

Supporting information

Structure-based design of a potent and selective YTHDC1 ligand

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*Bochenkova, Francesco Errani, Amedeo Caflisch**

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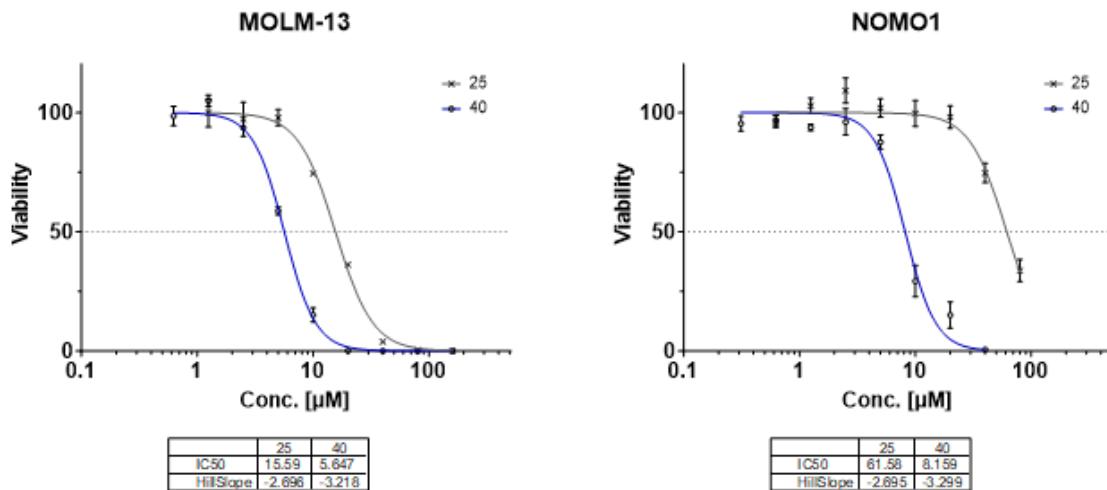
Winterthurerstrasse 190, CH-8057 Zurich, Switzerland

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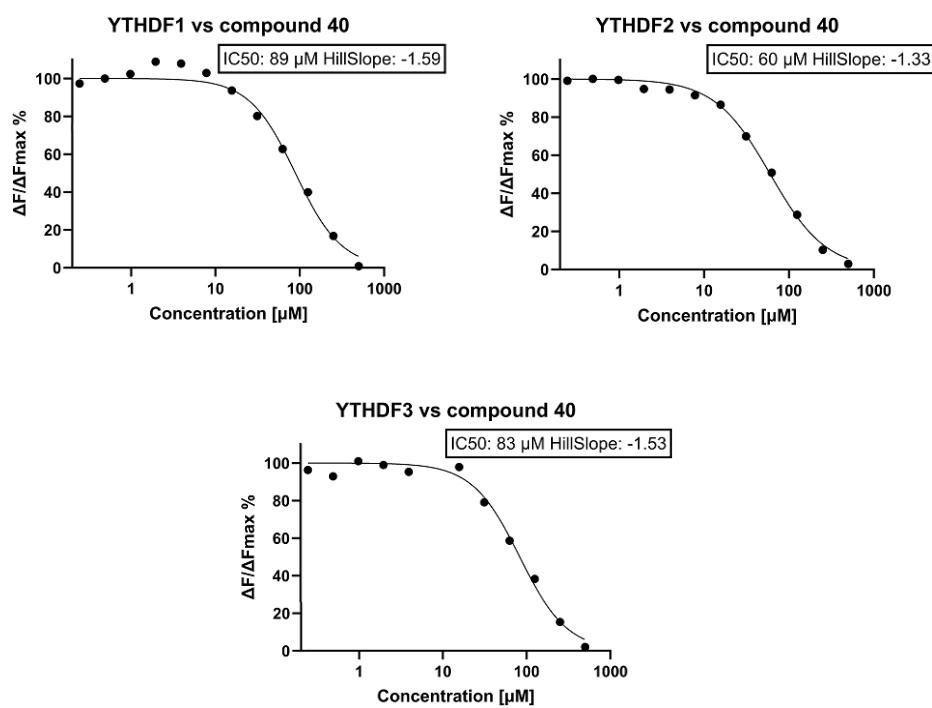
caflisch@bioc.uzh.ch

- 1. Figure S1:** Dose-response curve for the antiproliferative effect of compound **40** against MOLM-13 and NOMO1 cell line.
- 2. Figure S2:** HTRF dose-response curves of compound **40** against YTHDF1, YTHDF2, and YTHDF3, respectively.
- 3. Figure S3:** Dose-response thermal shift of YTHDF1, YTHDF2, YTHDF3, and YTHDC2 in presence of compound **40**.
- 4. GST-YTHDC1 HTRF dose-response curves**
- 5. NMR traces of final compounds**
- 6. HPLC traces of final compounds**

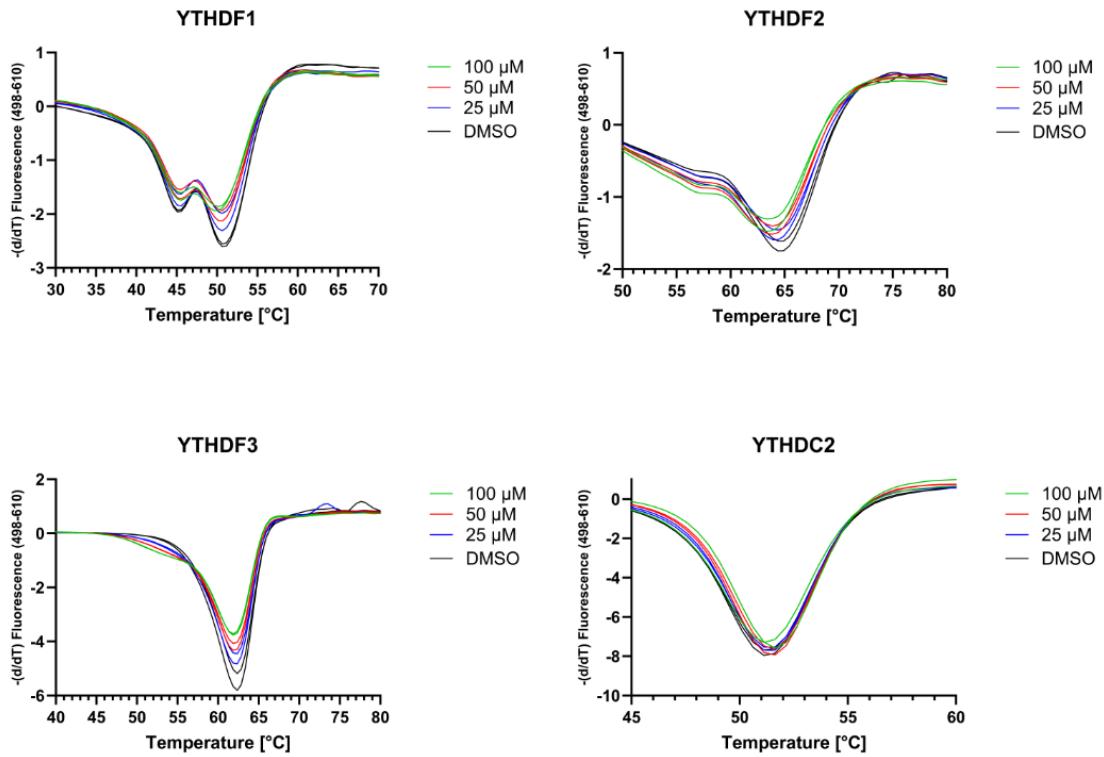
1. Figure S1: Dose-response curve for the antiproliferative effect of compound **40** against MOLM-13 and NOMO1 cell lines.



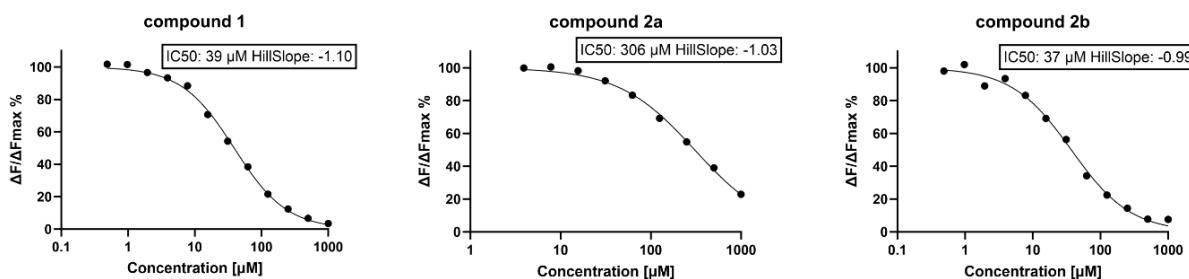
2. Figure S2: HTRF dose-response curves of compound **40** against YTHDF1, YTHDF2, and YTHDF3, respectively.

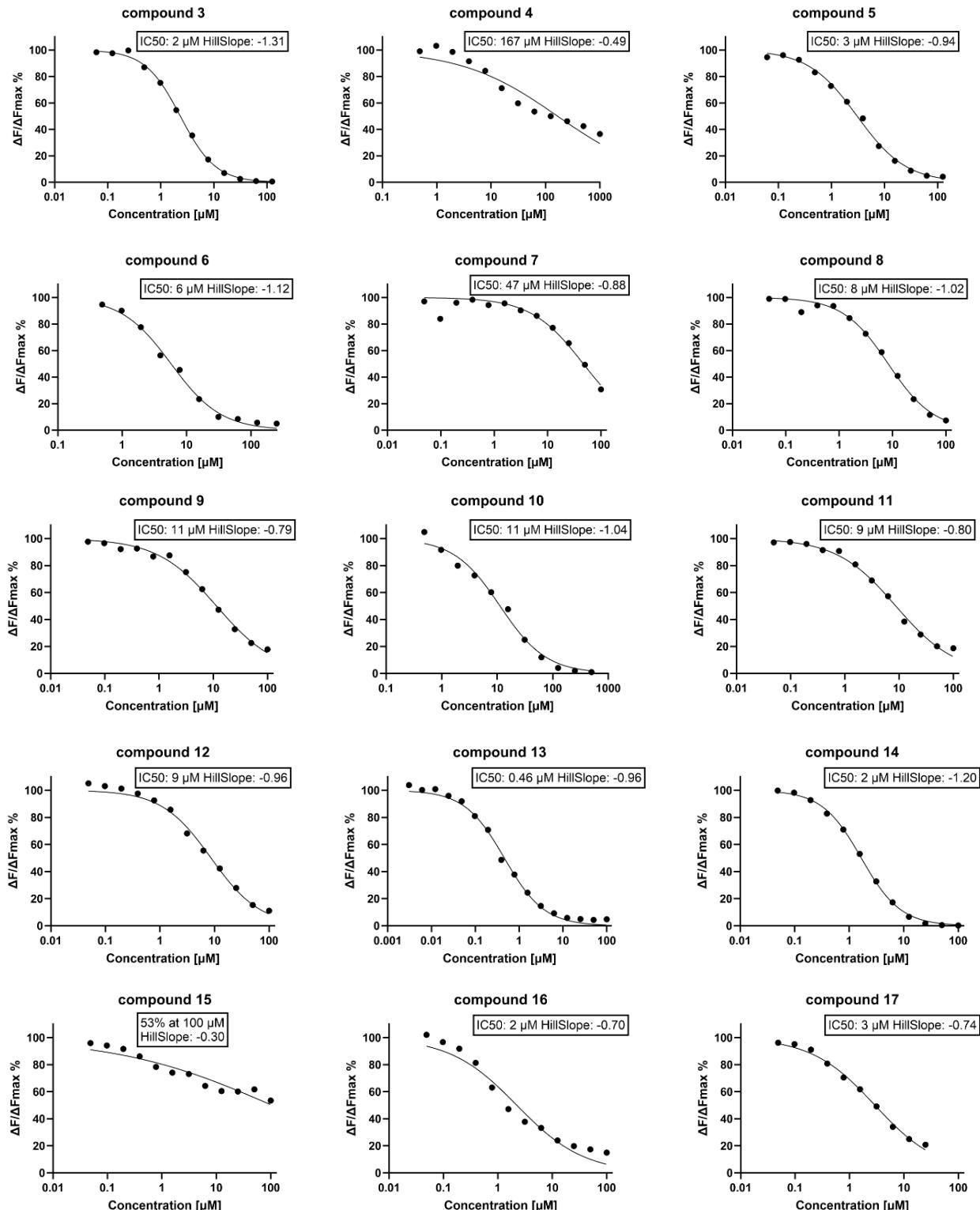


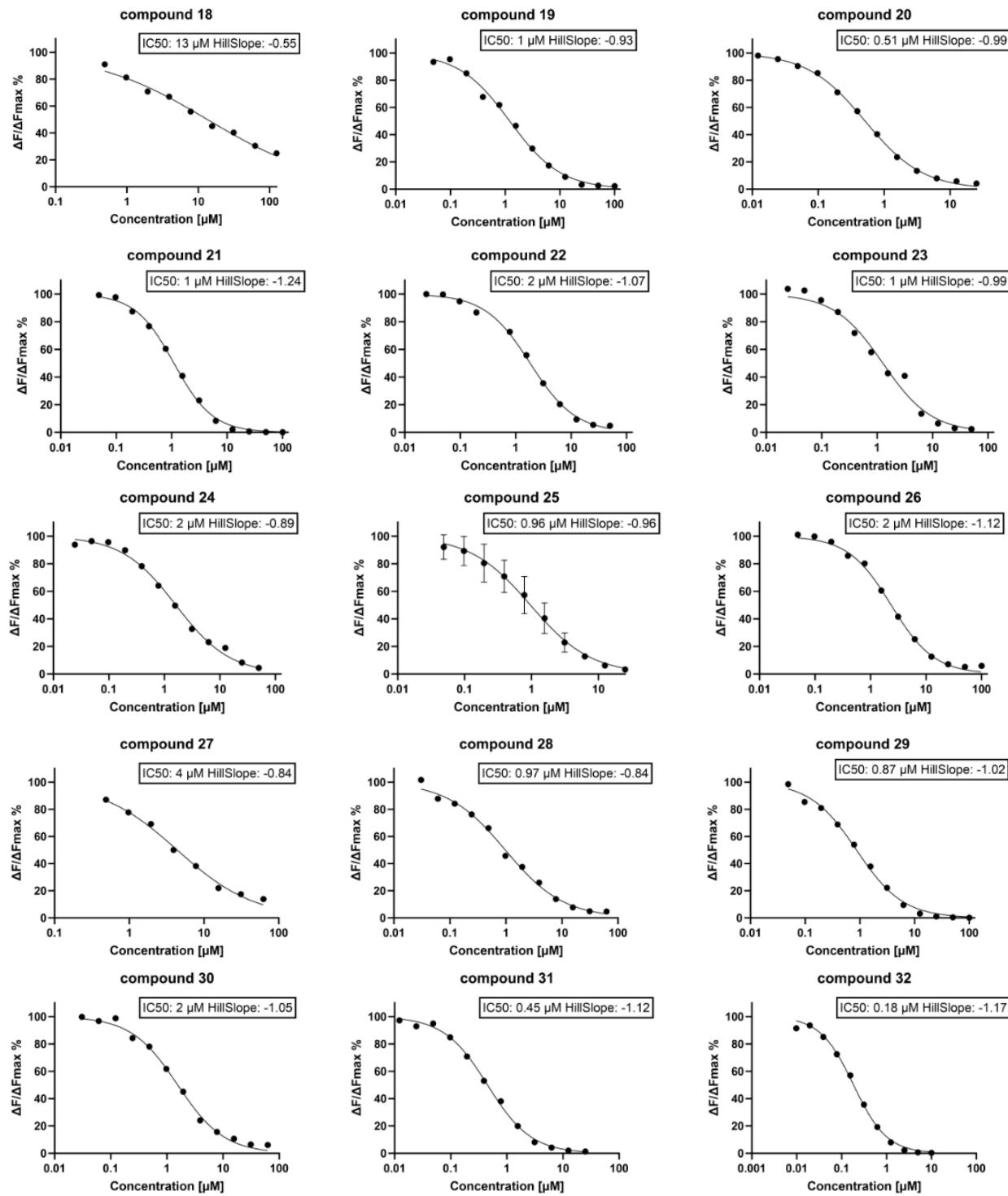
3. Figure S3: Dose-response thermal shift of YTHDF1, YTHDF2, YTHDF3, and YTHDC2 in presence of compound **40**.

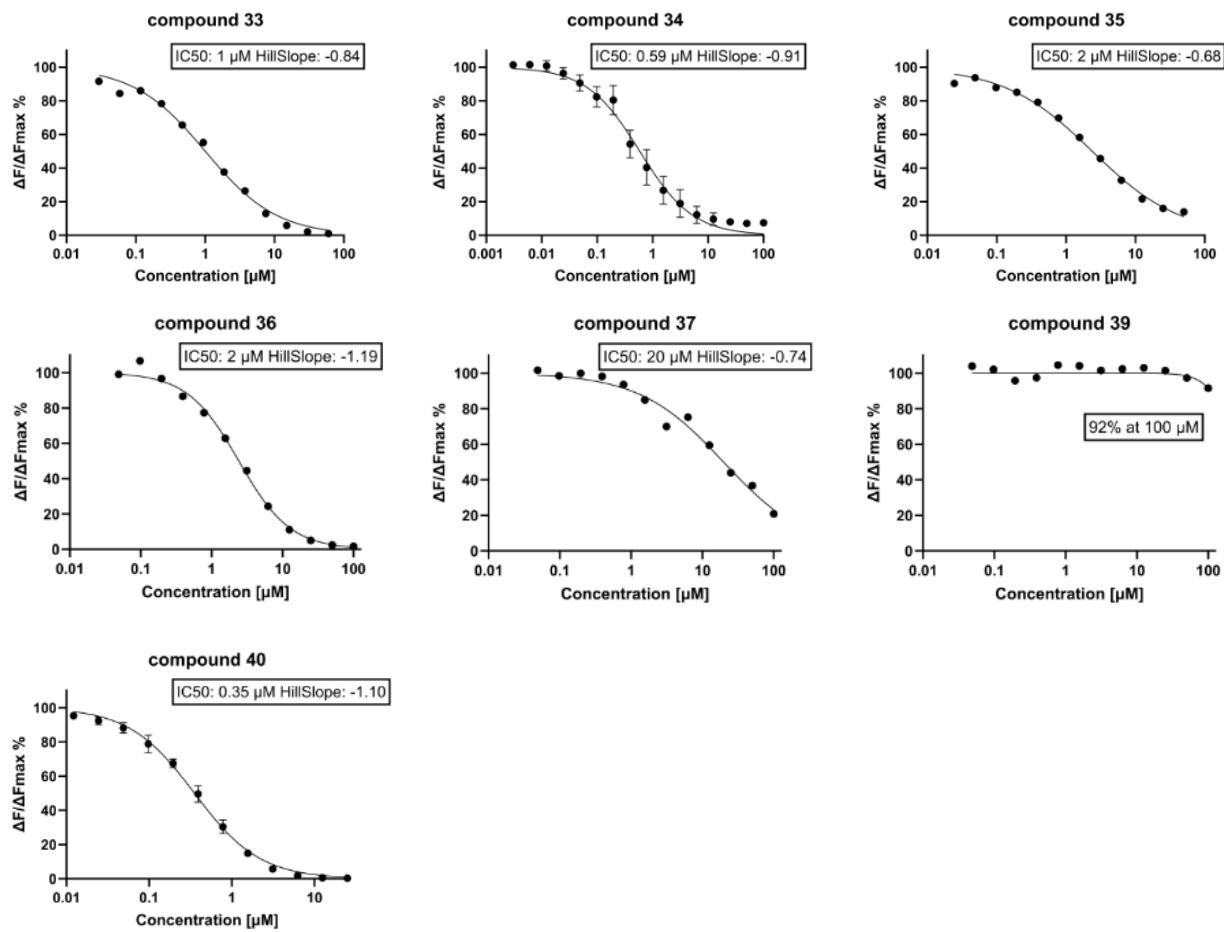


4. GST-YTHDC1 HTRF dose-response curves. With the exceptions of compounds **2b**, **4**, **7**, **8**, **9**, **15**, **24**, **29**, **33**, and **39** the curves come from the average of two or more biological replicates, and each biological replicate is the average of two technical replicates. The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



