source (ESI). PE refers to light petroleum ether.

2. Synthesis of substituted guanidine hydrochlorides 4c-g, 4i,j

Guanidines **4c-g**, **4i,j** were prepared according to the Scheme 1

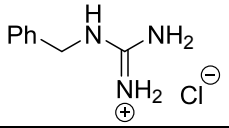
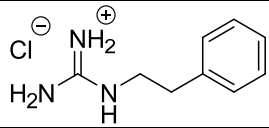
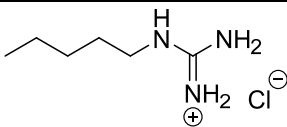
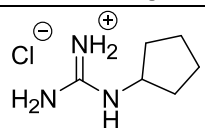
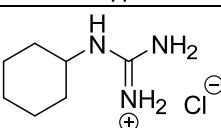
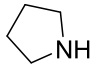
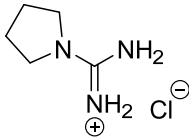
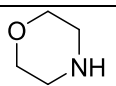
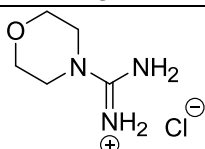


Scheme 1

General procedure. Substituted guanidines were prepared according to the literature procedure.¹ To a stirred solution of 1H-pyrazole-1-carboxamide hydrochloride (1.00 g; 6.8 mmol; 1.00 equiv.) and DIPEA (1.24 mL; 7.2 mmol; 1.05 equiv.) in MeCN (25 mL), benzylamine (782 μ L; 7.2 mmol; 1.05 equiv.) was added. The reaction mixture was stirred at ambient temperature overnight and precipitated solid filtered and washed with MeCN and Et₂O to obtain pure product **4c** as an off-white solid.

The guanidines prepared are shown in the Table 1.

Table 1

Entry	R or Amine	Product	Yield
4c	Bn		85%
4d	Phenethyl		69%
4e	<i>n</i> -Pentyl		89%
4f	<i>cy</i> -Pentyl		81%
4g	<i>cy</i> -Hexy		80%
4i			72%
4j			75%

¹ An T.; Kang B.; Kang S.; Pac J.; Youk J.; Lin D.; Lee Y. *Chem. Commun.* **2019**, 55, 10222.

3. Synthesis of 2-aminoquinazolines (3, 5a-j, 7a-f, 8a-f)

3.1. General procedure for the synthesis of 2-aminoquinazolines

A mixture of guanidine hydrochloride **2a** (765 mg, 8 mmol) and potassium hydroxide (441mg, 8 mmol) was dissolved in MeOH (30 mL) and stirred for 10 min at room temperature. Then 2-formylbenzeneboronic acid (400 mg, 2.67 mmol) was added to the mixture in one portion, followed by CuI (76 mg, 0.4 mmol). Then the mixture heated at 70 °C overnight. The reaction mixture evaporated under reduced pressure and partitioned between of aqueous ammonia (30 mL) and of ethyl acetate (120 mL). The organic layer washed with brine, dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The crude product was purified by trituration with ethyl acetate (3 mL) to afford 2-aminoquinazoline **3** (198 mg, 51%) as slightly beige solid.

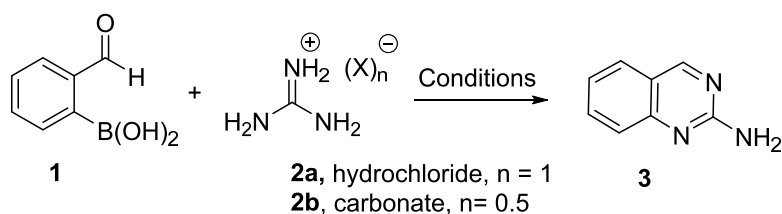
3.2. Preparation of aminoquinazoline **5a** from 2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (**9a**)

Prepared according to general procedure using *N*-methylguanidine hydrochloride **4a** to obtain *N*-methylquinazoline-2-amine **5a**. Purified by silica gel column chromatography eluting with EtOAc in PE (gradient from 20 to 50%) to obtain 109 mg of product **5a**, 58% yield.

3.3. Preparation of aminoquinazoline **5a** from potassium 2-formylphenyl-trifluoroborate (**9b**)

A mixture of *N*-methylguanidine hydrochloride **4a** (310 mg, 2.83 mmol) and potassium hydroxide (260 mg, 4.72 mmol) was dissolved in MeOH (20 mL) and stirred for 10 min at room temperature. Then, potassium 2-formylphenyl trifluoroborate (200 mg, 0.95 mmol) was added in one portion, followed by CuI (27 mg, 0.14 mmol). Then the mixture heated at 70 °C overnight. The reaction mixture evaporated under reduced pressure and partitioned between of aqueous ammonia (20 mL) and of ethyl acetate (40 mL). The organic layer washed with brine, dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography eluting with EtOAc in PE (gradient from 20 to 50%) to obtain 76 mg of the product **5a** as yellowish solid, 50% yield.

3.4. Reaction conditions screened for the synthesis of quinazoline 3

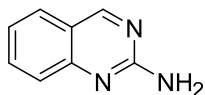


Entry ^a	Solvent, t ^o , time	2	Catalyst/oxidant system	Base	Additive	Yield of 3
1	MeOH, 70 °C, 17 h	2a 1.5 eq	CuI 15 mol%, air	Cs ₂ CO ₃ 2.5 eq	-	30%
2	MeOH, 70 °C, 17 h	2a 1.5 eq	CuI 15 mol%, air	Cs ₂ CO ₃ 2.5 eq	TMEDA, 30 mol%	23%
3	MeOH, 70 °C, 17 h	2a 1.5 eq	CuI 15 mol%, air	K ₂ CO ₃ 2.5 eq	-	31%
4	MeOH, 70 °C, 17 h	2a 2.5 eq	CuI 15 mol%, air	K ₂ CO ₃ 3 eq	-	44%
5	MeOH, 70 °C, 17 h	2a 3.5 eq	CuI 15 mol%, air	K ₂ CO ₃ 3.5 eq	-	46%
6	MeOH, 70 °C, 17 h	2a 5 eq	CuI 15 mol%, air	K ₂ CO ₃ 5 eq	-	14%
7	MeOH, 70 °C, 17 h	2b 3 eq	CuI 15 mol%, air	-	-	13%
8	MeOH, 70 °C, 17 h	2b 3 eq	CuI 15 mol%, air	KOH 3 eq	-	17%
9	MeOH, 70 °C, 17 h	2a 3 eq	CuI 15 mol%, air	KOH, 3 eq	-	51% (65%) ^b
10	MeOH, 70 °C, 17 h	2a 3 eq	CuI 5 mol%, air	KOH, 3 eq	-	11%
11	MeOH, 70 °C, 17 h	2a 3 eq	CuI 30 mol%, air	KOH, 3 eq	-	41%
12	MeOH, 70 °C, 17 h	2a 1.5 eq	CuI 15 mol%, air	KOH, 1.5 eq	-	34%
13	EtOH, 90 °C, 17 h	2a 3 eq	CuI 15 mol%, air	KOH 3 eq	-	52%
14	i-PrOH, 90 °C, 17 h	2a 3 eq	CuI 15 mol%, air	KOH 3 eq	-	n.r.
15	MeOH, 70 °C, 17 h	2a 2.5 eq	Cu(OAc) ₂ 15 mol%, air	K ₂ CO ₃ , 3 eq	-	35%
16	DMF, 60 °C, 17 h	2a 1.5 eq	Cu(OAc) ₂ 20 mol%, air	Cs ₂ CO ₃ 2.5 eq	2,2'-BiPy, 2 eq	n.r.
17	MeOH, 70 °C, 17 h	2a 2.5 eq	CuCl 15 mol%, air	K ₂ CO ₃ 3 eq	-	23%
18	MeOH, 70 °C, 17 h	2a 3 eq	CuI 15 mol%, O ₂ ^c	KOH, 3 eq	-	56%
19	MeOH, 70 °C, 17 h	2a 3 eq	CuI 15 mol%; 4 eq 35% aq H ₂ O ₂	KOH, 3 eq	-	40%

^aReaction was performed in open flask, until otherwise noted; ^bThe yield was determined by NMR using 1,3,5-trimethoxybenzene as internal standard; ^c1 atm of O₂.

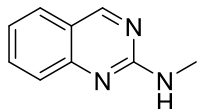
4. Characterization data of 2-aminoquinazolines 3, 5a-j, 7a-f, 8a-f.

2-Aminoquinazoline (3)



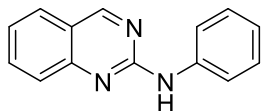
Prepared according to general procedure. Purified by trituration with EtOAc, white beige solid, 51% (198 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (s, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.67 (t, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 6.82 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 162.4, 160.9, 151.2, 134.1, 127.9, 124.5, 122.0, 119.5. LCMS: C₈H₈N₃ [M+H]⁺; calculated 146.17, found 146.16. Corresponds to the reported data.²

N-Methylquinazolin-2-amine (5a)



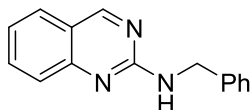
Prepared according to general procedure using commercially available *N*-methylguanidine hydrochloride (4a). Purified by silica gel column chromatography (gradient 20% to 50% EtOAc in PE), R_f 0.63 (EtOAc), yellowish solid; m.p. 81-83 °C, 63% (134 mg). ¹H NMR (400 MHz, Chloroform-*d*) δ 9.03 (s, 1H), 7.72 – 7.56 (m, 3H), 7.22 (t, *J* = 7.9 Hz, 1H), 5.43 (br. s, 1H), 3.12 (d, *J* = 4.0 Hz, 3H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 162.01, 160.50, 152.44, 134.37, 127.79, 125.83, 122.72, 120.75, 28.77; HRMS: C₉H₁₀N₃ [M+H]⁺; calculated 160.0875, found 160.0881

N-phenylquinazolin-2-amine (5b)



Prepared according to general procedure using commercially available phenylguanidine carbonate (4b). The crude product was purified by silica gel column chromatography using EtOAc: PE (1:3), R_f 0.68 (EtOAc:PE, 1:3) to obtain 168 mg of the slightly beige solid, 56%. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.09 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.80 – 7.71 (m, 3H), 7.44 (s, 1H), 7.41 – 7.30 (m, 3H), 7.08 (t, *J* = 7.4 Hz, 1H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 161.99, 156.96, 151.68, 139.77, 134.52, 129.11, 127.57, 126.50, 123.93, 122.69, 121.02, 119.15. LCMS C₁₄H₁₂N₃ [M+H]⁺; calculated 222.26, found 222.35. Corresponds to the reported data.³

N-Benzylquinazolin-2-amine (5c)

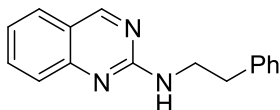


² Liu, Q.; Zhao, U.; Fu, H.; Cheng, C. *Synlett* **2013**, 24, 2089-2094.

³ Leitch J. A.; McMullin C. L.; Paterson A. J.; Mahon M. F.; Bhonoah Y.; Frost C. G. *Angew. Chem. Int. Ed.* **2017**, 56, 15131.

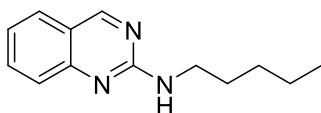
Prepared according to general procedure, using *N*-benzylguanidine hydrochloride (**4c**). Crude material dissolved in EtOAc:PE 1:1 and undissolved materials discarded. After evaporation of organic phase residue crystallized from EtOAc:PE (1:10) to obtain pure product as a beige solid, Rf 0.56 (EtOAc:PE 1:3), 66% (210 mg). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.87 (s, 1H), 7.87 – 7.57 (m, 3H), 7.56 – 7.20 (m, 6H), 6.03 (s, 1H), 4.83 (d, *J* = 5.2 Hz, 2H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 162.17, 159.63, 152.28, 139.33, 134.33, 127.90, 127.69, 127.41, 125.81, 122.77, 120.51, 45.85, 45.73. LCMS C₁₅H₁₄N₃ [M+H]⁺; calculated 236.29, found 236.37. Corresponds to the reported data.⁴

N-Phenethylquinazolin-2-amine (**5d**)



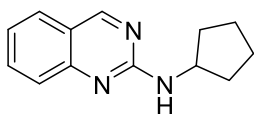
Prepared according to general procedure, using *N*-phenethylguanidine hydrochloride (**4d**). Purified by silica gel column chromatography using 10 to 40% EtOAc in PE gradient, Rf 0.46 (EtOAc:PE 1:3), slightly yellow solid, 52% (175 mg). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.92 (s, 1H), 7.79 – 7.54 (m, 3H), 7.36 – 7.17 (m, 6H), 5.37 (s, 1H), 3.81 (q, *J* = 7.0 Hz, 2H), 2.97 (t, *J* = 7.0 Hz, 2H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 162.06, 159.67, 152.34, 139.45, 134.28, 129.02, 128.72, 127.67, 126.52, 122.66, 120.39, 42.93, 35.82. LCMS C₁₆H₁₆N₃ [M+H]⁺; calculated 250.32, found 250.43. Corresponds to the reported data.⁴

N-Pentylquinazolin-2-amine (**5e**)



Prepared according to general procedure, using *N*-(*n*-pentyl)guanidine hydrochloride (**4e**). Purified by silica gel column chromatography using 10 to 40% EtOAc in PE gradient, Rf 0.55 (EtOAc:PE 1:3), light yellow crystalline solid; m.p. 76-78 °C, 54% (187 mg). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.95 (s, 1H), 7.74 – 7.52 (m, 3H), 7.21 (t, *J* = 8.0 Hz, 1H), 5.27 (s, 1H), 3.65 – 3.46 (m, 2H), 1.67 (p, *J* = 7.4 Hz, 2H), 1.40 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 159.87, 152.38, 134.27, 127.68, 125.65, 122.51, 120.29, 41.75, 29.44, 29.30, 22.59, 14.17. HRMS: C₁₃H₁₈N₃ [M+H]⁺; calculated 216.1501, found 216.1508.

N-cyclopentylquinazolin-2-amine (**5f**)

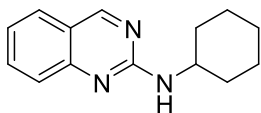


Prepared according to general procedure, using *N*-cyclopentylguanidine hydrochloride (**4f**). Purified by silica gel column chromatography using 10 to 40% EtOAc in PE gradient, Rf 0.46 (EtOAc:PE 1:3), yellow solid; m.p. 75-77 °C, 55% (198 mg). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.95 (s, 1H), 7.73 – 7.52 (m, 3H), 7.20 (t, *J* = 8.0 Hz, 1H), 5.27 (d, *J* = 6.0 Hz, 1H), 4.44 (h, *J* = 6.8 Hz, 1H), 2.12 (m, 2H), 1.84 – 1.60 (m, 4H), 1.53 (m, 2H). ¹³C NMR

⁴ Li, F.; Chen, L.; Kang, Q.; Cai, J.; Zhu, G. *New J. Chem.*, **2013**, *37*, 624.

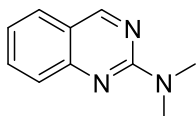
(101 MHz, Chloroform-*d*) δ 161.95, 159.54, 152.42, 127.64, 125.67, 122.42, 120.22, 53.11, 33.47, 23.82. HRMS: C₁₃H₁₆N₃ [M+H]⁺; calculated 214.1344, found 214.1347.

***N*-Cyclohexylquinazolin-2-amine (5g)**



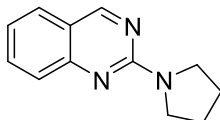
Prepared according to general procedure using *N*-cyclohexylguanidine hydrochloride (**4g**) (prepared from cyclohexylamine according to exemplary procedure B). Purified by silica gel column chromatography using 20 to 50% EtOAc in PE gradient, R_f 0.56 (EtOAc:PE 1:3), slightly yellow solid, 37% (113 mg). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.94 (s, 1H), 7.64 (m, 2H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.19 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 5.20 (d, *J* = 7.6 Hz, 1H), 4.01 (dtd, *J* = 14.4, 7.3, 6.4, 4.1 Hz, 1H), 2.11 (m, 2H), 1.77 (m, 2H), 1.65 (m, 1H), 1.54 – 1.35 (m, 2H), 1.34 – 1.16 (m, 3H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 162.07, 152.49, 134.19, 127.64, 125.62, 122.38, 120.24, 49.75, 33.37, 25.93, 25.00. LCMS C₁₄H₁₈N₃ [M+H]⁺; calculated 228.31, found 228.42. Corresponds to the reported data.⁵

***N,N*-Dimethylquinazolin-2-amine (5h)**



Prepared according to general procedure using commercially available 1,1-dimethylguanidine sulphate (**4h**). The crude product was purified by silica gel column chromatography using 1:3 EtOAc:PE, R_f 0.79 (EtOAc:PE 1:3) to obtain 100 mg of the white solid, 43%. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.99 (s, 1H), 7.66 – 7.60 (m, 2H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.20 – 7.14 (m, 1H), 3.31 (s, 6H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 161.38, 160.06, 152.60, 134.08, 127.57, 125.66, 122.12, 119.24, 37.43. LCMS C₁₀H₁₂N₃ [M+H]⁺; calculated 174.22, found 174.28. Corresponds to the reported data.⁶

2-(Pyrrolidin-1-yl)quinazoline (5i)



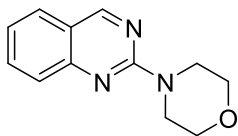
Prepared according to general procedure using pyrrolidine-1-carboximidamide hydrochloride (**4i**). Purified by silica gel column chromatography using 10 to 40% EtOAc in PE gradient, R_f 0.17 (EtOAc:PE 1:10), light yellow solid, 47% (108 mg). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.99 (s, 1H), 7.67 – 7.55 (m, 3H), 7.19 – 7.12 (m, 1H), 3.77 – 3.65 (m, 4H), 2.08 – 1.98 (m, 4H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 161.53, 158.22, 152.76, 134.09, 127.68, 125.55, 121.88, 119.43, 47.01, 25.71. LCMS C₁₂H₁₄N₃ [M+H]⁺; calculated 200.26, found 200.33. Corresponds to the reported data.⁷

⁵ Wang H. X.; Wei T. Q.; Xu P.; Wang S. Y.; Ji S. J. *J. Org. Chem.* **2018**, *83*, 21, 13491.

⁶ Suzuki, Y.; Takemura, Y.; Iwamoto, K.; Higashino, T.; Miyashita, A. *Chem. Pharm. Bull.* **1998**, *46*, 199.

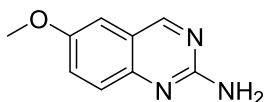
⁷ Huang, X.; Yang, H.; Fu, H.; Qiao, R.; Zhao, Y. *Synthesis* **2009**, *16*, 2679.

