Supplementary information

Enhanced inhibitory activity of compounds containing purine scaffolds compared to protein kinase CK2α considering crystalline water

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Trajectory files (zip) of the MD simulation of compounds 2–7 can be downloaded from https://doi.org/10.7910/DVN/MMVYEC

1. Molecular dynamics simulations

1.1 Complex structures of compounds and CK2α after MD simulation

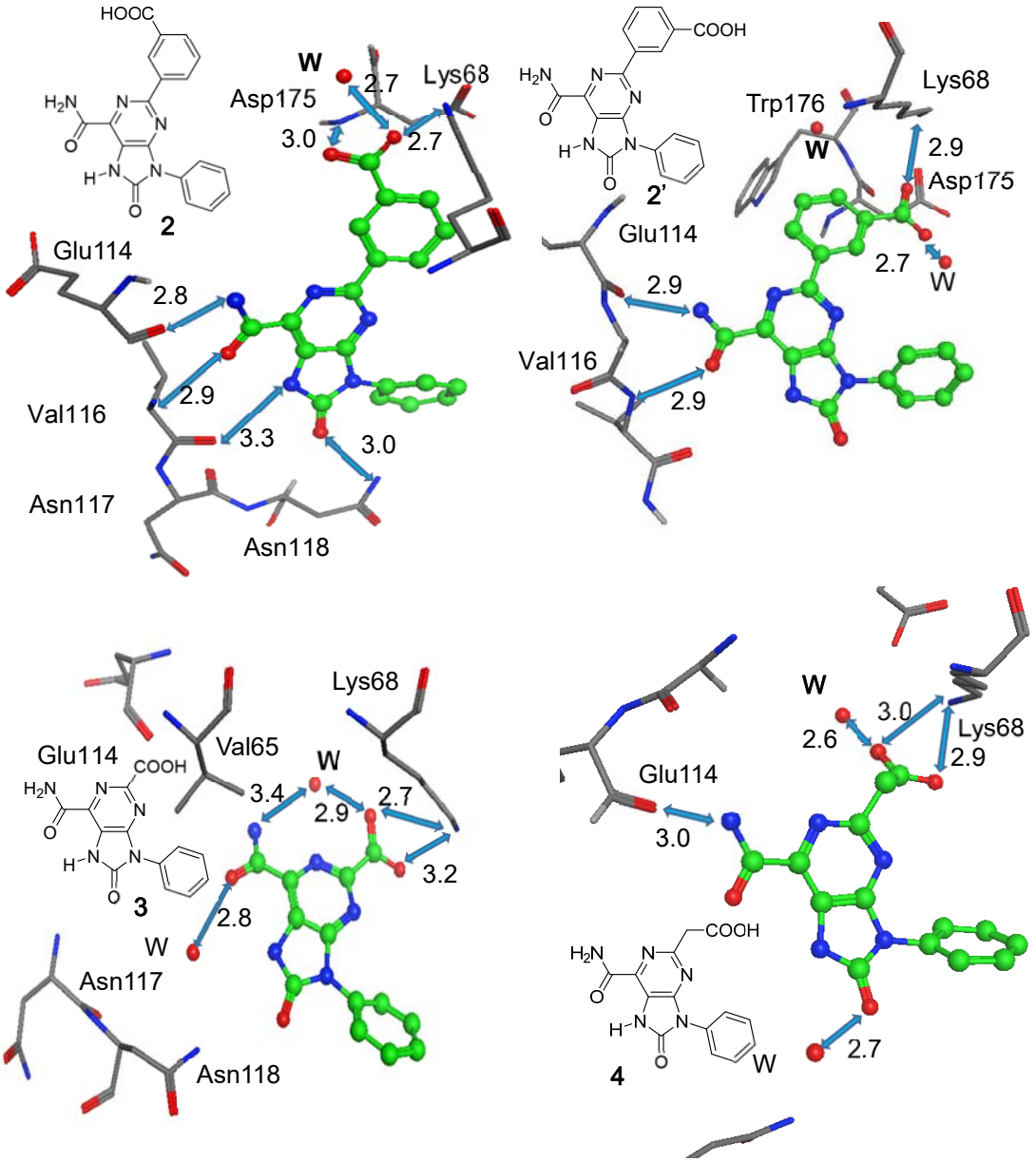

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Figure S1-1. Complex structures of design compounds and CK2α after MD simulation

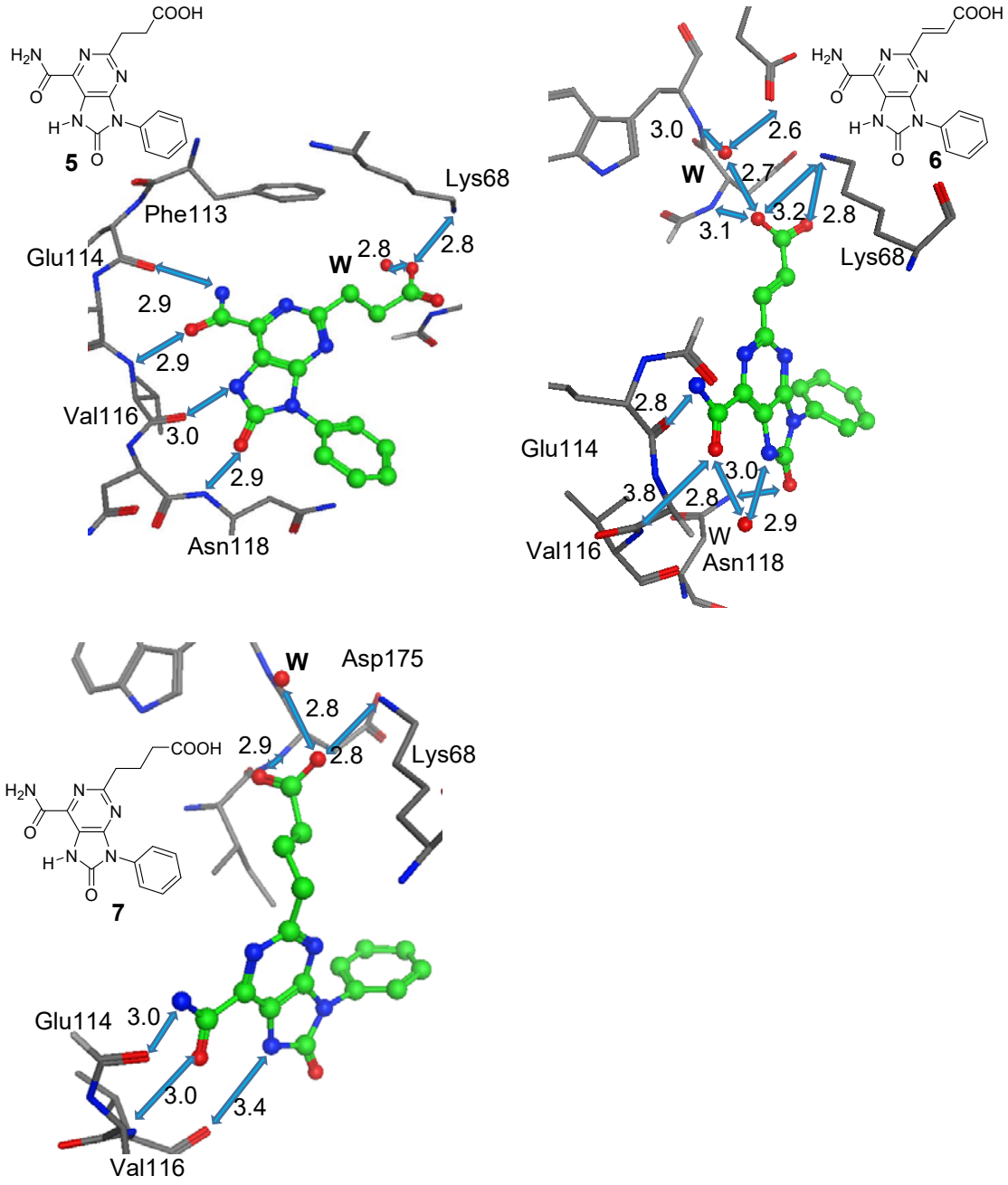


Figure S1-2. Complex structures of design compounds and CK2α after MD simulation

1.2 Detailed data of calculation results

Table S1-1. RMSD, ΔG_{PBSA} and ΔG_{bind} of compound 1

Run	RMSD (Å)	ΔG_{PBSA} (kcal/mol)	ΔG_{bind} (kcal/mol)
1	2.12	−27.8	−2.67
2	3.10	−40.9	−6.73
3	2.92	−40.7	0.0
4	2.31	−35.8	−7.50
5	2.32	−35.3	−7.9
Average	2.55	−36.1	−5.0
±MAE	0.36	3.8	2.9

(MAE：Mean Absolute Error)

Table S1-2. Component analysis of ΔG_{PBSA} of compound 1

Run	E_{vdw}	E_{ele}	E_{PB}	E_{SA}	$E_{interaction}$	$E_{desolvation}$	$E_{NonPolar}$	E_{Polar}	ΔG_{PBSA}
1	−42.4	−163.9	181.9	−3.4	−206.3	178.5	−45.8	18.1	−27.8
2	−40.1	−146.3	148.9	−3.4	−186.5	145.5	−43.5	2.6	−40.9
3	−40.6	−171.0	174.3	−3.4	−211.7	171.0	−44.0	3.3	−40.7
4	−40.1	−151.4	158.9	−3.3	−191.4	155.6	−43.4	7.6	−35.8
5	−40.7	−133.7	142.5	−3.4	−174.4	139.1	−44.0	8.8	−35.3
Average	−40.8	−153.3	161.3	−3.4	−194.0	157.9	−44.2	8.1	−36.1

Table S2-1. RMSD, ΔG_{PBSA} and ΔG_{bind} of compound 2

Run	RMSD (Å)	ΔG_{PBSA} (kcal/mol)	ΔG_{bind} (kcal/mol)
1	3.39	−35.5	−14.0
2	3.71	−367	−13.6
3	3.30	−37.1	−3.2
4	3.68	−36.4	−2.3
5	3.21	−36.4	−1.2
Average	3.46	−36.4	−6.9
±MAE	0.19	0.4	5.6

Table S2-2. Component analysis of ΔG_{PBSA} of compound 2

Run	E_{vdw}	E_{ele}	E_{PB}	E_{SA}	$E_{interaction}$	$E_{desolvation}$	$E_{NonPolar}$	E_{Polar}	ΔG_{PBSA}
1	−38.6	−143.1	149.4	−3.2	−181.7	146.2	−41.8	6.3	−35.5

2	−39.3	−156.1	162.0	−3.3	−195.4	158.8	−42.6	5.9	−36.7
3	−39.7	−162.1	168.0	−3.3	−201.9	164.7	−43.0	5.9	−37.1
4	−40.2	−152.5	159.5	−3.3	−192.6	156.2	−43.4	7.0	−36.4
5	−38.8	−142.8	148.4	−3.2	−181.6	145.3	−42.0	5.6	−36.4
Average	−39.3	−151.3	157.5	−3.2	−190.7	154.2	−42.6	6.1	−36.4

Table S3-1. RMSD, ΔG_{PBSA} and ΔG_{bind} of compound 2'

Run	RMSD (Å)	ΔG_{PBSA} (kcal/mol)	ΔG_{bind} (kcal/mol)
1	3.05	−39.6	16.2
2	2.51	−40.2	6.3
3	1.26	−34.6	1.5
4	1.48	−34.5	−4.5
5	2.22	−37.7	10.6
Average	2.10	−37.3	6.0
±MAE	0.59	2.2	6.0

Table S3-2. Component analysis of ΔG_{PBSA} of compound 2'

