Electronic Supporting Information

Direct Regioselective C-H Cyanation of Purines

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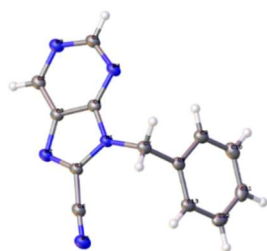
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† These authors contributed equally to this work.

Contents

1. The single crystal data of **2a** [CCDC: 2217776]

Crystal Data.

$C_{13}H_9N_5$, M =235.25, triclinic, a = 7.2138(13) Å, b = 7.7046(14) Å, c = 11.7853(19) Å, α = 104.439(15)°, β = 93.907(14)°, γ = 116.014(17)°, U = 558.08(17) Å^3, T = 113.50(14), space group P-1 (no. 2), Z = 2, μ(Mo Kα) = 0.091, 3968 reflections measured, 2193 unique (R_{int} = 0.0299) which were used in all calculations. The final $wR(F_2)$ was 0.1088 (all data).

Table S1: Structure refinement for **2a**

Identification code	**2a**
Empirical formula	$C_{13}H_9N_5$
Formula weight	235.25
Temperature / K	113.50(14)
Crystal system	triclinic
Space group	P-1
a / Å, b / Å, c / Å	7.2138(13), 7.7046(14), 11.7853(19)
α/°, β/°, γ/°	104.439(15), 93.907(14), 116.014(17)
Volume / Å^3	558.08(17)
Z	2
Q_{calc} / mg mm^{-3}	1.400
μ / mm^{-1}	0.091
F(000)	244
Crystal size / mm^3	0.54 × 0.28 × 0.21
2Θ range for data collection	6.12 to 51.98°
Index ranges	-8 ≤ h ≤ 8, -9 ≤ k ≤ 9, -14 ≤ l ≤ 14
Reflections collected	3968
Independent reflections	2193[R(int) = 0.0299 (inf-0.9Å)]
Data/restraints/parameters	2193/0/163
Goodness-of-fit on F^2	1.072
Final R indexes [I>2σ (I) i.e. F$_o$>4σ (F$_o$)]	R$_1$ = 0.0452, wR$_2$ = 0.0993
Final R indexes [all data]	R$_1$ = 0.0571, wR$_2$ = 0.1088
Largest diff. peak/hole / e Å^{-3}	0.240/-0.281
Flack Parameters	N
Completeness	0.9991

2. Optimization of the reactions

2.1 The screening of reactant loading
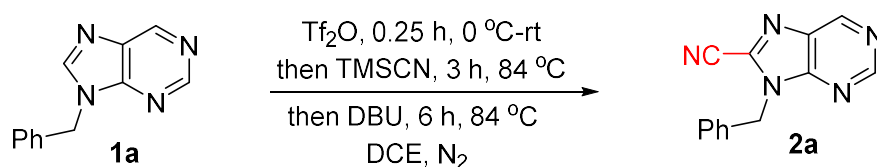
entry	Tf$_2$O (equiv)	TMSCN (equiv)	DBU (equiv)	2a (%)[a]
1	1.2	2.0	1.3	53
1	1.5	2.0	1.7	43
2	2.0	2.0	2.2	43
3	1.2	3.0	1.3	38

Reaction conditions: Tf$_2$O added to substrate **1a** (0.2 mmol) in DCE (2 mL) at 0 °C under N$_2$, stirred 1 h, then TMSCN added warmed to 84 °C for 3 h, and DBU added, warmed to 84 °C for 6 h before quench with NaHCO$_3$. [a.] All yields are obtained from isolated compounds.

2.2 The screening of the reaction time
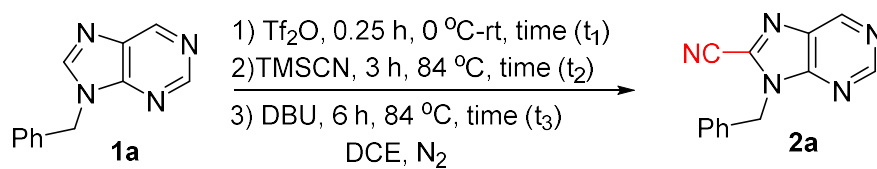
entry	t_1/h	t_2/h	t_3/h	2a%[a]
1	0.25	3	6	54
2	0.5	3	6	47
3	0.75	3	6	50
4	1	3	6	53
5	1.25	3	6	45
6	1.5	3	6	45
7	0.25	0	6	41
8	0.25	1	6	47
9	0.25	2	6	48
10	0.25	4	6	43
11	0.25	3	2	43
12	0.25	3	4	47
13	0.25	3	6	54
14	0.25	3	8	36
15	0.25	3	10	43

Reaction conditions: Tf$_2$O (1.2 eq) added to **1a** (0.2 mmol) in DCE (2 mL) at 0 °C under N$_2$, stirred t_1 (h), then TMSCN (2.0 eq) added warmed to 84 °C for t_2 (h), and DBU (1.3 eq) added, warmed to 84 °C for t_3 (h) before quench with NaHCO$_3$. [a.] All yields are obtained from isolated compounds.

3. **Copies of ¹H and ¹³C-NMR spectra of cyanopurines 2**

9-Benzyl-9H-purine-8-carbonitrile (**2a**)

¹H NMR (400 MHz, CDCl₃)
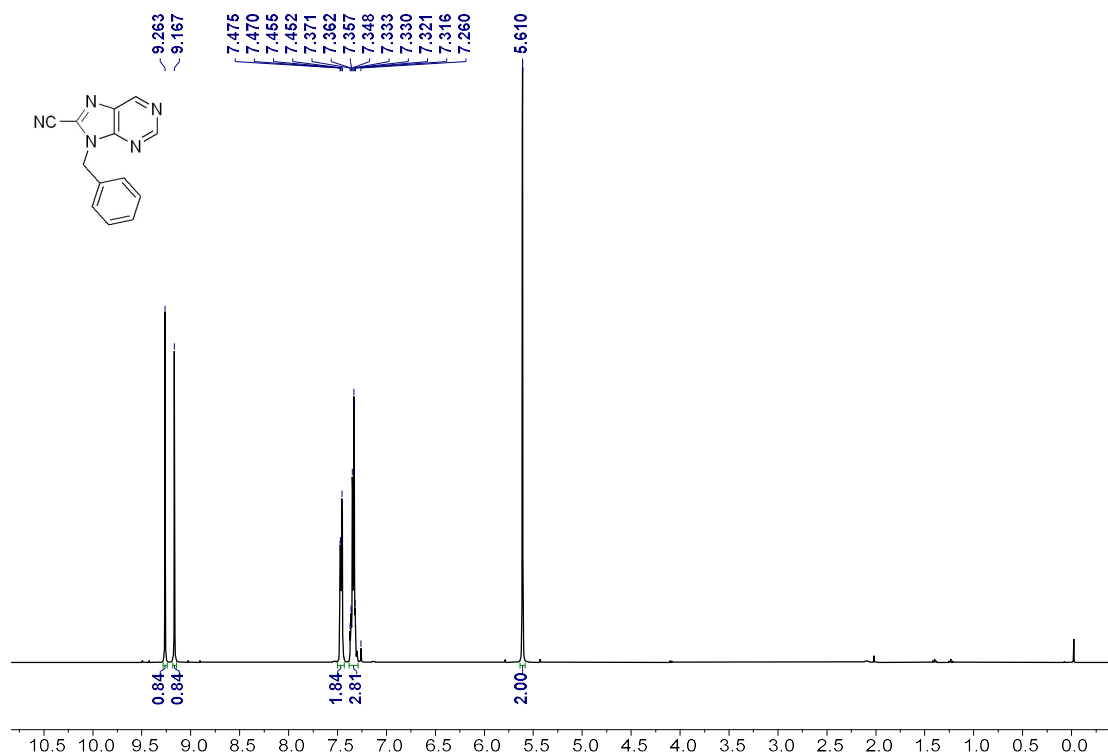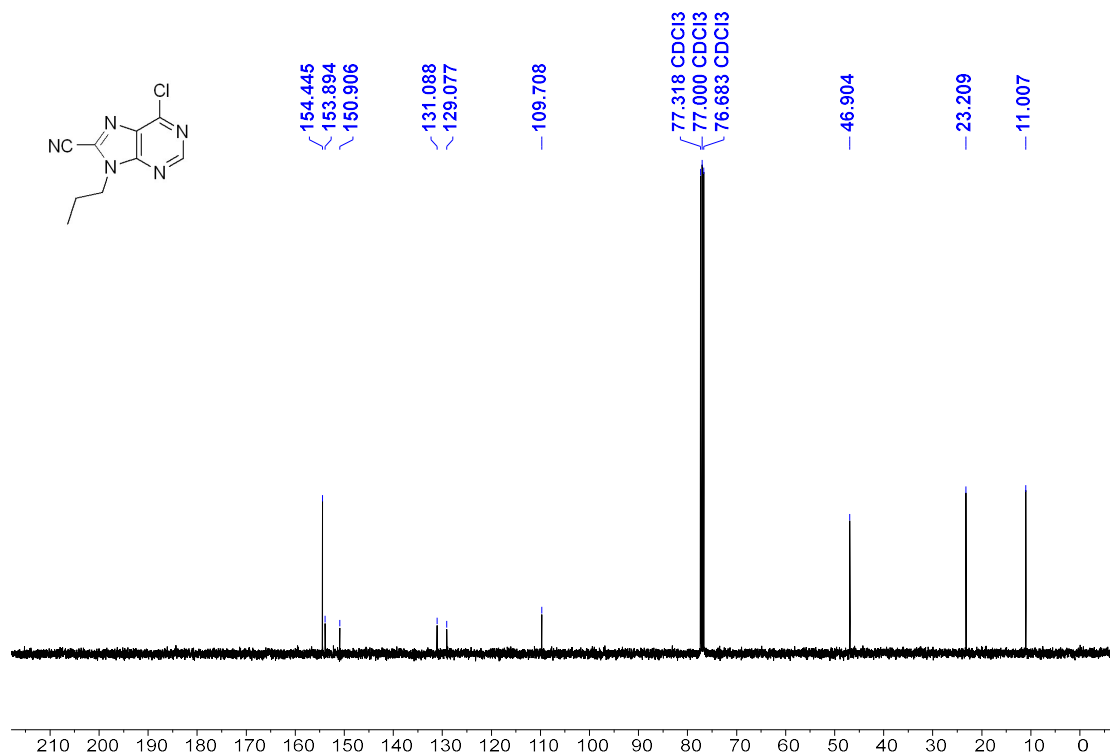

¹³C NMR (101 MHz, CDCl₃)
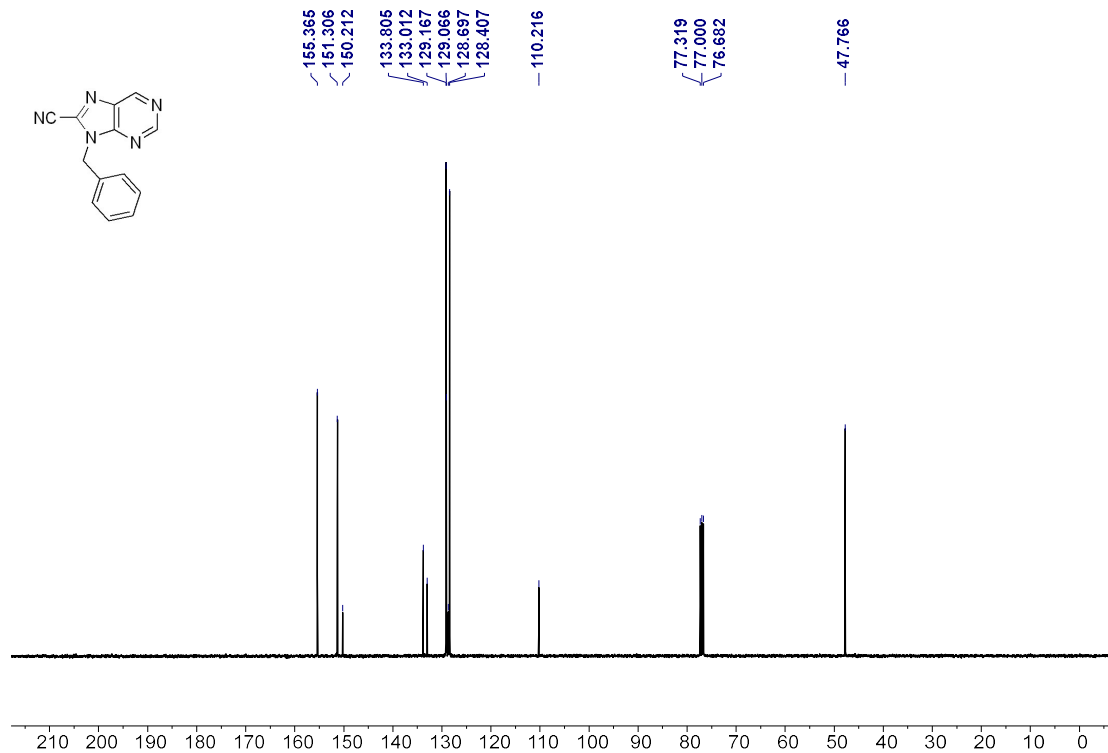
6-chloro-9-propyl-9H-purine-8-carbonitrile (**2b**)
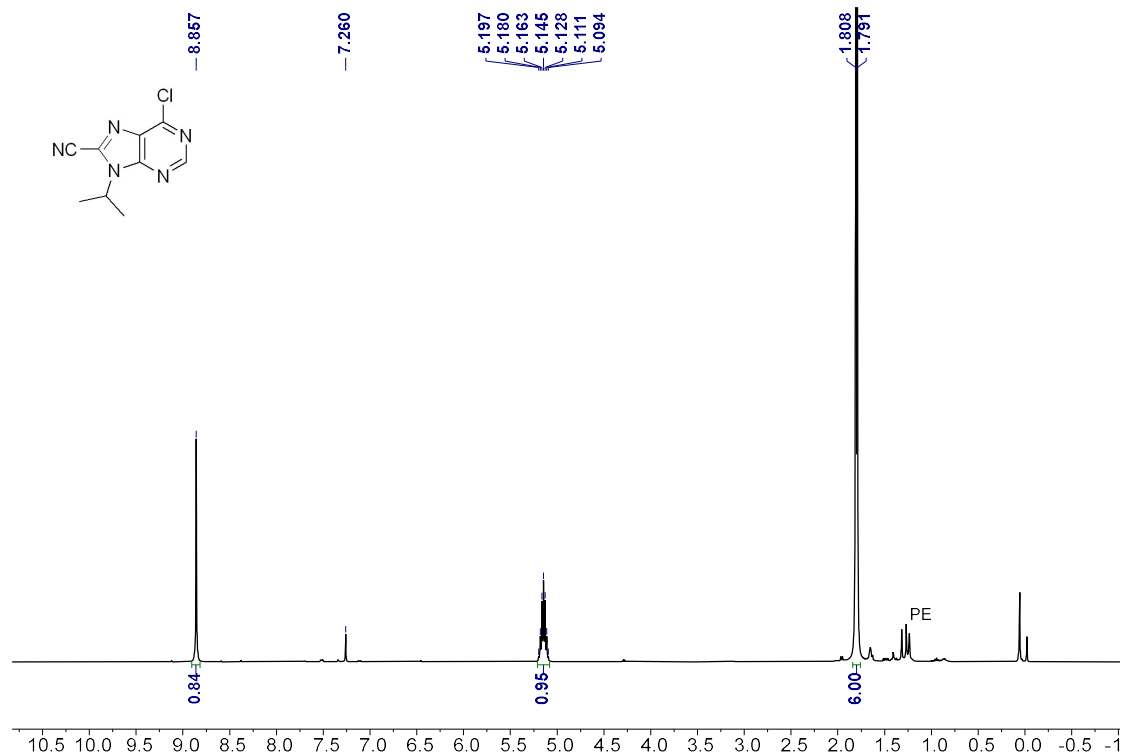
¹H NMR (400 MHz, CDCl₃)
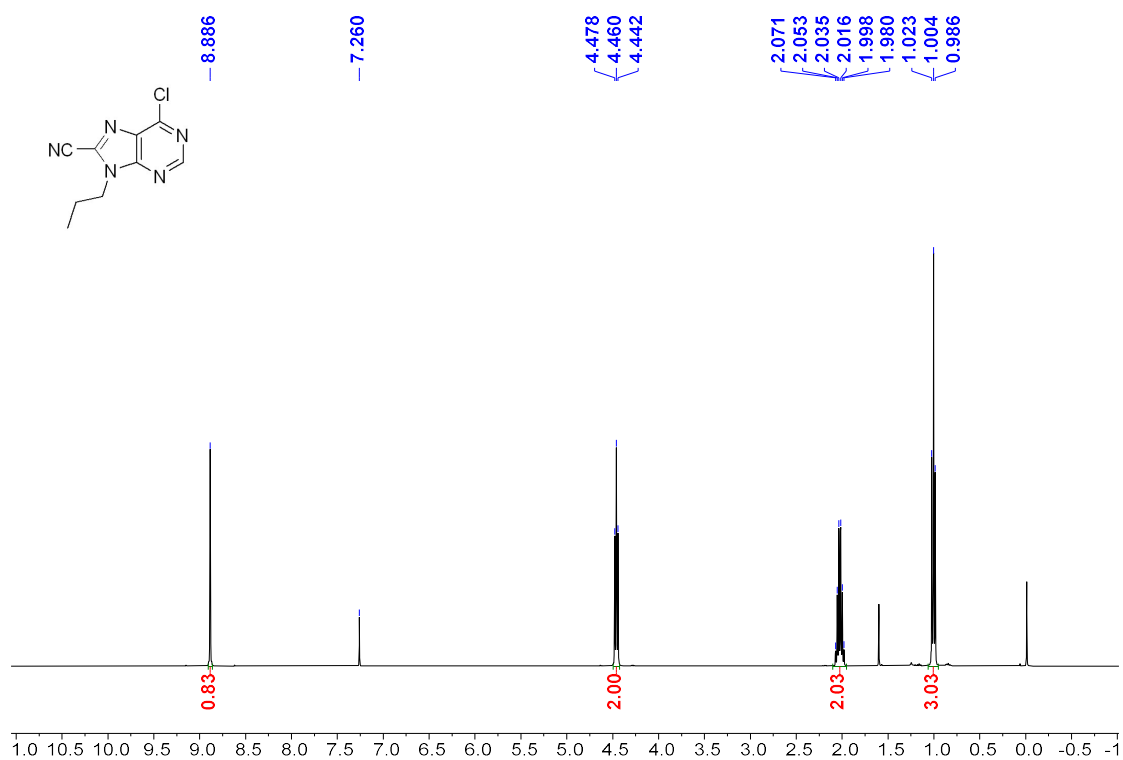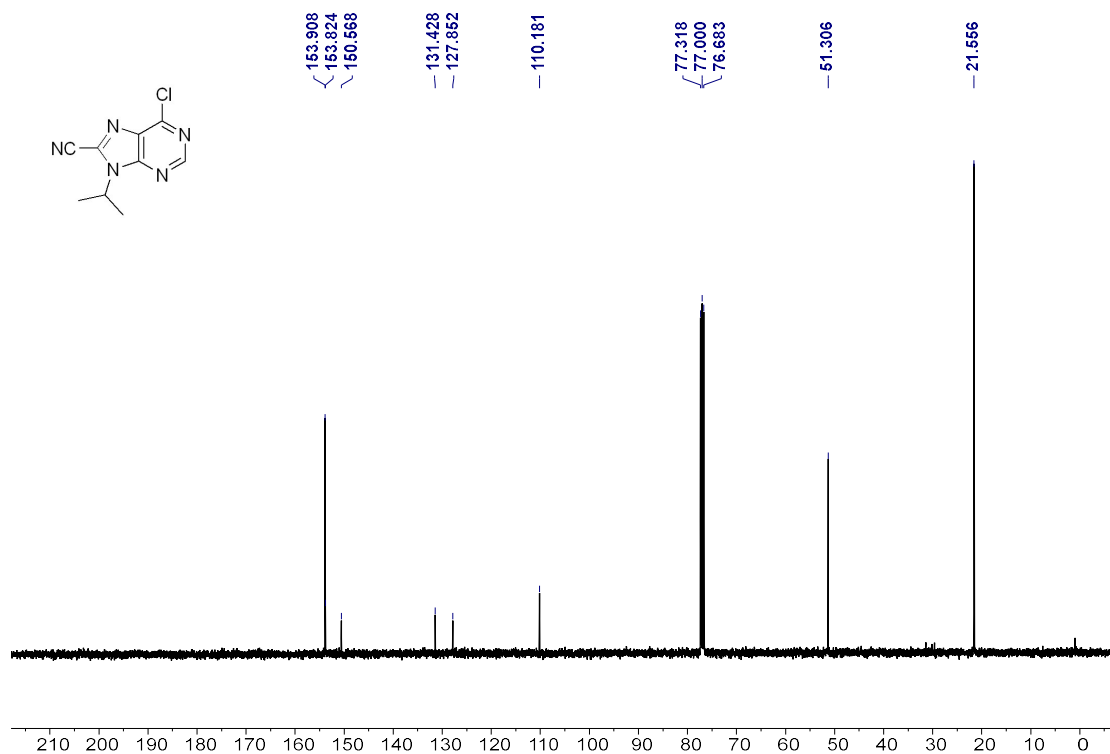

¹³C NMR (101 MHz, CDCl₃)

6-chloro-9-isopropyl-9H-purine-8-carbonitrile (**2c**)
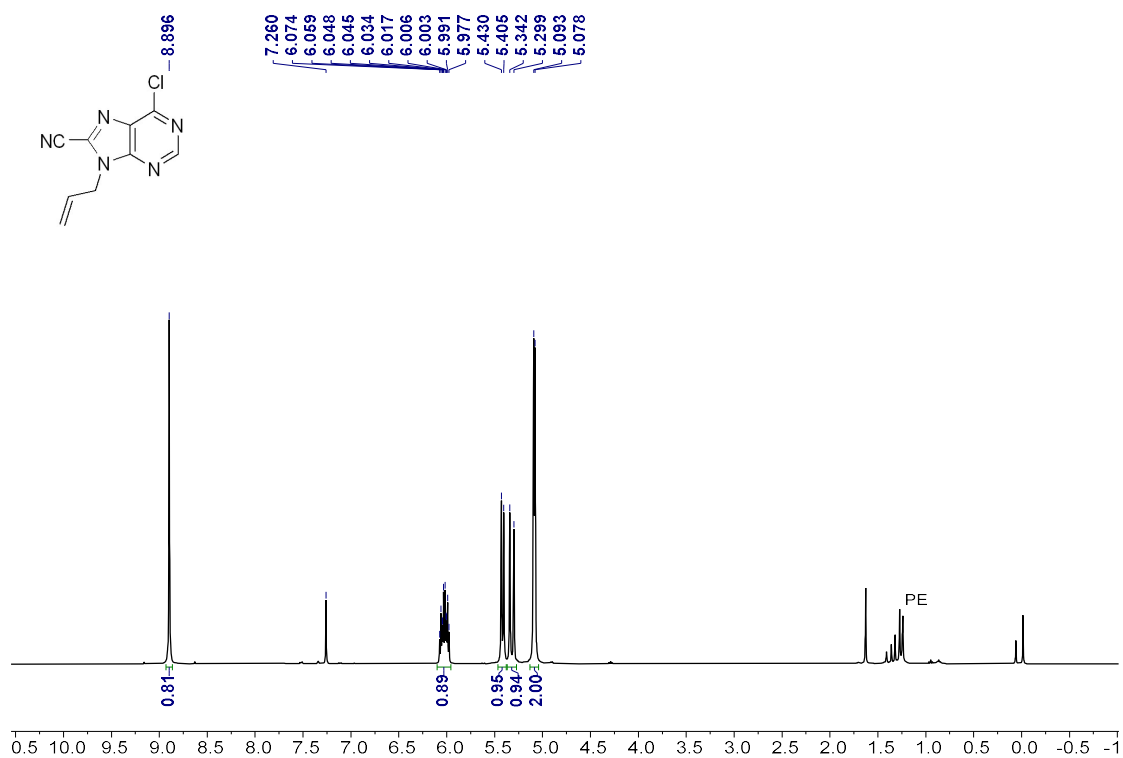
^{1}H NMR (400 MHz, CDCl$_3$)

