Additional Supporting Information

Solvent directed regioselective benzylation of adenine

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Table of content:

PART A.1

HMBC and HQSC ^{1}H-^{13}C correlation spectra (400.13 MHz) for the Figure indicated spectra of N9-benzyladenine in [D_6]DMSO, $CDCl_3$ and [D_4]MeOD solvent, y-axis: ^{13}C NMR (ppm), x-axis: ^{1}H NMR (ppm)

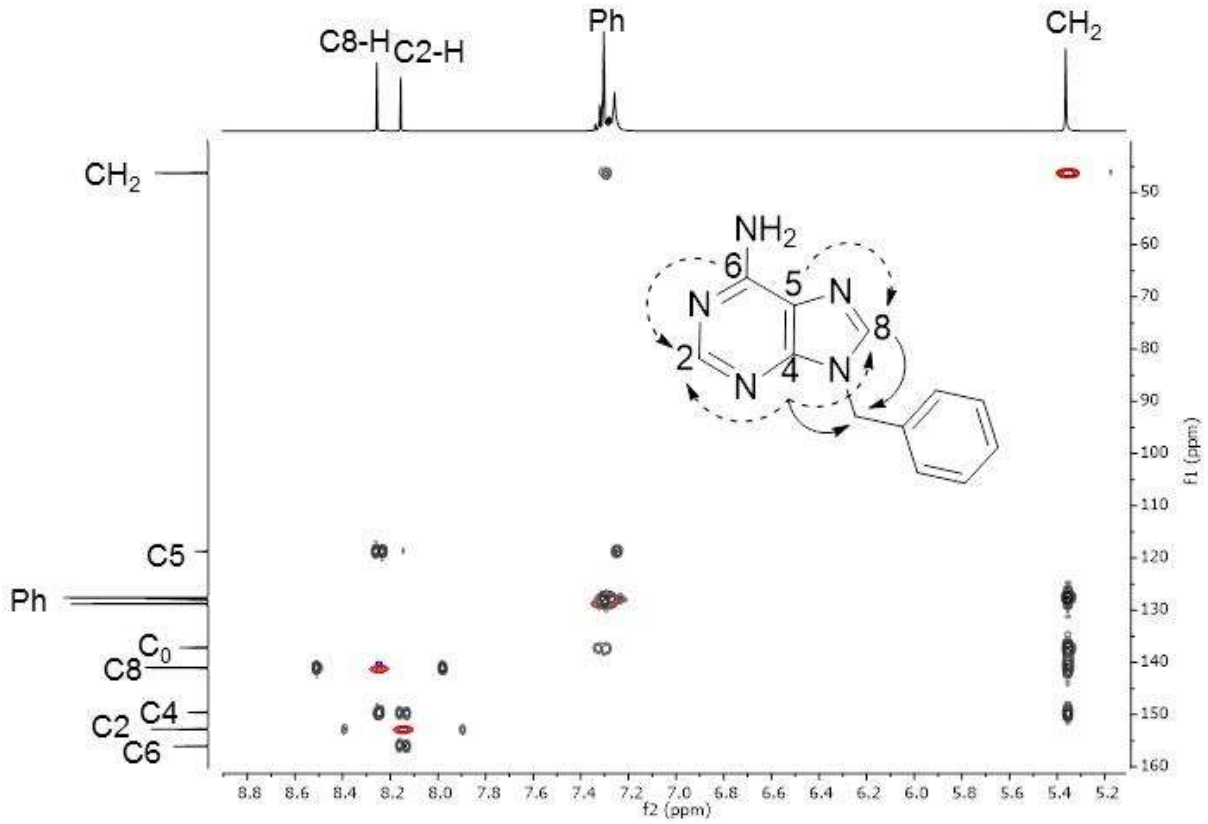


Figure S1 HMBC (black ^{1}H-^{13}C correlations) and HSQC (red ^{1}H-^{13}C correlations) in [D_6]DMSO.

C5 is the only purine ring carbon that is bonded to a single nitrogen atom and therefore resonates most upfield of all the purine ring carbons in the ^{13}C NMR spectra in all three solvents, resonating at 118.8 ppm in [D_6]DMSO. In the HMBC spectrum, the C5 peak shows a strong 3-bond correlation to the nearest proton C8-H (8.26 ppm) - Figure S1, black ^{1}H-^{13}C correlations. HSQC spectroscopy was used to identify the chemical shift of C8 (141 ppm) based on the

correlation with C8-H – Figure S1, red ^{1}H-^{13}C correlations. The C8-H also shows 3-bond coupling to C4 (149.6 ppm) in the HMBC spectrum. HMBC and HSQC spectra were used to continue mapping the chemical shifts of the atoms of the purine ring: C4 shows long range coupling to C2-H (8.16 ppm) which in turn couples to C2 (152.8 ppm, 1 bond, HSQC) and C6 (156.1 ppm, 3 bond, HMBC).

In addition, spectra showing the NH_2 peak upfield of but partly overlapping with the benzene ring protons showed an additional HMBC correlation from the C5 to the NH_2. When the sample being analysed by NMR was particularly concentrated, a weak 4-bond correlation from C5 to C2-H could also be observed. The position of the benzyl group on N9 was demonstrated by correlations from C4 and C8 to the benzyl CH_2 (5.36 ppm). Coupling between the CH_2 and the carbons of the benzene ring were also observed in the HMBC spectrum, and in particular allowed the quaternary benzene carbon peak to be identified (137.2 ppm).

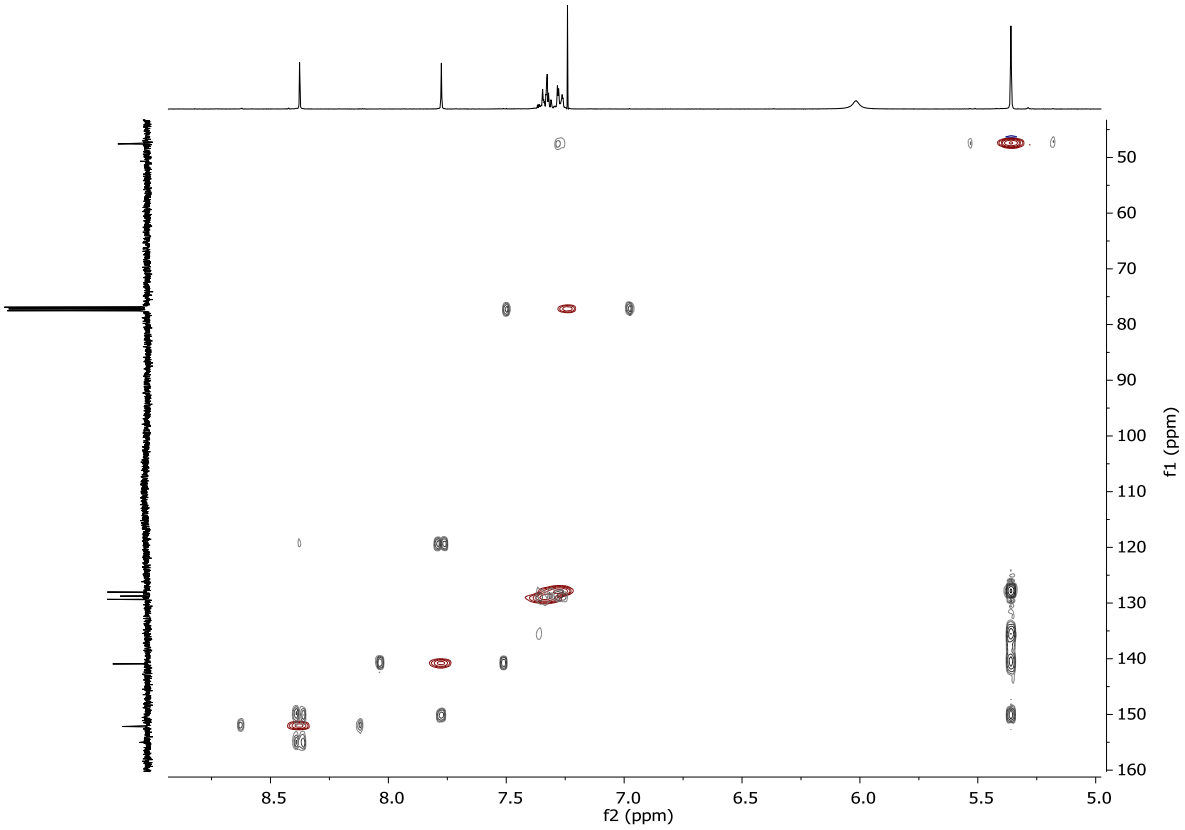


Figure S2 HMBC (black ^{1}H-^{13}C correlations) and HSQC (red ^{1}H-^{13}C correlations) in $CDCl_3$.