4-(Quinazolin-2-yl)morpholine (5j)



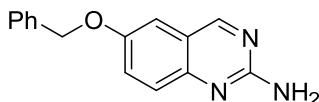
Prepared according to general procedure using morpholine-1-carboximidamide hydrochloride (**4j**). Purified by silica gel column chromatography using 10 to 30% EtOAc in PE gradient, R_f 0.26 (EtOAc:PE 1:10), yellow crystalline solid, 39% (114 mg). ¹H NMR (400 MHz, Chloroform-*d*) δ 9.01 (s, 1H), 7.71 – 7.63 (m, 2H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.26 – 7.20 (m, 1H), 4.01 – 3.92 (m, 4H), 3.85 – 3.78 (m, 4H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 161.60, 159.38, 152.32, 134.29, 127.55, 125.86, 122.89, 119.95, 67.11, 44.72. LCMS C₁₂H₁₄N₃O [M+H]⁺; calculated 216.26, found 216.35. Corresponds to the reported data.⁸

6-Methoxyquinazolin-2-amine (7a)



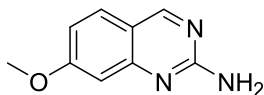
Prepared according to general procedure from boronic acid **6a** and guanidine hydrochloride (**2a**). Purified by trituration with EtOAc, beige solid, 55% (27 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.02 (s, 1H), 7.37 (s, 2H), 7.23 (s, 1H), 6.57 (s, 2H), 3.82 (s, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 160.8, 160.0, 154.0, 147.6, 126.2, 126.1, 119.7, 105.7, 55.4. LCMS: C₉H₁₀N₃O [M+H]⁺; calculated 176.19, found 176.26. Corresponds to the reported data.⁹

6-(Benzyloxy)quinazolin-2-amine (7b)



Prepared according to general procedure from boronic acid **6b** and guanidine hydrochloride (**2a**). Purified by trituration with EtOH, beige solid; m.p. 149-150 °C, 32% (79 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.01 (s, 1H), 7.66 – 7.21 (m, 8H), 6.61 (s, 2H), 5.15 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 160.84, 160.07, 153.01, 147.70, 136.80, 128.45, 127.93, 127.84, 126.53, 126.17, 119.61, 107.13, 69.62; HRMS: C₁₅H₁₄N₃O [M+H]⁺; calculated 252.1137, found 252.1136.

7-Methoxyquinazolin-2-amine (7c)



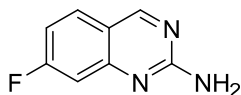
Prepared according to general procedure from boronic acid **6c** and guanidine hydrochloride (**2a**). Re-crystallized from EtOH, beige solid; m.p. 222-224 °C, 17% (26 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.90 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.70 (s, 2H), 3.85 (s, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 163.84,

⁸ Huang, X.; Yang, H.; Fu, H.; Qiao, R.; Zhao, Y. *Synthesis* **2009**, *16*, 2679.

⁹ Liu, Q.; Zhao, U.; Fu, H.; Cheng, C. *Synlett* **2013**, *24*, 2089-2094.

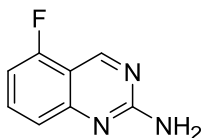
161.21, 160.83, 154.14, 129.20, 114.91, 114.18, 103.44, 55.41. HRMS: C₉H₁₀N₃O [M+H]⁺; calculated 176.0824, found 176.0820

7-Fluoroquinazolin-2-amine (7d)



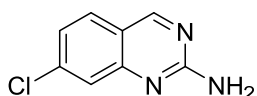
Prepared according to general procedure from boronic acid **6d** and guanidine hydrochloride (**2a**). Re-crystallized from EtOH, white beige solid, 36% (52 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.09 (s, 1H), 7.93 – 7.84 (m, 1H), 7.14 – 7.06 (m, 2H), 6.99 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.71 (d, *J* = 250.4 Hz), 162.08, 161.29, 153.55 (d, *J* = 14.5 Hz), 131.03 (d, *J* = 11.7 Hz), 116.89, 111.68 (d, *J* = 25.2 Hz), 108.18 (d, *J* = 20.6 Hz); ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -104.1. LCMS C₈H₇FN₃ [M+H]⁺; calculated 164.16, found 164.30. Corresponds to the reported data.¹⁰

5-Fluoroquinazolin-2-amine (7e)



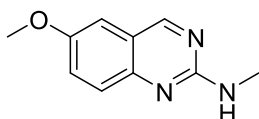
Prepared according to general procedure from boronic acid **6e** and guanidine hydrochloride (**2a**). Re-crystallized from EtOH, white yellow solid; m.p. 223-225 °C, 52% (76 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.25 (s, 1H), 7.72 – 7.60 (m, 1H), 7.23 (d, *J* = 10 Hz, 1H), 7.10 (s, 2H), 6.96 (d, *J* = 10 Hz, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 161.22, 158.54 (d, *J* = 255.2 Hz), 156.06, 153.11, 134.45 (d, *J* = 10.1 Hz), 120.94, 109.50 (d, *J* = 15.7 Hz), 105.85 (d, *J* = 18.7 Hz); ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -124.16. HRMS: C₈H₇FN₃ [M+H]⁺; calculated 164.0624, found 164.0621.

7-Chloroquinazolin-2-amine (7f)



Prepared according to general procedure from boronic acid **6f** and guanidine hydrochloride (**2a**). Re-crystallized from EtOH, beige solid; decomp. >275 °C, 35% (52 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.12 (s, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.05 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 162.40, 161.31, 152.53, 138.71, 129.93, 123.22, 122.34, 117.97, 40.19; HRMS: C₈H₇ClN₃ [M+H]⁺; calculated 180.0328, found 180.0331.

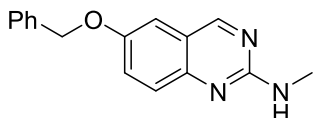
6-Methoxy-N-methylquinazolin-2-amine (8a)



¹⁰ Taylor N. J.; Emer E.; Preshlock S.; Schedler M.; Tredwell M.; Verhoog S.; Mercier J.; Genicot C.; Gouverneur V. *J. Am. Chem. Soc.* **2017**, *139*, 8267.

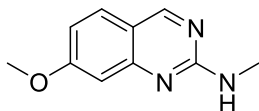
Prepared according to general procedure from boronic acid **6a** and *N*-methylguanidine hydrochloride **4a**. Purified by silica gel column chromatography eluting with EtOAc, Rf 0.54 (EtOAc), yellow solid; m.p. 144-145 °C, 59% (94 mg). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.89 (s, 1H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.35 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.96 (d, *J* = 2.8 Hz, 1H), 5.23 (s, 1H), 3.87 (s, 3H), 3.09 (d, *J* = 4.9 Hz, 3H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 160.54, 159.78, 155.00, 148.31, 127.21, 126.70, 120.37, 105.25, 55.68, 28.75; HRMS: C₁₀H₁₂N₃O [M+H]⁺; calculated 190.0980, found 190.0983.

6-(benzyloxy)-*N*-methylquinazolin-2-amine (8b)



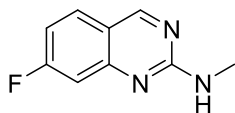
Prepared according to general procedure from boronic acid **6b** and *N*-methylguanidine hydrochloride (**4a**). Purified by silica gel column chromatography using 20% to 60% EtOAc in PE gradient, Rf 0.38 (EtOAc:PE 1:1), yellowish solid; m.p. 130-132 °C, 57% (150 mg). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.88 (s, 1H), 7.58 (d, *J* = 9.2 Hz, 1H), 7.51 – 7.32 (m, 6H), 7.05 (d, *J* = 2.8 Hz, 1H), 5.23 (s, 1H), 5.12 (s, 2H), 3.10 (d, *J* = 5.1 Hz, 3H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 160.67, 159.78, 154.12, 148.30, 136.70, 128.80, 128.28, 127.67, 127.23, 127.13, 120.32, 70.55, 28.76. HRMS: C₁₆H₁₆N₃O [M+H]⁺; calculated 266.1293, found 266.1292.

7-Methoxy-*N*-methylquinazolin-2-amine (8c)



Prepared according to general procedure from boronic acid **6c** and *N*-methylguanidine hydrochloride (**4a**). Purified by silica gel column chromatography eluting with EtOAc, Rf 0.54 (EtOAc), slightly yellow solid; m.p. 105-107 °C, 48% (77 mg). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.81 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 6.94 (s, 1H), 6.84 (dd, *J* = 8.8, 2.3 Hz, 1H), 5.24 (s, 1H), 3.92 (s, 3H), 3.11 (d, *J* = 4.5 Hz, 3H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 164.72, 160.92, 160.43, 154.70, 128.97, 115.84, 115.51, 104.21, 55.68, 28.66. HRMS: C₁₀H₁₂N₃O [M+H]⁺; calculated 190.0980, found 190.0981.

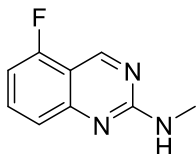
7-Fluoro-*N*-methylquinazolin-2-amine (8d)



Prepared according to general procedure from boronic acid **6d** and *N*-methylguanidine hydrochloride (**4a**). Purified by silica gel column chromatography eluting with EtOAc, Rf 0.65 (EtOAc), white solid; m.p. 135-137 °C, 52% (83 mg). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.91 (s, 1H), 7.64 (dd, *J* = 8.8, 6.2 Hz, 1H), 7.22 (d, *J* = 9.7 Hz, 1H), 6.96 (td, *J* = 8.7, 2.4 Hz, 1H), 5.46 (s, 1H), 3.11 (d, *J* = 4.8 Hz, 3H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 167.95, 165.42, 161.37, 160.73, 154.23, 154.09, 130.20, 130.09, 112.86, 112.61, 109.95,

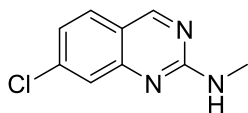
109.75; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -103.00. HRMS: $\text{C}_9\text{H}_9\text{FN}_3$ $[\text{M}+\text{H}]^+$; calculated 178.0781, found: 178.0782.

5-Fluoro-*N*-methylquinazolin-2-amine (8e)



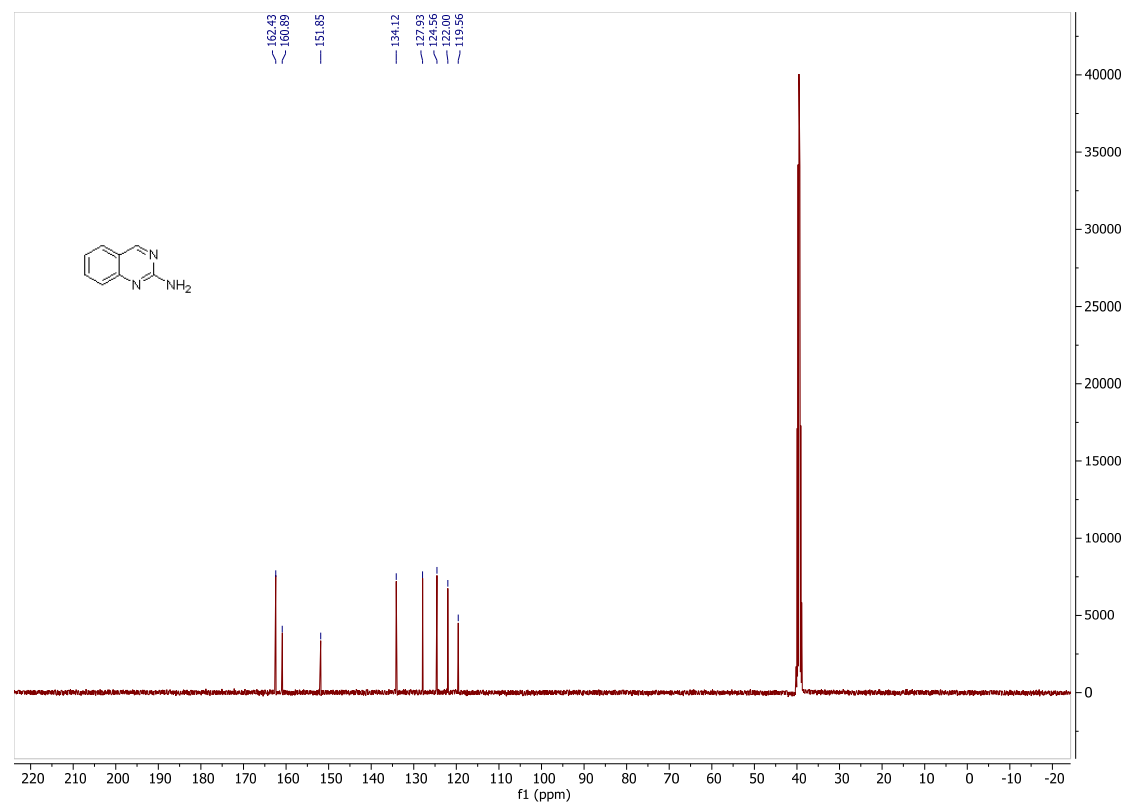
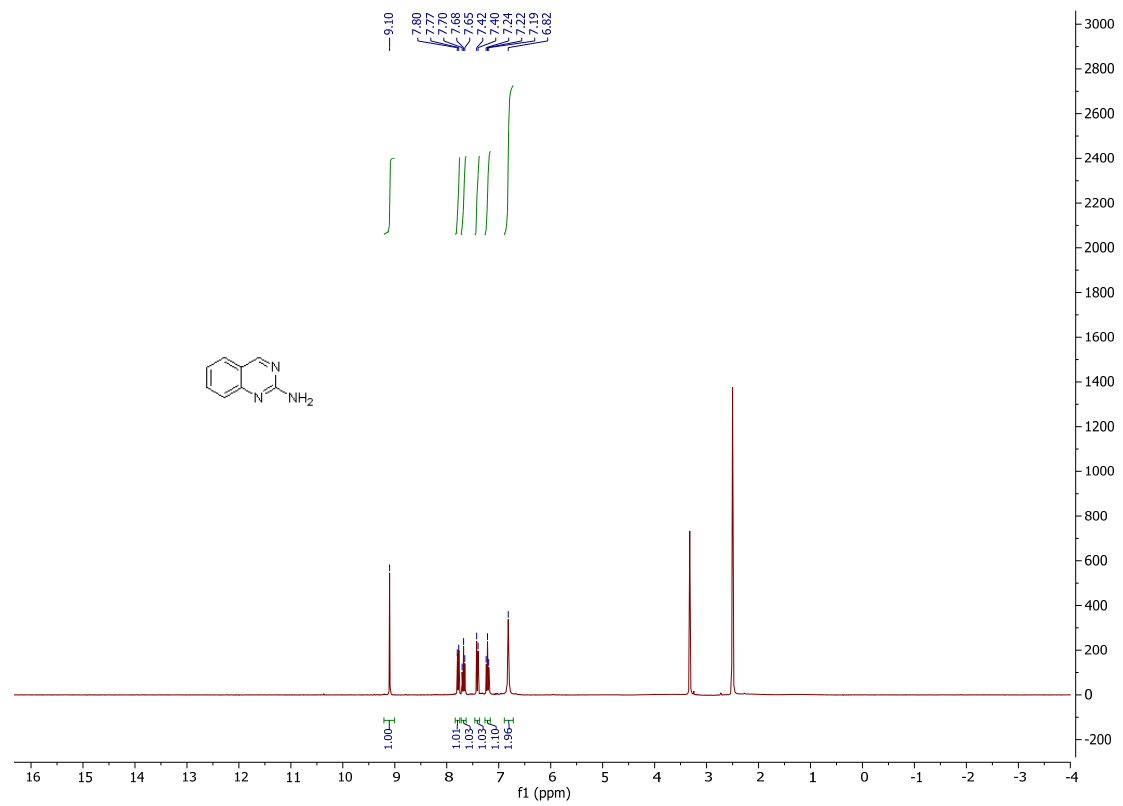
Prepared according to general procedure from boronic acid **6e** and *N*-methylguanidine hydrochloride (**4a**). Purified by silica gel column chromatography using 10% to 40% EtOAc in PE gradient, Rf 0.41 (EtOAc:PE 1:3), white beige solid; m.p. 142-144 °C, 46% (74 mg). ^1H NMR (400 MHz, Chloroform-*d*) δ 9.37 (s, 1H), 7.58 (q, $J = 7.9$ Hz, 1H), 7.39 (d, $J = 8.3$ Hz, 1H), 6.88 – 6.76 (m, 1H), 5.55 (s, 1H), 3.12 (s, 3H); ^{13}C NMR (101 MHz, DMSO-*d*₆) δ 160.67, 158.12, 153.45, 134.39, 134.29, 121.73, 106.48, 28.60; ^{19}F NMR (376 MHz, DMSO-*d*₆) δ -128.79. HRMS: $\text{C}_9\text{H}_9\text{FN}_3$ $[\text{M}+\text{H}]^+$; calculated 178.0781, found: 178.0779.