^{13}C NMR (101 MHz, CDCl$_3$)
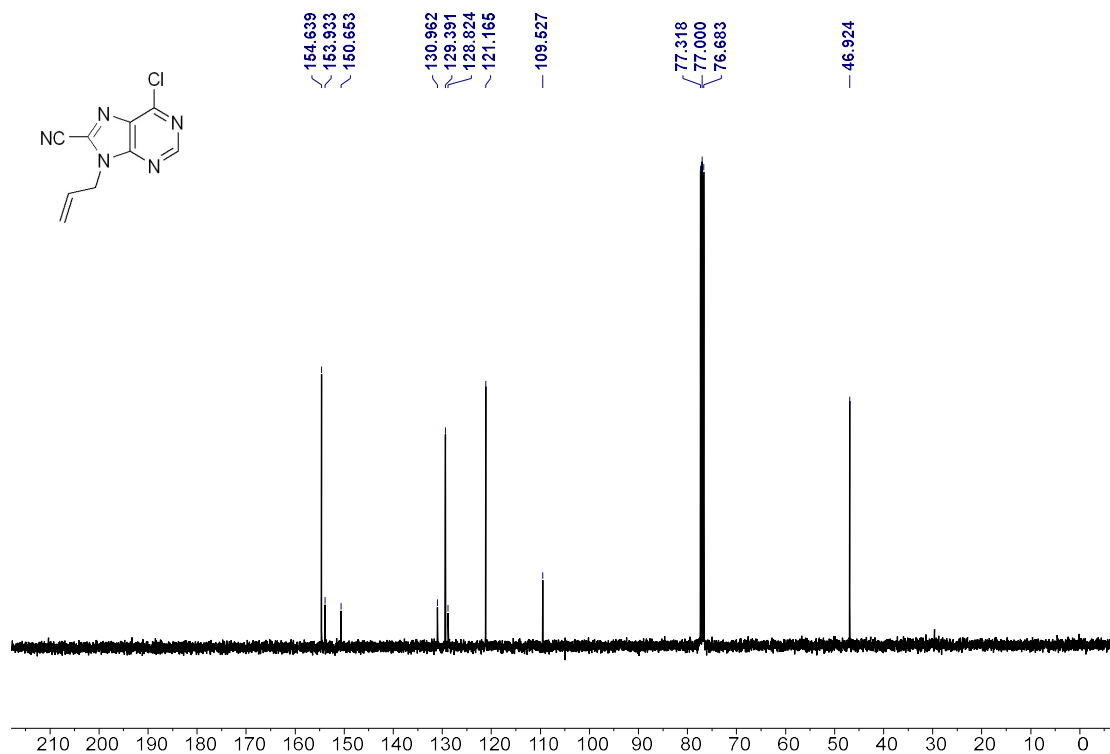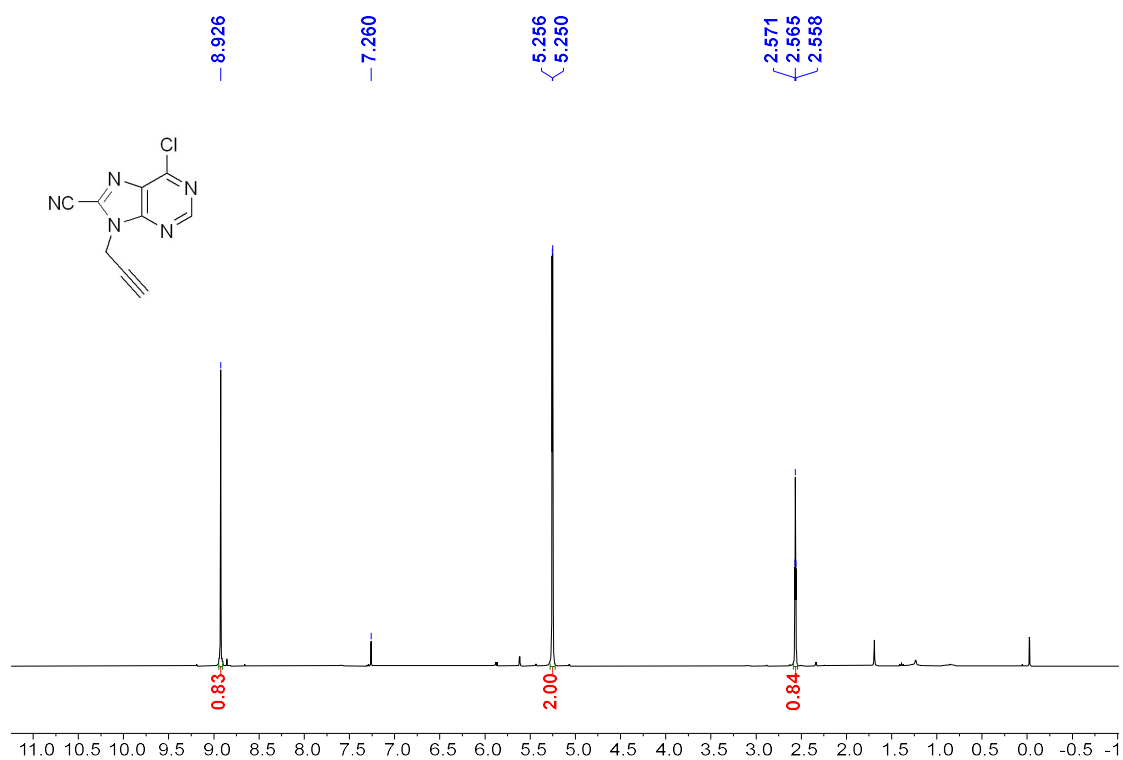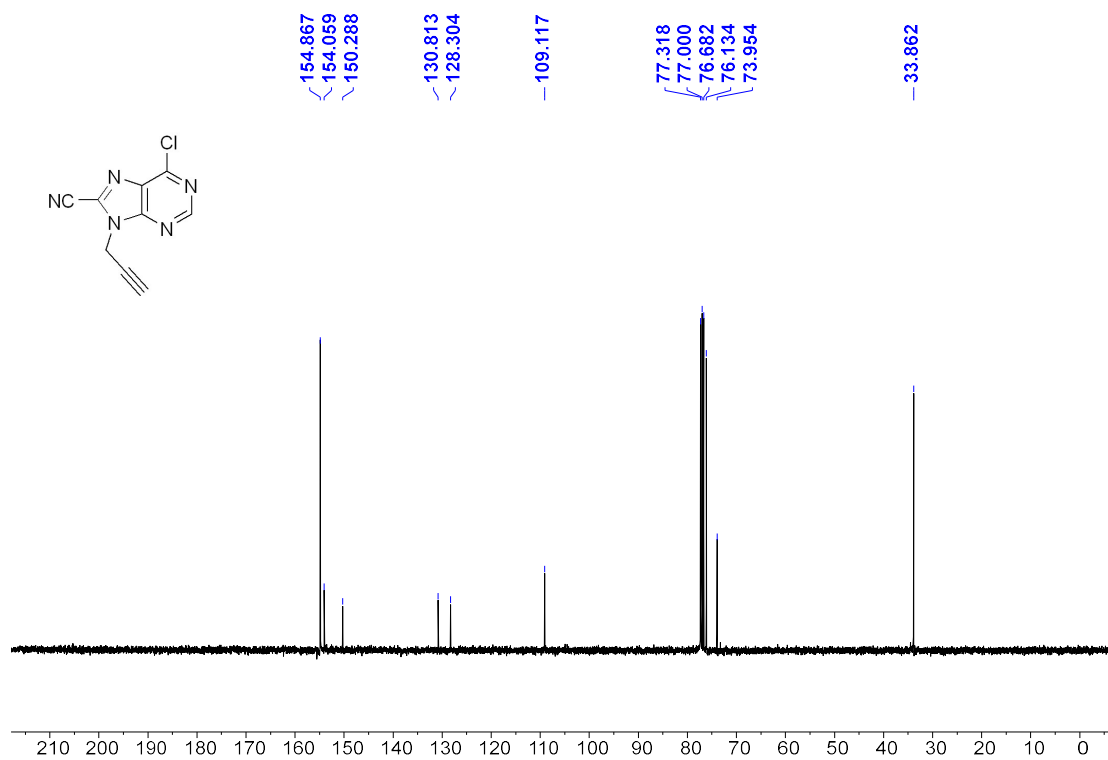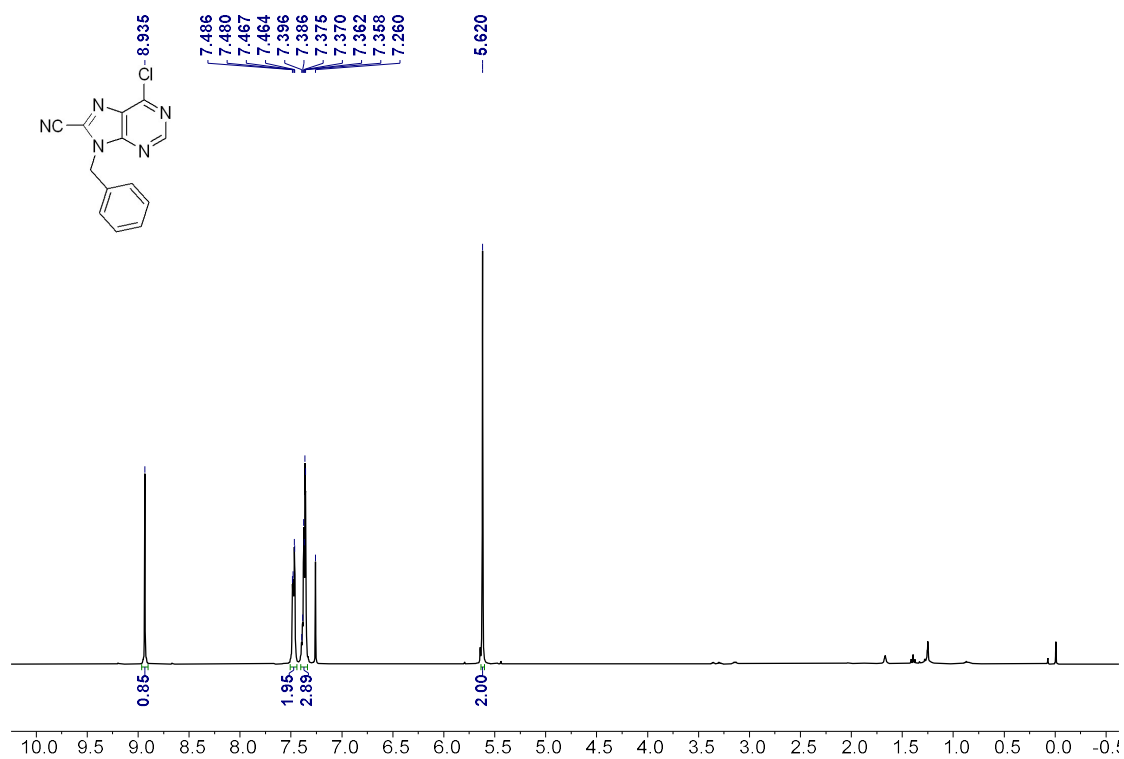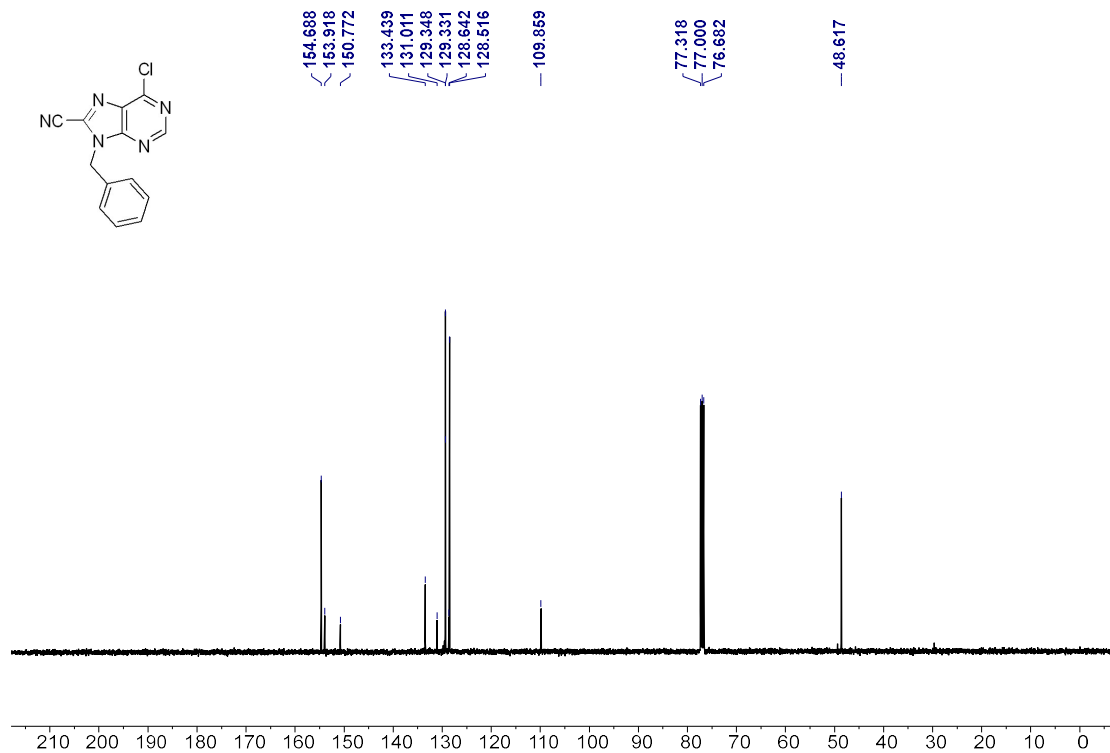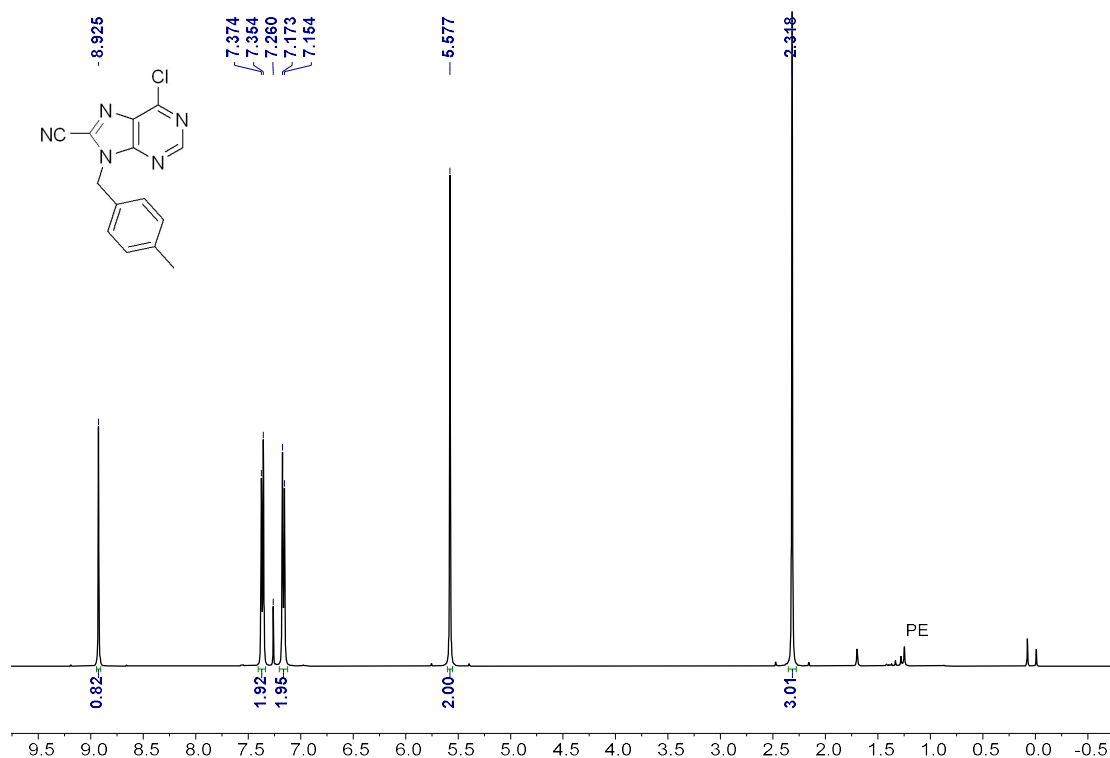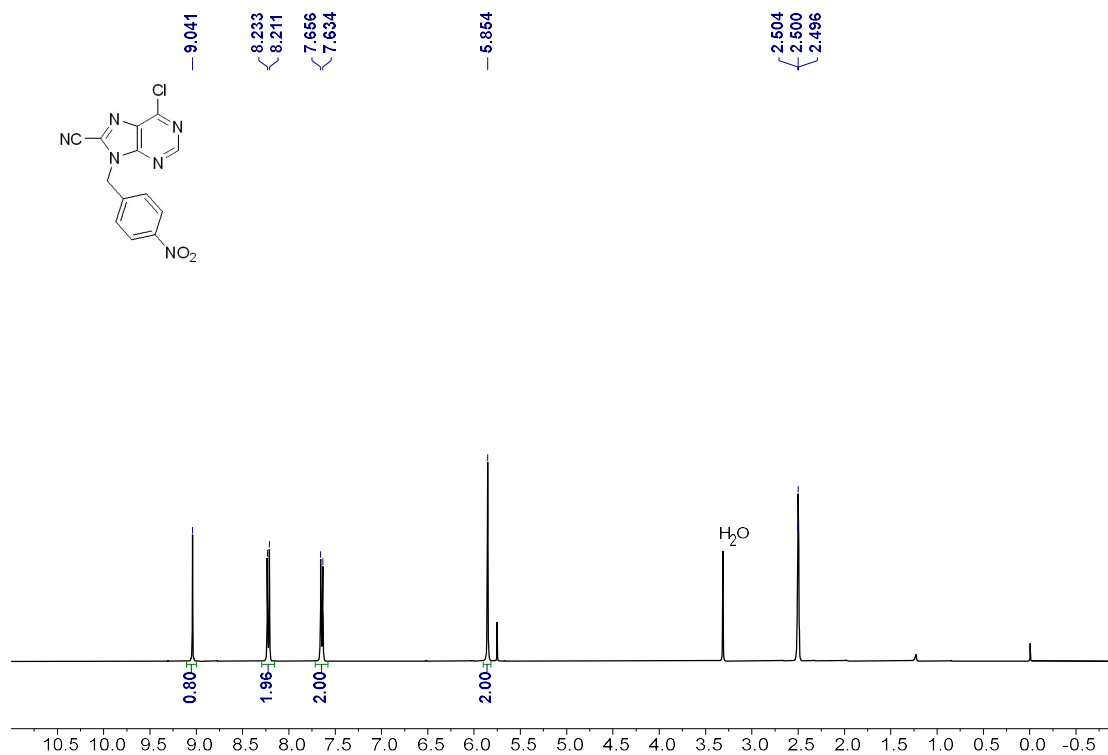
9-allyl-6-chloro-9H-purine-8-carbonitrile (**2d**)

¹H NMR (400 MHz, CDCl₃

¹³C NMR (101 MHz, CDCl₃)

6-Chloro-9-(propargyl)-9H-purine-8-carbonitrile (**2e**)

¹H NMR (400 MHz, CDCl₃)

¹³C NMR (101 MHz, CDCl₃)

9-benzyl-6-chloro-9H-purine-8-carbonitrile (**2f**)

^{1}H NMR (400 MHz, CDCl$_3$)

^{13}C NMR (101 MHz, CDCl$_3$)

6-chloro-9-(4-methylbenzyl)-9H-purine-8-carbonitrile (**2g**)
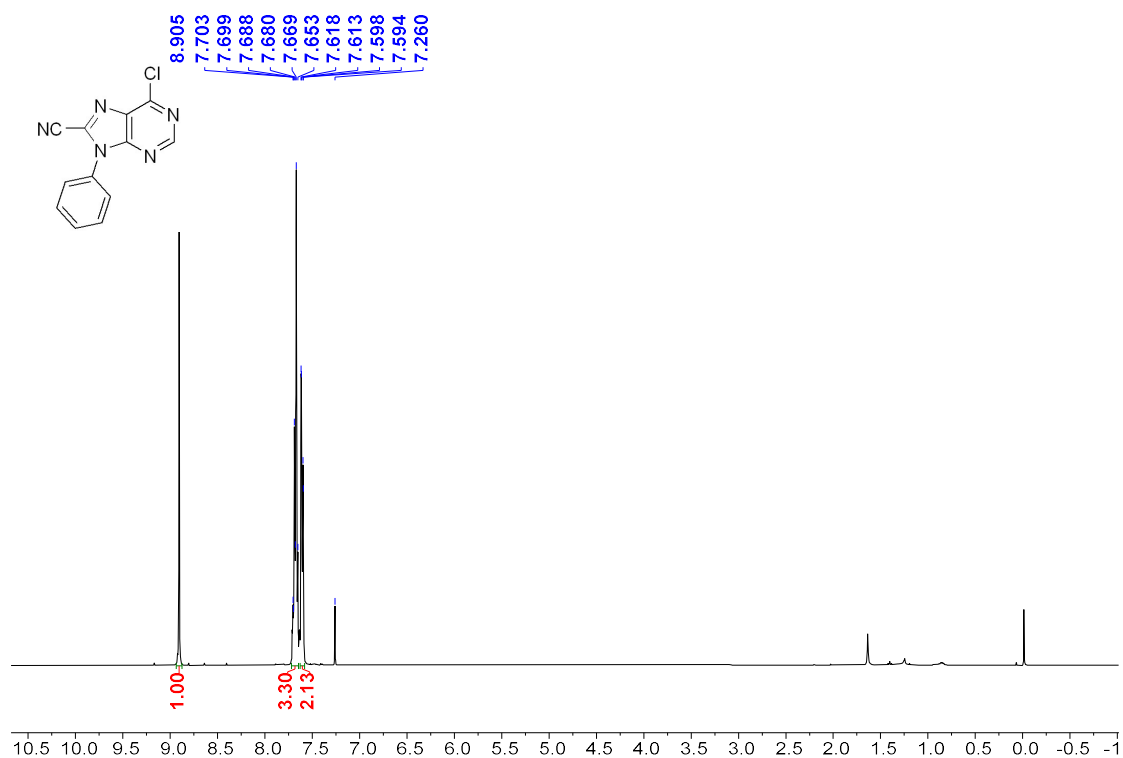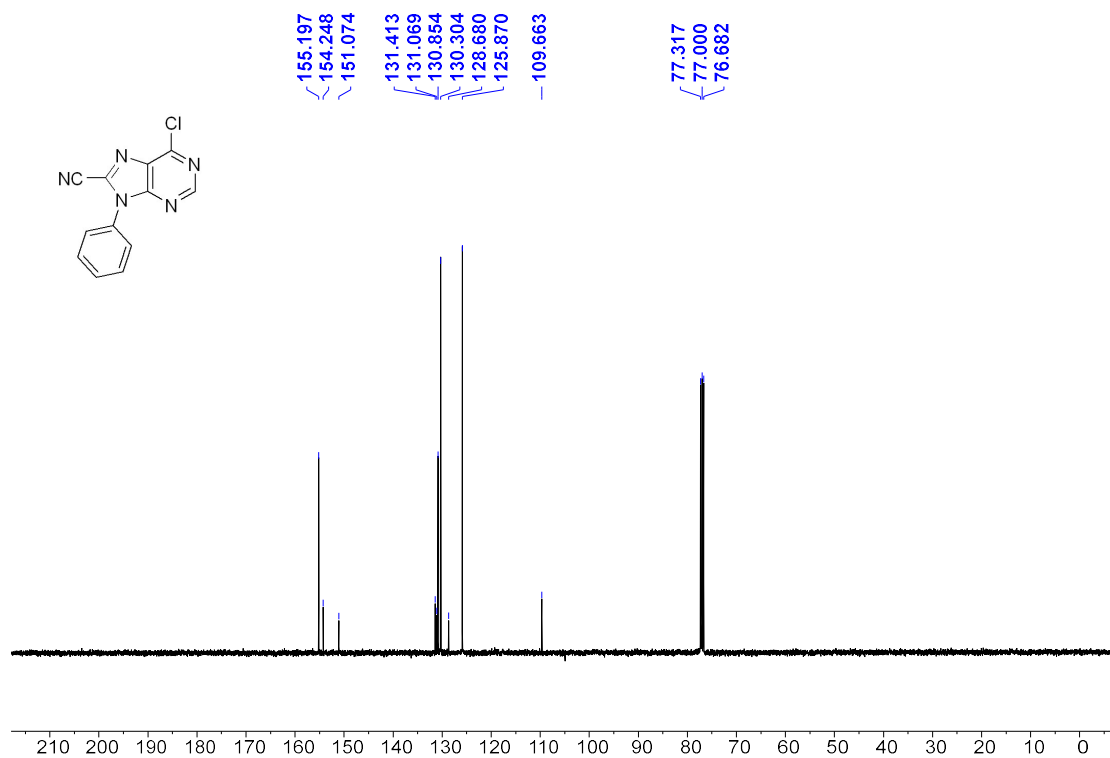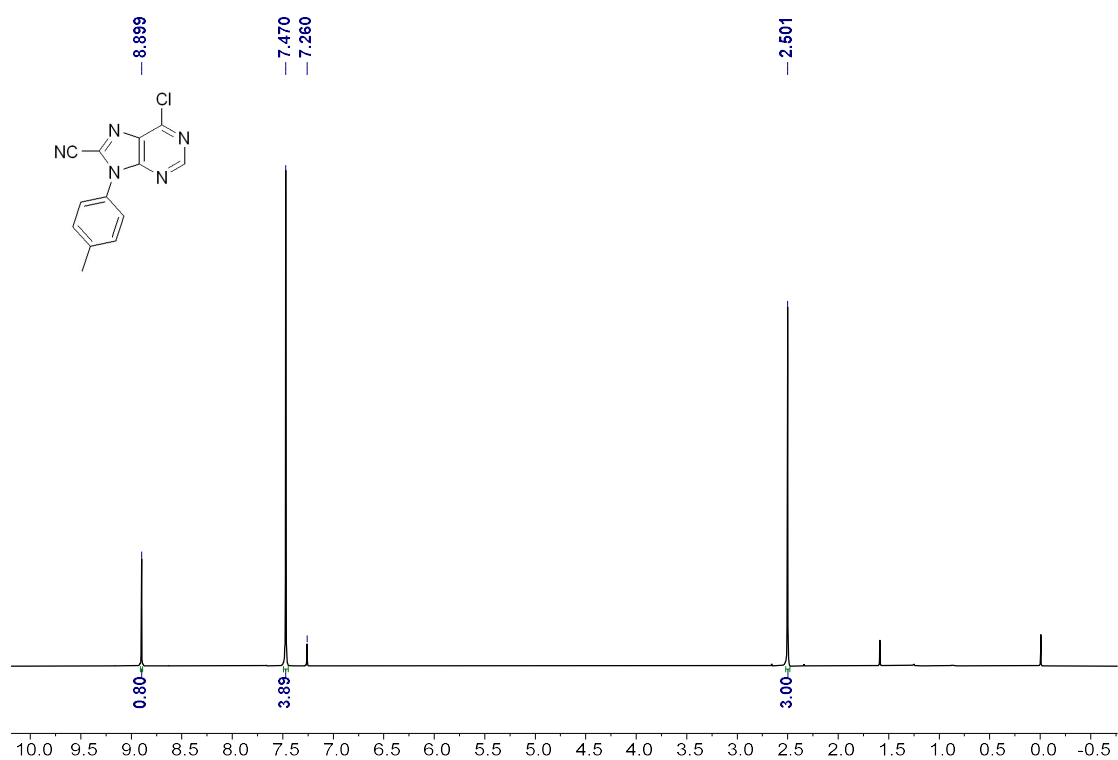
^{1}H NMR (400 MHz, CDCl$_3$)