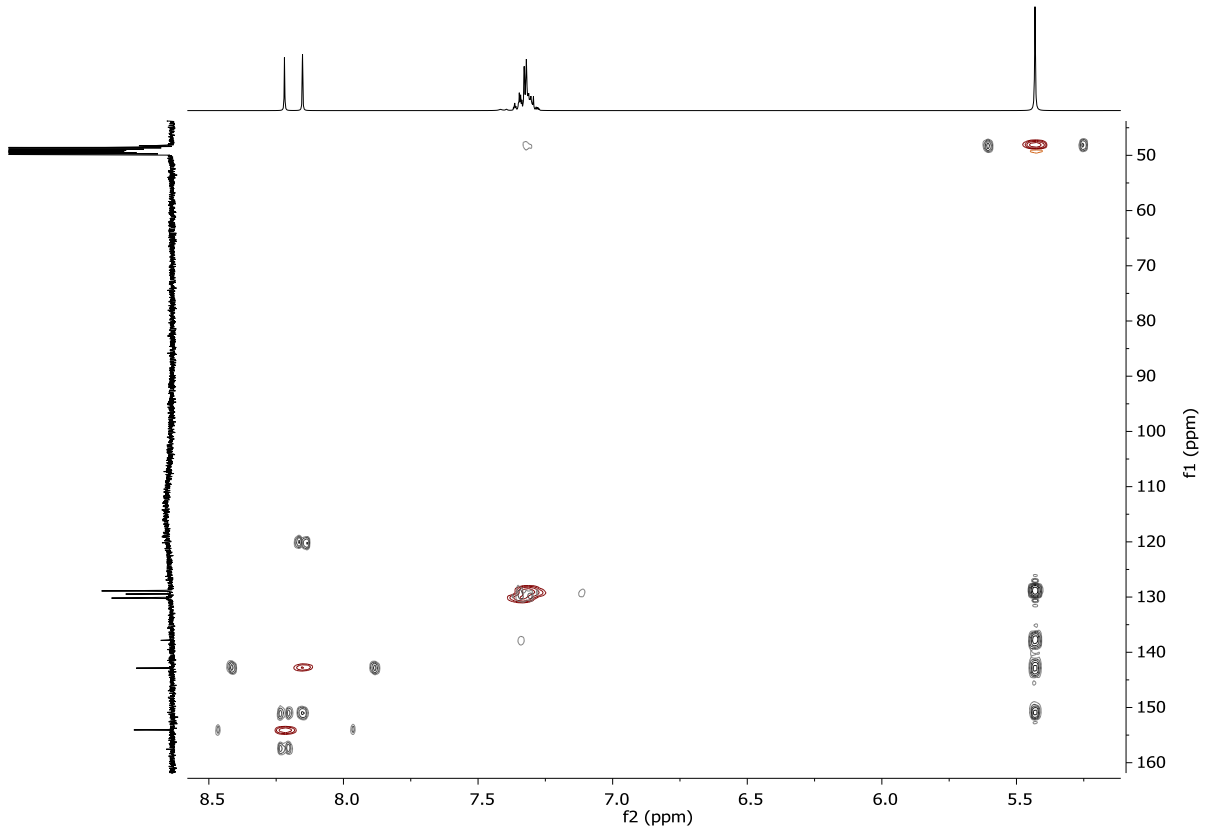


Figure S3 HMBC (black ^{1}H-^{13}C correlations) and HSQC (red ^{1}H-^{13}C correlations) in [D_4]MeOD.

PART A.2

HMBC and HQSC ^{1}H-^{13}C correlation spectra (400.13 MHz) for the Figure indicated spectra of N3-benzyladenine in [D_6]DMSO, $CDCl_3$ and [D_4]MeOD solvent, y-axis: ^{13}C NMR (ppm), x-axis: ^{1}H NMR (ppm)

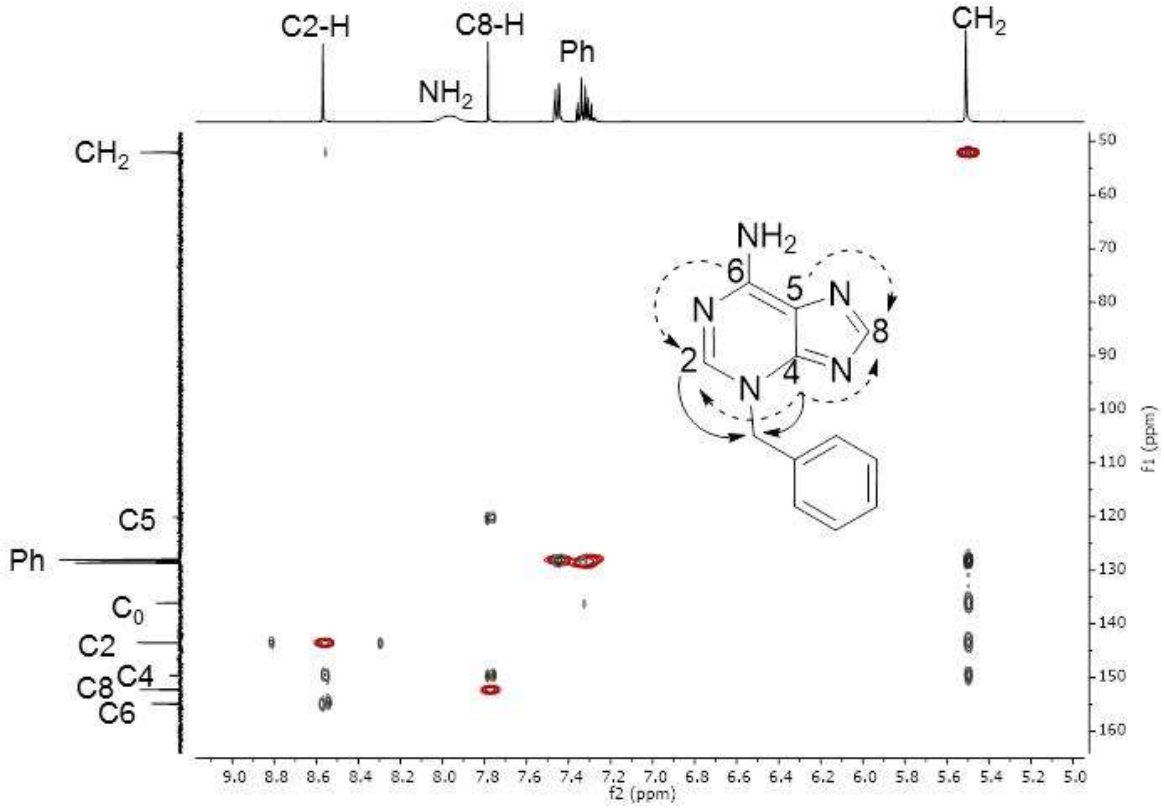


Figure S4 HMBC (black ^{1}H-^{13}C correlations) and HSQC (red ^{1}H-^{13}C correlations) in [D_6]DMSO.

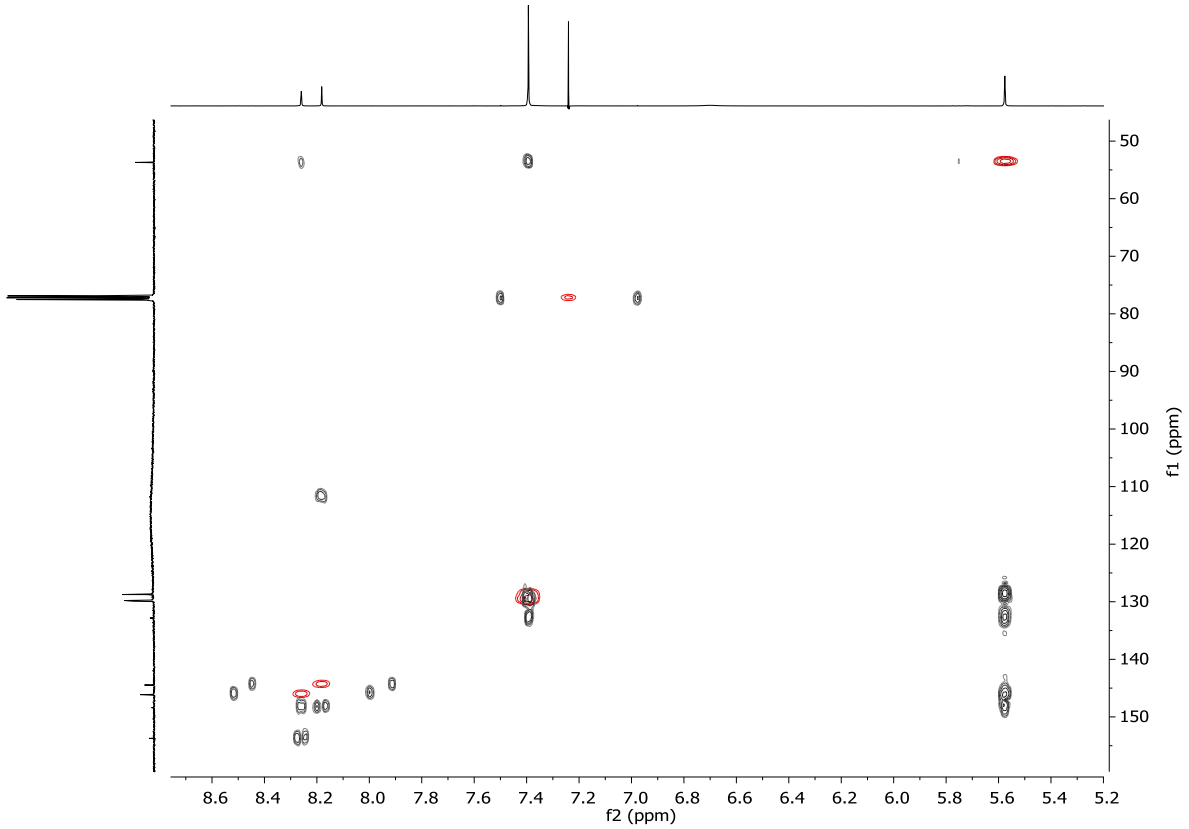


Figure S5 HMBC (black ^{1}H-^{13}C correlations) and HSQC (red ^{1}H-^{13}C correlations) in [D_4]MeOD.

