

# Supporting information

## Structure-based design of a potent and selective YTHDC1 ligand

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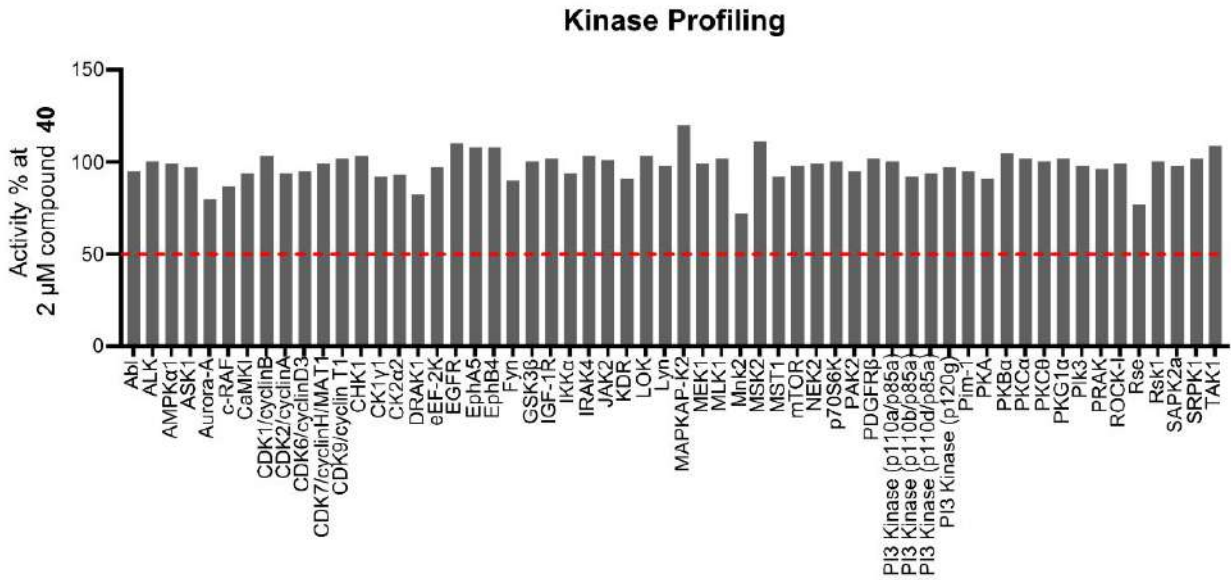
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[caflisch@bioc.uzh.ch](mailto:caflisch@bioc.uzh.ch)

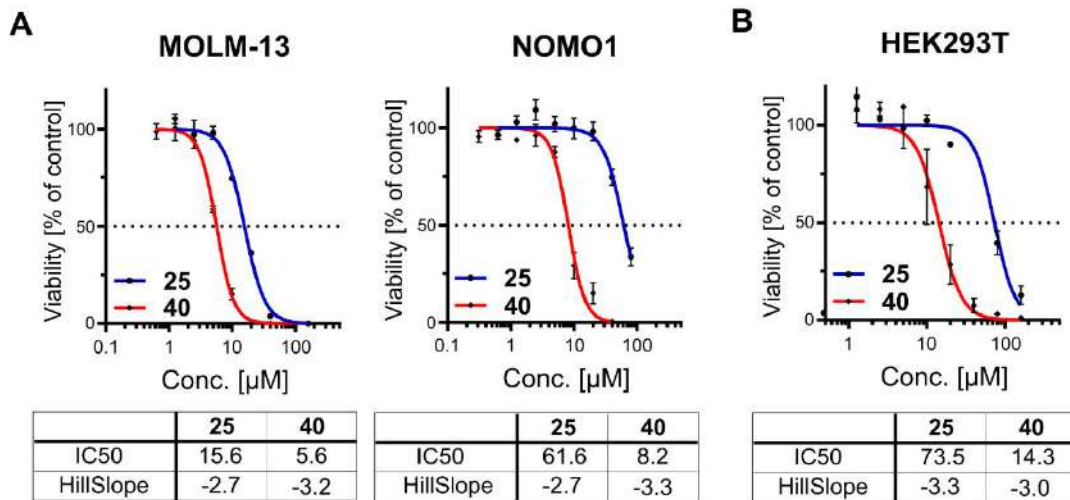
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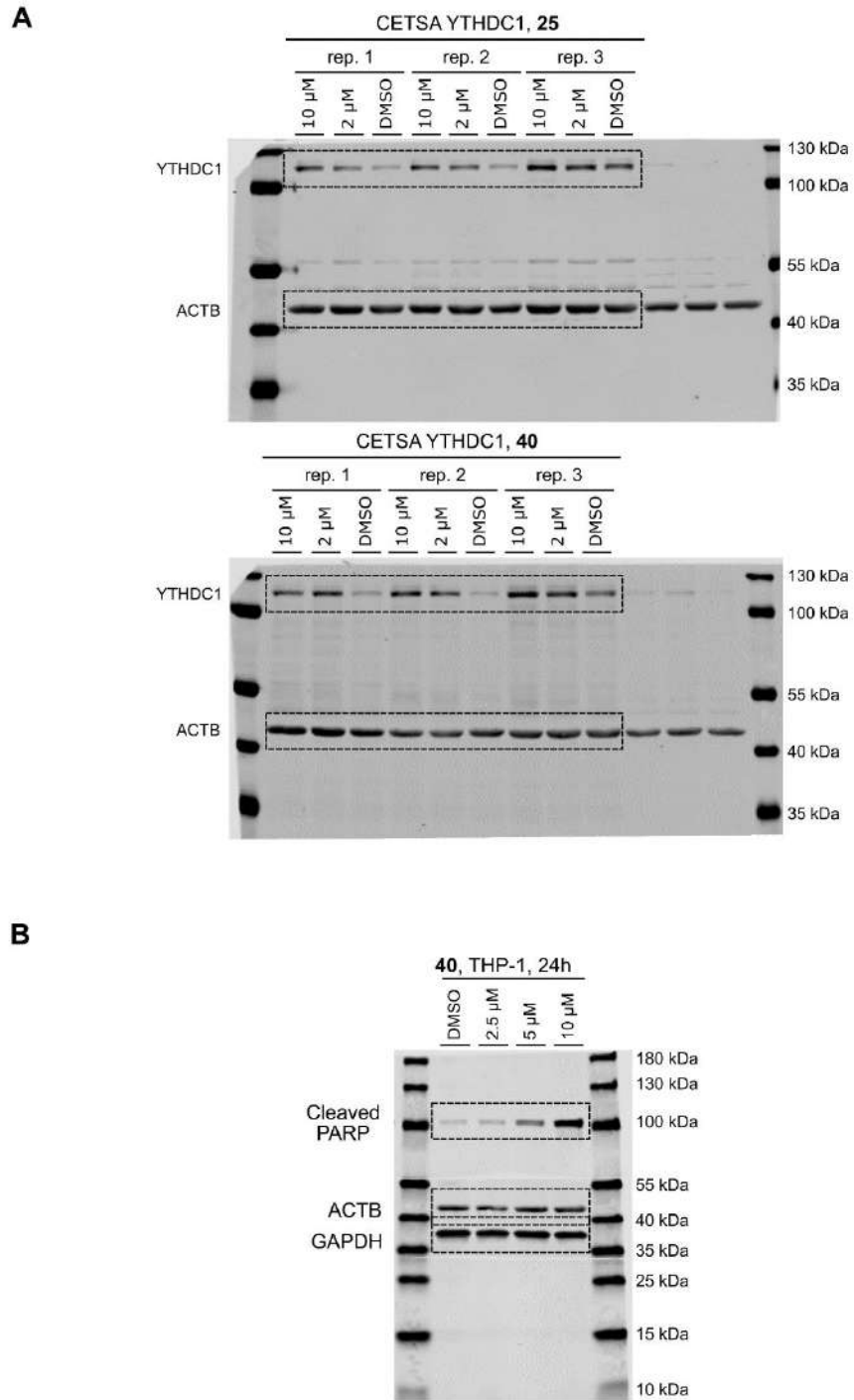
1. **Figure S1** - Inhibitory activity of compound **40** at 2  $\mu$ M on a panel of 58 kinases



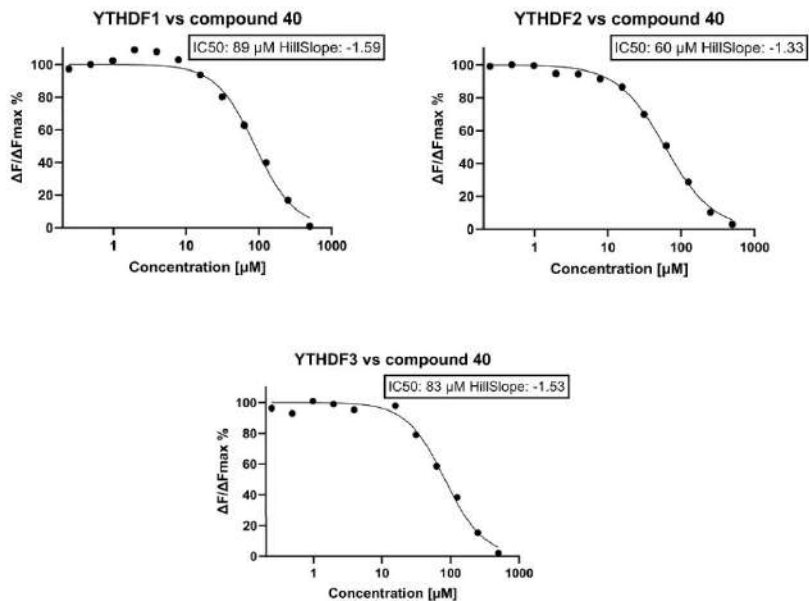
2. **Figure S2**: Dose-response curve for the antiproliferative effect of compound **40** against (A) MOLM-13, NOMO-1 and (B) HEK293T cell lines.



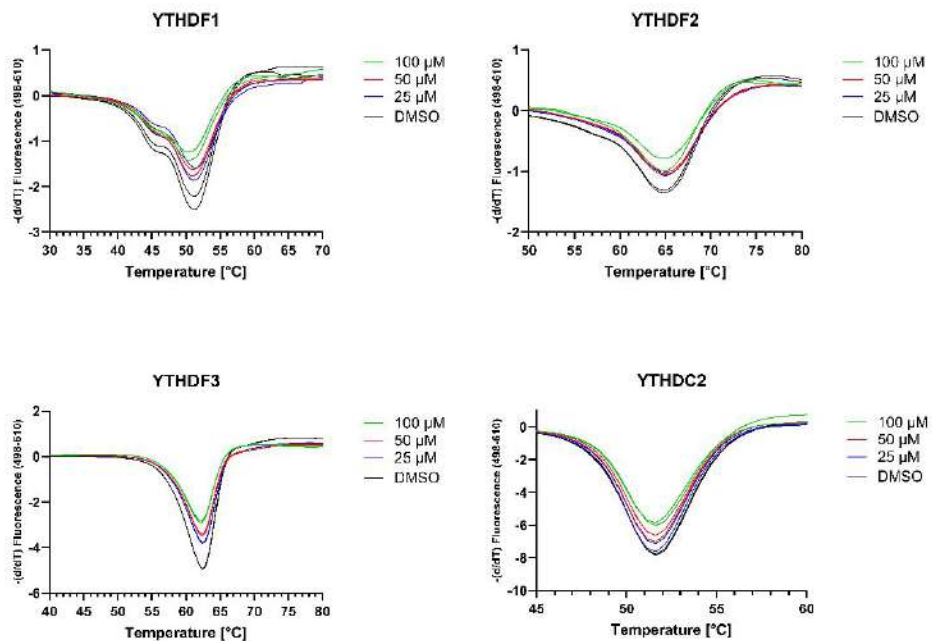
3. **Figure S3:** Representative Western blot membranes for the data presented in Figure 4.  
 (A) CETSA YTHDC1 (B) Cleaved PARP



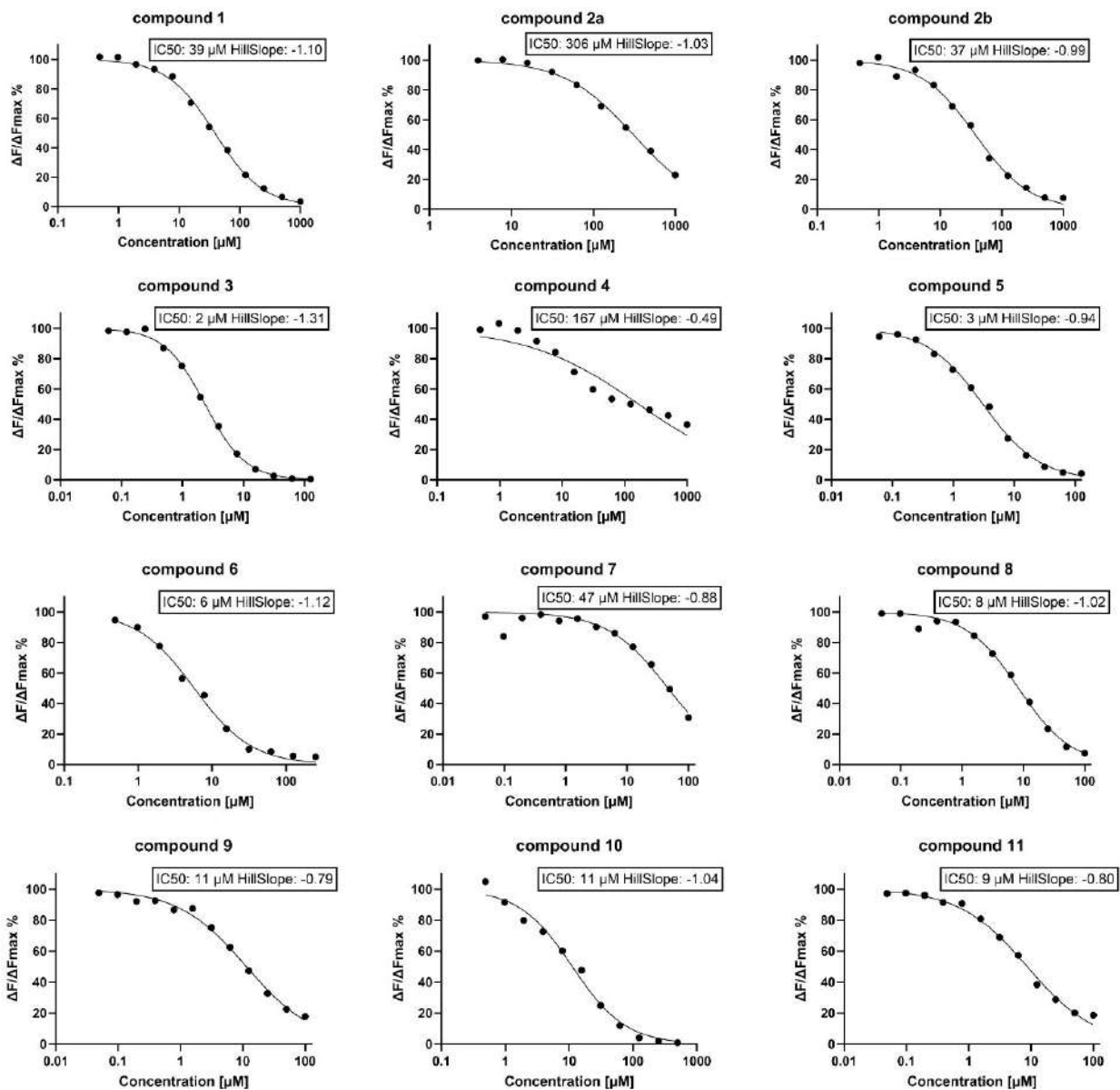
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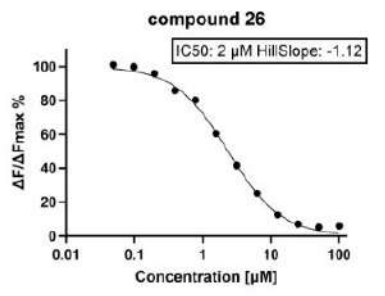
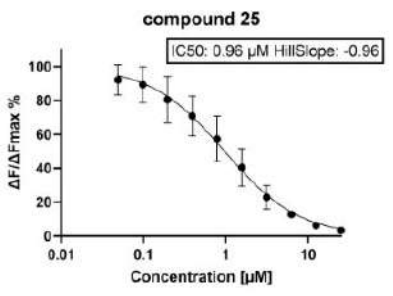
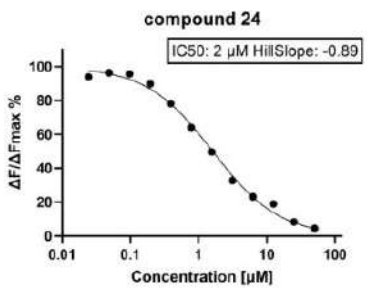
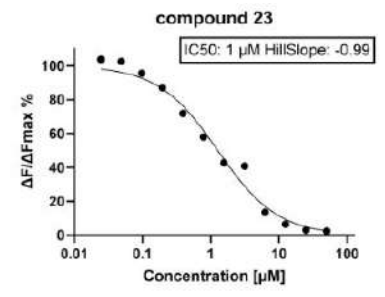
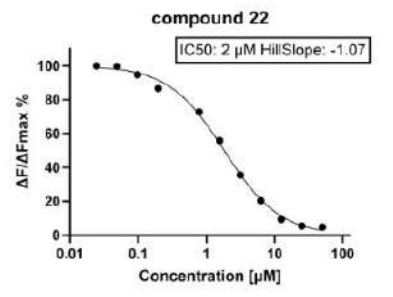
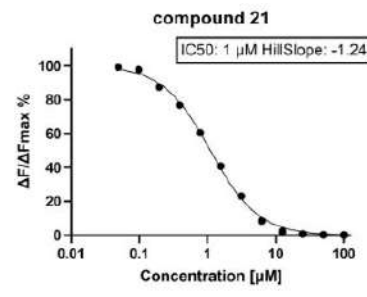
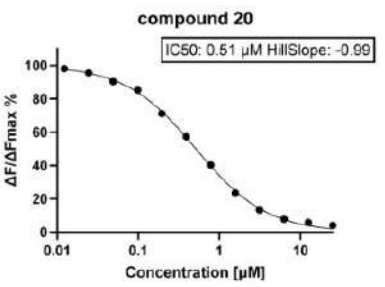
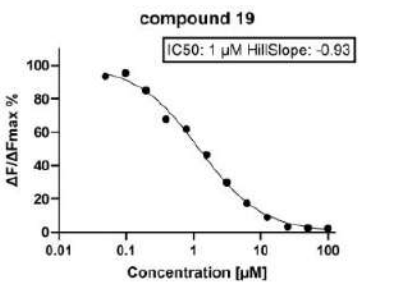
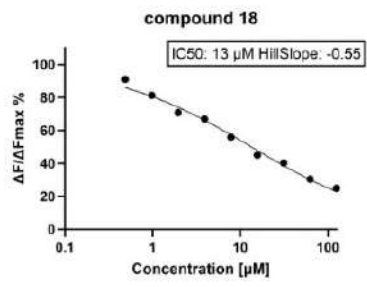
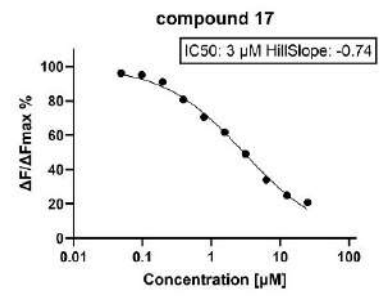
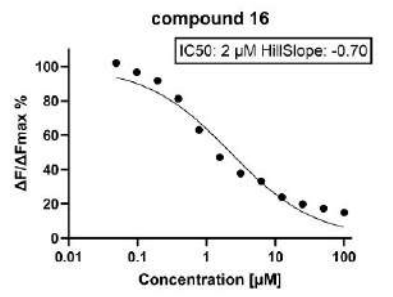
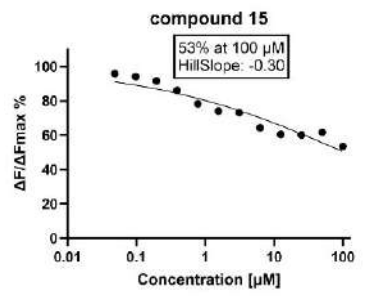
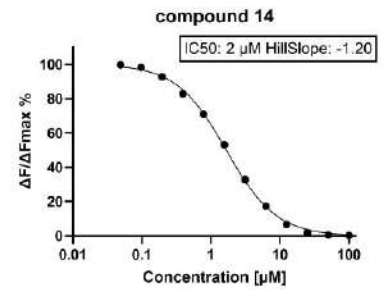
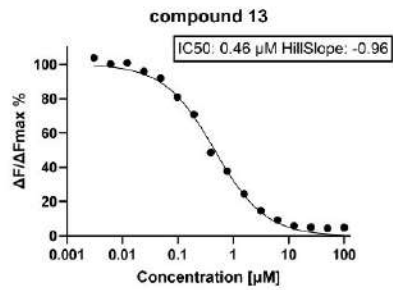
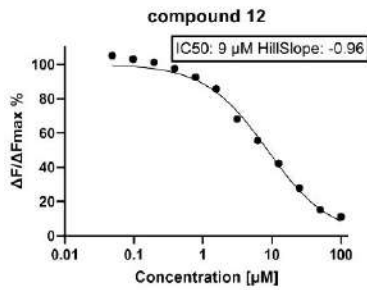


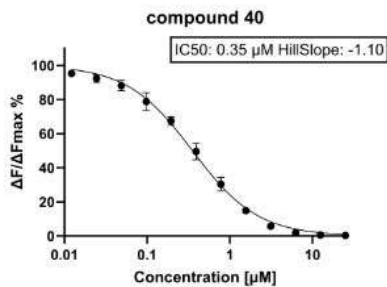
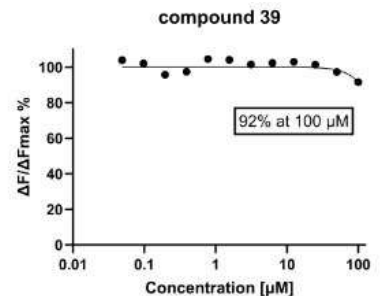
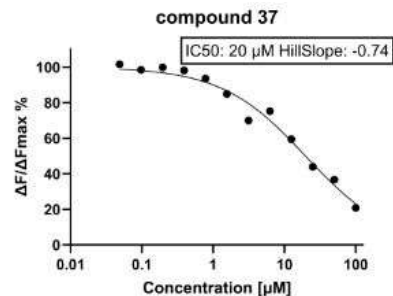
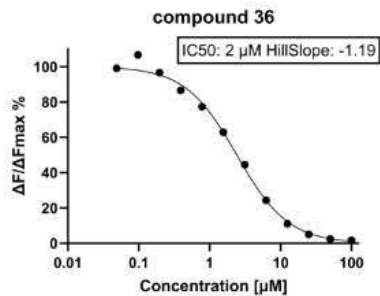
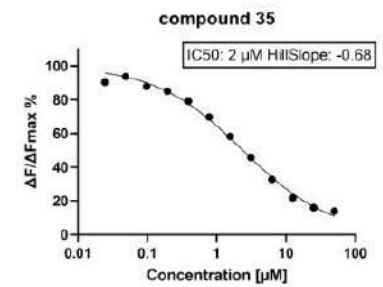
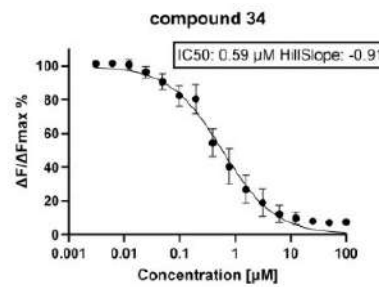
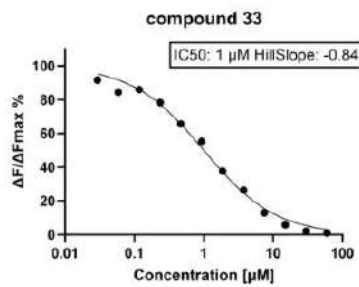
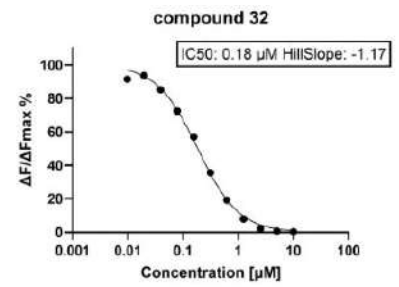
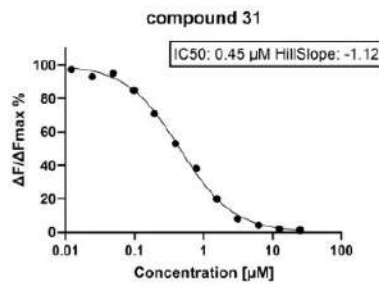
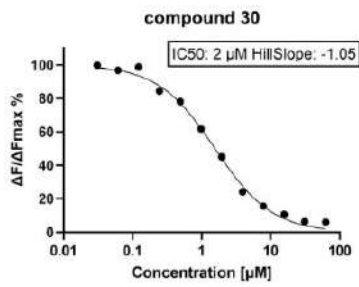
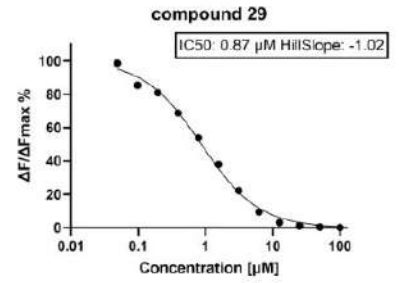
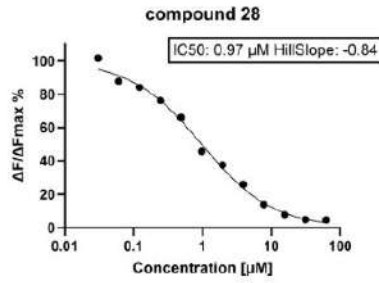
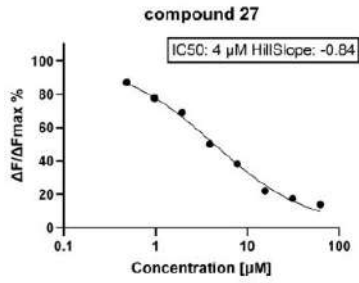
5. **Figure S5:** Dose-response thermal shift of YTHDF1, YTHDF2, YTHDF3, and YTHDC2 in presence of compound 40.



6. **GST-YTHDC1 HTRF dose-response curves.** With the exceptions of compounds **2b**, **4**, **7**, **8**, **9**, **15**, **24**, **29**, **33**, and **39** the curves come from the average of two or more biological replicates, and each biological replicate is the average of two technical replicates. The error bars represent the standard deviation for the biological triplicates and quadruplicate. Compound **38** was only tested in single dose at 5 micromolar (103%).

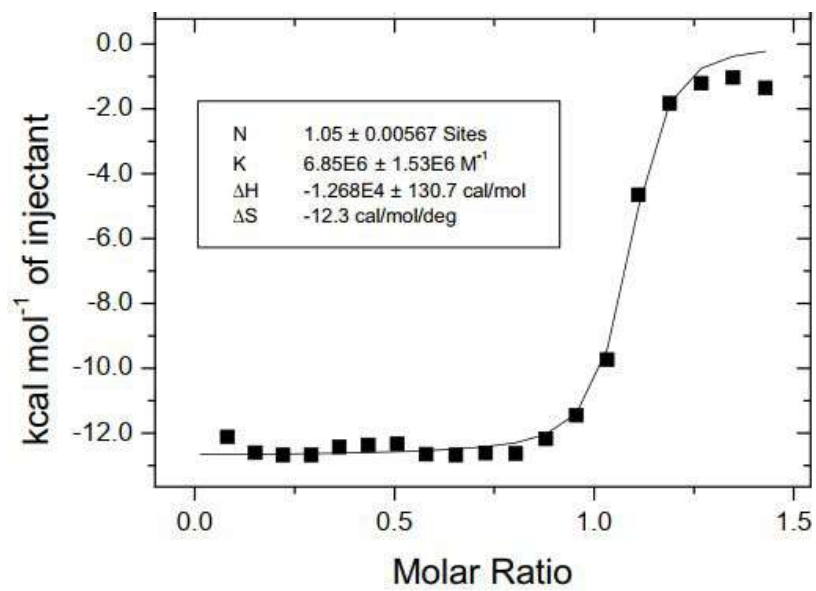






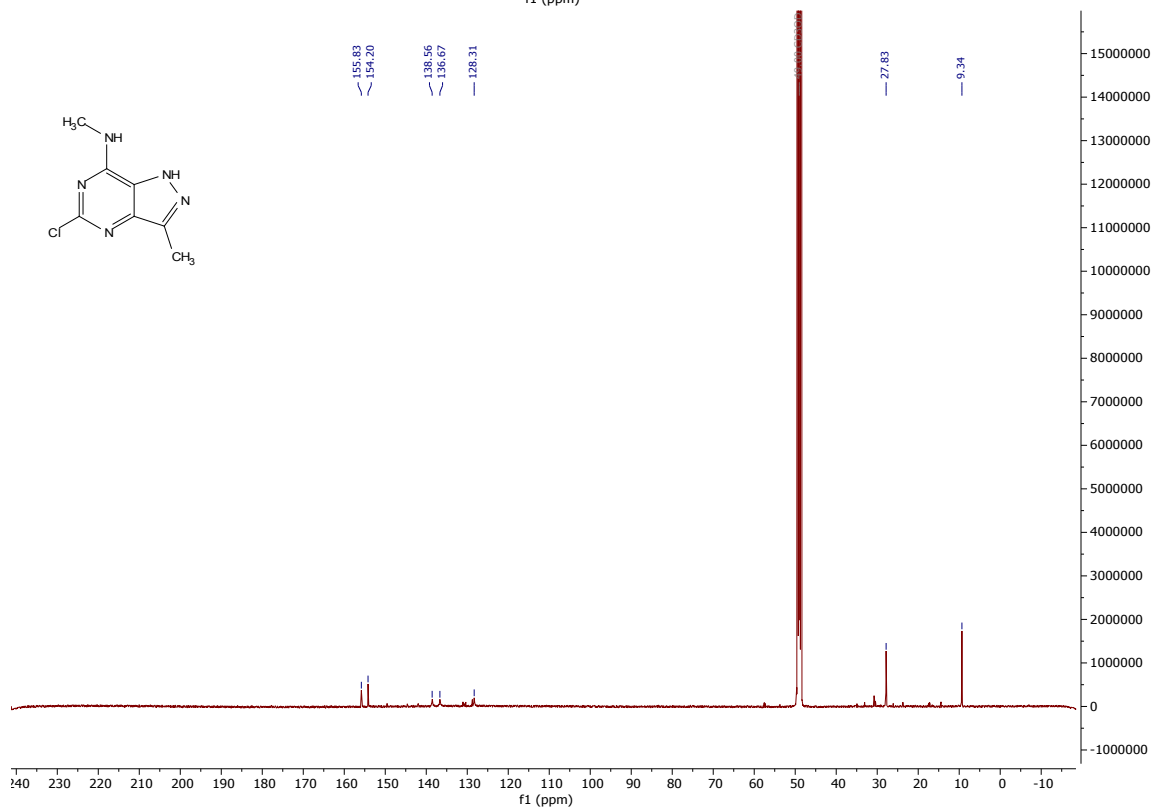
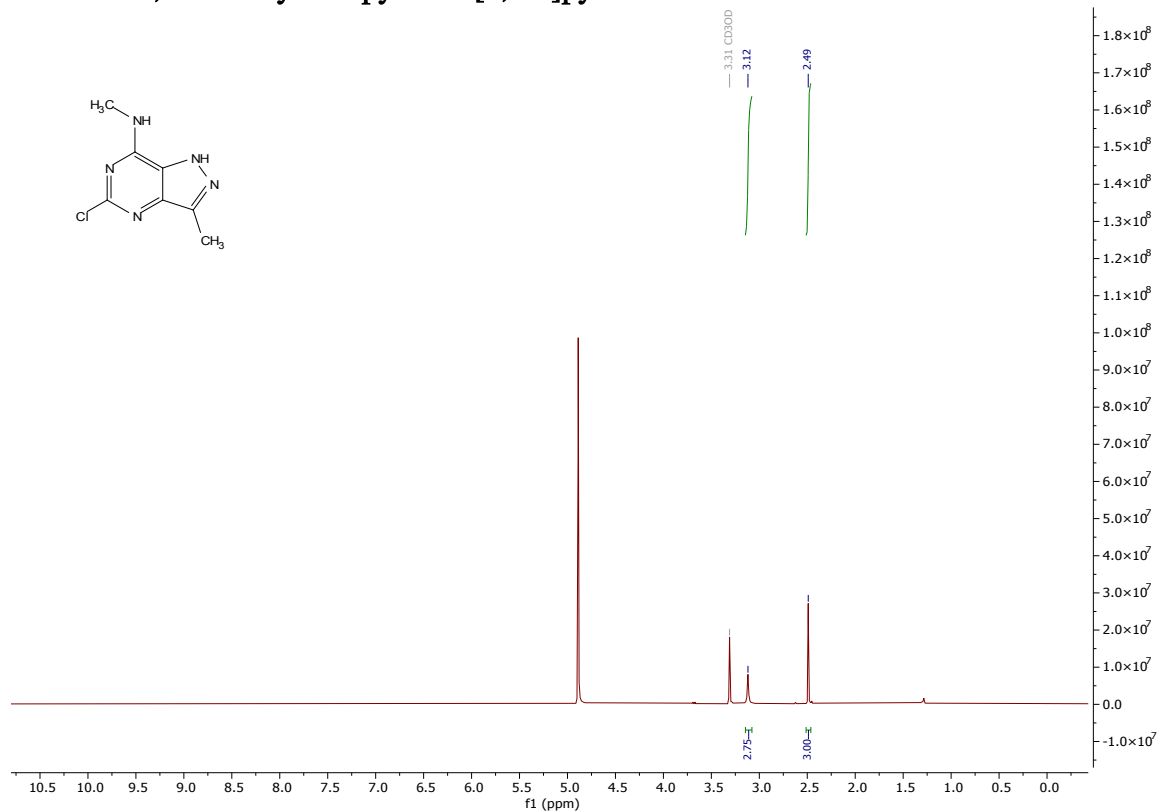


7. Figure S6: Isothermal titration calorimetry curve of compound 3

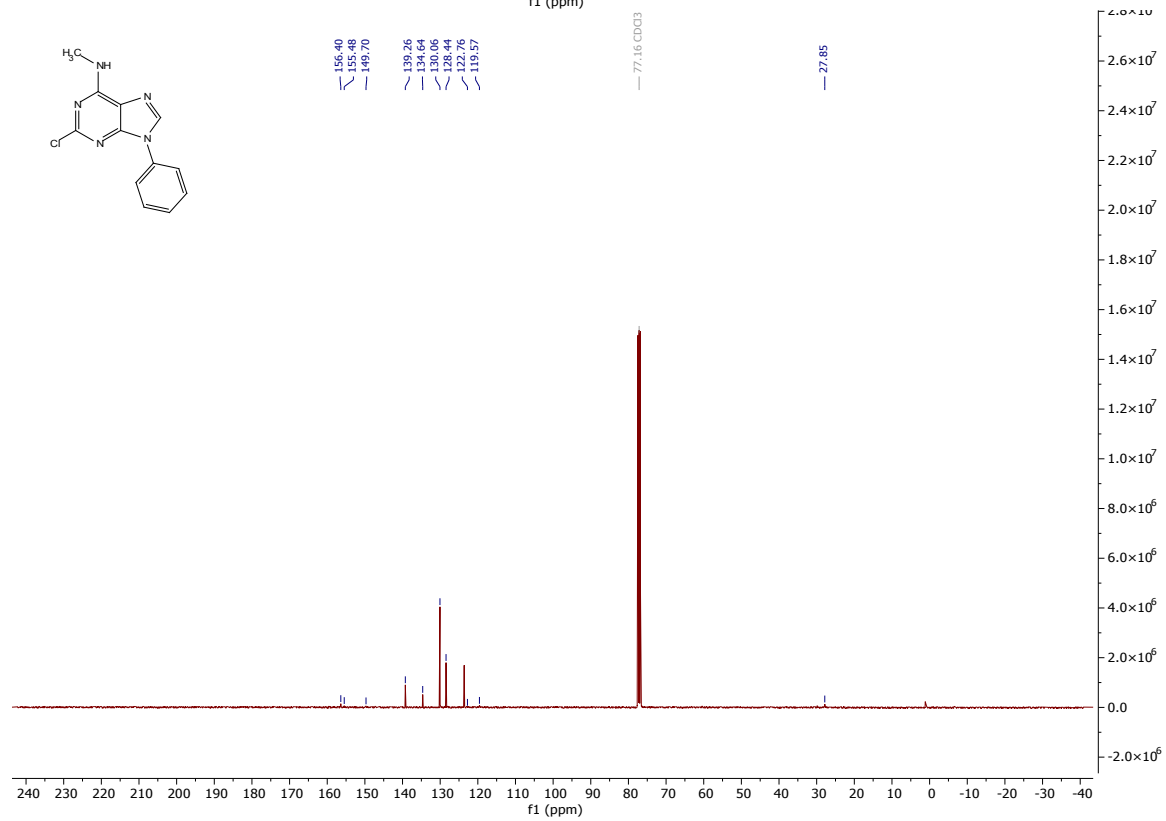
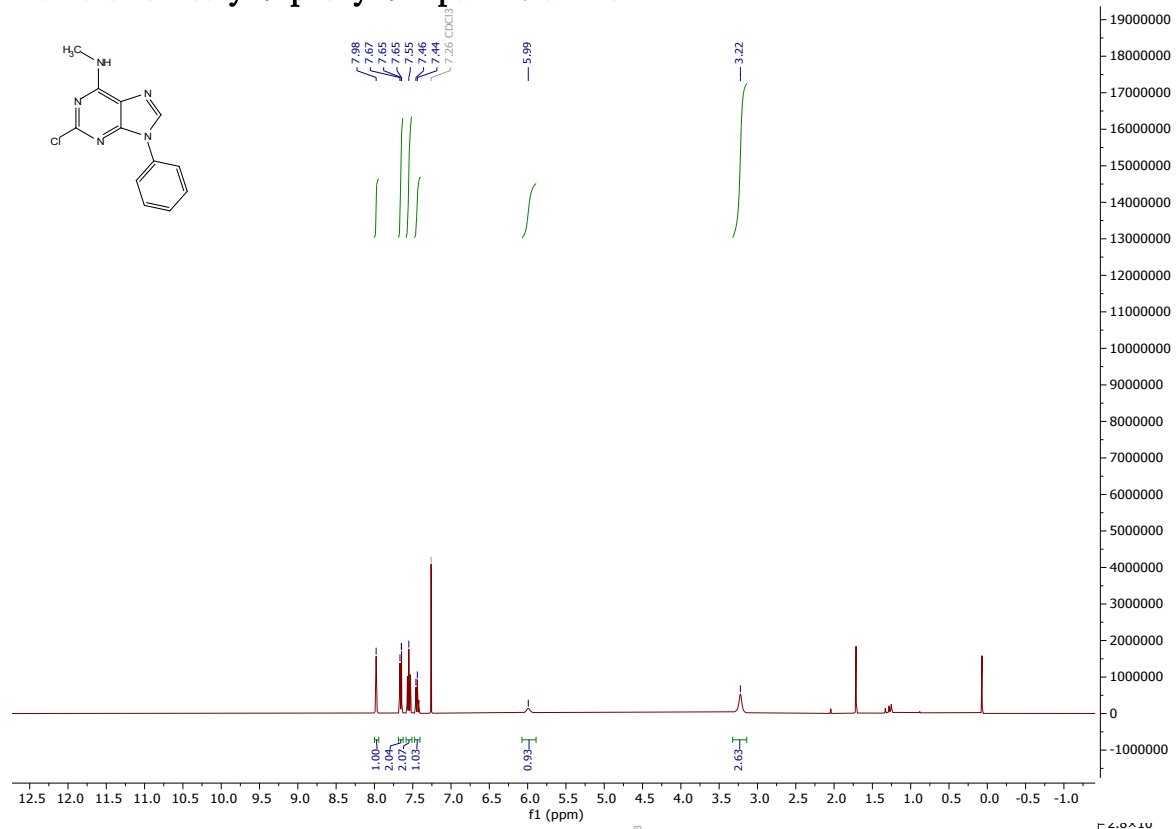