Run	E_{vdw}	E_{ele}	E_{PB}	E_{SA}	$E_{interaction}$	$E_{desolvation}$	$E_{NonPolar}$	E_{Polar}	ΔG_{PBSA}
1	−44.6	−128.8	137.1	−3.4	−173.4	133.8	−48.0	8.4	−39.6
2	−45.1	−165.0	173.5	−3.6	−210.1	169.9	−48.7	8.5	−40.2
3	−43.0	−133.1	144.9	−3.3	−176.1	141.6	−46.4	11.8	−34.6
4	−43.9	−133.4	146.2	−3.3	−177.3	142.9	−47.3	12.8	−34.5
5	−44.1	−144.1	153.9	−3.4	−188.2	150.5	−47.4	9.8	−37.7
Average	−44.2	−140.9	151.1	−3.4	−185.0	147.7	−47.5	10.2	−37.3

Table S4-1. RMSD, ΔG_{PBSA} and ΔG_{bind} of compound 3

Run	RMSD (Å)	ΔG_{PBSA} (kcal/mol)	ΔG_{bind} (kcal/mol)
1	3.08	−16.0	21.7
2	2.47	−18.4	14.0
3	2.79	−23.3	15.3
4	4.65	−18.2	18.4
5	2.12	−23.4	9.3
Average	3.02	−19.9	15.7
±MAE	0.67	2.8	3.4

Table S4-2. Component analysis of ΔG_{PBSA} of compound 3

Run	E_{vdw}	E_{ele}	E_{PB}	E_{SA}	$E_{interaction}$	$E_{desolvation}$	$E_{NonPolar}$	E_{Polar}	ΔG_{PBSA}
1	−33.0	−119.3	138.8	−2.6	−152.3	136.2	−35.6	19.5	−16.0
2	−32.7	−143.4	160.4	−2.6	−176.1	157.7	−35.3	17.0	−18.4
3	−32.6	−148.0	159.8	−2.5	−180.6	157.3	−35.1	11.8	−23.3
4	−34.0	−170.0	188.5	−2.7	−203.9	185.8	−36.7	18.5	−18.2
5	−33.9	−138.7	151.9	−2.7	−172.6	149.2	−36.6	13.2	−23.4
Average	−33.2	−143.9	159.9	−2.6	−177.1	157.3	−35.8	16.0	−19.9

Table S5-1. RMSD, ΔG_{PBSA} and ΔG_{bind} of compound 4

Run	RMSD (Å)	ΔG_{PBSA} (kcal/mol)	ΔG_{bind} (kcal/mol)
1	2.02	−31.8	−6.33
2	1.98	−29.6	5.1
3	2.86	−21.3	10.6
4	2.05	−32.6	4.7
5	2.00	−29.3	3.1
Average	2.18	−28.9	3.5
±MAE	0.27	3.0	4.1

Table S5-2. Component analysis of ΔG_{PBSA} of compound 4

Run	E_{vdw}	E_{ele}	E_{PB}	E_{SA}	$E_{interaction}$	$E_{desolvation}$	$E_{NonPolar}$	E_{Polar}	ΔG_{PBSA}
1	−37.3	−134.4	142.8	−2.9	−171.7	140.0	−40.2	8.4	−31.8
2	−35.6	−136.8	145.7	−2.9	−172.4	142.8	−38.5	8.9	−29.6
3	−34.1	−139.0	154.5	−2.8	−173.0	151.7	−36.9	15.5	−21.3
4	−35.1	−151.0	156.3	−2.8	−186.1	153.5	−37.8	5.2	−32.6
5	−36.3	−146.9	156.8	−2.9	−183.2	153.9	−39.2	9.9	−29.3
Average	−35.7	−141.6	151.2	−2.8	−177.3	148.4	−38.5	9.6	−28.9

Table S6-1. RMSD, ΔG_{PBSA} and ΔG_{bind} of compound 5

Run	RMSD (Å)	ΔG_{PBSA} (kcal/mol)	ΔG_{bind} (kcal/mol)
1	2.53	−37.8	−3.4
2	2.40	−39.0	10.3
3	1.89	−32.6	2.1
4	2.11	−35.2	−5.5

5	1.94	−37.9	−6.0
Average	2.17	−36.5	−0.5
±MAE	0.23	2.1	5.4

Table S6-2. Component analysis of ΔG_{PBSA} of compound 5

Run	E_{vdw}	E_{ele}	E_{PB}	E_{SA}	$E_{interaction}$	$E_{desolvation}$	$E_{NonPolar}$	E_{Polar}	ΔG_{PBSA}
1	−36.7	−160.9	162.7	−2.9	−197.6	159.8	−39.6	1.8	−37.8
2	−35.8	−173.8	173.5	−2.8	−209.6	170.6	−38.6	−0.3	−39.0
3	−33.3	−151.4	155.0	−2.9	−184.7	152.1	−36.2	3.6	−32.6
4	−35.1	−163.4	166.2	−3.0	−198.5	163.2	−38.1	2.8	−35.2
5	−35.5	−169.1	169.6	−2.9	−204.5	166.7	−38.4	0.5	−37.9
Average	−35.3	−163.7	165.4	−2.9	−199.0	162.5	−38.2	1.7	−36.5

Table S7-1. RMSD, ΔG_{PBSA} and ΔG_{bind} of compound 6

Run	RMSD (Å)	ΔG_{PBSA} (kcal/mol)	ΔG_{bind} (kcal/mol)
1	2.02	−36.1	−7.2
2	1.46	−36.3	−10.3
3	1.66	−34.4	4.1
4	1.96	−39.2	−21.1
5	2.51	−41.9	−16.2
Average	1.92	−37.6	−10.1
±MAE	0.29	2.4	6.87

Table S7-2. Component analysis of ΔG_{PBSA} of compound 6

Run	E_{vdw}	E_{ele}	E_{PB}	E_{SA}	$E_{interaction}$	$E_{desolvation}$	$E_{NonPolar}$	E_{Polar}	ΔG_{PBSA}
1	−36.2	−161.2	164.2	−2.9	−197.4	161.3	−39.1	3.0	−36.1
2	−36.6	−157.3	160.5	−2.9	−193.8	157.6	−39.5	3.2	−36.3
3	−36.6	−166.8	172.1	−3.0	−203.5	169.1	−39.6	5.2	−34.4
4	−36.0	−141.2	141.1	−3.0	−177.3	138.1	−39.1	−0.1	−39.2
5	−36.8	−157.7	155.5	−2.9	−194.5	152.6	−39.7	−2.2	−41.9
Average	−36.4	−156.8	158.7	−2.9	−193.3	155.7	−39.4	1.8	−37.6

Table S8-1. RMSD, ΔG_{PBSA} and ΔG_{bind} of compound 7

Run	RMSD (Å)	ΔG_{PBSA} (kcal/mol)	ΔG_{bind} (kcal/mol)

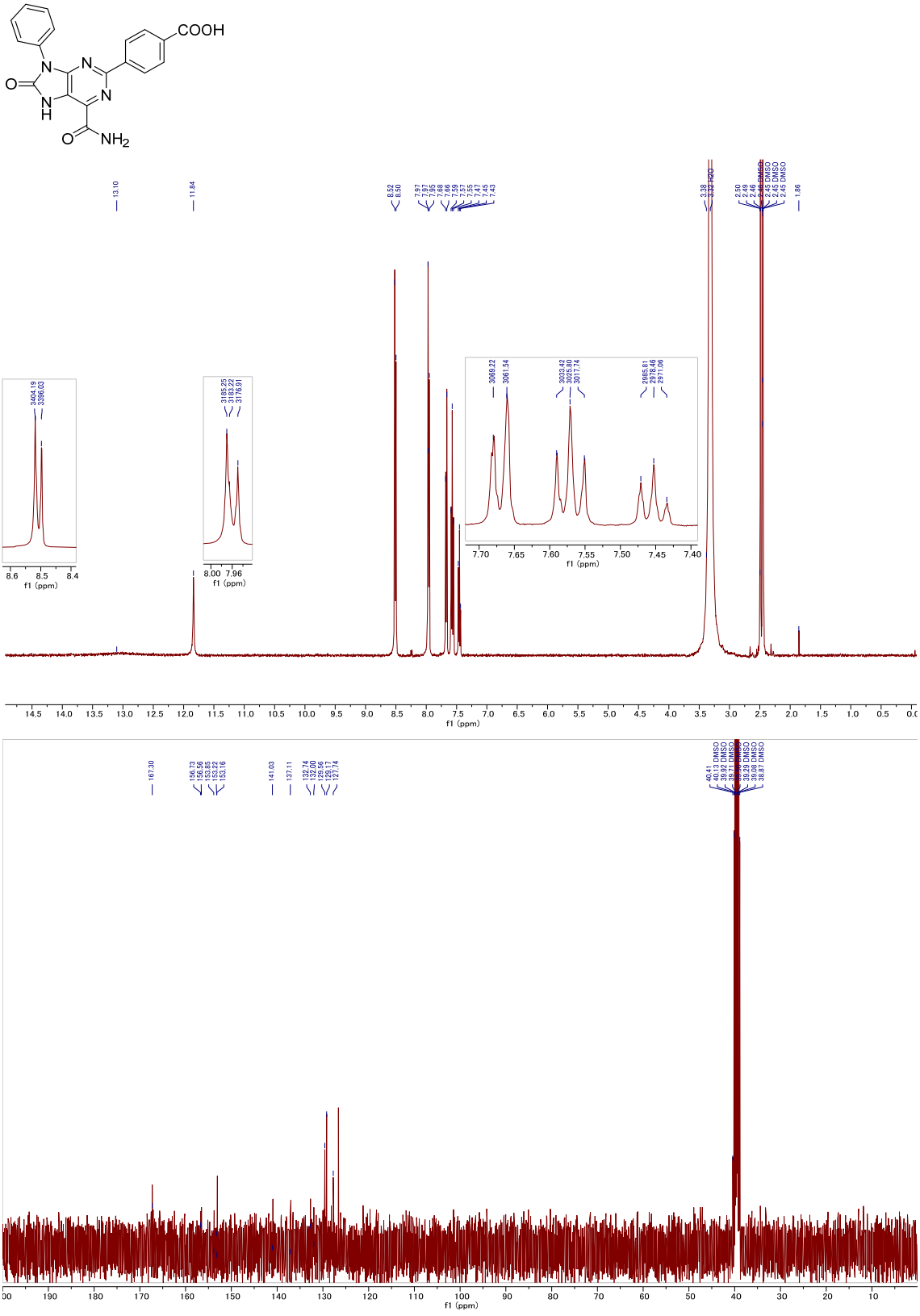
1	2.69	−35.4	6.8
2	2.10	−30.7	16.3
3	2.71	−27.8	38.8
4	1.80	−26.5	1.7
5	2.17	−32.7	4.3
Average	2.29	−30.6	13.6
±MAE	0.32	2.8	11.2

Table S8-2. Component analysis of ΔG_{PBSA} of compound 7

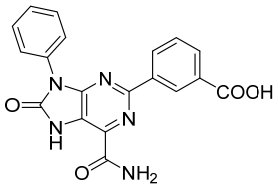
Run	E_{vdw}	E_{ele}	E_{PB}	E_{SA}	$E_{interaction}$	$E_{desolvation}$	$E_{NonPolar}$	E_{Polar}	ΔG_{PBSA}
1	−38.4	−130.5	136.6	−3.1	−168.9	133.5	−41.5	6.1	−35.4
2	−36.3	−151.7	160.4	−3.1	−187.9	157.3	−39.4	8.8	−30.7
3	−35.8	−145.1	156.3	−3.2	−180.9	153.1	−39.0	11.2	−27.8
4	−39.4	−152.1	168.1	−3.1	−191.5	165.0	−42.5	16.0	−26.5
5	−40.8	−148.7	159.9	−3.1	−189.5	156.7	−43.9	11.2	−32.7
Average	−38.1	−145.6	156.3	−3.1	−183.7	153.1	−41.3	10.7	−30.6