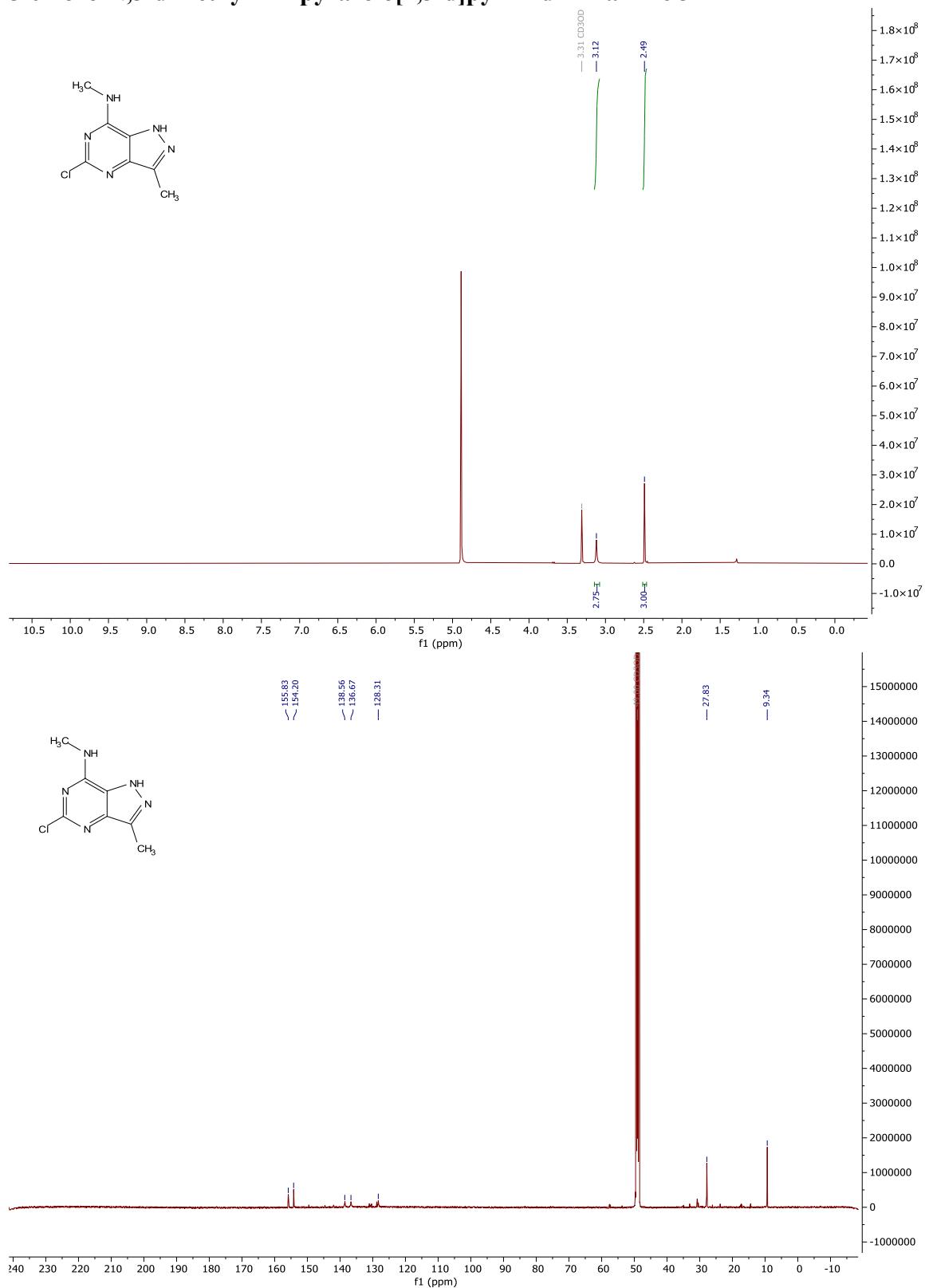




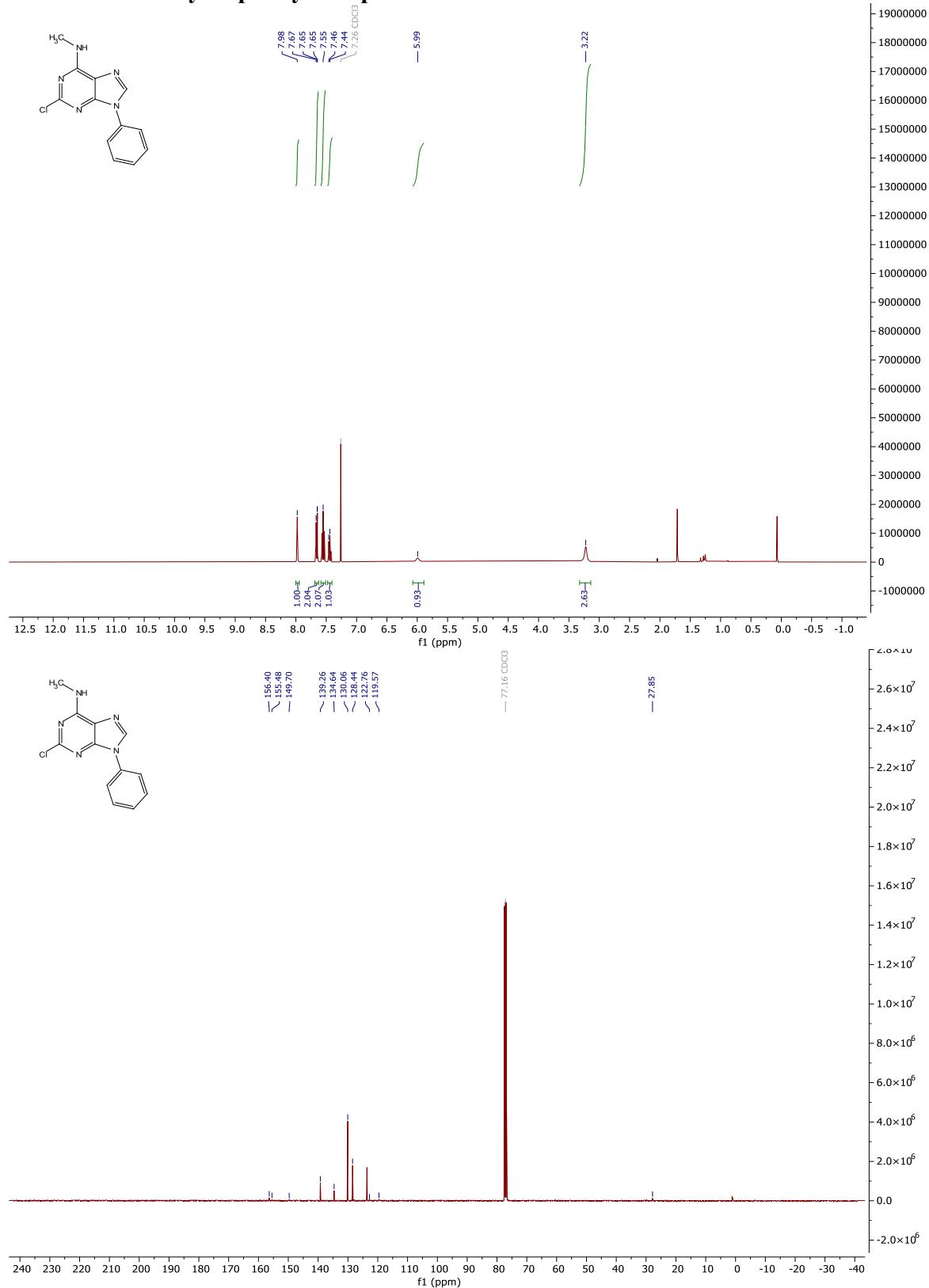


5. NMR traces of final compounds

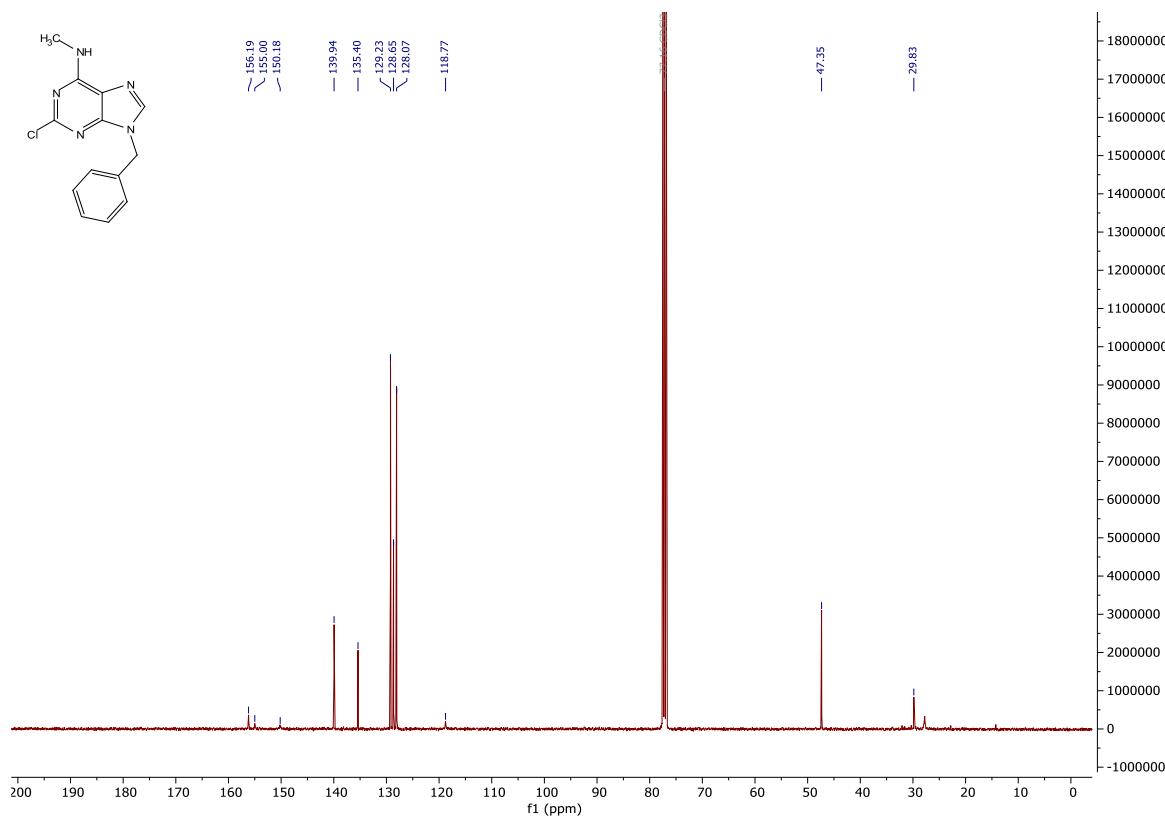
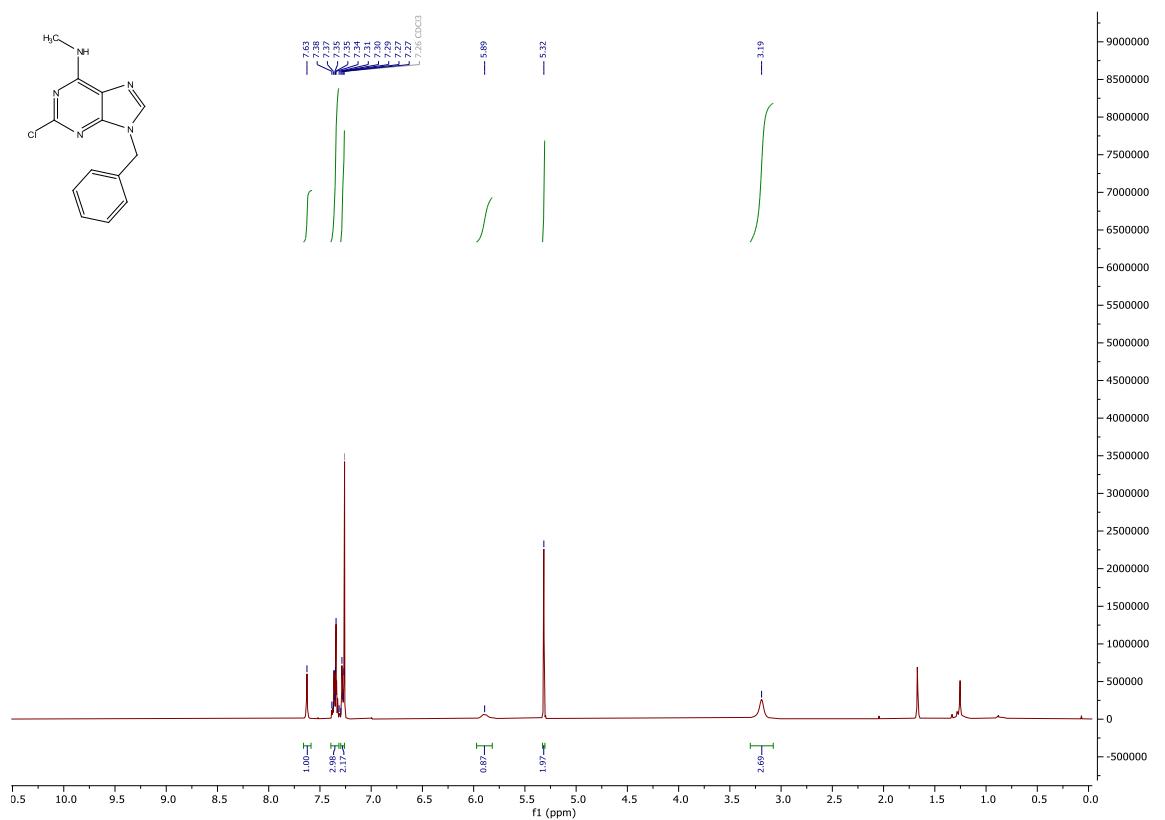
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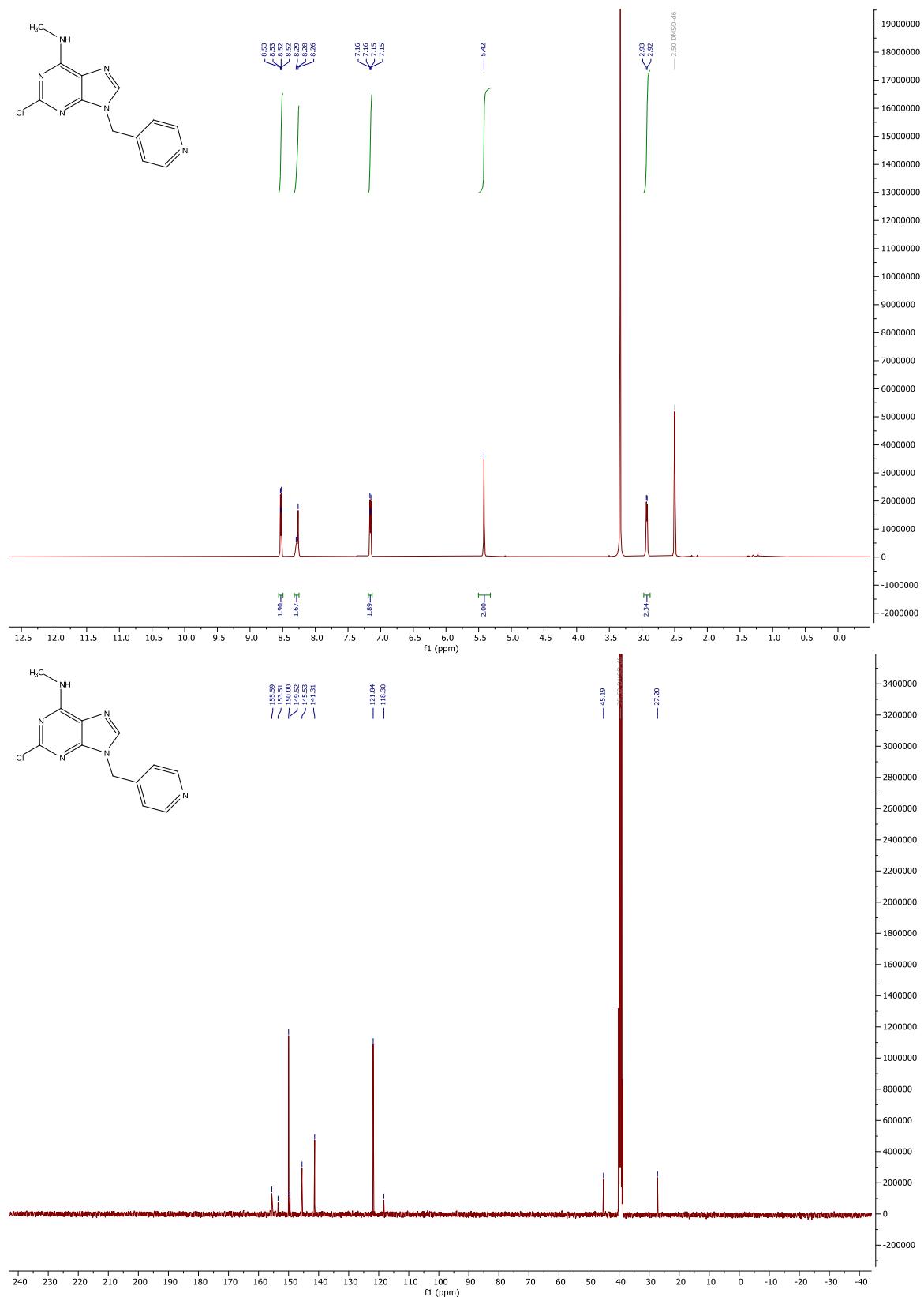
2-chloro-N-methyl-9-phenyl-9H-purin-6-amine 4



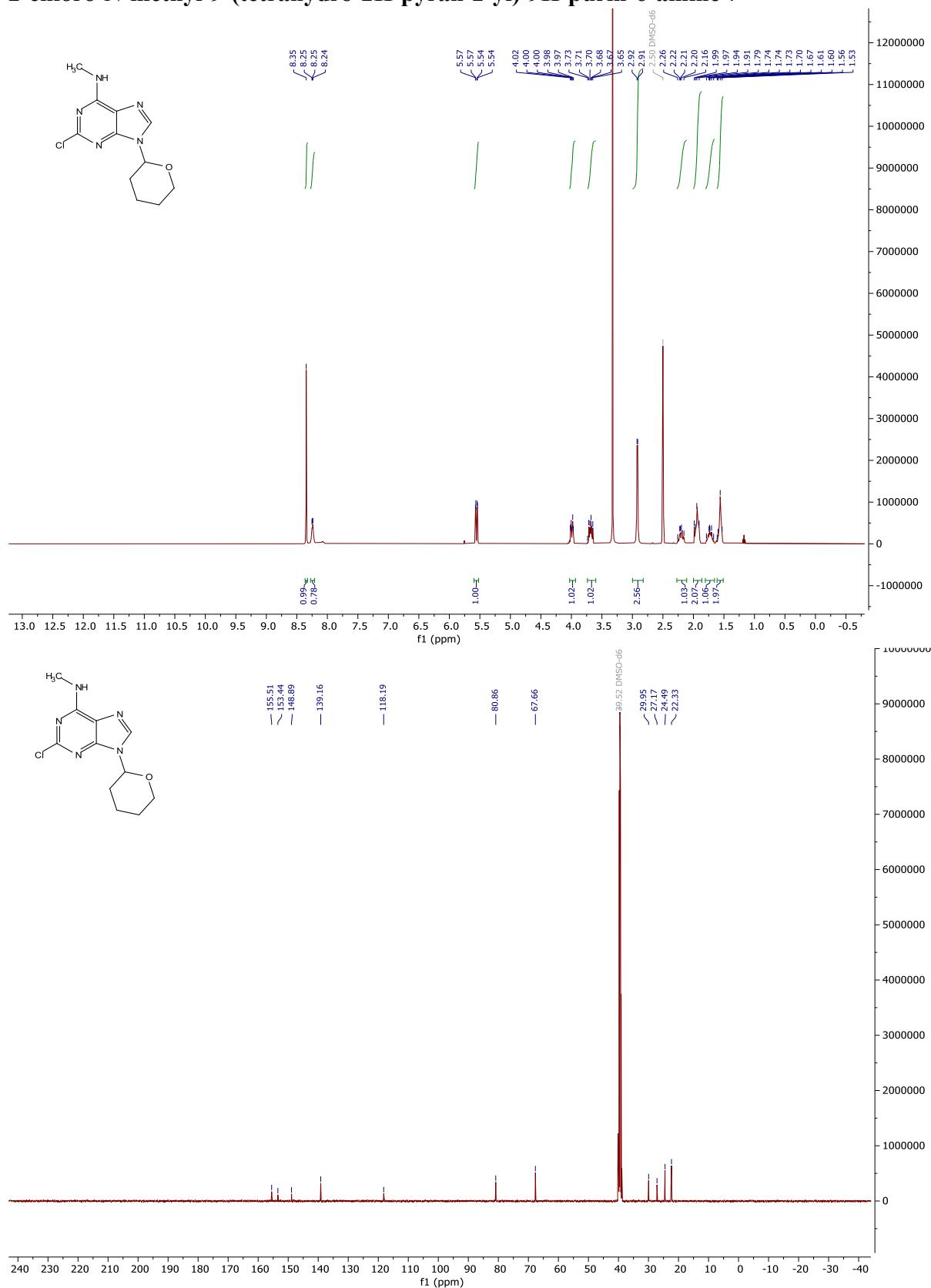
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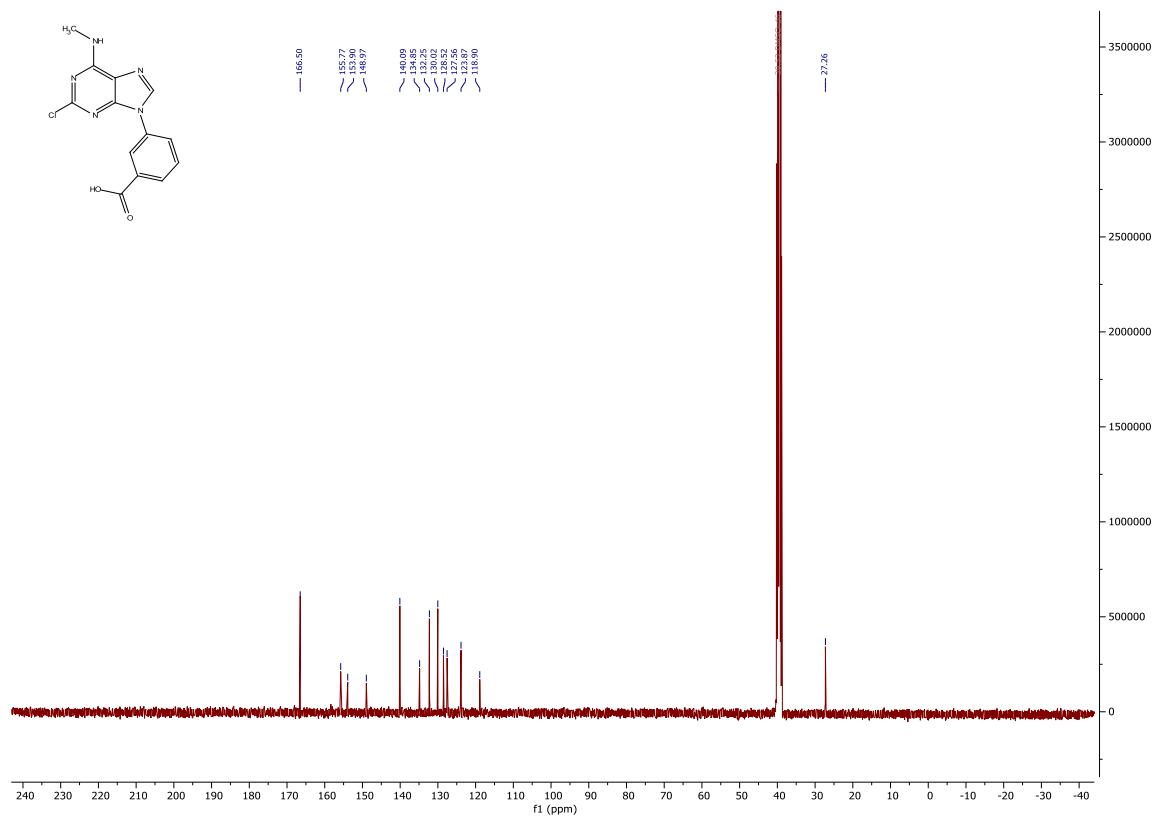
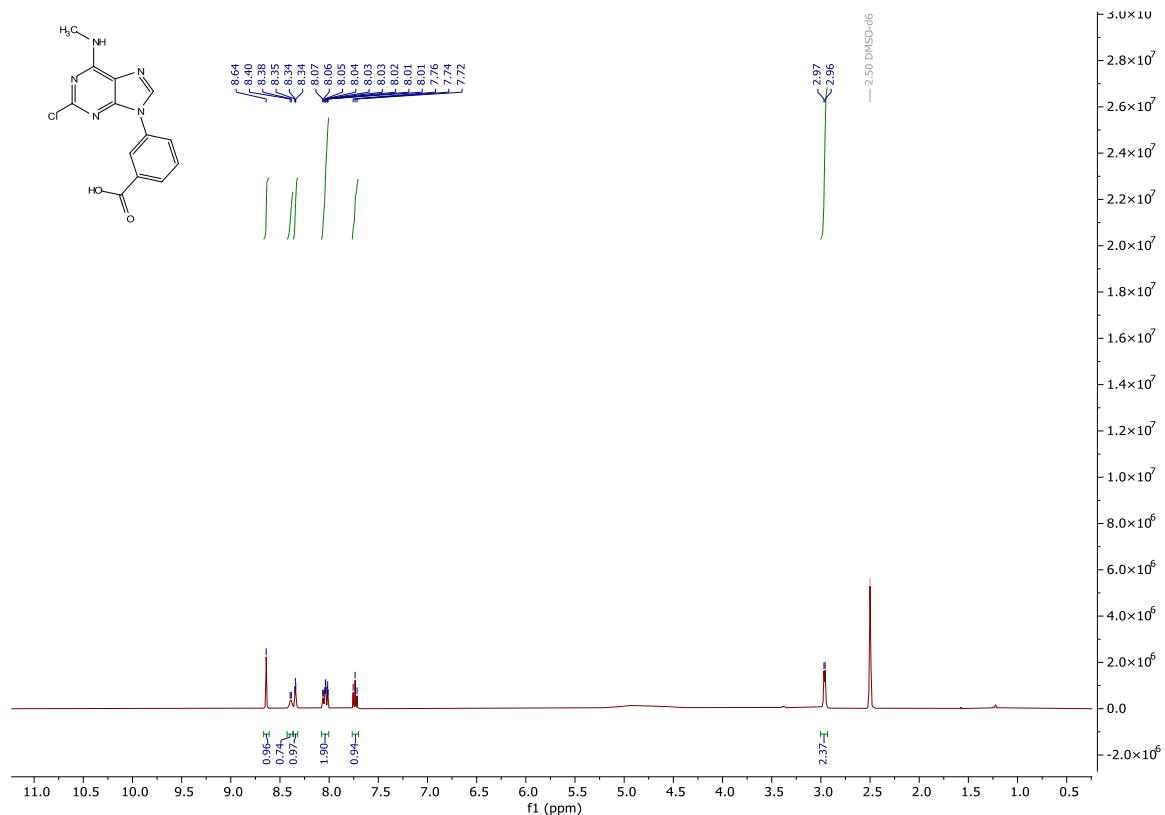
2-chloro-N-methyl-9-(pyridin-4-ylmethyl)-9H-purin-6-amine 6



