Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Intramolecular Cyclization of Imidazo[1,2-*a*]pyridines *via* a Silver Mediated/ Palladium Catalyzed C-H Activation Strategy

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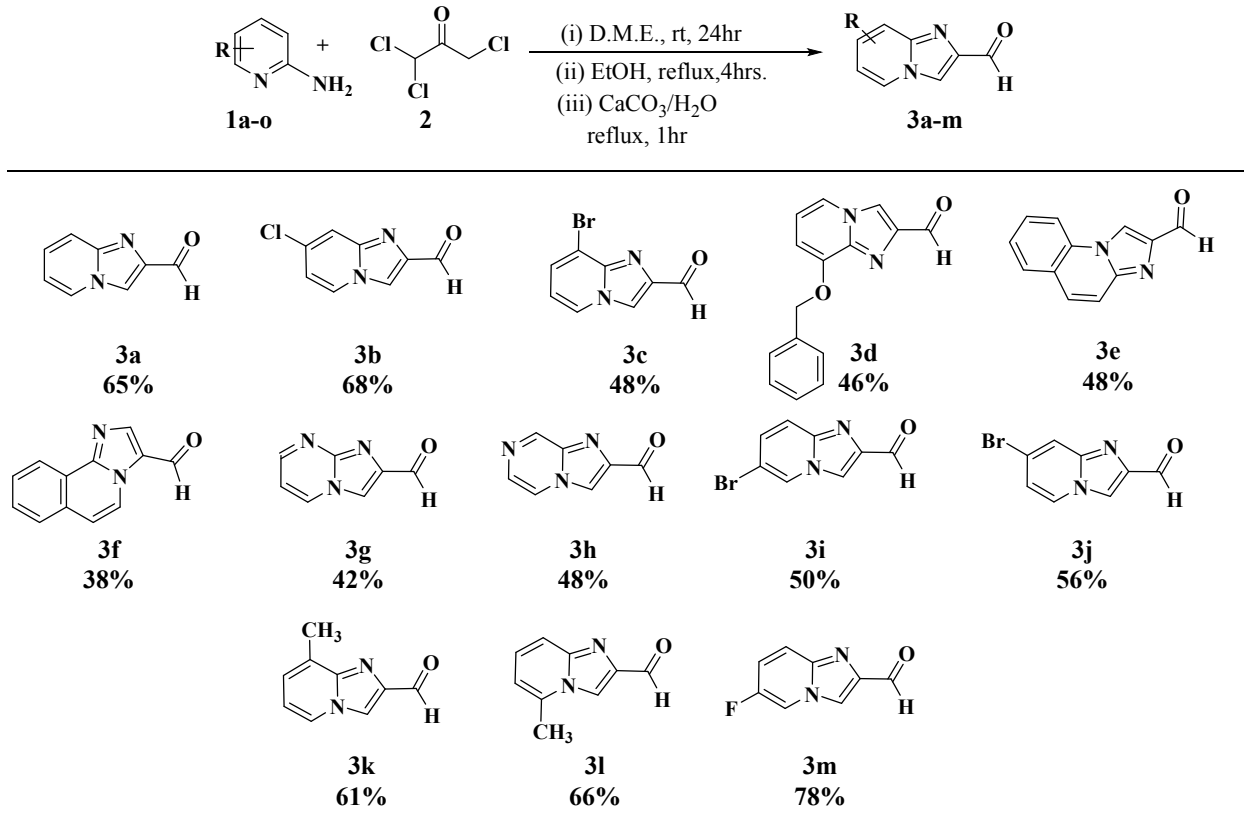
I. General Experimental Methods

General Methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on an Agilent 400 NMR spectrometer. Deuterated chloroform and deuterated dimethyl sulfoxide were used as solvents, unless stated otherwise. The spectra were calibrated against the residual solvent peak or TMS. Chemical shifts (δ) and coupling constants (*J*) are given in ppm (parts per million) and Hz (Hertz). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet. Purity of final compounds was assessed using a Thermo Finnigan LCQ Deca with a Thermo Surveyor LCMS system at wavelengths of 214 and 254 nm and confirmed >95%. All commercially available compounds were used without purification.

II. General experimental procedures

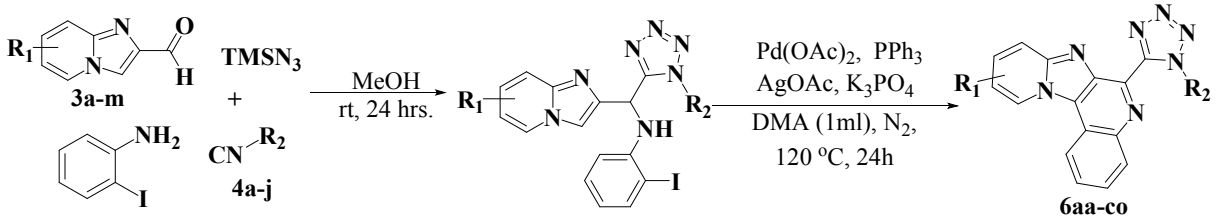
General procedure for synthesis of Imidazo[1,2-*a*]pyridine-2-carbaldehydes 3a-m.

Imidazo[1,2-*a*]pyridine carbaldehydes were synthesized by an established two-step process.[1] 1,1,3-trichloroacetone in dimethoxyethane (10 mL) was added to a solution of 2-aminopyridine (63 mmol) in dimethoxyethane (60 mL) and the reaction mixture was stirred at room temperature for 12 h. The precipitate was separated by filtration, suspended in ethanol (80 mL), and refluxed for 4 h till the solid dissolved completely. The reaction mixture was evaporated and extracted thoroughly with dichloromethane (50 mL). The combined extracts were dried over anhydrous sodium sulfate and evaporated using a rotary vacuum pump. The resulting dichloromethylimidazo[1,2-*a*]pyridine and 2.5 g calcium carbonate were suspended in 25 ml of water. The mixture was refluxed for 1 h and filtered. The filtrate was extracted with dichloromethane (50 mL). The combined extracts were dried over anhydrous sodium sulfate and evaporated using a rotary vacuum pump. The residue was purified on a silica gel column (1% MeOH in DCM) to obtained the product imidazo[1,2-*a*]pyridine-2-carbaldehyde (**3a**) as a solid.



Scheme 1: Synthesis of Imidazo[1,2-*a*]pyridine-2-carbaldehydes

1. General procedure for the synthesis of tetrazolyl pyrido imidazo[4,5-*c*]quinolone 6aa-6co.



Scheme 2: Synthesis of tetrazolyl pyrido imidazo[4,5-*c*]quinolones

2-Iodoaniline (0.04 mmol), substituted imidazo[1,2-*a*]pyridine-2-carbaldehydes (0.04 mmol), trimethyl silyl azide (0.04 mmol), and the corresponding isocyanide (0.04 mmol) were stirred in methanol (5ml) at rt for 24 hr. The reaction was monitored by LCMS, concentrated, dissolved in dimethylacetamide (2.0 mL), and degassed with N_2. Palladium acetate (10 mol %), triphenyl phosphine (20 mol %), AgOAc (1.5 equiv.), and K_3PO_4 (2.0 equiv.) were added to the reaction. The reaction was sealed and heated to 120 °C for 24 h. The reaction was monitored *via* LCMS, filtered, diluted with DCM (5ml), washed with water (2 x 3 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by flash

chromatography with 50-70% ethyl acetate/heptane or 1-5% DCM/methanol to afford the desired product (**6aa-co**) as a solid, which was confirmed by ^{1}H and ^{13}C NMR spectroscopy.

2. Extensive Optimization of the C-H activation step

Pd catalyst Optimization

The Ugi adduct [*N*-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(imidazo[1,2-*a*]pyridin-2-yl)methyl)-2-iodoaniline] (0.04 mmol), a Pd catalyst (S No. 1-6,10 mol %), triphenyl phosphine (20 mol %), AgOAc (1.5 equiv.), and K_3PO_4 (2.0 equiv.) were added to a vial containing degassed dimethylacetamide (2.0 mL). The reaction vessel was sealed and heated to 120 °C for 24 h. After completion of the reaction, the reaction yield of the desired product was determined by LCMS.

Table 1: Pd catalyst Optimization

S No.	Pd Catalyst	Yield (%)
1.	$PdCl_2$	16
2.	$Pd_2(dba)_3$	14
3.	$Pd(OAc)_2$	85
4.	$Pd(TFA)_2$	22
5.	$Pd(PPh_3)_4$	50
6.	$PdBr_2$	<5

Ag catalyst Optimization

The Ugi adduct [*N*-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(imidazo[1,2-*a*]pyridin-2-yl)methyl)-2-iodoaniline] (0.04 mmol), palladium acetate (10 mol %), triphenyl phosphine (20 mol %), a silver catalyst (S No. 1-6, 1.5 equiv.), and K_3PO_4 (2.0 equiv.) were added to a vial containing degassed dimethylacetamide (2.0 mL). The reaction vessel was sealed and heated to 120 °C for 24 h. After completion of the reaction, the reaction yield of the desired product was determined by LCMS.

Table 2: Ag catalyst Optimization

S No.	Ag Catalyst	Yield (%)
1.	AgI	11
2.	$AgNO_3$	12
3.	Ag_2O	nd
4.	Ag_2CO_3	<5
5.	AgOAc	85
6.	$AgBF_4$	nd

Ligand Optimization

The Ugi adduct [*N*-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(imidazo[1,2-*a*]pyridin-2-yl)methyl)-2-iodoaniline] (0.04 mmol), palladium acetate (10 mol %), a ligand (S No. 1-5, 20 mol %), AgOAc (1.5 equiv.), and K_3PO_4 (2.0 equiv.) were added to a vial containing degassed dimethylacetamide (2.0 mL). The reaction vessel was sealed and heated to 120 °C for 24 h. After completion of the reaction, the reaction yield of the desired product was determined by LCMS.

Table 3: Ligand Optimization

S No.	Ligand	Yield (%)
1.	PPh_3	85
2.	S-Phos	nd
3.	$P(OMe)_3$	10
4.	2,2′-Bipyridine	nd
5.	PMe_2Ph	nd

Base Optimization

The Ugi adduct [*N*-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(imidazo[1,2-*a*]pyridin-2-yl)methyl)-2-iodoaniline] (0.04 mmol), palladium acetate (10 mol %), triphenyl phosphine (20 mol %), AgOAc (1.5 equiv.), a base (S No. 1-6, 2.0 equiv.) were added to a vial containing degassed dimethylacetamide (2.0 mL). The reaction vessel was sealed and heated to 120 °C for 24 h. After completion of the reaction, the reaction yield of the desired product was determined by LCMS.

Table 4: Base Optimization

S No.	Bases	Yield (%)
1.	Na_2CO_3	15
2.	Cs_2CO_3	20
3.	K_2CO_3	18
4.	K^+*t*-BuO^-	26
5.	K_3PO_4	85
6.	KOH	12

Solvent Optimization

The Ugi adduct [*N*-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(imidazo[1,2-*a*]pyridin-2-yl)methyl)-2-iodoaniline] (0.04 mmol), palladium acetate (10 mol %), triphenyl phosphine (20 mol %), AgOAc (1.5 equiv.), and K_3PO_4 (2.0 equiv.) was added to a vial containing a degassed solvent (S No. 1-7, 2 mL). The reaction vessel was sealed and heated to 120 °C for 24 h. After completion of the reaction, the reaction yield of the desired product was determined by LCMS.

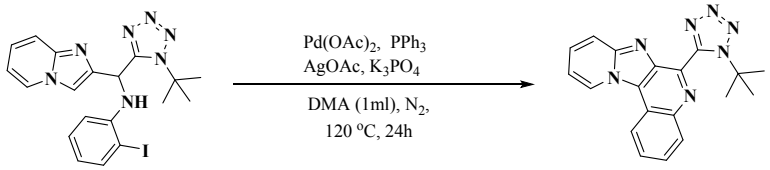
Table 5: Solvent Optimization

S No.	Solvents	Yield (%)
1.	DMF	34
2.	DMSO	nd
3.	Toluene	22
4.	DMA	85
5.	NMP	26
6.	Ethanol	nd
7.	TFE	nd

3. Control experiments for investigating the C-H activation reaction mechanism

To confirm the C-H activation reaction mechanism, a set of control experiments were performed. For this, the Ugi-adduct **5a** was synthesized by adding 2-iodoaniline (1 eq.), imidazo[1,2-*a*]pyridine-2-carbaldehydes (1 eq.), trimethylsilyl azide (1 eq.), and the corresponding isocyanide (1 eq.) and stirred in methanol (6 ml) at rt for 24hrs. After the completion of the reaction, the reaction mixture was concentrated and the Ugi adduct **5a** was isolated. Next, the C-H activation reaction was performed with variations from the standard conditions as follows: palladium acetate (10 mol %), triphenyl phosphine (20 mol %), AgOAc (1.5 eq.), and K_3PO_4 (2.0 eq.) in dimethylacetamide (2.0 mL) (Table 1). The reaction yield was monitored with LCMS.

Performing the reaction without base afforded less than 10% of the desired cyclo-aromatized product. No product was detected in the absence of $Pd(OAc)_2$, PPh_3, or AgOAc, suggesting all components are necessary.

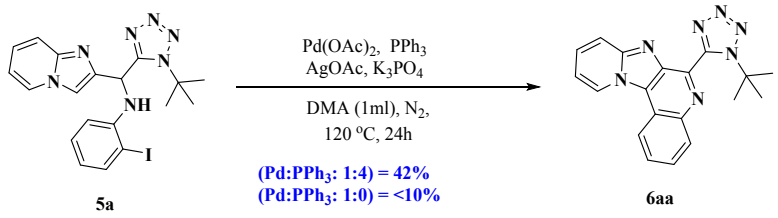


5a **6aa**

S No.	Variation in reaction conditions	Yield[a]
1.	No Base	<10%
2.	No $Pd(OAc)_2$	nd
3.	No AgOAc	10%

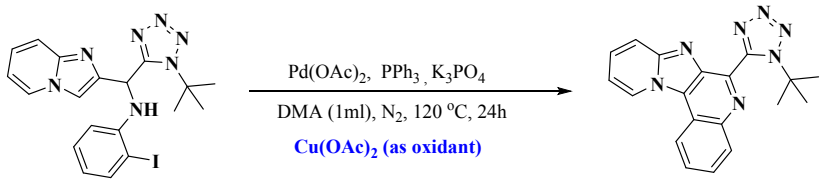
[a]LC yield

When the ratio of Pd:PPh_3 is decreased from 1:2 to 1:0 the product yield decreases, suggesting PPh_3 has multiple roles.



5a **6aa**

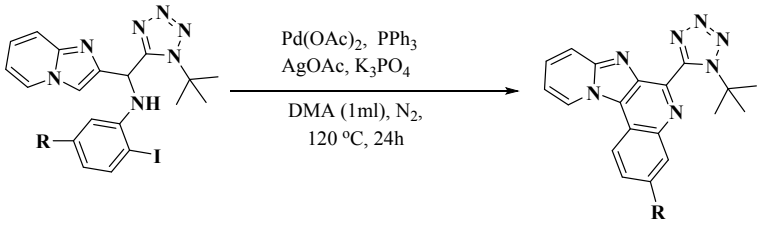
When AgOAc was replaced by $Cu(OAc)_2$ (1.5 eq.) only 24% of the product was obtained, reinforcing the fact that AgOAc is important beyond acting as an oxidant.



5a **6aa, 24%**

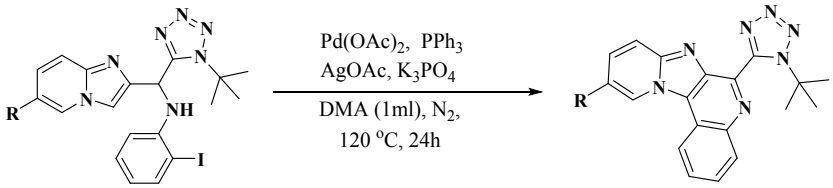
Additionally, competition experiments were also performed by adding equal amounts of starting Ugi substrates subjected to our standard optimized conditions for the C-H activation step.

Differently substituted imidazopyridines (Me *vs* Br) formed Me substituted products preferentially. Similarly, a methyl electron donating group on 2-iodoaniline displayed higher reactivity than a bromine electron withdrawing group. This suggests that oxidative addition is reversible and occurs before the rate-limiting step.[2,3]



5bk; R = CH_3 (1eq.)
5bl; R = NO_2 (1eq.)

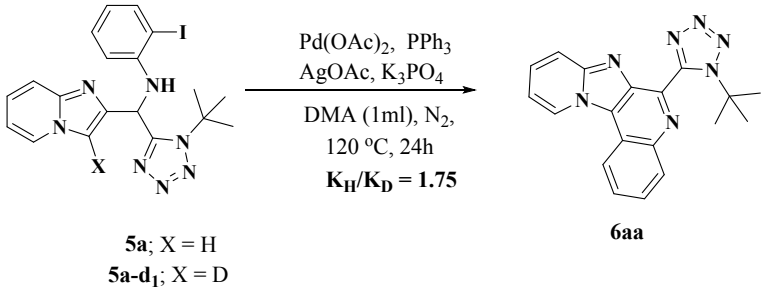
6bk; R = CH_3, 54%
6bl; R = NO_2, traces
6bk:6bl = 54:1



5bf; R= CH_3 (1eq.)
5bi; R= Br (1eq.)

6bf:6bi = 82:1

Kinetic Isotope Effect Experiments



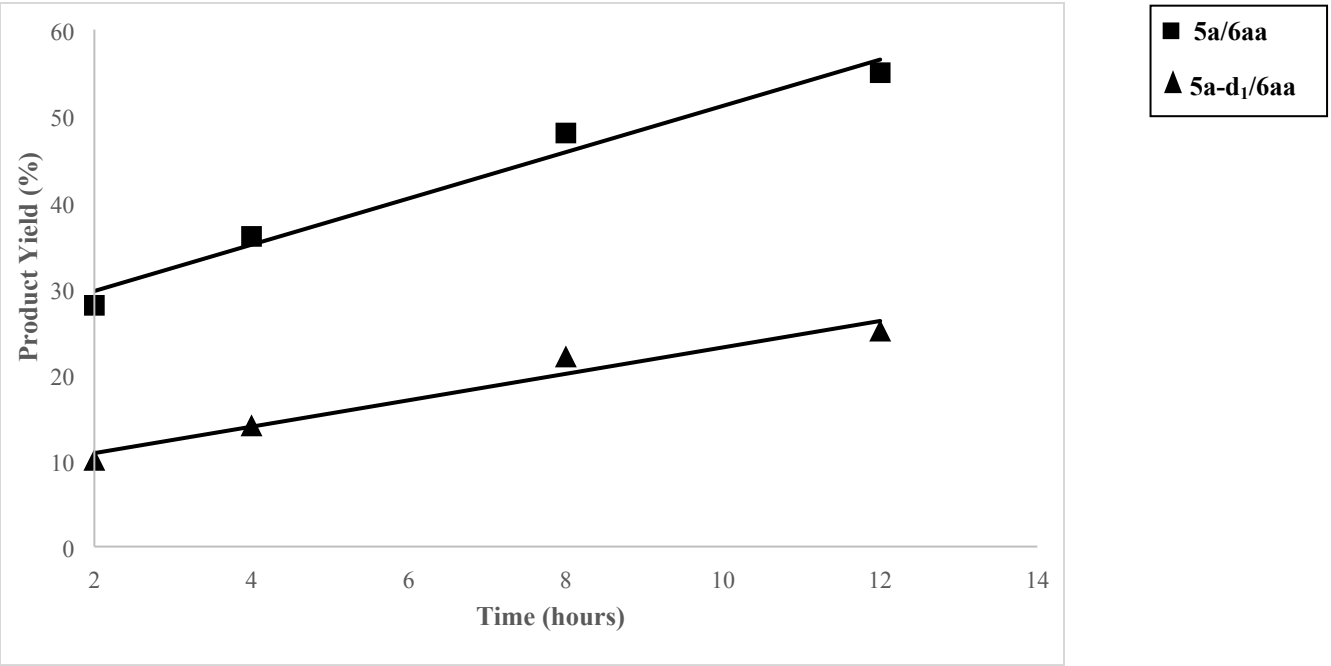
5a; X = H
5a-d$_1$; X = D

6aa

Scheme 3: Reaction scheme to study kinetic isotope effect

Ugi adduct, *N*-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(imidazo[1,2-*a*]pyridin-2-yl)methyl)-2-iodoaniline **5a** (0.02 mmol) or *N*-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(imidazo[1,2-*a*]pyridin-2-yl)methyl)-2-iodoaniline **5a-d$_1$** (0.02 mmol), were added to two separate dried reaction vessels, equipped with a magnetic stir bar along with palladium acetate (10 mol %), triphenyl phosphine (20 mol %), AgOAc (1.5 equiv.), K_3PO_4 (2.0 equiv.) and degassed dimethylacetamide (2.0 mL). Each reaction was stirred at 120 ^oC under argon for a select period of time. Following, the reaction mixture was cooled to room temperature, filtered, and extracted with DCM (5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and analyzed by LCMS using *p*-nitrobenzaldehyde as an internal standard.

S No.	2h	4h	8h	12h
5a/6aa (% yield)	28	36	48	55
5a-d$_1$-6aa (% yield)	10	14	22	25



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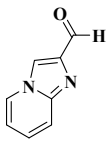
1. S. Dalapati, B. K. Paul, S. Jana, N. Guchhait, *Sens. Actuators, B.* **2011**, *157*, 615-620.
2. C. Colletto, S. Islam, F. J.-Hernandez, I. Larrosa, *J. Am. Chem. Soc.* **2016**, *138*, 1677−1683.
3. (a) B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 12898−12899; (b) E. V. Vinogradova, B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2012**, *134*, 11132−11135.

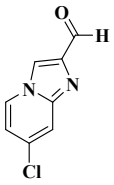
III. Experimental data of intermediates and final compounds

Imidazo[1,2-*a*]pyridine-2-carbaldehyde (3a)



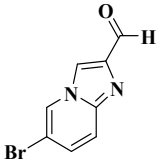
Dark yellow solid; Yield: 65%; R_f = 0.30 (50% EtOAc/Hexane); Melting point:108-110°C;^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H), 8.68 (d, J = 0.7 Hz, 1H), 8.65 (dt, J = 5.7, 1.2 Hz, 1H), 7.71 – 7.68 (m, 1H), 7.44 – 7.40 (m, 1H), 7.06 (td, J = 6.8, 5.7 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 188.22, 145.53, 143.36, 128.53, 127.63, 118.93, 118.67, 114.48; LCMS (ESI): Calculated for $[M]^+$ $C_8H_6N_2O$ 147.0514, found 147.1508

7-chloroimidazo[1,2-*a*]pyridine-2-carbaldehyde (3b)



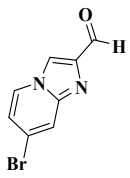
Brown solid; Yield: 68%; R_f = 0.29 (50% EtOAc/Hexane); Melting point:181-183°C;^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.15 (s, 1H), 8.12 (dd, J = 7.3, 0.8 Hz, 1H), 7.70 – 7.69 (m, 1H), 6.92 (dd, J = 7.3, 2.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.54, 145.44, 144.32, 133.15, 126.81, 117.90, 116.39, 115.60; LCMS (ESI): Calculated for $[M+H]^+$ $C_8H_5ClN_2O$ 181.0124, found 181.0826.

6-bromoimidazo[1,2-*a*]pyridine-2-carbaldehyde (3i)



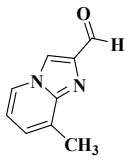
Dark yellow solid; Yield: 50%; R_f = 0.32 (50% EtOAc/Hexane); Melting point:208-210°C;^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.36 (s, 1H), 8.13 (s, 1H), 7.60 (d, J = 9.7 Hz, 1H), 7.36 (dd, J = 9.7, 1.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.65, 144.09, 130.33, 130.31, 126.53, 119.88, 115.22, 109.40; LCMS (ESI): Calculated for $[M]^+$ $C_8H_5BrN_2O$ 225.9565, found 225.3767.

7-bromoimidazo[1,2-*a*]pyridine-2-carbaldehyde (3j)



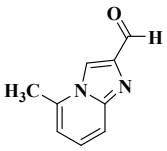
Yellow solid; Yield: 56%; R_f = 0.36 (50% EtOAc/Hexane); Melting point: 110-112°C;^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.14 (s, 1H), 8.05 (d, J = 7.3 Hz, 1H), 7.90 (s, 1H), 7.03 (d, J = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.56, 140.81, 126.72, 126.71, 121.36, 120.52, 118.64, 115.55; LCMS (ESI): Calculated for $[M]^+$ $C_8H_5BrN_2O$ 225.0450, found 225.2704.

8-methylimidazo[1,2-*a*]pyridine-2-carbaldehyde (3k)



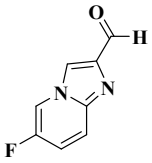
Dark brown solid; Yield: 61%; R_f = 0.34 (50% EtOAc/Hexane); Melting point:121-122°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.15 (s, 1H), 8.04 (d, J = 6.8 Hz, 1H), 7.08 – 7.06 (m, 1H), 6.81 (t, J = 6.9 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.05, 146.46, 143.17, 129.40, 124.93, 124.31, 116.12, 114.50, 17.08; LCMS (ESI): Calculated for $[M+H]^+$ $C_9H_8N_2O$ 161.0670, found 161.2260.

5-methylimidazo[1,2-*a*]pyridine-2-carbaldehyde (3l)



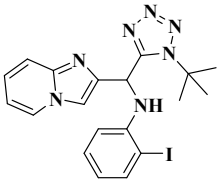
Dark brown solid; Yield: 66%; R_f = 0.41 (50% EtOAc/Hexane); Melting point:169-170°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.60 (s, 1H), 7.60 (d, *J* = 9.8 Hz, 1H), 7.40-7.38 (d, *J* = 2.4 Hz, 1H), 6.93 (d, *J* = 6.8 Hz, 1H), 2.68 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 188.23, 146.01, 143.34, 137.09, 127.79, 116.73, 116.14, 113.31, 18.47; LCMS (ESI): Calculated for $[M+H]^+$ $C_9H_8N_2O$ 161.0670, found 161.2346.

6-fluoroimidazo[1,2-*a*]pyridine-2-carbaldehyde (3m)



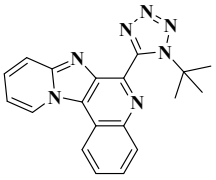
Light yellow solid; Yield: 78%; R_f = 0.42 (50% EtOAc/Hexane); Melting point:165-167°C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 10.14 (s, 1H), 8.18 (s, 1H), 8.14 – 8.12 (m, 1H), 7.72 – 7.68 (m, 1H), 7.26 – 7.22 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.57, 154.17(d, *J* = 243.41Hz), 144.72, 143.46, 120.05(d, *J* = 10.1Hz), 119.44(d, *J* = 26.26Hz), 116.38, 113.04(d, *J* = 40.4Hz); LCMS (ESI): Calculated for $[M+H]^+$ $C_8H_5FN_2O$ 165.0419, found 165.2369.

***N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(imidazo[1,2-*a*]pyridin-2-yl)methyl)-2-iodoaniline (5a)**



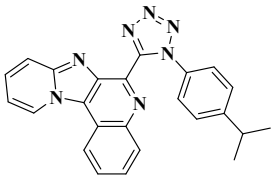
Orange-yellow solid; Yield: 89%; R_f = 0.40 (50% EtOAc/Hexane);^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, *J* = 6.8 Hz, 1H), 7.97 (s, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 9.1 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 6.96 – 6.92 (m, 2H), 6.65 (d, *J* = 8.5 Hz, 1H), 6.54 (t, *J* = 7.5 Hz, 1H), 5.76 (d, *J* = 8.5 Hz, 1H), 1.72 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.11, 145.68, 144.54, 144.00, 139.35, 129.78, 127.66, 125.76, 120.49, 117.16, 112.92, 112.88, 111.48, 86.93, 62.62, 49.48, 29.77; LCMS (ESI): Calculated for $[M]^+$ $C_{19}H_{20}IN_7$ 473.3255, found 473.8524.

6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6aa)



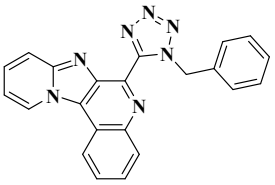
Light yellow solid; Yield: 85%; R_f = 0.45 (50% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.14 (d, *J* = 7.1 Hz, 1H), 8.53 (d, *J* = 8.3 Hz, 1H), 8.38 (d, *J* = 8.4 Hz, 1H), 7.87 (t, *J* = 9.2 Hz, 2H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.57 (m, 1H), 7.21 (t, *J* = 6.9 Hz, 1H), 1.69 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 150.68, 148.28, 142.49, 142.30, 137.49, 131.64, 129.41, 129.06, 127.34, 127.22, 127.02, 119.55, 119.21, 118.42, 113.72, 62.52, 30.04; HRMS (EI): Calculated for $[M+H]^+$ $C_{19}H_{17}N_7$ 344.1579, found 344.1618.

6-(1-(4-isopropylphenyl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6ab)



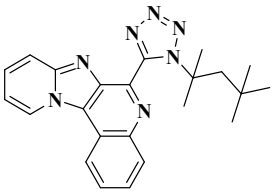
Off-white solid; Yield: 68% ; R_f = 0.60 (50% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, J = 6.9 Hz, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 9.4 Hz, 1H), 7.86 (t, J = 7.6 Hz, 1H), 7.74 (t, J = 7.7 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H), 2.93 (s, J = 8.0 Hz, 1H), 1.23 (d, J = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.98, 150.77, 148.32, 148.30, 142.40, 132.97, 131.80, 129.57, 129.20, 127.45, 127.32, 127.31, 127.17, 126.92, 125.46, 119.81, 119.10, 118.49, 113.80, 33.87, 23.79; HRMS (EI): Calculated for $[M+H]^+$ $C_{24}H_{19}N_{77}$ 406.1735, found 406.1782.

6-(1-benzyl-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6ac)



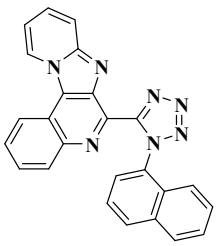
Dark yellow solid, Yield: 90%; R_f = 0.53 (50% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (d, J = 7.1 Hz, 1H), 8.59 (dd, J = 8.3, 0.9 Hz, 1H), 8.45 (dd, J = 8.3, 1.2 Hz, 1H), 8.16 (d, J = 9.2 Hz, 1H), 7.92 (td, J = 7.7,1.4 Hz, 1H), 7.85 (td, J = 7.6,1.3 Hz, 1H), 7.66 – 7.62 (m, 1H), 7.36 (d, J = 2.1 Hz, 1H), 7.36 – 7.33 (m, 2H), 7.23 – 7.20 (m, 3H), 6.41 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.45, 148.60, 142.10, 138.93, 136.61, 134.75, 131.51, 129.37, 129.23, 128.67, 128.28, 128.06, 127.83, 127.43, 127.04, 120.17, 119.21, 118.61, 113.72, 52.86; HRMS (EI): Calculated for $[M+H]^+$ $C_{22}H_{15}N_7$ 378.1422, found 378.1406.

6-(1-(2,4,4-trimethylpentan-2-yl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6ad)



Light brown solid; Yield: 73%; R_f = 0.46 (50% EtOAc/Hexane);^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (d, J = 7.1 Hz, 1H), 8.52 (d, J = 8.2 Hz, 1H), 8.36 (d, J = 8.3 Hz, 1H), 7.89 – 7.83 (m, 2H), 7.78 (t, J = 7.0 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.19 (t, J = 6.9 Hz, 1H), 2.23 (s, 2H), 1.63 (s, 6H), 0.91 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.95, 148.34, 142.78, 142.21, 137.88, 131.62, 129.16, 128.96, 127.24, 127.19, 126.98, 119.63, 119.21, 118.47, 113.56, 65.98, 53.84, 31.82, 30.78, 30.17; HRMS (EI): Calculated for $[M+H]^+$ $C_{23}H_{25}N_7$ 400.2142, found 400.2245.

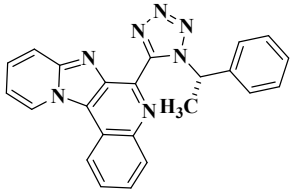
6-(1-(naphthalen-1-yl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinoline(6ae)



Bright-yellow solid; Yield: 55% ; R_f = 0.319 (5% Methanol in DCM); ^{1}H NMR (400 MHz, $CDCl_3$ in DMSO-d_6) δ 9.62 (d, J = 7.1 Hz, 1H), 8.92 (d, J = 8.3 Hz, 1H), 8.27 (d, J = 2.1 Hz, 1H), 8.09 (d, J = 7.3 Hz, 1H), 7.96 – 7.89 (m, 5H), 7.76 (d, J = 7.2 Hz, 2H), 7.63 – 7.54 (m, 3H), 7.33 (t, J = 6.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$ in DMSO-d_6) δ 142.20, 133.20, 132.62, 132.26, 131.16, 130.87, 129.60, 129.42, 129.28, 129.23, 128.62, 128.05, 127.90, 127.75, 127.69, 127.69, 127.66,

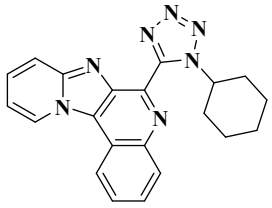
127.59, 124.44, 122.84, 120.83, 120.80, 118.74, 118.69, 114.14; HRMS (EI): Calculated for $[M+H]^+$ $C_{25}H_{15}N_7$ 414.1422, found 414.1463.

(*S*)-6-(1-(1-phenylethyl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6af)



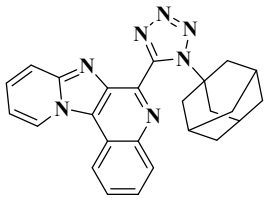
Light brown solid; Yield: 70%; R_f= 0.50 (50% EtOAc/Hexane);^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, J = 7.1 Hz, 1H), 8.46 (d, J = 8.0 Hz, 1H), 8.37 (d, J = 6.8 Hz, 1H), 8.01 (d, J = 9.3 Hz, 1H), 7.80 (td, J = 7.7, 7.1, 1.4 Hz, 1H), 7.75 (td, J = 7.7, 7.1, 1.4 Hz, 1H), 7.56-.52 (m,1H), 7.39 (d, J = 7.3 Hz, 2H), 7.24 – 7.12 (m, 4H), 7.06 (q, J = 7.1 Hz, 1H), 2.16 (d, J = 7.1 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.29, 148.48, 142.02, 140.15, 139.28, 136.82, 131.40, 129.23, 129.07, 128.60, 128.07, 127.64, 127.27, 127.02, 126.84, 119.93, 119.14, 118.42, 113.58, 59.38, 22.32; HRMS (EI): Calculated for $[M+H]^+$ $C_{23}H_{17}N_7$ 392.1579, found 392.161.

6-(1-cyclohexyl-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinoline(6ag)



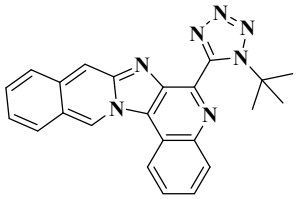
Light brown solid; Yield: 72%; R_f= 0.47 (50% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$)δ 9.17 (d, J = 7.1 Hz, 1H), 8.56 (d, J = 8.3 Hz, 1H), 8.38 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 9.3 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.22 (t, J = 6.9 Hz, 1H), 5.39-5.32 (m,1H), 2.36-2.33 (m, 2H), 2.21-2.12 (m, 2H), 2.00-1.97 (m, 2H), 1.79 – 1.74 (m, 1H), 1.49-1.37 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.90, 148.31, 142.76, 142.19, 137.86, 131.62, 129.09, 128.91, 127.20, 127.13, 126.96, 119.64, 119.16, 118.45, 113.50, 65.93, 53.79, 31.77, 30.74, 30.12; HRMS (EI): Calculated for $[M+H]^+$ $C_{21}H_{19}N_7$ 370.1735, found 370.1779.