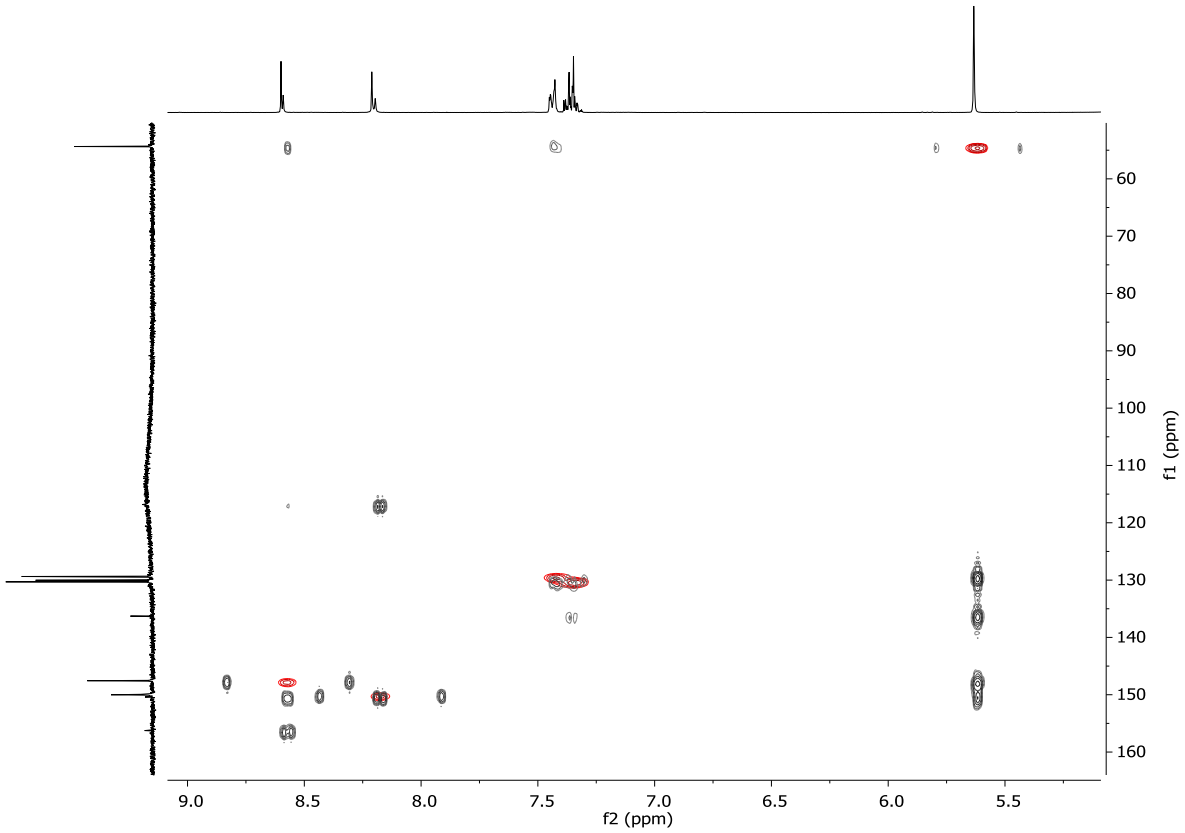


Figure S6 HMBC (black ^{1}H-^{13}C correlations) and HSQC (red ^{1}H-^{13}C correlations) in $CDCl_3$.

PART B.1

^{1}H (400.13 MHz) and ^{13}C (101 MHz) spectra for the Figure indicated spectra of N9-benzyladenine in $[D_6]DMSO$, $CDCl_3$ and $[D_4]MeOD$ solvent.

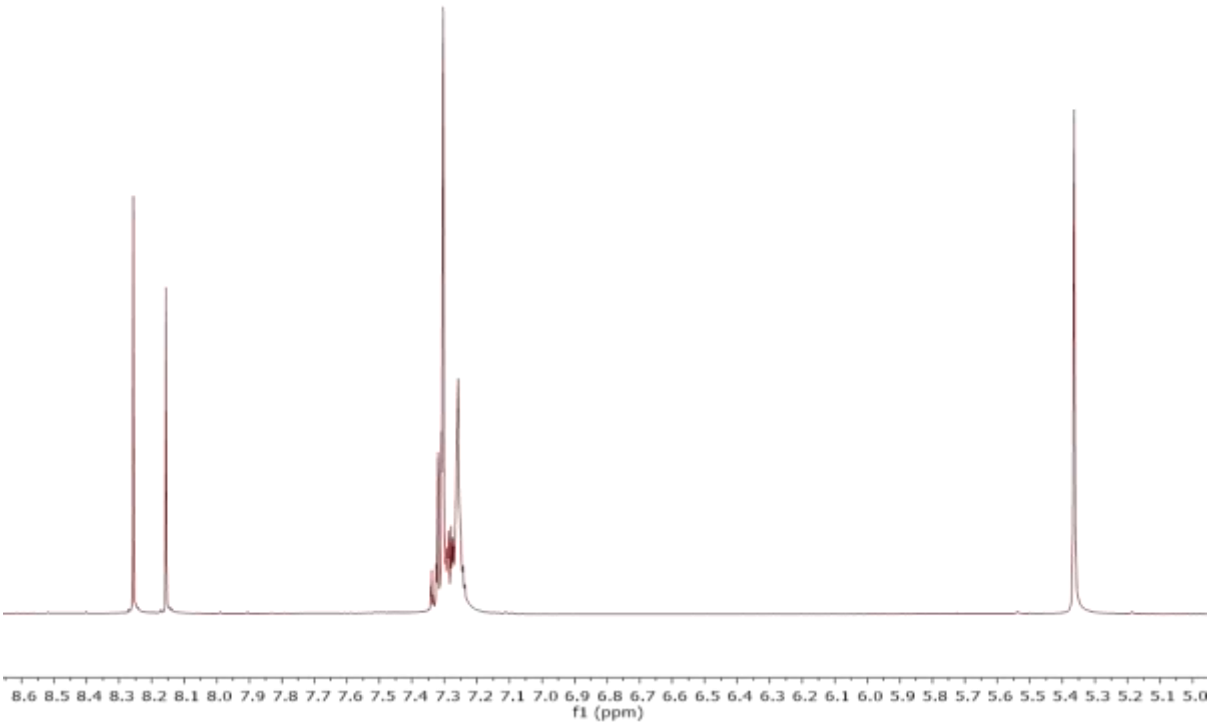


Figure S7 ^{1}H NMR spectrum (ppm) in $[D_6]DMSO$.

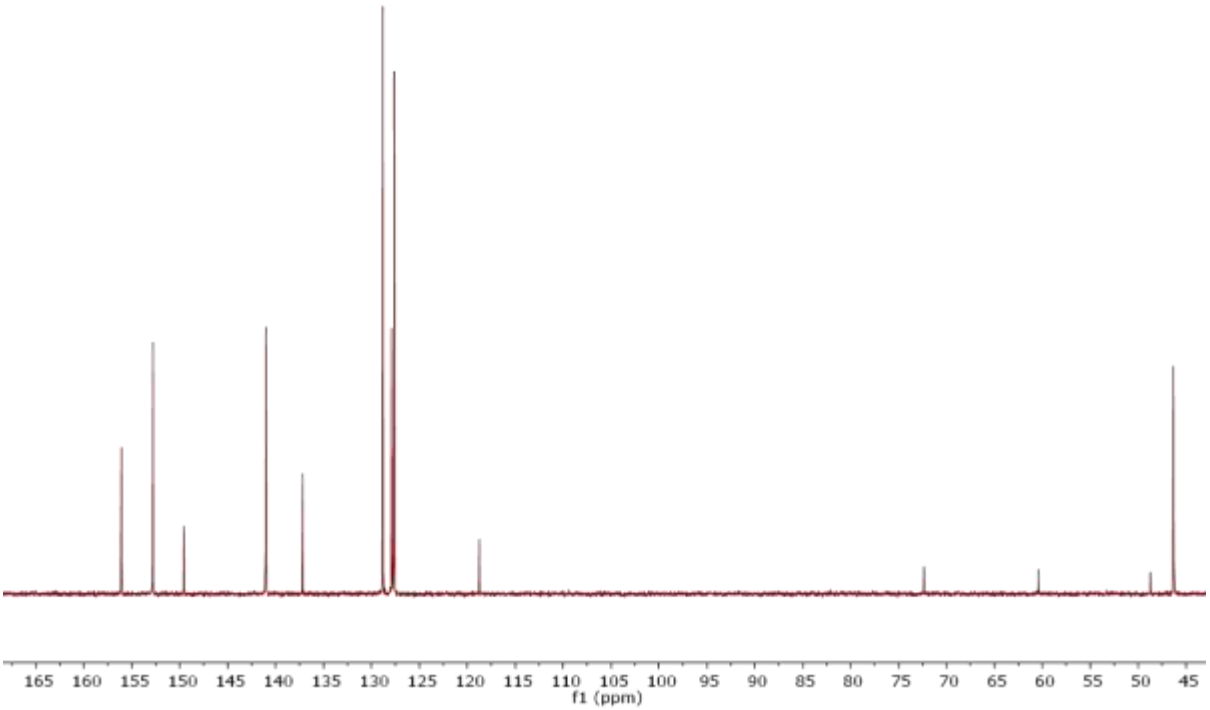


Figure S8 ^{13}C NMR spectrum (ppm) in [D_6]DMSO.

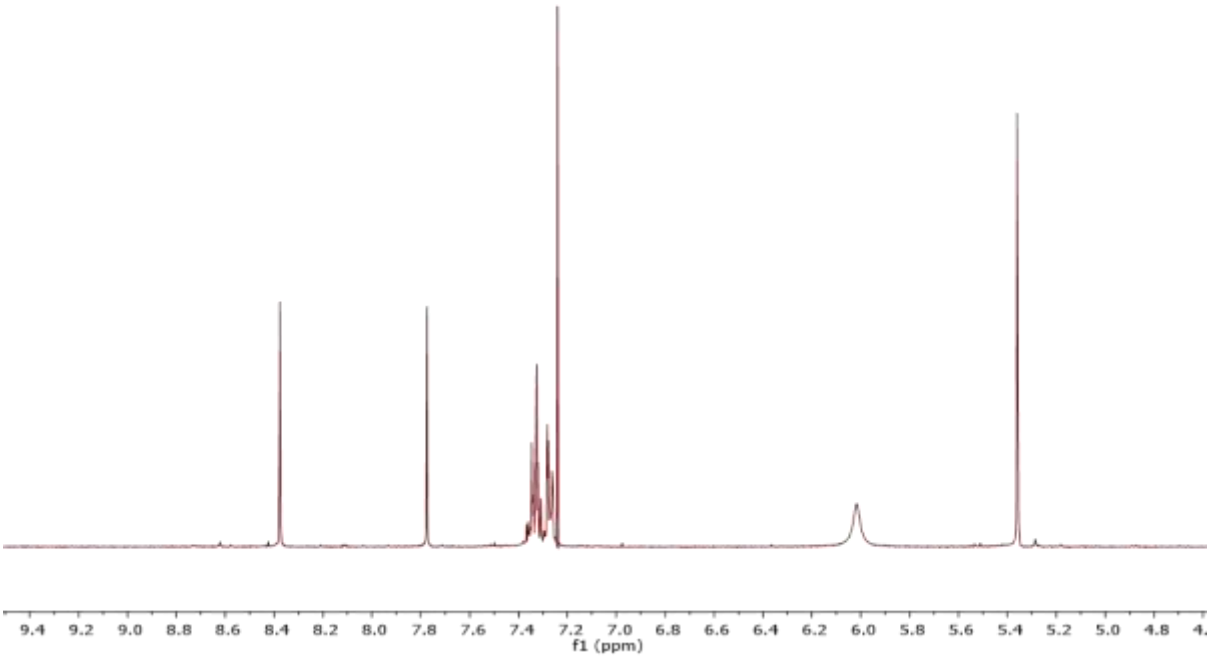


Figure S9 ^{1}H NMR spectrum (ppm) in $CDCl_3$.