7-Chloro-*N*-methylquinazolin-2-amine (8f)

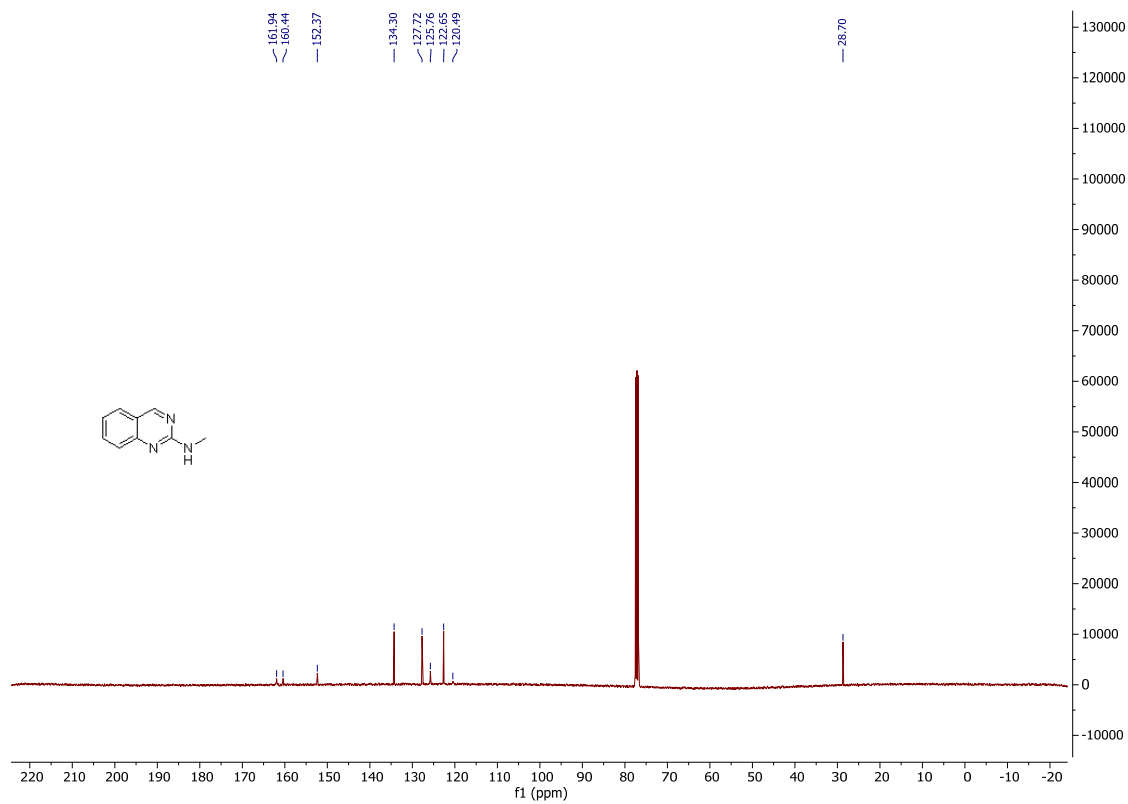
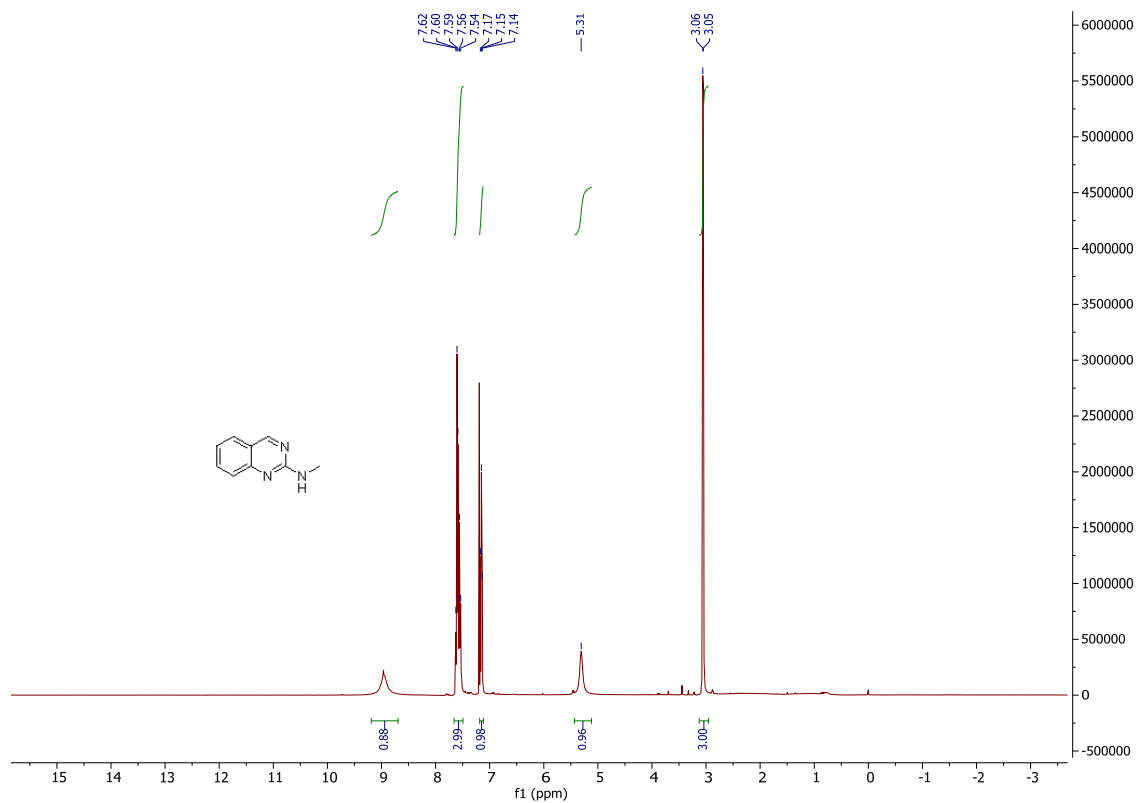


Prepared according to general procedure from boronic acid **6f** and *N*-methylguanidine hydrochloride (**4a**). Purified by silica gel column chromatography in EtOAc, Rf 0.69 (EtOAc), white yellow solid; decomp. >80 °C, 55% (86 mg). ^1H NMR (400 MHz, DMSO-*d*₆) δ 9.08 (s, 1H), 7.80 (d, $J = 8.5$ Hz, 1H), 7.54 (s, 1H), 7.48 (s, 1H), 7.20 (dd, $J = 8.5, 1.9$ Hz, 1H), 2.88 (d, $J = 4.7$ Hz, 3H); ^{13}C NMR (101 MHz, DMSO-*d*₆) δ 161.88, 160.41, 152.33, 129.92, 123.62, 122.21, 118.01, 27.92. HRMS: $\text{C}_9\text{H}_9\text{ClN}_3$ $[\text{M}+\text{H}]^+$; calculated 194.0485, found: 194.0484.

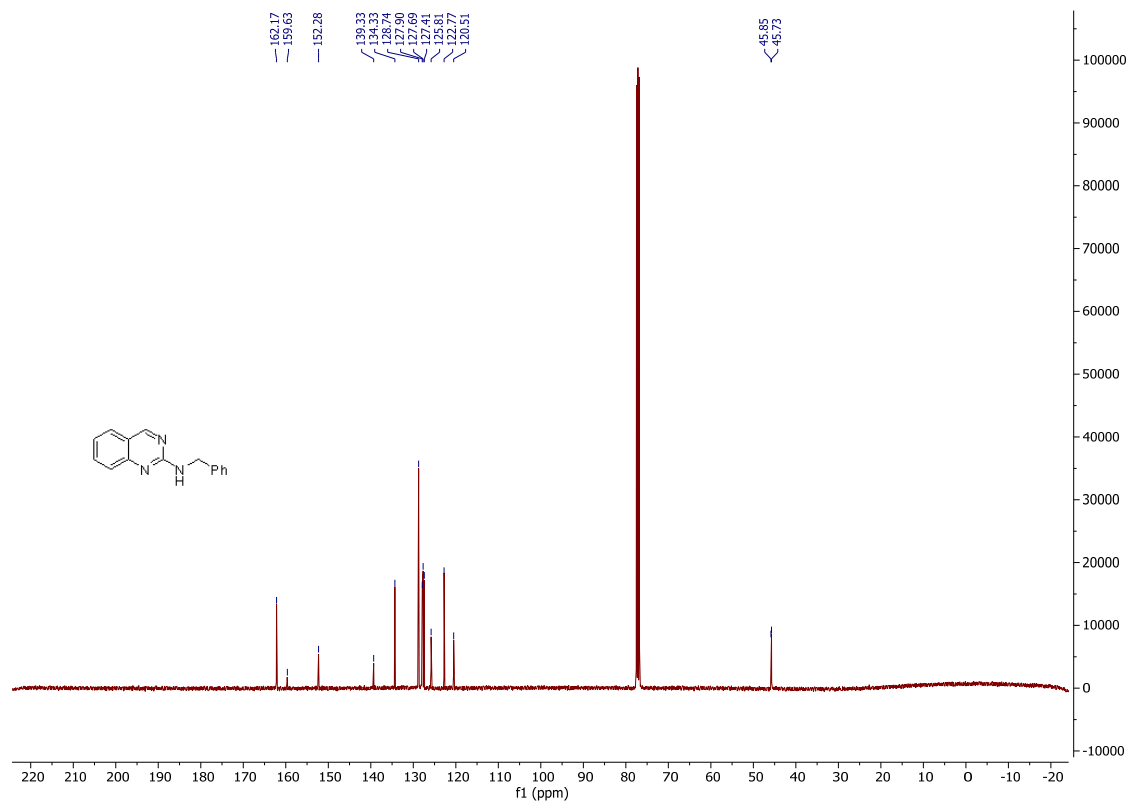
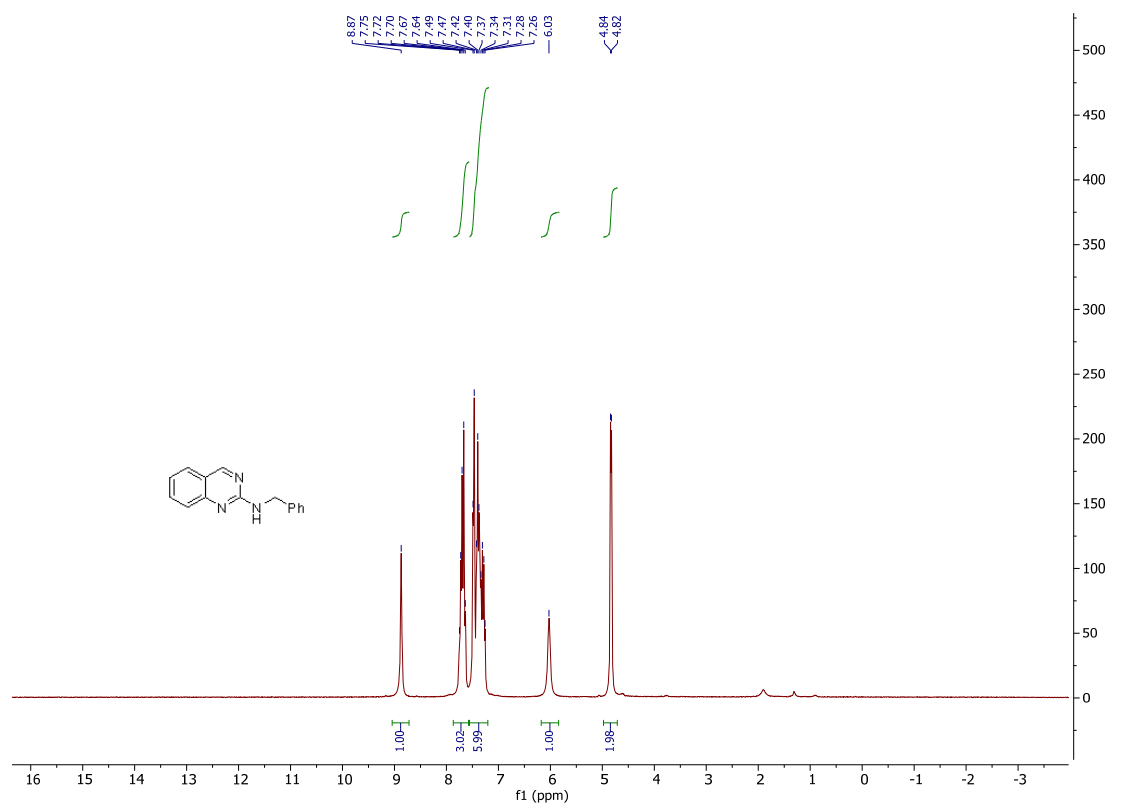
5. Copies of NMR spectra 2-aminoquinazoline (3)



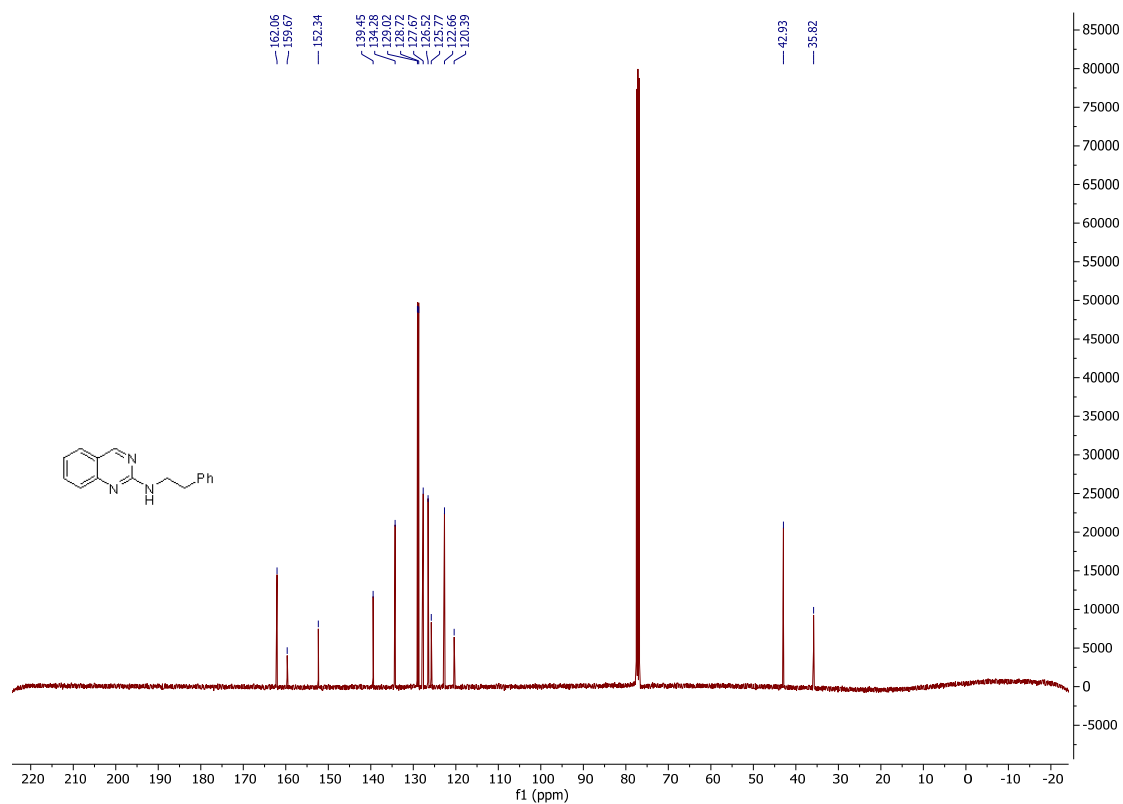
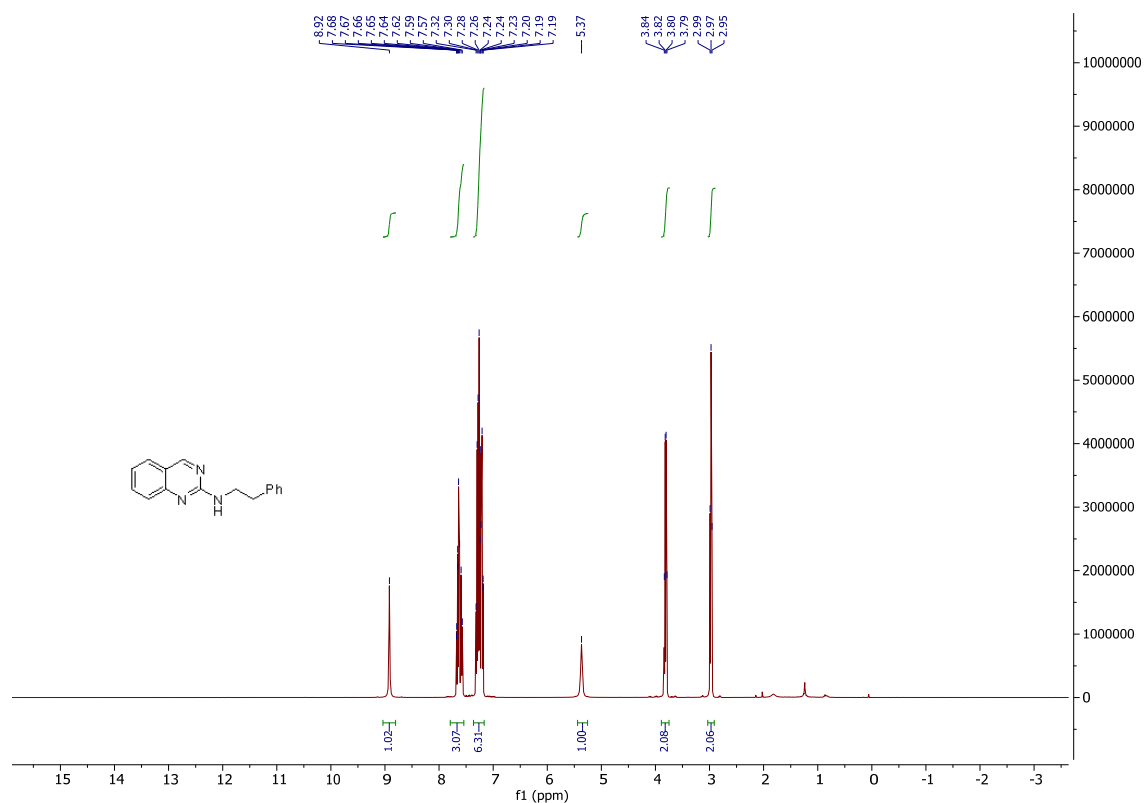
N-methylquinazolin-2-amine (5a)



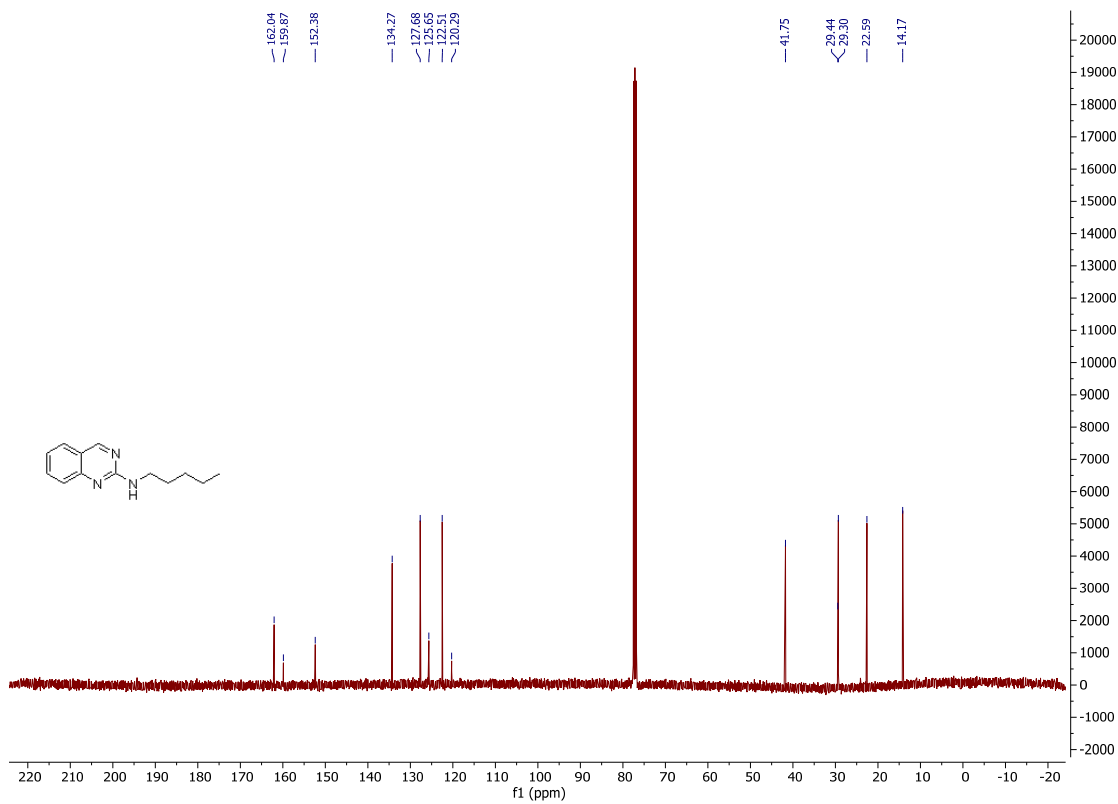
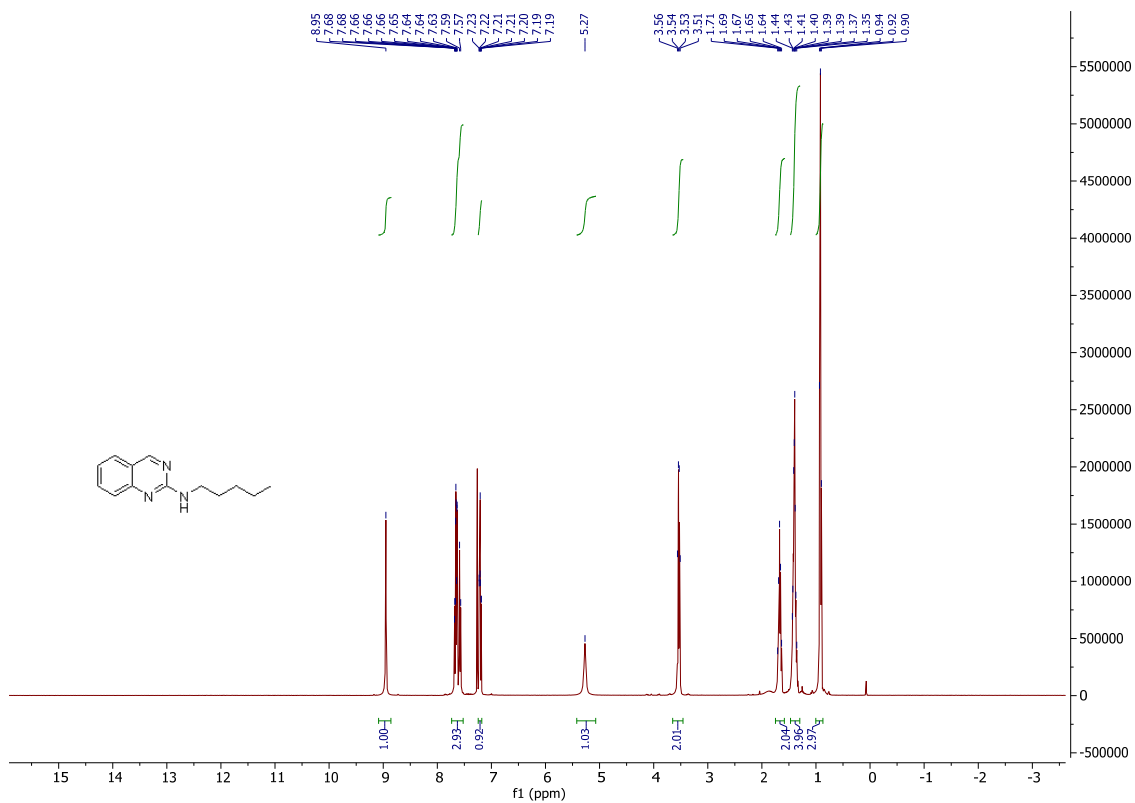
N-benzylquinazolin-2-amine (5c)