6-(1-(adamantan-1-yl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinoline (6ah)



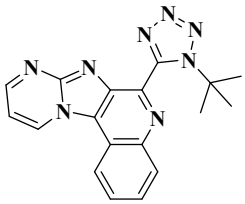
Off-white solid; Yield: 80%; R_f = 0.51 (50% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, J = 7.1 Hz, 1H), 8.57 (d, J = 8.4 Hz, 1H), 8.41 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.3 Hz, 1H), 7.89 (t, J = 8.0 Hz, 1H), 7.81 (t, J = 7.7 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.22 (t, J = 6.9 Hz, 1H), 2.38 – 2.36 (m, 6H), 2.09 – 2.06 (m, 3H), 1.64 – 1.57 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.43, 148.14, 142.60, 142.32, 137.22, 131.56, 129.59, 129.11, 127.48, 127.29, 127.01, 119.52, 119.29, 118.41, 113.86, 63.37, 42.08, 35.60, 29.53; LCMS (ESI): Calculated for $[M+H]^+$ $C_{25}H_{23}N_7$ 422.2048, found 422.4697.

6-(1-(tert-butyl)-1*H*-tetrazol-5-yl)isoquinolino[2',3':1,2]imidazo[4,5-*c*]quinoline (6ba)



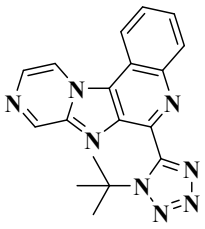
Light yellow solid; Yield: 90%; R_f = 0.69 (50% EtOAc/Hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 – 8.82 (m, 1H), 8.75 (d, J = 8.4 Hz, 1H), 8.46 – 8.42 (m, 1H), 8.24 – 8.20 (m, 2H), 7.98 – 7.93 (m, 3H), 7.84 (d, J = 9.5 Hz, 1H), 7.78 (t, J = 7.5 Hz, 1H), 1.60 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 150.80, 149.72, 143.38, 142.14, 138.64, 134.44, 133.55, 131.21, 131.19, 130.01, 129.22, 128.56, 128.01, 126.78, 124.82, 122.98, 119.00, 118.93, 117.68, 62.79, 29.87; HRMS (EI): Calculated for $[M+H]^+$ $C_{23}H_{19}N_7$ 394.1735, found 394.1779.

6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)pyrimido[1',2':1,2]imidazo[4,5-*c*]quinoline (6bb)



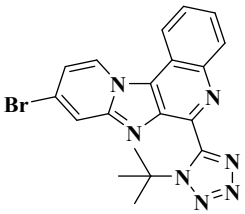
Off-white solid; Yield: 92%; R_f = 0.42 (5% Methanol in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 – 8.94 (m, 3H), 8.30 (d, J = 7.5 Hz, 1H), 7.95 – 7.86 (m, 2H), 7.11 – 7.06 (m, 1H), 1.80 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.30, 151.84, 150.60, 148.30, 144.19, 136.26, 133.83, 130.17, 129.66, 128.81, 123.70, 121.94, 118.91, 109.07, 64.04, 30.10; HRMS (EI): Calculated for $[M+H]^+$ $C_{18}H_{16}N_8$ 345.1531, found 345.1568.

6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)pyrazino[1',2':1,2]imidazo[4,5-*c*]quinolone (6bc)



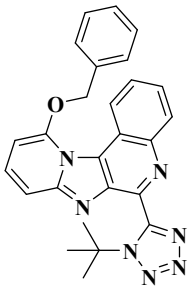
Light brown solid; Yield*: 56% (Isolated yield# 29%); R_f = 0.39 (5% Methanol in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 9.00 (dd, J = 4.8, 1.4 Hz, 1H), 8.57 (d, J = 8.2 Hz, 1H), 8.44 (d, J = 7.2 Hz, 1H), 8.29 (d, J = 4.8 Hz, 1H), 7.97 (t, J = 7.7 Hz, 1H), 7.91 (t, J = 7.0 Hz, 1H), 1.71 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.28, 147.22, 143.75, 142.78, 141.78, 137.46, 131.75, 129.91, 129.65, 128.54, 126.60, 119.96, 119.55, 118.10, 62.70, 30.07; HRMS (EI): Calculated for $[M+H]^+$ $C_{18}H_{16}N_8$ 345.1531, found 345.1566.

9-bromo-6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinoline (6bd)



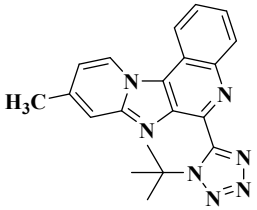
White solid; Yield*: 49% (Isolated yield# 22%); R_f = 0.48 (50% EtOAc/Hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 9.19 (d, J = 8.3 Hz, 1H), 8.43 (d, J = 8.2 Hz, 1H), 8.05 (t, J = 7.0 Hz, 1H), 8.00 – 7.94 (m, 3H), 1.57 (s, 9H);^{13}C NMR (101 MHz, DMSO-d_6) δ 150.74, 147.08, 142.58, 142.29, 137.79, 134.07, 131.09, 129.71, 129.23, 128.37, 127.55, 122.05, 119.84, 118.56, 108.16, 62.80, 29.84; HRMS (EI): Calculated for $[M]^+$ $C_{19}H_{16}BrN_7$ 422.29, found 422.0726.

11-(benzyloxy)-6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinoline (6be)



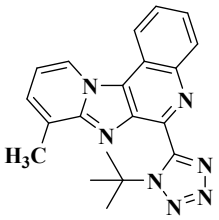
White solid; Yield*: 42% (Isolated yield 17%)#; R_f = 0.532 (5% Methanol in DCM); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (t, J = 4.0 Hz, 1H), 9.06 (d, J = 8.5 Hz, 1H), 8.42 (d, J = 8.3 Hz, 1H), 8.04 (t, J = 7.0 Hz, 1H), 7.96 (t, J = 7.1 Hz, 1H), 7.56 (d, J = 6.8 Hz, 2H), 7.47 – 7.40 (m, 3H), 7.30 (d, J = 3.6 Hz, 2H), 5.44 (s, 2H), 1.59 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 150.88, 148.28, 143.57, 142.67, 142.25, 137.06, 136.37, 134.06, 131.17, 129.67, 128.99, 128.71, 128.57, 128.17, 121.92, 121.25, 118.76, 114.23, 107.98, 70.77, 55.35, 29.78; HRMS (EI): Calculated for $[M+H]^+$ $C_{26}H_{23}N_7O$ 450.1998, found 450.2037.

6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-9-methylpyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6bf)



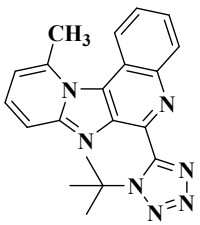
Off-white solid; Yield: 52%; R_f = 0.259 (5% Methanol in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.59 (d, J = 8.5 Hz, 1H), 8.41 (d, J = 8.4 Hz, 1H), 7.91 – 7.80 (m, 3H), 7.45 (d, J = 9.4 Hz, 1H), 2.58 (s, 3H), 1.70 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.77, 147.65, 142.70, 142.29, 137.89, 132.52, 131.69, 128.80, 127.13, 126.84, 124.44, 123.47, 119.24, 119.00, 118.66, 62.46, 30.04, 18.74; HRMS (EI): Calculated for $[M+H]^+$ $C_{20}H_{19}N_7$ 358.1735, found 358.1777.

6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-8-methylpyrido[1',2':1,2]imidazo[4,5-*c*]quinoline (6bg)



Pale yellow solid; Yield: 71%; R_f = 0.349 (5% Methanol in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, J = 7.0 Hz, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 8.3 Hz, 1H), 7.86 (t, J = 7.7 Hz, 1H), 7.78 (t, J = 7.7 Hz, 1H), 7.35 (d, J = 6.8 Hz, 1H), 7.09 (t, J = 6.9 Hz, 1H), 2.67 (s, 3H), 1.68 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.82, 149.09, 142.97, 142.38, 137.68, 131.69, 129.93, 128.76, 127.39, 127.29, 127.08, 124.72, 119.10, 118.69, 113.49, 62.49, 30.01, 17.62; HRMS (EI): Calculated for $[M+H]^+$ $C_{20}H_{19}N_7$ 358.1735, found 358.1772.

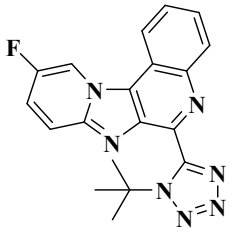
6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-11-methylpyrido[1',2':1,2]imidazo[4,5-*c*]quinoline (6bh)



Pale yellow solid; Yield: 56%; R_f = 0.279 (5% Methanol in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 – 8.37 (m, 2H), 7.79 – 7.73 (m, 3H), 7.52 – 7.48 (m, 1H), 6.92 (d, J = 6.5 Hz, 1H), 3.18 (s, 3H), 1.69 (s, 9H);^{13}C NMR (101 MHz, $CDCl_3$) δ 151.01, 150.74, 142.93, 142.64, 138.79, 138.55, 131.36, 129.97, 128.91, 127.56, 126.65, 123.62, 119.21, 117.18, 115.49, 62.42, 30.05, 24.15; LCMS (ESI): Calculated for $[M+Na]^+$ $C_{20}H_{19}N_7$ 380.1594, found 380.0731.

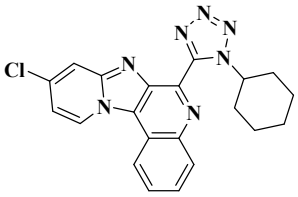
* LCMS Yield # Isolated Yields are low due to poor solubility.

6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-10-fluoropyrido[1',2':1,2]imidazo[4,5-*c*]quinoline (6bi)



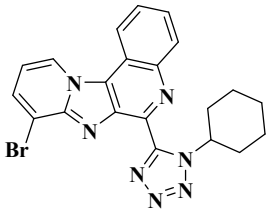
Light brown solid; Yield: 58%; R_f = 0.417 (5% Methanol in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.45 (d, J = 8.3 Hz, 1H), 8.01 – 7.92 (m, 2H), 7.86 (t, J = 7.7 Hz, 1H), 7.57 (t, J = 8.8 Hz, 1H), 1.71 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.47, 151.28 (d, J = 159.58 Hz), 146.01, 142.89, 142.33, 138.38, 136.80, 131.84, 129.24, 127.75, 122.01(d, J = 26.23Hz), 120.45(d, J = 9.09Hz), 118.99, 118.29, 113.85 (d, J = 42.4Hz), 62.59, 30.05; HRMS (EI): Calculated for $[M+H]^+$ $C_{19}H_{16}N_7F$ 362.1485, found 362.1523.

9-chloro-6-(1-cyclohexyl-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6ca)



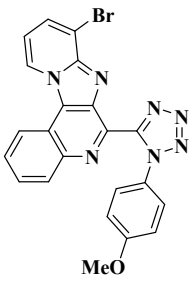
Yellow solid; Yield: 87%; R_f = 0.51 (50% EtOAc/Hexane);^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, J = 7.5 Hz, 1H), 8.50 (d, J = 8.3 Hz, 1H), 8.37 (d, J = 8.1 Hz, 1H), 8.01 (s, 1H), 7.88 (t, J = 7.7 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 5.36-5.29 (m, 1H), 2.30-2.35 (m, 2H), 2.20-2.12 (m, 2H), 2.01-1.96 (m, 2H), 1.79-1.74 (m, 1H), 1.46 – 1.36 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.95, 148.26, 142.50, 139.55, 137.32, 136.13, 131.84, 131.77, 129.36, 127.71, 127.30, 119.06, 118.49, 118.09, 115.51, 59.77, 32.99, 25.55, 25.06; LCMS (ESI): Calculated for $[M+H]^+$ $C_{21}H_{18}ClN_7$ 404.1346, found 404.4328.

8-bromo-6-(1-cyclohexyl-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6cb)



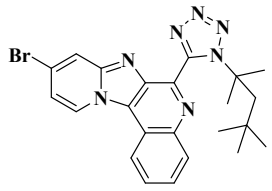
Light brown solid; Yield: 51%* (Isolated Yield: 22%)#; R_f = 0.55 (50% EtOAc/Hexane);^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (brs, 1H), 9.18 (dd, J = 8.3, 1.3 Hz, 1H), 8.43 (dd, J = 8.2, 1.3 Hz, 1H), 8.06-8.01 (m, 2H), 8.00 – 7.94 (m, 2H), 4.93 (tt, J = 7.8, 3.9 Hz, 1H), 2.32 – 2.24 (m, 2H), 2.06 – 1.95 (m, 2H), 1.89 – 1.84 (m, 2H), 1.68 – 1.64 (m, 1H), 1.37-1.30 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 150.70, 147.00, 142.44, 139.72, 137.15, 134.00, 131.26, 129.77, 129.07, 128.35, 128.10, 121.89, 119.95, 118.53, 108.19, 59.06, 25.11, 25.00; LCMS (ESI): Calculated for $[M+2]^+$ $C_{21}H_{18}BrN_7$ 448.3230, found 448.3231

6-(1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6cc)



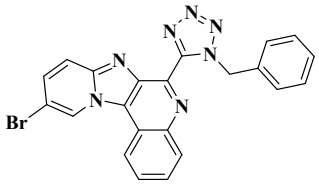
Pale yellow solid; Yield: 28%; R_f = 0.416 (5% Methanol in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, J = 6.1 Hz, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.16 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 8.3 Hz, 1H), 7.86 (t, J = 7.7 Hz, 1H), 7.74 (t, J = 7.7 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.51 (d, J = 7.8 Hz, 2H), 7.21 (t, J = 6.9 Hz, 1H), 6.89 (d, J = 7.8 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.36, 151.14, 148.56, 142.37, 139.19, 137.24, 131.88, 129.21, 129.08, 128.14, 127.48, 127.21, 127.05, 127.00, 119.98, 119.02, 118.57, 114.00, 113.55, 55.52; HRMS (EI): Calculated for $[M+H]^+$ $C_{22}H_{15}N_7O$ 394.1372, found 394.1408.

9-bromo-6-(1-(2,4,4-trimethylpentan-2-yl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6cd)



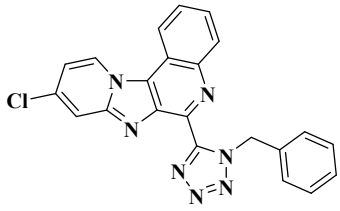
White solid; Yield: 58%* (Isolated Yield 22%)#; R_f = 0.447 (5% Methanol in DCM); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 9.20 (d, *J* = 8.5 Hz, 1H), 8.39 (d, *J* = 9.4 Hz, 1H), 8.08 – 8.03 (m, 2H), 8.01 – 7.95 (m, 3H), 2.07 (s, 2H), 1.55 (s, 6H), 0.86 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 150.94, 147.02, 142.73, 142.14, 137.85, 134.39, 134.10, 130.96, 129.73, 129.25, 128.45, 122.09, 119.81, 118.55, 108.14, 65.98, 53.11, 31.77, 30.70, 29.99; HRMS (EI): Calculated for $[M]^+$ $C_{23}H_{24}BrN_7$ 478.3980, found 478.1344.

6-(1-benzyl-1*H*-tetrazol-5-yl)-10-bromopyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6ce)



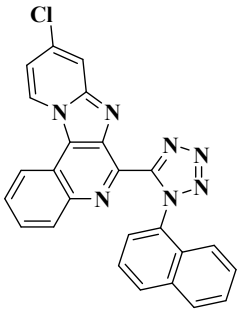
Brown solid; 53% yield; R_f = 0.48 (50% EtOAc/Hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 9.16 (d, *J* = 8.2 Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 8.05 (t, *J* = 10.2 Hz, 2H), 7.97 (t, *J* = 7.5 Hz, 2H), 7.68 – 7.59 (m, 2H), 7.30-7.29 (m, 3H), 6.15 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 151.20, 147.03, 142.28, 135.39, 134.02, 132.44, 131.95, 131.86, 131.14, 129.83, 129.25, 129.13, 129.07, 128.62, 128.39, 121.86, 119.97, 118.45, 109.99, 108.21, 52.15; HRMS (EI): Calculated for $[M+2]^+$ $C_{22}H_{14}BrN_7$ 458.0507, found 458.0547.

6-(1-benzyl-1*H*-tetrazol-5-yl)-9-chloropyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6cf)



Yellow solid; Yield: 65%* (Isolated Yield 37%)#; R_f = 0.539 (5% Methanol in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.07 (d, *J* = 7.3 Hz, 1H), 8.51 (d, *J* = 7.9 Hz, 1H), 8.44 (d, *J* = 8.2 Hz, 1H), 8.10 (brs, 1H), 7.93-7.84 (m, 2H), 7.35 – 7.31 (m, 2H), 7.22 – 7.17 (m, 4H), 6.39 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 150.28, 148.43, 142.27, 138.93, 136.11, 134.67, 131.64, 129.46, 128.69, 128.32, 128.02, 127.89, 127.81, 127.17, 119.05, 118.67, 118.26, 115.52, 109.99, 52.91; HRMS (EI): Calculated for $[M+H]^+$ $C_{22}H_{14}ClN_7$ 412.1033, found 412.1078.

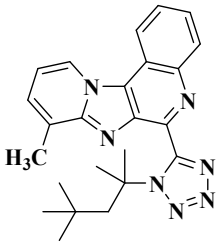
* LCMS Yield # Yields are low due to poor solubility.



9-chloro-6-(1-(naphthalen-1-yl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6cg)

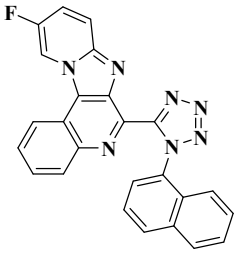
White solid; Yield: 52%* (isolated Yield 32%)#; R_f = 0.775 (5% Methanol in DCM); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.71 (d, J = 7.5 Hz, 1H), 8.99 (d, J = 8.4 Hz, 1H), 8.36 (brs, 1H), 8.23 (brs, 1H), 8.15 (d, J = 8.3 Hz, 1H), 8.02 – 7.96 (m, 4H), 7.86 (t, J = 8.0 Hz, 1H), 7.66 – 7.60 (m, 3H), 7.41 (d, J = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) 151.45, 148.51, 142.27, 138.88, 137.64, 136.13, 133.23, 132.64, 132.02, 131.11, 130.72, 129.87, 129.76, 128.80, 128.28, 128.24, 128.20, 128.08, 127.88, 124.55, 122.90, 121.34, 118.48, 117.40, 115.04; HRMS (EI): Calculated for $[M+H]^+$ $C_{25}H_{14}ClN_7$ 448.1033, found 448.1060.

8-methyl-6-(1-(2,4,4-trimethylpentan-2-yl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6ch)



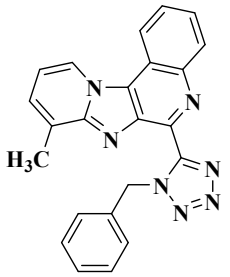
White solid; Yield: 68%* (Isolated Yield 45%)#; R_f = 0.371 (5% Methanol in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, J = 7.1 Hz, 1H), 8.57 (d, J = 8.3 Hz, 1H), 8.43 (d, J = 8.3 Hz, 1H), 7.89 (t, J = 7.6 Hz, 1H), 7.81 (t, J = 7.2 Hz, 1H), 7.36 (d, J = 6.8 Hz, 1H), 7.10 (t, J = 6.9 Hz, 1H), 2.69 (s, 3H), 2.18 (s, 2H), 1.64 (s, 6H), 0.91 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.03, 149.06, 143.29, 142.40, 137.84, 131.79, 130.06, 128.69, 127.40, 127.16, 127.04, 124.67, 119.09, 118.76, 113.42, 65.85, 53.92, 31.75, 30.70, 30.14, 17.59; HRMS (EI): Calculated for $[M+H]^+$ $C_{24}H_{27}N_7$ 414.2361, found 414.2400.

10-fluoro-6-(1-(naphthalen-1-yl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6ci)



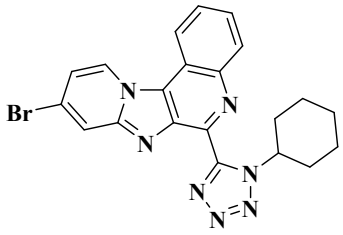
Yellow solid; Yield: 50%* (Isolated Yield 31%)#; R_f = 0.535 (5% Methanol in DCM); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89- 9.88 (m, 1H), 9.08 (d, J = 8.4 Hz, 1H), 8.36 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.12 – 8.08 (m, 1H), 8.01 – 7.94 (m, 5H), 7.85 (t, J = 8.0 Hz, 1H), 7.67 – 7.59 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.94 (d, J = 291.89 Hz), 152.15, 151.47, 146.48, 142.03, 139.25, 137.81, 133.22, 132.64, 132.04, 131.03, 129.75, 128.79, 128.22, 128.19, 127.87, 124.55, 123.45 (d, J = 26.26 Hz), 122.89, 122.71, 121.53, 121.34, 119.70 (d, J = 9.09 Hz), 118.54, 116.49 (d, J = 41.41 Hz); HRMS (EI): Calculated for $[M+H]^+$ $C_{25}H_{14}FN_7$ 432.1328, found 432.1373.

* LCMS Yield # Yields are low due to poor solubility.



6-(1-benzyl-1*H*-tetrazol-5-yl)-8-methylpyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6cj)

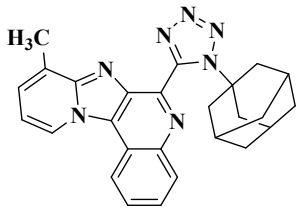
Dark yellow solid; Yield: 55%* (Isolated Yield 25%)#; R_f = 0.319 (5% Methanol in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 – 8.34 (m, 2H), 7.93 (d, J = 9.1 Hz, 1H), 7.79 – 7.76 (m, 2H), 7.55-7.51 (m, 1H), 7.34 (d, J = 5.2 Hz, 2H), 7.21-7.19 (m, 3H), 6.93 (d, J = 6.8 Hz, 1H), 6.36 (s, 2H), 3.13 (s, 3H).); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.30, 150.63, 142.60, 138.92, 138.42, 138.02, 134.73, 131.04, 129.95, 129.63, 128.64, 128.25, 128.08, 127.62, 126.67, 123.69, 119.26, 117.58, 115.56, 52.77, 23.95; HRMS (EI): Calculated for $[M+H]^+$ $C_{23}H_{17}N_7$ 392.1579, found 392.1622.



9-bromo-6-(1-cyclohexyl-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6ck)

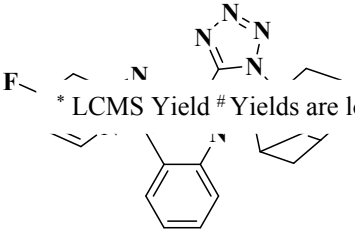
Off-white solid; Yield: 69%; R_f = 0.48 (50% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.57 (d, J = 8.4 Hz, 1H), 8.44 (d, J = 8.3 Hz, 1H), 8.06 (d, J = 9.7 Hz, 1H), 7.97 (t, J = 7.6 Hz, 1H), 7.89 (t, J = 7.6 Hz, 1H), 7.69 (d, J = 9.2 Hz, 1H), 5.41 (m, 1H), 2.38 – 2.33 (m, 2H), 2.22 – 2.14 (m, 2H), 2.04 – 1.96 (m, 2H), 1.69 – 1.67 (m, 1H), 1.49 – 1.41 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.89, 146.76, 142.57, 139.88, 137.01, 132.84, 131.92, 129.45, 127.85, 127.49, 126.97, 120.75, 119.17, 118.23, 108.46, 59.83, 33.01, 25.58, 25.08; LCMS (ESI): Calculated for $[M+2]^+$ $C_{21}H_{18}BrN_7$ 450.0820, found 450.4240.

6-(1-(adamantan-1-yl)-1*H*-tetrazol-5-yl)-8-methylpyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6cl)



Light yellow solid; Yield: 72%; R_f = 0.70 (50% EtOAc/Hexane); 1H NMR (400 MHz, DMSO-d_6) δ 9.55 (d, J = 7.0 Hz, 1H), 9.01 (d, J = 7.7 Hz, 1H), 8.36 (dd, J = 8.3, 1.2 Hz, 1H), 7.99 – 7.95 (m, 1H), 7.91 – 7.87 (m, 1H), 7.58 (d, J = 6.8 Hz, 1H), 7.26 (t, J = 6.9 Hz, 1H), 2.59-2.55 (m, 3H), 2.22-2.19 (m, 6H), 1.98-1.93 (m, 3H), 1.54-1.42 (m, 7H); 13C NMR (101 MHz, DMSO-d_6) δ 150.77, 149.15, 142.08, 142.01, 137.43, 131.16, 129.60, 129.04, 128.33, 128.02, 127.85, 127.26, 121.22, 118.81, 114.15, 63.35, 41.93, 35.30, 29.25, 17.61; LCMS (ESI): Calculated for $[M+H]^+$ $C_{26}H_{25}N_7$ 436.2205, found 436.5080.

6-(1-(adamantan-1-yl)-1*H*-tetrazol-5-yl)-9-fluoropyrido[1',2':1,2]imidazo[4,5-*c*]quinoline (6cm)

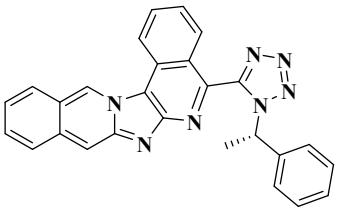


Brown solid; Yield: 58%; R_f= 0.70 (50% EtOAc/Hexane); ^{1}H NMR (400

* LCMS Yield # Yields are low due to poor solubility.

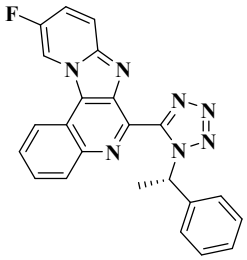
MHz, DMSO-d_6) δ 9.85 (dd, *J* = 4.7, 2.0 Hz, 1H), 9.08 (d, *J* = 7.7 Hz, 1H), 8.36 (dd, *J* = 8.3, 1.1 Hz, 1H), 8.05 (dd, *J* = 10.1, 5.2 Hz, 1H), 8.00 – 7.95 (m, 1H), 7.93 – 7.86 (m, 2H), 2.17-2.11 (m, 6H), 1.98-1.93 (m, 3H), 1.53-1.41 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.35 (d, *J* = 237.35 Hz), 150.54, 146.50, 142.86, 142.00, 138.48, 131.08, 129.63, 128.36 (d, *J* = 3.03 Hz),128.28, 123.37 (d, *J* = 27.27 Hz), 121.67, 119.75 (d, *J* = 9.09 Hz), 118.59, 116.56 (d, *J* = 43.43 Hz), 63.25, 42.04, 35.27, 29.23; LCMS (ESI): Calculated for $[M+H]^+$ $C_{25}H_{22}FN_7$ 440.1954, found 440.5656.

(*S*)-5-(1-(1-phenylethyl)-1*H*-tetrazol-5-yl)imidazo[1,2-b:4,5-*c*']diisoquinoline (6cn)



Brown solid; yield: 82%; R_f = 0.72 (50% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.96 – 8.90 (brm, 1H), 8.85 (d, *J* = 7.5 Hz, 1H), 8.56 (d, *J* = 8.1 Hz, 1H), 8.42 (d, *J* = 7.9 Hz, 1H), 7.86 – 7.79 (m, 3H), 7.76 – 7.71 (m, 2H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.24 – 7.17 (m, 2H), 6.94 (q, *J* = 6.5 Hz, 1H), 2.20 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 150.67, 147.73, 142.95, 139.95, 139.03, 136.19, 131.56, 130.76, 130.41, 129.55, 128.84, 128.74, 128.59, 128.11, 127.53, 126.97, 126.88, 125.93, 123.60, 122.89, 119.41, 118.30, 114.71, 59.34, 22.29; LCMS (ESI): Calculated for $[M+H]^+$ $C_{27}H_{19}N_7$ 442.1735, found 442.3128.

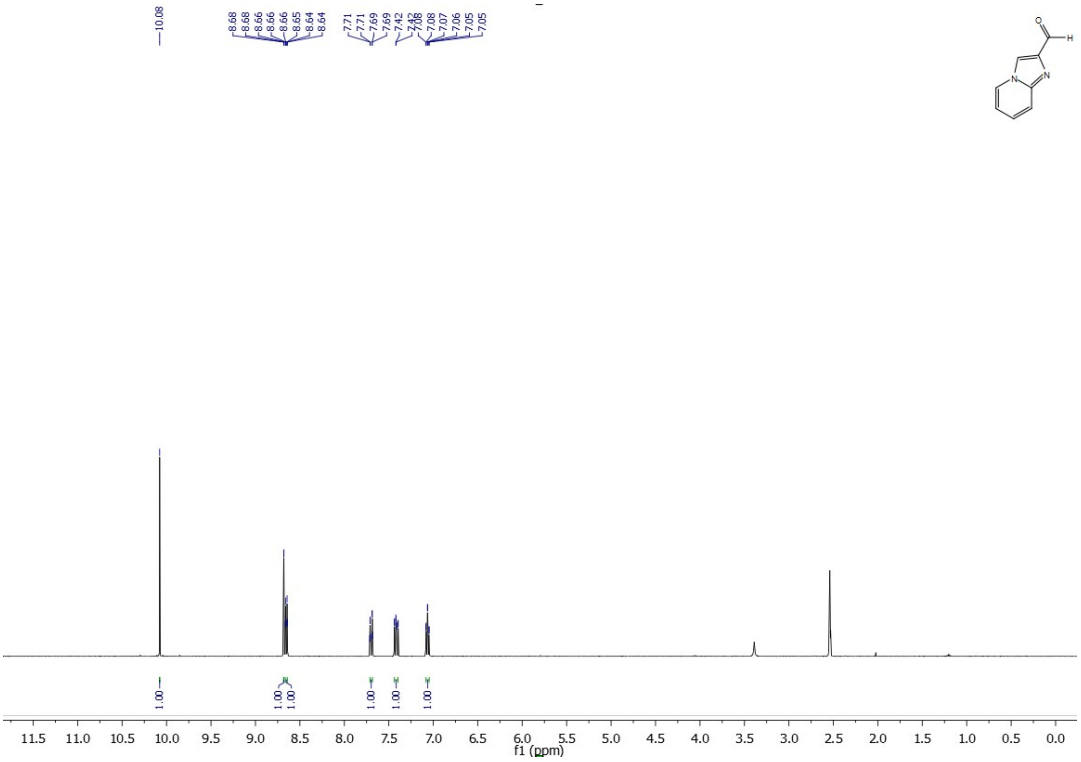
(*S*)-10-fluoro-6-(1-(1-phenylethyl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6co)

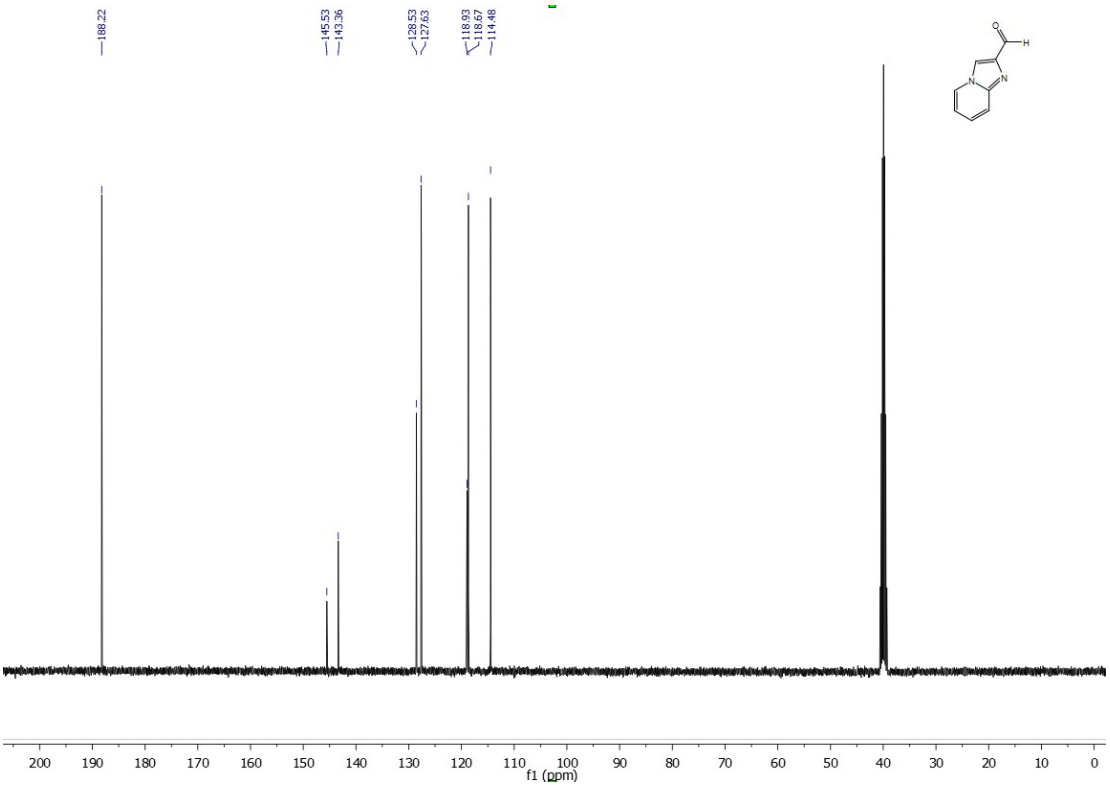


Dark-yellow solid; Yield: 87%; R_f = 0.563 (5% Methanol in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (brs, 1H), 8.52 – 8.45 (m, 2H), 8.14 – 8.09 (m, 1H), 7.94 (t, *J* = 7.6 Hz, 1H), 7.87 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 2H), 7.25 – 7.16 (m, 3H), 7.12 (q., *J* = 7.1 Hz, 1H), 2.18 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.49, 151. (d, *J* = 205.03 Hz), 146.18, 142.09, 140.15, 139.74, 137.62 (d, *J* = 2.02 Hz), 131.61, 129.32, 128.64, 128.43 (d, *J* = 3.03 Hz),128.11, 127.70, 126.83, 121.92 (d, *J* = 26.26 Hz), 120.81 (d, *J* = 9.09 Hz), 118.63(d, *J* = 67.67 Hz), 113.92, 113.50, 59.49, 22.34; HRMS (EI): Calculated for $[M+H]^+$ $C_{23}H_{16}FN_7$ 410.1485, found 410.1510.