## 8. NMR traces of final compounds

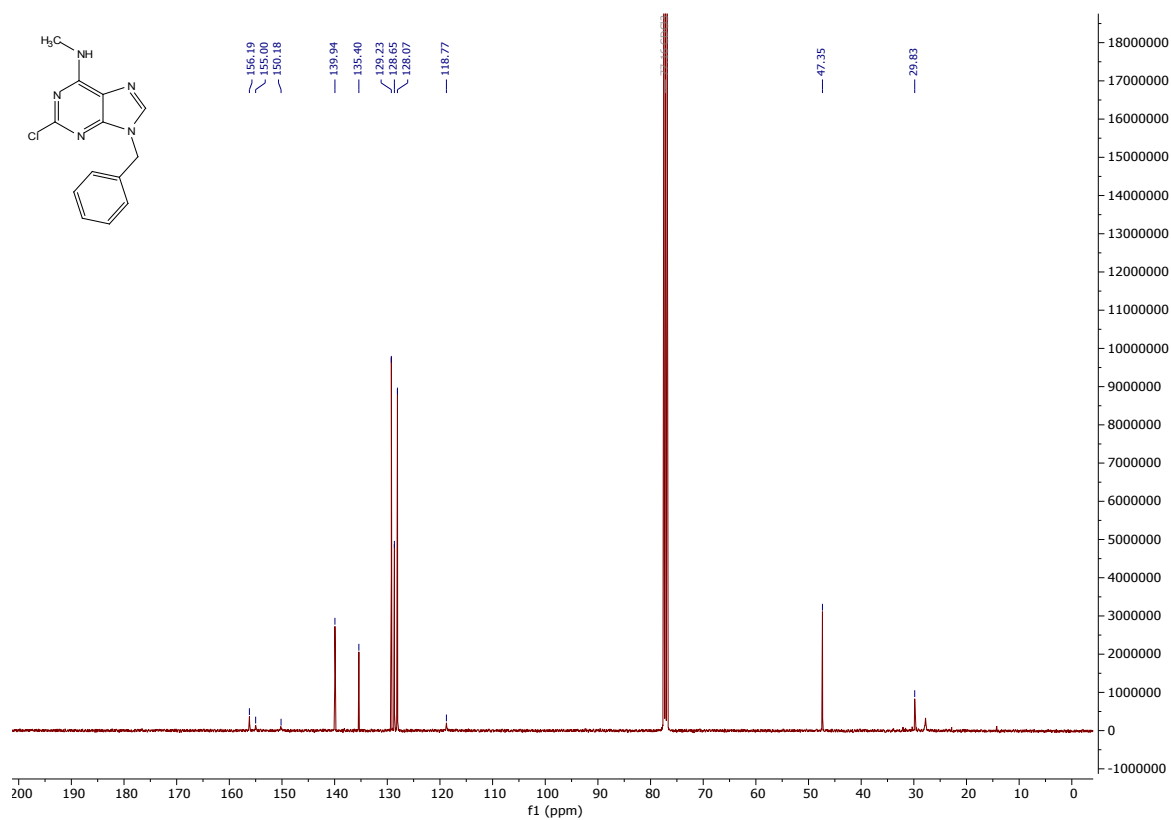
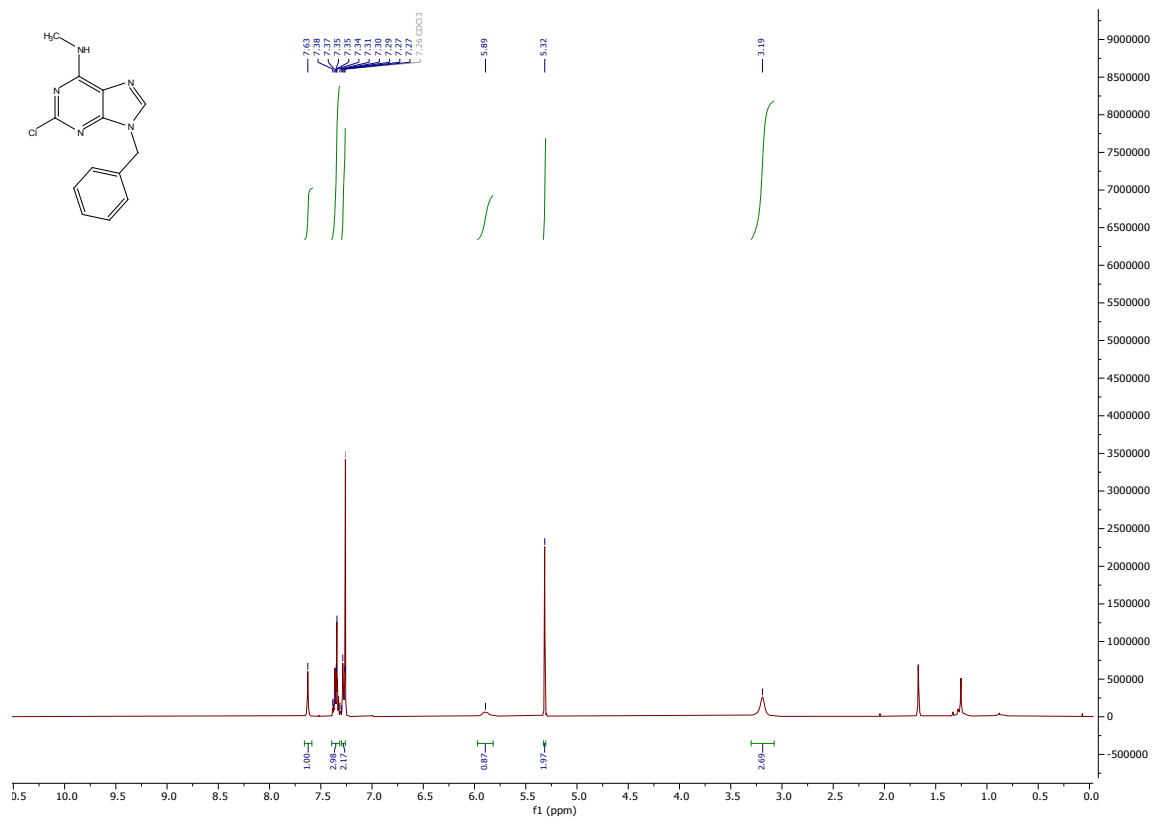
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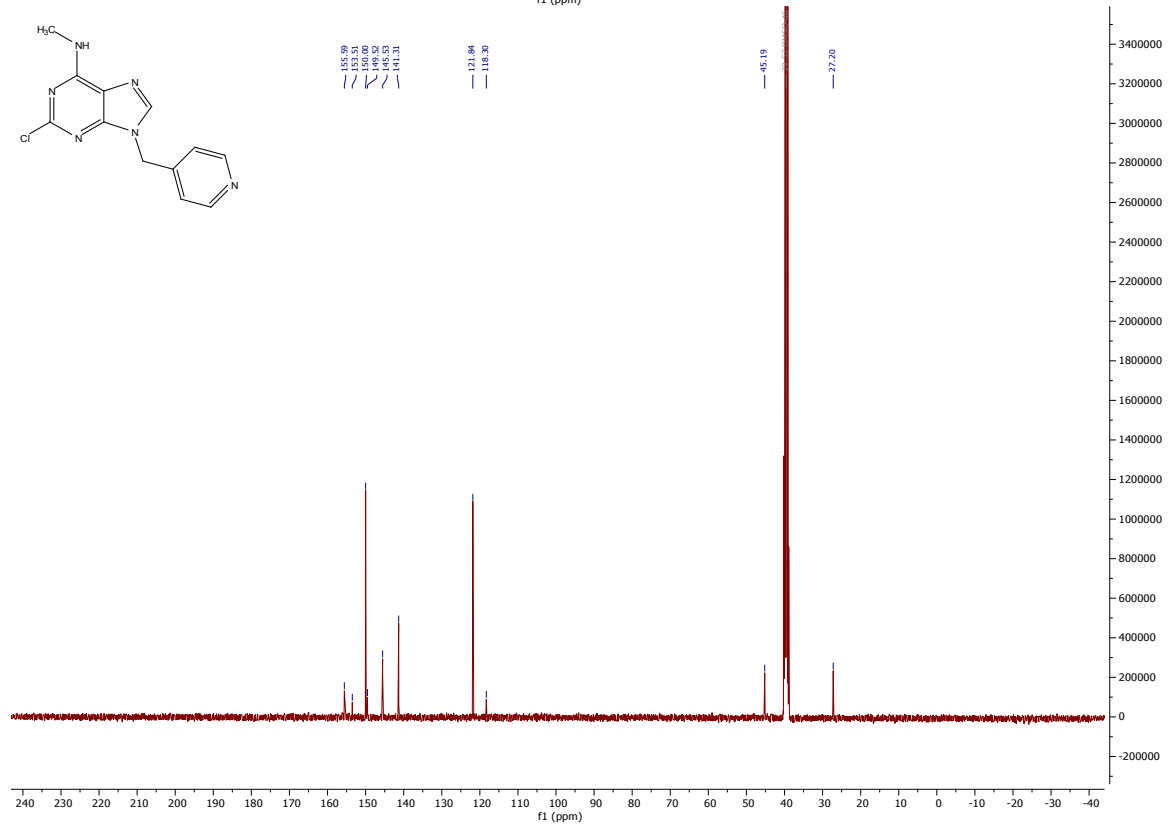
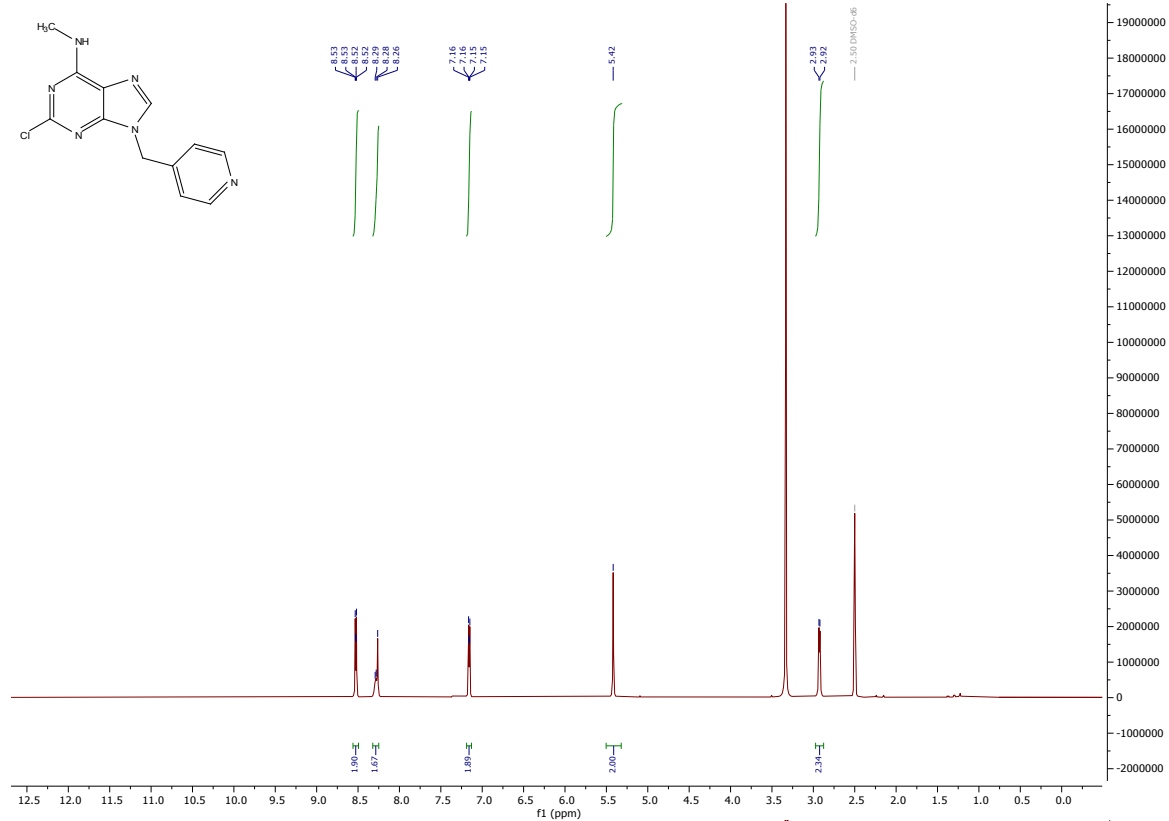
# 2-chloro-N-methyl-9-phenyl-9H-purin-6-amine 4



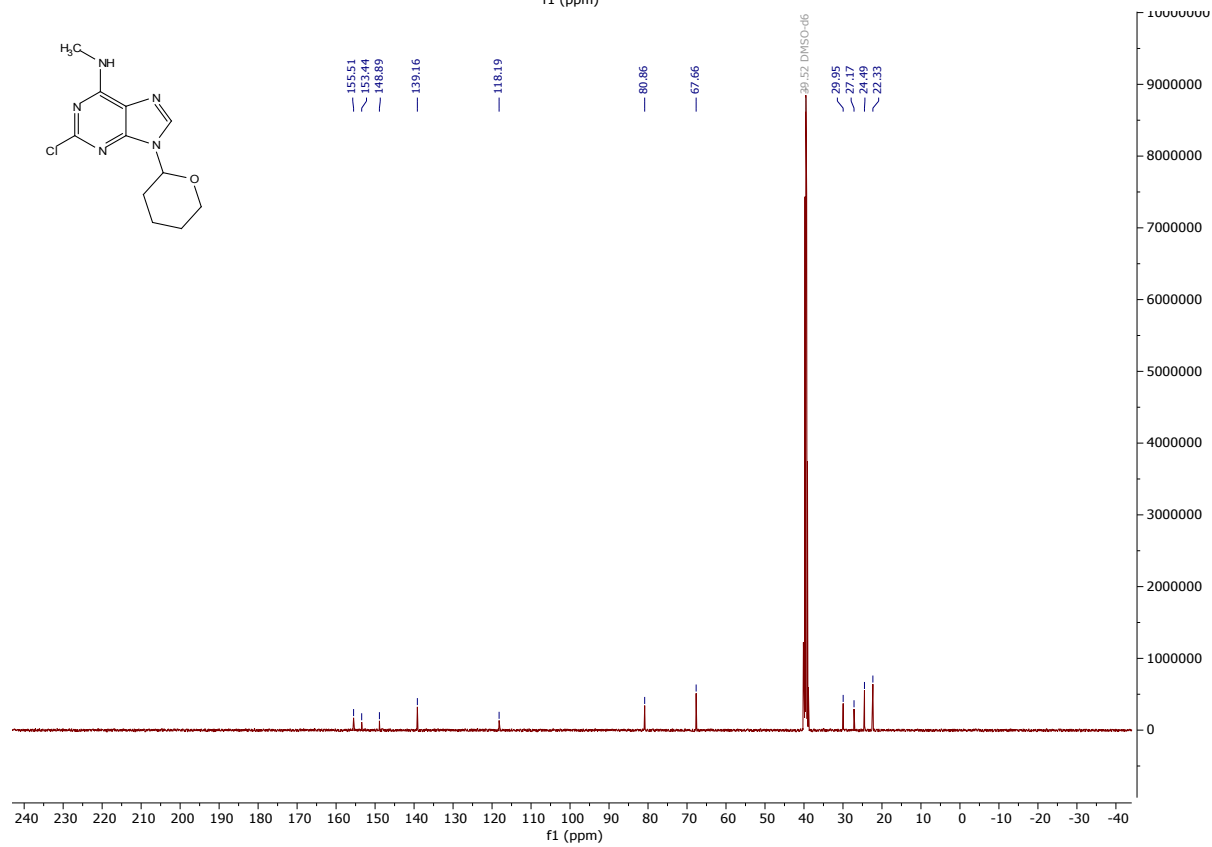
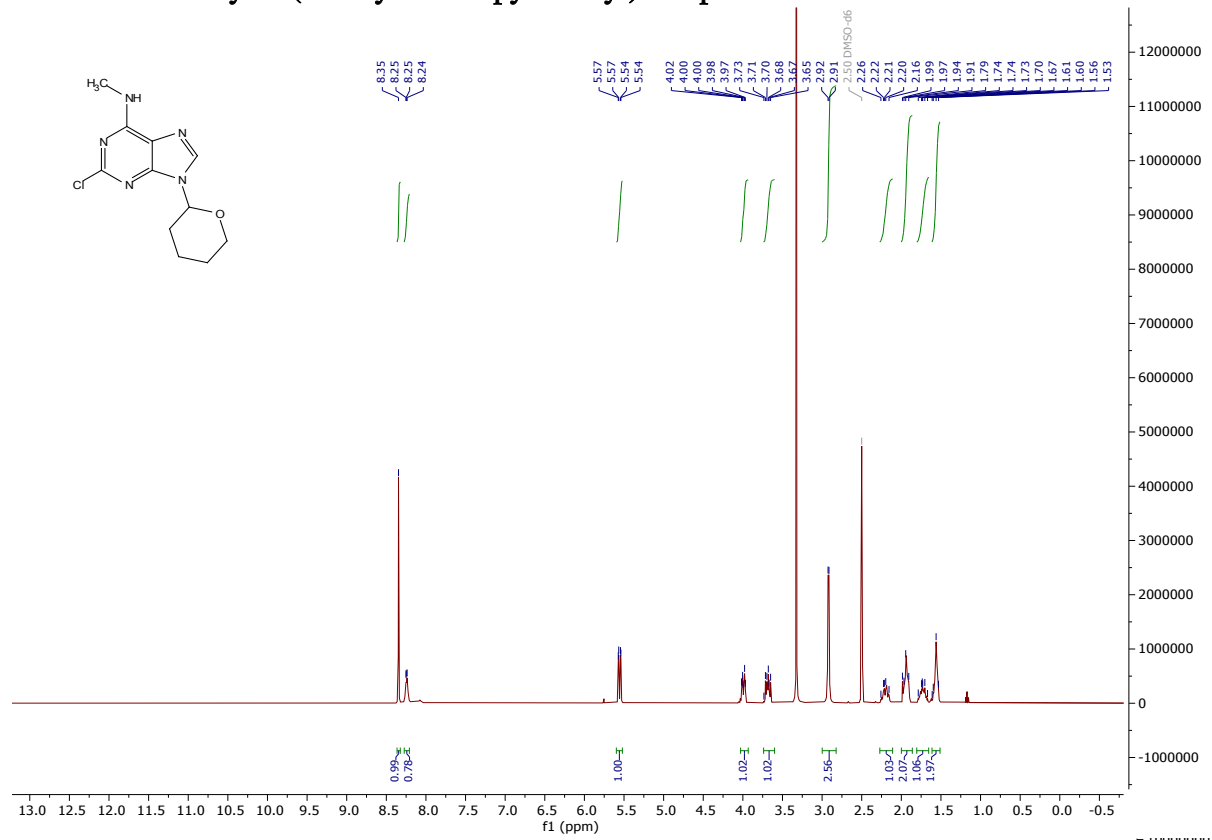
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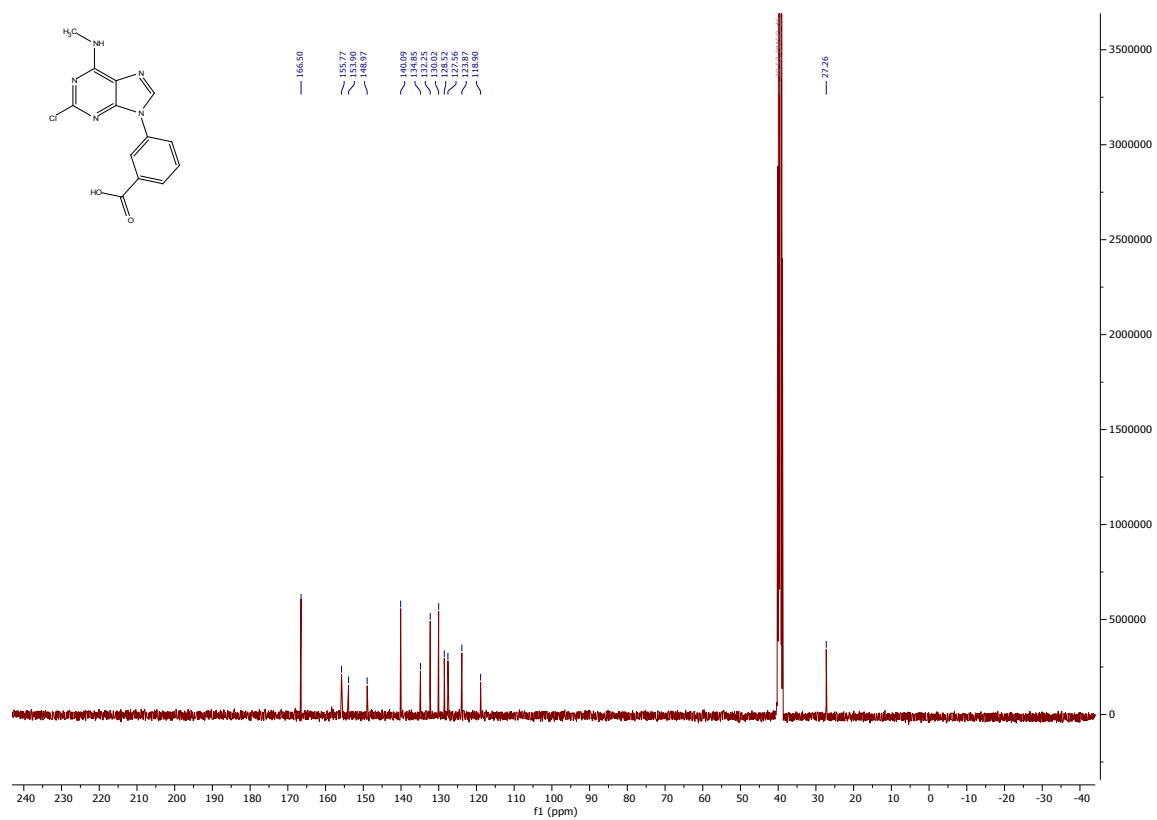
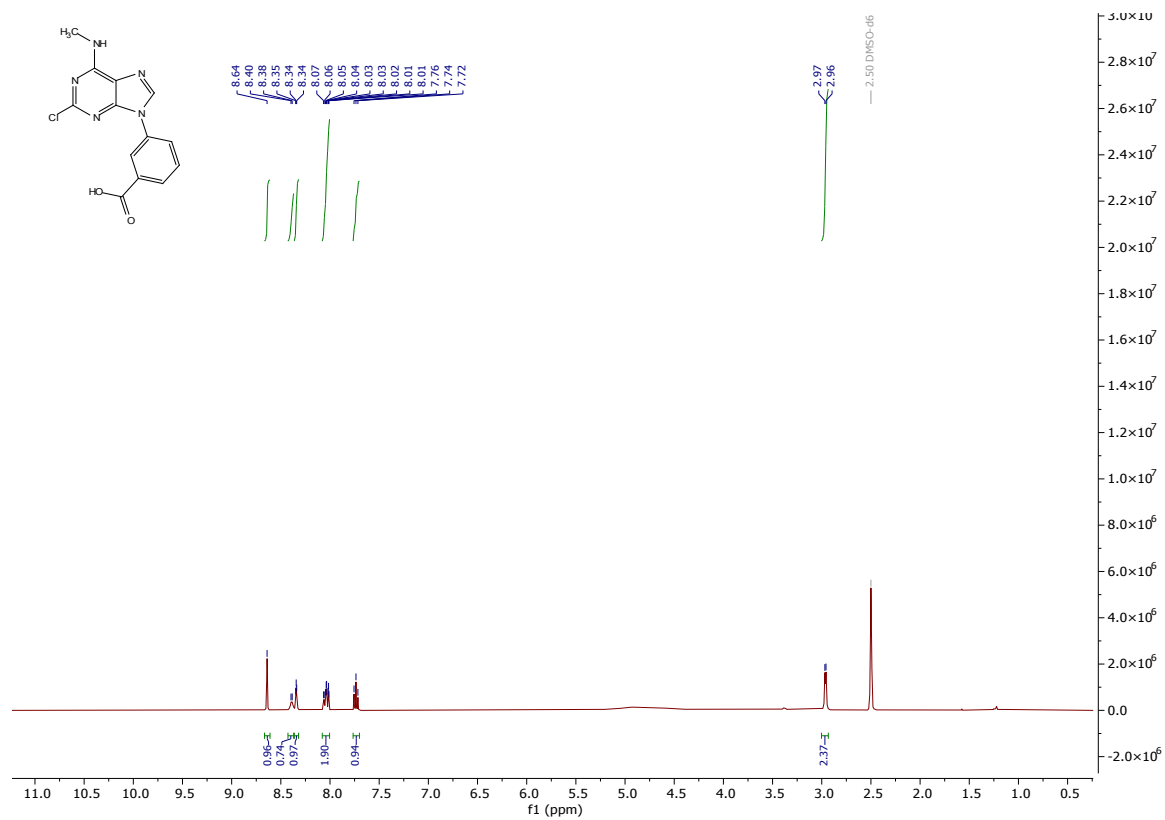
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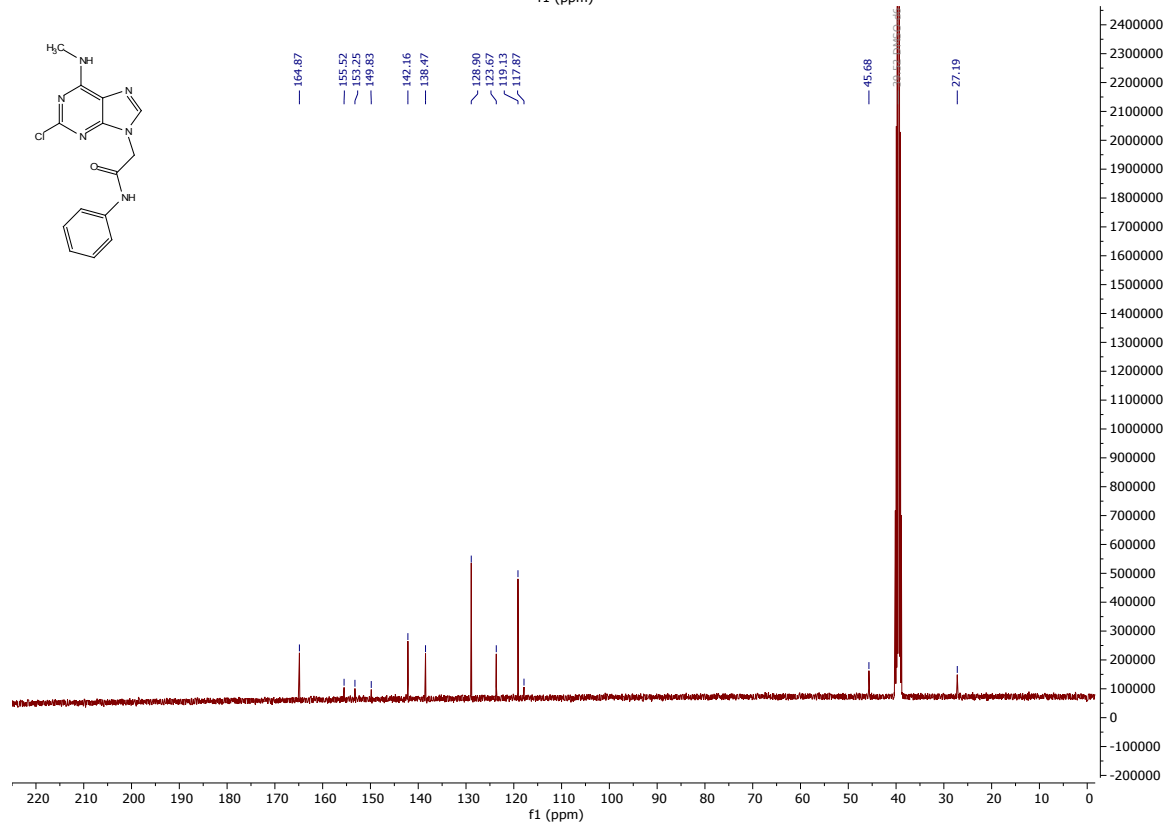
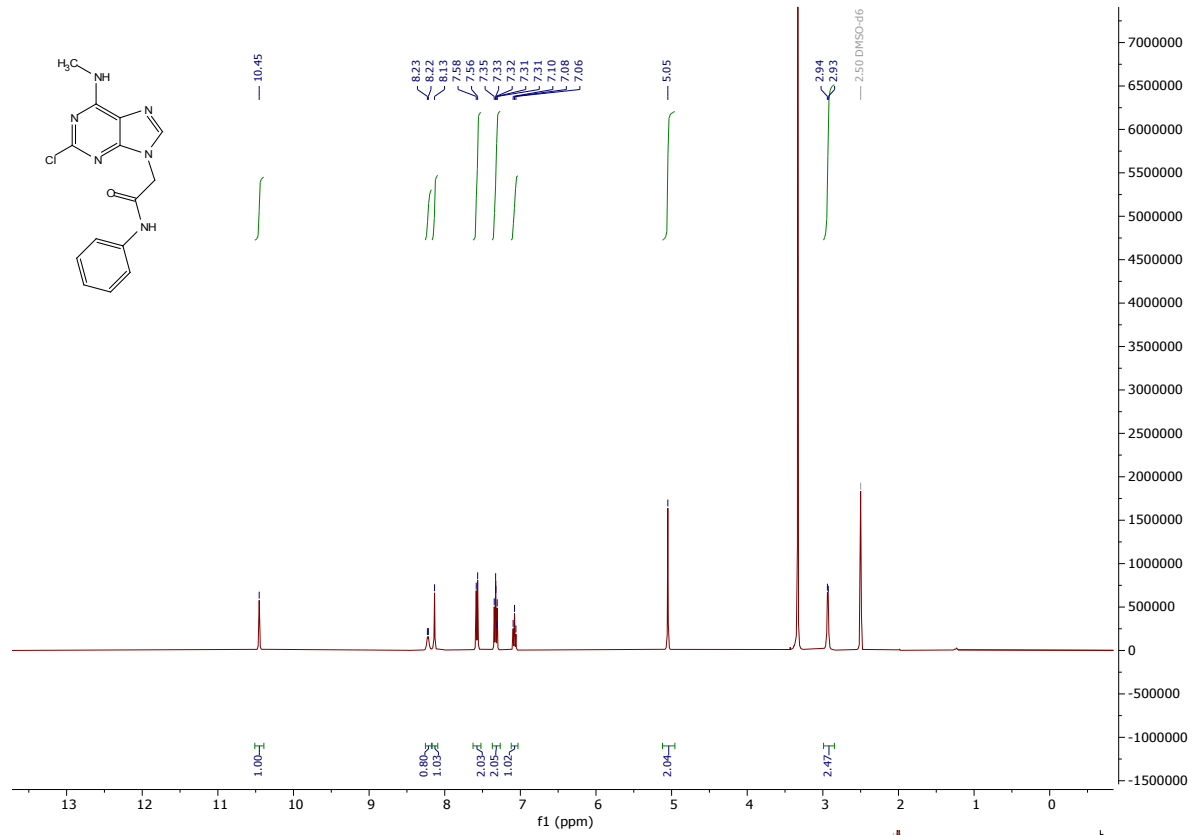
2-chloro-N-methyl-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-amine 7



### 3-(2-chloro-6-(methylamino)-9H-purin-9-yl)benzoic acid 10

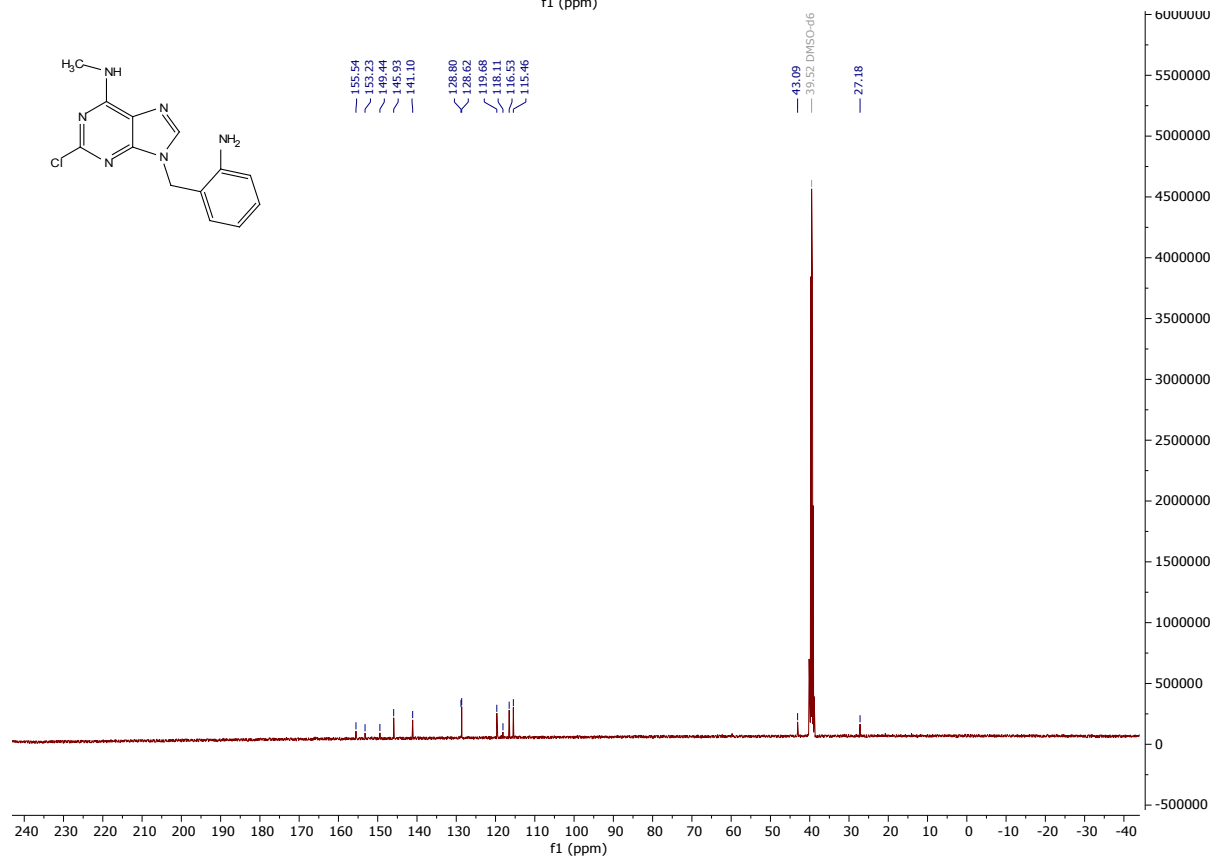
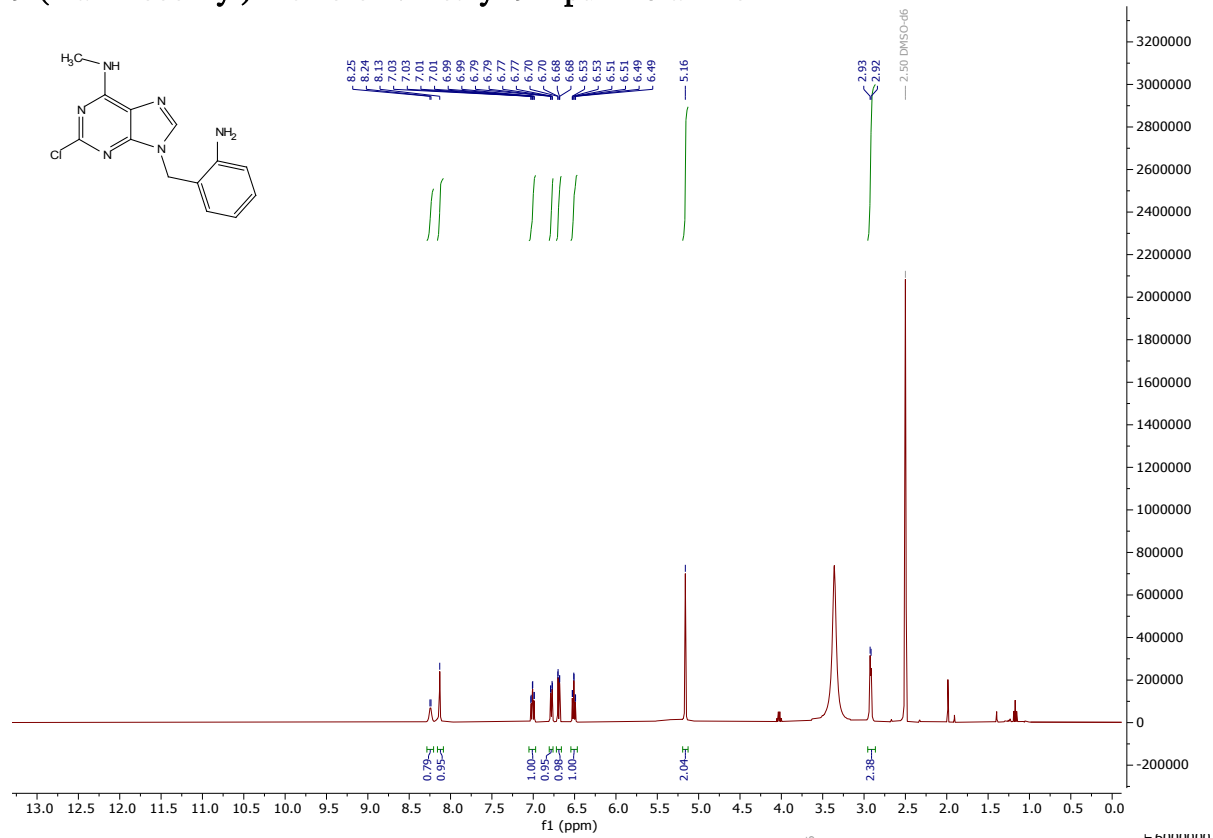


