Ortho-lithiation driven one-pot synthesis of quinazolines *via* [2+2+2] cascade annulation of halofluorobenzenes with nitriles

Jen-Chun Hsueh, Fu-En Szu, Yin-Yin Yu, Man-kit Leung*

Department of Chemistry, National Taiwan University, Taipei 106, Taiwan

Email: mkleung@ntu.edu.tw

List of content:

General Procedure for the synthesis of compound (19), (22), (23) and (26).

A two-neck flask under argon atmosphere was charged with Cs_2CO_3 (488.7 mg, 1.5 mmol), 5-fluoro-2,4-diphenylquinazoline or 8-fluoro-2,4-diphenylquinazoline (1.0 mmol), 9H-carbozole/9'H-9,3':6',9''-tercarbazole (1.5 mmol), Dry and de-aerated Dimethyl sulfoxide (1 mL) was added. The mixture was heated to 130 °C and stirred for 24 h. Then, the crude product was extracted with dichloromethane and brine, then dried over anhydrous $MgSO_4$. The solvent was evaporated by vacuum and the crude product was purified by column chromatography on silica gel (DCM/Hexane = 1/2 or 1/4).

General Procedure for the synthesis of compound (20), (21), (24) and (25).

A two-neck flask under argon atmosphere was charged with $Pd_2(dba)_3$ (229 mg, 0.1 mmol), 6-bromo-2,4-diphenylquinazoline or 7-bromo-2,4-diphenylquinazoline (720 mg, 2.0 mmol), sodium tert-butoxide (721 mg, 3.0 mmol), XPhos (238mg, 0.2mmol) and 9H-carbozole/9'H-9,3':6',9''-tercarbazole (2.2 mmol). Dry and de-aerated toluene (10 mL) was added. The mixture was refluxed for 15 h. After cooling, the reaction mixture was diluted with dichloromethane and filtered through celite, then dried over anhydrous $MgSO_4$. The solvent was evaporated by vacuum and the crude product was purified by column chromatography on silica gel (DCM/Hexane = 1/3).

Photophysical data for compound 19-26

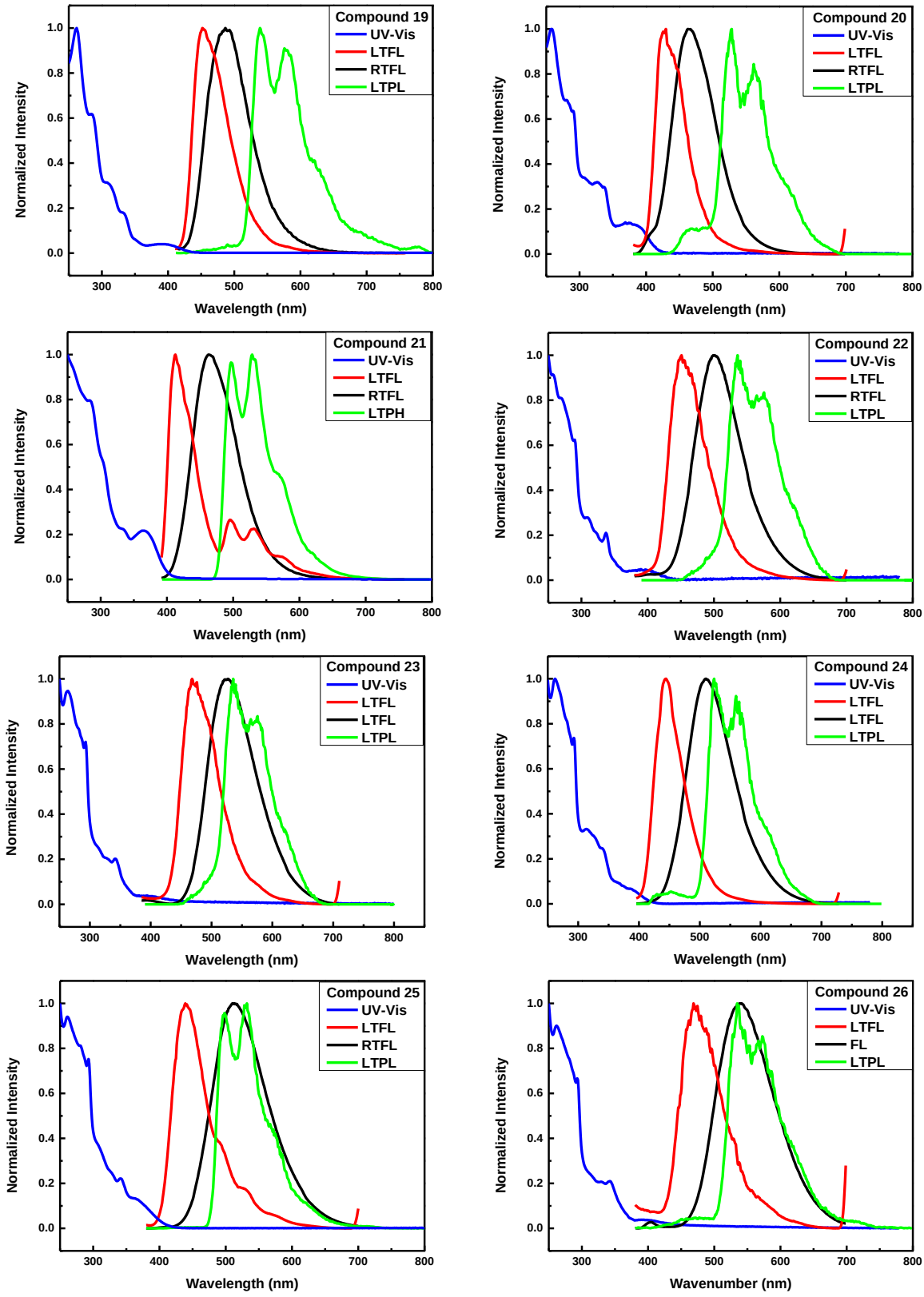


Figure S1. UV/Vis and photoluminescence spectrum for compound **19-26**.

Compound **19-26** was prepared at a concentration of 1.0×10^{-5}M in spectroscopic grade Tetrahydrofuran (THF), and UV-visible absorption spectrum and fluorescence emission spectrum (FL) were collected at room temperature. Subsequently, the compound was dissolved in spectroscopic grade 2-Methyltetrahydrofuran (2-MeTHF) at the same concentration, and low temperature fluorescence emission spectrum (LTFL) and low temperature phosphorescence emission spectrum (LTPH) were measured at 77 K.

Table S1. UV/Vis and photoluminescence data for compound **19-26**.

Compound	$\lambda_{onset}{}^{abs}$ (nm)	E_g (eV)	$\lambda_{max}{}^{RTFL}$, $\lambda_{max}{}^{LTFL}$, $^{c}\lambda_{onset}{}^{LTPH}$ (nm)	E_T (eV)	Φ^{*} (%)
19	422	2.94	487, 452, 512	2.42	0.46
20	399	3.11	463, 430, 491	2.53	0.82
21	420	2.95	463, 413, 476	2.42	0.14
22	413	3.00	499, 451, 494	2.51	0.17
23	428	2.90	527, 468, 508	2.44	0.29
24	406	3.06	510, 445, 494	2.51	0.69
25	401	3.09	514, 439, 475	2.61	0.46
26	425	2.92	542, 469, 503	2.47	0.16

*Fluorescence quantum yield was determined relative to coumarin 6 in toluene as standard (Φ = 78%) at 300 K.

Experiment data for the synthesis of quinazoline with 1,3-difluorobenzne and alkyl cyanide.

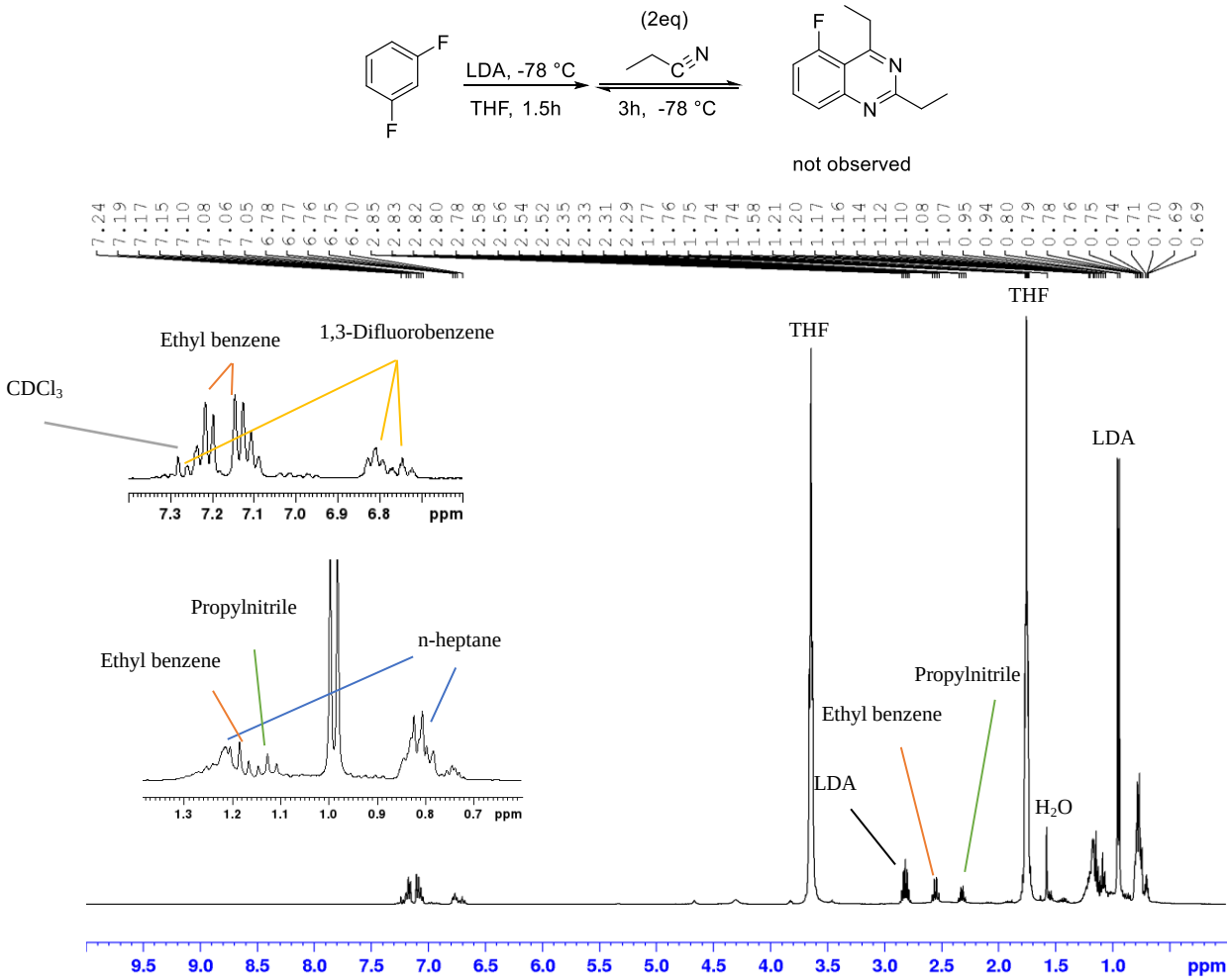


Figure S2. The ^{1}H NMR (in $CDCl_3$) of the crude product derived from the reaction of 1,3-difluorobenzene and propylnitrile. Ethyl benzene and n-heptane are the solvent in the solution of LDA.

Experiment data for the synthesis of quinazoline (18)

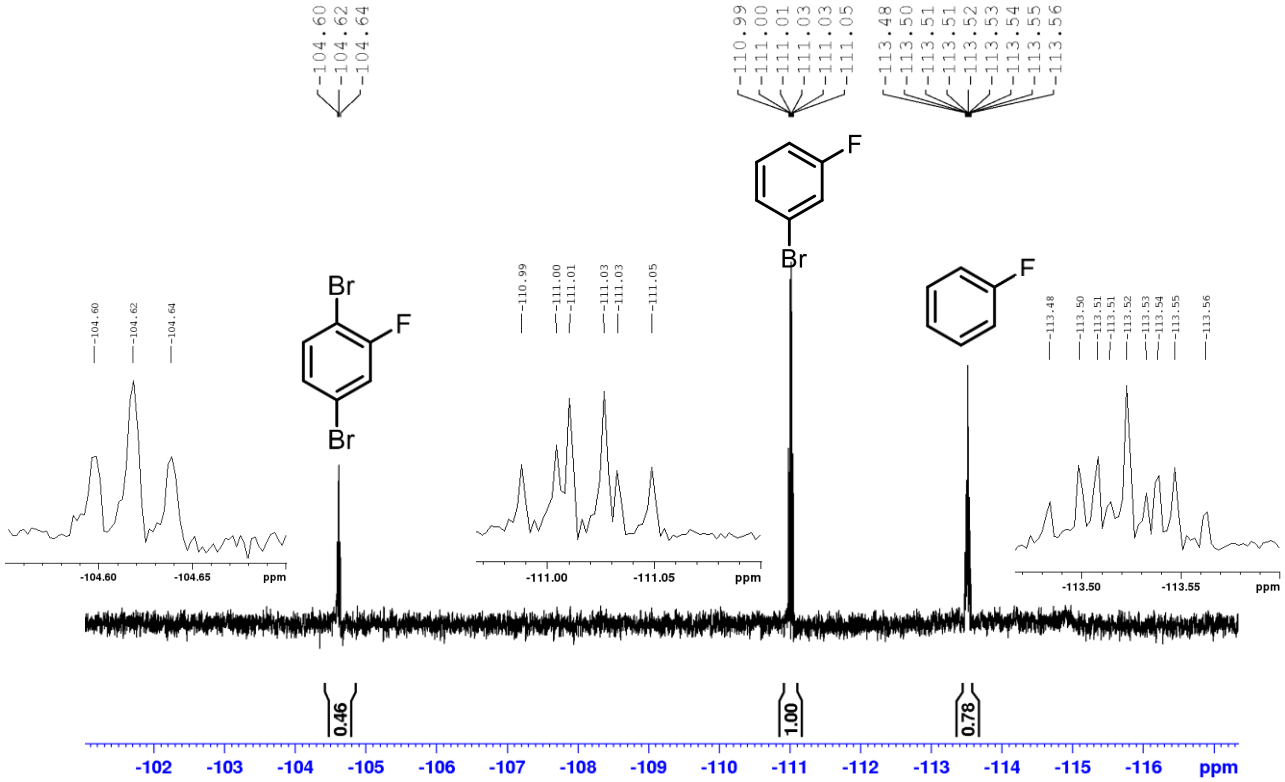


Figure S3. ^{19}F NMR spectrum (in $CDCl_3$) of 1,4-dibromo-2-fluorobenzene after bromine-lithium exchange with *n*-butyllithium. The crude was quenched by water.

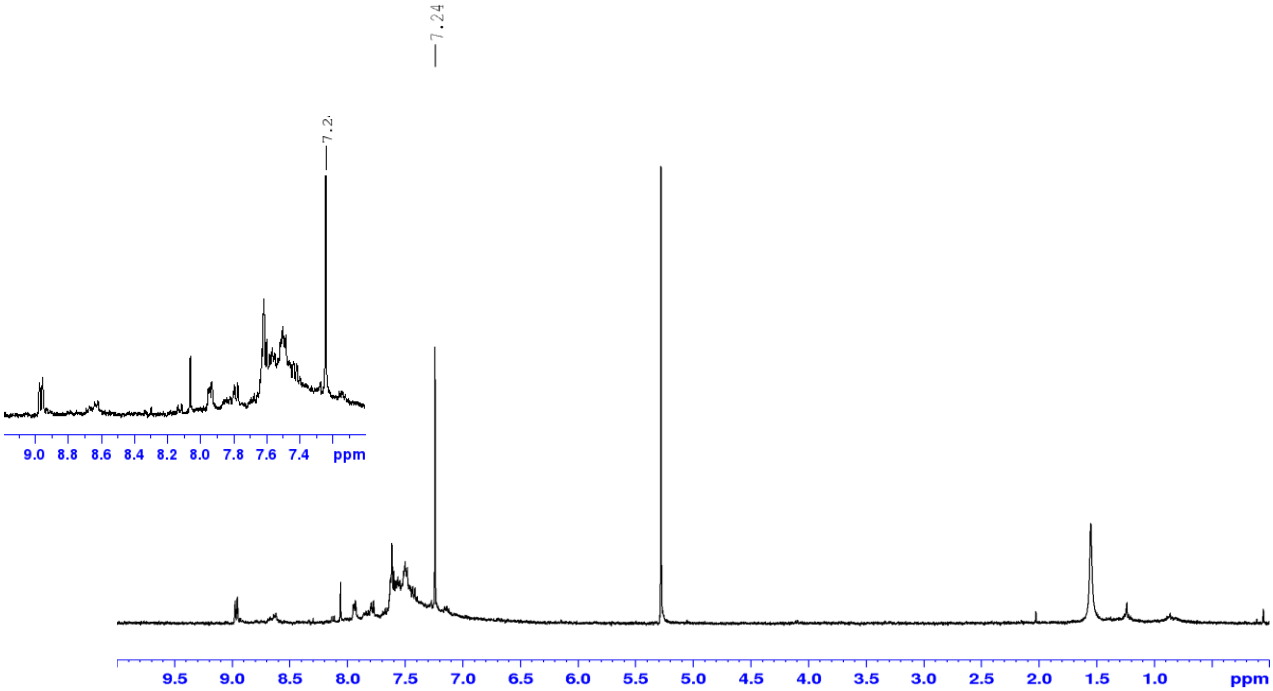
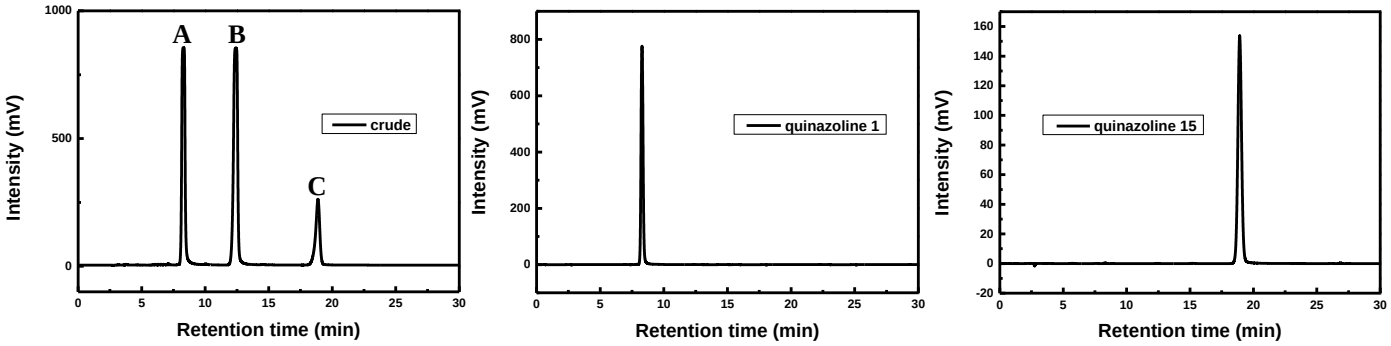


Figure S4. The lithiated intermediated **I-5** could initiate the condensation of benzonitrile to form oligomer product, the ^1H NMR ($CDCl_3$) is shown above.

Experiment data for the synthesis of quinazoline with 1,3-difluorobenzene, benzonitrile and 3,5-dimethylbenzonitrile.



NO.	Area	Retention Time (min)	Quinazoline
A	15498350	8.296	1
B	19540150	12.407	27、28
C	6029028	18.882	15

Figure S5. HPLC chromatogram of the quinazoline mixture derived from the reaction of 1,3-difuorobenzene, benzonitrile and 3,5-dimethylbenzonitrile.