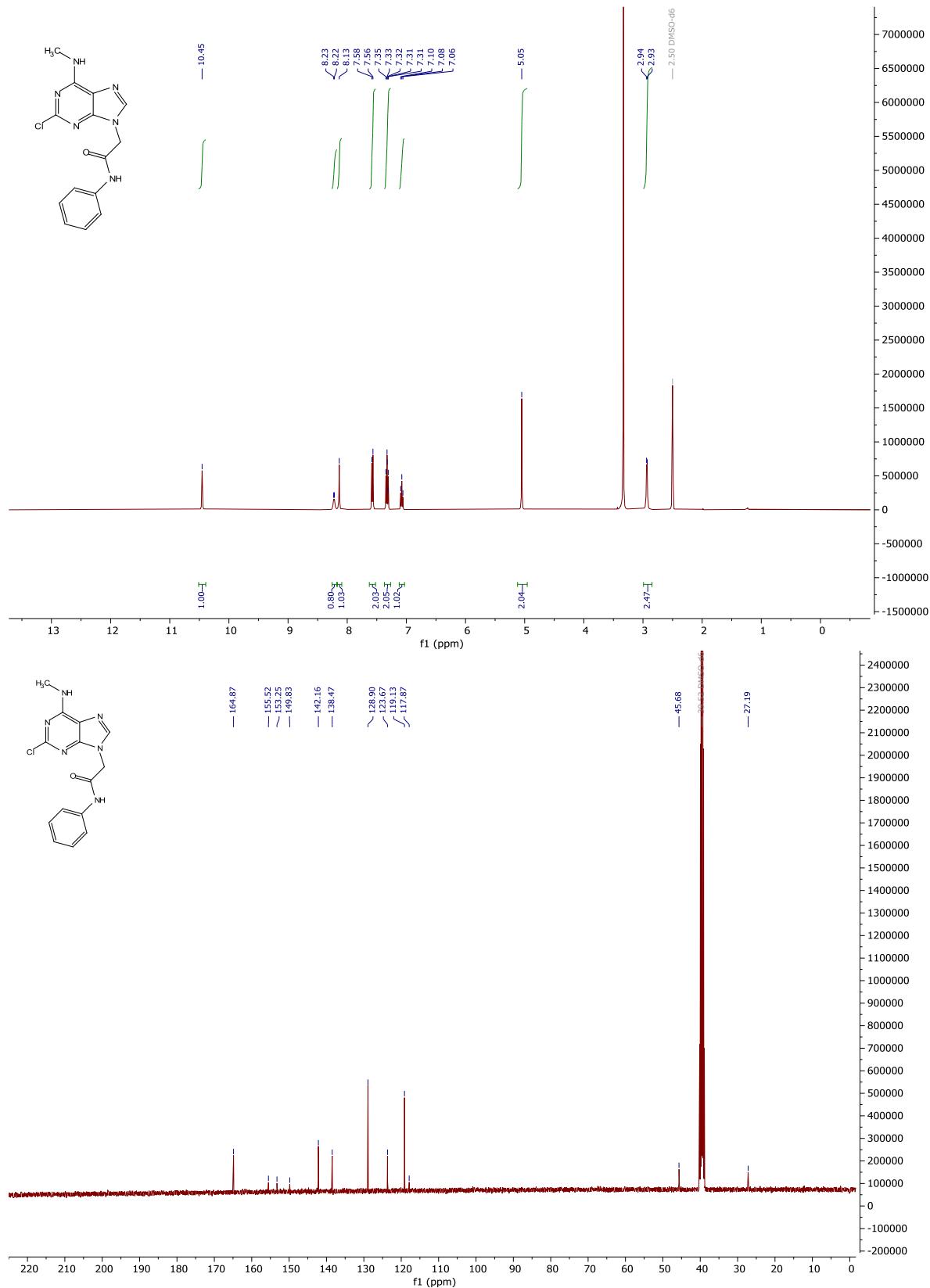
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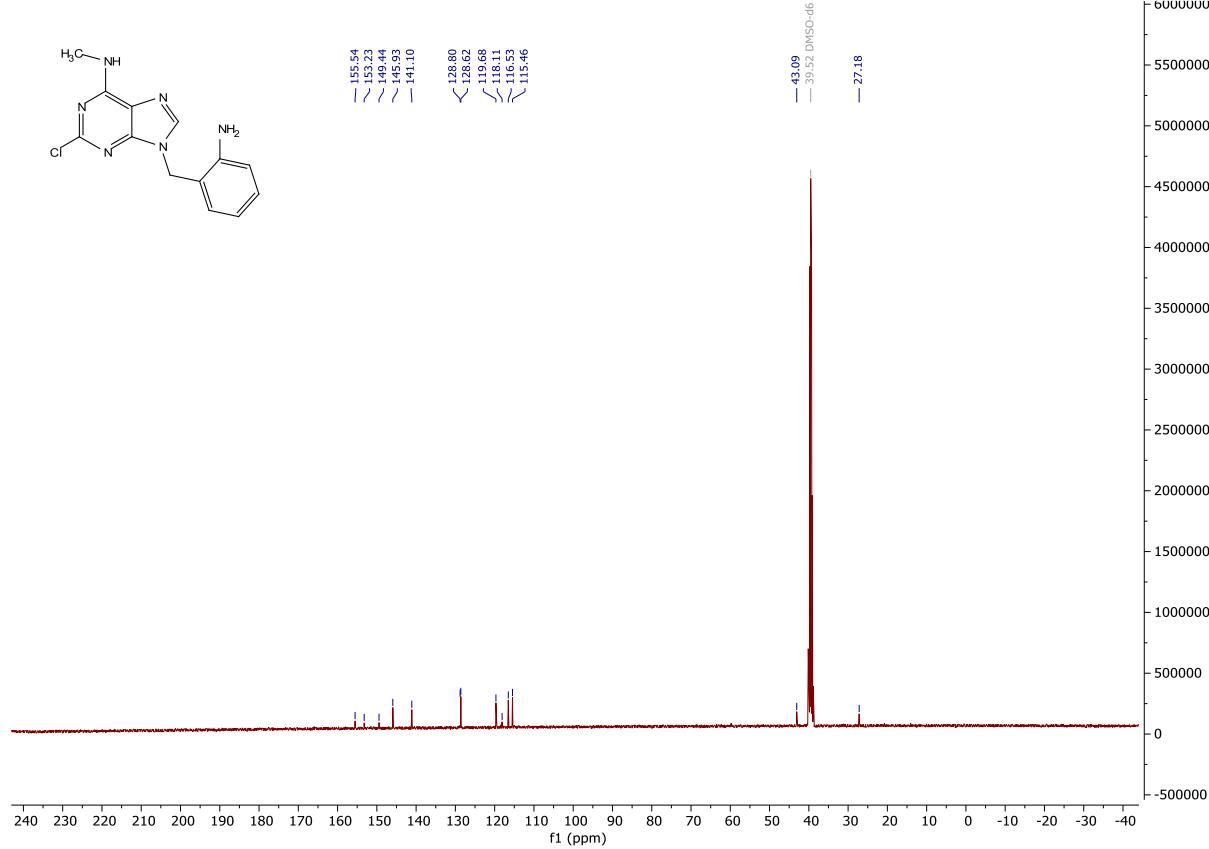
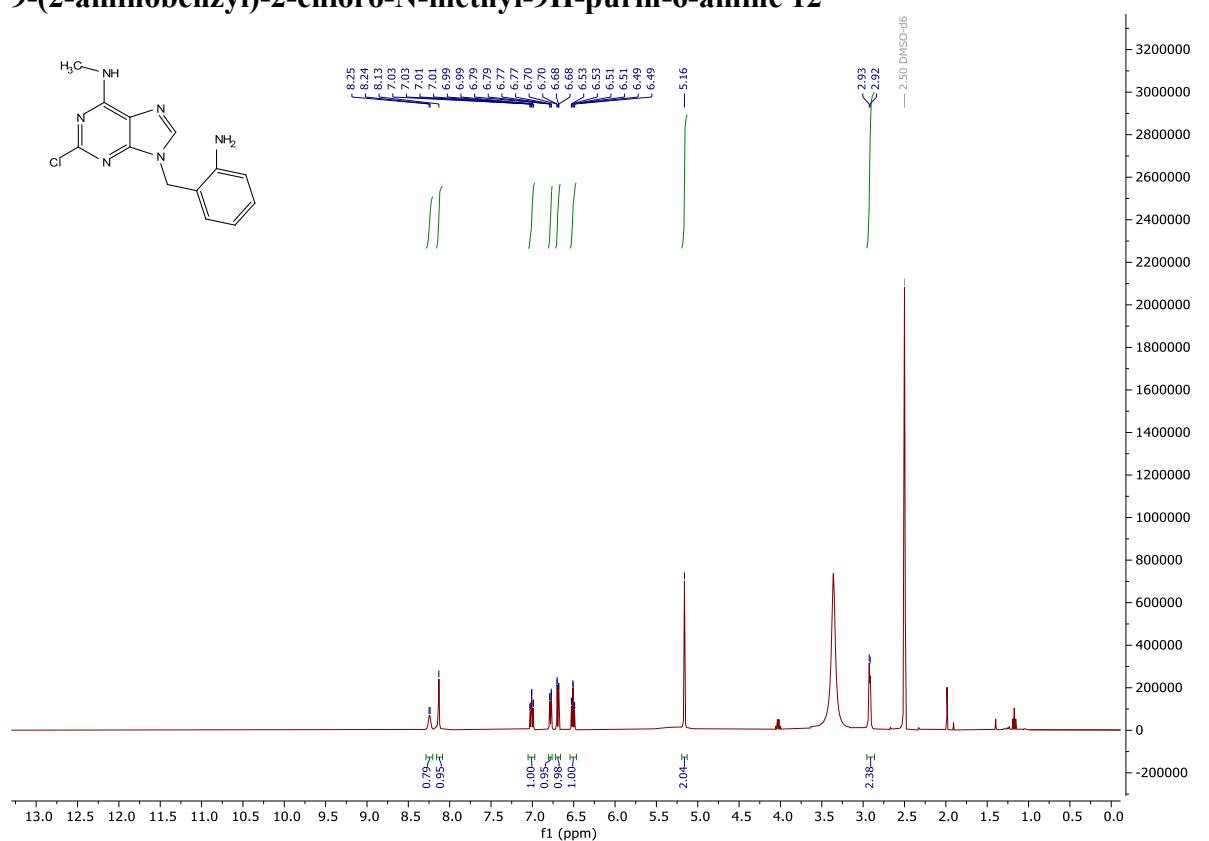
3-(2-chloro-6-(methylamino)-9H-purin-9-yl)benzoic acid 10



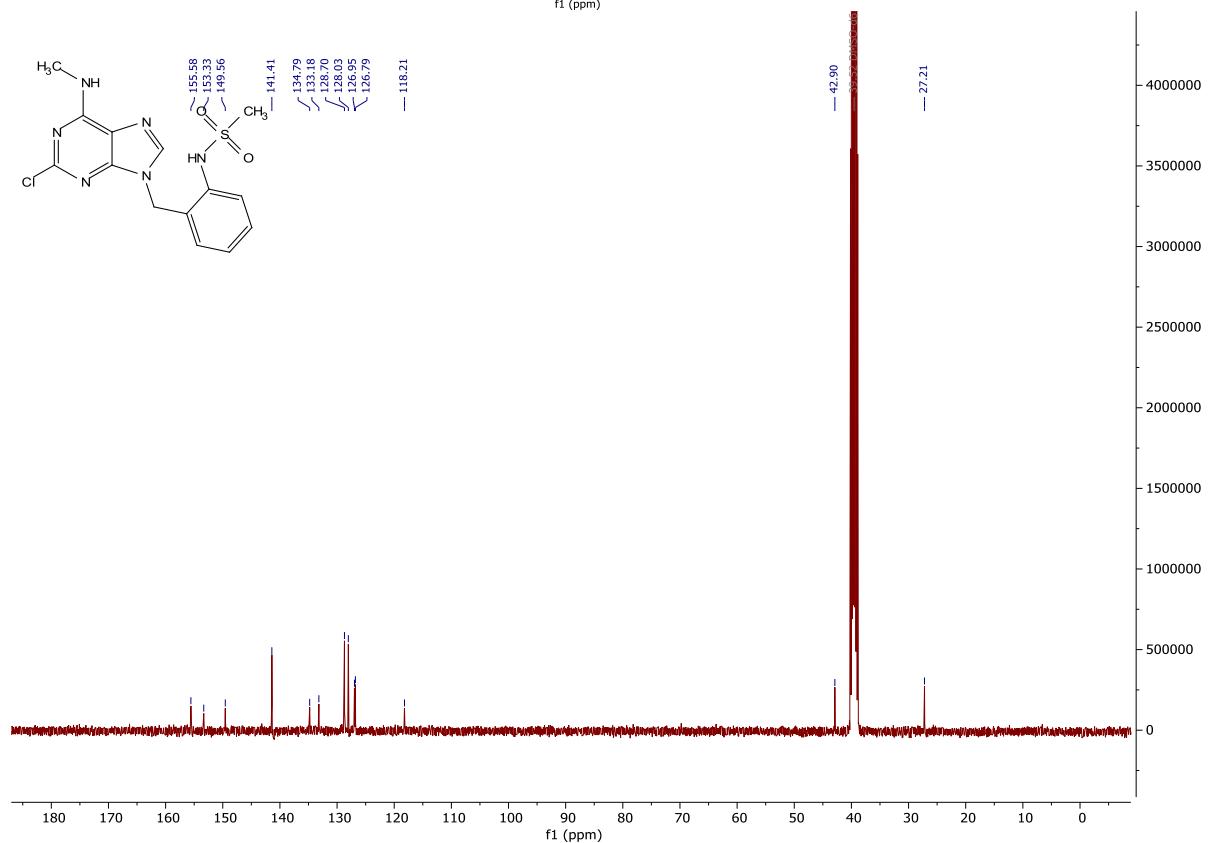
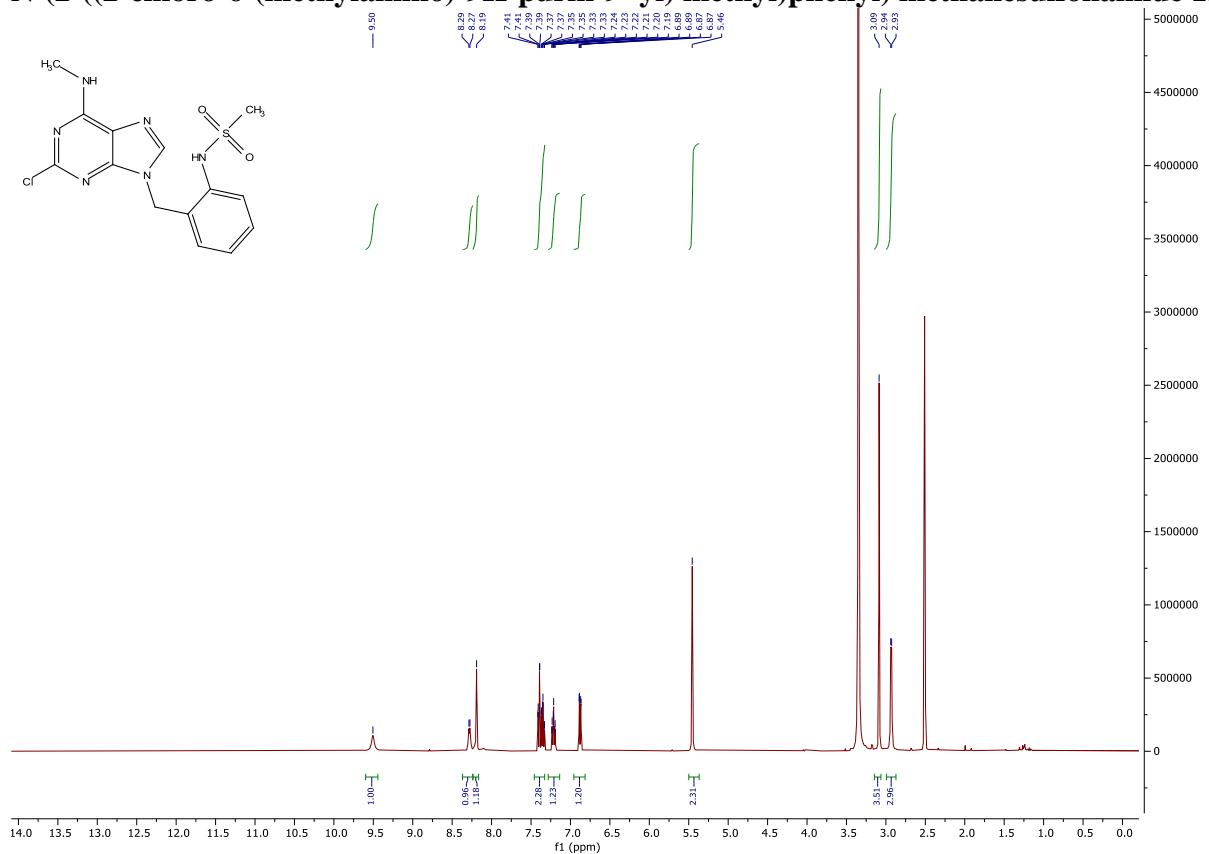
2-(2-chloro-6-(methylamino)-9H-purin-9-yl)-N-phenylacetamide 11