^{13}C NMR (101 MHz, CDCl$_3$)
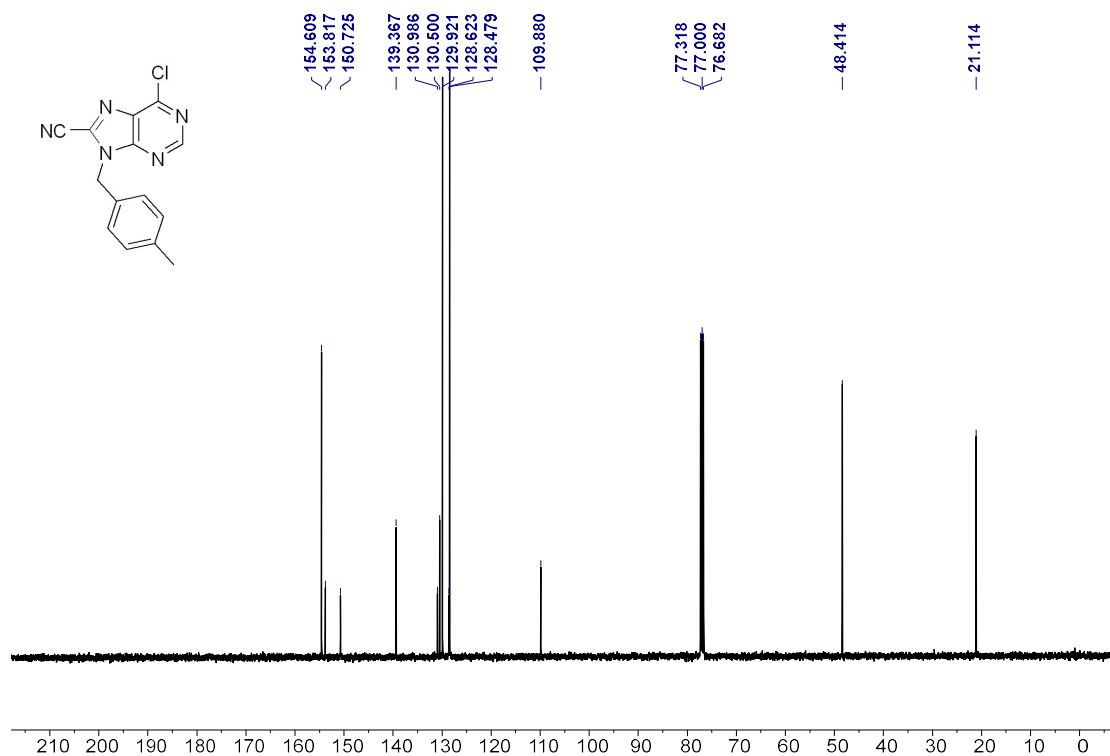
6-chloro-9-(4-nitrobenzyl)-9H-purine-8-carbonitrile (**2h**)

¹H NMR (400 MHz, DMSO-*d₆*)

¹³C NMR (101 MHz, DMSO-*d₆*)
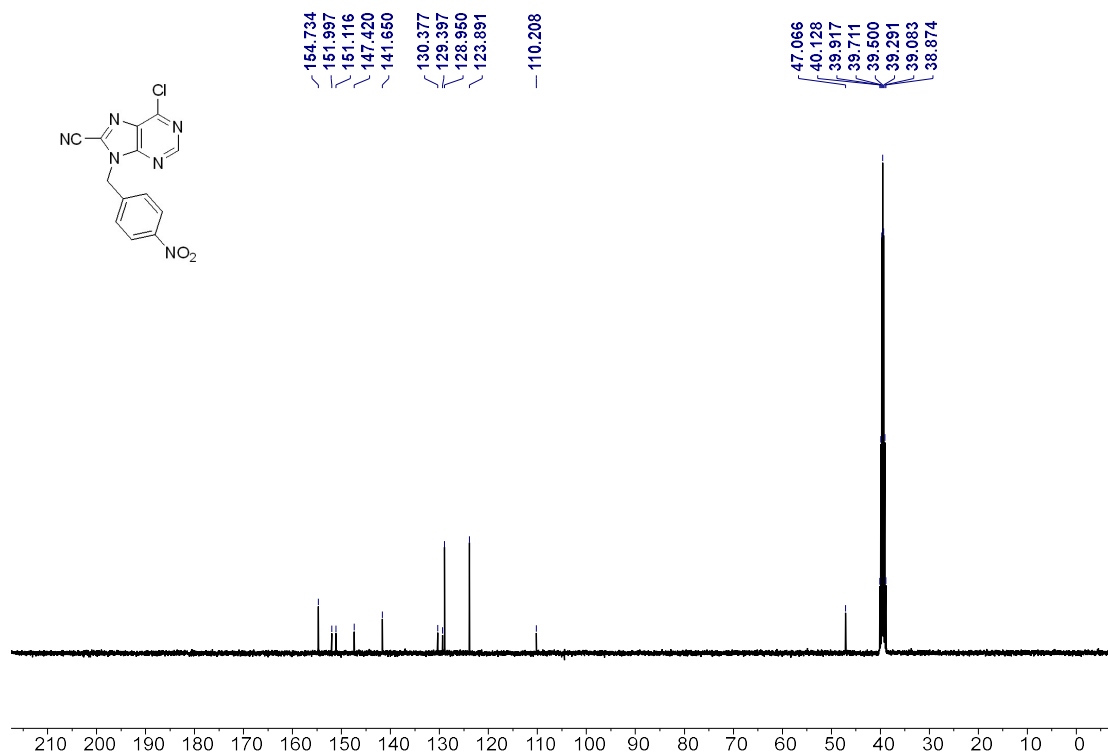
6-chloro-9-(4-methoxybenzyl)-9H-purine-8-carbonitrile (**2i**)

^{1}H NMR (400 MHz, CDCl$_3$)
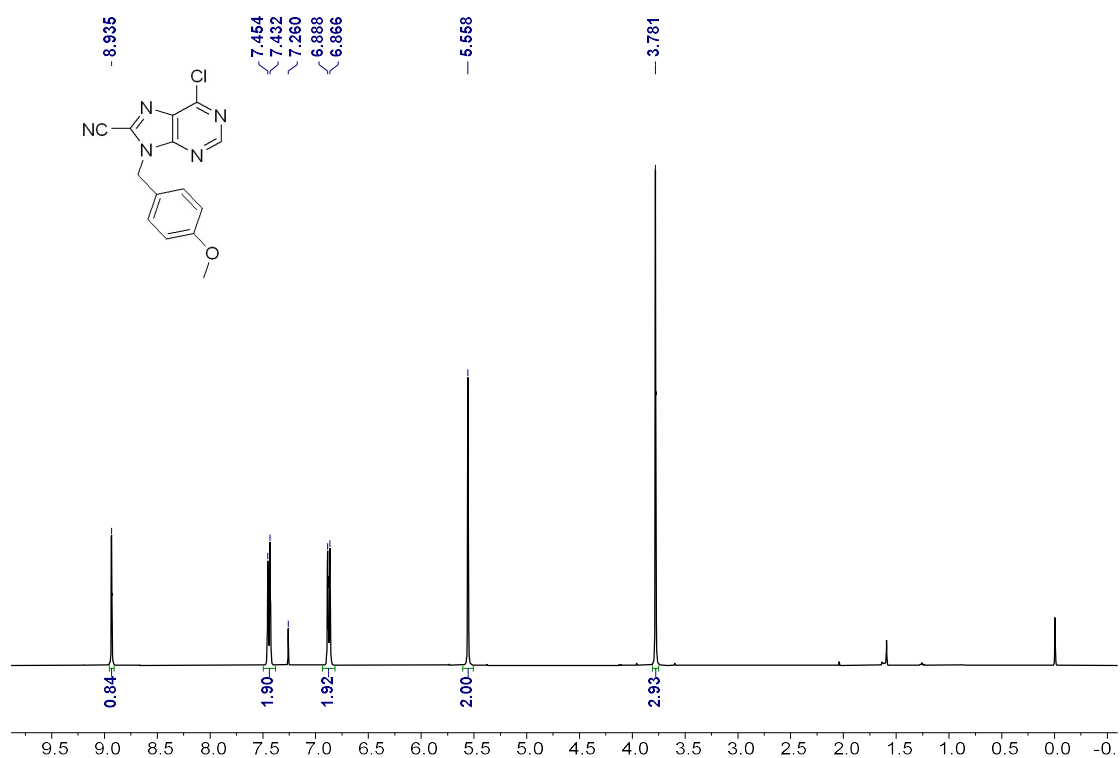
^{13}C NMR (101 MHz, CDCl$_3$)
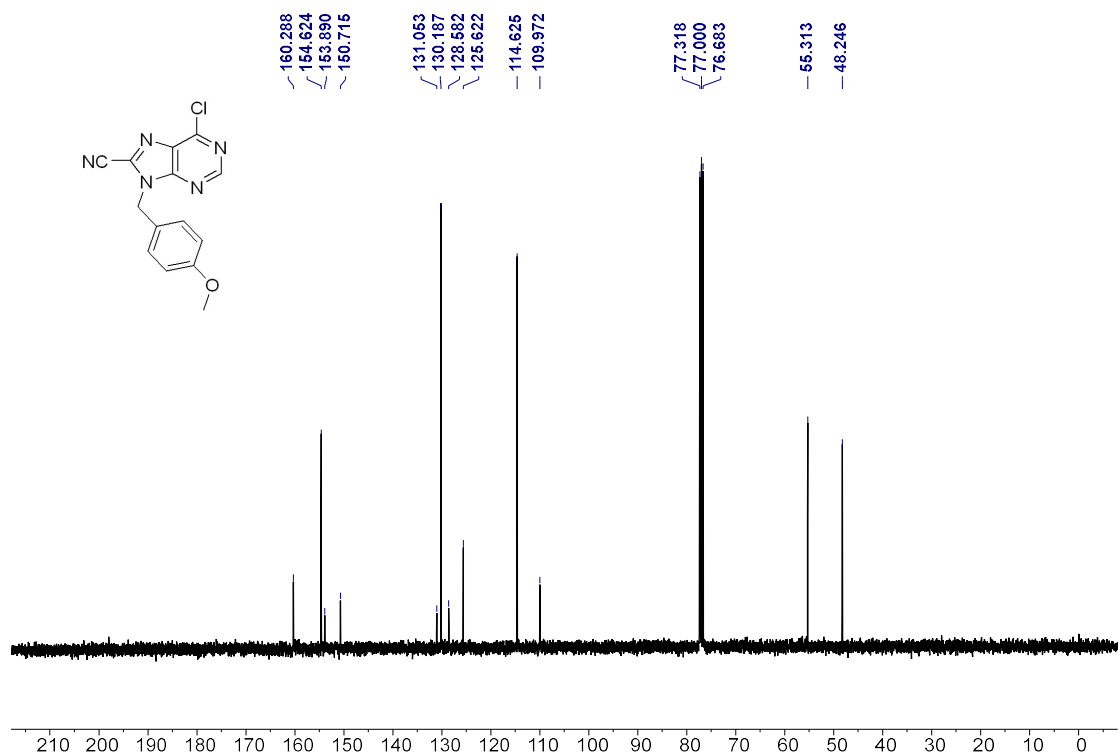
Ethyl-2-(6-chloro-8-cyano-9H-purin-9-yl) acetate (**2j**)
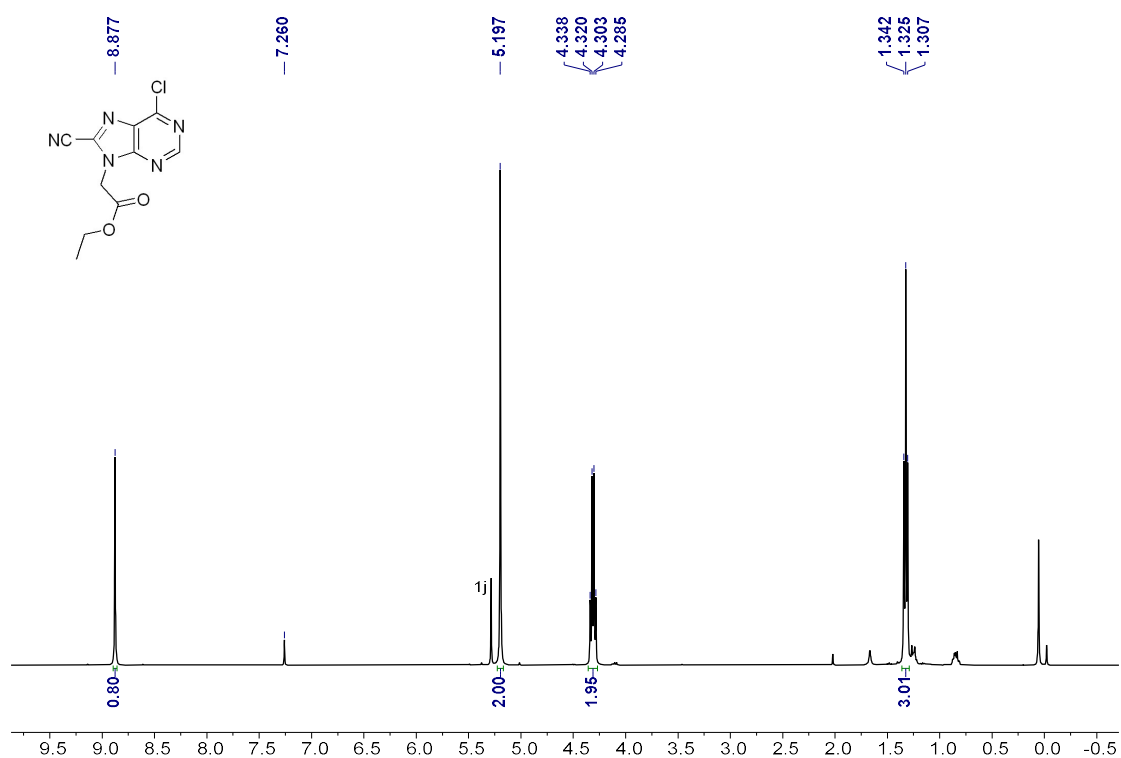
¹H NMR (400 MHz, CDCl₃)
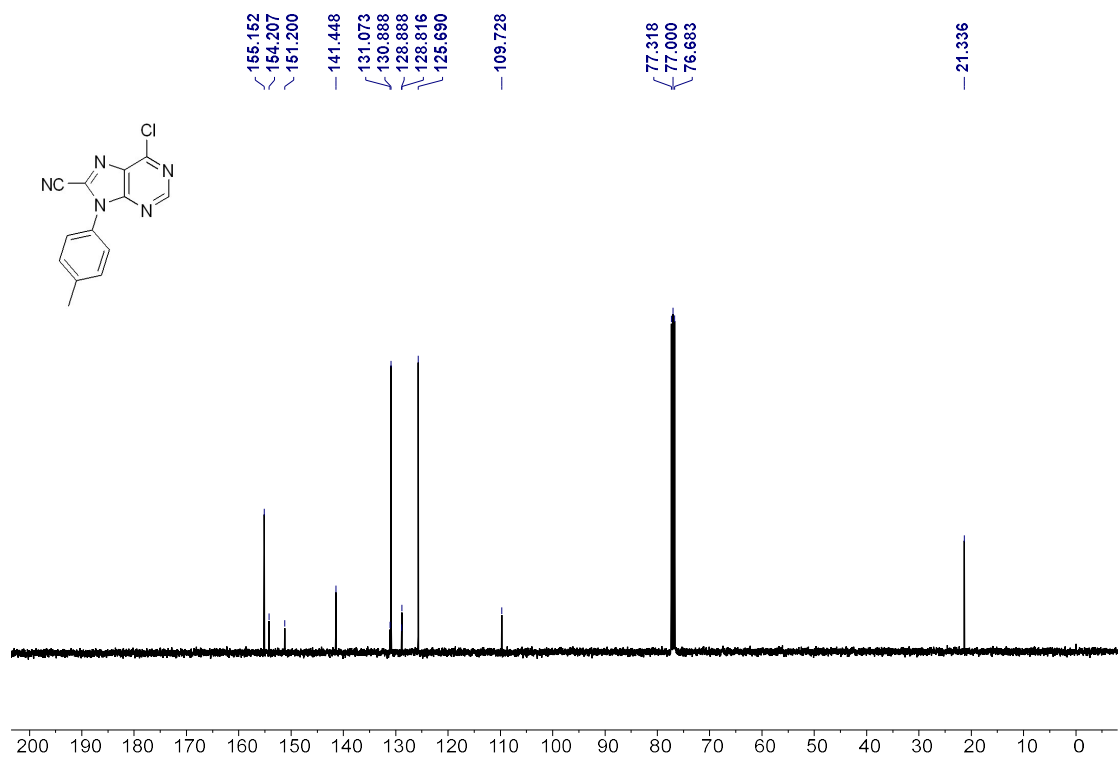

¹³C NMR (101 MHz, CDCl₃)
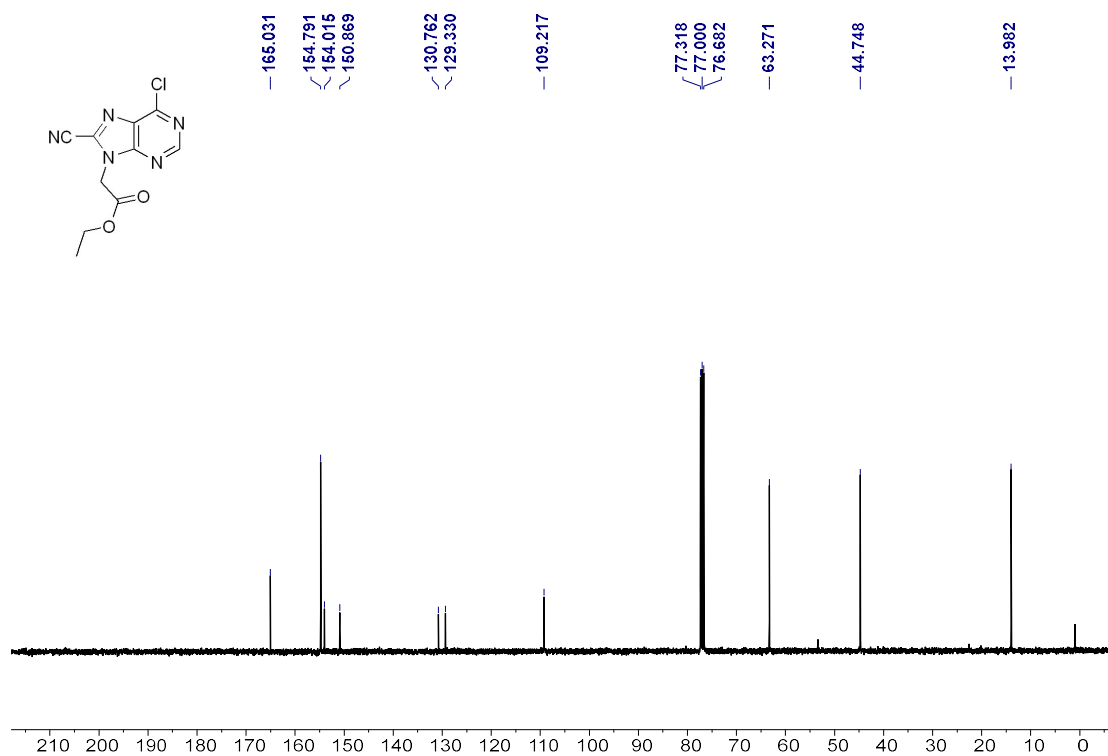
6-chloro-9-(2-(4-chlorophenyl)-2-oxoethyl)-9H-purine-8-carbonitrile (**2k**)