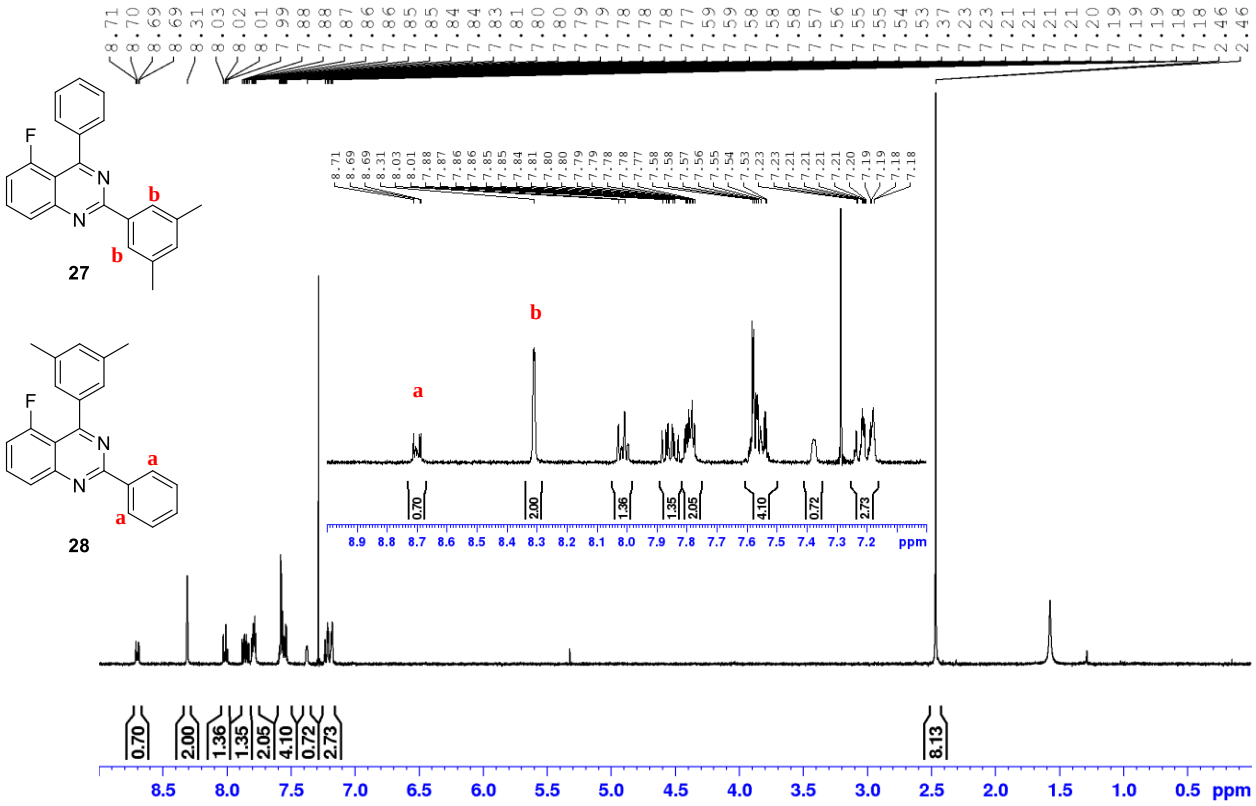
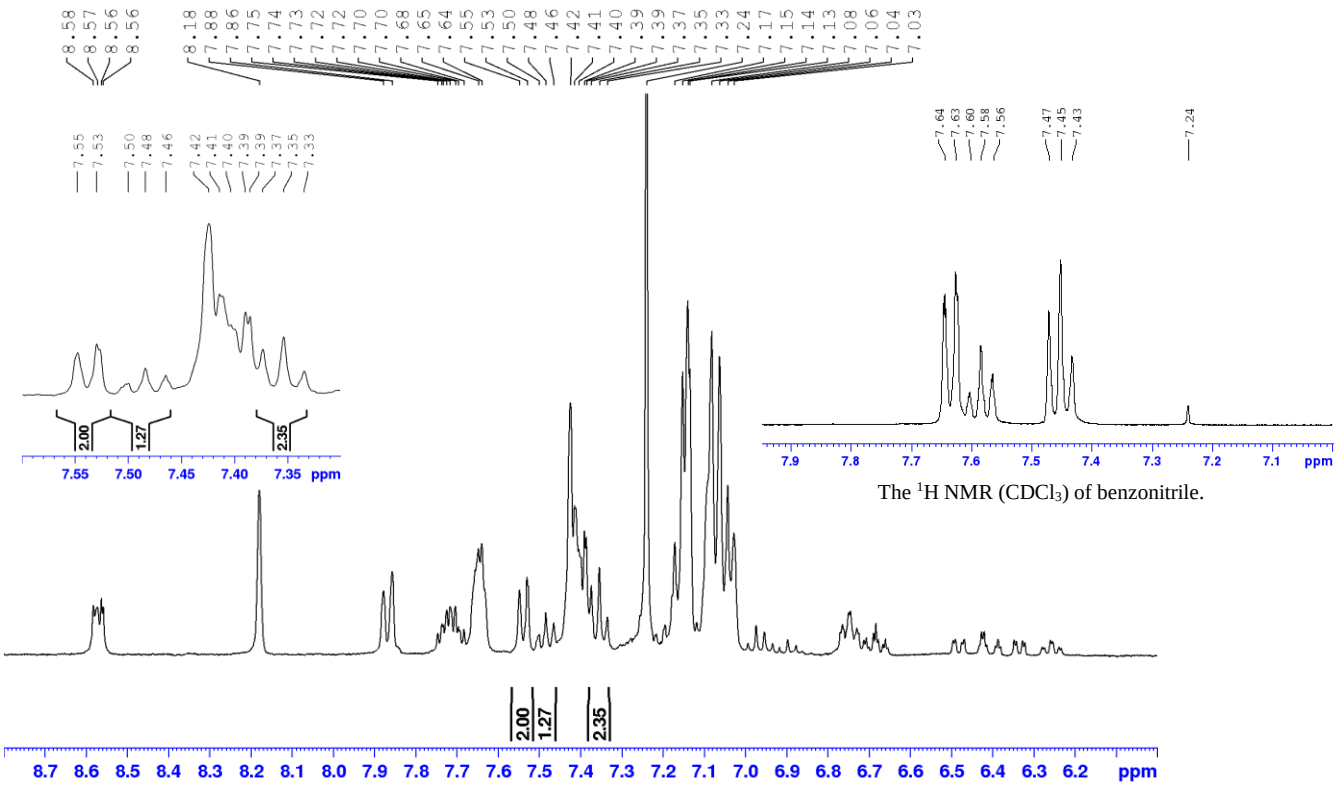


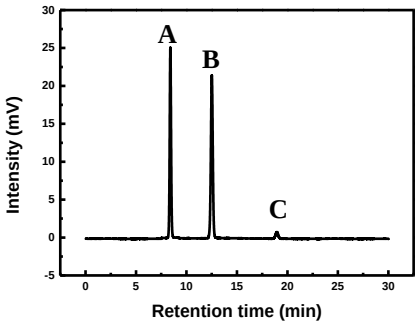
Figure S6. The ^{1}H NMR of peak **B**, which derived from the reaction of 1,3-difluorobenzene, benzonitrile and 3,5-dimethylbenzonitrile. The multiplet (δ 8.72-8.62 ppm) is the characteristic peak of quinazoline **28**, while singlet (δ 8.31 ppm) is the characteristic peak of quinazoline **27**, and the ratio between **27** and **28** is approximately (1:0.35).

Experiment data for the synthesis of quinazoline with 2,6-difluorobenzophenone imine and 3,5-dimethylbenzonitrile



The ^{1}H NMR ($CDCl_3$) of benzonitrile.

Figure S7. Starting from **2,6-difluorobenzophenone imine**, lithiation was carried out by LDA, followed by reaction with 3,5-dimethylbenzonitrile to produce quinazoline. The ^{1}H NMR spectrum ($CDCl_3$) of the crude above shows the presence of benzonitrile, suggesting that **2,6-difluorobenzophenone imine** could undergo reversible reaction to form benzonitrile and intermediate **I-6**.



NO.	Area	Retention Time (min)	Quinazoline
A	245236	8.405	1
B	287755	12.512	27、28
C	16337	18.943	15

Figure S8. The HPLC chromatogram of quinazoline mixture derived from the reaction of **2,6-difluorobenzophenone imine** and 3,5-dimethylbenzonitrile. The result also suggests that the existence of quinazoline **1**、**15**、**27**、**28**.

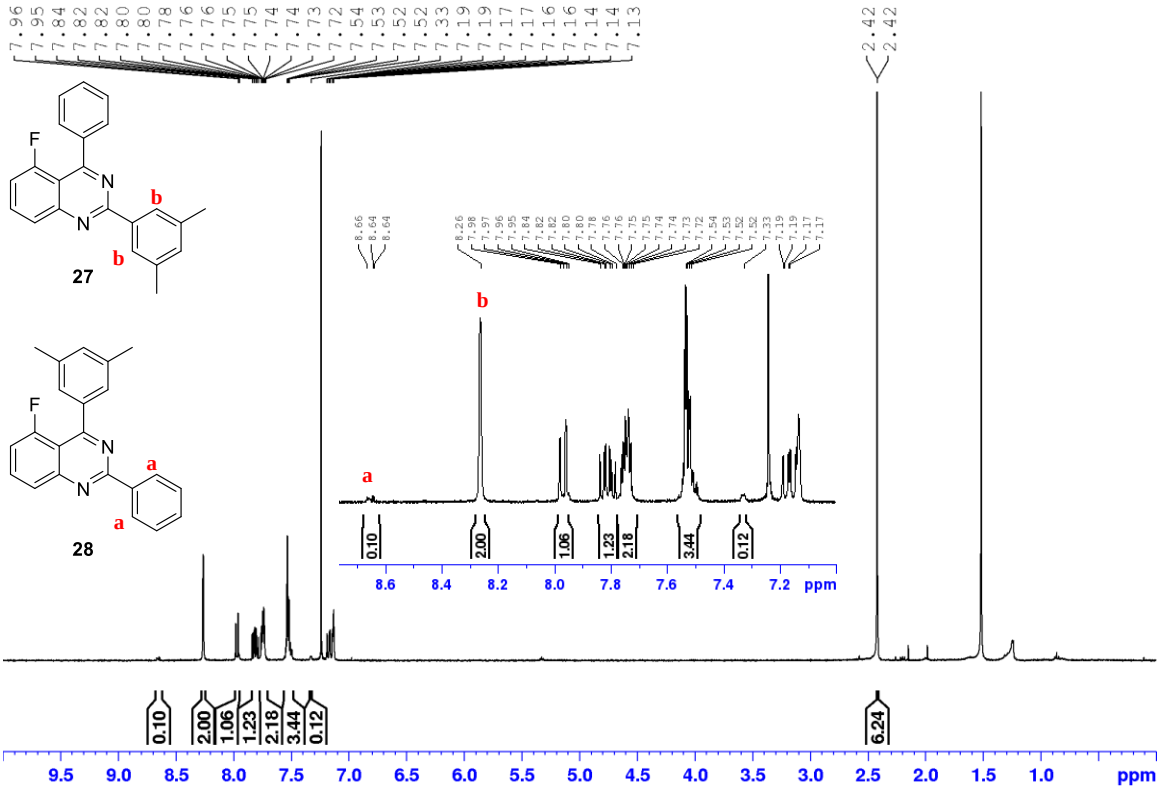
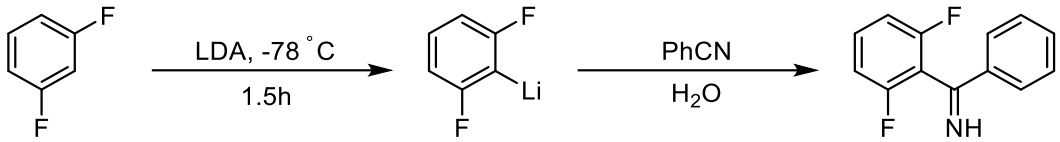


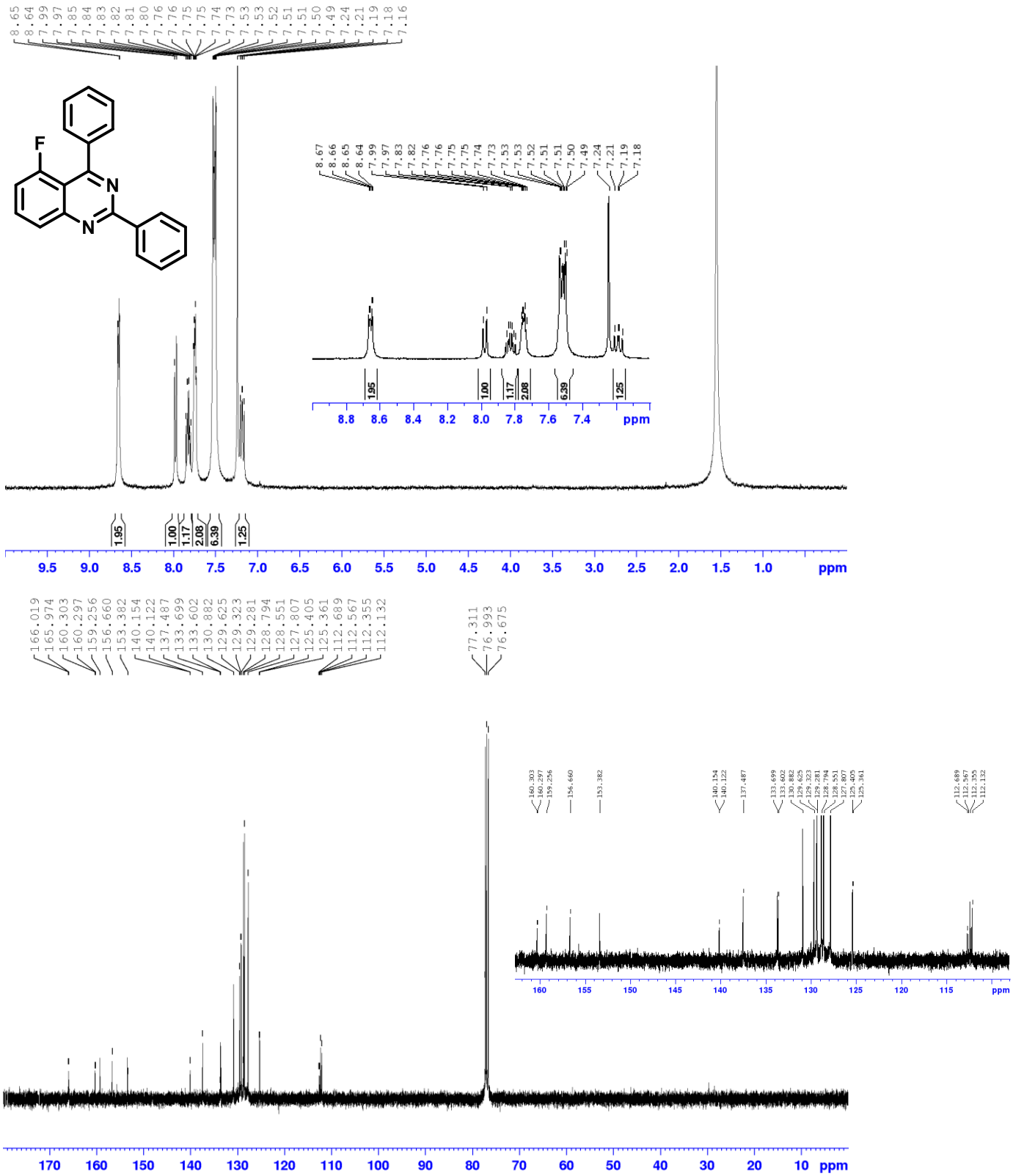
Figure S9. The ^{1}H NMR ($CDCl_3$) of peak **B**, which derived from the reaction of **2,6-difluorobenzophenone imine** and 3,5-dimethylbenzonitrile. The multiplet (δ 8.67-8.63 ppm) is the characteristic peak of quinazoline **28**, while singlet (δ 8.26 ppm) is the characteristic peak of quinazoline **27**, and the ratio between **27** and **28** is approximately (1:0.05).

General procedures for the synthesis of 2,6-difluorobenzophenone imine

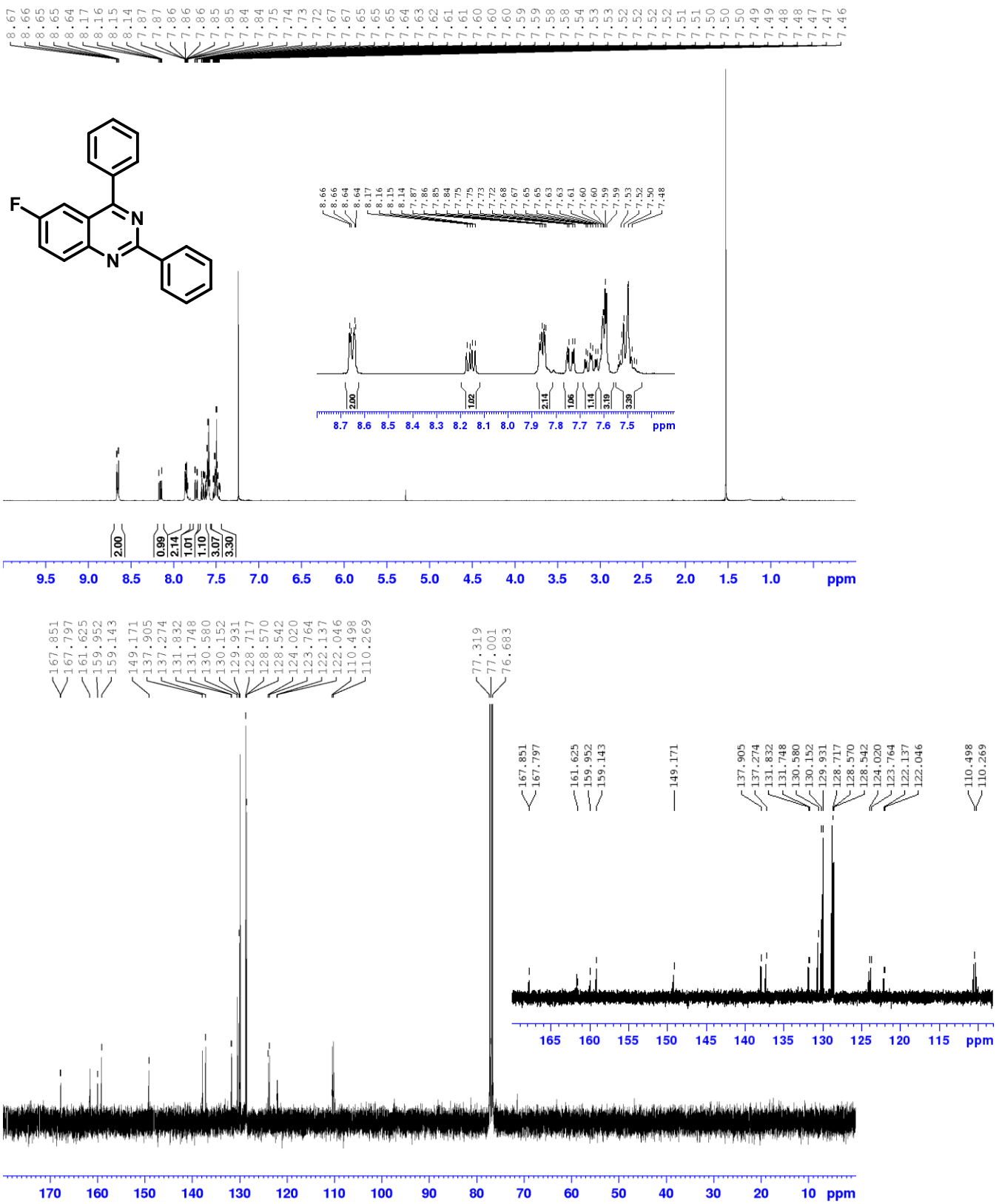


A sealed Schlenk tube under argon atmosphere was charged with anhydrous THF (2 ml) and 1,3-Difluorobenzene (2 mmol), following by cooling down the mixture to -78 °C. A solution of lithium diisopropylamide (2M in THF, 4.4 mmol) was added dropwise to the above mixture and stirred for 1.5 h, then anhydrous benzonitrile (2.2 mmol) was injected. The mixture was stirred for 3.0 h at -78 °C. The mixture was quenched by water. The combined organic layer was extracted with dichloromethane and brine, then dried over anhydrous $MgSO_4$. The solvent was evaporated by vacuum and the crude product was purified by column chromatography on silica gel (DCM) to give **2,6-difluorobenzophenone imine** (68%).

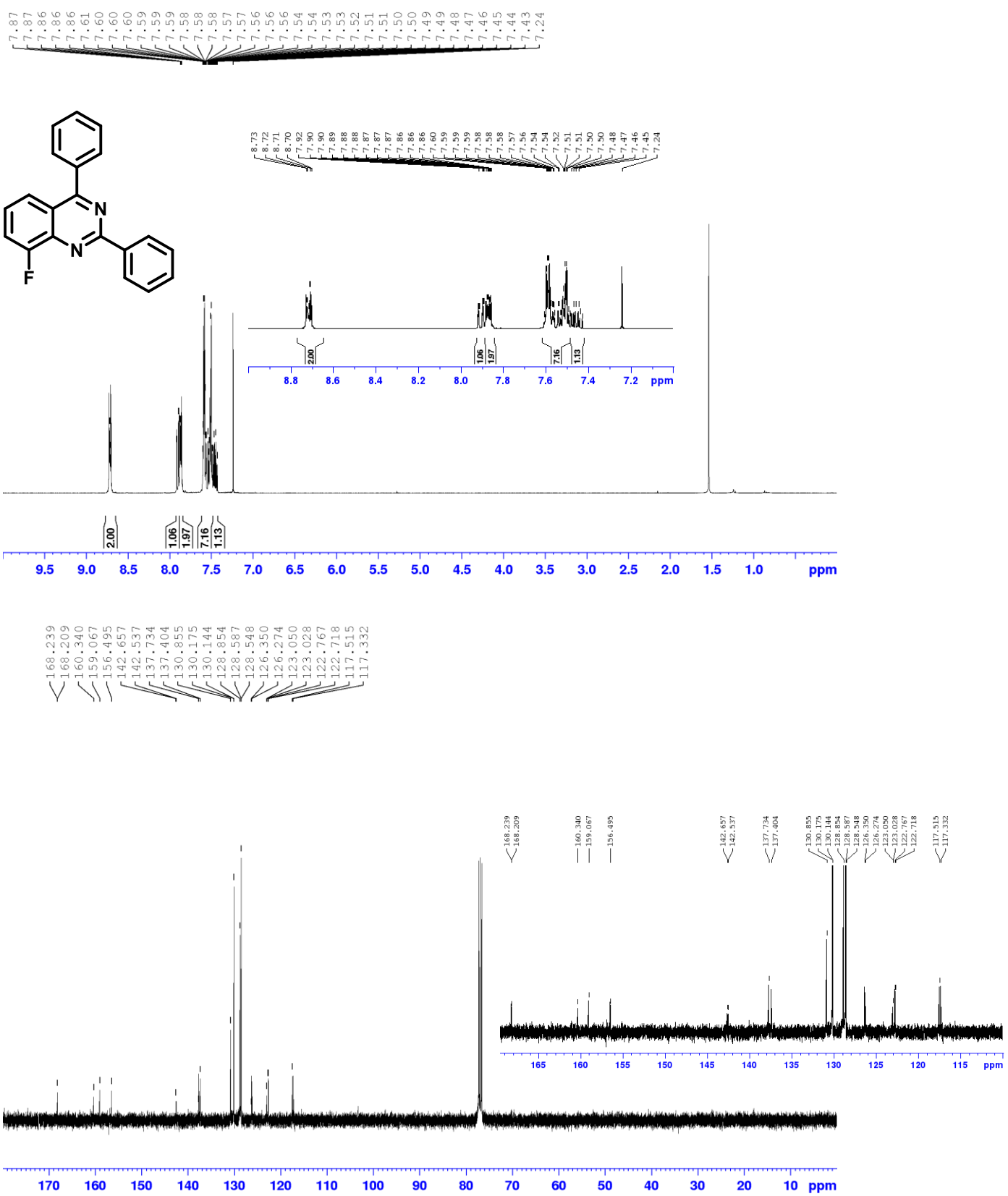
^{1}H and ^{13}C NMR spectra of compounds