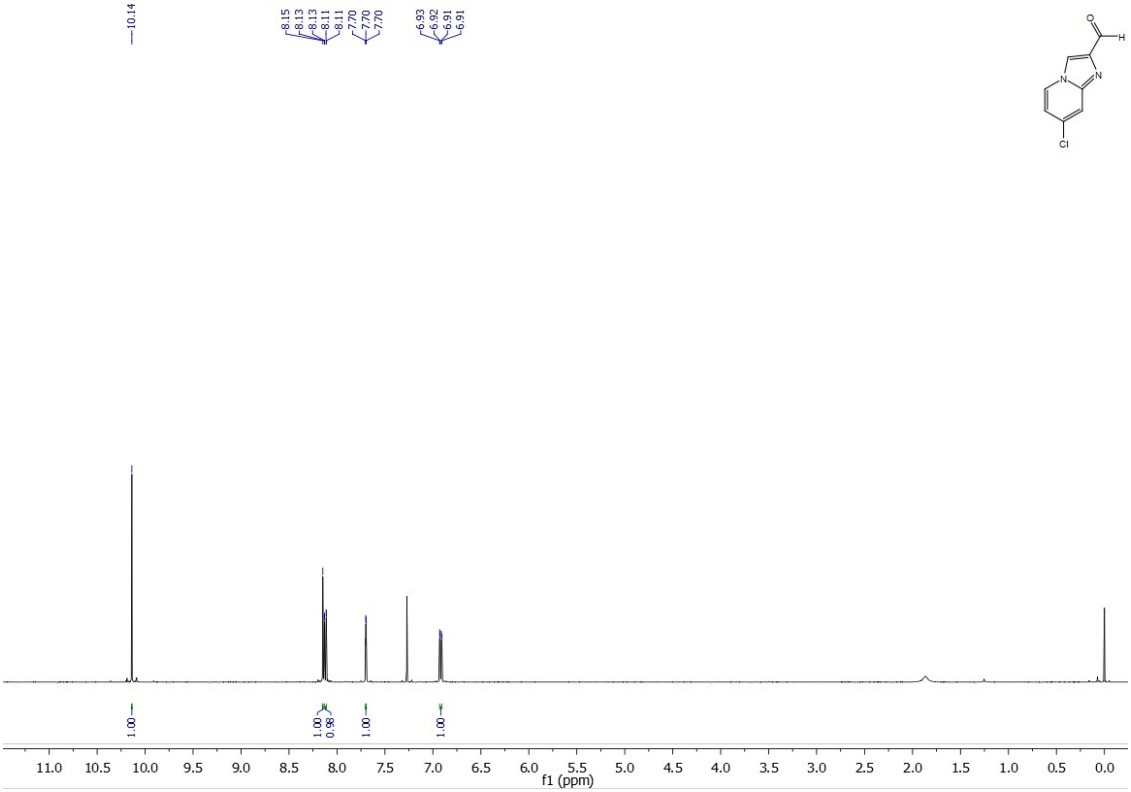
IV. ^{1}H NMR and ^{13}C NMR spectra of final compounds

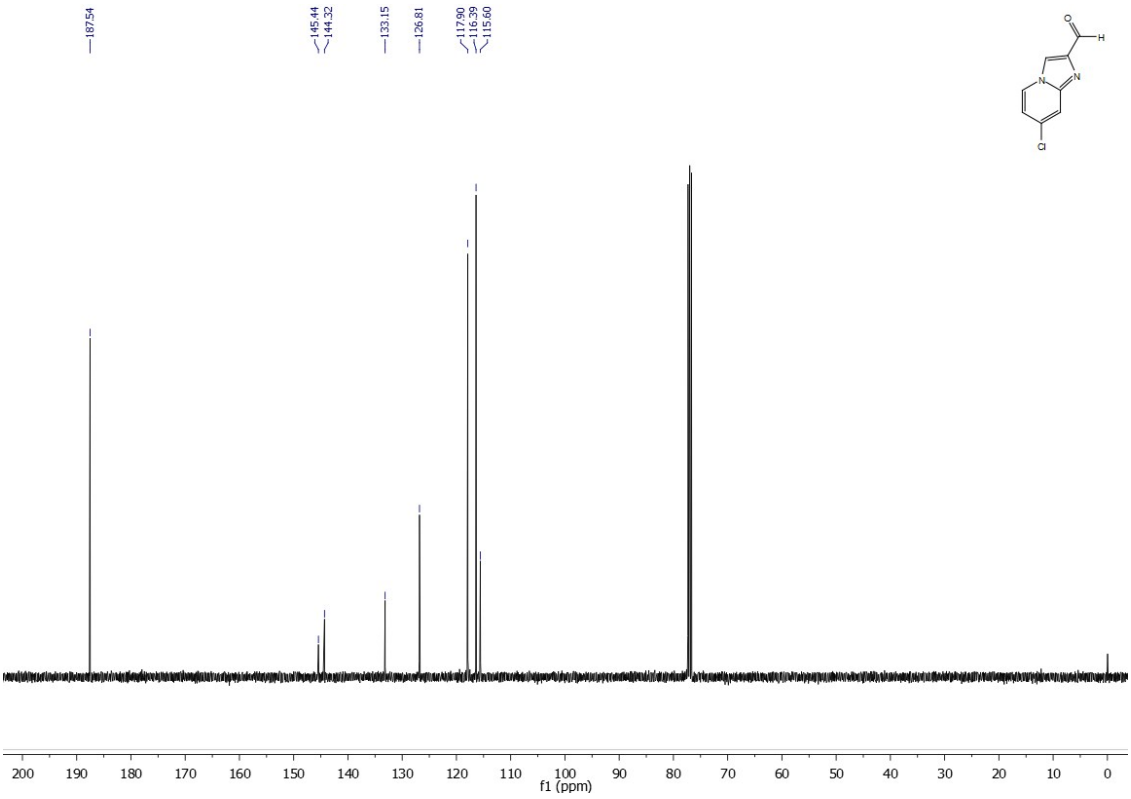
^{1}H NMR and ^{13}C NMR for Imidazo[1,2-*a*]pyridine-2-carbaldehyde (3a)



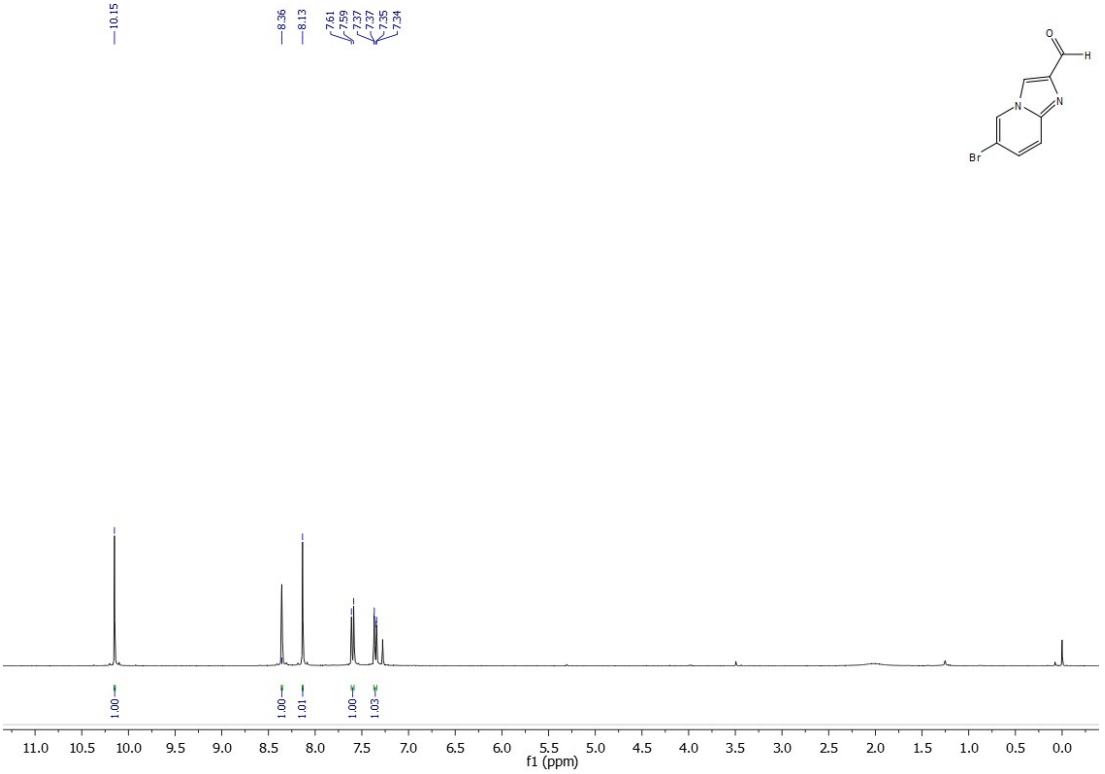


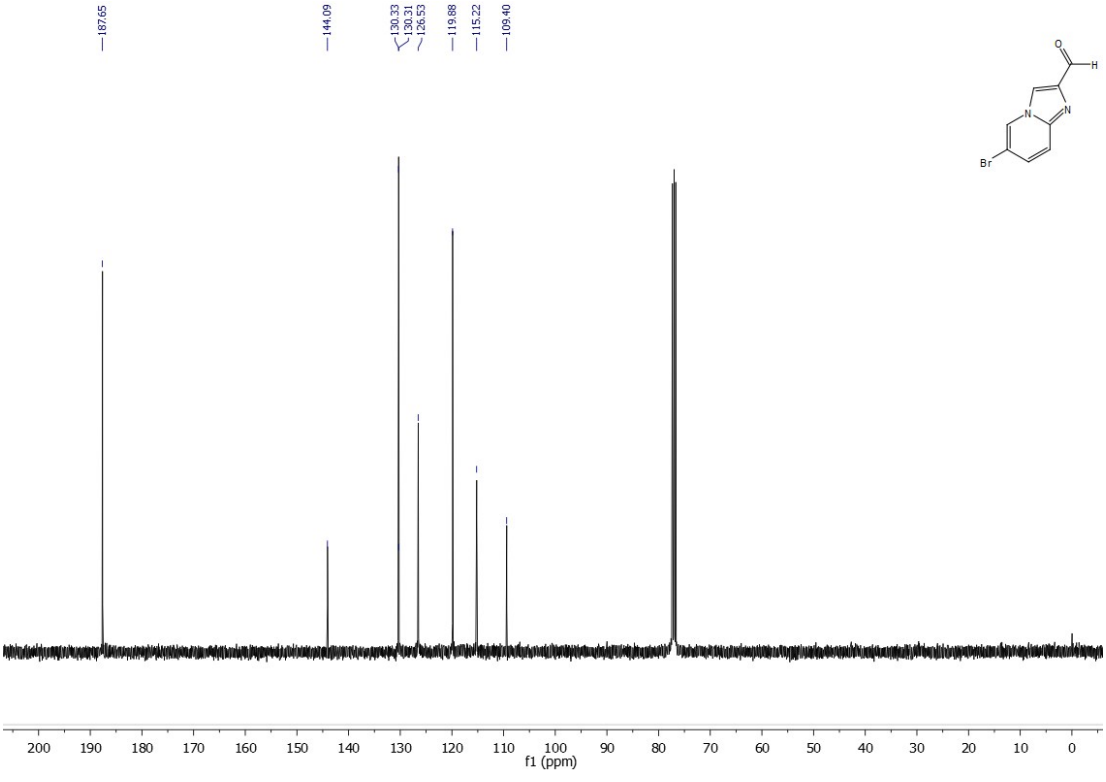
^{1}H NMR and ^{13}C NMR for 7-chloroimidazo[1,2-*a*]pyridine-2-carbaldehyde (3b)



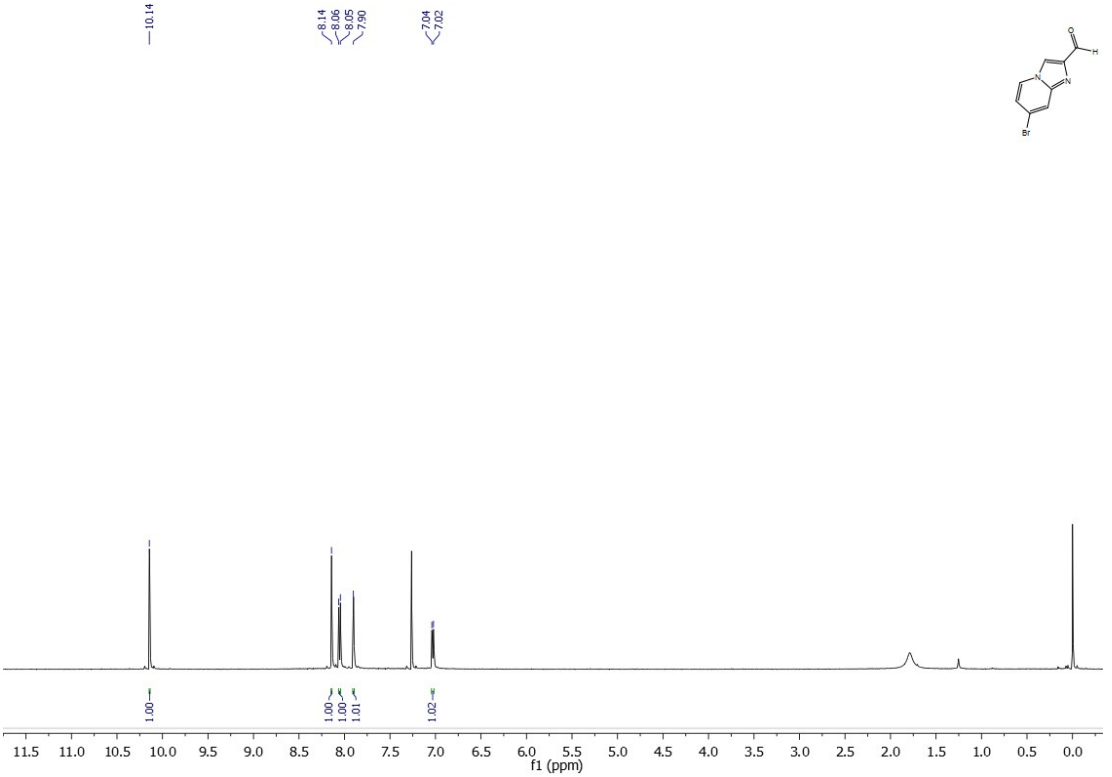


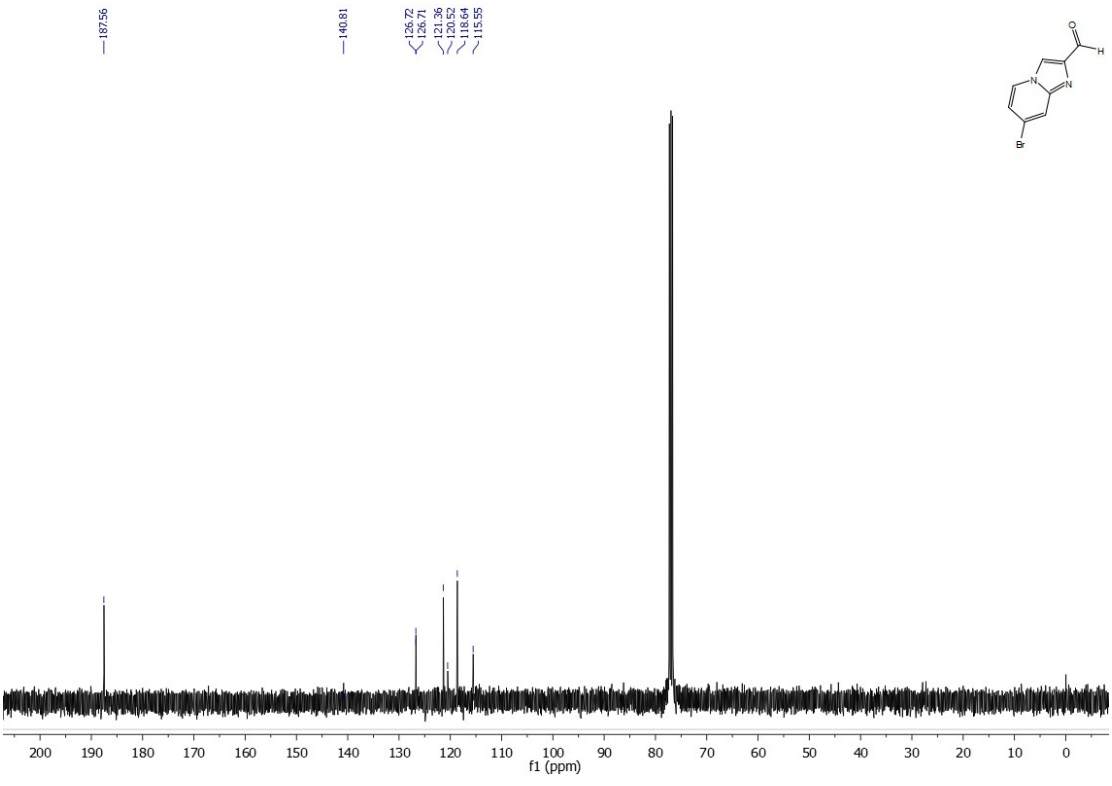
^{1}H NMR and ^{13}C NMR for 6-bromoimidazo[1,2-*a*]pyridine-2-carbaldehyde (3i)



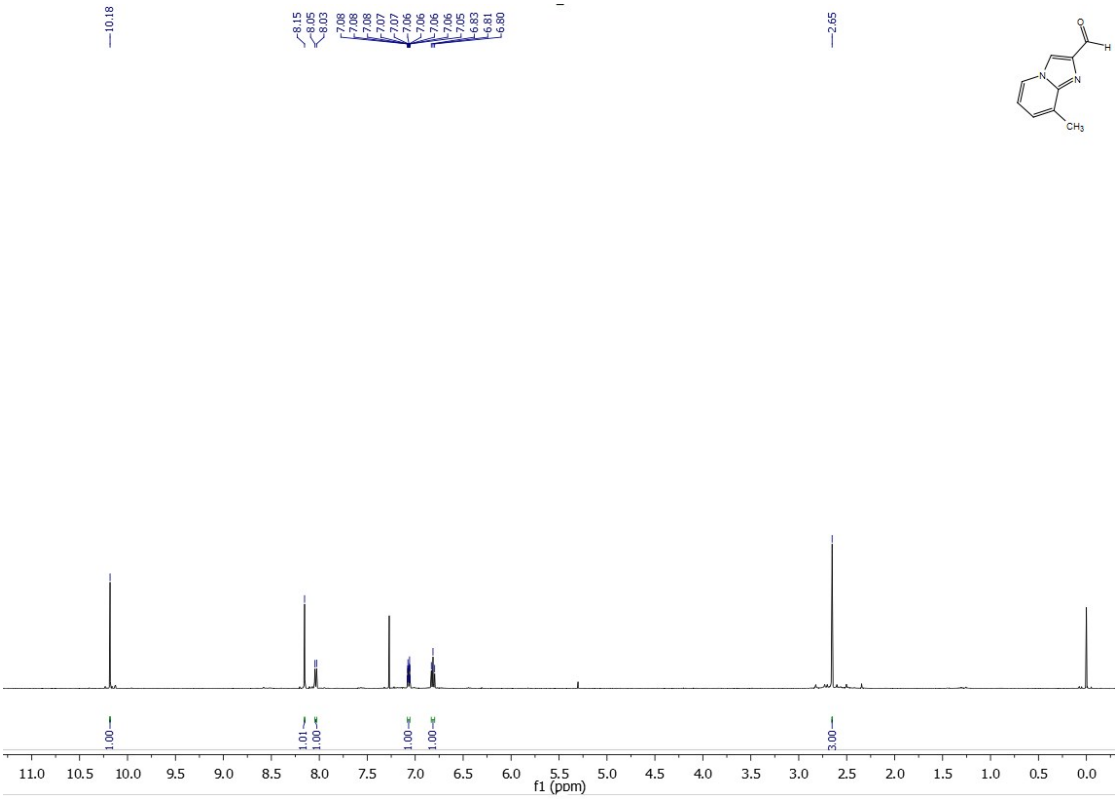


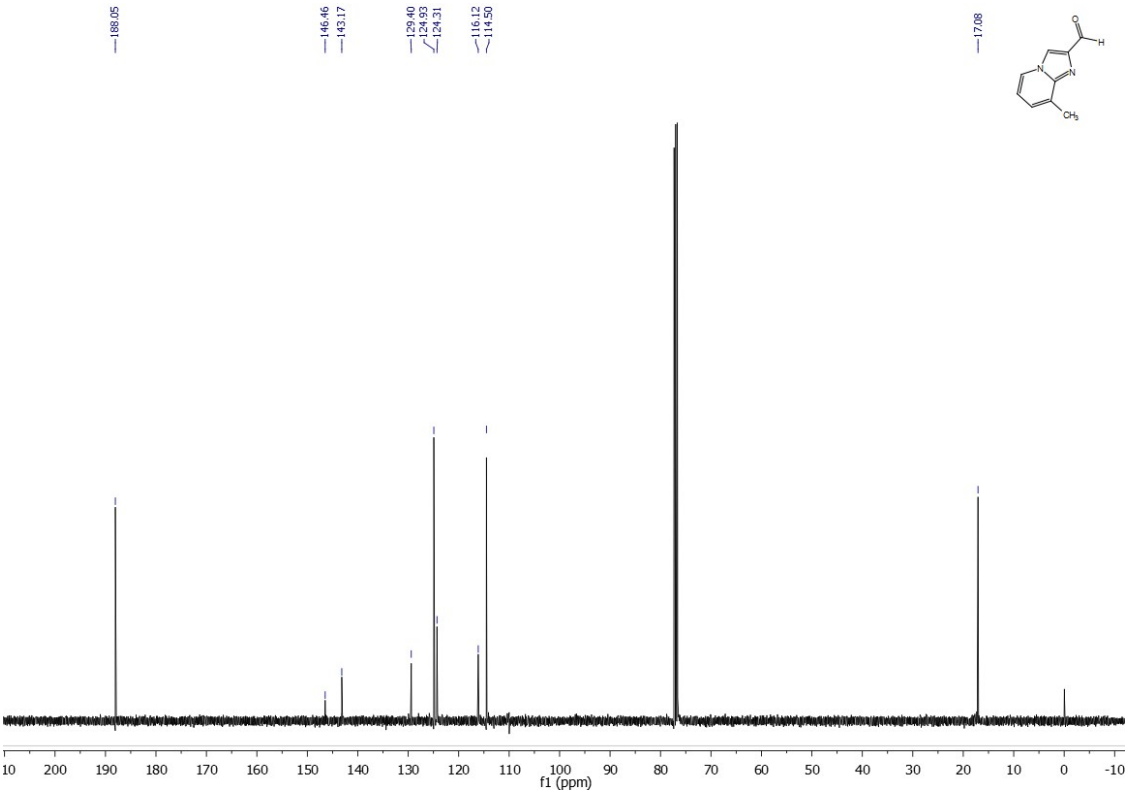
^{1}H NMR and ^{13}C NMR for 7-bromoimidazo[1,2-*a*]pyridine-2-carbaldehyde (3j)



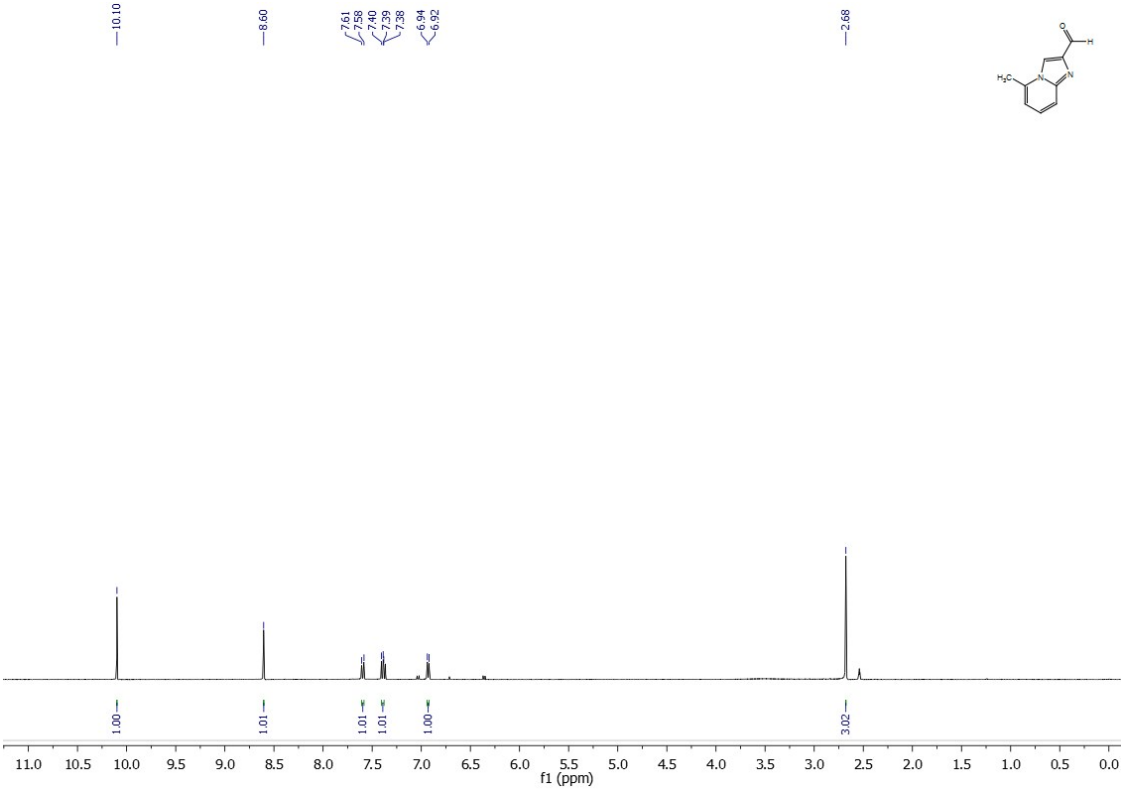


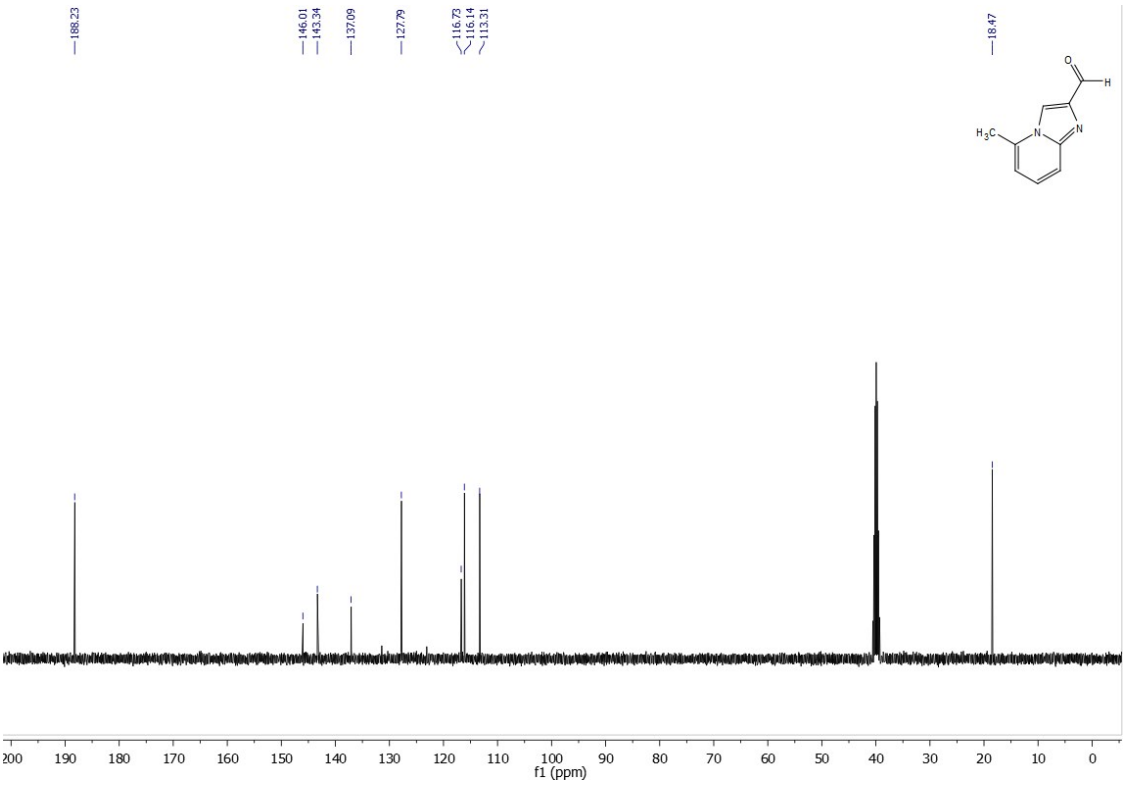
^{1}H NMR and ^{13}C NMR for 8-methylimidazo[1,2-*a*]pyridine-2-carbaldehyde (3k)



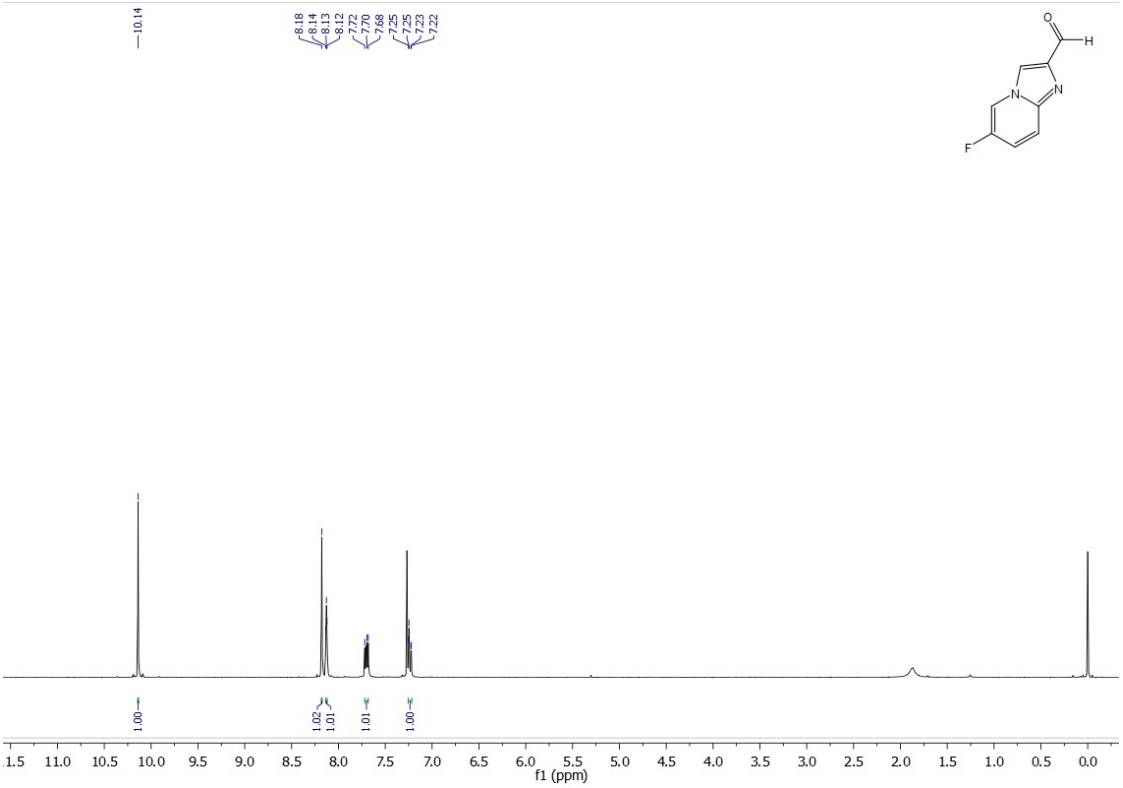


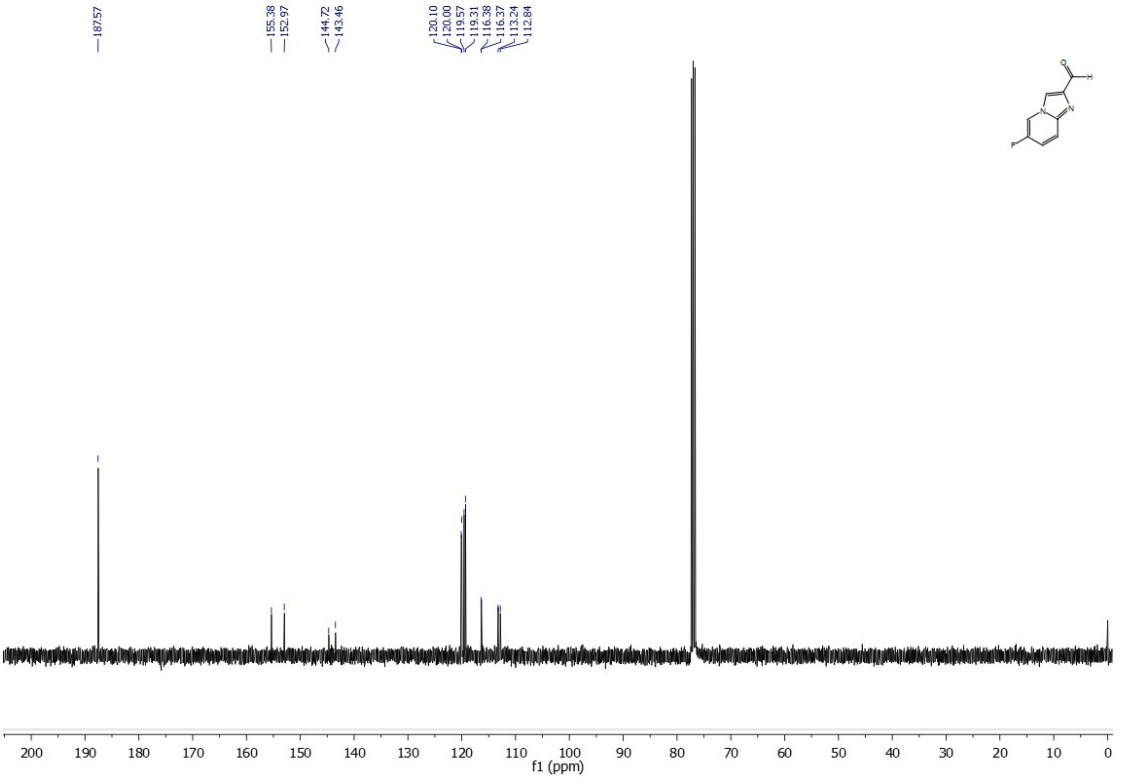
^{1}H NMR and ^{13}C NMR for 5-methylimidazo[1,2-a]pyridine-2-carbaldehyde (3l)