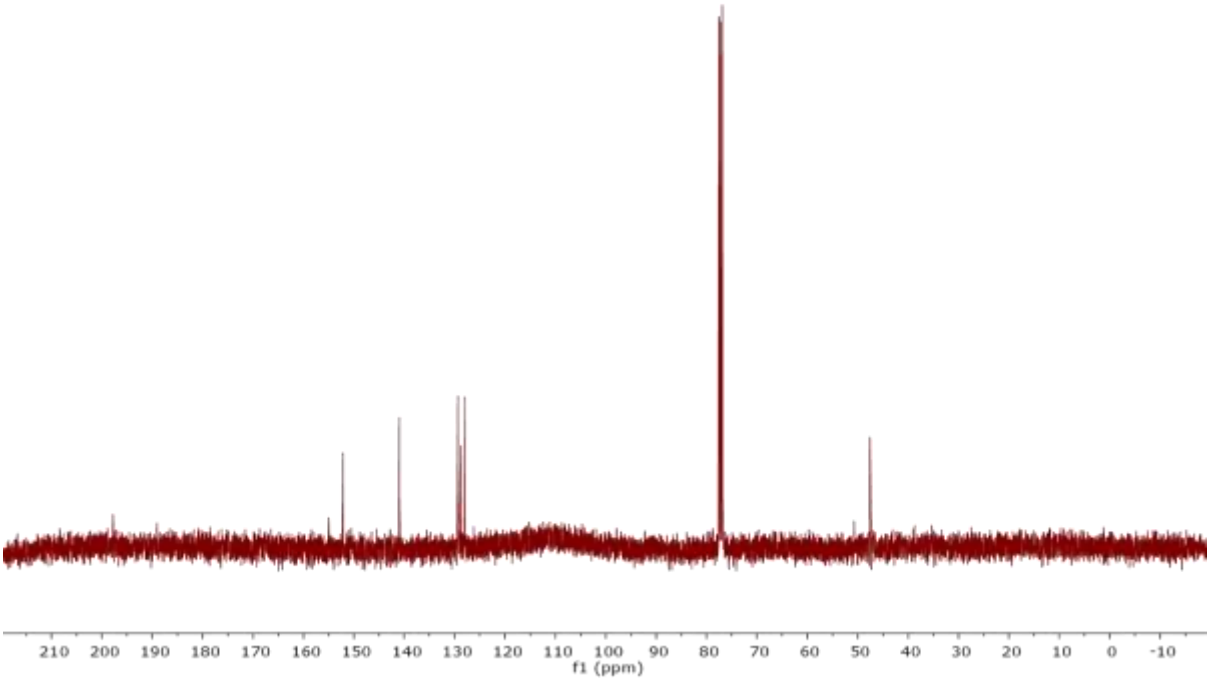


Figure S10 ^{13}C NMR spectrum (ppm) in $CDCl_3$.

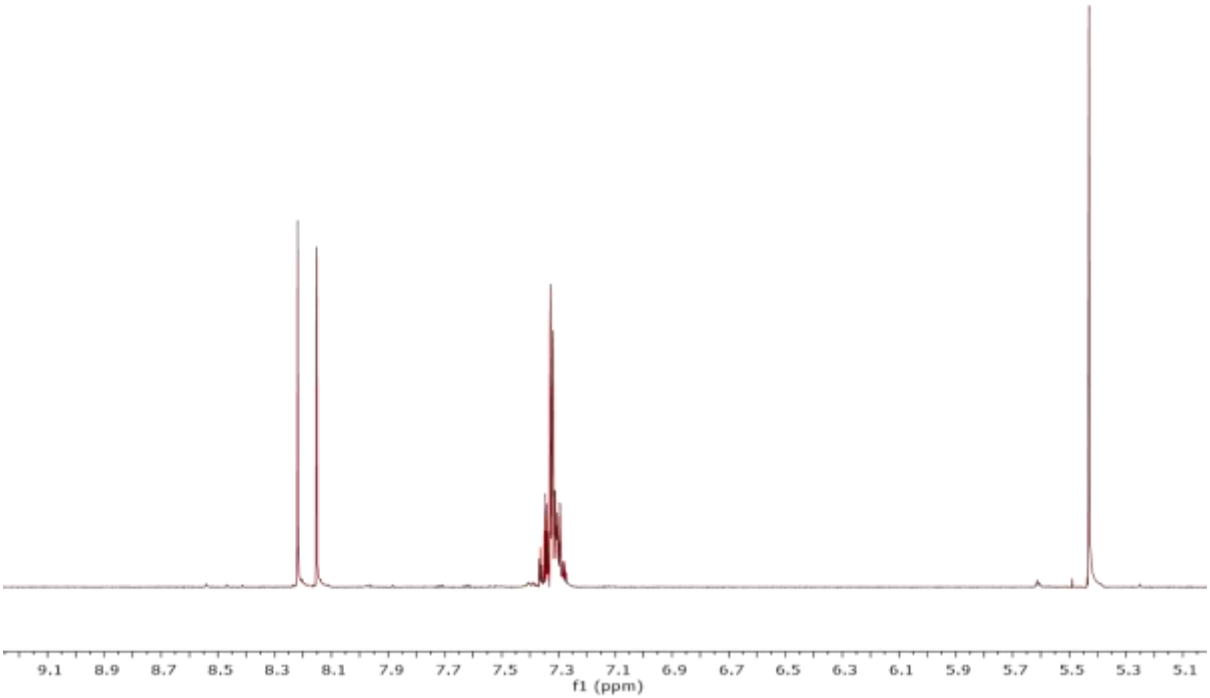


Figure S11 ^{1}H NMR spectrum (ppm) in $[D_4]$MeOD.

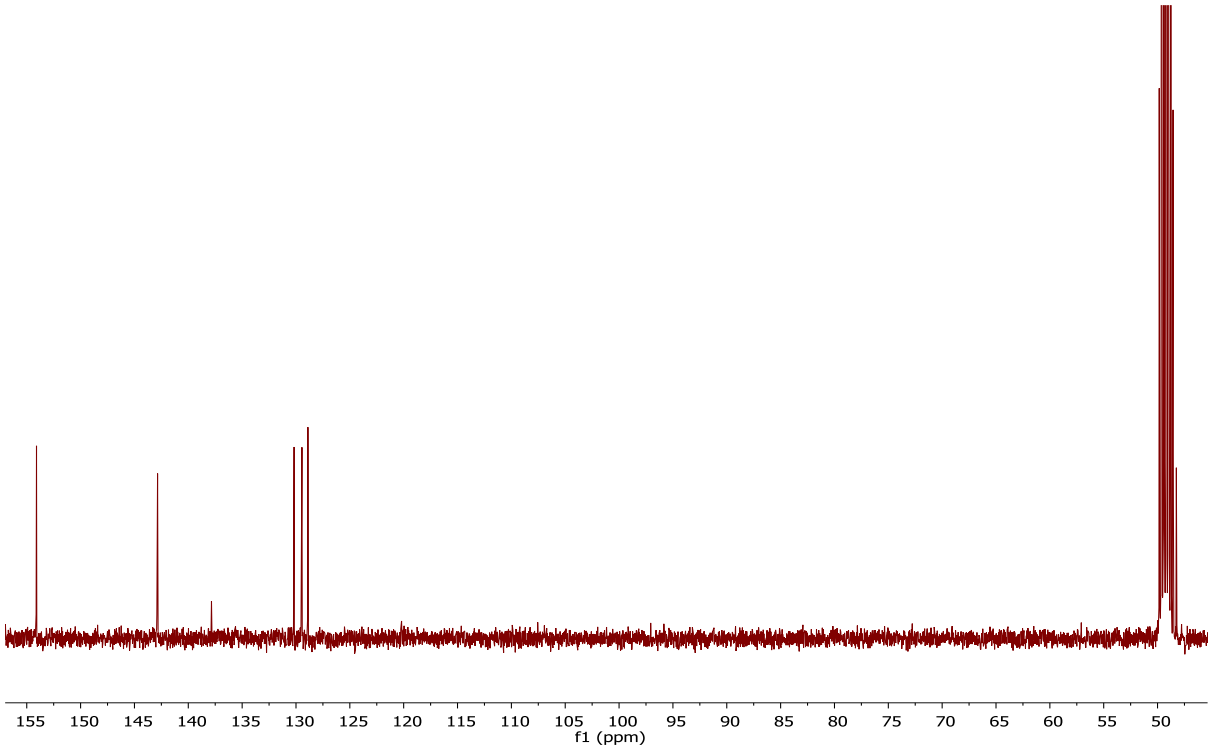


Figure S12 ^{13}C NMR spectrum (ppm) in [D_4]MeOD.

PART B.2

^{1}H (400.13 MHz) and ^{13}C (101 MHz) spectra for the Figure indicated spectra of N3-benzyladenine in [D_6]DMSO, $CDCl_3$ and [D_4]MeOD solvent.