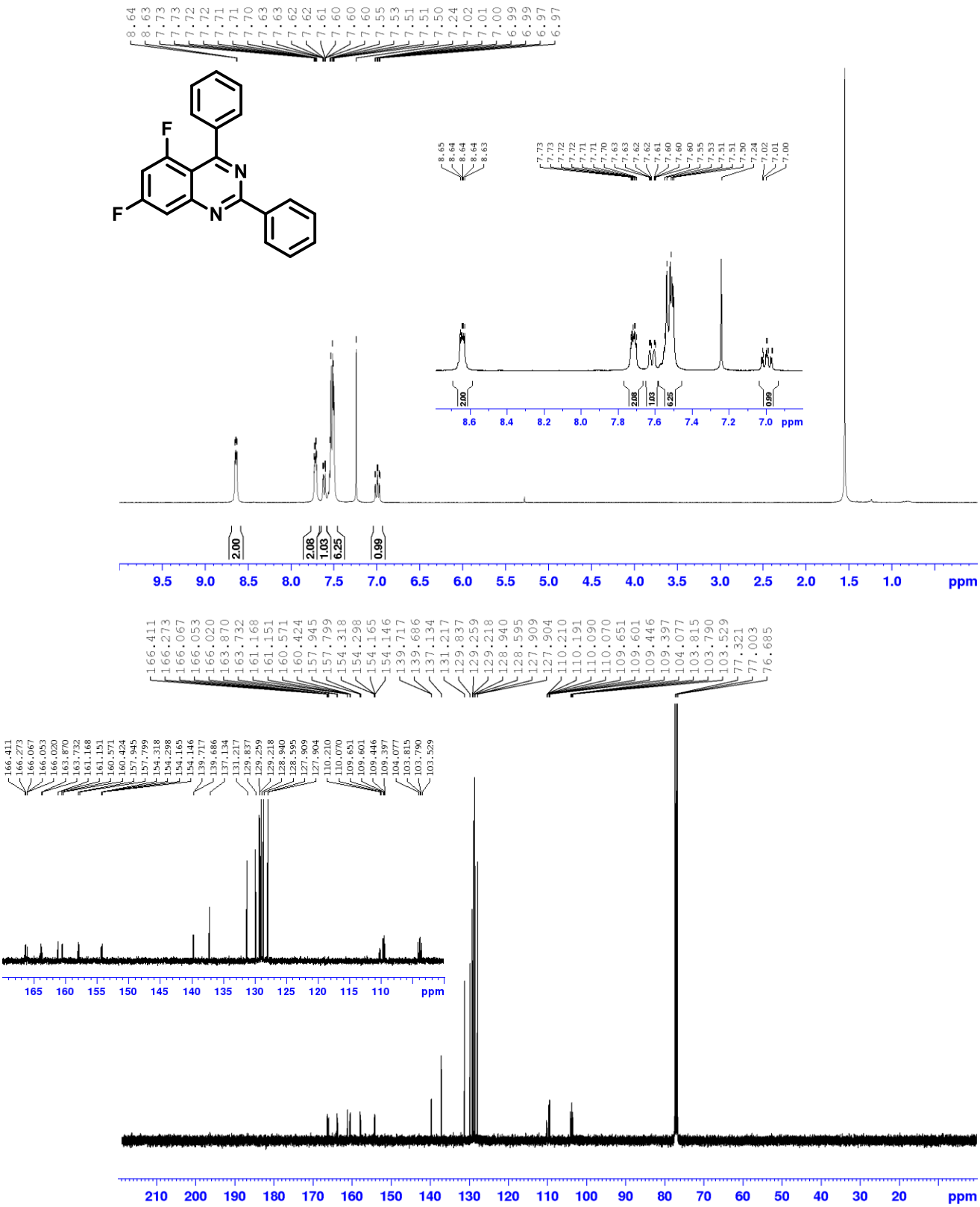
^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **1**



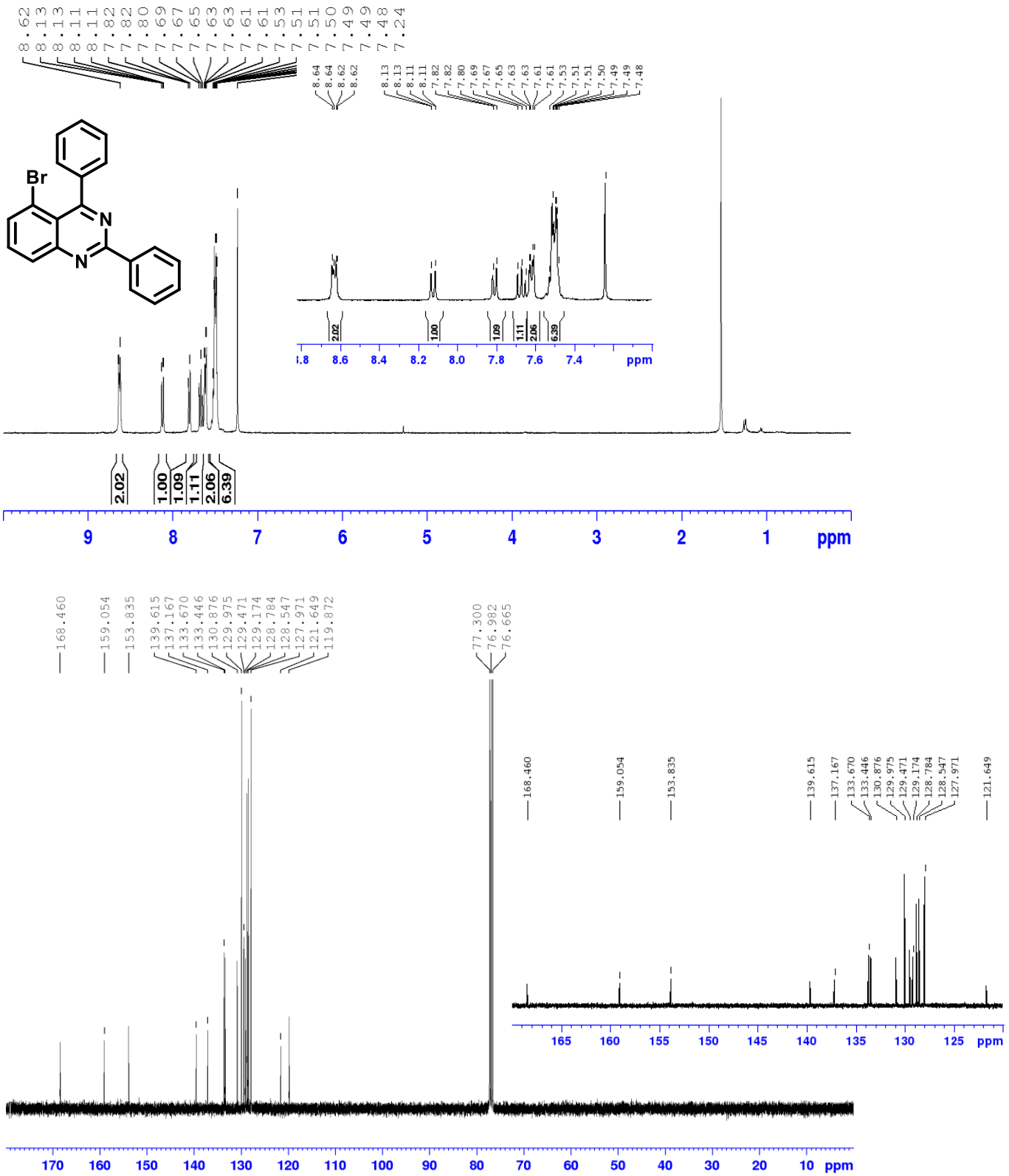
^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **2**



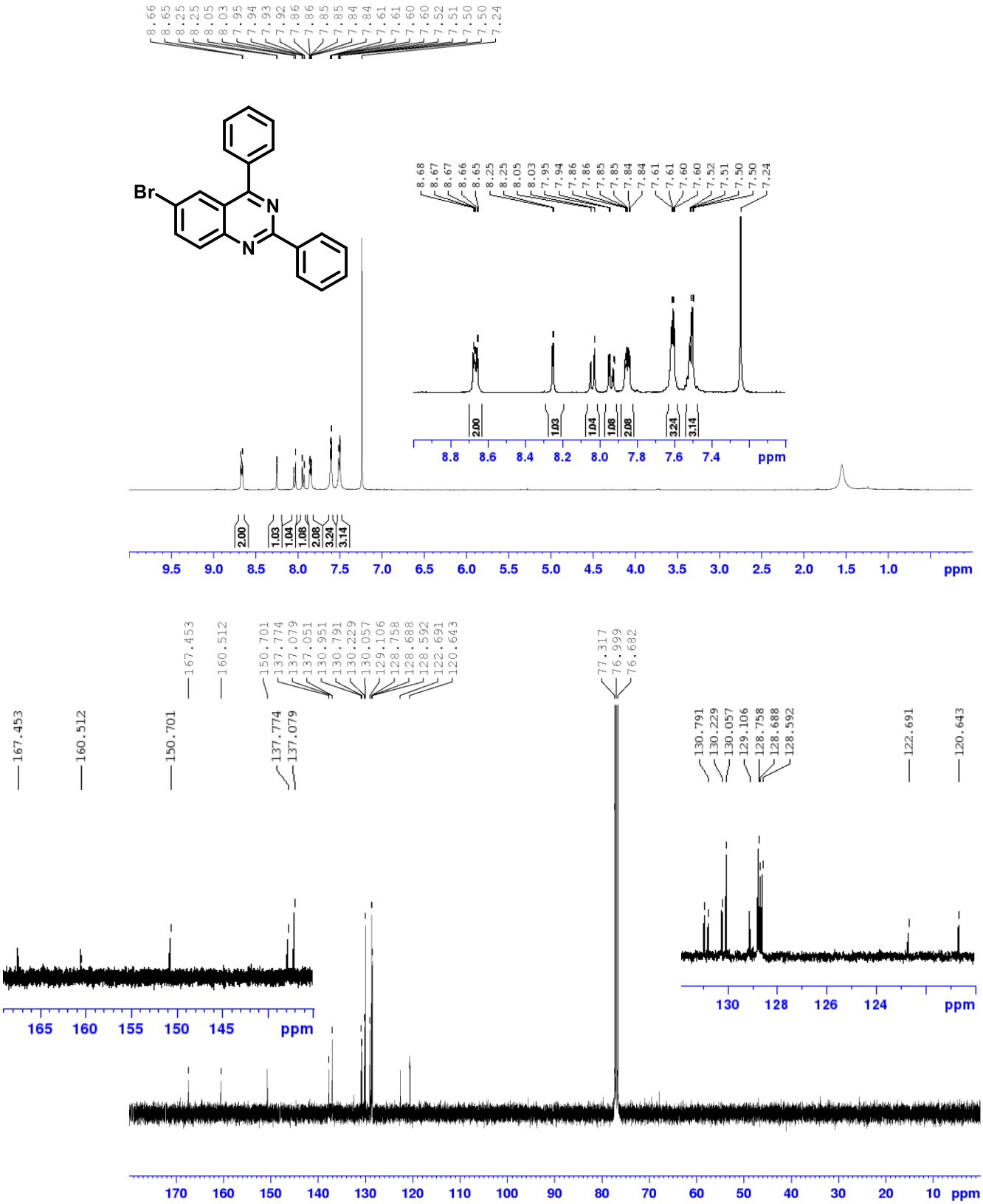
^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **3**



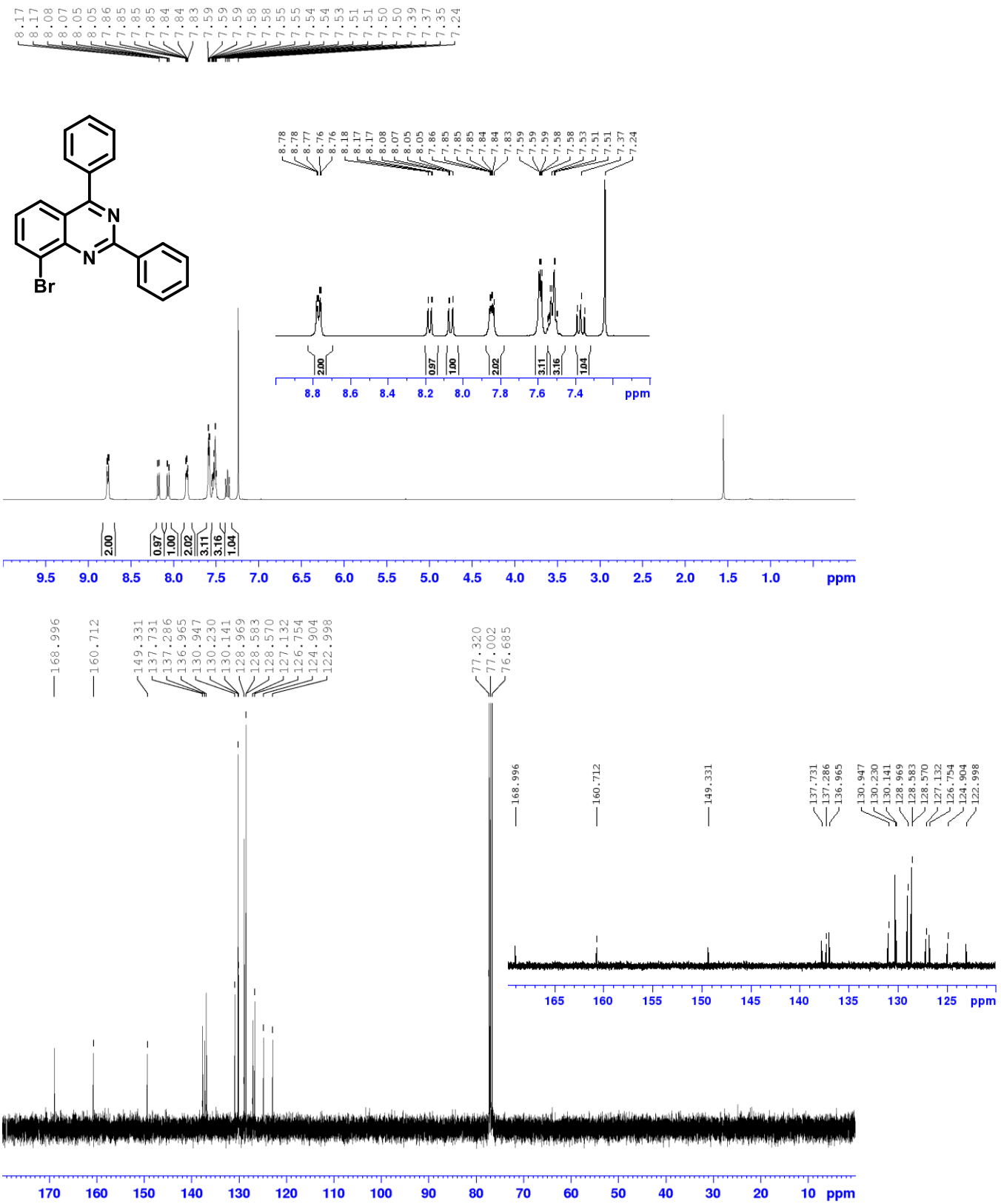
^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **4**



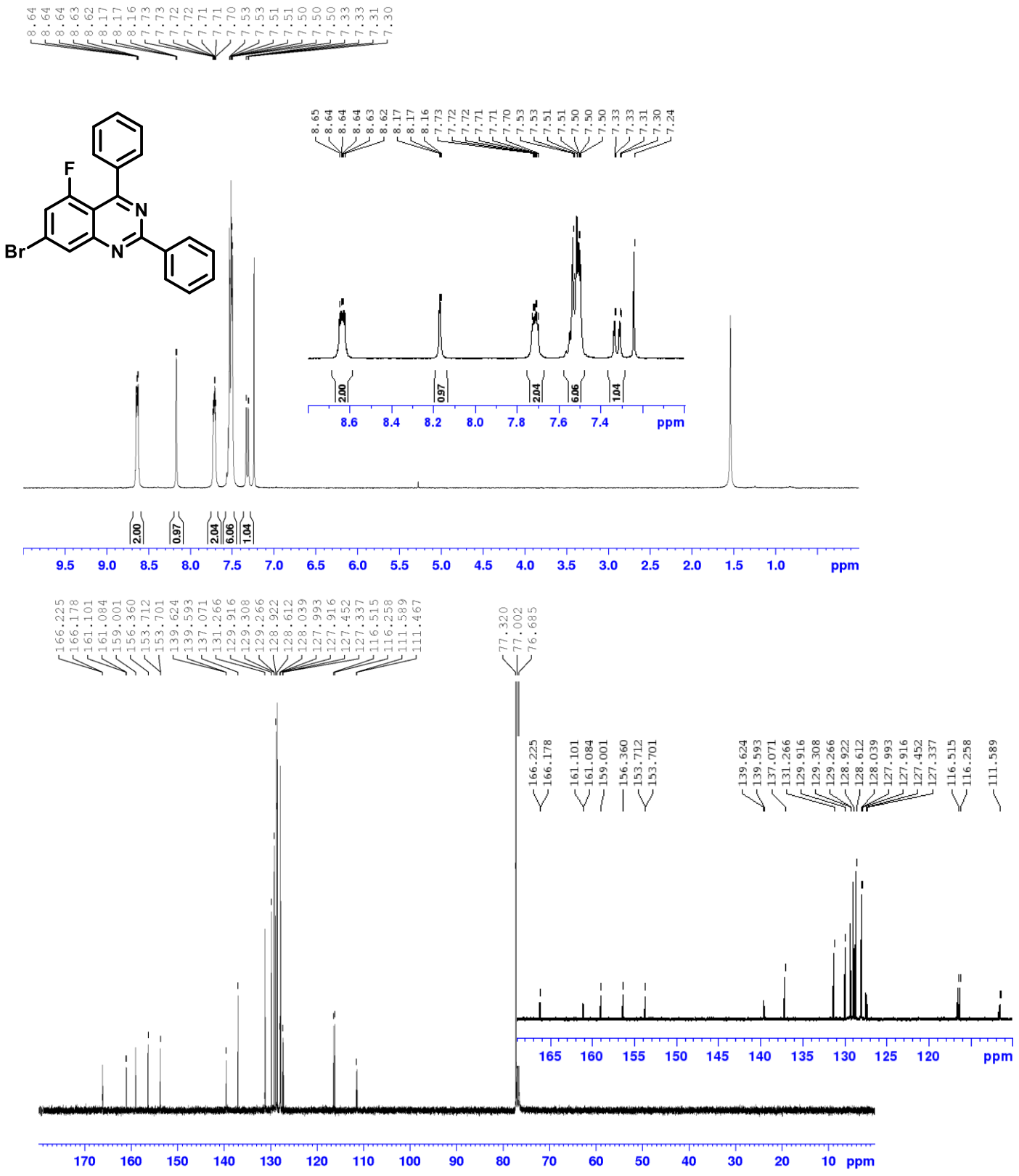
^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **5**



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **6**

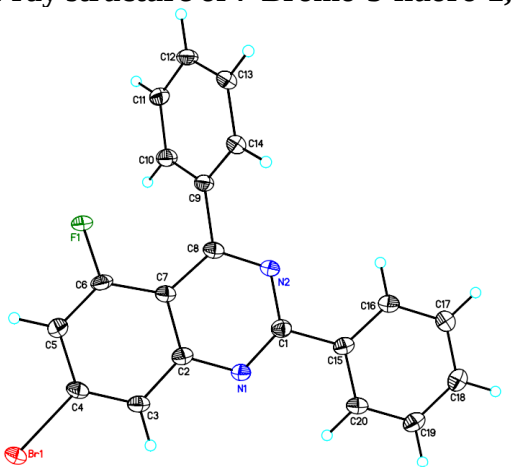


^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **7**



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **8**

X-ray structure of 7-Bromo-5-fluoro-2,4-diphenylquinazoline (8) (CCDC 2248146).



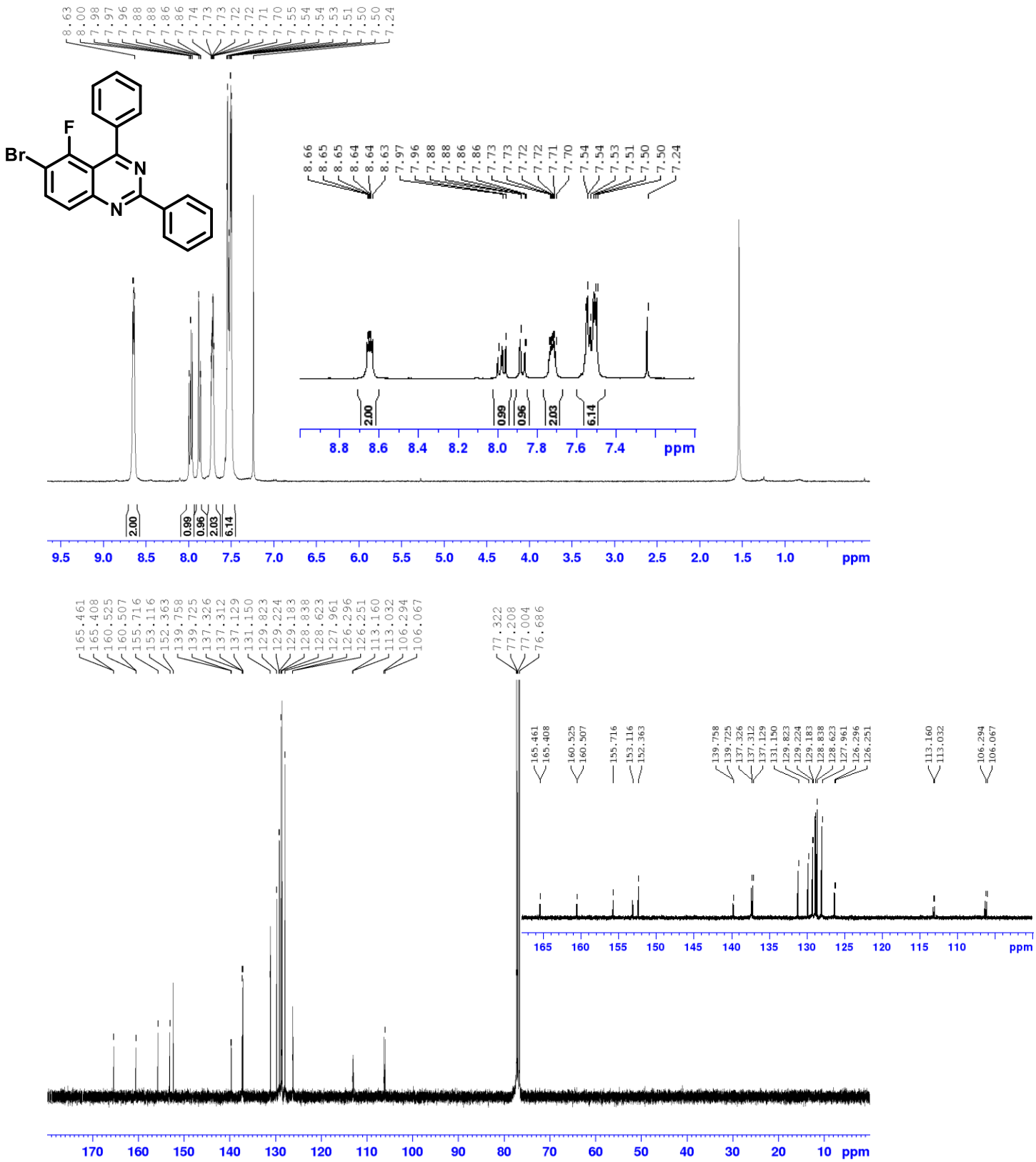
The single crystals of compound **8** were obtained by slow evaporation of its DCM/hexane (3/1) solution.