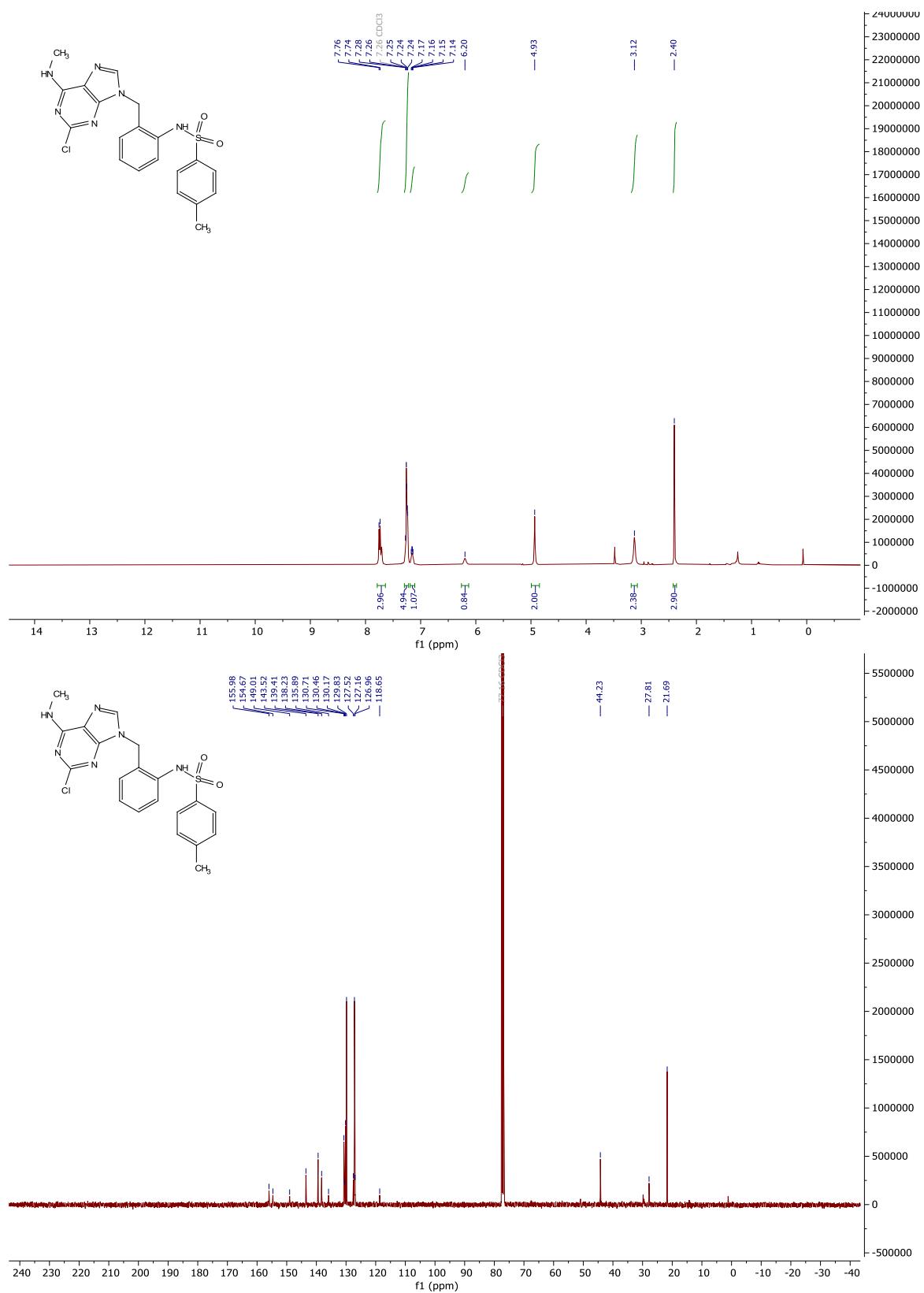
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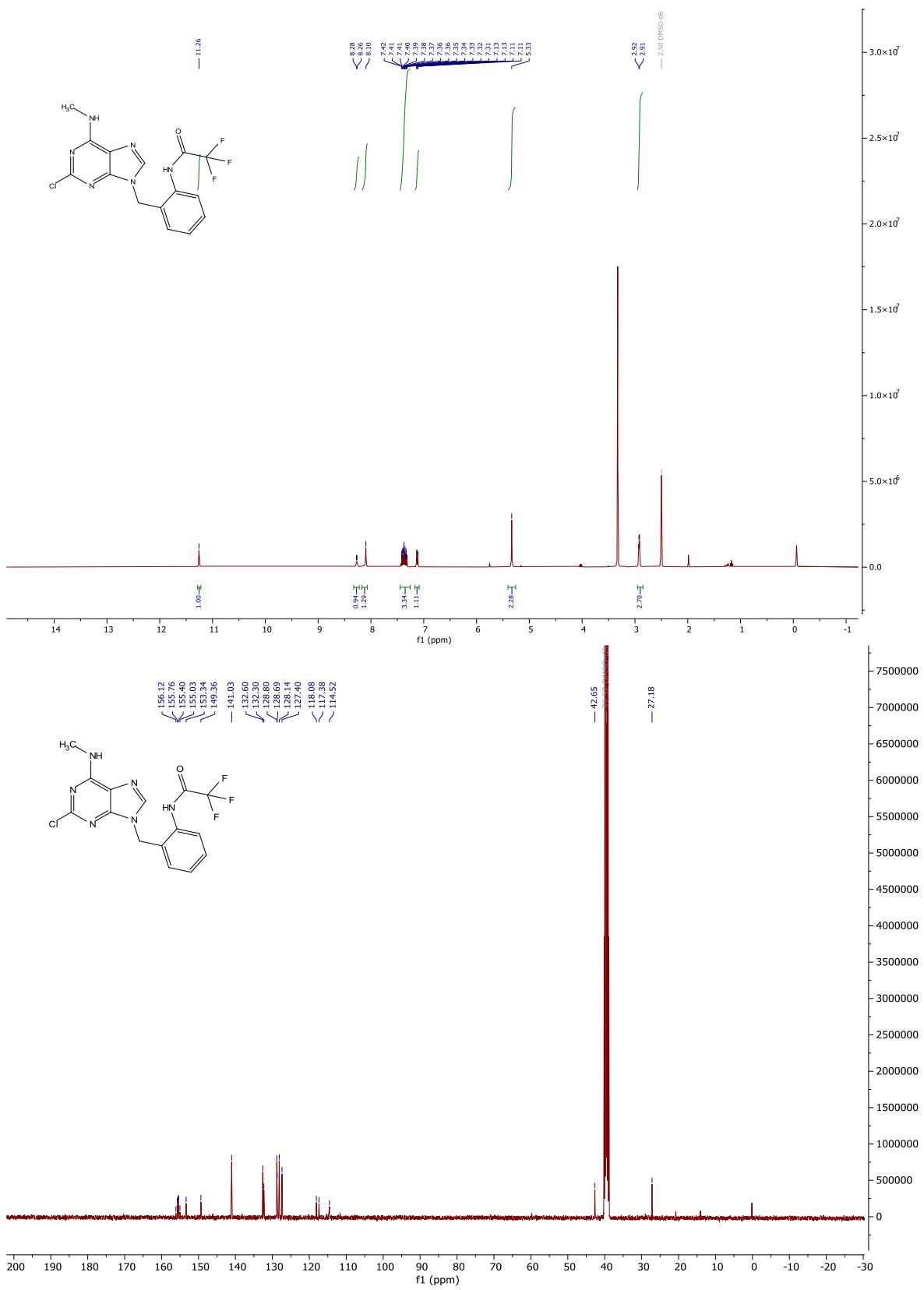
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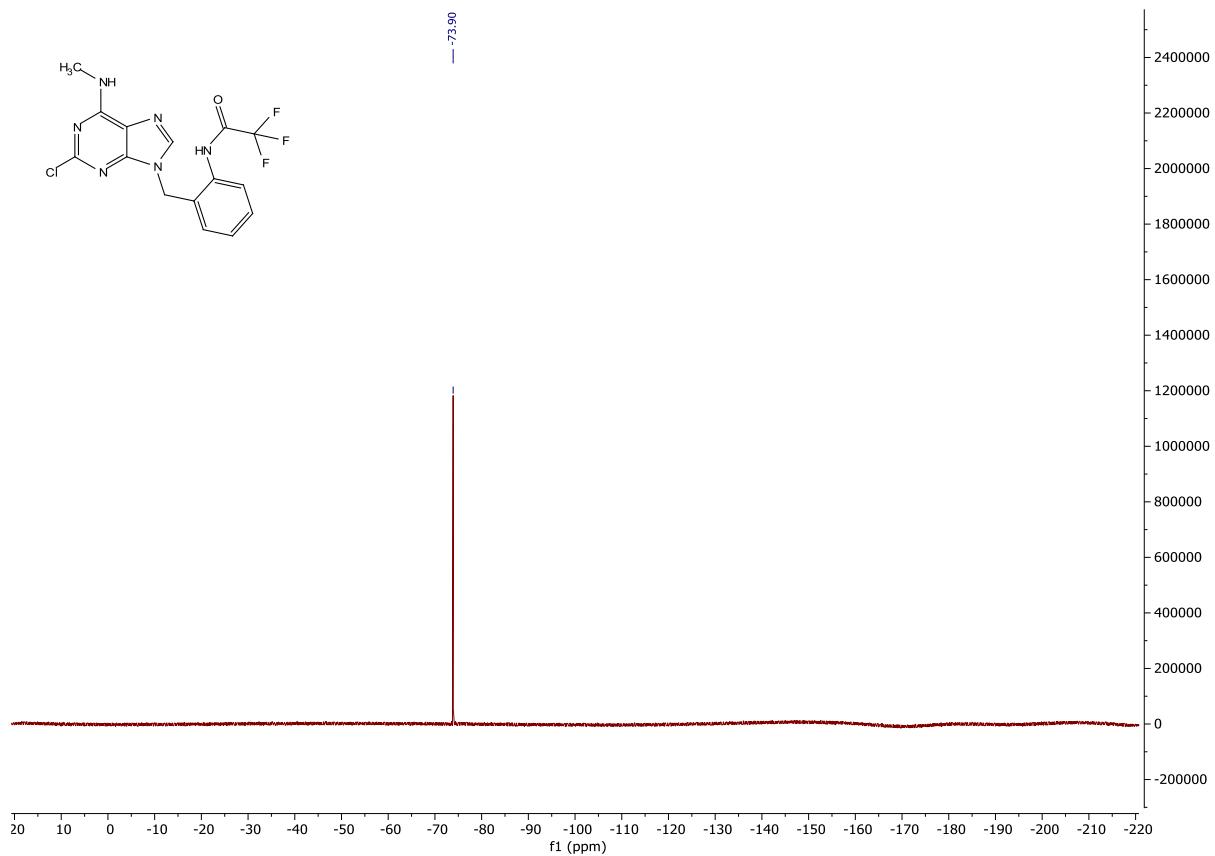


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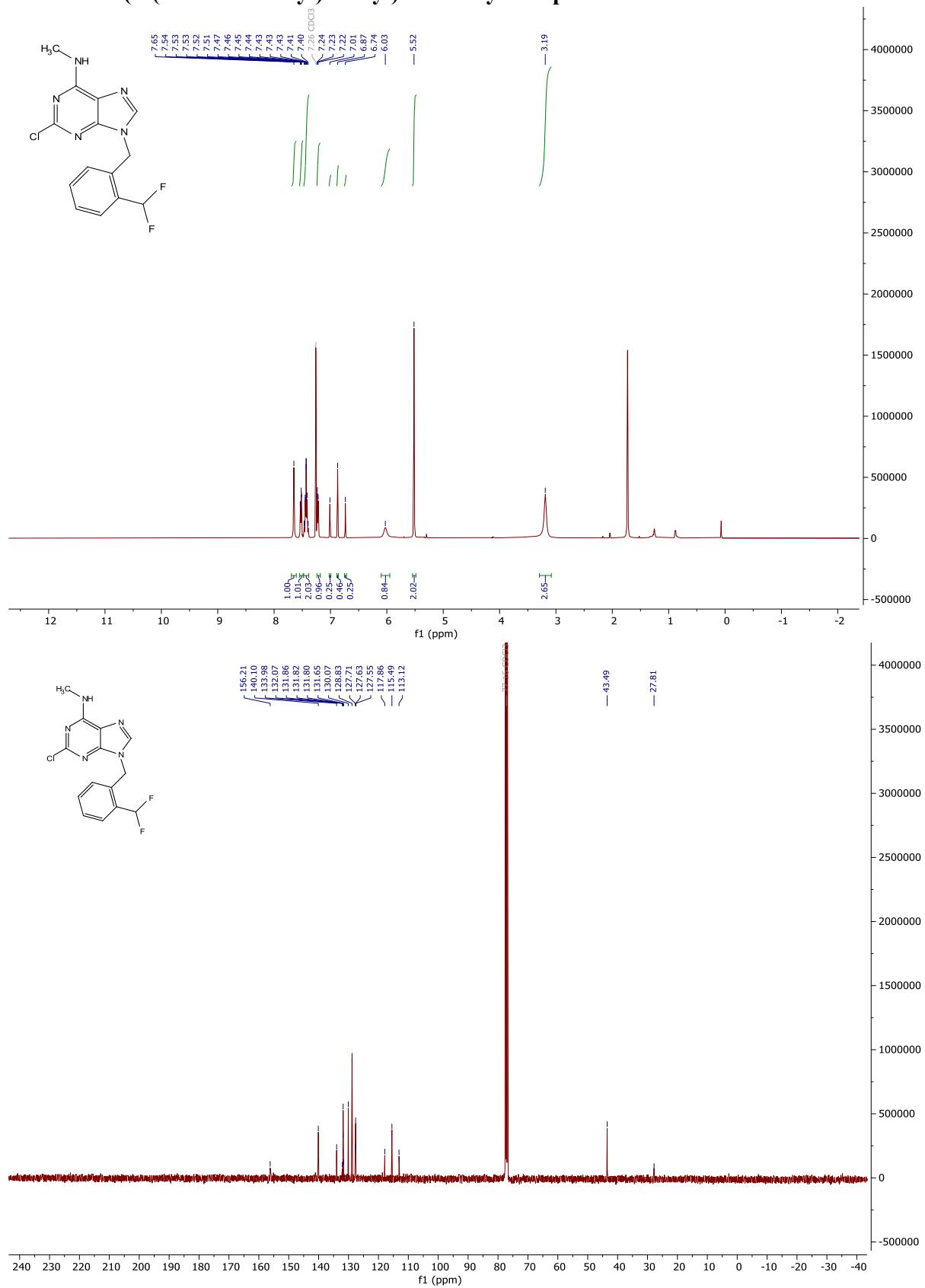


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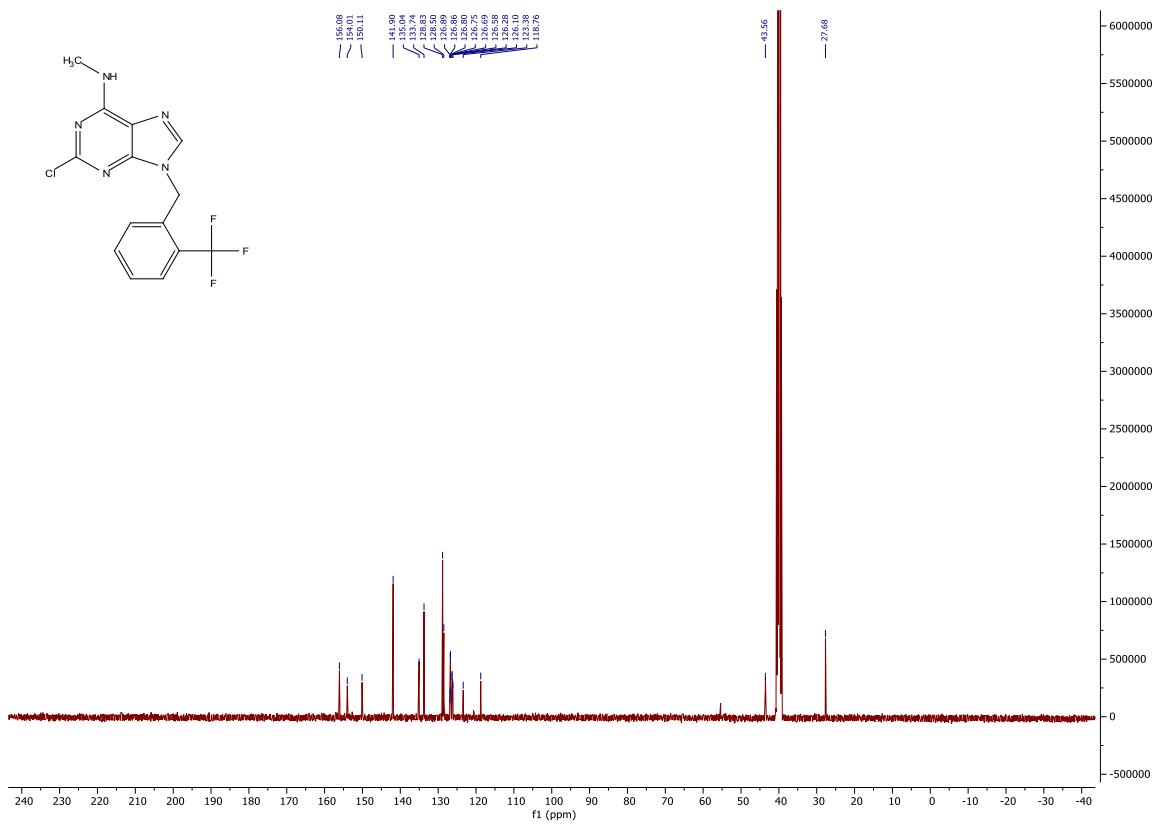
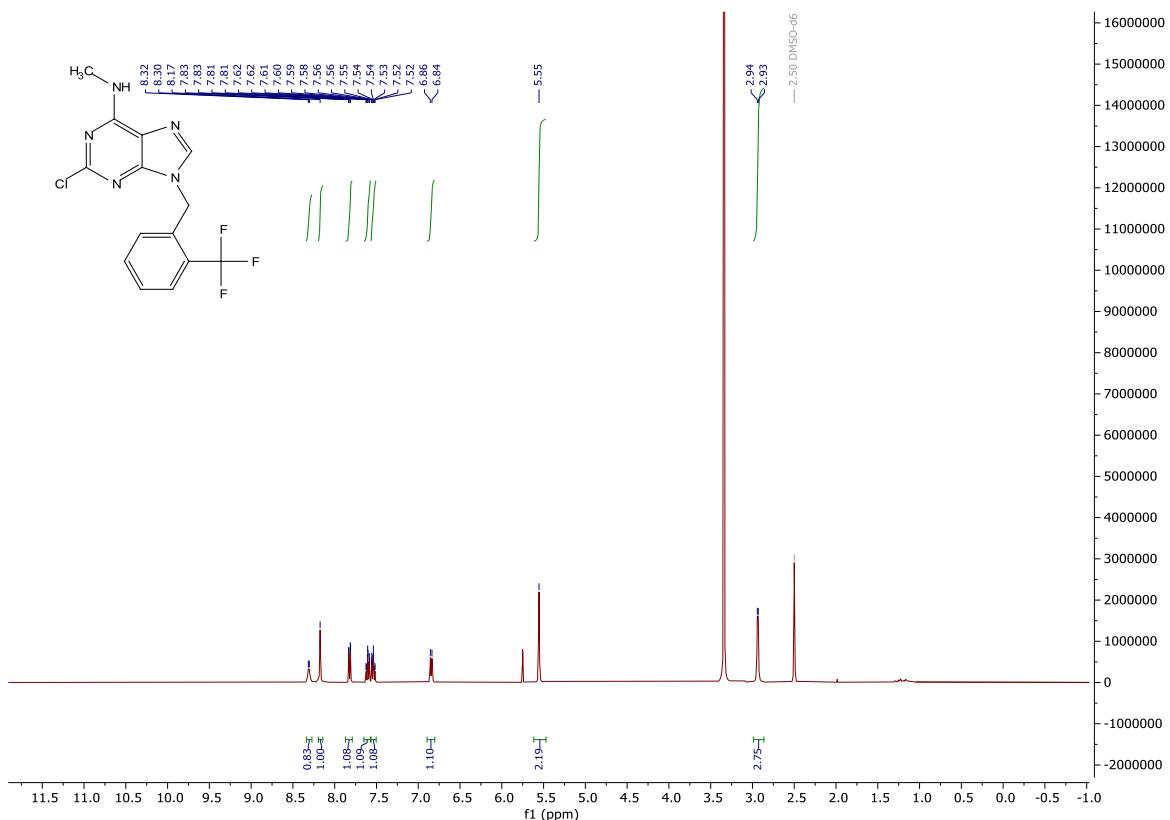