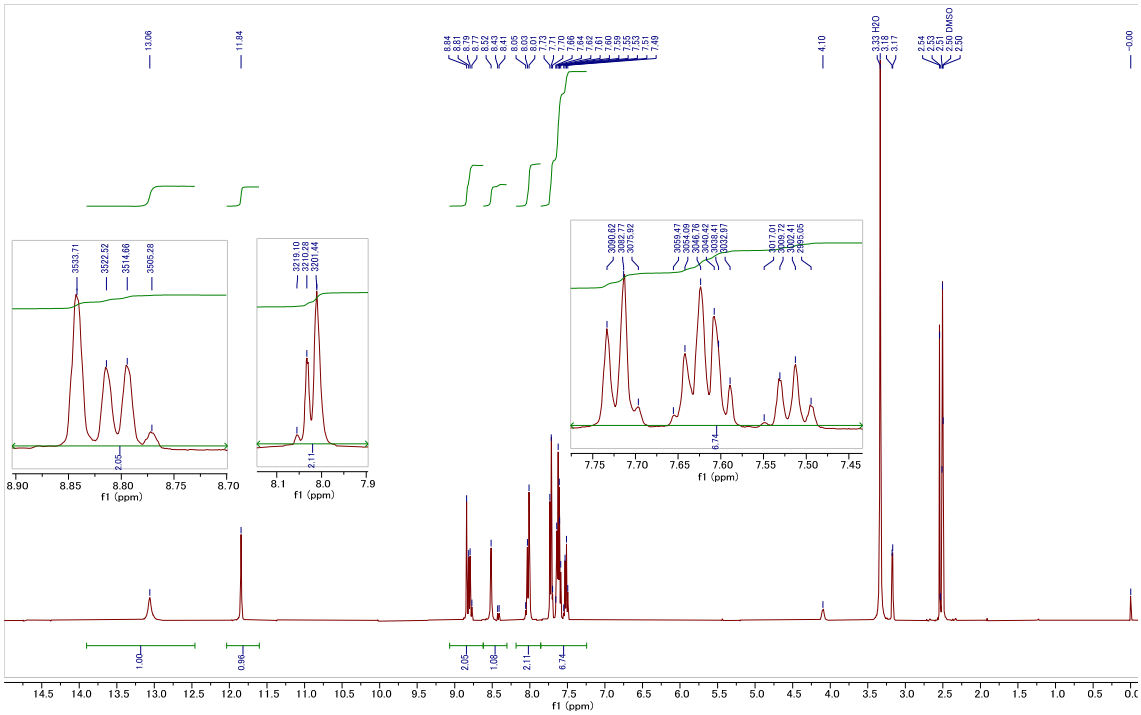
2. Spectral data

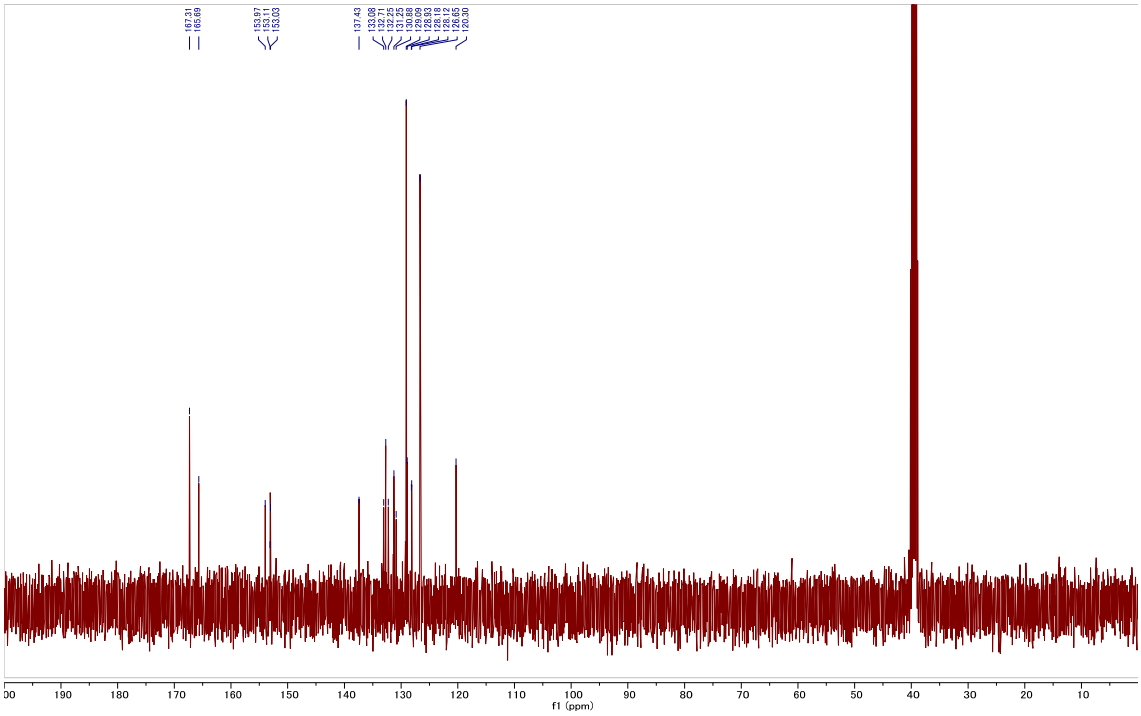
2 4-(6-Carbamoyl-8-oxo-9-phenyl-8,9-dihydro-7*H*-purin-2-yl)benzoic acid (1)



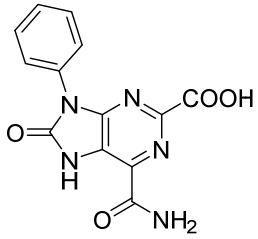
3-(6-Carbamoyl-8-oxo-9-phenyl-8,9-dihydro-7*H*-purin-2-yl)benzoic acid (2)

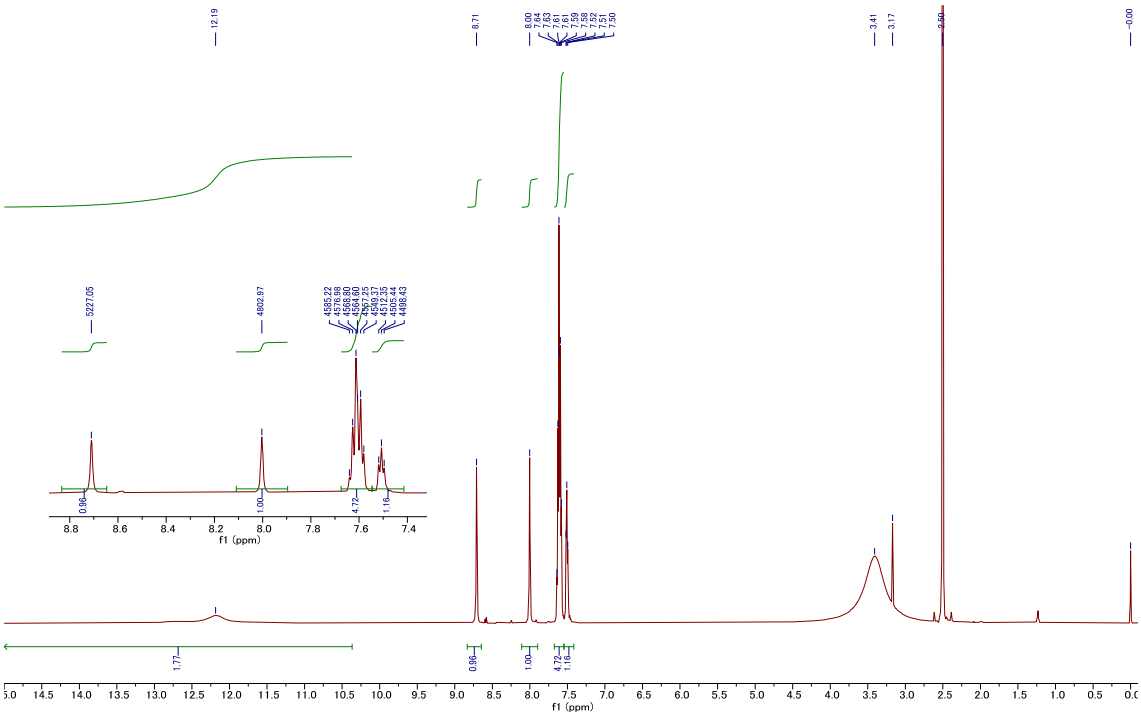


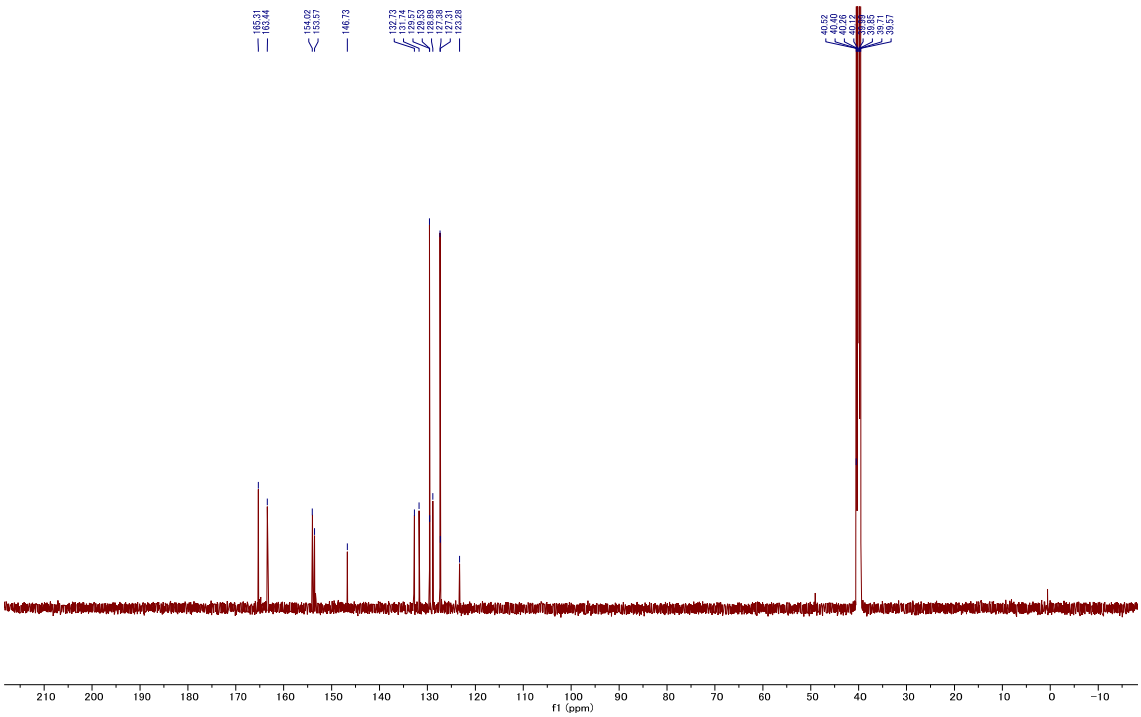




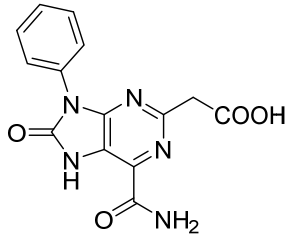
6-Carbamoyl-8-oxo-9-phenyl-8,9-dihydro-7*H*-purine-2-carboxylic acid (3)