Empirical formula	C20 H12 Br F N2	
Formula weight	379.23	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 4.1687(2) Å	α= 68.5349(18)°.
	b = 12.4116(7) Å	β= 85.512(2)°.
	c = 15.8272(9) Å	γ = 81.5452(19)°.
Volume	753.56(7) $Å^3$	
Z	2	
F(000)	380	
Density (calculated)	1.671 Mg/m^3	
Wavelength	1.54178 Å	
Cell parameters reflections used	9966	
Theta range for Cell parameters	3.00 to 74.40°.	
Absorption coefficient	3.835 mm^{-1}	
Temperature	100(2) K	
Crystal size	0.250 x 0.080 x 0.050 mm^3	

Data collection

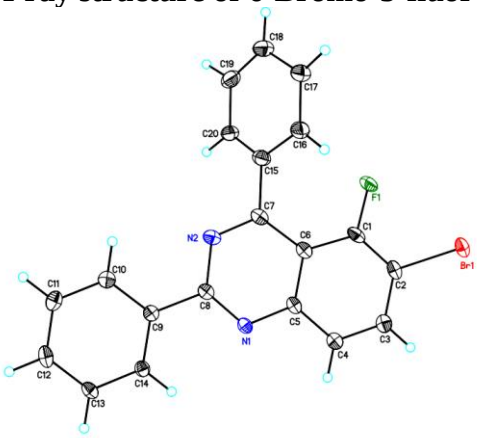
Diffractometer	Bruker AXS D8 VENTURE, PhotonIII_C28
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.7584
No. of measured reflections	11806
No. of independent reflections	2948 [R(int) = 0.0420]
No. of observed [I>2_igma(I)]	2837
Completeness to theta = 67.679°	98.3 %

Theta range for data collection	3.001 to 74.430°.
	Refinement
Final R indices [I>2sigma(I)]	R1 = 0.0298, wR2 = 0.0811
R indices (all data)	R1 = 0.0312, wR2 = 0.0825
Goodness-of-fit on F^2	1.079
No. of reflections	2948
No. of parameters	217
No. of restraints	0
Largest diff. peak and hole	0.437 and -0.735 e.$Å^{-3}$



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **9**

X-ray structure of 6-Bromo-5-fluoro-2,4-diphenylquinazoline (9) (CCDC 2248148).



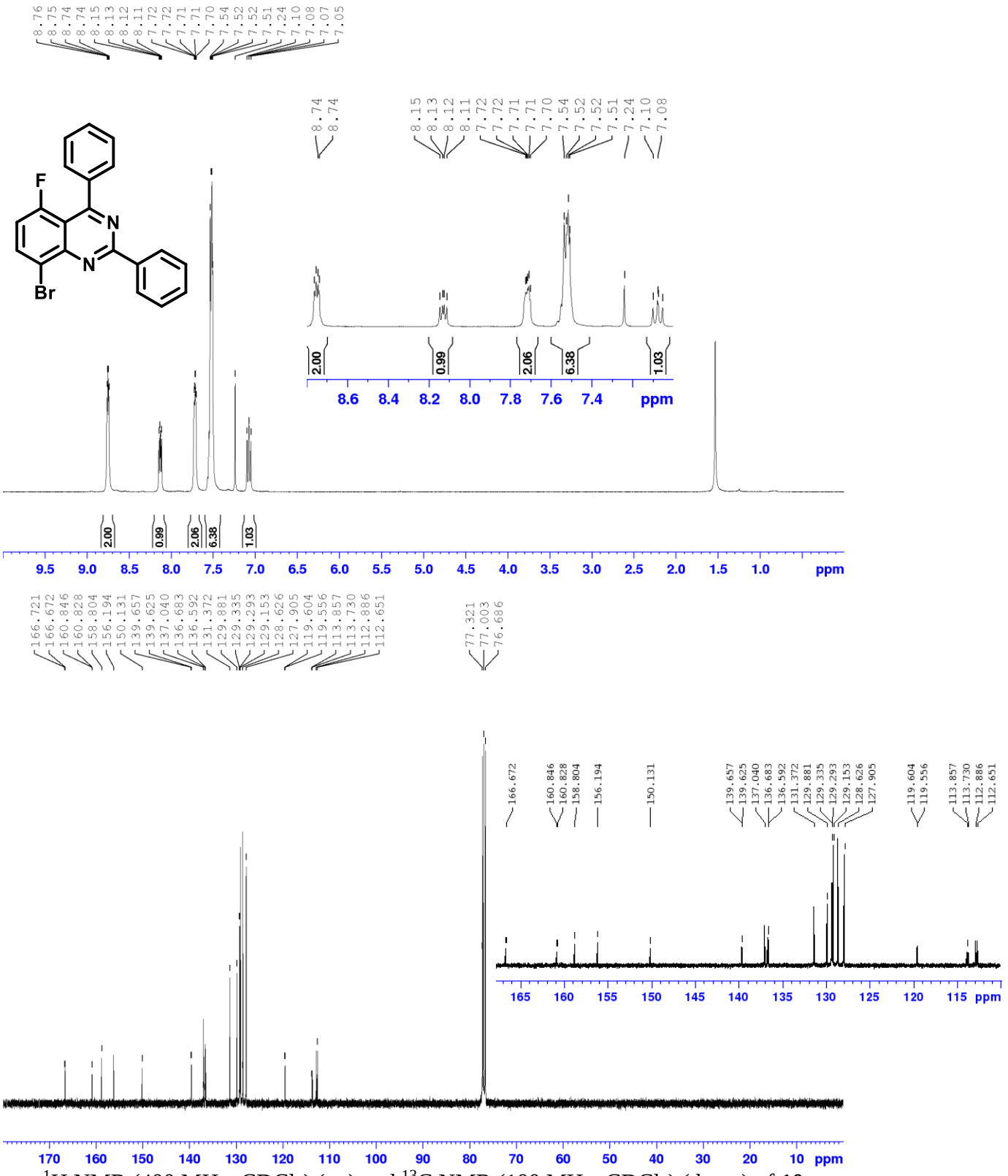
The single crystals of compound **9** were obtained by slow evaporation of its DCM/hexane (3/1) solution.

Empirical formula	C20 H12 Br F N2	
Formula weight	379.23	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 16.4004(10) Å	α= 90°.
	b = 4.9641(3) Å	β= 107.5625(18)°.
	c = 19.8649(12) Å	γ = 90°.
Volume	1541.88(16) $Å^3$	
Z	4	
F(000)	760	
Density (calculated)	1.634 Mg/m^3	
Wavelength	1.54178 Å	
Cell parameters reflections used	9173	
Theta range for Cell parameters	2.83 to 78.08°.	
Absorption coefficient	3.749 mm^{-1}	
Temperature	100(2) K	
Crystal size	0.400 x 0.100 x 0.050 mm^3	

Data collection

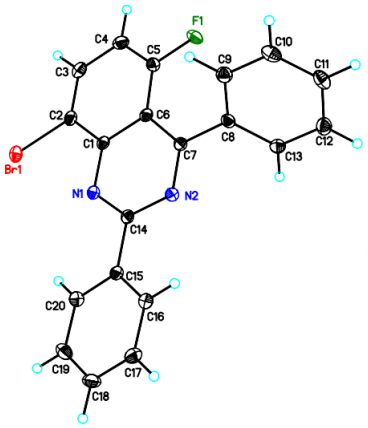
Diffractometer	Bruker AXS D8 VENTURE, PhotonIII_C28
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.7660
No. of measured reflections	28264
No. of independent reflections	3206 [R(int) = 0.0394]
No. of observed [I>2_igma(I)]	3128
Completeness to theta = 67.679°	99.6 %
Theta range for data collection	2.826 to 78.665°.

Refinement	
Final R indices [I>2sigma(I)]	R1 = 0.0412, wR2 = 0.1008
R indices (all data)	R1 = 0.0421, wR2 = 0.1013
Goodness-of-fit on F^2	1.195
No. of reflections	3206
No. of parameters	248
No. of restraints	390
Largest diff. peak and hole	0.591 and -0.980 e.$Å^{-3}$



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **10**

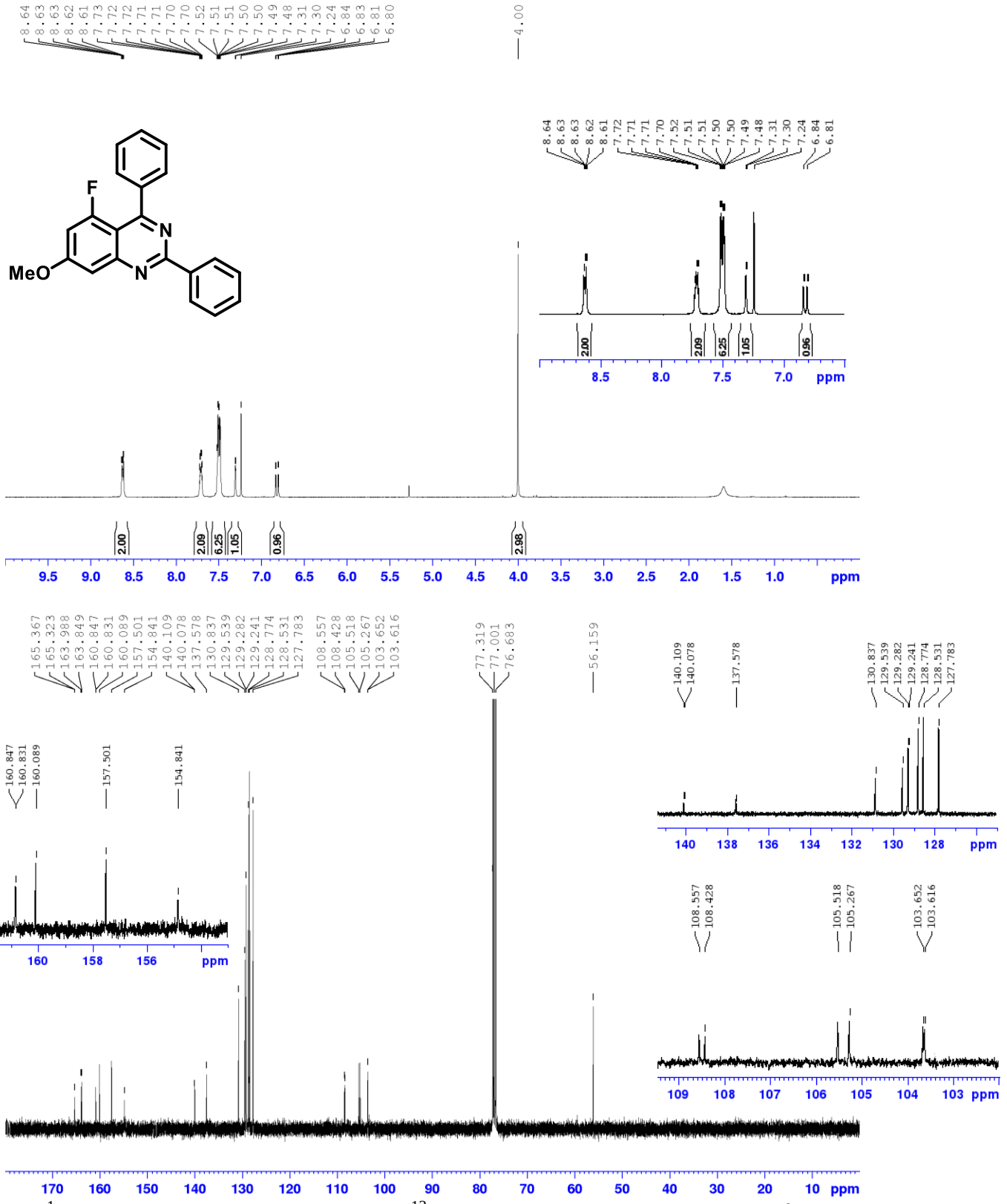
X-ray structure of 8-bromo-5-fluoro-2,4-diphenylquinazoline (10) (CCDC 2248147).



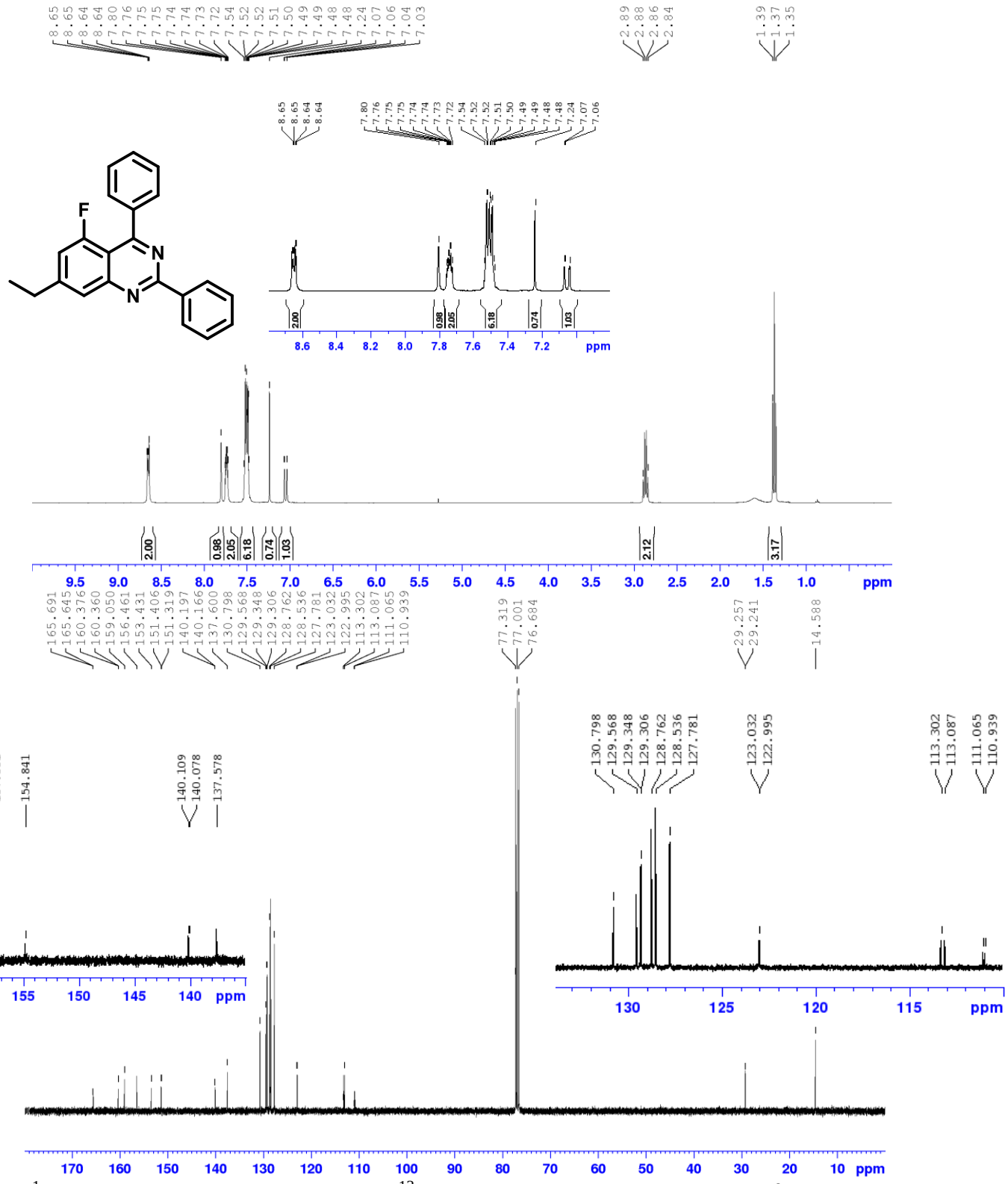
The single crystals of compound **10** were obtained by slow evaporation of its DCM/hexane (3/1) solution.

Empirical formula	C20 H12 Br F N2	
Formula weight	379.23	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.3882(2) Å	α= 93.6965(6)°.
	b = 9.8687(3) Å	β= 93.9425(6)°.
	c = 21.9346(6) Å	γ = 101.9771(6)°.
Volume	1555.69(8) $Å^3$	
Z	4	
F(000)	760	
Density (calculated)	1.619 Mg/m^3	
Wavelength	1.54178 Å	
Cell parameters reflections used	9874	
Theta range for Cell parameters	4.05 to 78.60°.	
Absorption coefficient	3.715 mm^{-1}	
Temperature	100(2) K	
Crystal size	0.350 x 0.250 x 0.100 mm^3	
	Data collection	
Diffractometer	Bruker AXS D8 VENTURE, PhotonIII_C28	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.6943	
No. of measured reflections	23763	
No. of independent reflections	6441 [R(int) = 0.0265]	
No. of observed [I>2_igma(I)]	6299	
Completeness to theta = 67.679°	99.3 %	

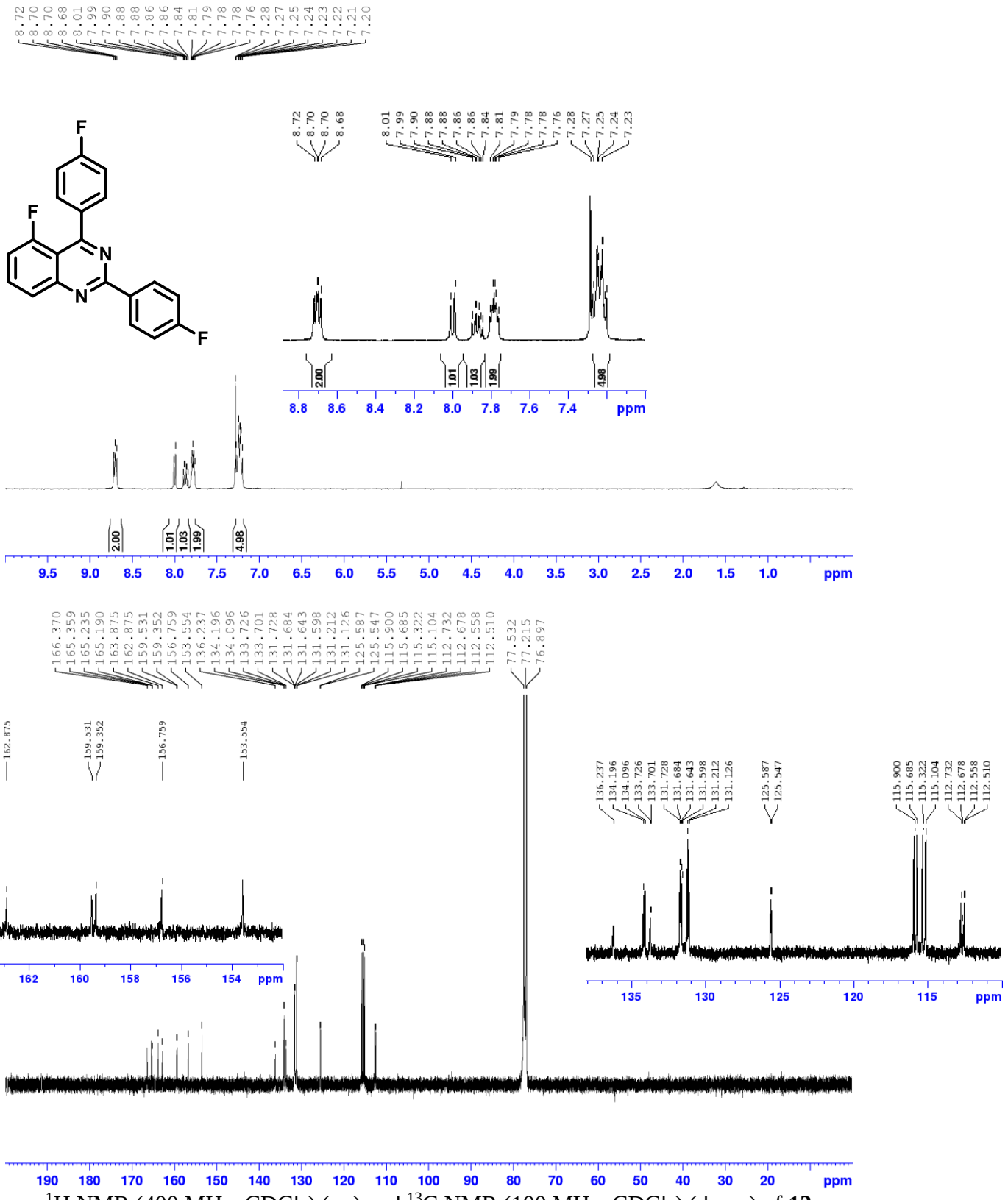
Theta range for data collection	2.025 to 79.111°.
	Refinement
Final R indices [I>2sigma(I)]	R1 = 0.0271, wR2 = 0.0751
R indices (all data)	R1 = 0.0283, wR2 = 0.0758
Goodness-of-fit on F^2	1.046
No. of reflections	6441
No. of parameters	433
No. of restraints	0
Largest diff. peak and hole	0.898 and -0.751 e.$Å^{-3}$



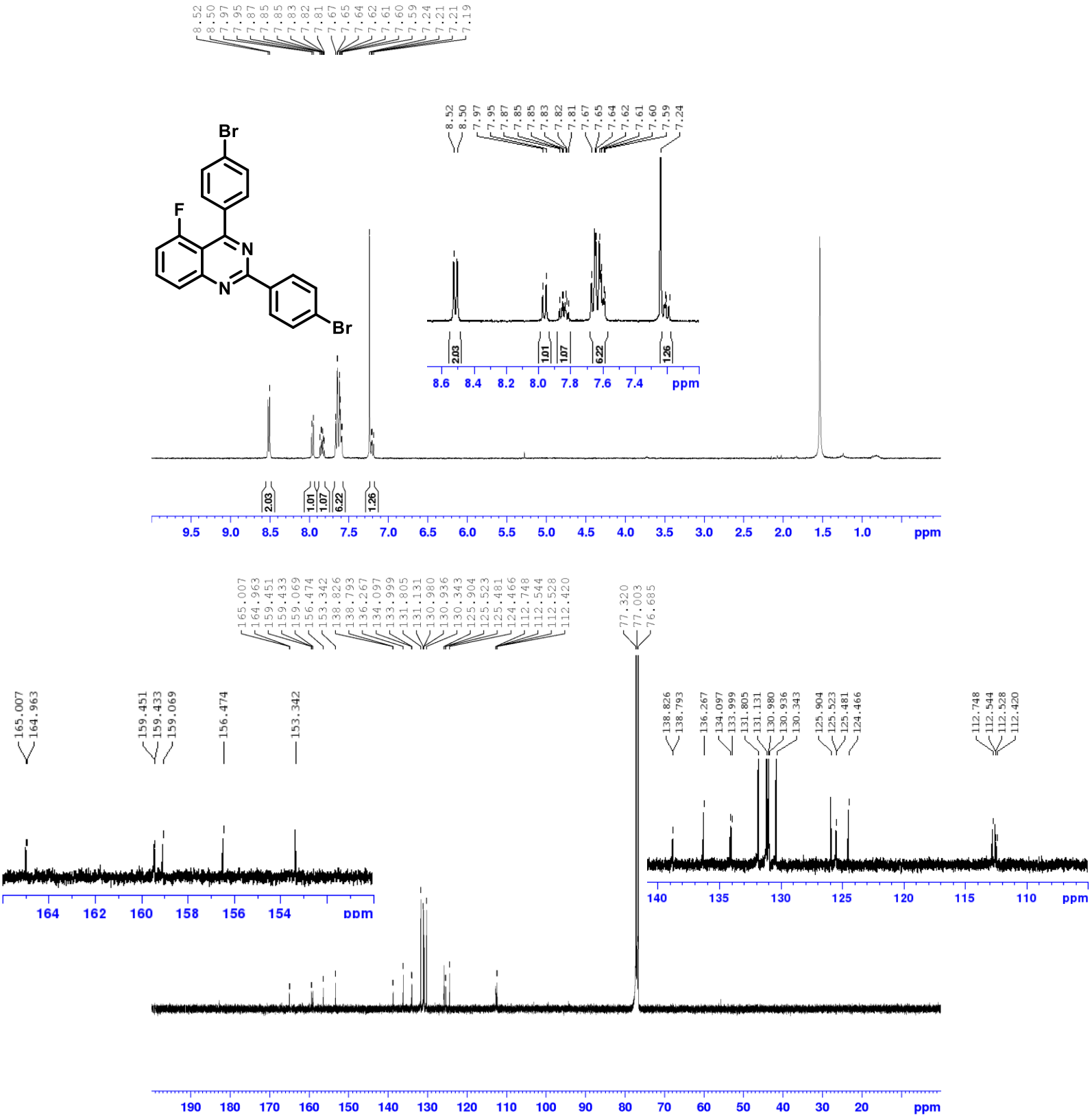
^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **11**