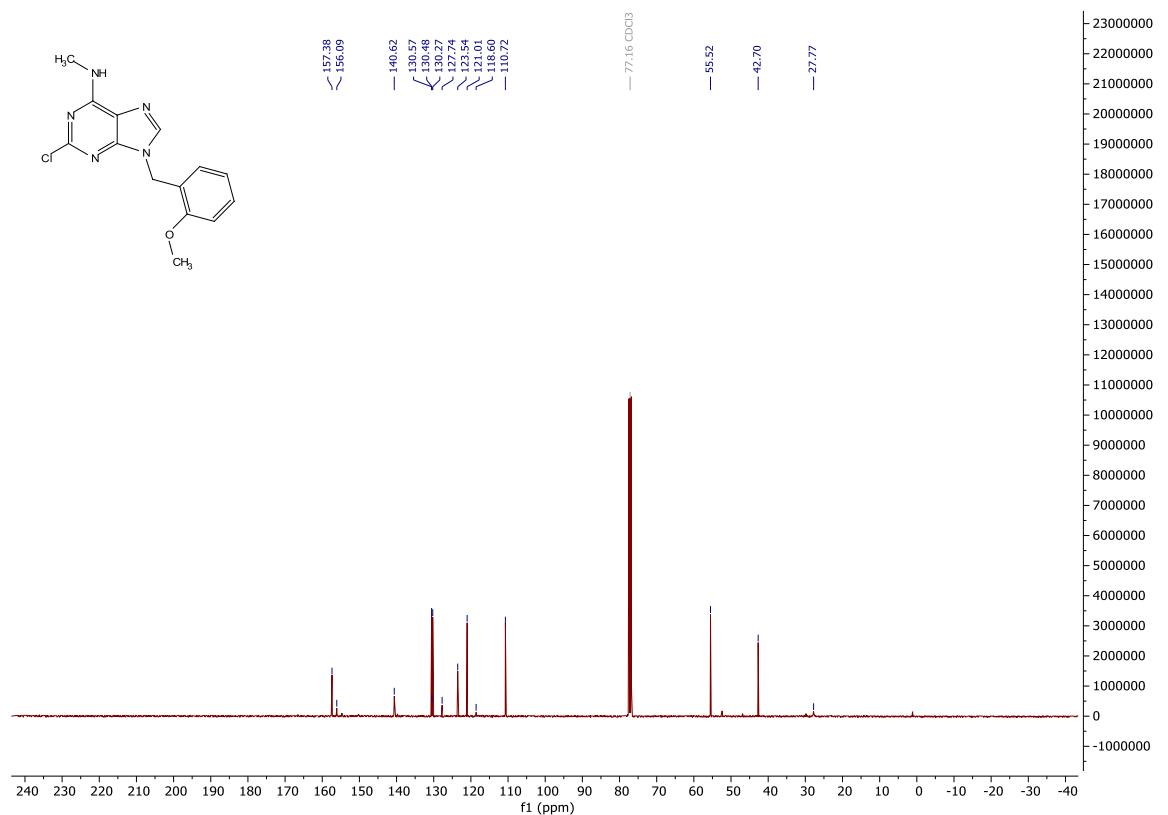
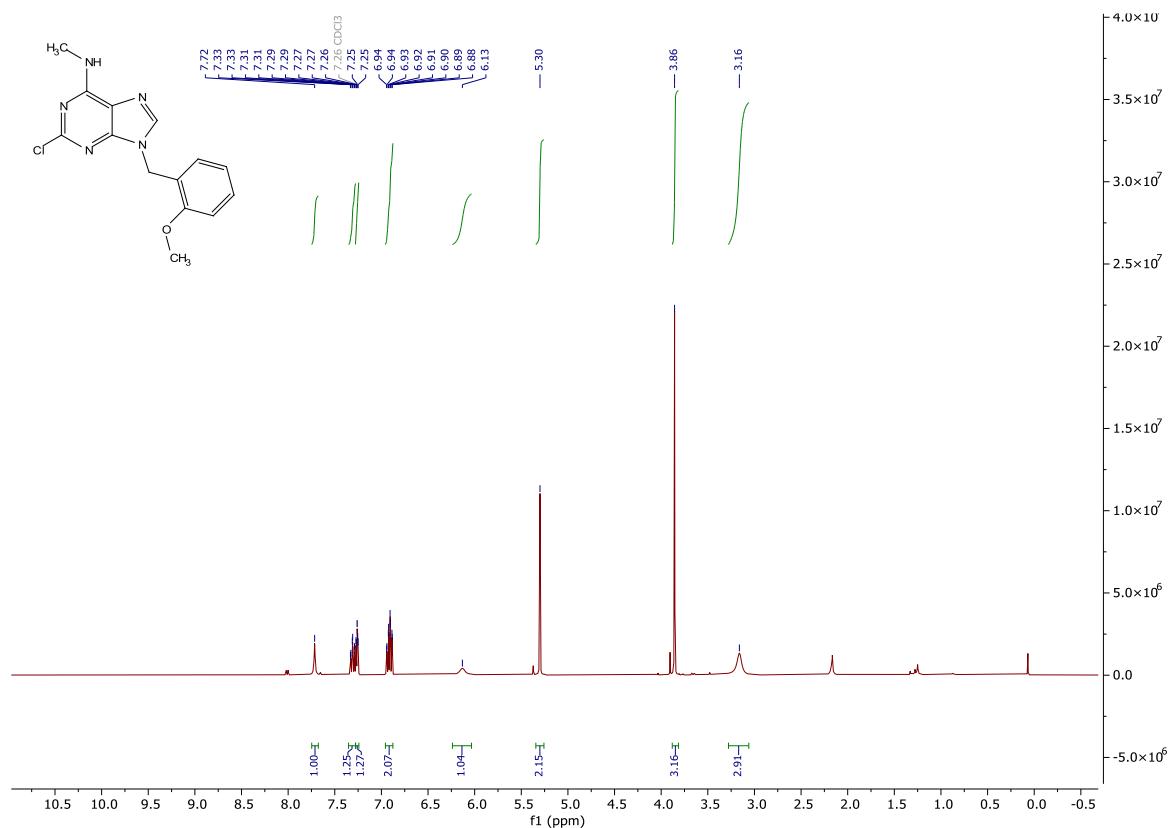
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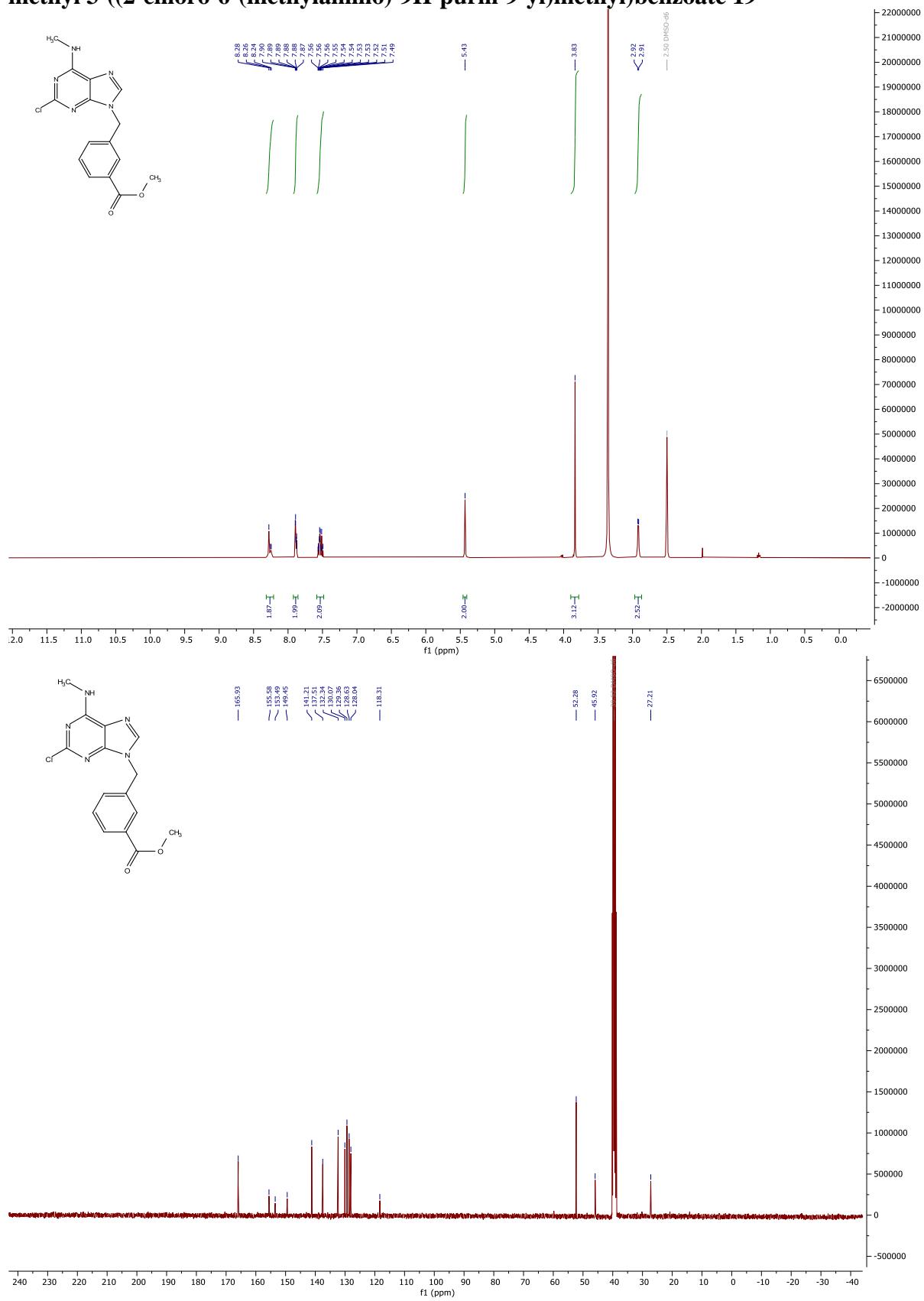
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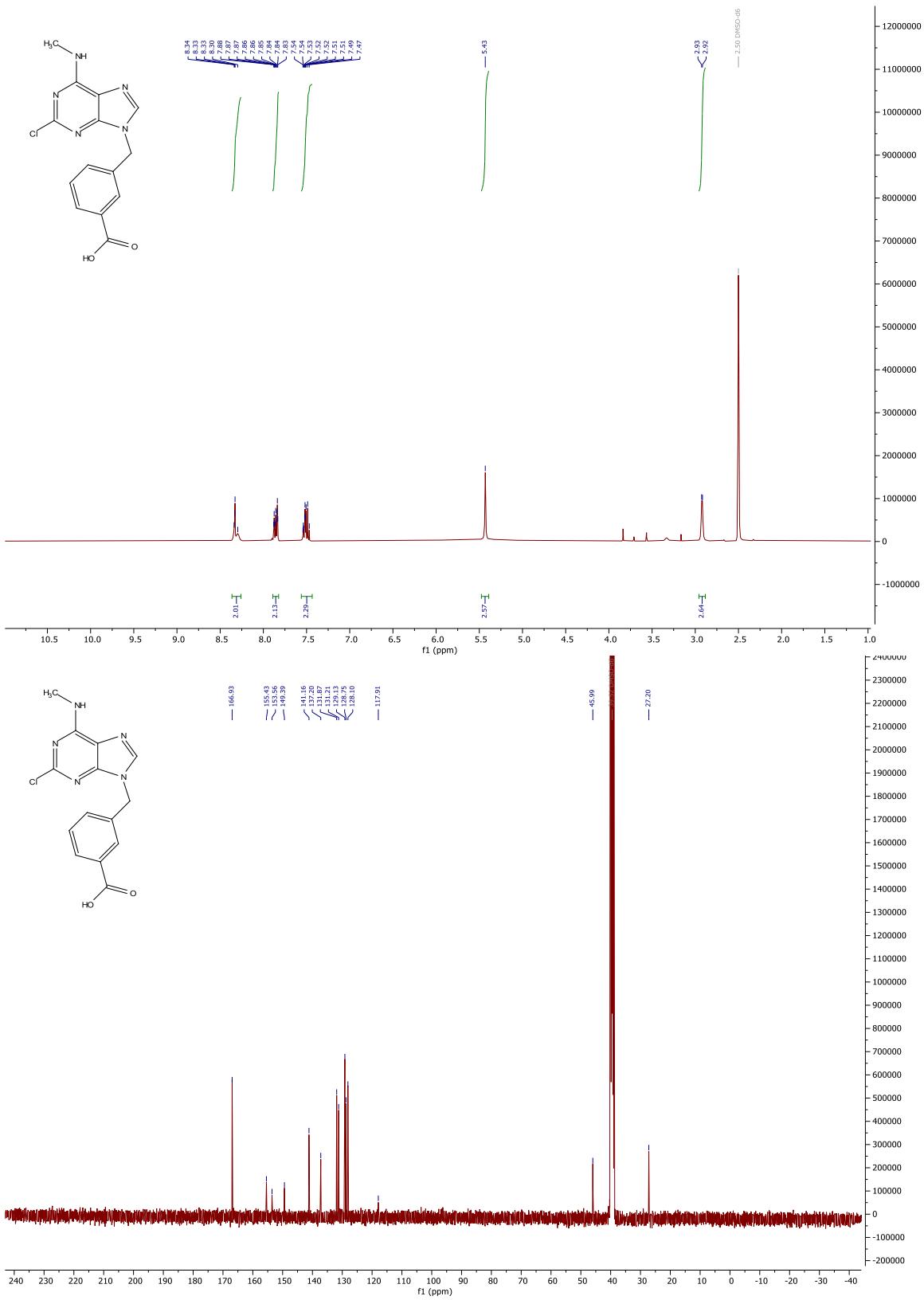
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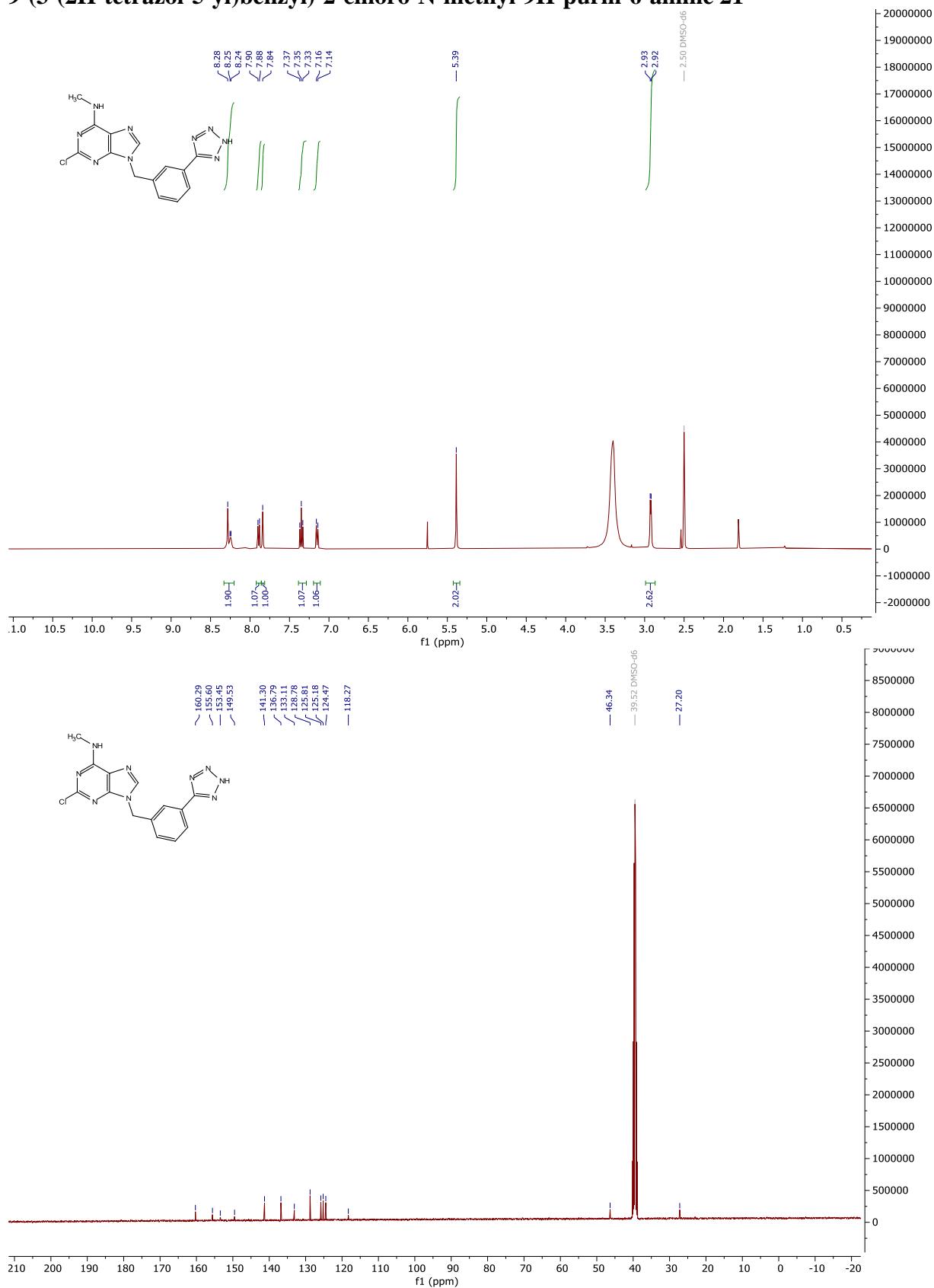
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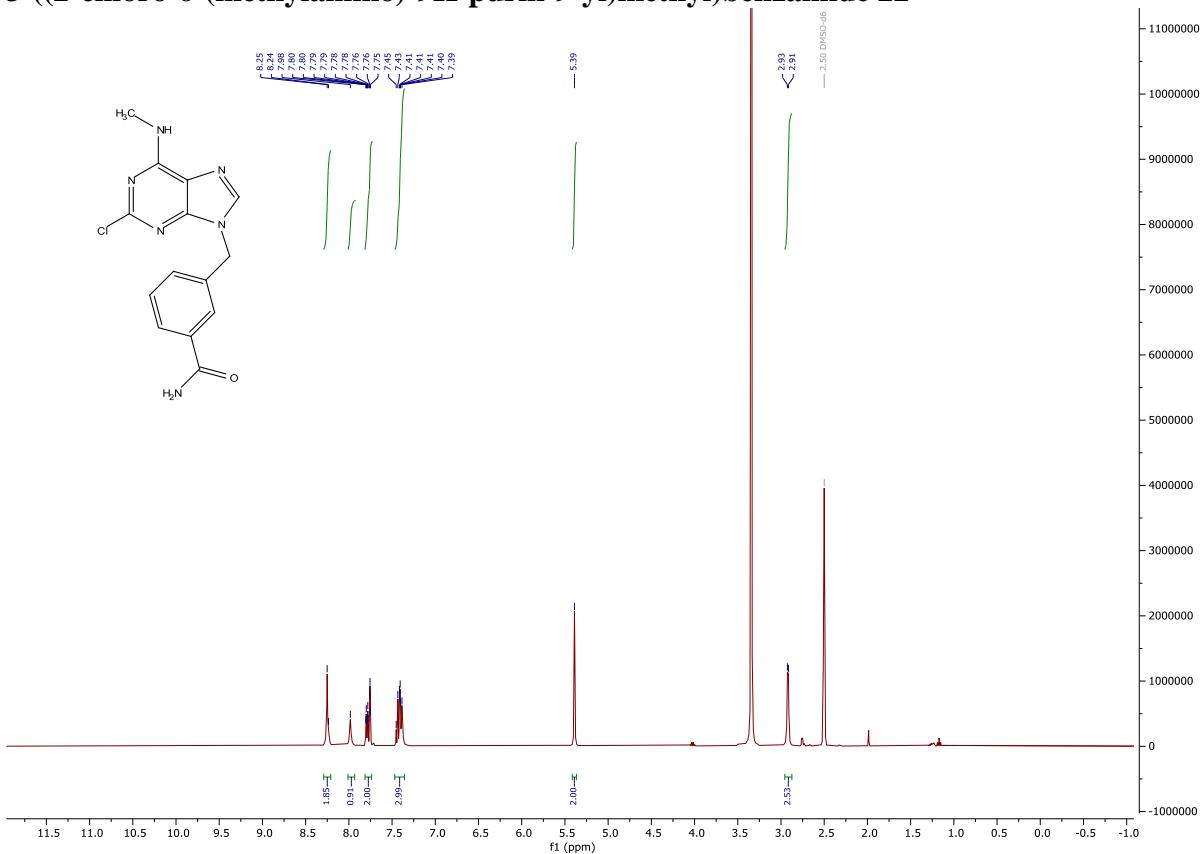
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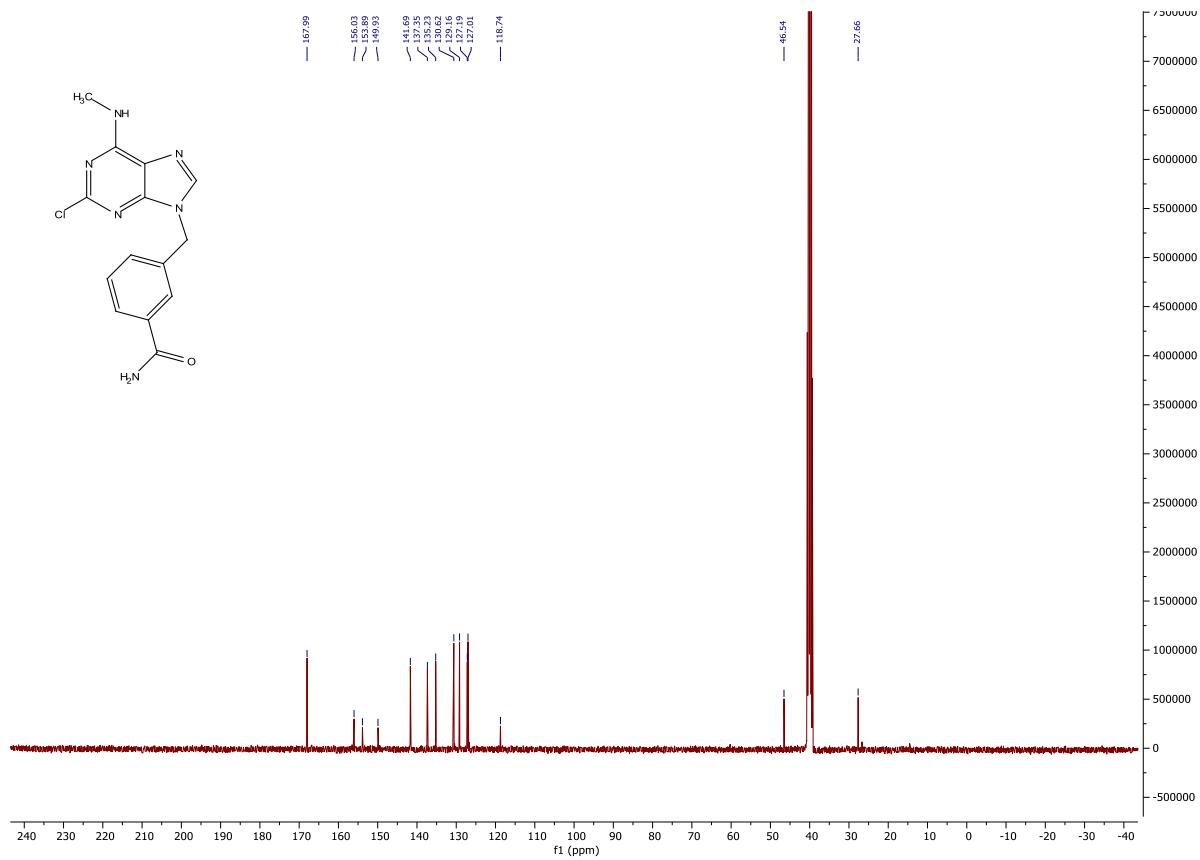


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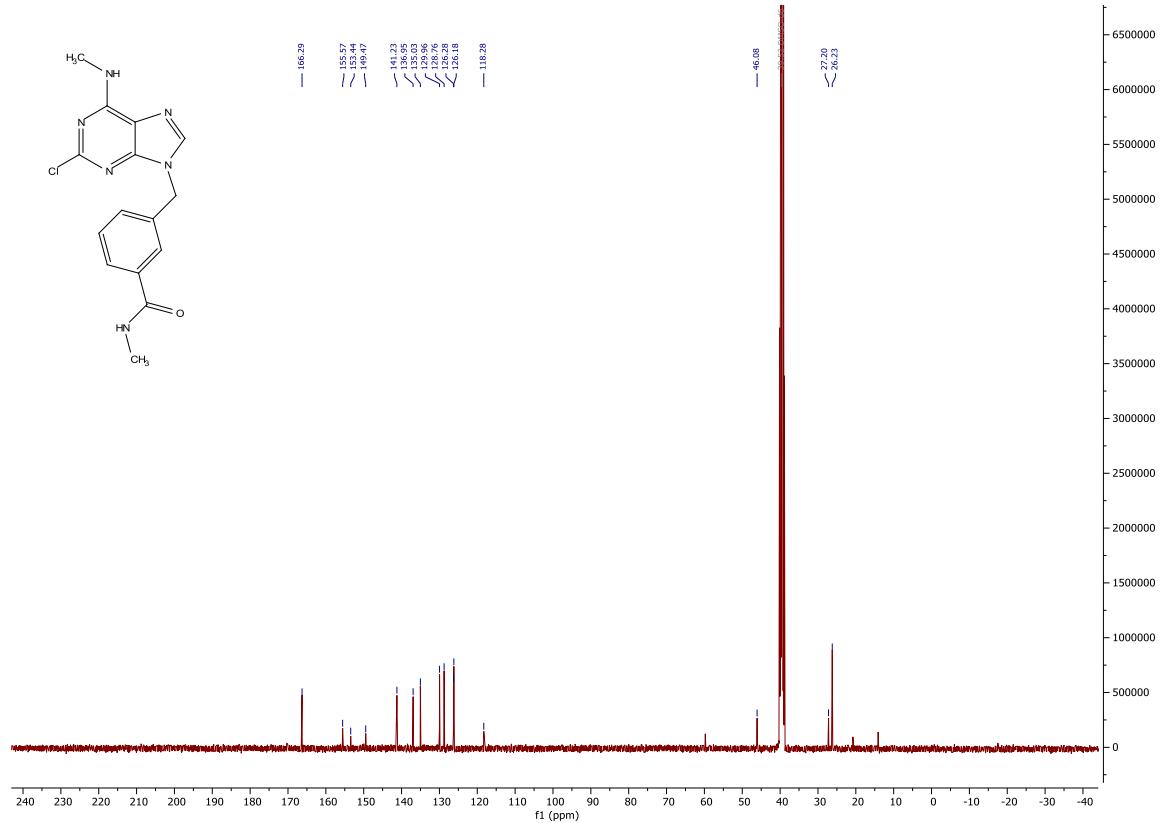
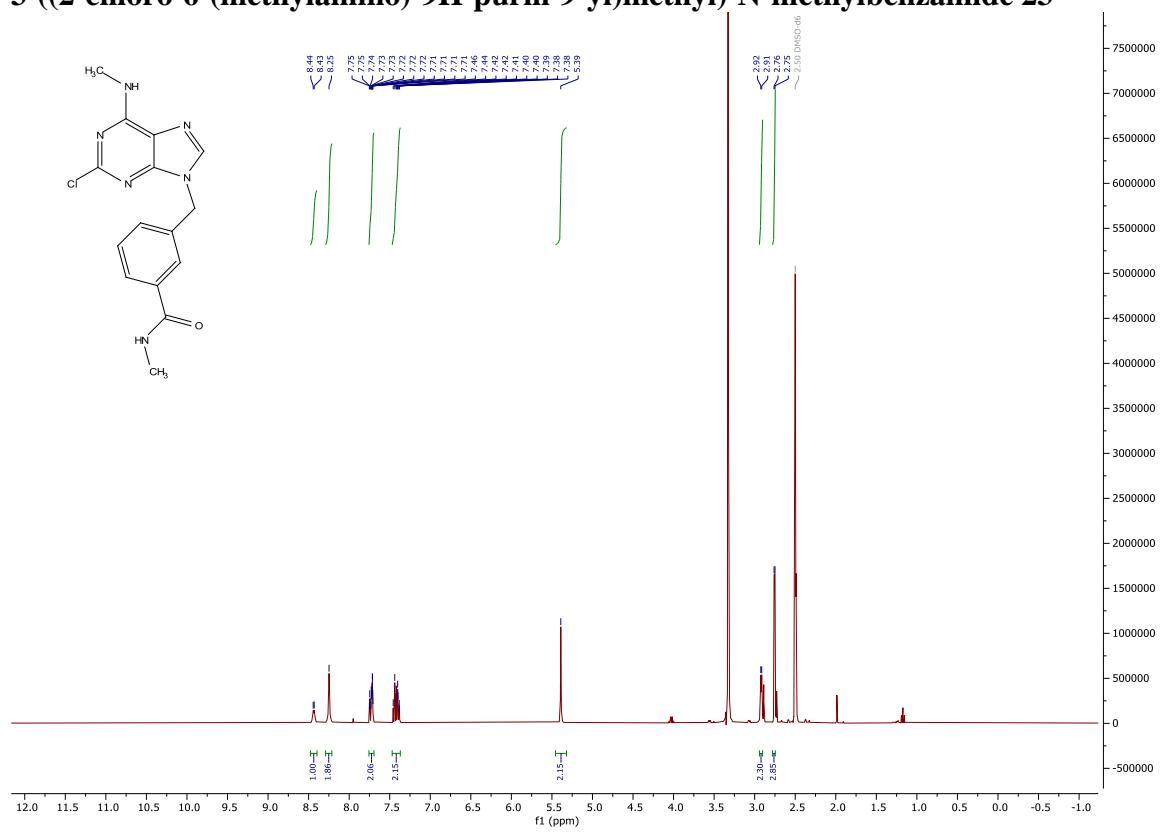


