Supporting Information

A one-pot synthesis of highly functionalized purines

Renaud Zelli,[†] Waël Zeinyeh,[†,‡] Romain Haudecoeur,[†] Julien Alliot,[†] Benjamin Boucherle,[†] Isabelle Callebaut,[§] and Jean-Luc Decout*[,†]

[†]Univ. Grenoble Alpes, CNRS, DPM, 38000 Grenoble, France.

[‡]Univ. Grenoble Alpes, CEA, CNRS, BIG-LCBM, 38000 Grenoble, France.

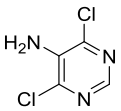
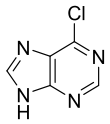
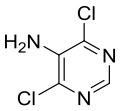
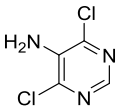
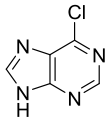
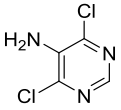
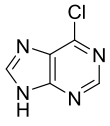
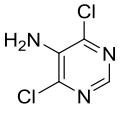
[§]IMPMC, Sorbonne Universités, UPMC Univ. Paris 06, UMR CNRS 7590, Muséum National d'Histoire Naturelle, IRD UMR 206, IUC, Case 115, 4 Place Jussieu, 75005 Paris Cedex 05, France.

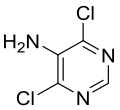
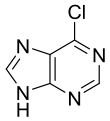
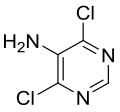
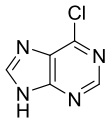
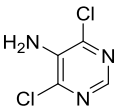
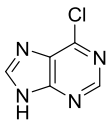
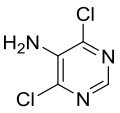
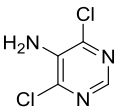
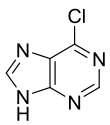
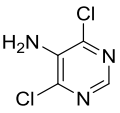
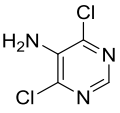
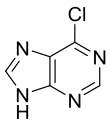
Table of Content

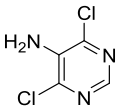
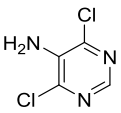
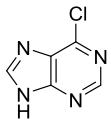
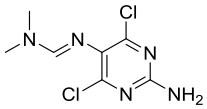
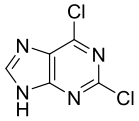
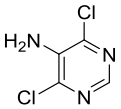
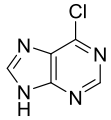
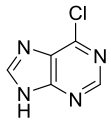
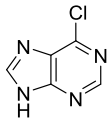
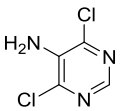
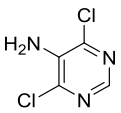
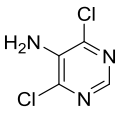
1. New and previously described compounds

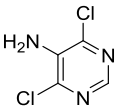
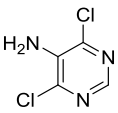
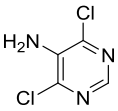
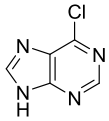
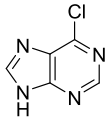
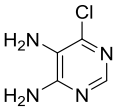
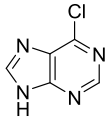
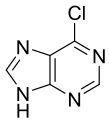
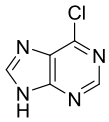
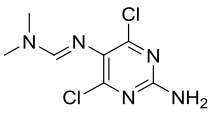
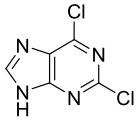
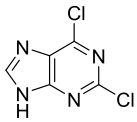
The following compounds are presented herein for the first time at the best of our knowledge: **6**, **7**, **13**, **14**, **17**, **18**, **19**, **20**, **21**, **27**, **28**, **29**, **30**, **31** and **38**.

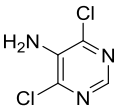
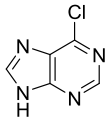
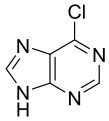
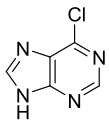
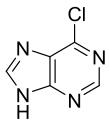
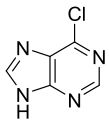
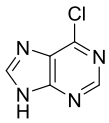
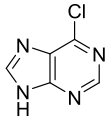
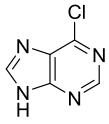
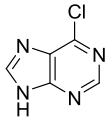
Concerning the compounds previously described in the literature, the main characteristics of the synthesis methodology are compared in the following table to those of the synthesis using Vilsmeier-type reagents. In each case the synthesis characteristics were described from commercially available starting materials. The new one-pot synthesis was mainly conducted with stoichiometric ratios of pyrimidines and amines.

Cd.	Method	Starting compound	Nb. of isolated steps	Global yield	Max. temperature / total reaction time
4	**This work**		**1**	**86%**	**100 °C / 16 h**
	Chan-Lam reaction[1]		1	41%	25 °C / 96 h
	Substitution / Closure from orthoester[2]		2	54%	140 °C / 10 h
5	**This work**		**1**	**85%**	**100 °C / 16 h**
	Chan-Lam reaction[1]		1	73%	25 °C / 96 h
9	**This work**		**1**	**81%**	**100 °C / 16 h**
	Chan-Lam reaction[1]		1	71%	25 °C / 96 h
	Substitution / Closure from orthoester[2]		2	58%	140 °C / 11 h

	Formylation / Substitution–cyclization[3]		2	77%	140 °C / 2 h
	C–N cross coupling reaction[4]		1	99%	40 °C / 2.5 h
10	**This work**		**1**	**86%**	**100 °C / 16 h**
	Chan-Lam reaction[5]		1	65%	25 °C / 72 h
11	**This work**		**1**	**85%**	**100 °C / 16 h**
	Chan-Lam reaction[1]		1	68%	25 °C / 96 h
	Substitution / Closure from orthoester[6]		2	29%	150 °C / 2 h
12	**This work**		**1**	**83%**	**100 °C / 16 h**
	Chan-Lam reaction[1]		1	52%	25 °C / 96 h
	Formylation / Substitution–cyclization[3]		2	90%	160 °C / 2 h
	Substitution / Closure from orthoester[6]		2	38%	150 °C / 1 h
	Chan-Lam reaction[7]		1	47%	25 °C / 96 h

16	**This work**		**1**	**54%**	**100 °C / 16 h**
	Substitution / Closure from orthoester[6]		2	33%	150 °C / 1 h
	Chan-Lam reaction[8]		1	35%	25 °C / 72 h
23	**This work**		**2**	**42%**	**70 °C / 72 h**
	Chan-Lam reaction[9]		1	18%	25 °C / 48 h
24	**This work**		**1**	**68%**	**120 °C / 16 h**
	Direct alkylation[10]		1	64%	25 °C / 14 h
	Direct alkylation[11]		1	63%	25 °C / 24 h
	Direct alkylation[12]		1	43%	25 °C / 3 h
25	**This work**		**1**	**64%**	**120 °C / 16 h**
	Formylation / Substitution–cyclization[3]		2	86%	160 °C / 2 h
	Substitution / Closure from orthoester[13]		2	62%	120 °C / 88 h

	Substitution / Closure from orthoester[14]		2	51%	120 °C / 12 h
	Substitution / Closure from orthoester[15]		2	14%	130 °C / 6 h
	This work		**2**	**94%**	**120 °C / 10 h**
26	Direct alkylation[16]		1	67%	50 °C / 20 h
	Direct alkylation[17]		1	61%	100 °C / 15 min
	This work		**2**	**40%**	**85 °C / 16 h**
	Silyl-promoted glycosylation[18]		1	94%	80 °C / 2.5 h
36	ACF-promoted glycosylation[19]		1	53%	200 °C / 0.5 h
	Silyl-promoted glycosylation[20]		1	56%	80 °C / 3–4 h
	This work		**3**	**14%**	**84 °C / 33 h**
38	(p-Tol)$_2$SO/Tf$_2$O-promoted glycosylation[21]		1	73%	25 °C / 2 h
	NPOE-promoted glycosylation[22]		1	85%	25 °C / 4 h

	This work		**3**	**55%**	**120 °C / 26 h**
	Direct alkylation[23]		1	6%	25 °C / 20 h
	Direct alkylation[24]		1	25%	25 °C / 22 h
	Direct alkylation[25]		1	30%	25 °C / 24–96 h
	Direct alkylation[26]		1	18%	25 °C / 72 h
39					
	Direct alkylation[27]		1	15%	25 °C / 3 h
	Mitsunobu reaction[28]		1	23%	25 °C / 10 h
	Organomagnesium-mediated alkylation[29]		1	88%	50 °C / 20 h
	N^9-Boc-oriented alkylation[30]		4	74%	25 °C / 5.5 h
	N^9-Trityl-oriented alkylation[31]		2	86%	25 °C / 4 h

(1) Bakkestuen, A. K.; Gundersen, L.-L. *Tetrahedron Lett.* **2003**, *44*, 3359–3362.

(2) Greenberg, S. M.; Ross, L. O.; Robins, R. K. *J. Org. Chem.* **1959**, *24*, 1314–1317.

(3) Dejmek, M.; Kovackova, S.; Zbornikova, E.; Hrebabecky, H.; Sala, M.; Dracinsky, M.; Nencka, R. *RSC Adv.* **2012**, *2*, 6970–6980.

(4) Niu, H.-Y.; Xia, C.; Qu, G.-R.; Zhang, Q.; Jiang, Y.; Mao, R.-Z.; Li, D.-Y.; Guo, H.-M. *Org. Biomol. Chem.* **2011**, *9*, 5039–5042.

(5) Morellato, L.; Huteau, V.; Pochet, S. *Tetrahedron Lett.* **2014**, *55*, 1625–1627.

(6) Aguado, L.; Camarasa, M.-J.; Pérez-Pérez, M.-J. *J. Comb. Chem.* **2009**, *11*, 210–212.

(7) Cerna, I.; Pohl, R.; Klepetarova, B.; Hocek, M. *J. Org. Chem.* **2008**, *73*, 9048–9054.

(8) Aguado, L.; Thibaut, H. J.; Priego, E.-M.; Jimeno, M.-L.; Camarasa, M.-J.; Neyts, J.; Pérez-Pérez, M.-J. *J. Med. Chem.* **2010**, *53*, 316–324.

(9) Bibian, M.; Rahaim, R. J.; Choi, J. Y.; Noguchi, Y.; Schürer, S.; Chen, W.; Nakanishi, S.; Licht, K.; Rosenberg, L. H.; Li, L.; Feng, Y.; Cameron, M. D.; Duckett, D. R.; Cleveland, J. L.; Roush, W. R. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4374–4380.

(10) Lambertucci, C.; Buccioni, M.; Dal Ben, D.; Kachler, S.; Marucci, G.; Spinaci, A.; Thomas, A.; Klotz, K.-N.; Volpini, R. *Med. Chem. Commun.* **2015**, *6*, 963–970.

(11) Dilek Celik, G.; Disli, A.; Oner, Y.; Acik, L. *Med. Chem. Res.* **2013**, *22*, 1470–1479.

(12) Purohit, C. S.; Mishra, A. K.; Verma, S. *Inorg. Chem.* **2007**, *46*, 8493–8495.

(13) Lambertucci, C.; Antonini, I.; Buccioni, M.; Dal Ben, D.; Kachare, D. D.; Volpini, R.; Klotz, K.-N.; Cristalli, G. *Bioorg. Med. Chem.* **2009**, *17*, 2812–2822.

(14) Zhang, C.; Shokat, K. M. *Tetrahedron* **2007**, *63*, 5832–5838.

(15) Montgomery, J.; Temple, C. *J. Am. Chem. Soc.* **1958**, *80*, 409–411.

(16) Guha, S.; Graf, J.; Göricke, B.; Diederichsen, U. *J. Pept. Sci.* **2013**, *19*, 415–422.

(17) Boëns, B.; Azouz, M.; Ouk, T.-S.; Zerrouki, R. *Nucleosides Nucleotides Nucleic Acids* **2013**, *32*, 69–80.

(18) Yadav, V.; Chu, C. K.; Rais, R. H.; Al Safarjalani, O. N.; Guarcello, V.; Naguib, F. N. M.; El Kouni, M. H. *J. Med. Chem.* **2004**, *47*, 1987–1996.

(19) Lautrette, S.; Granet, R.; Krausz, P. *Chem. Commun.* **2004**, 586–587.

(20) Manfredini, S.; Baraldi, P. G.; Bazzanini, R.; Guarneri, M.; Simoni, D. *J. Chem. Soc. Chem. Commun.* **1994**, 583–584.

(21) Liu, G.-J.; Zhang, X.-T.; Xing, G.-W. *Chem. Commun.* **2015**, *51*, 12803–12806.

(22) Fraser-Reid, B.; Ganney, P.; Ramamurty, V. S.; Gomez, A. M.; Lopez, J. C. *Chem. Commun.* **2013**, *49*, 3251–3253.

(23) Laufer, S. A.; Domeyer, D. M.; Scior, T. R. F.; Albrecht, W.; Hauser, D. R. J. *J. Med. Chem.* **2005**, *48*, 710–722.

(24) Gundersen, L.-L.; Bakkestuen, A. K.; Aasen, A. J.; Overas, H.; Rise, F. *Tetrahedron* **1994**, *50*, 9743–9756.

(25) Dalby, C.; Bleasdale, C.; Clegg, W.; Elsegood, M. R. J.; Golding, B. T.; Griffin, R. J. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1696–1697.

(26) McKenzie, T.; Epstein, J. W. *J. Org. Chem.* **1982**, *47*, 4881–4884.

(27) Montgomery, J. A.; Temple, C. *J. Am. Chem. Soc.* **1961**, *83*, 630–635.

(28) Toyota, A.; Katagiri, N.; Kaneko, C. *Synth. Commun.* **1993**, *23*, 1295–1305.

(29) Chen, S.; Graceffa, R. F.; Boezio, A. A. *Org. Lett.* **2016**, *18*, 16–19.

(30) Kotek, V.; Tobrman, T.; Dvorak, D. *Synthesis* **2012**, *44*, 610–618.

(31) Kotek, V.; Chudikova, N.; Tobrman, T.; Dvorak, D. *Org. Lett.* **2010**, *12*, 5724–5727.

2. Material and methods

All starting materials were commercially available research-grade chemicals and used without further purification. Reactions were monitored by analytical TLC on silica gel (Alugram Sil G/UV_{254}) from Macherey-Nagel with fluorescent indicator UV_{254}. NMR analyses were performed by the analytical service of Institut de Chimie Moléculaire de Grenoble (ICMG). ^{1}H NMR spectra were recorded on a Bruker Avance 400 at 400 MHz. ^{13}C NMR spectra were recorded either on a Bruker Avance 400 or on a Bruker Avance 500, respectively at 100 or 125 MHz. Chemical shifts are reported in ppm (parts per million) relative to the residual signal of the solvent in which the spectrum was recorded [^{1}H: δ(d_6-DMSO) = 2.50 ppm, $\delta(CDCl_3)$ = 7.26 ppm, $\delta(CD_3OD)$ = 3.31 ppm; ^{13}C: δ(d_6-DMSO) = 39.5 ppm, $\delta(CDCl_3)$ = 77.2 ppm, $\delta(CD_3OD)$ = 49.0 ppm]. Coupling constants are reported in Hertz (Hz). Liquid chromatography purifications were performed on a Grace Reveleris X1 apparatus, using Grace Resolv silica gel cartridges (40 µm). HRMS analyses were obtained from the Mass Spectrometry Service, ICOA, at the University of Orléans, France, using a HRMS Q-Tof MaXis spectrometer. Compounds **1**–**3** were purchased from commercial sources.

3. General procedures

General method I (2-H/Me 9-arylpurines 4–13 and 15–18). To a solution of a pyrimidine (1 equiv) in anhydrous dioxane (2 mL/mmol) under argon atmosphere, an aniline derivative (1 equiv) and PTSA.H_2O (0.5 equiv) were added successively, and the solution was refluxed for 16 h. After cooling, a 0.2 M solution of a dimethyliminium chloride (2 equiv) in anhydrous DMF, was then added dropwise and the resulting mixture was stirred at room temperature for another 30 minutes. The solution was diluted in CH_2Cl_2 (5 mL/mmol) and washed with a saturated aqueous solution of $NaHCO_3$ (5 mL/mmol). The aqueous layer was extracted 3 times with CH_2Cl_2 and the resulting organic layer was then dried over $MgSO_4$. After concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel to afford the compound.

General method II (2-amino 9-arylpurines 19 and 20). To a solution of pyrimidine (1 equiv) in anhydrous dioxane (2 mL/mmol) under argon atmosphere, an aniline derivative (1 equiv) and PTSA.H_2O (0.5 equiv) were added successively, and the solution was refluxed for 6 h. After cooling, a 0.2 M solution of a dimethyliminium chloride (3 equiv) in anhydrous DMF was then added dropwise and the resulting mixture was stirred for another 1 h. Water (5 mL/mmol) was then slowly added and the resulting mixture was stirred at room temperature for 18 h. The solution was diluted in AcOEt (5 mL/mmol) and washed with a saturated aqueous solution of $NaHCO_3$ (5 mL/mmol). The aqueous layer was extracted 3 times with AcOEt and the resulting organic layer was then dried over $MgSO_4$. After concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel to afford the compound.

General method III (2,6-dichloro 9-arylpurines 21–23). To a solution of pyrimidine **S1** (1.2 equiv) in anhydrous DMF (10 mL/mmol), an aniline derivative (1 equiv) and PTSA.H_2O or benzenesulfonic acid (1 equiv) were added successively, and the solution was stirred at room temperature for 72 h. The solution was diluted in AcOEt (5 mL/mmol) and washed with a saturated aqueous solution of $NaHCO_3$ (5 mL/mmol). The resulting organic layer was then dried over $MgSO_4$. After concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel to afford the compound.

General method IV (9-alkylpurines 24–27). To a solution of pyrimidine (1 equiv) in butan-1-ol (2 mL/mmol), an aniline derivative (1 equiv) and DIPEA (2 equiv) were added successively, and the solution was refluxed for 16 h. After cooling, the mixture was concentrated under reduced pressure. A 0.2 M solution of a dimethyliminium chloride (2 equiv) in anhydrous DMF was then added dropwise and the resulting mixture was stirred for another 2 h at 40 °C. The solution was diluted in CH_2Cl_2 or AcOEt (5 mL/mmol) and washed with a saturated aqueous solution of $NaHCO_3$ (5 mL/mmol). The aqueous layer was extracted 3 times with CH_2Cl_2 or AcOEt and the resulting organic layer was then

dried over $MgSO_4$. After concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel to afford the compound.

General method V (8-alkyl-9-arylpurine 28 and 8-aryl-9-arylpurines 29 and 32). Preparation of solution **A**: To a solution of the corresponding pyrimidine (1 equiv) in anhydrous dioxane (2 mL/mmol) under argon atmosphere, were successively added 4-bromoaniline (1 equiv) and PTSA.H_2O (1 equiv). The solution was stirred at reflux for 16 h and then concentrated under reduced pressure. The residue was diluted in AcOEt (5 mL/mmol) and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted 3 times with AcOEt and the resulting organic layer was then dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was solubilized in anhydrous 1,2-dimethoxyethane (10 mL/mmol) to give solution **A**.

Preparation of solution **B**: To a solution of the corresponding amide (3 equiv) in dry 1,2-dichloroethane (4 mL/mmol) under argon atmosphere, was added oxalyl chloride (3 equiv) and the resulting mixture was stirred at 35 °C for 2 h to give solution **B**.

Solution **A** was then added dropwise to solution **B** at 35 °C. The resulting mixture was stirred 2 h at 35 °C followed by 2 h at reflux and then diluted with CH_2Cl_2 (5 mL/mmol) and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted 3 times with CH_2Cl_2 and the resulting organic layer was then dried over $MgSO_4$ then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the compound.

General method VI (ribonucleosides 36–38). To a solution of the corresponding amidine (1 equiv) in anhydrous 1,2-dichloroethane (10 mL/mmol) under argon atmosphere, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (1 equiv) and TMSOTf (1 equiv) were added successively, and the resulting mixture was refluxed for 16 h. After cooling, the solution was diluted in CH_2Cl_2 (20 mL/mmol) and washed with a saturated aqueous solution of $NaHCO_3$ (20 mL/mmol). The aqueous layer was extracted three times with CH_2Cl_2 and the resulting organic layer was then dried over $MgSO_4$. After concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel to afford the compound.

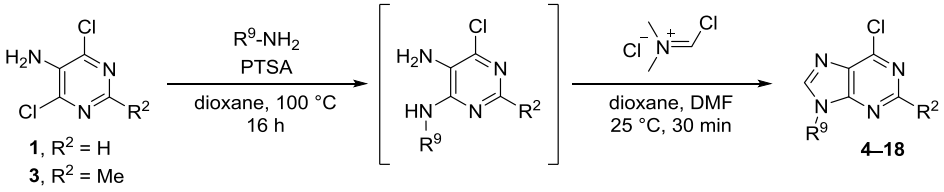
4. Detailed higher scale example

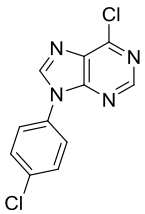
9-(4-Bromophenyl)-6-chloro-8-phenyl-9*H*-purine (29). Preparation of solution **A**: To a solution of 5-amino-4,6-dichloropyrimidine (1.00 g, 6.10 mmol) in anhydrous dioxane (12 mL) under argon atmosphere, were successively added 4-bromoaniline (1.05 g, 6.10 mmol) and PTSA.H_2O (580 mg, 3.05 mmol). The solution was stirred at reflux for 16 h and then concentrated under reduced pressure. The residue was diluted in AcOEt (100 mL) and washed with a saturated aqueous solution of $NaHCO_3$.

The aqueous layer was extracted 3 times with AcOEt and the resulting organic layer was then dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was solubilized in anhydrous 1,2-dimethoxyethane (45 mL) to give solution **A**. Preparation of solution **B**: To a solution of *N*,*N*-dimethylbenzamide (1.82 g, 12.2 mmol) in dry 1,2-dichloroethane (12 mL) under argon atmosphere, was added oxalyl chloride (1.55 g, 12.2 mmol) and the resulting mixture was stirred at 35 °C for 2 h to give solution **B**. Solution **A** was then added dropwise to solution **B** at 35 °C. The resulting mixture was stirred 2 h at 35 °C followed by 2 h at reflux and then diluted with CH_2Cl_2 (30 mL) and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted 3 times with CH_2Cl_2 and the resulting organic layer was then dried over $MgSO_4$ then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **29** (1.64 g, 70%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H, CH_{ar}), 7.71–7.57 (m, 4H, 4 CH_{ar}), 7.52–7.43 (m, 1H, CH_{ar}), 7.43–7.34 (m, 2H, 2 CH_{ar}), 7.30–7.17 (m, 2H, 2 CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9 (C_q), 154.1 (C_q), 152.4 (CH_{ar}), 150.8 (C_q), 133.5 (C_q), 133.3 (CH_{ar}), 131.8 (C_q), 131.3 (CH_{ar}), 129.9 (CH_{ar}), 128.9 (CH_{ar}), 128.1 (C_q), 123.8 (C_q). HRMS (ESI) calc. for $C_{17}H_{11}BrClN_4$ $[M + H]^+$ 384.9850, found 384.9853.

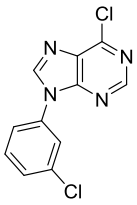
5. Synthesis and characterization

5.1. Preparation of 9-arylpurines 4–18

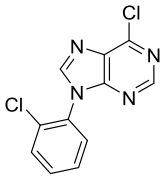




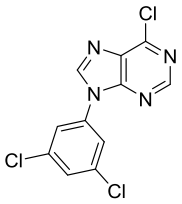
6-Chloro-9-(4-chlorophenyl)-9*H*-purine (4). This compound was synthesized through general method I from 5-amino-4,6-dichloropyrimidine, 4-chloroaniline and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **4** (139 mg, 86%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H, CH_{ar}), 8.39 (s, 1H, CH_{ar}), 7.71–7.67 (m, 2H, 2 CH_{ar}), 7.61–7.57 (m, 2H, 2 CH_{ar}). ^{13}C NMR (400 MHz, $CDCl_3$) δ 152.9 (CH_{ar}), 152.1 (C_q), 151.5 (C_q), 143.8 (CH_{ar}), 135.1 (C_q), 132.5 (C_q), 132.3 (C_q), 130.5 (CH_{ar}), 124.9 (CH_{ar}). HRMS (ESI) calc. for $C_{11}H_7Cl_2N_4$ $[M + H]^+$ 265.0042, found 265.0039.



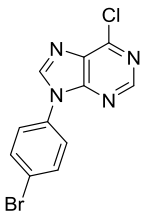
6-Chloro-9-(3-chlorophenyl)-9*H*-purine (5). This compound was synthesized through general method I from 5-amino-4,6-dichloropyrimidine, 3-chloroaniline and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **5** (136 mg, 84%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H, CH_{ar}), 8.41 (s, 1H, CH_{ar}), 7.79 (t, 1H, J = 2.0 Hz, CH_{ar}), 7.66–7.63 (m, 1H, CH_{ar}), 7.54 (t, 1H, J = 8.0 Hz, CH_{ar}), 7.50–7.47 (m, 1H, CH_{ar}). ^{13}C NMR (400 MHz, $CDCl_3$) δ 153.0 (CH_{ar}), 152.1 (C_q), 151.5 (C_q), 143.7 (CH_{ar}), 136.0 (C_q), 135.1 (C_q), 132.3 (C_q), 131.3 (CH_{ar}), 129.3 (CH_{ar}), 123.9 (CH_{ar}), 121.6 (CH_{ar}). HRMS (ESI) calc. for $C_{11}H_7Cl_2N_4$ $[M + H]^+$ 265.0042, found 265.0042.



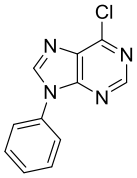
6-Chloro-9-(2-chlorophenyl)-9*H*-purine (6). This compound was synthesized through general method I from 5-amino-4,6-dichloropyrimidine, 2-chloroaniline and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **6** (36 mg, 22%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H, CH_{ar}), 8.29 (s, 1H, CH_{ar}), 7.67–7.64 (m, 1H, CH_{ar}), 7.56–7.50 (m, 3H, 3 CH_{ar}). ^{13}C NMR (400 MHz, $CDCl_3$) δ 153.0 (CH_{ar}), 152.3 (C_q), 151.9 (C_q), 145.4 (CH_{ar}), 131.5 (CH_{ar}), 131.5 (C_q), 131.4 (C_q), 131.2 (CH_{ar}), 131.1 (C_q), 129.1 (CH_{ar}), 128.4 (CH_{ar}). HRMS (ESI) calc. for $C_{11}H_7Cl_2N_4$ $[M + H]^+$ 265.0042, found 265.0042.



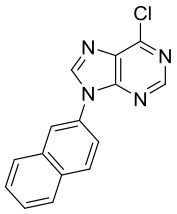
6-Chloro-9-(3,5-dichlorophenyl)-9*H*-purine (7). This compound was synthesized through general method I from 5-amino-4,6-dichloropyrimidine, 3,5-dichloroaniline, and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **7** (146 mg, 80%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H, CH_{ar}), 8.41 (s, 1H, CH_{ar}), 7.74 (d, 2H, *J* = 1.8 Hz, 2 CH_{ar}), 7.51 (t, 1H, *J* = 1.8 Hz, CH_{ar}). ^{13}C NMR (400 MHz, $CDCl_3$) δ 153.2 (CH_{ar}), 152.4 (C_q), 151.3 (C_q), 143.2 (CH_{ar}), 136.7 (C_q), 135.7 (C_q), 132.4 (C_q), 129.2 (CH_{ar}), 121.8 (CH_{ar}). HRMS (ESI) calc. for $C_{11}H_6Cl_3N_4$ $[M + H]^+$ 298.9653, found 298.9650.



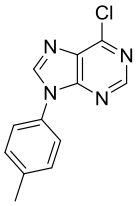
9-(4-Bromophenyl)-6-chloro-9*H*-purine (8). This compound was synthesized through general method I from 5-amino-4,6-dichloropyrimidine, 4-bromoaniline and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent CH_2Cl_2/MeOH) to afford compound **8** (177 mg, 94%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H, CH_{ar}), 8.39 (s, 1H, CH_{ar}), 7.77–7.73 (m, 2H, 2 CH_{ar}), 7.65–7.62 (m, 2H, 2 CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9 (CH_{ar}), 152.1 (C_q), 151.5 (C_q), 143.7 (CH_{ar}), 133.4 (CH_{ar}), 133.1 (C_q), 132.3 (C_q), 125.1 (CH_{ar}), 123.0 (C_q). HRMS (ESI) calc. for $C_{11}H_7BrClN_4$ $[M + H]^+$ 308.9537, found 308.9539.



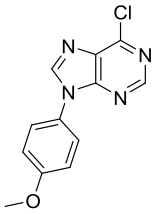
6-Chloro-9-phenyl-9*H*-purine (9). This compound was synthesized through general method I from 5-amino-4,6-dichloropyrimidine, aniline and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent CH_2Cl_2/MeOH) to afford compound **9** (114 mg, 81%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H, CH_{ar}), 8.41 (s, 1H, CH_{ar}), 7.72–7.69 (m, 2H, 2 CH_{ar}), 7.62–7.58 (m, 2H, 2 CH_{ar}), 7.53–7.49 (m, 1H, CH_{ar}). ^{13}C NMR (400 MHz, $CDCl_3$) δ 152.8 (CH_{ar}), 151.8 (C_q), 151.6 (C_q), 144.3 (CH_{ar}), 134.0 (C_q), 132.3 (C_q), 130.2 (CH_{ar}), 129.1 (CH_{ar}), 123.7 (CH_{ar}). HRMS (ESI) calc. for $C_{11}H_8ClN_4$ $[M + H]^+$ 231.0432, found 231.0431.



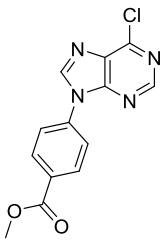
6-Chloro-9-(naphthalen-2-yl)-9*H*-purine (10). This compound was synthesized through general method I from 5-amino-4,6-dichloropyrimidine, 2-naphthylamine and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent CH_2Cl_2/MeOH) to afford compound **10** (147 mg, 86%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H, CH_{ar}), 8.52 (s, 1H, CH_{ar}), 8.18 (d, 1H, J = 2.1 Hz, CH_{ar}), 8.07 (d, 1H, J = 8.8 Hz, CH_{ar}), 7.97–7.93 (m, 2H, 2 CH_{ar}), 7.81 (dd, 1H, J = 8.8 Hz, 2.1 Hz, CH_{ar}), 7.63–7.58 (m, 2H, 2 CH_{ar}). ^{13}C NMR (400 MHz, $CDCl_3$) δ 152.8 (CH_{ar}), 151.9 (C_q), 151.8 (C_q), 144.4 (CH_{ar}), 133.5 (C_q), 132.9 (C_q), 132.3 (C_q), 131.4 (C_q), 130.4 (CH_{ar}), 128.3 (CH_{ar}), 128.1 (CH_{ar}), 127.7 (CH_{ar}), 127.5 (CH_{ar}), 122.3 (CH_{ar}), 121.4 (CH_{ar}). HRMS (ESI) calc. for $C_{15}H_{10}ClN_4$ $[M + H]^+$ 281.0589, found 281.0590.



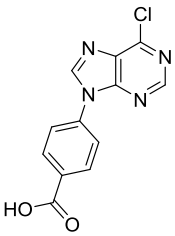
6-Chloro-9-(4-methylphenyl)-9*H*-purine (11). This compound was synthesized through general method I from 5-amino-4,6-dichloropyrimidine, 4-methylaniline and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **11** (127 mg, 85%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H, CH_{ar}), 8.37 (s, 1H, CH_{ar}), 7.60–7.55 (m, 2H, 2 CH_{ar}), 7.44–7.37 (m, 2H, 2 CH_{ar}), 2.46 (CH_3). ^{13}C NMR (400 MHz, $CDCl_3$) δ 152.8 (CH_{ar}), 151.8 (C_q), 151.7 (C), 144.4 (CH_{ar}), 139.5 (C_q), 132.2 (C_q), 131.5 (C_q), 130.8 (CH_{ar}), 123.7 (CH_{ar}), 21.3 (CH_3). HRMS (ESI) calc. for $C_{12}H_{10}ClN_4$ $[M + H]^+$ 245.0589, found 245.0590.



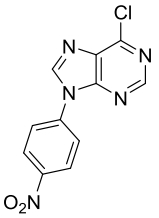
6-Chloro-9-(4-methoxyphenyl)-9*H*-purine (12). This compound was synthesized through general method I from 5-amino-4,6-dichloropyrimidine, 4-methoxyaniline and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **12** (132 mg, 83%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H, CH_{ar}), 8.33 (s, 1H, CH_{ar}), 7.59–7.54 (m, 2H, 2 CH_{ar}), 7.12–7.07 (m, 2H, 2 CH_{ar}), 3.89 (CH_3). ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.1 (C_q), 152.7 (CH_{ar}), 151.8 (C_q), 151.7 (C_q), 144.6 (CH_{ar}), 132.1 (C_q), 126.7 (C_q), 125.5 (CH_{ar}), 115.4 (CH_{ar}), 55.8 (CH_3). HRMS (ESI) calc. for $C_{12}H_{10}ClN_4O$ $[M + H]^+$ 261.0538, found 261.0536.



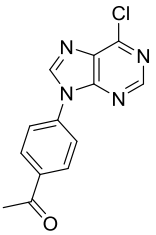
Methyl 4-(6-chloro-9*H*-purin-9-yl)benzoate (13). This compound was synthesized through general method I from 5-amino-4,6-dichloropyrimidine, methyl 4-aminobenzoate and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **13** (141 mg, 80%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H, CH_{ar}), 8.48 (s, 1H, CH_{ar}), 8.30–8.27 (m, 2H, 2 CH_{ar}), 7.91–7.88 (m, 2H, 2 CH_{ar}), 3.98 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (C_q) 153.0 (CH_{ar}), 152.2 (C_q), 151.5 (C_q), 143.6 (CH_{ar}), 137.8 (C_q), 132.5 (C_q), 131.7 (CH_{ar}), 130.5 (C_q), 123.0 (CH_{ar}), 52.7 (CH_3). HRMS (ESI) calc. for $C_{13}H_{10}ClN_4O_2$ $[M + H]^+$ 289.0487, found 289.0489.



4-(6-Chloro-9*H*-purin-9-yl)benzoic acid (14). To a solution of 5-amino-4,6-dichloropyrimidine (100 mg, 0.61 mmol) in anhydrous dioxane (1.25 mL/mmol) under argon atmosphere, 4-aminobenzoic acid (84 mg, 0.61 mmol) and PTSA.H_2O (58 mg, 0.31 mmol) were added successively, and the solution was refluxed for 16 h. After cooling, the mixture was filtered and the resulting solid was washed with dioxane. 4.5 mL of a 0.2 M solution of (chloromethylene)dimethyliminium chloride (115 mg, 0.9 mmol) in anhydrous DMF was then added dropwise to the solid under argon atmosphere and the resulting mixture was stirred for 30 minutes. Water (300 µL) was added and the resulted mixture was concentrated under reduced pressure. The resulting solid was washed with water and dried to afford compound **14** (120 mg, 72%) as a white solid. ^{1}H NMR (400 MHz, *d*$_6$-DMSO) δ 13.26 (bs, 1H, CO_2H) 9.22 (s, 1H, CH_{ar}), 8.89 (s, 1H, CH_{ar}), 8.22–8.14 (m, 2H, 2 CH_{ar}), 8.14–8.07 (m, 2H, 2 CH_{ar}). ^{13}C NMR (100 MHz, *d*$_6$-DMSO) δ 166.5 (C_q) 152.3 (CH_{ar}), 151.4 (C_q), 149.8 (C_q), 146.1 (CH_{ar}), 137.6 (C_q), 131.7 (C_q), 130.7 (CH_{ar}), 130.3 (C_q), 123.1 (CH_{ar}). HRMS (ESI) calc. for $C_{12}H_8ClN_4O_2$ $[M + H]^+$ 275.0330, found 275.0326.