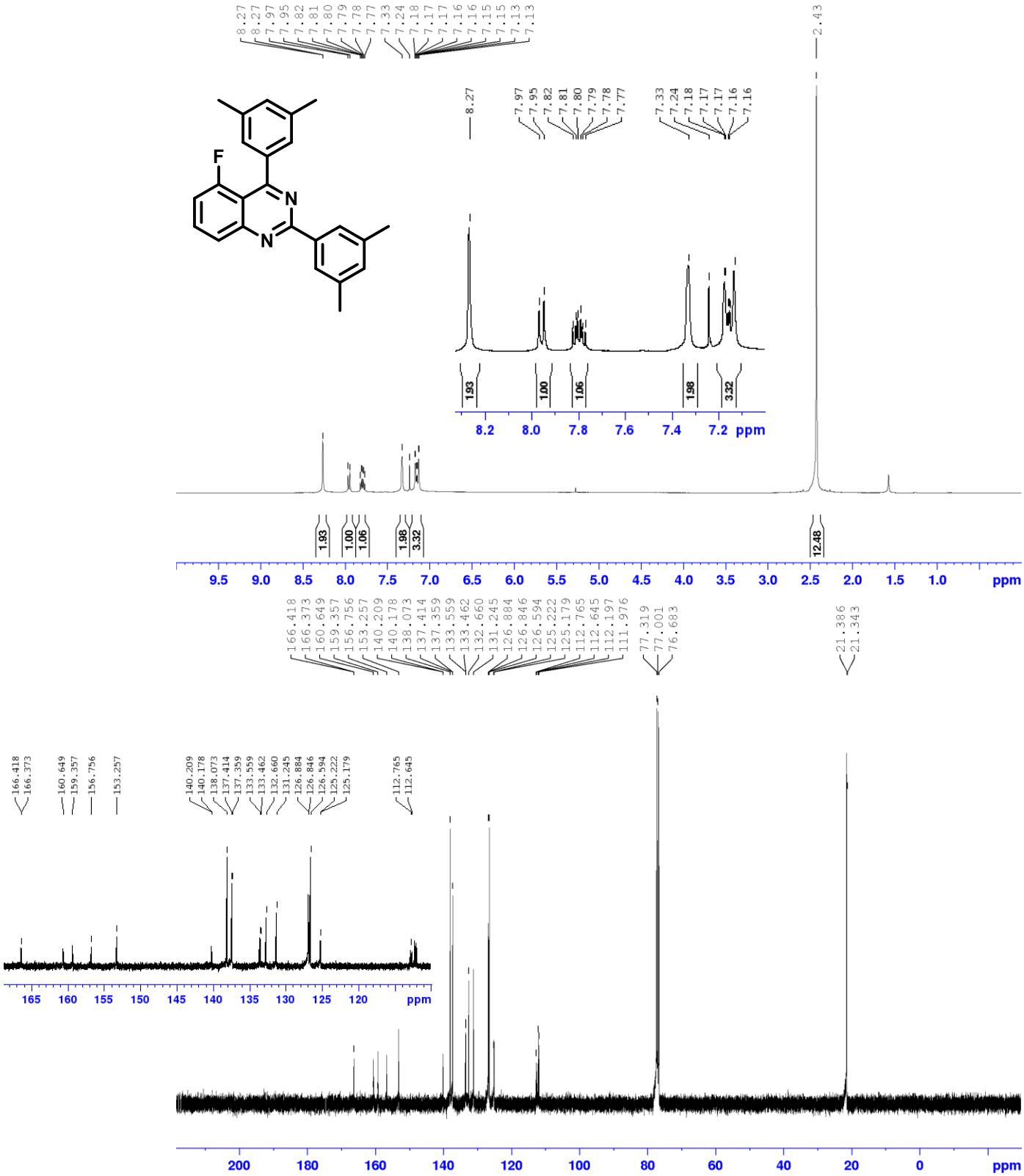
^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **12**



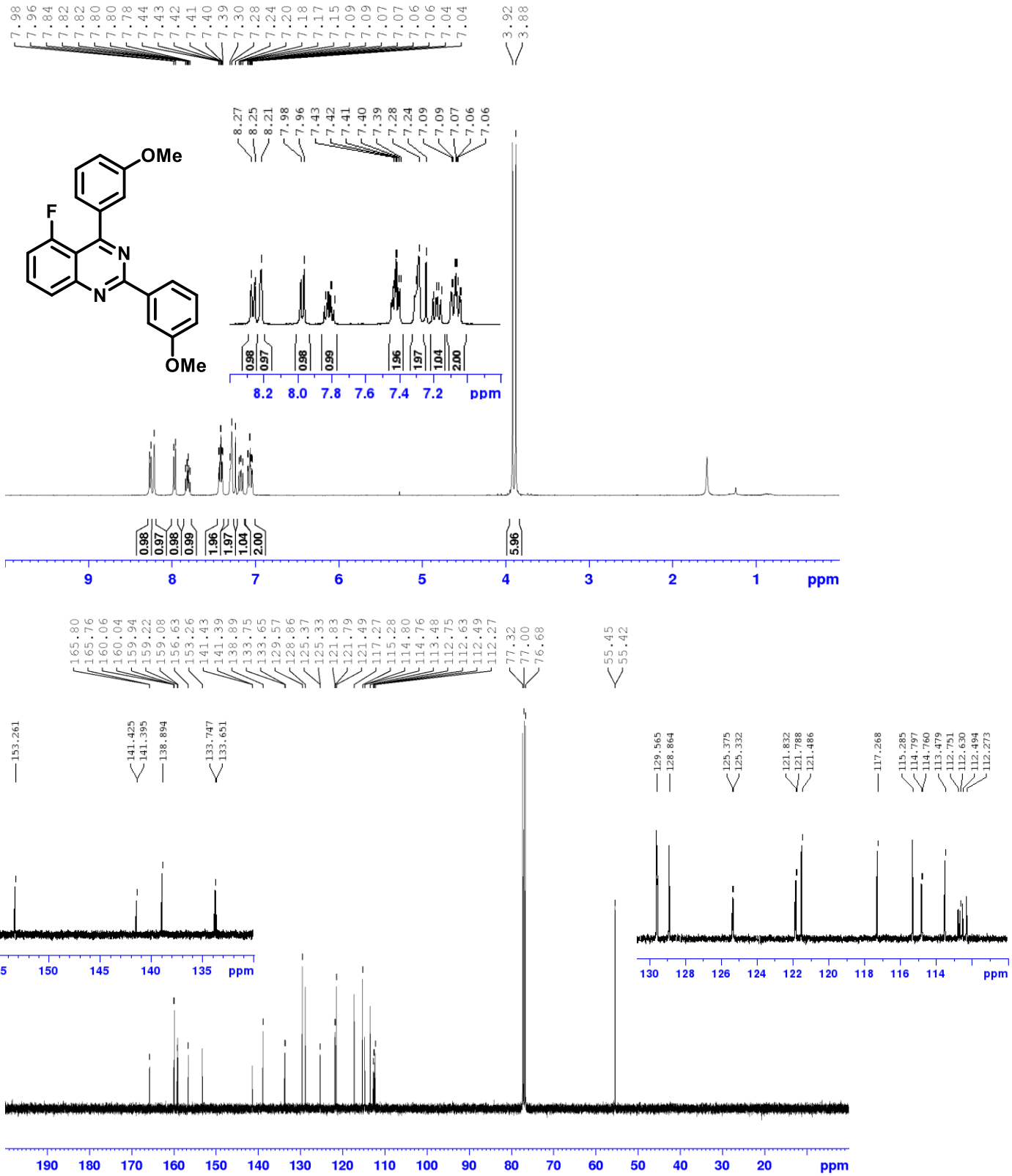
^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **13**



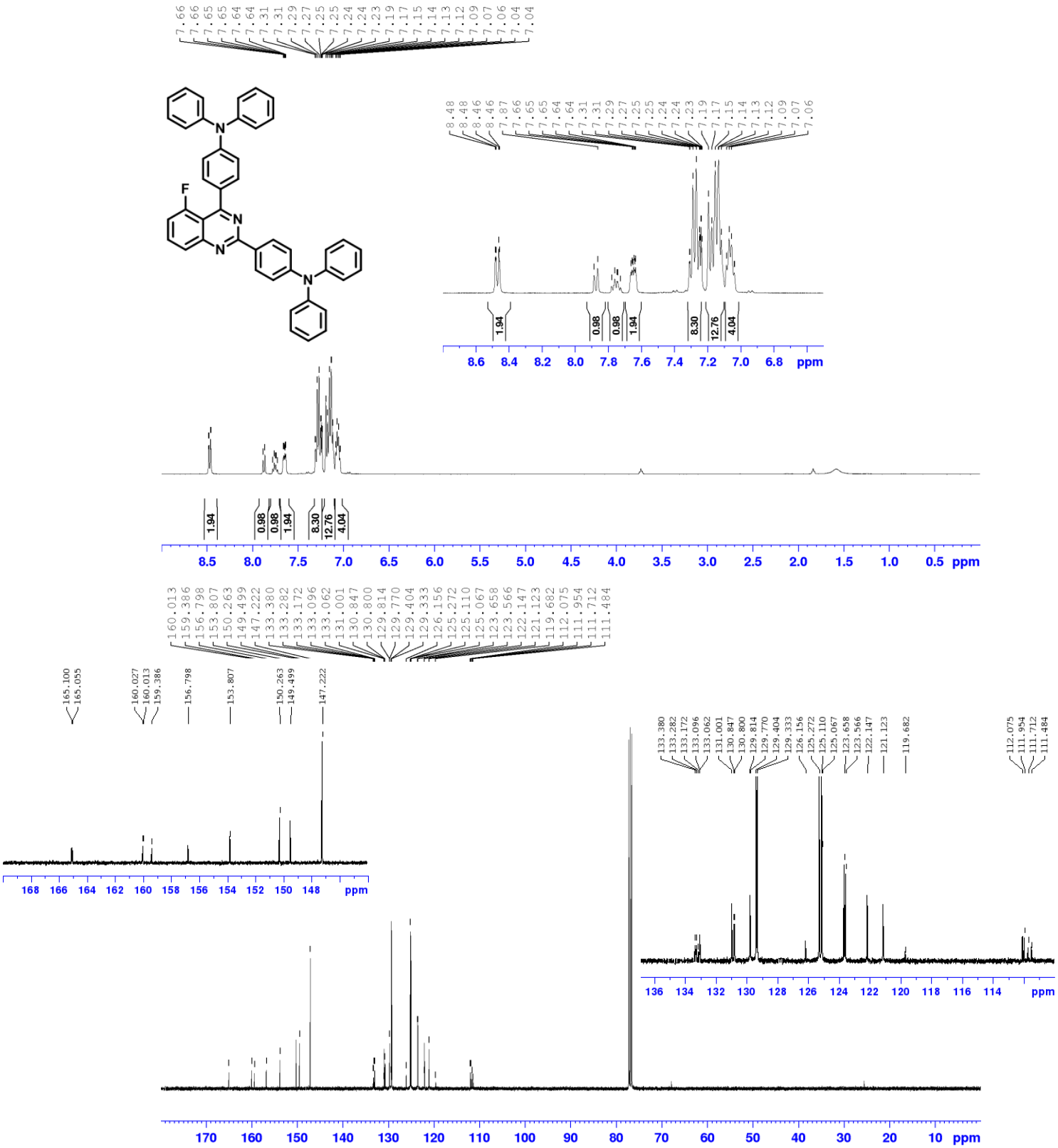
^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **14**



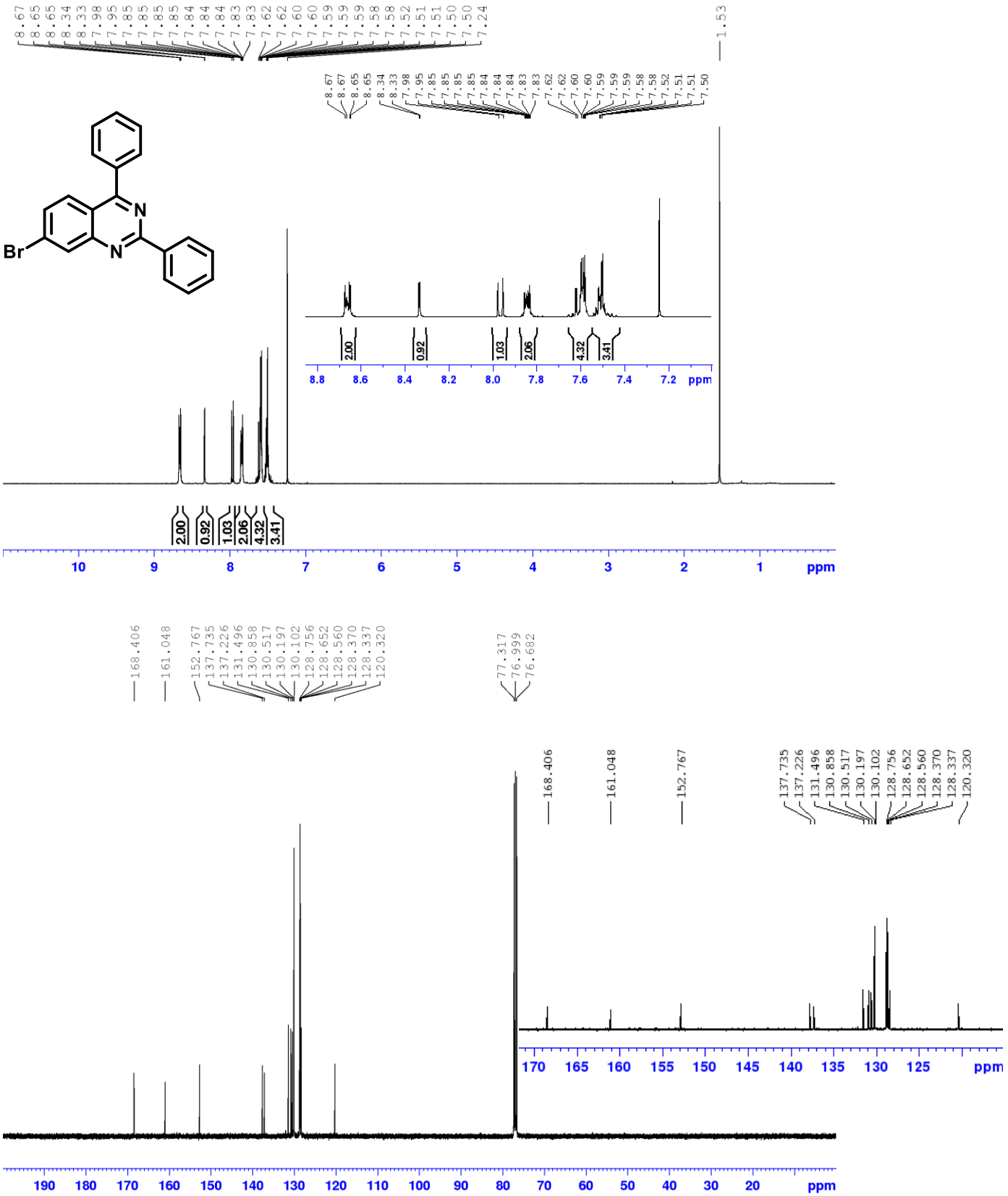
^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **15**



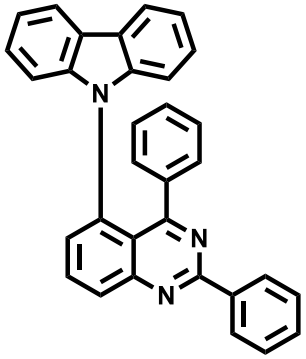
^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **16**



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **17**



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **18**

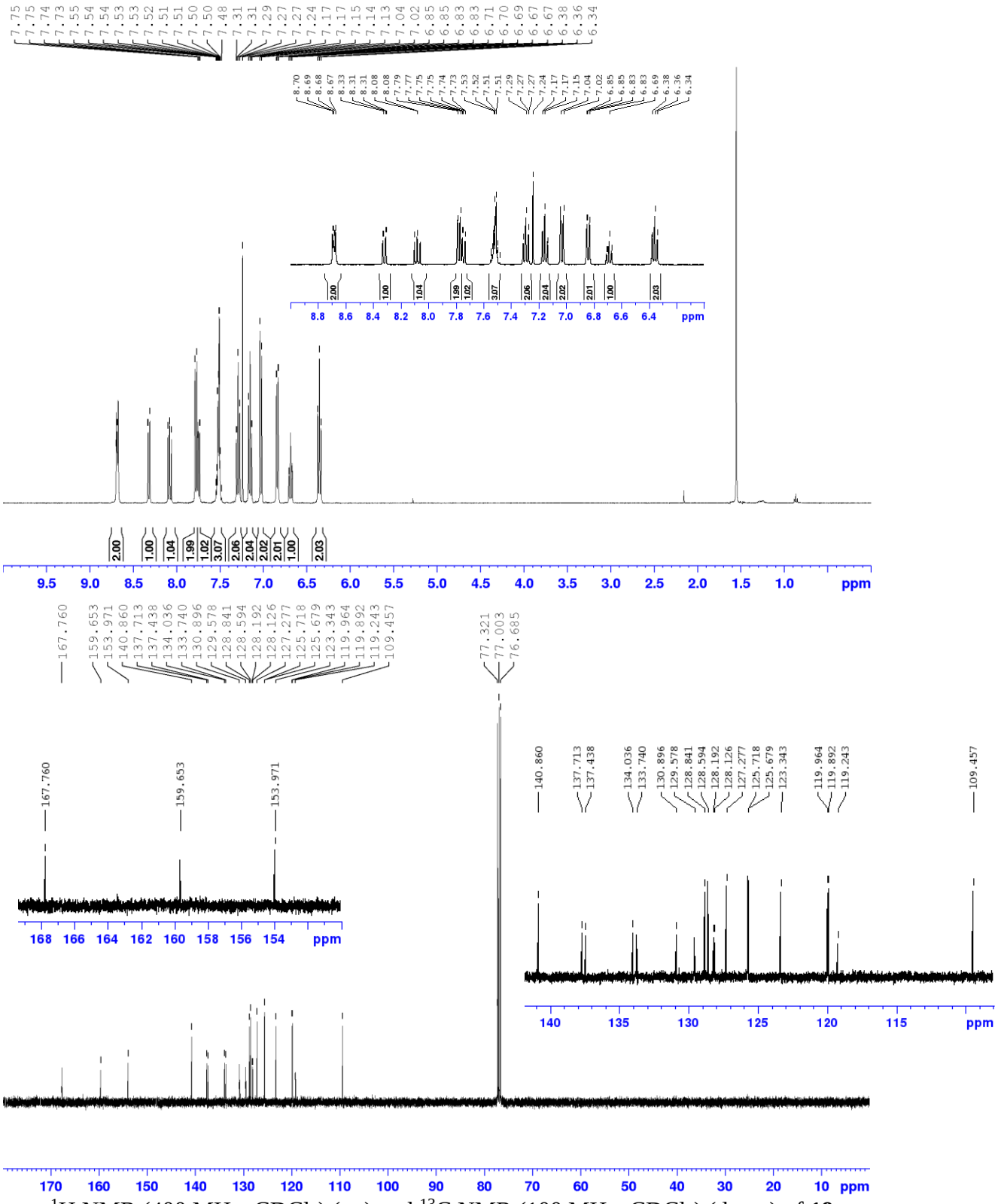


9-(2,4-Diphenylquinazolin-5-yl)-9H-carbazole (19). Yellow solid (331 mg, 74%); mp:196-200 °C.

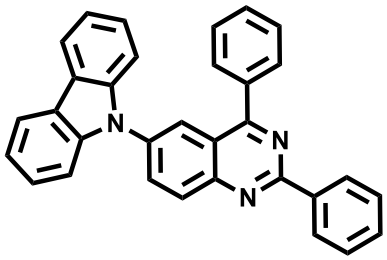
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71-8.65 (m, 2H), 8.32 (dd, J = 8.4, 1.1 Hz, 1H), 8.08 (t, J = 7.4 Hz, 1H), 7.78 (d, J = 7.7 Hz, 2H), 7.74 (dd, J = 7.5, 1.2 Hz, 1H), 7.56-7.49 (m, 3H), 7.33-7.26 (m, 2H), 7.18-7.12 (m, 2H), 7.03 (d, J = 8.8 Hz, 2H), 6.84 (dd, J = 7.0 Hz, 1.2 Hz, 2H), 6.69 (d, J = 7.5Hz, 1H), 6.36 (t, J = 7.8 Hz, 2H).

^{13}C NMR (100 MHZ, $CDCl_3$) δ 167.8, 159.7, 154.0, 140.9, 137.7, 137.4, 134.0, 133.7, 130.9, 129.6, 128.8, 128.6, 128.2, 128.1, 127.3, 125.71, 125.68, 123.3, 119.96, 119.89, 119.2, 109.5.

HRMS (FAB) estimated for $C_{32}H_{22}N_3$ $(M+H)^+$ m/z = 448.1814, found 448.1813.