^{1}H NMR (400 MHz, CDCl$_3$)
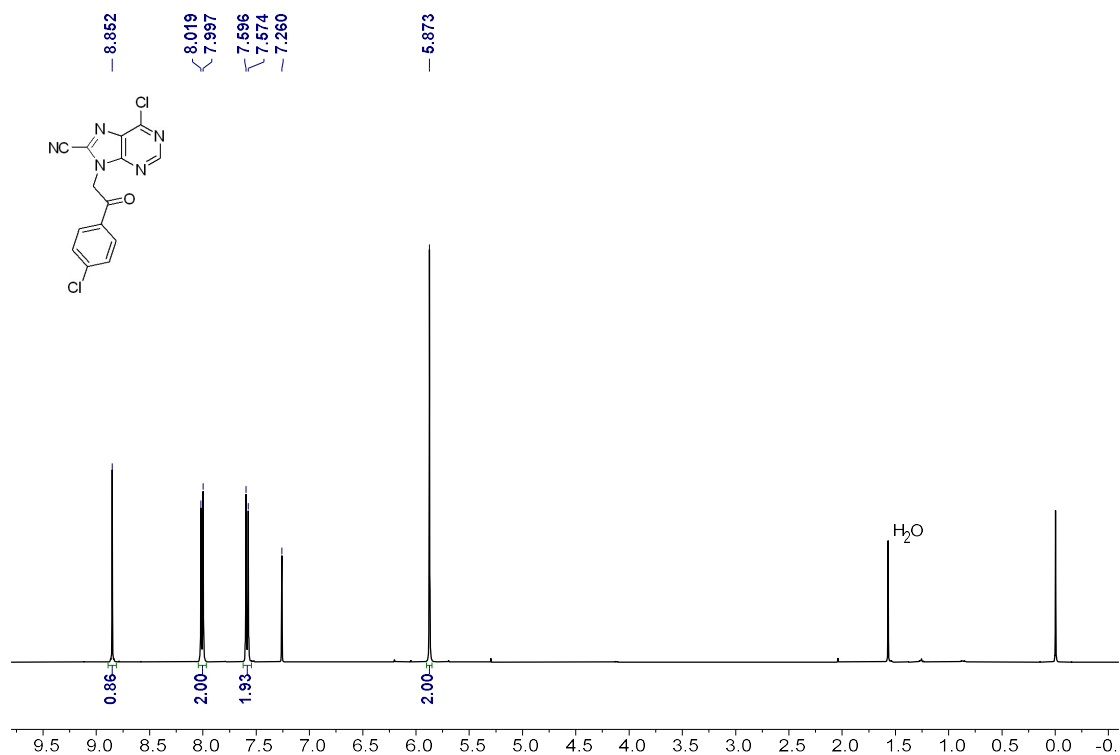
^{13}C NMR (101 MHz, CDCl$_3$)
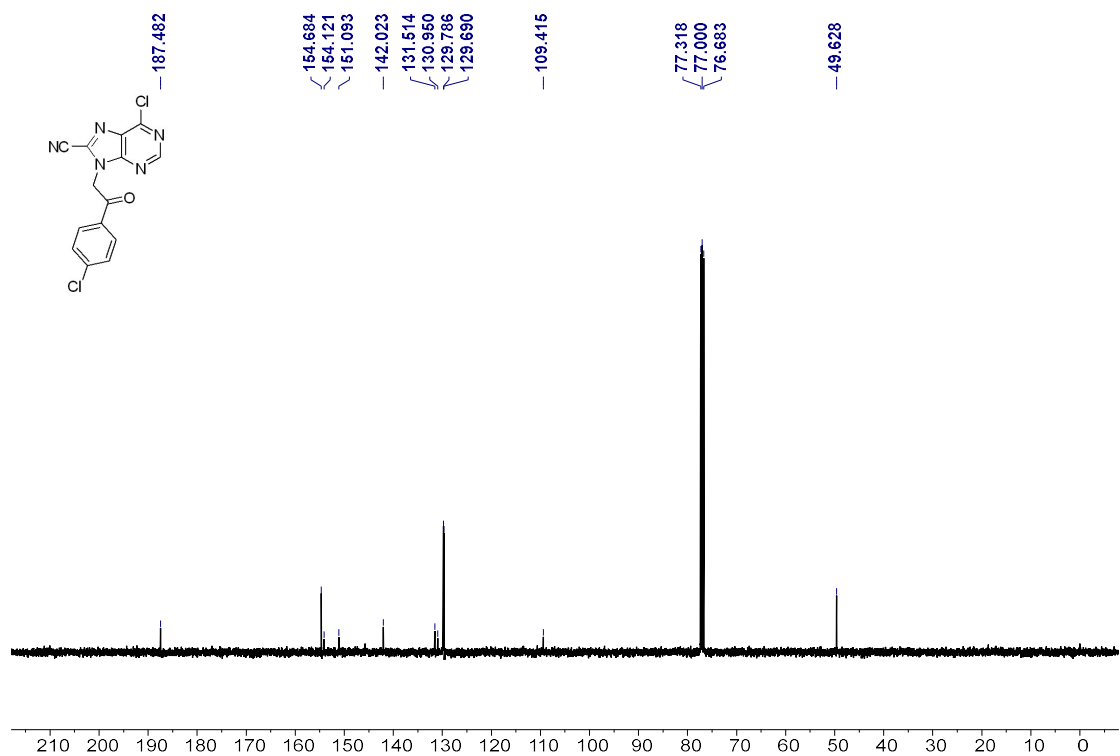
6-chloro-9-phenyl-9H-purine-8-carbonitrile (**21**)

^{1}H NMR (400 MHz, CDCl₃)

^{13}C NMR (101 MHz, CDCl₃)

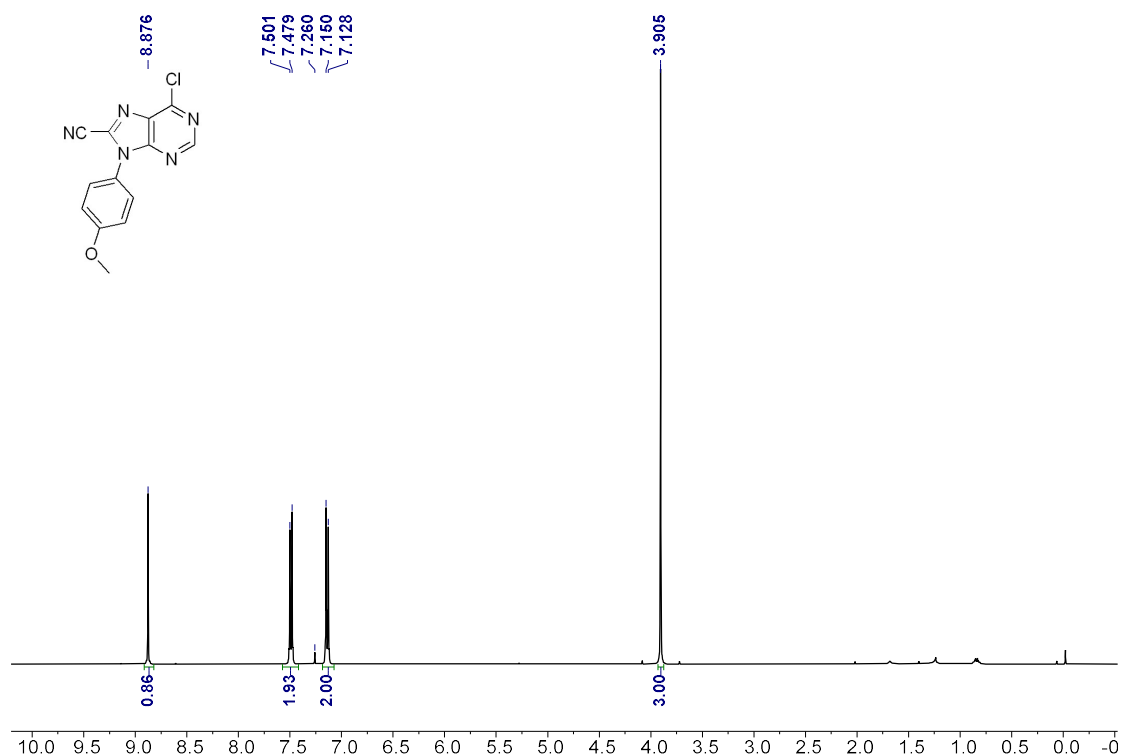*6-chloro-9-(p-tolyl)-9H-purine-8-carbonitrile* (**2m**)

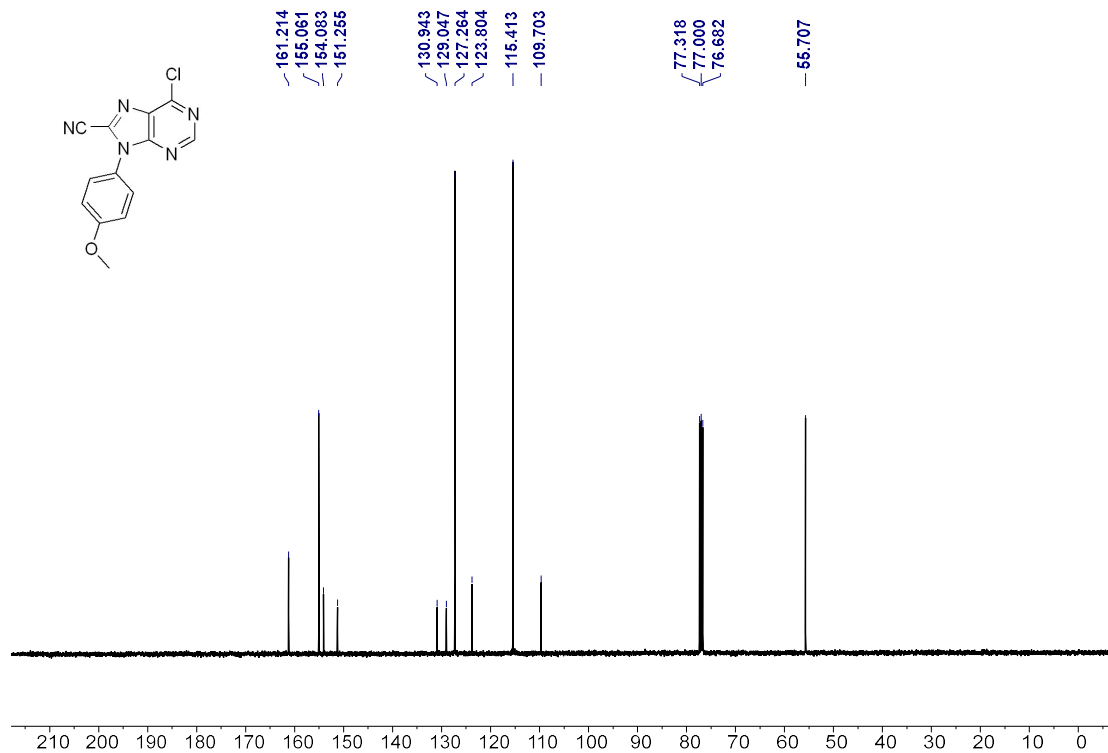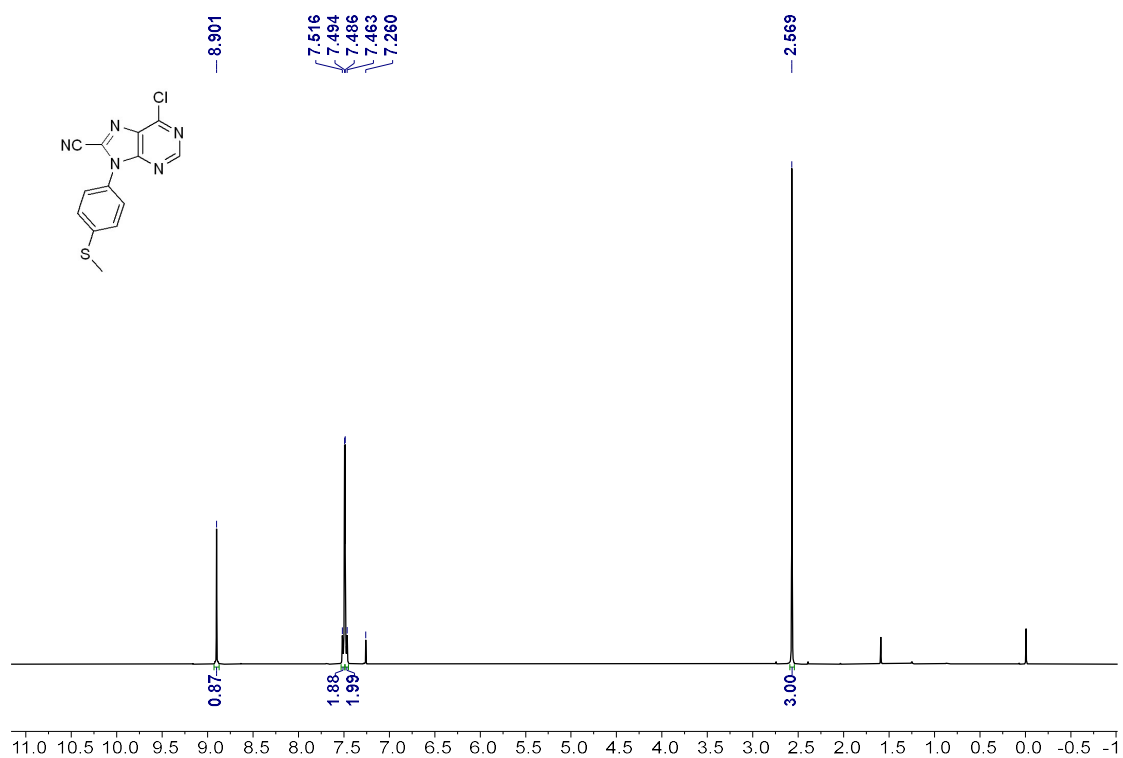^{1}H NMR (400 MHz, CDCl$_3$)
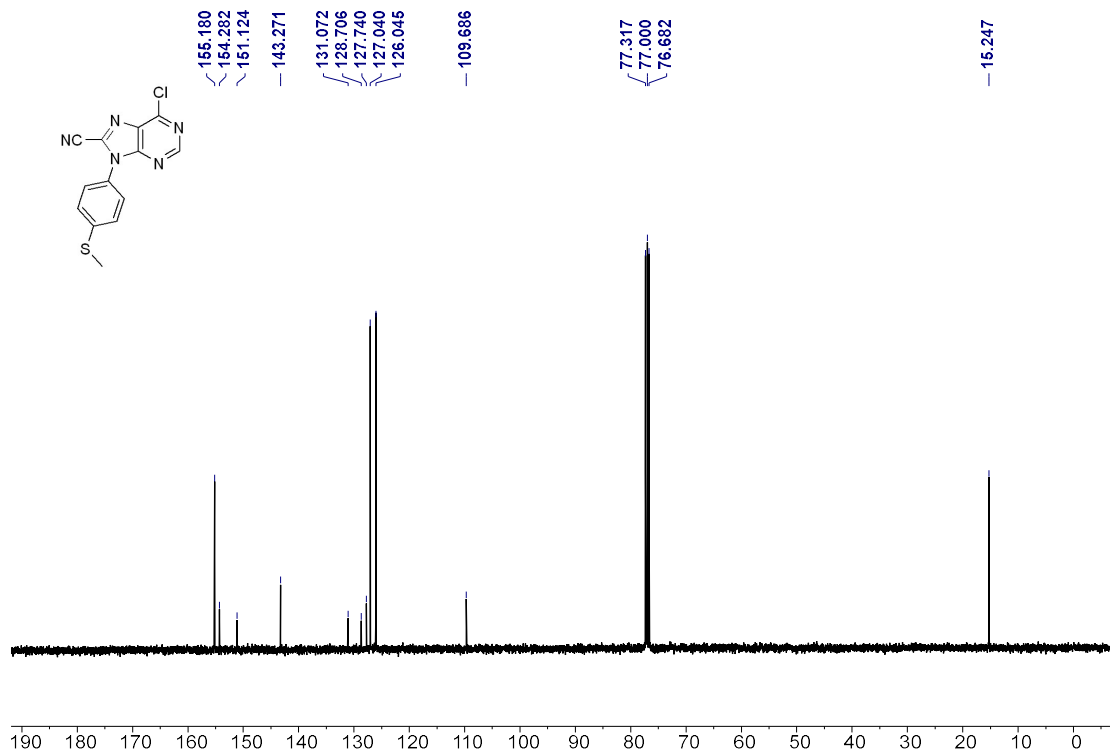

^{13}C NMR (101 MHz, CDCl$_3$)

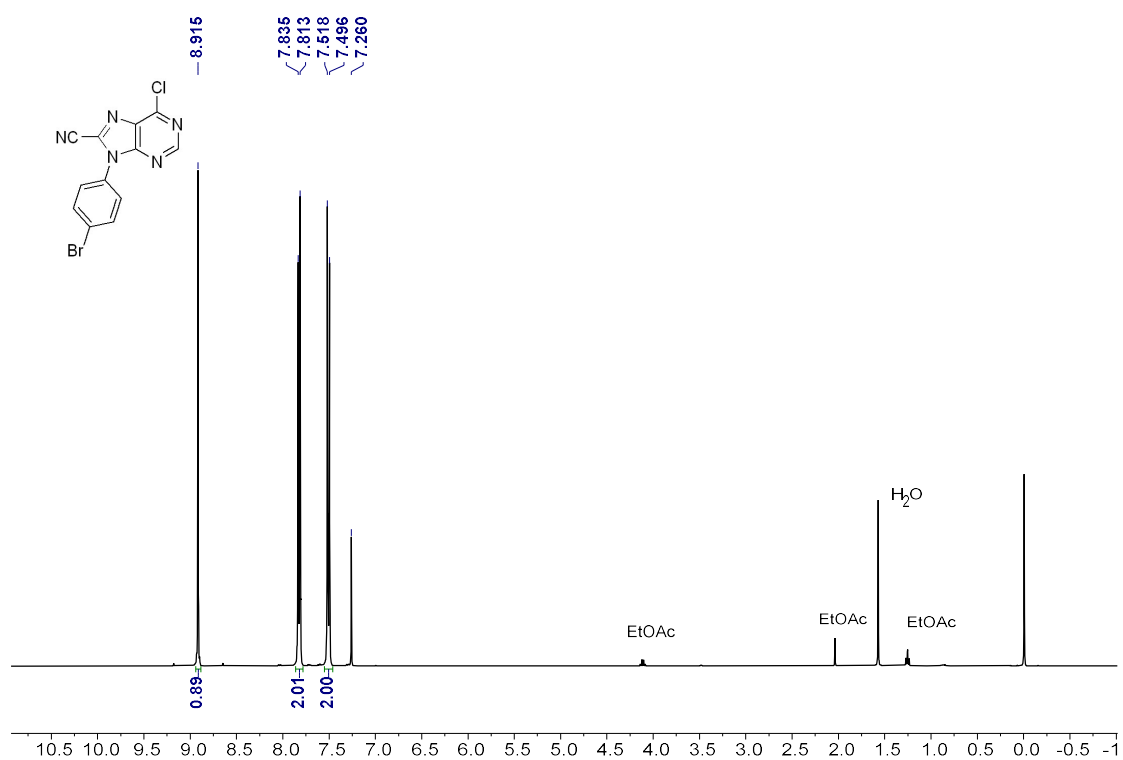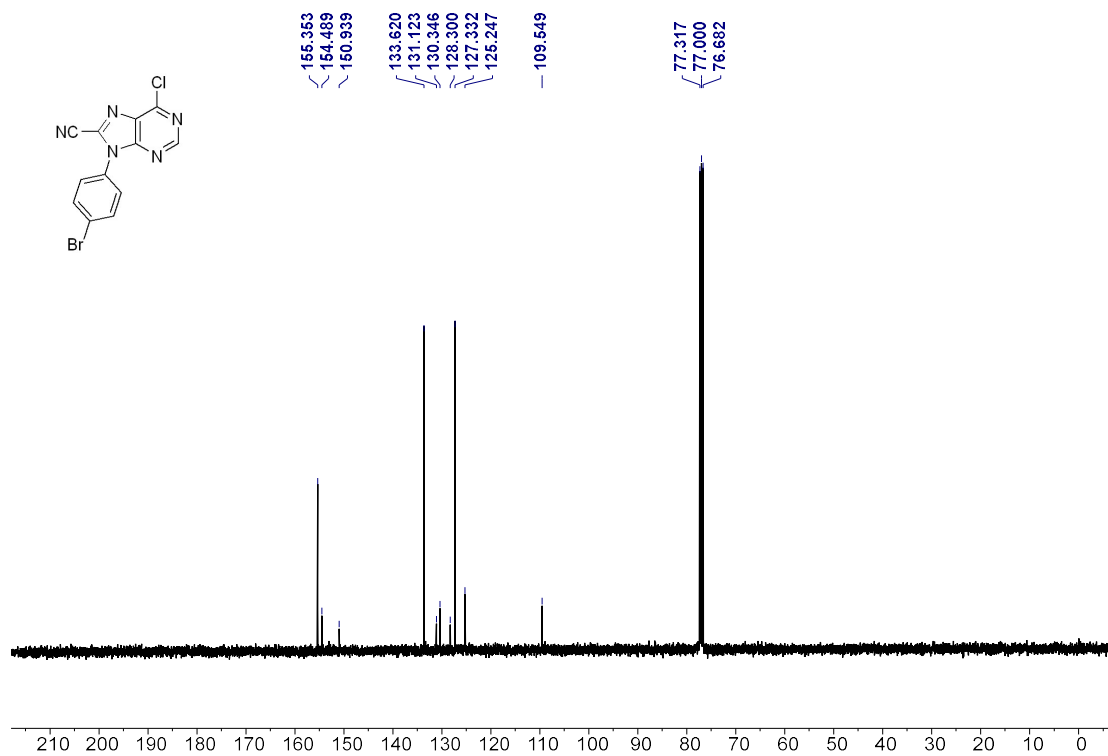*6-chloro-9-(4-methoxyphenyl)-9H-purine-8-carbonitrile (2n)*

¹H NMR (400 MHz, CDCl₃)

8.876
7.501
7.479
7.260
7.150
7.128
3.905

0.86
1.93
2.00
3.00

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0

¹³C NMR (101 MHz, CDCl₃)

161.214
155.061
154.083
151.255
130.943
129.047
127.264
123.804
115.413
109.703
77.318
77.000
76.682
55.707

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

6-chloro-9-(4-(methylthio) phenyl)-9H-purine-8-carbonitrile (**2o**)

¹H NMR (400 MHz, CDCl₃)

¹³C NMR (101 MHz, CDCl₃)

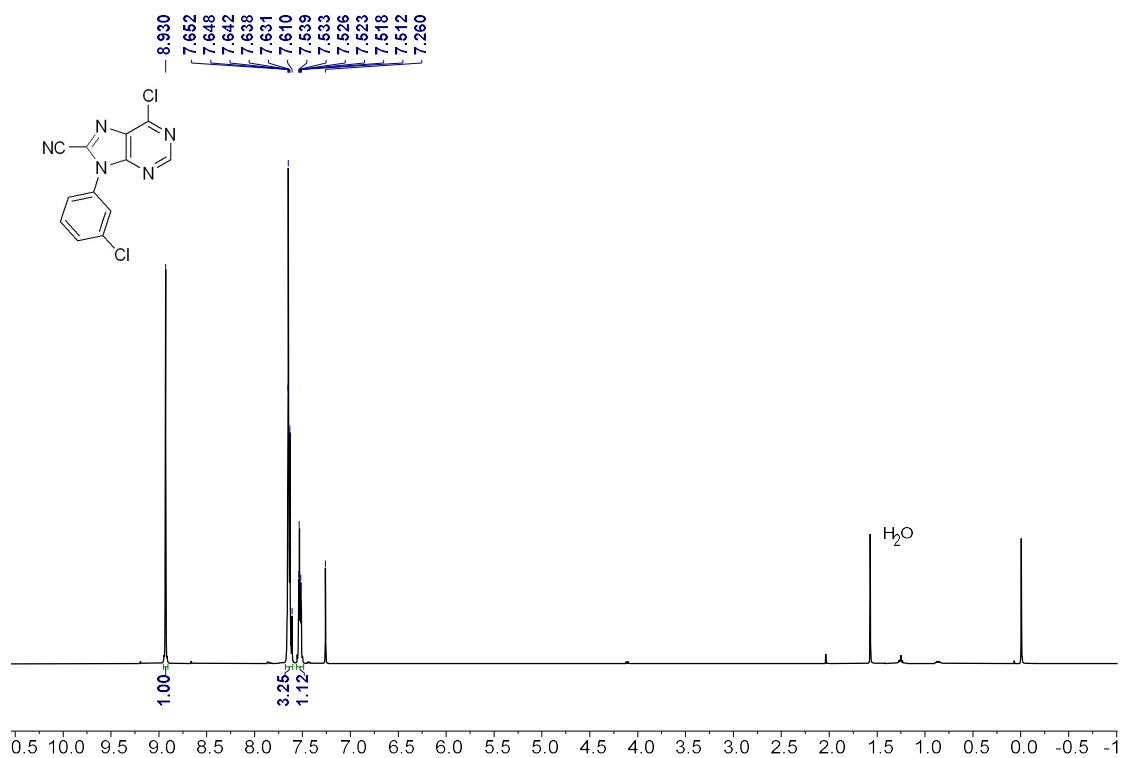*9-(4-bromophenyl)-6-chloro-9H-purine-8-carbonitrile* (**2p**)
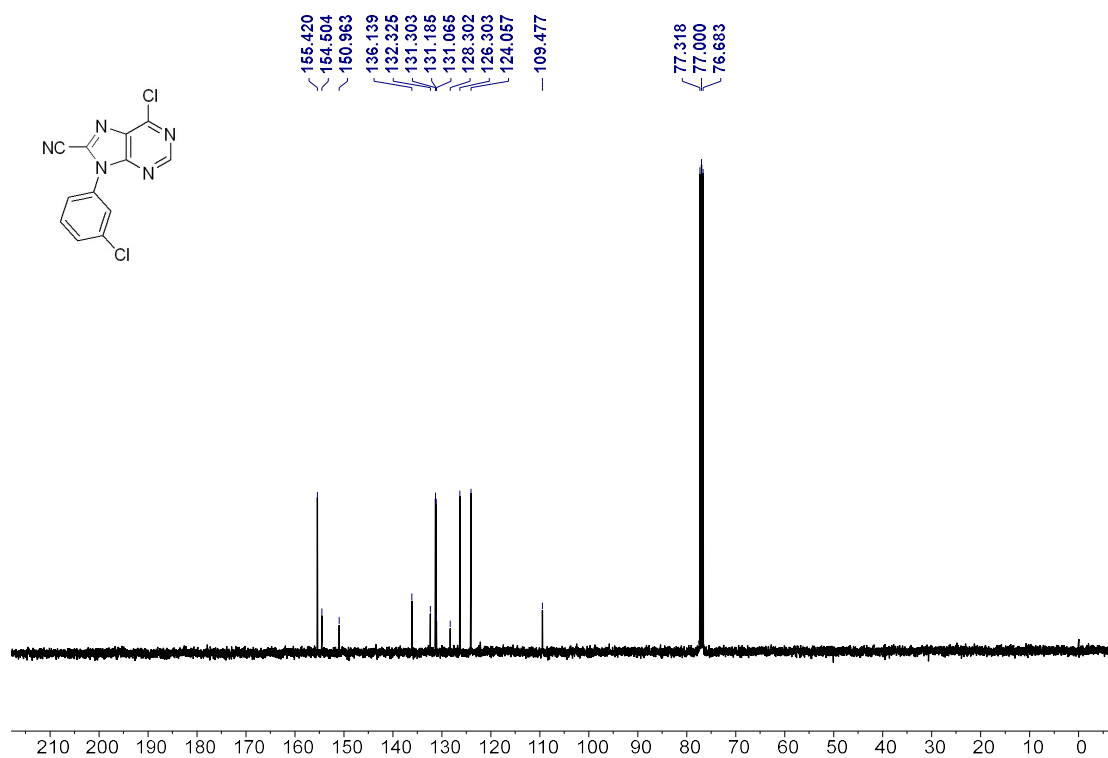
¹H NMR (400 MHz, CDCl₃)