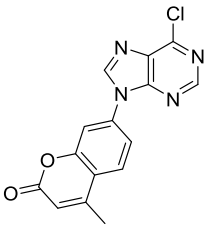


6-Chloro-9-(4-nitrophenyl)-9*H*-purine (15). This compound was synthesized through general method I from 5-amino-4,6-dichloropyrimidine, 4-nitroaniline and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent toluene/AcOEt) to afford compound **15** (106 mg, 63%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H, CH_{ar}), 8.52 (s, 1H, CH_{ar}), 8.51–8.48 (m, 2H, 2 CH_{ar}), 8.11–8.07 (m, 2H, 2 CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3 (CH_{ar}), 152.6 (C_q), 151.4 (C_q), 147.3 (C_q), 143.0 (CH_{ar}), 139.3 (C_q), 132.7 (C_q), 125.8 (CH_{ar}), 123.5 (CH_{ar}). HRMS (ESI) calc. for $C_{11}H_7ClN_5O_2$ $[M + H]^+$ 276.0283, found 276.0282.

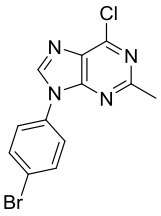


1-(4-(6-Chloro-9*H*-purin-9-yl)phenyl) ethyl ketone (16). This compound was synthesized through general method I from 5-amino-4,6-dichloropyrimidine, 4'-aminoacetophenone and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent CH_2Cl_2/MeOH) to afford compound **16**

(90 mg, 54%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H, CH_{ar}), 8.49 (s, 1H, CH_{ar}), 8.20–8.18 (m, 2H, 2 CH_{ar}), 7.93–7.91 (m, 2H, 2 CH_{ar}), 2.67 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6 (CO), 153.0 (CH_{ar}), 152.2 (C_q), 151.5 (C_q), 143.5 (CH_{ar}), 137.8 (C_q), 137.0 (C_q), 132.5 (C_q), 130.3 (CH_{ar}), 123.1 (CH_{ar}), 26.8 (CH_3). HRMS (ESI) calc. for $C_{13}H_{10}ClN_4O$ $[M + H]^+$ 273.0538, found 273.0536.

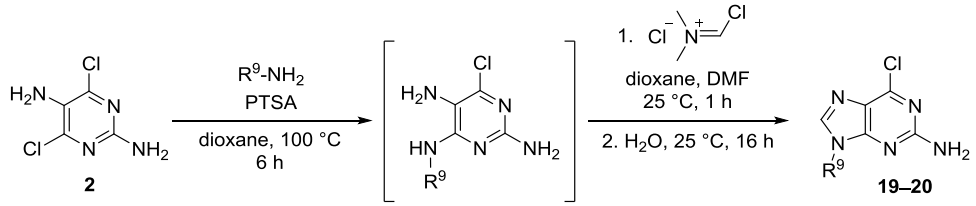


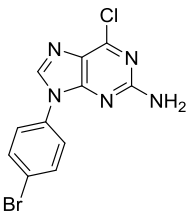
7-(6-Chloro-9*H*-purin-9-yl)-4-methyl-2*H*-chromen-2-one (17). This compound was synthesized through general method I from 5-amino-4,6-dichloropyrimidine, 7-amino-4-methylcoumarin and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent CH_2Cl_2/MeOH) to afford compound **17** (110 mg, 58%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H, CH_{ar}), 8.50 (s, 1H, CH_{ar}), 7.86 (d, 1H, *J* = 2.1 Hz, CH_{ar}), 7.84 (d, 1H, *J* = 8.5 Hz, CH_{ar}), 7.77 (dd, 1H, *J* = 8.5 Hz, 2.1 Hz, CH_{ar}), 6.40 (d, 1H, *J* = 1.2 Hz, CH_{ar}), 2.52 (d, 3H, *J* = 1.2 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9 (CO), 154.5 (C_q), 153.2 (CH_{ar}), 152.4 (C_q), 151.5 (C_q), 151.5 (C_q), 143.3 (CH_{ar}), 136.6 (C_q), 132.6 (C_q), 126.5 (CH_{ar}), 120.2 (C_q), 118.6 (CH_{ar}), 116.2 (CH_{ar}), 111.7 (CH_{ar}), 18.9 (CH_3). HRMS (ESI) calc. for $C_{15}H_{10}ClN_4O_2$ $[M + H]^+$ 313.0487, found 313.0487.



9-(4-Bromophenyl)-6-chloro-2-methyl-9*H*-purine (18). This compound was synthesized through general method I from 5-amino-4,6-dichloro-2-methylpyrimidine, 4-bromoaniline and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **18** (145 mg, 80%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H, CH_{ar}), 7.74–7.72 (m, 2H, 2 CH_{ar}), 7.64–7.61 (m, 2H, 2 CH_{ar}), 2.80 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.7 (C_q), 152.0 (C_q), 151.4 (C_q), 143.1 (CH_{ar}), 133.3 (CH_{ar}), 133.3 (C_q), 130.0 (C_q), 125.1 (CH_{ar}), 122.7 (C_q), 26.0 (CH_3). HRMS (ESI) calc. for $C_{12}H_9BrClN_4$ $[M + H]^+$ 322.9694, found 322.9693.

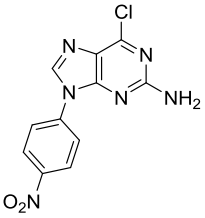
5.2. Preparation of 2-amino-9-arylpurines 19–20





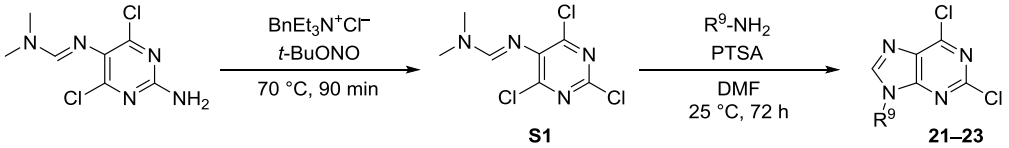
9-(4-Bromophenyl)-6-chloro-9*H*-purin-2-amine (19). This compound was synthesized through general method II from 2,5-diamino-4,6-dichloropyrimidine, 4-bromoaniline and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent toluene/AcOEt) to afford compound **19**

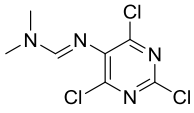
(151 mg, 83%) as an off-white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.54 (s, 1H, CH_{ar}), 7.85–7.75 (m, 4H, 4 CH_{ar}), 7.07 (bs, 2H, NH_2). ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.2 (C_q), 153.5 (C_q), 150.0 (C_q), 141.6 (CH_{ar}), 134.0 (C_q), 132.3 (CH_{ar}), 125.2 (CH_{ar}), 123.7 (C_q), 120.4 (C_q). HRMS (ESI) calc. for $C_{11}H_8BrClN_5$ $[M + H]^+$ 323.9646, found 323.9646.



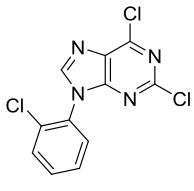
6-Chloro-9-(4-nitrophenyl)-9*H*-purin-2-amine (20). This compound was synthesized through general method II from 2,5-diamino-4,6-dichloropyrimidine, 4-nitroaniline and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent toluene/AcOEt) to afford compound **20** (111 mg, 68%) as a yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.72 (s, 1H, CH_{ar}), 8.45–8.42 (m, 2H, 2 CH_{ar}), 8.26–8.22 (m, 2H, 2 CH_{ar}), 7.18 (bs, 2H, NH_2). ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.3 (C_q), 153.5 (C_q), 150.3 (C_q), 145.7 (C_q), 141.2 (CH_{ar}), 140.1 (C_q), 124.9 (CH_{ar}), 123.9 (C_q), 123.1 (CH_{ar}). HRMS (ESI) calc. for $C_{11}H_8ClN_6O_2$ $[M + H]^+$ 291.0392, found 291.0390.

5.3. Preparation of 2-chloro-9-arylpurines 21–23 and intermediate S1



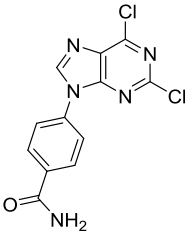


***N'*-(2,4,6-Trichloropyrimidin-5-yl)-*N*,*N*-dimethylformamidine (S1).** To a suspension of *N*'-(2-amino-4,6-dichloropyrimidin-5-yl)-*N*,*N*-dimethylformamidine (1.5 g, 6.4 mmol) and benzyltriethylammonium chloride (6.6 g, 28.9 mmol) in 1,2-dichloroethane (50 mL), *tert*-butyl nitrite (7.7 mL, 64 mmol) was added, and the mixture was heated at 70 °C under argon atmosphere for 90 minutes. After cooling, the solution was concentrated under reduced pressure, and the residue was taken up in CH_2Cl_2 and water. The organic layer was washed twice with water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **S1** (0.70 g, 44%) as a yellowish solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.87 (s, 1H), 3.06 (s, 3H), 2.99 (s, 3H). ^{13}C NMR (125 MHz, d_6-DMSO) δ 156.7 (CH), 153.8 (C_q), 147.0 (C_q), 141.2 (C_q), 39.8 (CH_3), 33.7 (CH_3). HRMS (ESI) calc. for $C_7H_8Cl_3N_4$ $[M + H]^+$ 252.9809, found 252.9809.

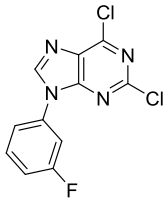


2,6-Dichloro-9-(2-chlorophenyl)-9*H*-purine (21). This compound was synthesized through general method III from 2-chloroaniline with slightly modified conditions (2.4 equiv of 2-chloroaniline were added, and the solution was heated to 50 °C for 48 h), and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **21** (67 mg, 56%) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ

9.01 (s, 1H, CH_{ar}), 7.85–7.77 (m, 2H, 2 CH_{ar}), 7.72–7.63 (m, 2H, 2 CH_{ar}). ^{13}C NMR (100 MHz, d_6-DMSO) δ 153.8 (C_q), 151.9 (C_q), 150.3 (C_q), 148.3 (CH_{ar}), 132.0 (CH_{ar}), 130.5 (C_q), 130.4 (CH_{ar}), 130.4 (C_q), 130.3 (C_q), 130.0 (CH_{ar}), 128.6 (CH_{ar}). HRMS (ESI) calc. for $C_{11}H_6Cl_3N_4$ $[M + H]^+$ 298.9653, found 298.9653.

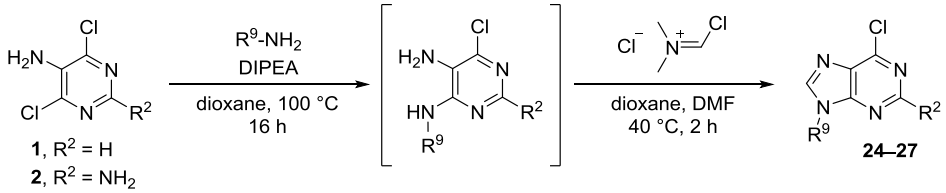


4-(2,6-Dichloro-9*H*-purin-9-yl)benzamide (22). This compound was synthesized through general method III from 4-aminobenzamide, and was purified by flash chromatography on silica gel (eluent CH_2Cl_2/MeOH) to afford compound **22** (42 mg, 86%) as a white solid. ^1H NMR (400 MHz, d_6-DMSO) δ 9.19 (s, 1H), 8.13–8.11 (m, 3H, 2 CH_{ar} + NH), 7.96–7.94 (m, 2H, 2 CH_{ar}), 7.55 (bs, 1H, NH). ^{13}C NMR (100 MHz, d_6-DMSO) δ 166.8 (CO), 152.9 (C_q), 151.7 (C_q), 150.2 (C_q), 147.1 (CH_{ar}), 135.8 (C_q), 134.3 (C_q), 131.3 (C_q), 128.9 (CH_{ar}), 123.3 (CH_{ar}). HRMS (ESI) calc. for $C_{12}H_8Cl_2N_5O$ $[M + H]^+$ 308.0100, found 308.0100.

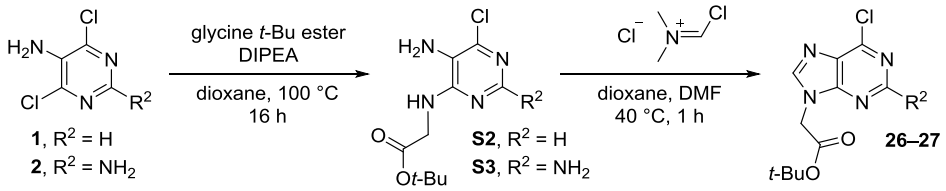


2,6-Dichloro-9-(3-fluorophenyl)-9*H*-purine (23). This compound was synthesized through general method III from 3-fluoroaniline, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **23** (43 mg, 95%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H, CH_{ar}), 7.64-7.55 (m, 1H, CH_{ar}), 7.54-7.45 (m, 2H, 2 CH_{ar}), 7.28-7.20 (m, 1H, CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (d, $J_{C,F}$ = 250.0 Hz, CF), 154.2 (C_q), 152.8 (C_q), 152.6 (C_q), 144.4 (CH_{ar}), 134.8 (d, $J_{C,F}$ = 10.1 Hz, C_q), 132.3 (d, $J_{C,F}$ = 9.1 Hz, CH_{ar}), 131.5 (C_q), 119.1 (d, $J_{C,F}$ = 3.4 Hz, CH_{ar}), 116.4 (d, $J_{C,F}$ = 21.1 Hz, CH_{ar}), 111.4 (d, $J_{C,F}$ = 25.5 Hz, CH_{ar}). HRMS (ESI) calc. for $C_{11}H_6Cl_2FN_4$ $[M + H]^+$ 282.9948, found 282.9947.

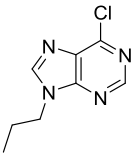
5.4. Preparation of 9-alkylpurines 24–27 and intermediates S2–S3



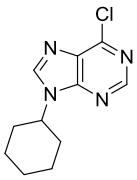
Alternative two-steps preparation of esters **26** and **27**



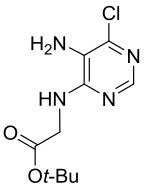
6-Chloro-9-propyl-9*H*-purine (24). This compound was synthesized through general method IV from 5-amino-4,6-dichloropyrimidine, propylamine and (chloromethylene)dimethyliminium chloride,



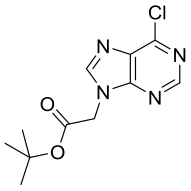
and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **24** (82 mg, 68%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H, CH_{ar}), 8.12 (s, 1H, CH_{ar}), 4.27 (t, 2H, *J* = 7.3 Hz, N*CH*$_2$), 1.96 (st, 2H, *J* = 7.3 Hz, *CH*$_2$CH$_3$), 0.98 (t, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0 (CH_{ar}, C_q), 151.2 (C_q), 145.3 (CH_{ar}), 131.8 (C_q), 46.3 (CH_2), 23.4 (CH_2), 11.3 (CH_3). HRMS (ESI) calc. for $C_8H_{10}ClN_4$ $[M + H]^+$ 197.0589, found 197.0589.



6-Chloro-9-cyclohexyl-9*H*-purine (25). This compound was synthesized through general method IV from 5-amino-4,6-dichloropyrimidine, cyclohexylamine and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent CH_2Cl_2/MeOH) to afford compound **25** (92 mg, 64%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H, CH_{ar}), 8.17 (s, 1H, CH_{ar}), 4.52 (tt, 1H, *J* = 12.0 Hz, 3.8 Hz, *c*-Hex), 2.19 (m, 2H, *c*-Hex), 1.96 (m, 2H, *c*-Hex), 1.83 (m, 3H, *c*-Hex), 1.52 (m, 2H, *c*-Hex), 1.32 (ddt, 1H, *J* = 16.7 Hz, 13.0 Hz, 6.5 Hz, *c*-Hex). ^{13}C NMR (400 MHz, $CDCl_3$) δ 151.7 (CH_{ar}), 151.6 (C_q), 151.1 (C_q), 143.3 (CH_{ar}), 131.9 (C_q), 55.5 (CH), 33.2 (CH_2), 25.6 (CH_2), 25.2 (CH_2). HRMS (ESI) calc. for $C_{11}H_{14}ClN_4$ $[M + H]^+$ 237.0902, found 237.0900.

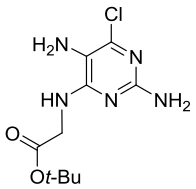


***Tert*-butyl (5-amino-6-chloropyrimidin-4-yl)glycinate (S2).** DIPEA (621 µL, 3.66 mmol) was added to a solution of 5-amino-4,6-dichloropyrimidine (100 mg, 0.61 mmol) and glycine *tert*-butyl ester hydrochloride (410 mg, 2.44 mmol) in butan-1-ol (1.5 mL). The resulting mixture was stirred at reflux for 8 h and then diluted in CH_2Cl_2 (3 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (3 mL). The aqueous layer was extracted 3 times with CH_2Cl_2 and the resulting organic layer was then dried over $MgSO_4$. After concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel (eluent AcOEt/cyclohexane) to afford compound **S2** (148 mg, 94%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H, CH_{ar}), 5.53 (bs, 1H, NH), 4.15 (s, 2H, *J* = 5.0 Hz, CH_2), 1.50 (s, 9H, 3 CH_3). ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.7 (C_q), 154.9 (C_q), 154.3 (C_q), 149.1 (CH_{ar}), 122.6 (C_q), 82.8 (C_q), 44.1 (CH_2), 28.2 (CH_3). HRMS (ESI) calc. for $C_{10}H_{16}ClN_4O_2$ $[M + H]^+$ 259.0956, found 259.0955.

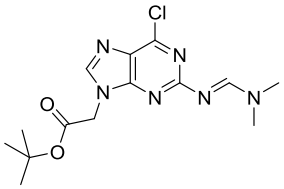


***Tert*-butyl 2-(6-chloro-9*H*-purin-9-yl)acetate (26).** This compound was synthesized through general method IV from 5-amino-4,6-dichloropyrimidine, glycine *tert*-butyl ester hydrochloride and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **24** (60 mg, 38%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H, CH_{ar}), 8.19 (s, 1H, CH), 4.95 (s, 2H, CH_2), 1.47 (s, 9H, 3 CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (C_q), 152.3 (CH_{ar}), 152.1 (C_q), 151.3 (C_q), 145.8 (CH_{ar}), 131.3 (C_q), 84.3 (C_q), 45.4 (CH_2), 28.1 (CH_3). HRMS (ESI) calc. for $C_{11}H_{14}ClN_4O_2$ $[M + H]^+$ 269.0800, found 269.0801.

Alternative preparation of 26 from S2. (Chloromethylene)dimethyliminium chloride (100 mg, 0.78 mmol) was added to a solution of pyrimidine **S2** (100 mg, 0.39 mmol) in dry DMF and the resulting solution was stirred under argon atmosphere at 40 °C for 2 h. The solution was then diluted in CH_2Cl_2 (2 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 mL). The aqueous layer was extracted 3 times with CH_2Cl_2 and the resulting organic layer was then dried over $MgSO_4$. After concentration under reduced pressure, compound **26** (108 mg**,** 100%) was obtained as a brown solid.



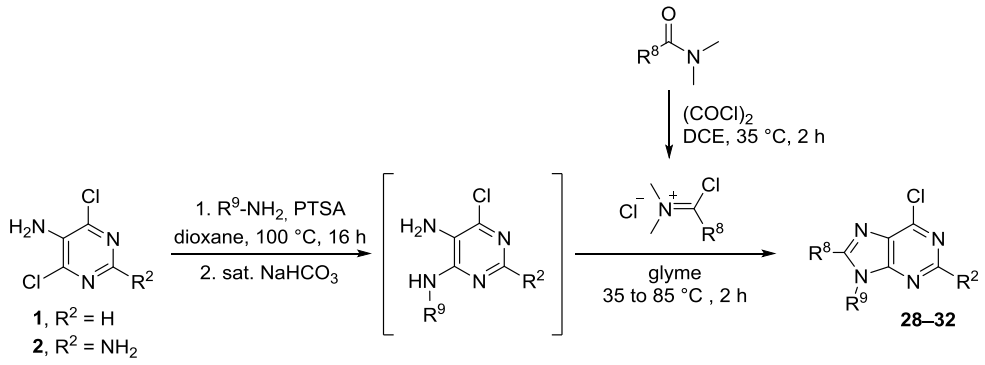
***Tert*-butyl (2,5-diamino-6-chloropyrimidin-4-yl)glycinate (S3)** DIPEA (570 µL, 3.36 mmol) was added to a solution of 2,5-amino-4,6-dichloropyrimidine (100 mg, 0.56 mmol) and glycine *tert*-butyl ester hydrochloride (376 mg, 2.24 mmol) in butan-1-ol (1.5 mL). The resulting mixture was stirred at reflux for 16 h and then diluted in CH_2Cl_2 (3 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (3 mL). The aqueous layer was extracted 3 times with CH_2Cl_2 and the resulting organic layer was then dried over $MgSO_4$. After concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel (eluent AcOEt/cyclohexane) to afford compound **S3** (95 mg, 62%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (bs, 1H, NH), 4.70 (bs, 2H, NH_2), 4.04 (s, 2H, J = 5.1 Hz, CH_2), 2.74 (bs, 2H, NH_2), 1.47 (s, 9H, 3 CH_3). ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.7 (C_q), 158.3 (C_q), 157.4 (C_q), 147.9 (C_q), 112.3 (C_q), 82.2 (C_q), 43.7 (CH_2), 28.1 (CH_3). HRMS (ESI) calc. for $C_{10}H_{17}ClN_5O_2$ $[M + H]^+$ 274.1065, found 274.1064.

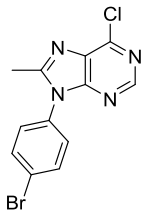


***Tert*-butyl 2-(6-chloro-2-(((dimethylamino)methylene)amino)-9*H*-purin-9-yl)acetate (27).** This compound was synthesized through general method IV from 5-amino-4,6-dichloropyrimidine, glycine *tert*-butyl ester hydrochloride and (chloromethylene)dimethyliminium chloride, and was purified by flash chromatography on silica gel (eluent CH_2Cl_2/MeOH) to afford compound **27** (37 mg, 20%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H, CH_{ar}), 7.94 (s, 1H, CH), 4.90 (s, 2H, CH_2), 3.18 (s, 6H, 2 CH_3), 1.46 (s, 9H, 3 CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2 (C_q), 162.4 (C_q), 159.1 (CH), 153.9 (C_q), 150.9 (C_q), 144.0 (CH_{ar}), 126.9 (C_q), 83.8 (C_q), 44.8 (CH_2), 41.5 (CH_3), 35.6 (CH_3), 28.1 (CH_3). HRMS (ESI) calc. for $C_{14}H_{20}ClN_6O_2$ $[M + H]^+$ 339.1331, found 339.1331.

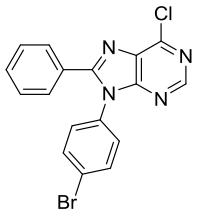
Alternative preparation of 27 from S3. (Chloromethylene)dimethyliminium chloride (141 mg, 1.1 mmol) was added to a solution of pyrimidine **S3** (100 mg, 0.35 mmol) in dry DMF and the resulting solution was stirred under argon atmosphere at 70 °C for 5 h. The solution was then diluted in CH_2Cl_2 (2 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 mL). The aqueous layer was extracted 3 times with CH_2Cl_2 and the resulting organic layer was then dried over $MgSO_4$. After concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel (eluent AcOEt/CH_2Cl_2) to afford compound **27** (100 mg, 85%) as a brown solid.

5.5. Preparation of 8-substituted 9-arylpurines 28–32

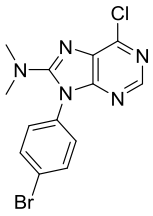




9-(4-Bromophenyl)-6-chloro-8-methyl-9*H*-purine (28). This compound was synthesized through general method V from 5-amino-4,6-dichloropyrimidine, 4-bromoaniline and *N*,*N*-dimethylacetamide, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **28** (145 mg, 74%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H, CH_{ar}), 7.78–7.74 (m, 2H, 2 CH_{ar}), 7.33–7.26 (m, 2H, 2 CH_{ar}), 2.62 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0 (C_q), 153.8 (C_q), 152.2 (CH_{ar}), 149.9 (C_q), 133.7 (CH_{ar}), 132.6 (C_q), 131.3 (C_q), 128.9 (CH_{ar}), 124.5 (C_q), 15.3 (CH_3). HRMS (ESI) calc. for $C_{12}H_9BrClN_4$ $[M + H]^+$ 322.9694, found 322.9695.

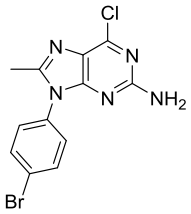


9-(4-Bromophenyl)-6-chloro-8-phenyl-9*H*-purine (29). This compound was synthesized through general method V from 5-amino-4,6-dichloropyrimidine, 4-bromoaniline and *N*,*N*-dimethylbenzamide, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **29** (183 mg, 78%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H, CH_{ar}), 7.71–7.57 (m, 4H, 4 CH_{ar}), 7.52–7.43 (m, 1H, CH_{ar}), 7.43–7.34 (m, 2H, 2 CH_{ar}), 7.30–7.17 (m, 2H, 2 CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9 (C_q), 154.1 (C_q), 152.4 (CH_{ar}), 150.8 (C_q), 133.5 (C_q), 133.3 (CH_{ar}), 131.8 (C_q), 131.3 (CH_{ar}), 129.9 (CH_{ar}), 128.9 (CH_{ar}), 128.1 (C_q), 123.8 (C_q). HRMS (ESI) calc. for $C_{17}H_{11}BrClN_4$ $[M + H]^+$ 384.9850, found 384.9853.



9-(4-Bromophenyl)-6-chloro--9*H*-purin-8-*N*,*N*-dimethylamine (30). A solution of 5-amino-4,6-dichloropyrimidine (100 mg, 0.61 mmol), 4-bromoaniline (105 mg, 0.61 mmol) and PTSA.H_2O (58 mg, 0.31 mmol) in dioxane (1.22 mL) was refluxed for 16 h. After colling, DIPEA (207 µL, 1.22 mL) was added and the solution was stirred for 5 min then concentrated under reduced pressure. The residue was solubilized in 1,2-dichloroethane (3 mL) and (dichloromethylene)dimethyliminium chloride (295 mg, 1.82 mmol) was added. The resulting mixture was refluxed for 1 h, diluted in CH_2Cl_2 (10 mL) and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted 3 times with CH_2Cl_2 and the resulting organic layer was dried over $MgSO_4$. After concentration under reduced pressure, the crude

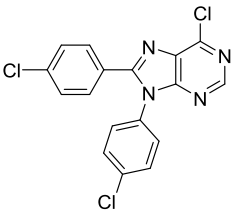
product was purified by flash chromatography on silica gel (eluent AcOEt/CH_2Cl_2) to afford compound **30** (150 mg, 77%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H, CH_{ar}), 7.74–7.69 (m, 2H, 2 CH_{ar}), 7.41–7.36 (m, 2H, 2 CH_{ar}), 2.97 (s, 6H, 2 CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6 (C_q), 154.7 (C_q), 149.5 (CH_{ar}), 144.3 (C_q), 134.2 (C_q), 133.4 (CH_{ar}), 131.4 (C_q), 128.3 (CH_{ar}), 123.4 (C_q), 40.9 (CH_3). HRMS (ESI) calc. for $C_{13}H_{12}BrClN_5$ $[M + H]^+$ 351.9959, found 351.9957.



9-(4-Bromophenyl)-6-chloro-8-methyl-9*H*-purin-2-amine (31). Preparation of solution **A**: To a solution of 2,5-amino-4,6-dichloropyrimidine (100 mg, 0.56 mmol) in anhydrous dioxane (1.13 mL) under argon atmosphere, were successively added 4-bromoaniline (97 mg, 0.56 mmol) and PTSA.H_2O (53 mg, 0.28 mmol). The solution was stirred at reflux for 6 h and then concentrated under reduced pressure. The residue was diluted in AcOEt (5 mL/mmol) and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted 3 times with AcOEt and the resulting organic layer was then dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was solubilized in anhydrous 1,2-dimethoxyethane (5.6 mL) to give solution **A**.

Preparation of solution **B**: To a solution of the *N*,*N*-dimethylacetamide (156 µL, 1,68 mmol) in dry 1,2-dichloroethane (6.7 mL) under argon atmosphere, was added oxalyl chloride (205 µL, 1.68 mmol) and the resulting mixture was stirred at 35 °C for 2 h to give solution **B**.

Solution **A** was then added dropwise to solution **B** at 35 °C. The resulting mixture was stirred 2 h at 35 °C followed by 2 h at reflux. Water (3 mL) was added and the resulting mixture was stirred for 16 h at 25 °C, then diluted with AcOEt (3 mL) and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted 3 times with AcOEt and the resulting organic layer was then dried over $MgSO_4$ then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt) to afford pure compound **31** (50 mg, 26%) as an off-white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.82–7.78 (m, 2H, 2 CH_{ar}), 7.53–7.49 (m, 2H, 2 CH_{ar}), 6.84 (bs, 2H, NH_2), 2.33 (s, 3H, CH_3). ^{13}C NMR (100 MHz, d_6-DMSO) δ 159.8 (C_q), 155.9 (C_q), 150.6 (C_q), 147.9 (C_q), 133.4 (C_q), 132.6 (CH_{ar}), 129.9 (CH_{ar}), 122.4 (C_q), 122.3 (C_q), 14.4 (CH_3). HRMS (ESI) calc. for $C_{12}H_{10}BrClN_5$ $[M + H]^+$ 337.9803, found 337.9799.

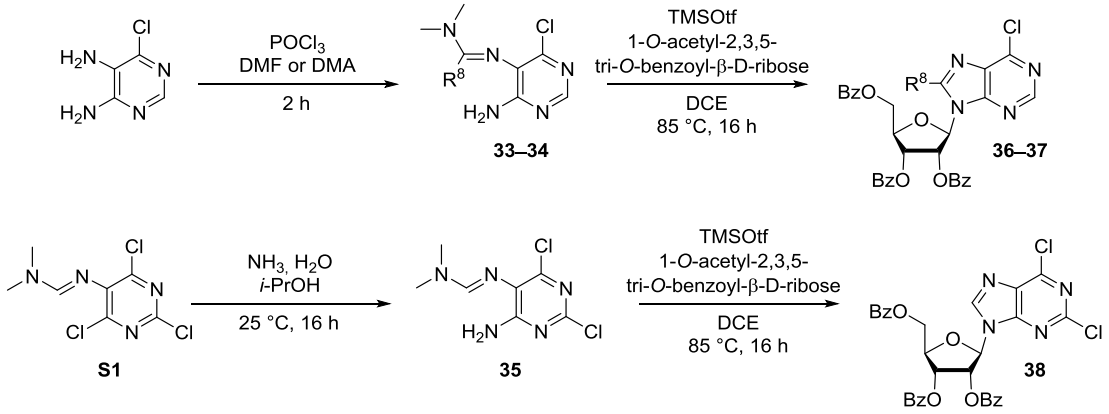


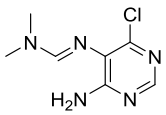
6-Chloro-8,9-bis(4-chlorophenyl)-9*H*-purine (32).[a] This compound was synthesized through general method V from 5-amino-4,6-dichloropyrimidine, 4-chloroaniline and 4-chloro-*N*,*N*-dimethylbenzamide, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **32** (66 mg, 88%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H, CH_{ar}), 7.59–7.52 (m, 4H, 4 CH_{ar}), 7.39–7.36 (m, 2H, 2 CH_{ar}), 7.32–7.28 (m, 2H, 2 CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2 (C_q), 153.7 (C_q), 152.6 (CH_{ar}), 151.0 (C_q), 137.9 (C_q), 136.1 (C_q), 132.8

(C_q), 131.8 (C_q), 131.2 (CH_{ar}), 130.5 (CH_{ar}), 129.3 (CH_{ar}), 128.7 (CH_{ar}), 126.6 (C_q). HRMS (ESI) calc. for $C_{17}H_{10}Cl_3N_4$ $[M + H]^+$ 374.9966, found 374.9965.

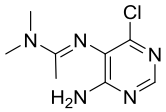
[a]The synthesis of the Vilsmeier-type reagent was adapted from Seballos-Resendiz, A.; Lechuga-Eduardo, H.; Barroso-Flores, J. Martinez-Otero, D.; Romero-Ortega, M. *Synthesis* **2016**, *48*, 2205–2212.

5.6. Preparation of pyrimidines 33–35 and nucleosides 36–38



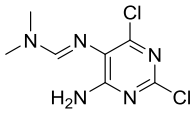


***N'*-(4-Amino-6-chloropyrimidin-5-yl)-*N*,*N*-dimethylformamidine (33).** A solution of 6-chloro-4,5-diaminopyrimidine (50 mg, 0.34 mmol) in anhydrous DMF (1 mL) under argon atmosphere was stirred at 0 °C for 10 min before addition of $POCl_3$ (33 µL). After another 2 h of stirring at 25 °C, a solution of saturated $NaHCO_3$ was added and the resulting mixture was extracted 3 times with AcOEt, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent CH_2Cl_2/MeOH) to afford compound **33** (40 mg, 60%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H, CH_{ar}), 7.65 (s, 1H, CH_{ar}), 3.07 (d, 6H, 2 CH_3). ^{13}C NMR (100 MHz, CD_3OD) δ 161.9 (C_q), 159.3 (CH), 151.9 (CH_{ar}), 147.1 (C_q), 128.8 (C_q), 40.6 (CH_3), 34.5 (CH_3). HRMS (ESI) calc. for $C_7H_{11}ClN_5$ $[M + H]^+$ 200.0697, found 200.0697.

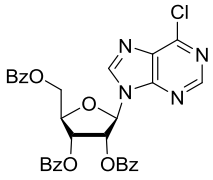


***N'*-(4-Amino-6-chloropyrimidin-5-yl)-*N*,*N*-dimethylacetamidine (34).** A solution of 6-chloro-4,5-diaminopyrimidine (50 mg, 0.34 mmol) in anhydrous *N*,*N*-dimethylacetamide (1 mL) under argon atmosphere was stirred at 0 °C for 10 min before addition of $POCl_3$ (99 µL). After another 2 h of stirring at 25 °C, a solution of saturated $NaHCO_3$ was added and the resulting mixture was extracted 3 times with AcOEt, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent CH_2Cl_2/MeOH) to afford compound **34** (57 mg, 80%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (s, 1H, CH_{ar}), 3.11 (s, 6H, 2 CH_3), 1.83 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CD_3OD) δ

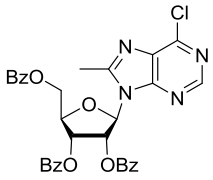
163.6 (C_q), 161.3 (C_q), 151.8 (CH_{ar}), 148.1 (C_q), 128.1 (C_q), 38.8 (CH_3), 16.0 (CH_3). HRMS (ESI) calc. for $C_8H_{13}ClN_5$ $[M + H]^+$ 214.0854, found 214.0856.