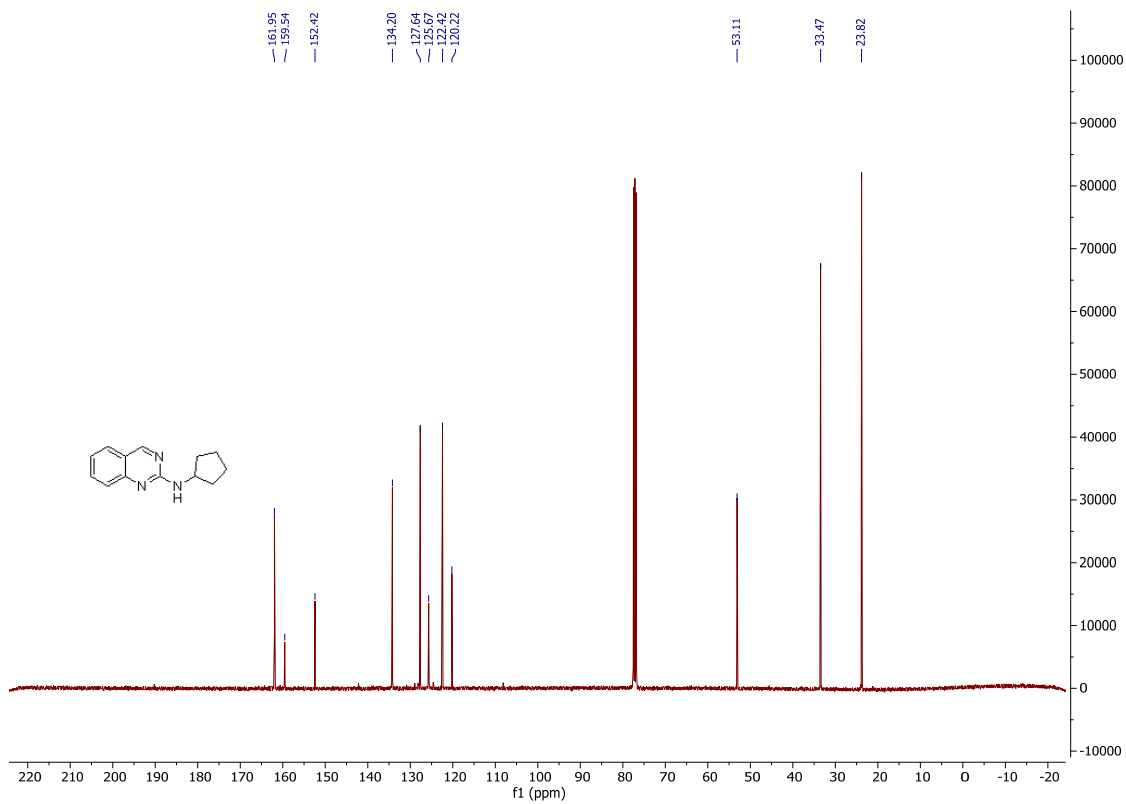
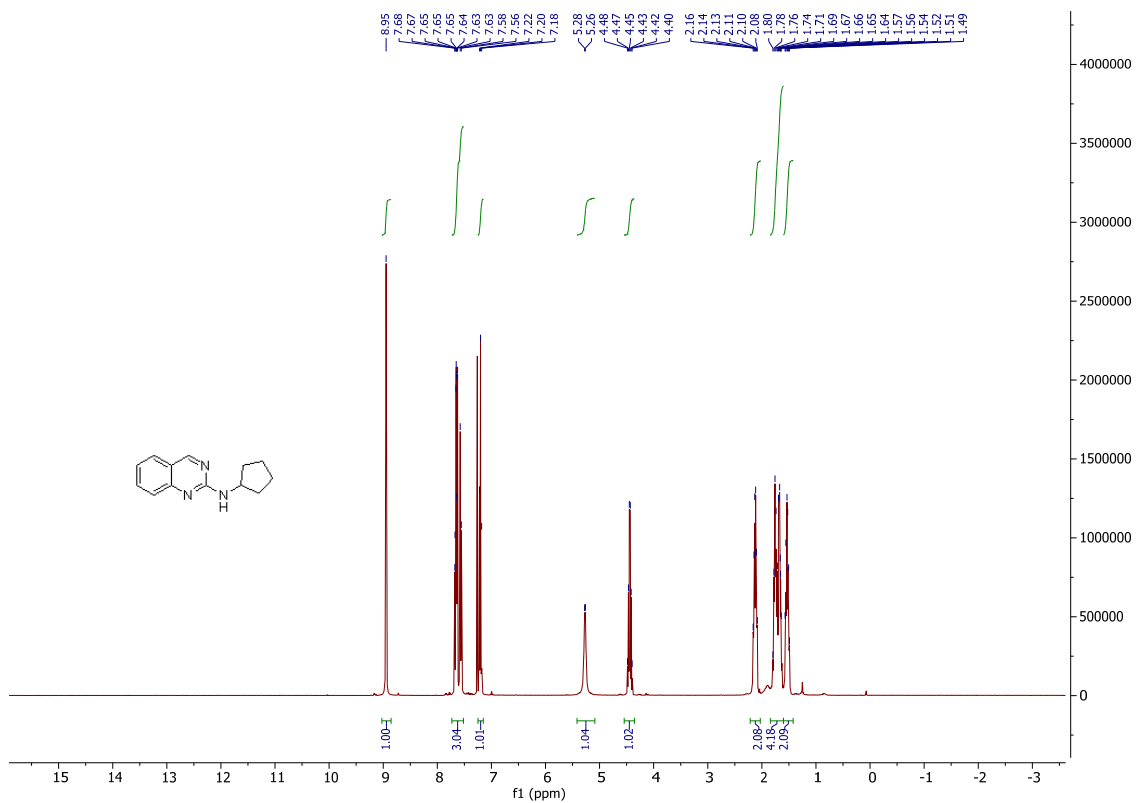
N-phenethylquinazolin-2-amine (5d)



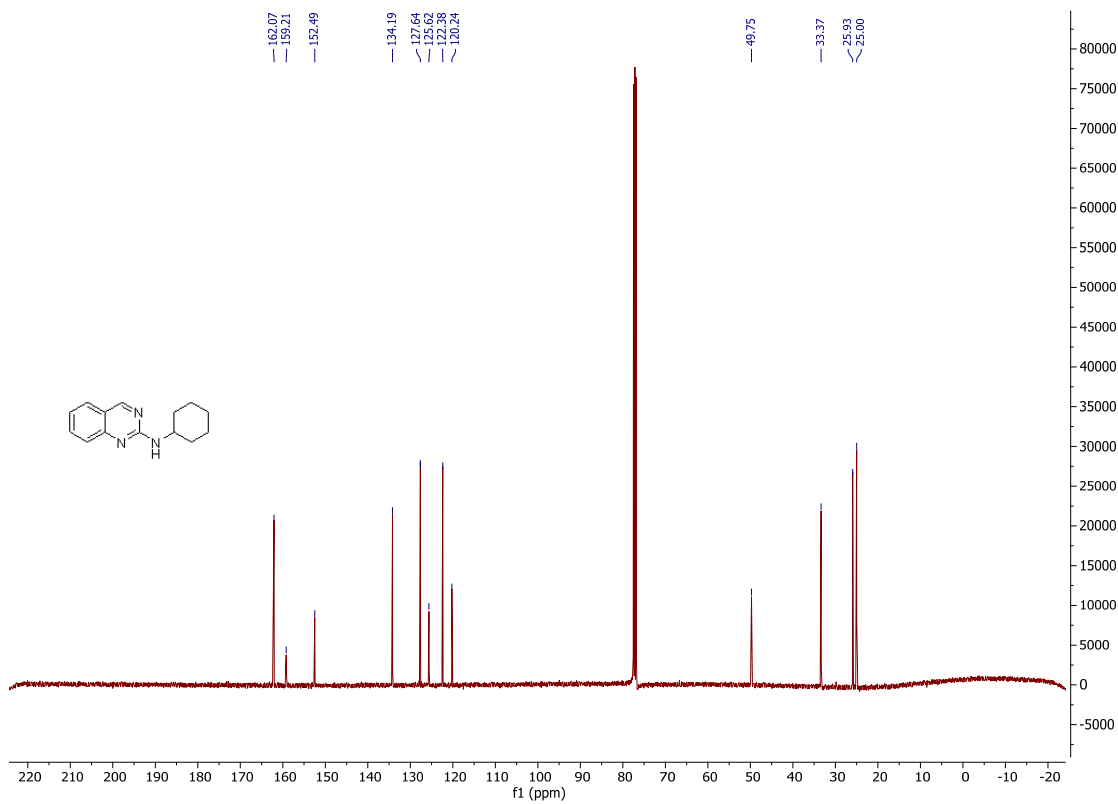
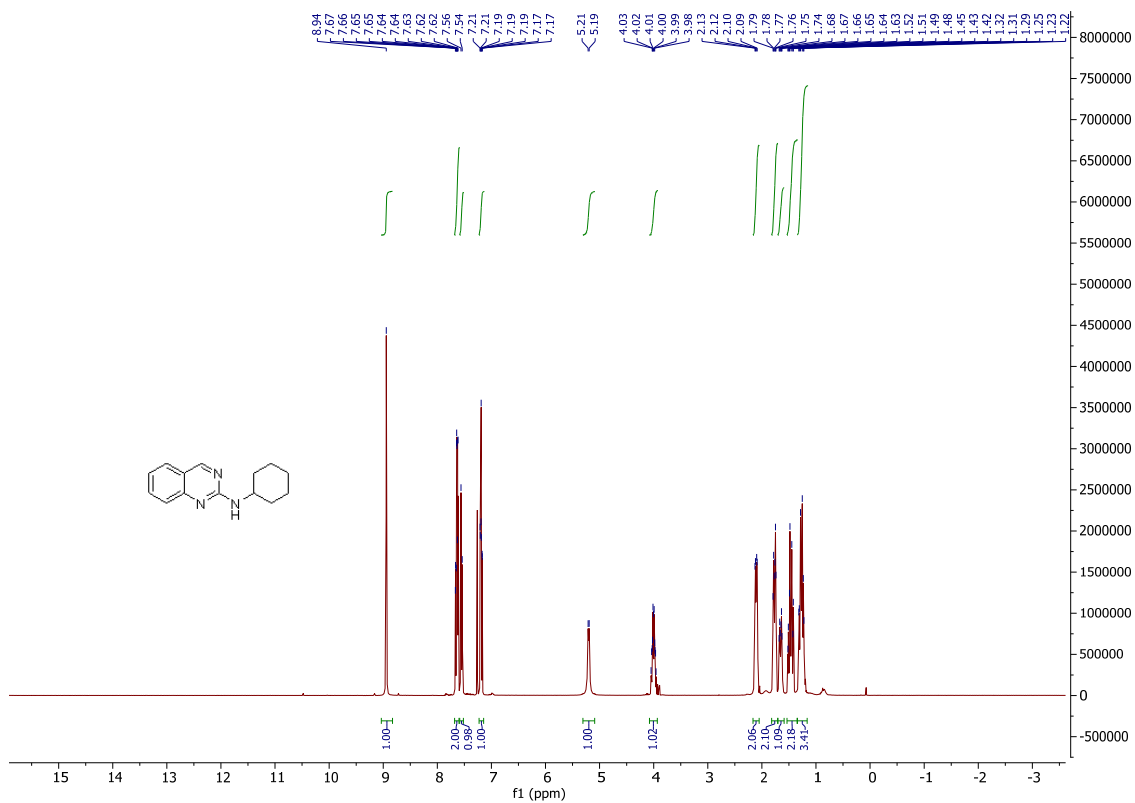
N-pentylquinazolin-2-amine (5e)



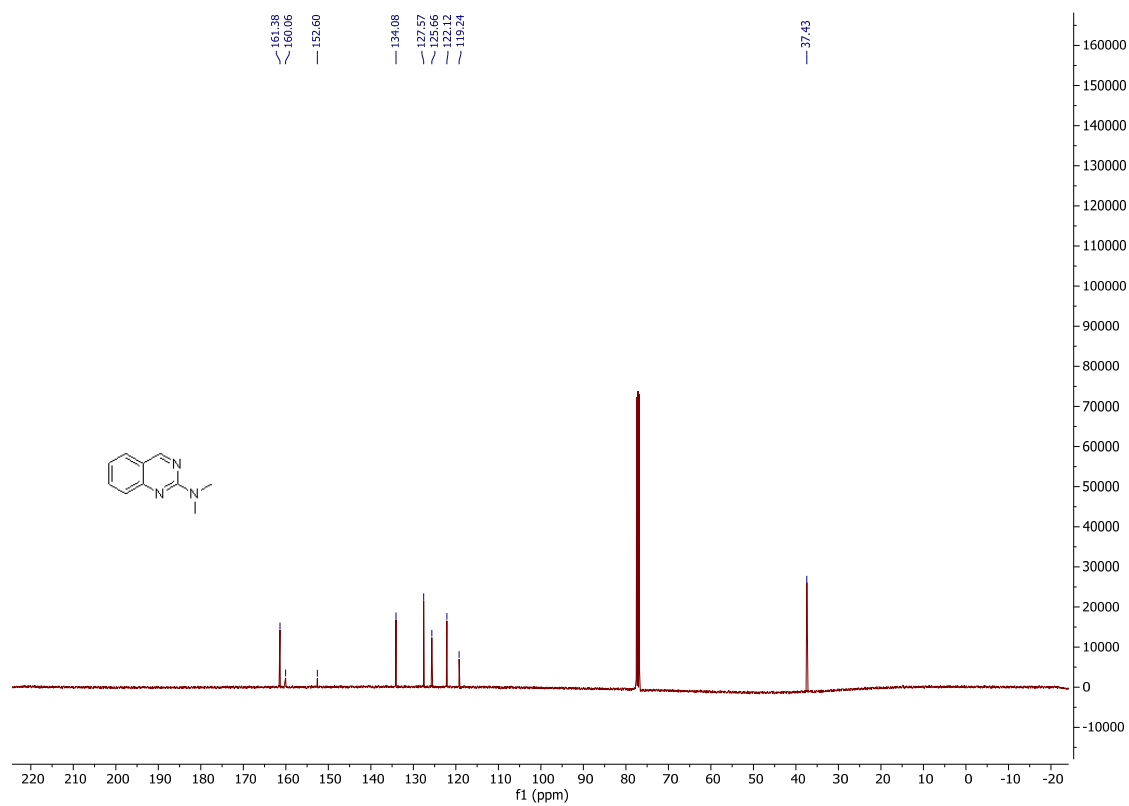
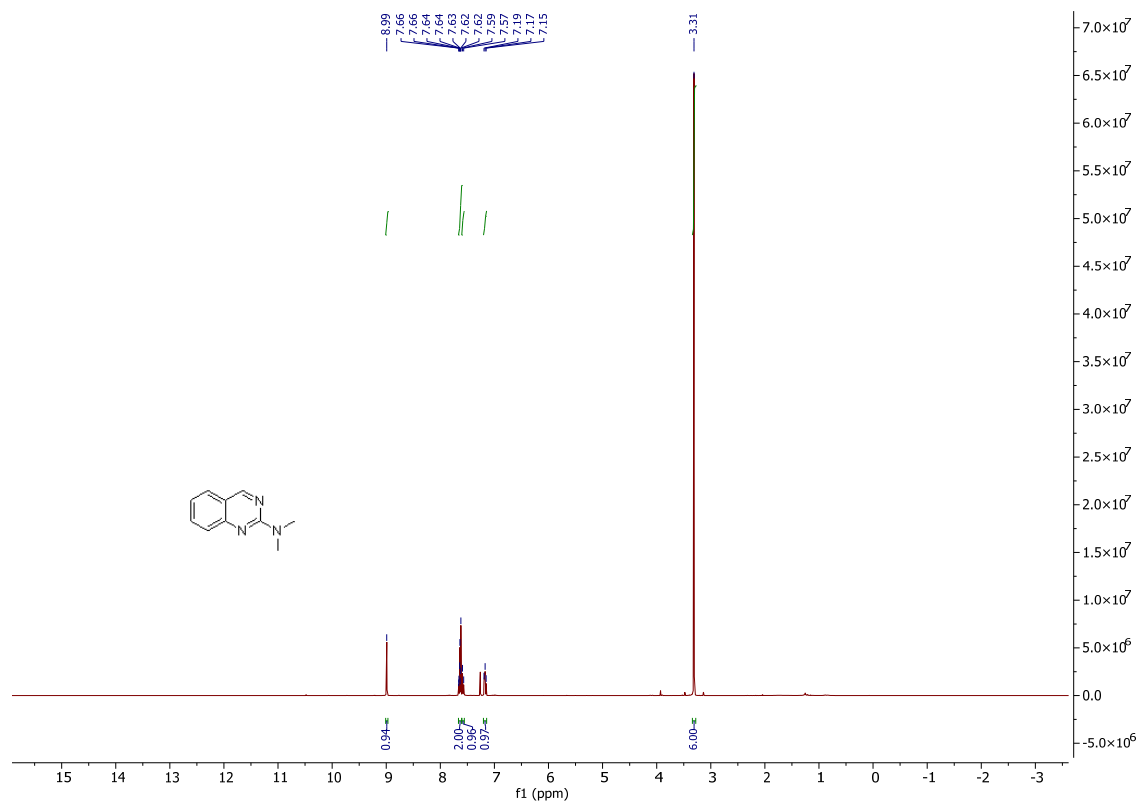
N-cyclopentylquinazolin-2-amine (5f)