¹³C NMR (101 MHz, CDCl₃)

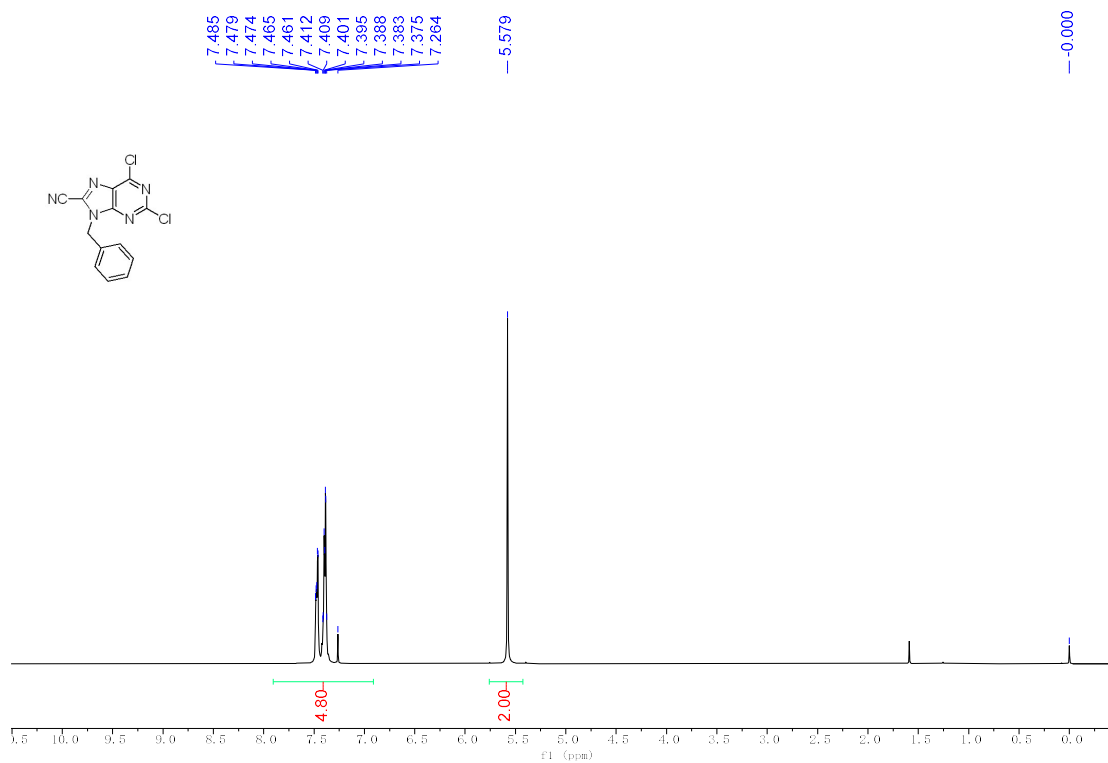*6-chloro-9-(3-chlorophenyl)-9H-purine-8-carbonitrile* (**2q**)

¹H NMR (400 MHz, CDCl₃)

¹³C NMR (101 MHz, CDCl₃)

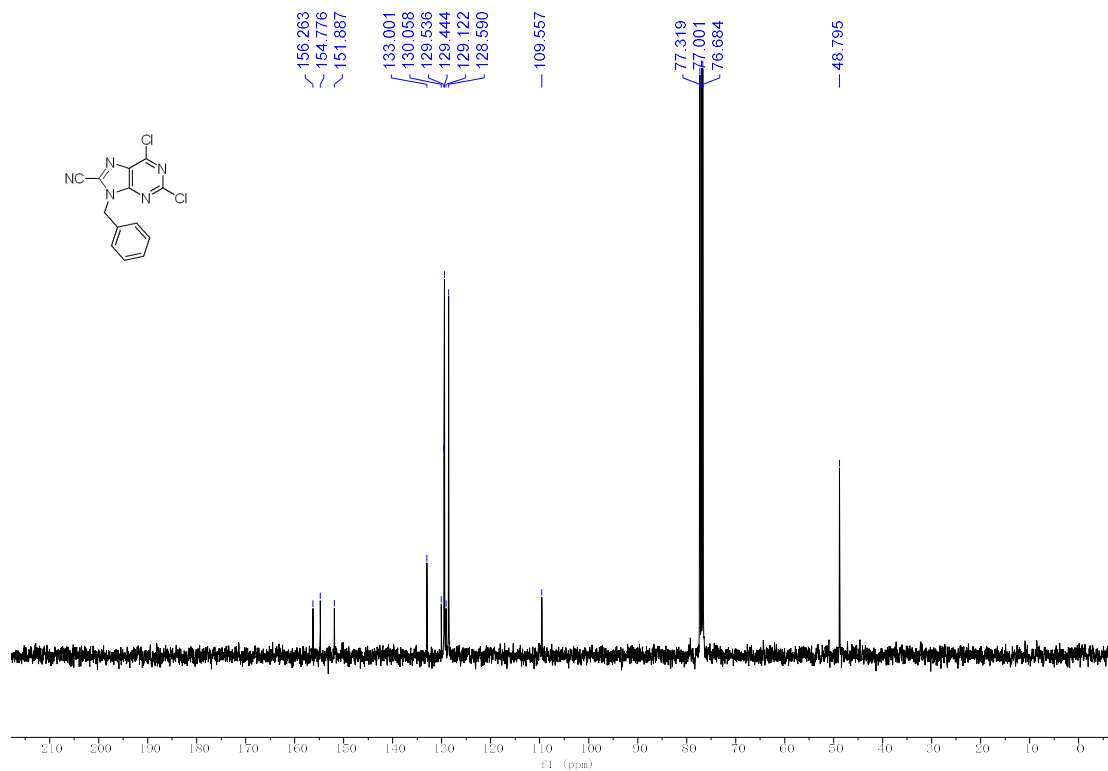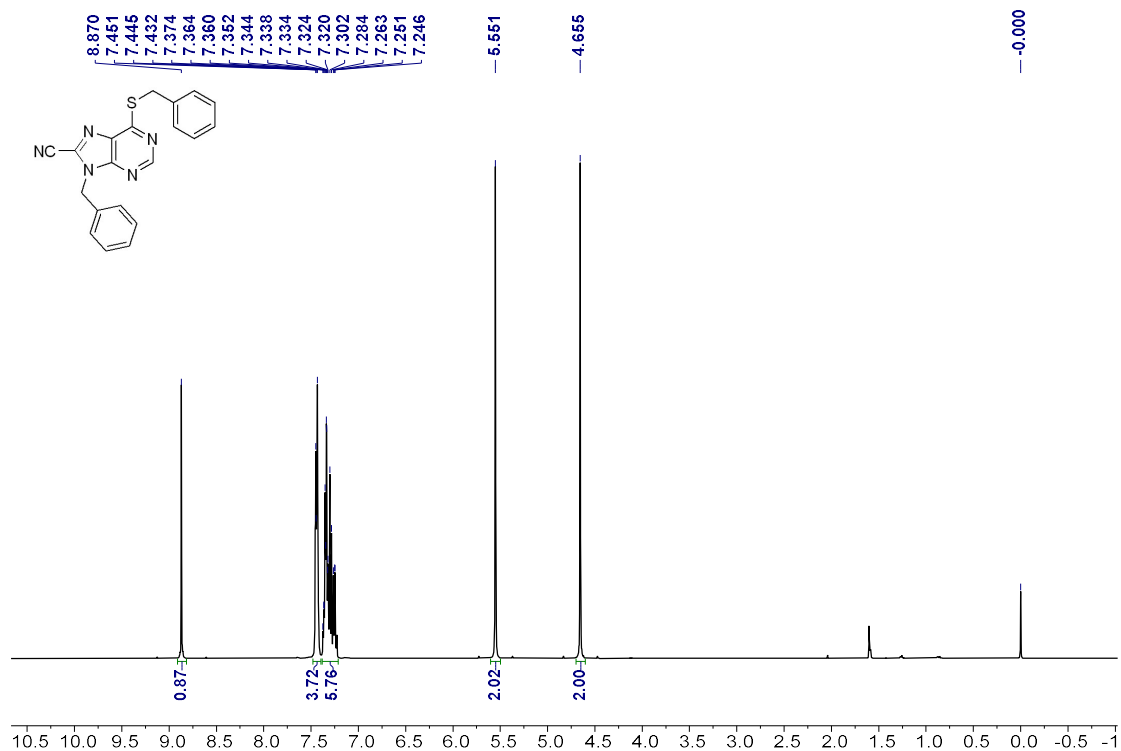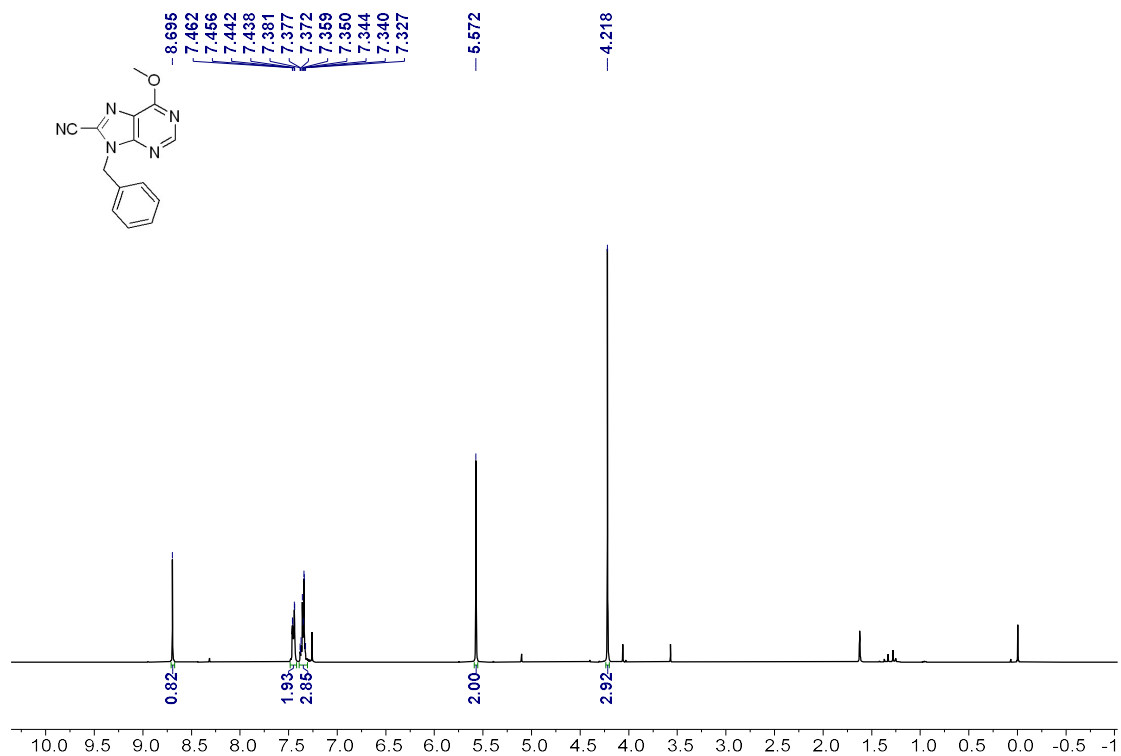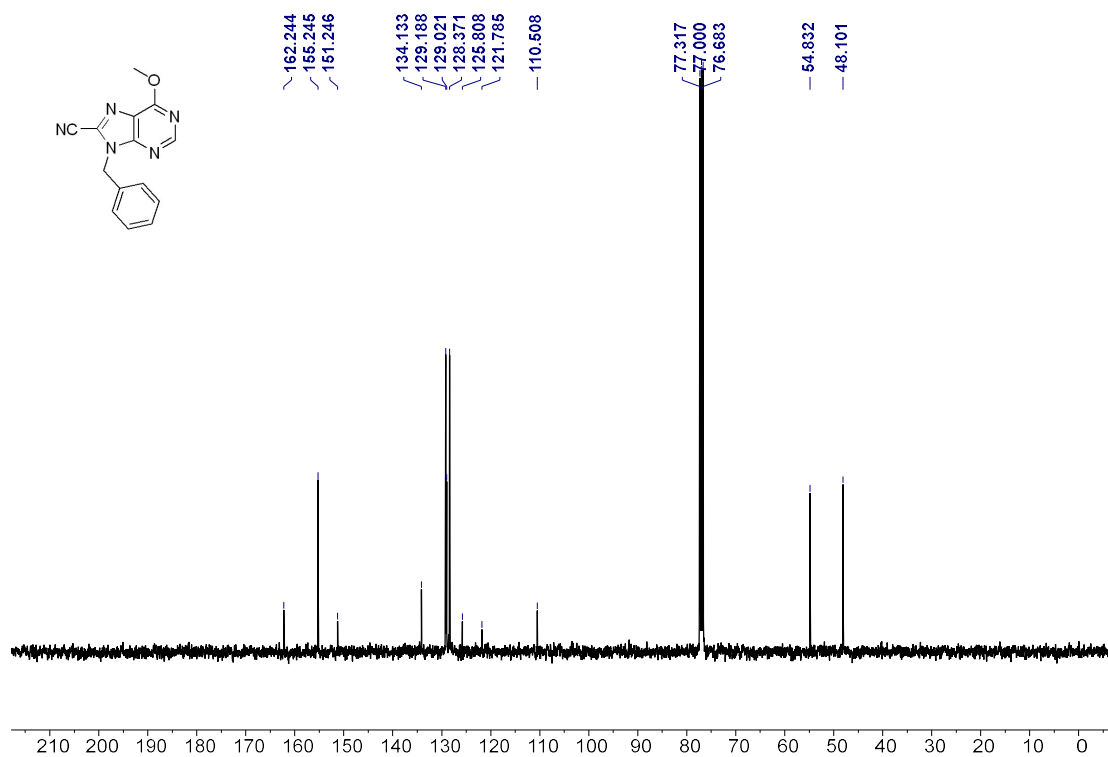*9-benzyl-2,6-dichloro-9H-purine-8-carbonitrile* (**2r**)

¹H NMR (400 MHz, CDCl₃)

7.485
7.479
7.474
7.465
7.461
7.412
7.409
7.401
7.395
7.388
7.383
7.375
7.264

5.579

−0.000

4.80   2.00

¹³C NMR (101 MHz, CDCl₃)

156.263
154.776
151.887

133.001
130.058
129.536
129.444
129.122
128.590

109.557

77.319
77.001
76.684

48.795

9-benzyl-6-(benzylthio)-9H-purine-8-carbonitrile (**2s**)

^{1}H NMR (400 MHz, CDCl$_3$)

^{13}C NMR (101 MHz, CDCl$_3$)
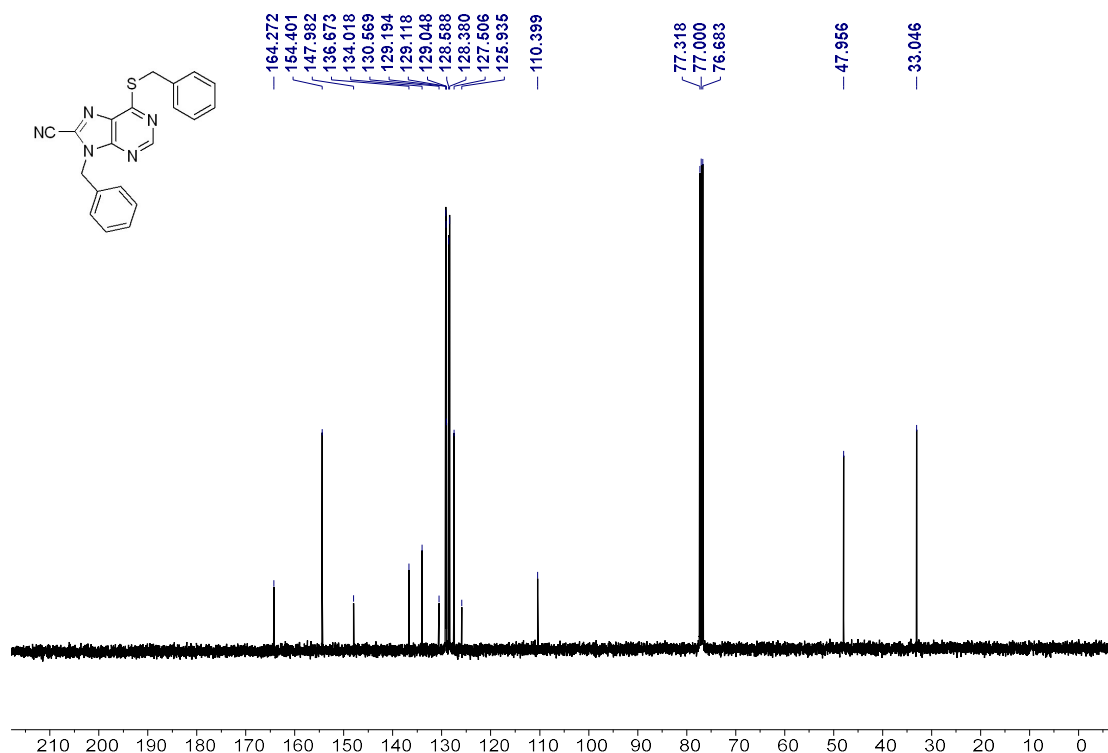
9-benzyl-6-methoxy-9H-purine-8-carbonitrile (**2t**)
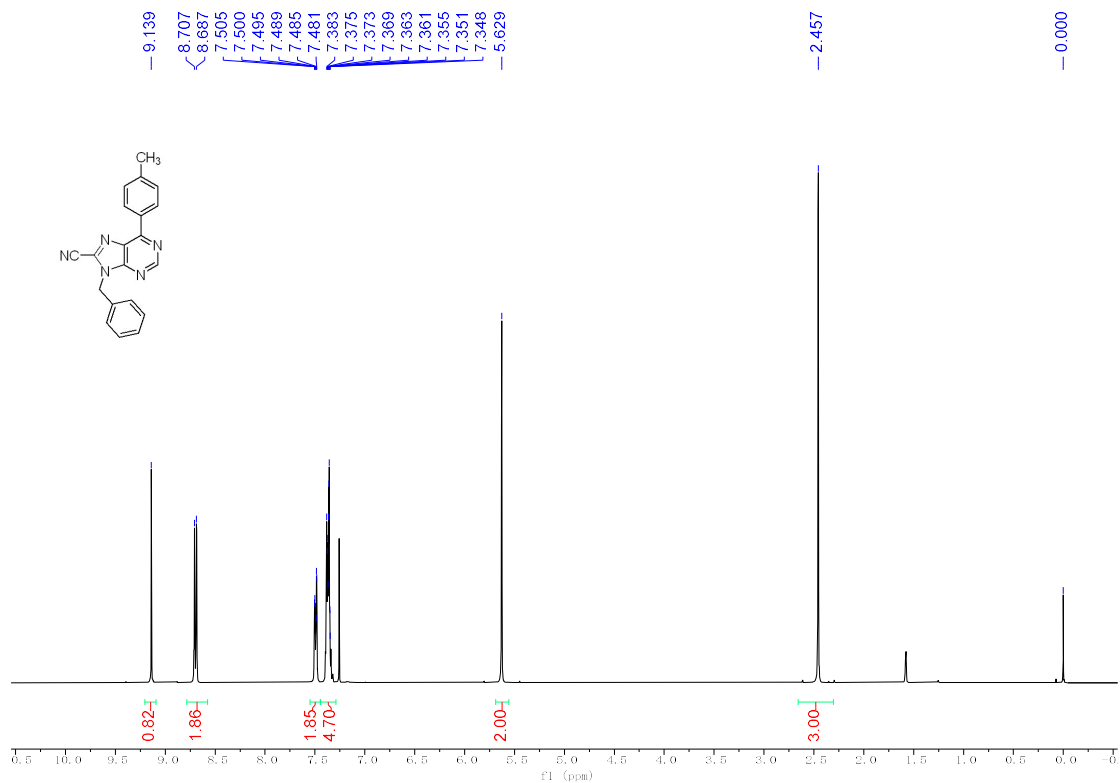
¹H NMR (400 MHz, CDCl₃)

8.695
7.462
7.456
7.442
7.438
7.381
7.377
7.372
7.359
7.350
7.344
7.340
7.327
5.572
4.218

0.82
1.93
2.85
2.00
2.92

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1

¹³C NMR (101 MHz, CDCl₃)

162.244
155.245
151.246
134.133
129.188
129.021
128.371
125.808
121.785
110.508
77.317
77.000
76.683
54.832
48.101

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

*9-Benzyl-6-(p-tolyl)-9H-purine-8-carbonitrile (**2u**)*

¹H NMR (400 MHz, CDCl₃)

¹³C NMR (101 MHz, CDCl₃)
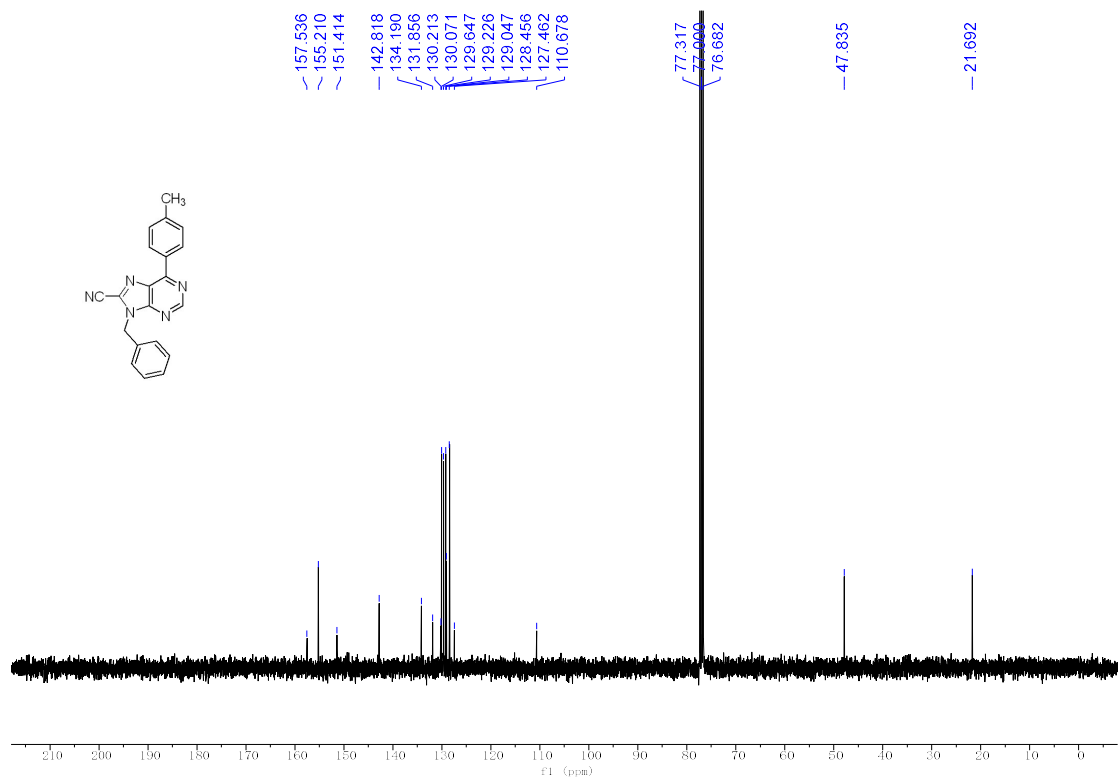
4.   The structural identification of 2v and 2v′