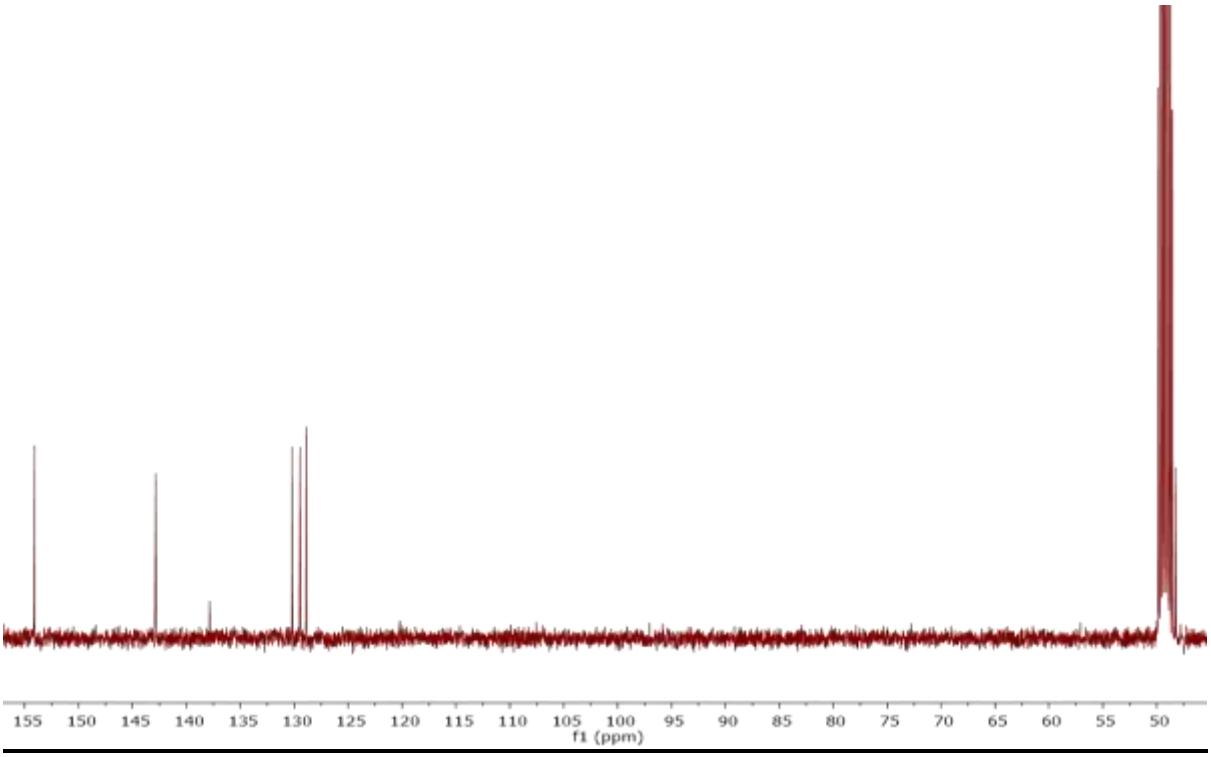


Figure S13 ^{1}H NMR spectrum (ppm) in [D_6]DMSO.

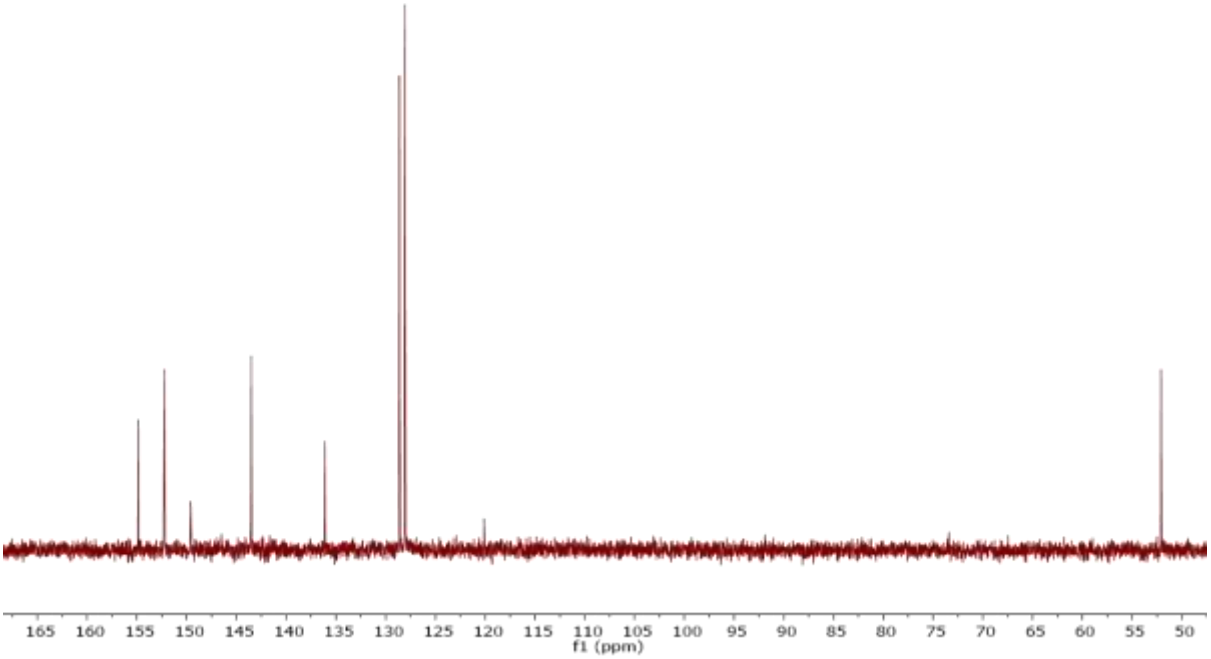


Figure S14 ^{13}C NMR spectrum (ppm) in $[D_6]DMSO$.

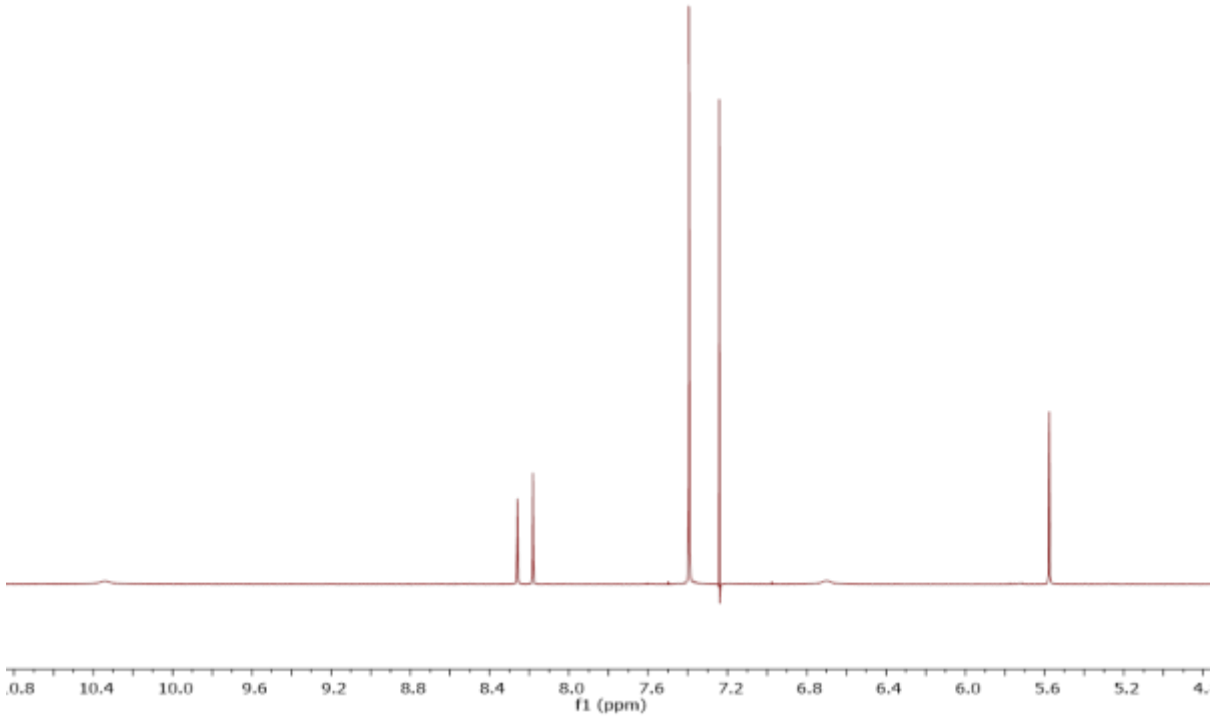


Figure S15 ^{1}H NMR spectrum (ppm) in $CDCl_3$.

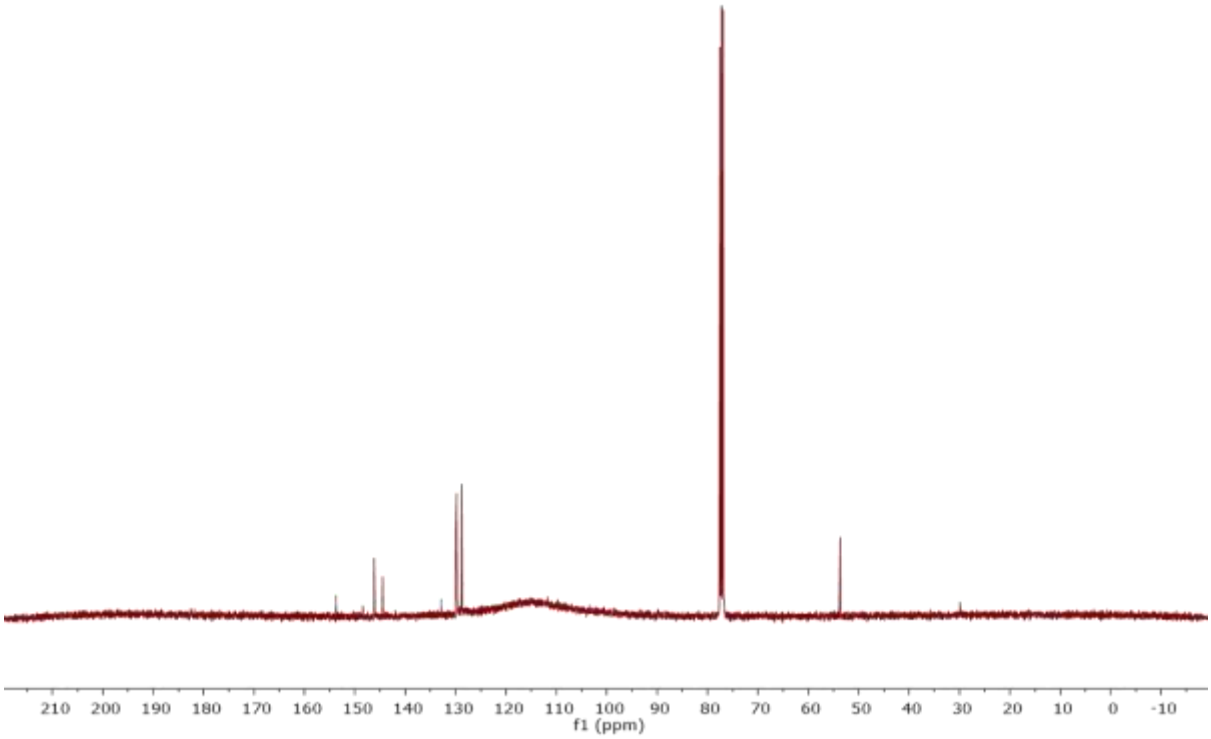


Figure S16 ^{13}C NMR spectrum (ppm) in $CDCl_3$.