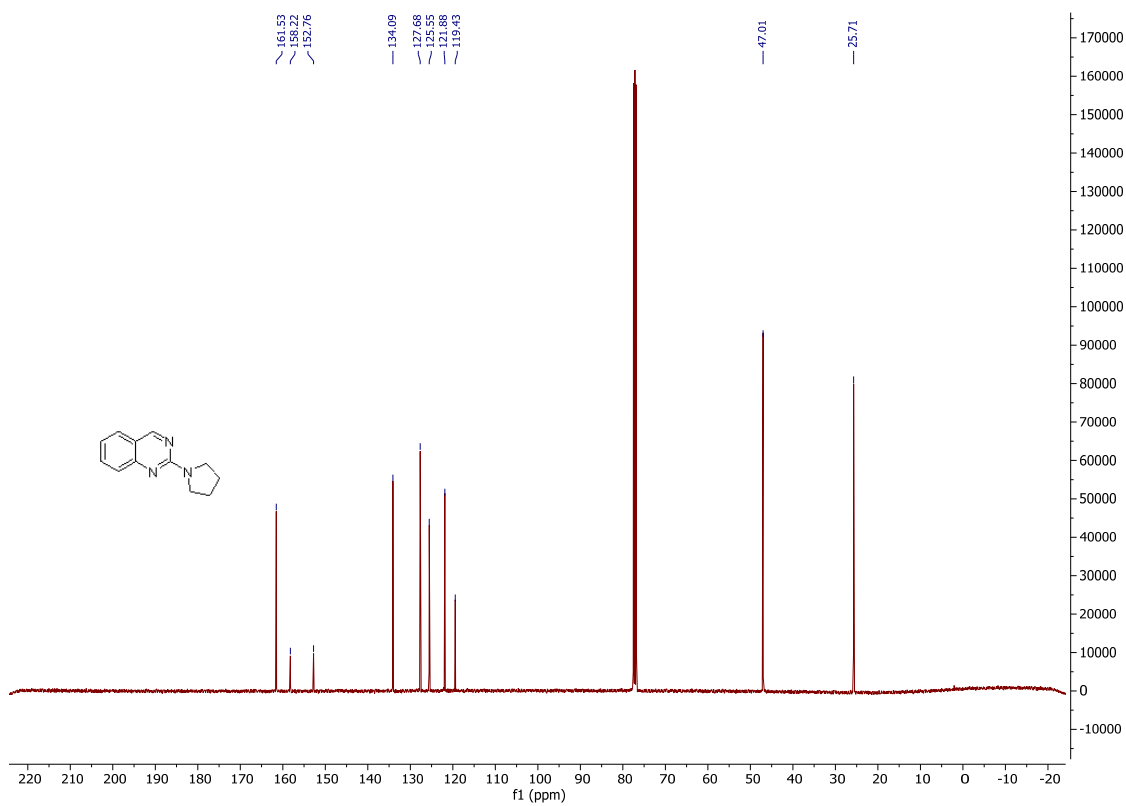
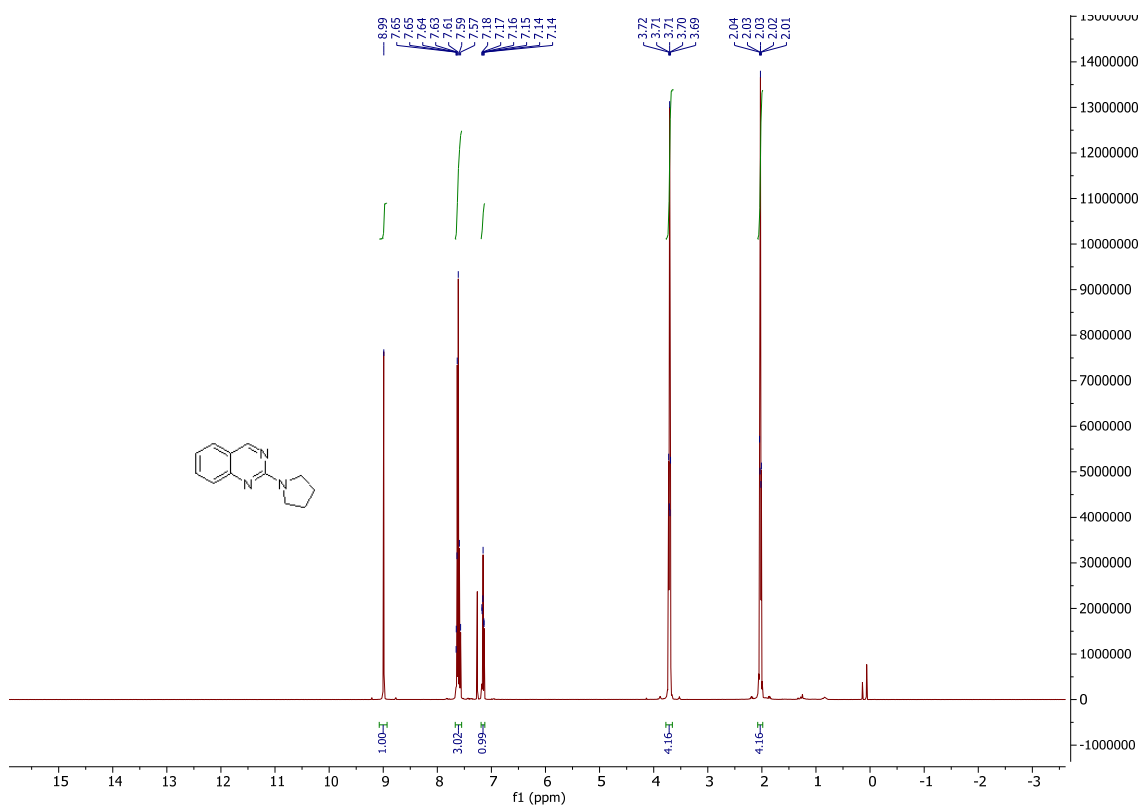
N-cyclohexylquinazolin-2-amine (5g)



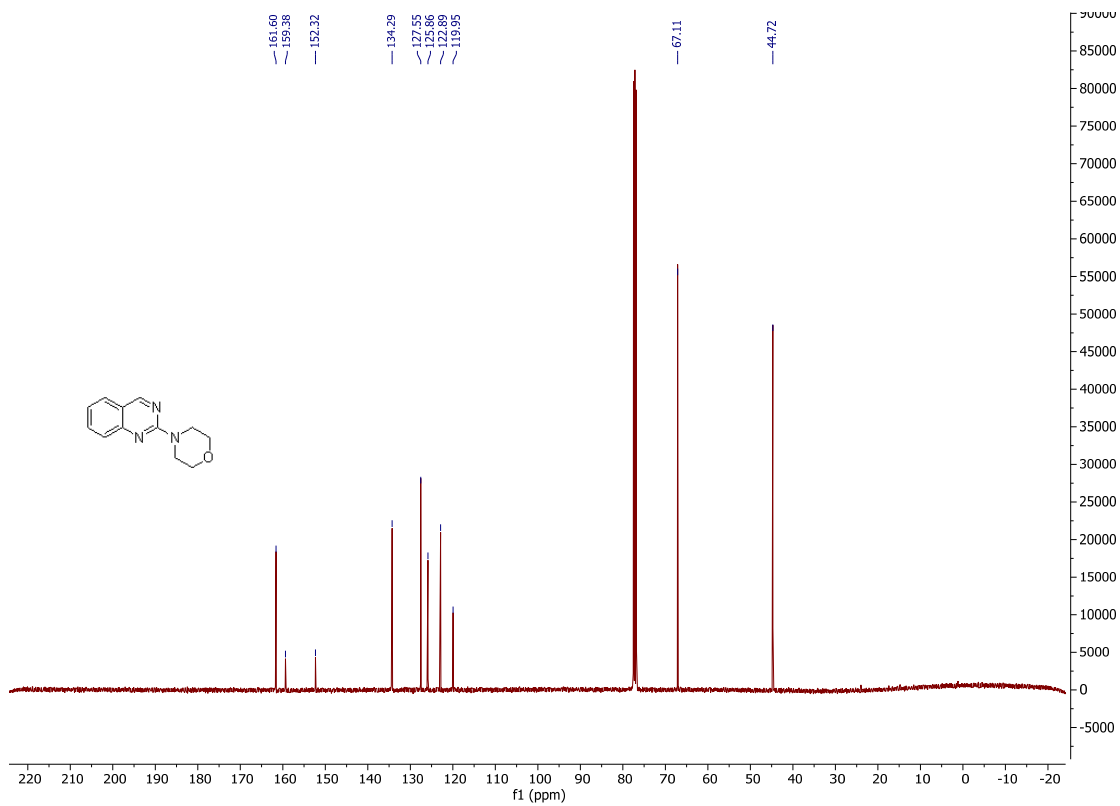
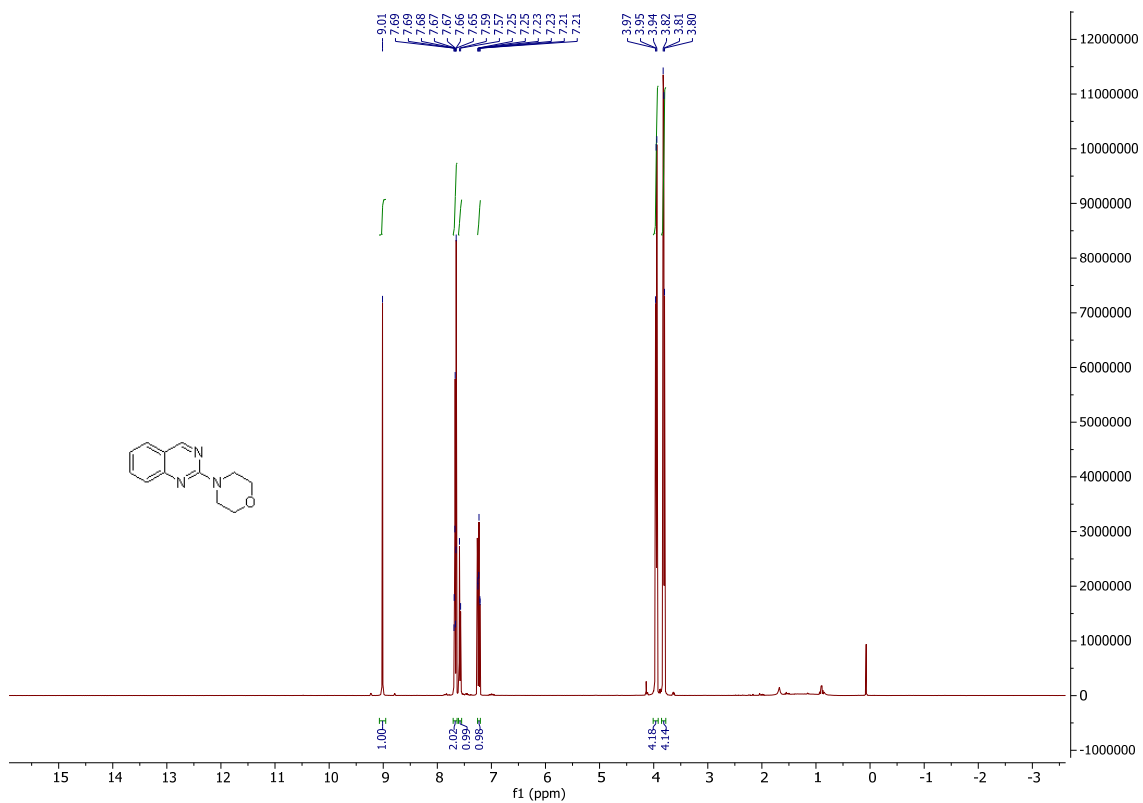
N,N-dimethylquinazolin-2-amine (5h)



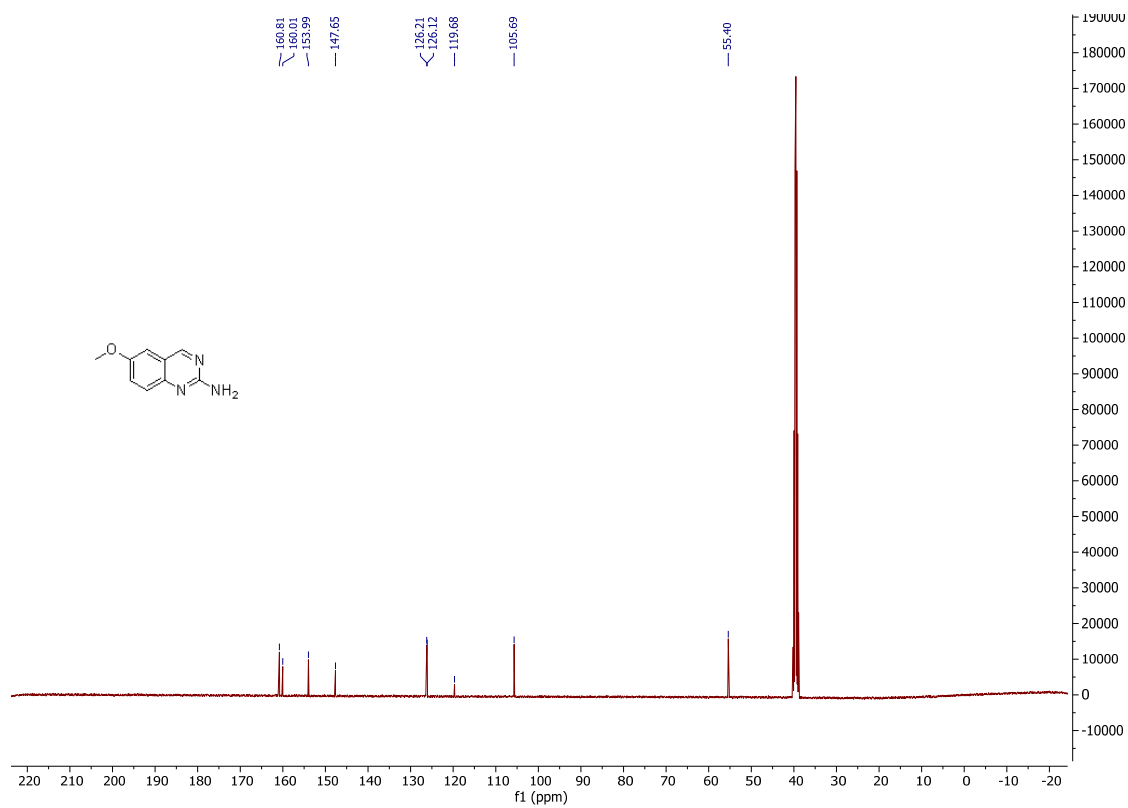
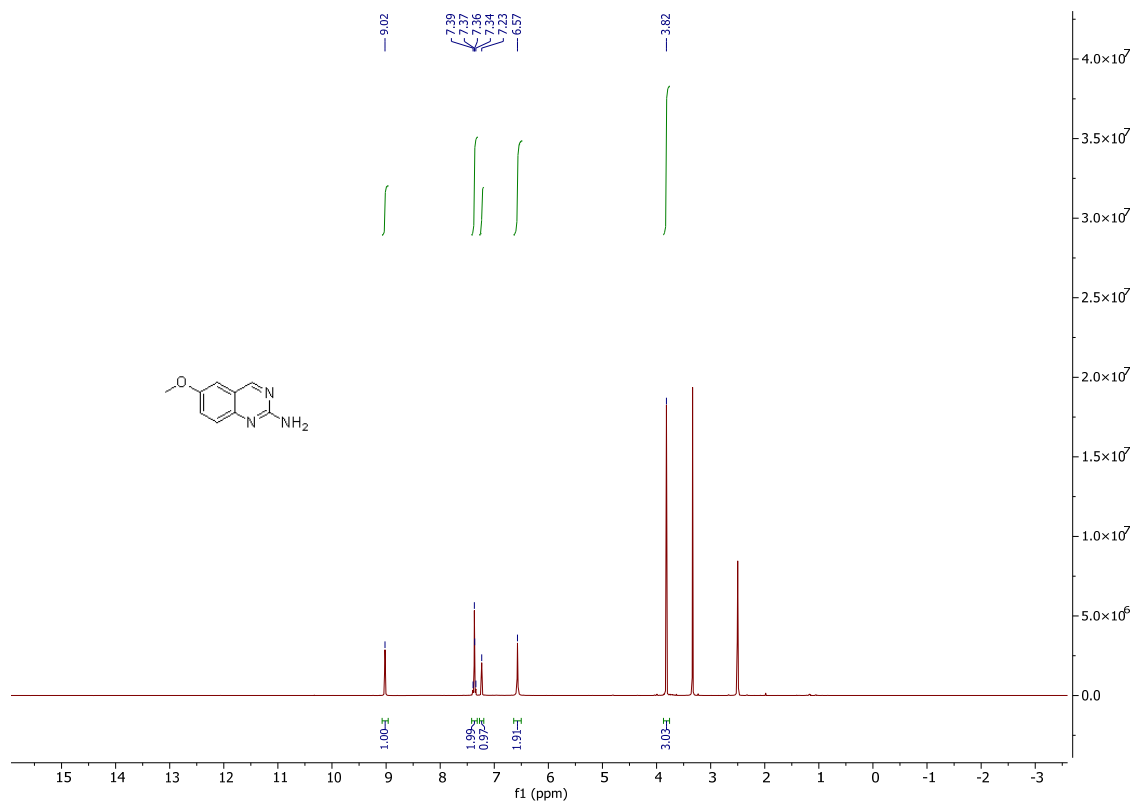
2-(pyrrolidin-1-yl)quinazoline (5i)