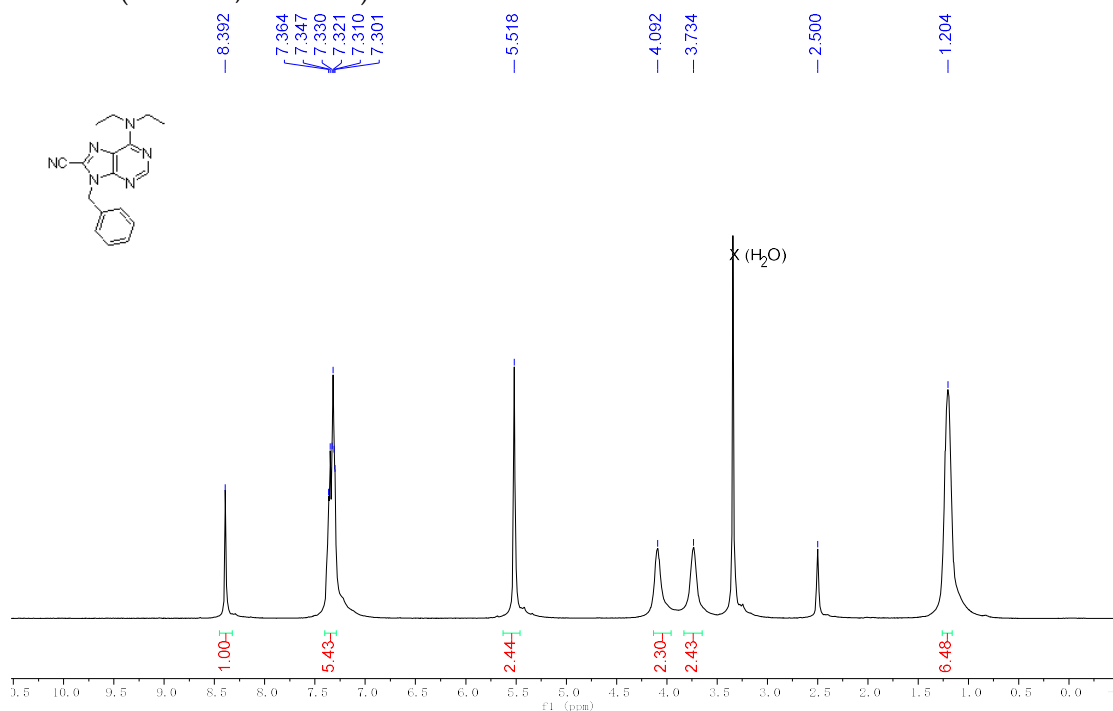*9-benzyl-6-(diethylamino)-9H-purine-8-carbonitrile* (**2v**)
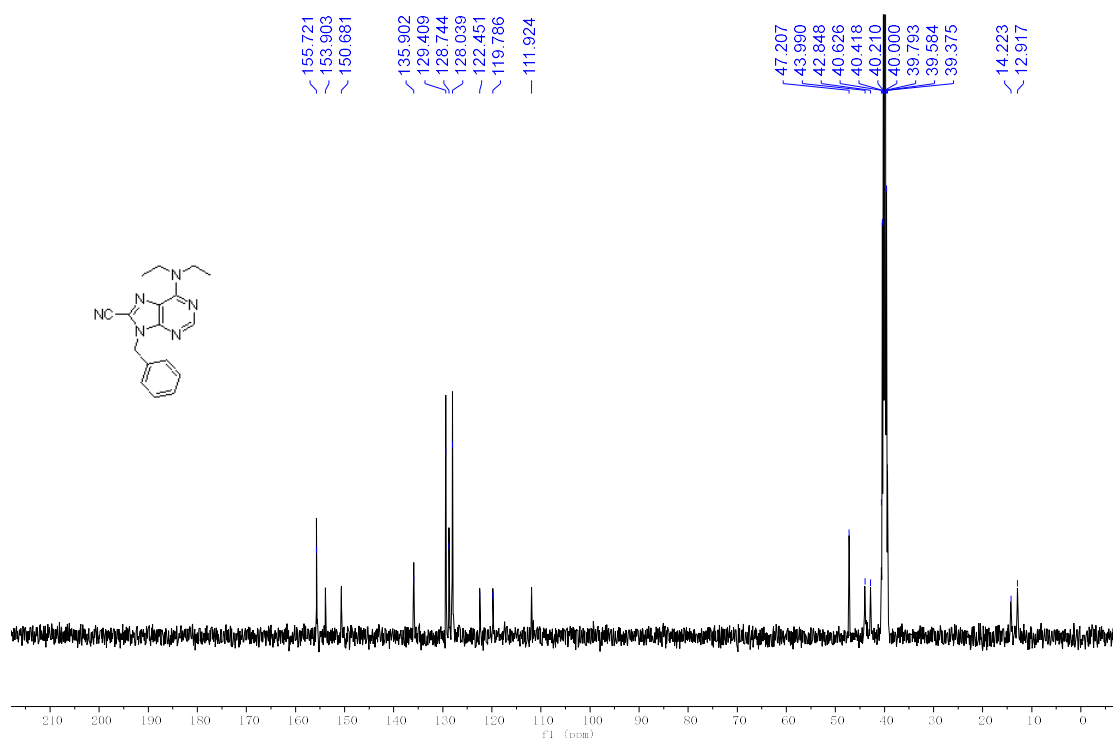
¹H NMR (400 MHz, CDCl₃)
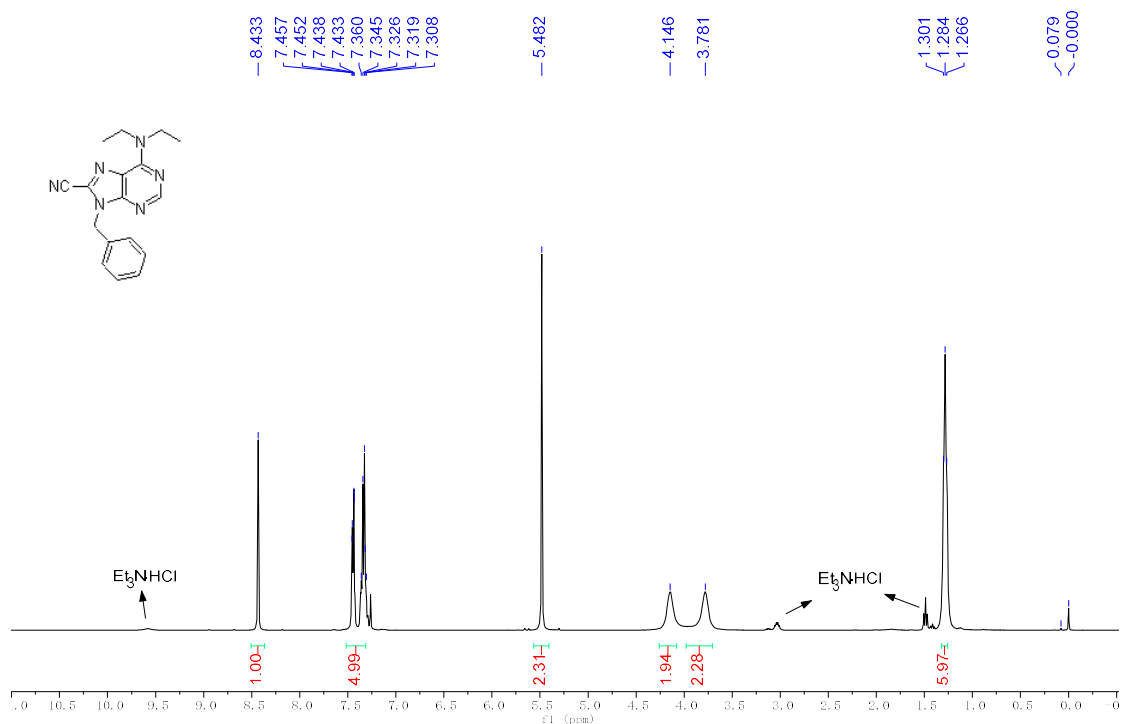
¹³C NMR (101 MHz, CDCl₃)
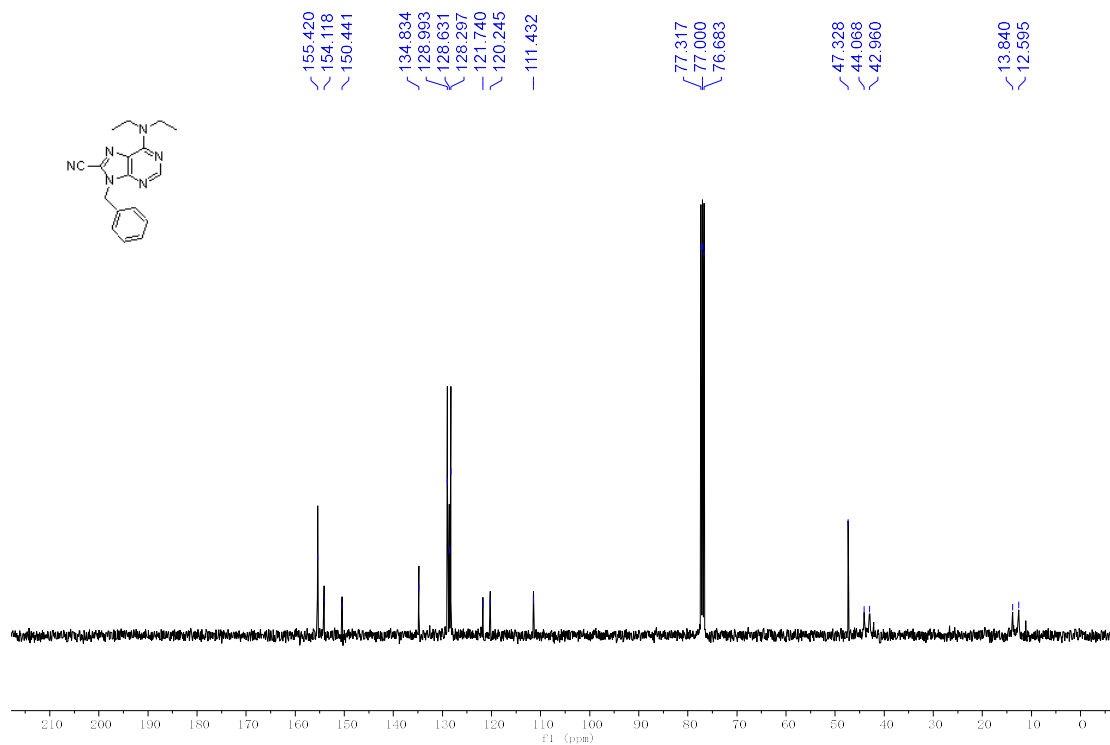
Et3N has been removed by washing with aq HCl and H, and the **2v** was test again in DMSO-d6 where a better carbon NMR data was obtained.
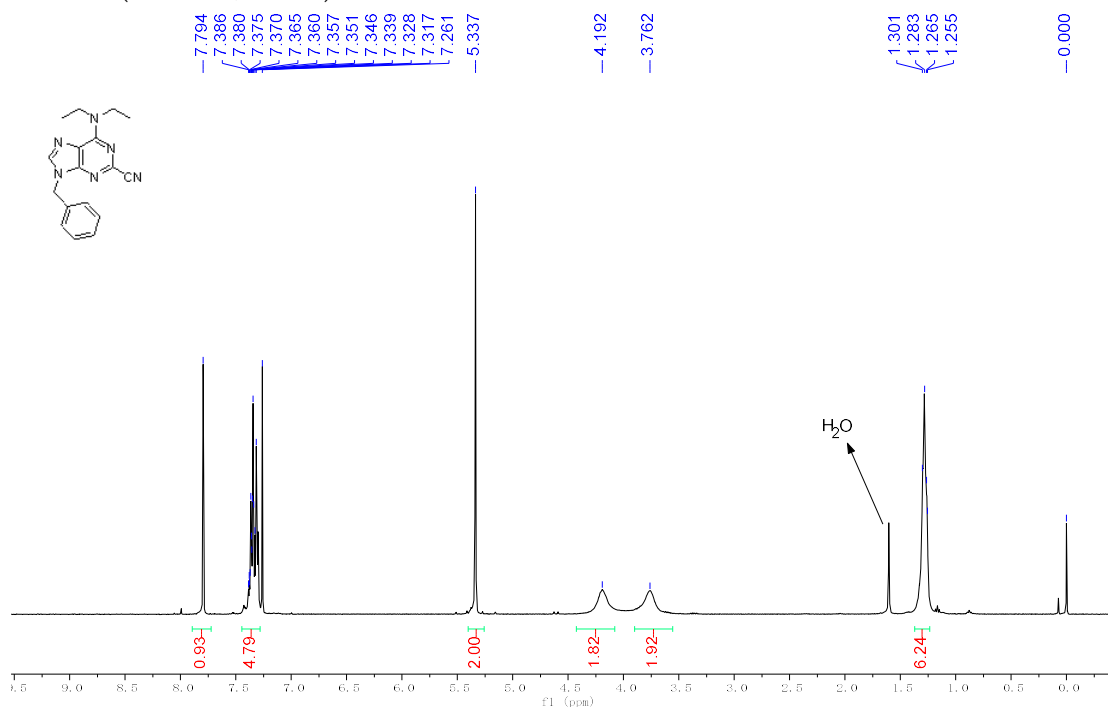
¹H NMR (400 MHz, DMSO-*d₆*)

¹³C NMR (101 MHz, DMSO-*d₆*)

9-benzyl-6-(diethylamino)-9H-purine-2-carbonitrile (**2v′**)

^{1}H NMR (400 MHz, CDCl$_3$)

^{13}C NMR (101 MHz, CDCl$_3$)

The ^{13}C NMR spectrum was tested twice; the first one was scanned for 164 times where the alkyl carbons in Et$_2$N were totally absent and the second one was scanned for 1250 times (~ 90 min) where the alkyl carbons in Et$_2$N were appeared, but they were still broad and weak apparently..
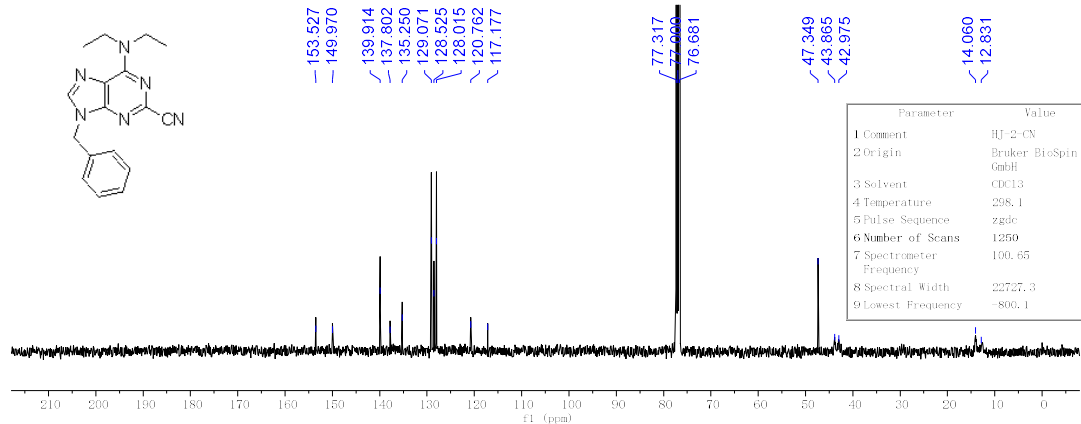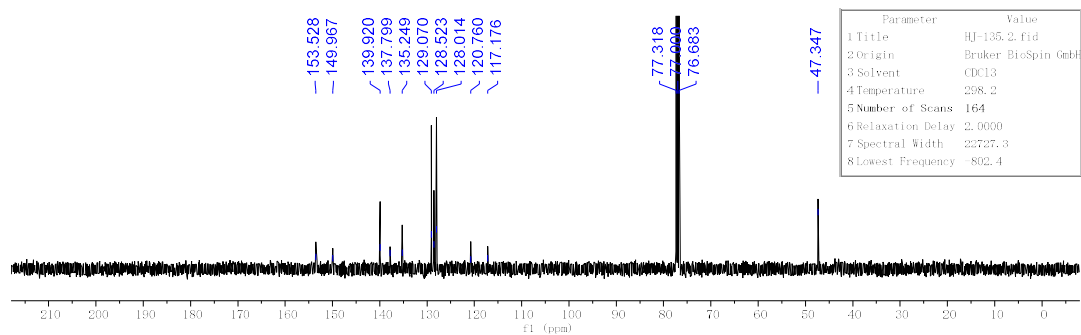
The HSQC of **2v'** was thus performed (NS = 2, 1TD = 128, ~ 10 min), where the cross peak of ^1J coupling between hydrogen and the weak carbons were obvious emerged. The HSQC spectrum highly supports the structure of **2v'**.
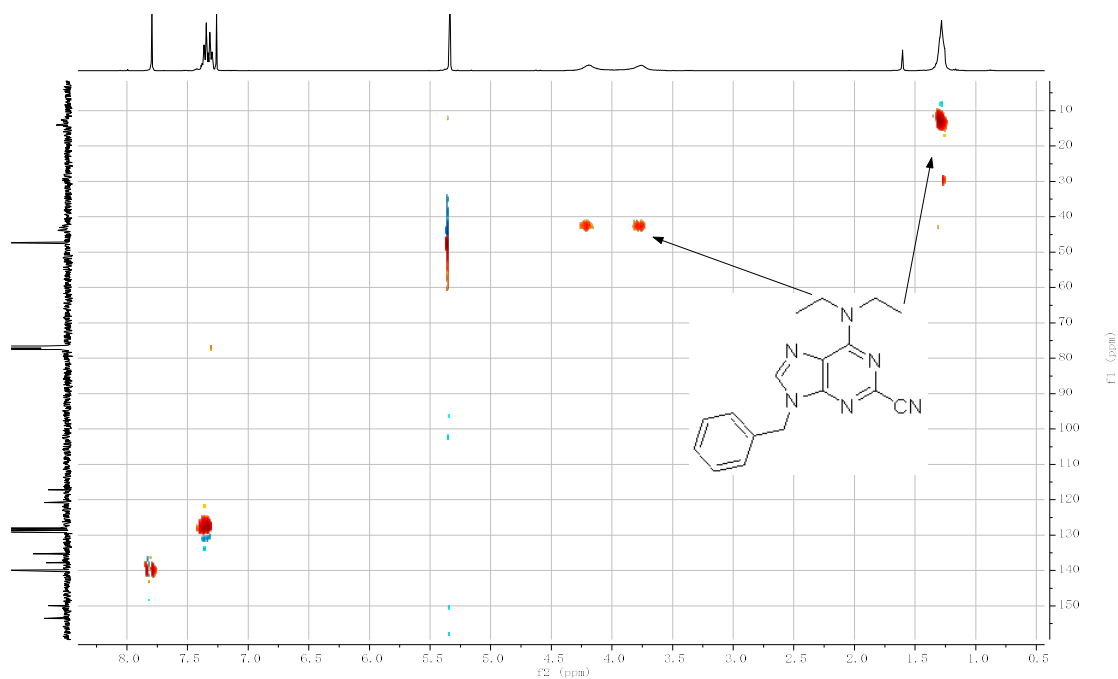
5. Copies of ¹H and ¹³C-NMR spectra of 3r, 4u, 5f, 5s & 6f