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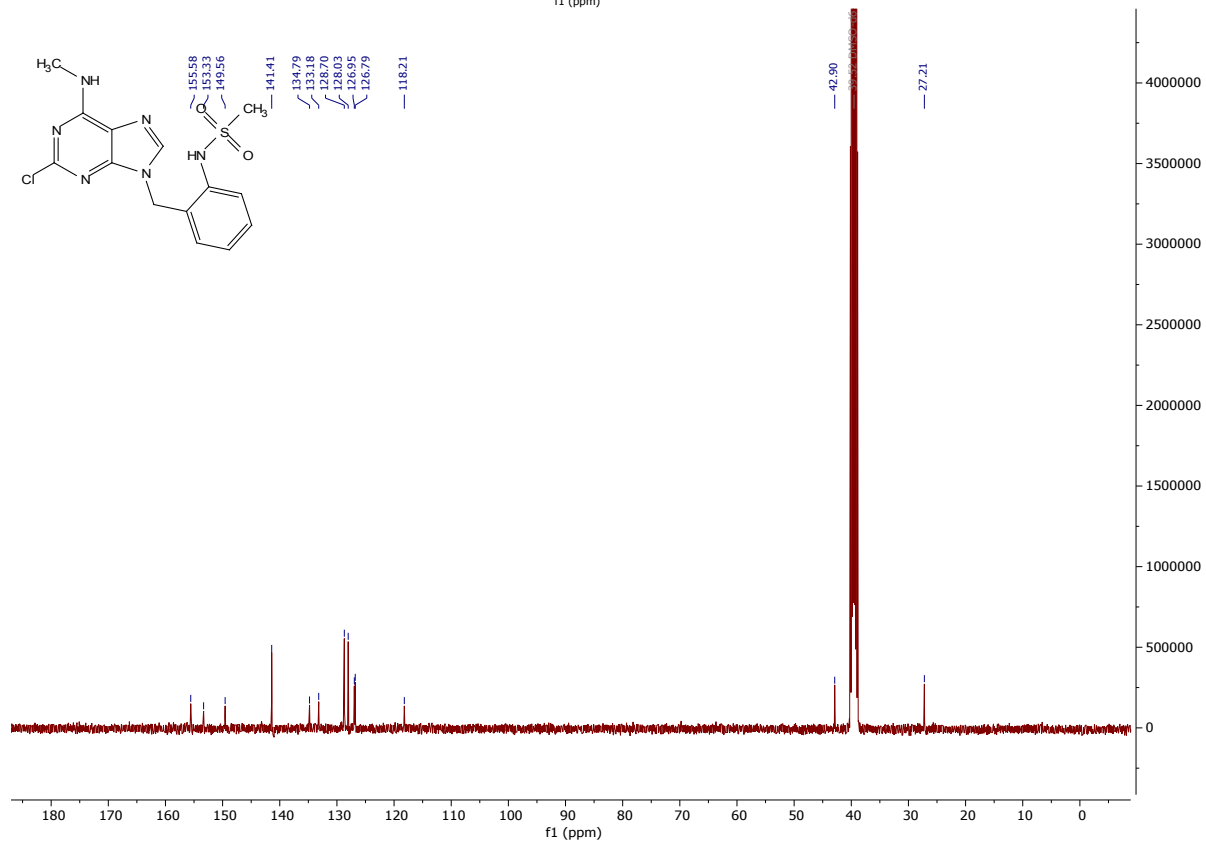
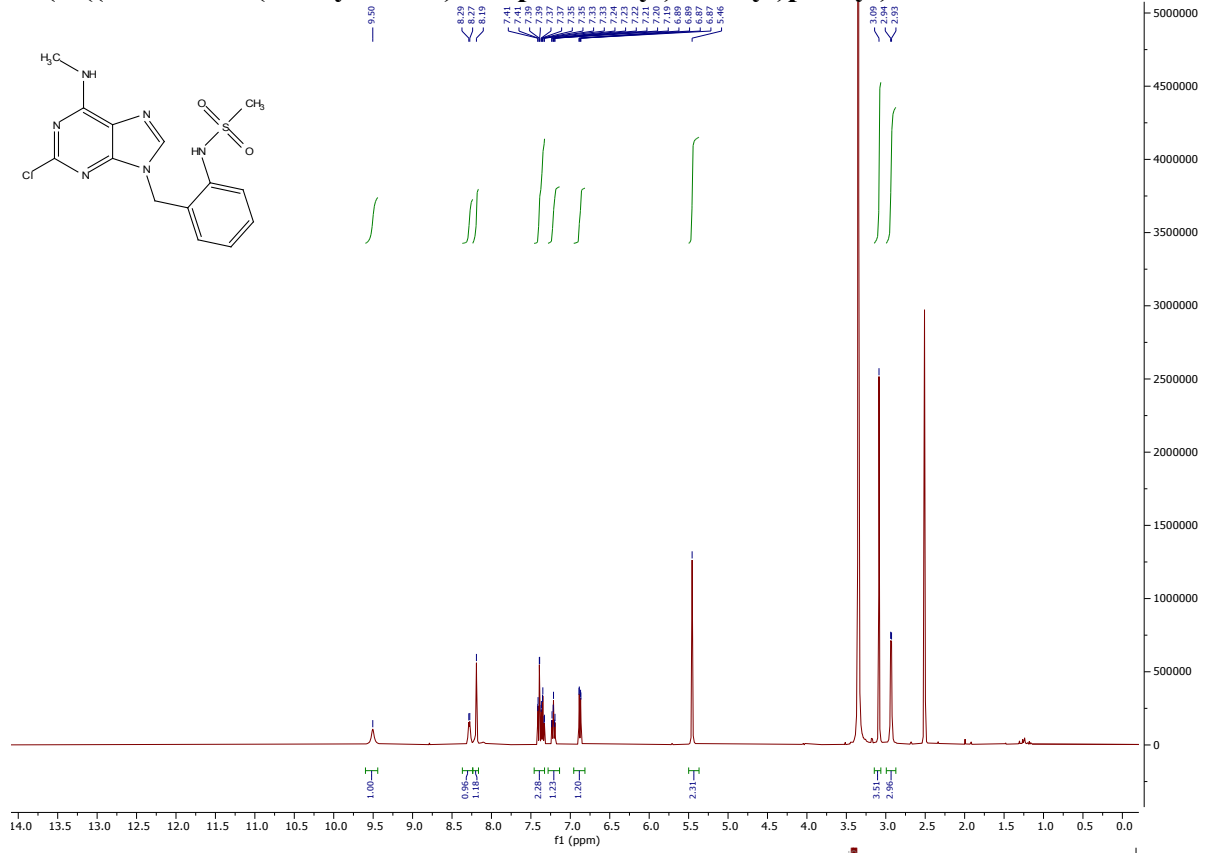




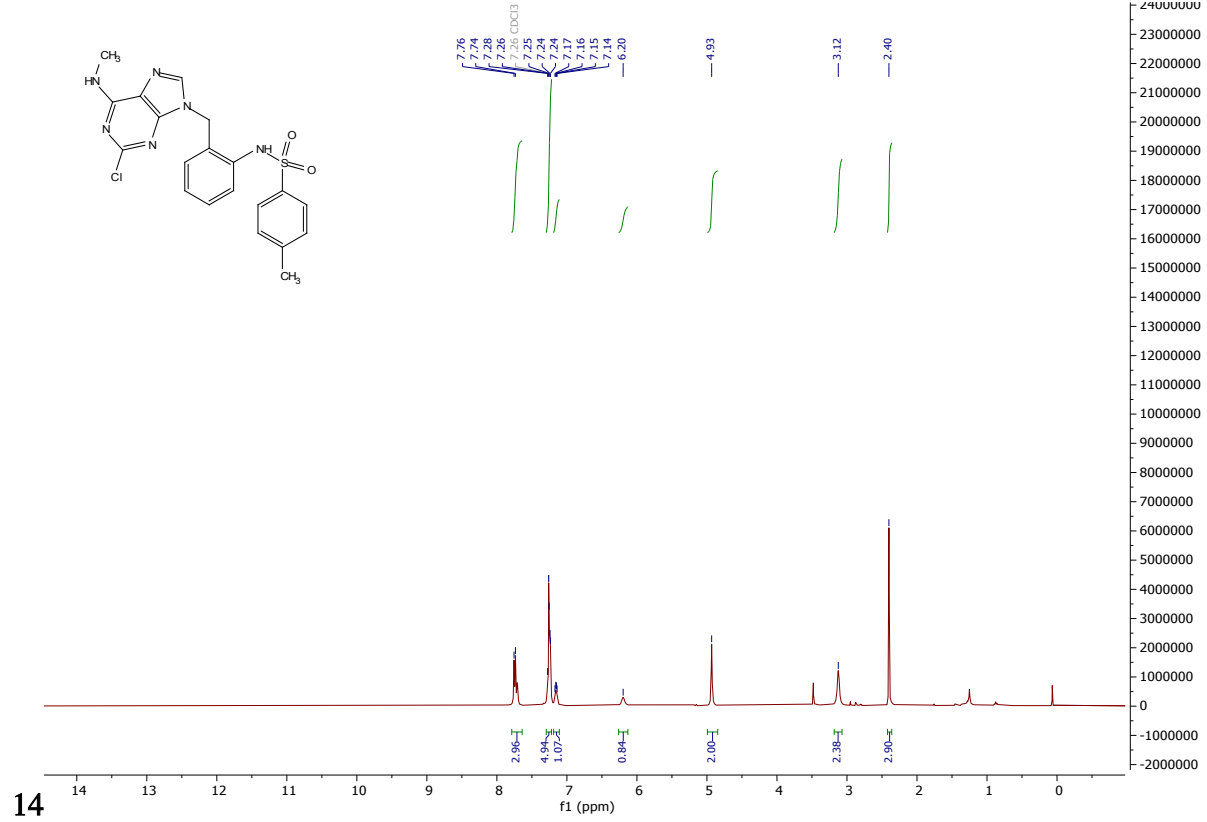
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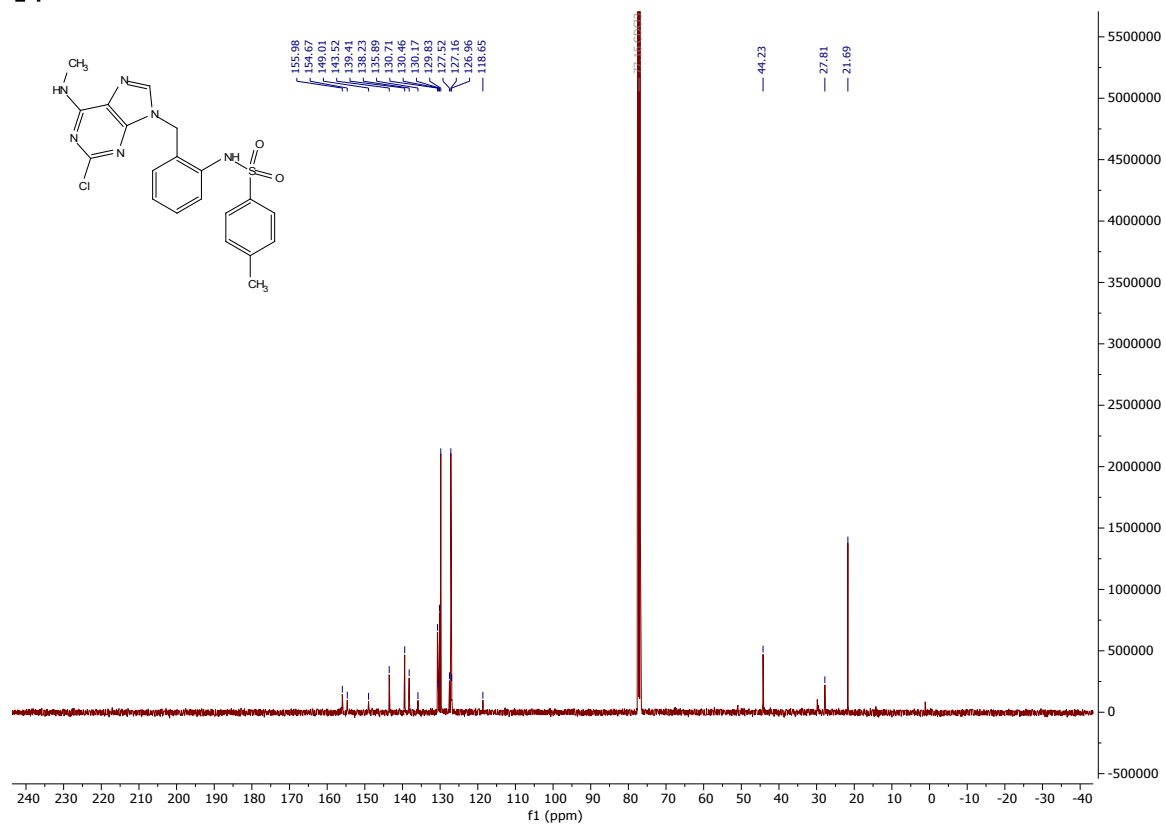
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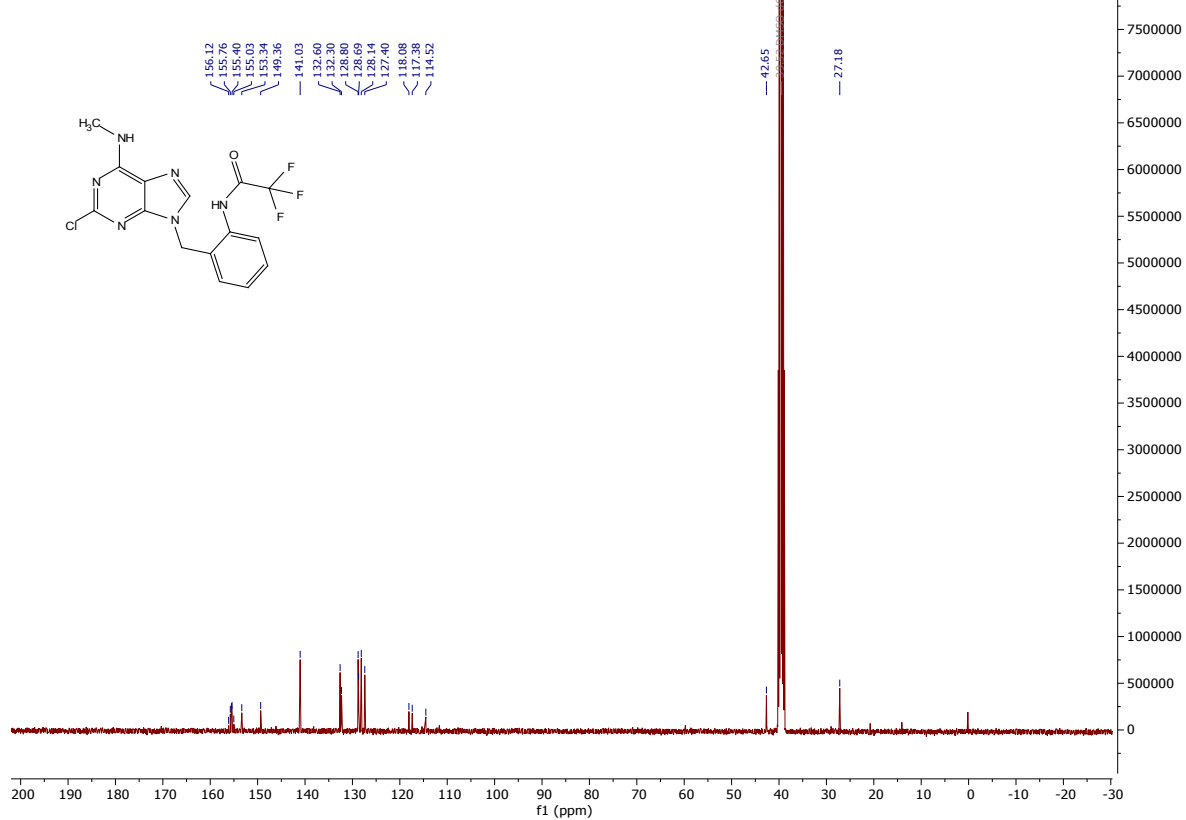
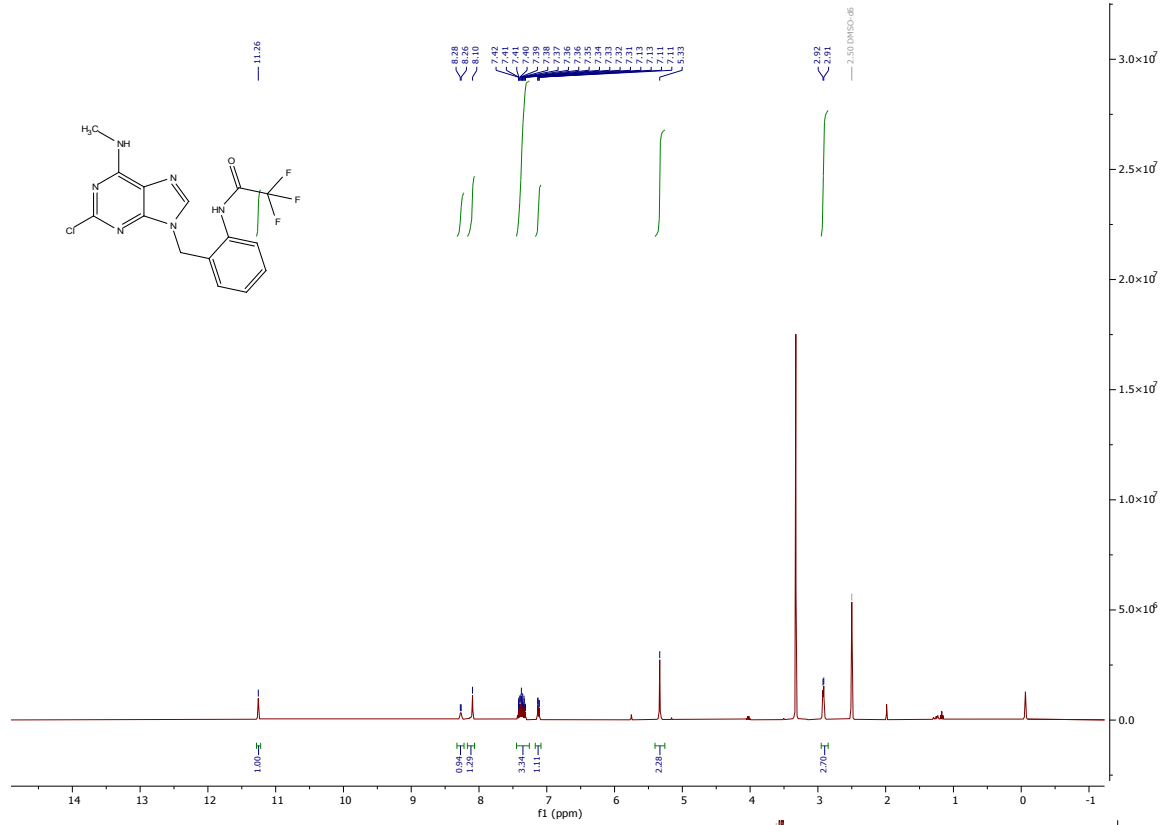
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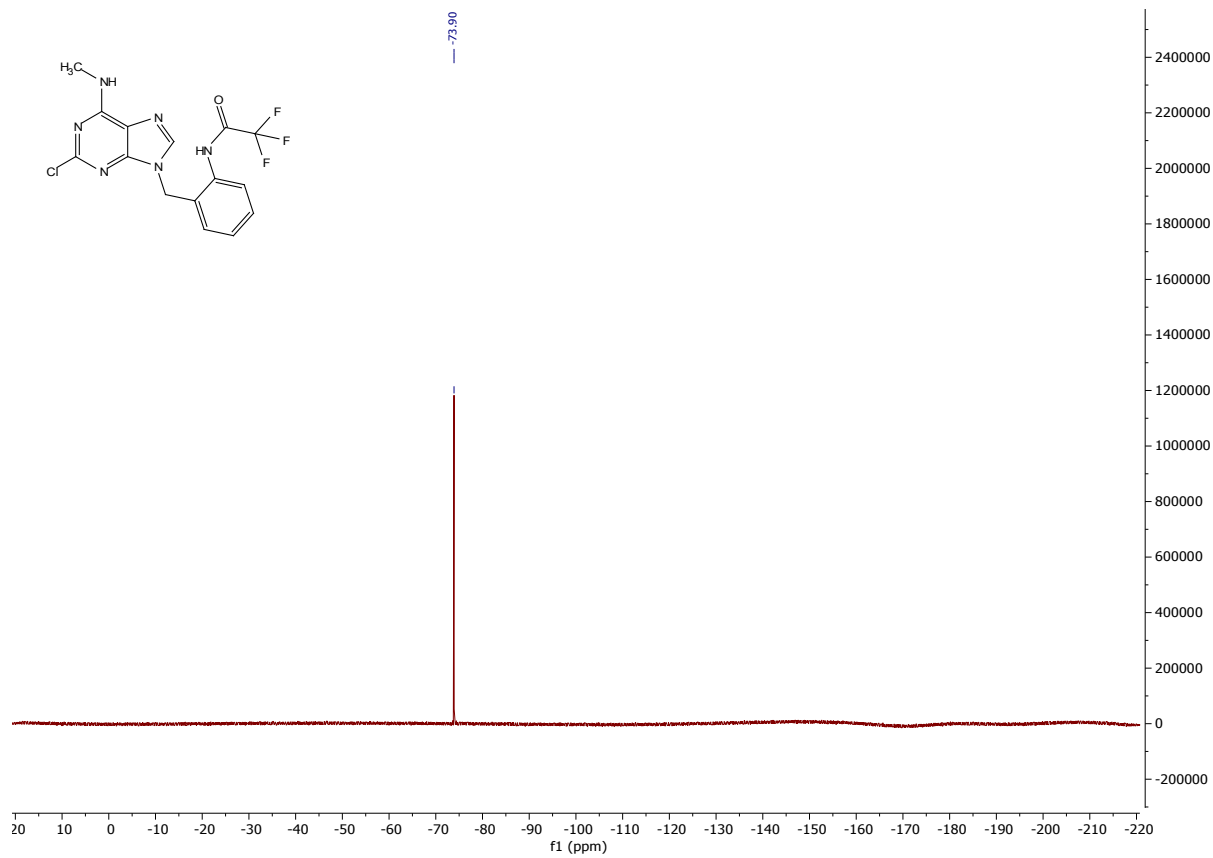


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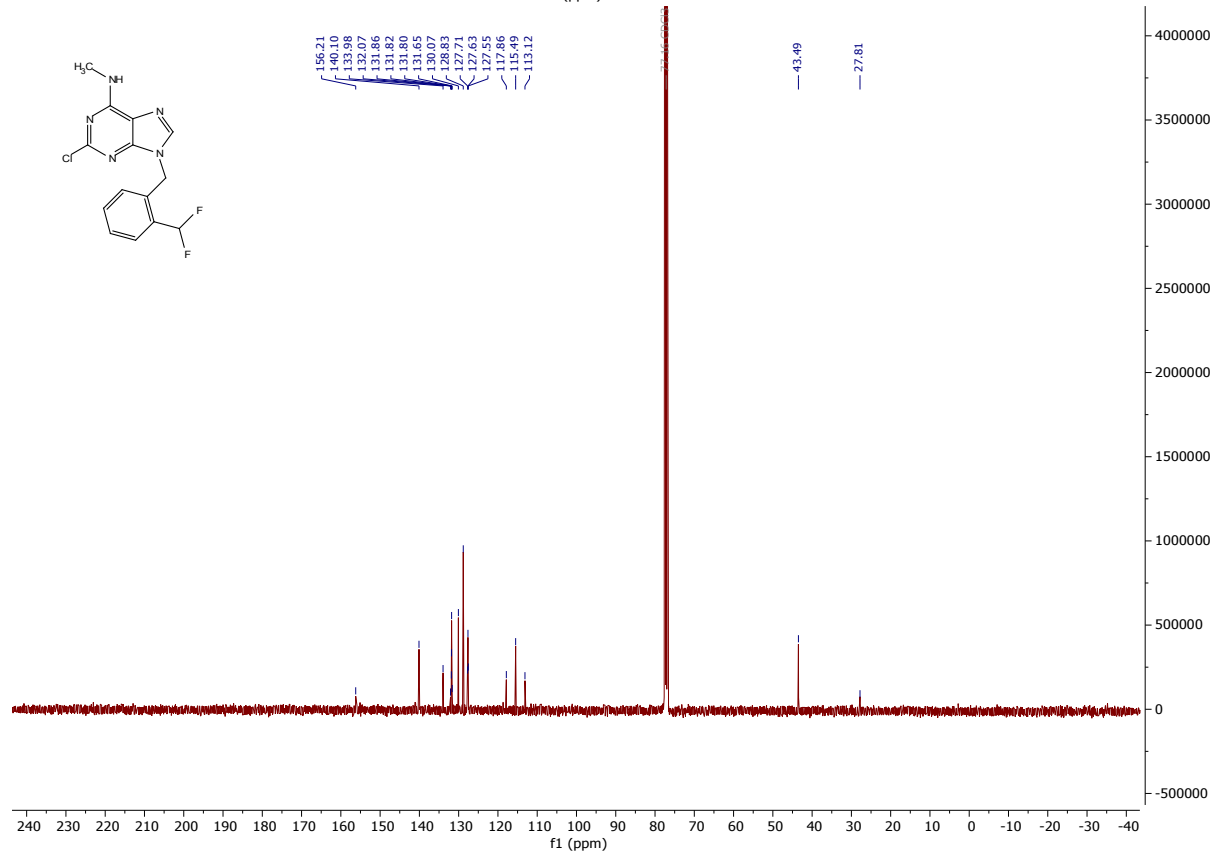
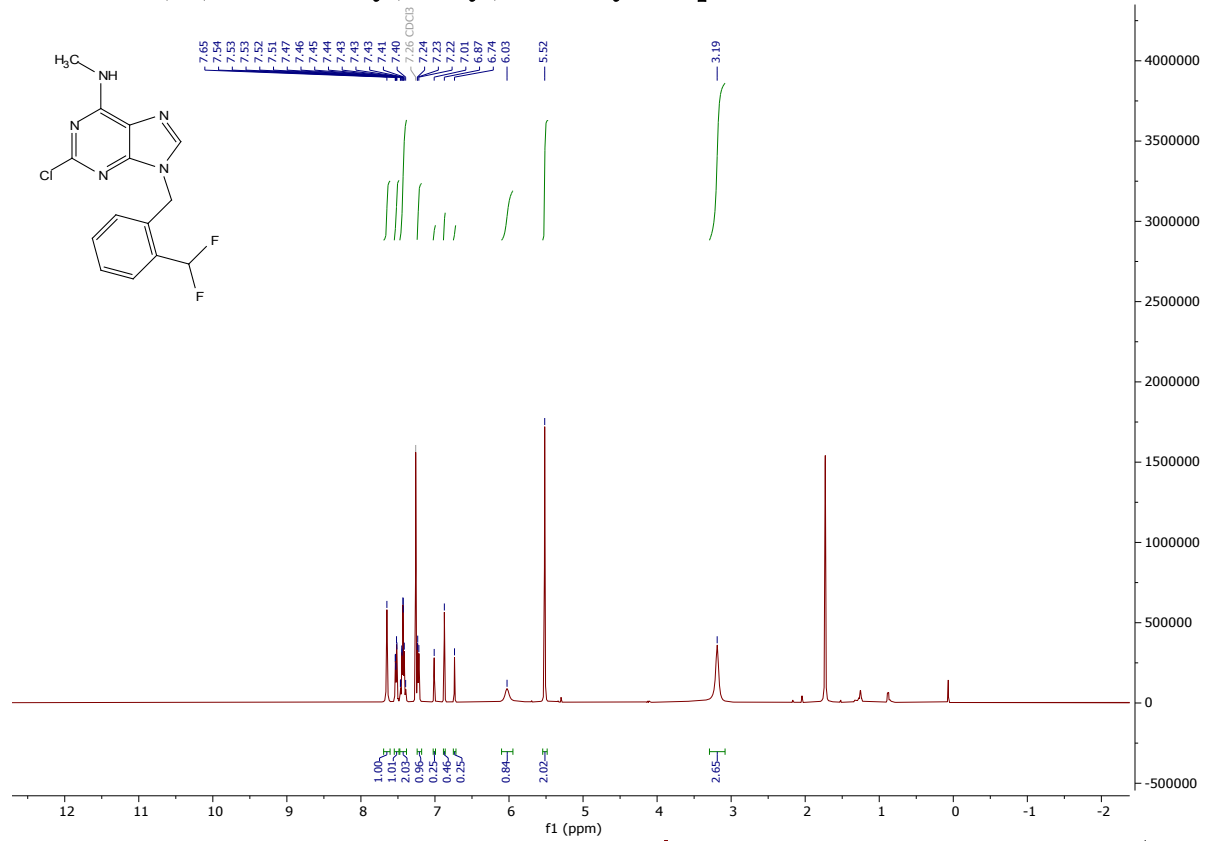


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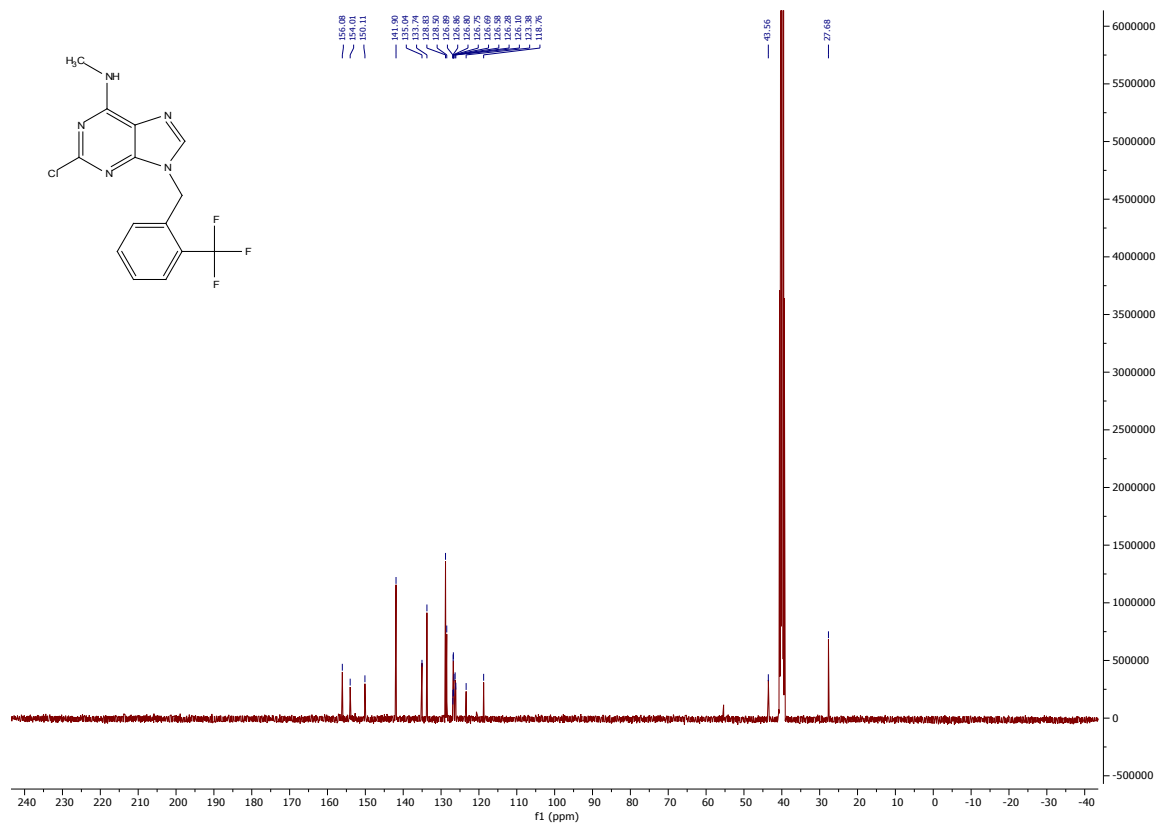
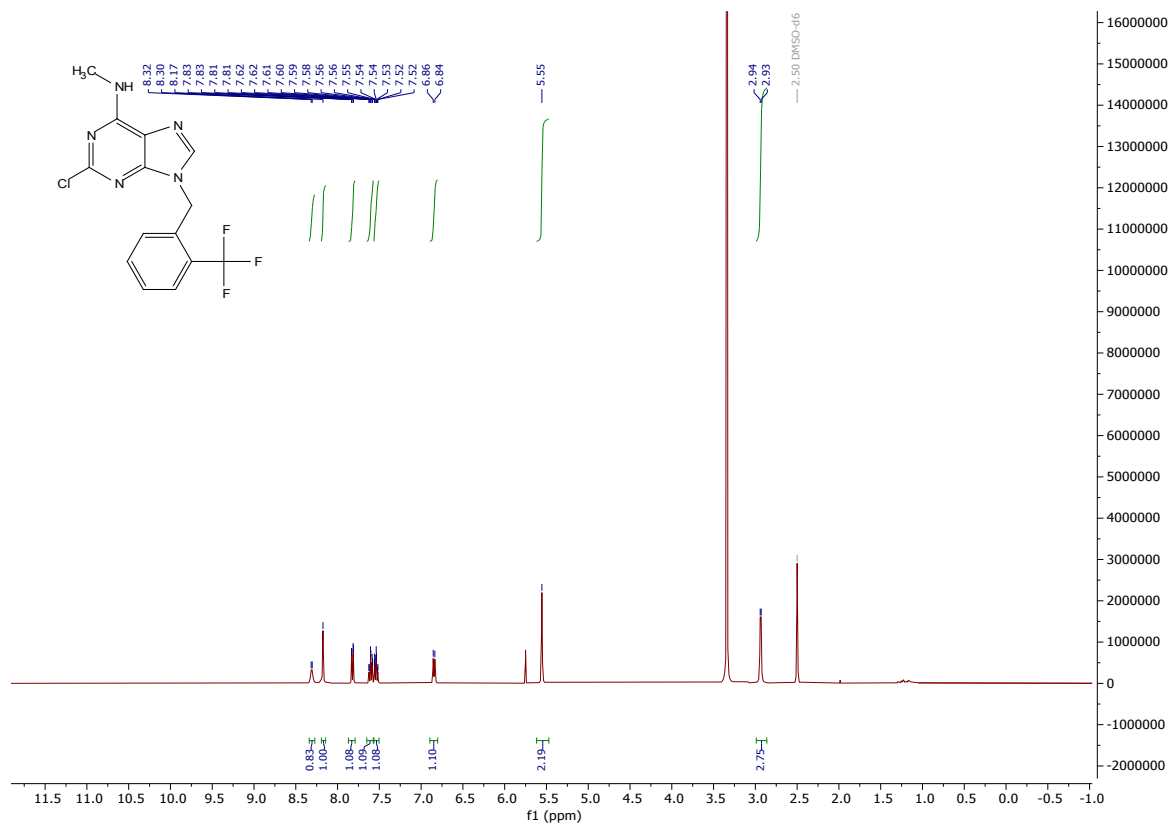




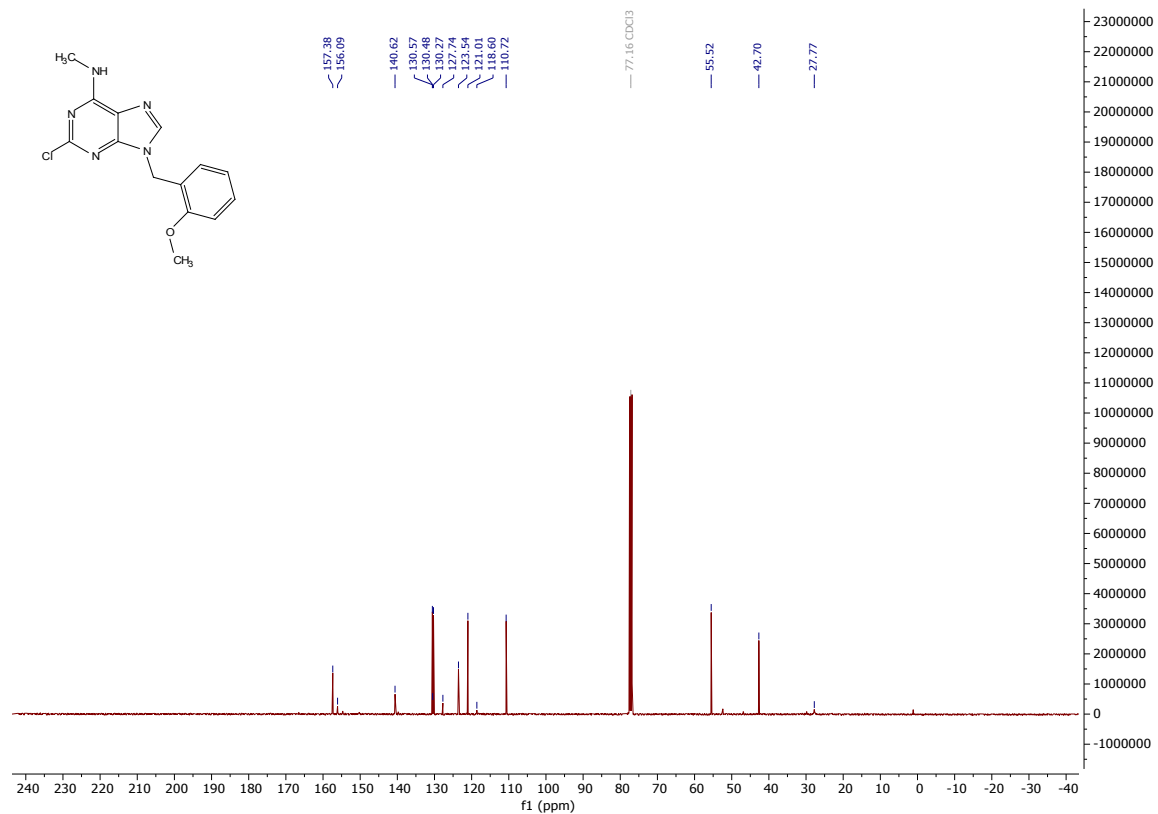
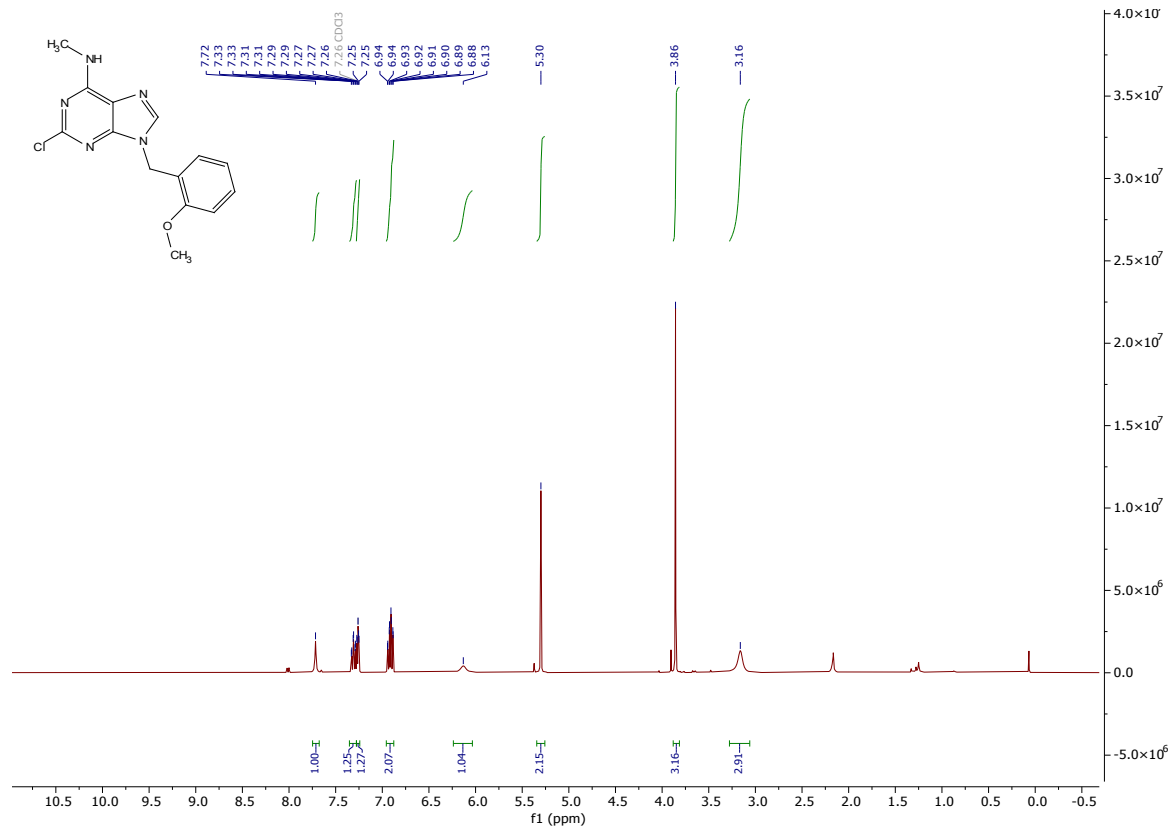
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# 2-chloro-N-methyl-9-(2-(trifluoromethyl)benzyl)-9H-purin-6-amine 17