***N'*-(4-Amino-2,6-dichloropyrimidin-5-yl)-*N*,*N*-dimethylformamidine (35).** A suspension of compound **S1** (200 mg, 0.79 mmol) in a mixture of propan-2-ol (15 mL) and 25% aqueous ammonia (25 mL) was stirred for 16 h at 25 °C. Propan-2-ol was then evaporated, and the aqueous layer was extracted with AcOEt. The organic layer was dried over $MgSO_4$ then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **35** as a white solid (150 mg, 81%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.69 (s, 1H, CH), 2.99 (s, 3H, CH_3), 2.95 (s, 3H, CH_3). ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.4 (C_q), 157.0 (CH), 149.4 (C_q), 144.1 (C_q), 126.4 (C_q), 39.7 (CH_3), 33.9 (CH_3). HRMS (ESI) calc. for $C_7H_9Cl_2N_5$ $[M + H]^+$ 234.0308, found 234.0309.

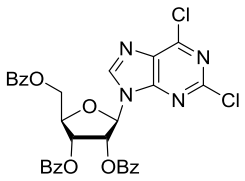


***(2R,3R,4R,5R)*-2-((Benzoyloxy)methyl)-5-(6-chloro-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl dibenzoate (36).** This compound was synthesized through general method VI from amidine **33**, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose and TMSOTf, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **36** (23 mg, 40%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H, H-2) 8.28 (s, 1H, H-8), 8.10–8.00 (m, 4H, 4 CH_{ar}), 7.95–7.87 (m, 2H, 2 CH_{ar}), 7.64–7.52 (m, 3H, 3 CH_{ar}), 7.49–7.32 (m, 6H, 6 CH_{ar}), 6.45 (d, 1H, $J_{1',2'}$ = 5.1 Hz, H-1'), 6.41 (dd, 1H, $J_{2',3'}$ = 5.5 Hz, H-2'), 6.25 (dd, 1H, $J_{3',4'}$ = 5.2 Hz, H-3'), 4.94 (dd, 1H, $J_{4',5'a}$ = 3.3 Hz, $J_{5'a,5'b}$ = 12.2 Hz, H-5'a), 4.85 (ddd, 1H, $J_{4',5'b}$ = 4.2 Hz, H-4'), 4.70 (dd, 1H, H-5'b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2 (CO), 165.4 (CO), 165.3 (CO), 152.5 (CH_{ar}), 151.8 (C_q), 151.4 (C_q), 144.1 (CH_{ar}), 134.1 (CH_{ar}), 134.0 (CH_{ar}), 133.7 (CH_{ar}), 132.5 (C_q), 130.1–129.7 (CH_{ar}), 129.4 (C_q),128.8 (C_q), 128.8–128.6 (CH_{ar}), 128.4 (C_q), 87.7 (CH), 81.2 (CH), 74.0 (CH), 71.5 (CH), 63.4 (CH_2). HRMS (ESI) calc. for $C_{31}H_{24}O_7ClN_4$ $[M + H]^+$ 599.1328, found 599.1332.



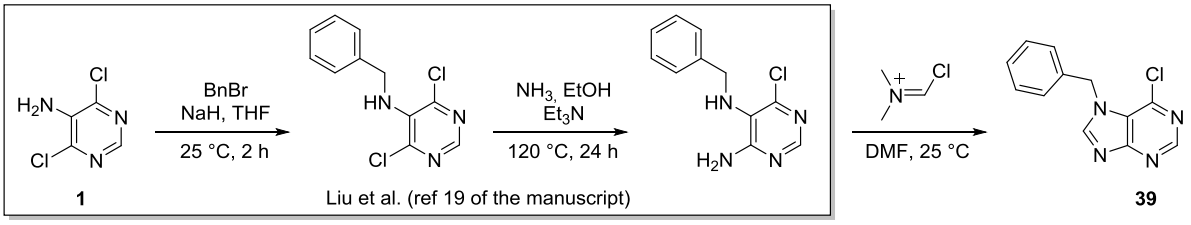
***(2R,3R,4R,5R)*-2-((Benzoyloxy)methyl)-5-(6-chloro-8-methyl-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl dibenzoate (37).** This compound was synthesized through general method VI from amidine **34**, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose and TMSOTf, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **37** (27 mg, 42%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H, H-2), 8.07–7.90 (m, 6H, 6 CH_{ar}), 7.62–7.52 (m, 3H, 3 CH_{ar}), 7.44–7.33 (m, 6H, 6 CH_{ar}), 6.56 (dd, 1H, $J_{1',2'}$ = 3.4 Hz, $J_{2',3'}$ = 6.1 Hz, H-2'), 6.45 (dd, 1H, $J_{3',4'}$ = 6.9 Hz, H-3'), 6.20 (d, 1H, H-1'), 4.92 (dd, 1H, $J_{4',5'a}$ = 3.3 Hz, $J_{5'a,5'b}$ = 12.2 Hz, H-5'a), 4.81 (ddd, 1H, $J_{4',5'b}$ = 4.6 Hz, H-4'), 4.65 (dd, 1H, H-5'b), 2.78 (3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1 (CO), 165.5 (CO), 165.4 (CO), 155.1 (C_q), 152.3 (C_q), 151.4 (CH_{ar}), 149.6 (C_q), 134.0 (CH_{ar}), 133.8 (CH_{ar}), 133.4 (CH_{ar}), 131.3 (C_q), 129.9–129.6 (CH_{ar}), 129.4 (C_q), 128.8 (C_q), 128.7–128.3 (CH_{ar}), 128.5 (C_q), 88.1 (CH), 80.2

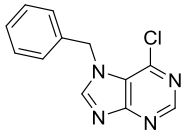
(CH), 73.8 (CH), 71.0 (CH), 62.8 (CH_2), 14.8 (CH_3). HRMS (ESI) calc. for $C_{32}H_{26}O_7ClN_4$ $[M + H]^+$ 613.1485, found 613.1483.



***(2R,3R,4R,5R)*-2-((Benzoyloxy)methyl)-5-(2,6-dichloro-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl dibenzoate (38).** This compound was synthesized through general method VI from amidine **35**, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose and TMSOTf, and was purified by flash chromatography on silica gel (eluent cyclohexane/AcOEt) to afford compound **38** (20 mg, 37%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H, H-8), 8.09–7.01 (m, 4H, 4 CH_{ar}), 7.96-7.90 (m, 2H, 2 CH_{ar}), 7.64–7.53 (m, 3H, 3 CH_{ar}), 7.48–7.34 (m, 6H, 6 CH_{ar}), 6.48 (d, 1H, $J_{1',2'}$ = 5.5 Hz, H-1'), 6.18 (dd, 1H, $J_{2',3'}$ = 5.7 Hz, H-2'), 6.13 (dd, 1H, $J_{3',4'}$ = 4.2 Hz, H-3'), 4.92 (dd, 1H, $J_{4',5'a}$ = 3.2 Hz, $J_{5'a,5'b}$ = 12.2 Hz, H-5'a), 4.87 (ddd, 1H, $J_{4',5'b}$ = 4.1 Hz, H-4'), 4.73 (dd, 1H, H-5'b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2 (CO), 165.5 (CO), 165.3 (CO), 153.7 (C_q), 152.8 (C_q), 152.5 (C_q), 144.0 (CH_{ar}), 134.1 (CH_{ar}), 134.0 (CH_{ar}), 133.8 (CH_{ar}), 131.5 (C_q), 130.2–129.7 (CH_{ar}), 129.2 (C_q), 129.0–128.7 (CH_{ar}), 128.6 (C_q), 128.3 (C_q), 87.2 (CH), 81.7 (CH), 74.5 (CH), 71.7 (CH), 63.6 (CH_2). HRMS (ESI) calc. for $C_{31}H_{23}O_7Cl_2N_4$ $[M + H]^+$ 633.0938, found 633.0936.

5.7. Preparation of 7-substituted purine 39





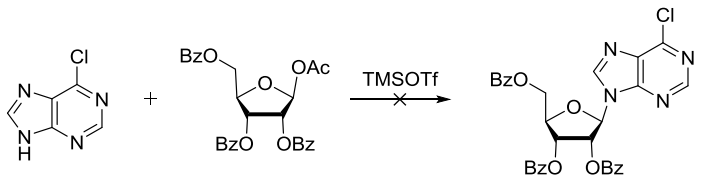
7-Benzyl-6-chloro-7*H*-purine (39). To a solution of N^5-Benzyl-6-chloropyrimidine-4,5-diamine (20 mg, 0.085 mmol) in dry DMF under argon atmosphere was added (chloromethylene)dimethyliminium chloride (16 mg, 0.128 mmol). The resulting solution was stirred for 30 min at 25 °C, diluted in CH_2Cl_2 (3 mL) and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted 3 times with CH_2Cl_2 and the resulting organic layer was then dried over $MgSO_4$. After concentration under reduced pressure, compound **39** (21 mg, 100%) was obtained as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.01 (s, 1H, CH_{ar}), 8.82 (s, 1H, CH_{ar}), 7.38–7.30 (m, 3H, 3 CH_{ar}), 7.20–7.18 (m, 2H, 2 CH_{ar}), 5.76 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (C_q), 152.8 (CH_{ar}), 149.2 (CH_{ar}), 143.4 (C_q), 134.7 (C_q), 129.6 (CH_{ar}), 129.1 (CH_{ar}), 127.2 (CH_{ar}), 122.7 (C_q), 50.9 (CH_2). HRMS (ESI) calc. for $C_{12}H_{10}ClN_4$ $[M + H]^+$ 245.0585, found 245.0589.

6. Additional experiments

6.1. Amidine 33 leads to 6-chloropurine in the presence of TMSOTf

To a solution of amidine **33** (5 mg, 0.025 mmol) in $CDCl_3$ (0.5 mL) was added TMSOTf (4.5 µL, 0.025 mmol). The resulting mixture was heated at 50 °C and the formation of 6-chloroadenine was monitored by ^{1}H NMR (400 MHz). After 5 h, the complete conversion of amidine **33** to 6-chloropurine was observed.

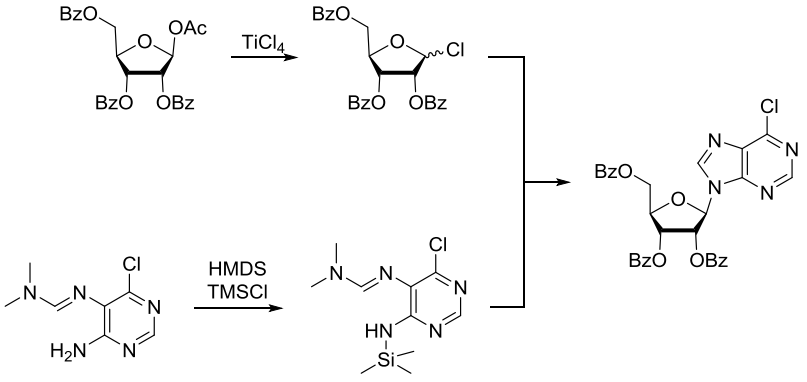
6.2. Non-silylated 6-chloropurine is not glycosylated in the presence of TMSOTf



To a solution of 6-chloroadenine (15 mg, 0.1 mmol) in anhydrous 1,2-dichloroethane (1 mL) under argon atmosphere, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (50 mg, 0.1 mmol) and TMSOTf (18 µL, 0.1 mmol) were added successively, and the resulting mixture was refluxed for 16 h. After concentration under reduced pressure, the ^{1}H NMR spectrum of the mixture ($CDCl_3$, 400 MHz) was recorded and it did not revealed formation of the corresponding nucleoside **36**.

6.3. Prior silylation of amidine 33 activates it for glycosylation

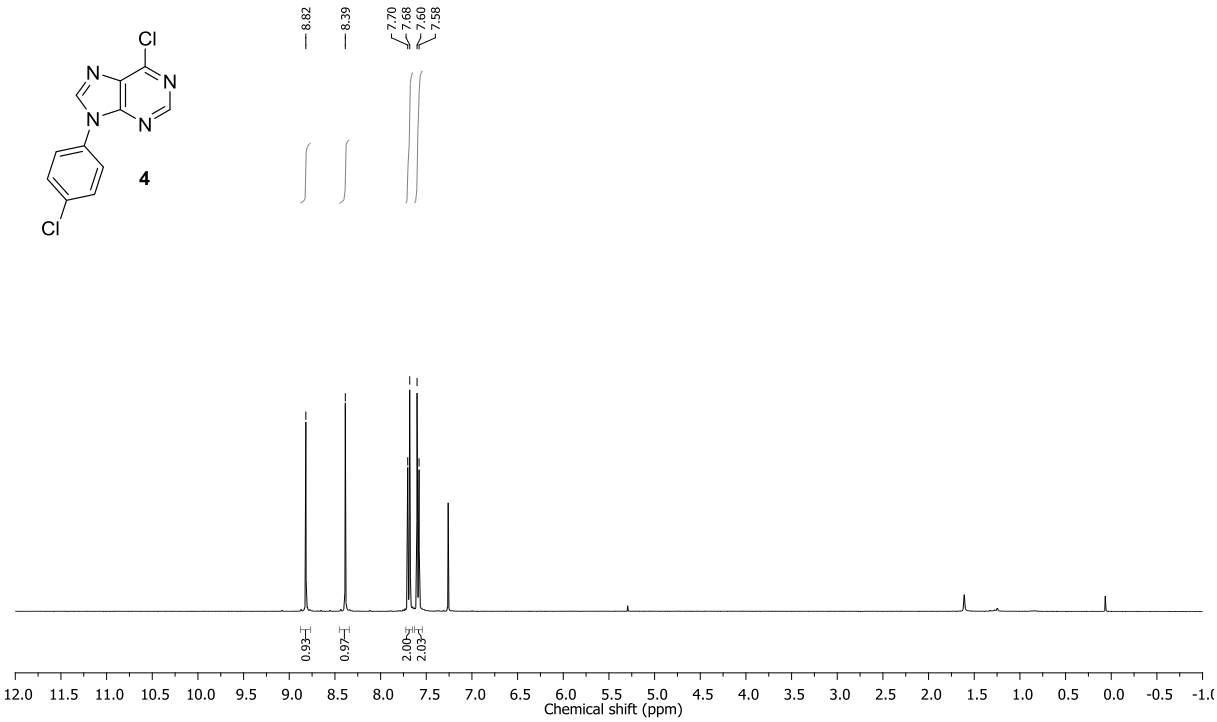
*The reaction of the anomeric isomer mixture of 2,3,5-tri-*O*-benzoyl-1-chlororibose and freshly silylated pyrimidine **33** led to the β-ribonucleoside **36** in 34% yield without formation of 9*H*-purine demonstrating purine formation from the silylated pyrimidine.*



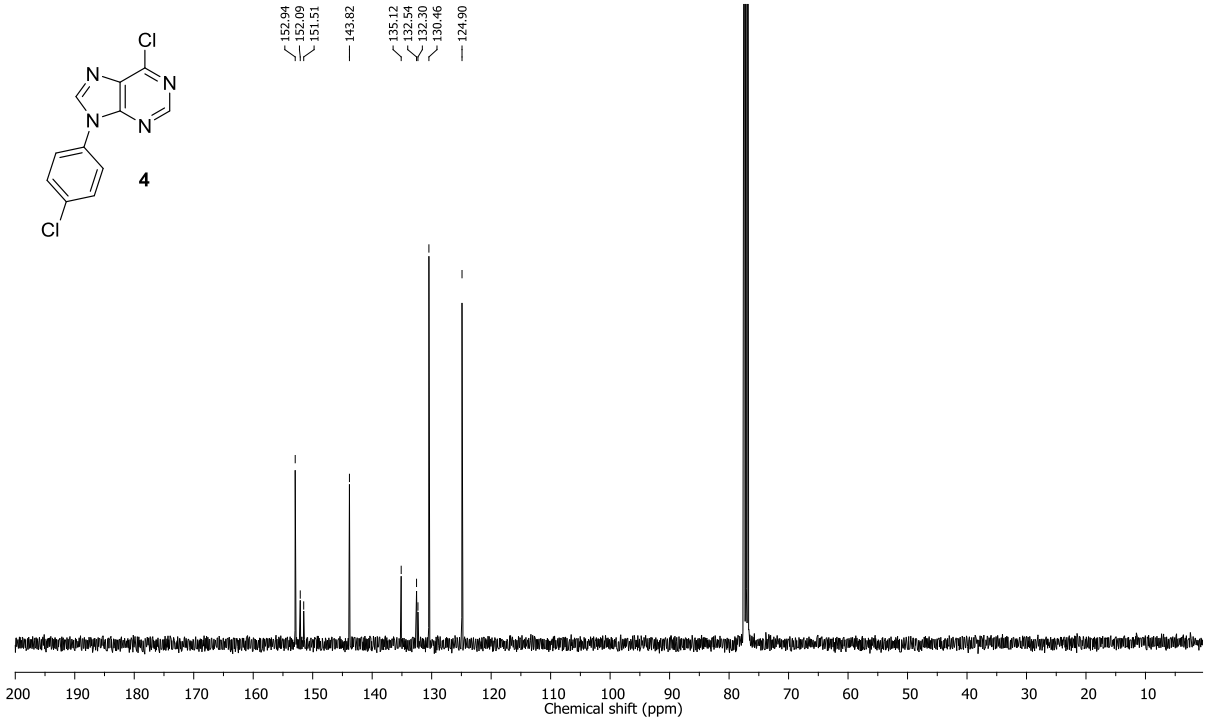
To a solution of amidine **33** (20 mg, 0.1 mmol) in dry acetonitrile (1 mL) was added HMDS (42 µL, 0.2 mmol) and TMSCl (38 µL, 0.3 mmol). The resulting mixture was stirred at reflux for 2 h and concentrated under reduced pressure. Dry acetonitrile (1 mL) was then added to the residue. Simultaneously, a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (100 mg, 0.2 mmol) in dry CH_2Cl_2 was treated with 180 µL of a 1 M solution of $TiCl_4$ in dry CH_2Cl_2. The resulting mixture was stirred at 25 °C for 1 h 30 before water (2 mL) was added. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Dry acetonitrile (1 mL) was then added to the residue and the resulting solution was added to the solution of silylated amidine previously prepared. After 16 h of stirring at reflux, CH_2Cl_2 (10 mL) and saturated aqueous solution of $NaHCO_3$ (10 mL) were added into the resulting mixture. The aqueous layer was extracted 3 times with CH_2Cl_2 and the resulting organic layer was then dried over $MgSO_4$. After concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel (eluent AcOEt/cyclohexane) to afford compound **36** (20 mg, 34%) as a colorless oil.

7. ^{1}H and ^{13}C NMR spectra

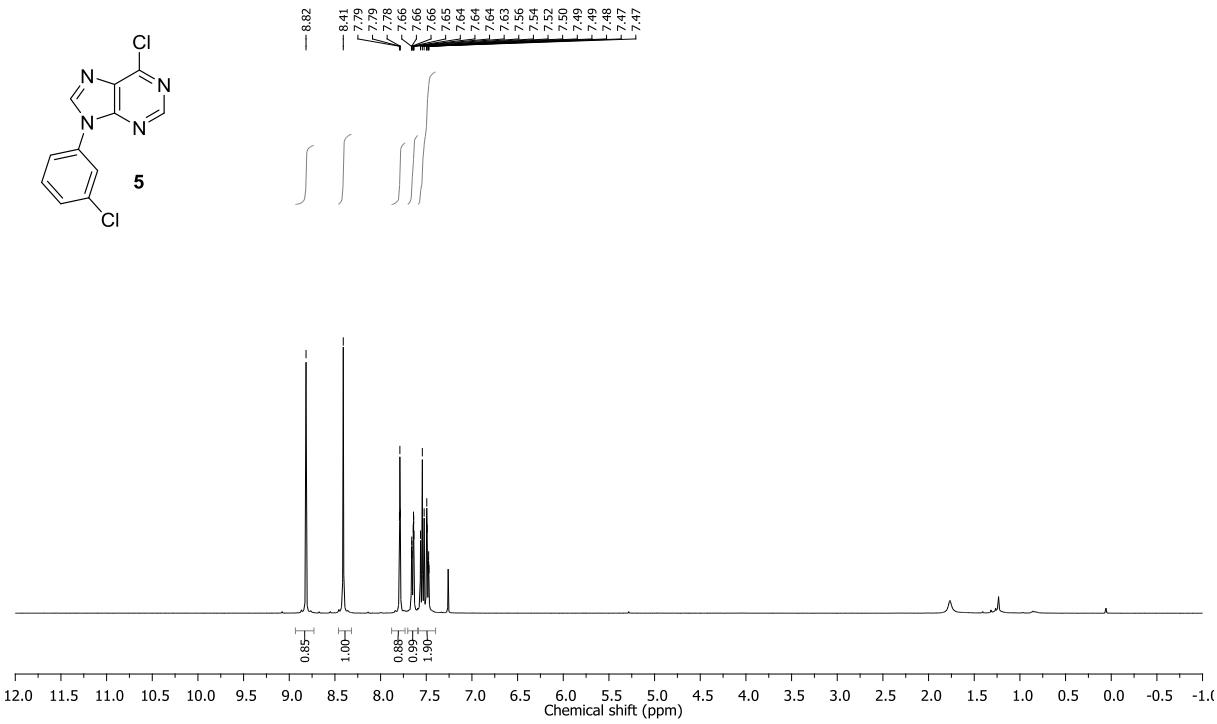
^{1}H NMR (400 MHz, $CDCl_3$)



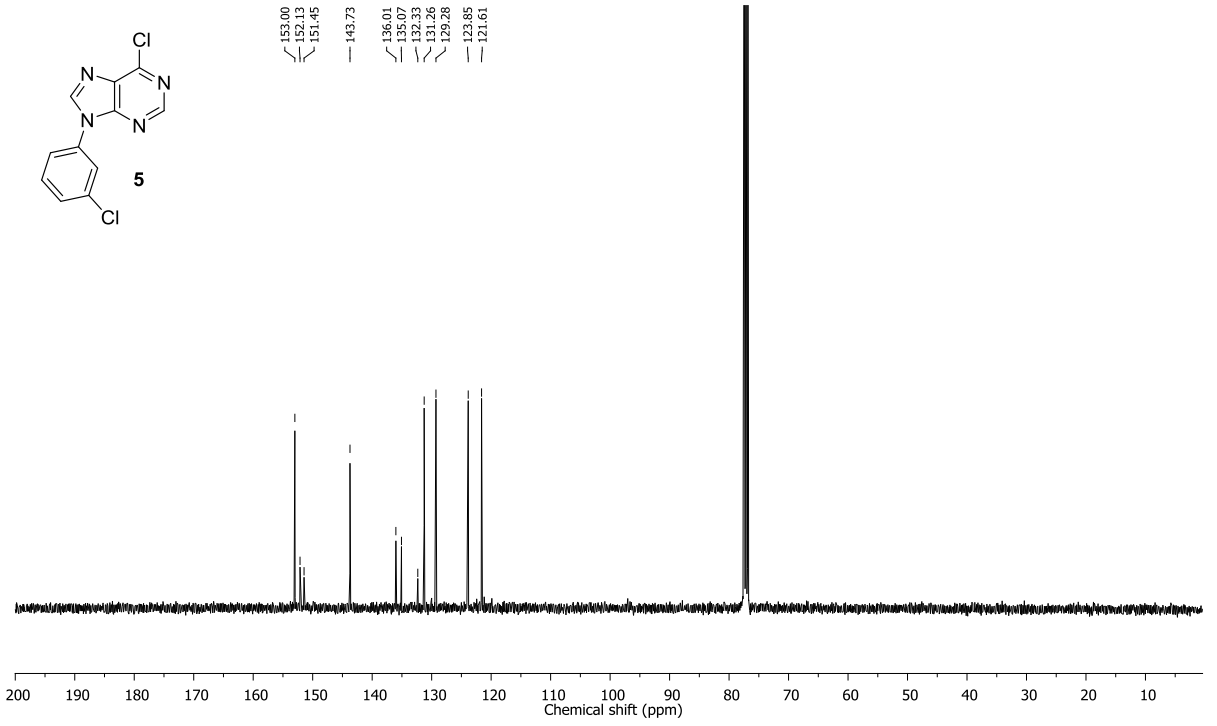
^{13}C NMR (100 MHz, $CDCl_3$)



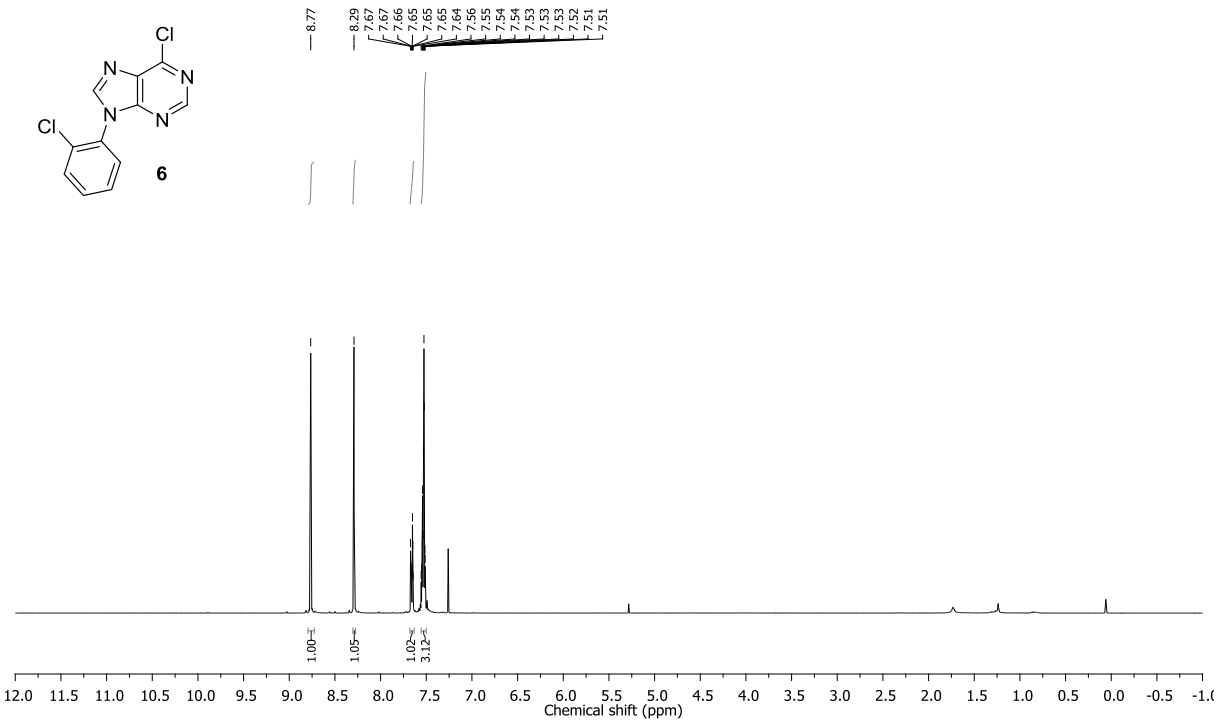
^{1}H NMR (400 MHz, $CDCl_3$)



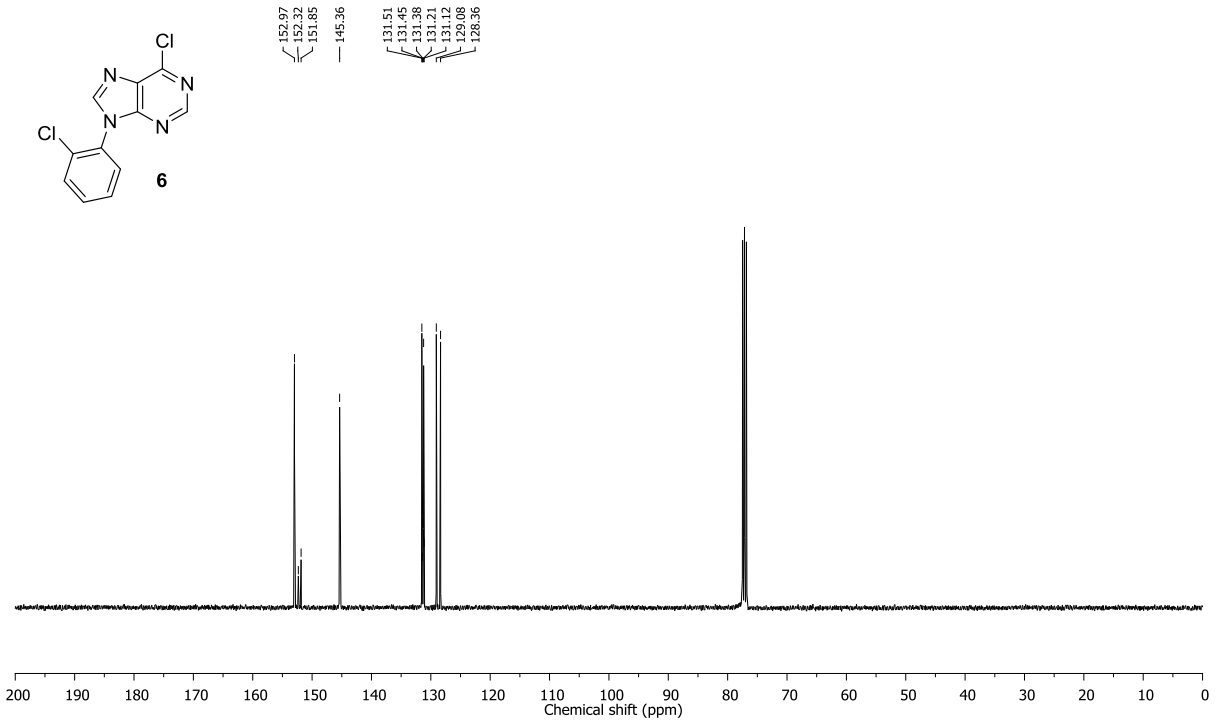
^{13}C NMR (100 MHz, $CDCl_3$)



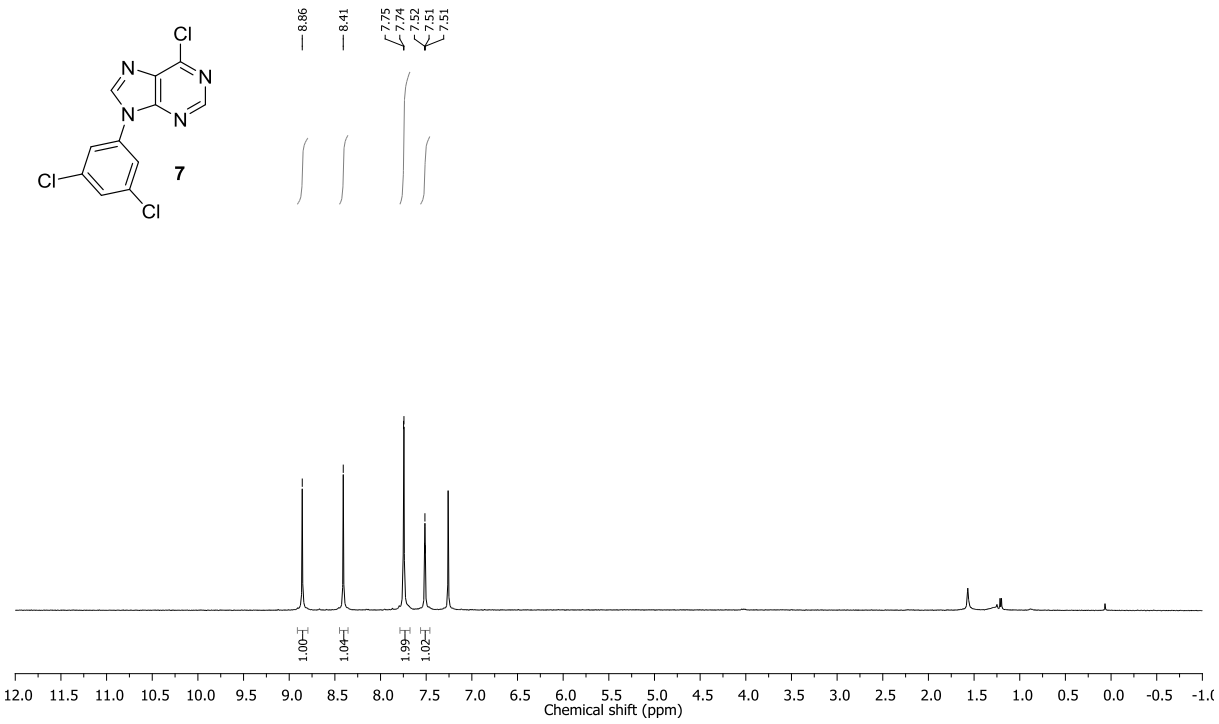
^{1}H NMR (400 MHz, $CDCl_3$)



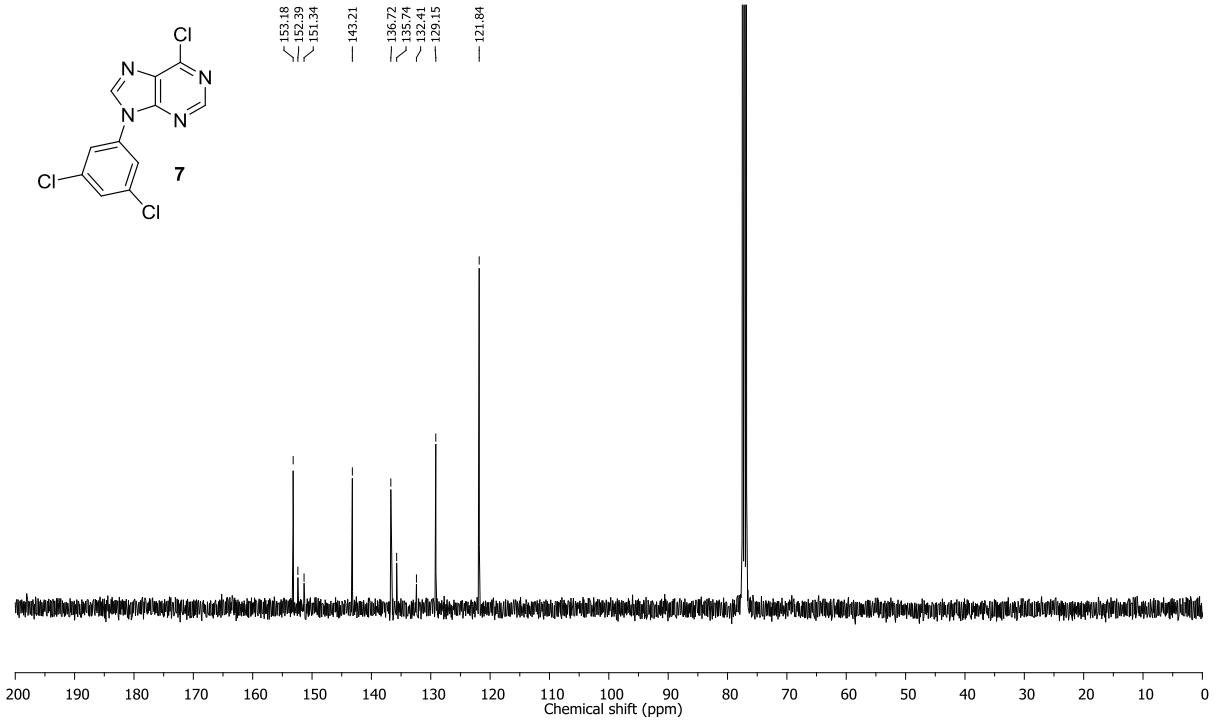
^{13}C NMR (100 MHz, $CDCl_3$)