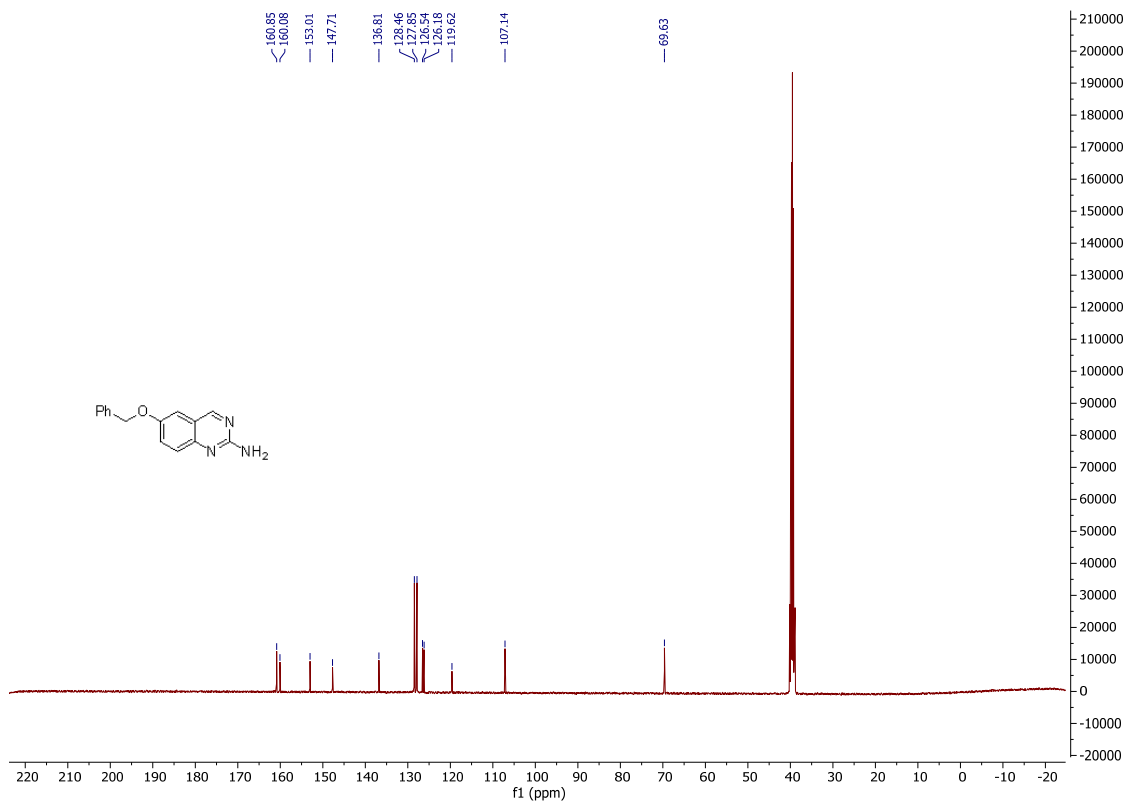
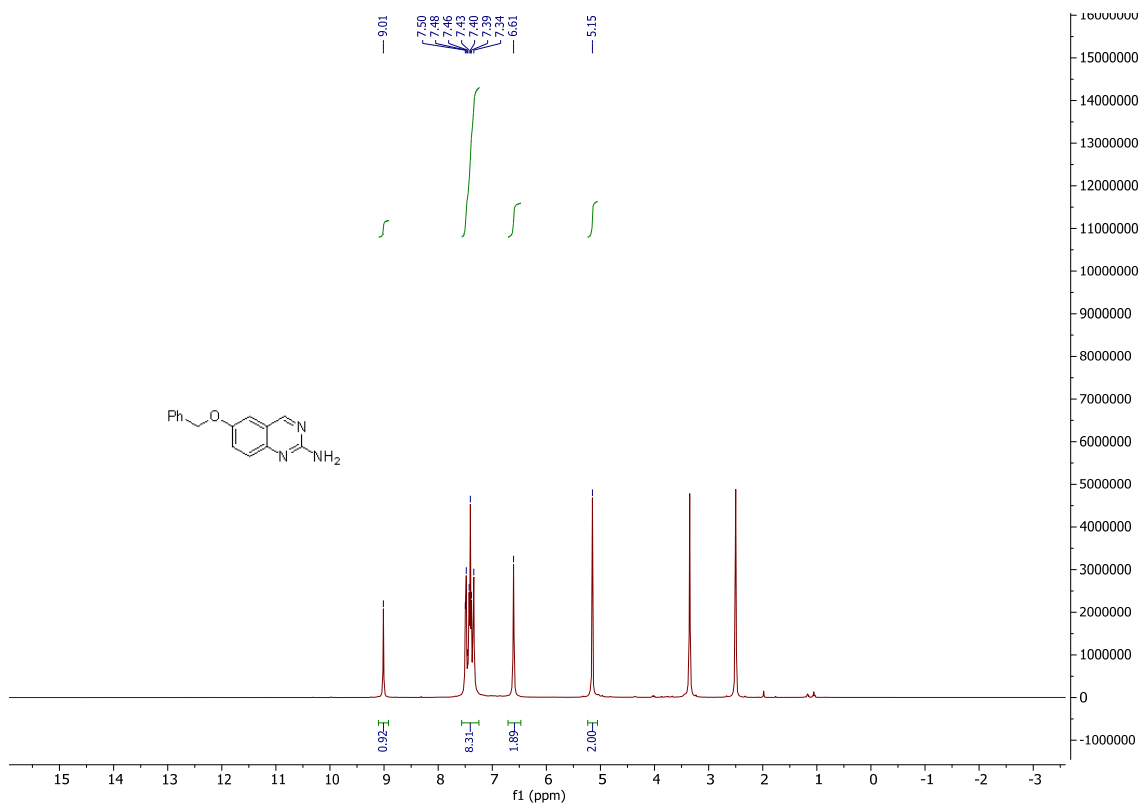
4-(quinazolin-2-yl)morpholine (5j)



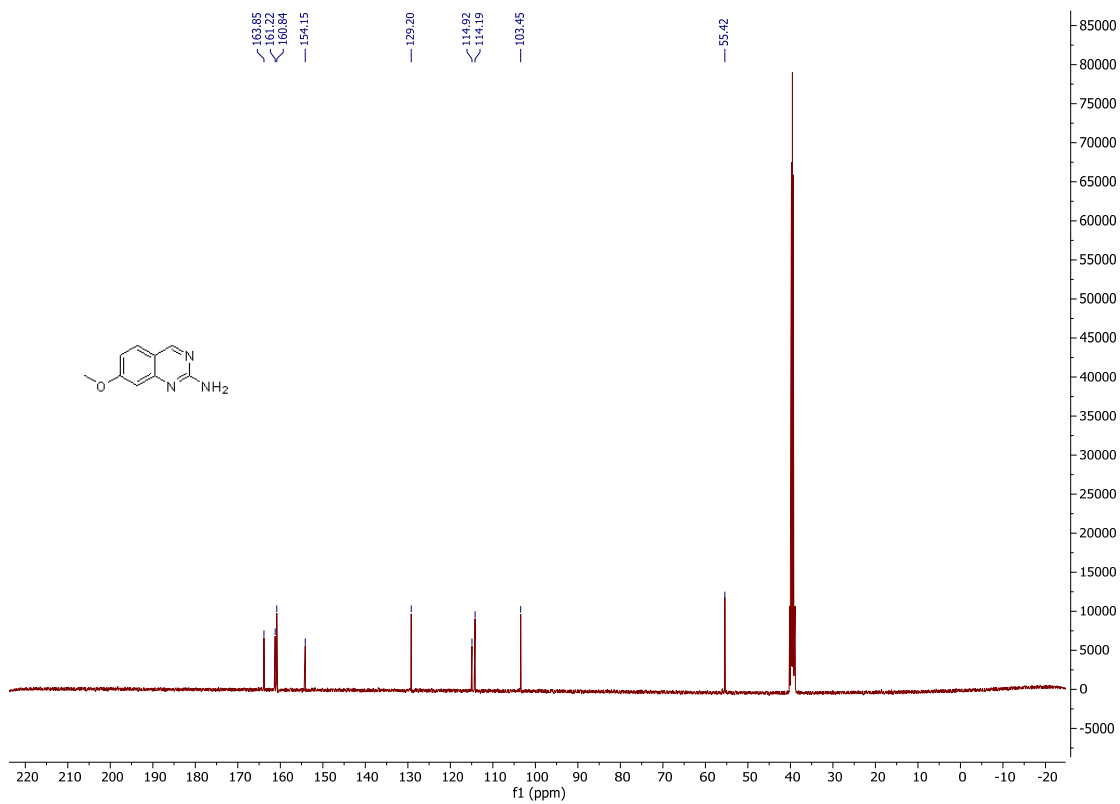
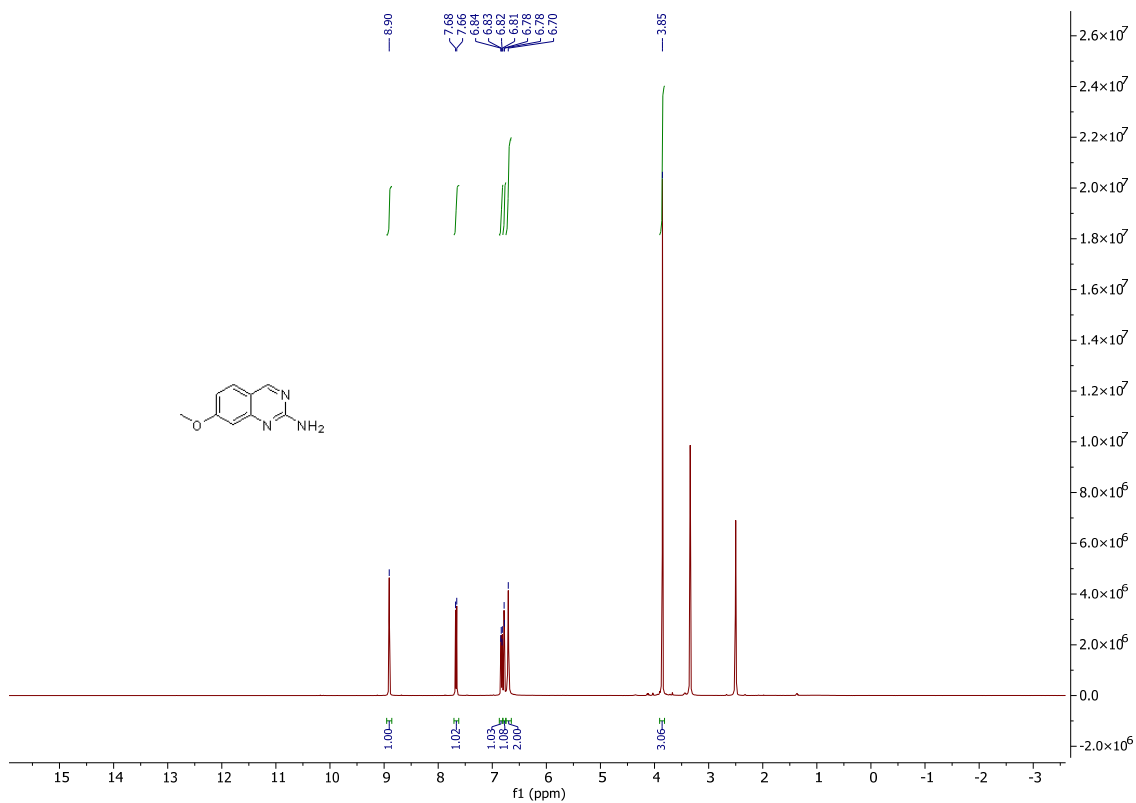
6-methoxyquinazolin-2-amine (7a)



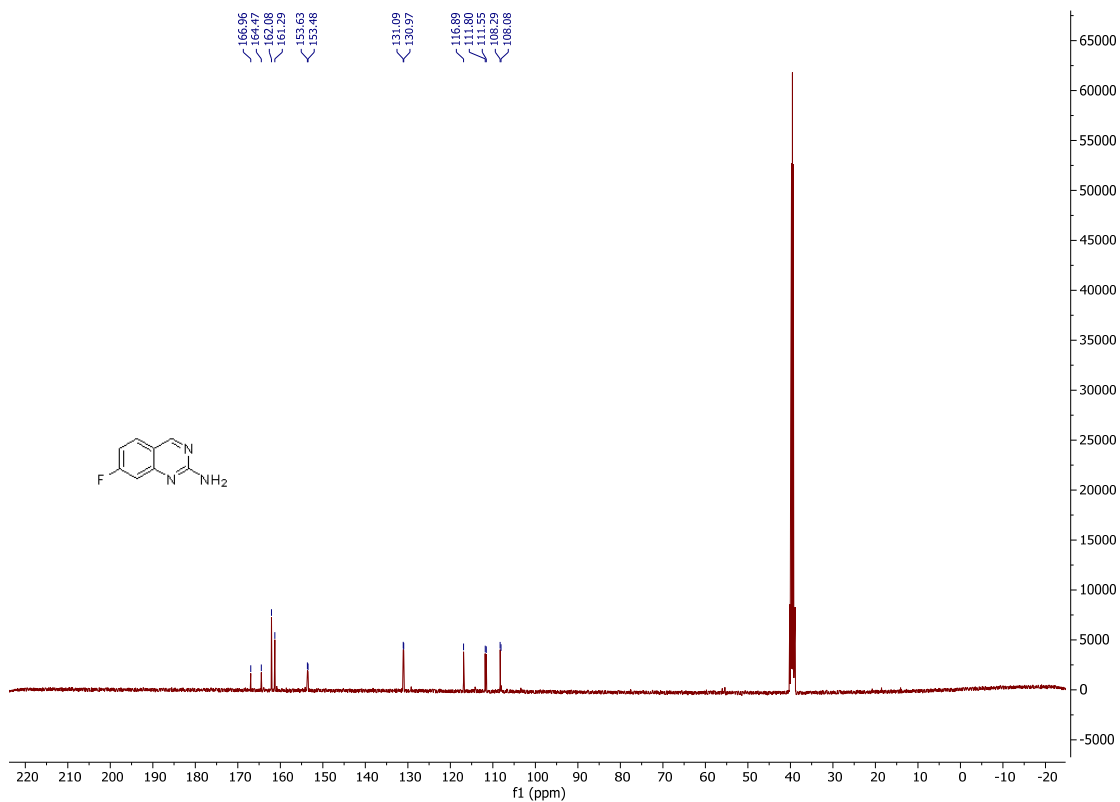
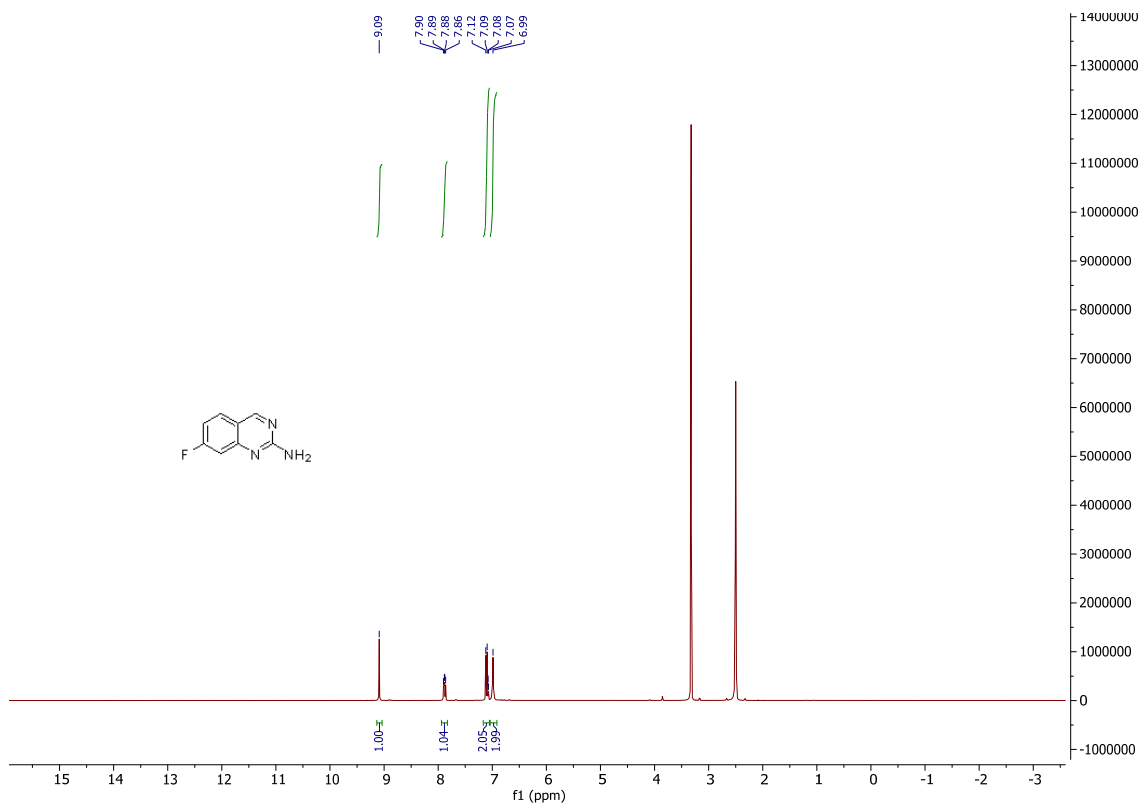
6-(benzyloxy)quinazolin-2-amine (7b)