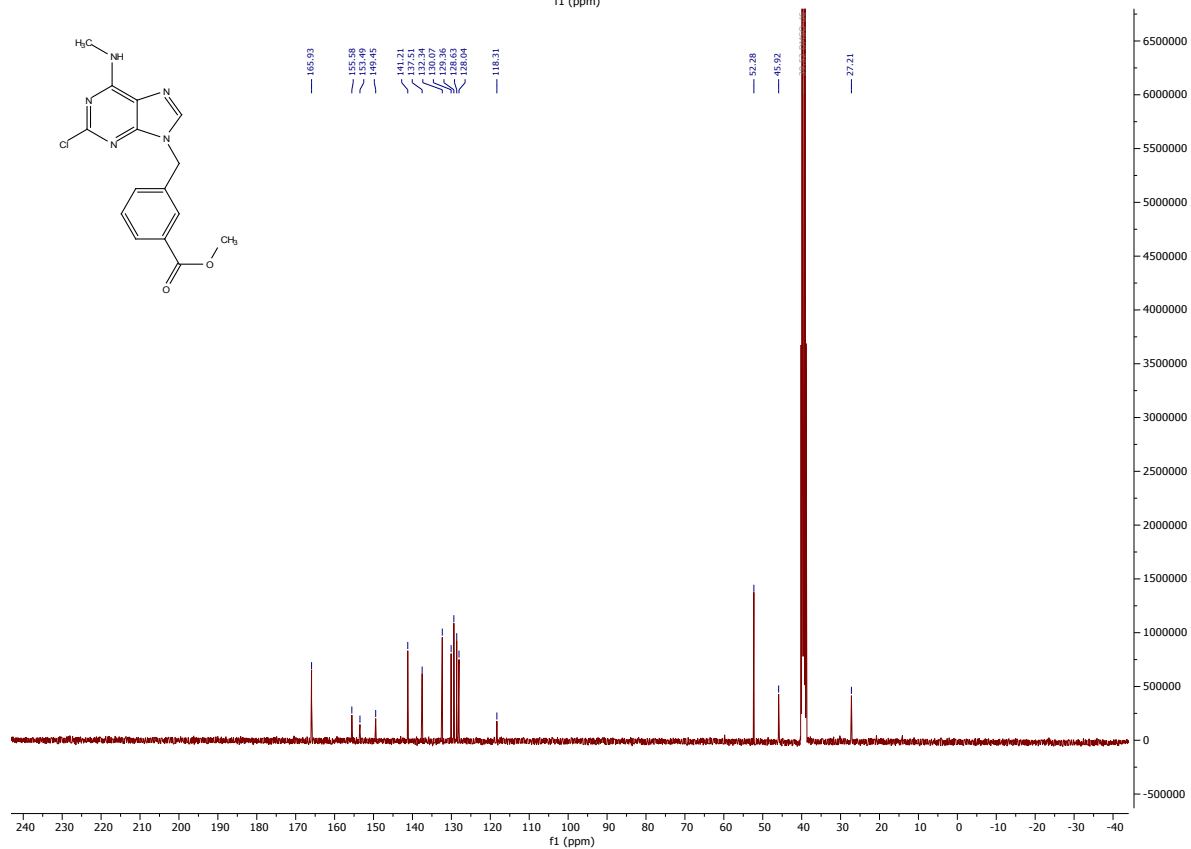
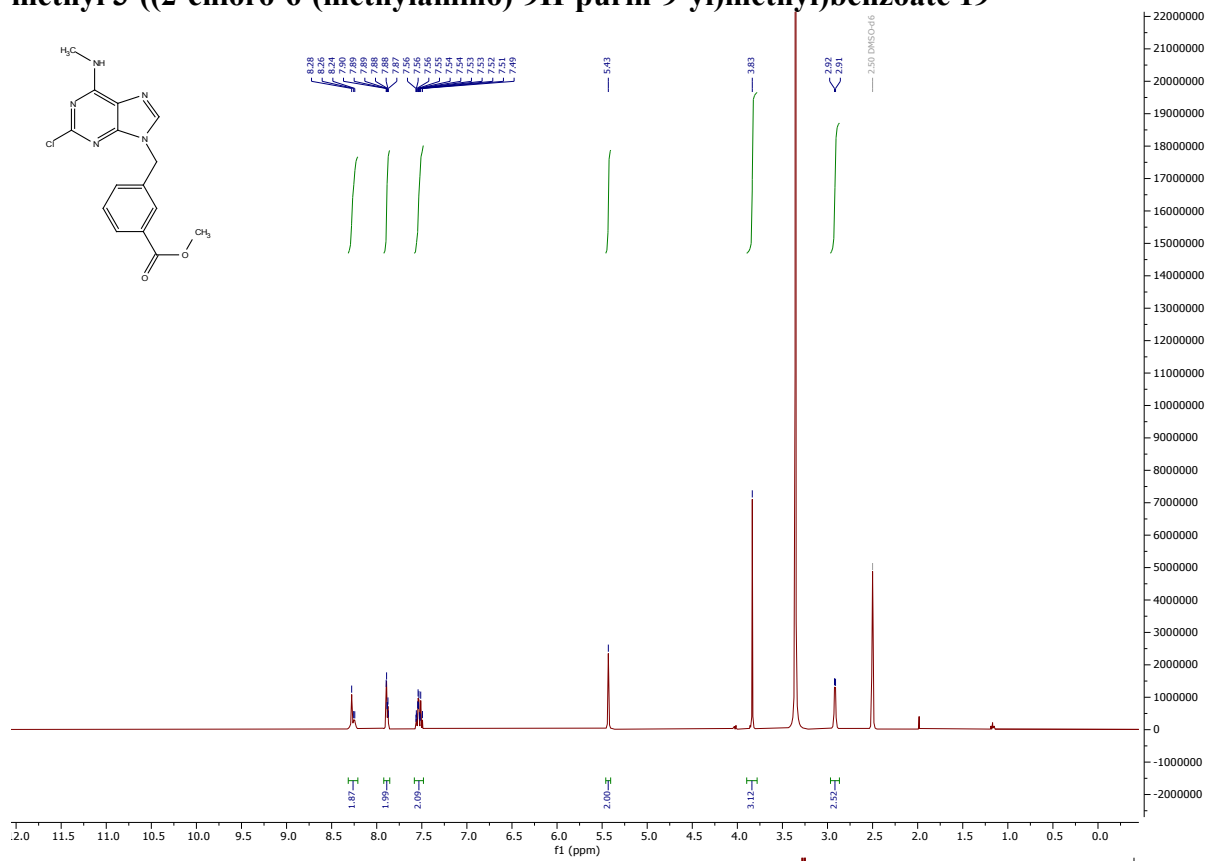


# 2-chloro-9-(2-methoxybenzyl)-N-methyl-9H-purin-6-amine 18

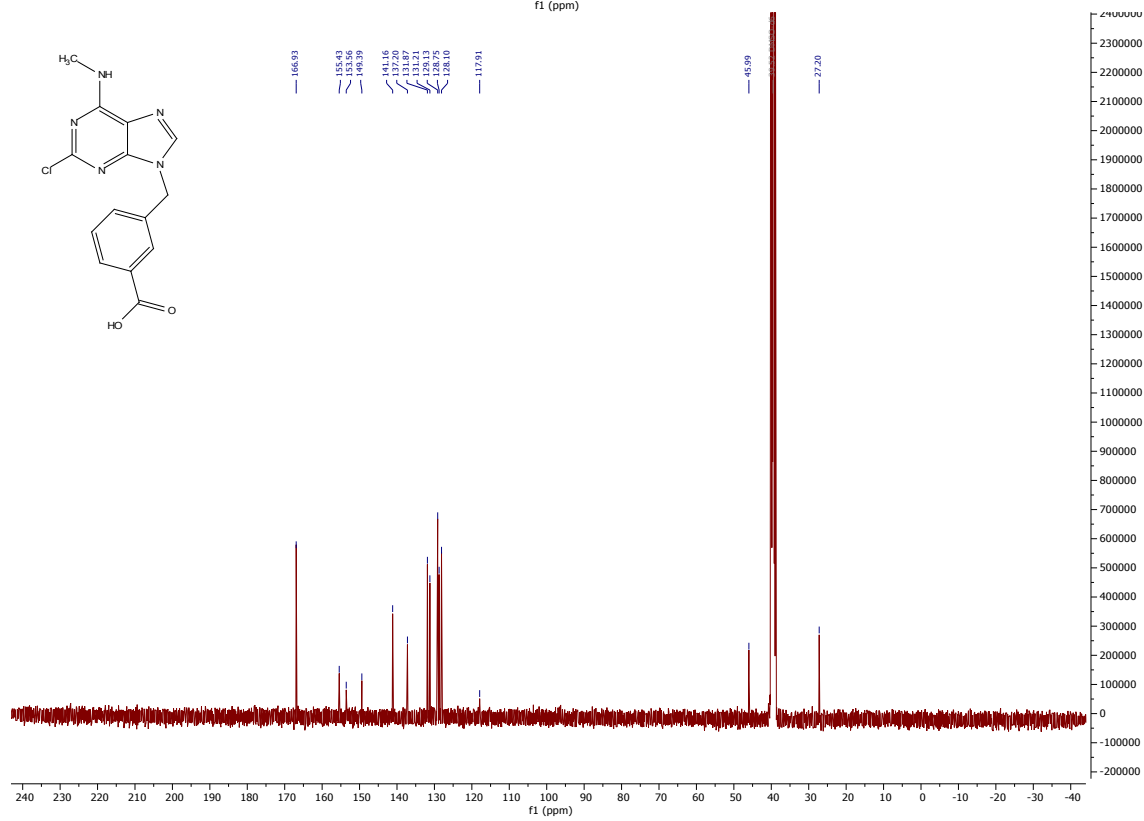
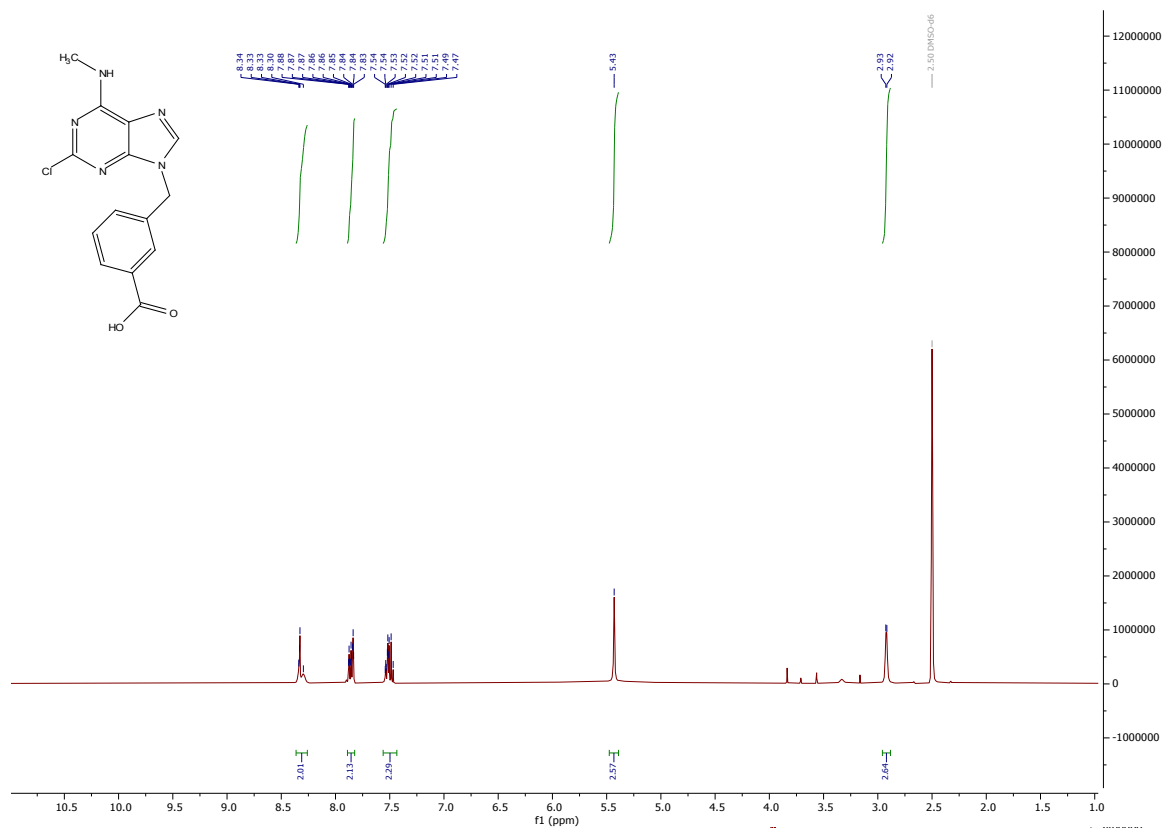




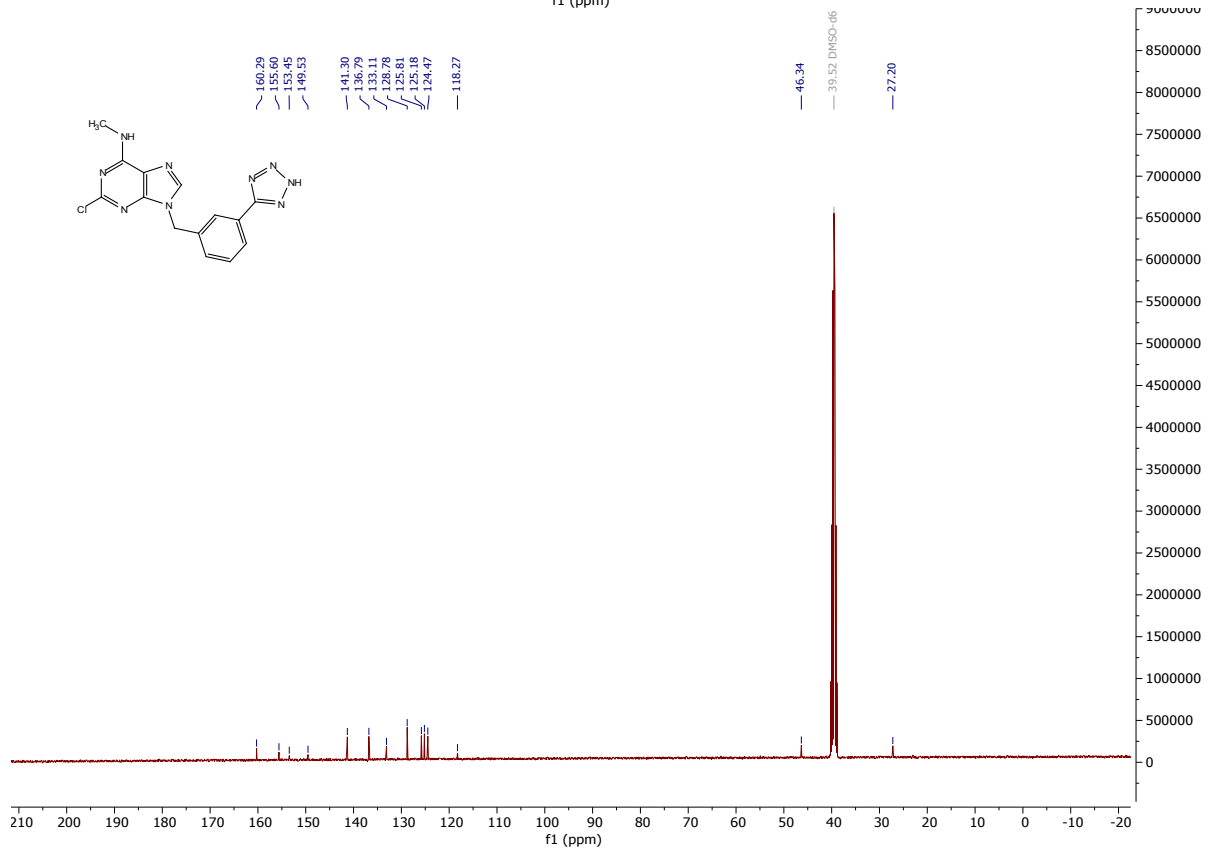
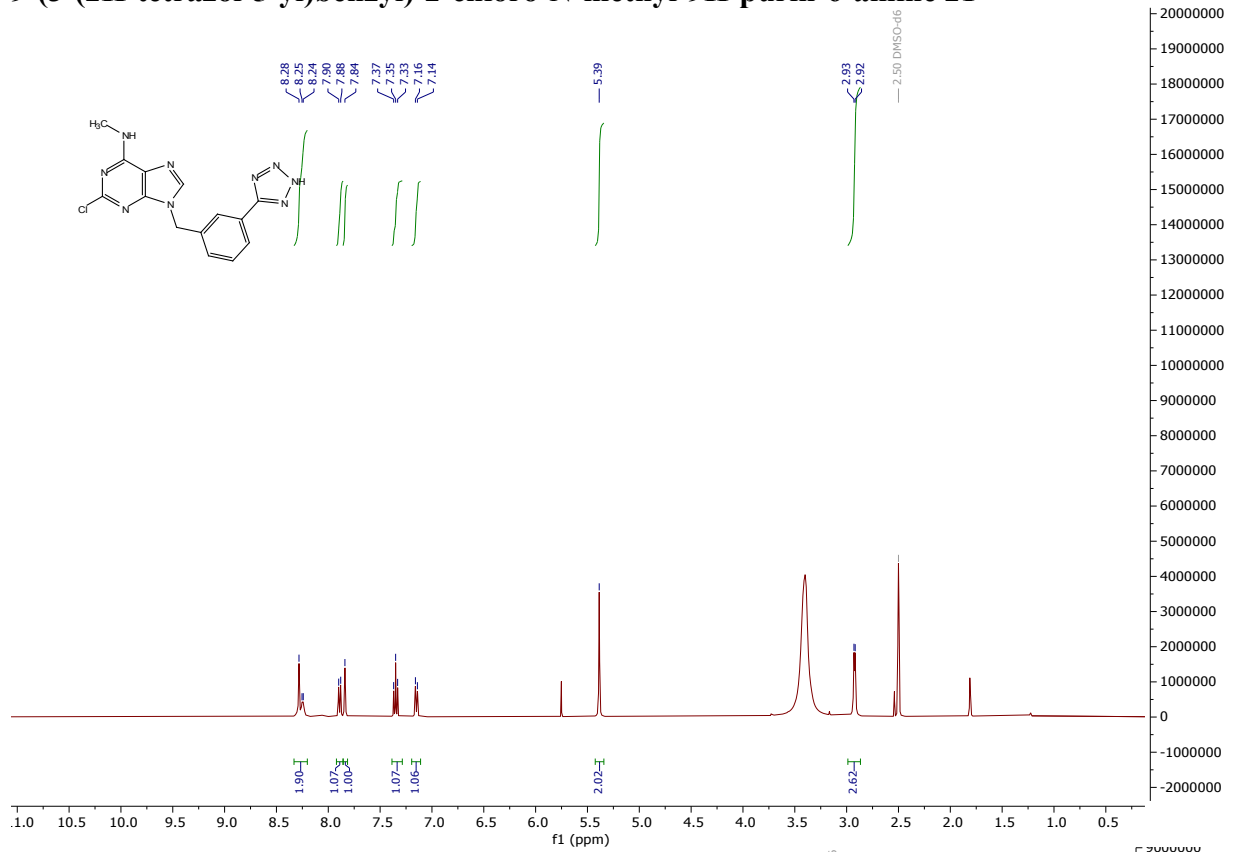
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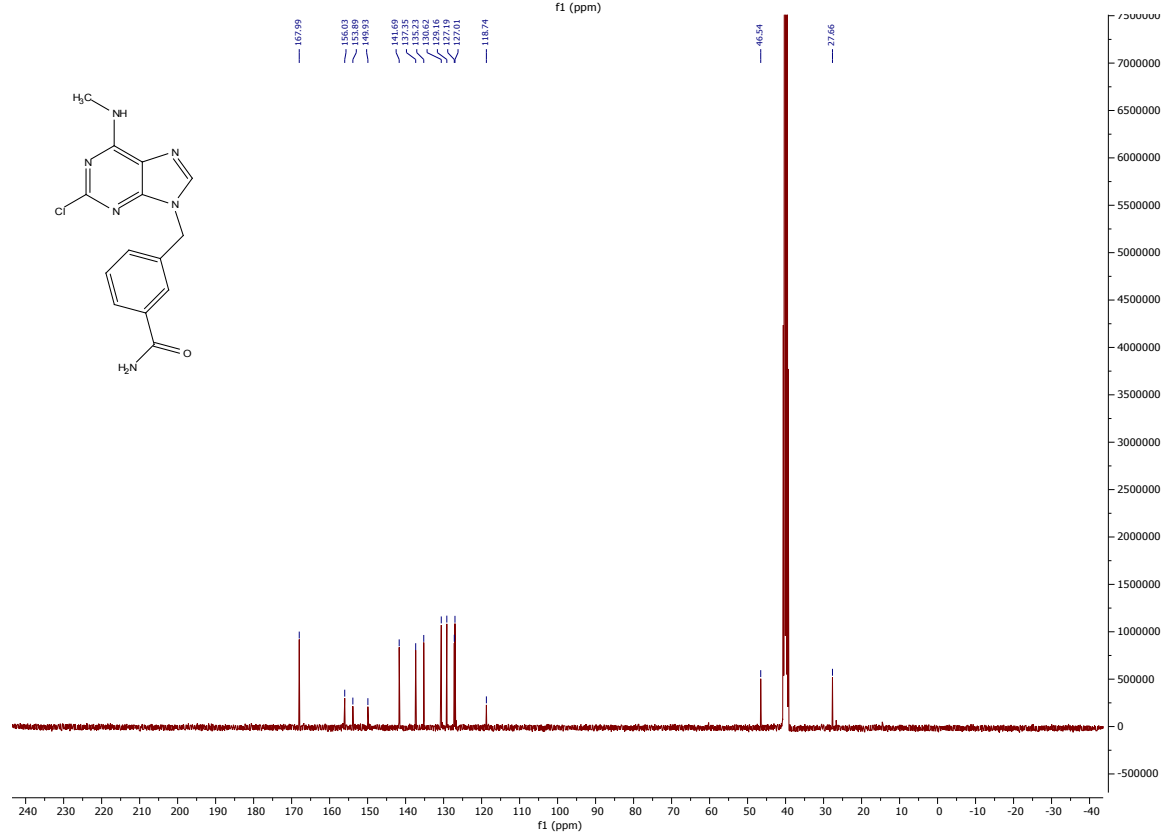
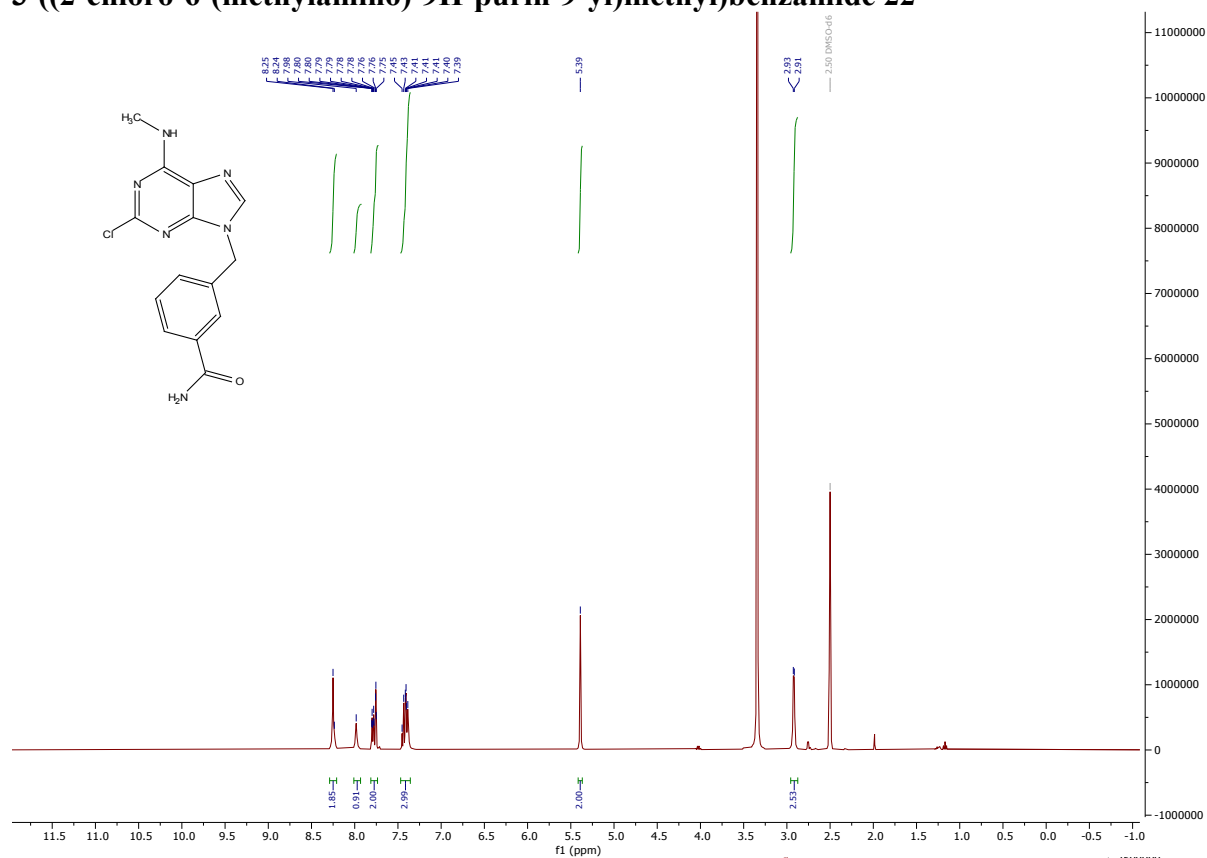
3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid 20



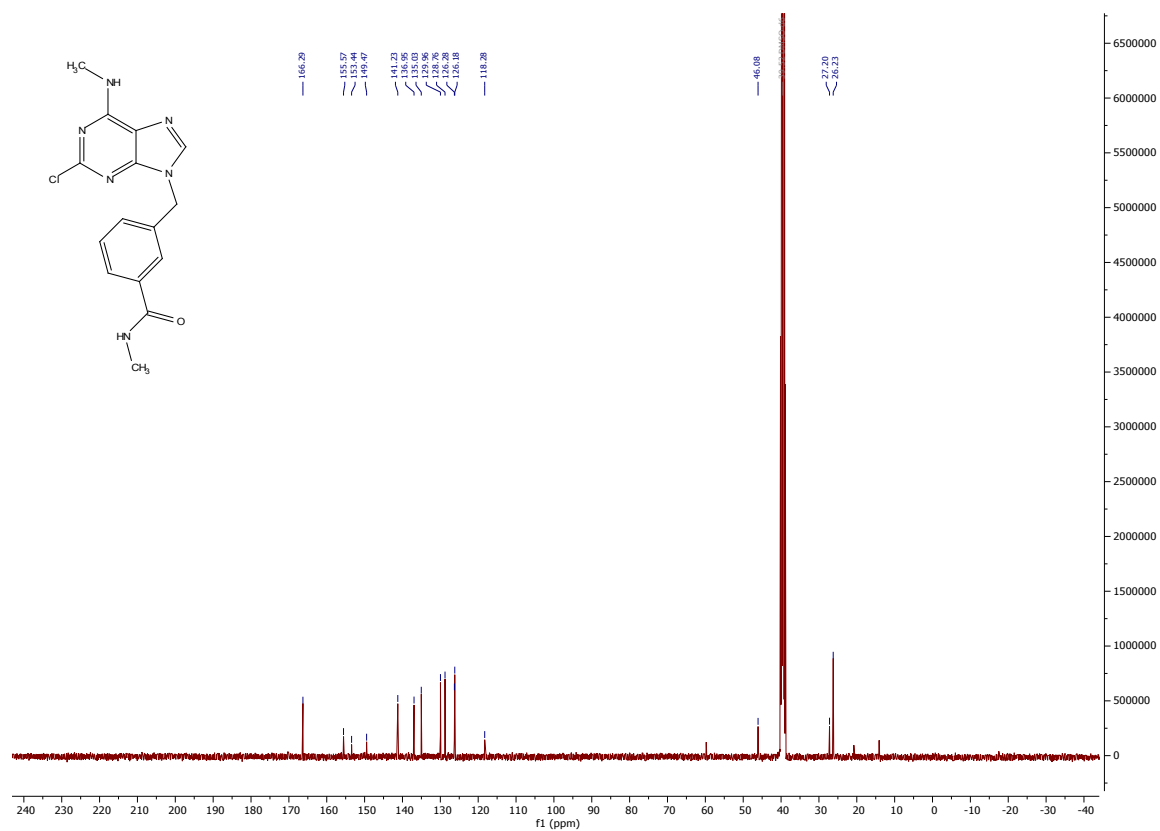
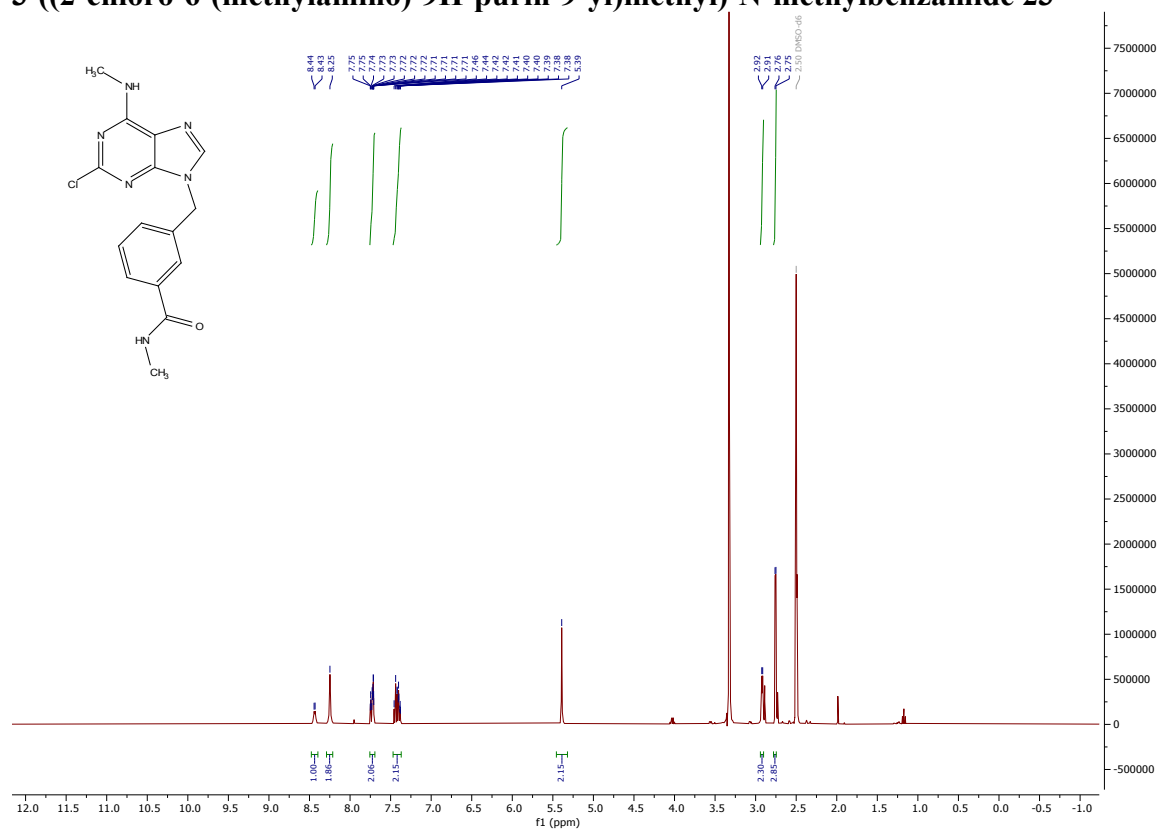
# 9-(3-(2H-tetrazol-5-yl)benzyl)-2-chloro-N-methyl-9H-purin-6-amine 21



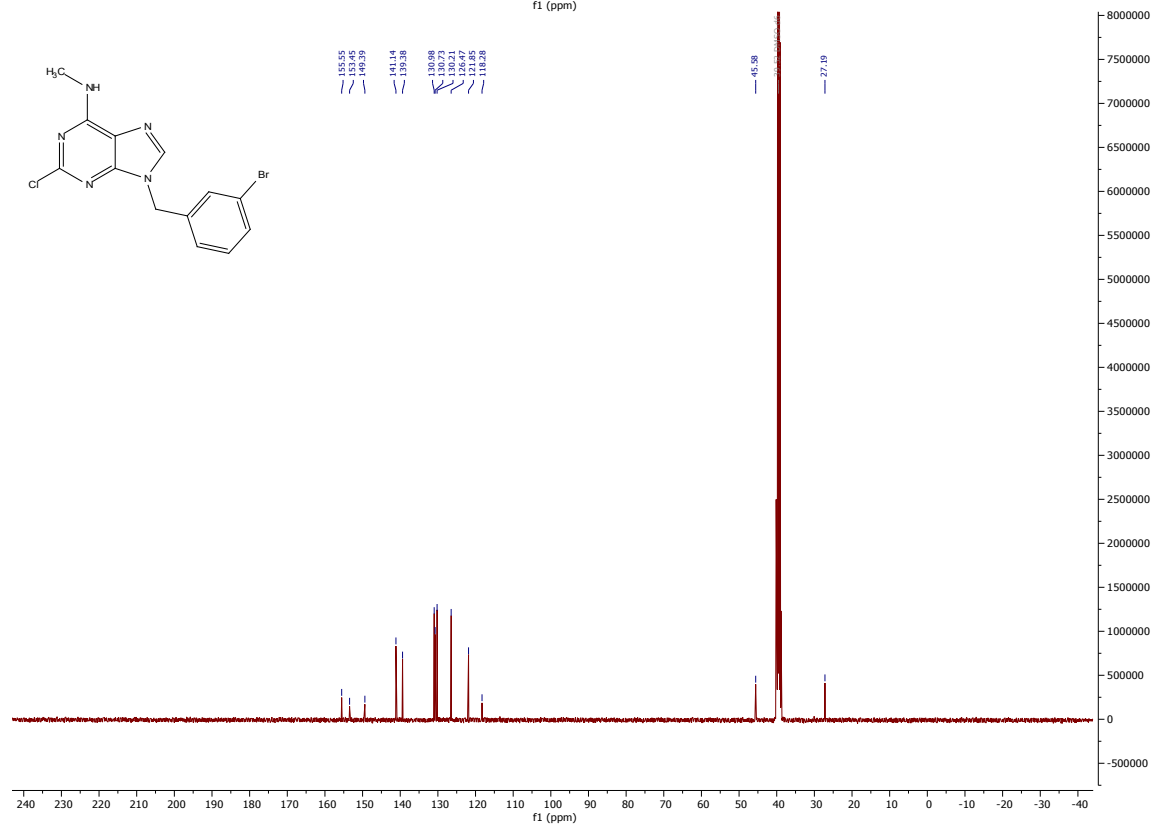
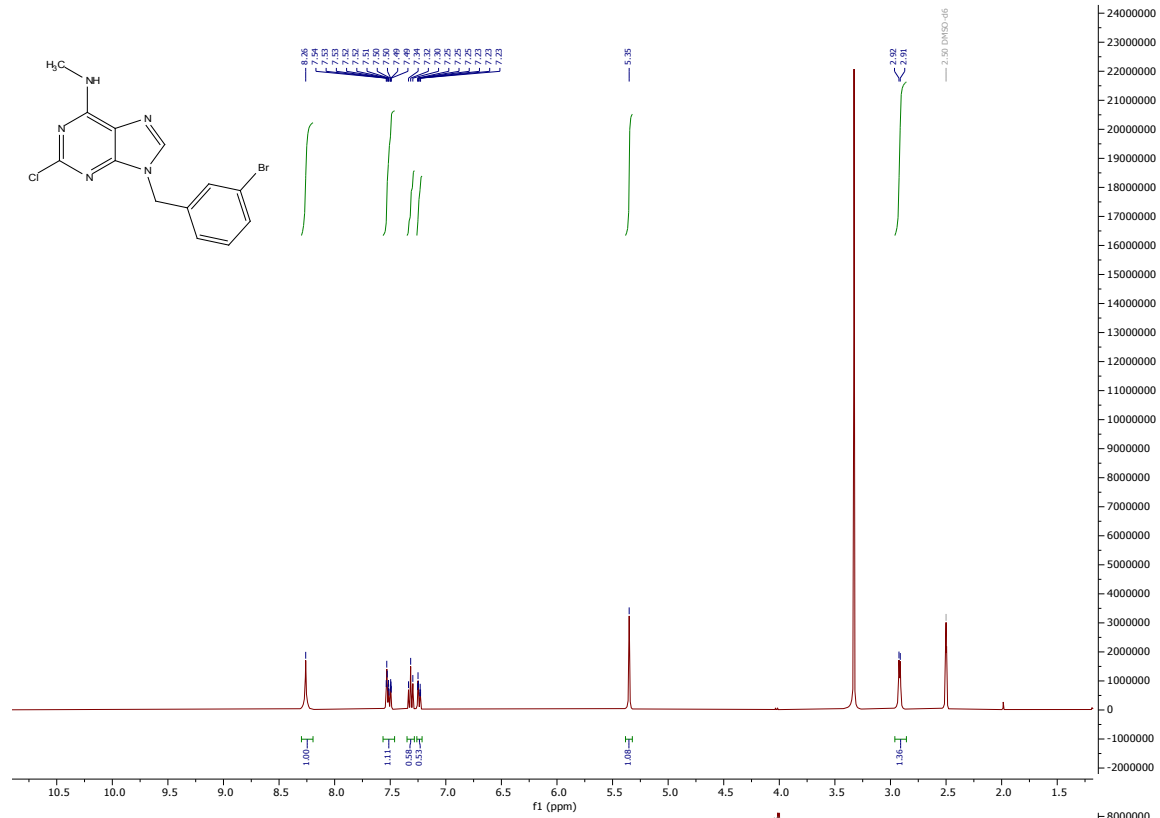
### 3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzamide 22