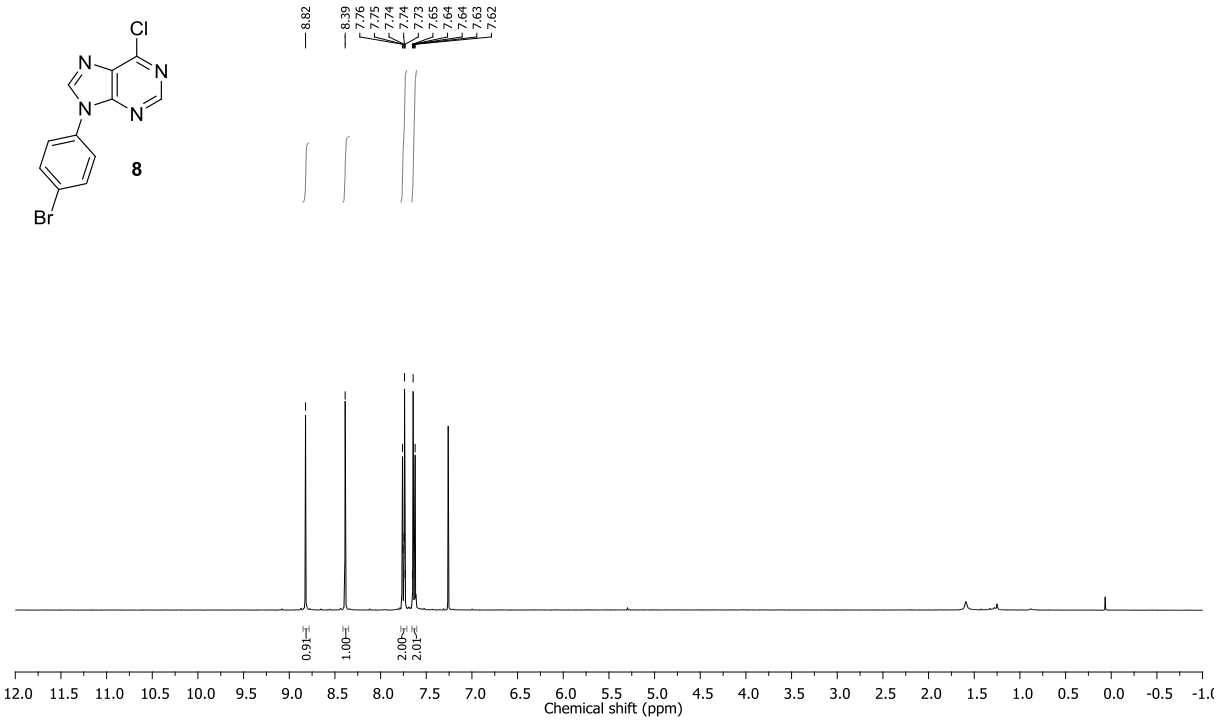
^{1}H NMR (400 MHz, $CDCl_3$)



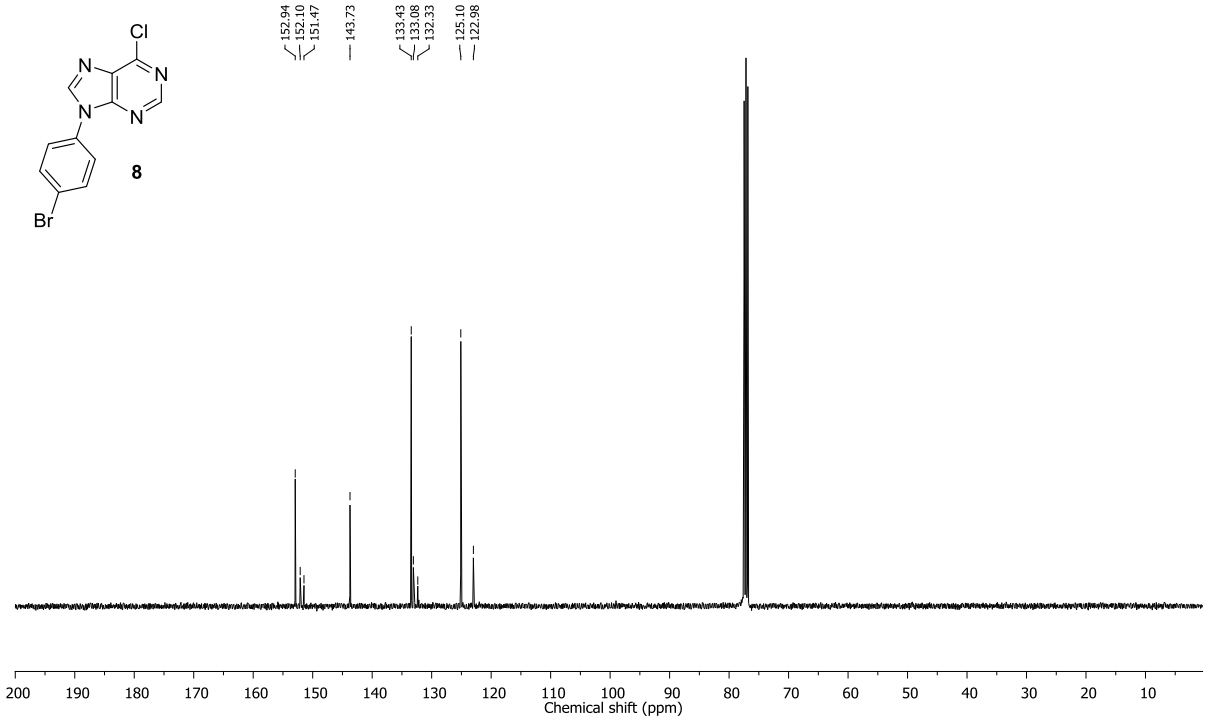
^{13}C NMR (100 MHz, $CDCl_3$)



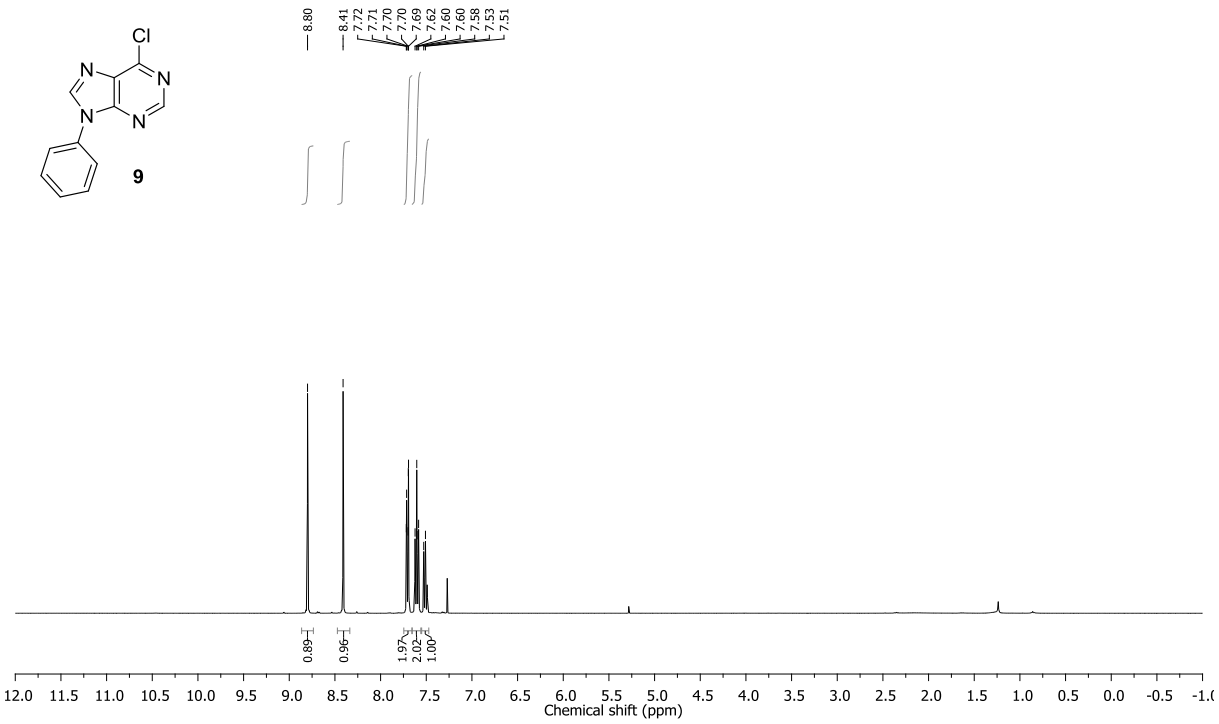
^{1}H NMR (400 MHz, $CDCl_3$)



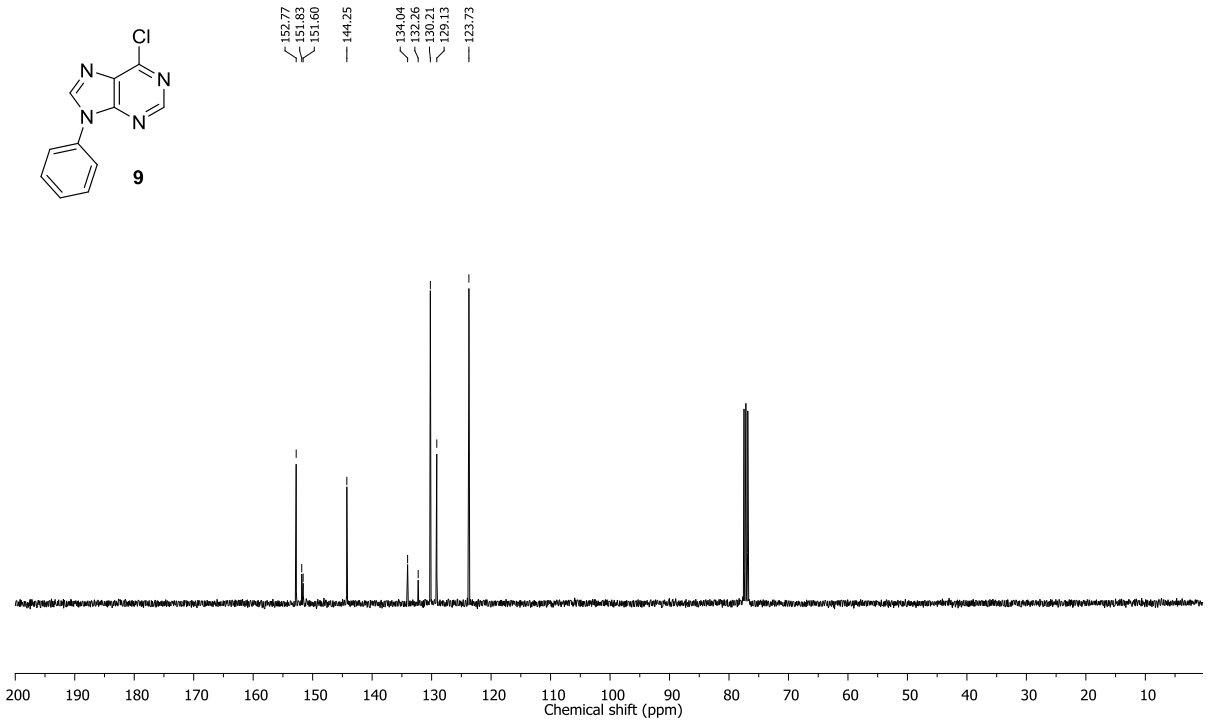
^{13}C NMR (100 MHz, $CDCl_3$)



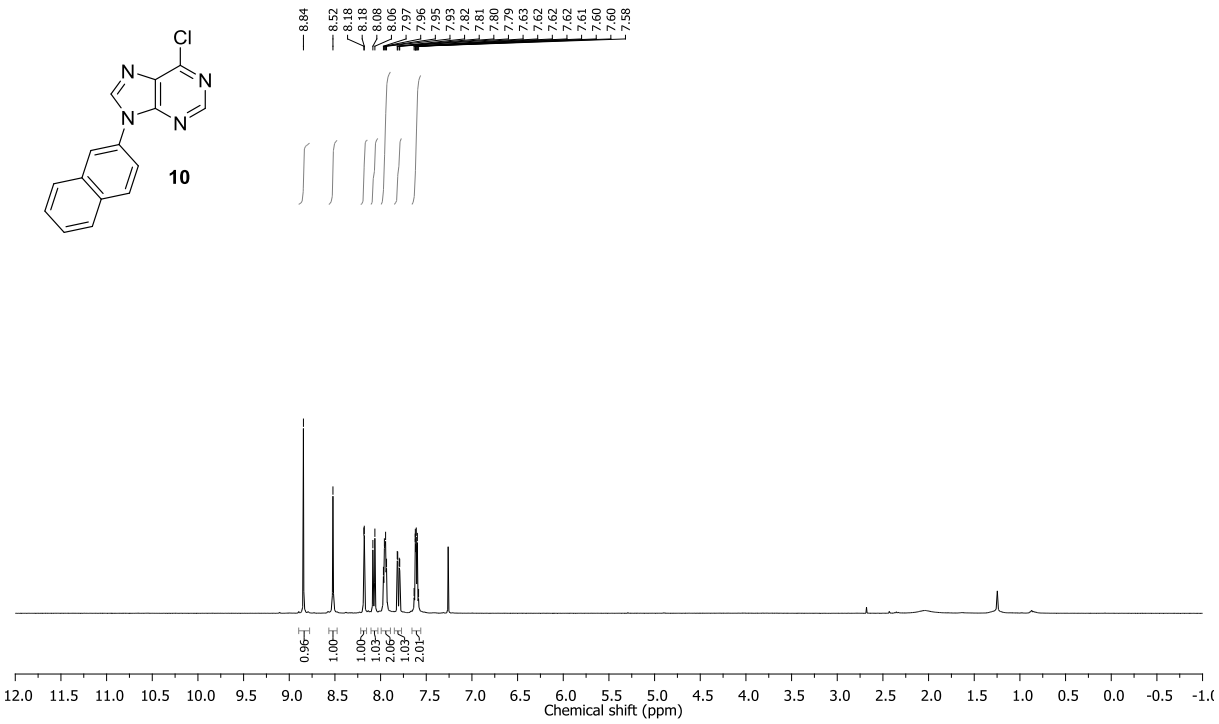
^{1}H NMR (400 MHz, $CDCl_3$)



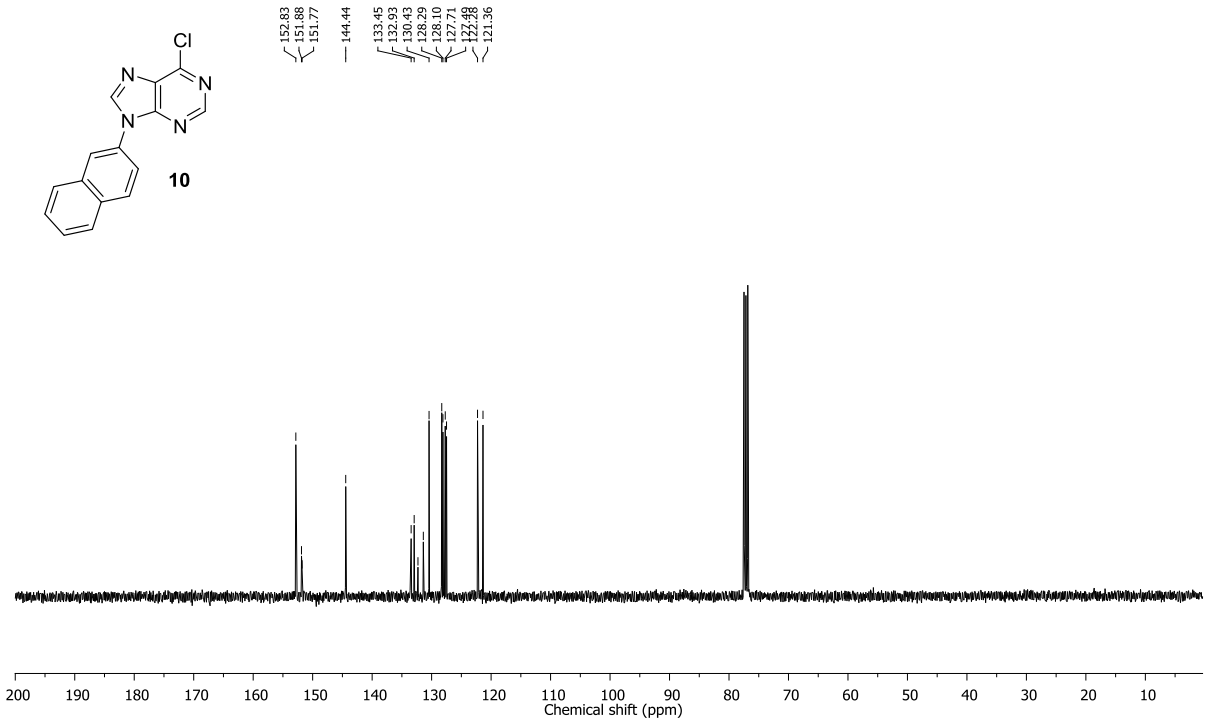
^{13}C NMR (100 MHz, $CDCl_3$)



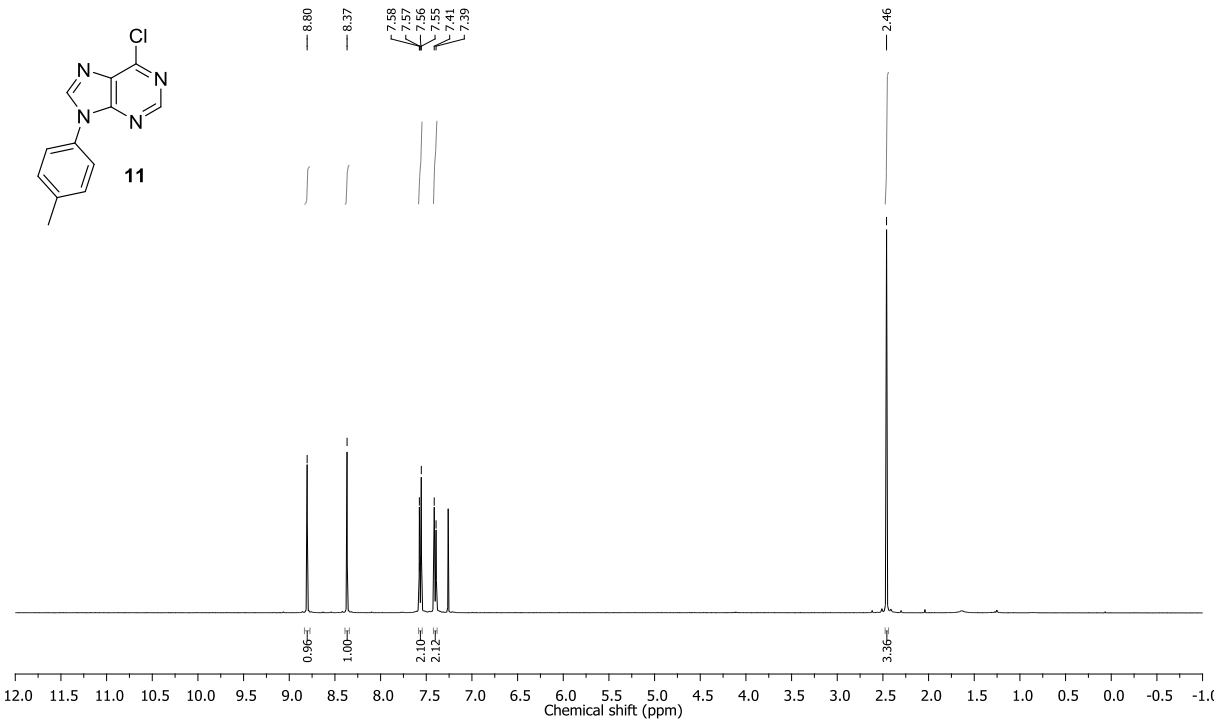
^{1}H NMR (400 MHz, $CDCl_3$)



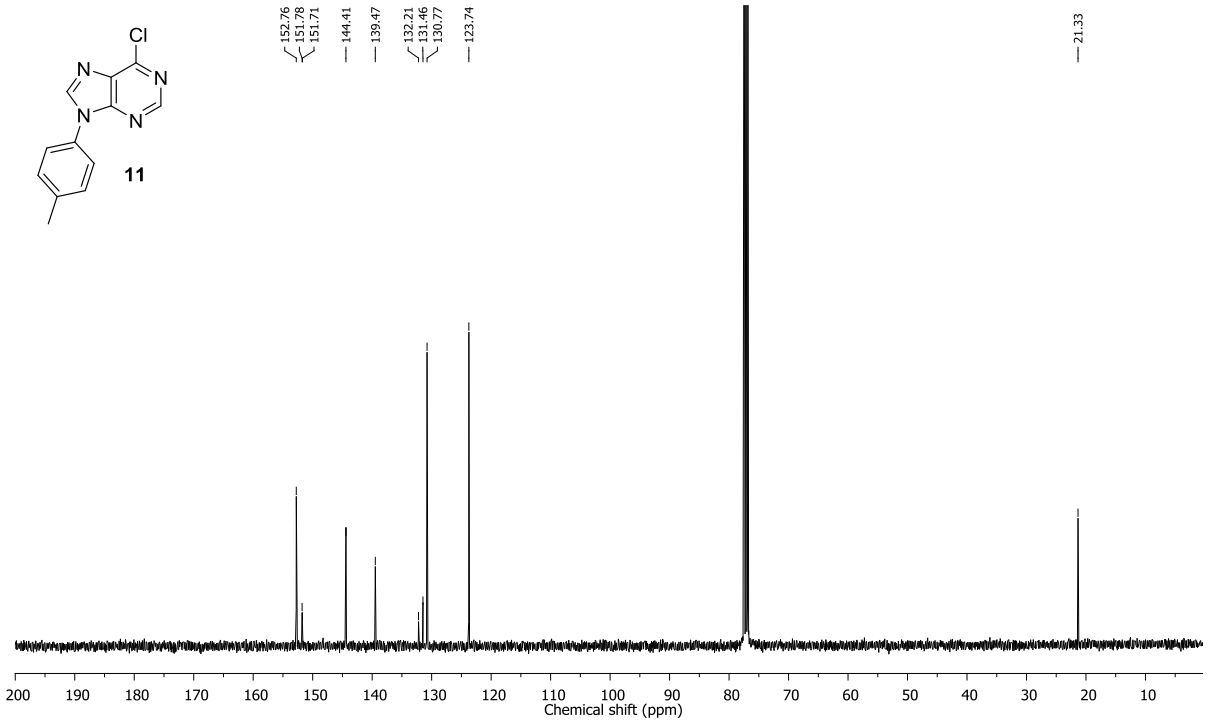
^{13}C NMR (100 MHz, $CDCl_3$)



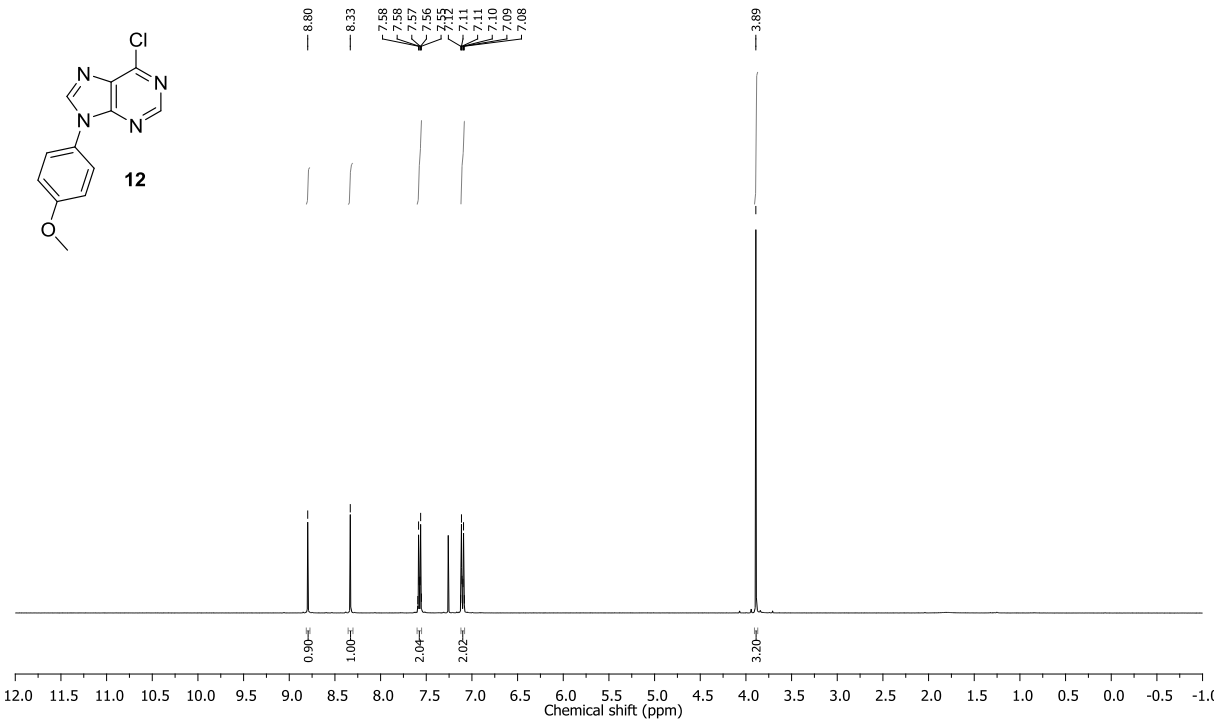
^{1}H NMR (400 MHz, $CDCl_3$)



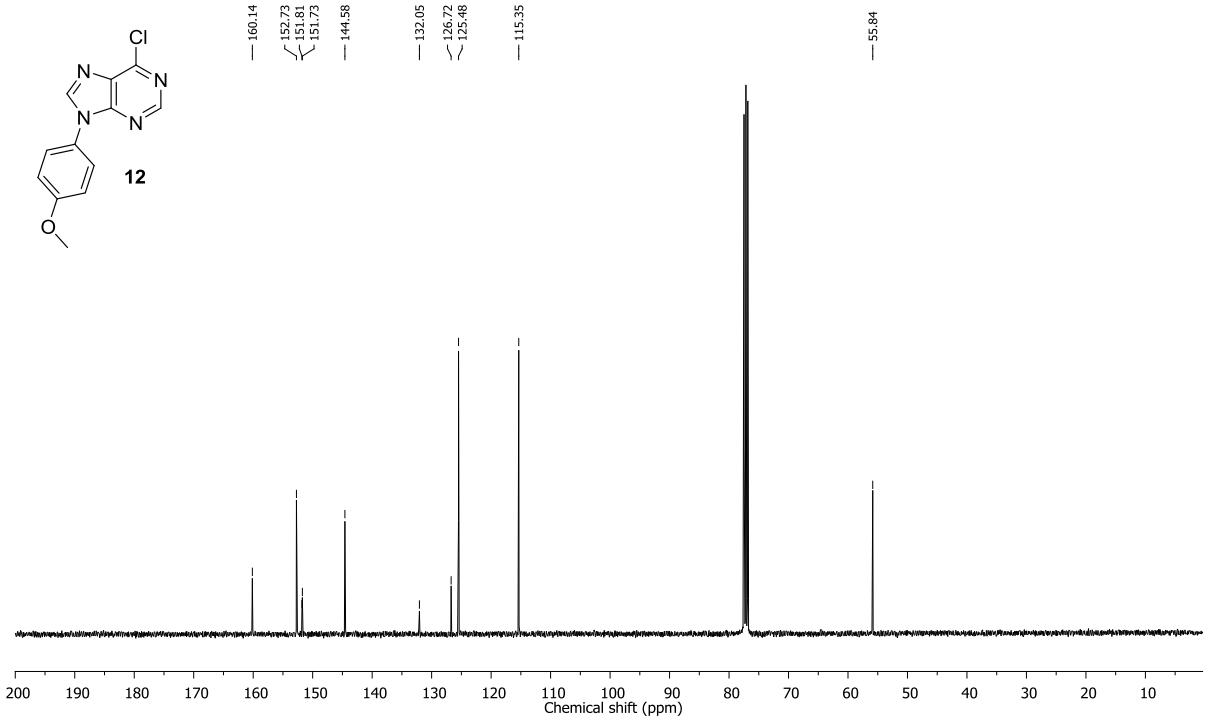
^{13}C NMR (100 MHz, $CDCl_3$)



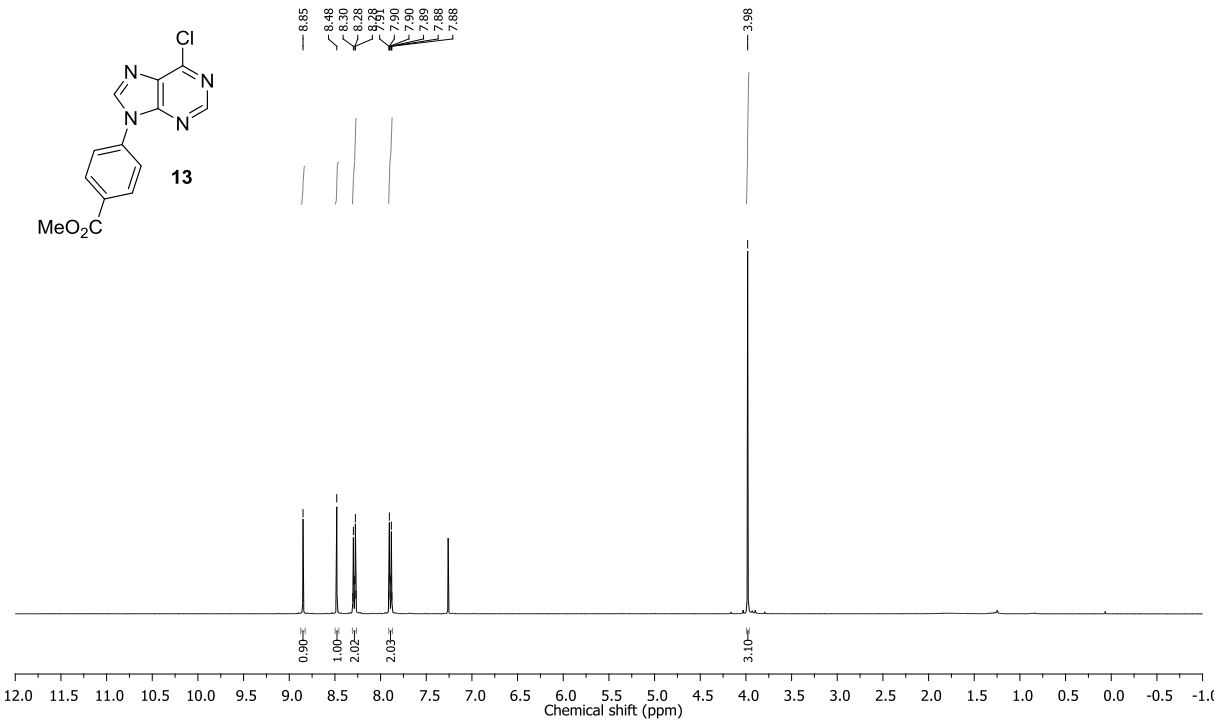
^{1}H NMR (400 MHz, $CDCl_3$)



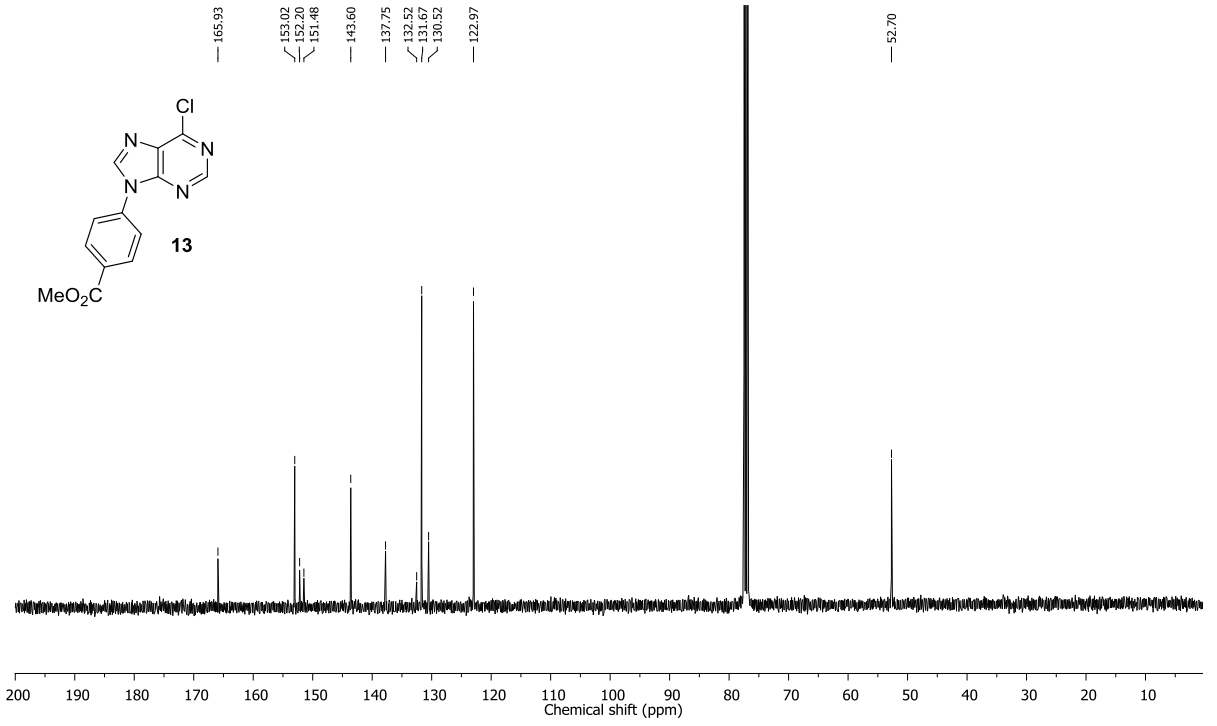
^{13}C NMR (100 MHz, $CDCl_3$)



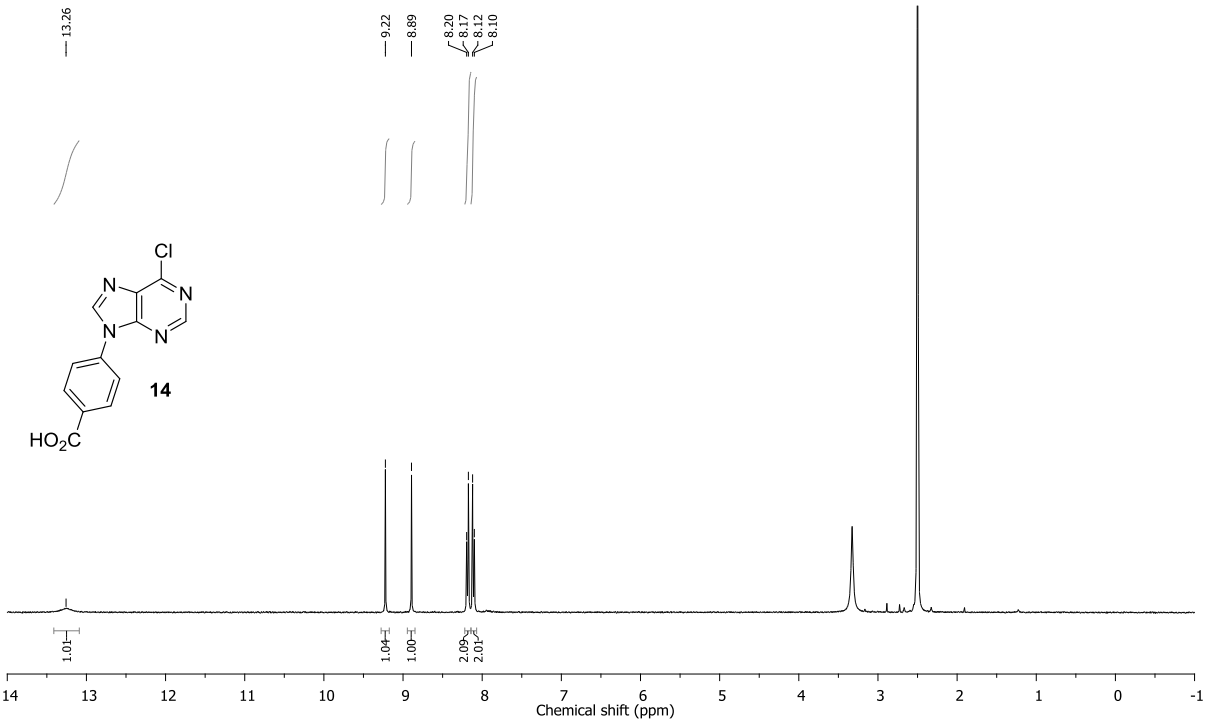
^{1}H NMR (400 MHz, $CDCl_3$)