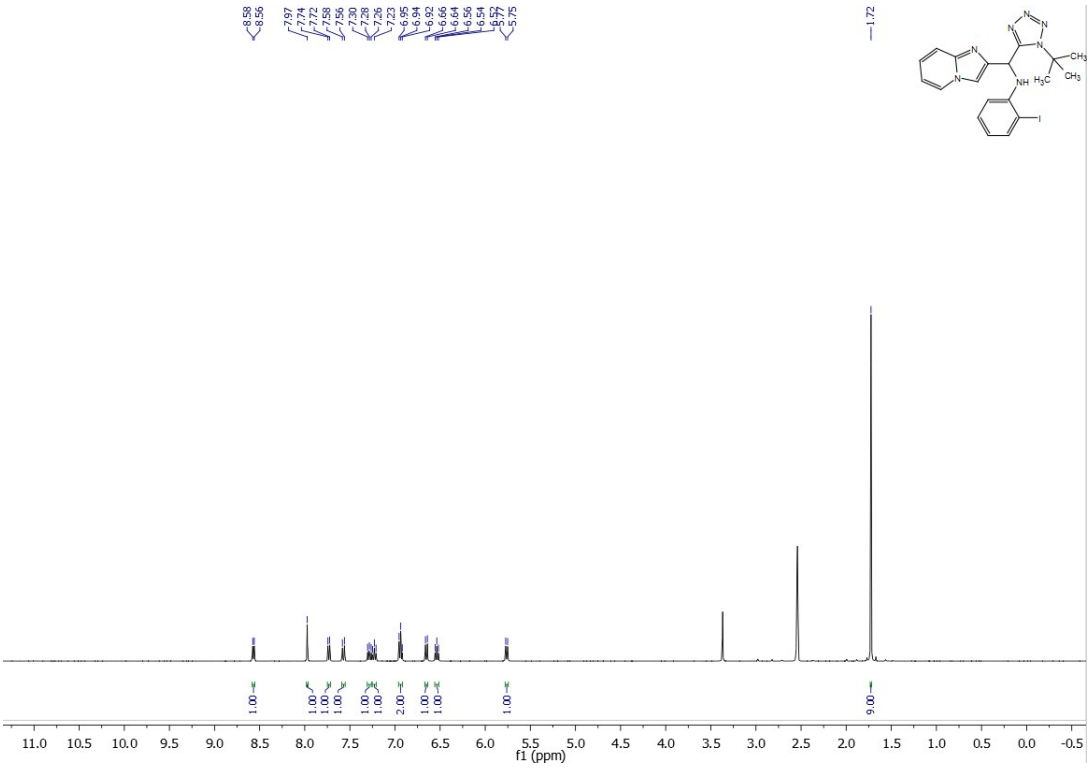


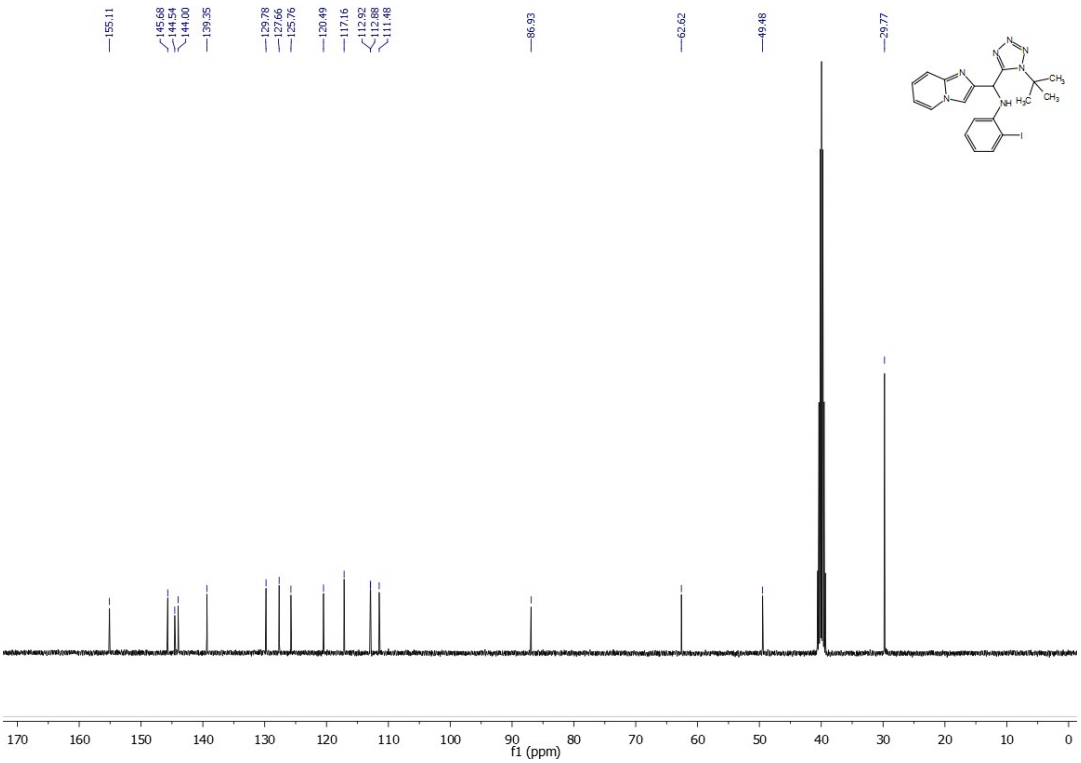
^{1}H NMR and ^{13}C NMR for 6-fluoroimidazo[1,2-a]pyridine-2-carbaldehyde (3m)



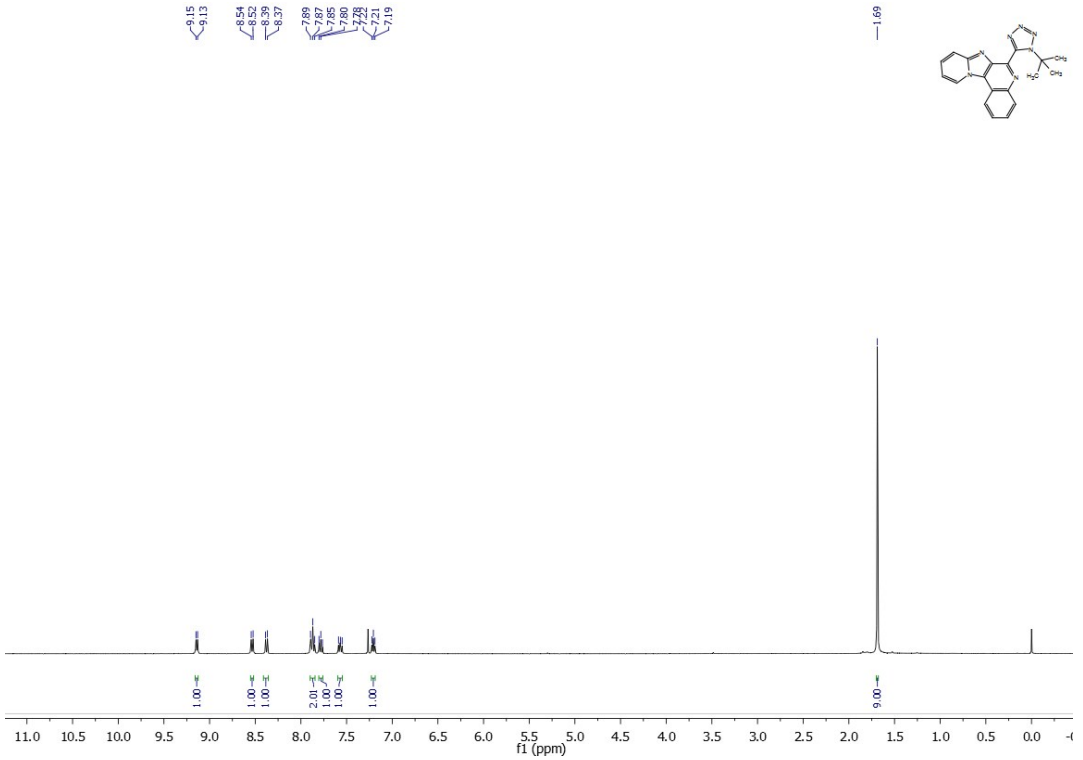


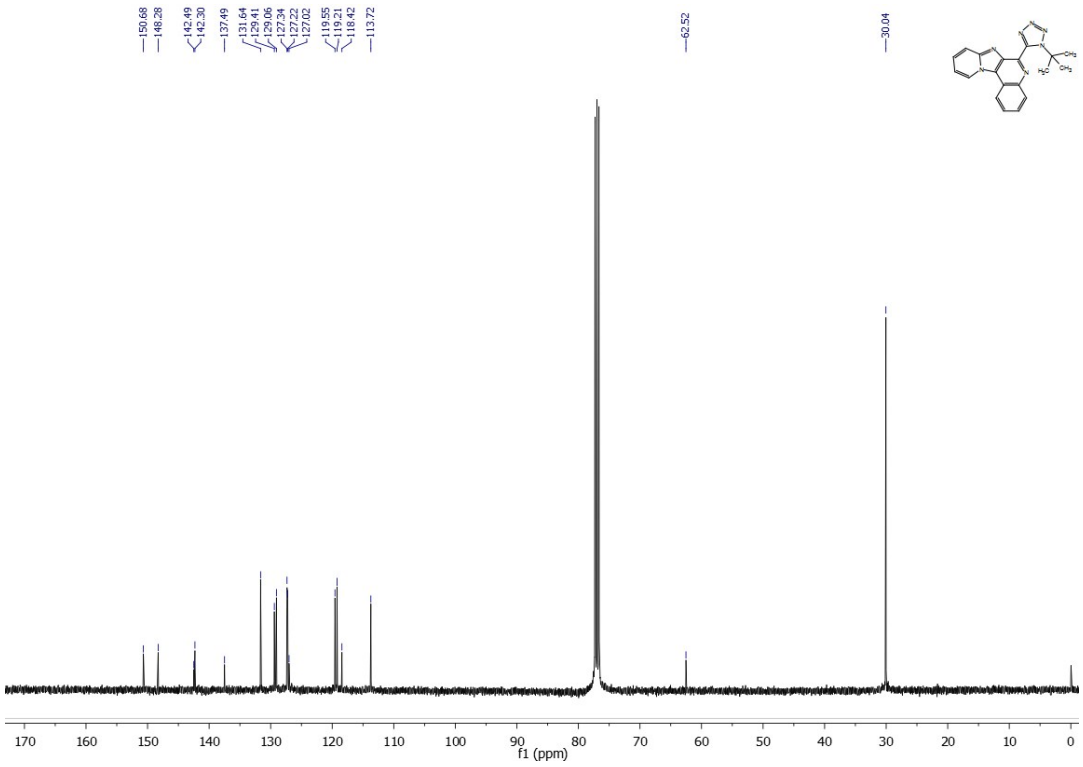
^{1}H NMR and ^{13}C NMR for N-((1-(tert-butyl)-1H-tetrazol-5-yl)(imidazo[1,2-a]pyridin-2-yl)methyl)-2-iodoaniline (5a)



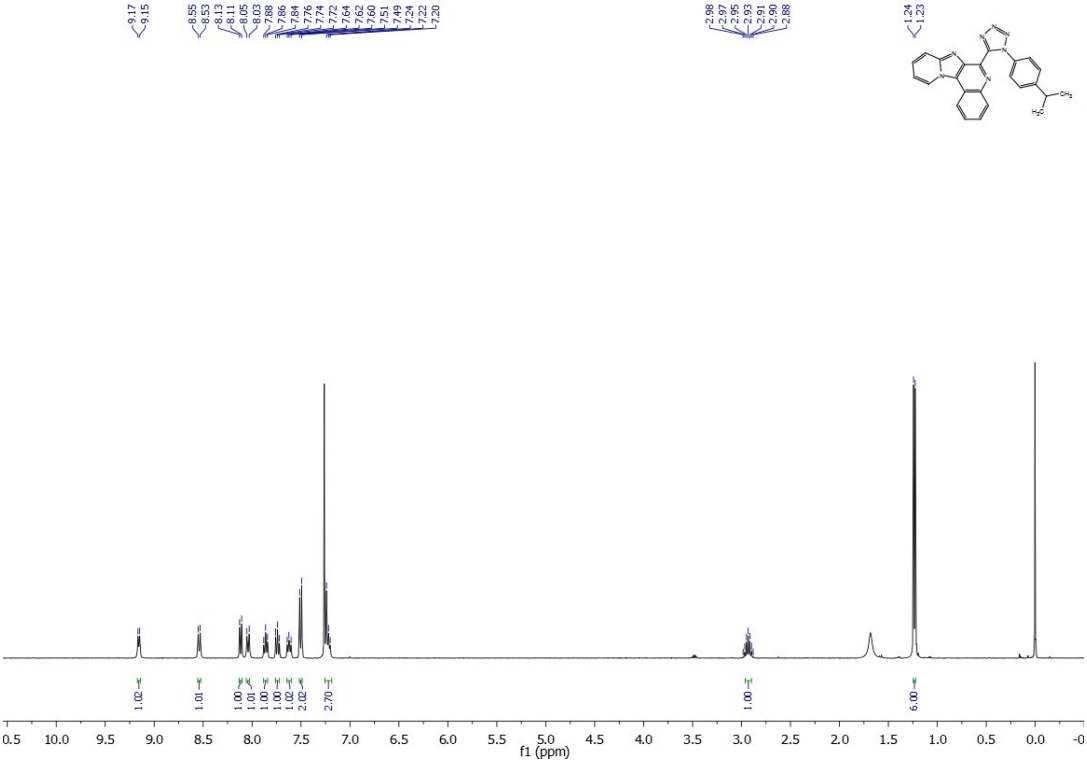


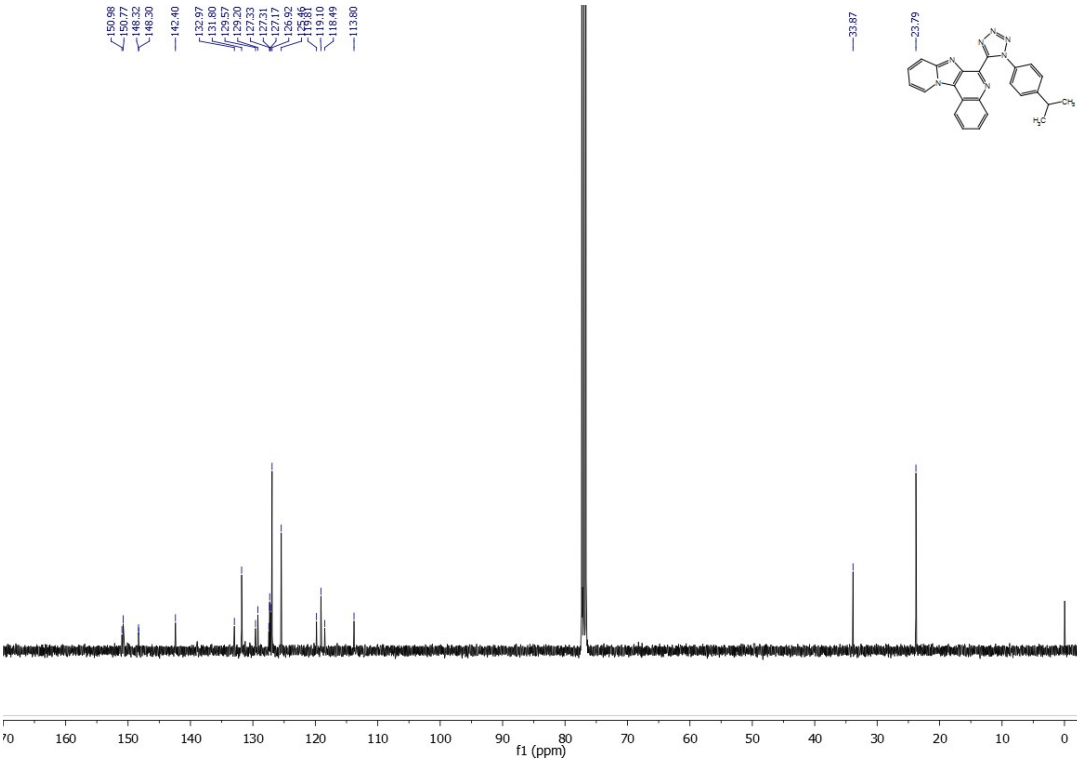
^{1}H NMR and ^{13}C NMR for 6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6aa)



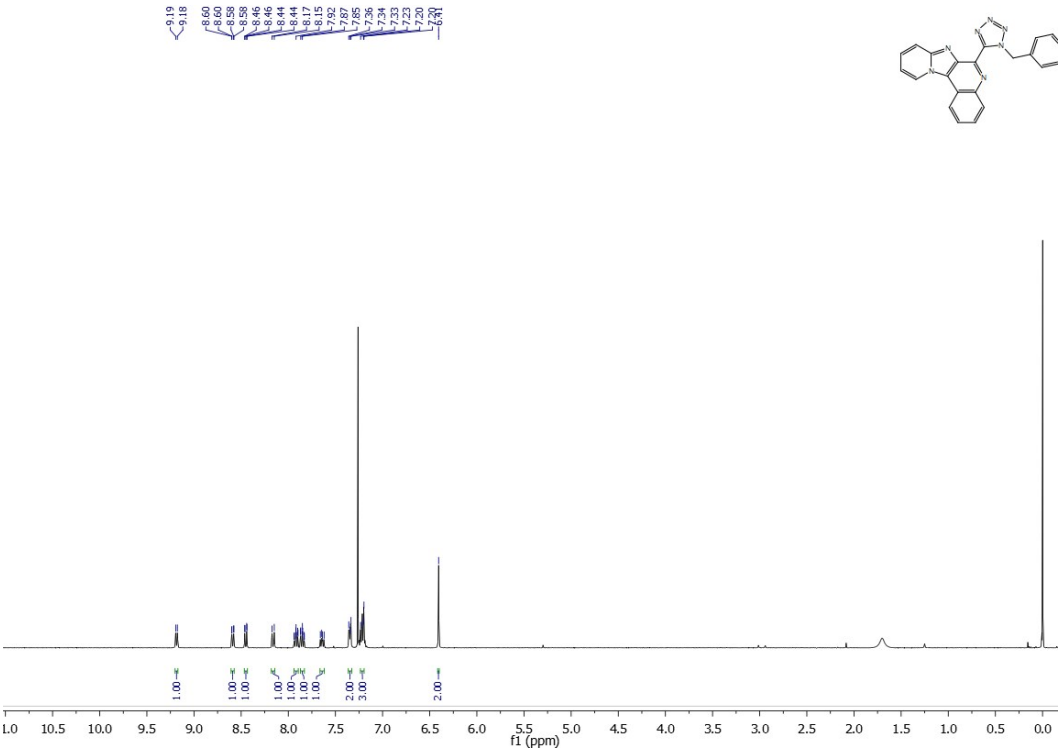


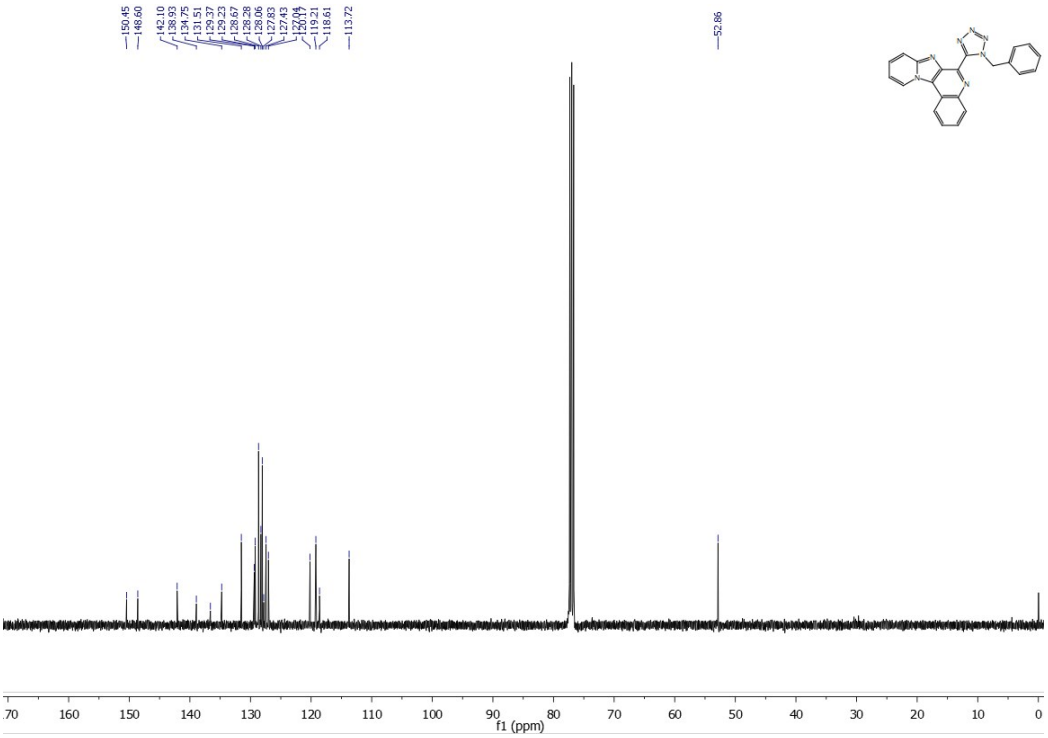
^{1}H NMR and ^{13}C NMR for 6-(1-(4-isopropylphenyl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6ab)



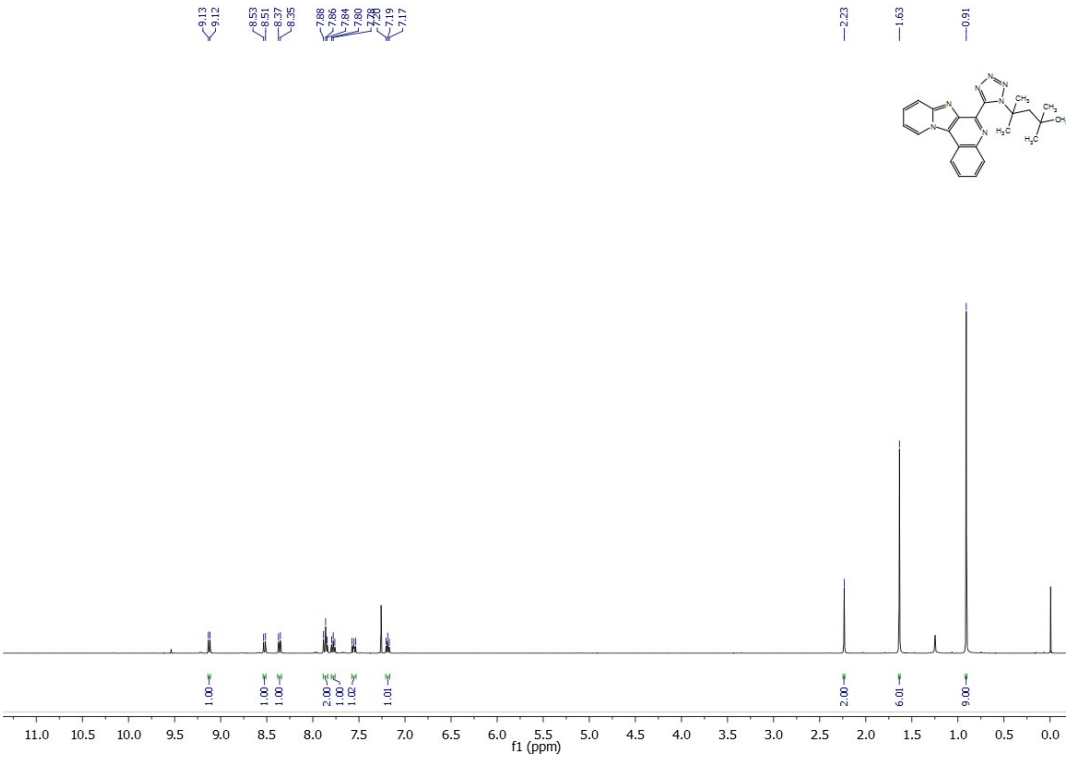


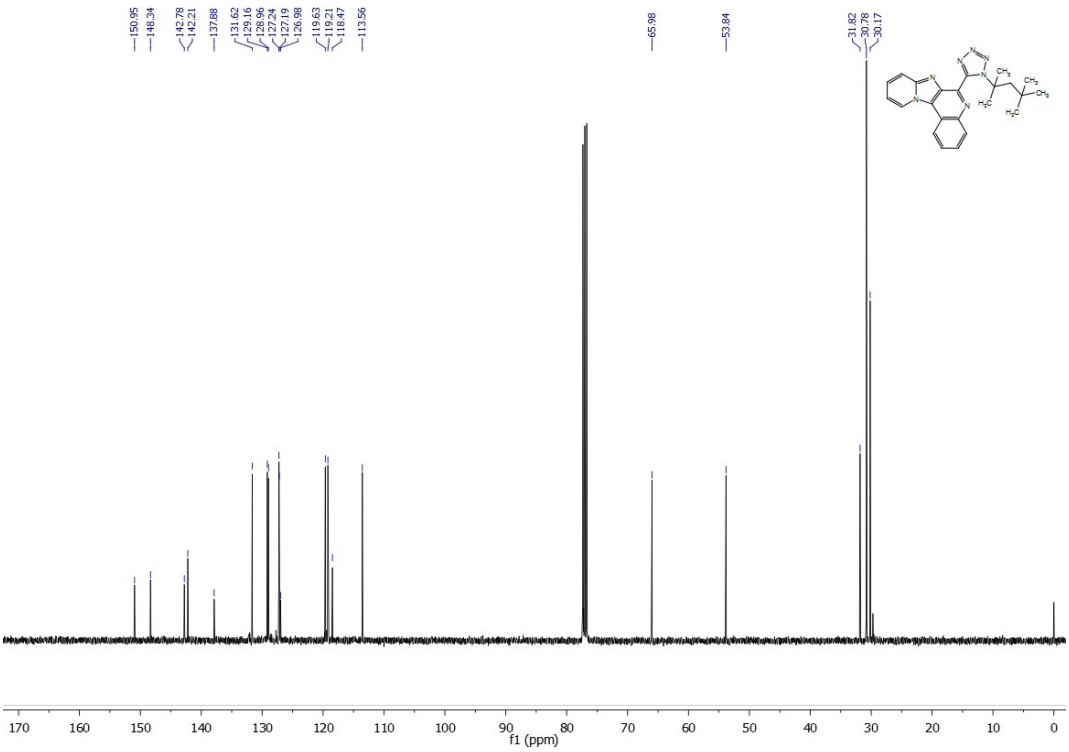
^{1}H NMR and ^{13}C NMR for 6-(1-benzyl-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-c]quinolone (6ac)



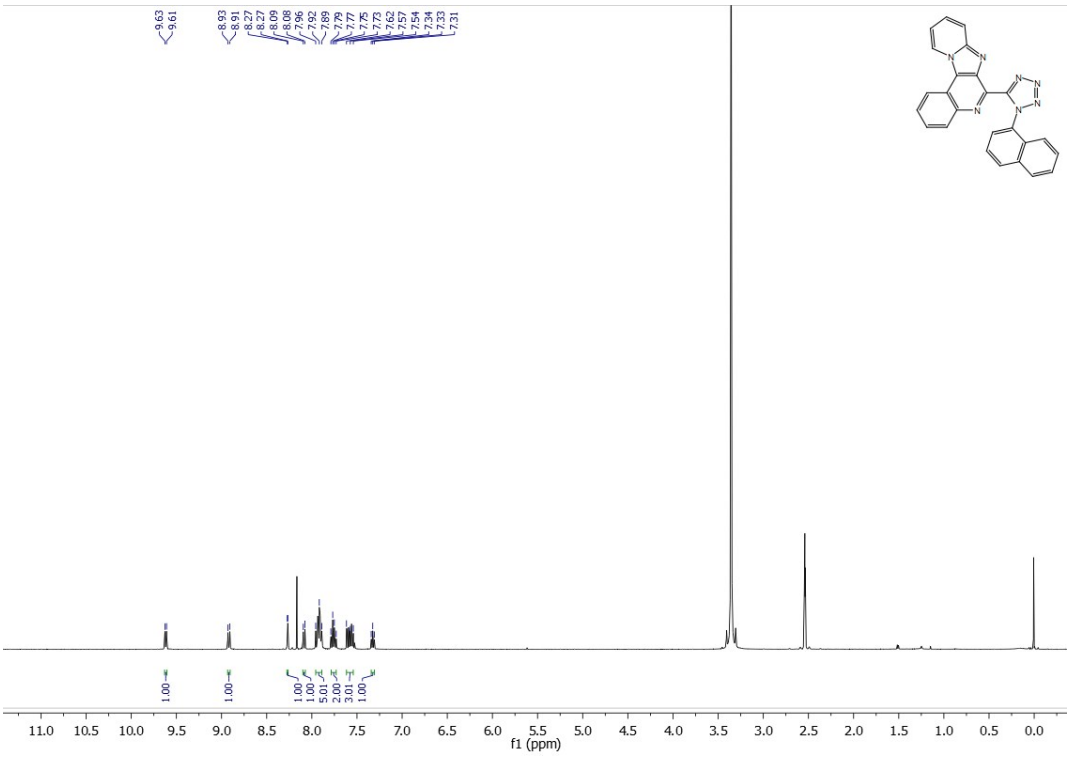


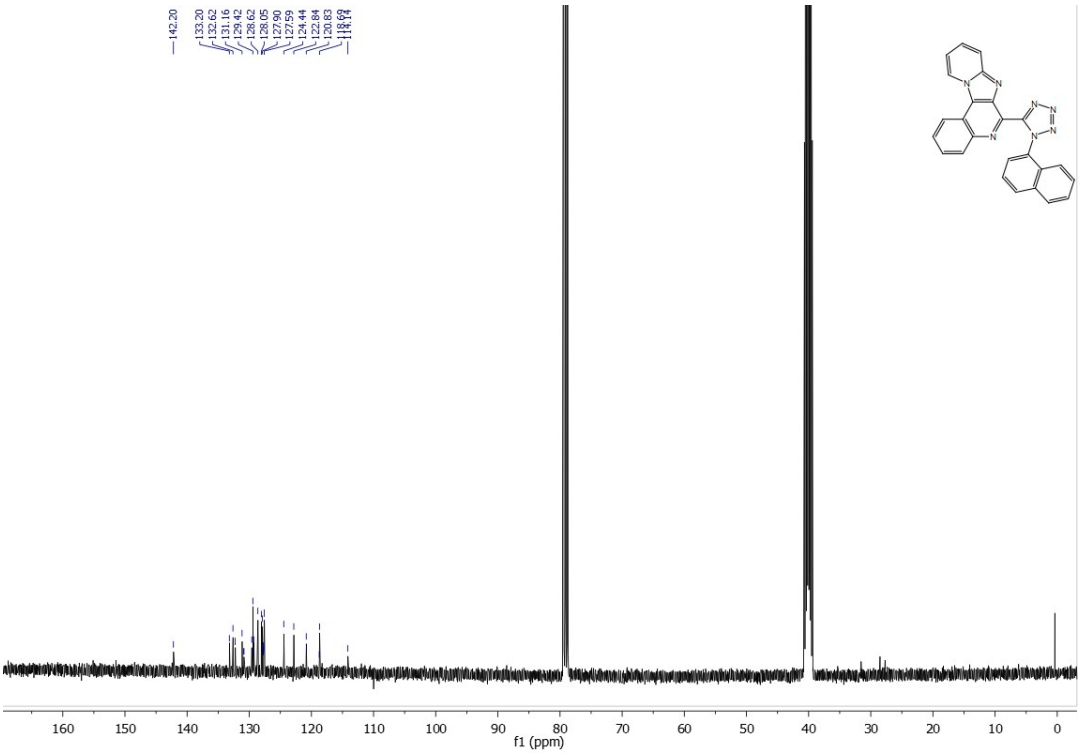
^{1}H NMR and ^{13}C NMR for 6-(1-(2,4,4-trimethylpentan-2-yl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-i]quinolone (6ad)



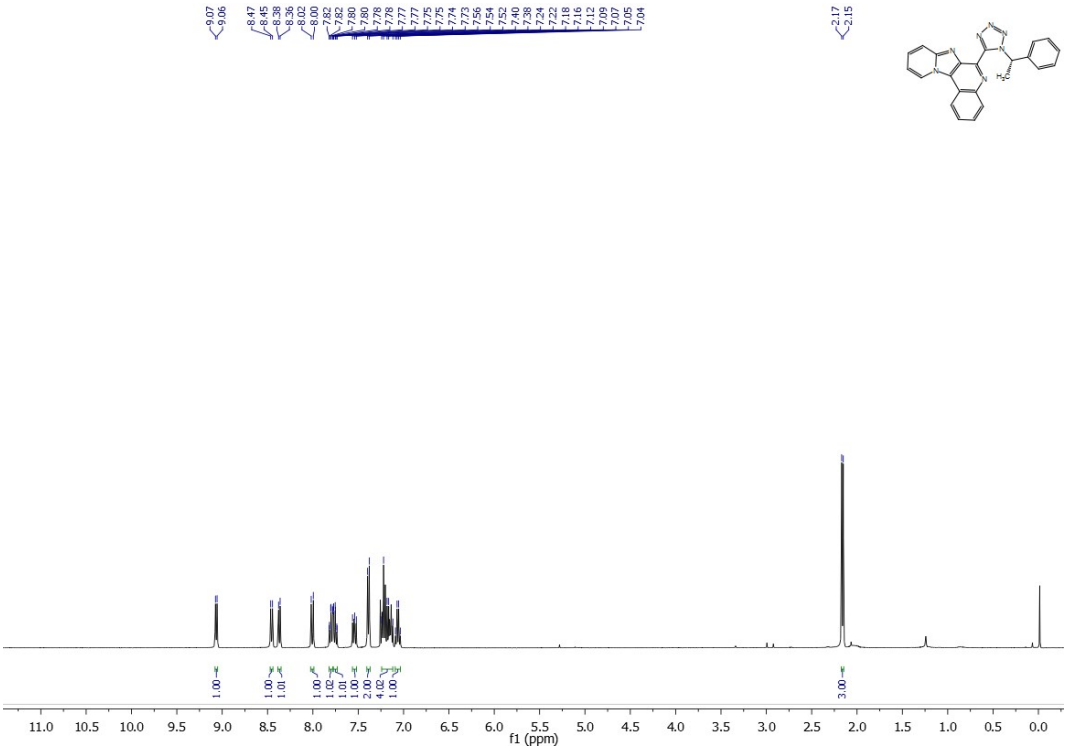


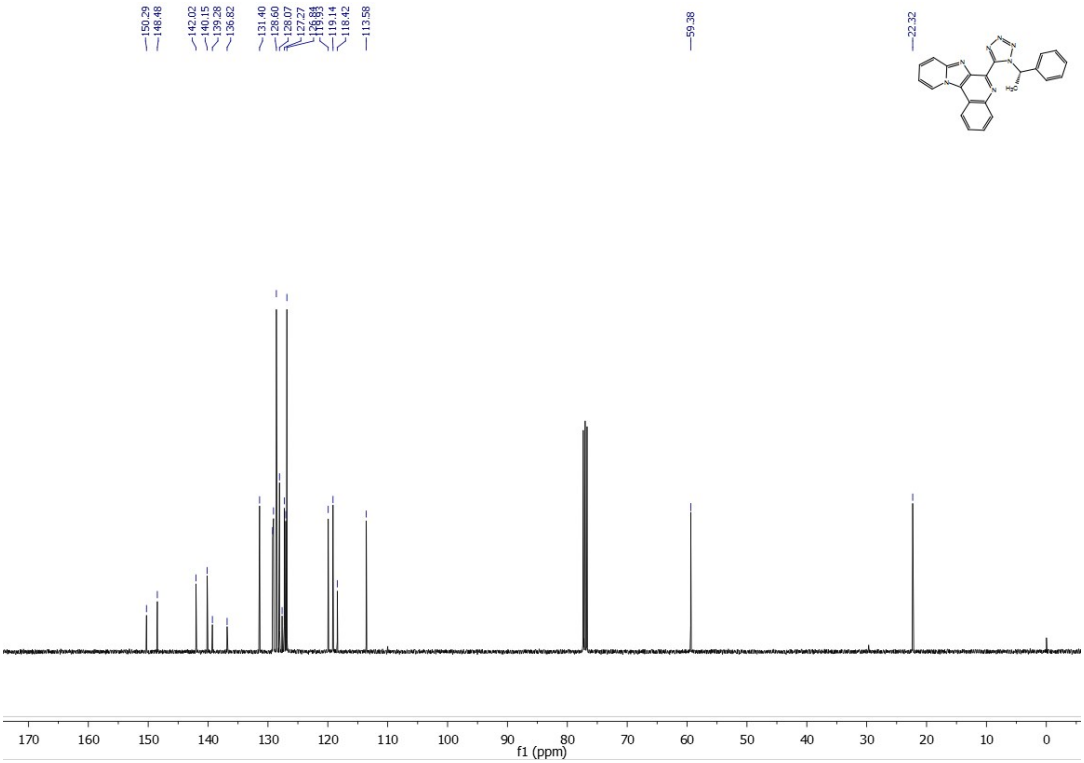
^{1}H NMR and ^{13}C NMR for 6-(1-(naphthalen-1-yl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinoline(6ae)