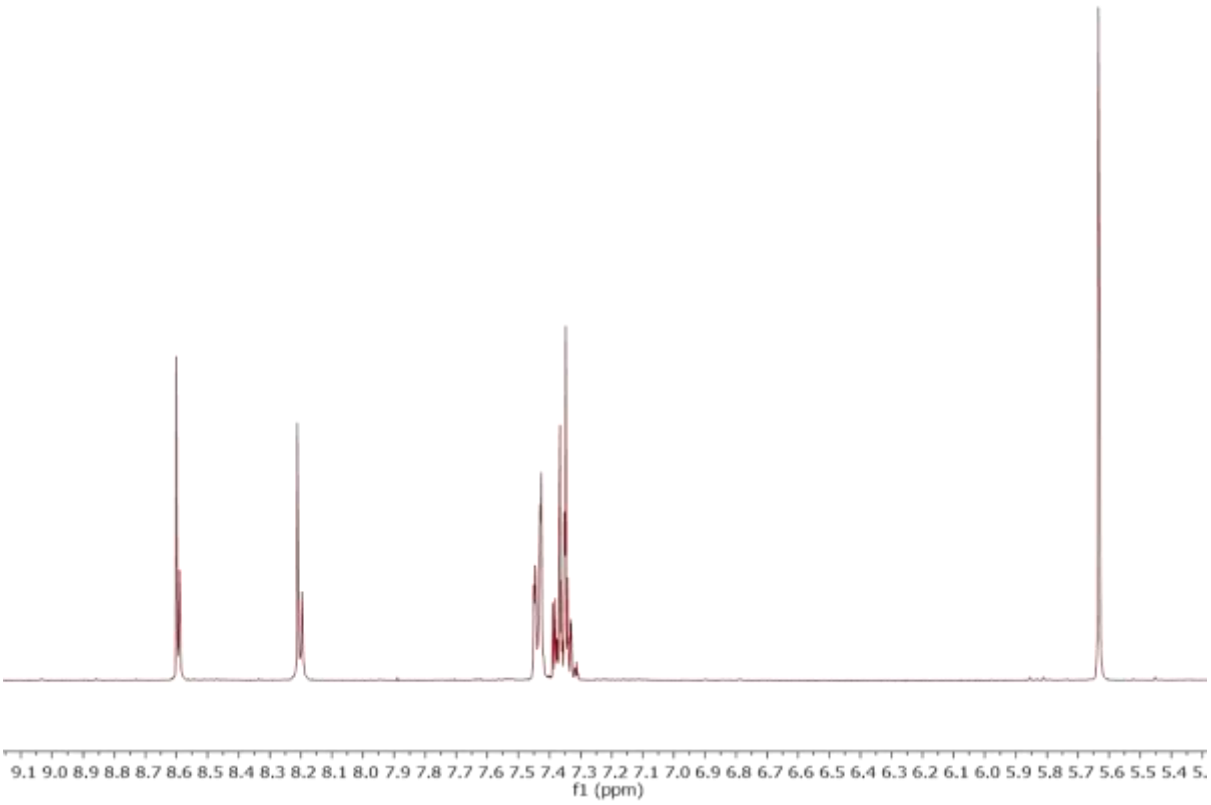


Figure S17 ^{1}H NMR spectrum (ppm) in [D_4]MeOD.

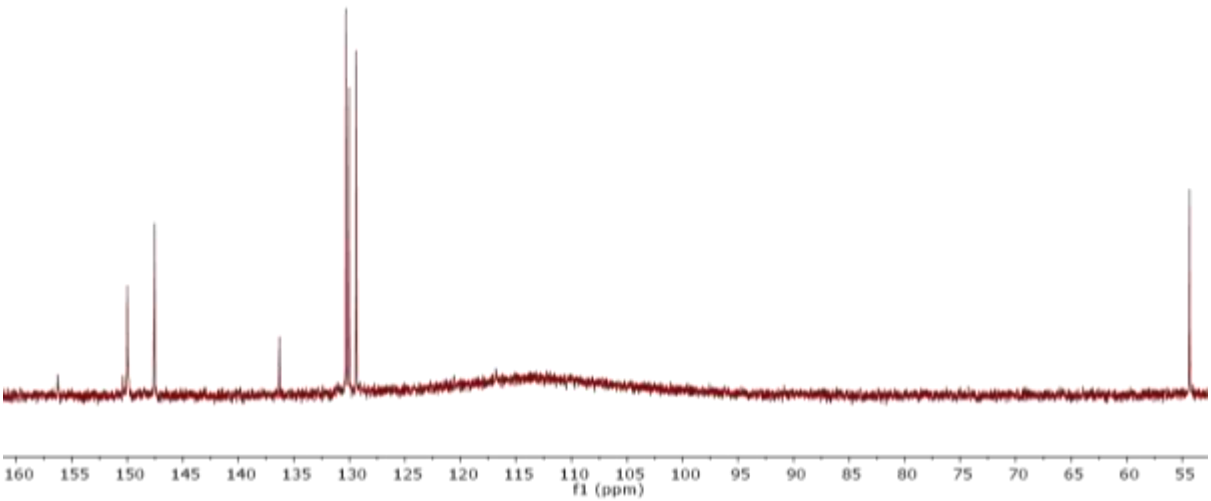


Figure S18 ^{13}C NMR spectrum (ppm) in [D_4]MeOD.

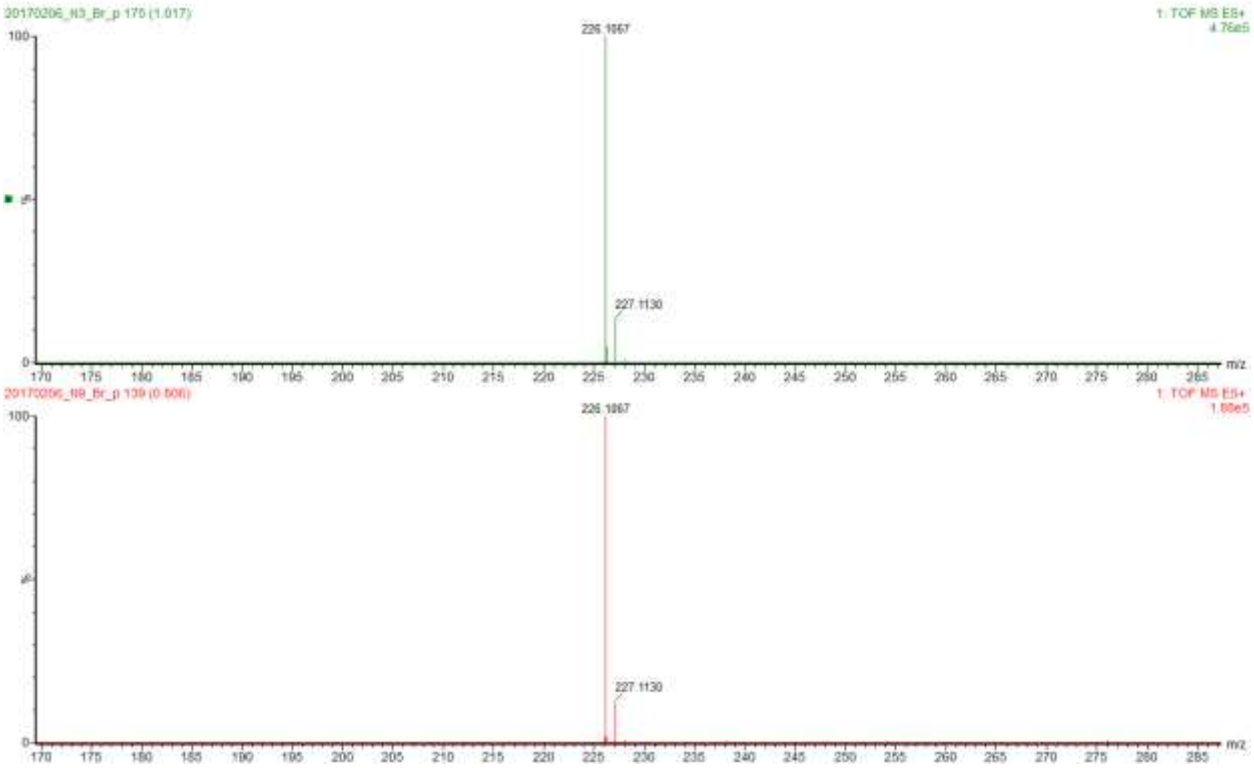


Figure S19: Mass spectra of N3-benzyladenine and N9-benzyladenine.

PART C

Computational prediction of ^{13}C NMR for N3-, N7- and N9-benzyladenine

To improve the accuracy of the prediction the computed spectrum for adenine was calibrated using the well-assigned adenine ^{13}C NMR chemical shits (Table S1). To this effect, we have used theoretical relative ^{13}C NMR chemical shifts values (obtained for adenine in [D_6]DMSO with TMS as a reference) to derive an expression to scale theoretical shifts to the experimental shifts. We attempted both linear and quadratic scaling, Figure S19. Our assumption was that these scaling expressions should be sufficient to predict the ^{13}C NMR chemical shifts for equivalent C-atoms of the adenine fragment in N9-Bn and its regio-isomers and enable us to identify the major and minor compounds formed with highest confidence possible. The scaling expressions were applied to calculated unscaled ^{13}C NMR shifts for N9-, N3- and N7-Bn to give the predicted ^{13}C NMR chemical shift values which are compared to the experimental values obtained in our laboratory.

Table S1 Computed and Experimental ^{13}C NMR shifts for adenine ([D_6]DMSO)

	C2	C4	C5	C6	C8
Calculated unscaled shifts	161.9	159.5	127.2	164.1	146.53
Experimental	152.4	150.6	118.2	155.6	139.2

The average ^{13}C NMR chemical shift for TMS and DMSO were calculated to be 183.35 ppm and 137.87 ppm respectively.