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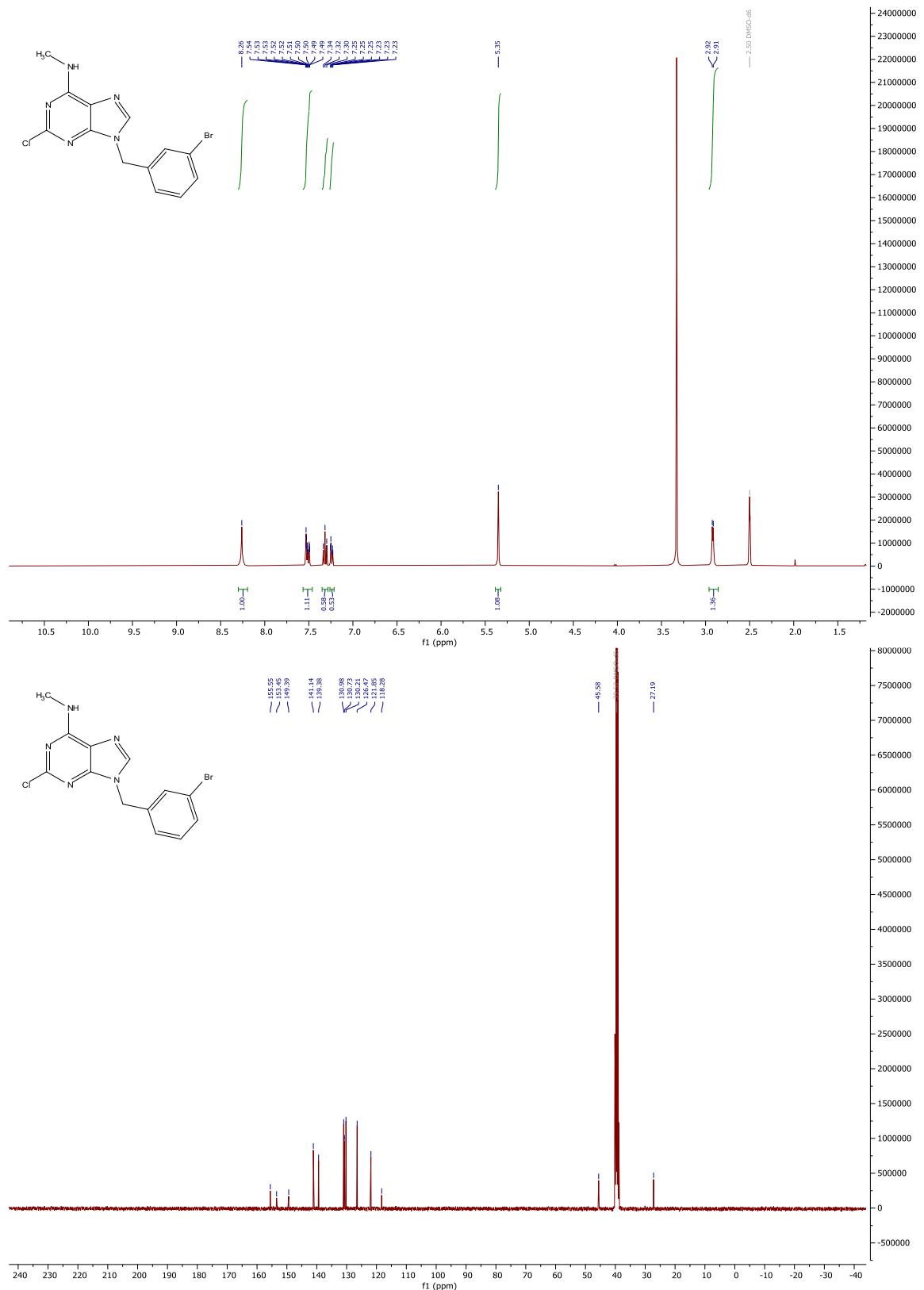




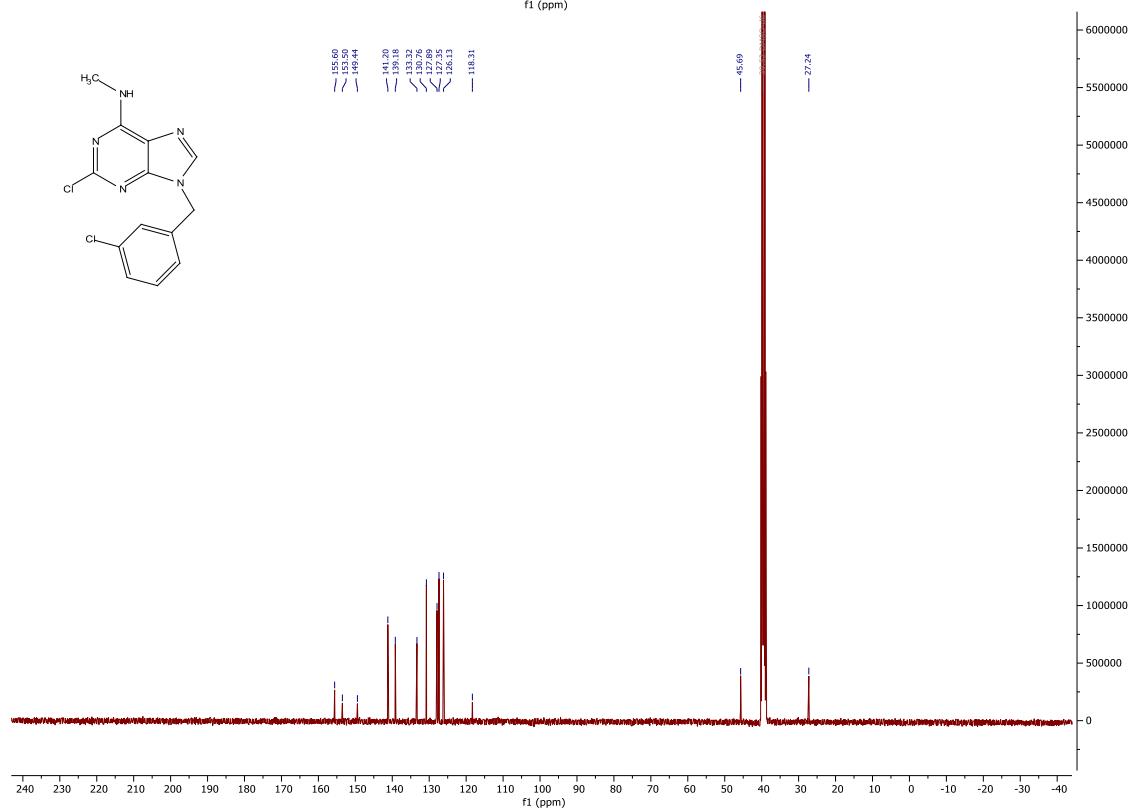
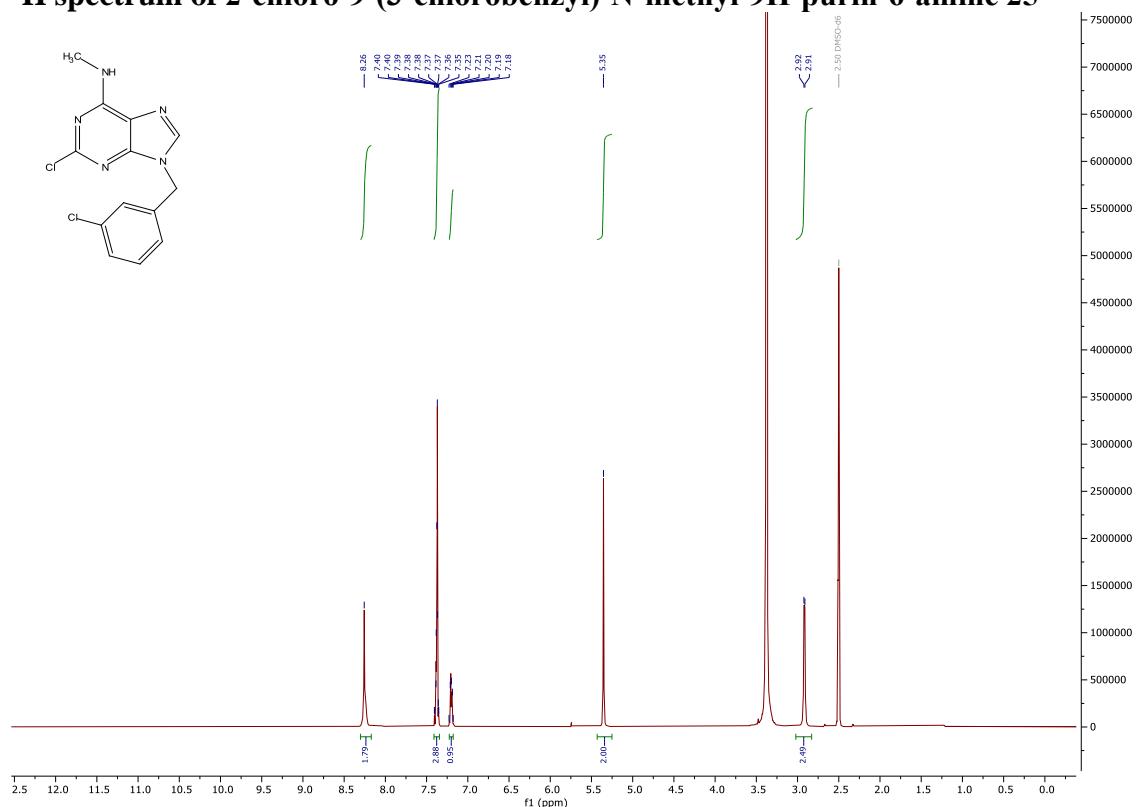
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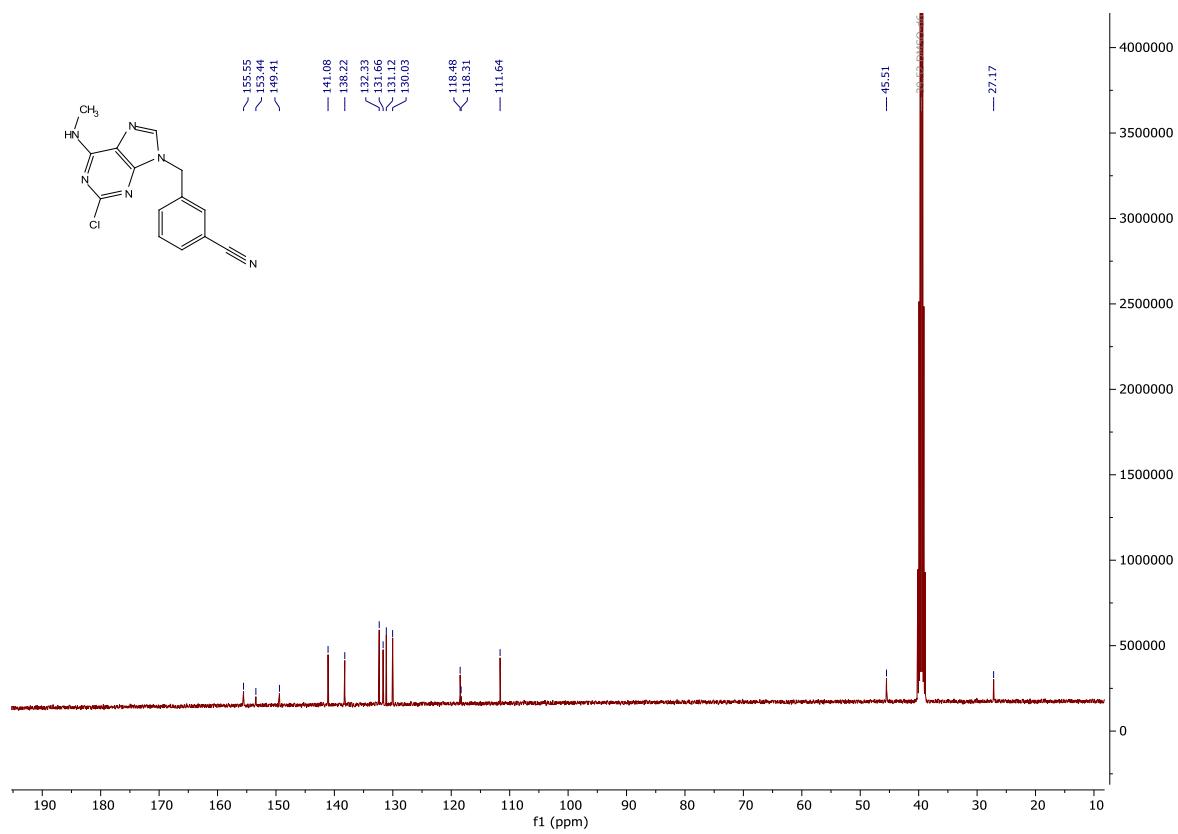
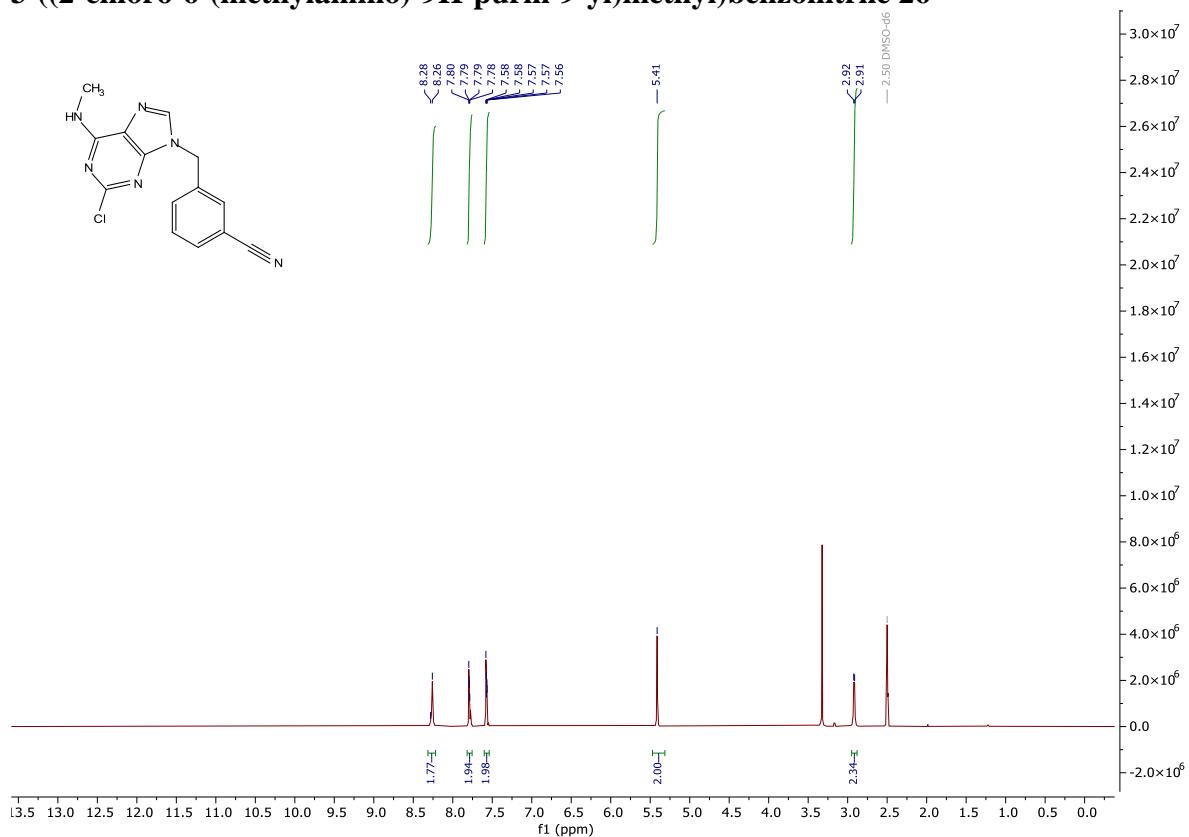
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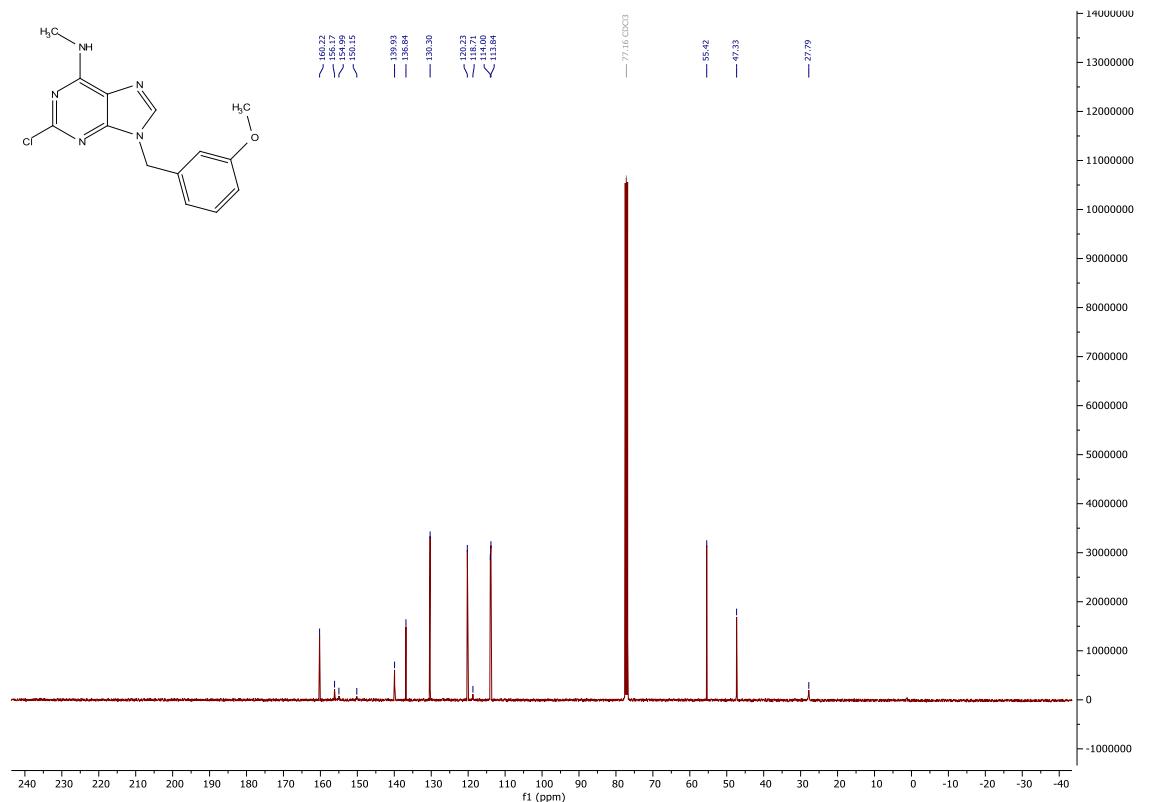
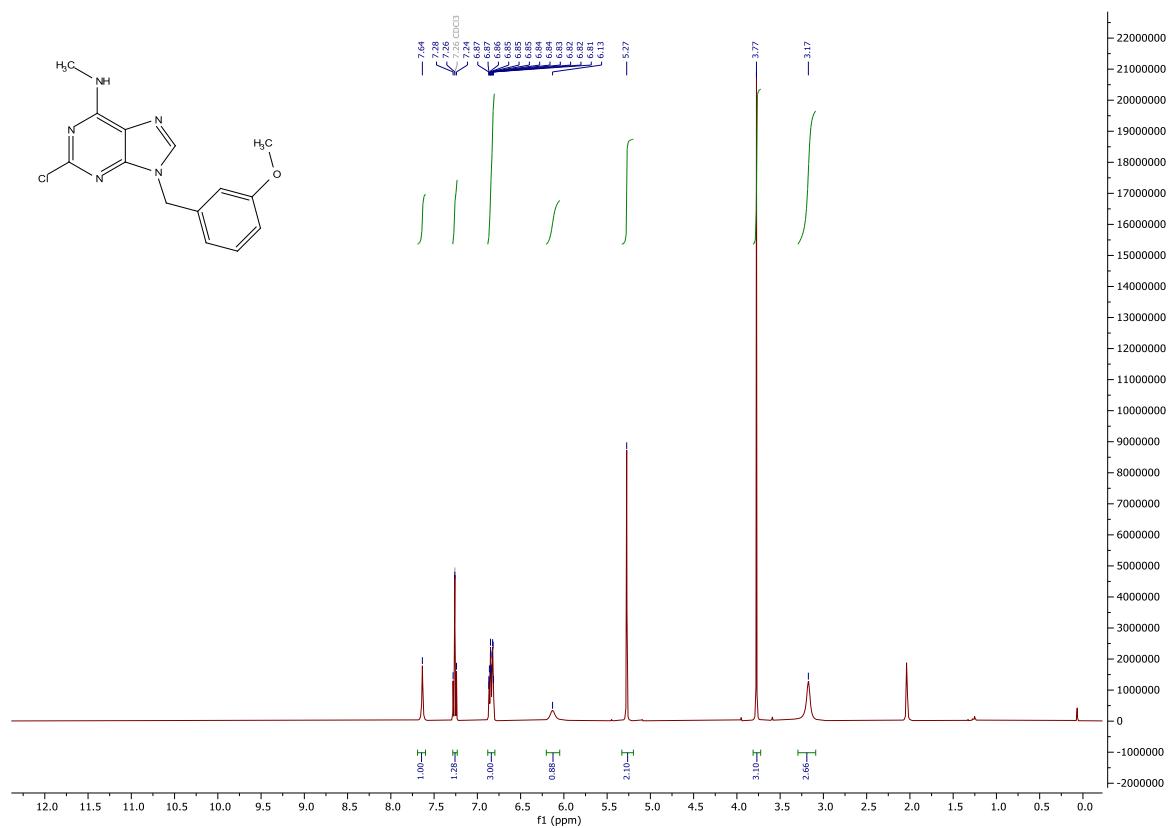
¹H spectrum of 2-chloro-9-(3-chlorobenzyl)-N-methyl-9H-purin-6-amine 25