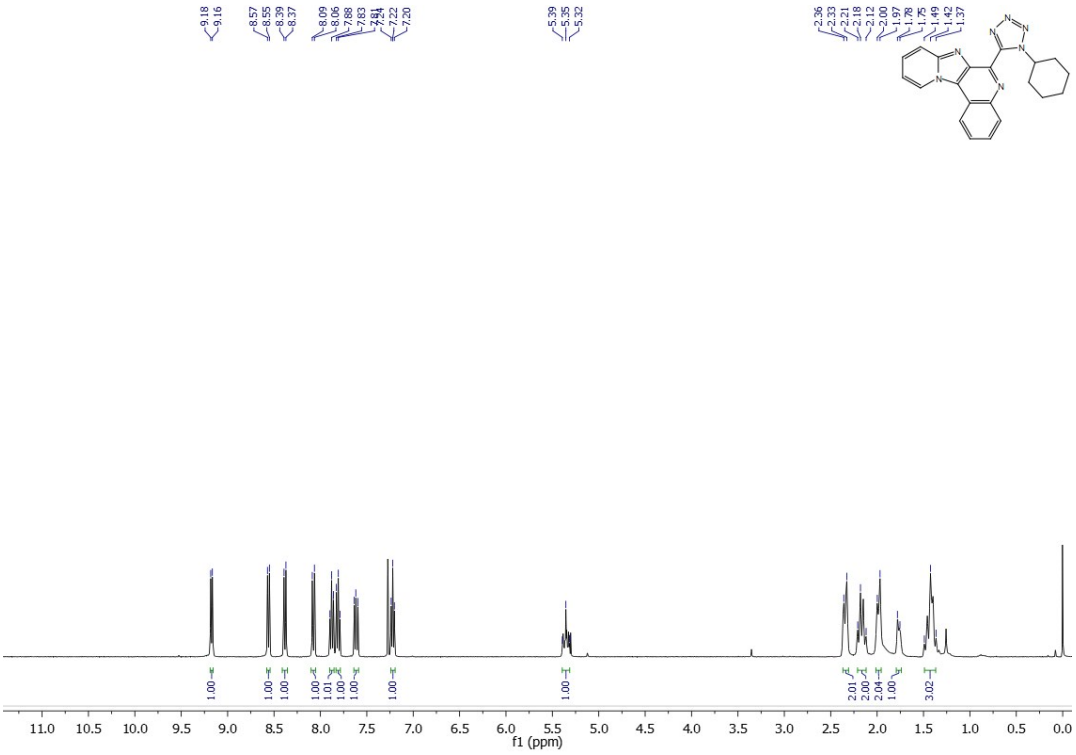


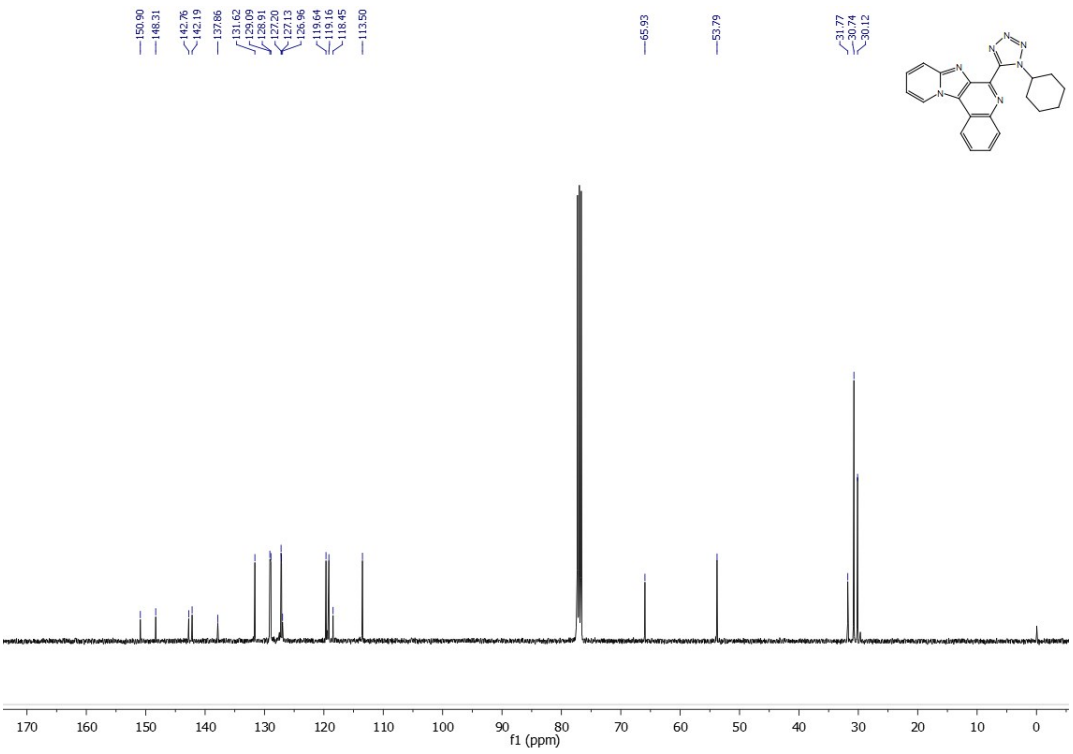
^{1}H NMR and ^{13}C NMR for (*S*)-6-(1-(1-phenylethyl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6af)



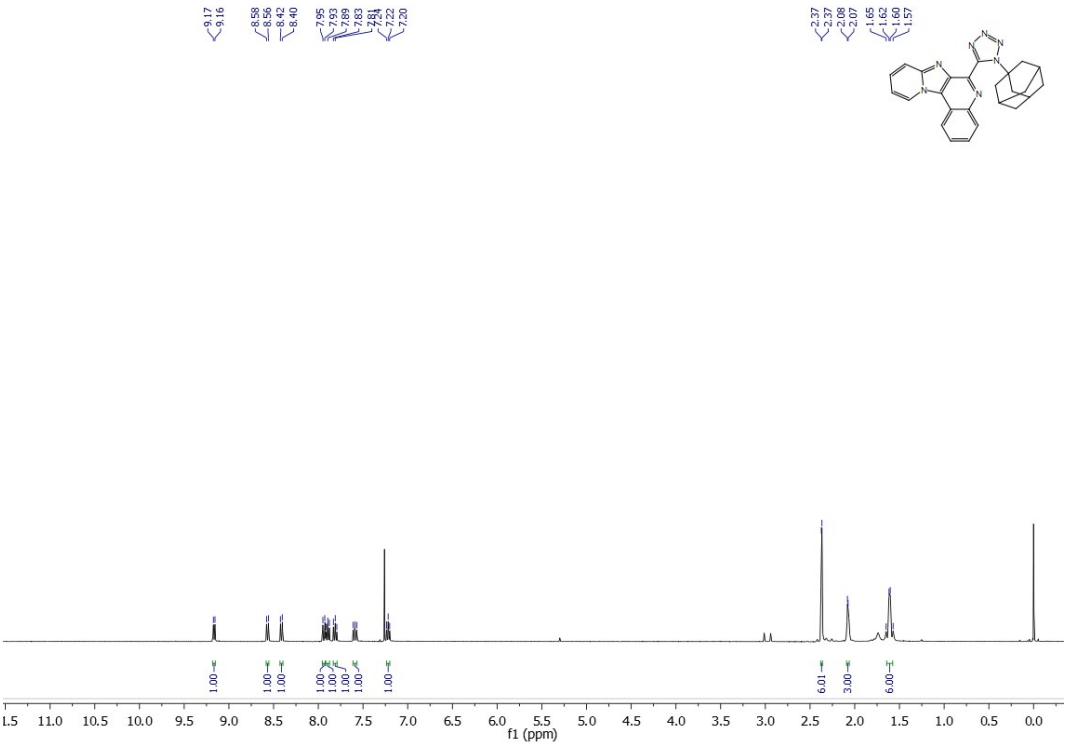


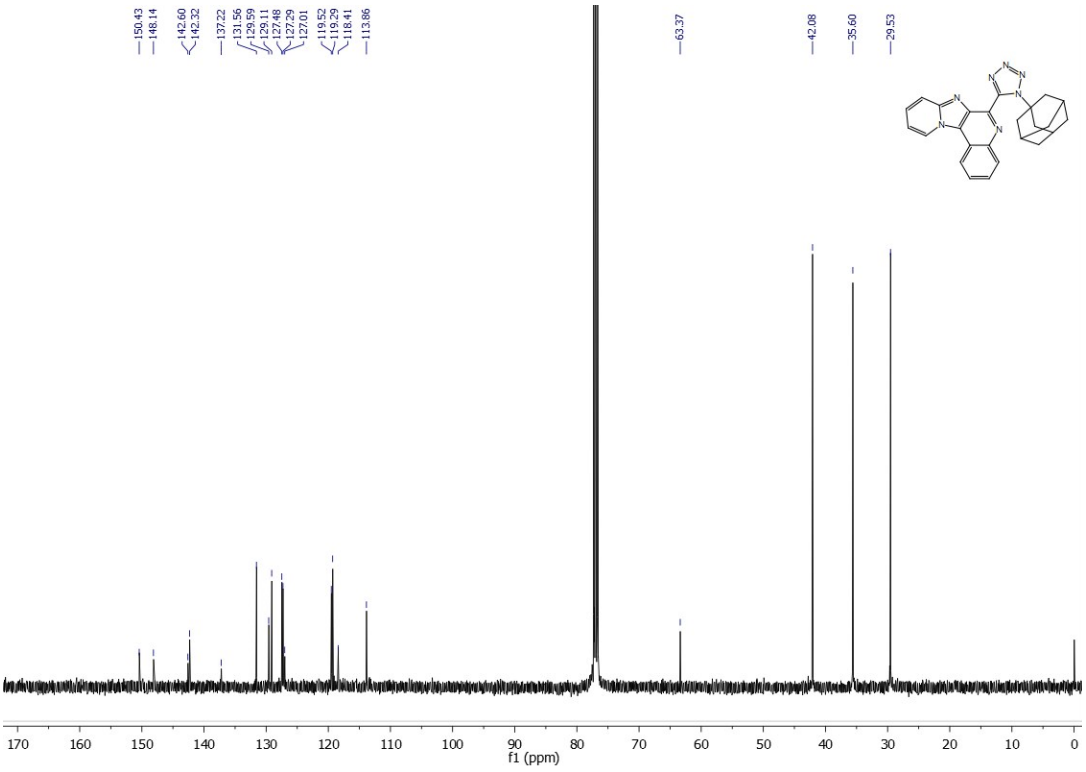
^{1}H NMR and ^{13}C NMR for 6-(1-cyclohexyl-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-c]quinoline(6ag)



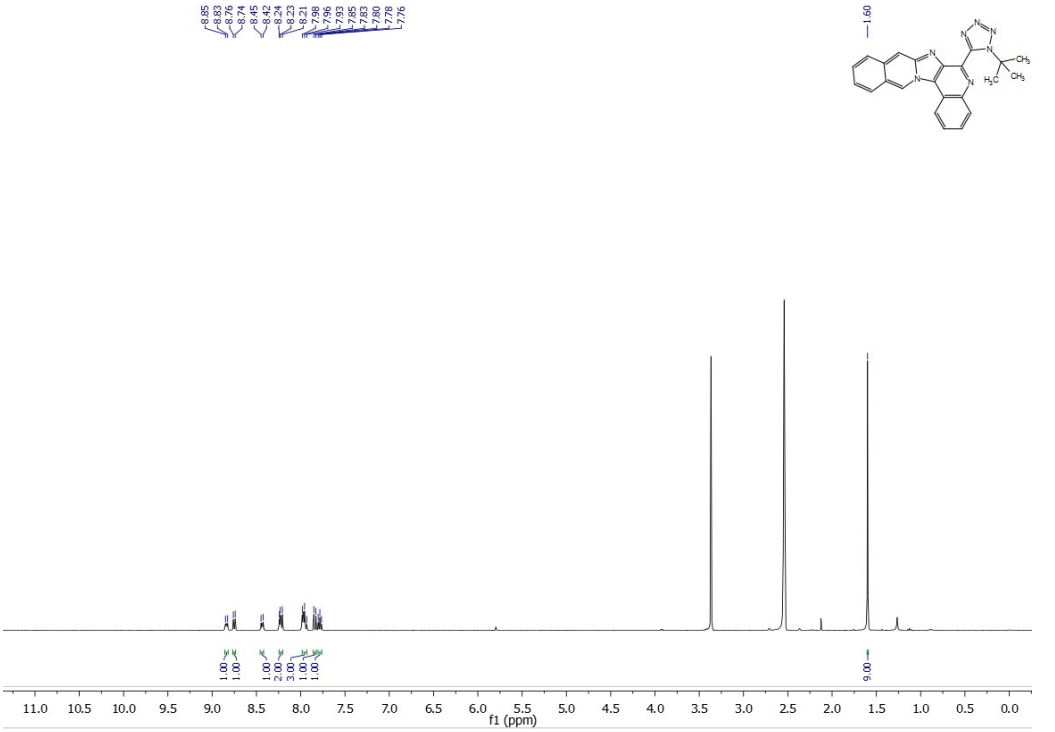


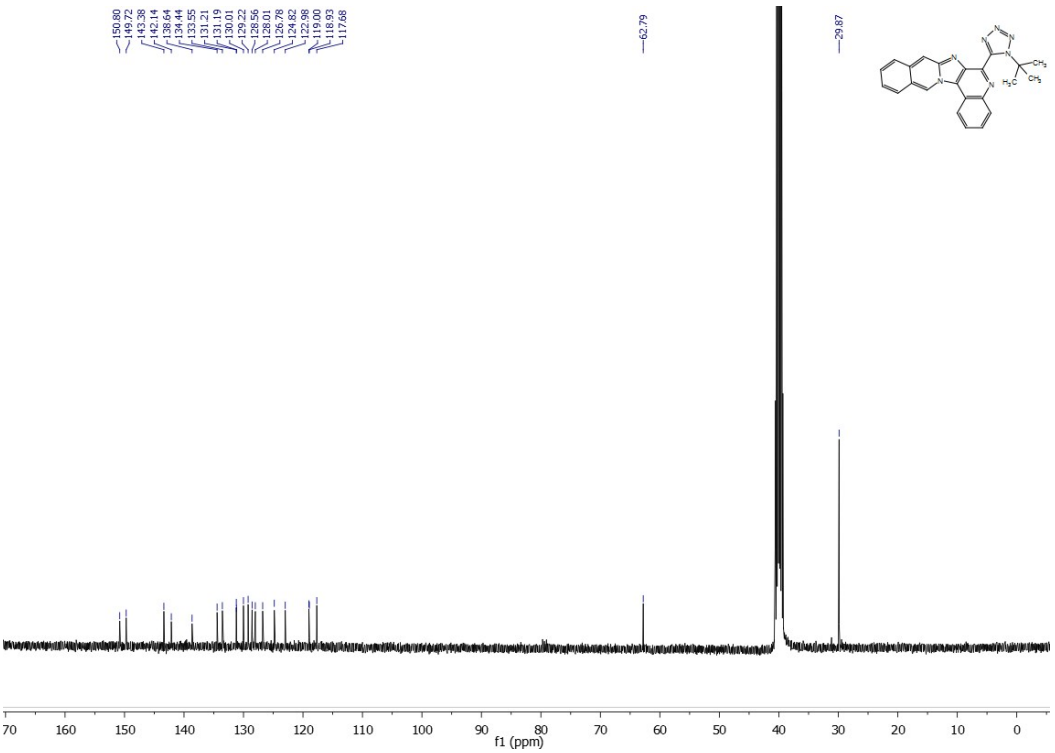
^{1}H NMR and ^{13}C NMR for 6-(1-(adamantan-1-yl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinoline (6ah)



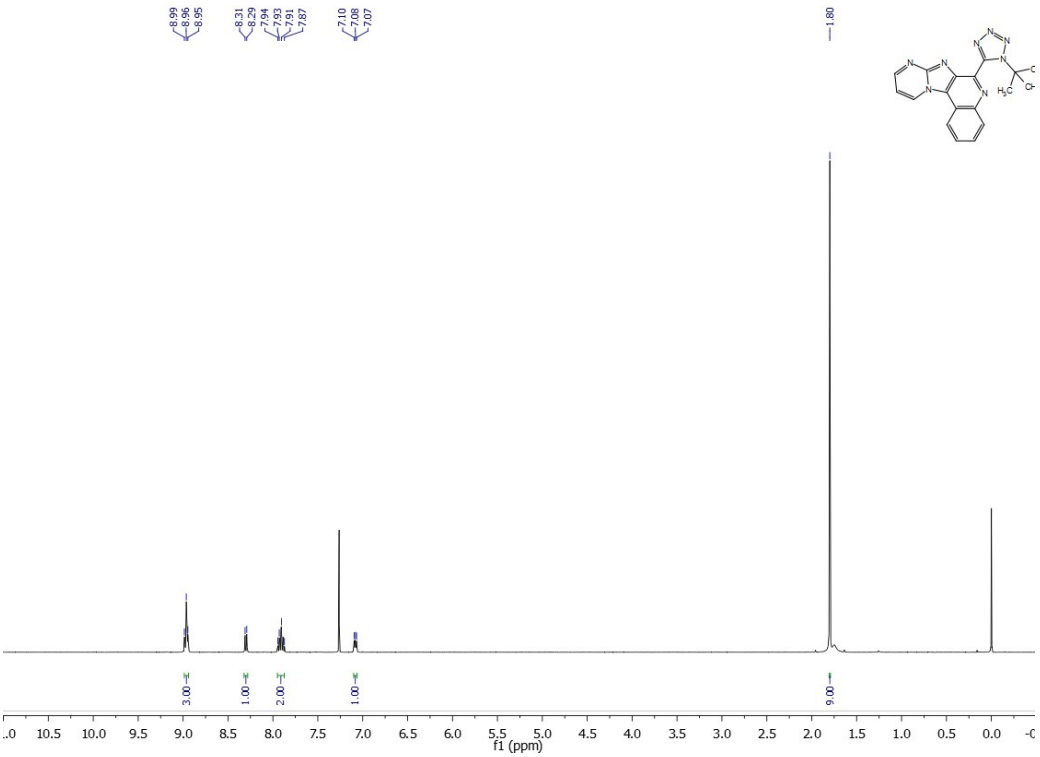


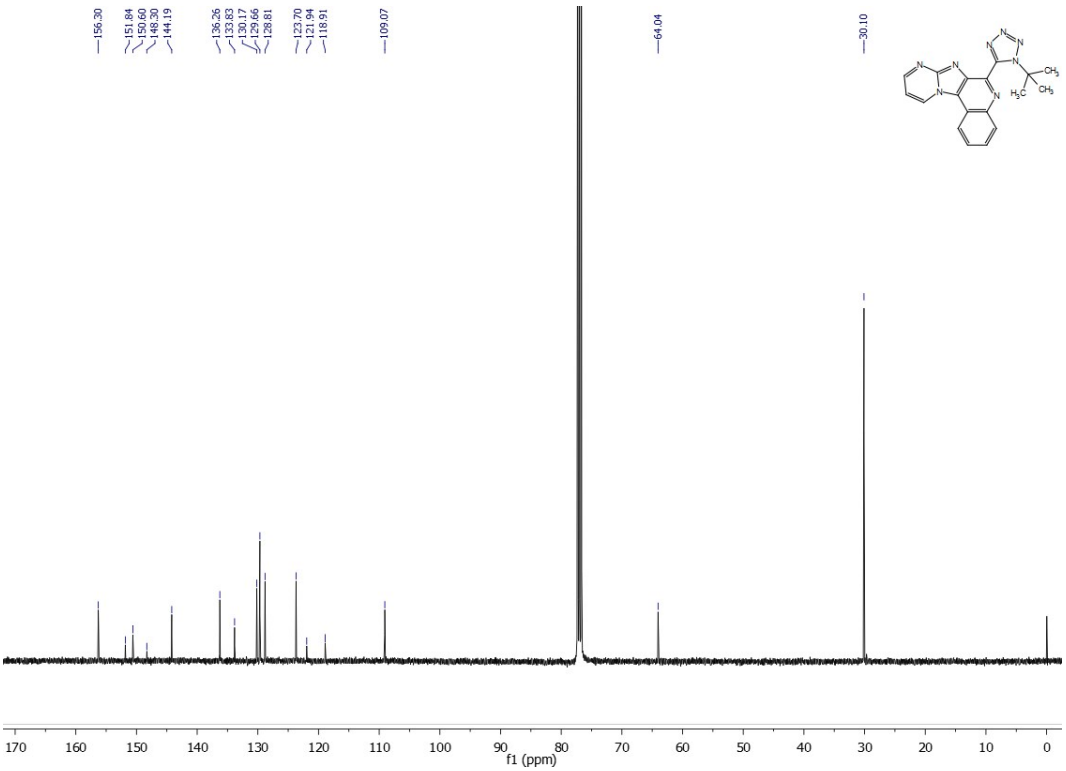
^{1}H NMR and ^{13}C NMR for 6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)isoquinolino[2',3':1,2]imidazo[4,5-*c*]quinoline (6ba)



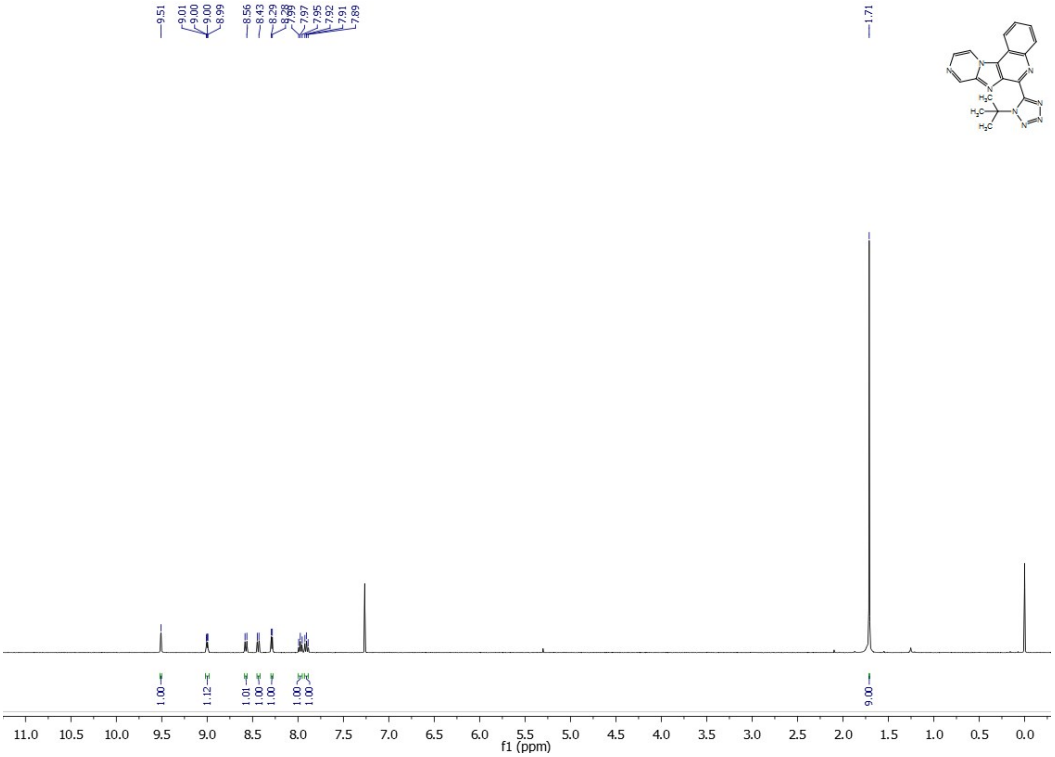


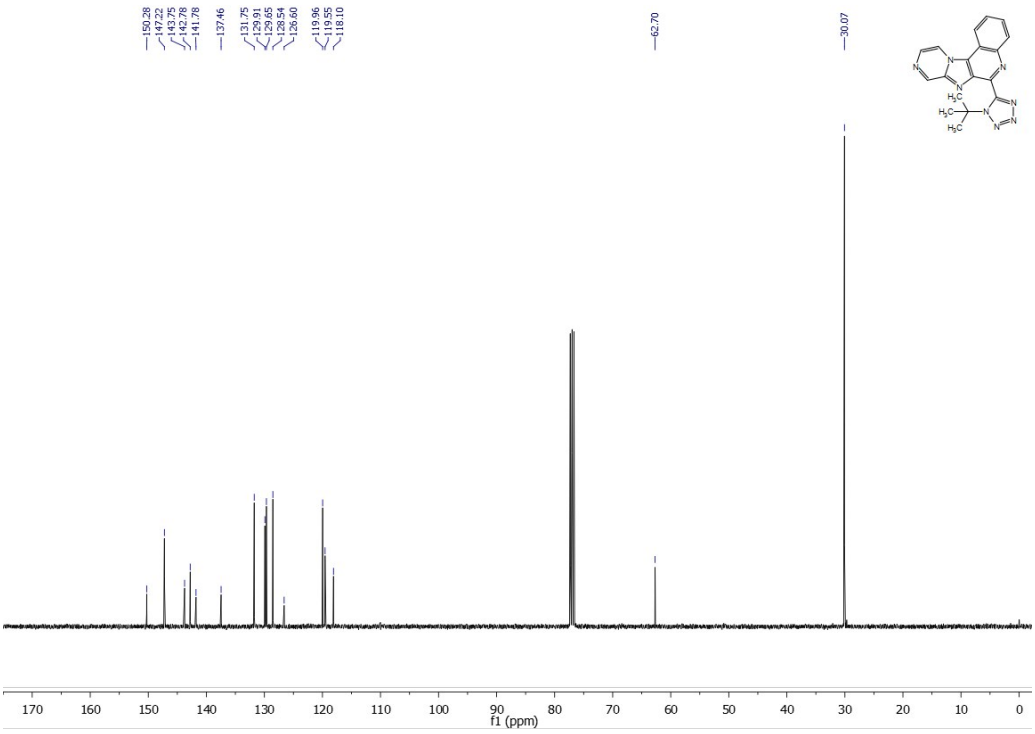
^{1}H NMR and ^{13}C NMR for 6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)pyrimido[1',2':1,2]imidazo[4,5-*c*]quinoline (6bb)



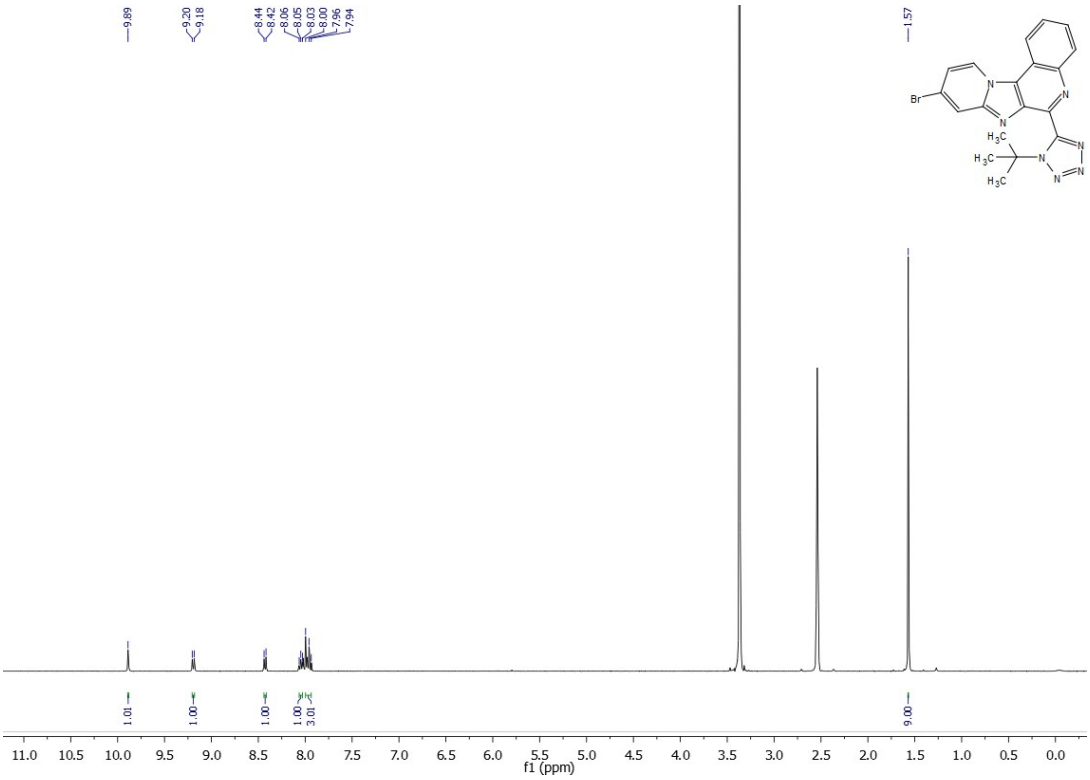


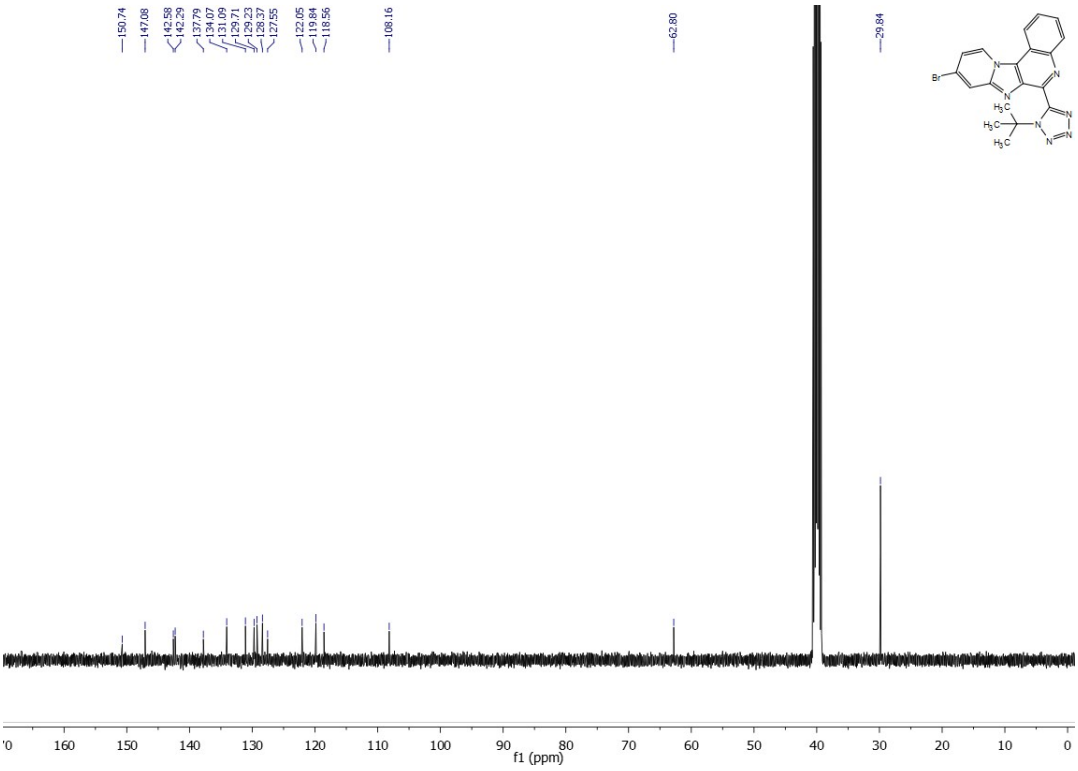
^{1}H NMR and ^{13}C NMR for 6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)pyrazino[1',2':1,2]imidazo[4,5-*c*]quinolone (6bc)



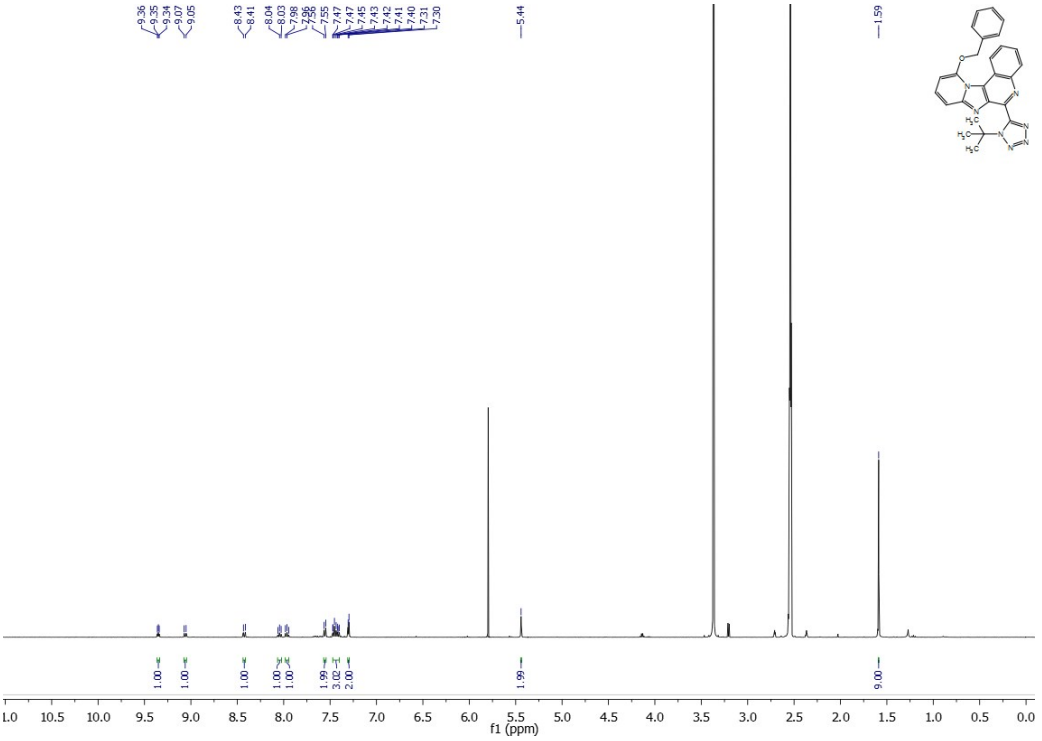


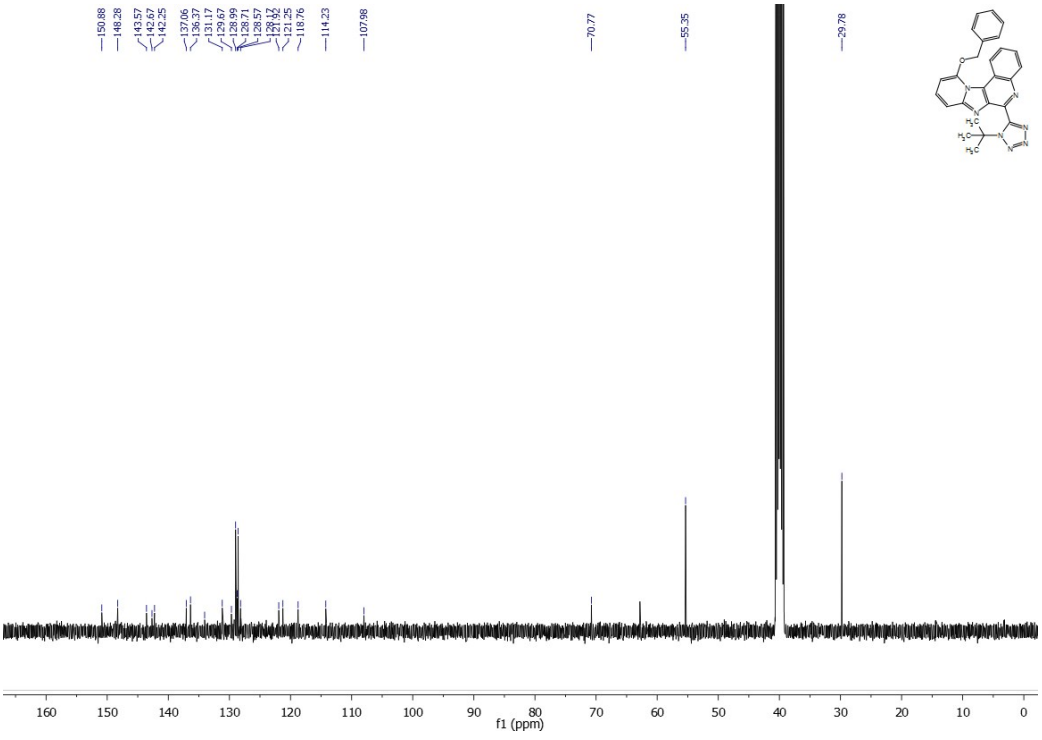
^{1}H NMR and ^{13}C NMR for 9-bromo-6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinoline (6bd)