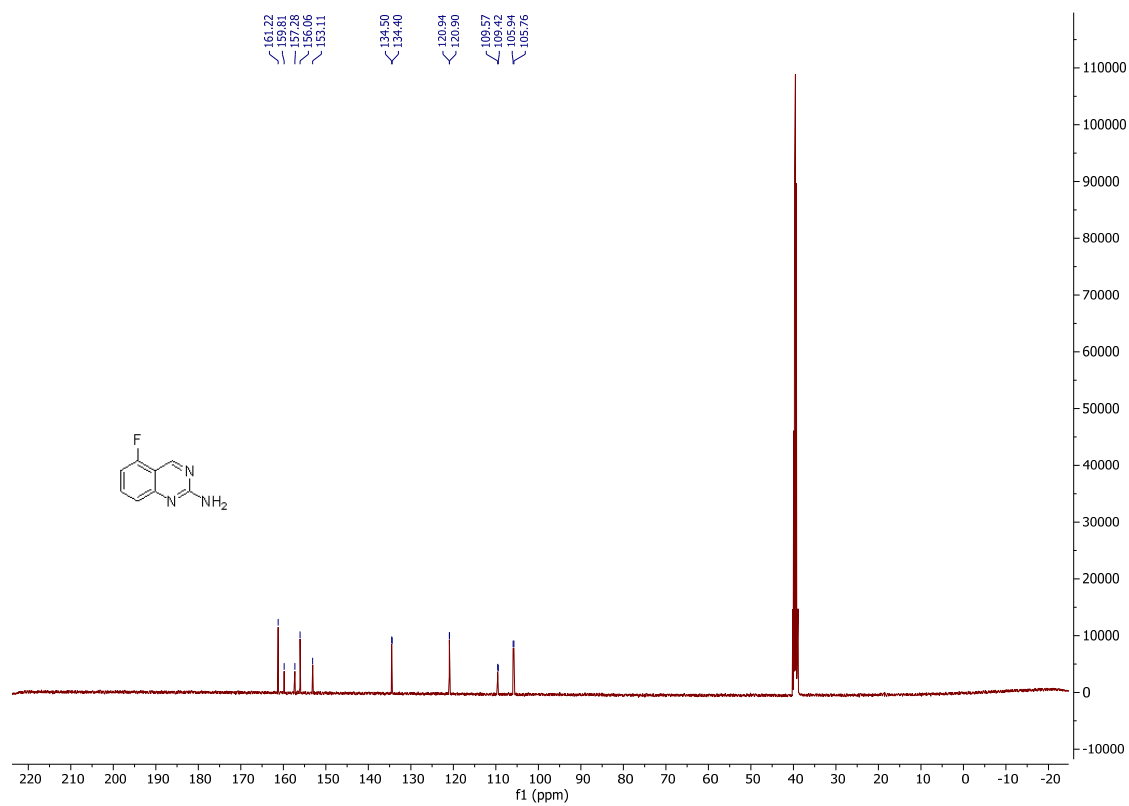
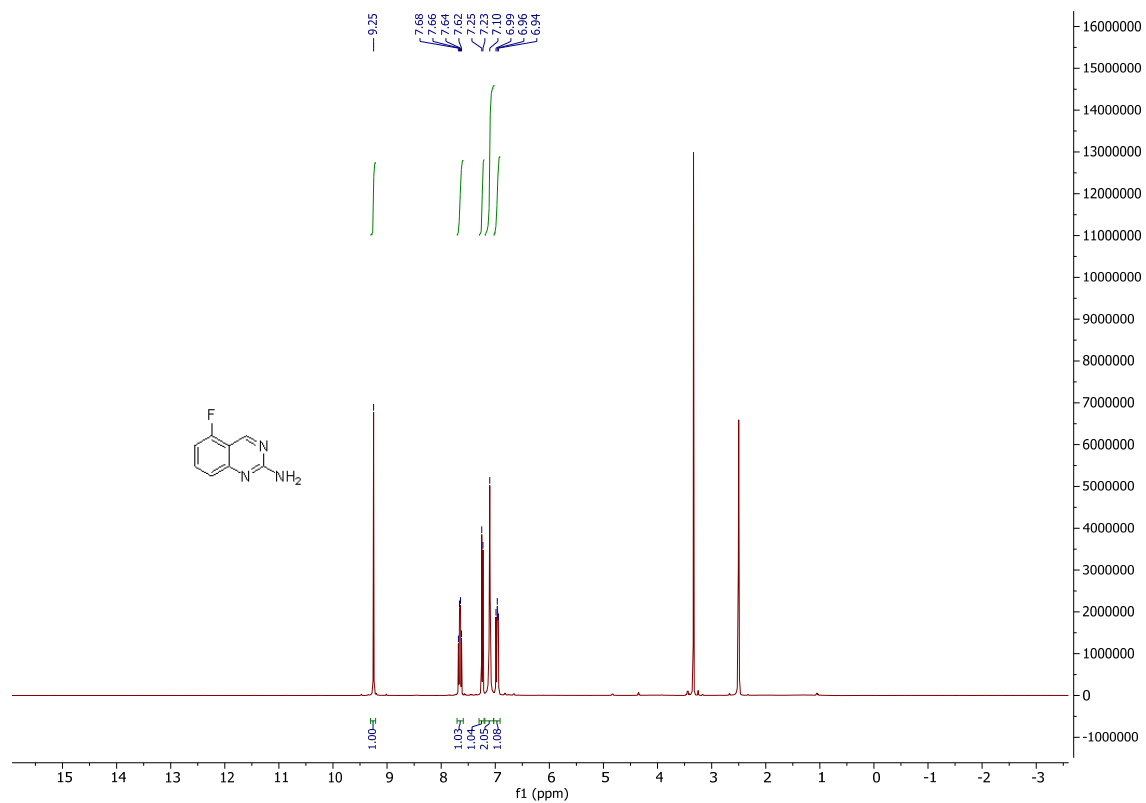
7-methoxyquinazolin-2-amine (7c)



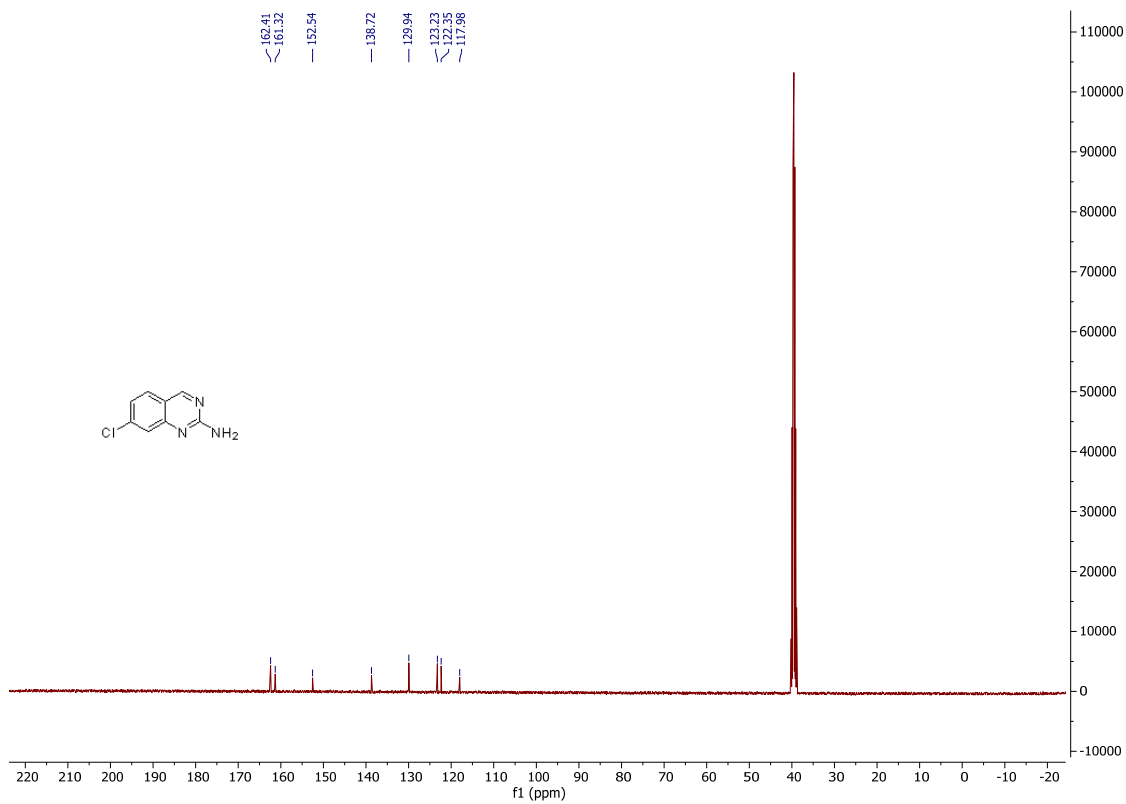
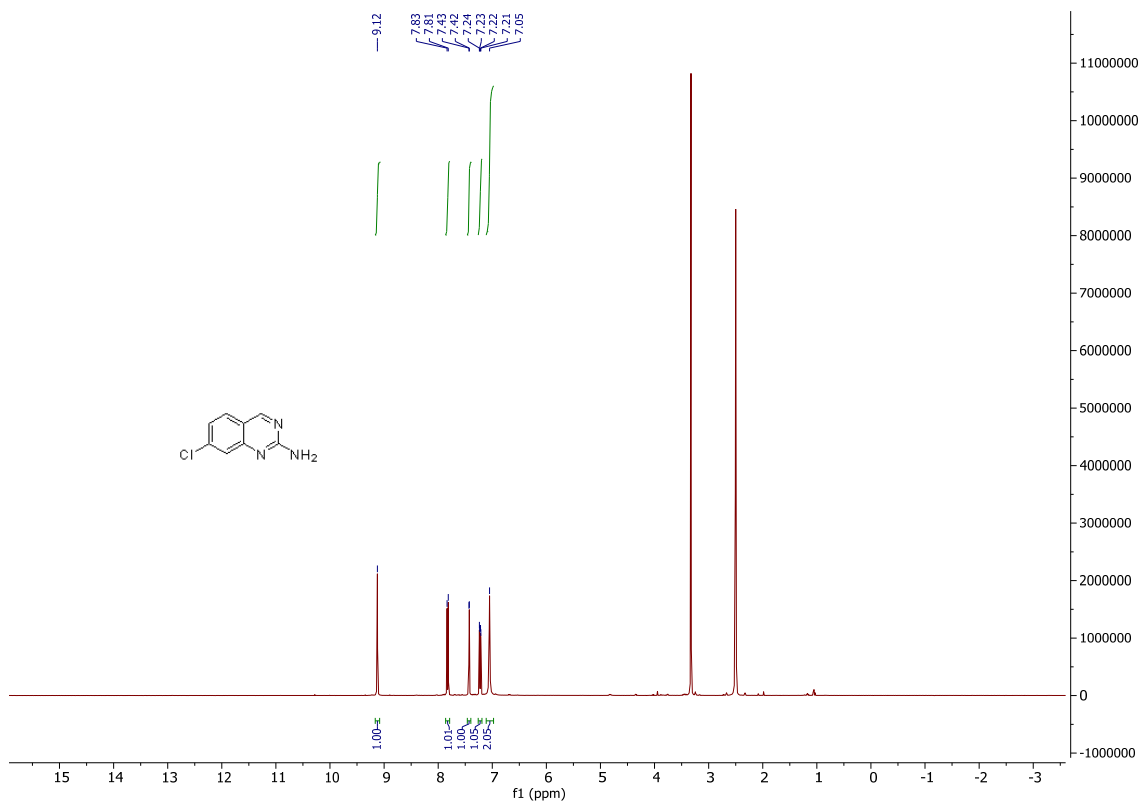
7-fluoroquinazolin-2-amine (7d)



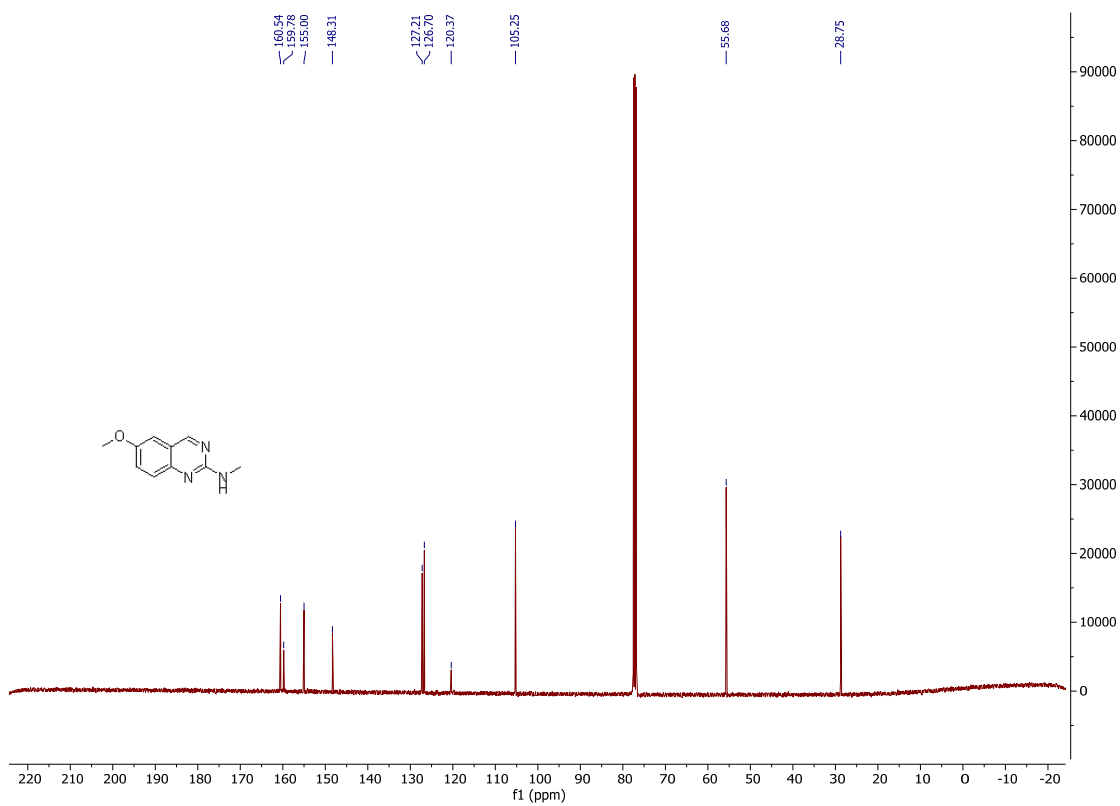
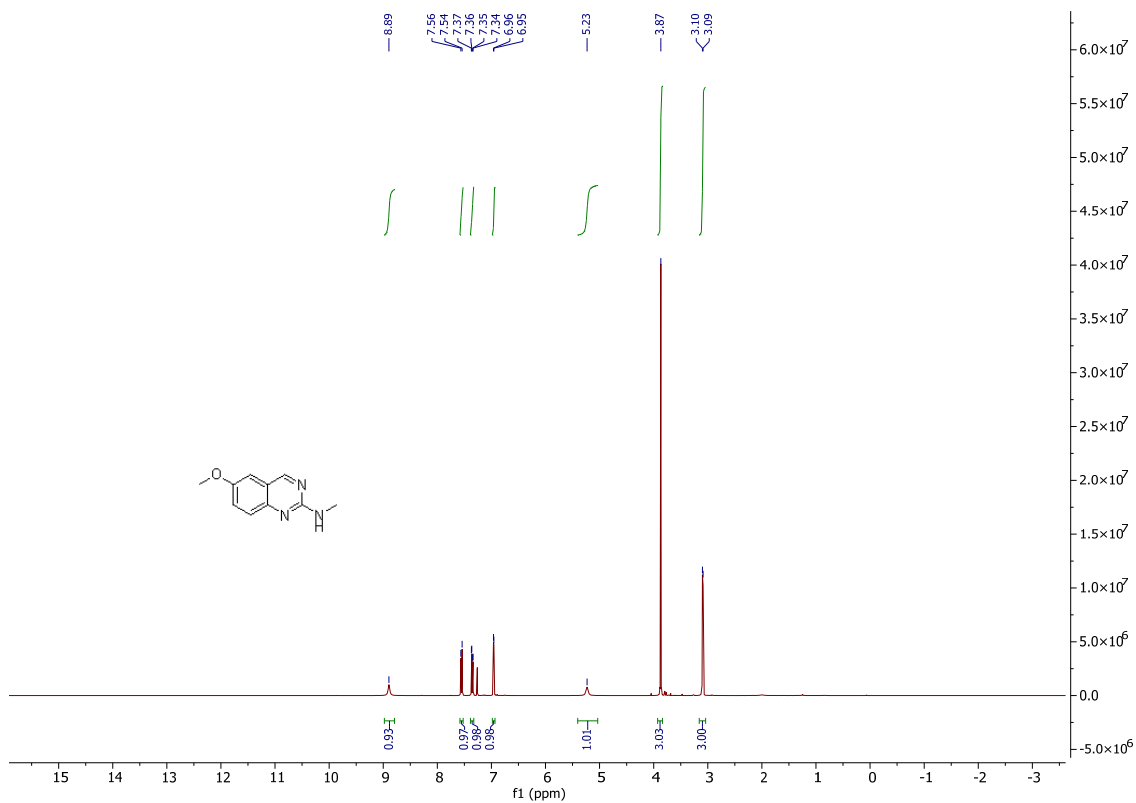
5-fluoroquinazolin-2-amine (7e)



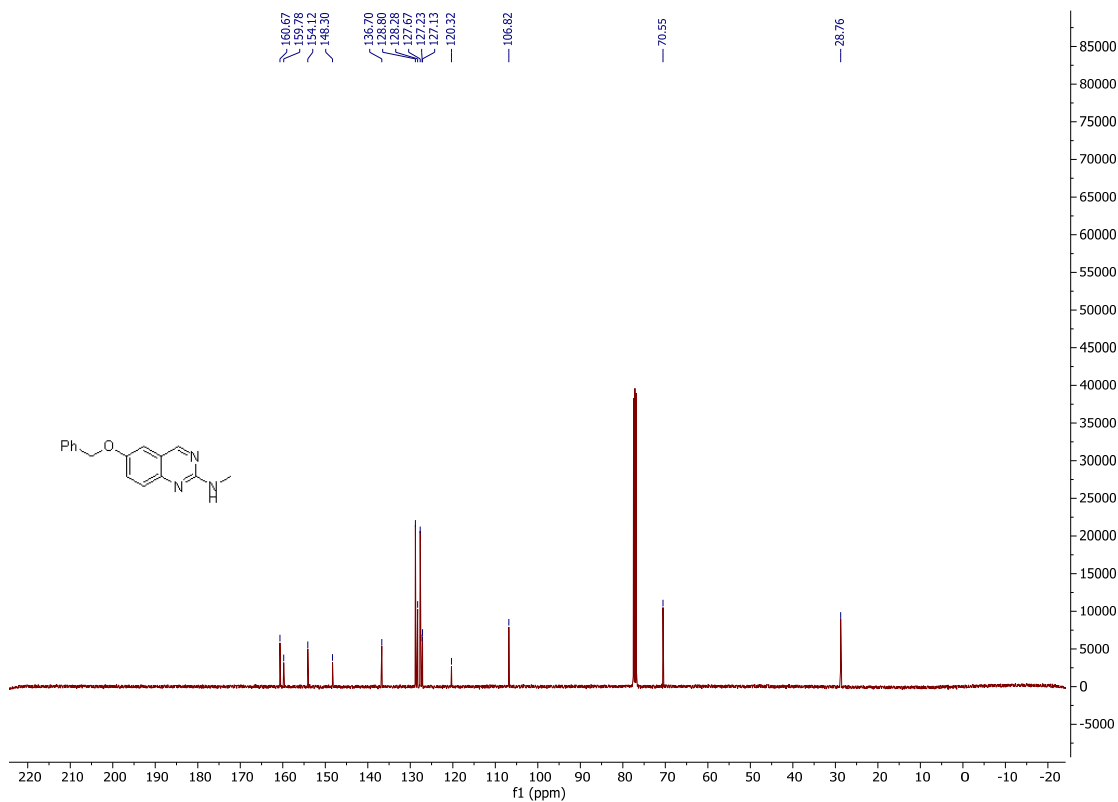
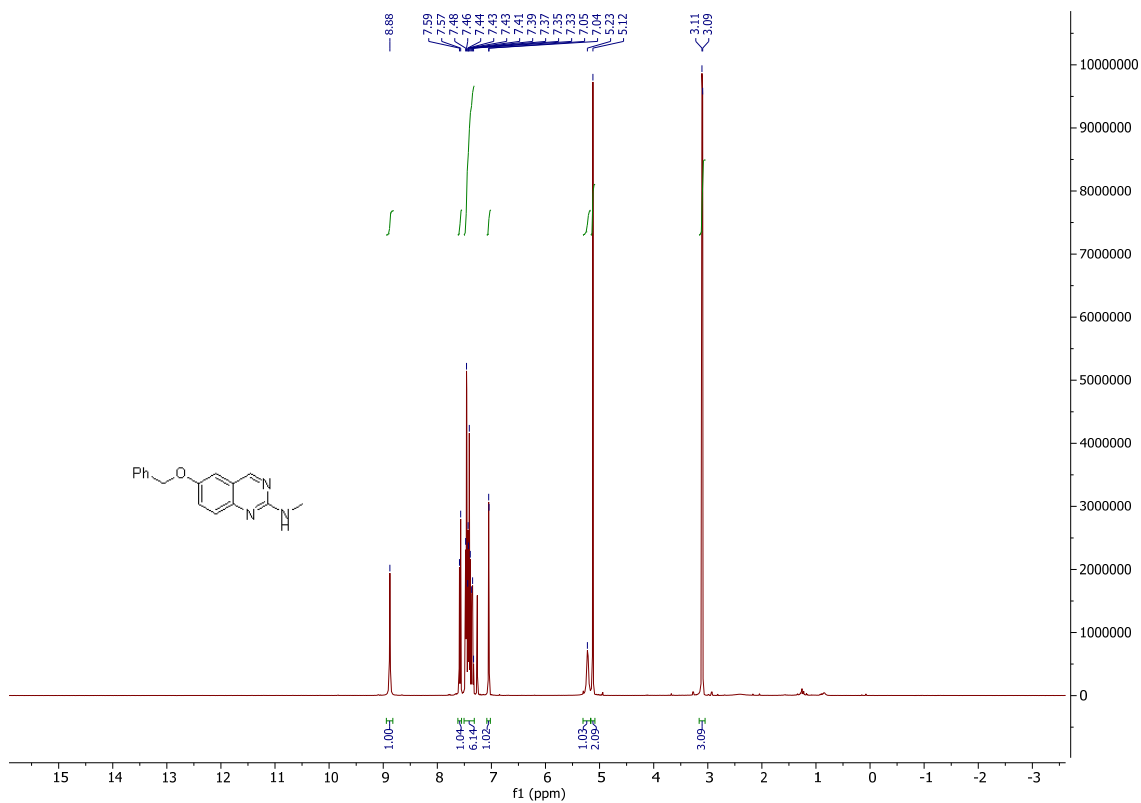
7-chloroquinazolin-2-amine (7f)