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **19**

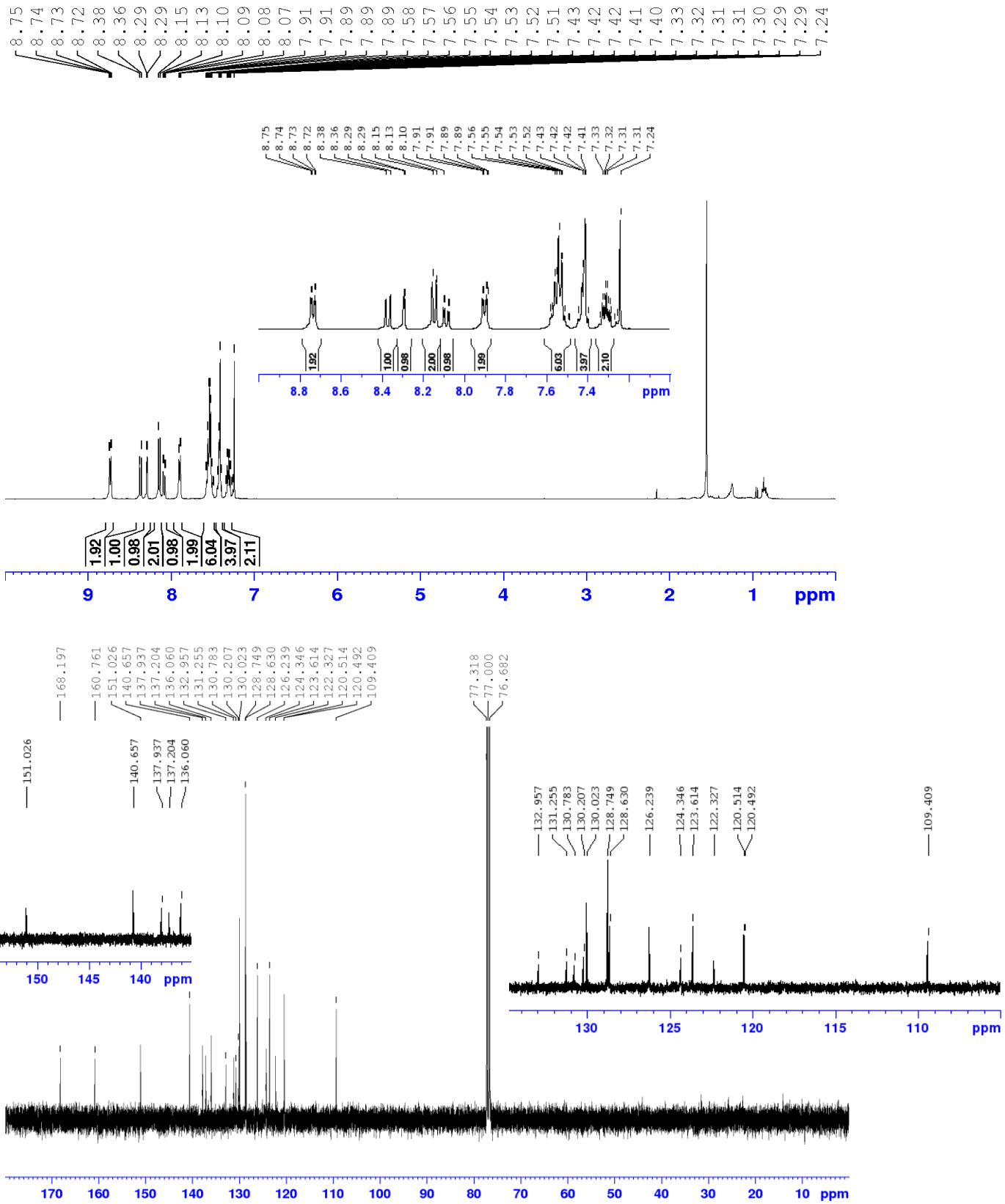


9-(2,4-Diphenylquinazolin-6-yl)-9H-carbazole (20). Yellow solid (349mg, 78%); mp:219-222 °C.

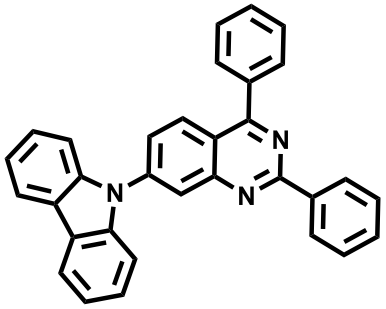
^{1}H NMR (400 MHz, CDCl3) δ 8.77-8.70 (m, 2H), 8.37 (d, J = 8.9 Hz, 1H), 8.29 (d, J = 2.2 Hz, 1H), 8.15 (d, J = 8.3 Hz, 2H), 8.09 (dd, J = 8.9, 2.2 Hz, 1H), 7.90 (dd, J = 7.8, 2.1 Hz, 2H), 7.60-7.48 (m, 6H), 7.47-7.38 (m, 4H), 7.36-7.28 (m, 2H).

^{13}C NMR (100 MHZ, CDCl3) δ 168.2, 160.8, 151.0, 140.7, 137.9, 137.2, 136.1, 133.0, 131.3, 130.8, 130.2, 130.0, 128.7, 128.6, 126.2, 124.3, 123.6, 122.3, 120.51, 120.49, 109.4.

HRMS (FAB) estimated for $C_{32}H_{22}N_3$ $(M+H)^+$ m/z = 448.1814, found 448.1818.



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **20**

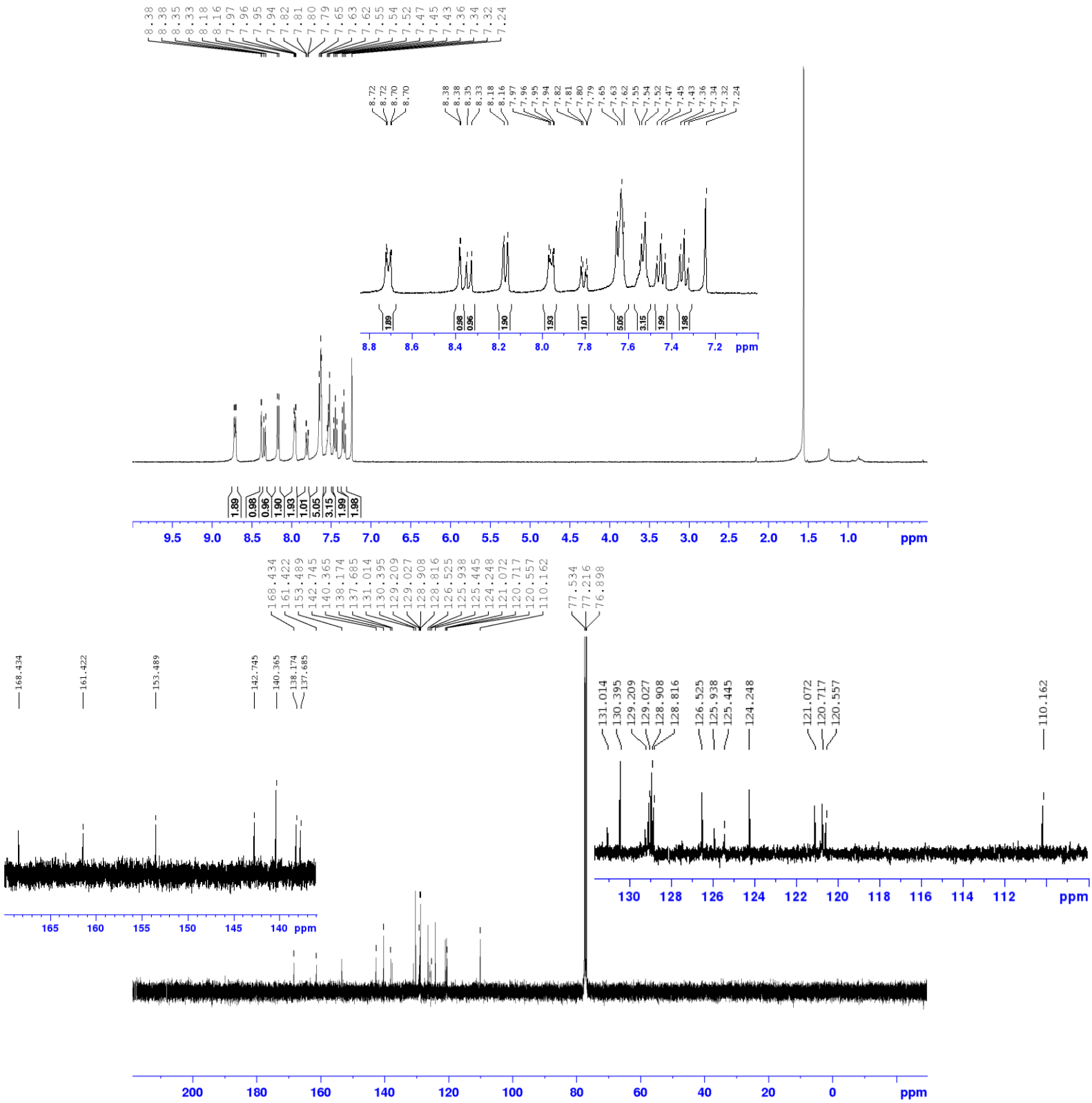


9-(2,4-diphenylquinazolin-7-yl)-9H-carbazole (21). Yellow solid (384mg, 86%); mp:219-221 °C.

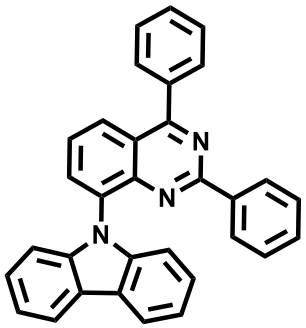
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75-8.68 (m, 2H), 8.38 (d, J = 1.9 Hz, 1H), 8.34 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.18 Hz, 2H), 8.00-7.93 (m, 2H), 7.81 (dd, J = 9.3, 2.2 Hz, 1H), 7.68-7.60 (m, 5H), 7.57-7.50 (m, 3H), 7.45 (t, J = 7.9 Hz, 2H), 7.34 (t, J = 7.3 Hz, 2H).

^{13}C NMR (100 MHZ, $CDCl_3$) δ 168.4, 161.4, 153.5, 142.7, 140.4, 138.2, 137.7, 131.0, 130.4, 129.2, 129.0, 128.9, 128.8, 126.5, 125.9, 125.4, 124.2, 121.1, 120.7, 120.6, 110.2.

HRMS (FAB) estimated for $C_{32}H_{22}N_3$ $(M+H)^+$ m/z = 448.1814, found 448.1807.



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **21**

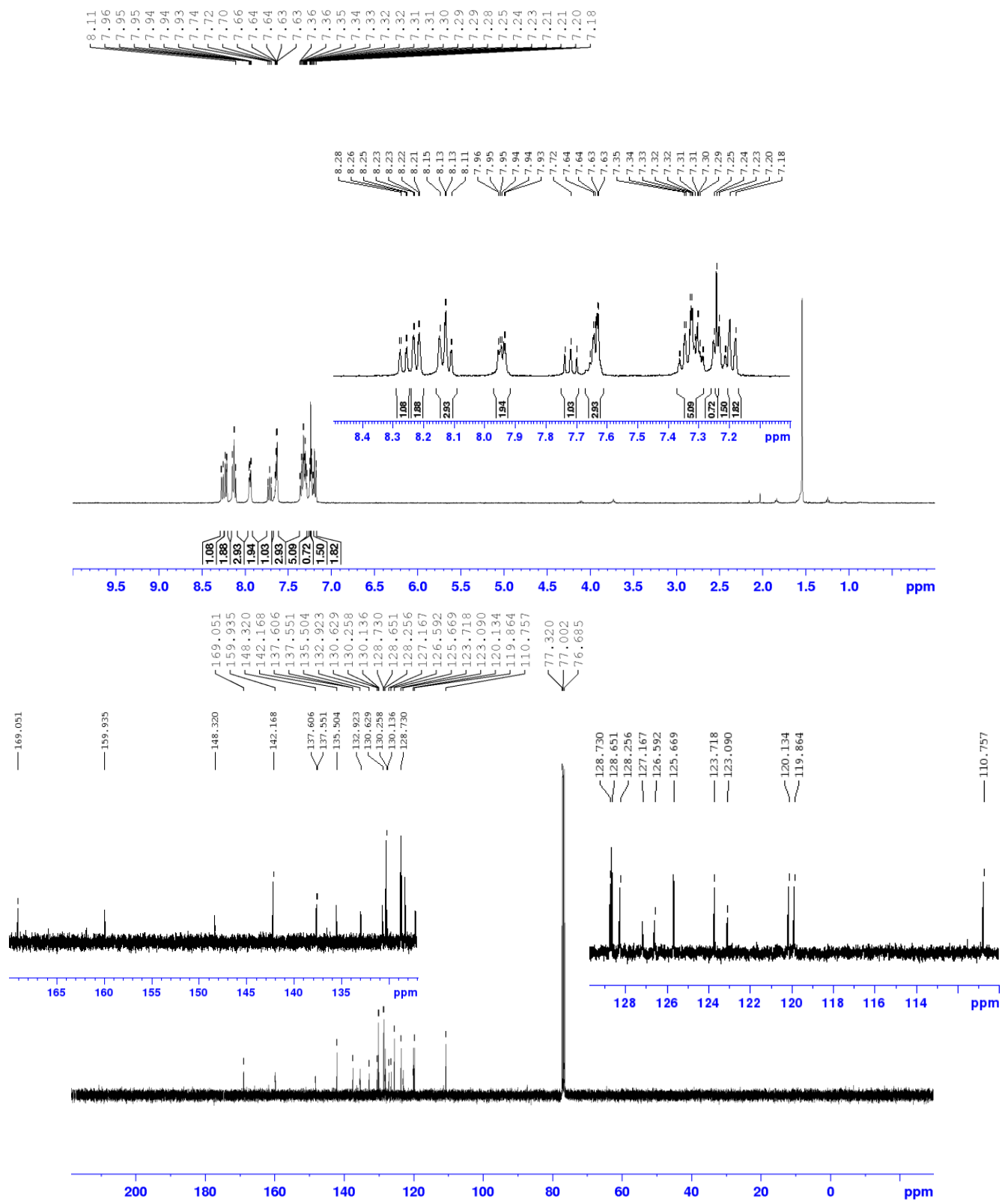


9-(2,4-diphenylquinazolin-8-yl)-9H-carbazole (22). Yellow solid (429 mg, 96%); mp:203-207 °C.

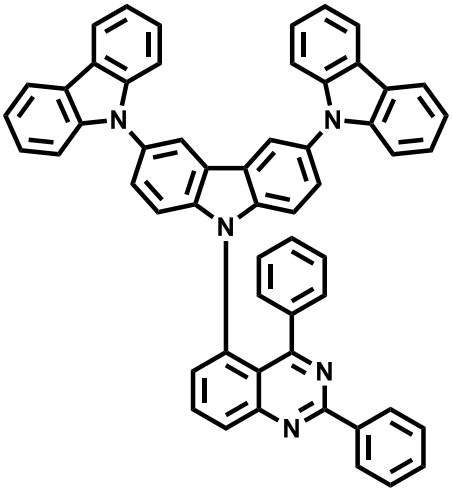
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, J = 9.1 Hz, 1.3 Hz, 1H), 8.22 (dd, J = 8.2 Hz, 1.2 Hz, 2H), 8.17-8.09 (m, 3H), 7.97-7.91 (m, 2H), 7.72 (t, J = 8.2 Hz, 1H), 7.67-7.61 (m, 3H), 7.38-7.28 (m, 5H), 7.23 (t, J = 7.7 Hz, 2H), 7.19 (d, J = 7.6 Hz, 2H).

^{13}C NMR (100 MHZ, $CDCl_3$) δ 169.1, 159.9, 148.3, 142.2, 137.6, 137.55, 135.5, 133.0, 130.6, 130.3, 130.1, 128.7, 128.65, 128.3, 127.2, 126.6, 125.7, 123.7, 123.1, 120.1, 119.9, 110.8.

HRMS (FAB) estimated for $C_{32}H_{22}N_3$ $(M+H)^+$ m/z = 448.1814, found 448.1813.



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **22**

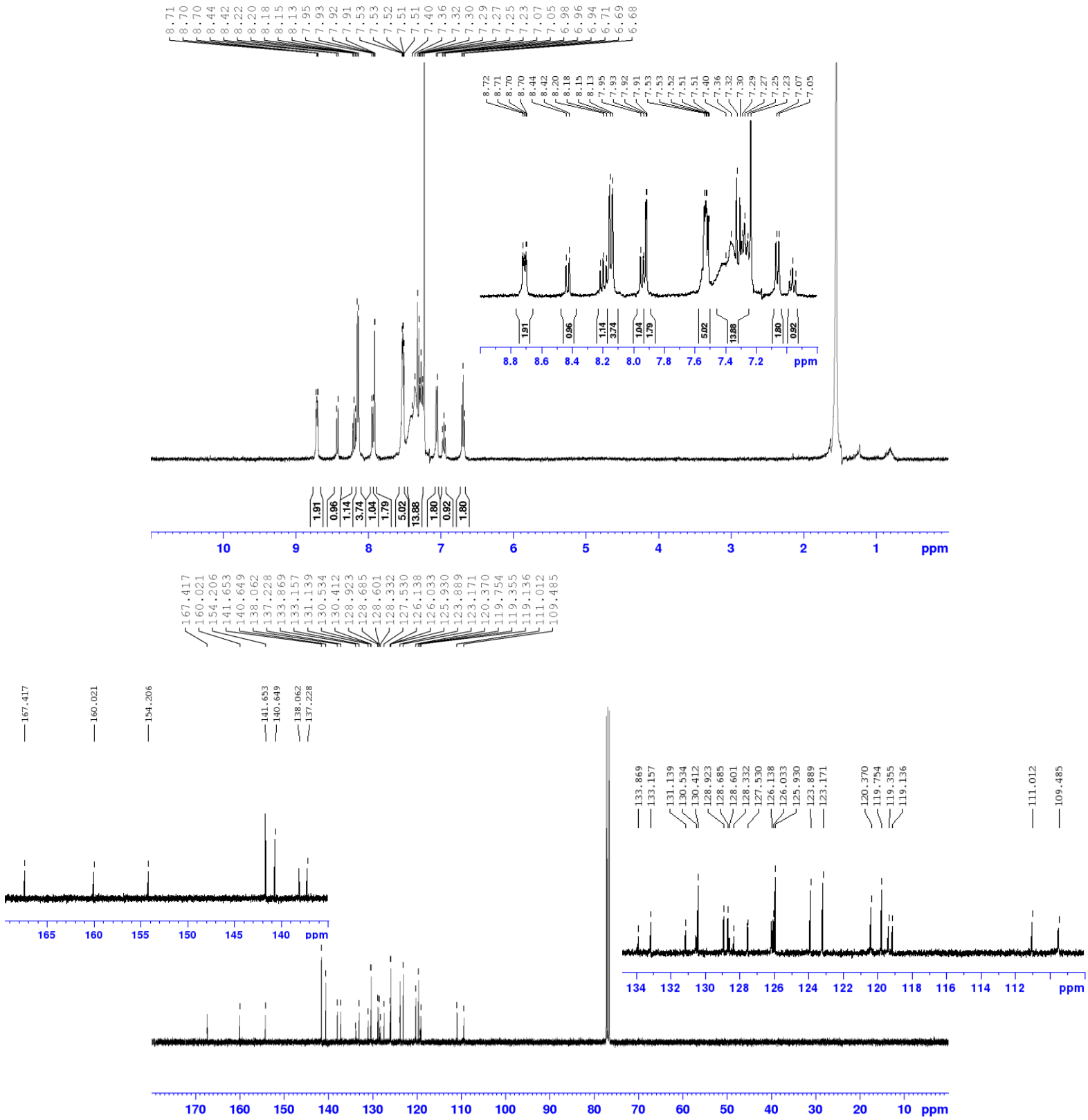


9'-(2,4-diphenylquinazolin-5-yl)-9'H-9,3':6',9''-tercarbazole (23). Yellow solid (699, 90%); mp:241-243 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73-8.68 (m, 2H), 8.43 (d, J = 8.4 Hz, 1H), 8.20 (t, J = 8.4 Hz, 1H), 8.14 (d, J = 8.1 Hz, 4H), 7.94 (d, J = 7.4 Hz, 1H), 7.91 (d, J = 1.7 Hz, 2H), 7.57-7.48 (m, 5H), 7.48-7.25 (m, 14H), 7.05 (d, J = 7.6 Hz, 2H), 6.96 (t, J = 7.6 Hz, 1H), 6.70 (t, J = 7.6 Hz, 2H).

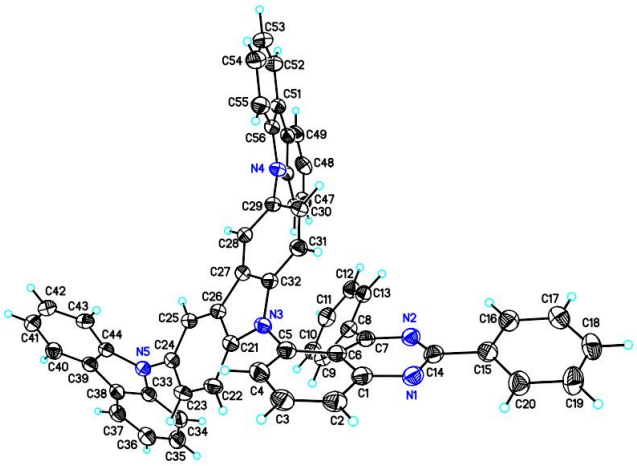
^{13}C NMR (100 MHZ, $CDCl_3$) δ 167.4, 160.0, 154.2, 141.7, 140.6, 138.1, 137.2, 133.9, 133.2, 131.1, 130.5, 130.4, 128.9, 128.7, 128.6, 128.3, 127.5, 126.1, 126.0, 125.9, 123.9, 123.2, 120.4, 119.8, 119.4, 119.1, 110.0, 109.5.

HRMS (FAB) estimated for $C_{56}H_{36}N_5$ $(M+H)^+$ m/z = 778.2971, found 778.2975.



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **23**

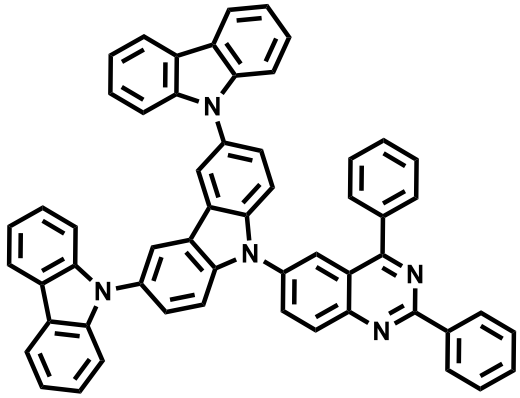
X-ray structure of 9'-(2,4-diphenylquinazolin-5-yl)-9'H-9,3':6',9''-tercarbazole (23) (CCDC 2250630).



The single crystals of compound **23** were obtained by slow evaporation of its DCM/hexane (3/1) solution.