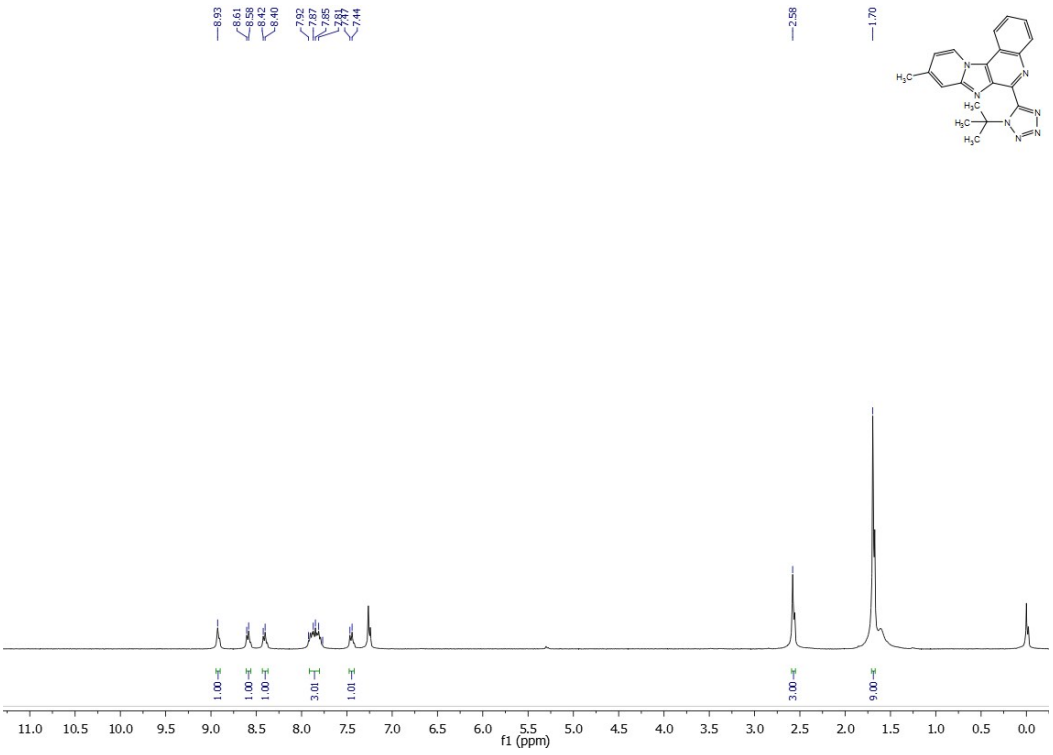


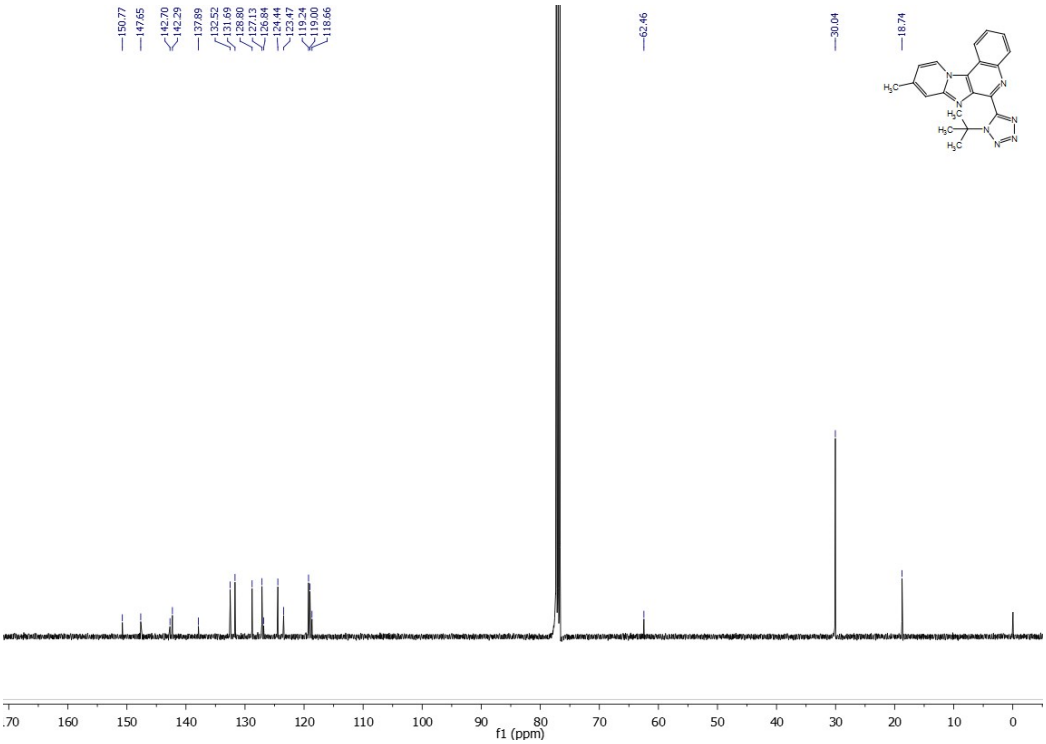
^{1}H NMR and ^{13}C NMR for 11-(benzyloxy)-6-(1-(tert-butyl)-1H-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-c]quinoline (6be)



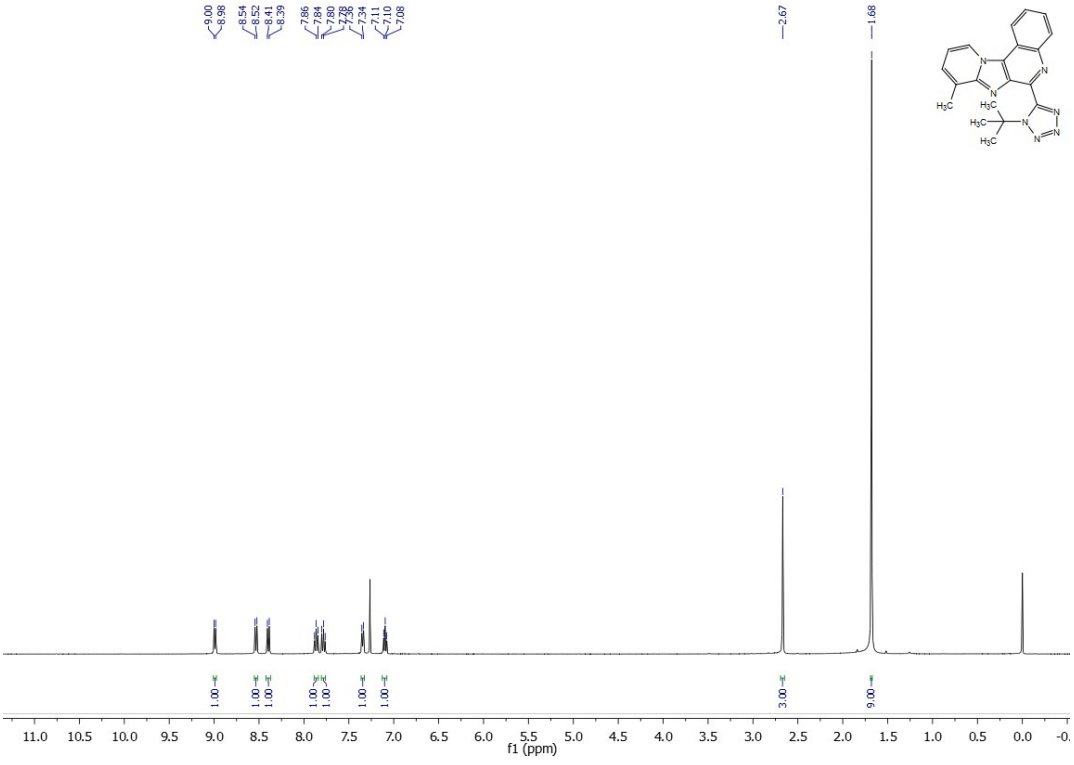


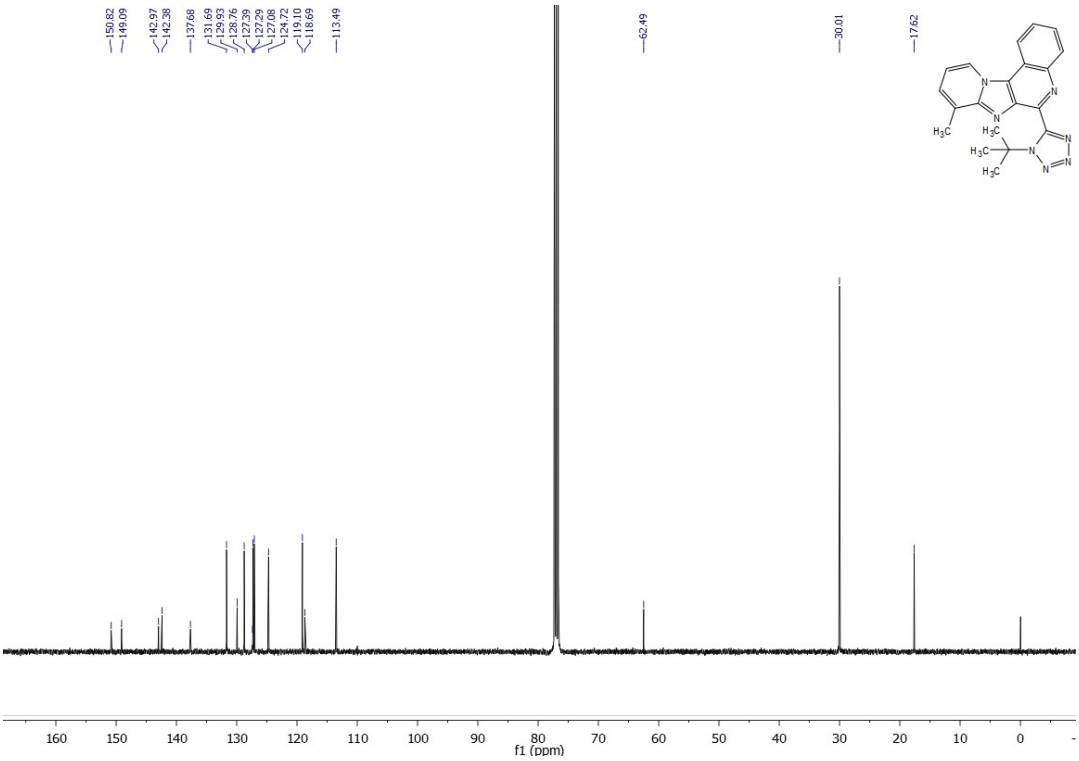
^{1}H NMR and ^{13}C NMR for 6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-9-methylpyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6bf)



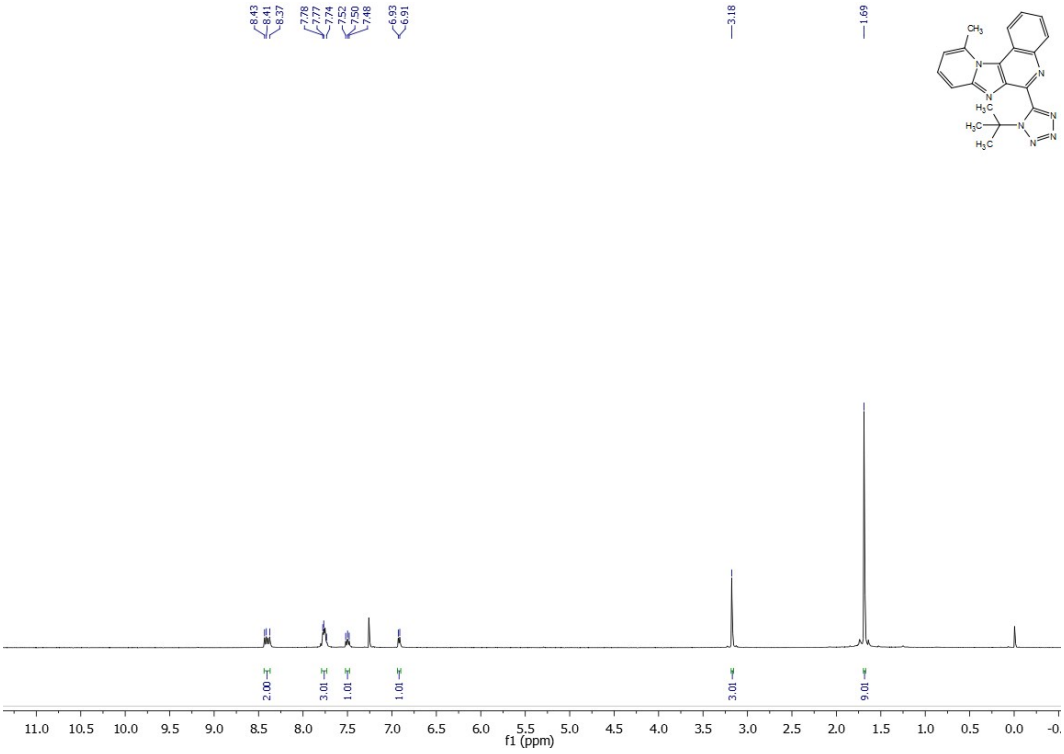


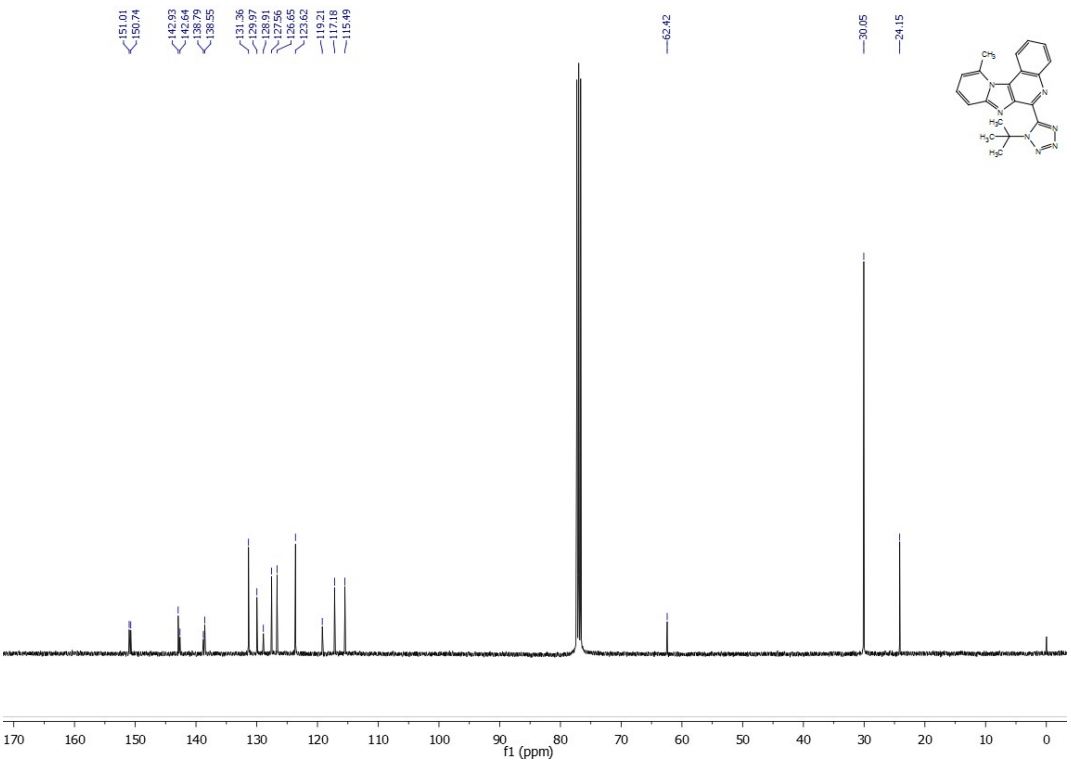
^{1}H NMR and ^{13}C NMR for 6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-8-methylpyrido[1',2':1,2]imidazo[4,5-*c*]quinoline (6bg)



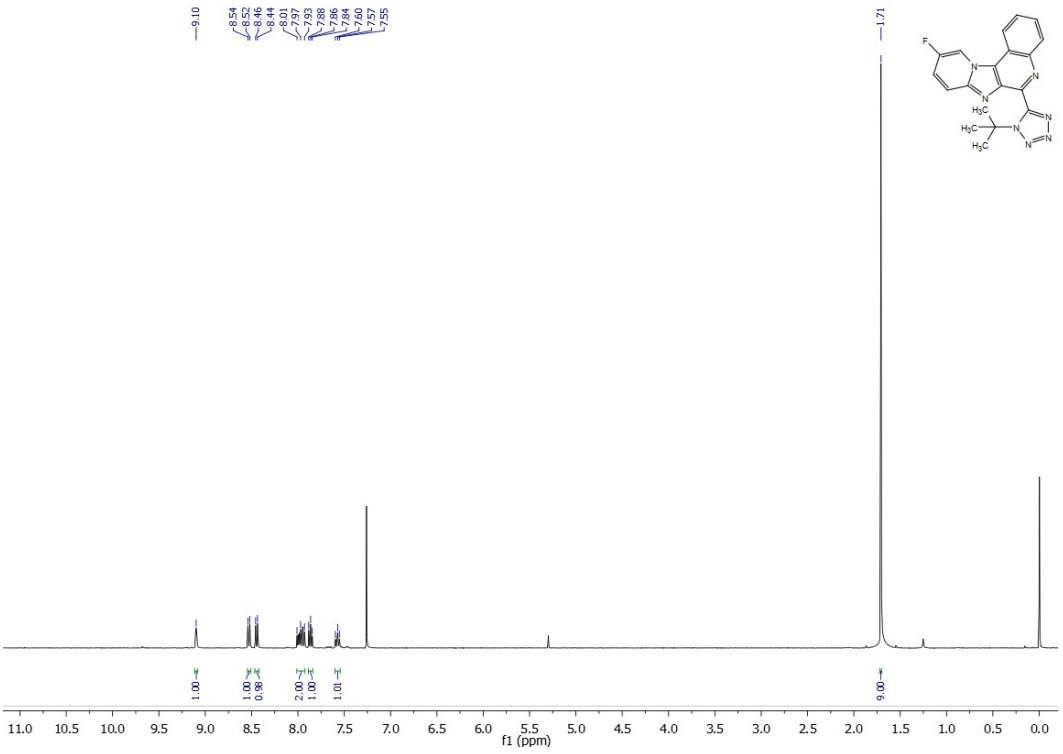


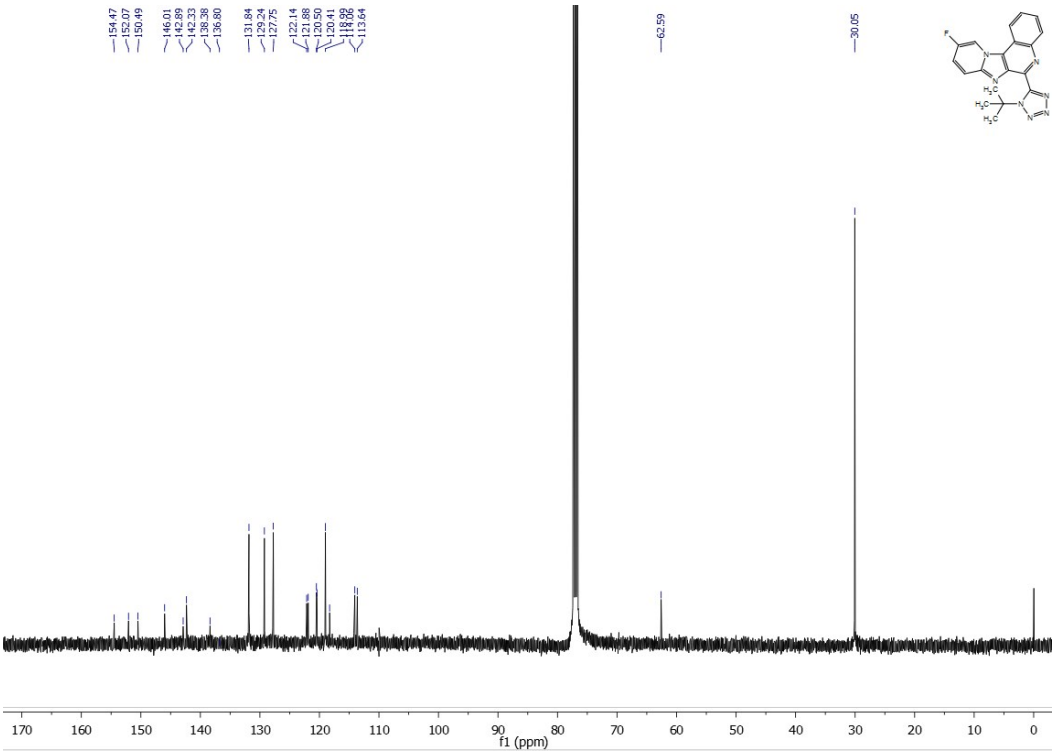
^{1}H NMR and ^{13}C NMR for 6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-11-methylpyrido[1',2':1,2]imidazo[4,5-*c*]quinoline (6bh)



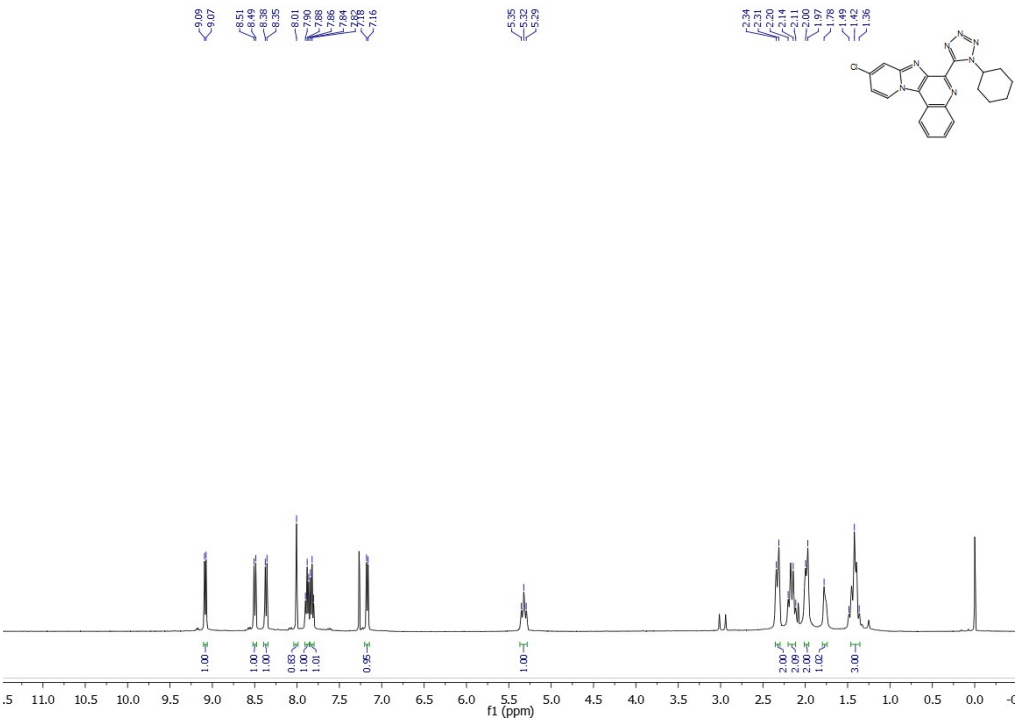


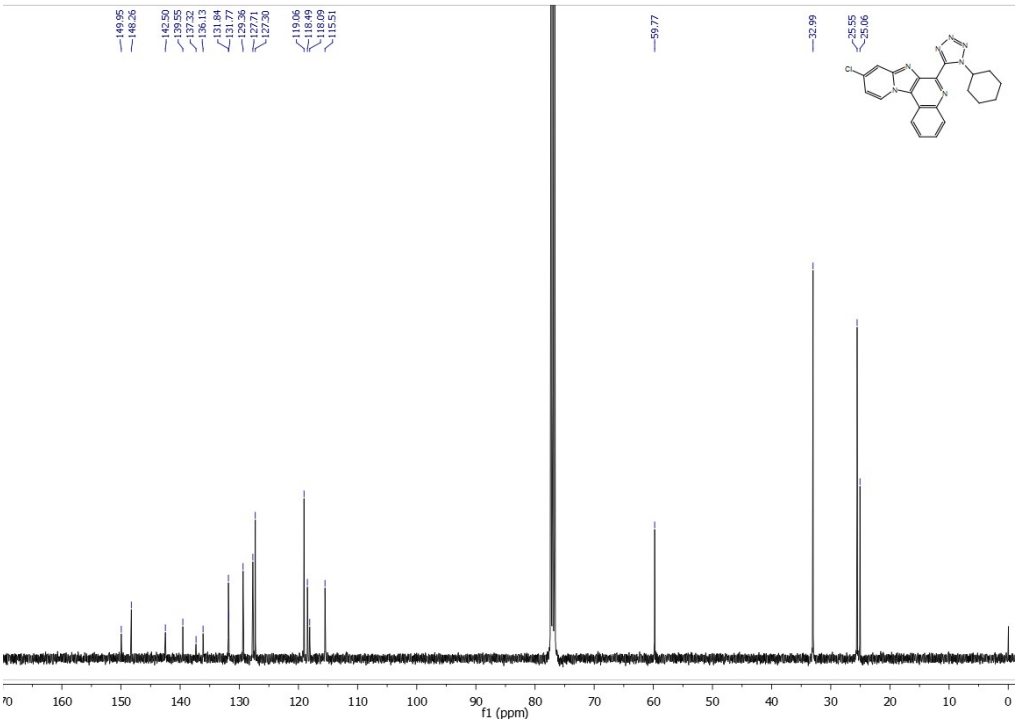
^{1}H NMR and ^{13}C NMR for 6-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-10-fluoropyrido[1',2':1,2]imidazo[4,5-*c*]quinoline (6bi)



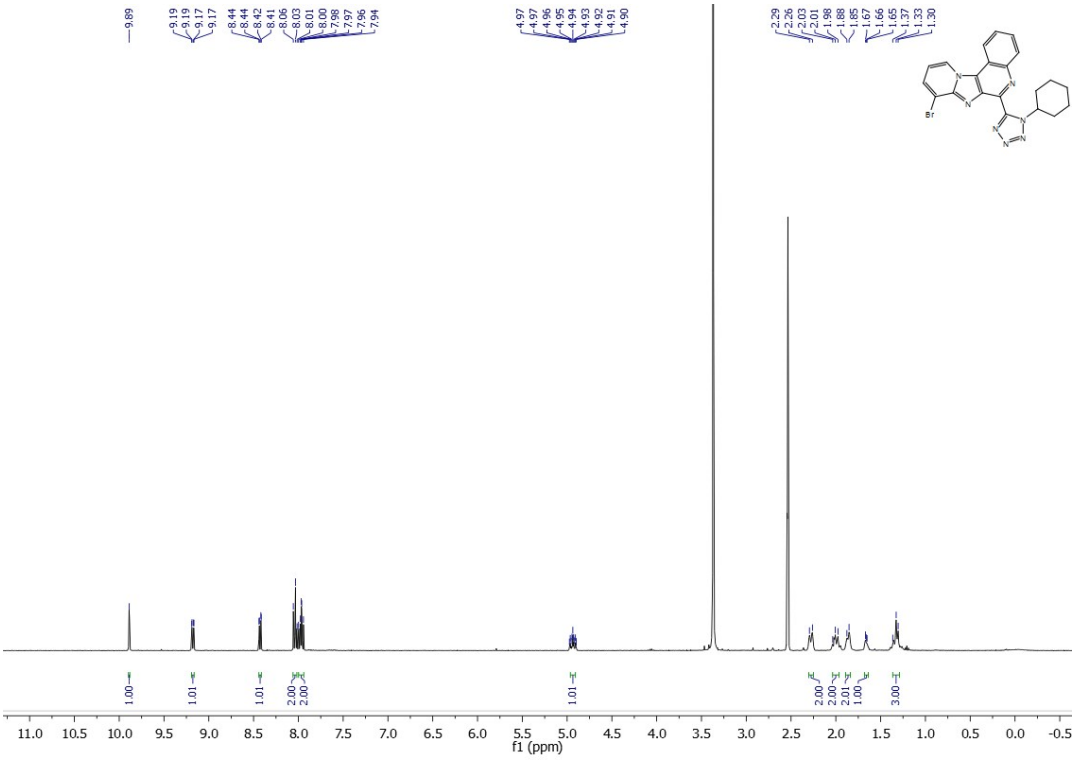


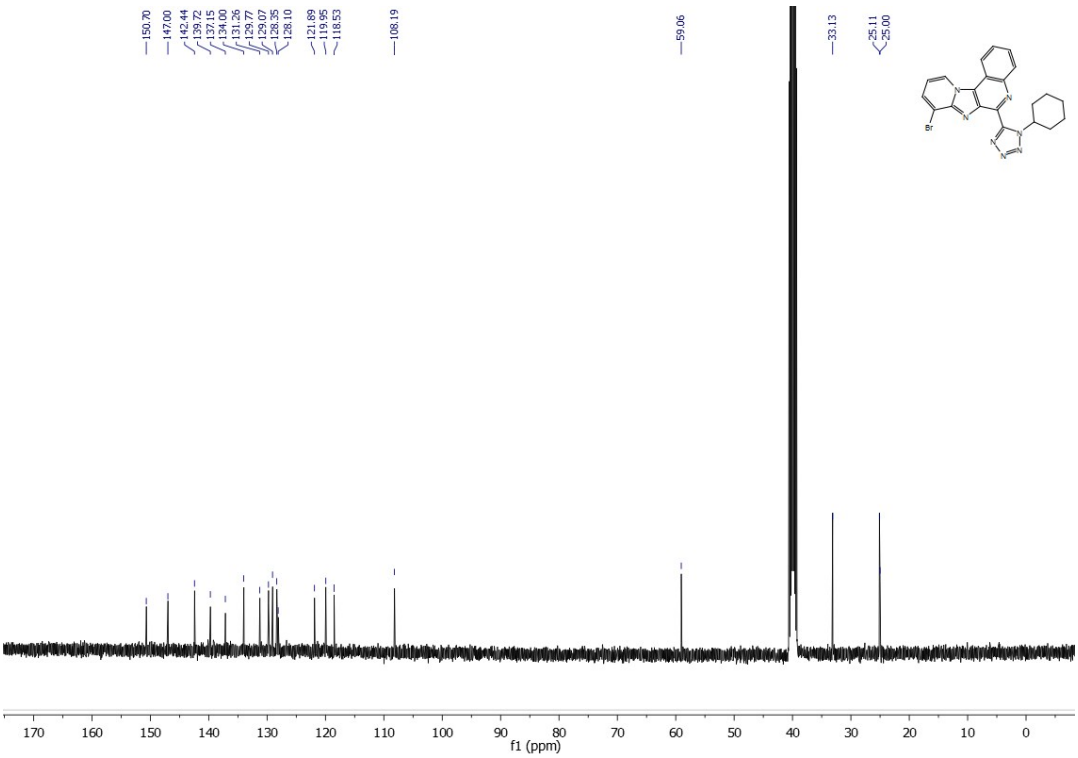
^{1}H NMR and ^{13}C NMR for 9-chloro-6-(1-cyclohexyl-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6ca)



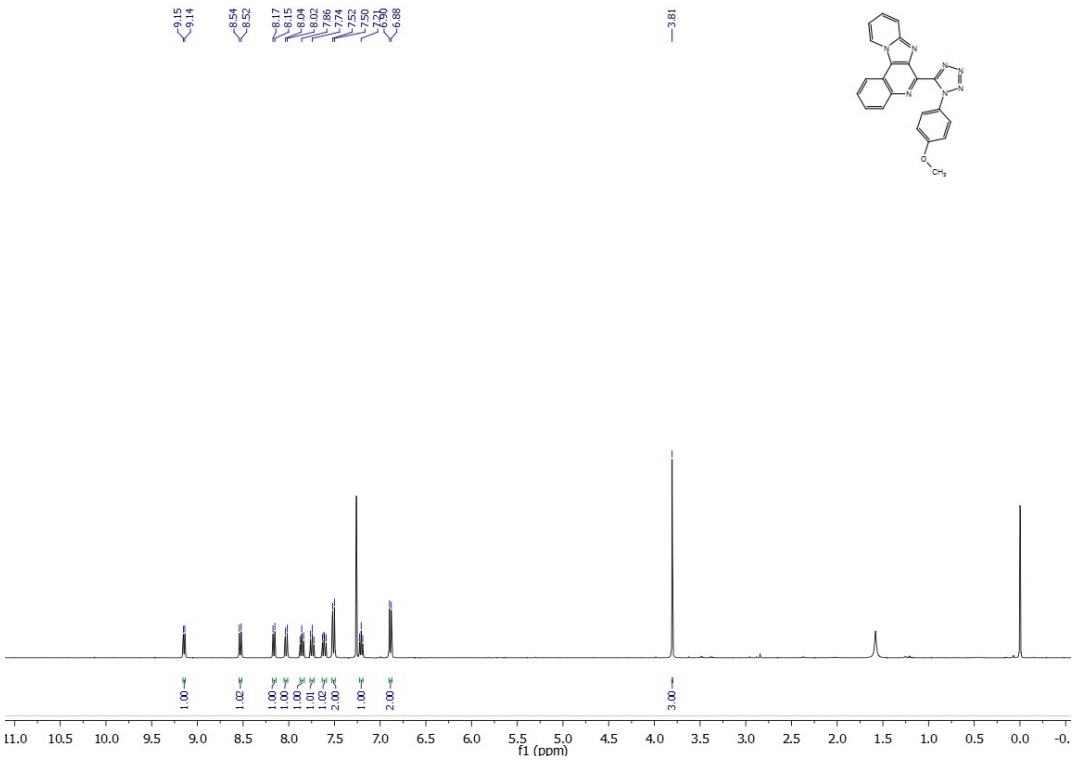


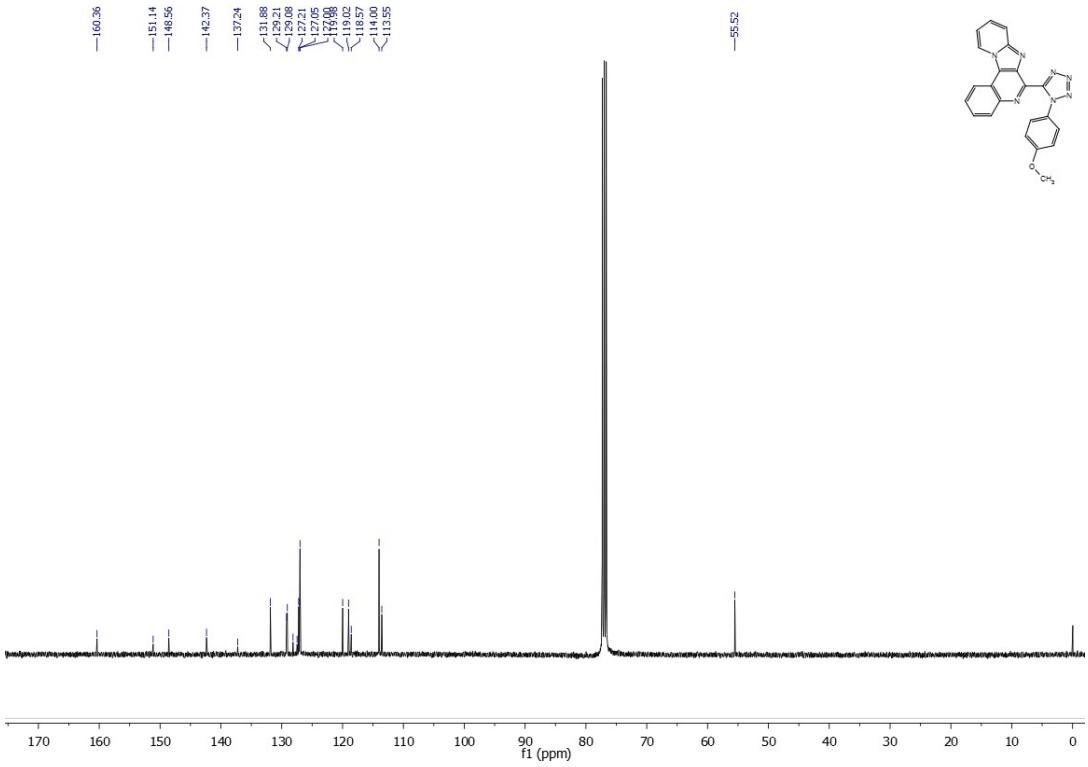
^{1}H NMR and ^{13}C NMR for 8-bromo-6-(1-cyclohexyl-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6cb)