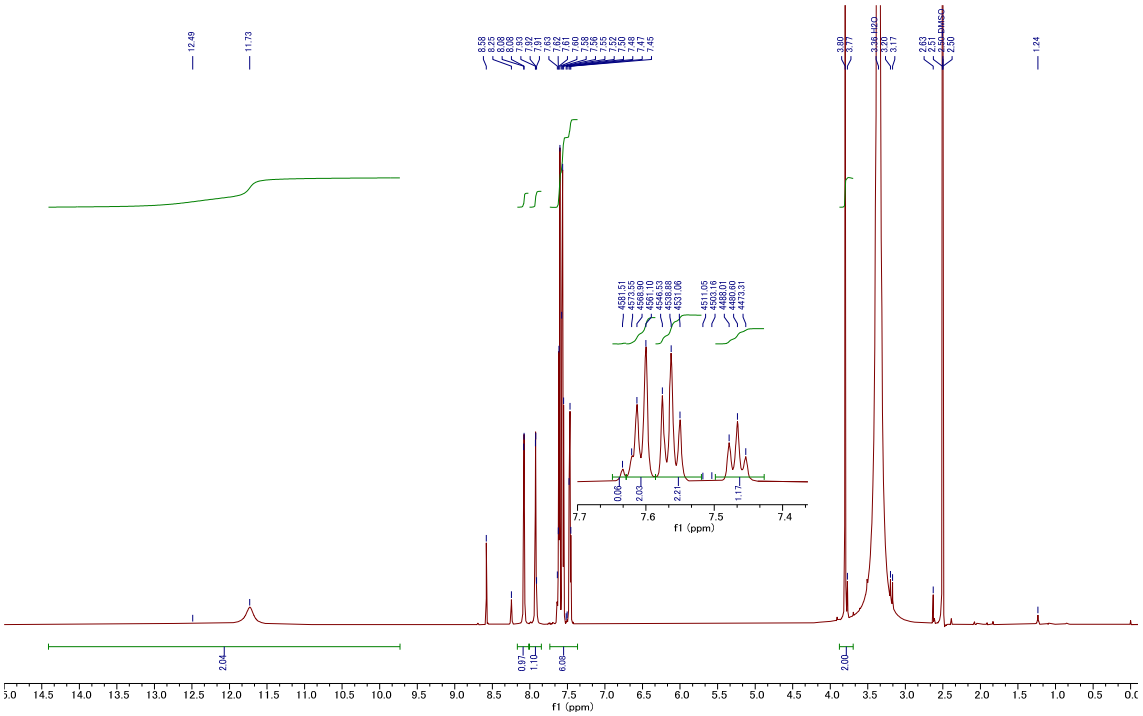


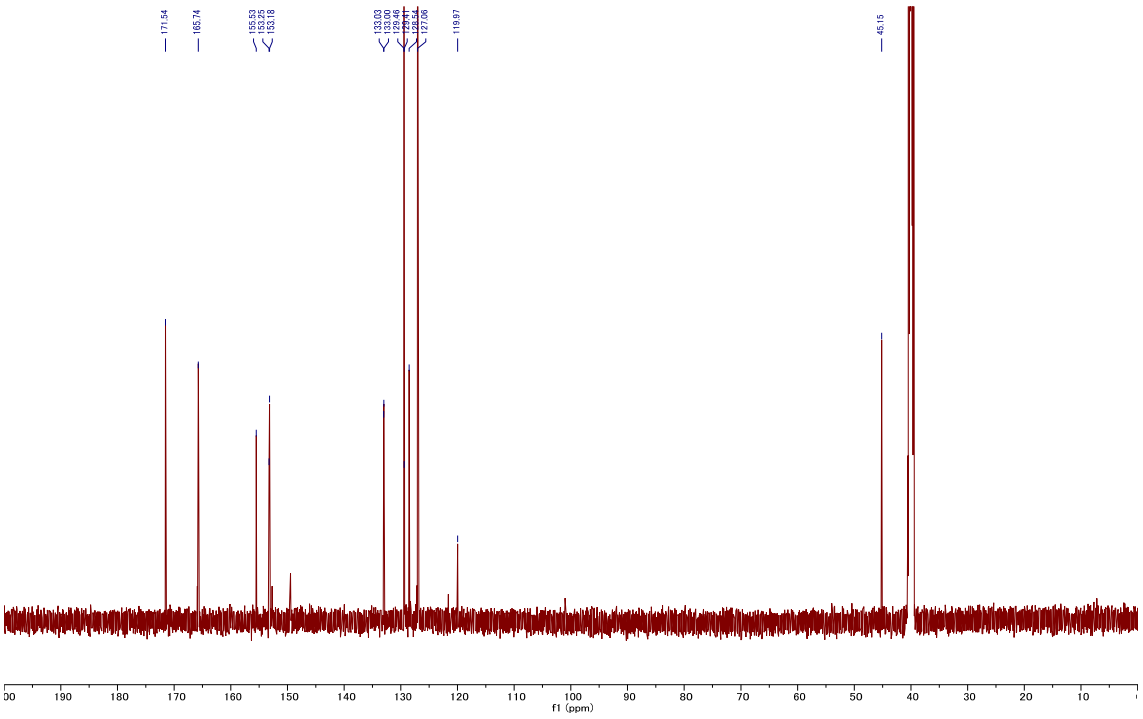




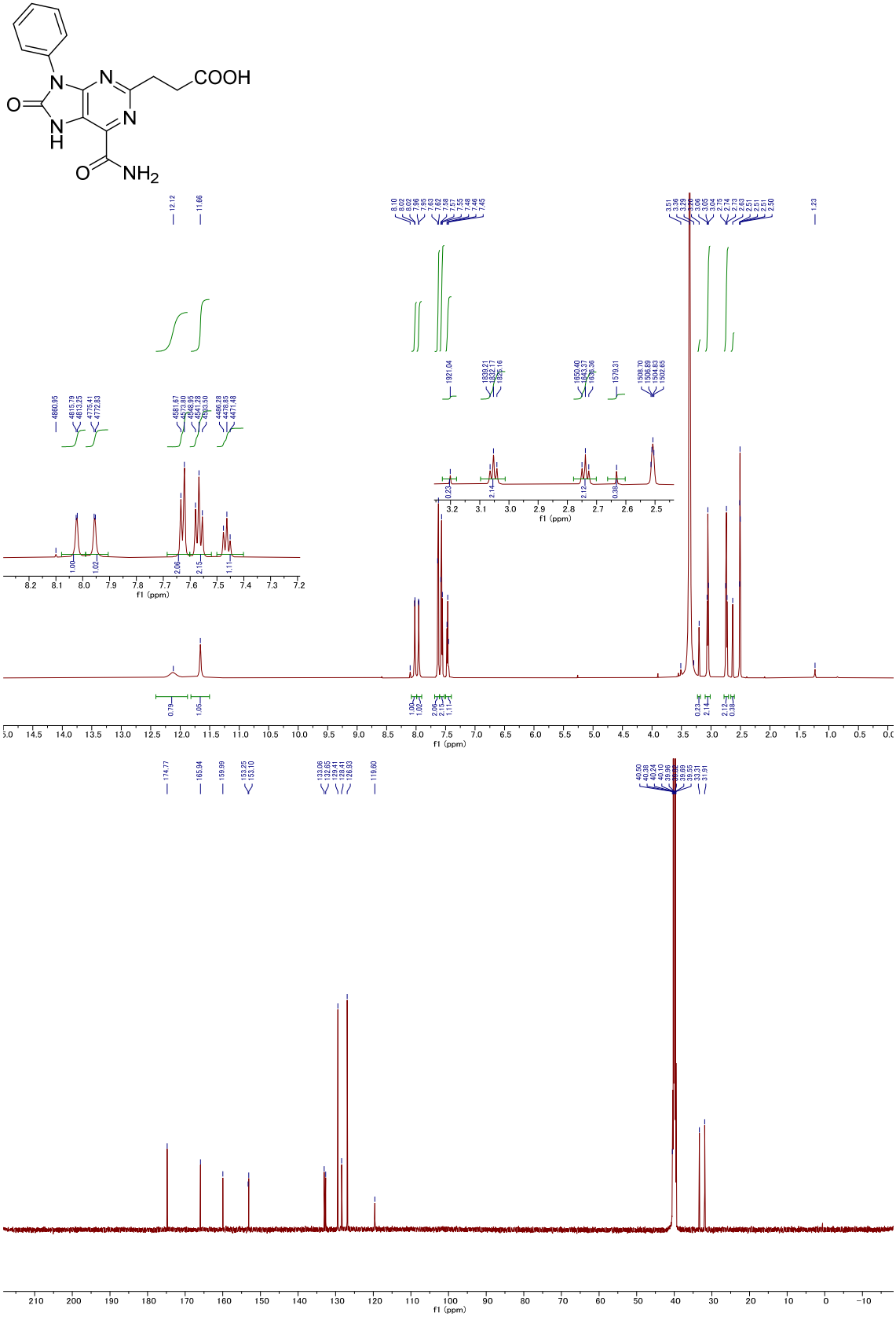
2-(6-Carbamoyl-8-oxo-9-phenyl-8,9-dihydro-7*H*-purin-2-yl)acetic acid (4)







3-(6-carbamoyl-8-oxo-9-phenyl-8,9-dihydro-7*H*-purin-2-yl)propanoic acid (5)