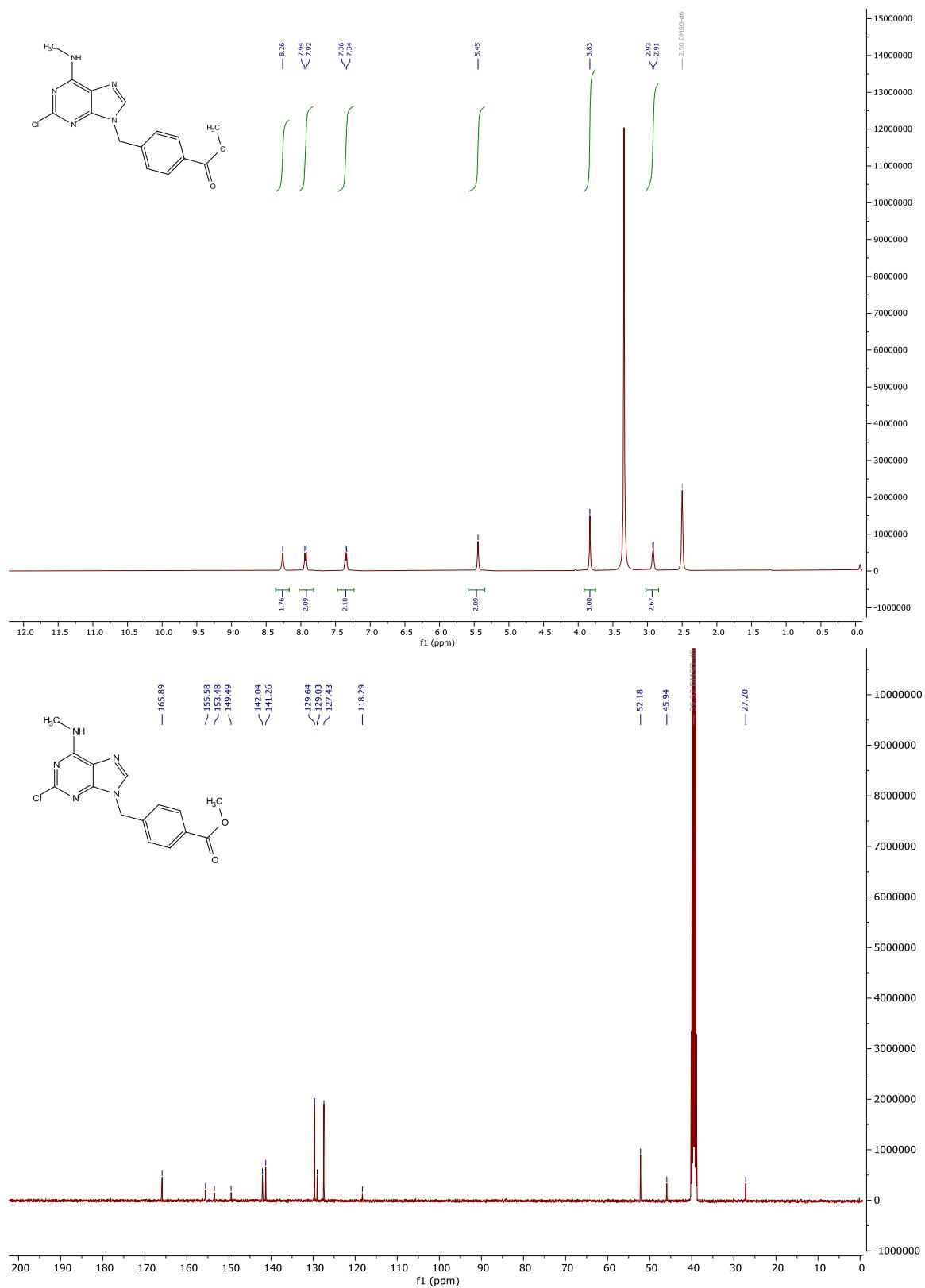
3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzonitrile 26



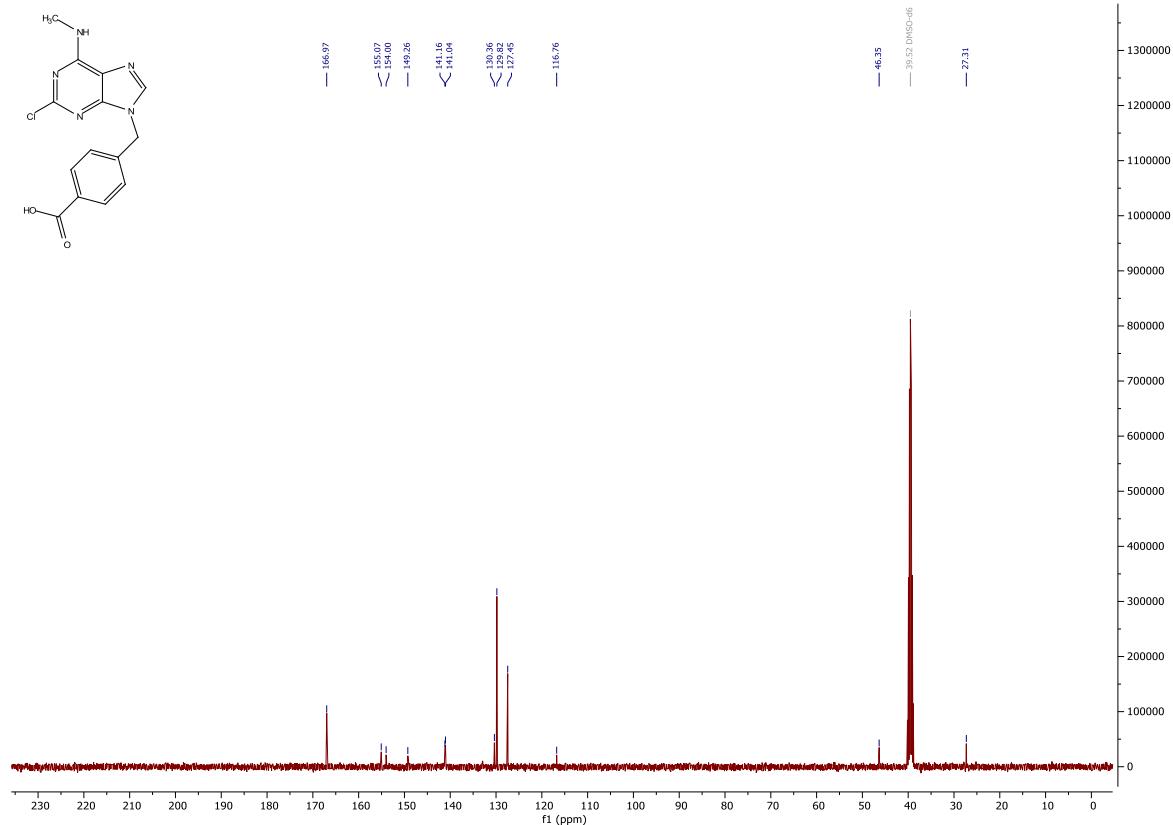
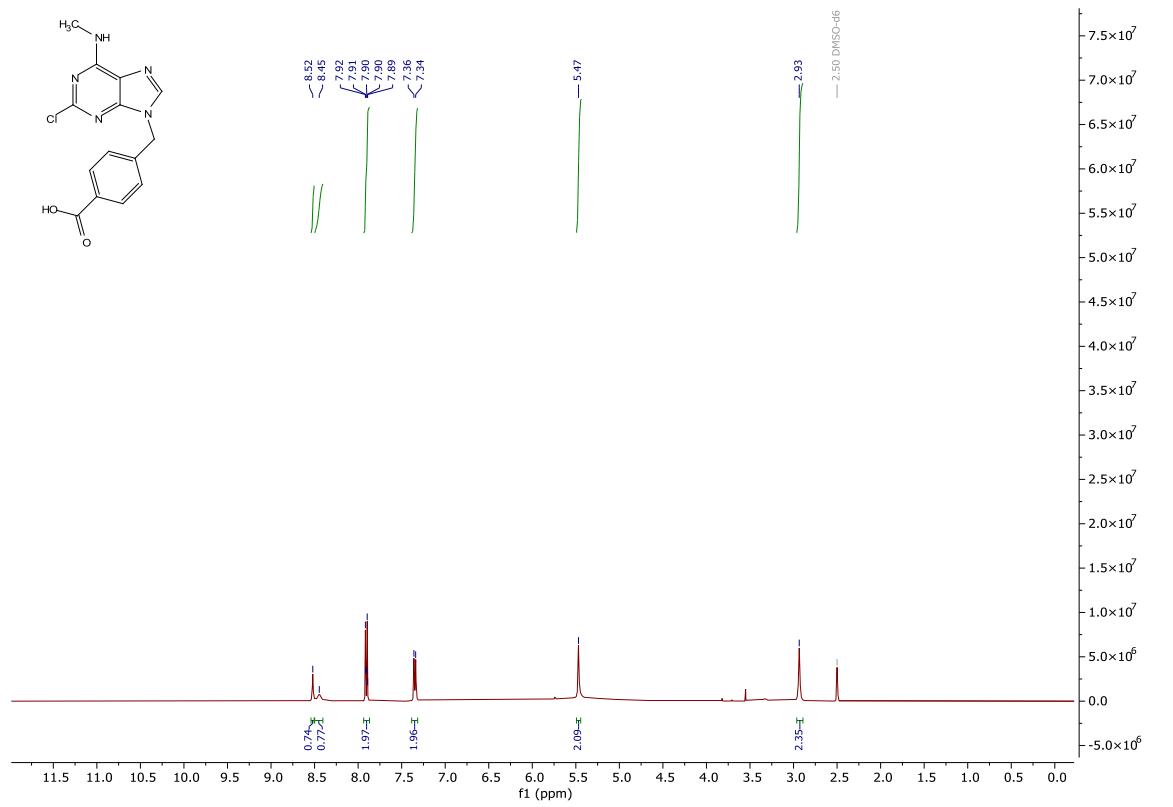
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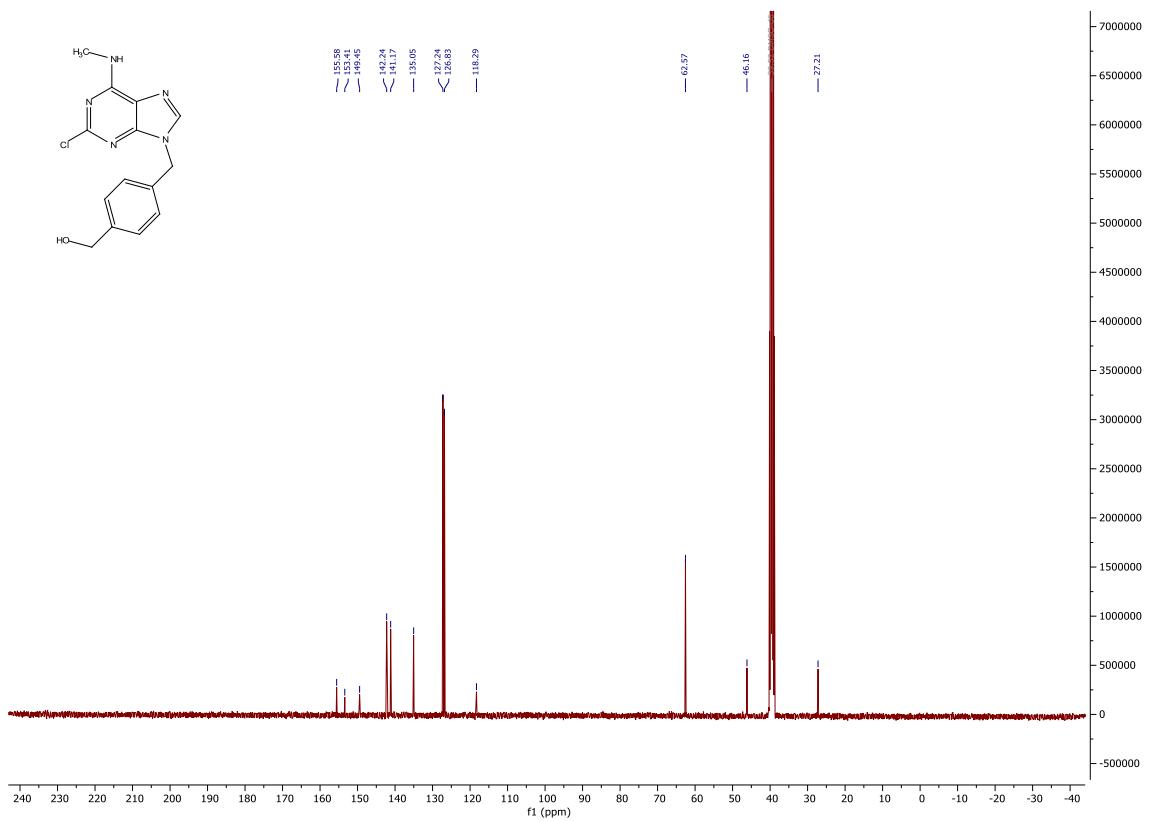
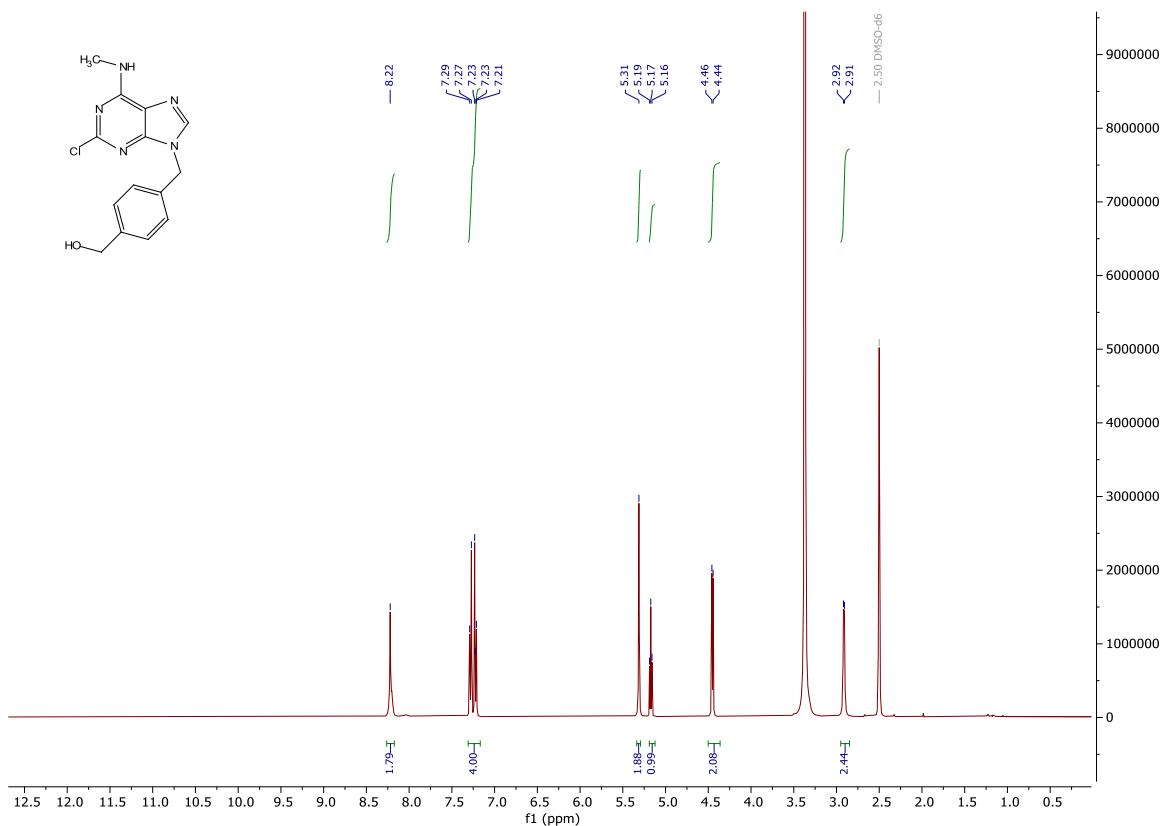
methyl 4-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoate 28



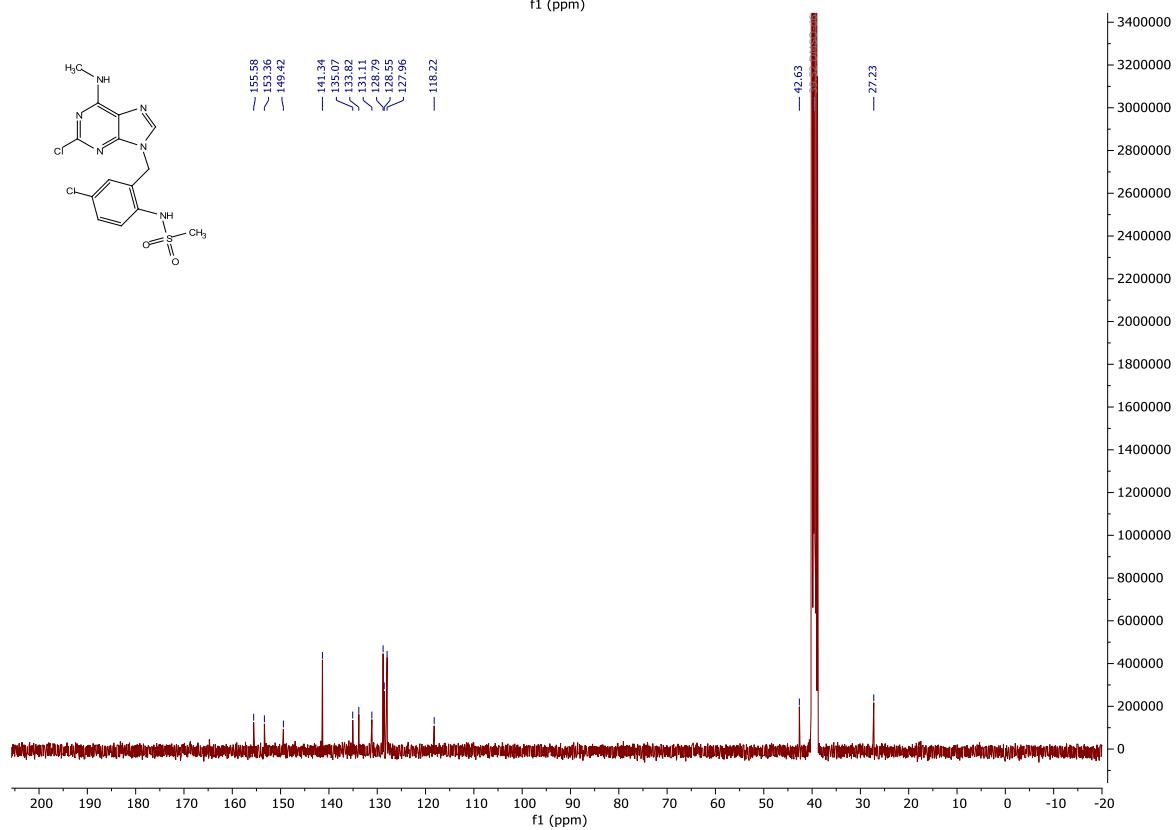
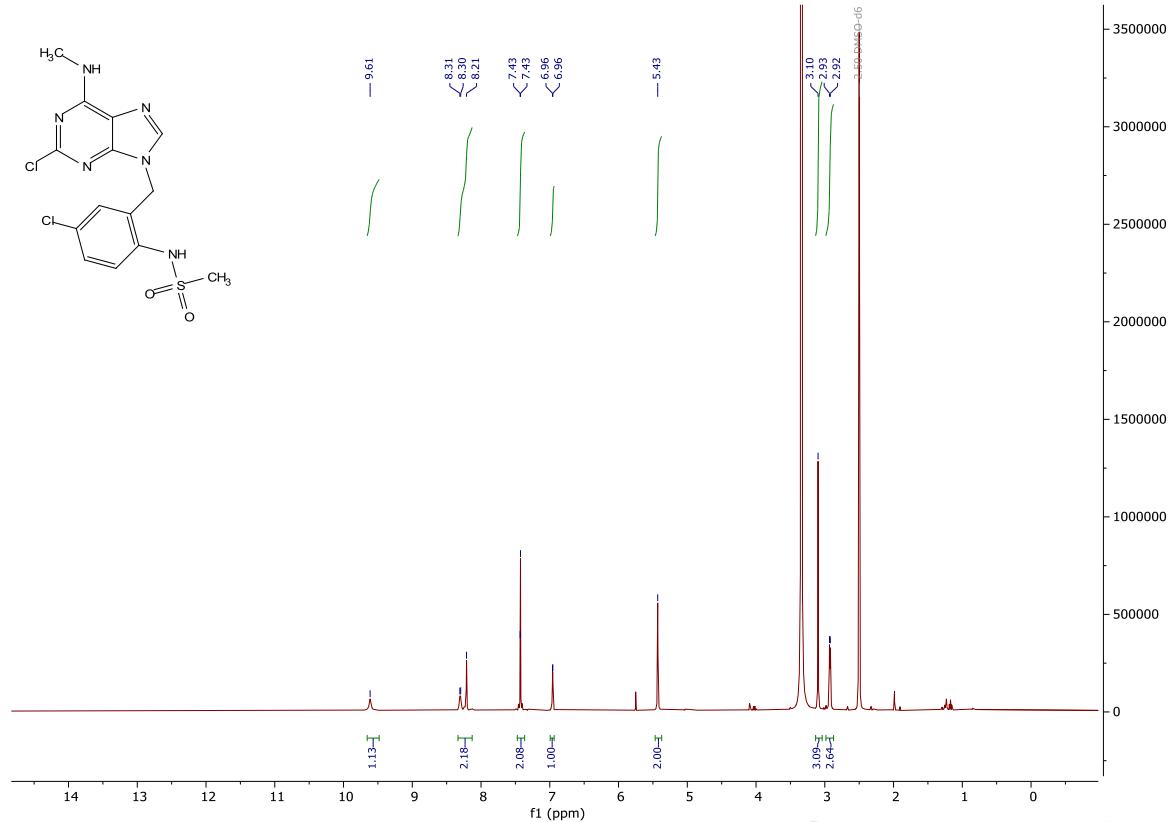
3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid 29



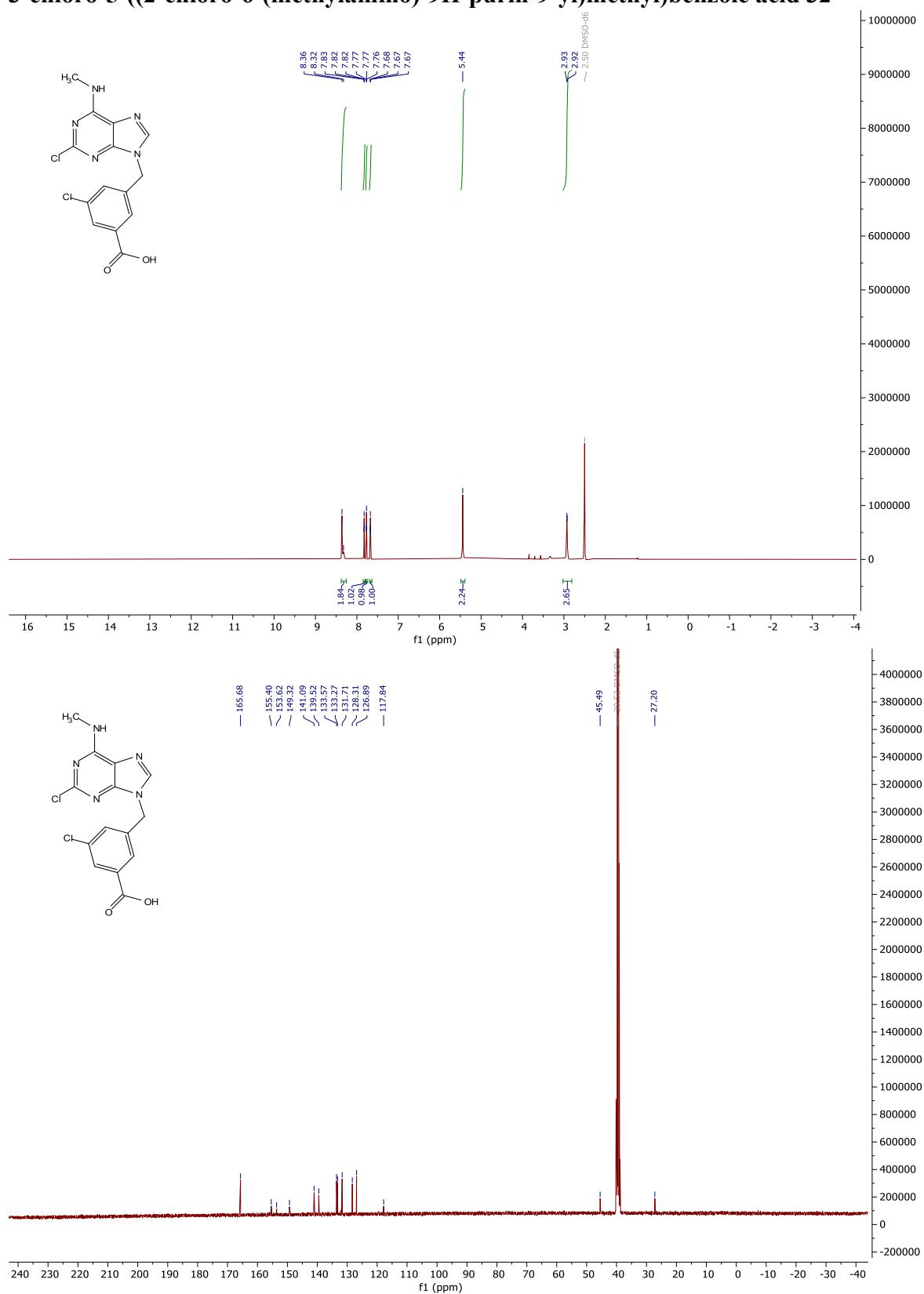
(4-((2,6-dichloro-9H-purin-9-yl)methyl)phenyl)methanol 30