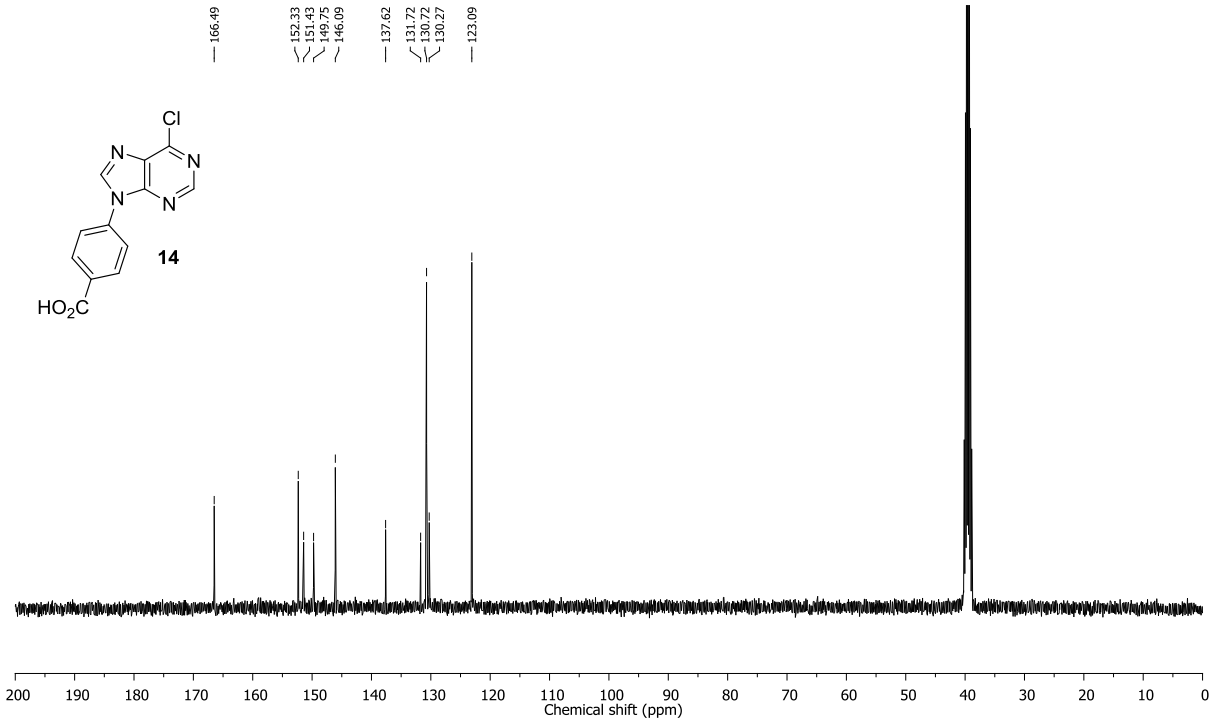
^{13}C NMR (100 MHz, $CDCl_3$)



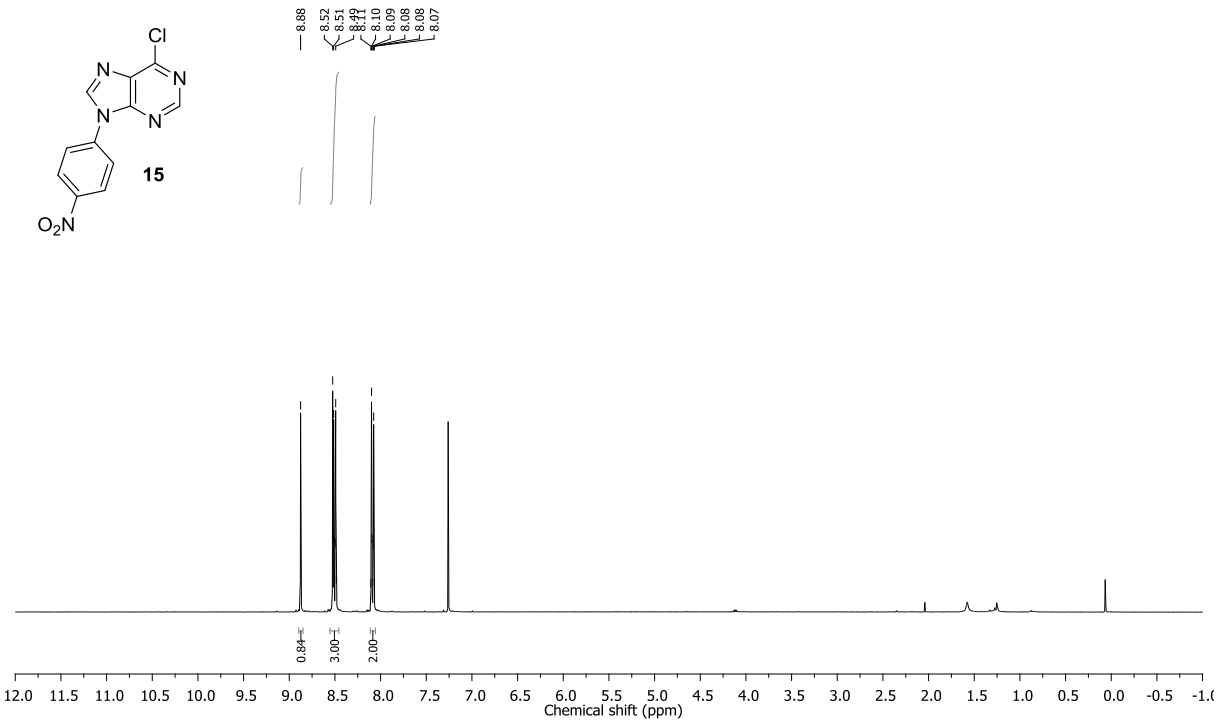
^{1}H NMR (400 MHz, d_6-DMSO)



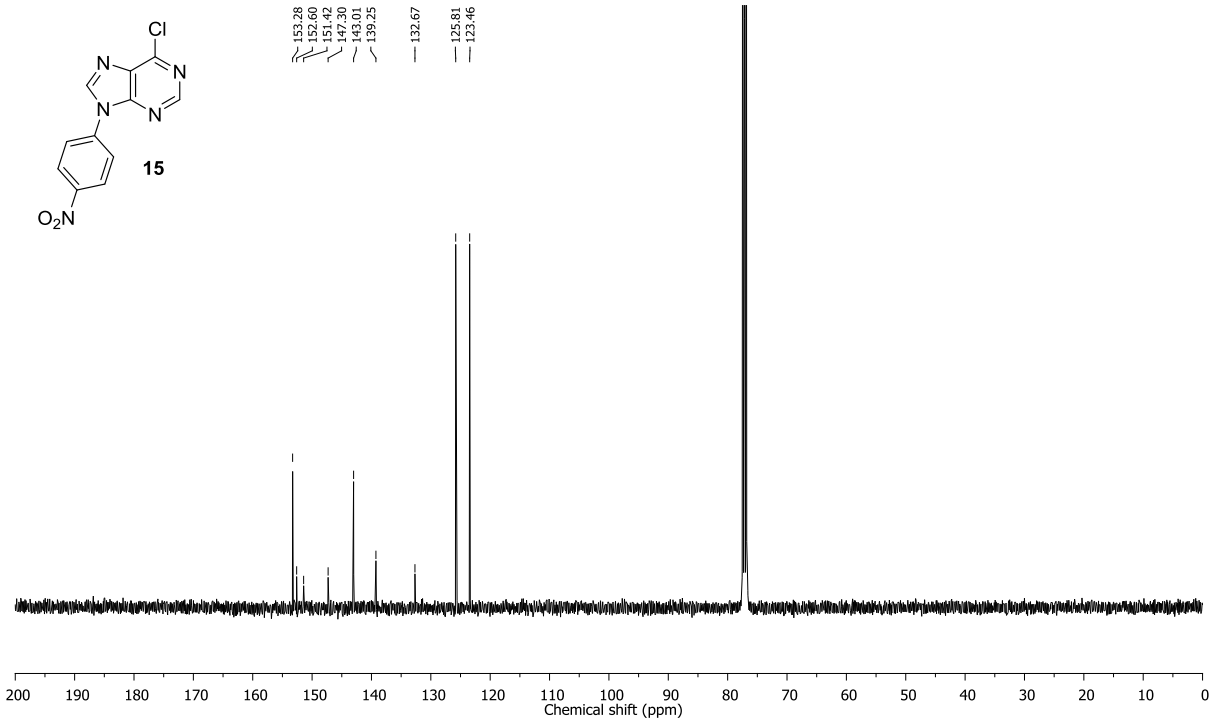
^{13}C NMR (100 MHz, d_6-DMSO)



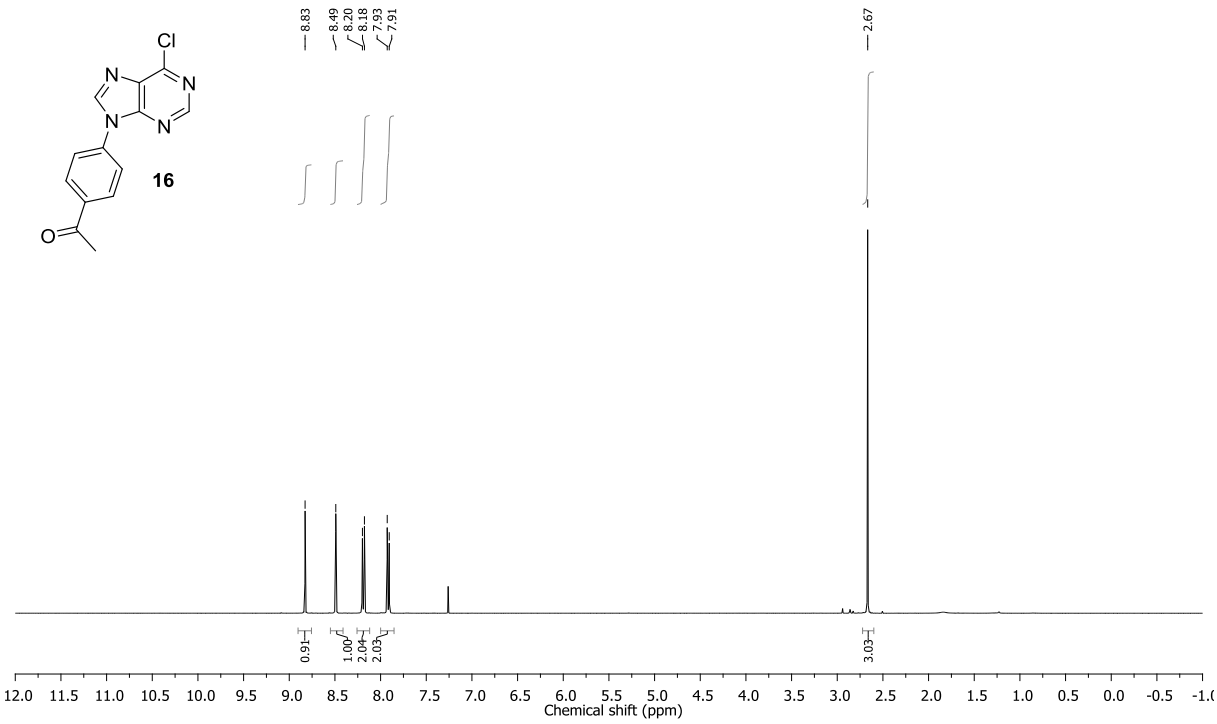
^{1}H NMR (400 MHz, $CDCl_3$)



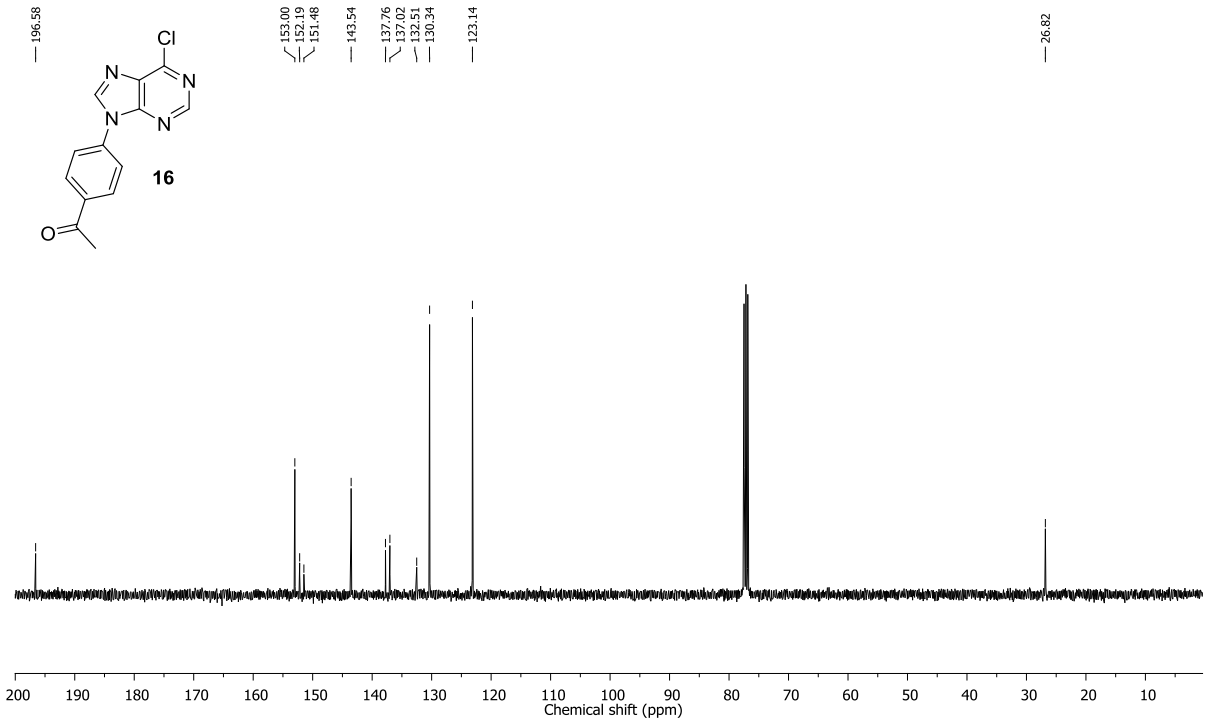
^{13}C NMR (100 MHz, $CDCl_3$)



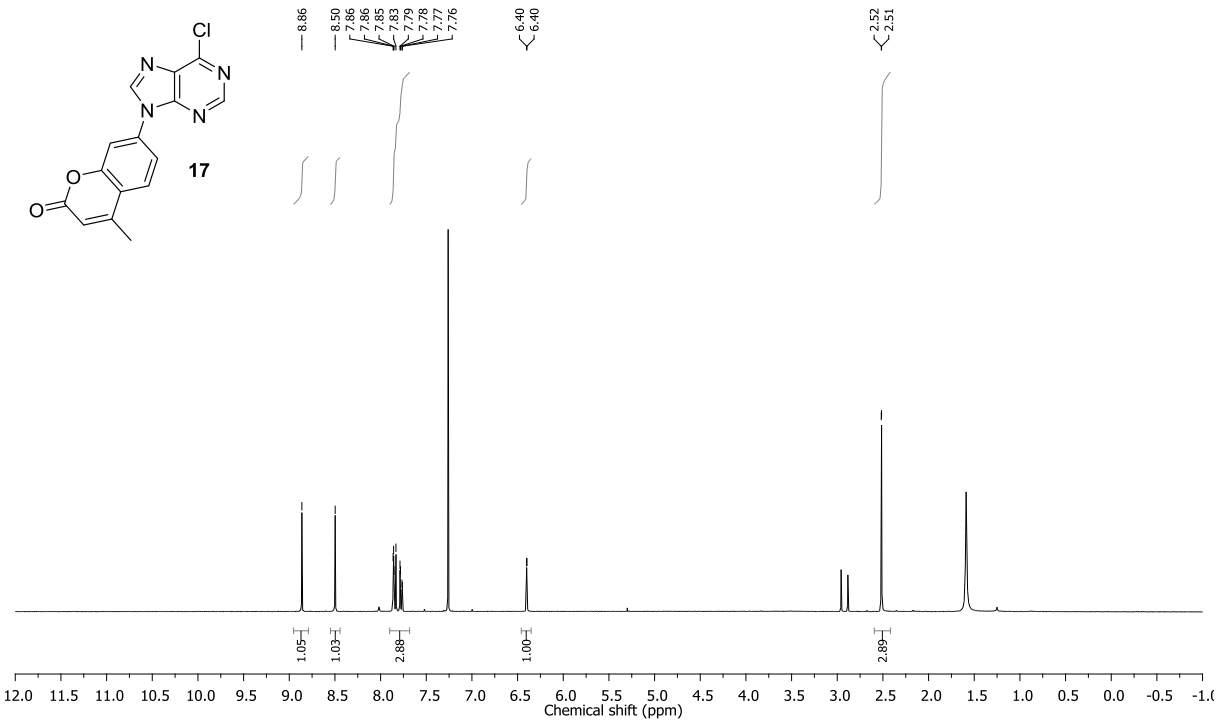
^{1}H NMR (400 MHz, $CDCl_3$)



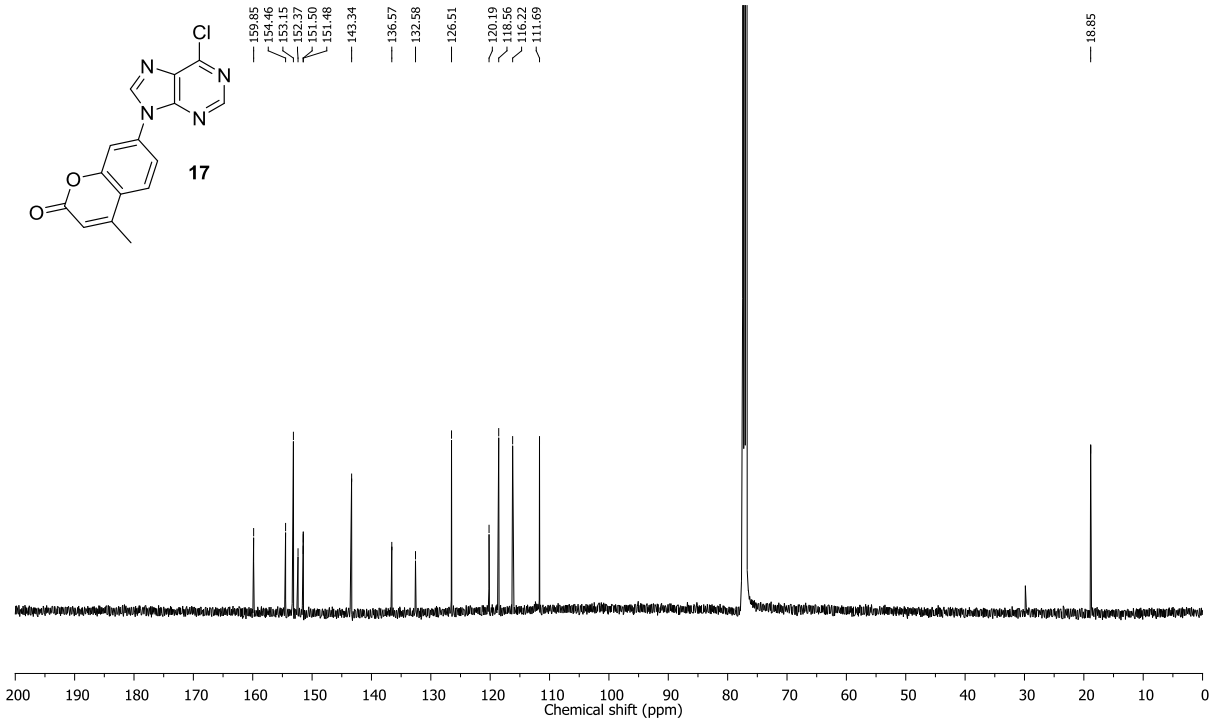
^{13}C NMR (100 MHz, $CDCl_3$)



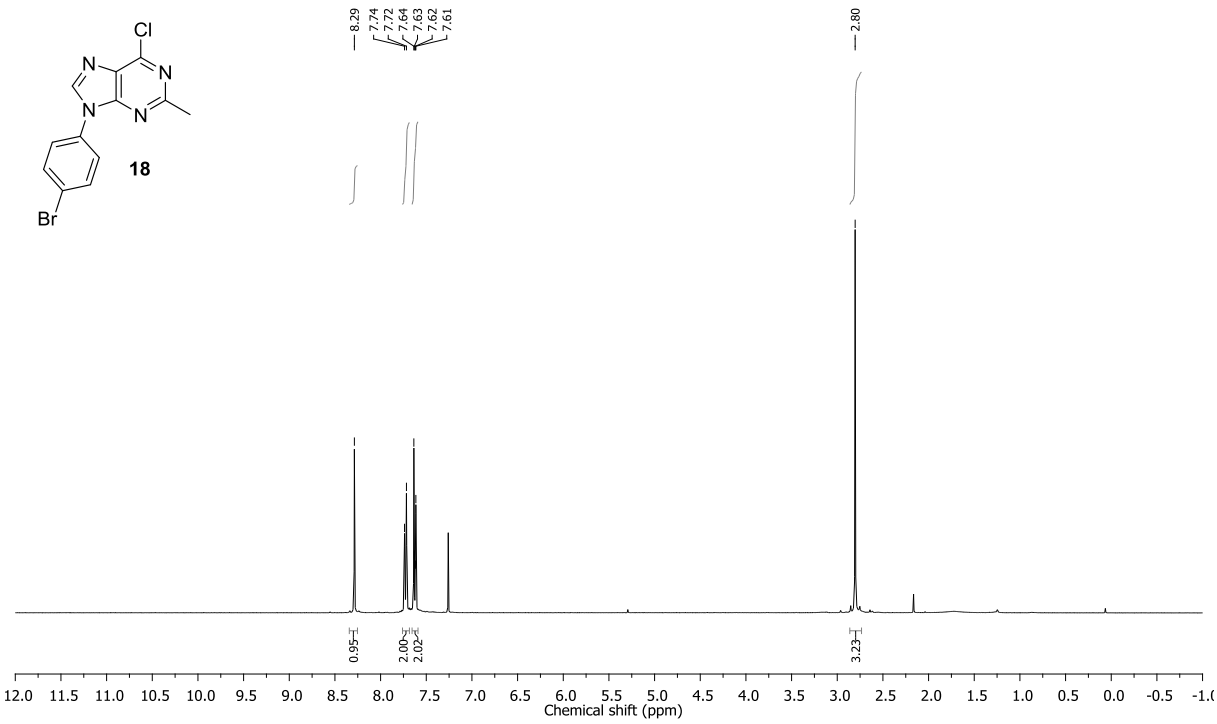
^{1}H NMR (400 MHz, $CDCl_3$)



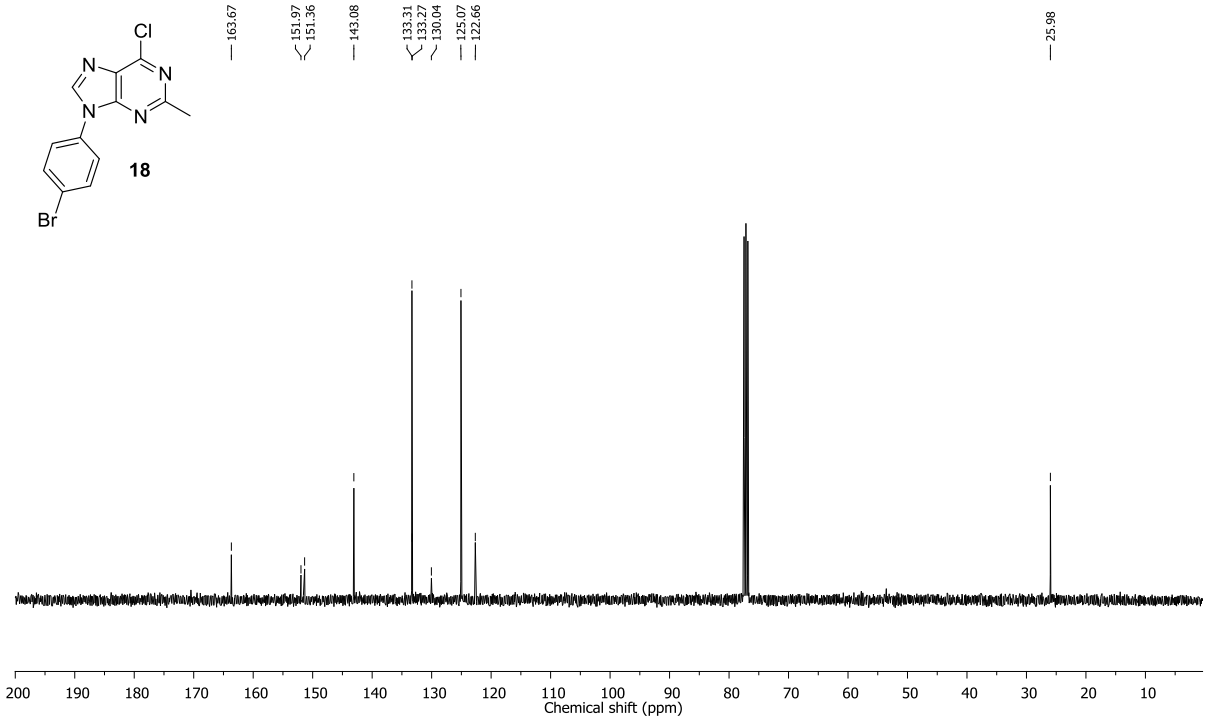
^{13}C NMR (125 MHz, $CDCl_3$)



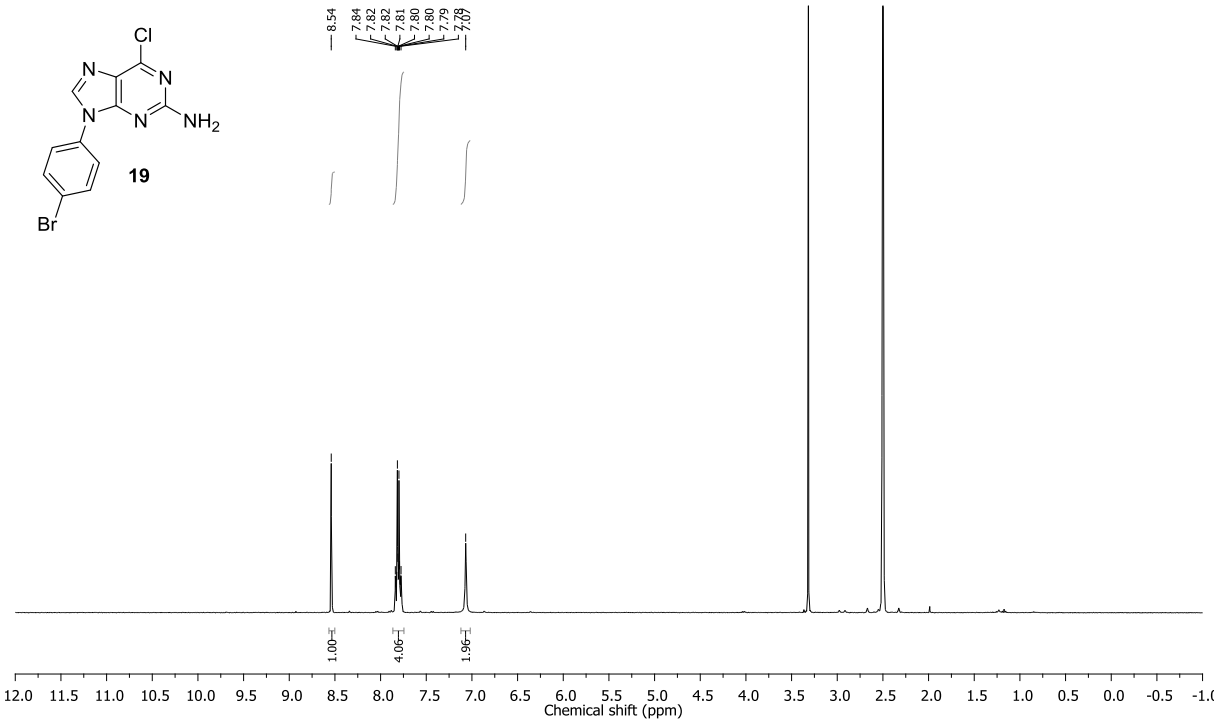
^{1}H NMR (400 MHz, $CDCl_3$)



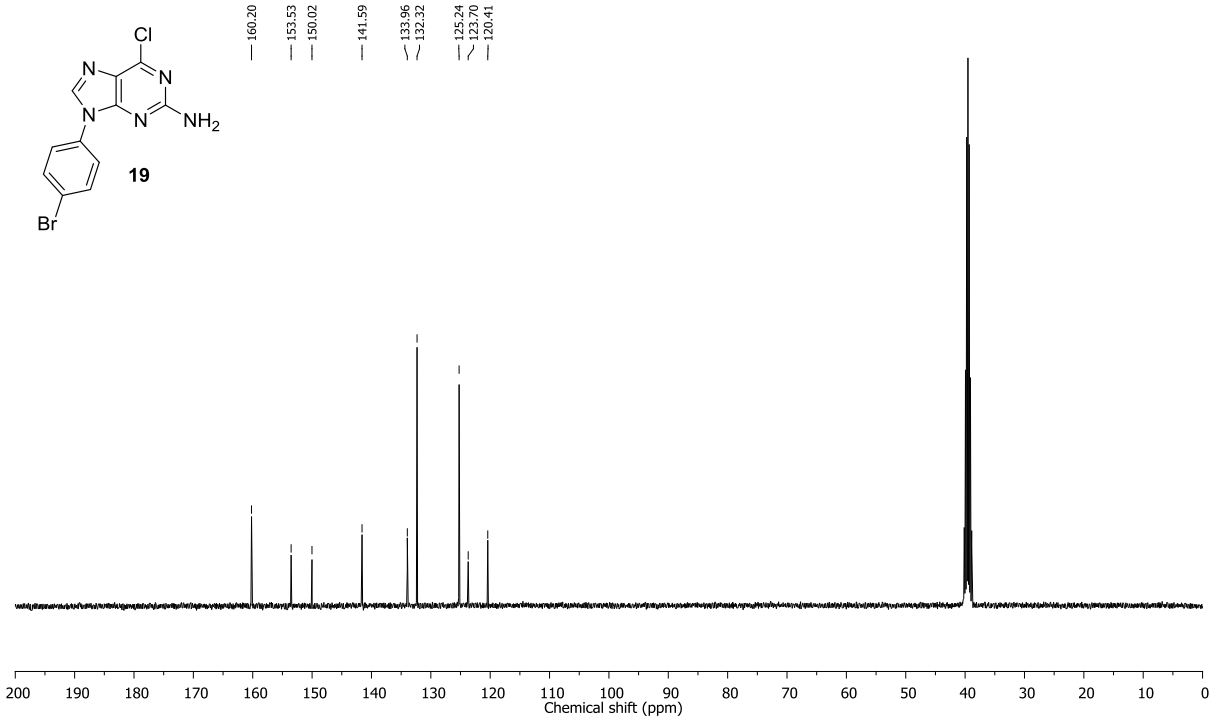
^{13}C NMR (100 MHz, $CDCl_3$)



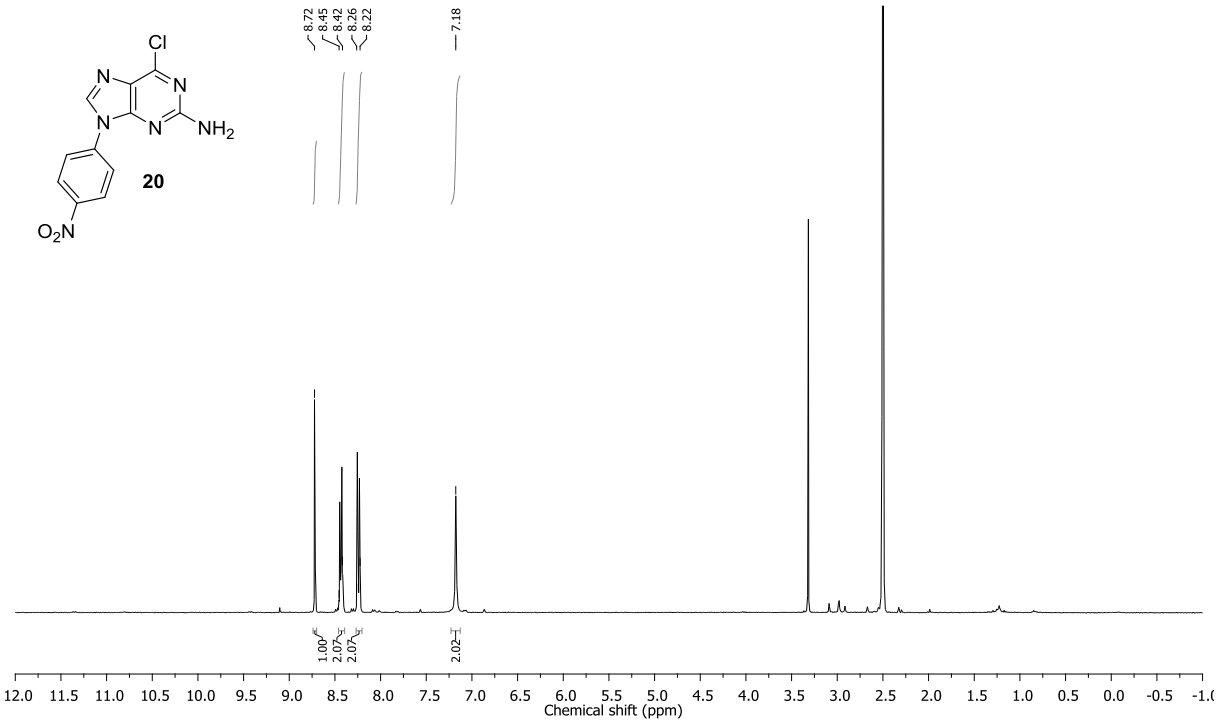
^{1}H NMR (400 MHz, d_6-DMSO)