Table S2 The absolute, computed ^{13}C NMR chemical shifts for adenine and regioisomers of benzyladenine

	C2	C4	C5	C6	C8
Adenine	21.4	23.8	56.2	19.3	36.8
N9-Bn	21.7	24.1	54.5	18.5	33.7
N3-Bn	31.8	23.6	52.9	21.0	20.2
N7-Bn	20.2	11.0	62.8	22.4	26.6

In the first step, the unscaled computed ^{13}C NMR chemical shift for each C-atom in adenine was determined as the difference between the computed shift of TMS and the C-atoms of adenine. These unscaled computed shifts were scaled to the experimental ^{13}C NMR chemical shift of adenine and a linear and quadratic scaling expression was obtained.

Table S3 All unscaled chemical shifts relative to TMS

	C2	C4	C5	C6	C8
Adenine	161.9	159.5	127.2	164.1	146.5
N9-Bn	161.6	159.2	128.9	164.9	149.7
N3-Bn	151.5	159.8	130.5	162.4	163.1
N7-Bn	163.1	172.3	120.6	160.9	156.7

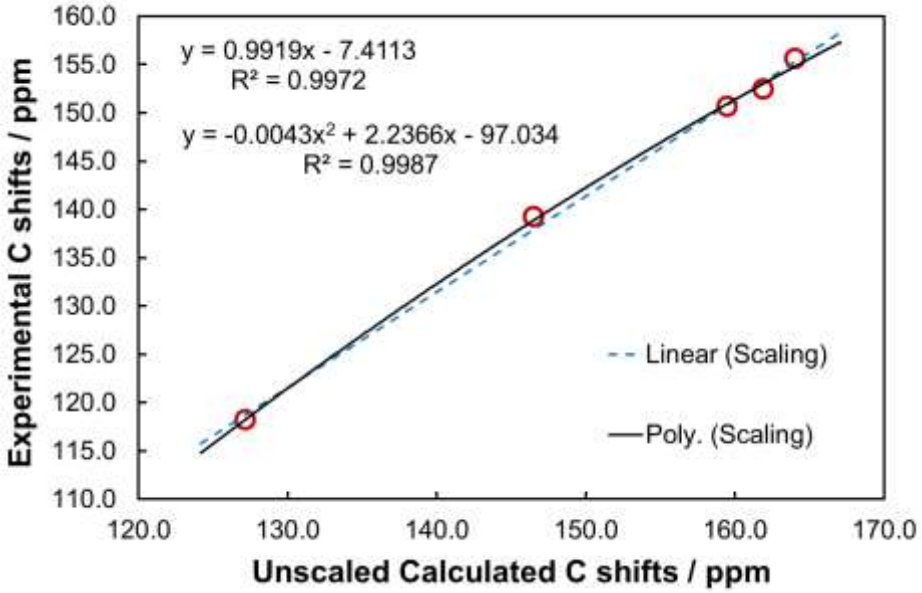


Figure S20 Graph to show the linear and quadratic scaling of theoretical, unscaled chemical shifts to the experimental shifts.

The predicted chemical shifts for each regio-isomer of benzyladenine were determined by substituting the unscaled computed ^{13}C chemical shifts into the linear and quadratic scaling expressions. The quadratic scaling yielded an excellent correlation between the predicted and experimental ^{13}C NMR values for all three isomers N9-, N3- and N7-Bn (Table S4) with the exception of C6 in N3-Bn ($\Delta\delta$-2.2 ppm).

Table S4 Predicted and Experimental ^{13}C NMR shifts for benzyladenine isomers using linear scaling

		C2	C4	C5	C6	C8
N9-Bn	Predicted	152.9	150.5	120.4	156.1	142.0
	Experimental	151.3	149.3	118.6	154.9	141.4
	Difference	-1.6	-1.2	-1.8	-1.2	0.4
N3-Bn	Predicted	142.9	151.1	122.0	153.7	154.4
	Experimental	143.5	149.6	120.1	154.9	152.2
	Difference	0.6	-1.5	-1.9	1.2	-2.2
N7-Bn	Predicted	154.4	163.5	112.2	152.2	148.1
	Literature[24]	152.6	159.3	110.8	151.8	147.5
	Difference	-1.8	-4.2	-1.4	-0.4	-0.6

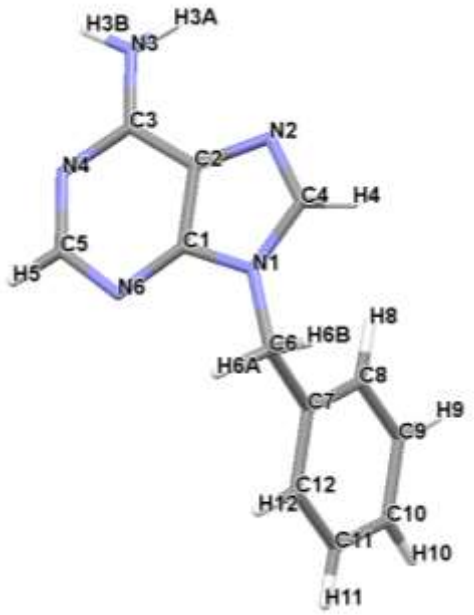
Table S5 Predicted and Experimental ^{13}C NMR shifts for benzyladenine isomers using quadratic scaling

		C2	C4	C5	C6	C8
N9-Bn	Predicted	152.1	150.1	119.8	154.8	142.3
	Experimental	151.3	149.3	118.6	154.9	141.4
	Difference	-0.8	-0.8	-1.2	0.1	0.0
N3-Bn	Predicted	143.2	150.6	121.6	152.8	153.4
	Experimental	143.5	149.6	120.1	154.9	152.2
	Difference	-0.3	-1.0	-1.5	2.1	-1.2
N7-Bn	Predicted	153.4	160.7	110.2	1521.5	147.9
	Literature [21]	152.6	159.3	110.8	151.8	147.5
	Difference	-0.8	-1.4	0.6	0.3	-0.4

PART D

Crystallographic Information of N9-benzyladenine and N3-benzyladenine

N9-benzyladenine



Formula	$C_{12}H_{11}N_5$
Compound name:	N9-benzyladenine
Space group	P 2_1/c
Cell lengths	**a** 11.7874(4) **b** 12.4129(4) **c** 7.1279(2)
Cell angles	**α** 90 **β** 90.7760(11) **γ** 90
Cell Volume	1042.83
Z, Z'	Z: 4 Z': 0
R-factor (%)	3.87

Table S6 Bond angles of N9-benzyladenine crystallographic structure

Atom1	Atom2	Atom3	Angle
C1	N1	C4	106.3(1)
C1	N1	C6	126.0(1)
C4	N1	C6	127.6(1)
C2	N2	C4	103.3(1)
H3A	N3	H3B	122(2)
H3A	N3	C3	119(1)
H3B	N3	C3	118(1)
C3	N4	C5	119.3(1)

C1	N6	C5	110.2(1)
N1	C1	N6	127.0(1)
N1	C1	C2	105.1(1)
N6	C1	C2	128.0(1)
N2	C2	C1	111.2(1)
N2	C2	C3	132.7(1)
C1	C2	C3	116.1(1)
N3	C3	N4	118.2(1)
N3	C3	C2	124.5(1)
N4	C3	C2	117.4(1)
N1	C4	N2	114.1(1)
N1	C4	H4	122(1)
N2	C4	H4	124(1)
N4	C5	N6	129.1(1)
N4	C5	H5	115.7(9)
N6	C5	H5	115.2(9)
N1	C6	H6A	107(1)
N1	C6	H6B	107(1)
N1	C6	C7	114.1(1)
H6A	C6	H6B	111(1)
H6A	C6	C7	109(1)
H6B	C6	C7	109(1)
C6	C7	C8	122.0(1)
C6	C7	C12	118.8(1)
C8	C7	C12	119.0(1)
C7	C8	H8	120(1)
C7	C8	C9	120.4(1)
H8	C8	C9	120(1)
C8	C9	H9	118(1)
C8	C9	C10	120.3(1)
H9	C9	C10	122(1)
C9	C10	H10	122(1)
C9	C10	C11	119.7(1)
H10	C10	C11	118(1)
C10	C11	H11	122(1)
C10	C11	C12	120.3(1)
H11	C11	C12	118(1)
C7	C12	C11	120.2(1)
C7	C12	H12	120(1)
C11	C12	H12	120(1)

Table S7 Bond distances (Å) of N9-benzyladenine crystallographic structure

Atom1	Atom2	Length

N1	C1	1.372(2)
N1	C4	1.368(2)
N1	C6	1.460(2)
N2	C2	1.388(2)
N2	C4	1.312(2)
N3	H3A	0.83(2)
N3	H3B	0.90(2)
N3	C3	1.341(2)
N4	C3	1.355(2)
N4	C5	1.343(2)
N6	C1	1.344(2)
N6	C5	1.328(2)
C1	C2	1.391(2)
C2	C3	1.412(2)
C4	H4	0.96(2)
C5	H5	0.96(2)
C6	H6A	1.00(2)
C6	H6B	0.98(2)
C6	C7	1.512(2)
C7	C8	1.389(2)
C7	C12	1.393(2)
C8	H8	1.00(2)
C8	C9	1.386(2)
C9	H9	0.99(2)
C9	C10	1.382(2)
C10	H10	0.95(2)
C10	C11	1.382(2)
C11	H11	0.96(2)
C11	C12	1.388(2)
C12	H12	0.96(2)

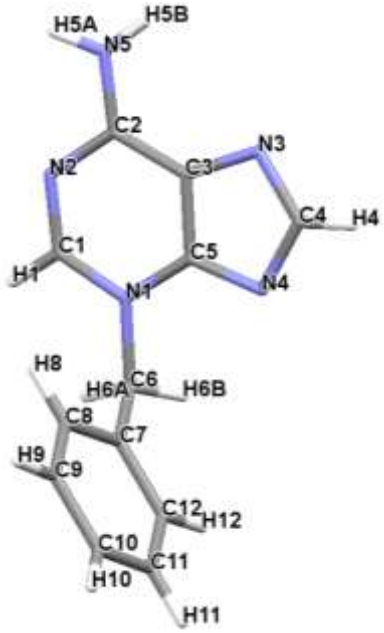
Table S8 Torsion angles of N9-benzyladenine crystallographic structure