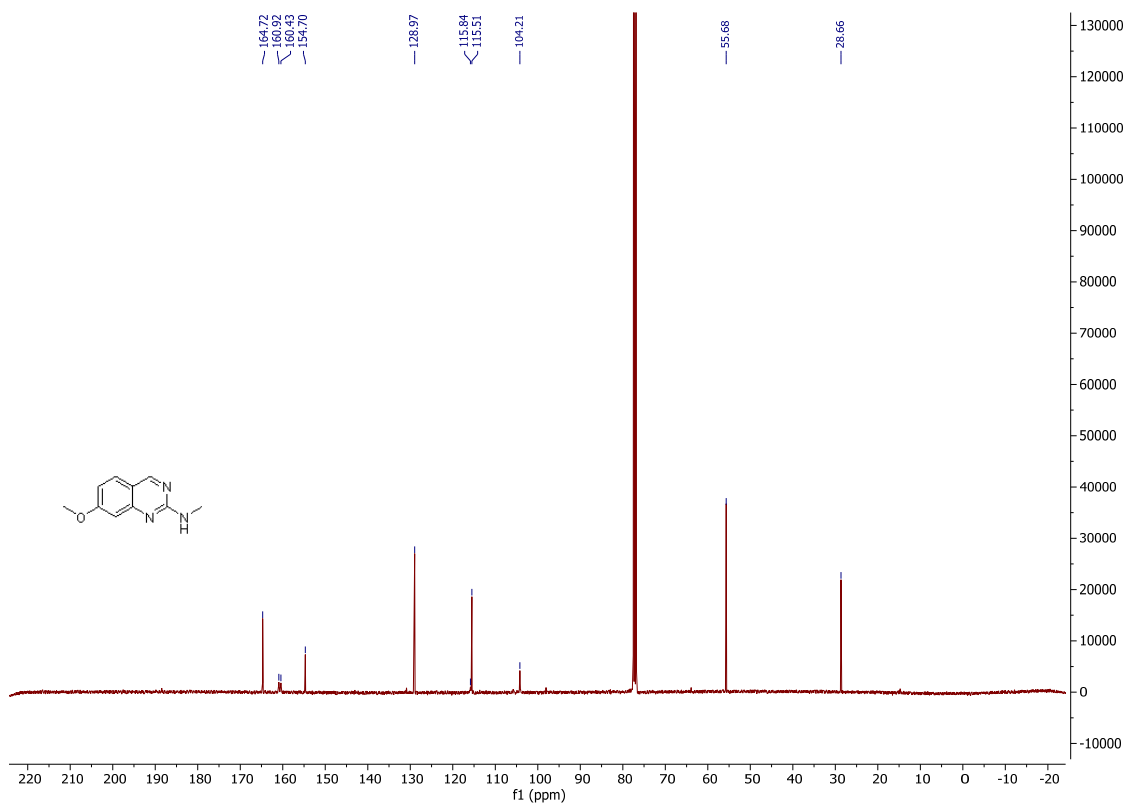
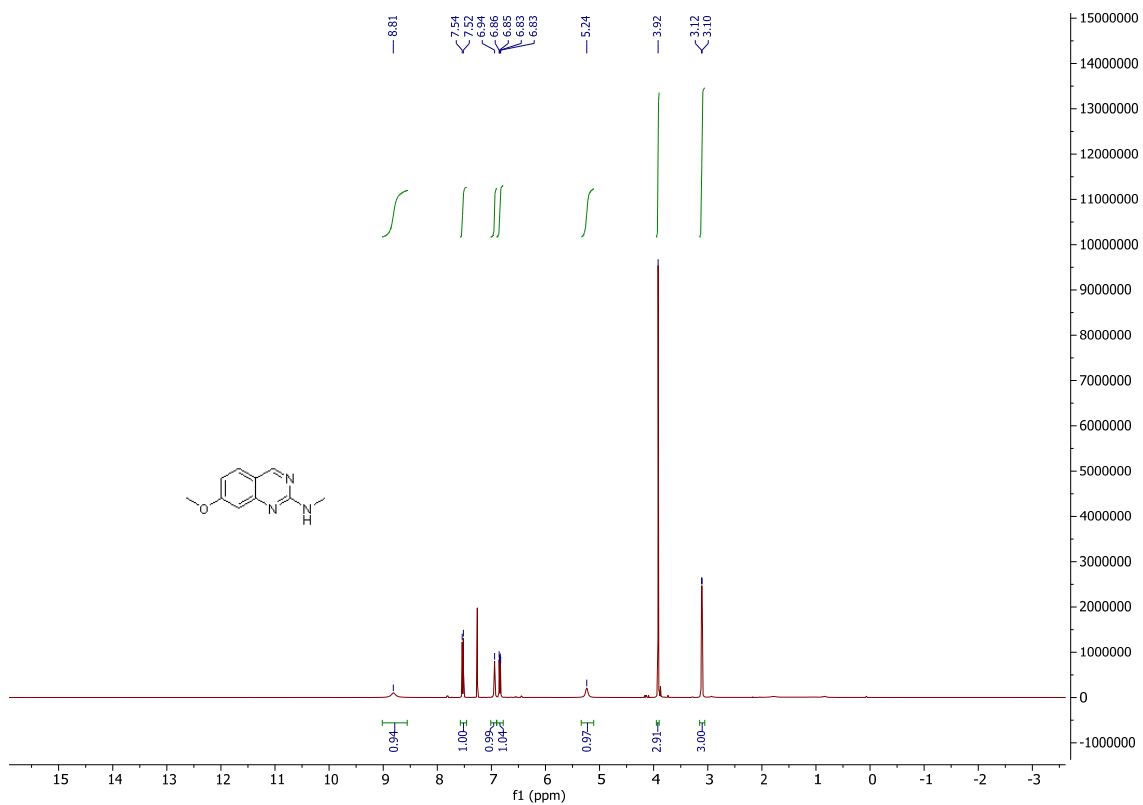
6-methoxy-N-methylquinazolin-2-amine (8a)



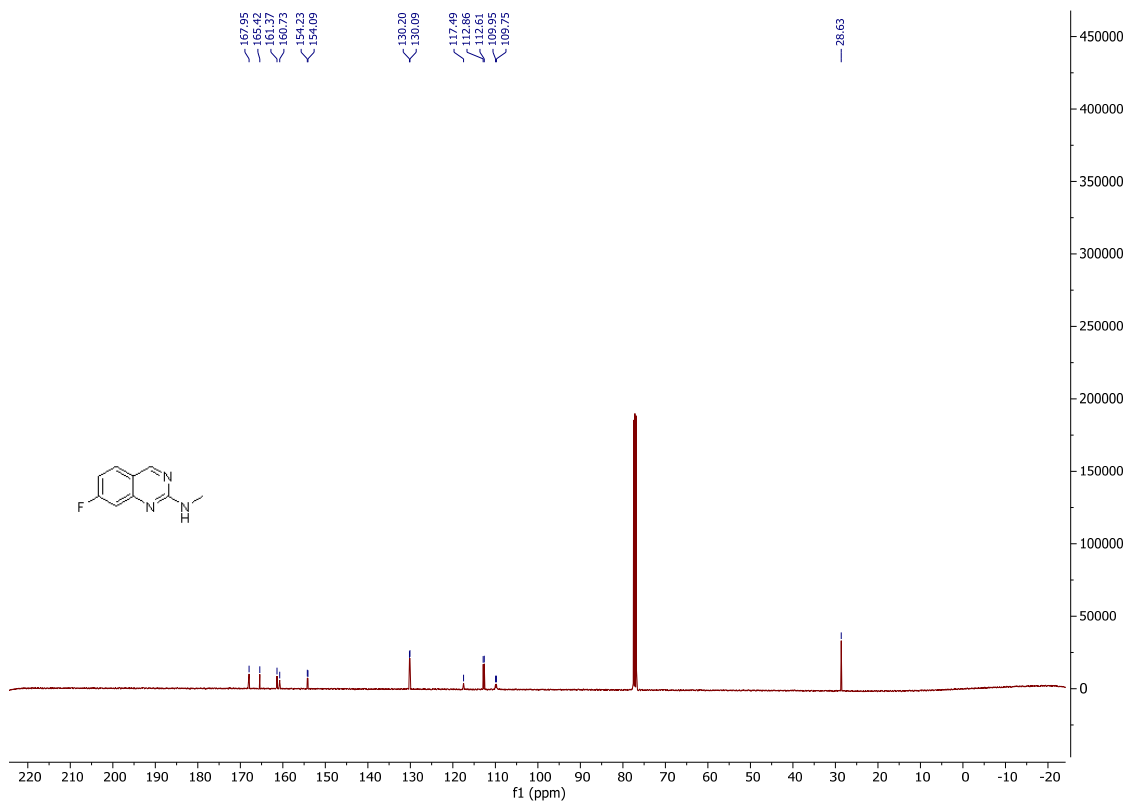
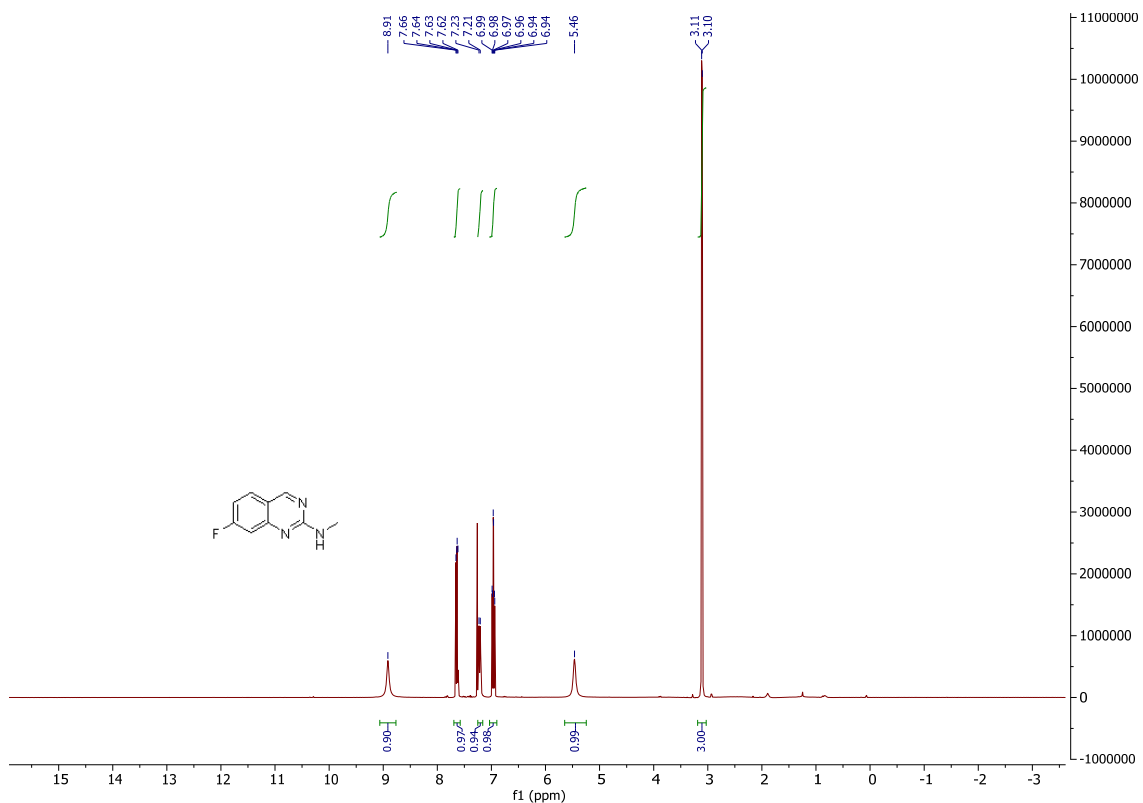
6-(benzyloxy)-N-methylquinazolin-2-amine (8b)



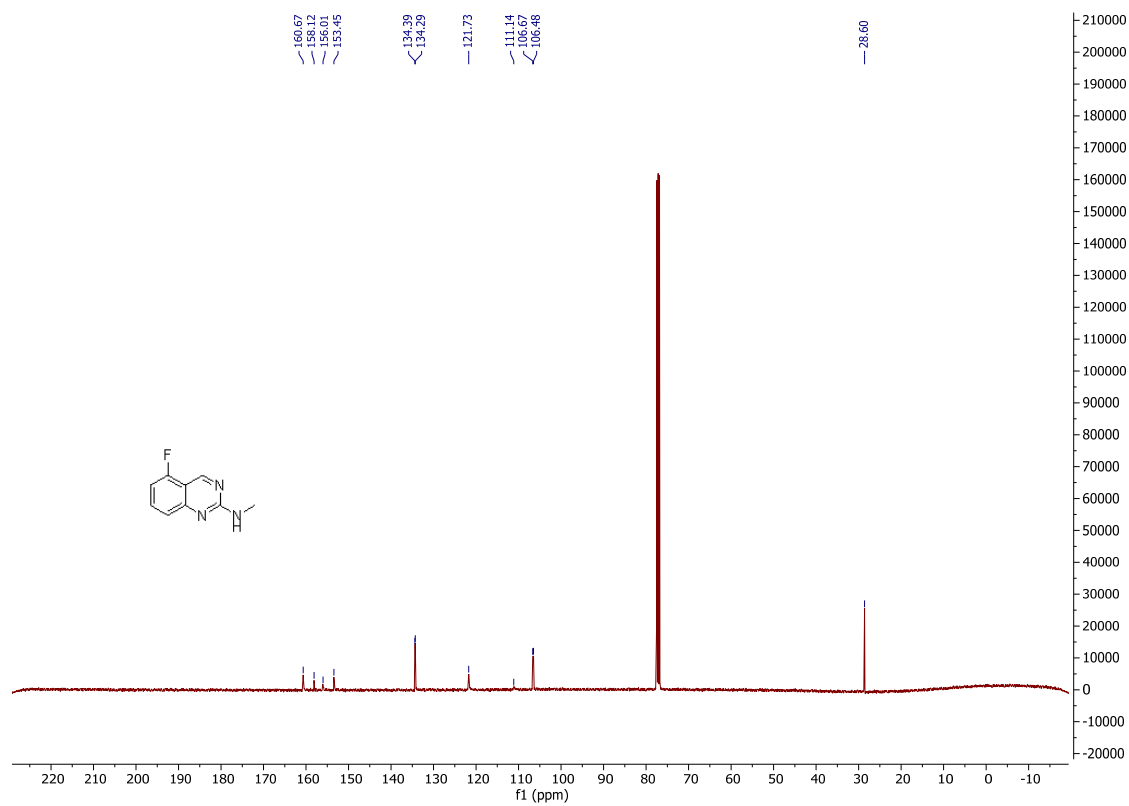
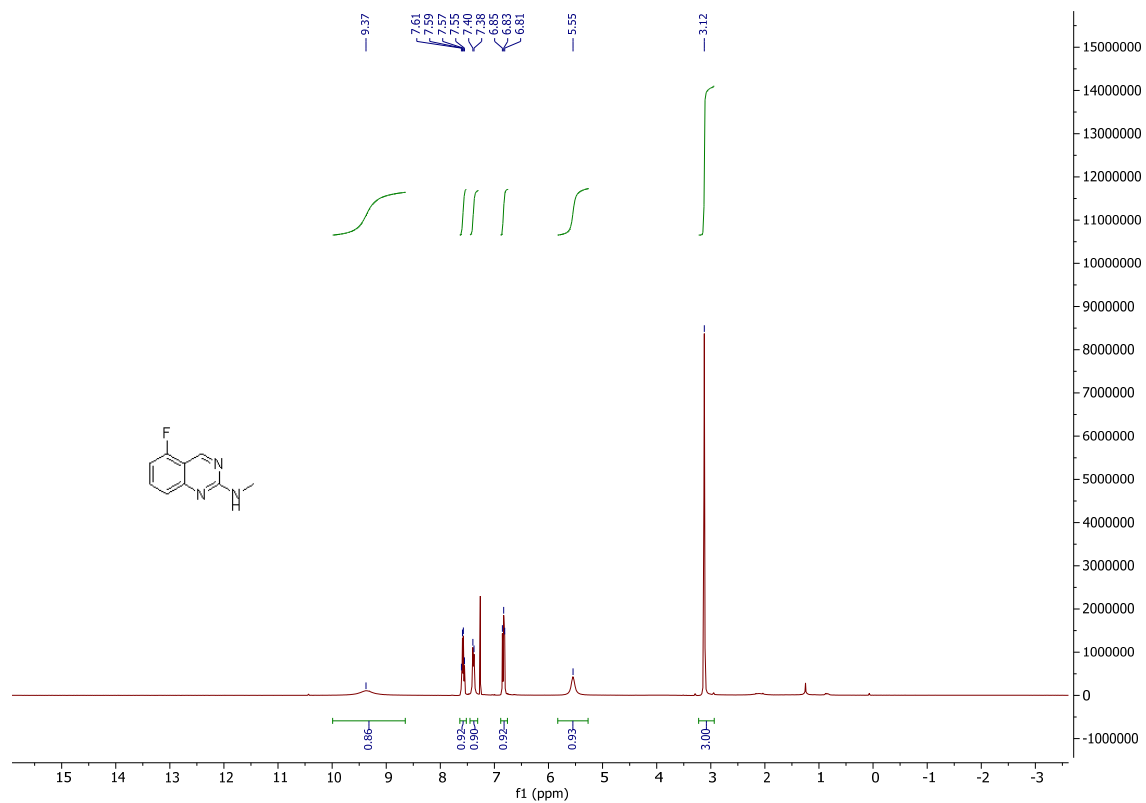
7-methoxy-N-methylquinazolin-2-amine (8c)



7-fluoro-N-methylquinazolin-2-amine (8d)



5-fluoro-N-methylquinazolin-2-amine (8e)



7-chloro-N-methylquinazolin-2-amine (8f)