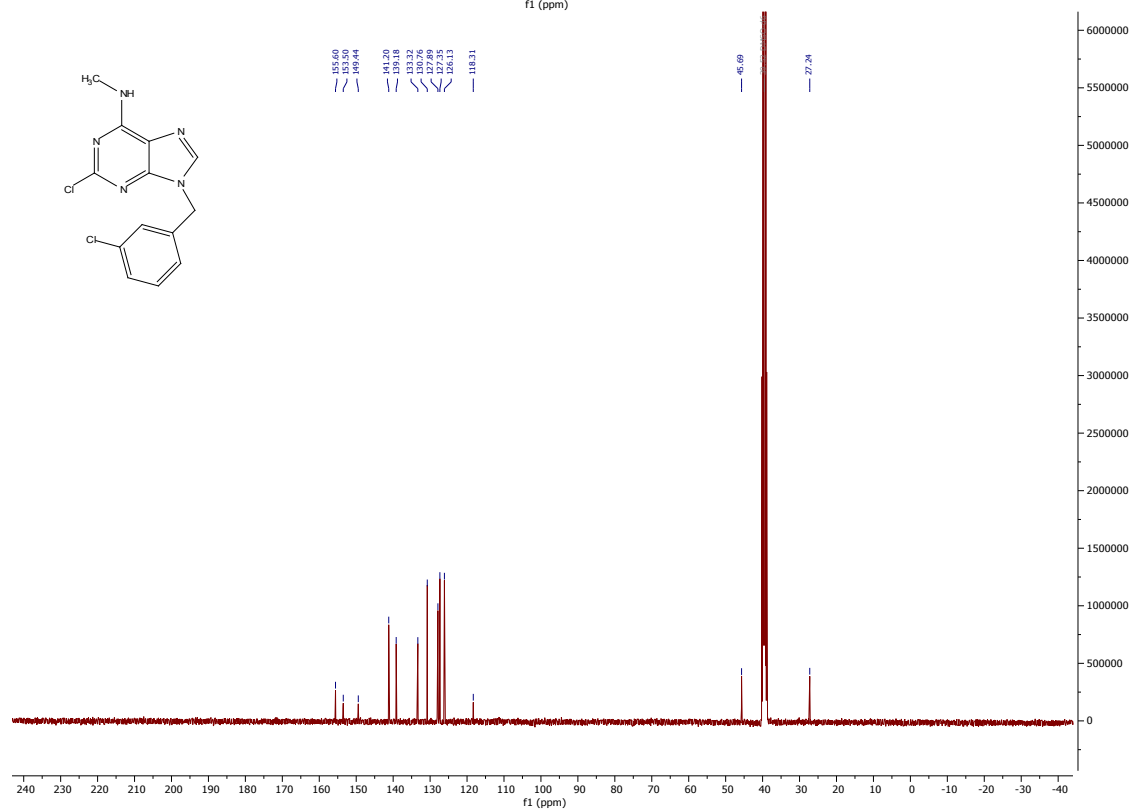
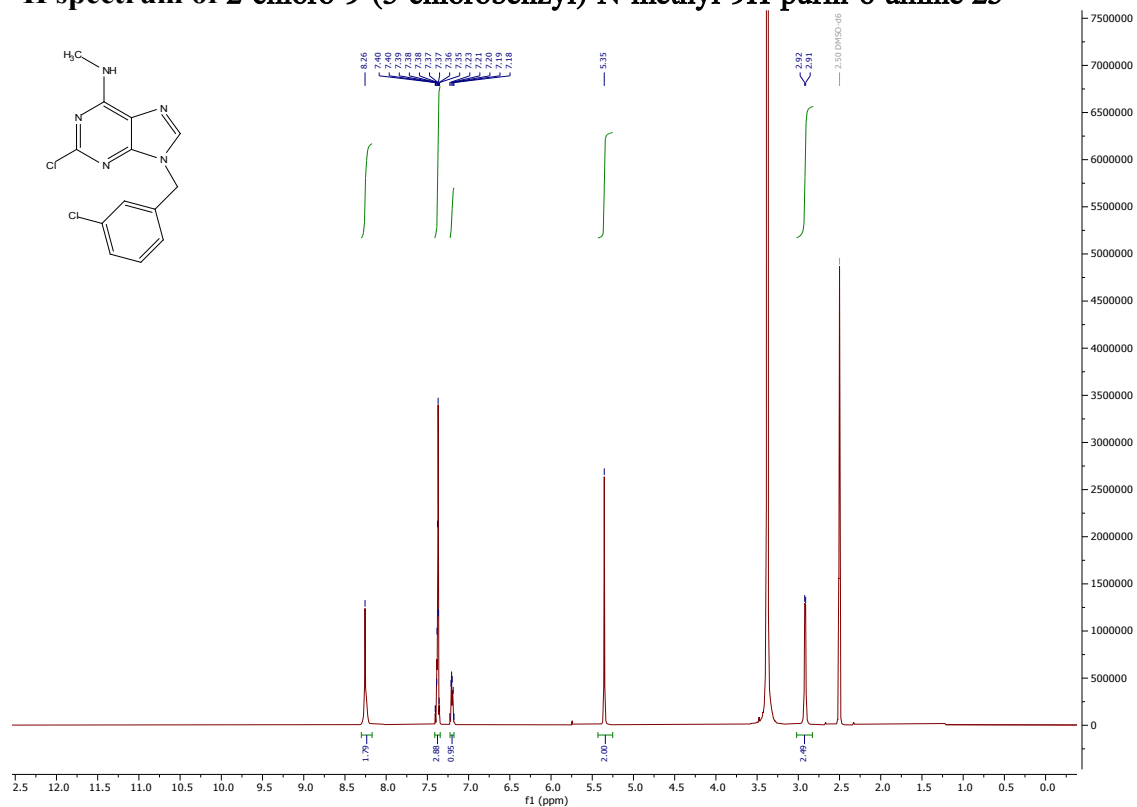
### 3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)-N-methylbenzamide 23



# 9-(3-bromobenzyl)-2-chloro-N-methyl-9H-purin-6-amine 24

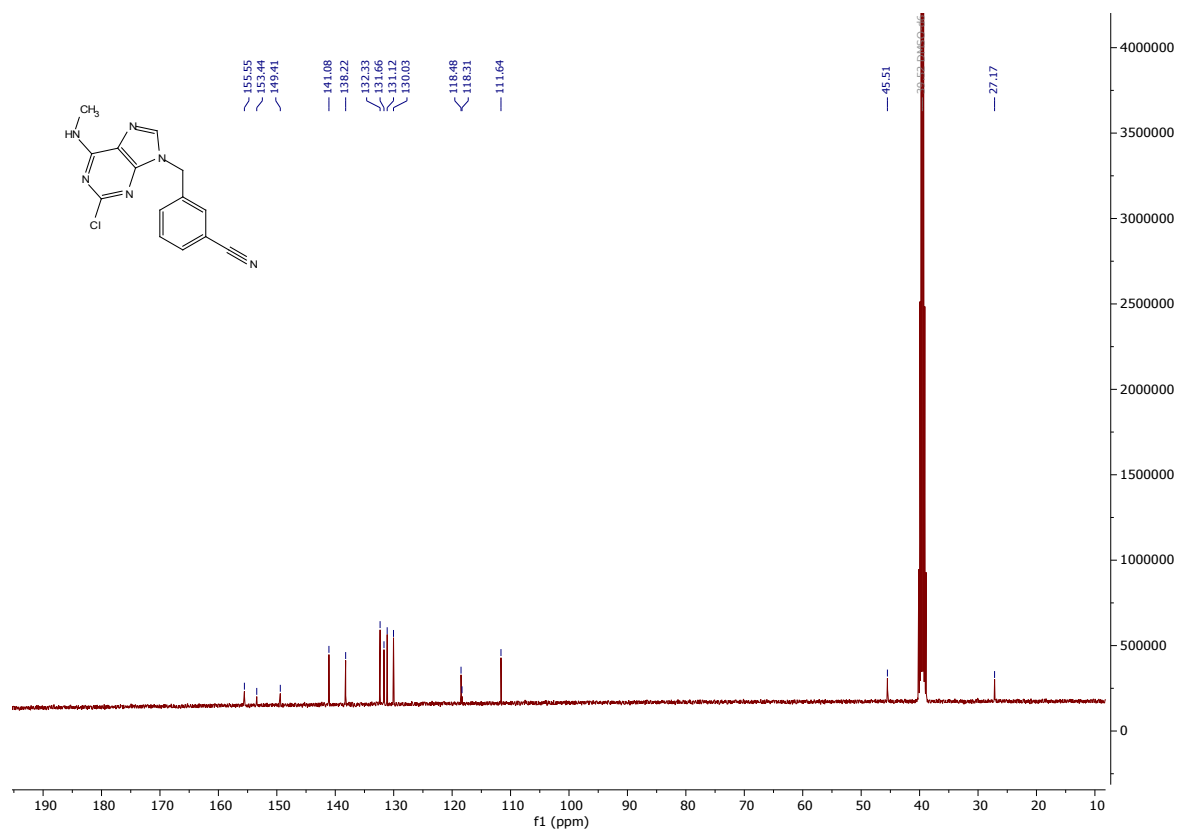
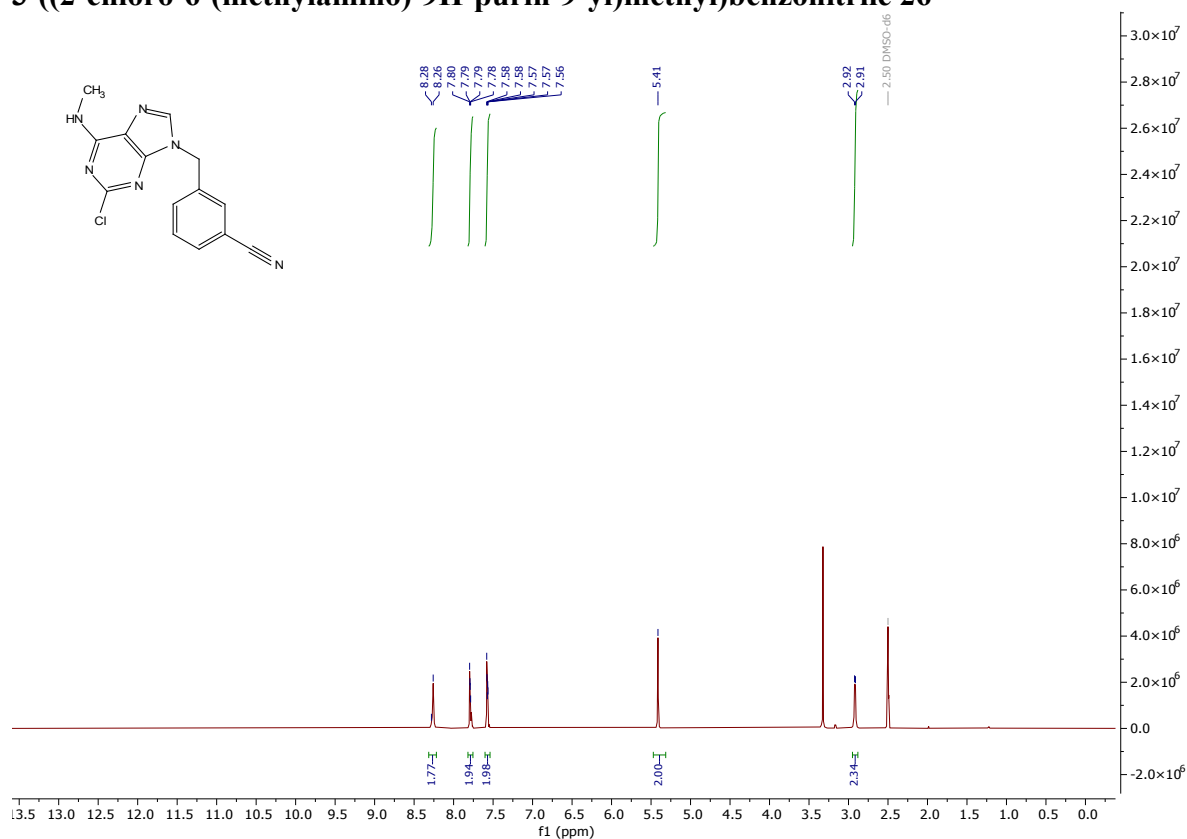


# <sup>1</sup>H spectrum of 2-chloro-9-(3-chlorobenzyl)-N-methyl-9H-purin-6-amine 25

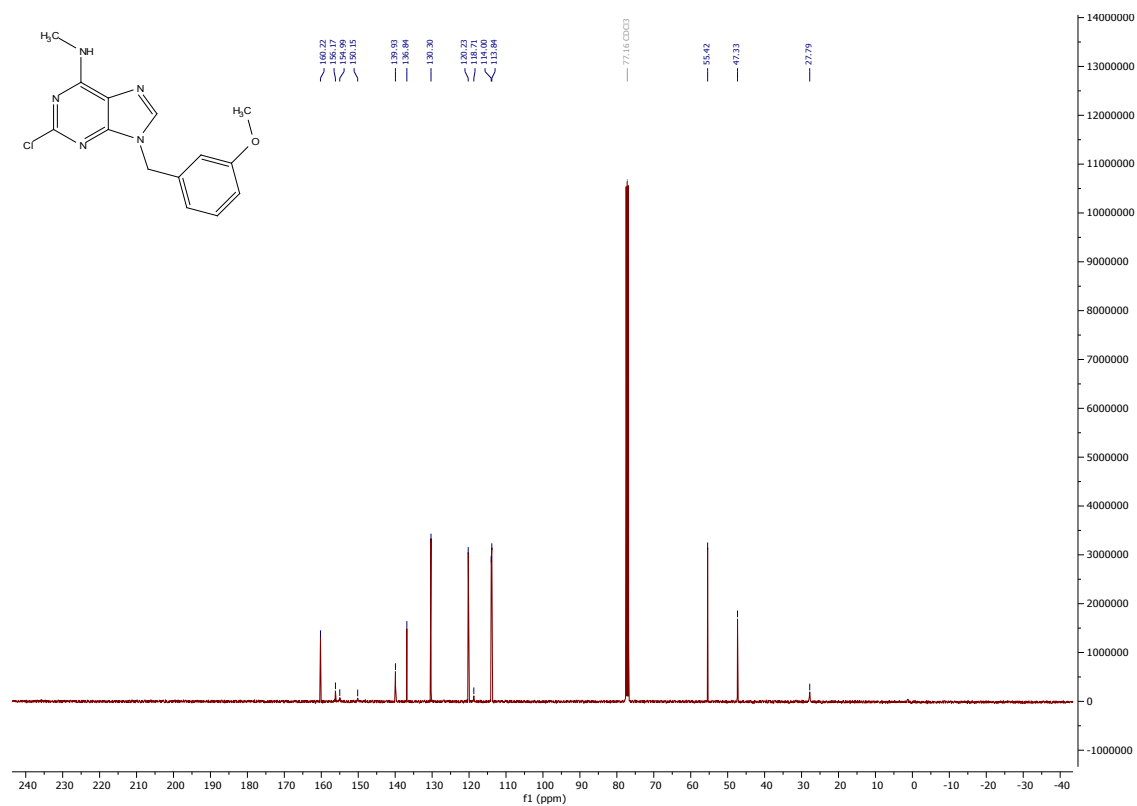
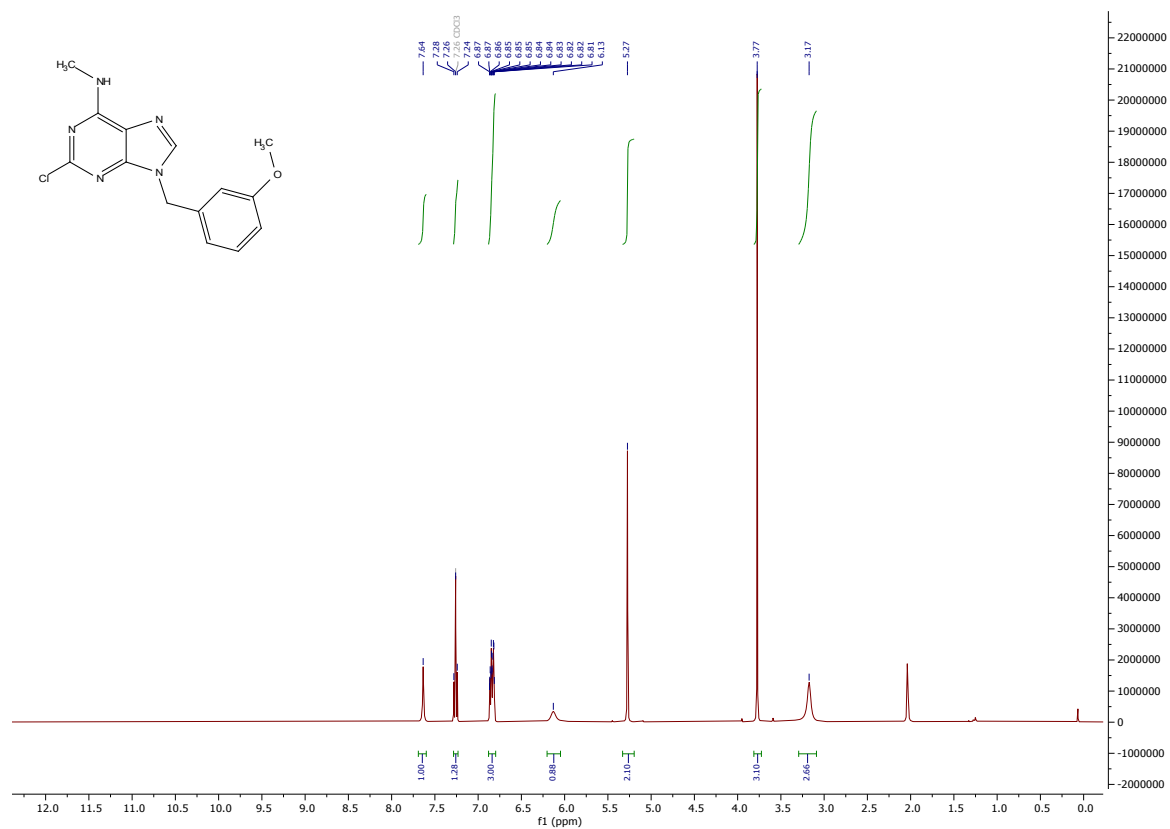




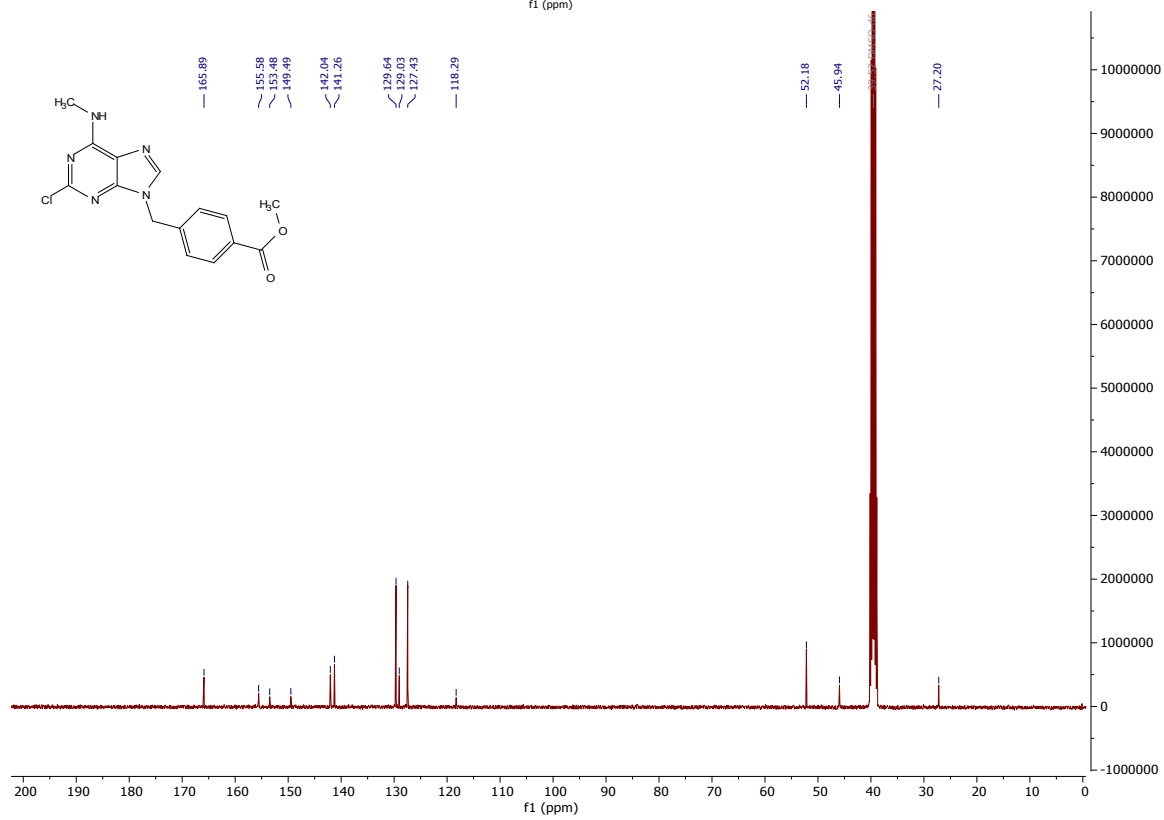
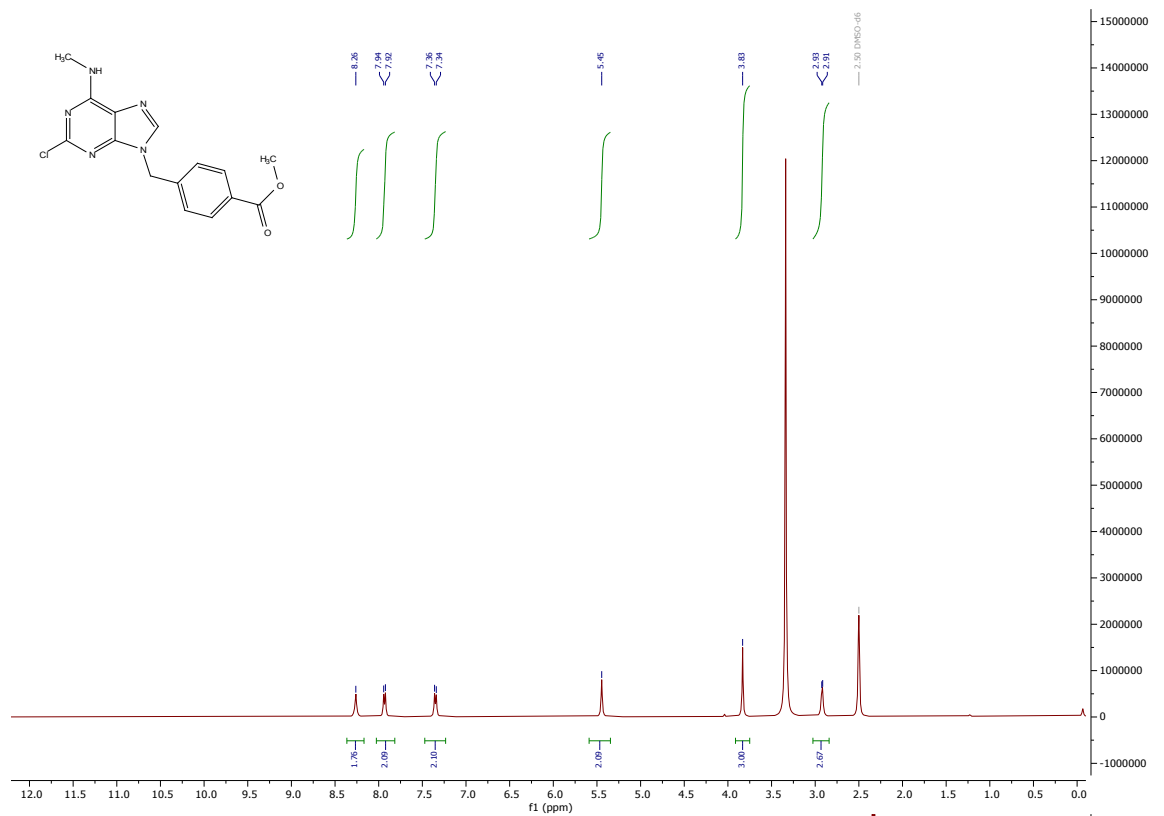
### 3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzonitrile 26



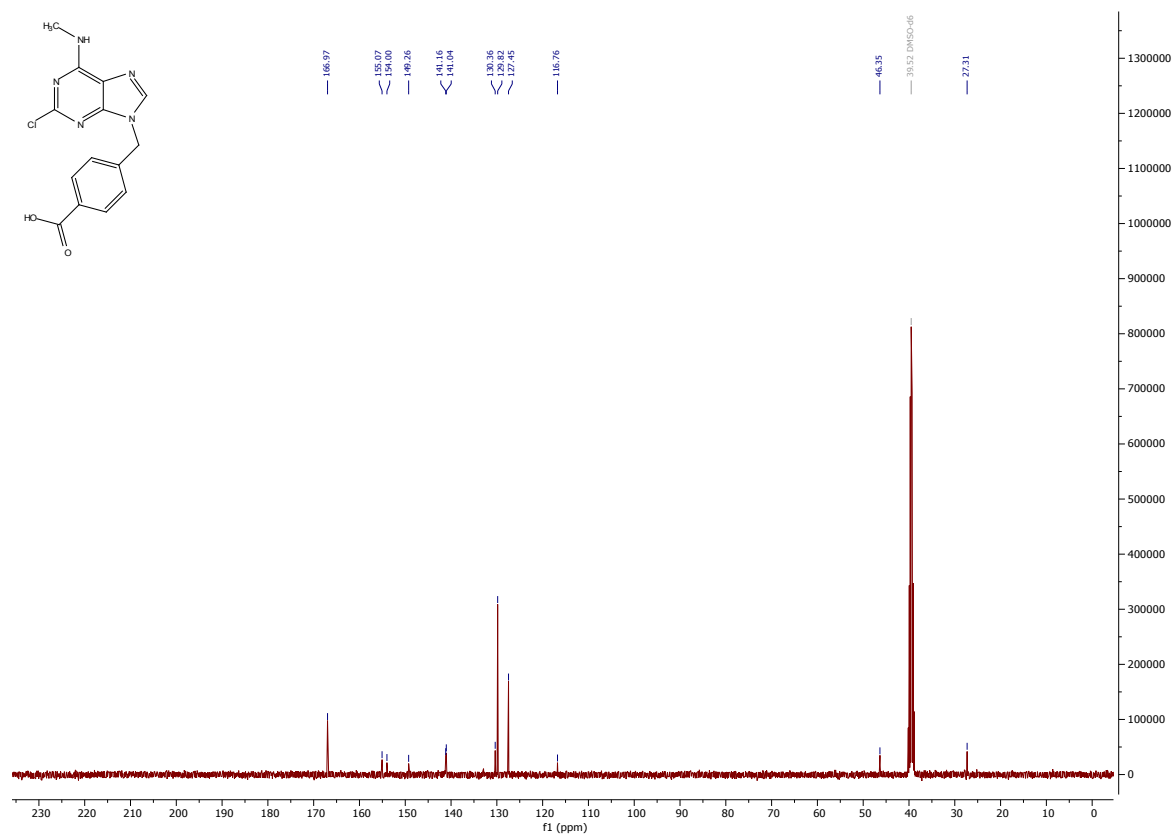
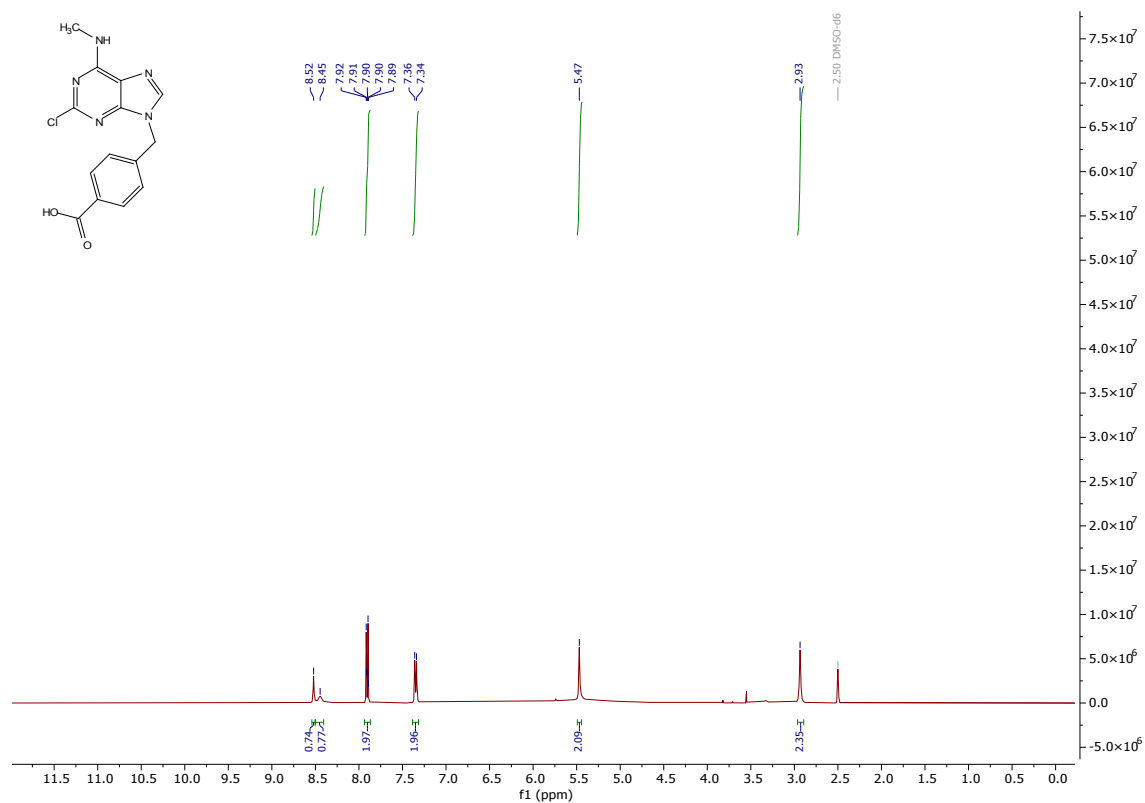
# 2-chloro-9-(3-methoxybenzyl)-N-methyl-9H-purin-6-amine 27



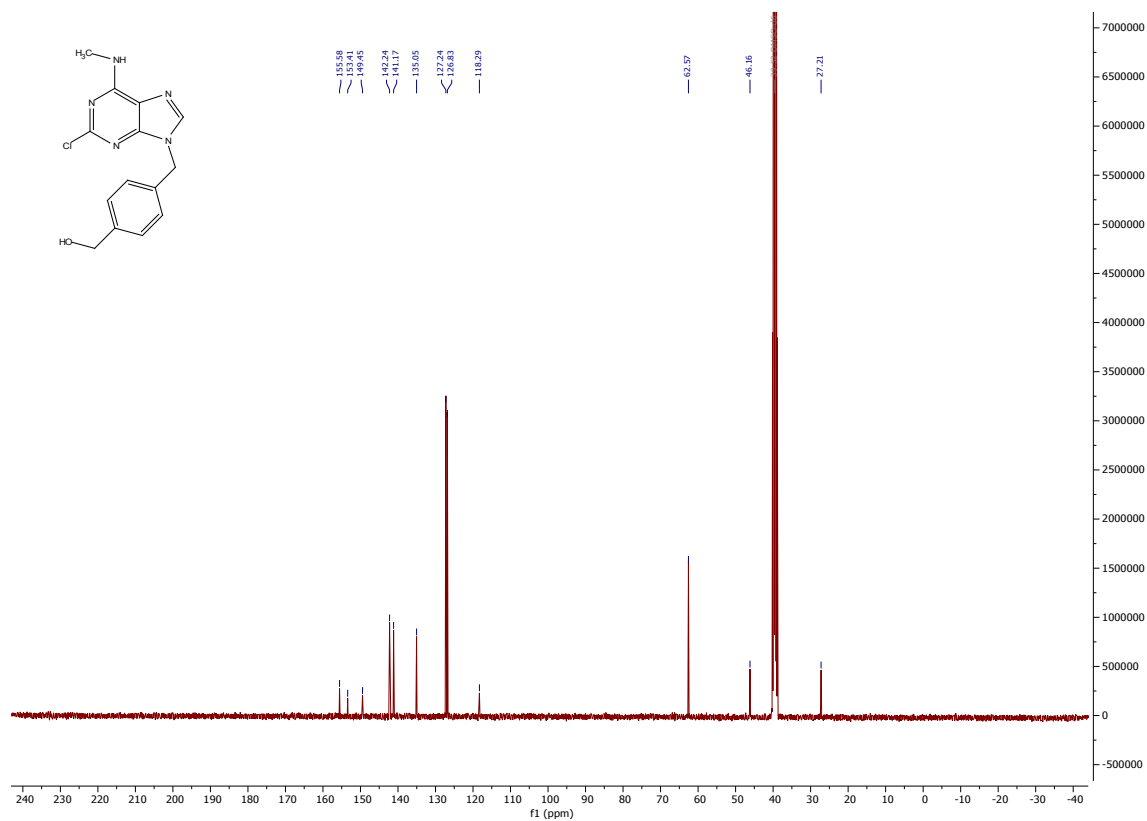
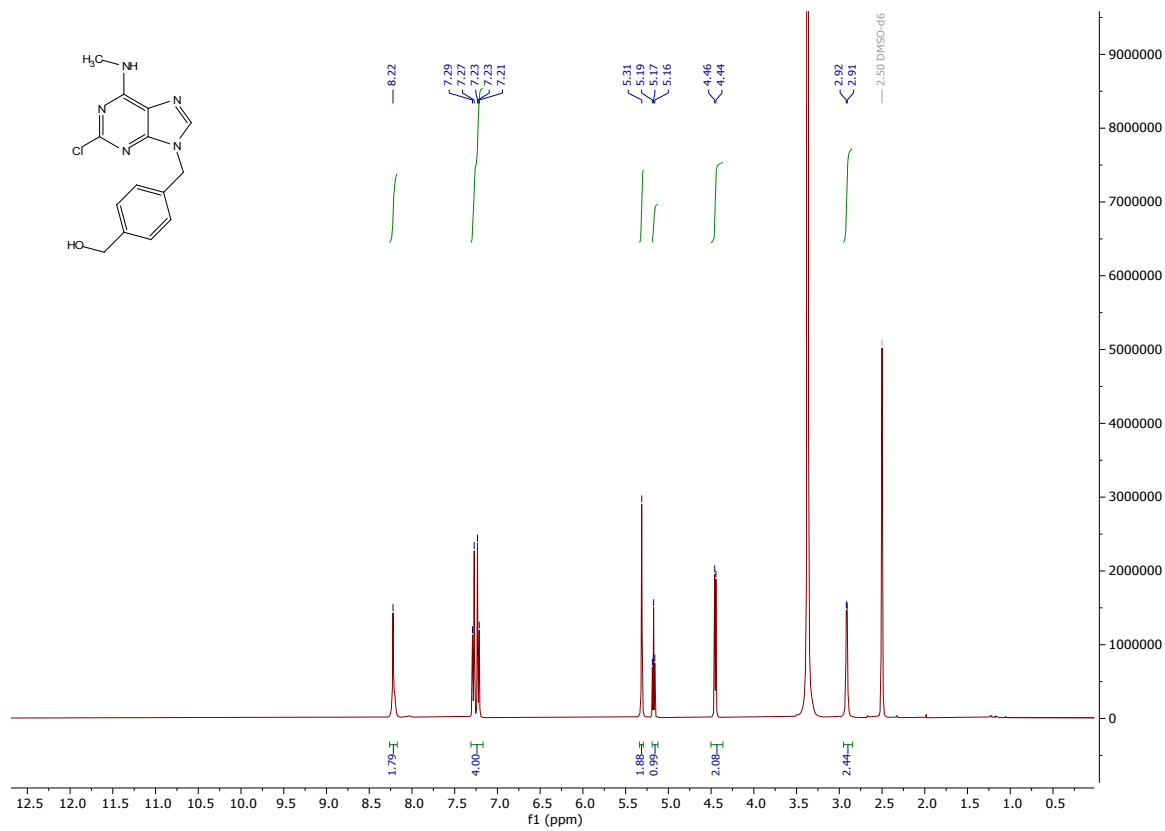
# methyl 4-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoate 28