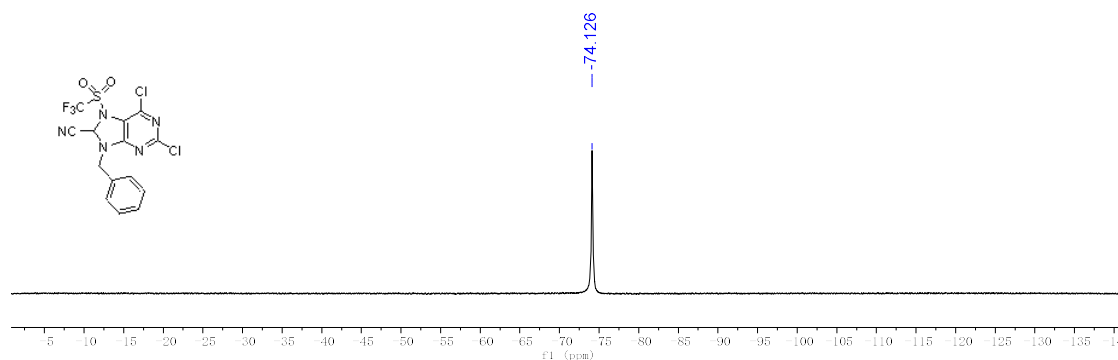*9-benzyl-2,6-dichloro-7-((trifluoromethyl)sulfonyl)-8,9-dihydro-7H-purine-8-carbonitrile* (**3r**)
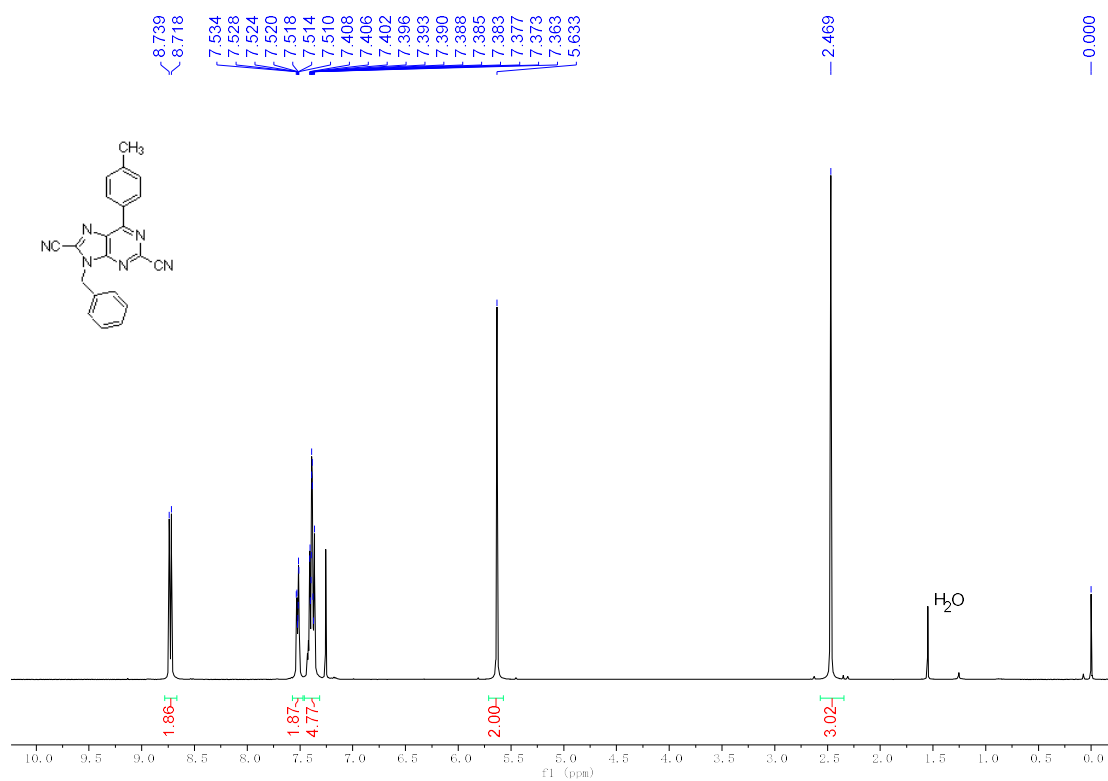
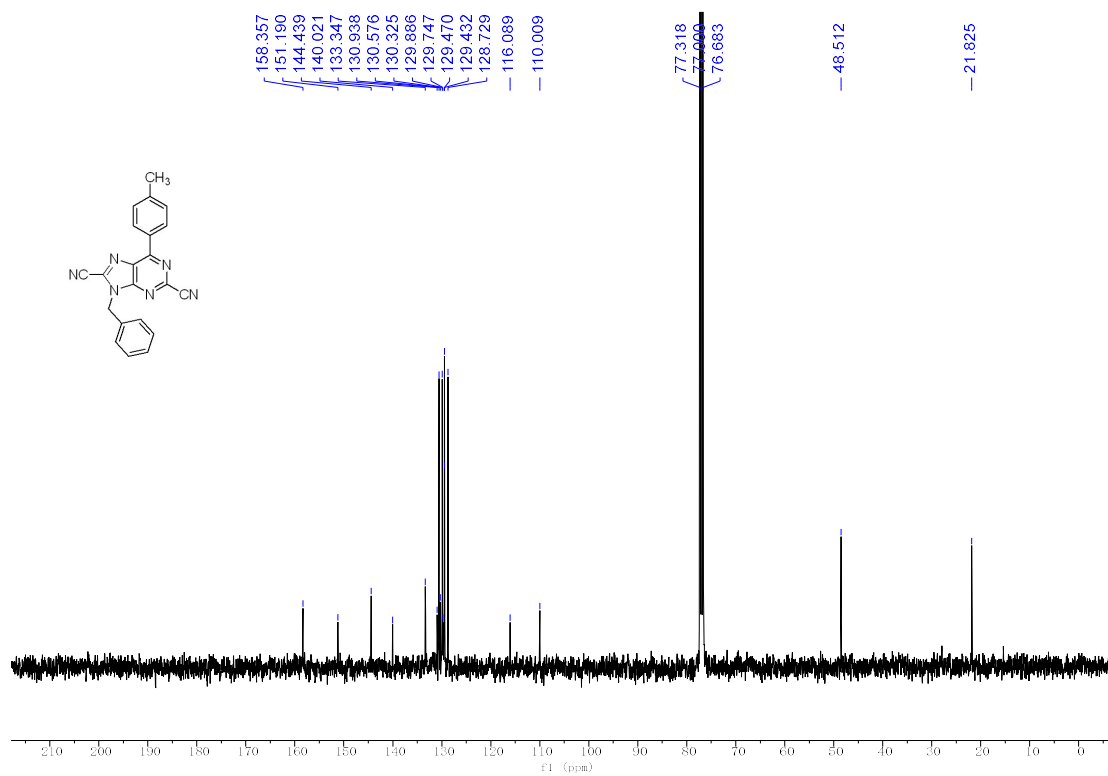¹H NMR (400 MHz, CDCl₃)
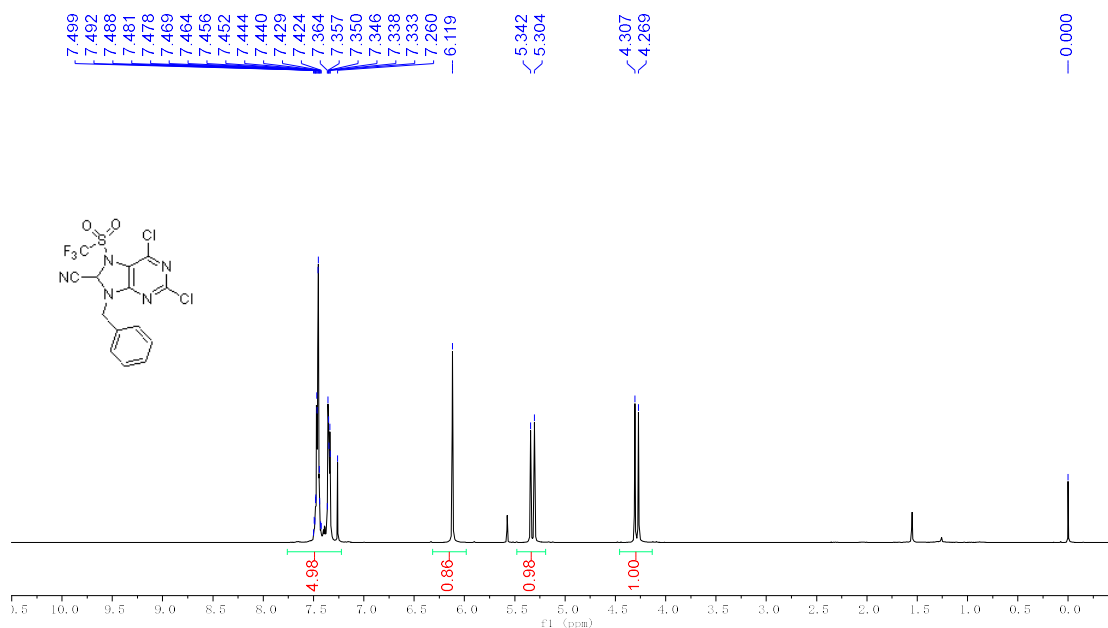
¹³C NMR (101 MHz, CDCl₃)
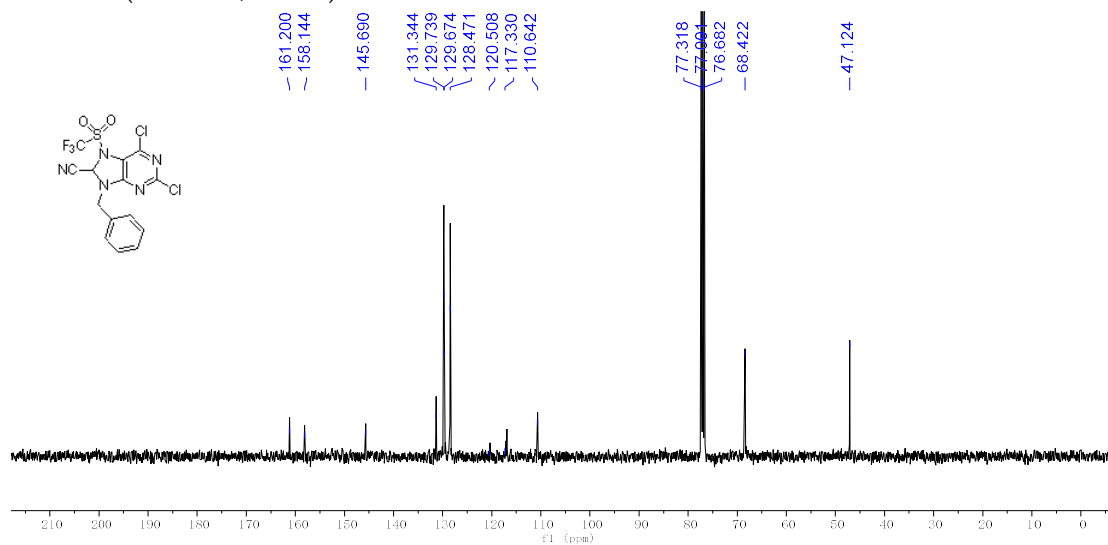
¹⁹F NMR (376 MHz, CDCl₃)

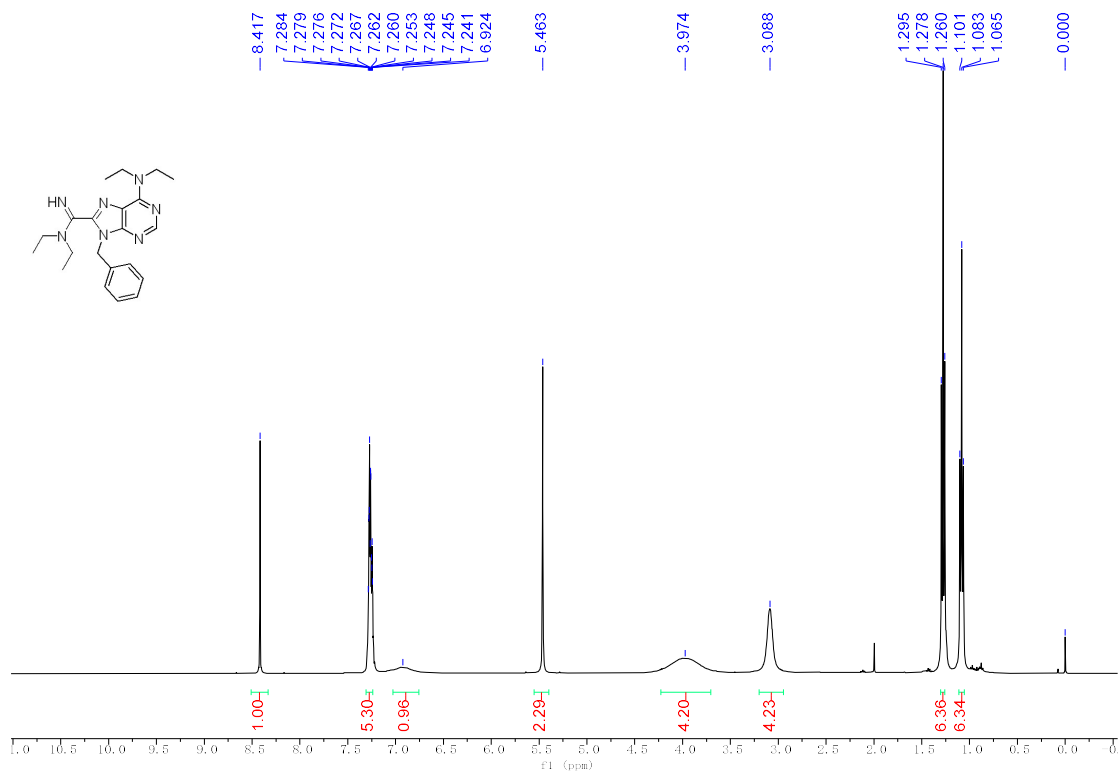*9-benzyl-6-(p-tolyl)-9H-purine-2,8-dicarbonitrile* (**4u**)
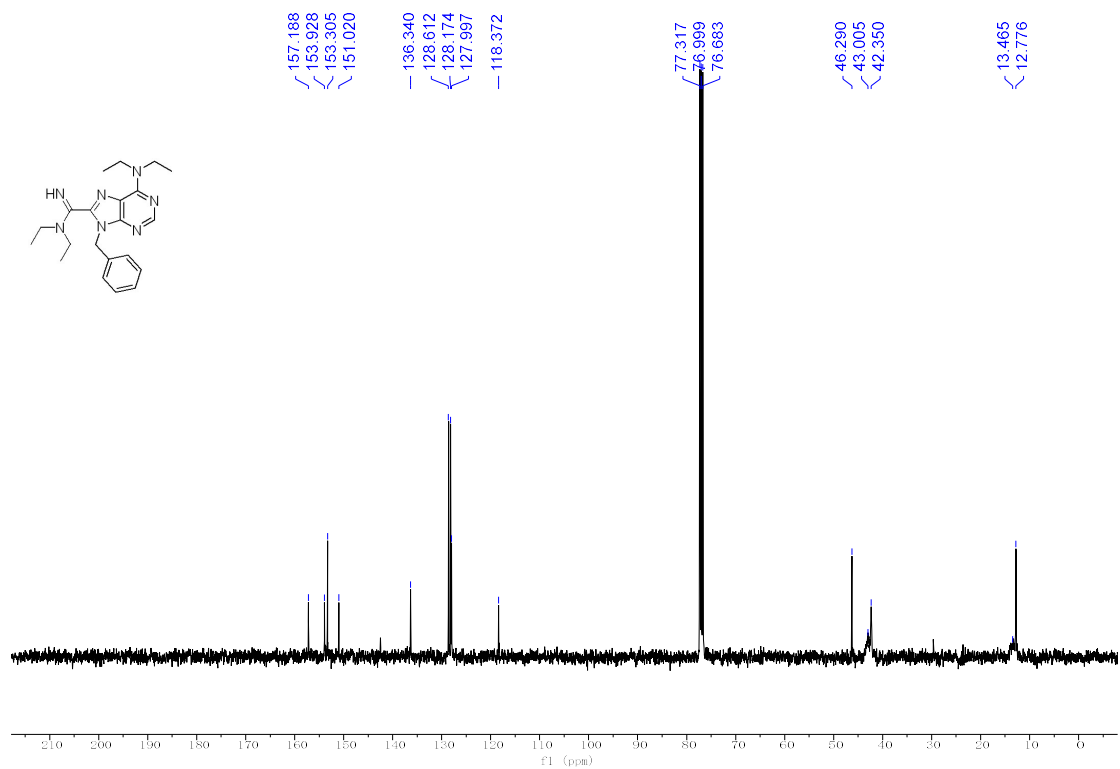
¹H NMR (400 MHz, CDCl₃)

¹³C NMR (101 MHz, CDCl₃)

9-benzyl-6-(diethylamino)-N,N-diethyl-9H-purine-8-carboximidamide (**5f**)
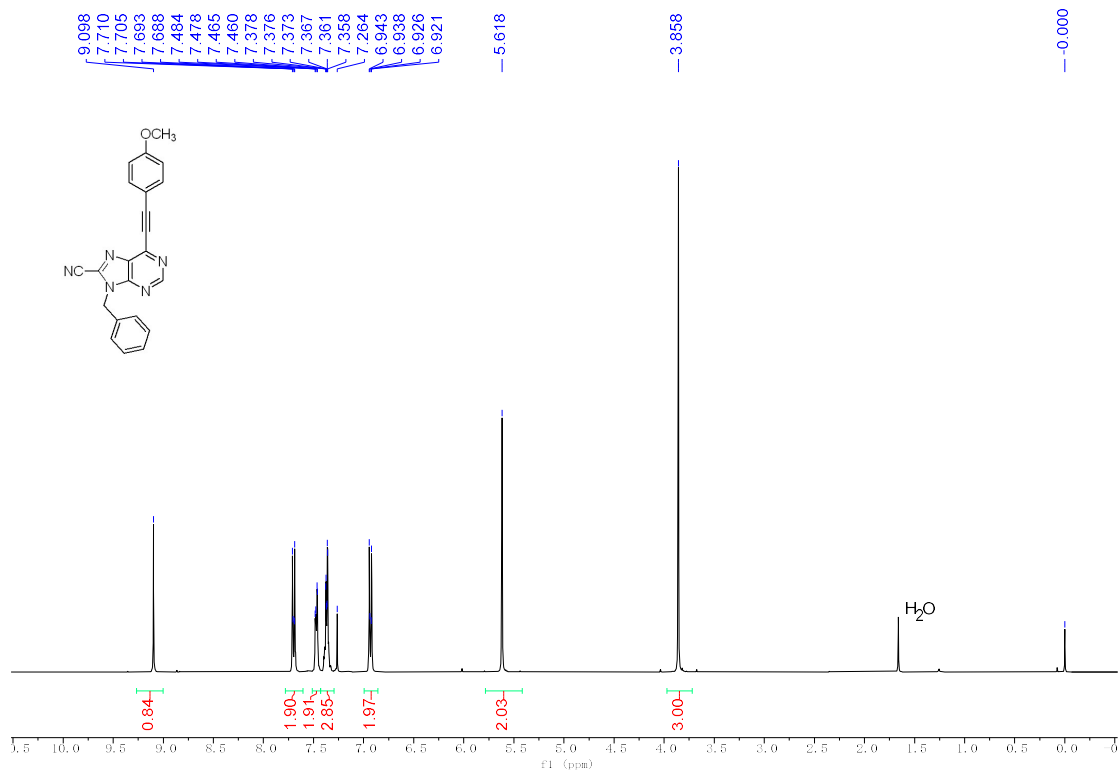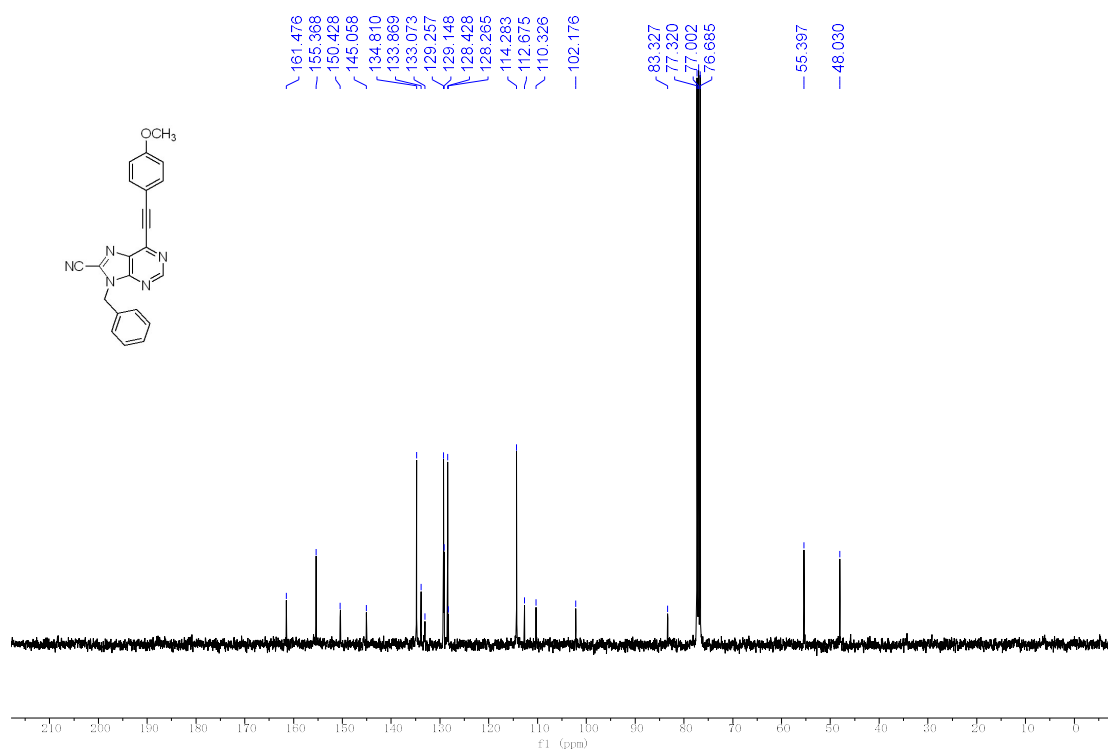
¹H NMR (400 MHz, CDCl₃)

¹³C NMR (101 MHz, CDCl₃)

9-benzyl-6-((4-methoxyphenyl)ethynyl)-9H-purine-8-carbonitrile (**6f**)
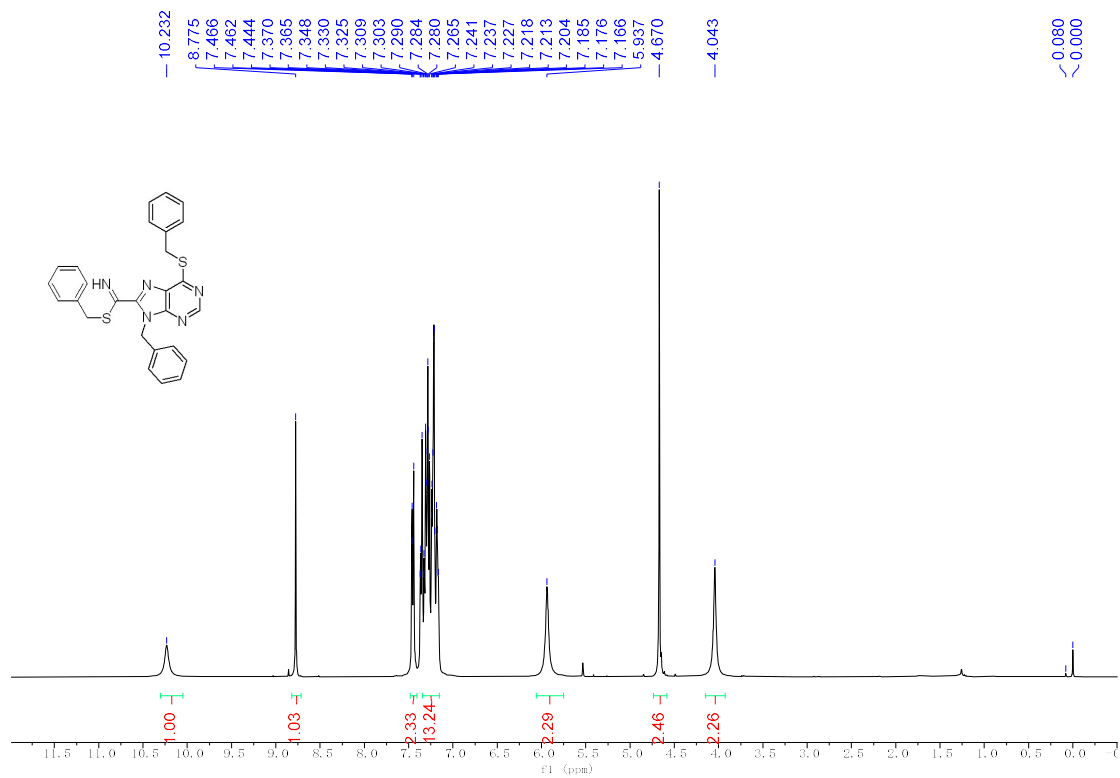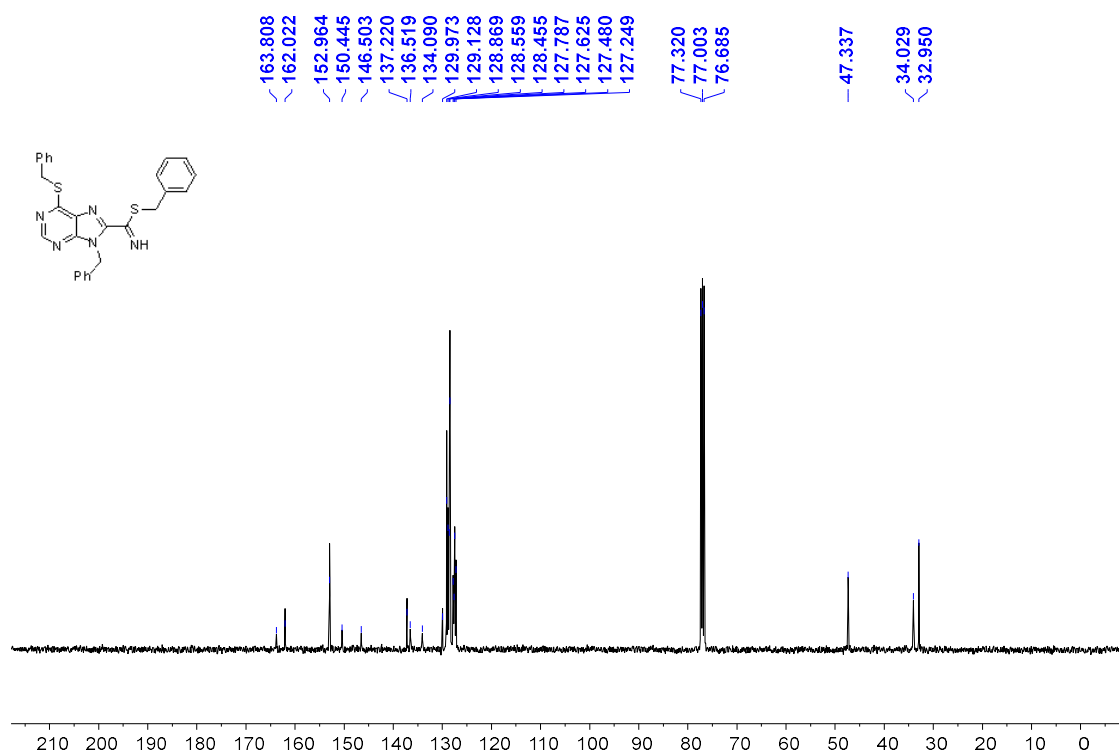
¹H NMR (400 MHz, CDCl₃)

¹³C NMR (101 MHz, CDCl₃)