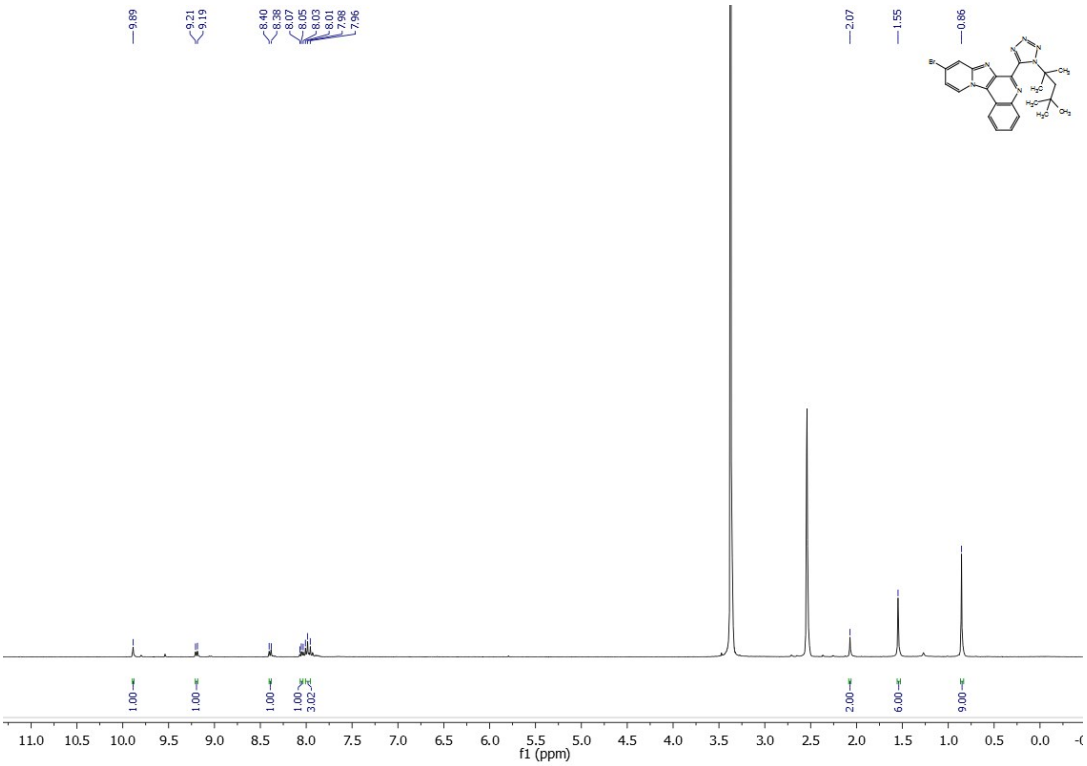


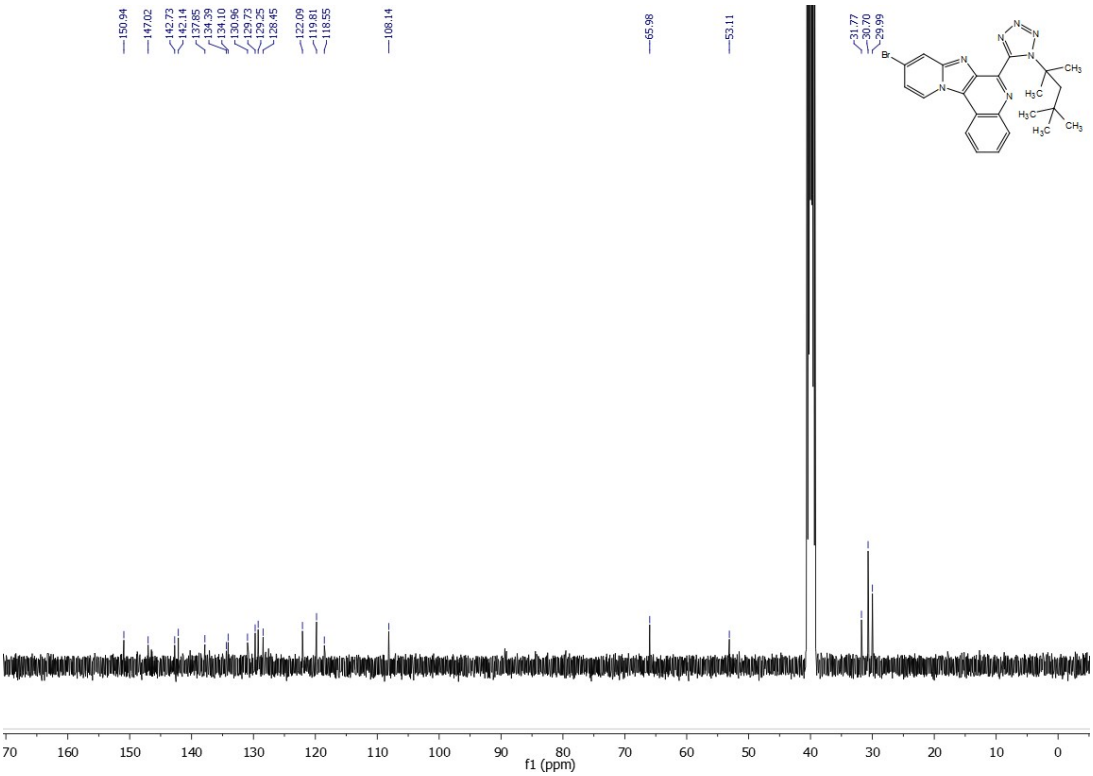
^{1}H NMR and ^{13}C NMR for 6-(1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6cc)



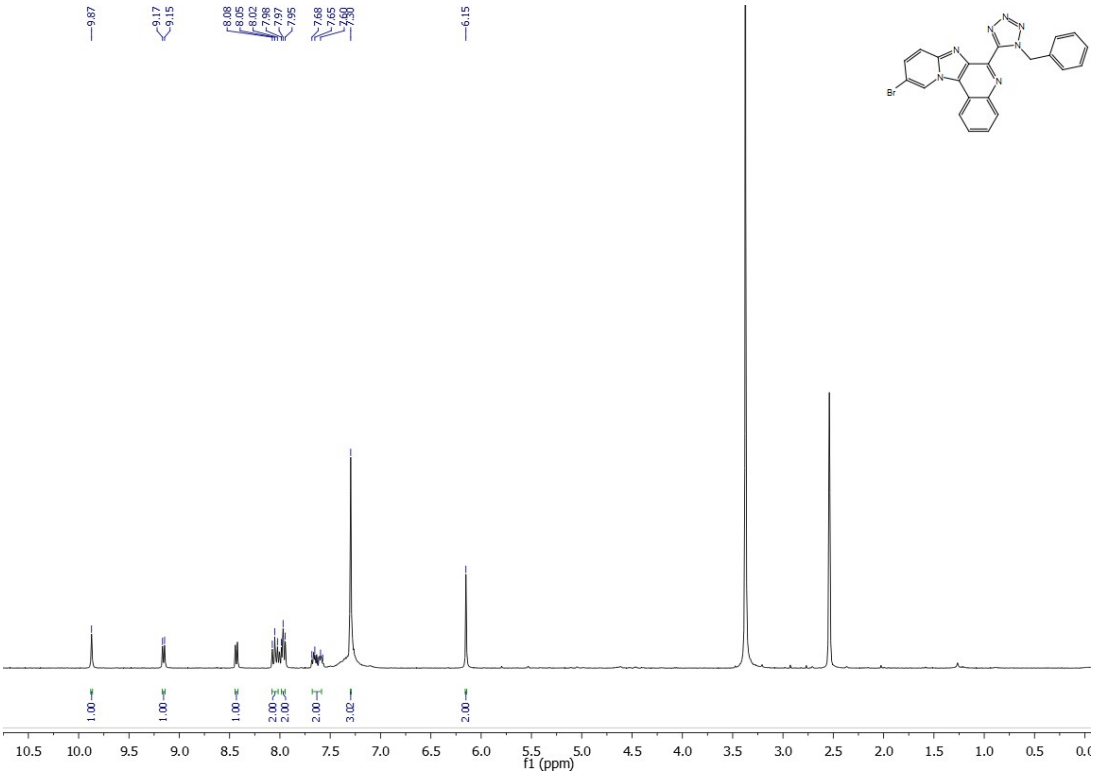


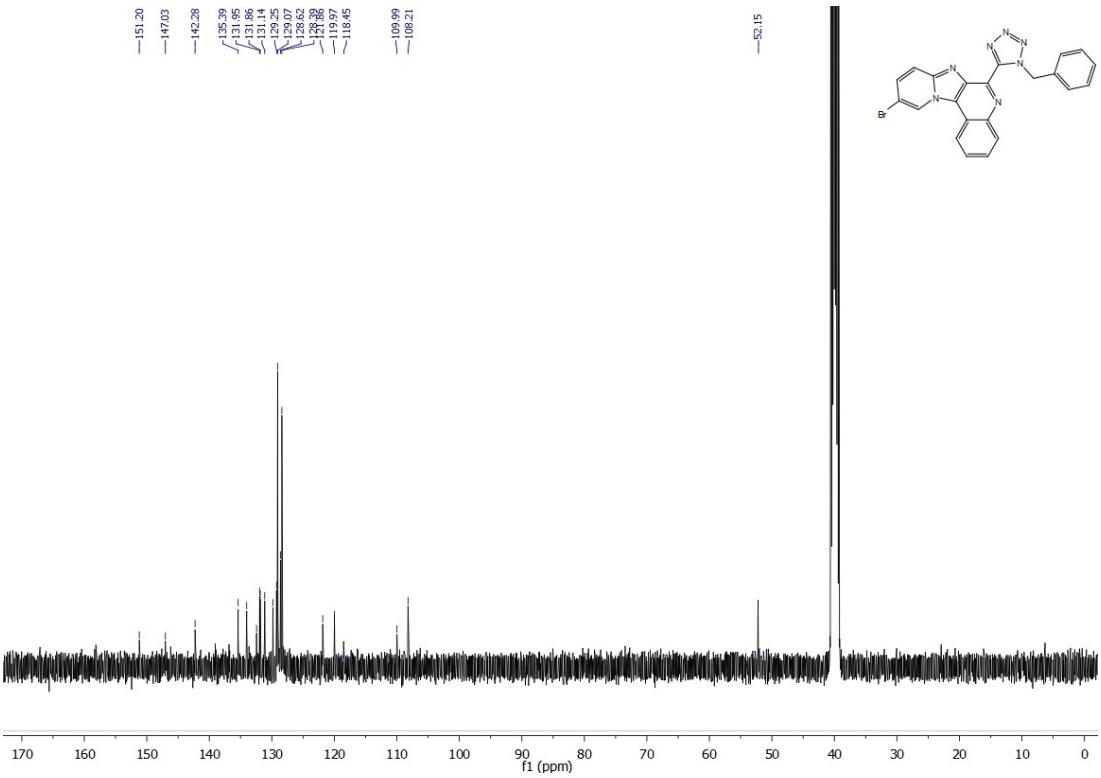
^{1}H NMR and ^{13}C NMR for 9-bromo-6-(1-(2,4,4-trimethylpentan-2-yl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6cd)


9.89
9.21
9.19
8.40
8.38
8.07
8.05
8.03
8.01
7.98
7.96
2.07
1.55
0.86
1.00
1.00
1.00
1.00
3.02
2.00
6.00
9.00
f1 (ppm)

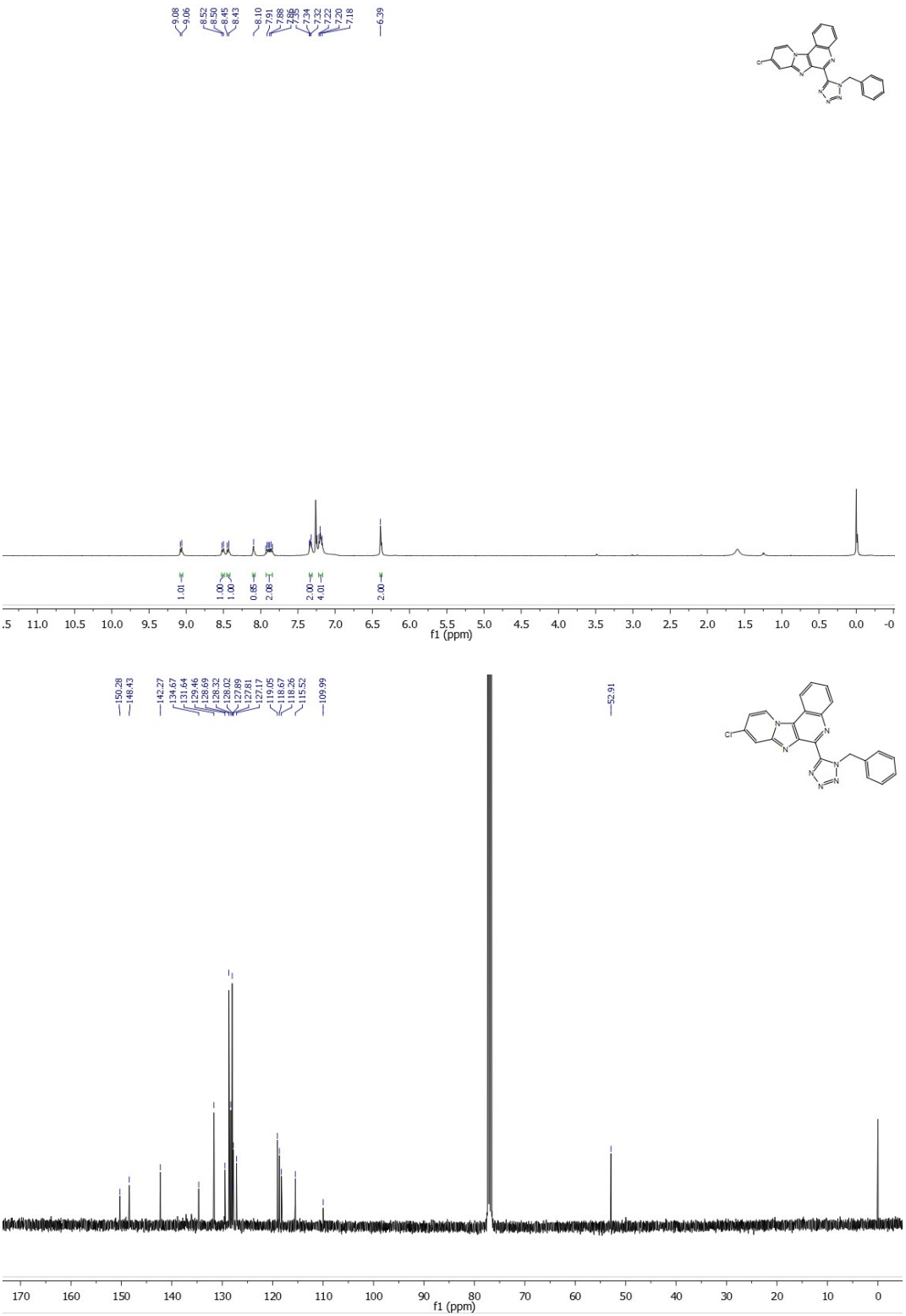

150.94
147.02
142.73
142.14
137.85
134.39
134.10
130.96
129.73
129.25
128.45
122.09
119.81
118.55
108.14
65.98
53.11
31.77
30.70
29.99
f1 (ppm)

^{1}H NMR and ^{13}C NMR for 6-(1-benzyl-1*H*-tetrazol-5-yl)-10-bromopyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6ce)

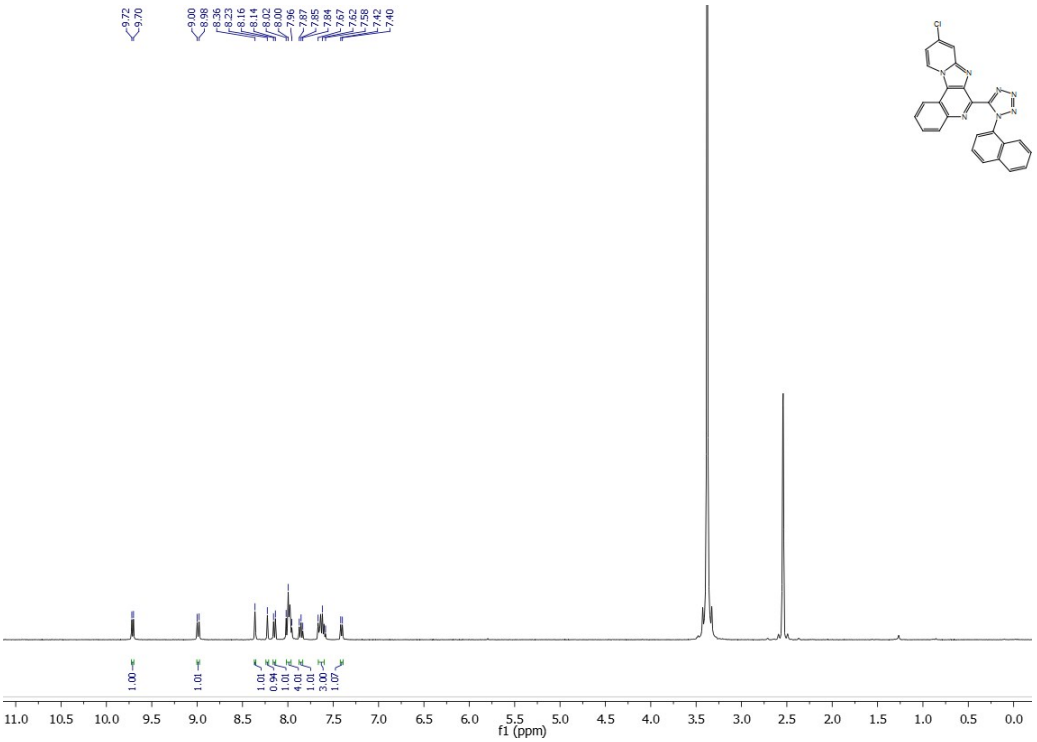


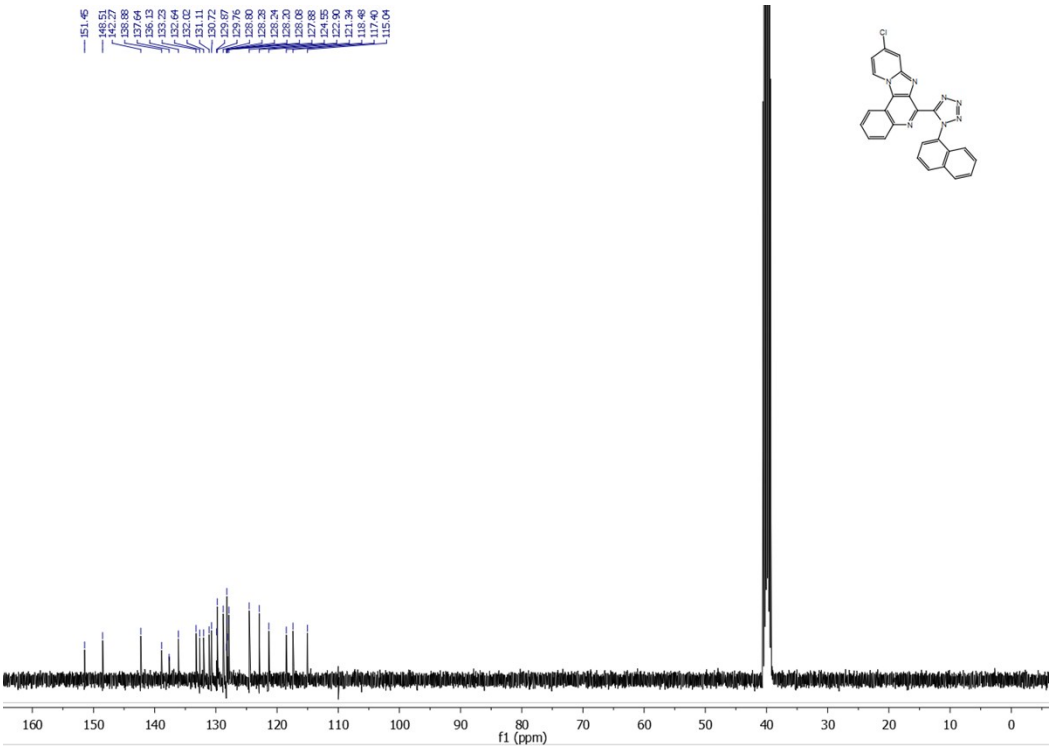


^{1}H NMR and ^{13}C NMR for 6-(1-benzyl-1*H*-tetrazol-5-yl)-9-chloropyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6cf)

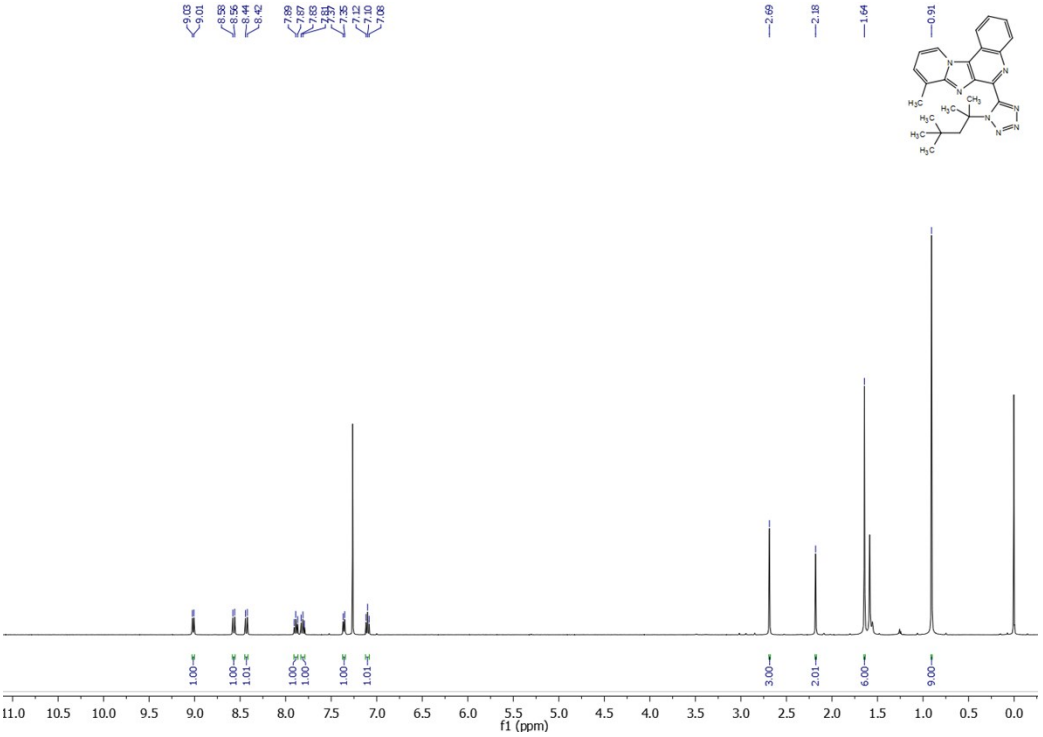


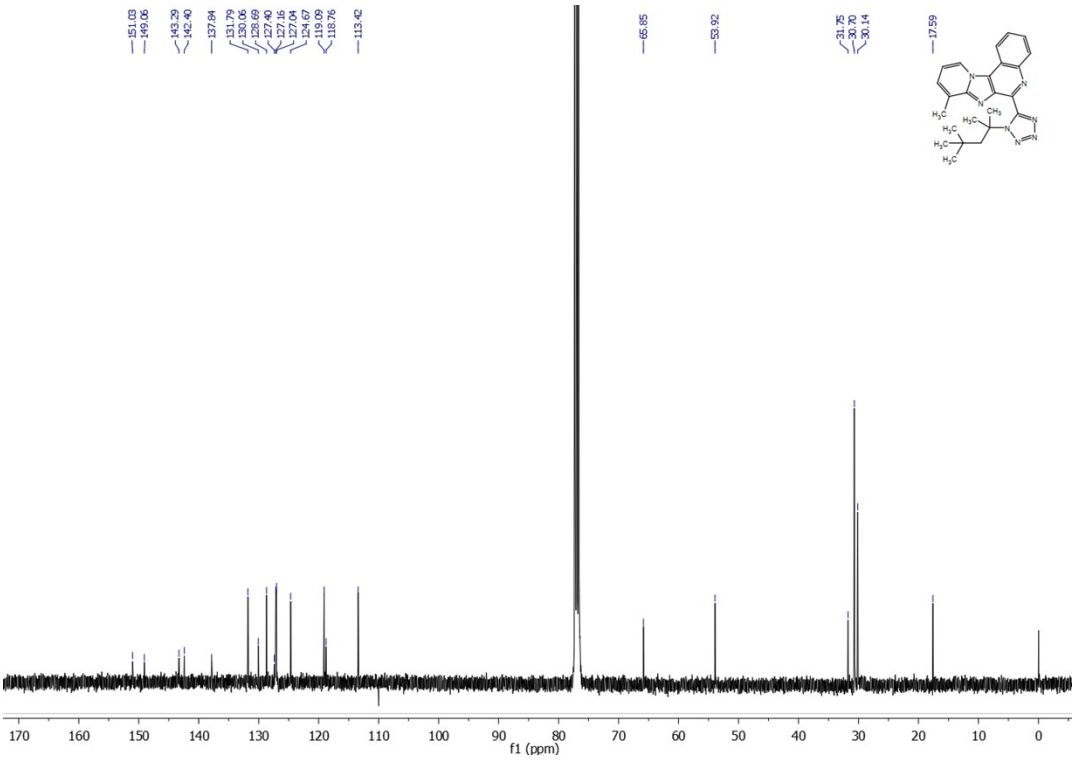
^{1}H NMR and ^{13}C NMR for 9-chloro-6-(1-(naphthalen-1-yl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6cg)



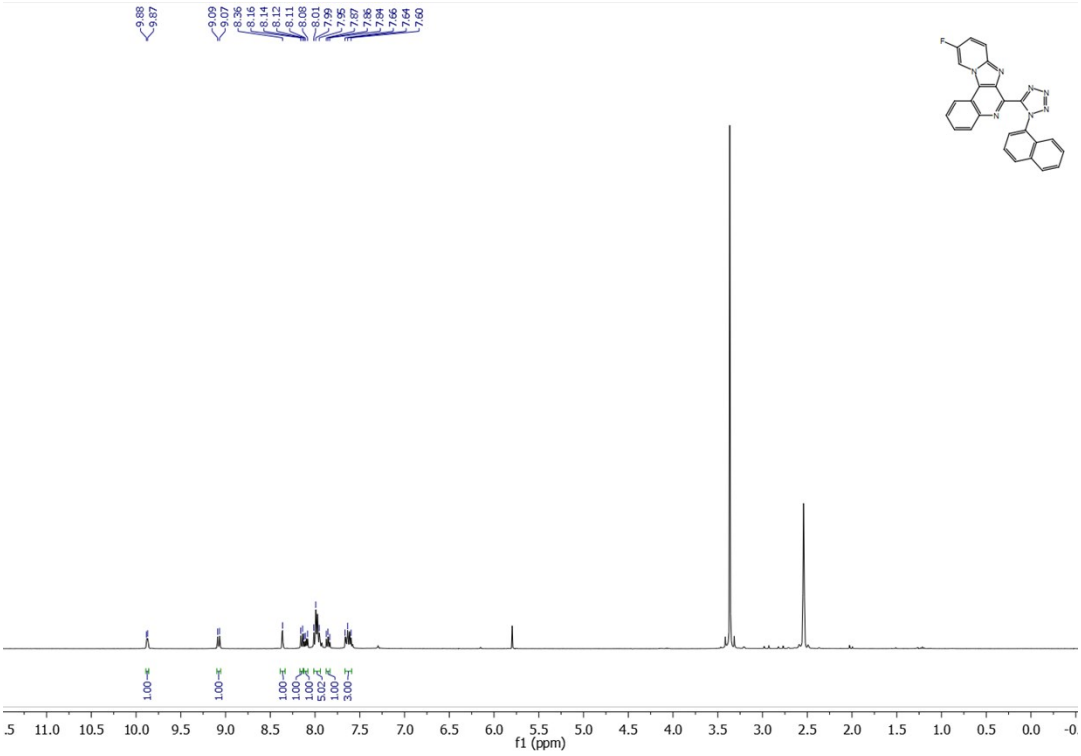


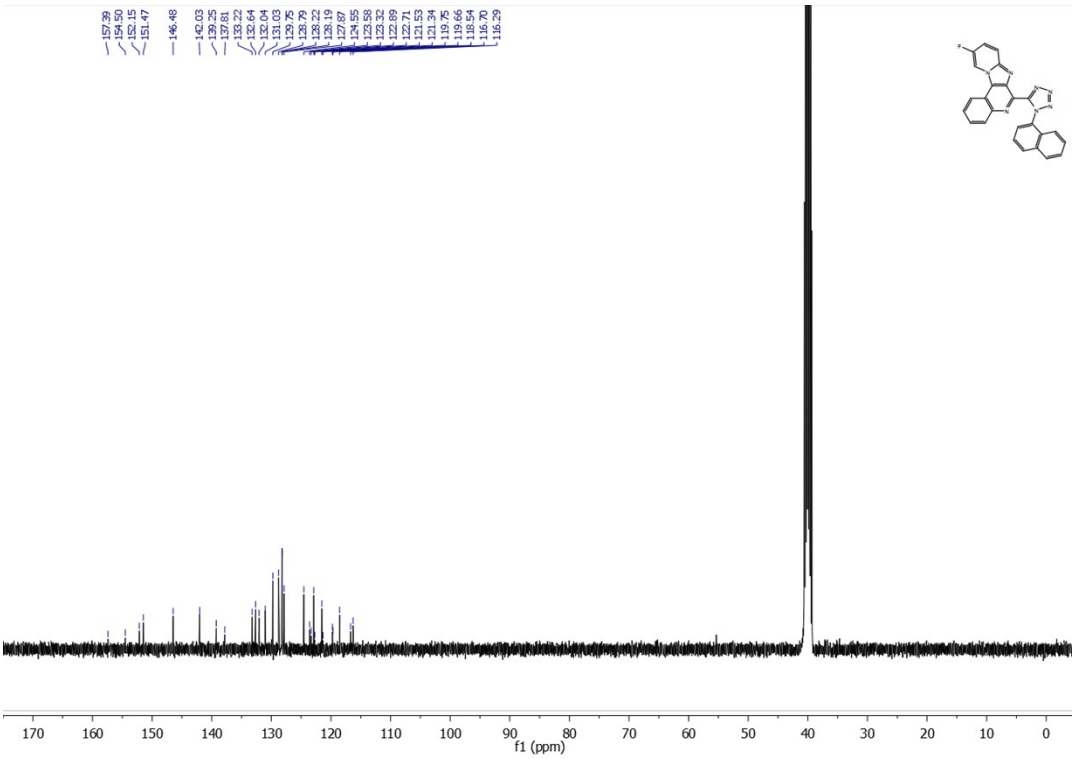
^{1}H NMR and ^{13}C NMR for 8-methyl-6-(1-(2,4,4-trimethylpentan-2-yl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6ch)



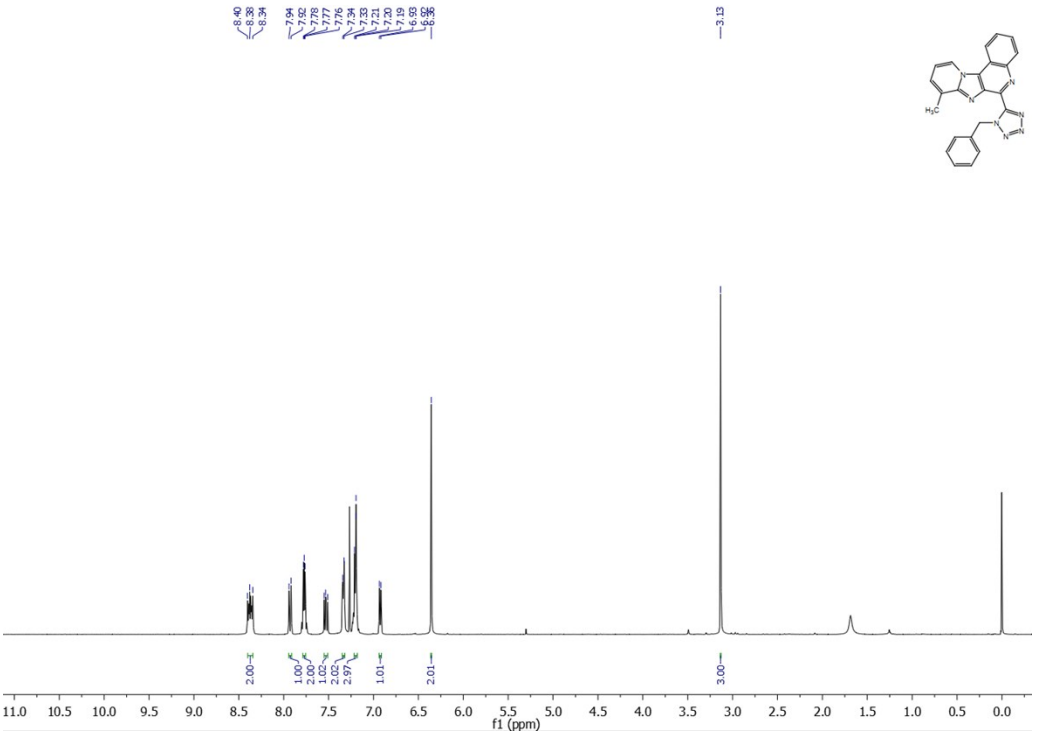


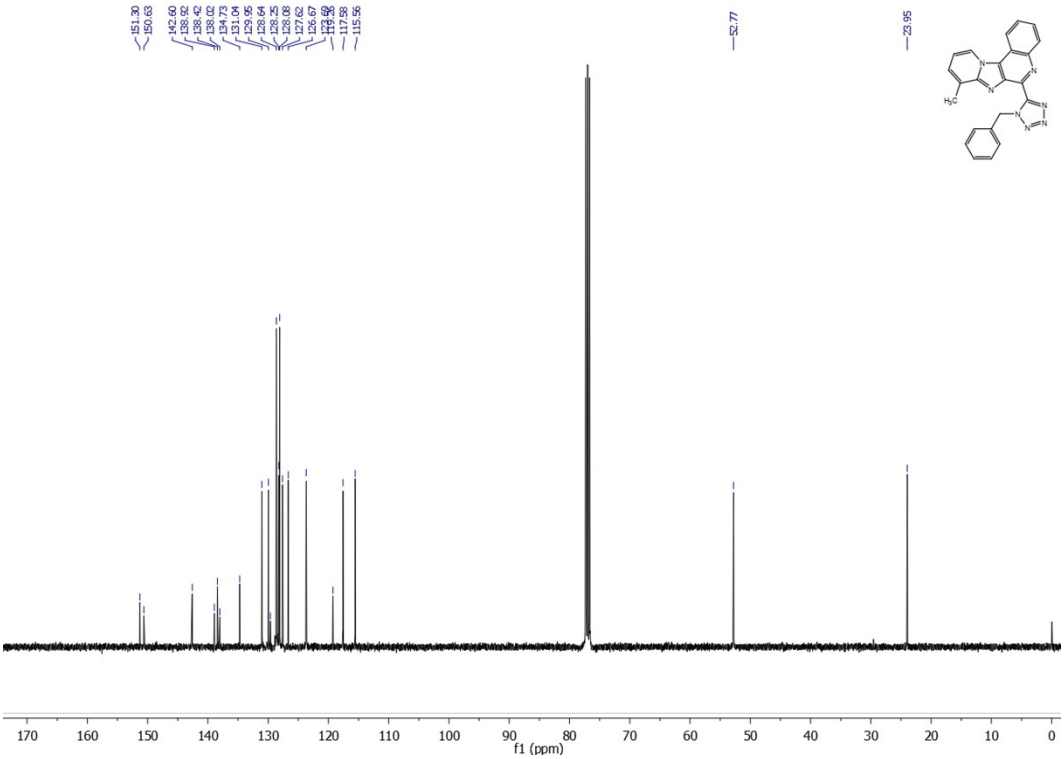
^{1}H NMR and ^{13}C NMR for 10-fluoro-6-(1-(naphthalen-1-yl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6ci)