Empirical formula	C56 H35 N5	
Formula weight	777.89	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 13.4479(4) Å	α= 90°.
	b = 14.7090(4) Å	β= 93.8572(13)°.
	c = 23.9088(7) Å	γ = 90°.
Volume	4718.6(2) $Å^3$	
Z	4	
F(000)	1624	
Density (calculated)	1.095 Mg/m^3	
Wavelength	1.54178 Å	
Cell parameters reflections used	9396	
Theta range for Cell parameters	3.53 to 78.37°.	
Absorption coefficient	0.502 mm^{-1}	
Temperature	100(2) K	
Crystal size	0.250 x 0.100 x 0.050 mm^3	
	Data collection	
Diffractometer	Bruker AXS D8 VENTURE, PhotonIII_C28	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.8516	
No. of measured reflections	94466	

No. of independent reflections	9891 [R(int) = 0.0389]
No. of observed [I>2_igma(I)]	8872
Completeness to theta = 67.679°	99.7 %
Theta range for data collection	3.530 to 78.868°.
Refinement	
Final R indices [I>2sigma(I)]	R1 = 0.0558, wR2 = 0.1716
R indices (all data)	R1 = 0.0608, wR2 = 0.1771
Goodness-of-fit on F^2	1.054
No. of reflections	9891
No. of parameters	550
No. of restraints	0
Largest diff. peak and hole	0.491 and -0.446 e.$Å^{-3}$

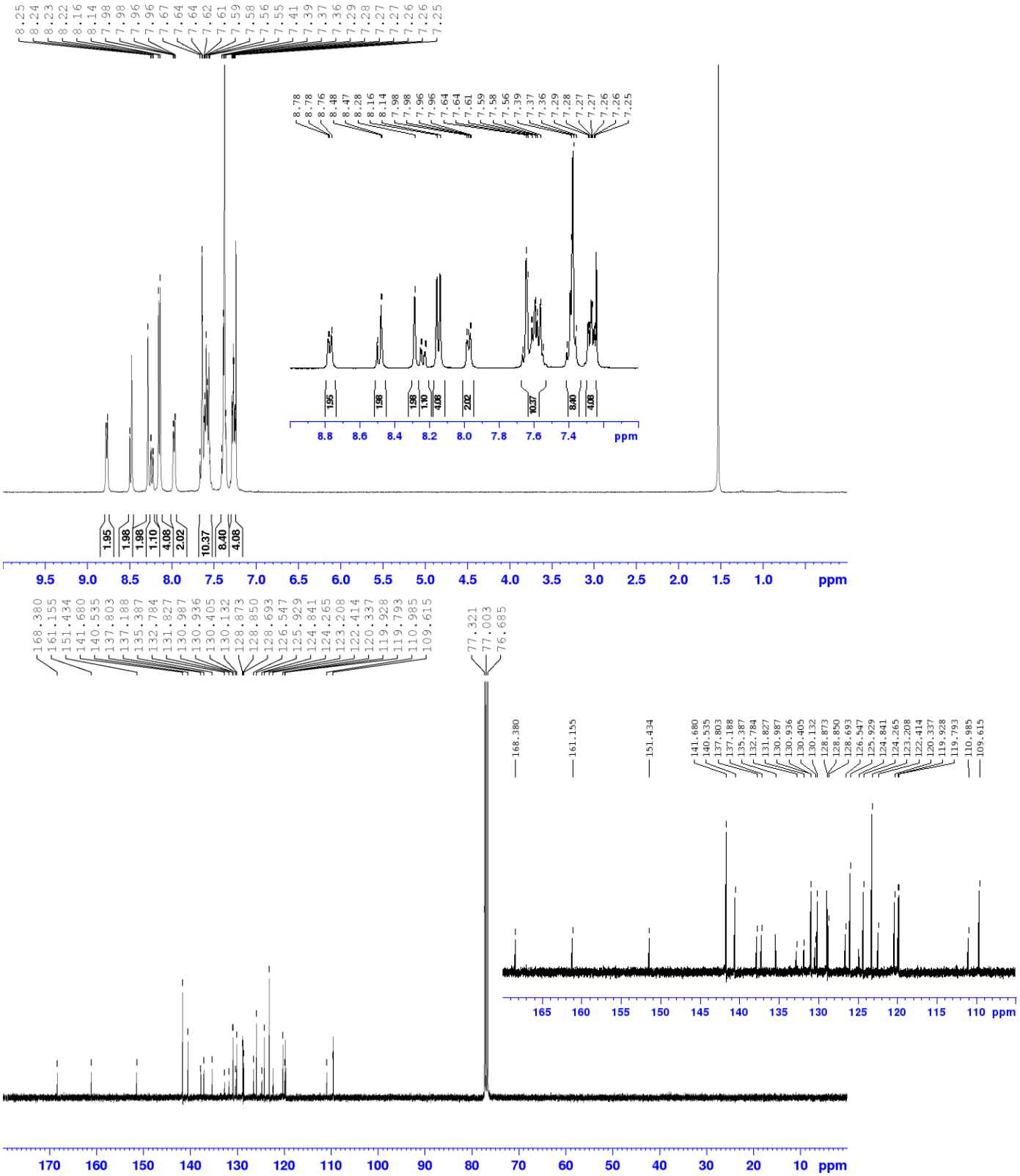


9'-(2,4-diphenylquinazolin-6-yl)-9'H-9,3':6',9''-tercarbazole (24). yellow solid (699 mg, 90%); mp:200-203 °C.

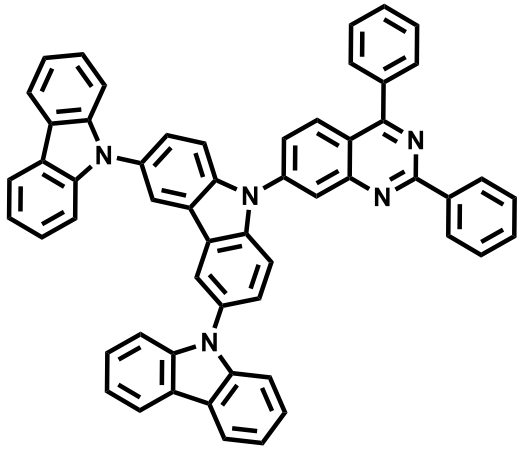
^{1}H NMR (400 MHz, CDCl3) δ 8.80-8.75 (m, 2H), 8.52-8.42 (m, 2H), 8.28 (s, 2H), 8.24 (dd, J = 9.0, 2.4 Hz, 1H), 8.15 (d, J = 8.1 Hz, 4H), 8.00-7.94 (m, 2H), 7.68-7.54 (m, 10H), 7.43-7.34 (m, 8H), 7.30-7.25 (m, 4H).

^{13}C NMR (100 MHZ, $CDCl_3$) δ 168.4, 161.2, 151.4, 141.7, 140.5, 137.8, 137.2, 135.4, 132.8, 131.8, 131.0, 130.9, 130.4, 130.1, 128.87, 128.85, 128.7, 126.5, 126.0, 124.8, 124.3, 123.2, 122.4, 120.3, 119.9, 119.8, 111.0, 109.6.

HRMS (FAB) estimated for $C_{56}H_{36}N_5$ $(M+H)^+$ m/z = 778.2971, found 778.2971.



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **24**

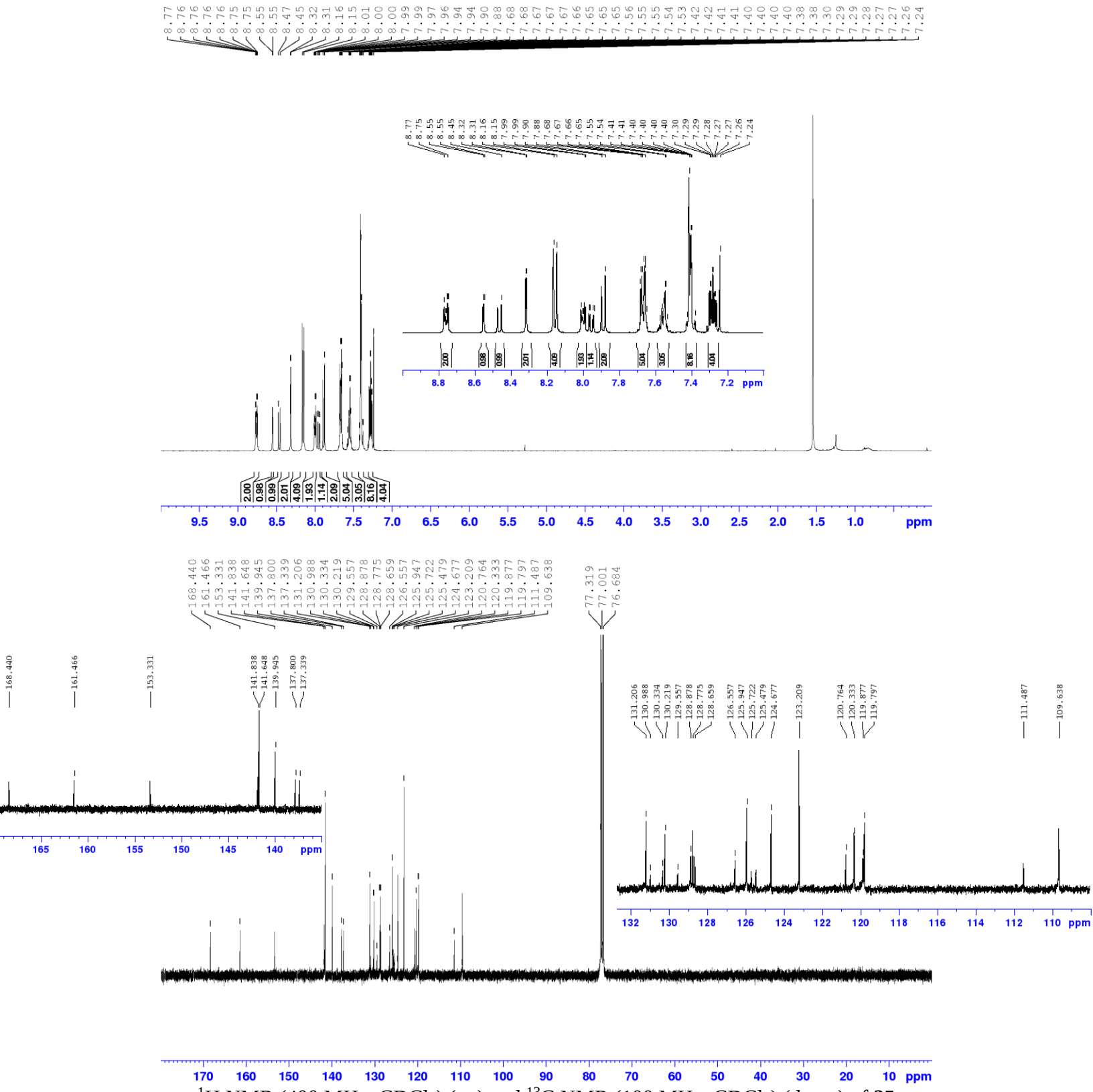


9'-(2,4-diphenylquinazolin-7-yl)-9'H-9,3':6',9''-tercarbazole (25). Yellow solid (637 mg, 82%); mp:>300 °C.

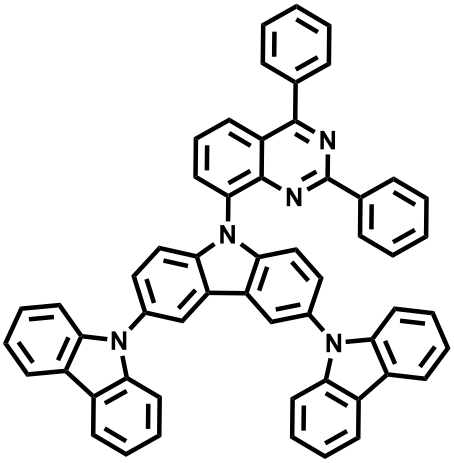
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79-8.74 (m, 2H), 8.55 (d, J = 2.1 Hz, 1H), 8.46 (d, J = 9.0 Hz, 1H), 8.31 (d, J = 2.0 Hz, 2H), 8.18-8.13 (m, 4H), 8.02-7.97 (m, 2H), 7.95 (dd, J = 9.0, 2.1 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.70-7.64 (m, 5H), 7.59-7.52 (m, 3H), 7.43-7.37 (m, 8H), 7.32-7.25 (m, 4H).

^{13}C NMR (100 MHZ, $CDCl_3$) δ 168.4, 161.5, 153.3, 141.8, 141.6, 139.9, 137.8, 137.3, 131.2, 131.0, 130.3, 130.2, 129.6, 128.9, 128.8, 128.7, 126.6, 125.9, 125.7, 125.5, 124.7, 123.2, 120.8, 120.3, 119.9, 119.8, 111.5, 109.6.

HRMS (FAB) estimated for $C_{56}H_{36}N_5$ $(M+H)^+$ m/z = 778.2971, found 778.2975.



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **25**

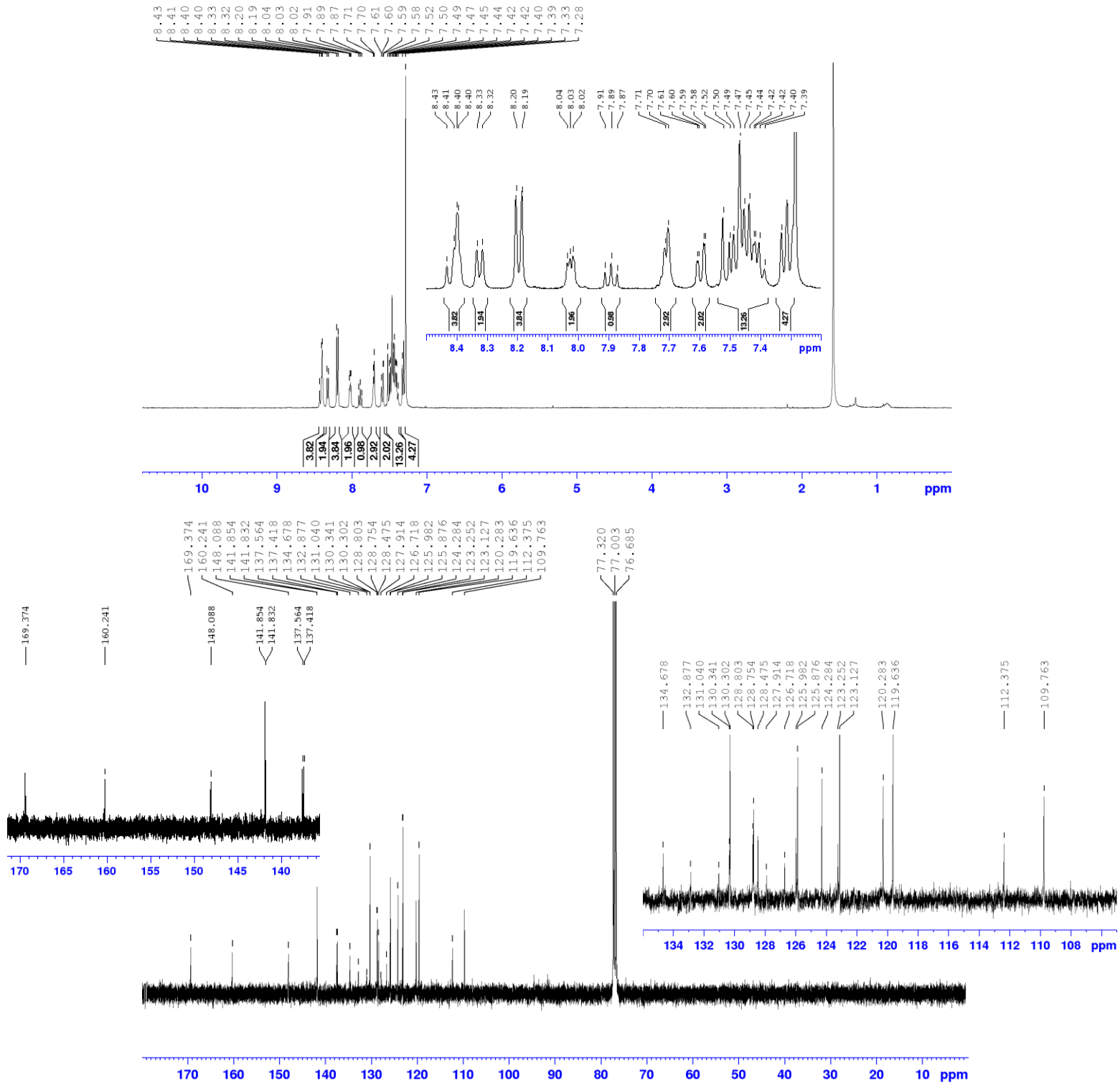


9'-(2,4-diphenylquinazolin-8-yl)-9'H-9,3':6',9''-tercarbazole (26). Yellow solid (559 mg, 72%); mp:222-226 °C.

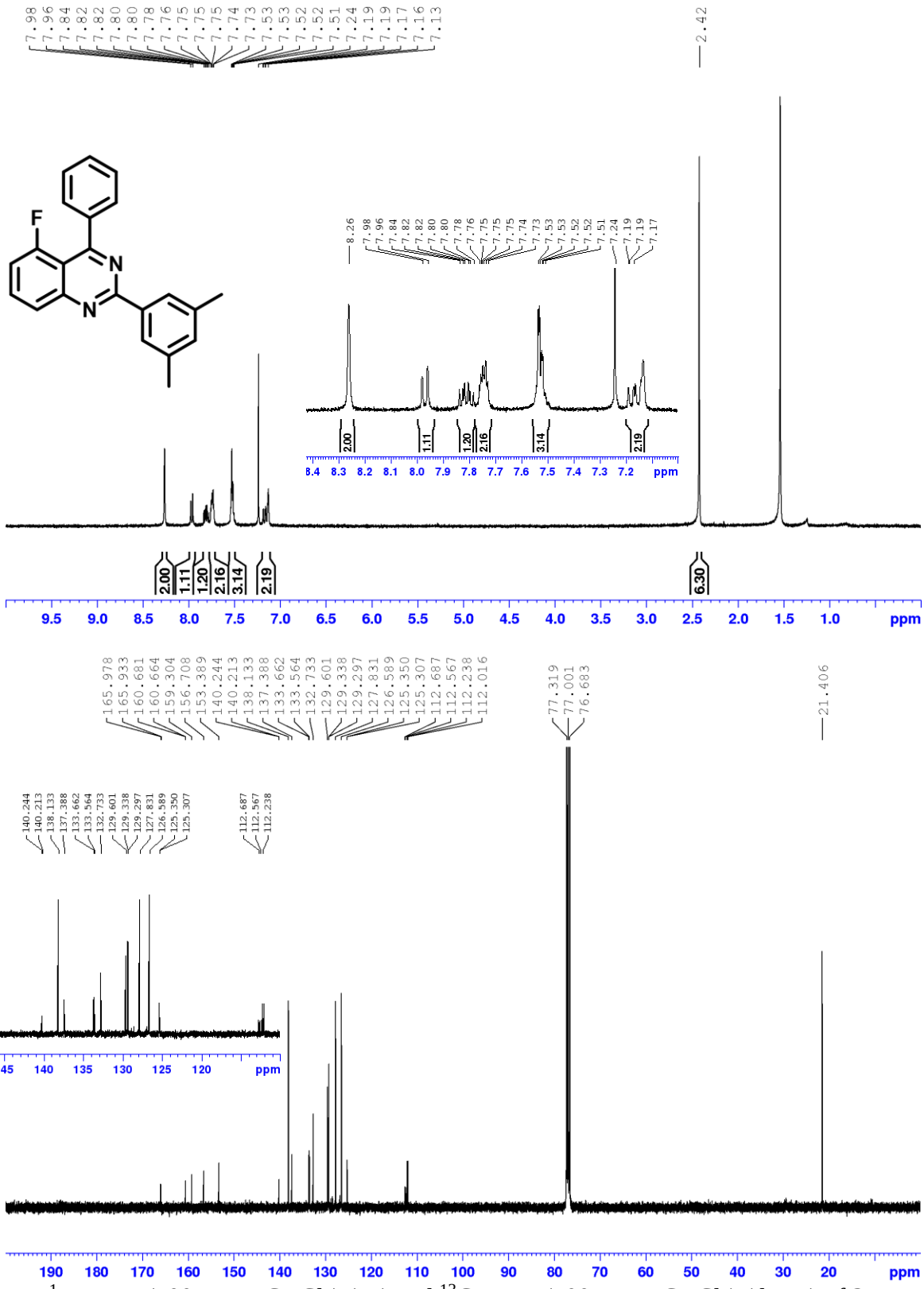
^{1}H NMR (400 MHz, CDCl3) δ 8.44-8.38 (m, 4H), 8.32 (d, J = 7.3 Hz, 2H), 8.20 (d, J = 7.56 Hz, 4H), 8.05-8.00 (m, 2H), 7.89 (t, J = 8.1 Hz, 1H), 7.74-7.68 (m, 3H), 7.60 (dd, J = 8.9, 1.6 Hz, 2H), 7.55-7.37 (m, 13H), 7.31 (t, J = 7.6 Hz, 4H).

^{13}C NMR (100 MHZ, CDCl3) δ 169.4, 160.2, 148.1, 141.9, 141.8, 137.6, 137.4, 134.7, 132.9, 131.0, 130.34, 130.30, 128.80, 128.75, 128.5, 127.9, 126.7, 126.0, 125.9, 124.3, 123.3, 123.1, 120.3, 119.6, 112.4, 109.8.

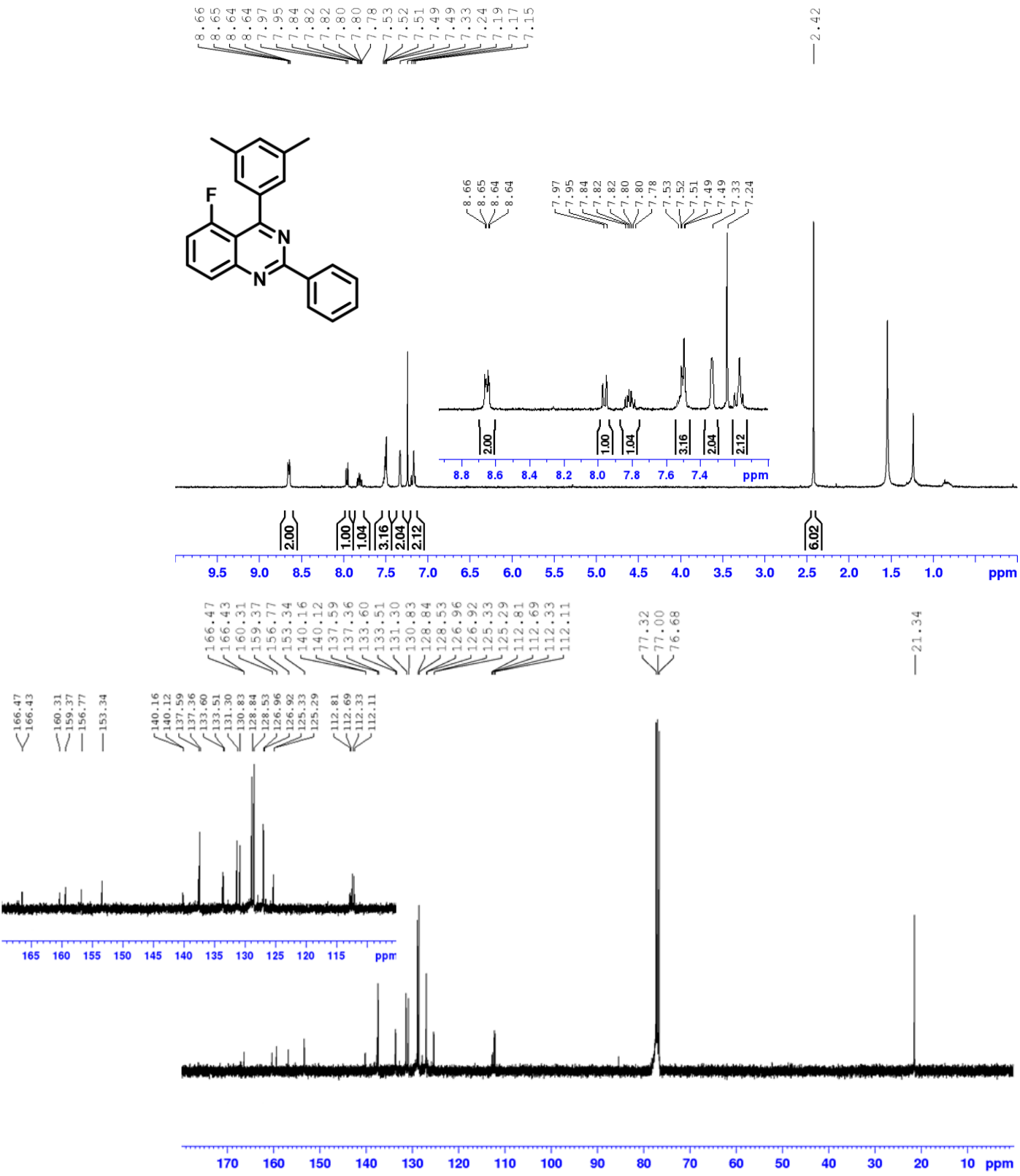
HRMS (FAB) estimated for $C_{56}H_{36}N_5$ $(M+H)^+$ m/z = 778.2971, found 778.2977.