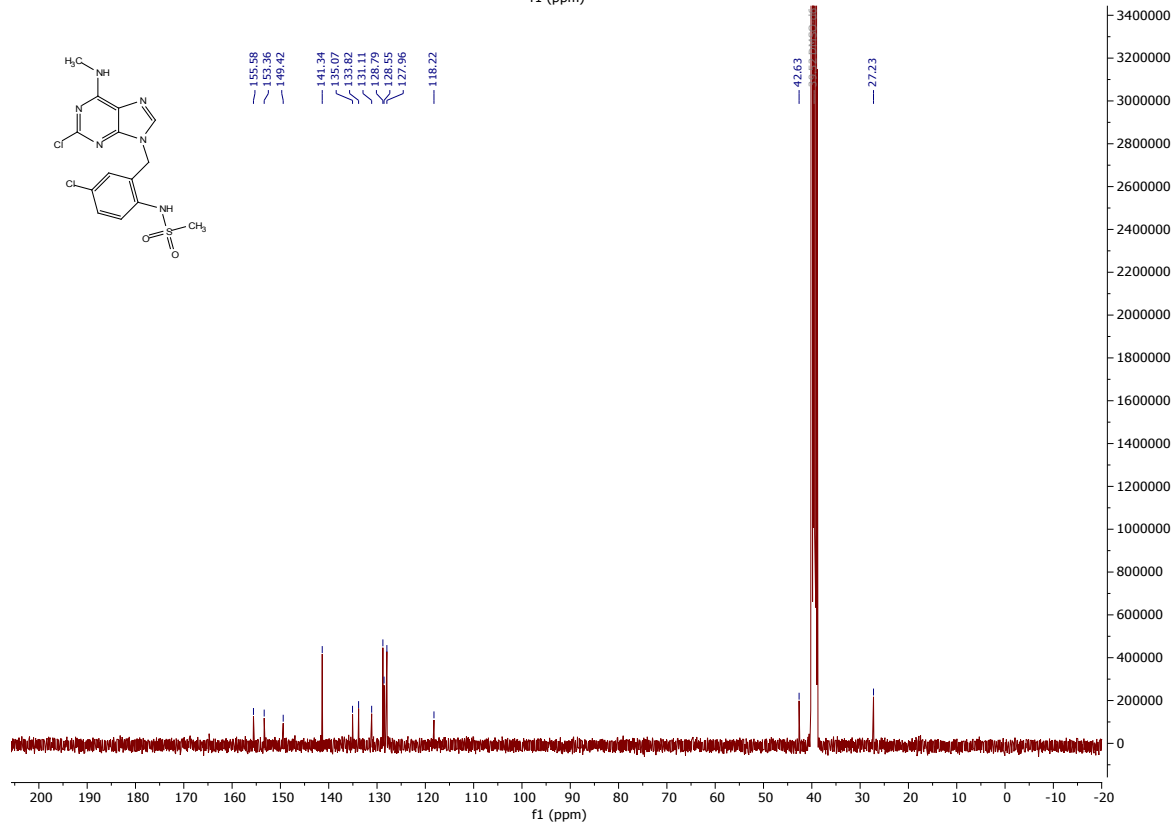
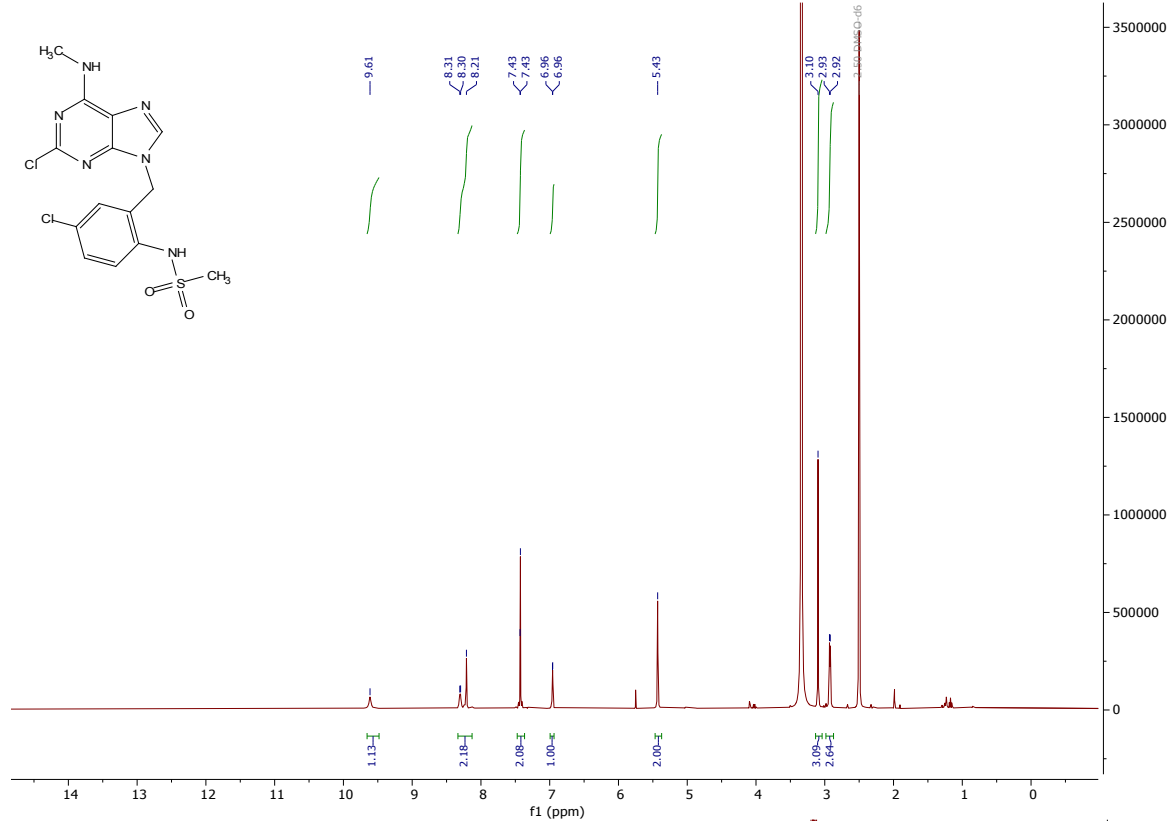
### 3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid 29



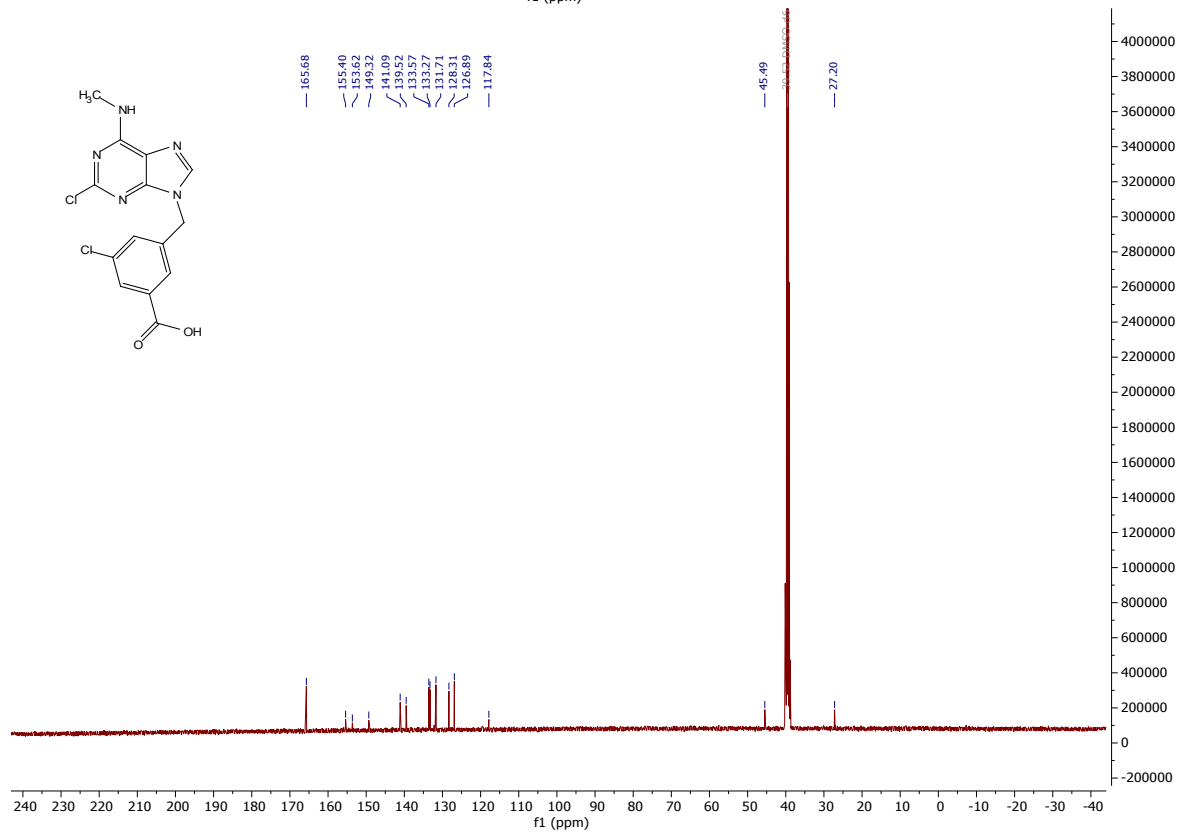
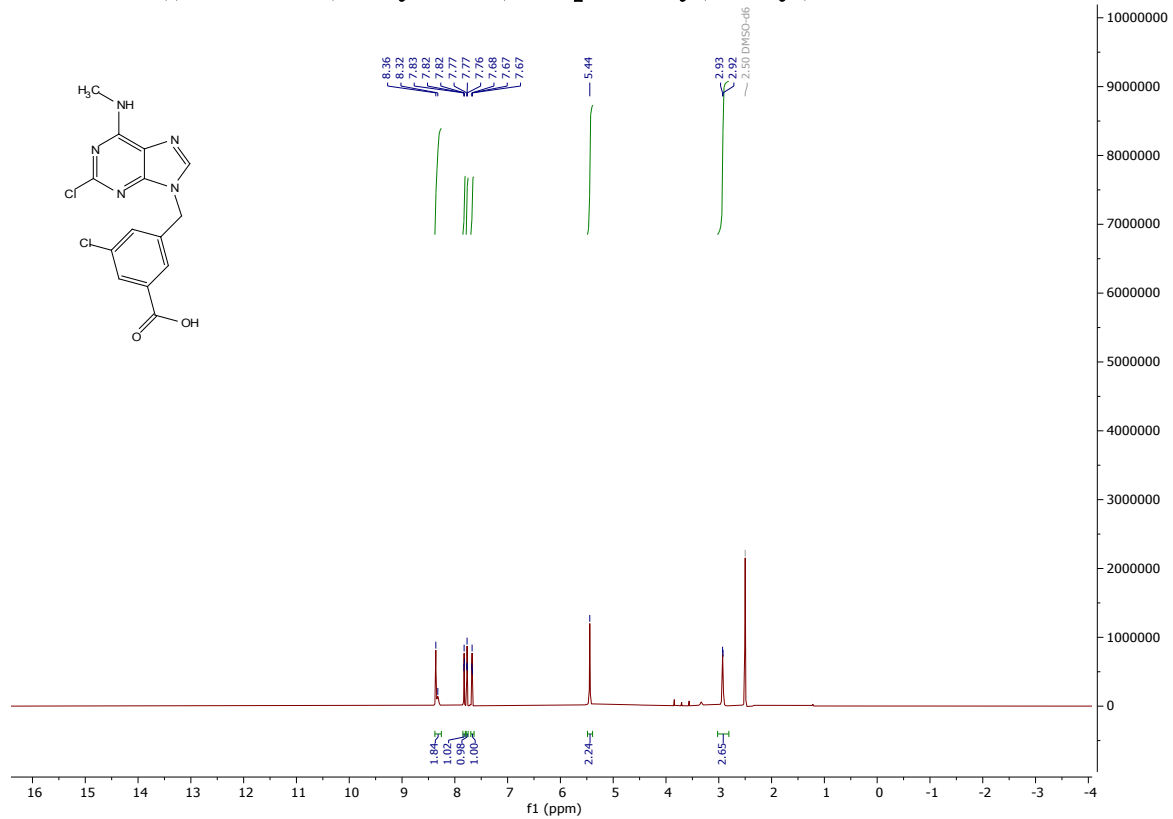
# (4-((2,6-dichloro-9H-purin-9-yl)methyl)phenyl)methanol 30



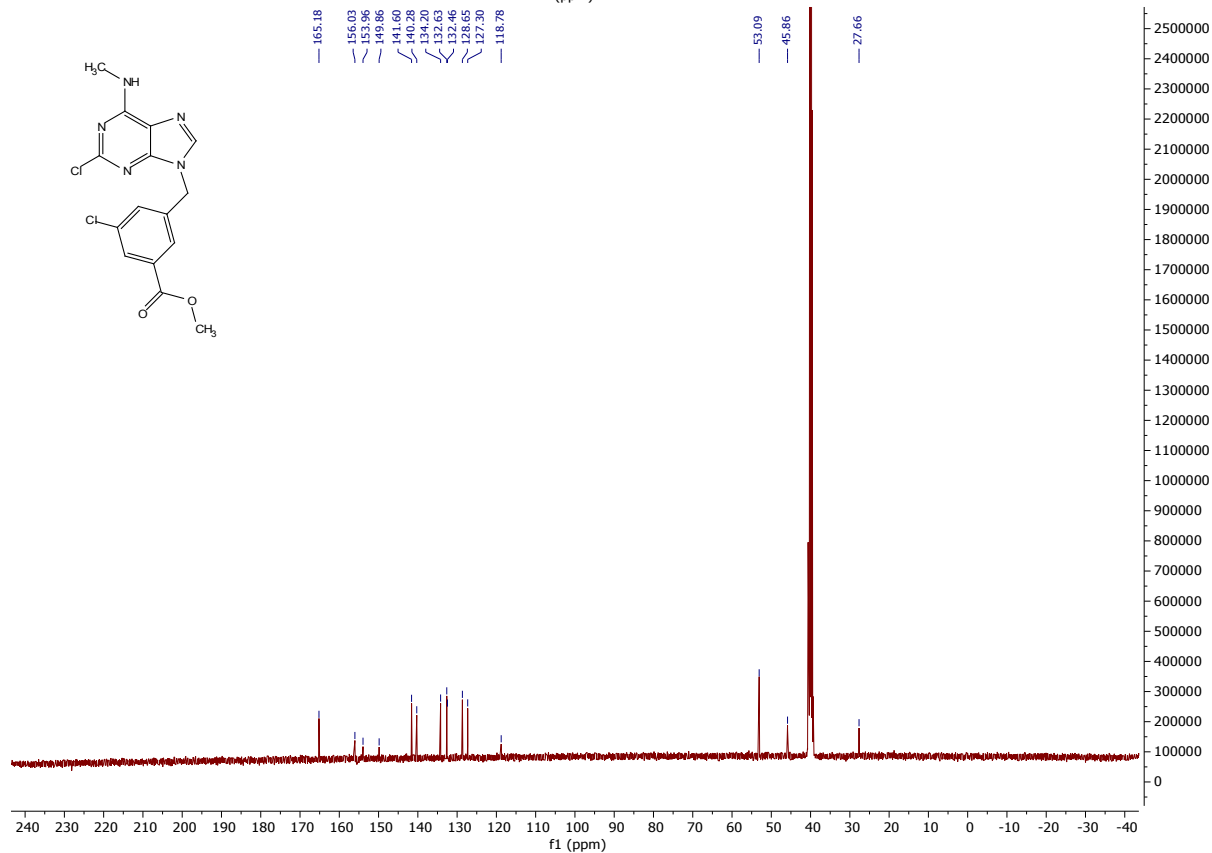
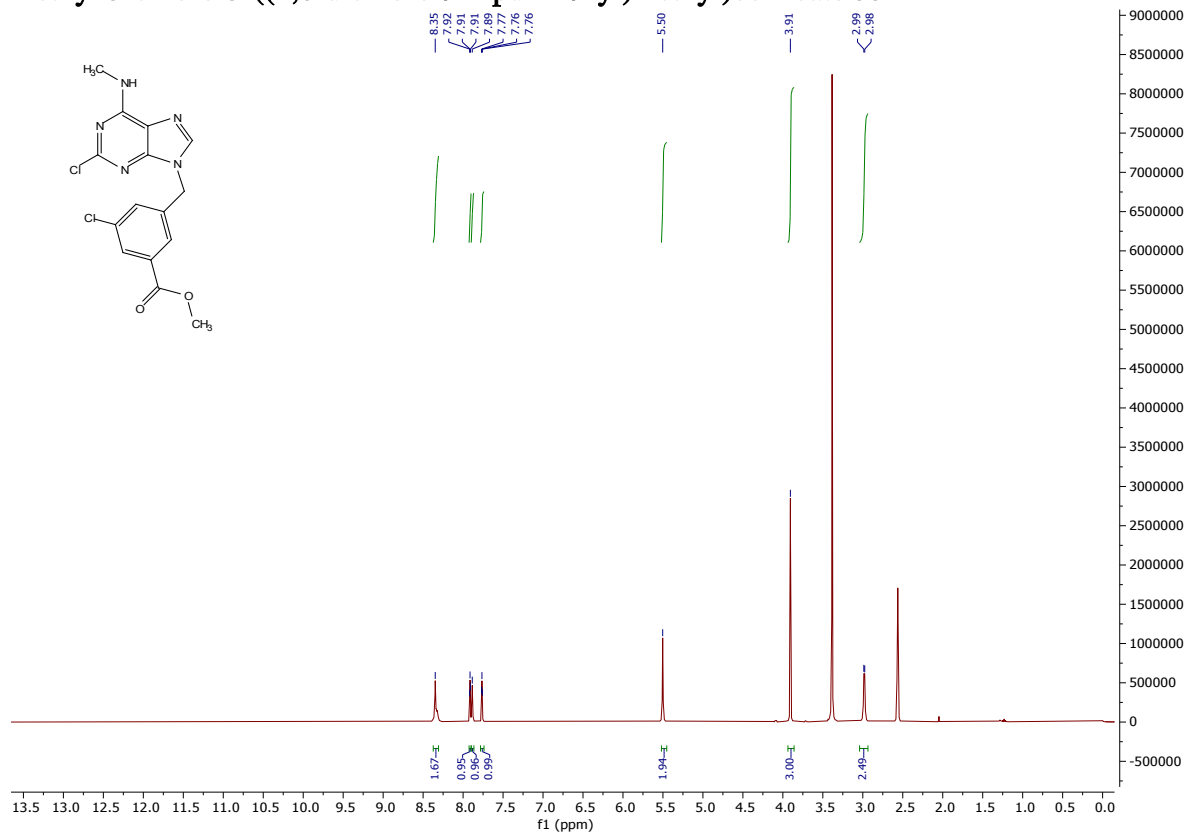
# N-(4-chloro-2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)methanesulfonamide 31



3-chloro-5-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid 32

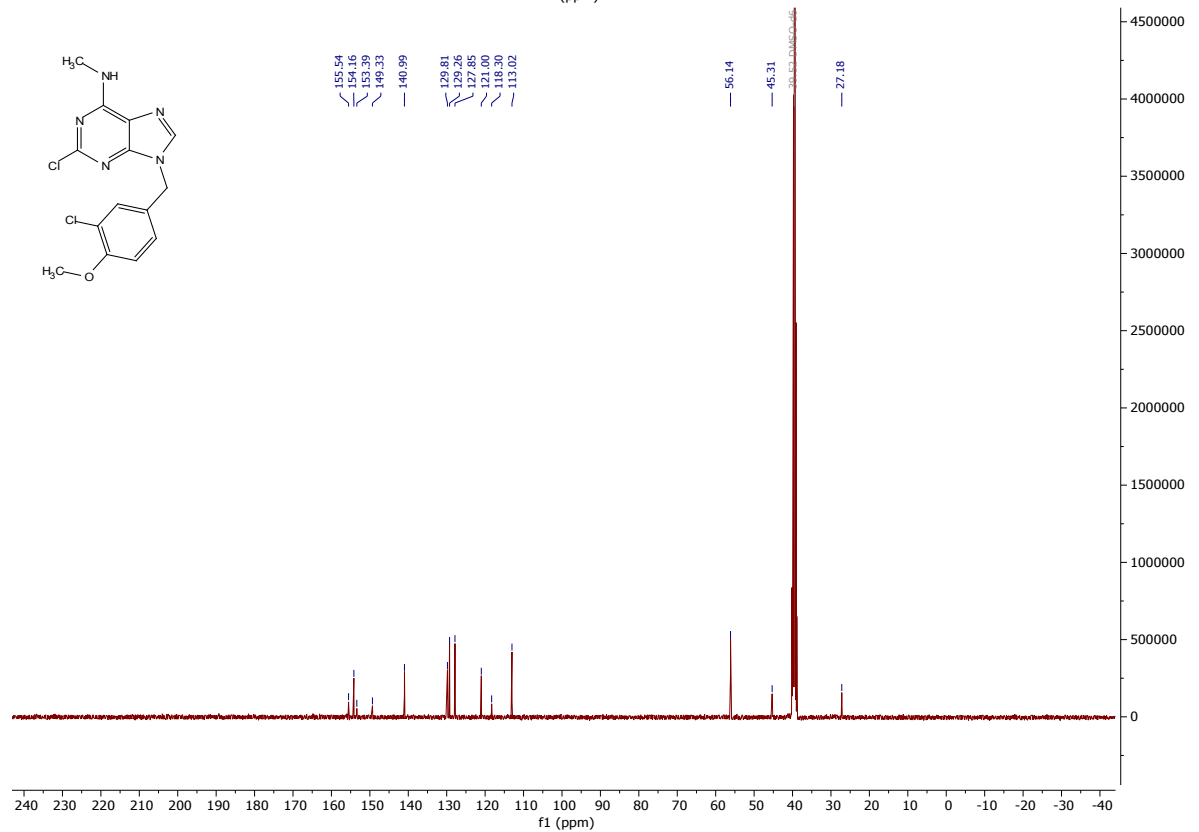
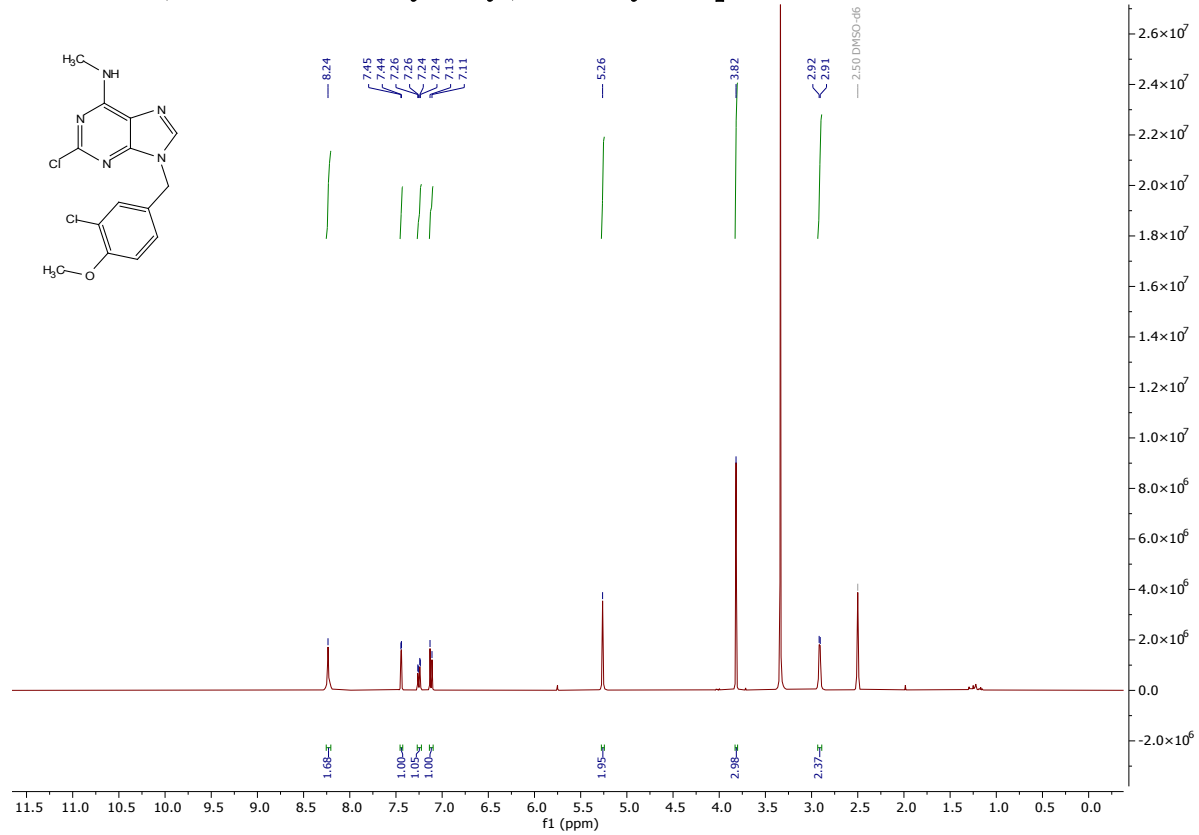


methyl 3-chloro-5-((2,6-dichloro-9H-purin-9-yl)methyl)benzoate 33

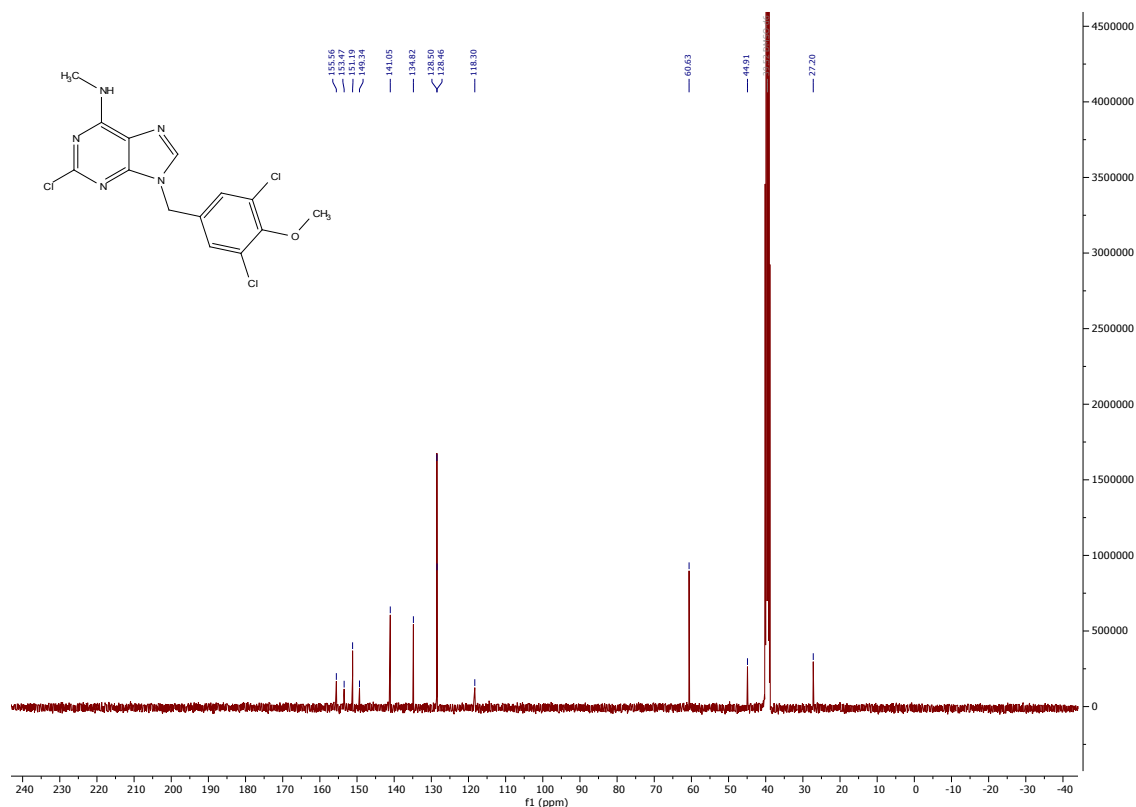
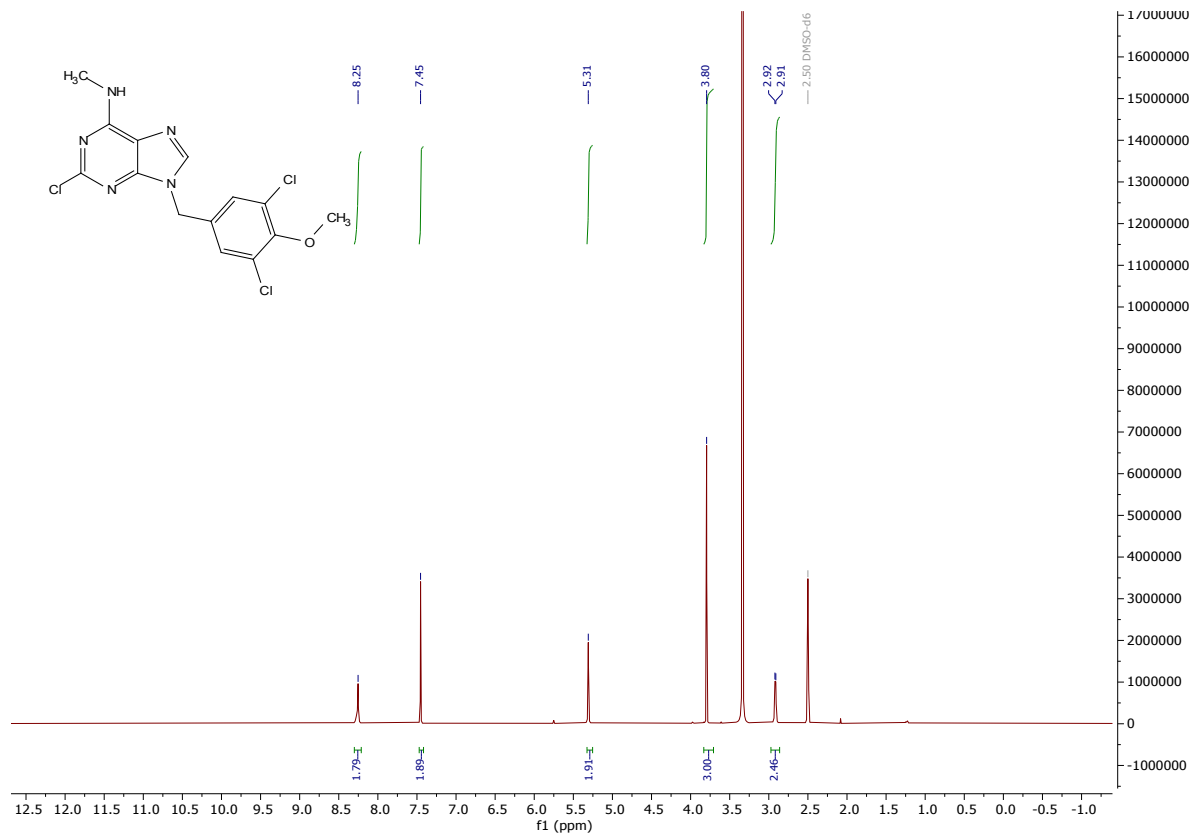




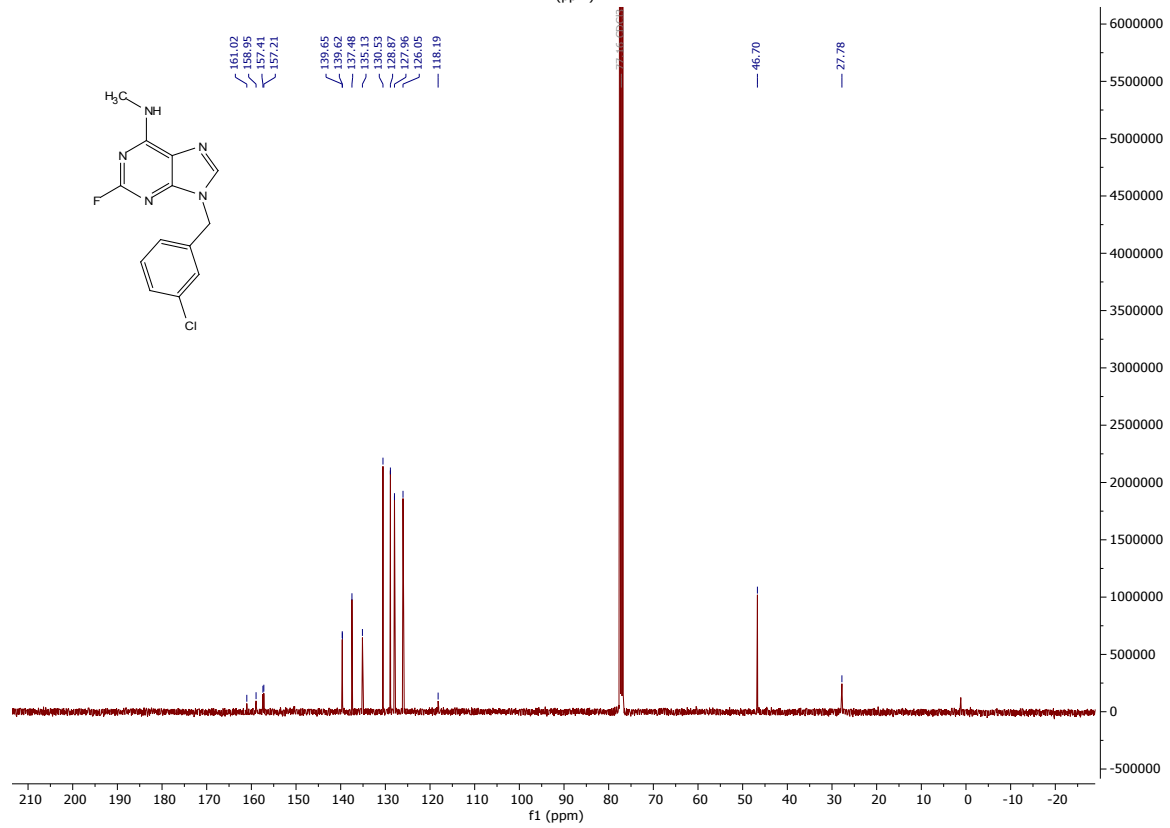
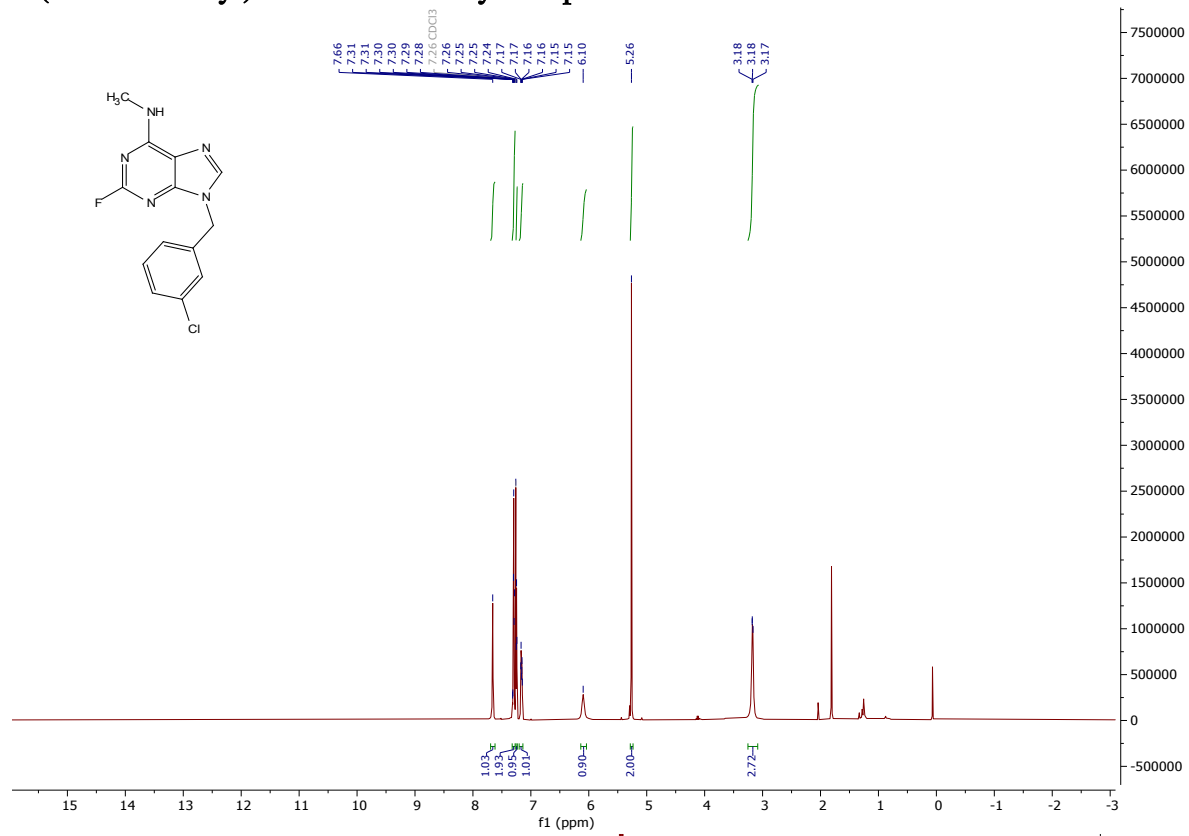
# 2-chloro-9-(3-chloro-4-methoxybenzyl)-N-methyl-9H-purin-6-amine 34



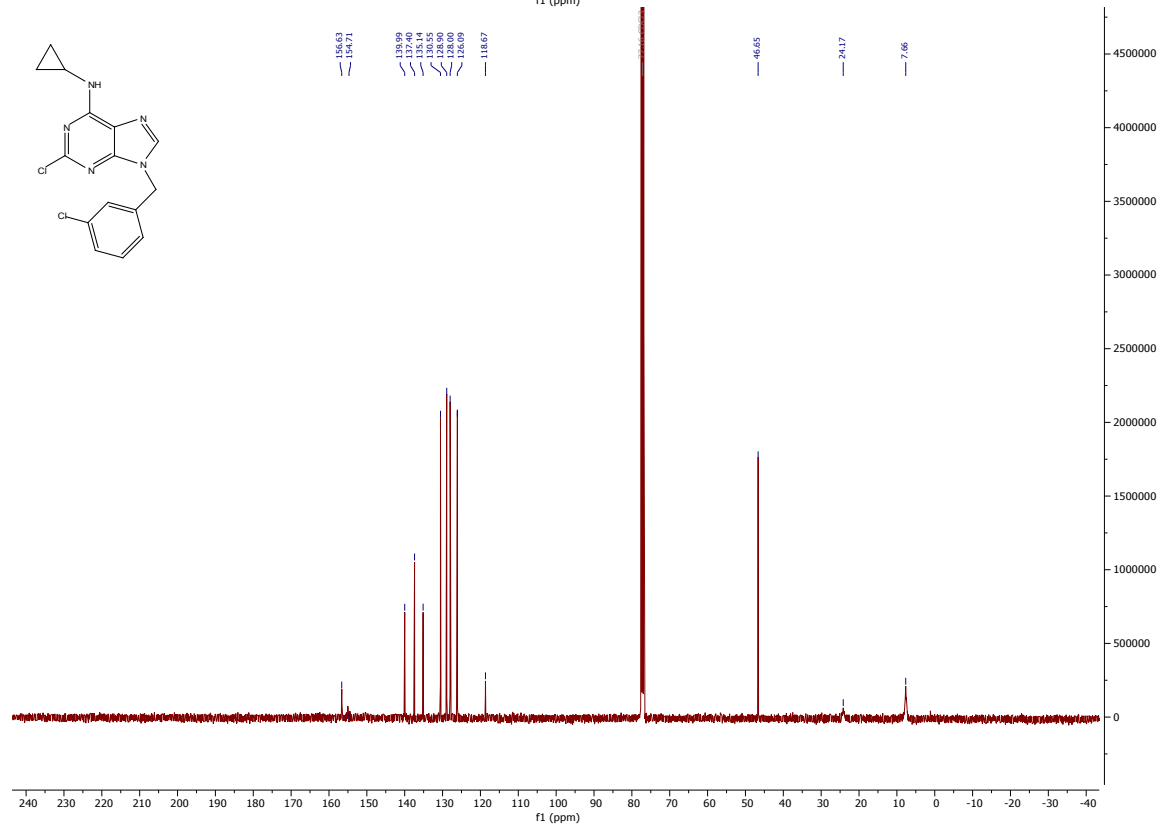
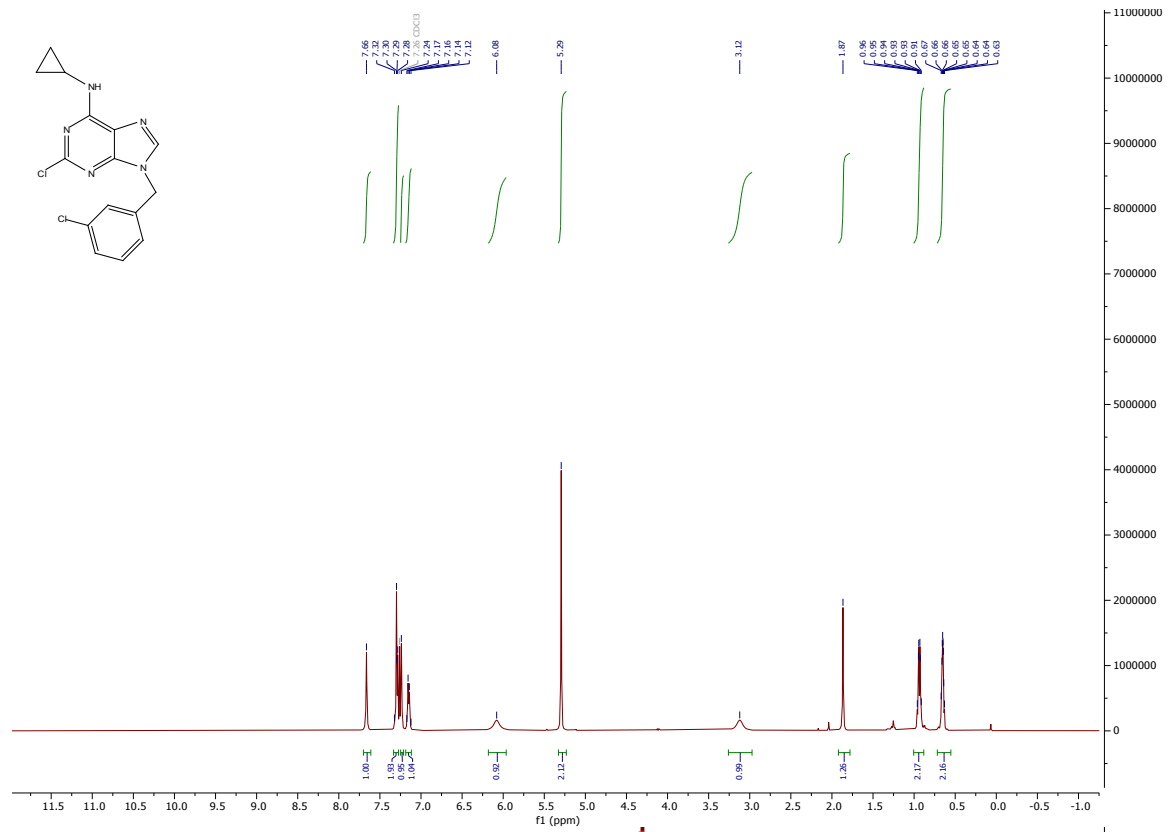
# 2-chloro-9-(3,5-dichloro-4-methoxybenzyl)-N-methyl-9H-purin-6-amine 35