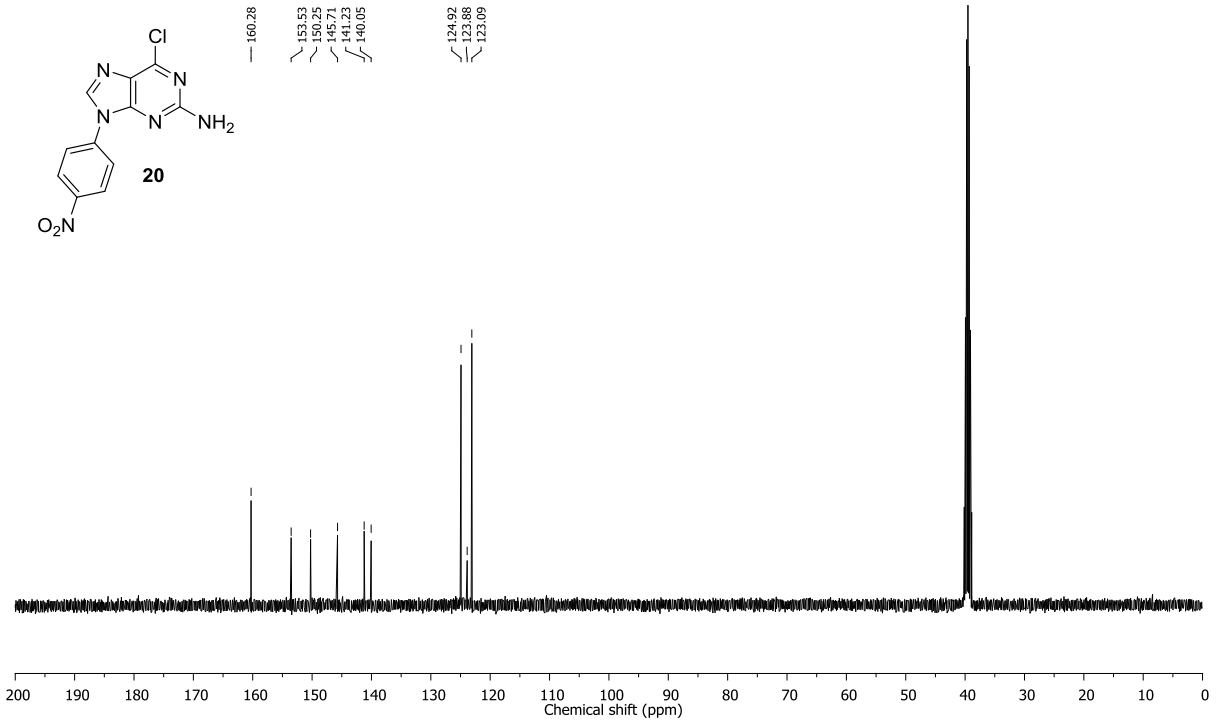
^{13}C NMR (100 MHz, d_6-DMSO)



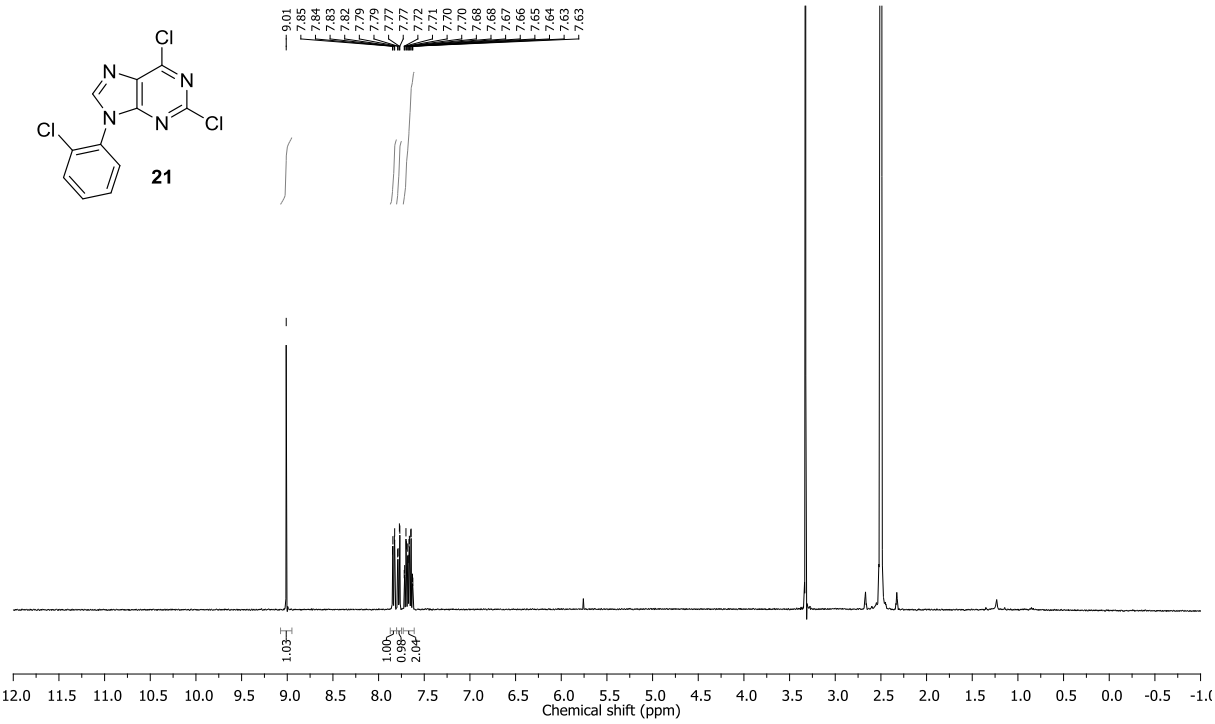
^{1}H NMR (400 MHz, d_6-DMSO)



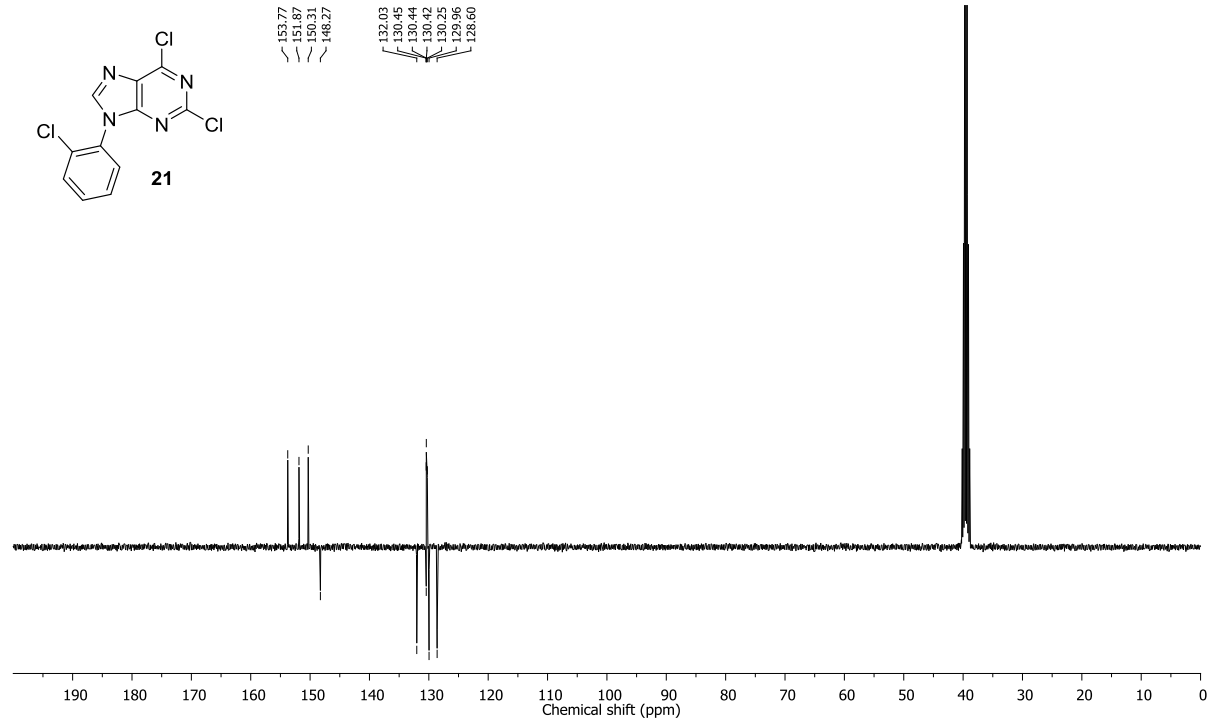
^{13}C NMR (100 MHz, d_6-DMSO)



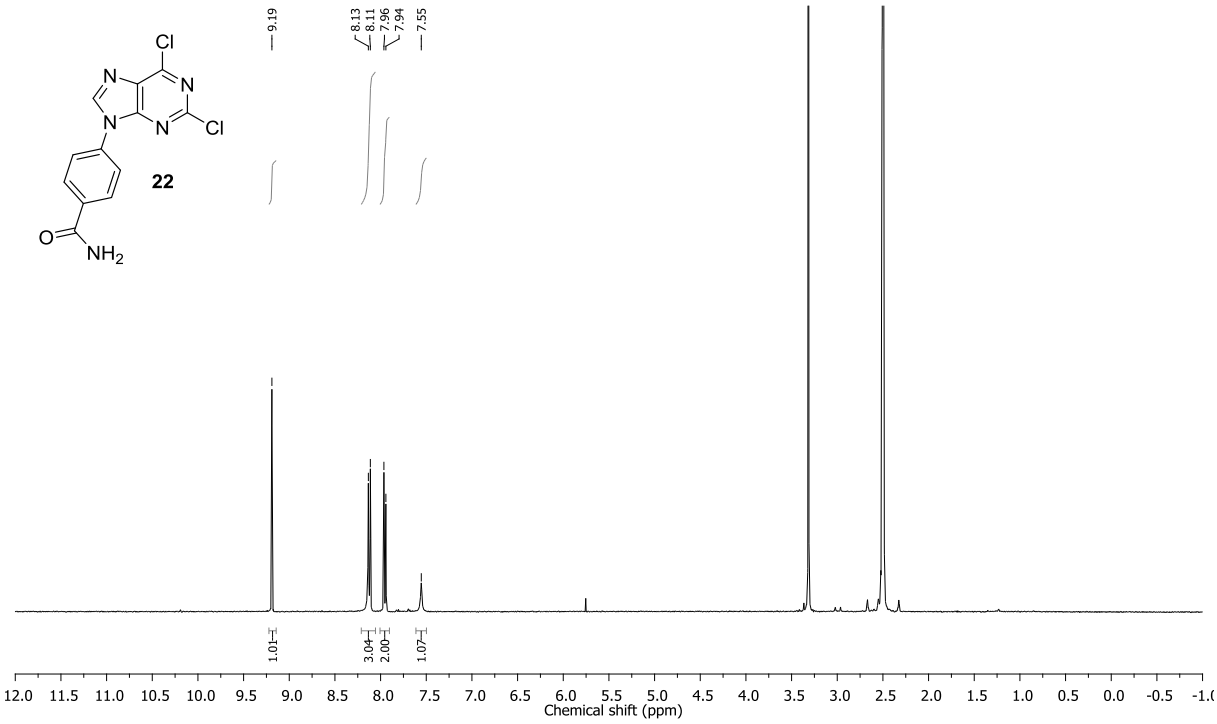
^{1}H NMR (400 MHz, d_6-DMSO)



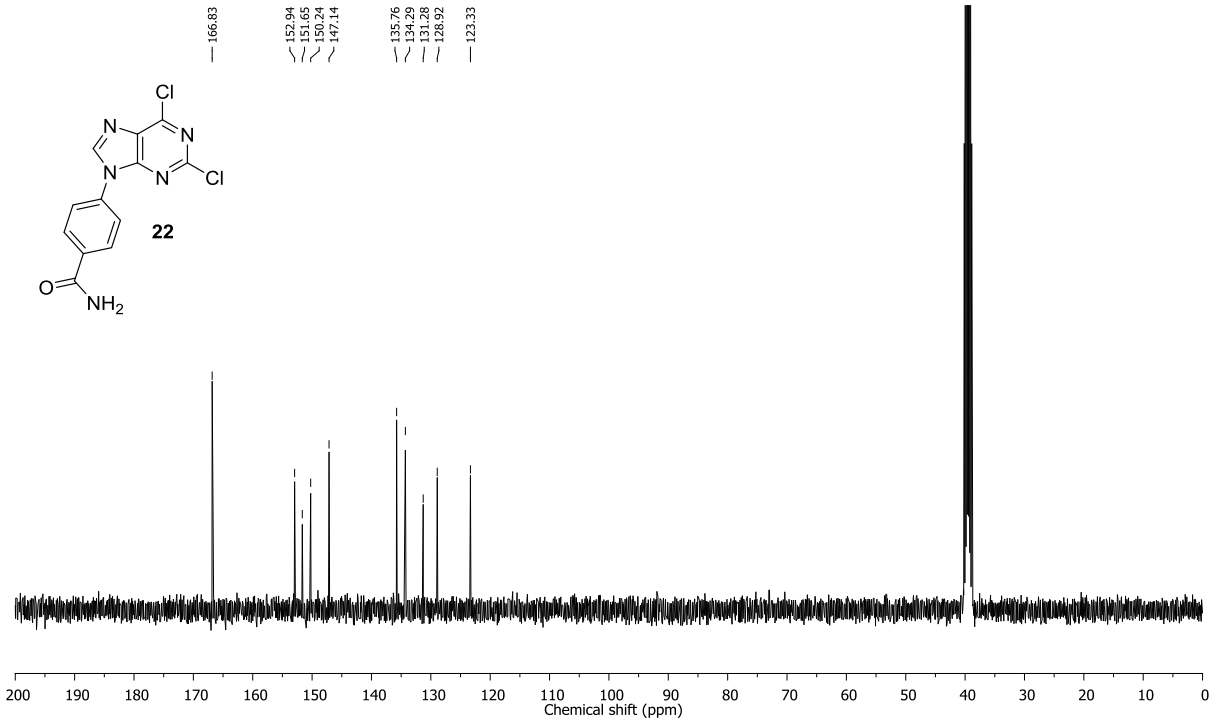
^{13}C NMR JMOD (100 MHz, d_6-DMSO)



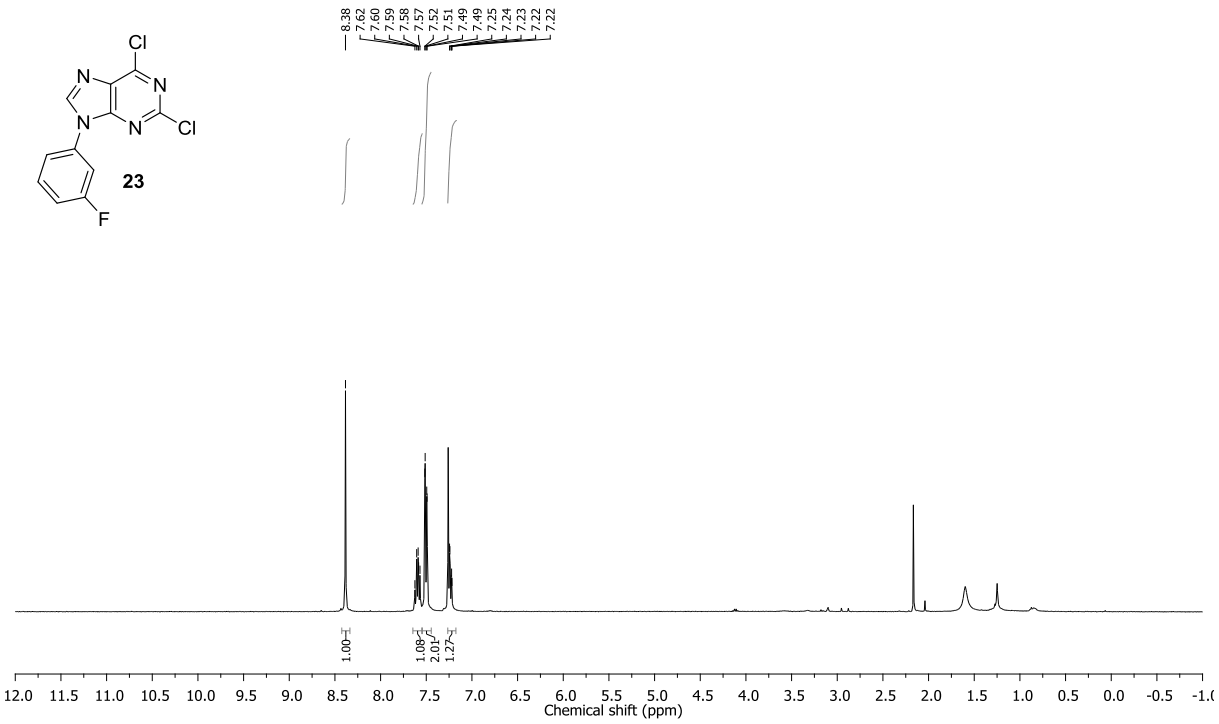
^{1}H NMR (400 MHz, d_6-DMSO)



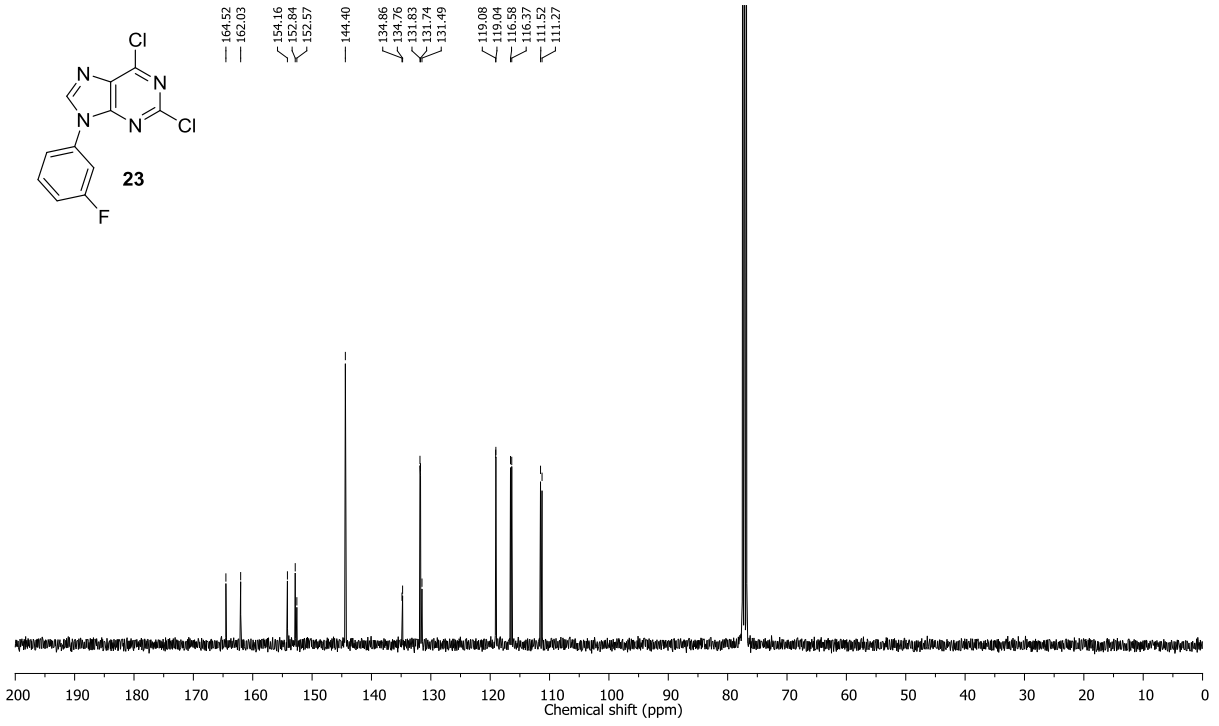
^{13}C NMR QUAT (100 MHz, d_6-DMSO)



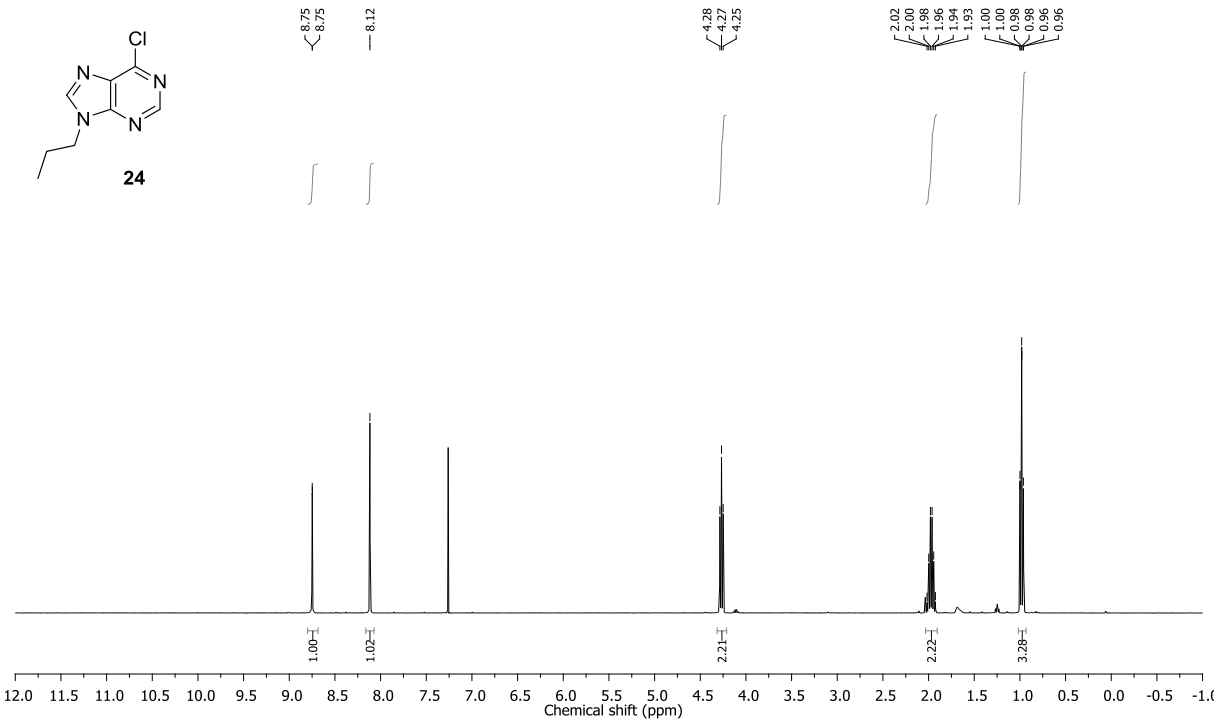
^{1}H NMR (400 MHz, $CDCl_3$)



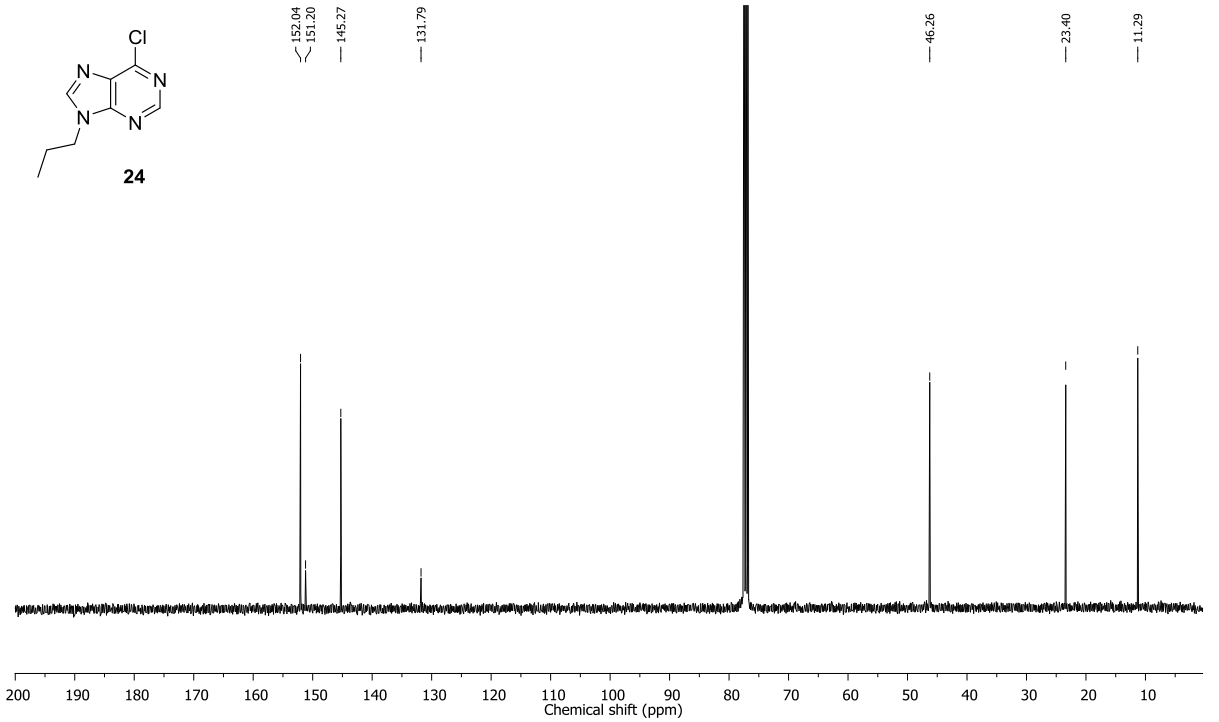
^{13}C NMR (100 MHz, $CDCl_3$)



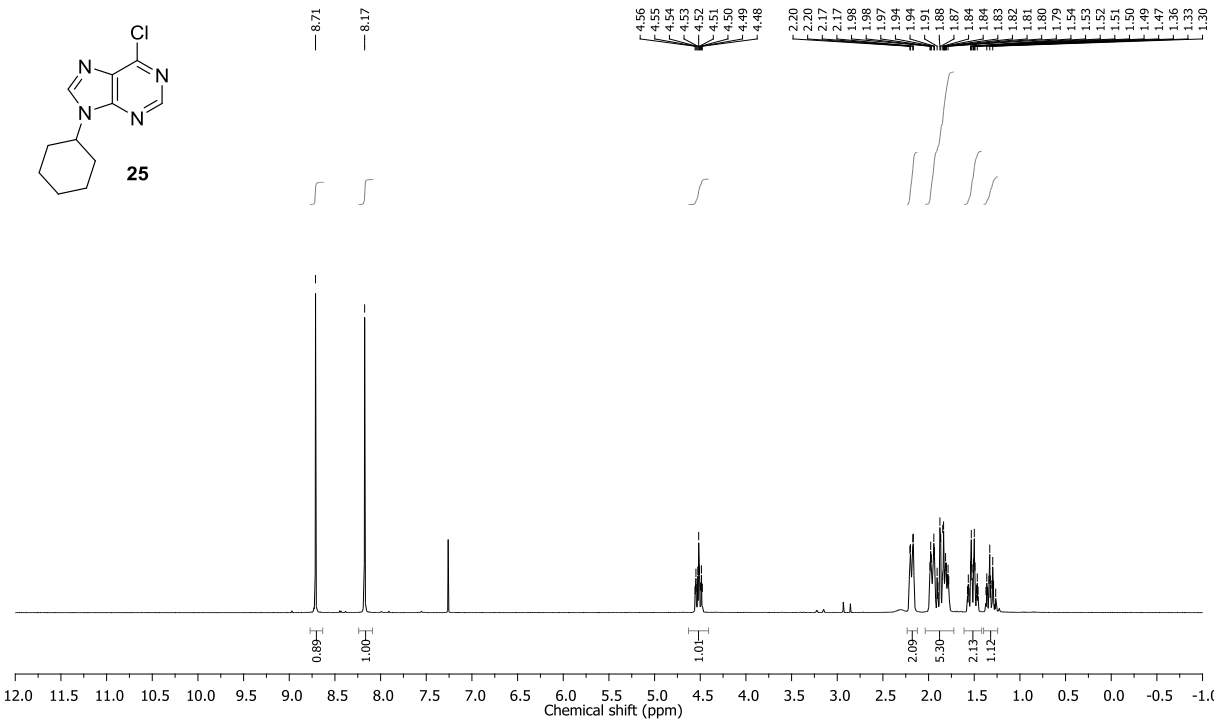
^{1}H NMR (400 MHz, $CDCl_3$)



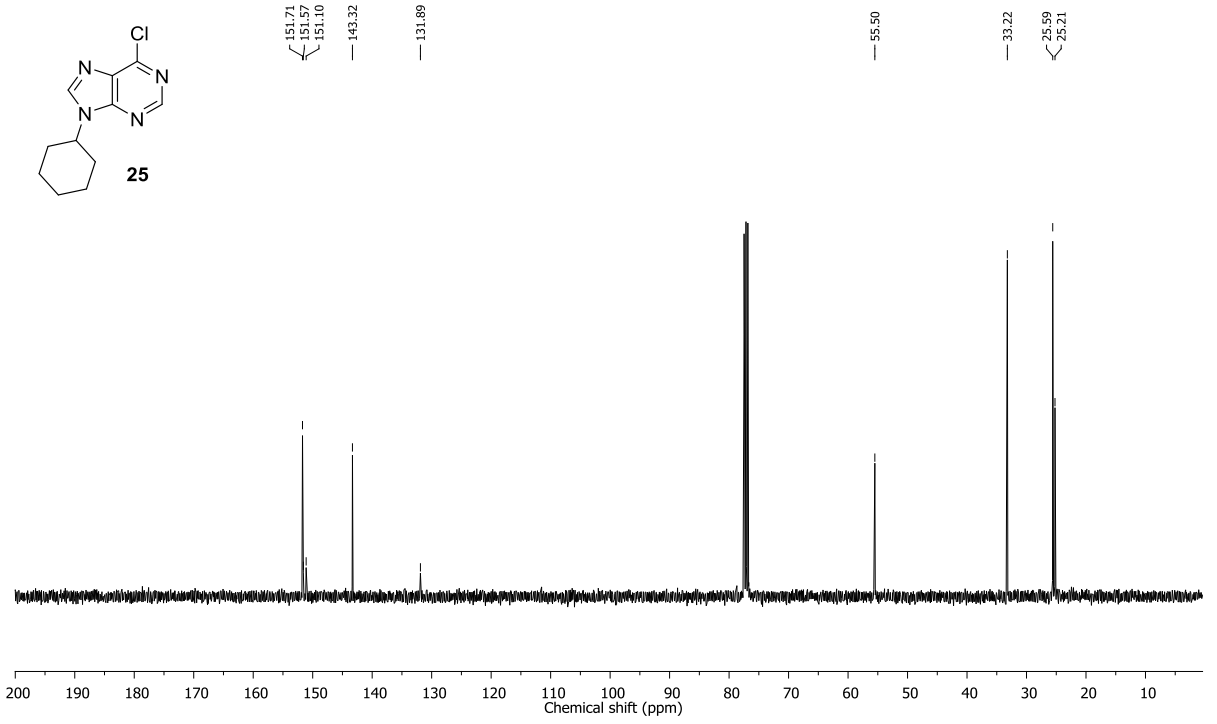
^{13}C NMR (100 MHz, $CDCl_3$)



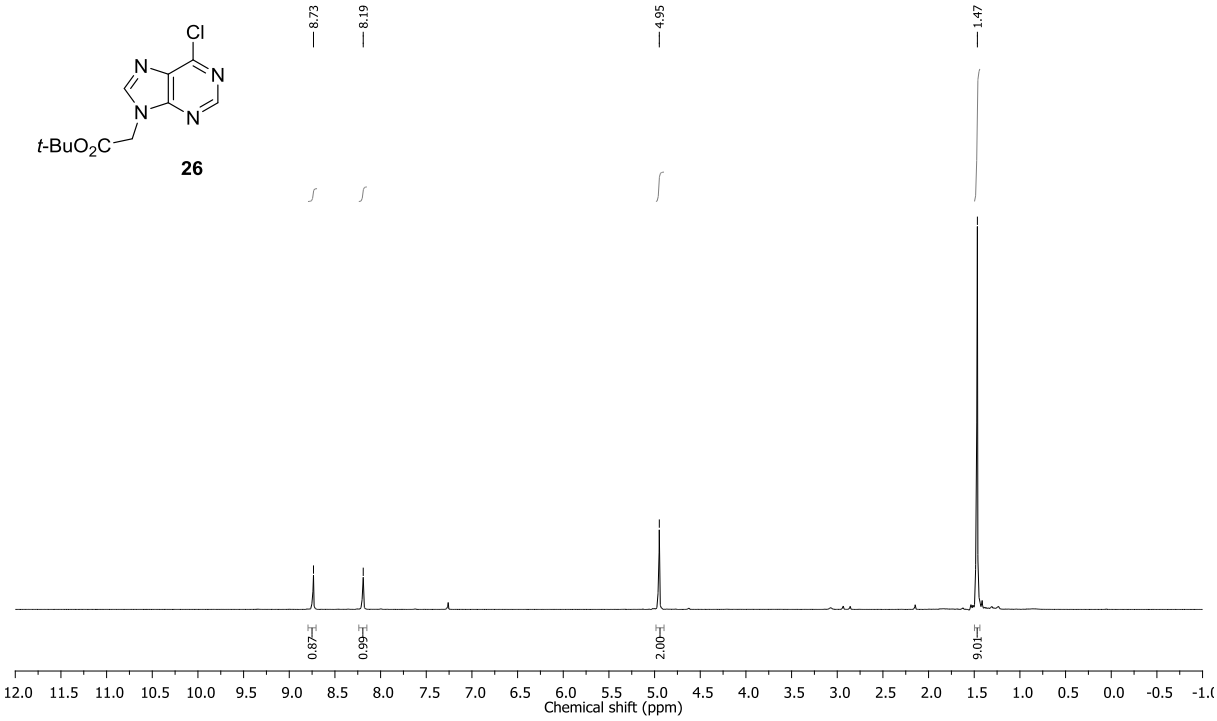
^{1}H NMR (400 MHz, $CDCl_3$)



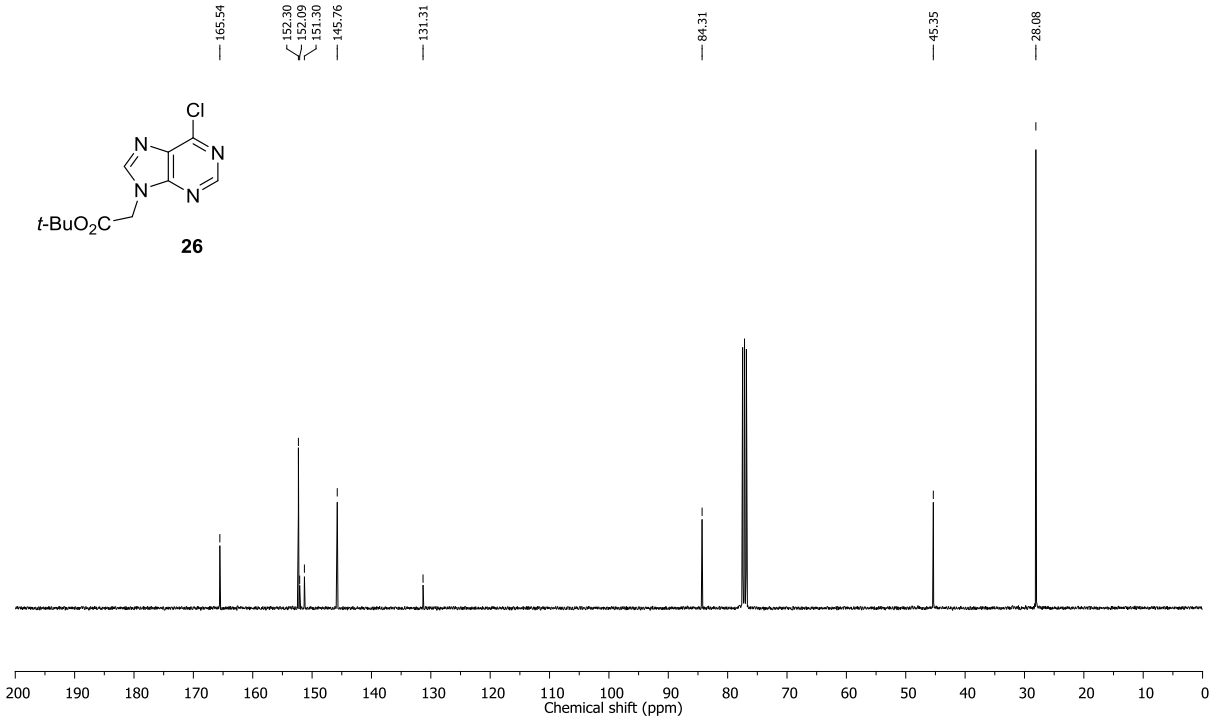
^{13}C NMR (100 MHz, $CDCl_3$)