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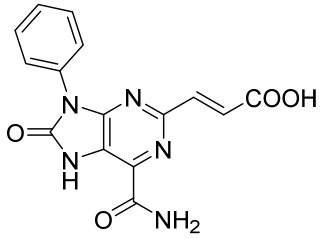
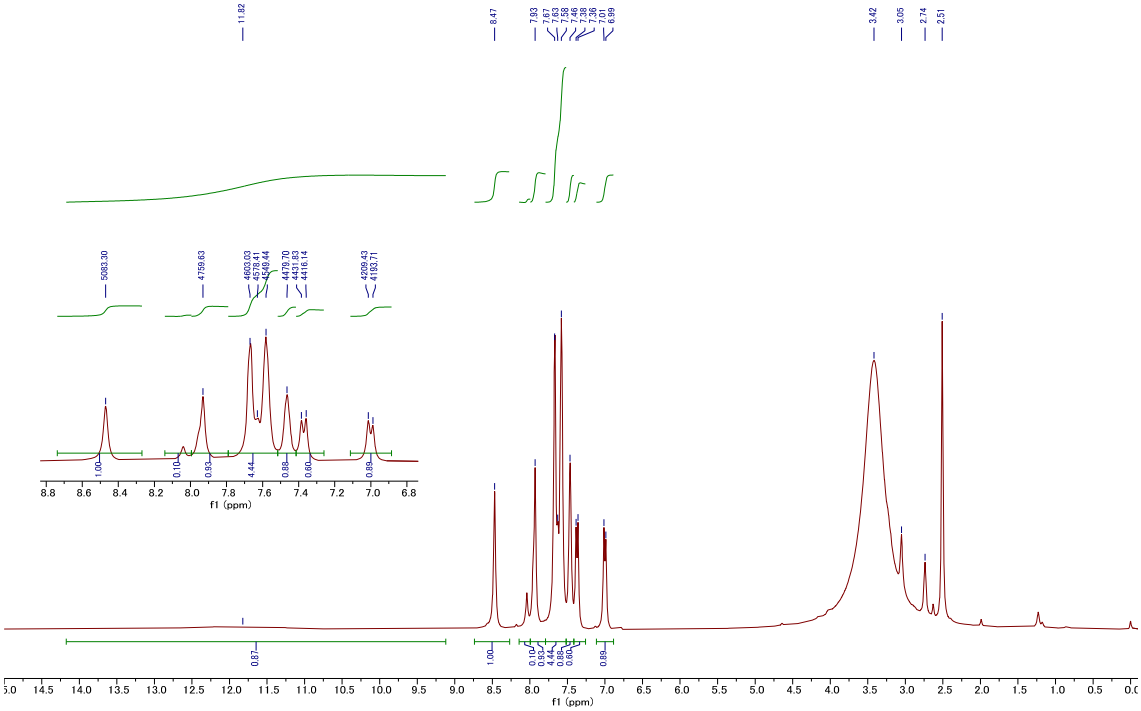
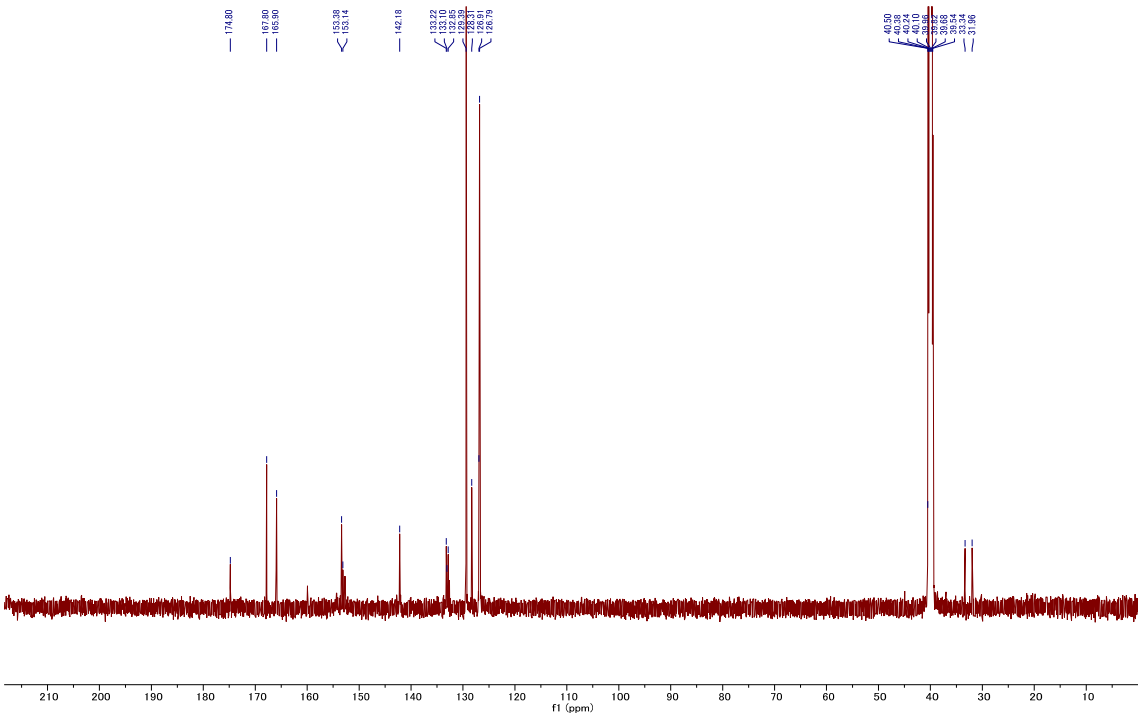
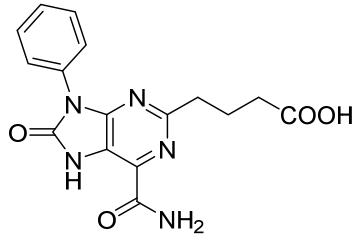
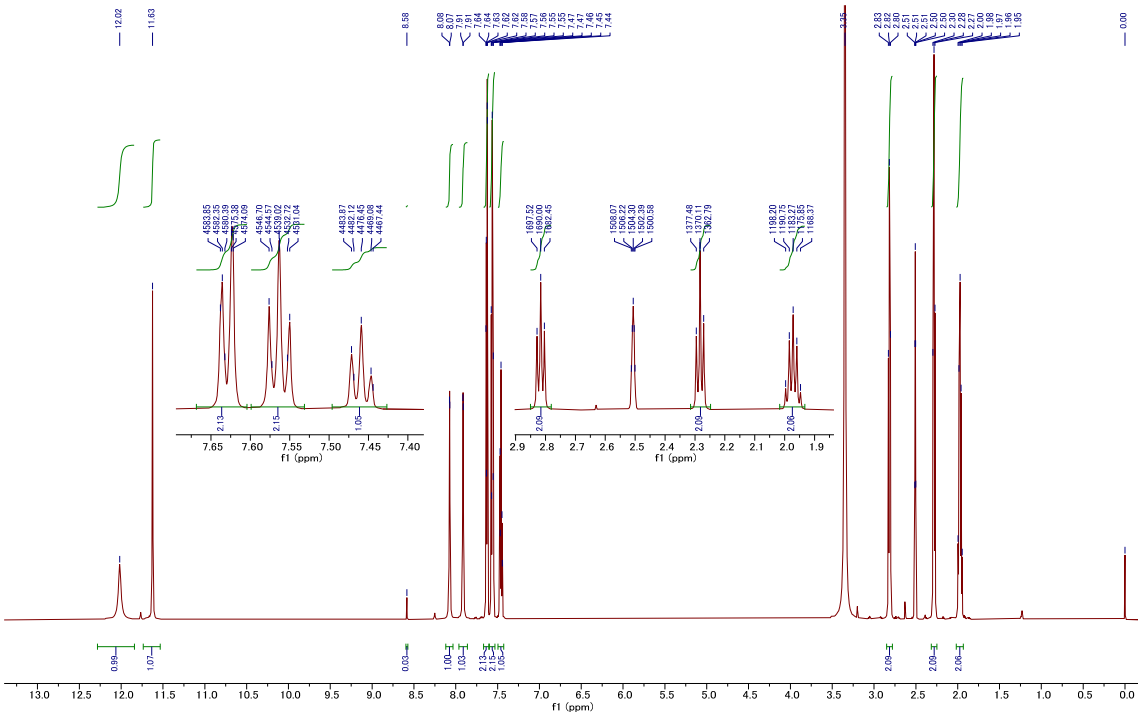


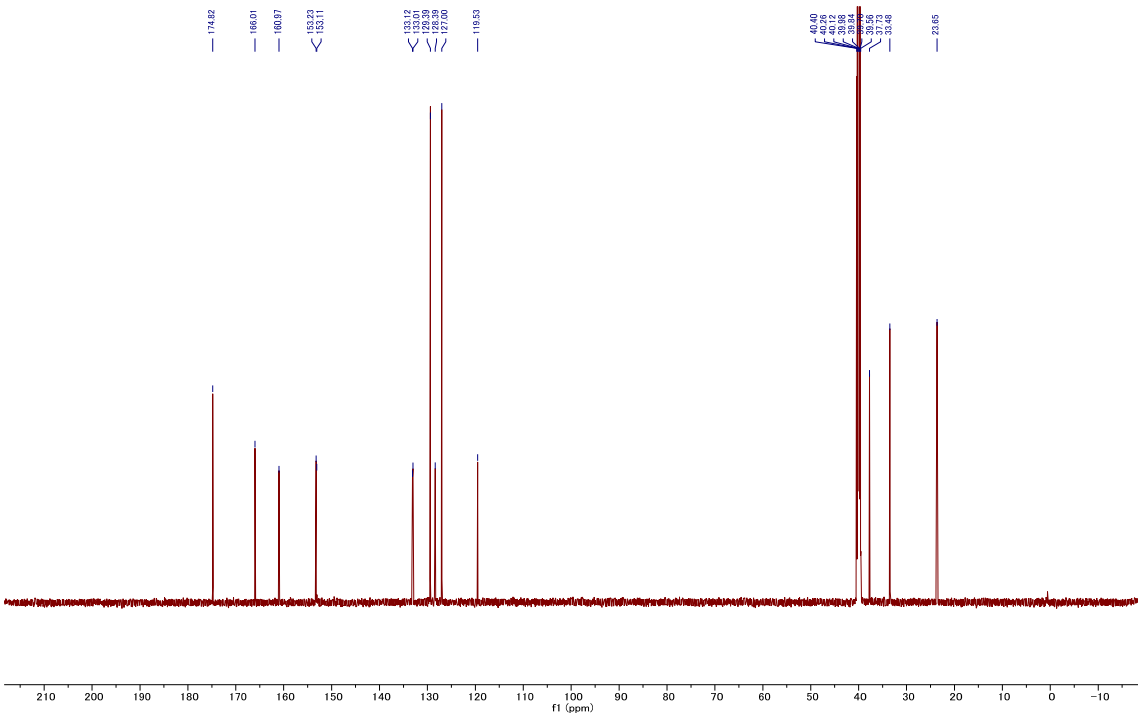




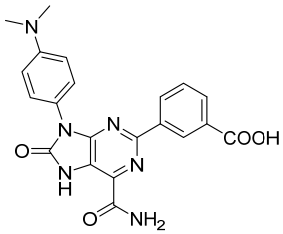
4-(6-carbamoyl-8-oxo-9-phenyl-8,9-dihydro-7*H*-purin-2-yl)butanoic acid (7)