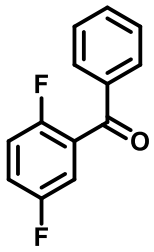
^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **26**



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **27**



^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **28**

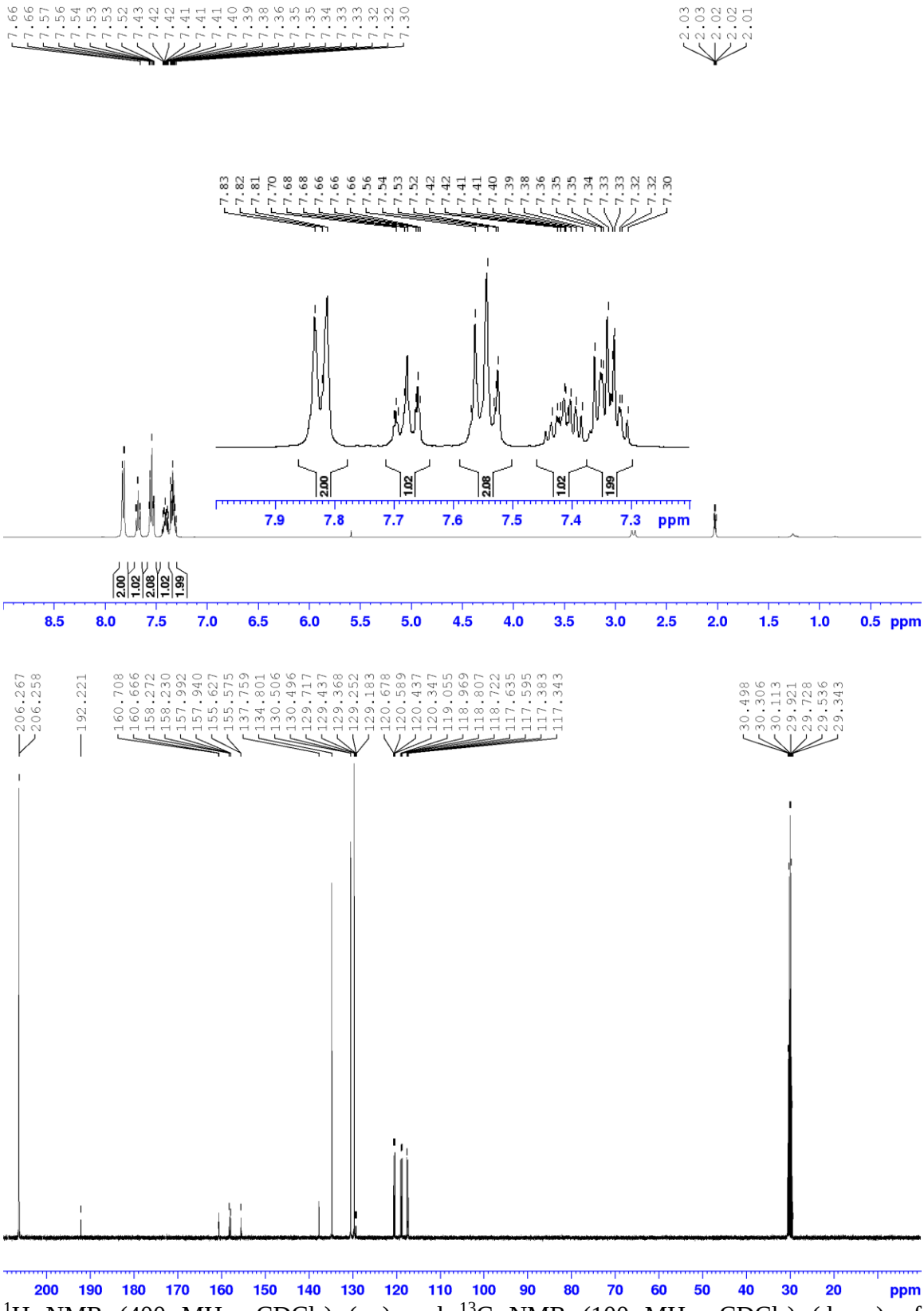


2,5-Difluorobenzophenone[7]. Colorless oil (157 mg, 36%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.3 Hz, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 7.4 Hz, 2H), 7.45-7.38 (m, 1H), 7.37-7.29 (m, 2H).

^{13}C NMR (100 MHZ, $CDCl_3$) δ 192.2, 159.3 (dd, J = 245.5, 4.4 Hz), 156.8 (dd, J = 237.4, 5.3 Hz), 137.8, 134.8, 130.5 (d, J = 1Hz), 129.7, 129.3 (dd, J = 18.8, 7.3 Hz), 120.5 (dd, J = 24.1, 8.8 Hz), 118.9 (dd, J = 25.0, 8.6 Hz), 117.5 (dd, J = 25.5, 4.2 Hz).

HRMS (ESI) estimated for $C_{13}H_9F_2N$ $(M+H)^+$ m/z = 219.0621, found 219.0617.



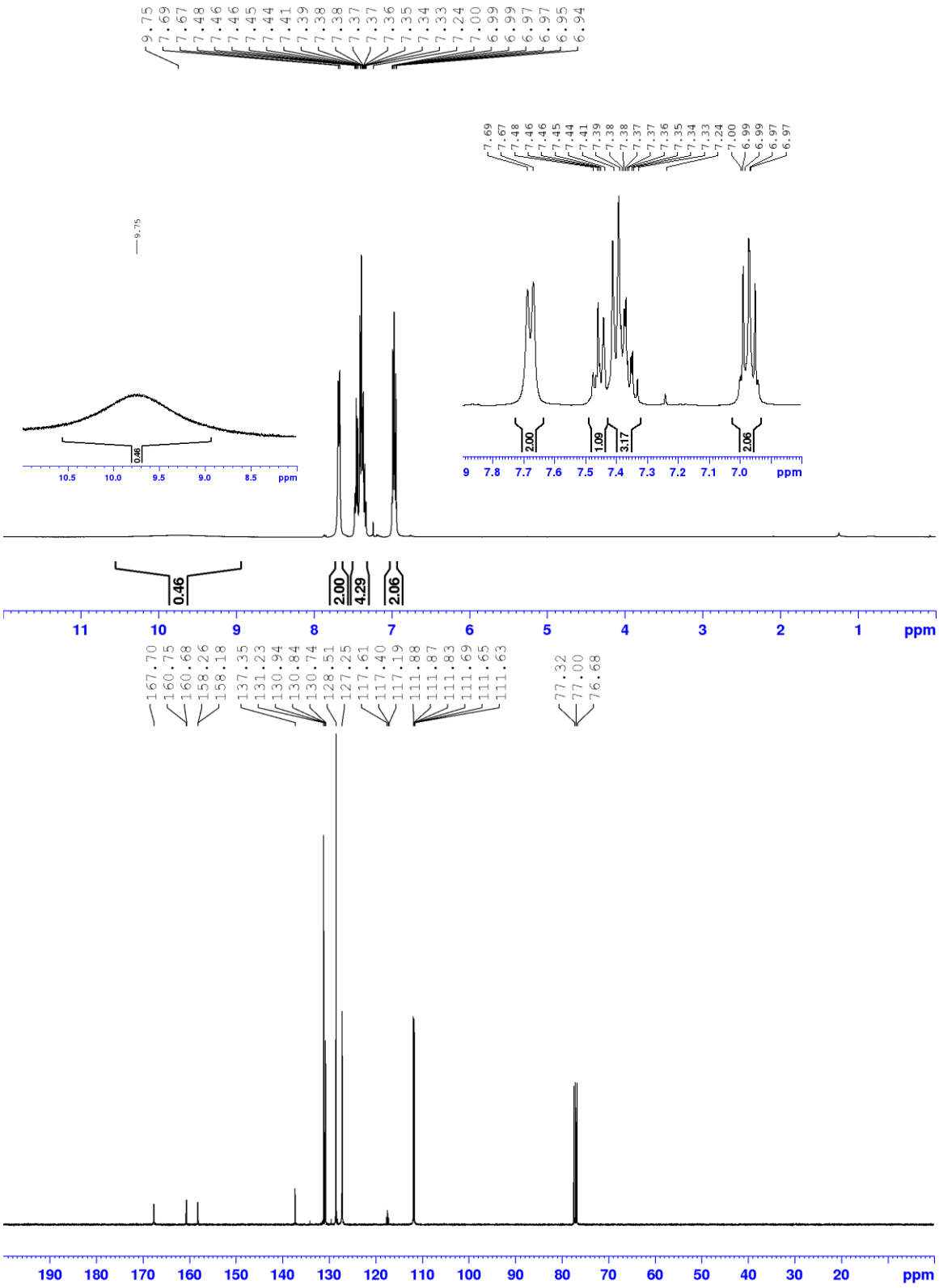
^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **2,5-Difluorobenzophenone**

2,6-Difluorobenzophenone imine. Yellow solid (300 mg, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (br, 1H), 7.67 (d, J = 7.5 Hz, 2H), 7.49-7.44 (m, 1H), 7.44-7.32 (m, 3H), 7.00-6.93 (m, 2H).

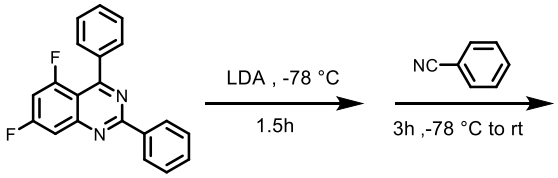
^{13}C NMR (100 MHZ, $CDCl_3$) δ 167.7, 159.5 (dd, J = 250.6, 7.6 Hz), 137.3, 131.2, 130.8 (t, J = 10.0 Hz), 128.5, 127.2, 117.4 (t, J = 20.1 Hz), 111.758 (dd, J = 18.1, 4.5 Hz), 111.756 (d, J = 25.4 Hz).

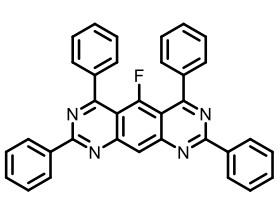
HRMS (ESI) estimated for $C_{13}H_{10}F_2N$ $(M+H)^+$ m/z = 218.0781, found 218.0788.



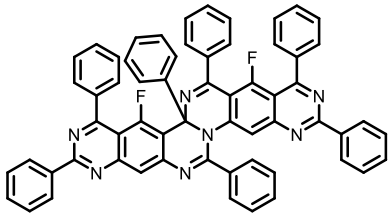
^{1}H NMR (400 MHz, $CDCl_3$) (up) and ^{13}C NMR (100 MHz, $CDCl_3$) (down) of **2,6-Difluorobenzophenone imine**

[2+2+2] Cascade Annulation of Quinazoline 4 With Nitriles

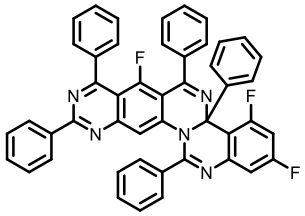




29, 4%



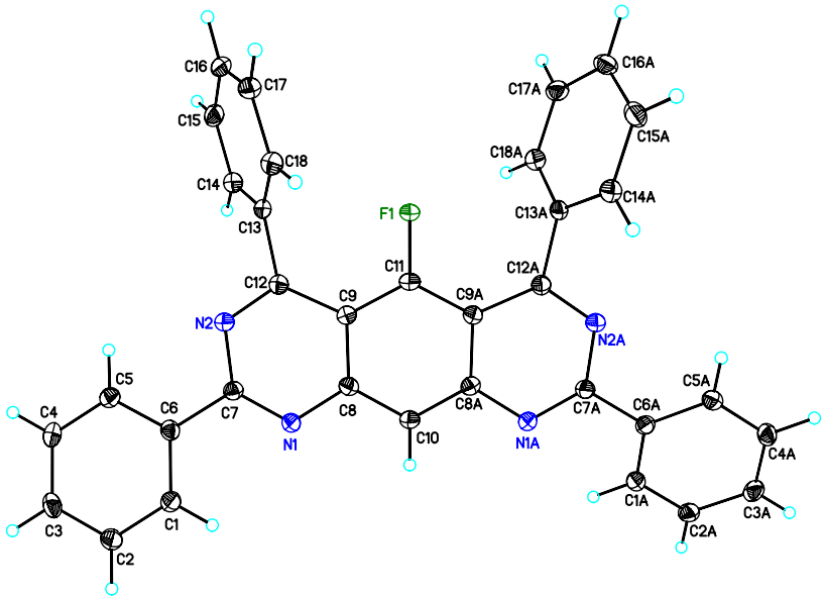
30, 16%



31, 6%

A sealed Schlenk tube under argon atmosphere was charged with anhydrous THF (4 ml) and halogen - substituted benzene (2 mmol), following by cooling down the mixture to -78 °C. A solution of lithium diisopropylamide (2M in THF, 4 mmol) was added dropwise to the above mixture and stirred for 1.5h, then anhydrous benzonitrile (4.4 mmol) was injected. The mixture was stirred for another 3 h at room temperature. The mixture was quenched by water. The combined organic layer was extracted with dichloromethane and brine, then dried over anhydrous $MgSO_4$. The solvent was evaporated by vacuum and the crude product was purified by column chromatography on silica gel (EA/Hexane = 1/4). The isolated product **29, 30, 31** was recrystallized in the solution of acetone and hexane (Acetone/Hexane = 1/3) and the structure was determined by X-ray crystallography.

X-ray structure of quinazoline (29) (CCDC 2248145).



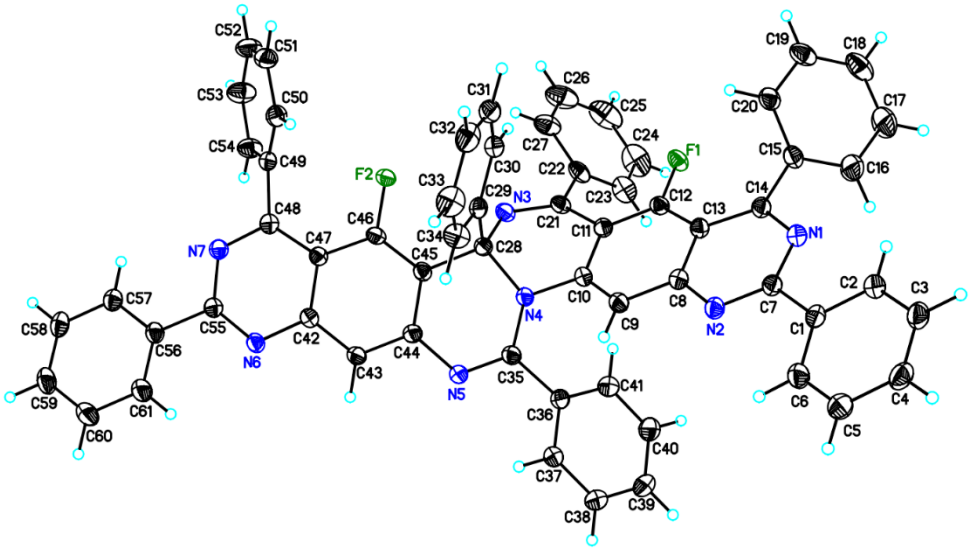
Empirical formula	C34 H21 F N4	
Formula weight	504.55	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 18.0446(6) Å	α= 90°.
	b = 11.8808(4) Å	β= 94.5198(12)°.
	c = 11.2129(4) Å	γ = 90°.
Volume	2396.39(14) Å^3	
Z	4	
F(000)	1048	
Density (calculated)	1.398 Mg/m^3	
Wavelength	1.54178 Å	
Cell parameters reflections used	9866	
Theta range for Cell parameters	4.46 to 77.83°.	
Absorption coefficient	0.711 mm^{-1}	
Temperature	100(2) K	
Crystal size	0.150 x 0.100 x 0.100 mm^3	

Data collection

Diffractometer	Bruker AXS D8 VENTURE, PhotonIII_C28
Absorption correction	Semi-empirical from equivalents

Max. and min. transmission	1.0000 and 0.9114
No. of measured reflections	28125
No. of independent reflections	2508 [R(int) = 0.0351]
No. of observed [I>2_igma(I)]	2388
Completeness to theta = 67.679°	99.4 %
Theta range for data collection	4.460 to 78.124°.
	Refinement
Final R indices [I>2sigma(I)]	R1 = 0.0377, wR2 = 0.1028
R indices (all data)	R1 = 0.0394, wR2 = 0.1050
Goodness-of-fit on F^2	1.012
No. of reflections	2508
No. of parameters	178
No. of restraints	0
Largest diff. peak and hole	0.259 and -0.263 e.$Å^{-3}$

X-ray structure of quinazoline (30) (CCDC 2248149).



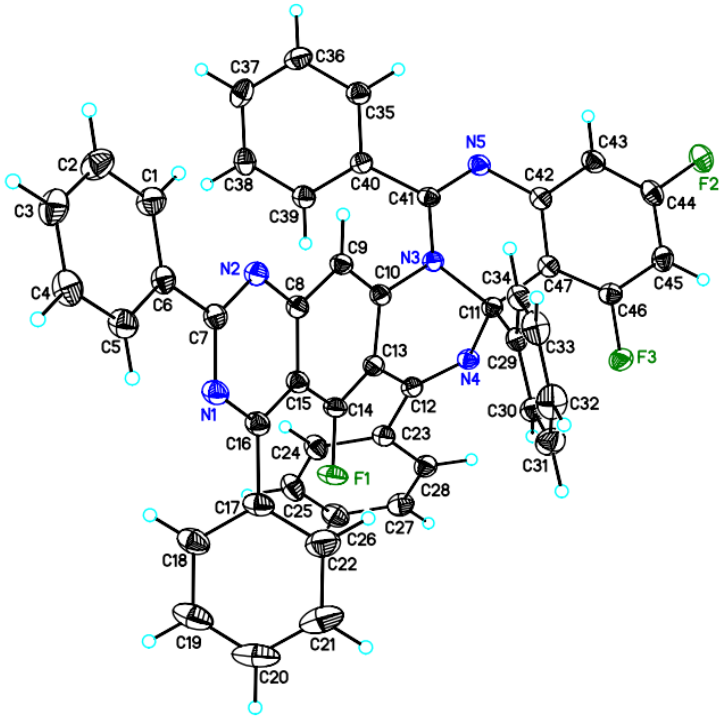
Empirical formula	C61 H37 F2 N7	
Formula weight	905.97	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.6106(2) Å	α= 109.3869(8)°.
	b = 13.7588(3) Å	β= 98.5209(8)°.
	c = 17.4536(4) Å	γ = 93.7331(8)°.
Volume	2581.46(9) $Å^3$	
Z	2	
F(000)	940	
Density (calculated)	1.166 Mg/m^3	
Wavelength	1.54178 Å	
Cell parameters reflections used	9907	
Theta range for Cell parameters	2.73 to 78.03°.	
Absorption coefficient	0.598 mm^{-1}	
Temperature	100(2) K	
Crystal size	0.150 x 0.150 x 0.100 mm^3	

Data collection

Diffractometer	Bruker AXS D8 VENTURE, PhotonIII_C28
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.9228
No. of measured reflections	47577
No. of independent reflections	10499 [R(int) = 0.0311]

No. of observed [I>2_igma(I)]	9669
Completeness to theta = 67.679°	98.9 %
Theta range for data collection	2.729 to 78.516°.
	Refinement
Final R indices [I>2sigma(I)]	R1 = 0.0426, wR2 = 0.1093
R indices (all data)	R1 = 0.0459, wR2 = 0.1128
Goodness-of-fit on F^2	1.003
No. of reflections	10499
No. of parameters	631
No. of restraints	0
Largest diff. peak and hole	0.317 and -0.250 e.$Å^{-3}$

X-ray structure of quinazoline (31) (CCDC 2248150).



Empirical formula	C47 H28 F3 N5	
Formula weight	719.74	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 16.0104(4) Å	α= 90°.
	b = 11.8607(3) Å	β= 102.6407(9)°.
	c = 18.9342(5) Å	γ = 90°.
Volume	3508.35(16) $Å^3$	
Z	4	
F(000)	1488	
Density (calculated)	1.363 Mg/m^3	
Wavelength	1.54178 Å	
Cell parameters reflections used	9187	
Theta range for Cell parameters	4.09 to 78.20°.	
Absorption coefficient	0.753 mm^{-1}	
Temperature	100(2) K	
Crystal size	0.250 x 0.200 x 0.150 mm^3	
	Data collection	
Diffractometer	Bruker AXS D8 VENTURE, PhotonIII_C28	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.8886
No. of measured reflections	69512
No. of independent reflections	7323 [R(int) = 0.0335]
No. of observed [I>2_igma(I)]	6916
Completeness to theta = 67.679°	99.3 %
Theta range for data collection	4.086 to 78.569°.
Refinement	
Final R indices [I>2sigma(I)]	R1 = 0.0392, wR2 = 0.1093
R indices (all data)	R1 = 0.0428, wR2 = 0.1154
Goodness-of-fit on F^2	1.054
No. of reflections	7323
No. of parameters	496
No. of restraints	0
Largest diff. peak and hole	0.370 and -0.312 e.$Å^{-3}$