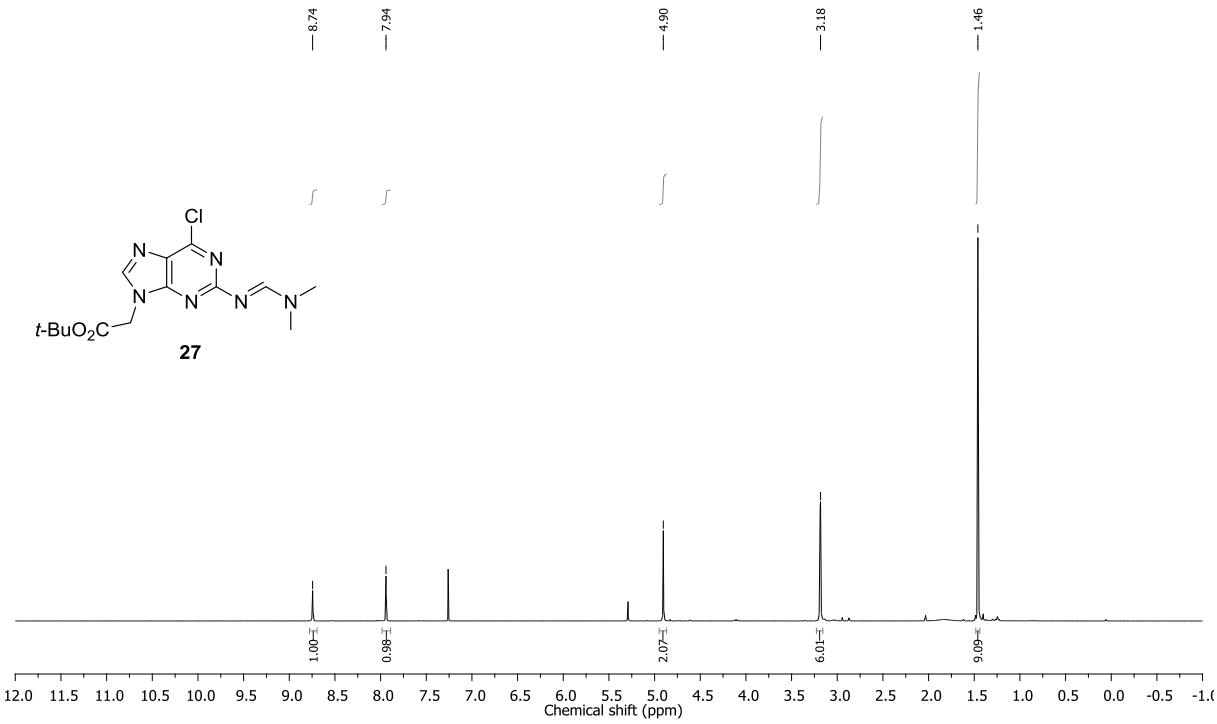
^{1}H NMR (400 MHz, $CDCl_3$)



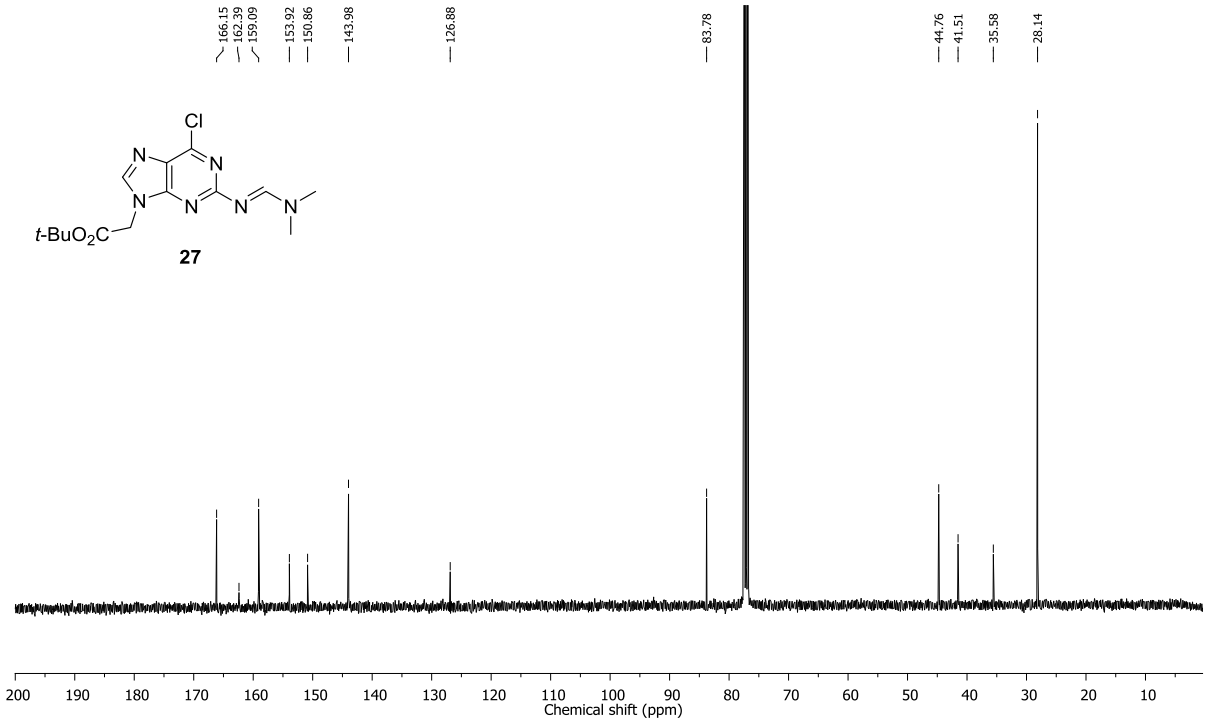
^{13}C NMR (100 MHz, $CDCl_3$)



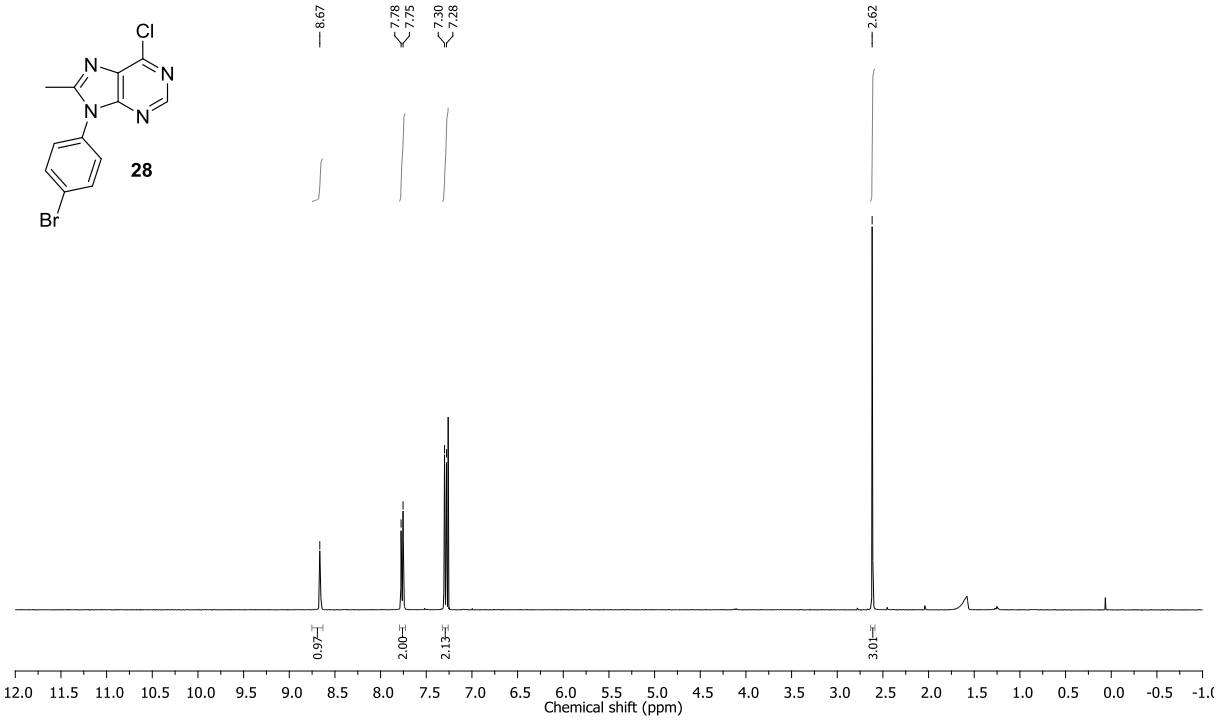
^{1}H NMR (400 MHz, $CDCl_3$)



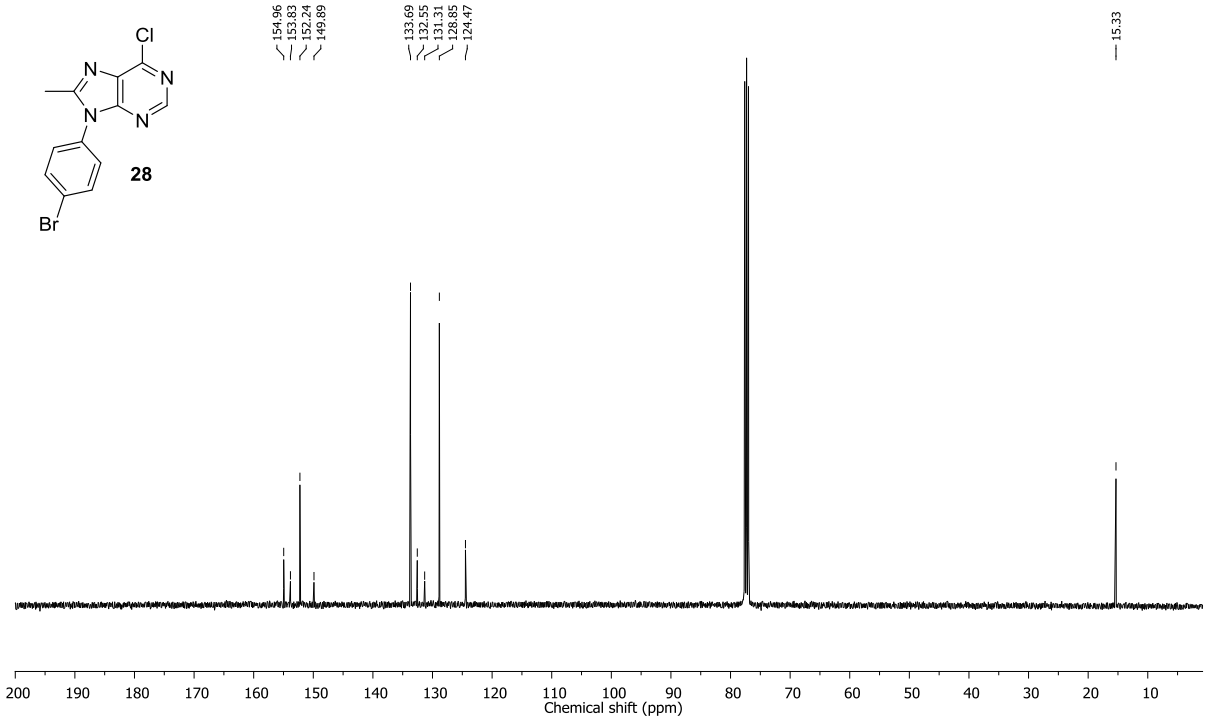
^{13}C NMR (100 MHz, $CDCl_3$)



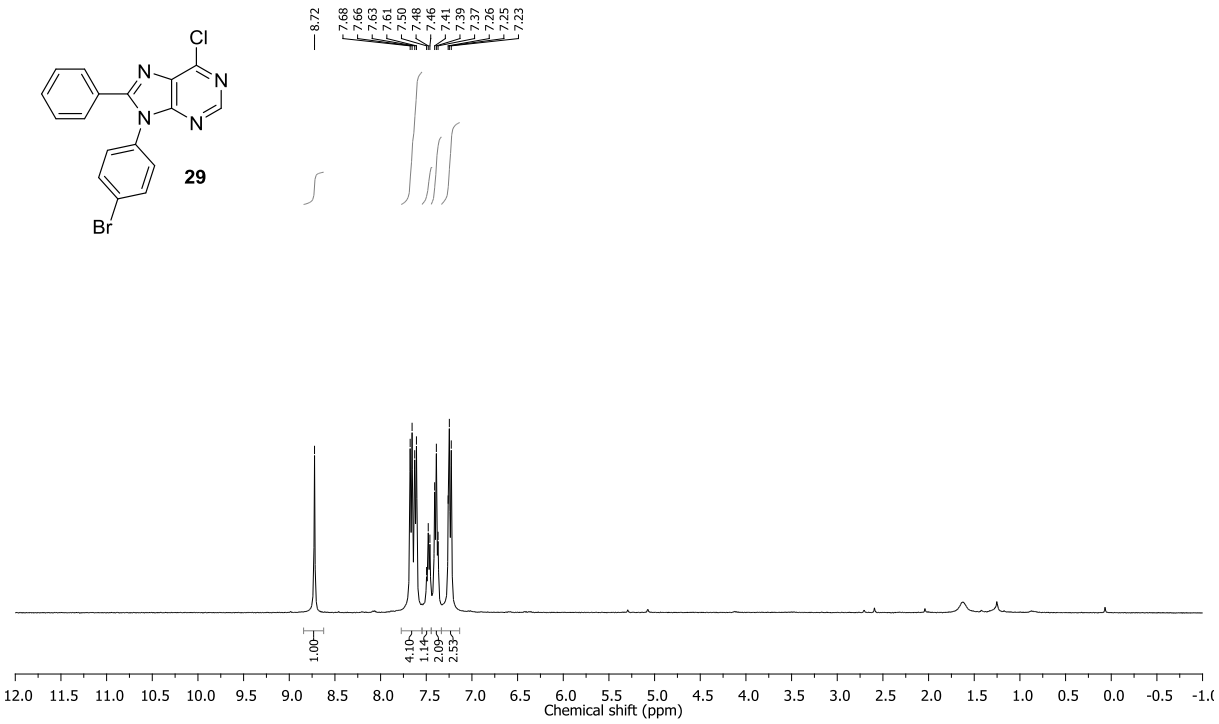
^{1}H NMR (400 MHz, $CDCl_3$)



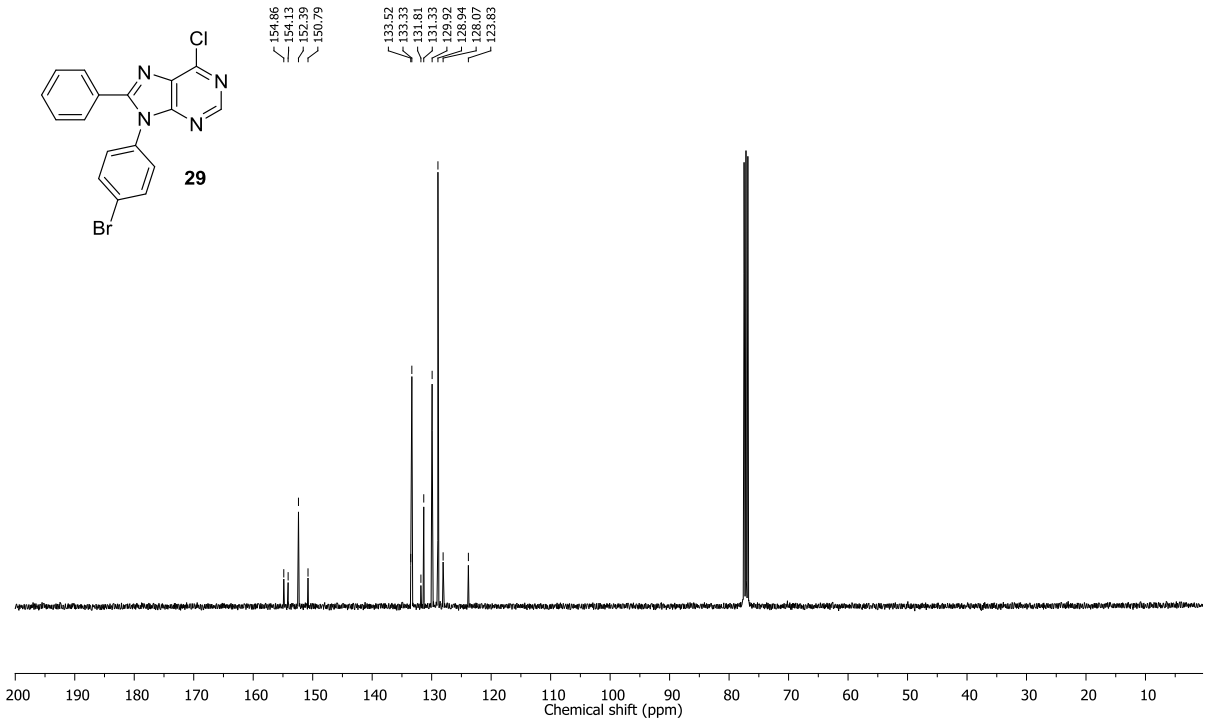
^{13}C NMR (100 MHz, $CDCl_3$)



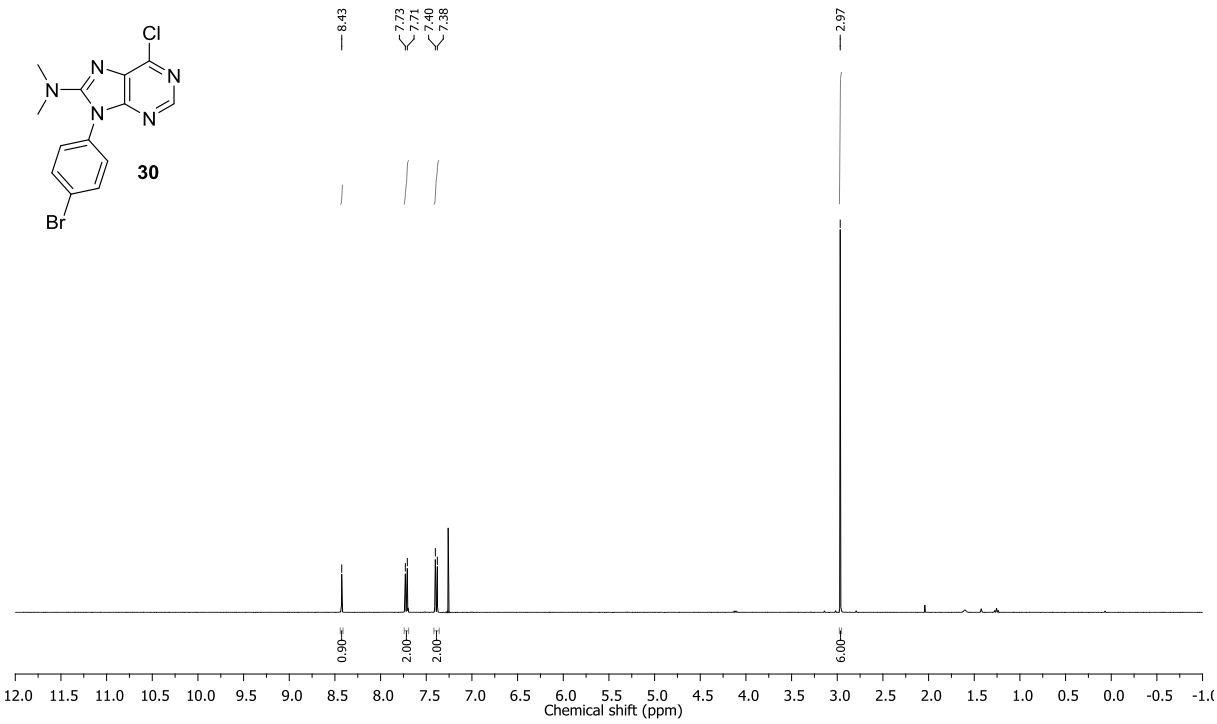
^{1}H NMR (400 MHz, $CDCl_3$)



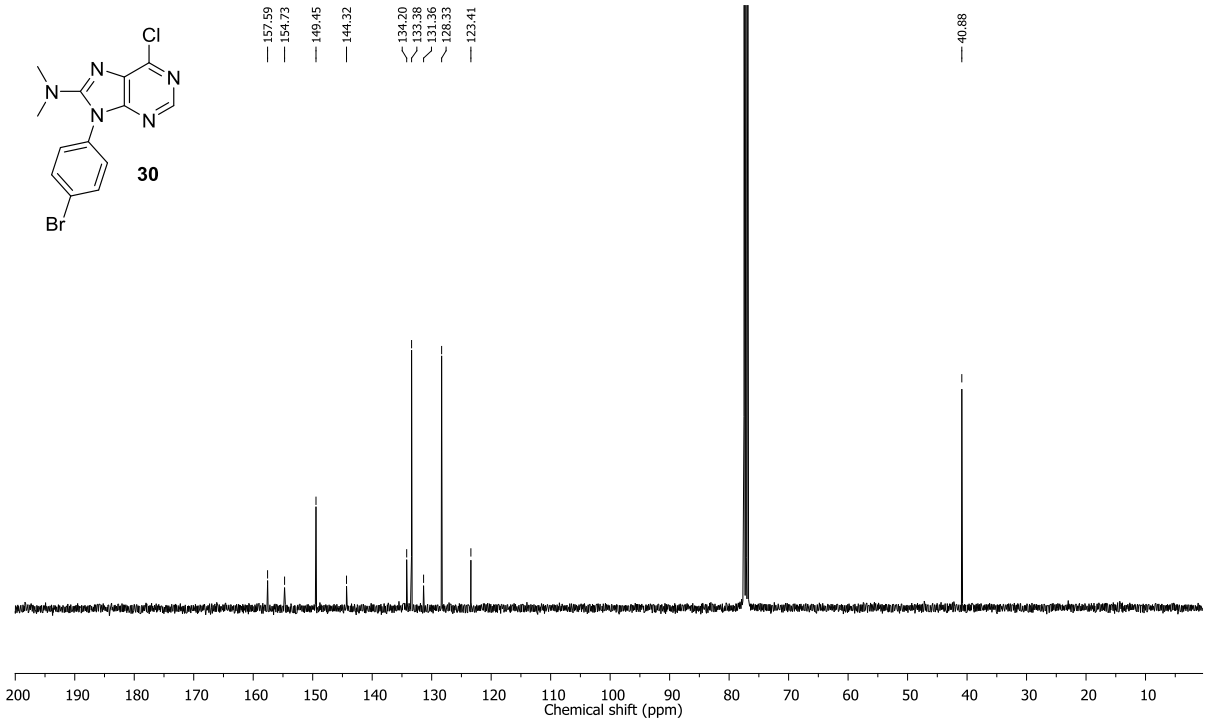
^{13}C NMR (100 MHz, $CDCl_3$)



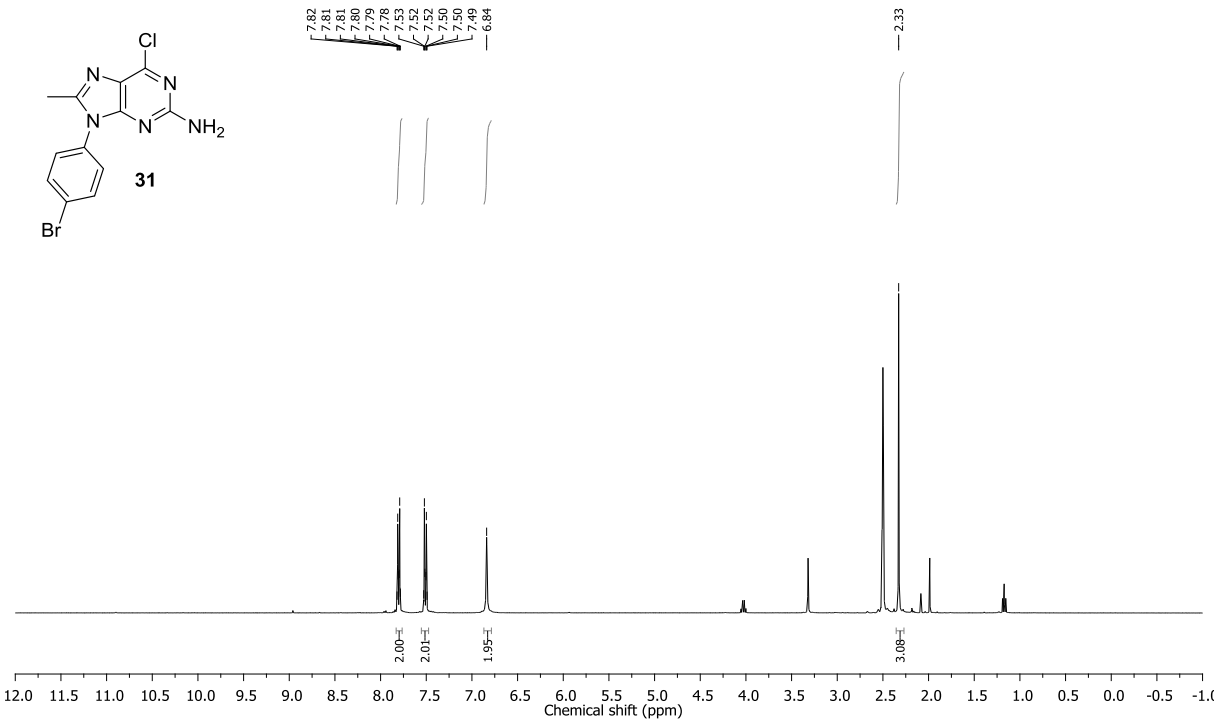
^{1}H NMR (400 MHz, $CDCl_3$)



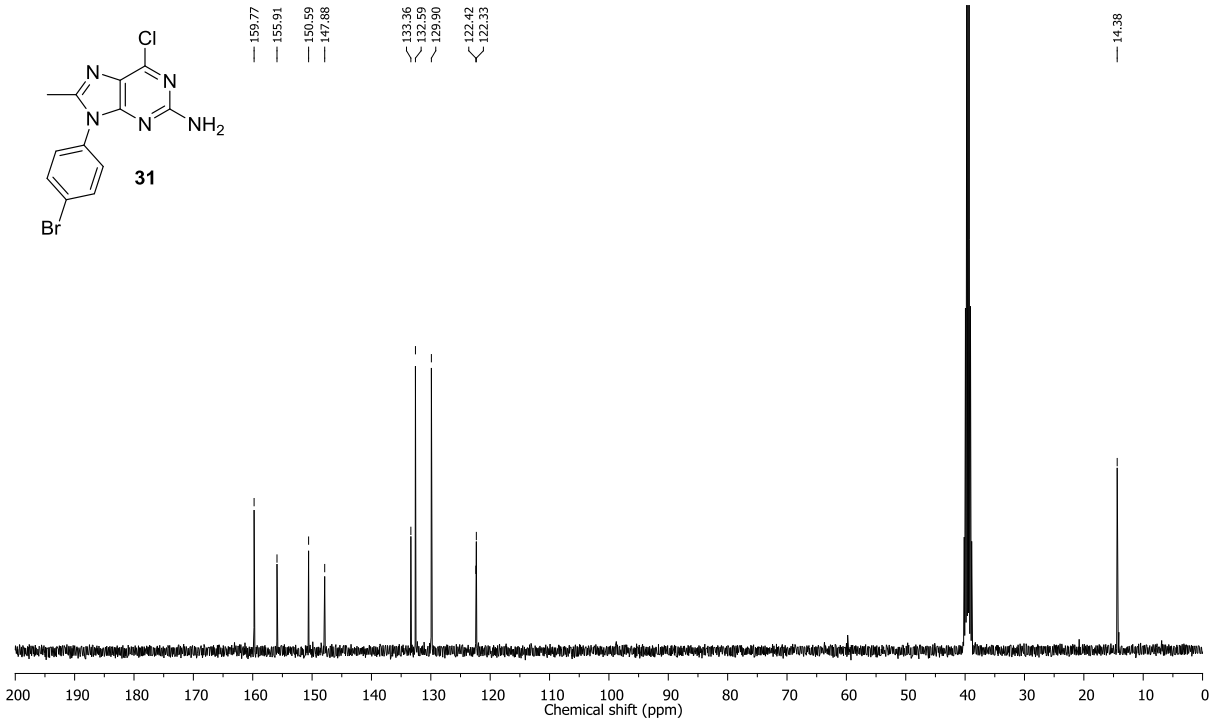
^{13}C NMR (100 MHz, $CDCl_3$)



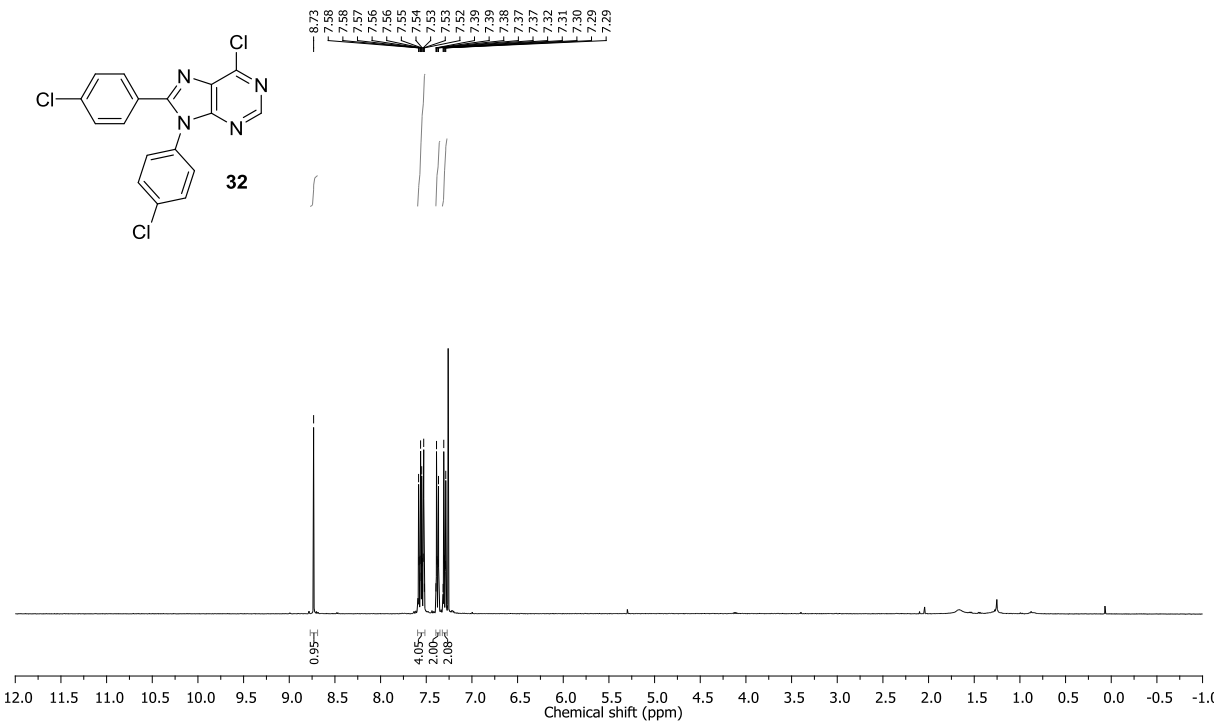
^{1}H NMR (400 MHz, d_6-DMSO)



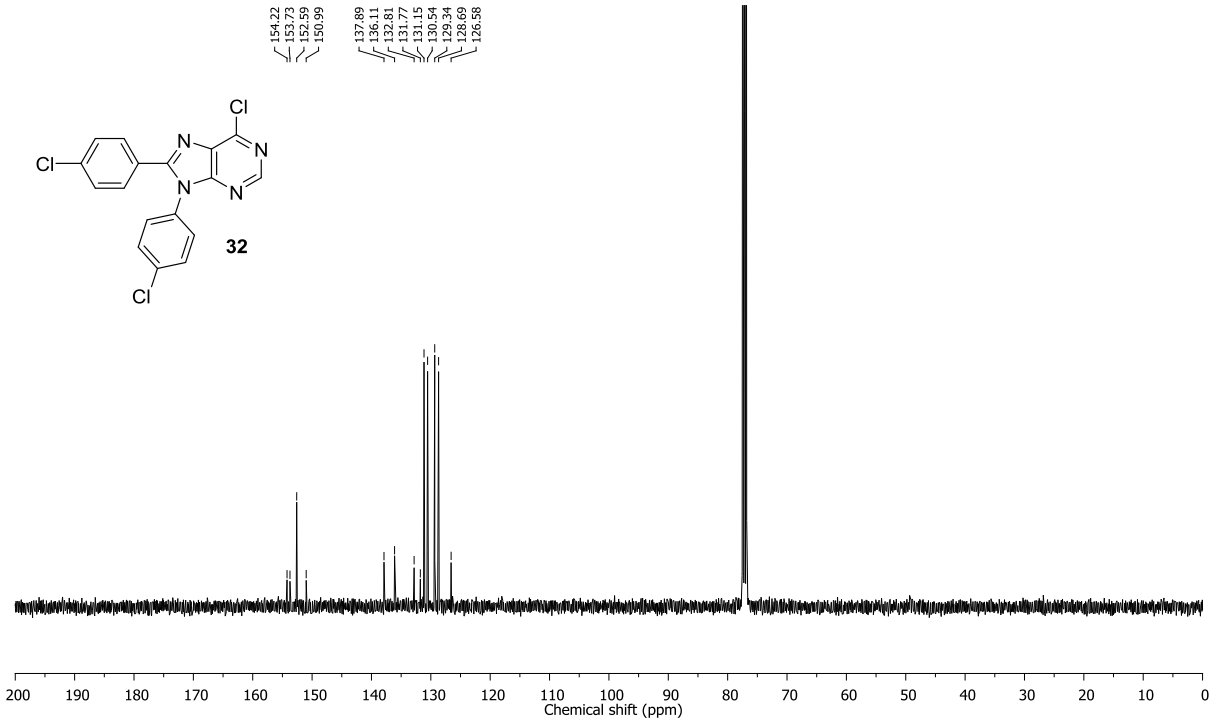
^{13}C NMR (100 MHz, d_6-DMSO)