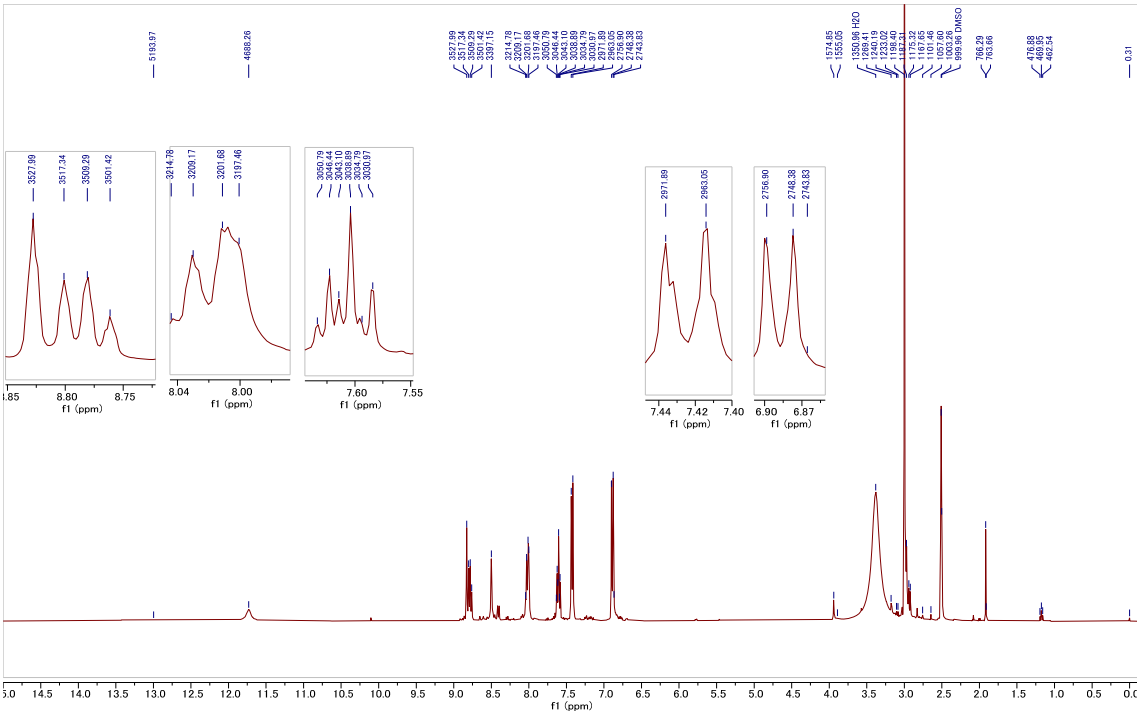


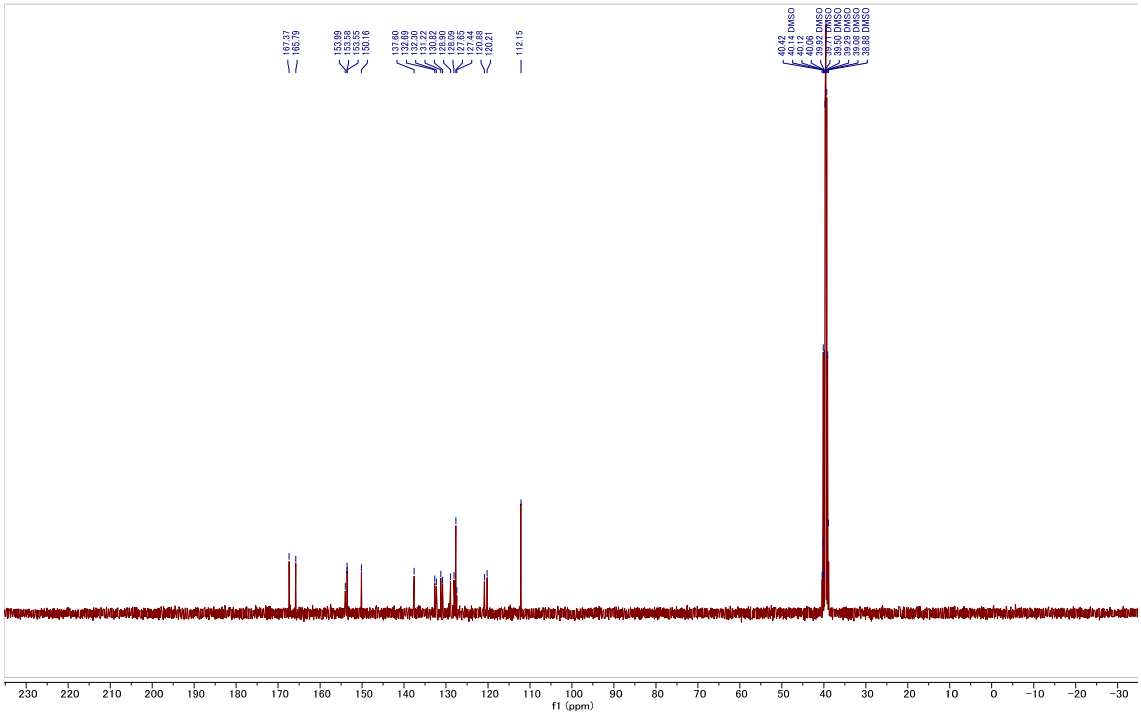




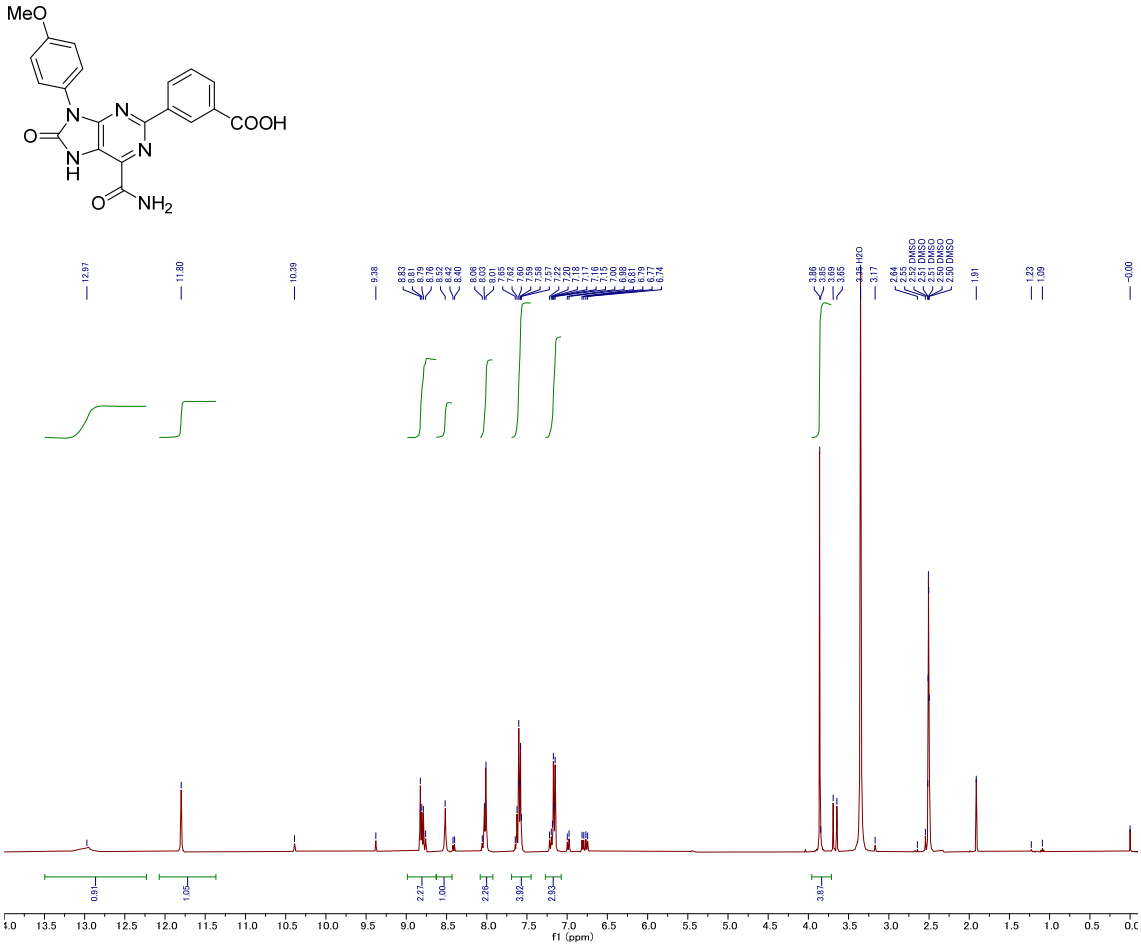
3-(6-carbamoyl-9-(4-(dimethylamino)phenyl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl) benzoic acid (8)

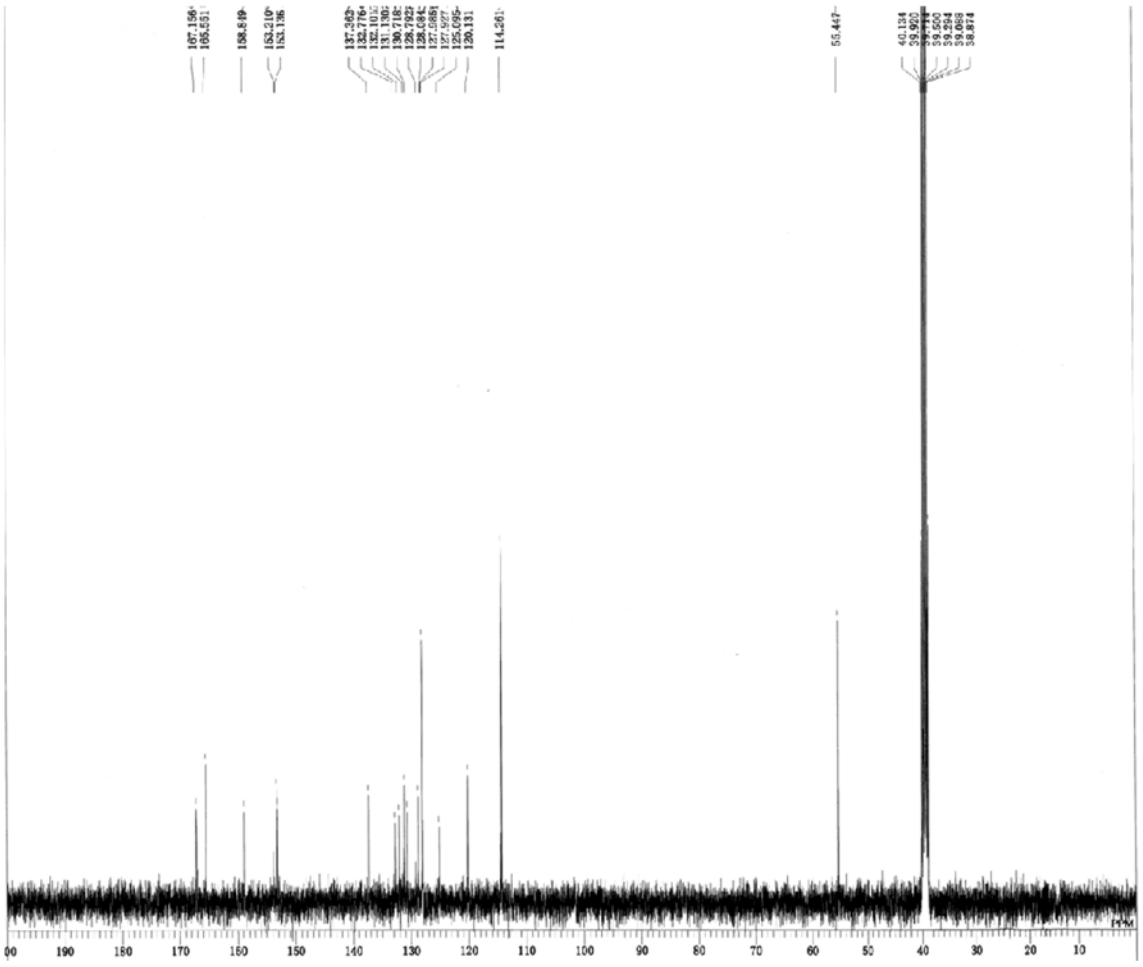




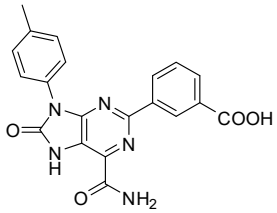


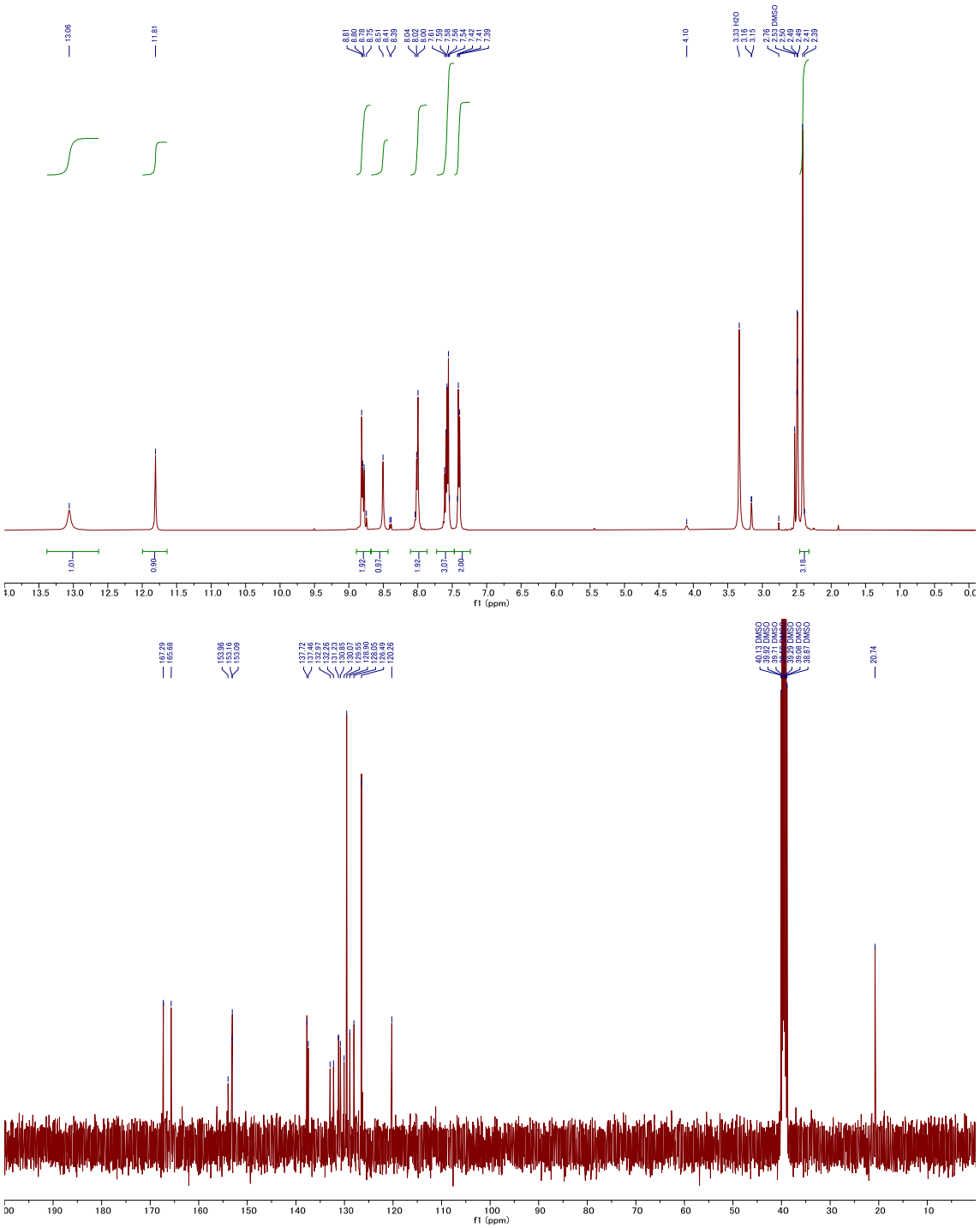
3-(6-Carbamoyl-9-(4-methoxyphenyl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)benzoic acid (9)