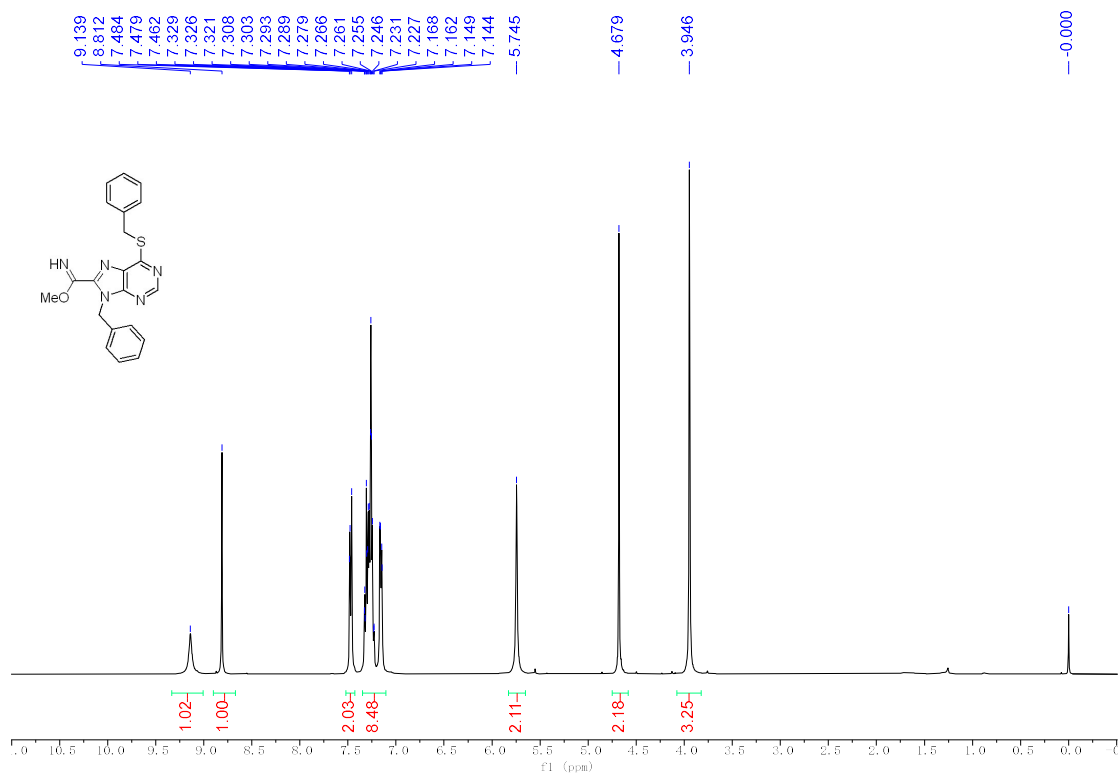*9-benzyl-6,8-bis(benzylthio)-9H-purine* (**5s**)

¹H NMR (400 MHz, CDCl₃)

¹³C NMR (101 MHz, CDCl₃)
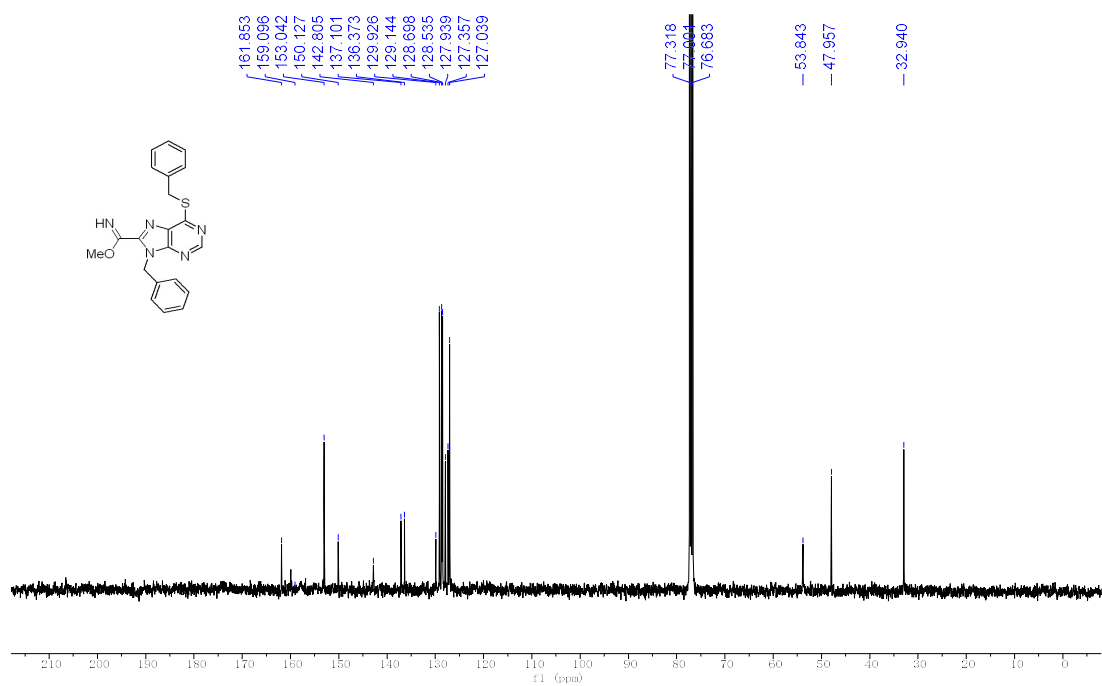
6. **Copies of ¹H and ¹³C-NMR spectra of 6s, 6s', 7s, 8s &10s.**

9-benzyl-6-(benzylthio)-*9H*-purine-8-carbimidate (**6s**)

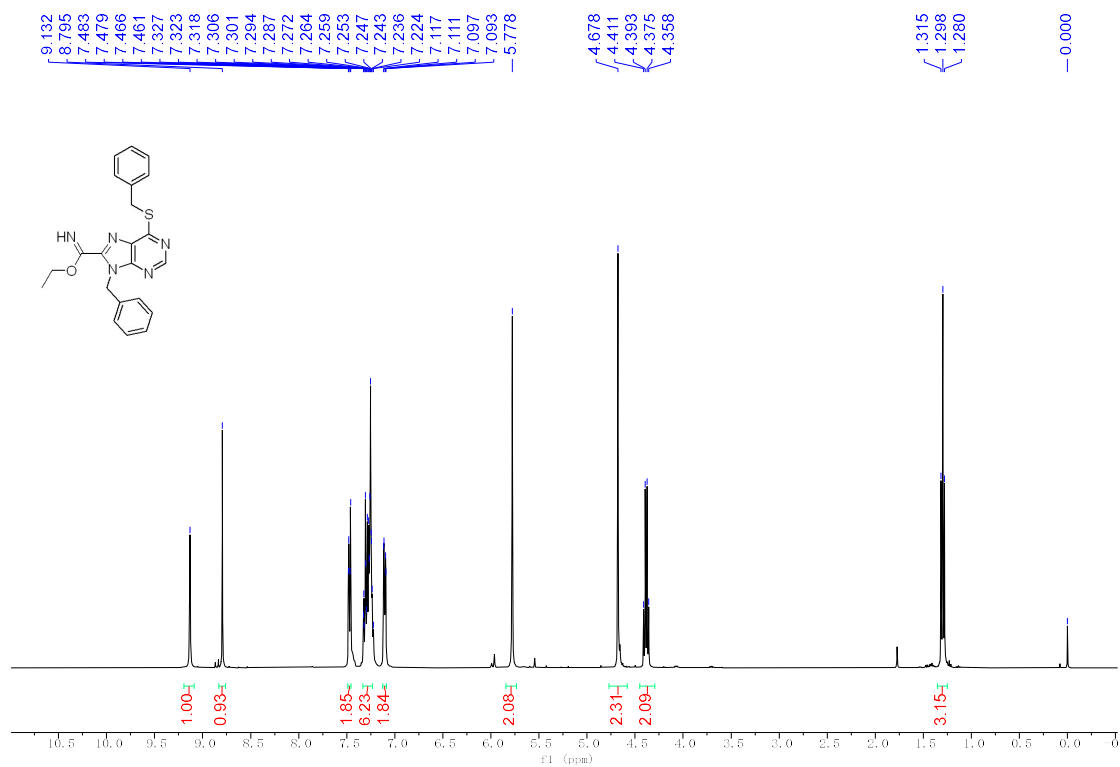¹H NMR (400 MHz, CDCl₃)
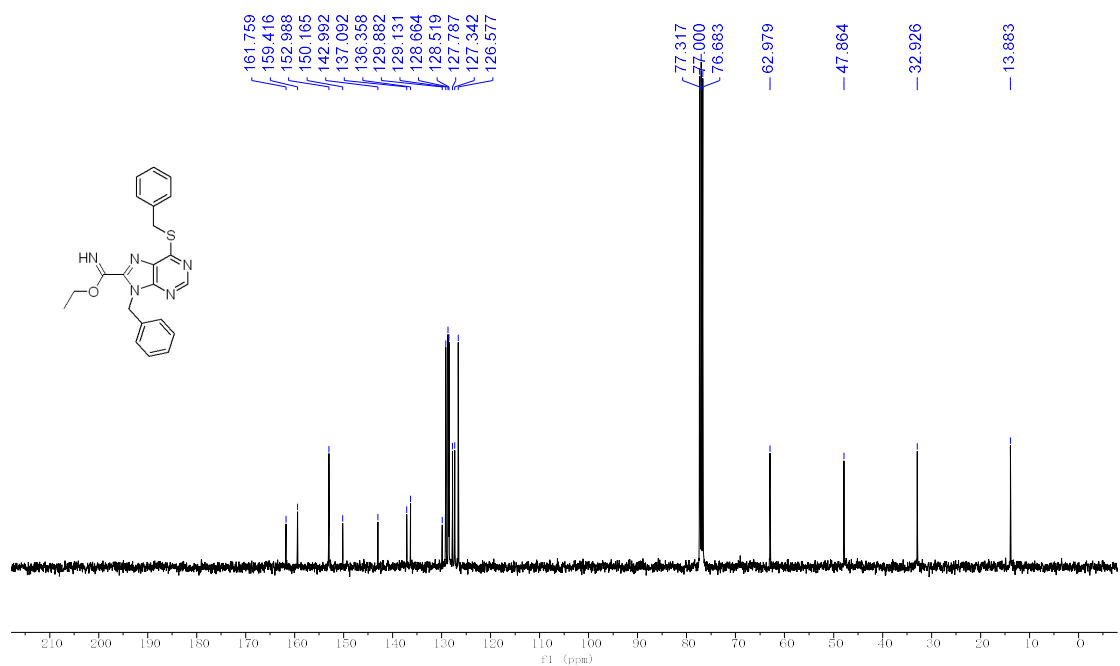

¹³C NMR (101 MHz, CDCl₃)

9-benzyl-6-(benzylthio)-9H-purine-8-carbimidate (**6s'**)
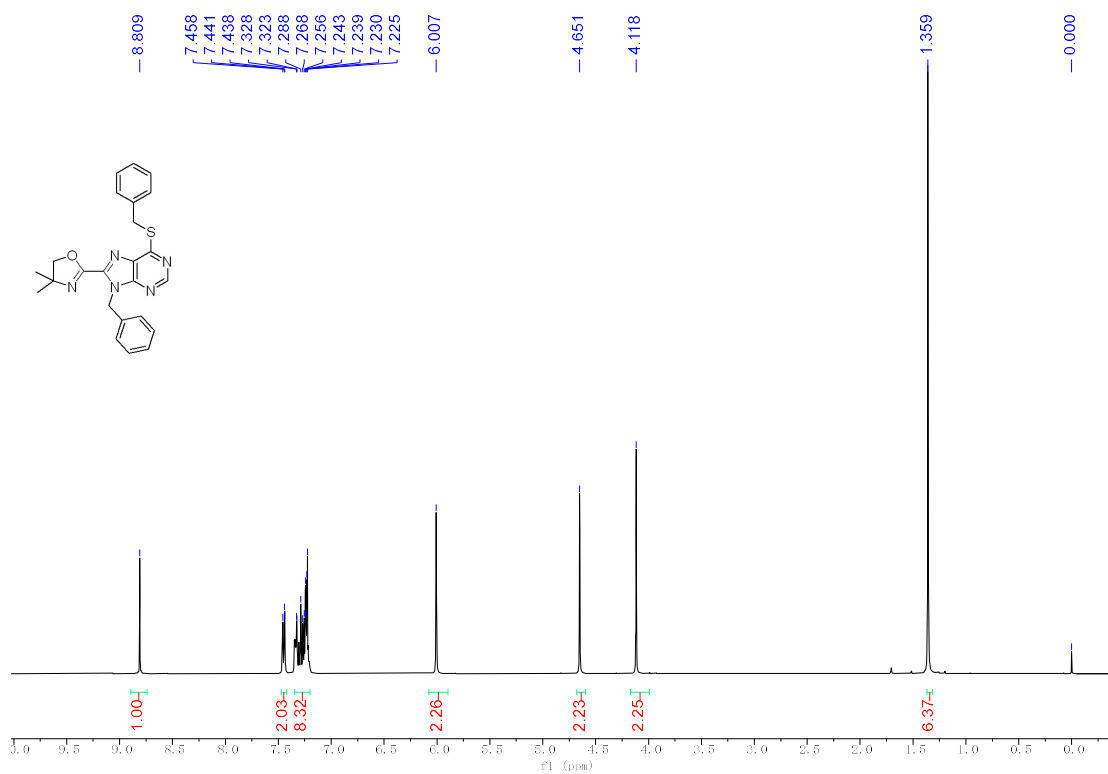
^{1}H NMR (400 MHz, CDCl$_3$)
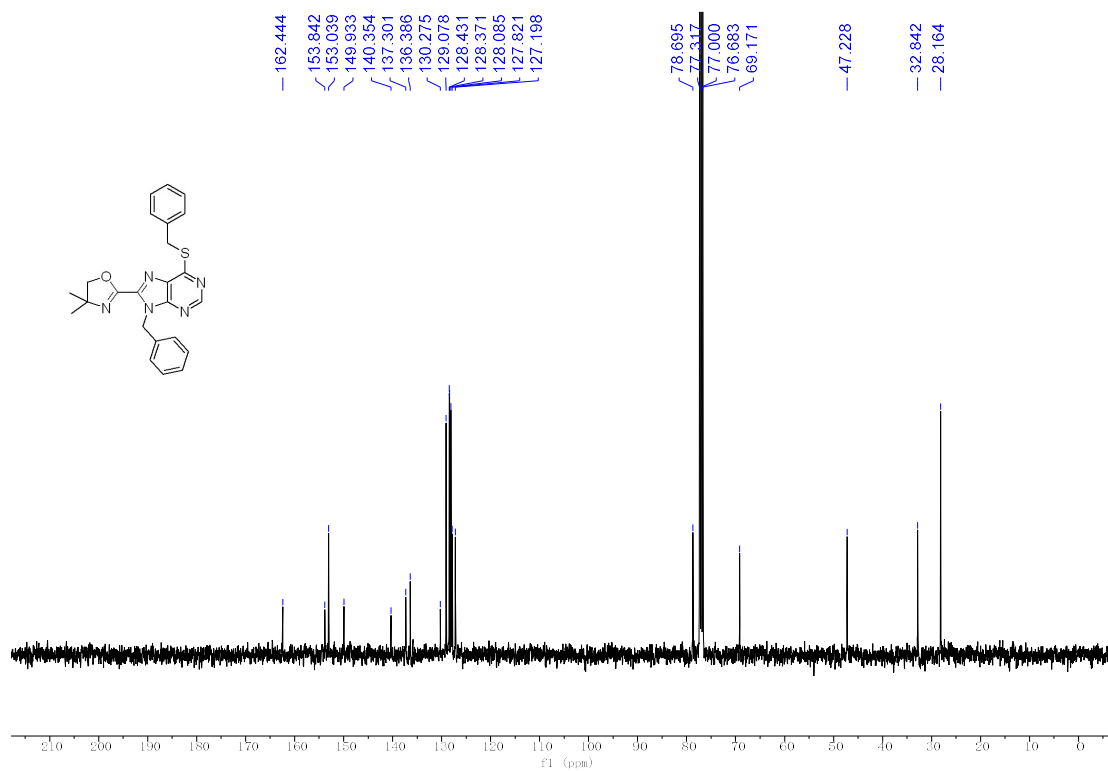

^{13}C NMR (101 MHz, CDCl$_3$)

2-(9-benzyl-6-(benzylthio)-*9H*-purin-8-yl)-4,4-dimethyl-4,5-dihydrooxazole (**7s**)
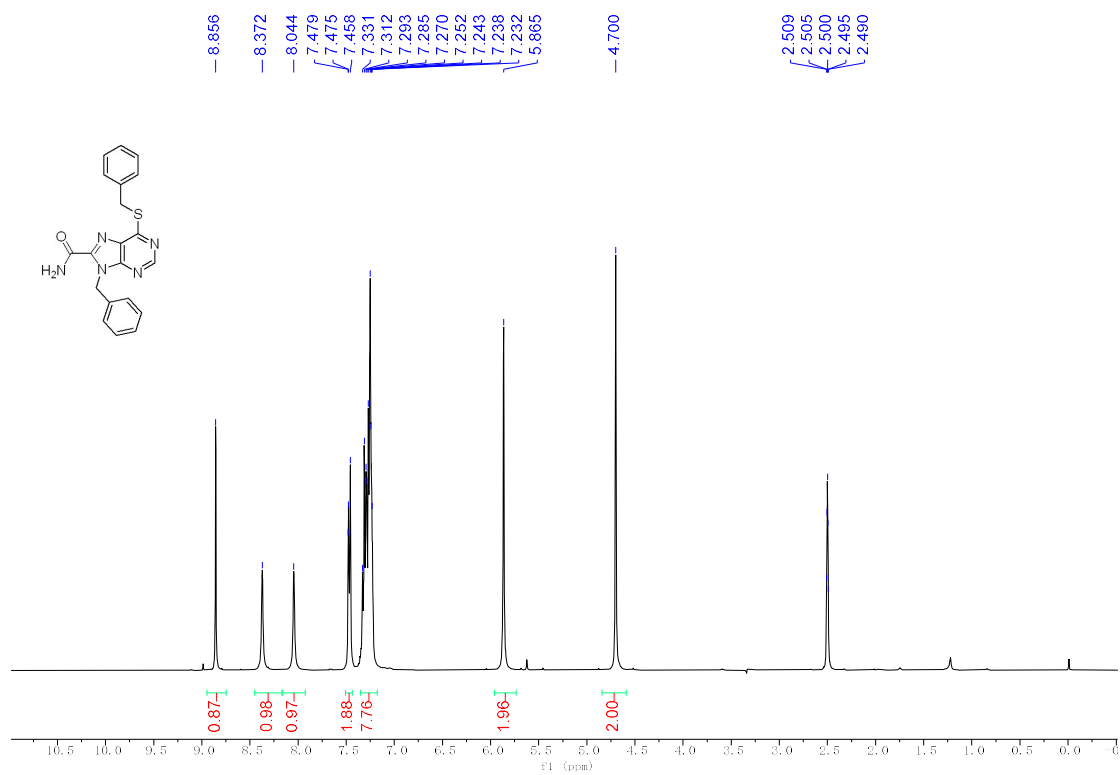
¹H NMR (400 MHz, CDCl₃)
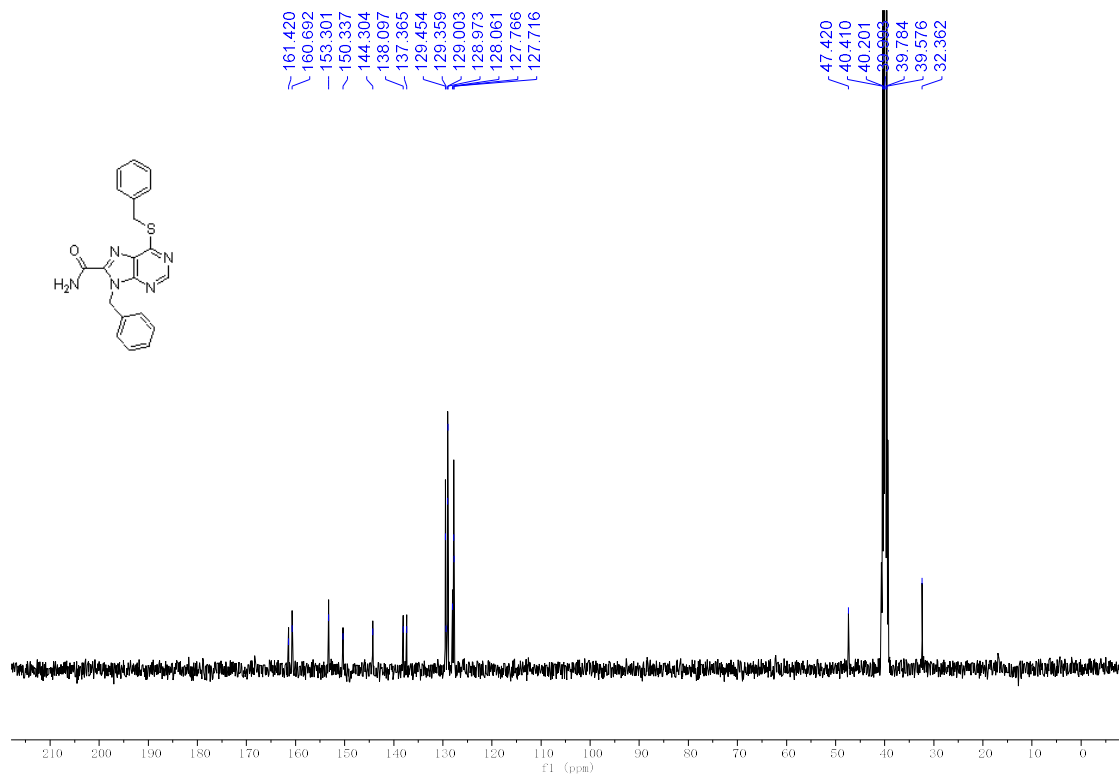

¹³C NMR (101 MHz, CDCl₃)

9-benzyl-6-(benzylthio)-*9H*-purine-8-carboxamide (**8s**)

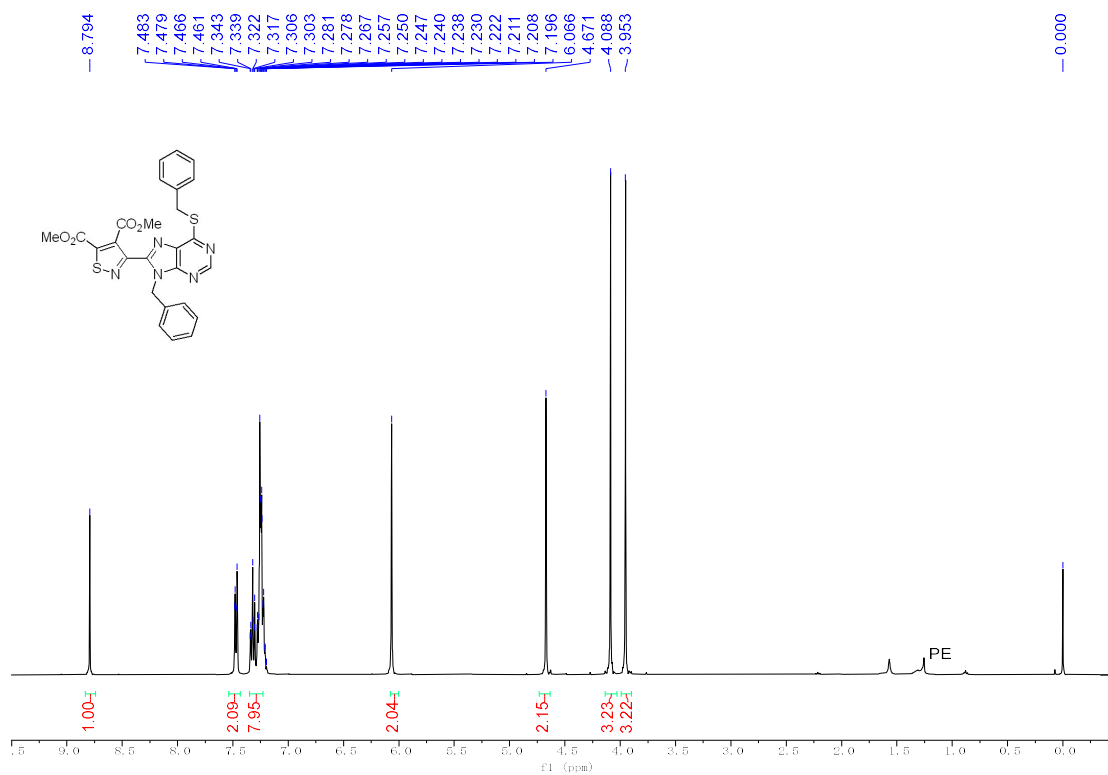¹H NMR (400 MHz, DMSO-*d₆*)

¹³C NMR (101 MHz, DMSO-*d₆*)

3-(9-benzyl-6-(benzylthio)-*9H*-purin-8-yl)isothiazole-4,5-dicarboxylate (**10s**)

¹H NMR (400 MHz, CDCl₃)

¹³C NMR (101 MHz, CDCl₃)