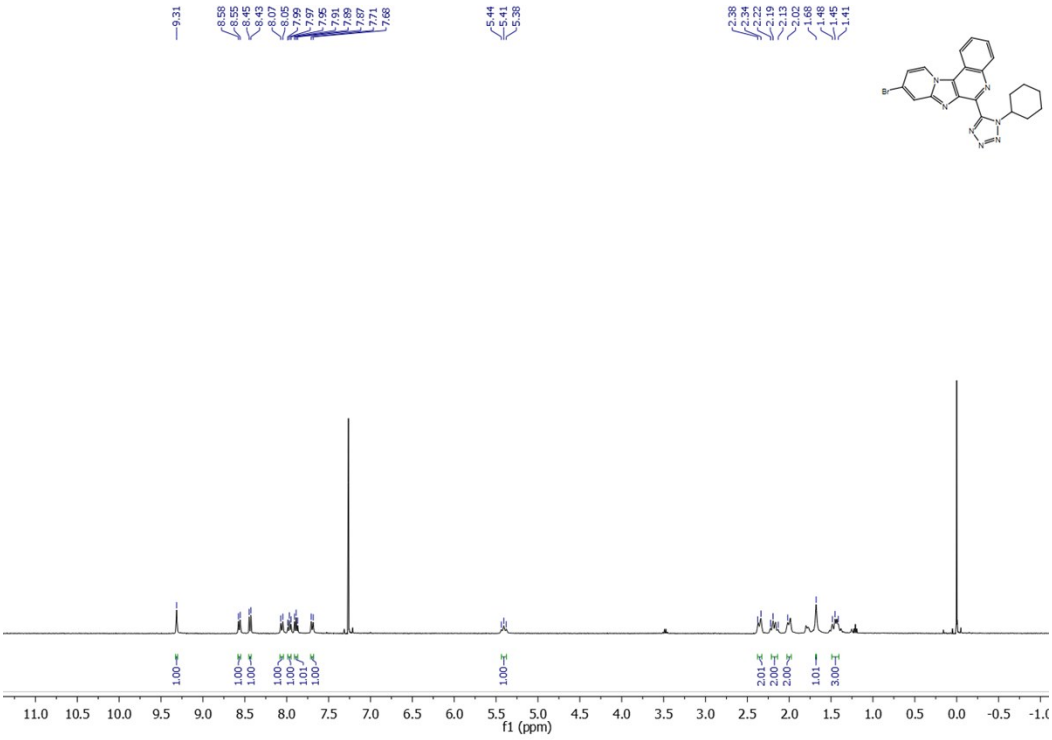


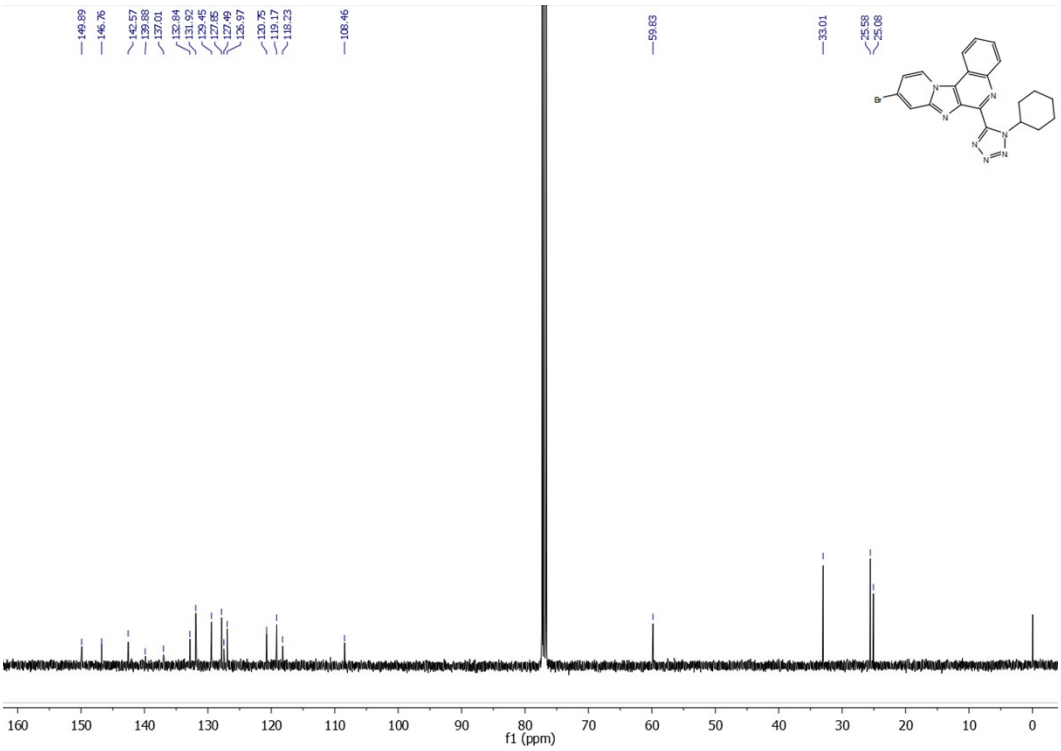
^{1}H NMR and ^{13}C NMR for 6-(1-benzyl-1*H*-tetrazol-5-yl)-8-methylpyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6cj)



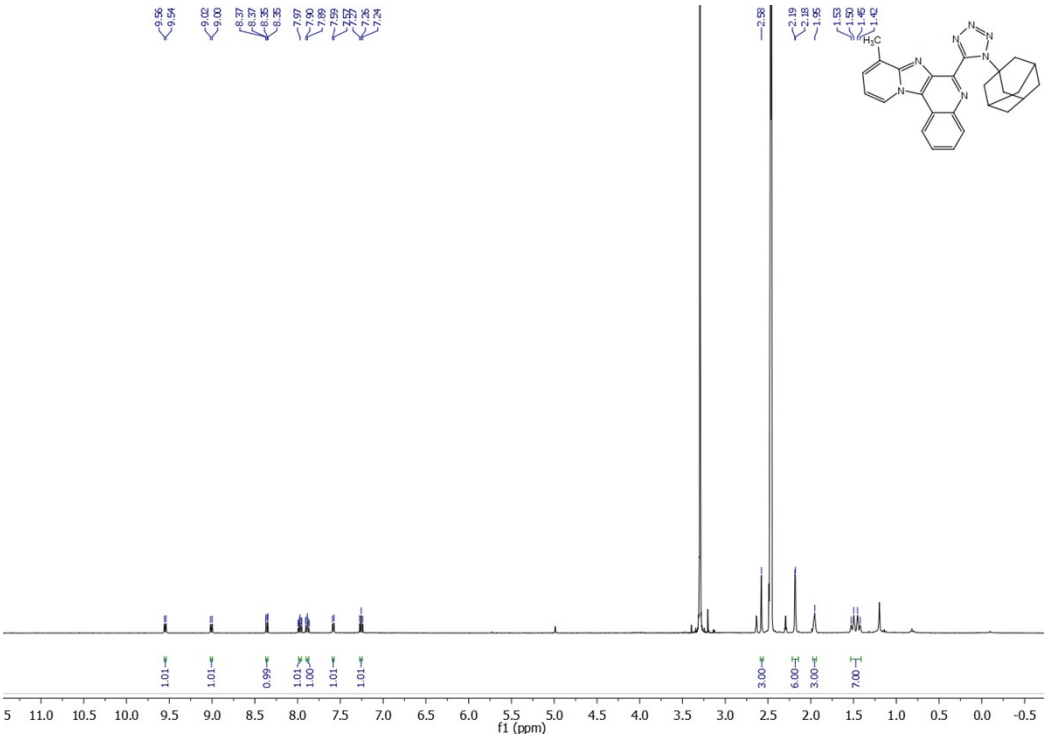


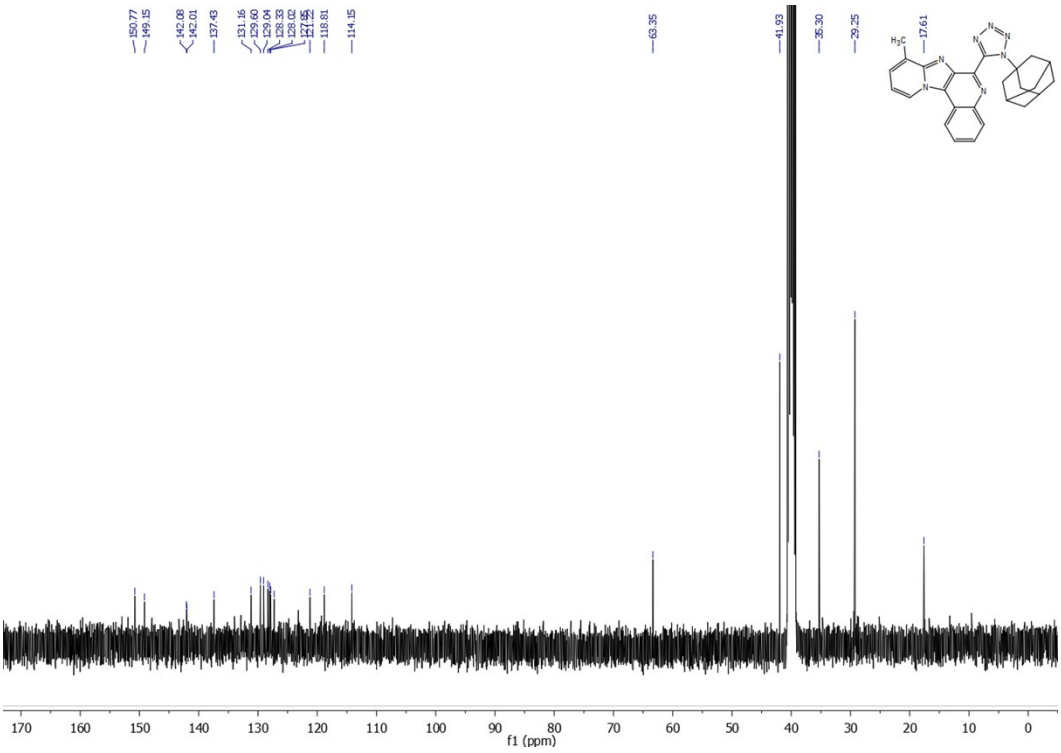
^{1}H NMR and ^{13}C NMR for 9-bromo-6-(1-cyclohexyl-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6ck)



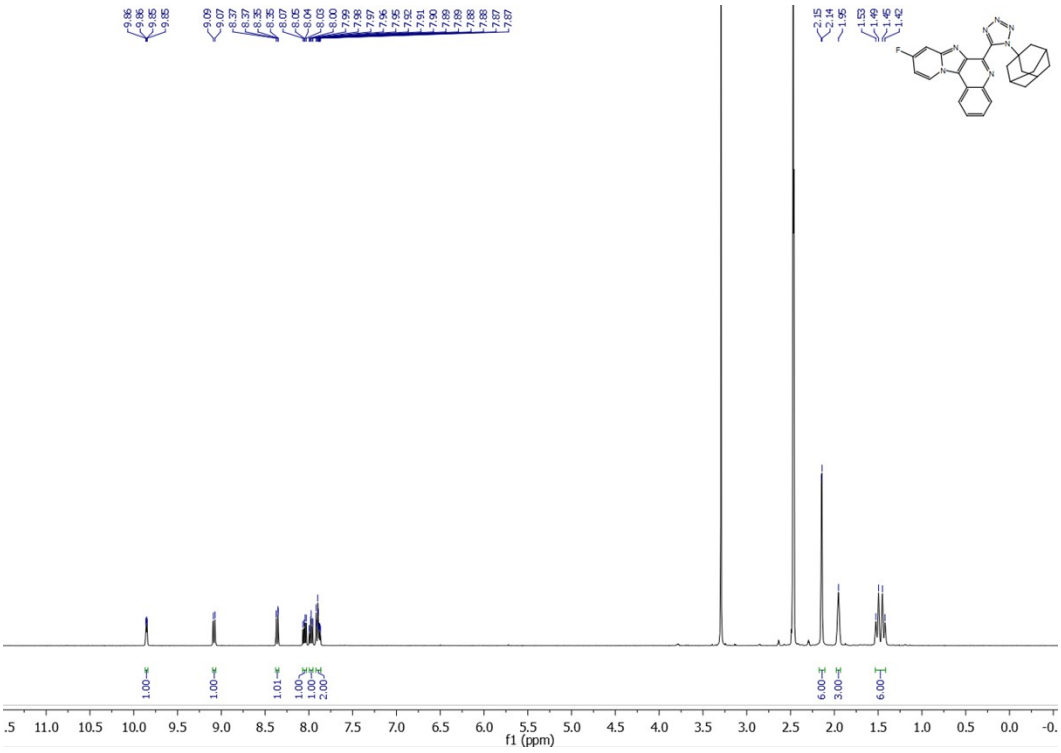


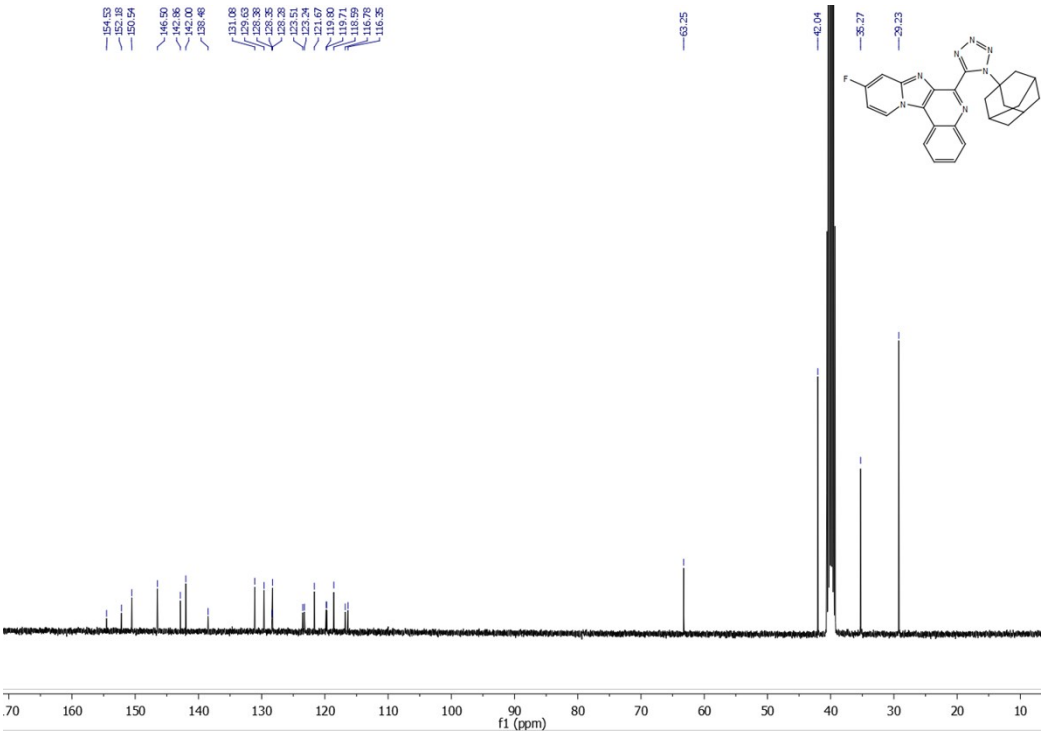
^{1}H NMR and ^{13}C NMR for 6-(1-(adamantan-1-yl)-1*H*-tetrazol-5-yl)-8-methylpyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6cl)



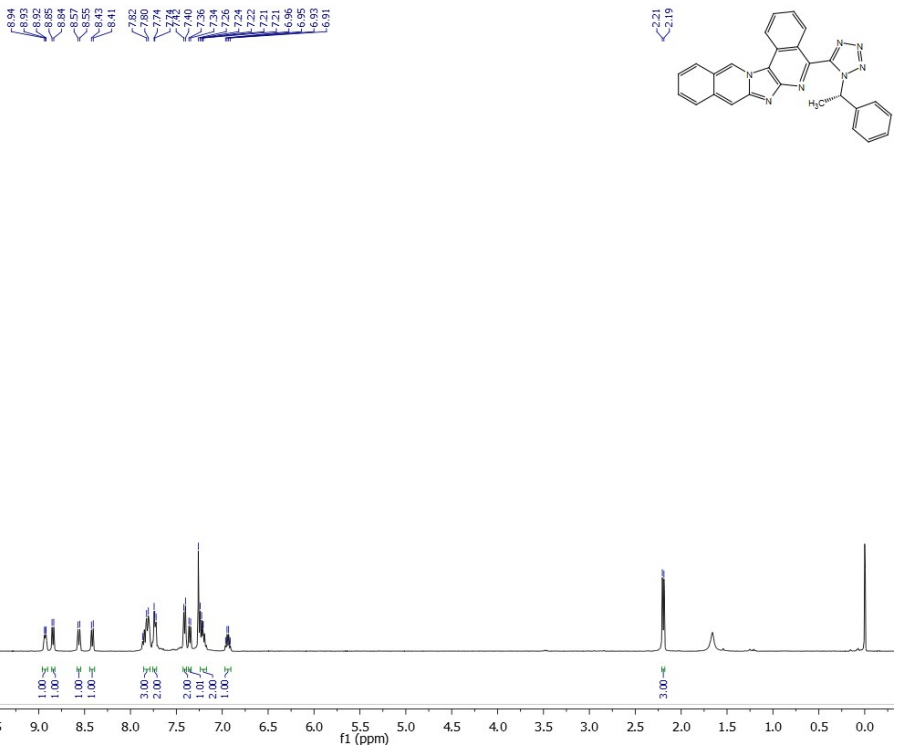


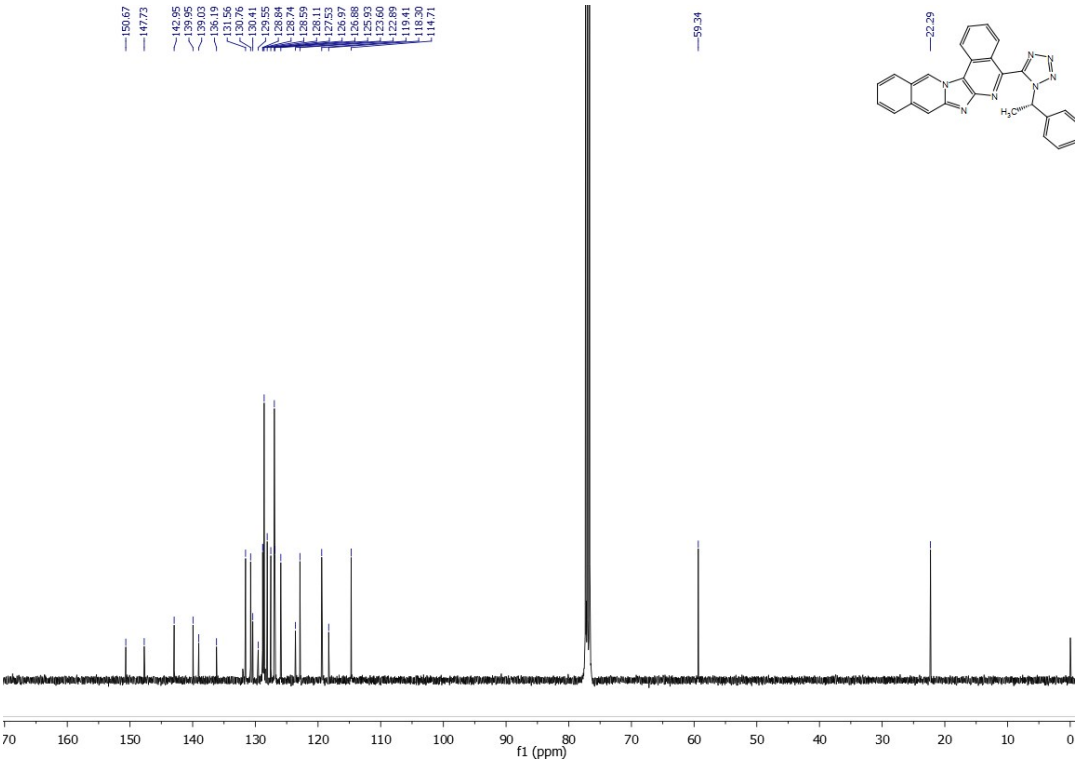
^{1}H NMR and ^{13}C NMR for 6-(1-(adamantan-1-yl)-1*H*-tetrazol-5-yl)-9-fluoropyrido[1',2':1,2]imidazo[4,5-*c*]quinoline (6cm)



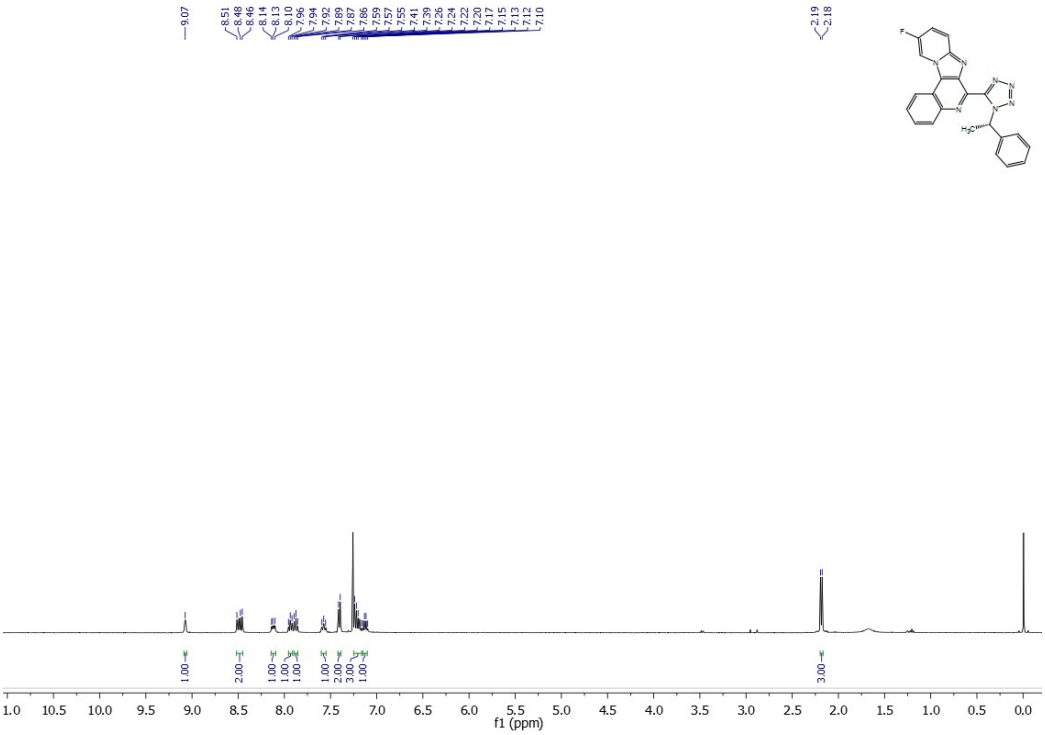


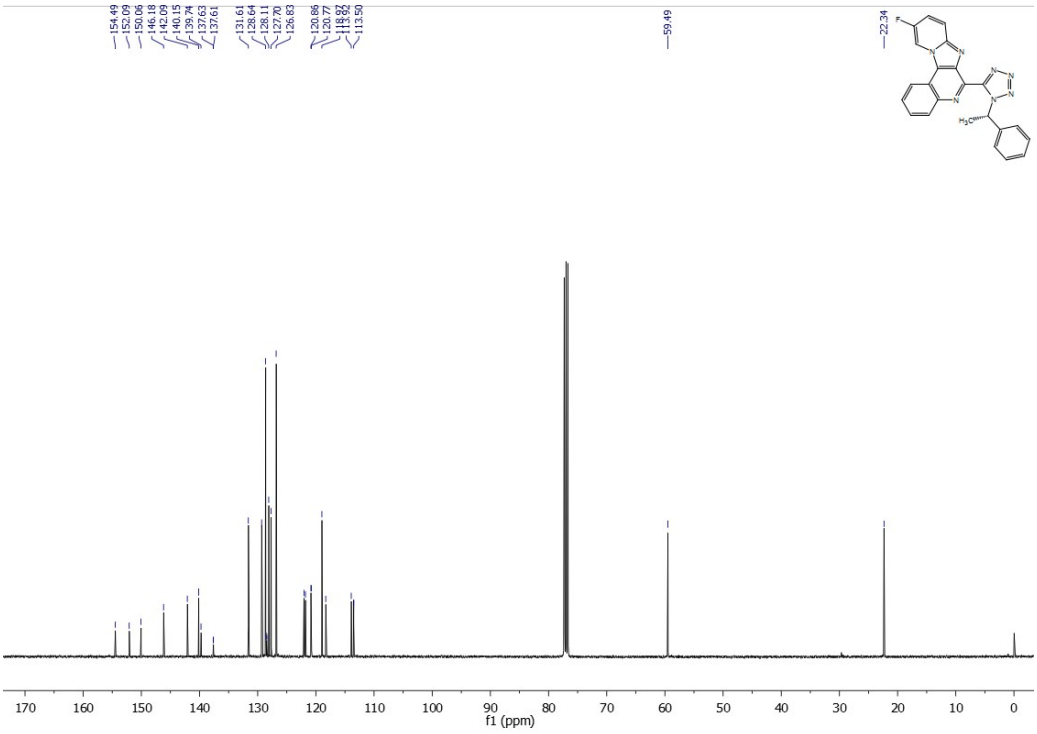
^{1}H NMR and ^{13}C NMR for (*S*)-5-(1-(1-phenylethyl)-1*H*-tetrazol-5-yl)imidazo[1,2-*b*:4,5-*c*']diisoquinoline (6cn)





^{1}H NMR and ^{13}C NMR for (*S*)-10-fluoro-6-(1-(1-phenylethyl)-1*H*-tetrazol-5-yl)pyrido[1',2':1,2]imidazo[4,5-*c*]quinolone (6co)





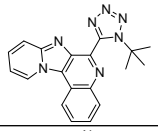
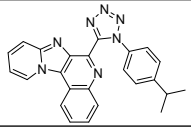
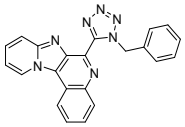
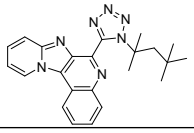
V. Cellular Assay Procedure for Solid Tumors

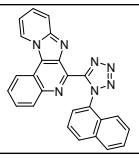
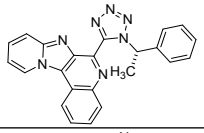
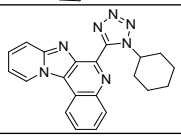
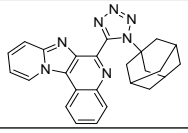
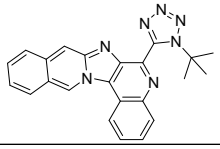
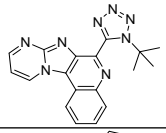
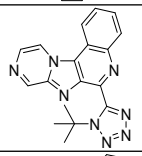
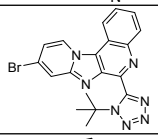
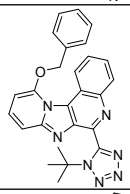
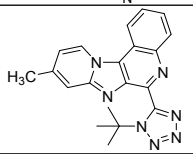
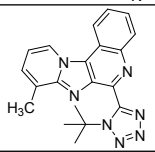
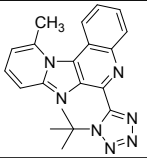
The MCF7 (human breast adenocarcinoma cell line) cells were obtained from American Type Culture Collection, Manassas, VA. MCF7 cells were cultured using the recommended Eagle's Minimum Essential Medium supplemented with 10% fetal bovine Serum. The cells were maintained at 37 °C in a humidified atmosphere with 5% CO and were sub-cultured two to three times per week. Cell viability assays were performed in 96-well plates (Sigma-Aldrich). Briefly, MCF7 cells were seeded at approximately 5 x 10^3 cells per well in 96 well plates containing 100 µl medium, and incubated for 24 hours. After 24 hours incubation at 37 °C, inhibitors were then dosed in concentrations ranging from 100 µm to 1nm. Cells were further incubated for three days, after which the amount of viable cells were quantified. 10 µl of Resazurin solution (Biotium) were added to each well and incubated for 6 h before reading at a fluorescence excitation/emission wavelength of 540/590nm. Fluorescence in each well was then measured using a microplate reader (Synergy neo2 multi-mode reader Biotek INC, Winooski, VT). Nonlinear regression method was used in graph pad prism for calculating IC_{50} values. A similar viability protocol was utilized for KM-12 and SKMEL-28 cells.

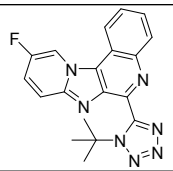
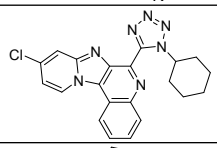
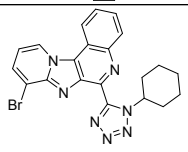
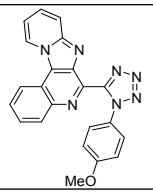
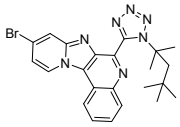
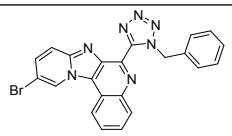
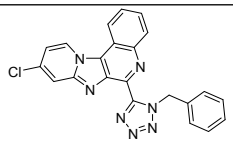
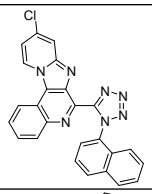
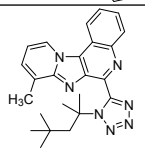
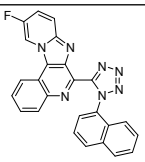
VI. Cellular Assay Procedure for Hematological Tumors

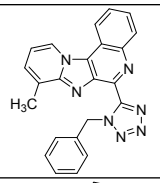
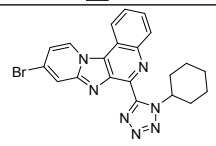
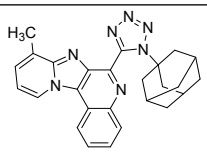
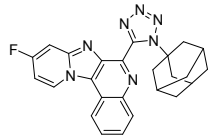
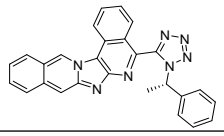
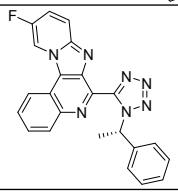
The human diffuse large B-cell lymphoma cell lines, VAL, RIVA, SUDHL6, and U2932 were previously obtained from Dr. Rimsza (Mayo Clinic Scottsdale) and HT and SUDHL4 were obtained from American Type Culture Collection. All cell lines were cultured in 10% FBS, 5% penicillin/streptomycin-supplemented Roswell Park Memorial Institute (RMPI) media and tested for mycoplasma every 6 months and last authenticated on 10/29/2018 using the University of Arizona Genetics Core (Tucson, AZ) with the PowerPlex 16 System (Promega). The cells were maintained at 37 °C in a humidified atmosphere with 5% CO and were sub-cultured one to two times per week. Cell viability assays were performed in 96-well plates with all cells seeded at approximately 5 x 10^4 cells per well containing 90 μl medium and incubated over-night. Inhibitors were then dosed with 11 two-fold concentration dilutions ranging from 10 µm to 10 nm. Cells were further incubated for three days, after which the amount of viable cells were quantified using the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium (MTS) colorimetric assay as per the manufacturer's protocol (Promega). Absorbance was measured using a microplate reader (Cytation 5 imaging reader Biotek) and nonlinear regression method was used in GraphPad Prism software (v6) for generating dose-response curves and calculating IC_{50} values.

VII. Anti-proliferative activity of synthesized compounds

S No.	Compound Code	Structure	Cell IC_{50} (μM) cell lines		
			MCF7	KM12	SKMEL
1.	**6aa**		41.14	47.17	35.83
2.	**6ab**		10.1	28.5	93.7
3.	**6ac**		68.02	14.6	50.86
4.	**6ad**		40.50	134.2	37.18

5.	**6ae**		41.50	nd	nd
6.	**6af**		3.0	6.6	19.3
7.	**6ag**		26.65	69.15	29.94
8.	**6ah**		nd	nd	nd
9.	**6ba**		33.62	nd	nd
10.	**6bb**		33.37	42.1	84.31
11.	**6bc**		60.92	nd	nd
12.	**6bd**		48.02	nd	nd
13.	**6be**		28.03	nd	nd
14.	**6bf**		56.67	nd	nd
15.	**6bg**		40.79	nd	nd
16.	**6bh**		33.91	nd	nd

17.	**6bi**		37.42	nd	nd
18.	**6ca**		19.94	142.6	48.18
19.	**6cb**		11.1	31.42	48.2
20.	**6cc**		43.42	nd	nd
21.	**6cd**		55.91	nd	nd
22.	**6ce**		32.56	nd	nd
23.	**6cf**		34.88	nd	nd
24.	**6cg**		32.48	nd	nd
25.	**6ch**		32.71	nd	nd
26.	**6ci**		nd	nd	nd

27.	**6cj**		21.46	nd	nd
28.	**6ck**		nd	nd	nd
29.	**6cl**		nd	nd	nd
30.	**6cm**		nd	nd	nd
31.	**6cn**		nd	nd	nd
32.	**6co**		nd	nd	nd

VIII. Activity of **6af** against Lymphoma cell lines