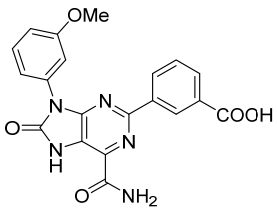


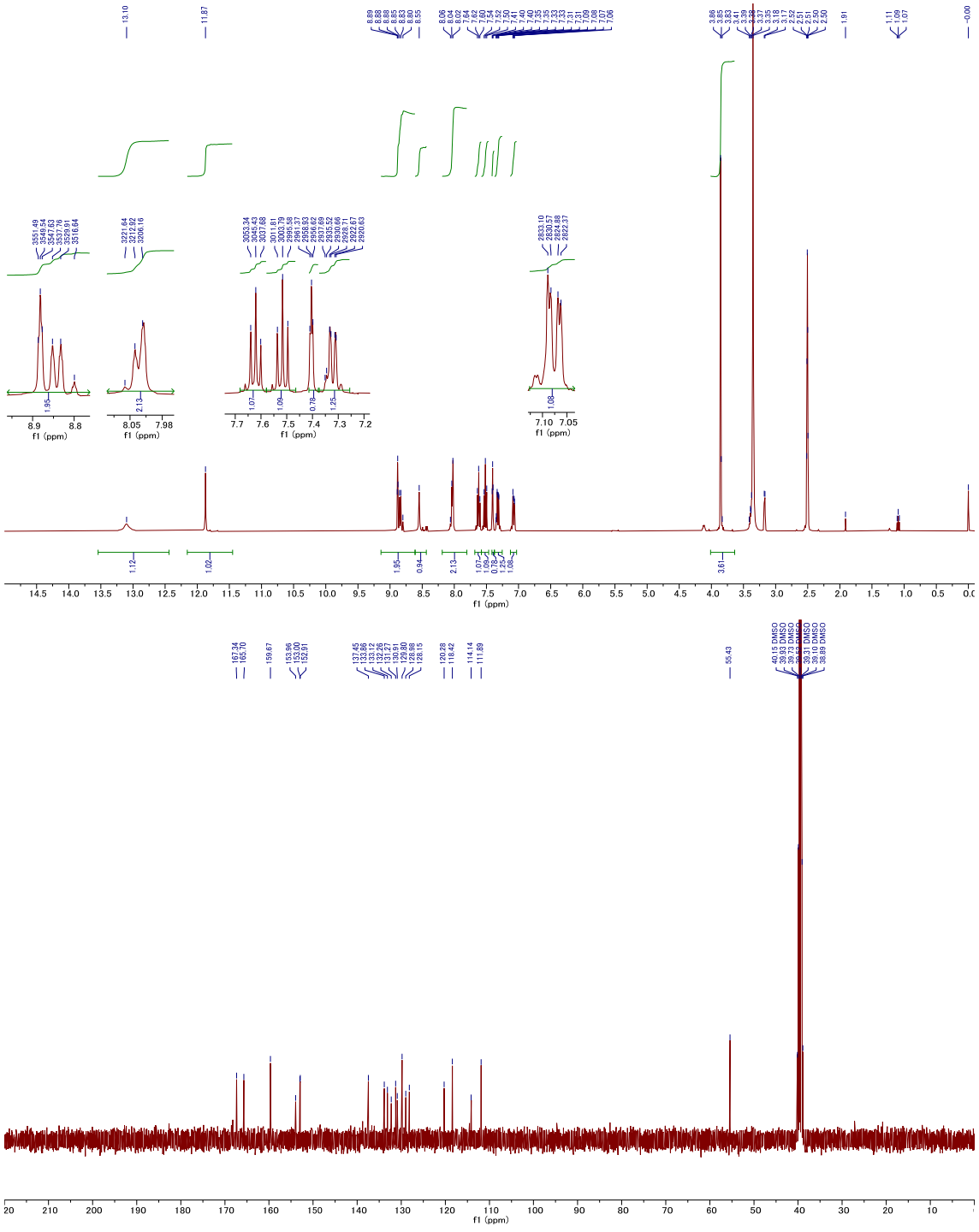
3-(6-Carbamoyl-8-oxo-9-(p-tolyl)-8,9-dihydro-7*H*-purin-2-yl)benzoic acid (10)



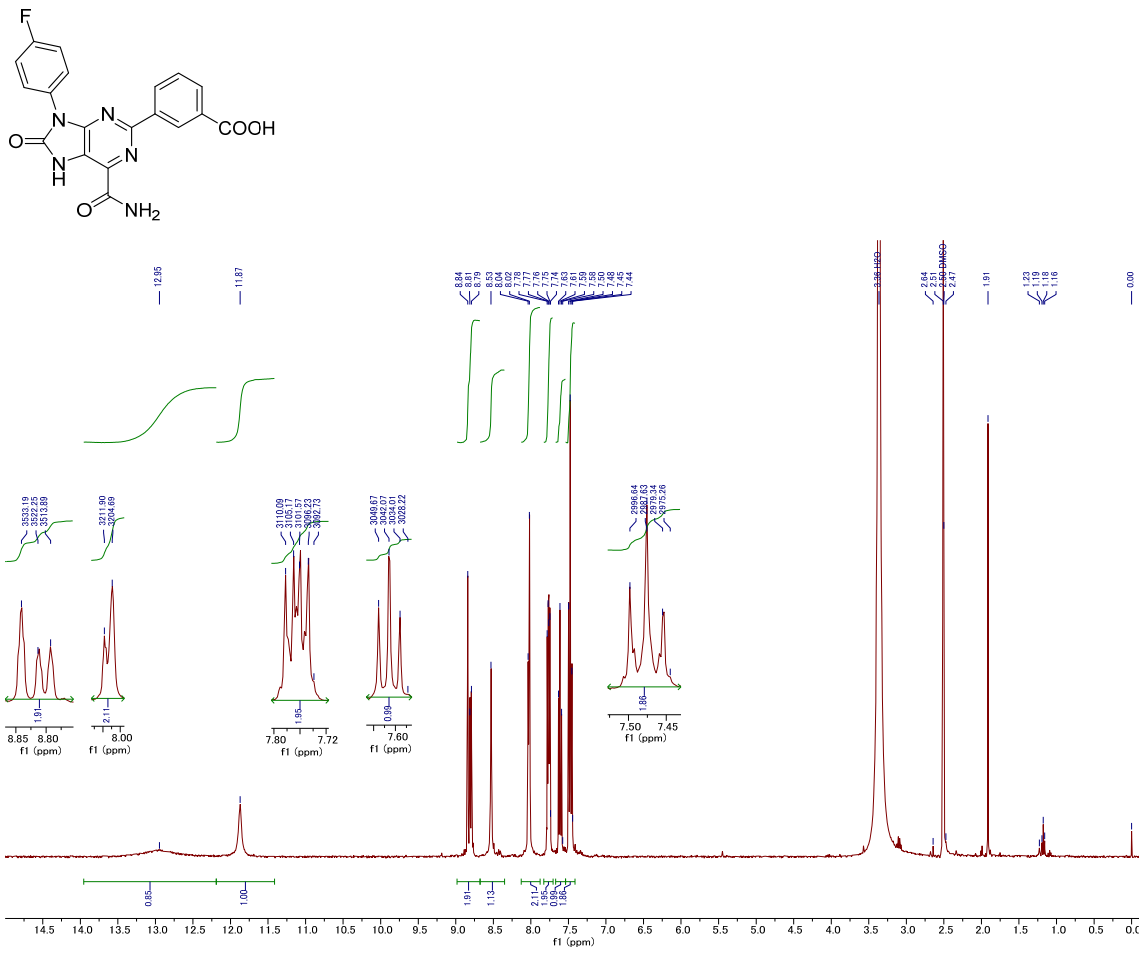


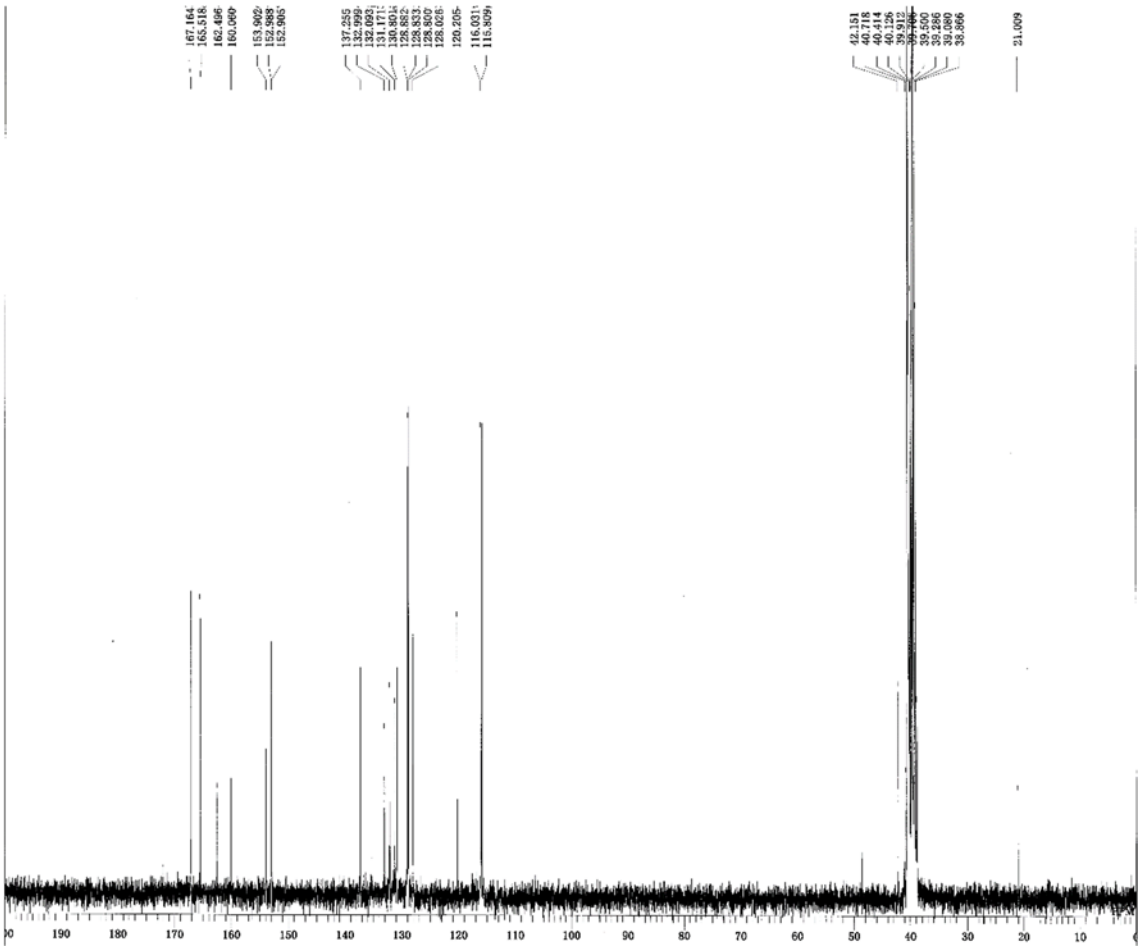
3-(6-Carbamoyl-9-(3-methoxyphenyl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)benzoic acid (11)