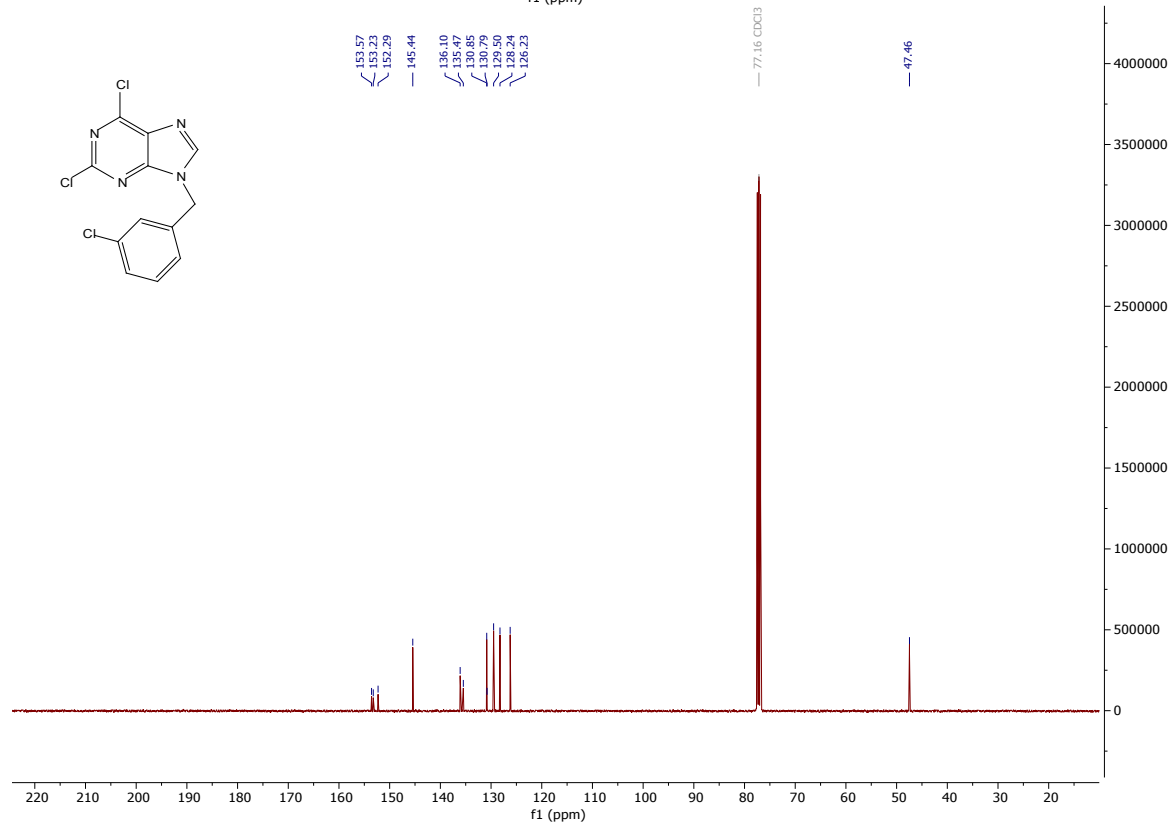
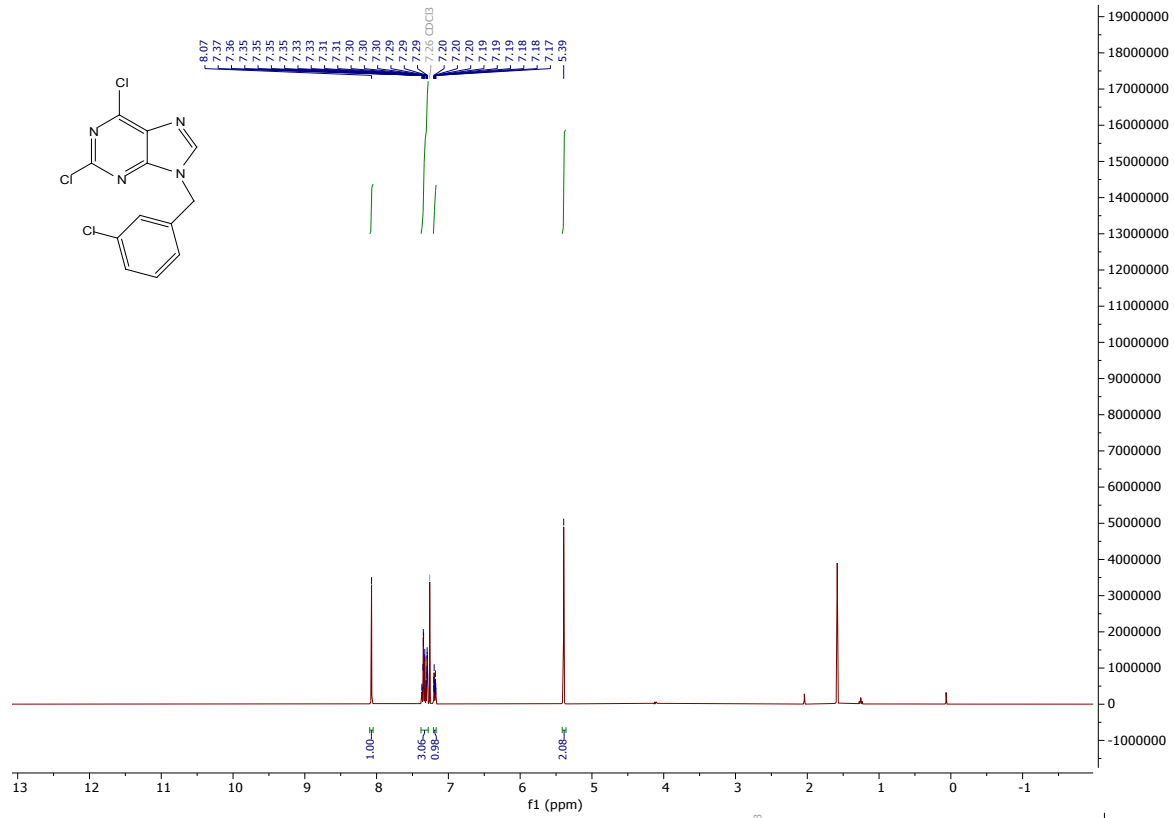
# 9-(3-chlorobenzyl)-2-fluoro-N-methyl-9H-purin-6-amine 36



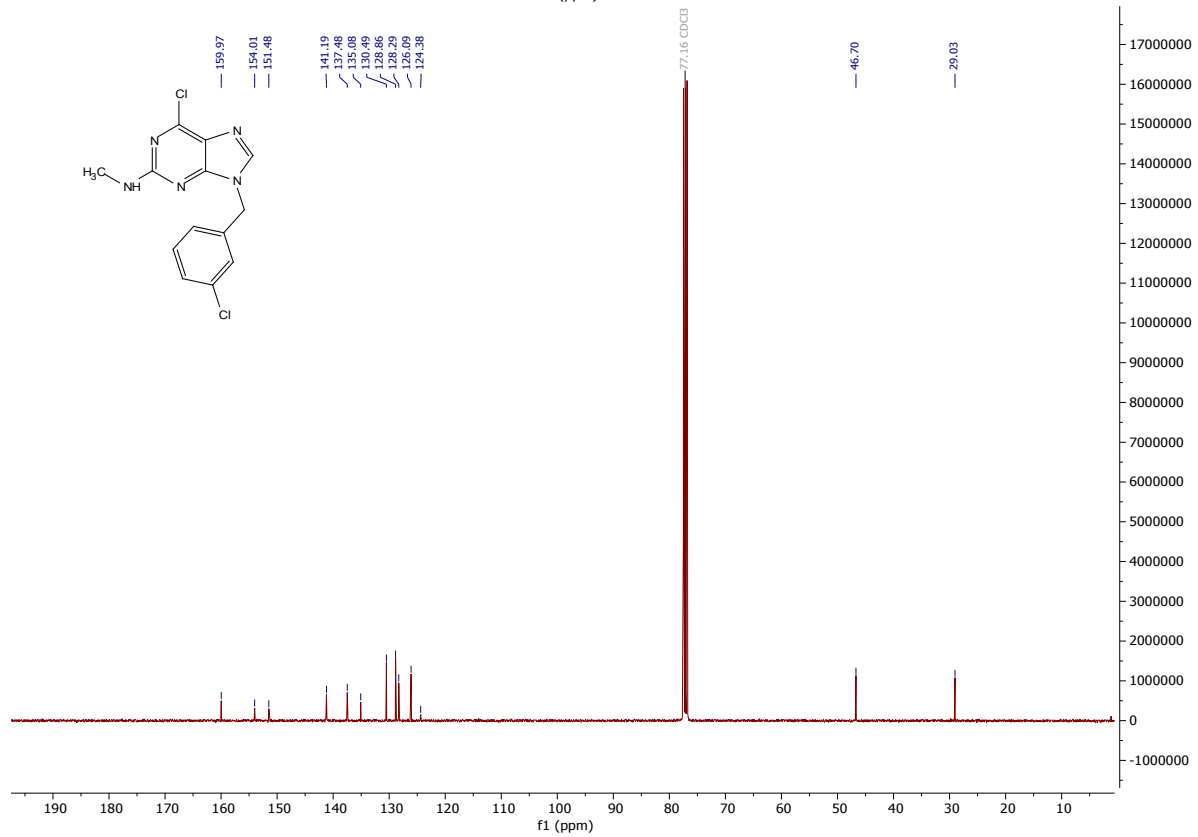
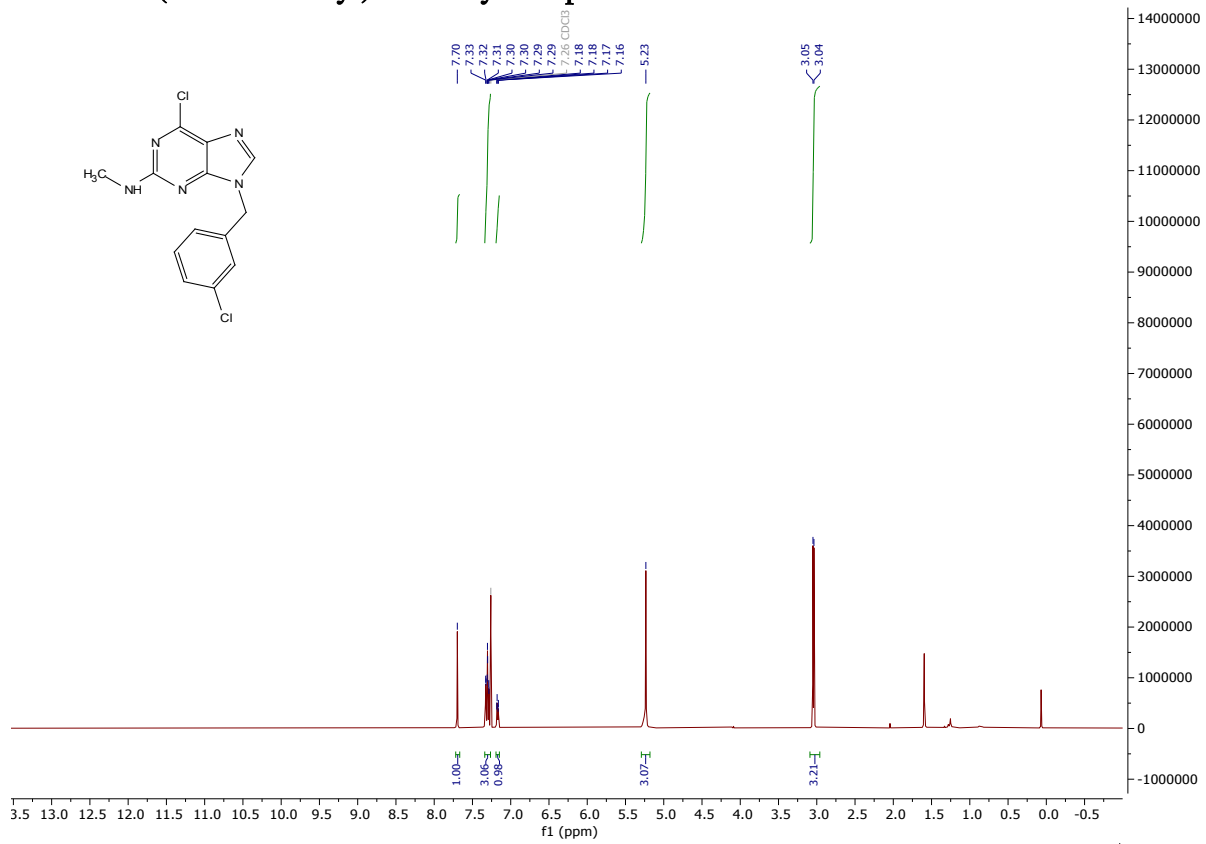
# 2-chloro-9-(3-chlorobenzyl)-N-cyclopropyl-9H-purin-6-amine 37



2,6-dichloro-9-(3-chlorobenzyl)-9H-purine 38

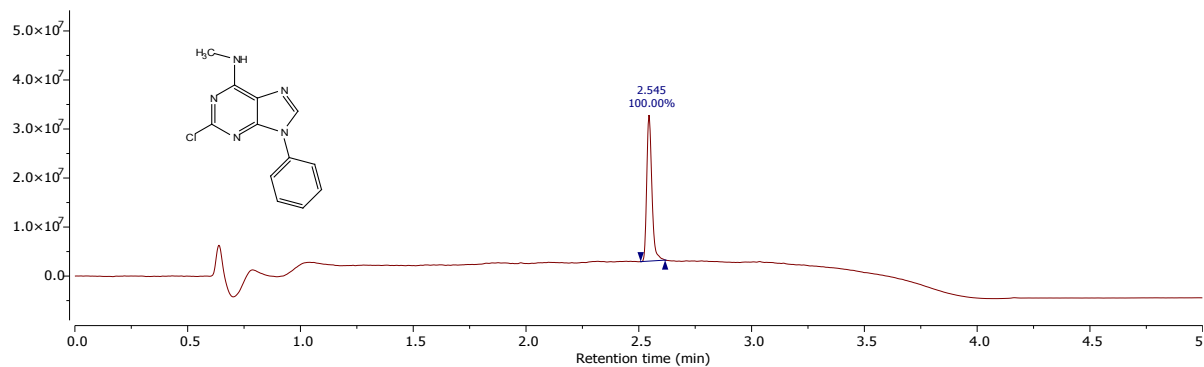


# 6-chloro-9-(3-chlorobenzyl)-N-methyl-9H-purin-2-amine 39

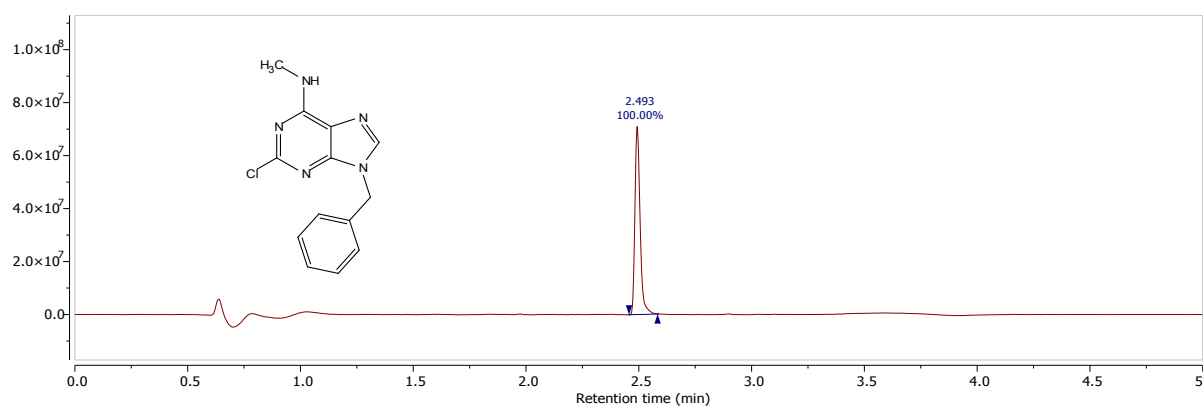


## 9. HPLC traces of final compounds

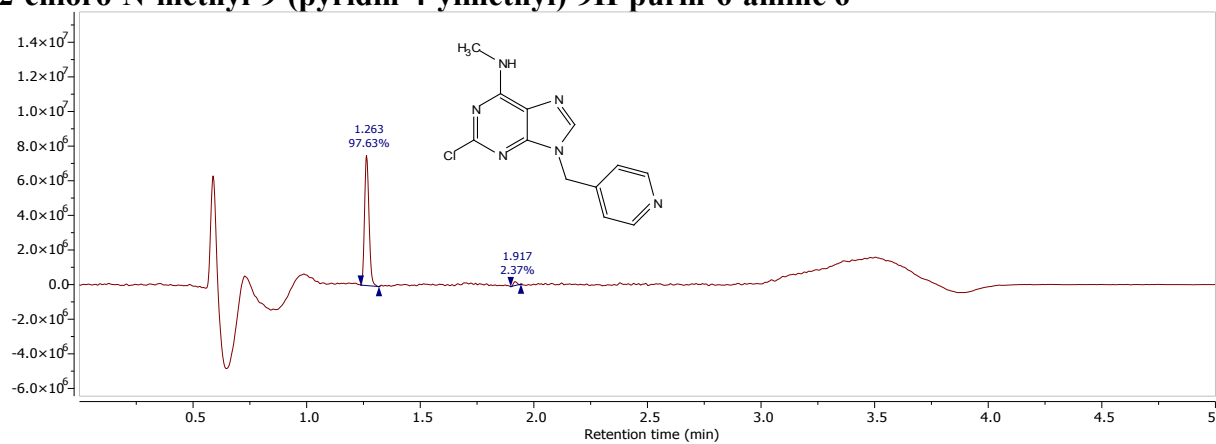
### 2-chloro-N-methyl-9-phenyl-9H-purin-6-amine 4



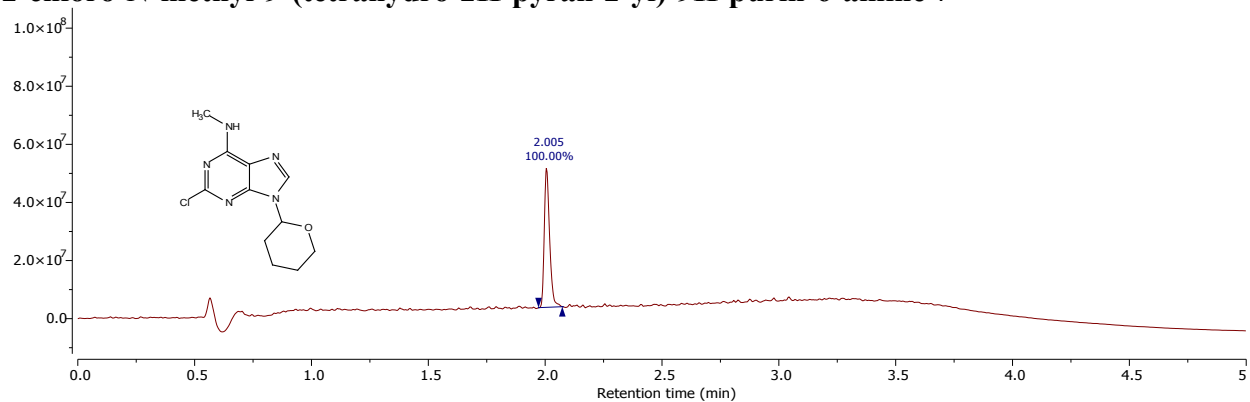
### 9-benzyl-2-chloro-N-methyl-9H-purin-6-amine 5



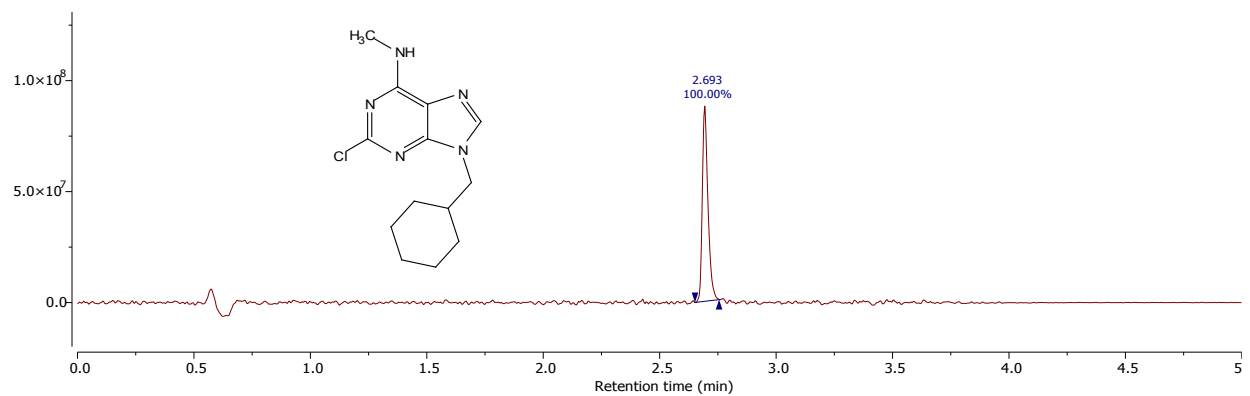
### 2-chloro-N-methyl-9-(pyridin-4-ylmethyl)-9H-purin-6-amine 6



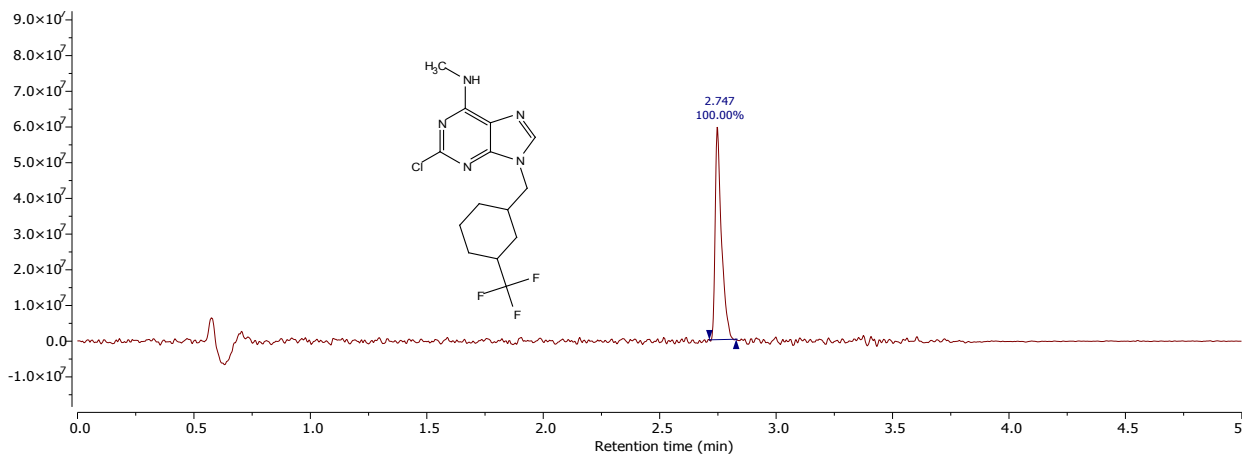
### 2-chloro-N-methyl-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-amine 7



### 2-chloro-9-(cyclohexylmethyl)-N-methyl-9H-purin-6-amine 8

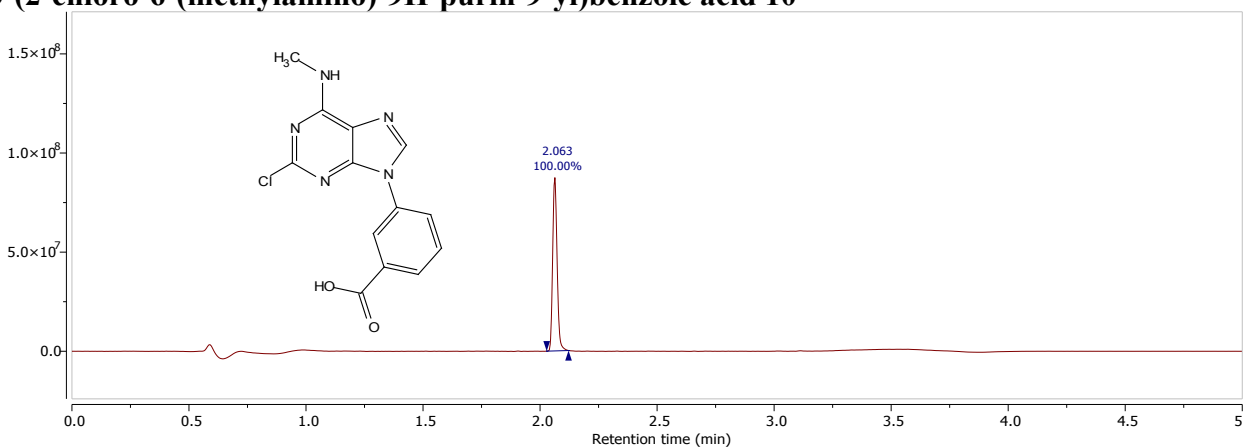


### 2-chloro-N-methyl-9-((3-(trifluoromethyl)cyclohexyl)methyl)-9H-purin-6-amine

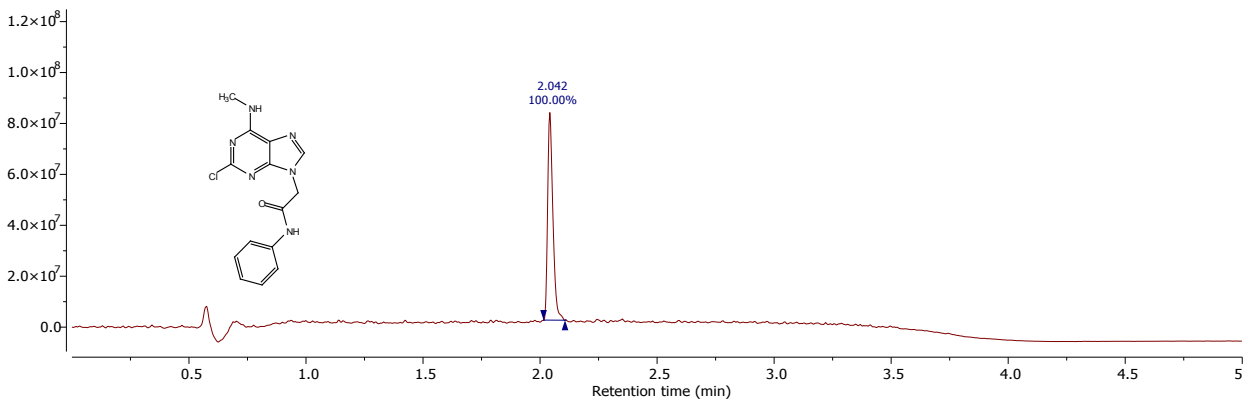




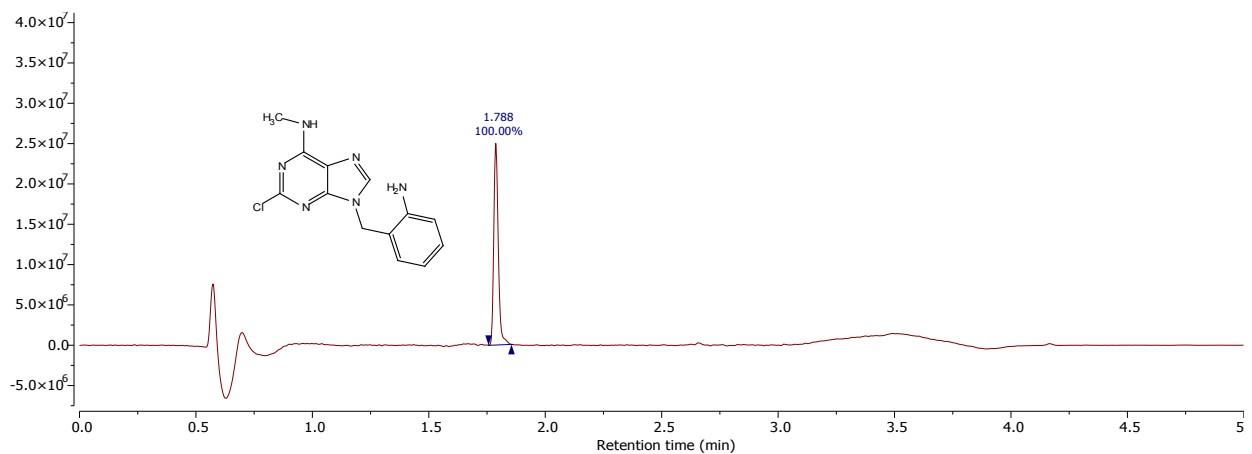
### 3-(2-chloro-6-(methylamino)-9H-purin-9-yl)benzoic acid 10



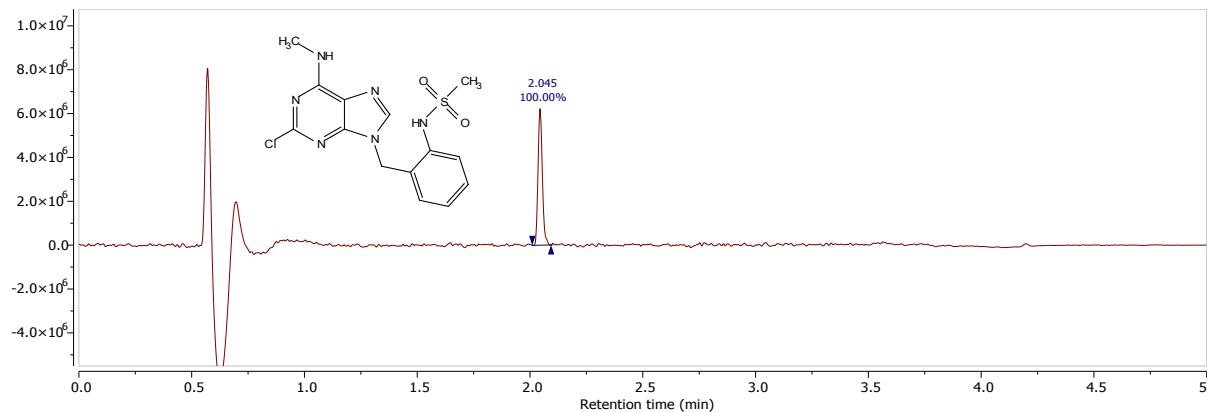
### 2-(2-chloro-6-(methylamino)-9H-purin-9-yl)-N-phenylacetamide 11



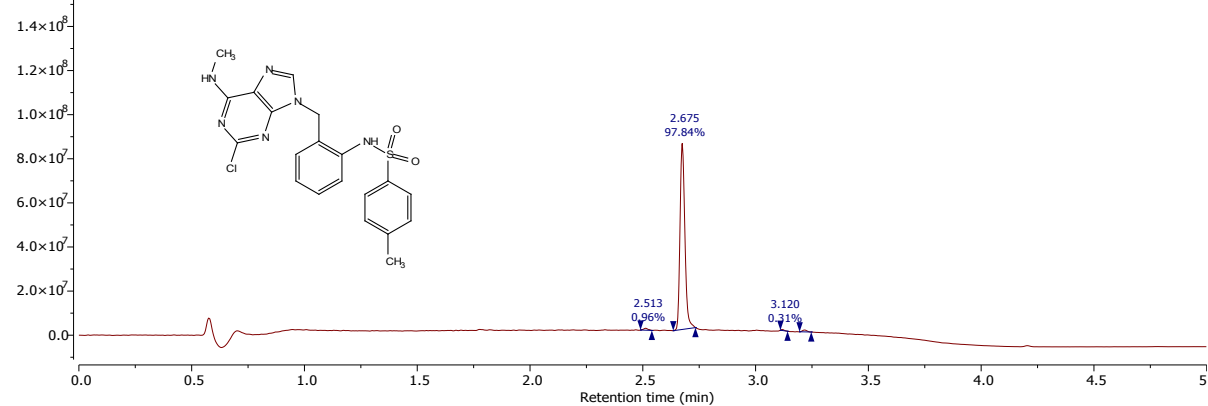
### 9-(2-aminobenzyl)-2-chloro-N-methyl-9H-purin-6-amine 12



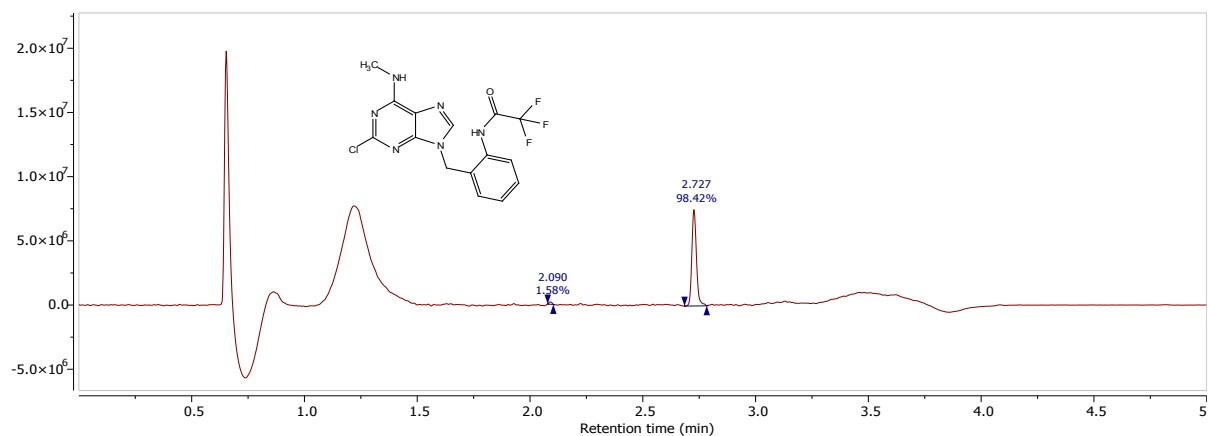
### N-(2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)methanesulfonamide 13



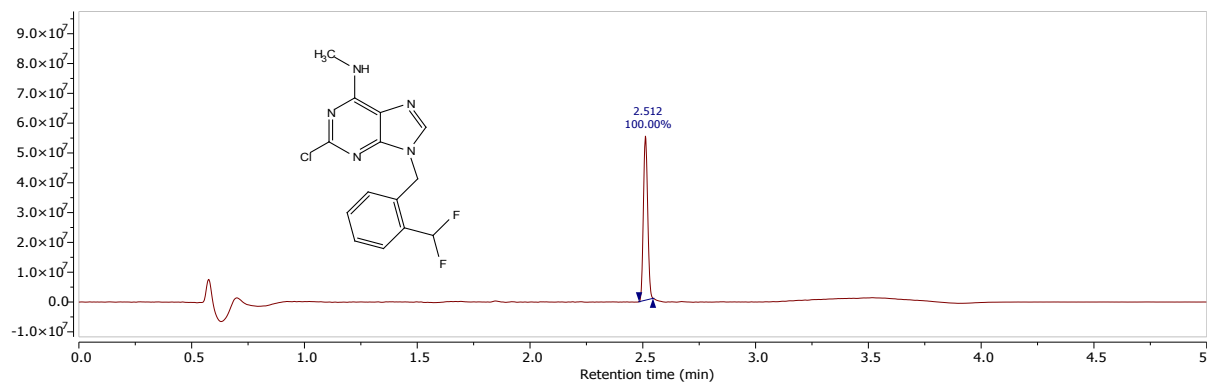
### N-(2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)-4-methylbenzenesulfonamide 14



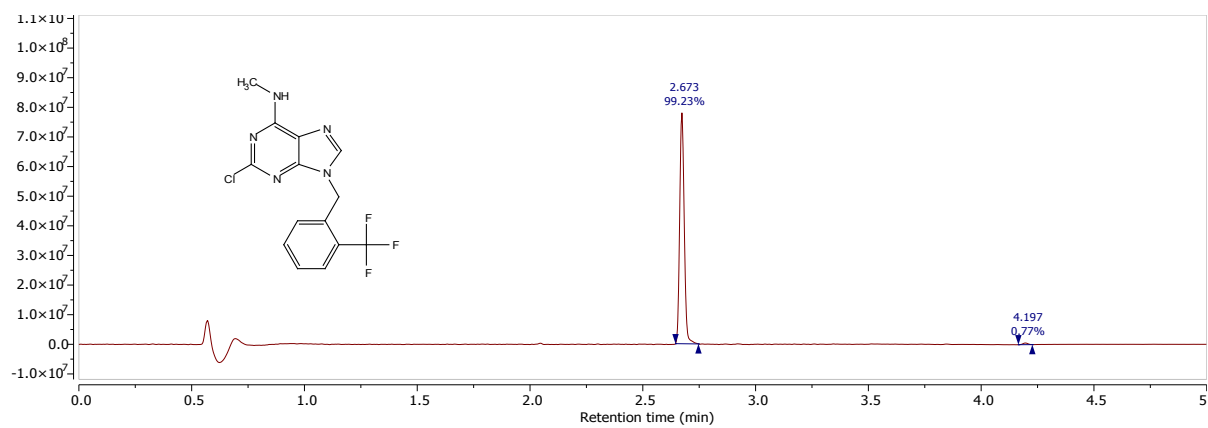
### N-(2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)-2,2,2-trifluoroacetamide 15