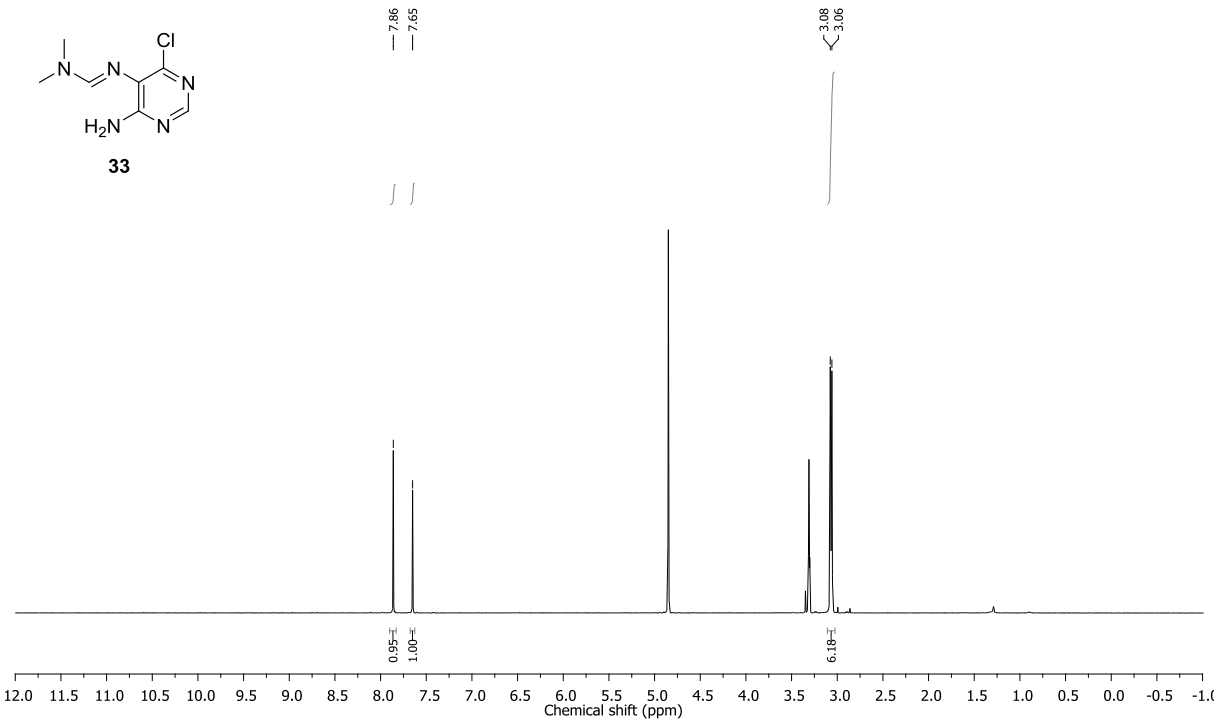
^{1}H NMR (400 MHz, $CDCl_3$)



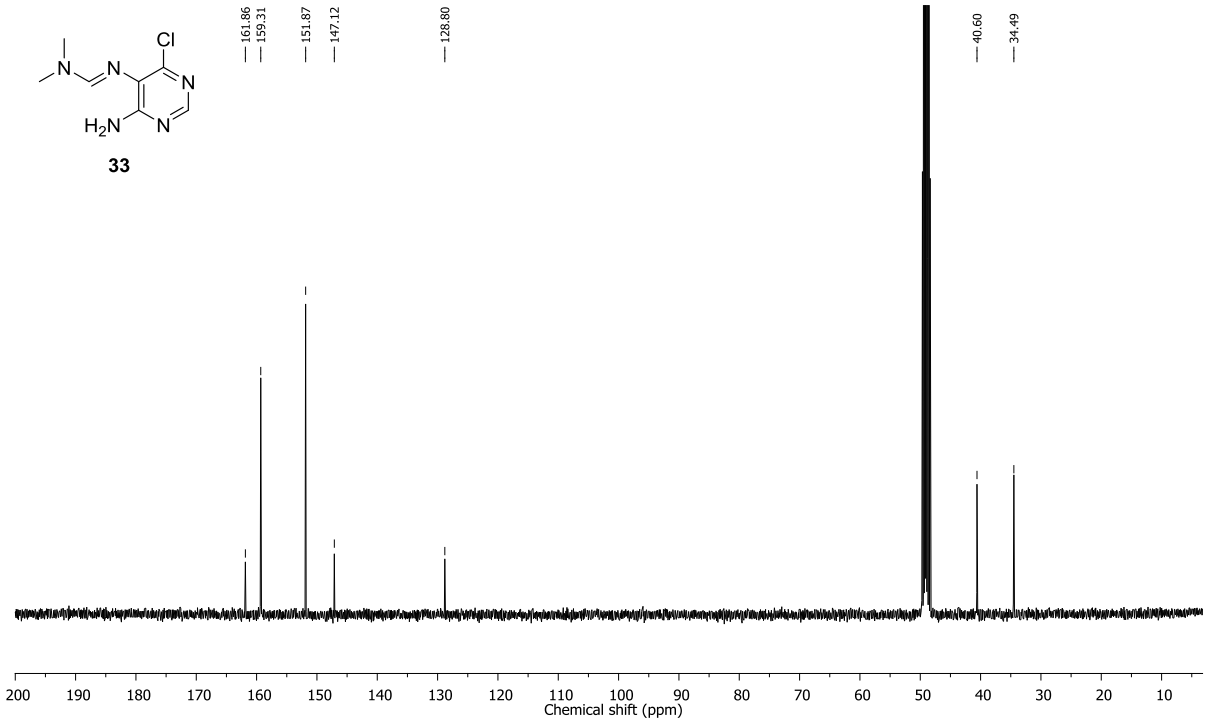
^{13}C NMR (100 MHz, $CDCl_3$)



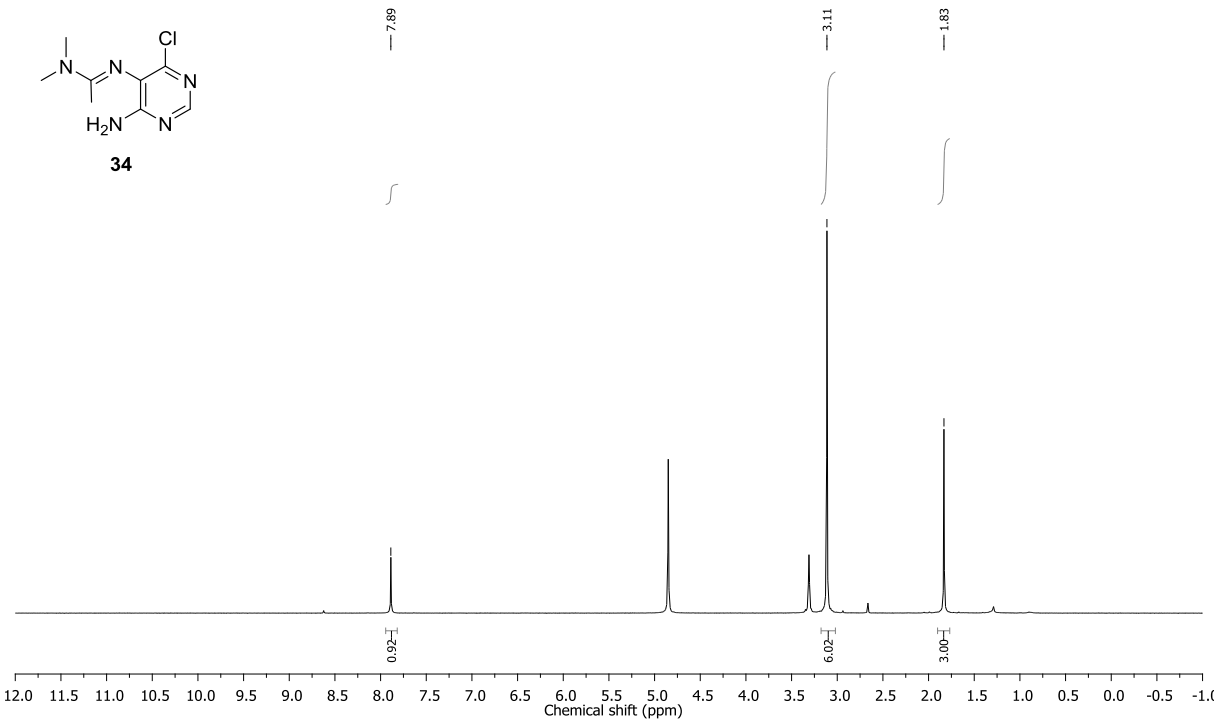
^{1}H NMR (400 MHz, CD_3OD)



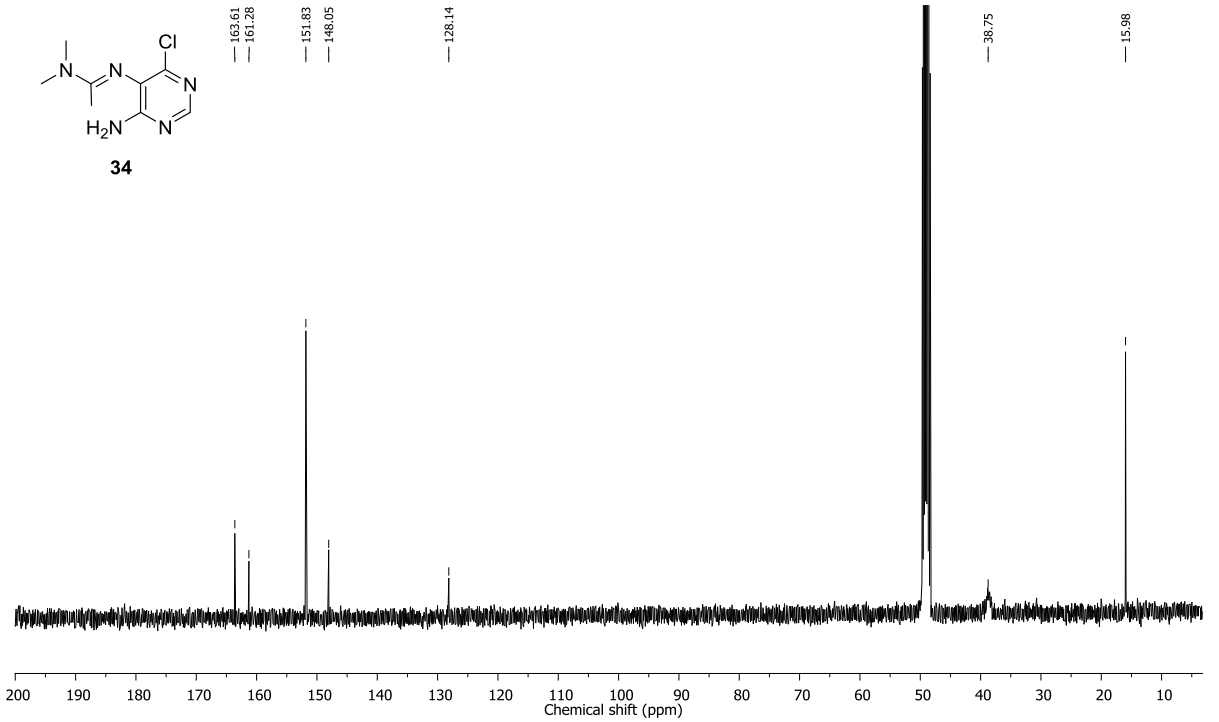
^{13}C NMR (100 MHz, CD_3OD)



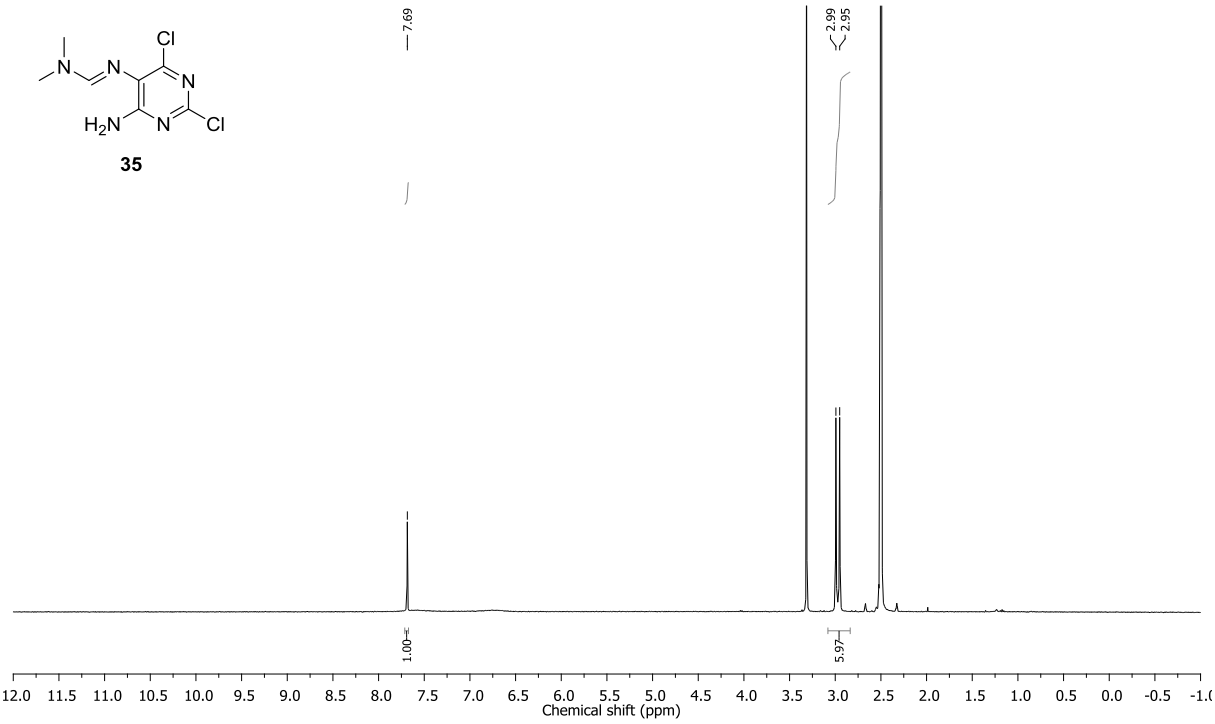
^{1}H NMR (400 MHz, CD_3OD)



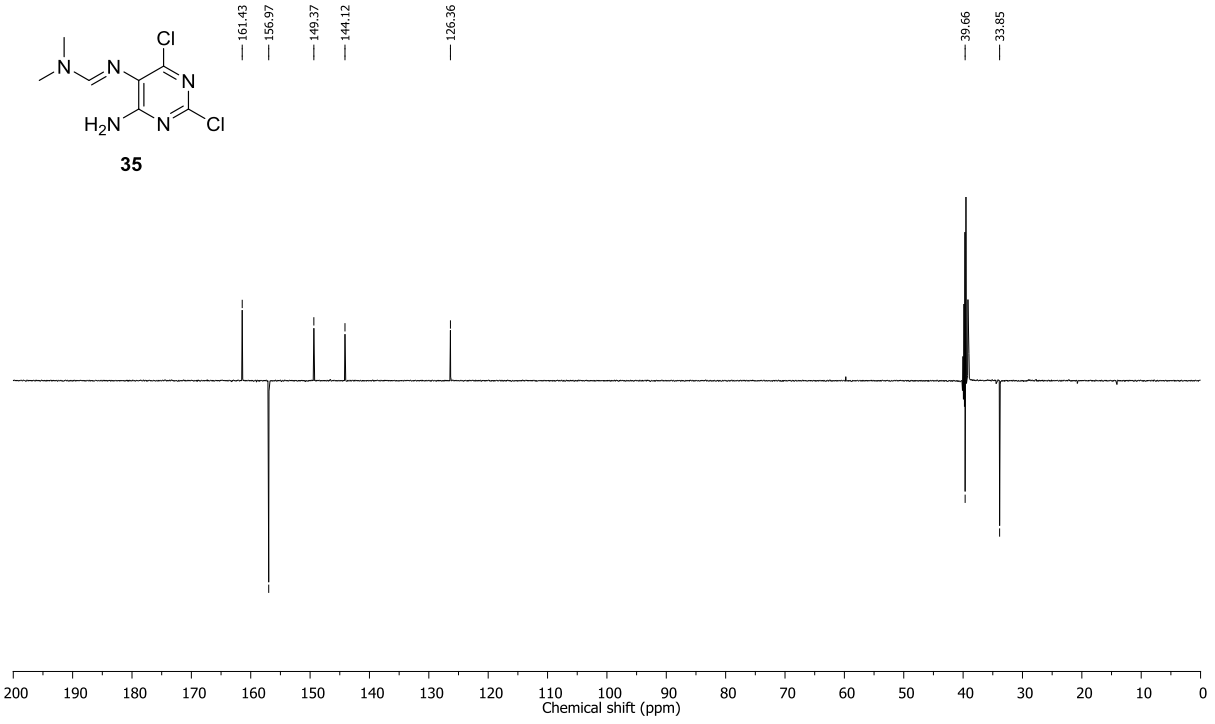
^{13}C NMR (100 MHz, CD_3OD)



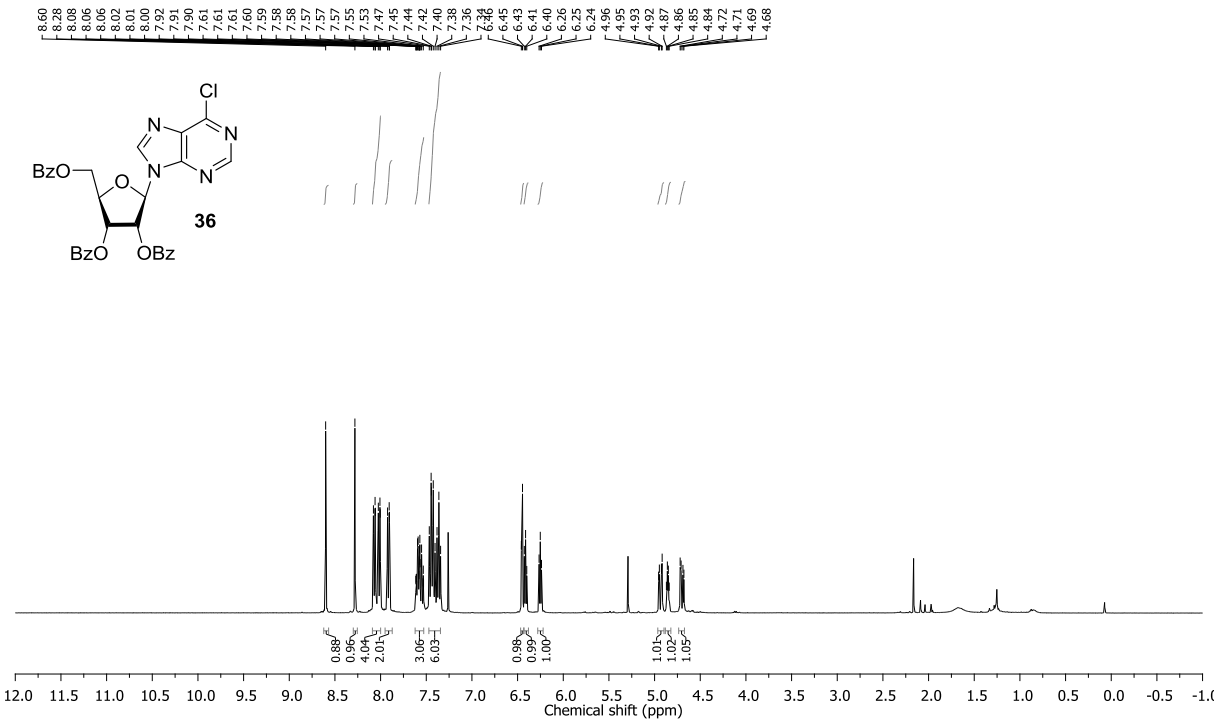
^{1}H NMR (400 MHz, d_6-DMSO)



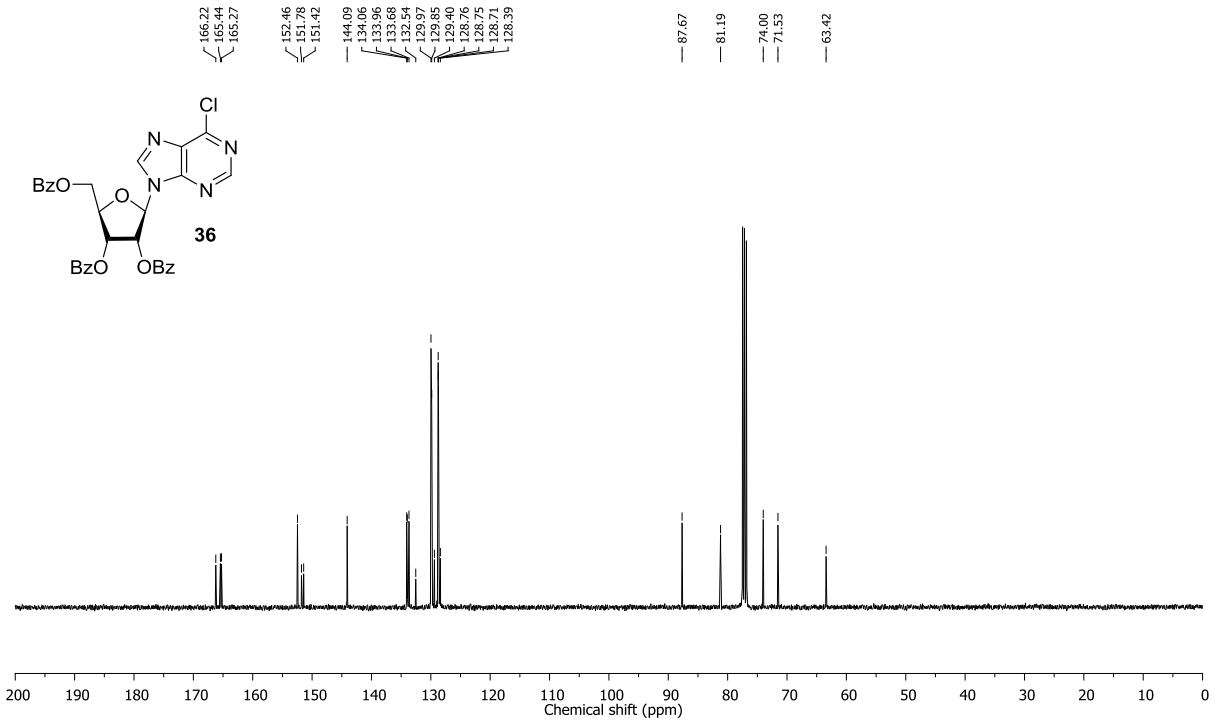
^{13}C NMR JMOD (100 MHz, d_6-DMSO)



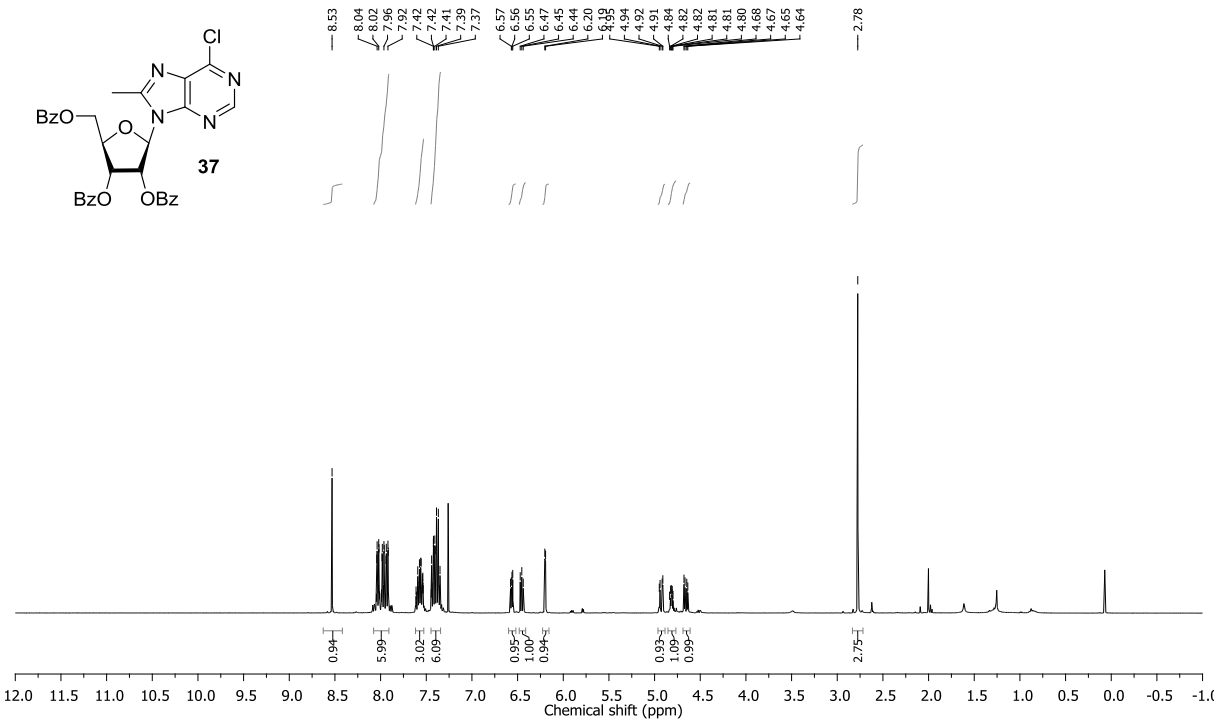
^{1}H NMR (400 MHz, $CDCl_3$)



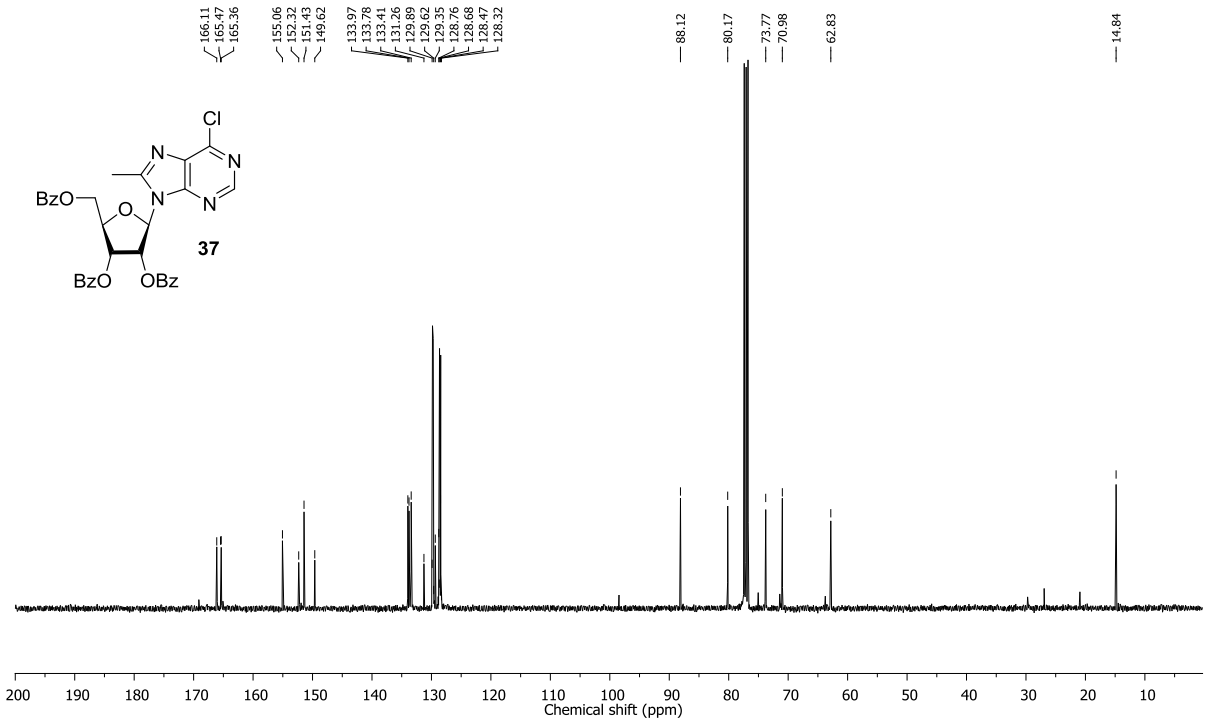
^{13}C NMR (100 MHz, $CDCl_3$)



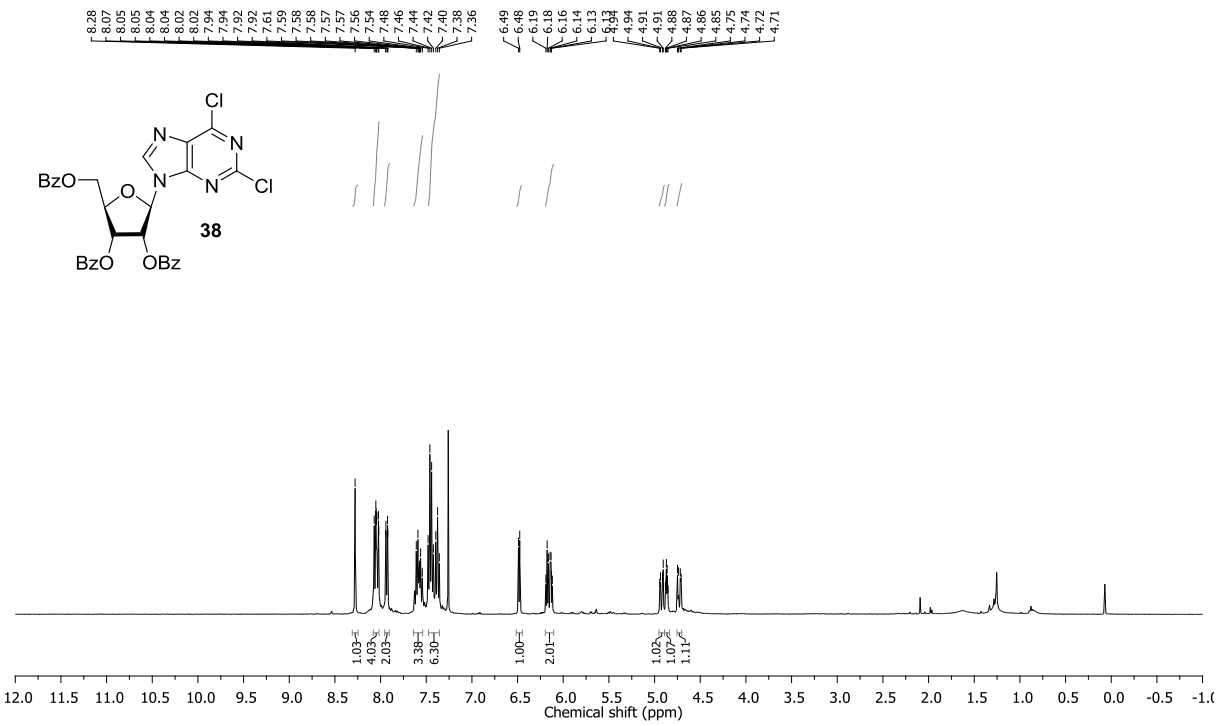
^{1}H NMR (400 MHz, $CDCl_3$)



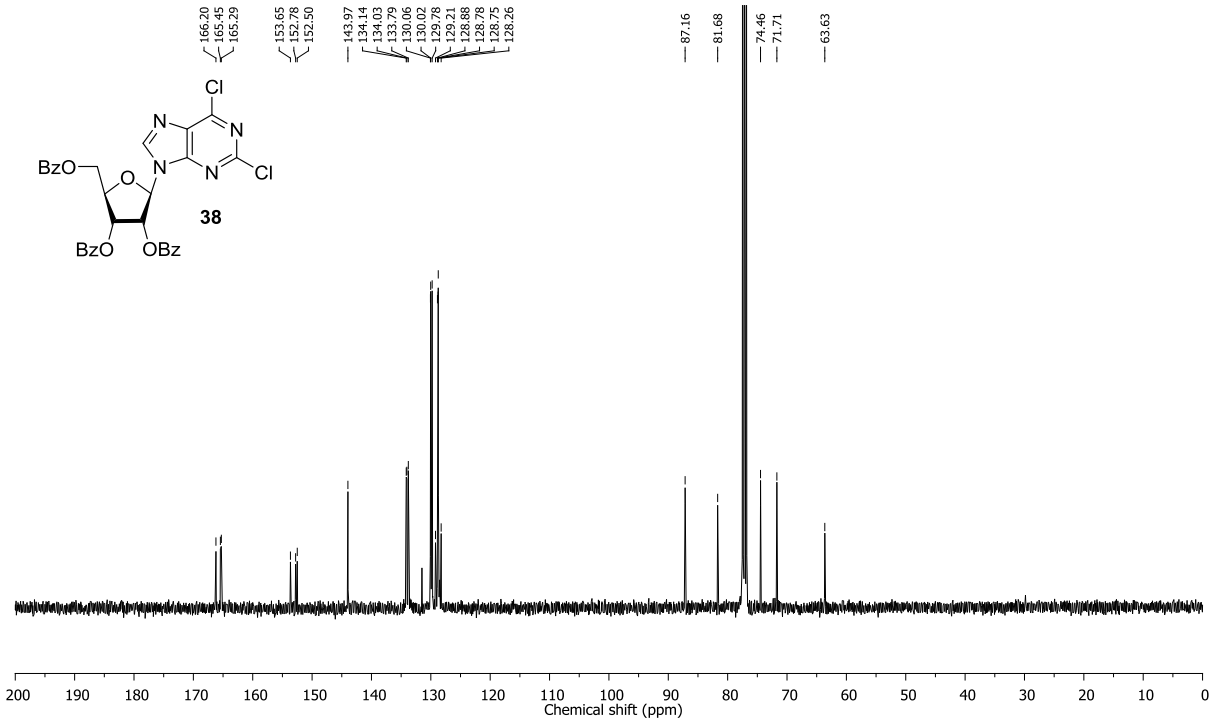
^{13}C NMR (100 MHz, $CDCl_3$)



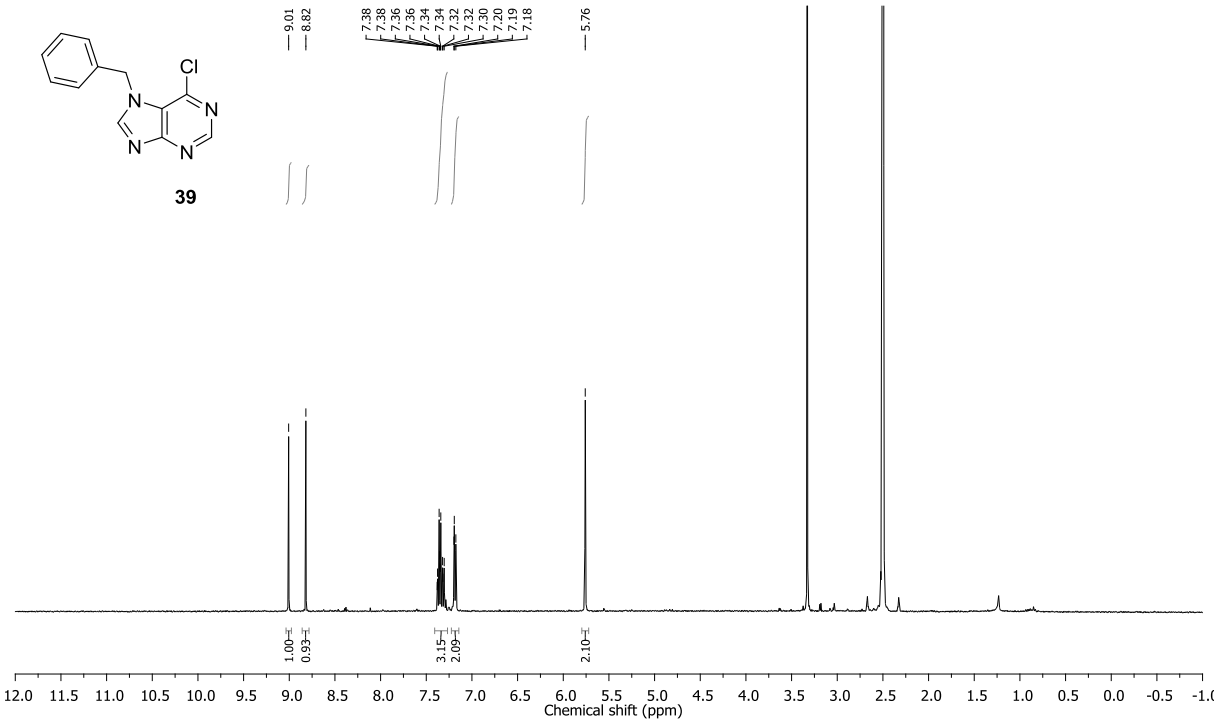
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, d_6-DMSO)



^{13}C NMR (100 MHz, $CDCl_3$)