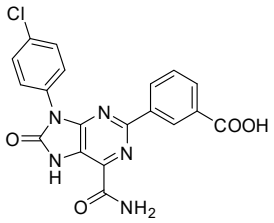


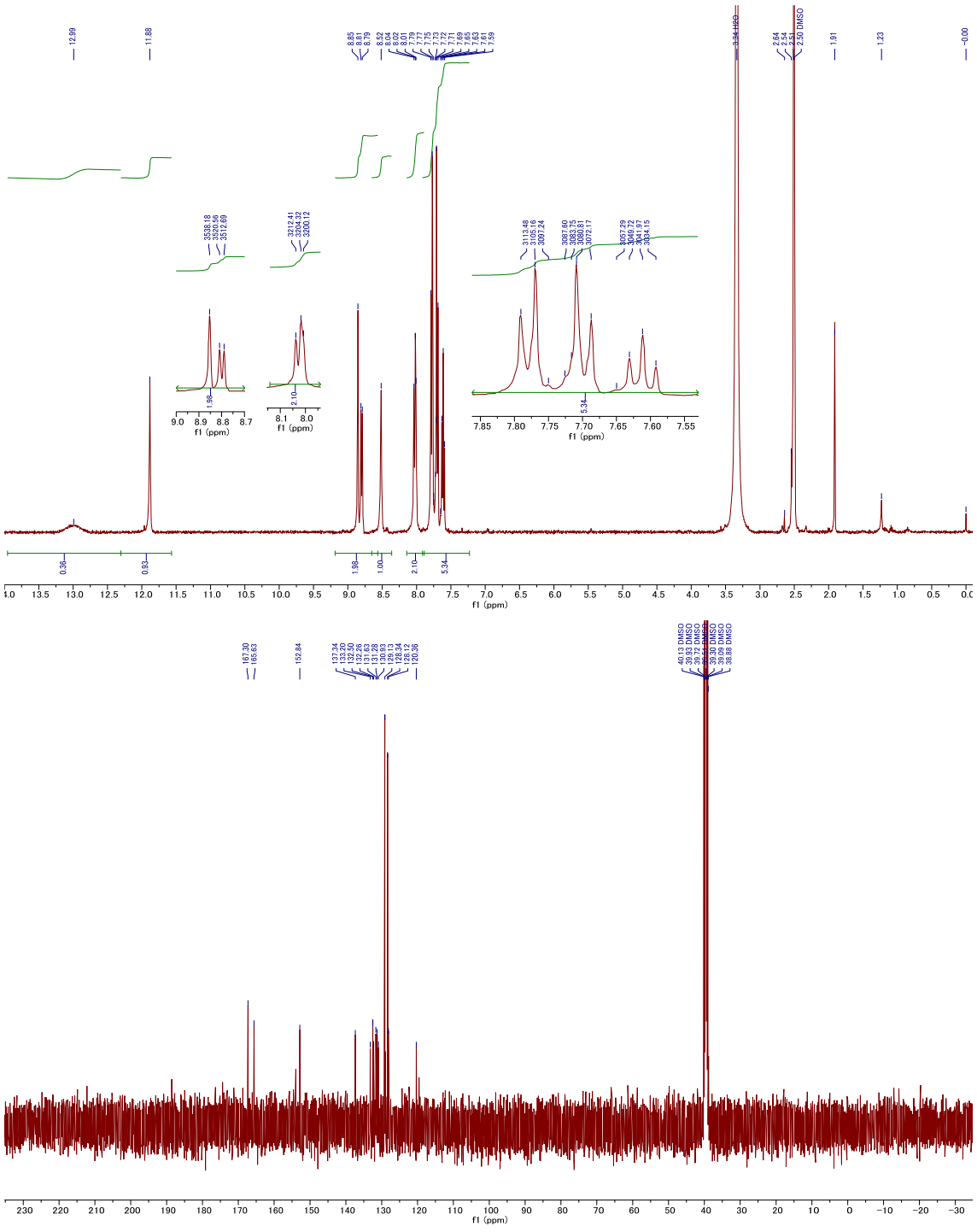
3-(6-Carbamoyl-9-(4-fluorophenyl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)benzoic acid(12)


F
O
N
N
H
N
N
COOH
O
NH2
12.95
11.67
8.84
8.81
8.79
8.53
8.04
8.02
7.78
7.77
7.76
7.75
7.74
7.63
7.61
7.59
7.58
7.50
7.48
7.45
7.44
3.36
2.64
2.51
2.47
1.91
1.23
1.19
1.18
1.16
0.00
f1 (ppm)

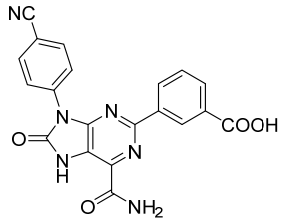


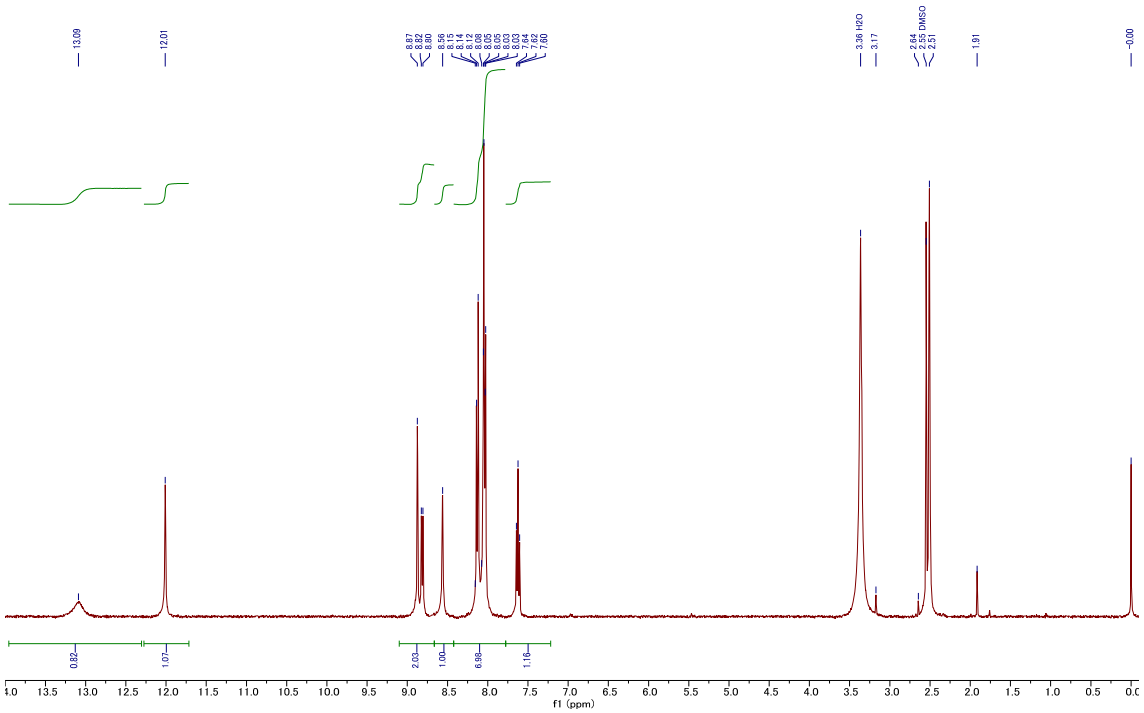
3-(6-Carbamoyl-9-(4-chlorophenyl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)benzoic acid (13)

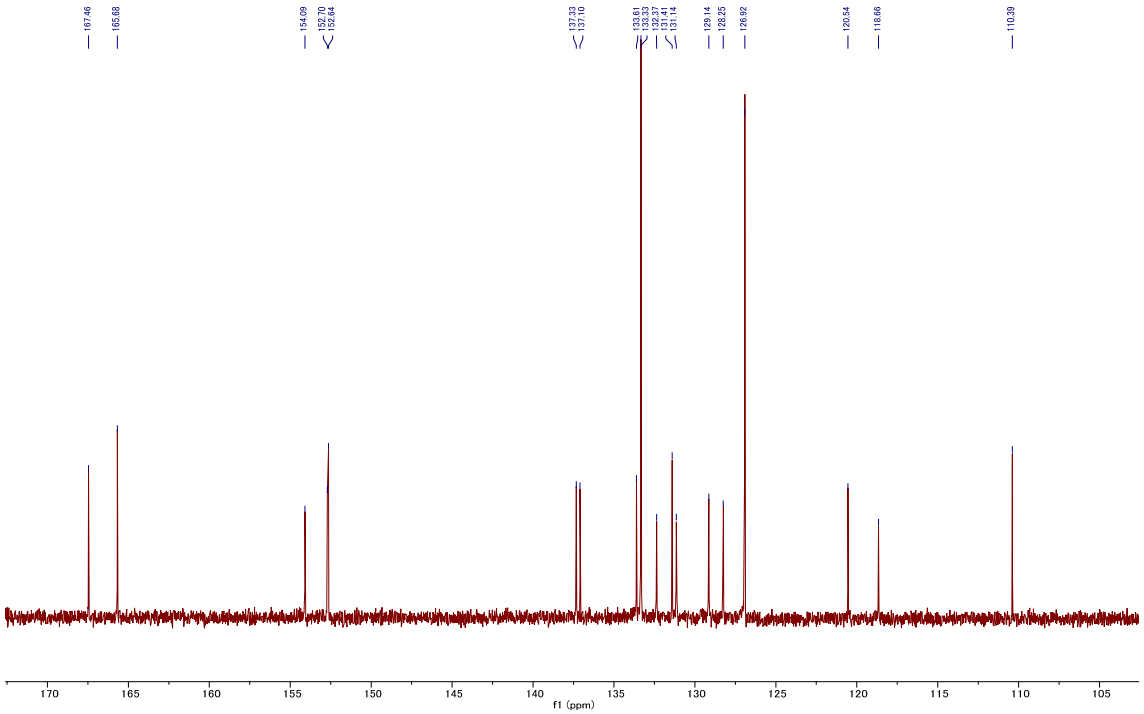




3-(6-Carbamoyl-9-(4-cyanophenyl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)benzoic acid (14)


NC
N
N
O
N
H
N
COOH
O
NH2


13.09
12.01
8.87
8.82
8.80
8.56
8.15
8.14
8.12
8.08
8.06
8.05
8.05
8.03
8.03
7.64
7.62
7.60
3.38 H2O
3.17
2.64
2.55 DMSO
2.51
1.91
-0.00
0.82
1.07
2.03
1.00
6.98
1.16
f1 (ppm)


167.46
165.88
154.09
152.70
152.64
137.33
137.10
133.61
133.33
132.37
131.41
131.14
129.14
128.25
126.92
120.54
118.66
110.39
f1 (ppm)

3-(6-carbamoyl-9-(4-nitrophenyl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)benzoic acid (15)