Atom1	Atom2	Atom3	Atom4	Torsion
C4	N1	C1	N6	-179.7(1)
C4	N1	C1	C2	-0.0(1)
C6	N1	C1	N6	0.4(2)
C6	N1	C1	C2	-179.9(1)
C1	N1	C4	N2	-0.2(2)
C1	N1	C4	H4	178(1)
C6	N1	C4	N2	179.7(1)
C6	N1	C4	H4	-2(1)
C1	N1	C6	H6A	-34(1)
C1	N1	C6	H6B	-152(1)

C1	N1	C6	C7	86.9(2)
C4	N1	C6	H6A	147(1)
C4	N1	C6	H6B	28(1)
C4	N1	C6	C7	-92.9(2)
C4	N2	C2	C1	-0.3(2)
C4	N2	C2	C3	178.6(2)
C2	N2	C4	N1	0.3(2)
C2	N2	C4	H4	-178(1)
H3A	N3	C3	N4	-168(1)
H3A	N3	C3	C2	11(1)
H3B	N3	C3	N4	2(1)
H3B	N3	C3	C2	-178(1)
C5	N4	C3	N3	177.3(1)
C5	N4	C3	C2	-2.2(2)
C3	N4	C5	N6	1.3(2)
C3	N4	C5	H5	-176(1)
C5	N6	C1	N1	177.9(1)
C5	N6	C1	C2	-1.7(2)
C1	N6	C5	N4	0.7(2)
C1	N6	C5	H5	178(1)
N1	C1	C2	N2	0.2(2)
N1	C1	C2	C3	-178.9(1)
N6	C1	C2	N2	179.9(1)
N6	C1	C2	C3	0.8(2)
N2	C2	C3	N3	3.0(2)
N2	C2	C3	N4	-177.6(1)
C1	C2	C3	N3	-178.2(1)
C1	C2	C3	N4	1.3(2)
N1	C6	C7	C8	32.3(2)
N1	C6	C7	C12	-152.4(1)
H6A	C6	C7	C8	152(1)
H6A	C6	C7	C12	-33(1)
H6B	C6	C7	C8	-87(1)
H6B	C6	C7	C12	88(1)
C6	C7	C8	H8	-4(1)
C6	C7	C8	C9	174.8(1)
C12	C7	C8	H8	-179(1)
C12	C7	C8	C9	-0.5(2)
C6	C7	C12	C11	-174.7(1)
C6	C7	C12	H12	7(1)
C8	C7	C12	C11	0.7(2)
C8	C7	C12	H12	-178(1)
C7	C8	C9	H9	-178(1)
C7	C8	C9	C10	-0.2(2)

H8	C8	C9	H9	1(2)
H8	C8	C9	C10	179(1)
C8	C9	C10	H10	178(1)
C8	C9	C10	C11	0.7(2)
H9	C9	C10	H10	-3(2)
H9	C9	C10	C11	179(1)
C9	C10	C11	H11	179(1)
C9	C10	C11	C12	-0.4(2)
H10	C10	C11	H11	2(2)
H10	C10	C11	C12	-178(1)
C10	C11	C12	C7	-0.3(2)
C10	C11	C12	H12	178(1)
H11	C11	C12	C7	180(1)
H11	C11	C12	H12	-2(2)

N3-benzyladenine



Formula	$C_{12}H_{11}N_5$
Compound name:	N3-benzyladenine
Space group	P 2_1/c
Cell lengths	**a** 7.2996(4) **b** 11.7426(6) **c** 12.4520(7)
Cell angles	**α** 90 **β** 100.998 **γ** 90
Cell Volume	1047.74
Z, Z'	Z: 4 Z': 0
R-factor (%)	3.41

Table S9 Bond angles of N9-benzyladenine crystallographic structure

Atom1	Atom2	Atom3	Angle
C1	N1	C5	116.39(9)
C1	N1	C6	122.39(9)
C5	N1	C6	121.21(8)
C1	N2	C2	119.10(9)
C3	N3	C4	101.71(8)
C4	N4	C5	100.73(8)
H5A	N5	H5B	120(1)
H5A	N5	C2	117.8(9)
H5B	N5	C2	120.7(9)
N1	C1	N2	126.2(1)
N1	C1	H1	115.7(8)
N2	C1	H1	118.1(8)
N2	C2	N5	117.72(9)
N2	C2	C3	118.62(9)
N5	C2	C3	123.7(1)
N3	C3	C2	132.77(9)
N3	C3	C5	107.98(9)
C2	C3	C5	119.19(9)
N3	C4	N4	118.12(9)
N3	C4	H4	120.1(8)
N4	C4	H4	121.8(8)
N1	C5	N4	128.09(9)
N1	C5	C3	120.45(9)
N4	C5	C3	111.46(9)
N1	C6	H6A	106.0(8)
N1	C6	H6B	107.3(9)
N1	C6	C7	113.64(9)
H6A	C6	H6B	109(1)
H6A	C6	C7	109.7(8)
H6B	C6	C7	111.0(9)
C6	C7	C8	121.9(1)
C6	C7	C12	118.9(1)
C8	C7	C12	119.2(1)
C7	C8	H8	119.4(8)
C7	C8	C9	120.2(1)
H8	C8	C9	120.3(8)
C8	C9	H9	119.0(9)
C8	C9	C10	120.4(1)
H9	C9	C10	120.6(9)
C9	C10	H10	121.0(9)
C9	C10	C11	119.6(1)

H10	C10	C11	119.4(9)
C10	C11	H11	119.3(9)
C10	C11	C12	120.1(1)
H11	C11	C12	120.5(9)
C7	C12	C11	120.5(1)
C7	C12	H12	118.4(9)
C11	C12	H12	121.1(9)

Table S10 Bond distances (Å) of N9-benzyladenine crystallographic structure

Atom1	Atom2	Length
N1	C1	1.350(1)
N1	C5	1.371(1)
N1	C6	1.471(2)
N2	C1	1.312(2)
N2	C2	1.367(1)
N3	C3	1.378(1)
N3	C4	1.338(1)
N4	C4	1.360(1)
N4	C5	1.342(1)
N5	H5A	0.87(1)
N5	H5B	0.89(1)
N5	C2	1.332(2)
C1	H1	0.97(1)
C2	C3	1.403(1)
C3	C5	1.397(2)
C4	H4	0.96(1)
C6	H6A	0.98(1)
C6	H6B	0.97(1)
C6	C7	1.512(2)
C7	C8	1.391(1)
C7	C12	1.389(2)
C8	H8	0.99(2)
C8	C9	1.388(2)
C9	H9	0.97(1)
C9	C10	1.386(2)
C10	H10	0.96(2)
C10	C11	1.384(2)
C11	H11	1.00(2)
C11	C12	1.390(2)
C12	H12	0.98(1)

Table S11 Torsion angles of N9-benzyladenine crystallographic structure

Atom1	Atom2	Atom3	Atom4	Torsion
C5	N1	C1	N2	0.0(2)
C5	N1	C1	H1	179.9(9)
C6	N1	C1	N2	-179.4(1)
C6	N1	C1	H1	0.5(9)
C1	N1	C5	N4	177.2(1)
C1	N1	C5	C3	-1.7(1)
C6	N1	C5	N4	-3.3(2)
C6	N1	C5	C3	177.78(9)
C1	N1	C6	H6A	17.2(9)
C1	N1	C6	H6B	133.6(9)
C1	N1	C6	C7	-103.3(1)
C5	N1	C6	H6A	-162.2(9)
C5	N1	C6	H6B	-45.8(9)
C5	N1	C6	C7	77.2(1)
C2	N2	C1	N1	1.8(2)
C2	N2	C1	H1	-178.0(9)
C1	N2	C2	N5	178.0(1)
C1	N2	C2	C3	-2.0(1)
C4	N3	C3	C2	176.8(1)
C4	N3	C3	C5	-0.4(1)
C3	N3	C4	N4	0.7(1)
C3	N3	C4	H4	-178(1)
C5	N4	C4	N3	-0.7(1)
C5	N4	C4	H4	178(1)
C4	N4	C5	N1	-178.6(1)
C4	N4	C5	C3	0.3(1)
H5A	N5	C2	N2	15(1)
H5A	N5	C2	C3	-165(1)
H5B	N5	C2	N2	-178(1)
H5B	N5	C2	C3	2(1)
N2	C2	C3	N3	-176.5(1)
N2	C2	C3	C5	0.4(1)
N5	C2	C3	N3	3.4(2)
N5	C2	C3	C5	-179.6(1)
N3	C3	C5	N1	179.10(9)
N3	C3	C5	N4	0.0(1)
C2	C3	C5	N1	1.5(1)
C2	C3	C5	N4	-177.61(9)
N1	C6	C7	C8	36.9(1)
N1	C6	C7	C12	-145.9(1)
H6A	C6	C7	C8	-81.5(9)
H6A	C6	C7	C12	95.6(9)

H6B	C6	C7	C8	158.0(9)
H6B	C6	C7	C12	-24.9(9)
C6	C7	C8	H8	-3(1)
C6	C7	C8	C9	177.8(1)
C12	C7	C8	H8	180(1)
C12	C7	C8	C9	0.7(2)
C6	C7	C12	C11	-177.0(1)
C6	C7	C12	H12	4(1)
C8	C7	C12	C11	0.2(2)
C8	C7	C12	H12	-179(1)
C7	C8	C9	H9	179(1)
C7	C8	C9	C10	-0.6(2)
H8	C8	C9	H9	-0(1)
H8	C8	C9	C10	-180(1)
C8	C9	C10	H10	180(1)
C8	C9	C10	C11	-0.4(2)
H9	C9	C10	H10	0(2)
H9	C9	C10	C11	-180(1)
C9	C10	C11	H11	180(1)
C9	C10	C11	C12	1.3(2)
H10	C10	C11	H11	-0(1)
H10	C10	C11	C12	-179(1)
C10	C11	C12	C7	-1.2(2)
C10	C11	C12	H12	178(1)
H11	C11	C12	C7	-180(1)
H11	C11	C12	H12	-1(1)