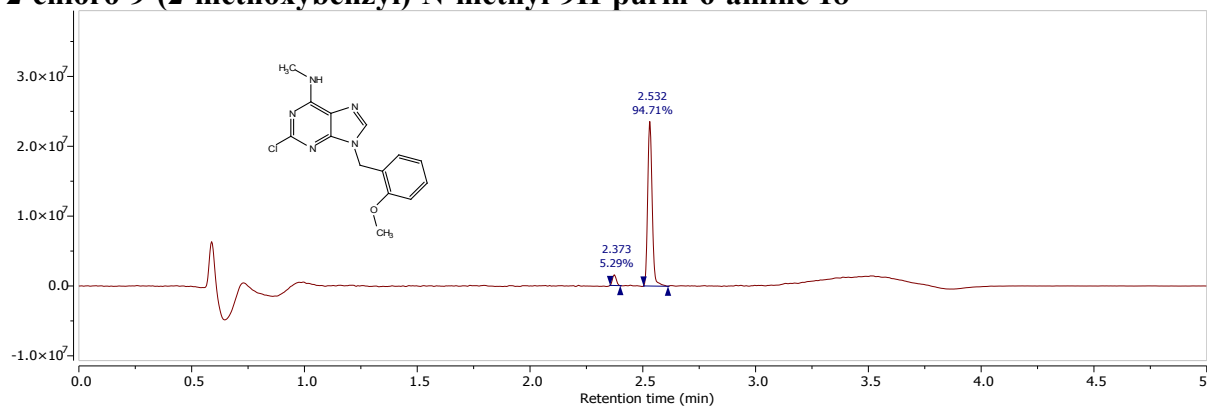
### 2-chloro-9-(2-(difluoromethyl)benzyl)-N-methyl-9H-purin-6-amine 16



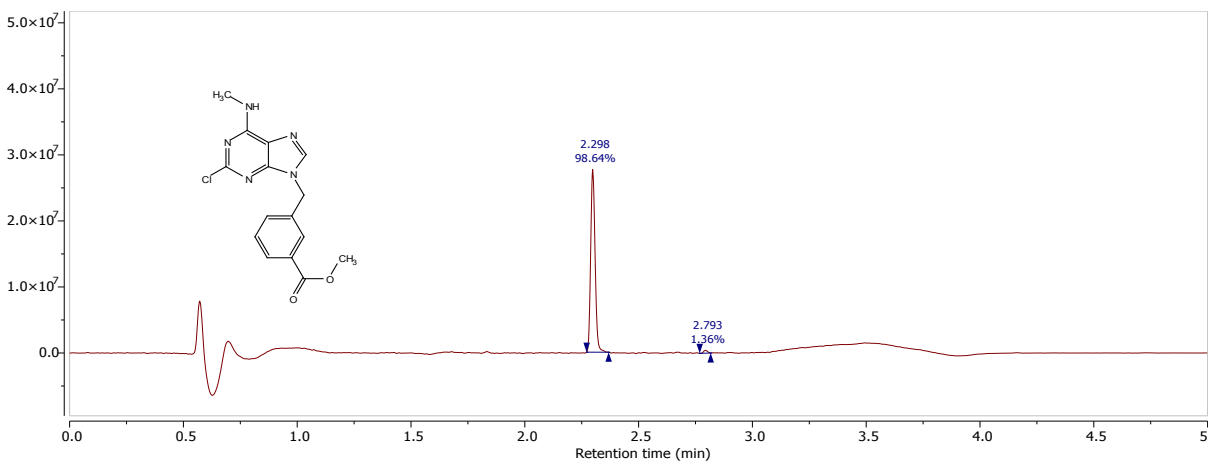
### 2-chloro-N-methyl-9-(2-(trifluoromethyl)benzyl)-9H-purin-6-amine 17



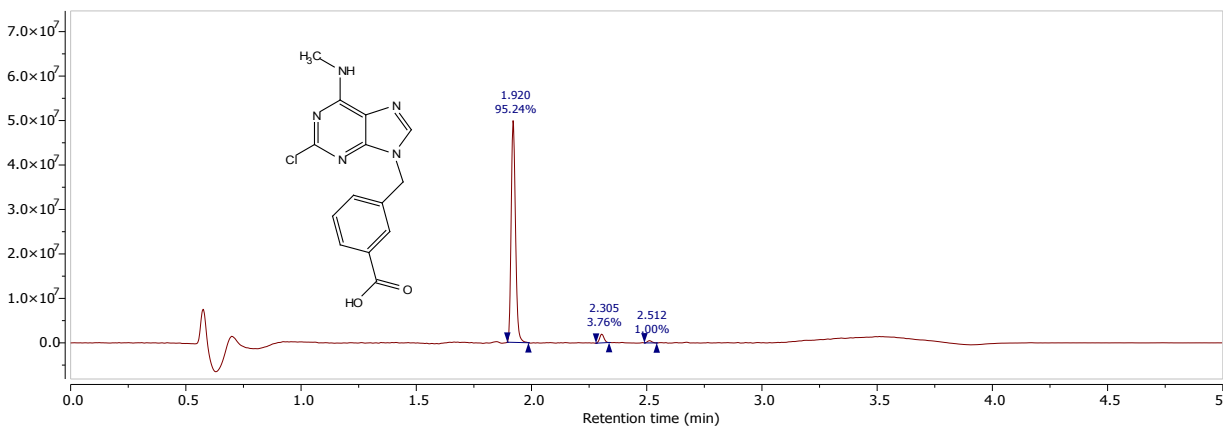
### 2-chloro-9-(2-methoxybenzyl)-N-methyl-9H-purin-6-amine 18



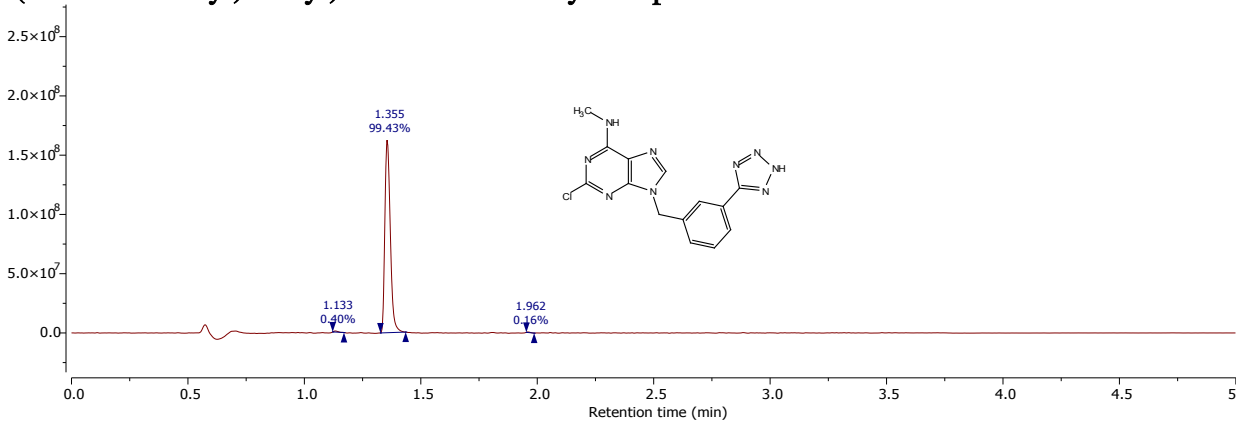
### methyl 3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoate 19



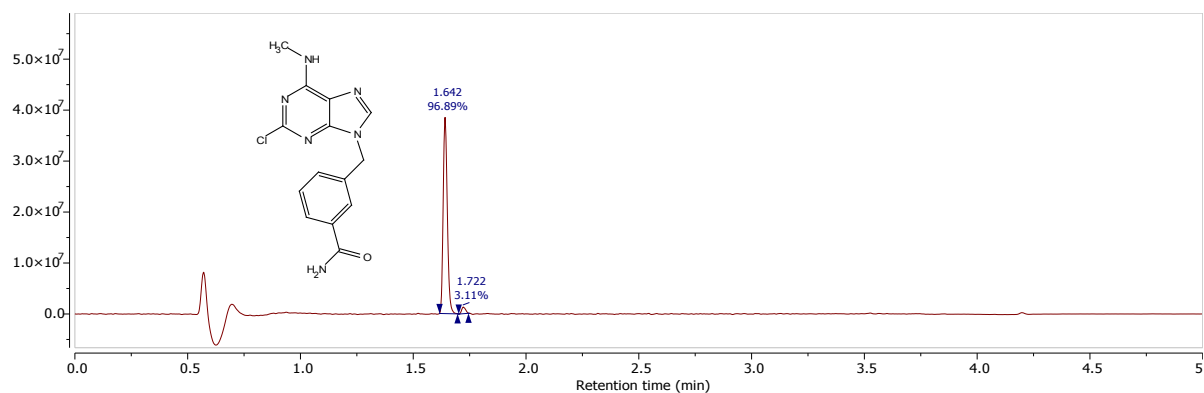
### 3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid 20



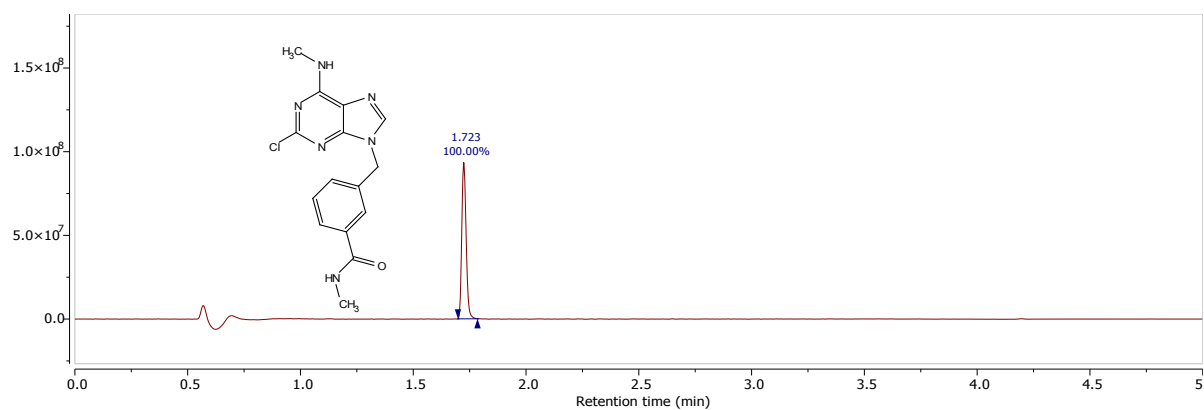
### 3-(2H-tetrazol-5-yl)benzyl)-2-chloro-N-methyl-9H-purin-6-amine 21



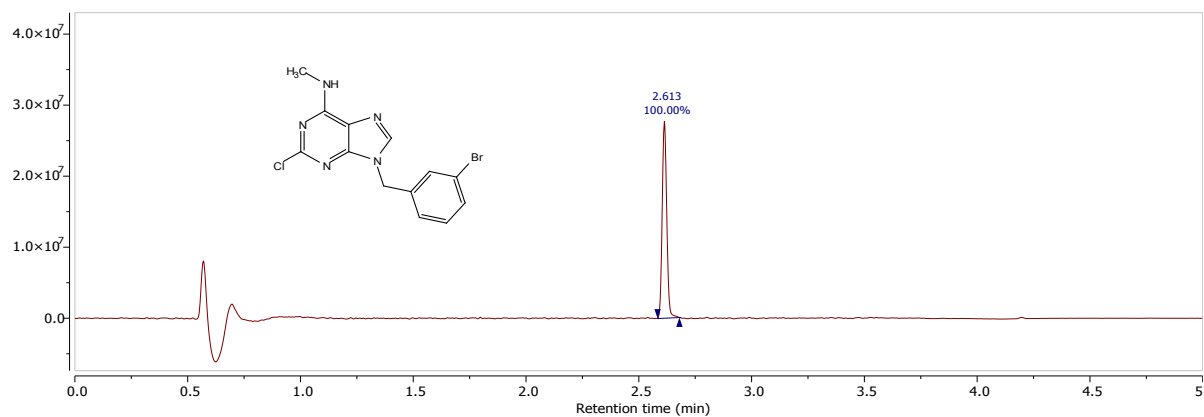
### 3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzamide 22



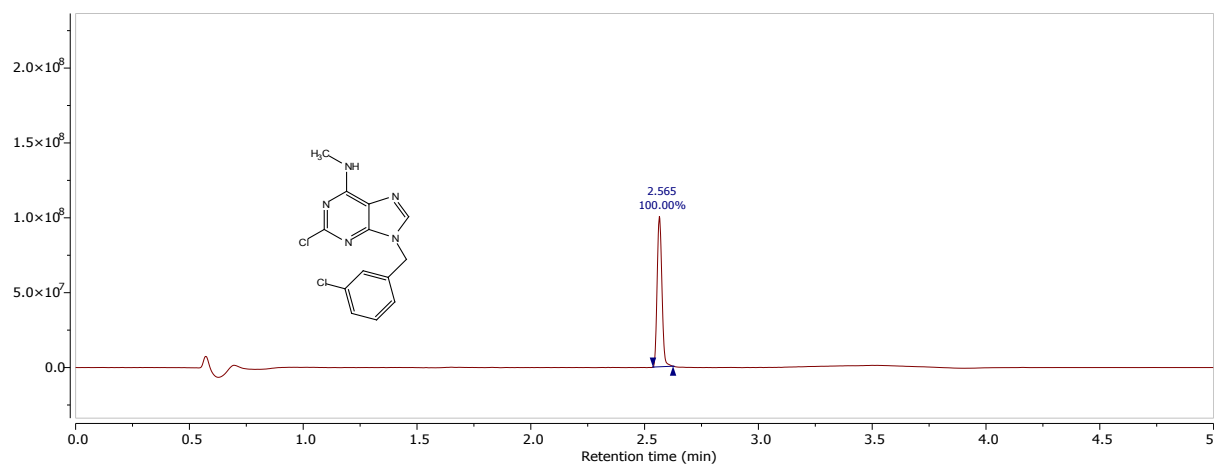
### 3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)-N-methyl benzamide 23



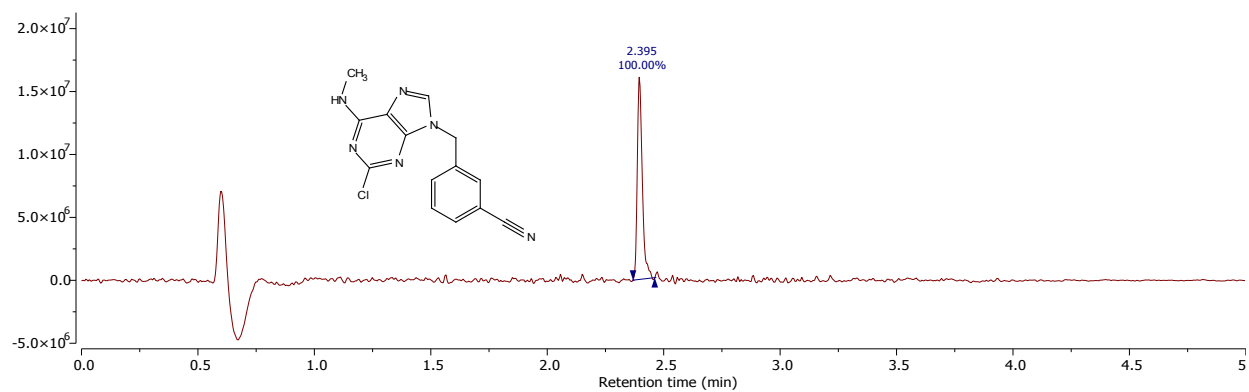
### 9-(3-bromobenzyl)-2-chloro-N-methyl-9H-purin-6-amine 24



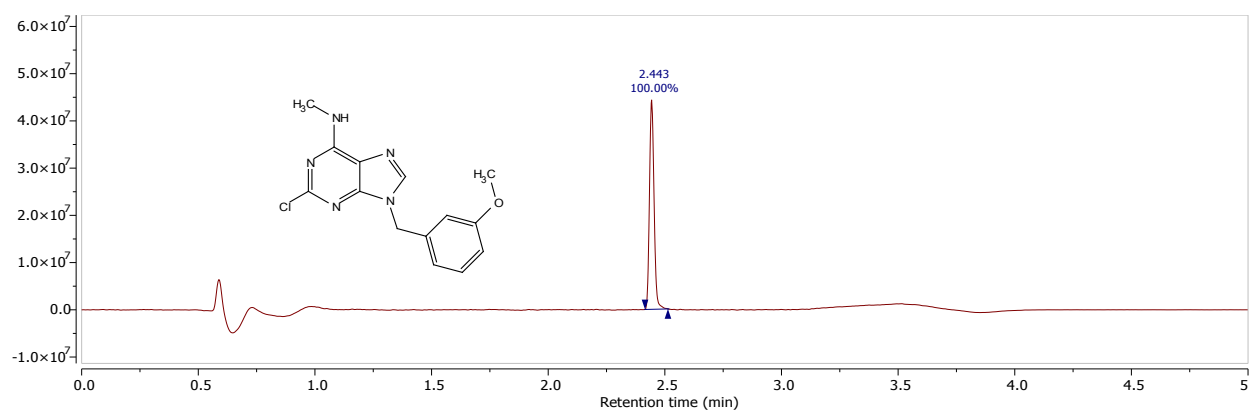
### 2-chloro-9-(3-chlorobenzyl)-N-methyl-9H-purin-6-amine 25



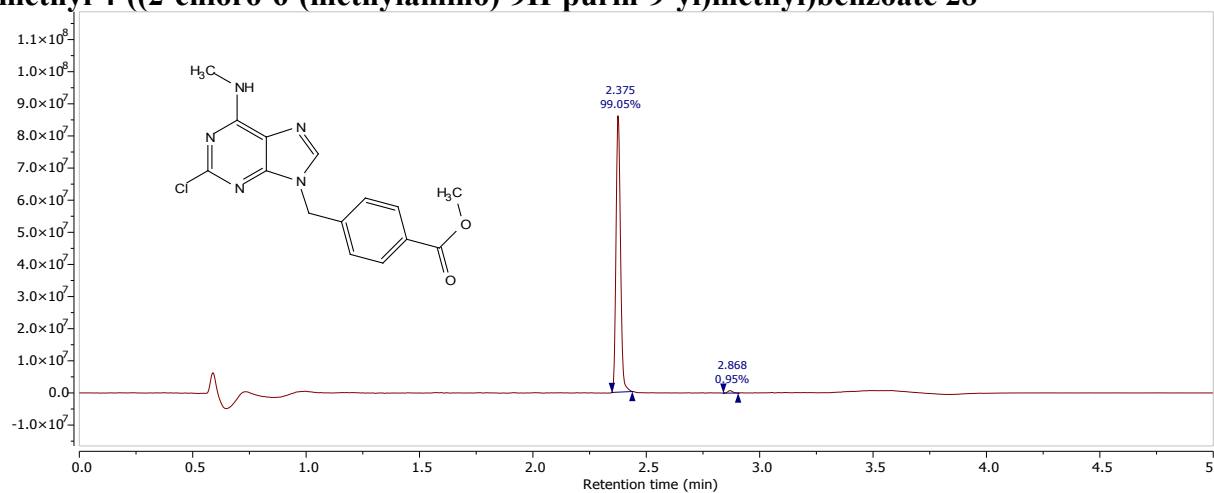
### 3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzonitrile 26



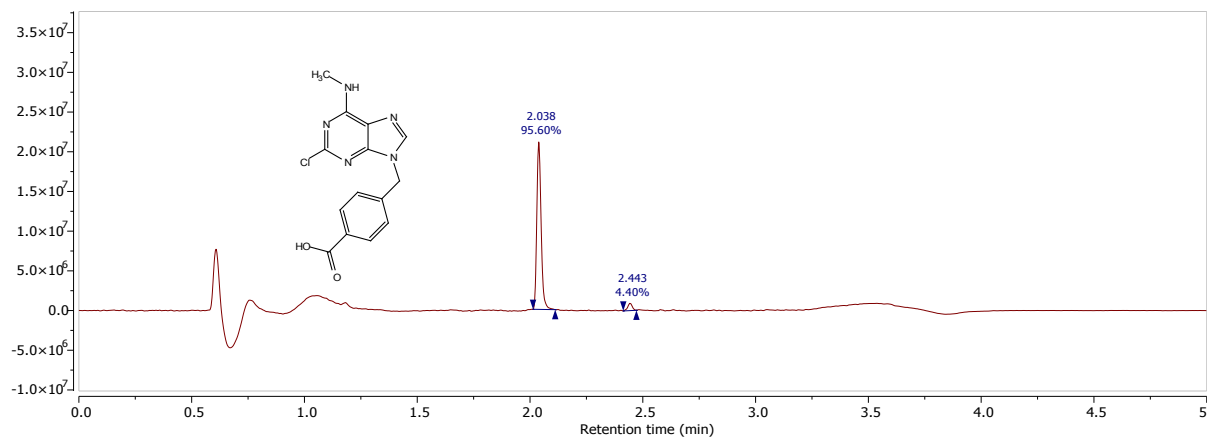
### 2-chloro-9-(3-methoxybenzyl)-N-methyl-9H-purin-6-amine 27



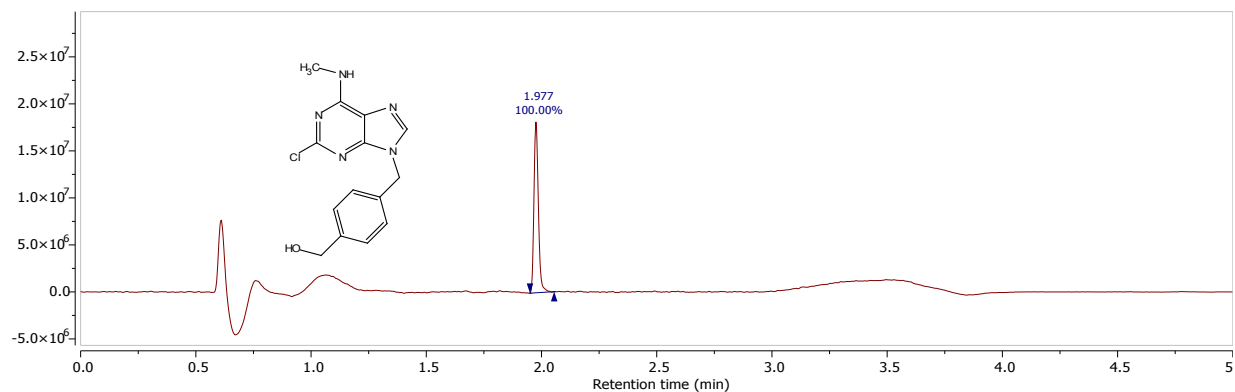
**methyl 4-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoate 28**



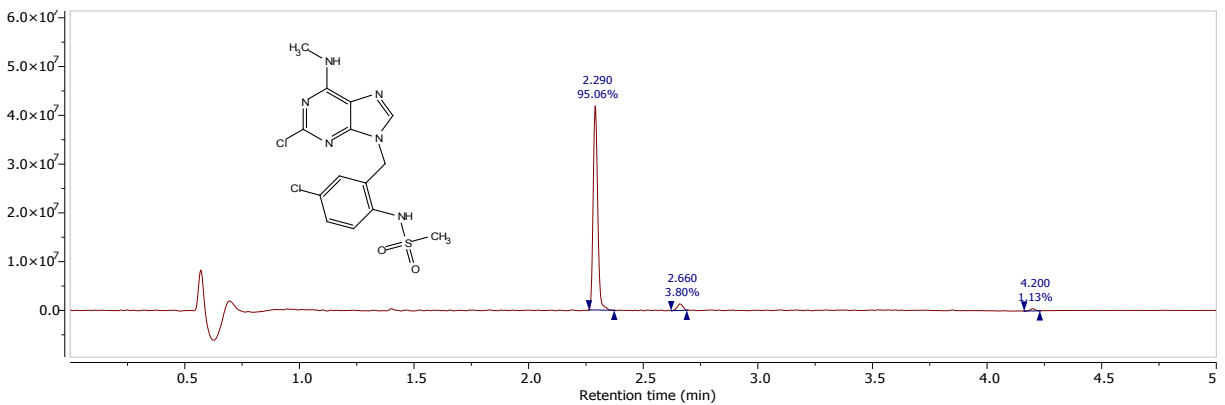
**3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid 29**



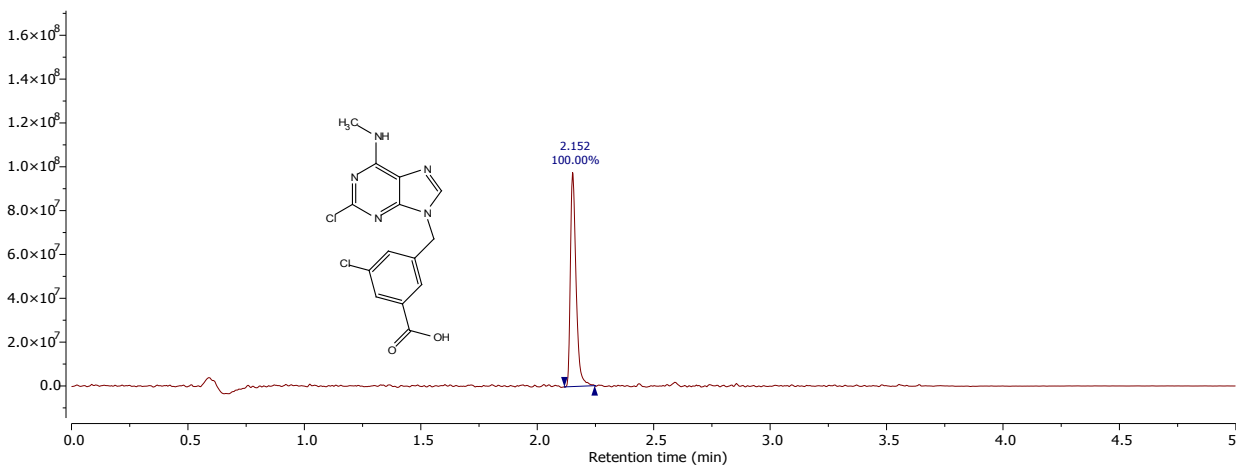
**(4-((2,6-dichloro-9H-purin-9-yl)methyl)phenyl)methanol 30**



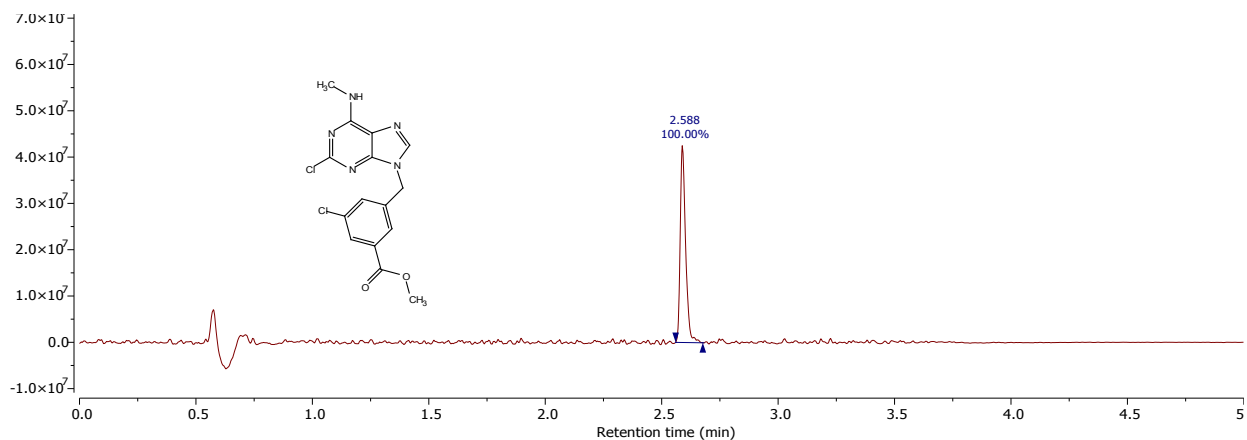
**N-(4-chloro-2-((2-chloro-6-(methylamino)-9H-purin-9-yl) methyl)phenyl) methanesulfonamide 31**



**3-chloro-5-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid 32**

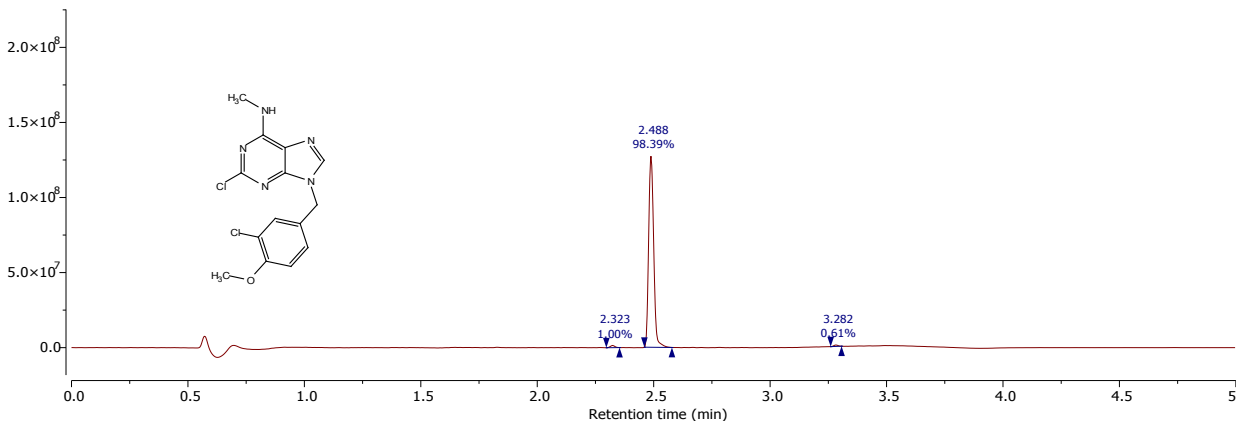


**methyl 3-chloro-5-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoate 33**

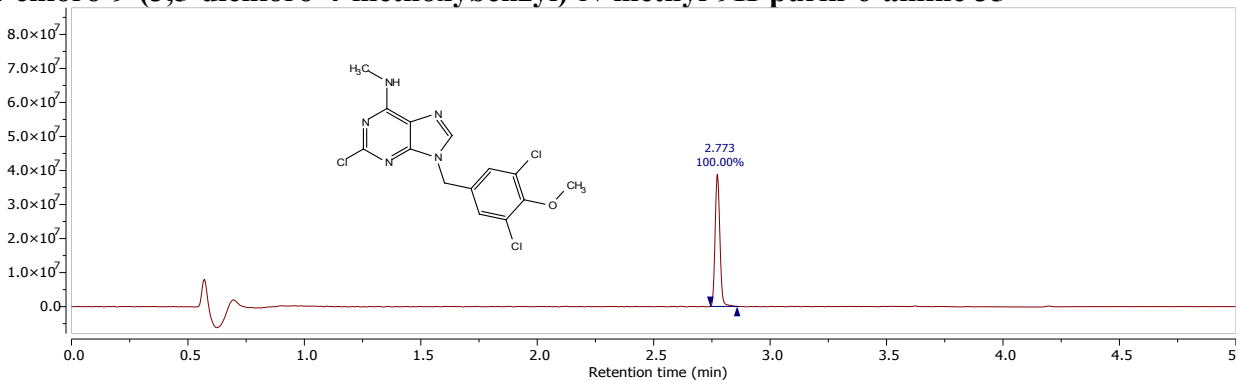




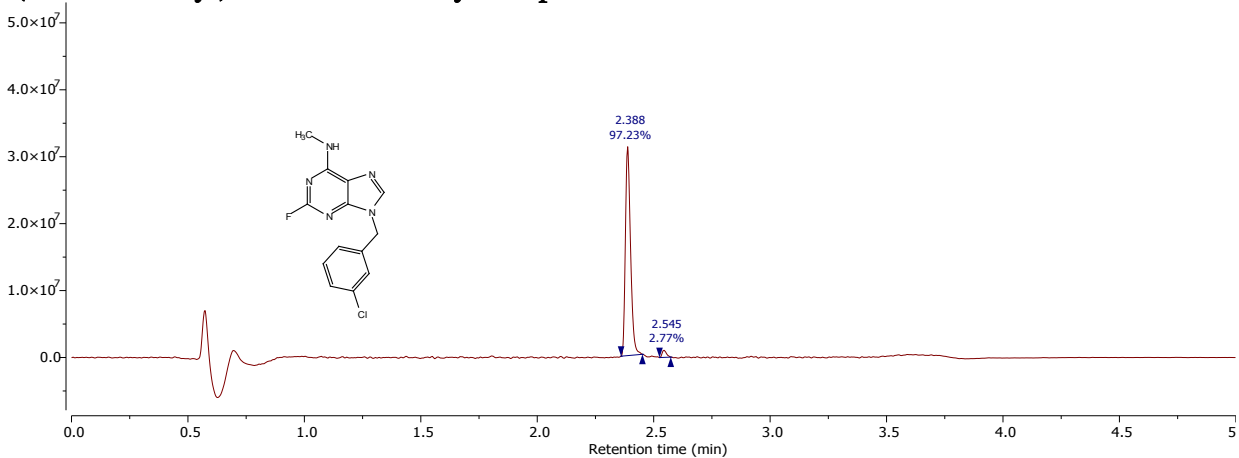
### 2-chloro-9-(3-chloro-4-methoxybenzyl)-N-methyl-9H-purin-6-amine 34



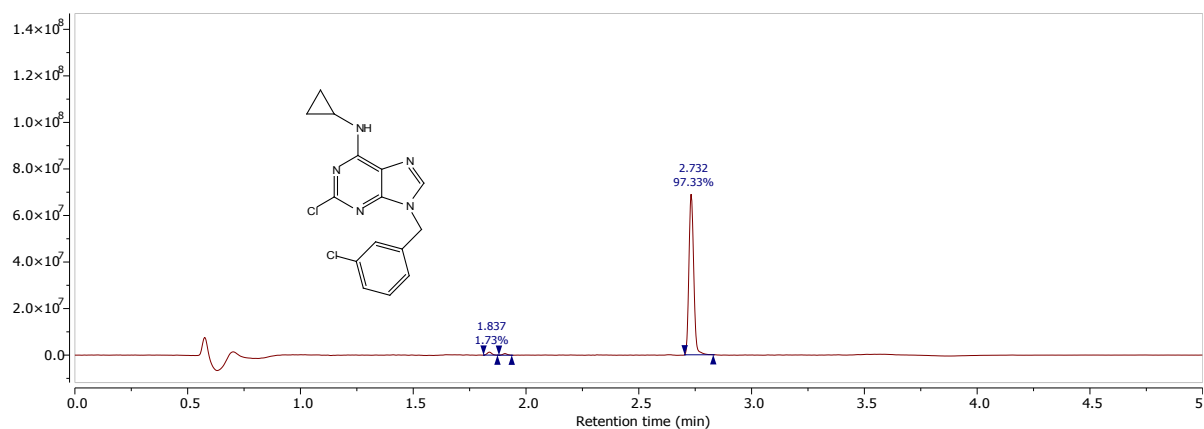
### 2-chloro-9-(3,5-dichloro-4-methoxybenzyl)-N-methyl-9H-purin-6-amine 35



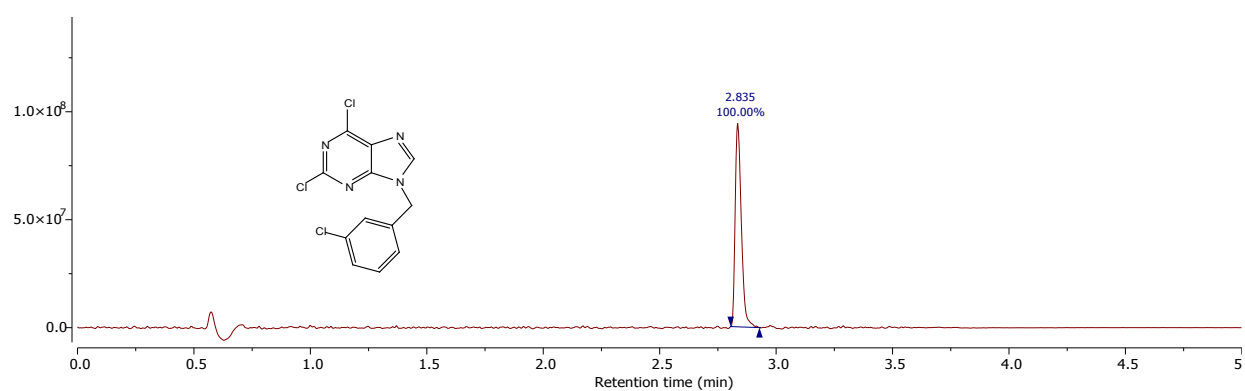
### 9-(3-chlorobenzyl)-2-fluoro-N-methyl-9H-purin-6-amine 36



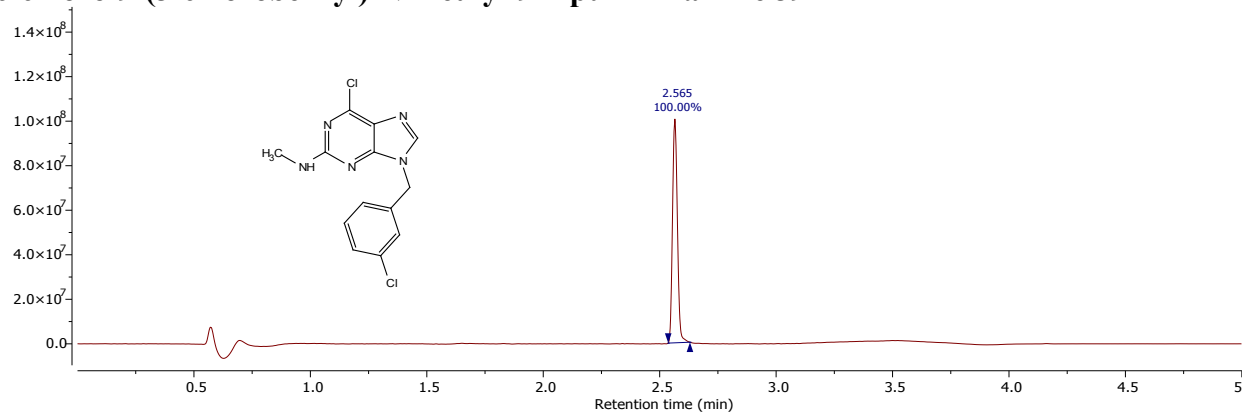
### 2-chloro-9-(3-chlorobenzyl)-N-cyclopropyl-9H-purin-6-amine 37



### 2,6-dichloro-9-(3-chlorobenzyl)-9H-purine 38



### 6-chloro-9-(3-chlorobenzyl)-N-methyl-9H-purin-2-amine 39



**5-chloro-3-(3-chlorobenzyl)-N-methyl-2H-pyrazolo[4,3-d]pyrimidin-7-amine 40**