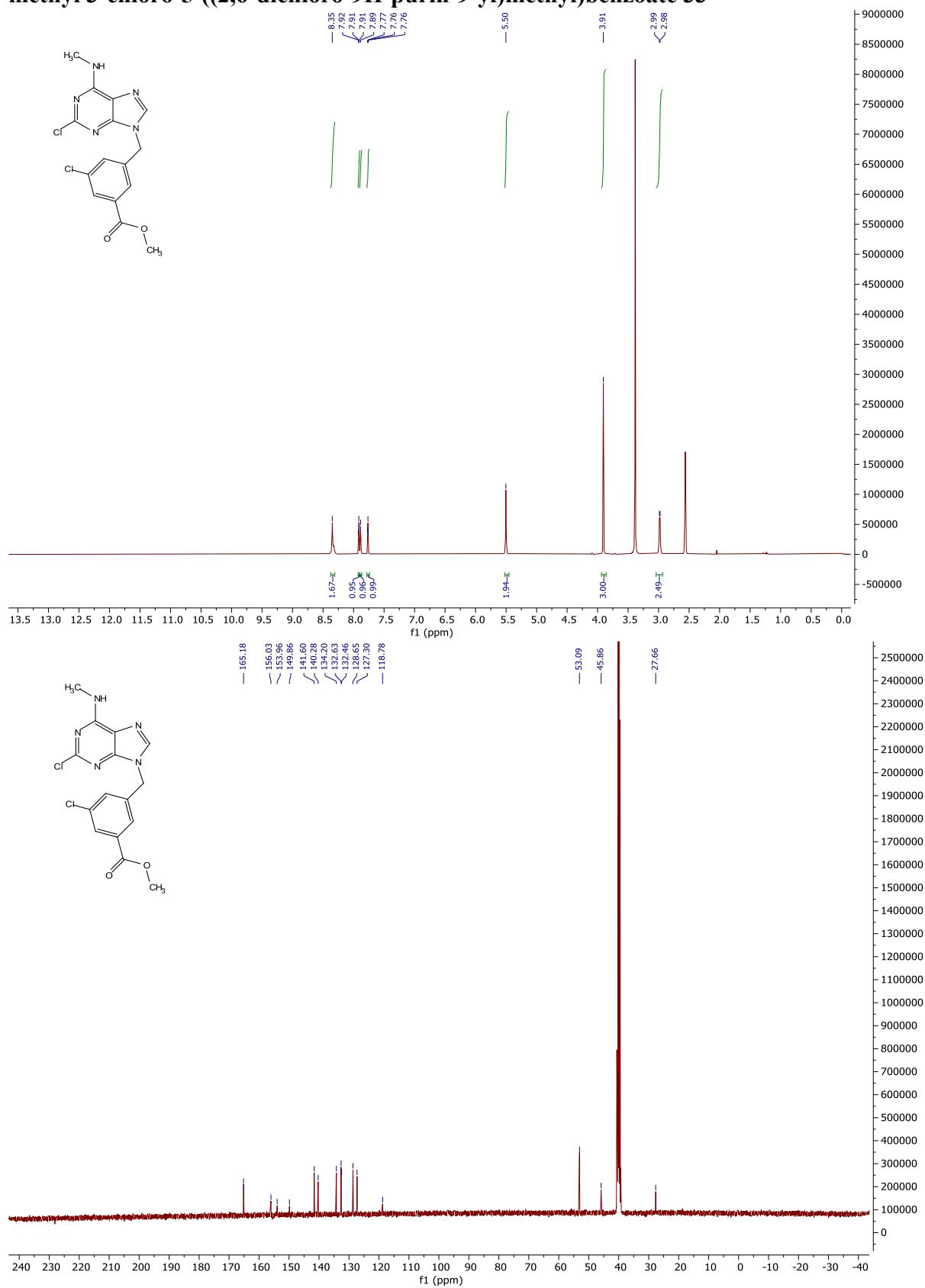
N-(4-chloro-2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl) methanesulfonamide 31



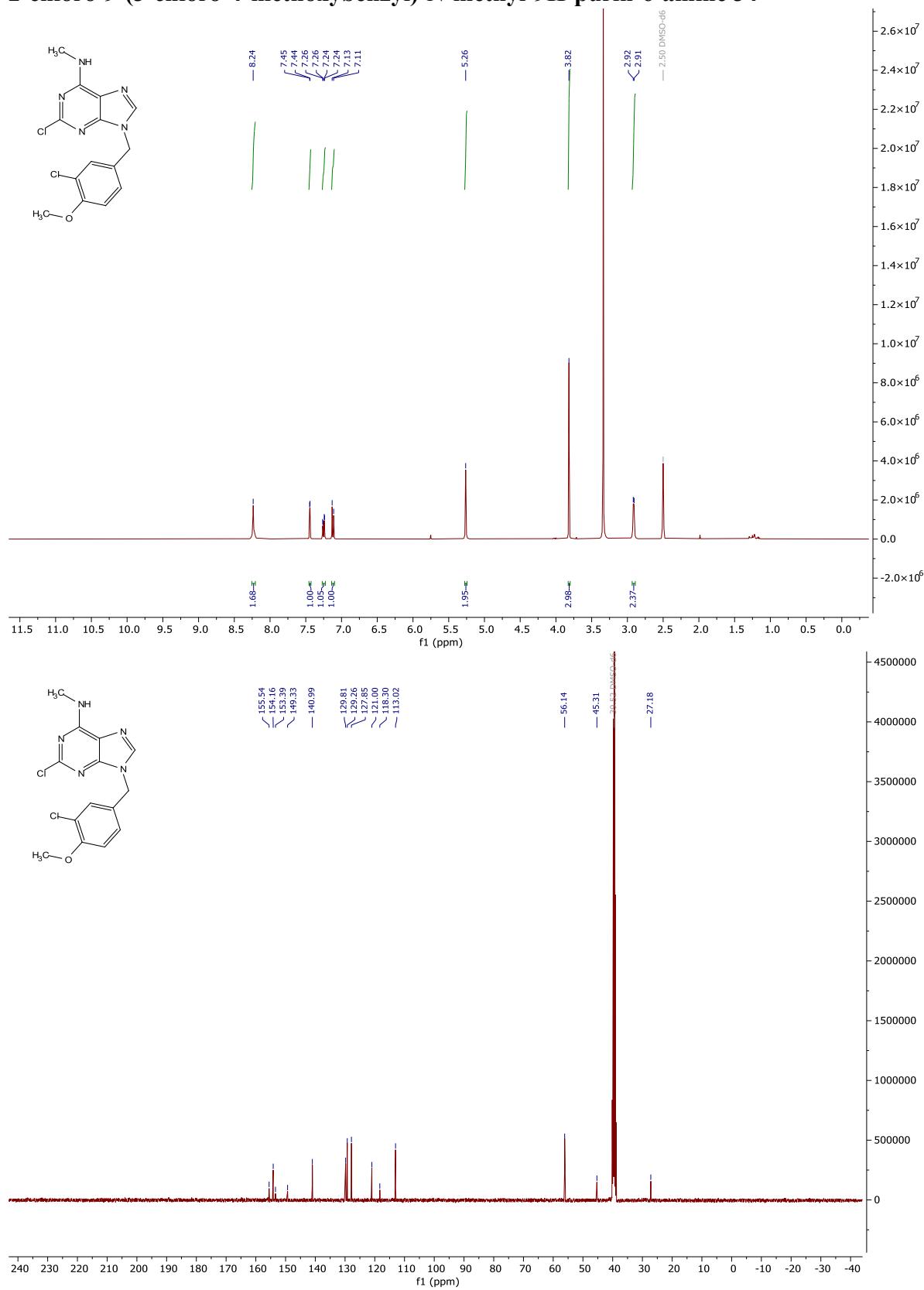
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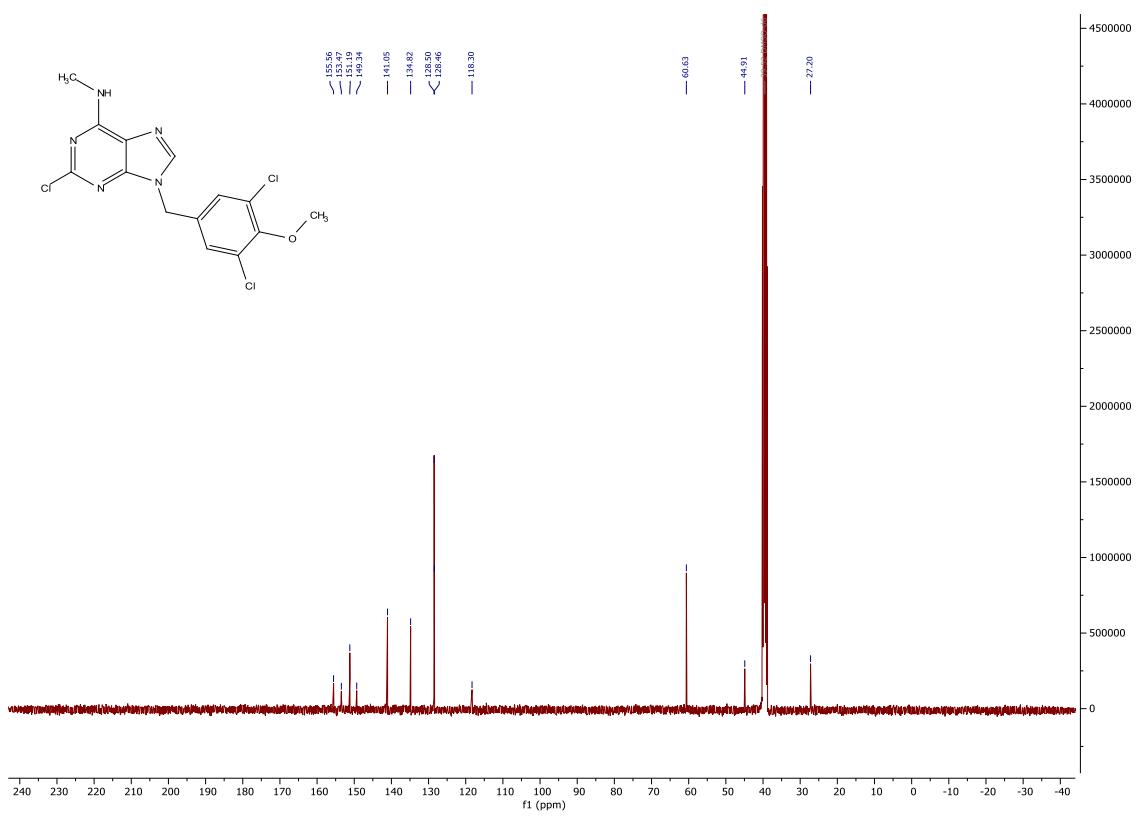
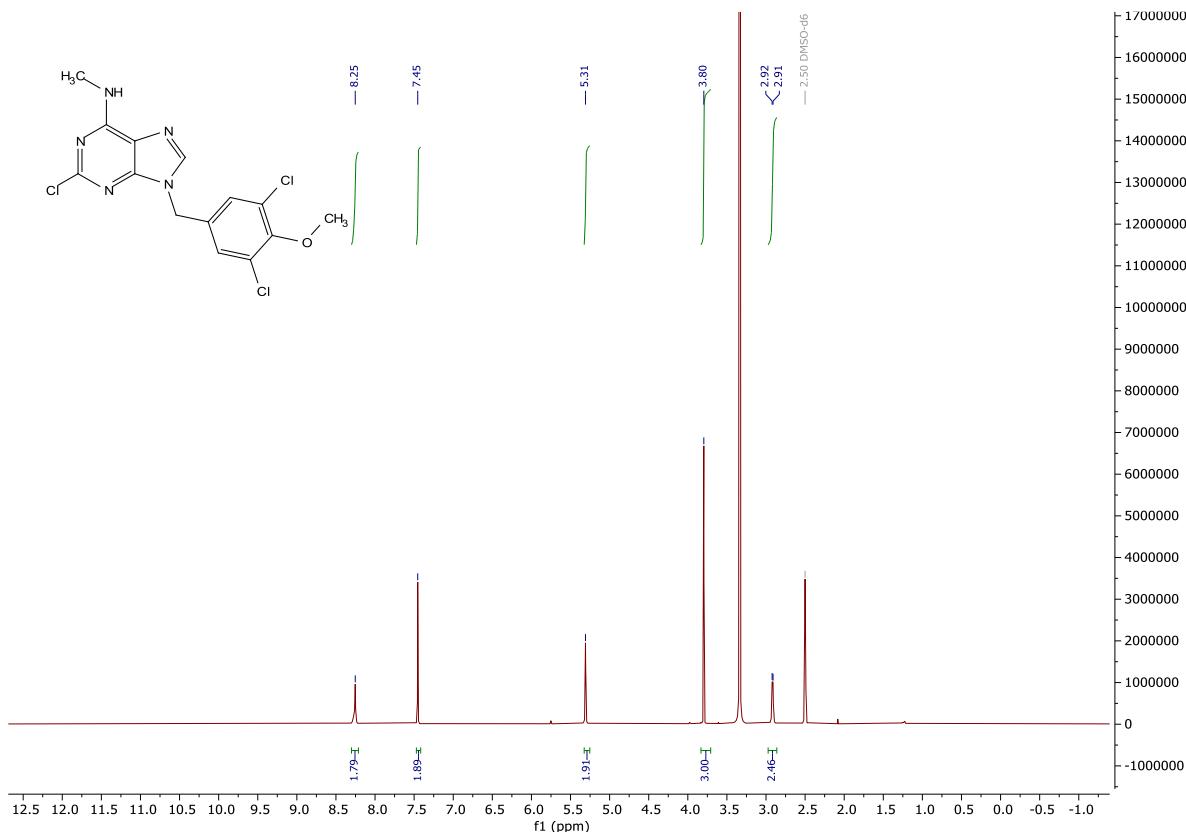
methyl 3-chloro-5-((2,6-dichloro-9H-purin-9-yl)methyl)benzoate 33



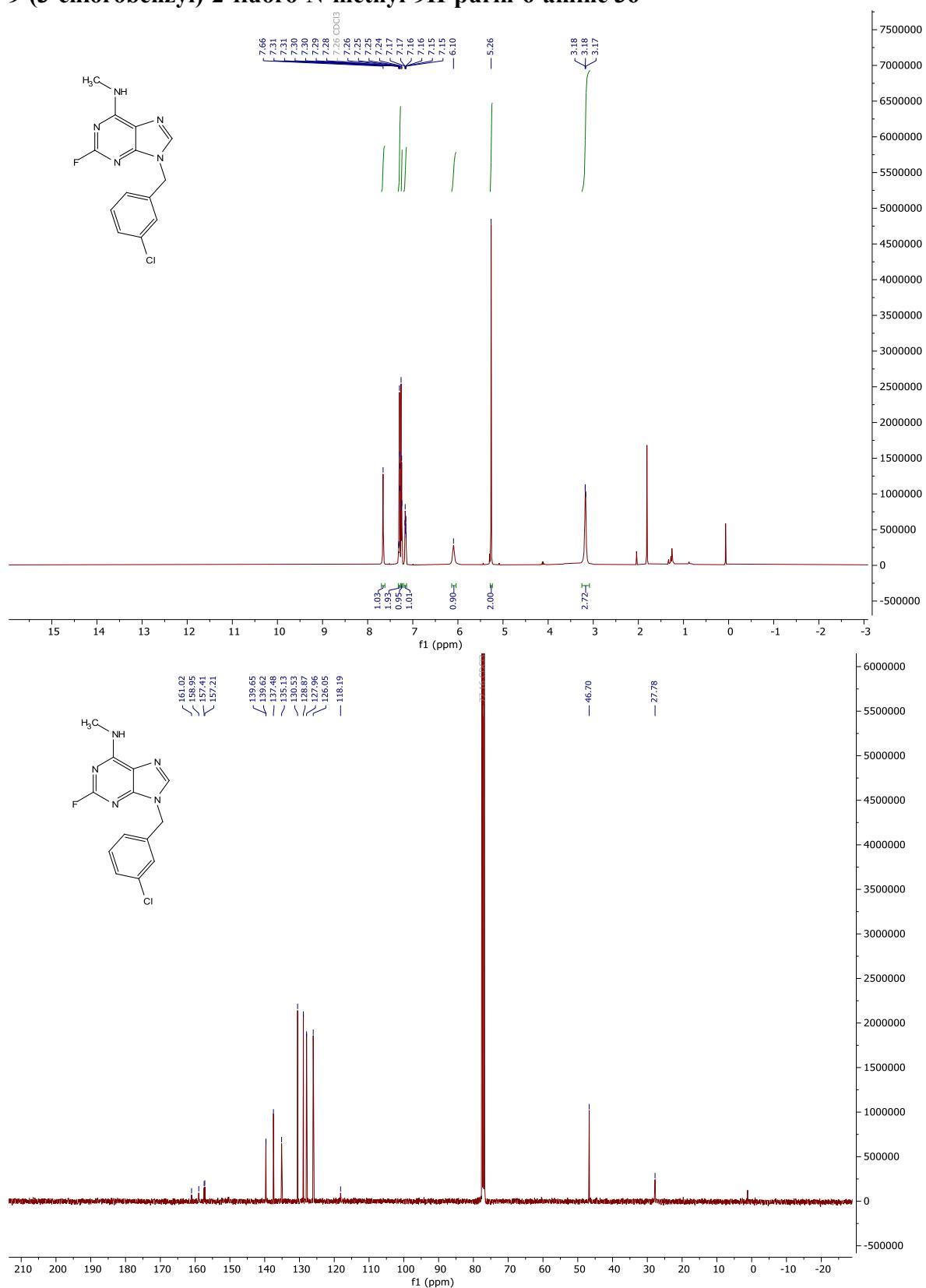
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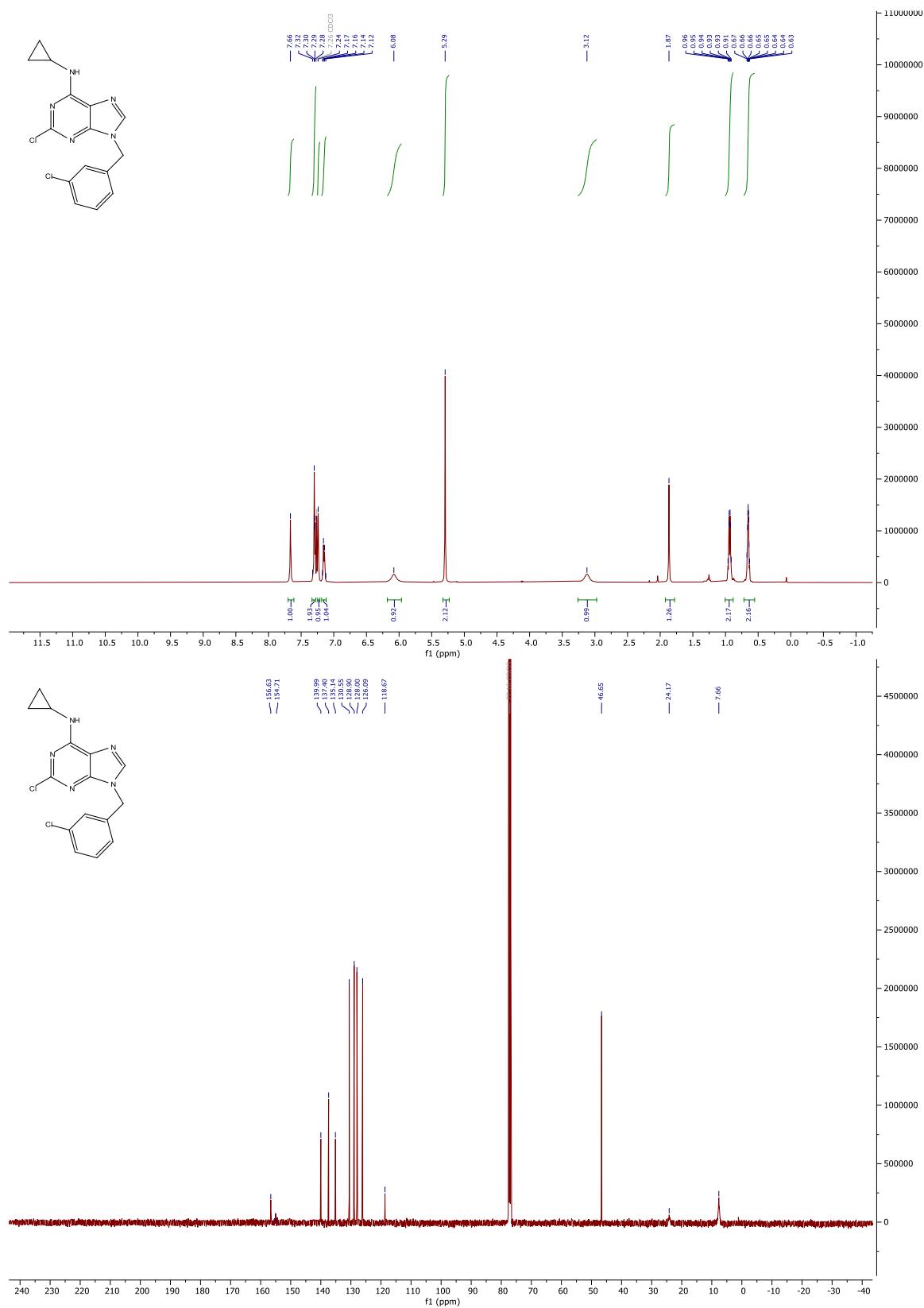
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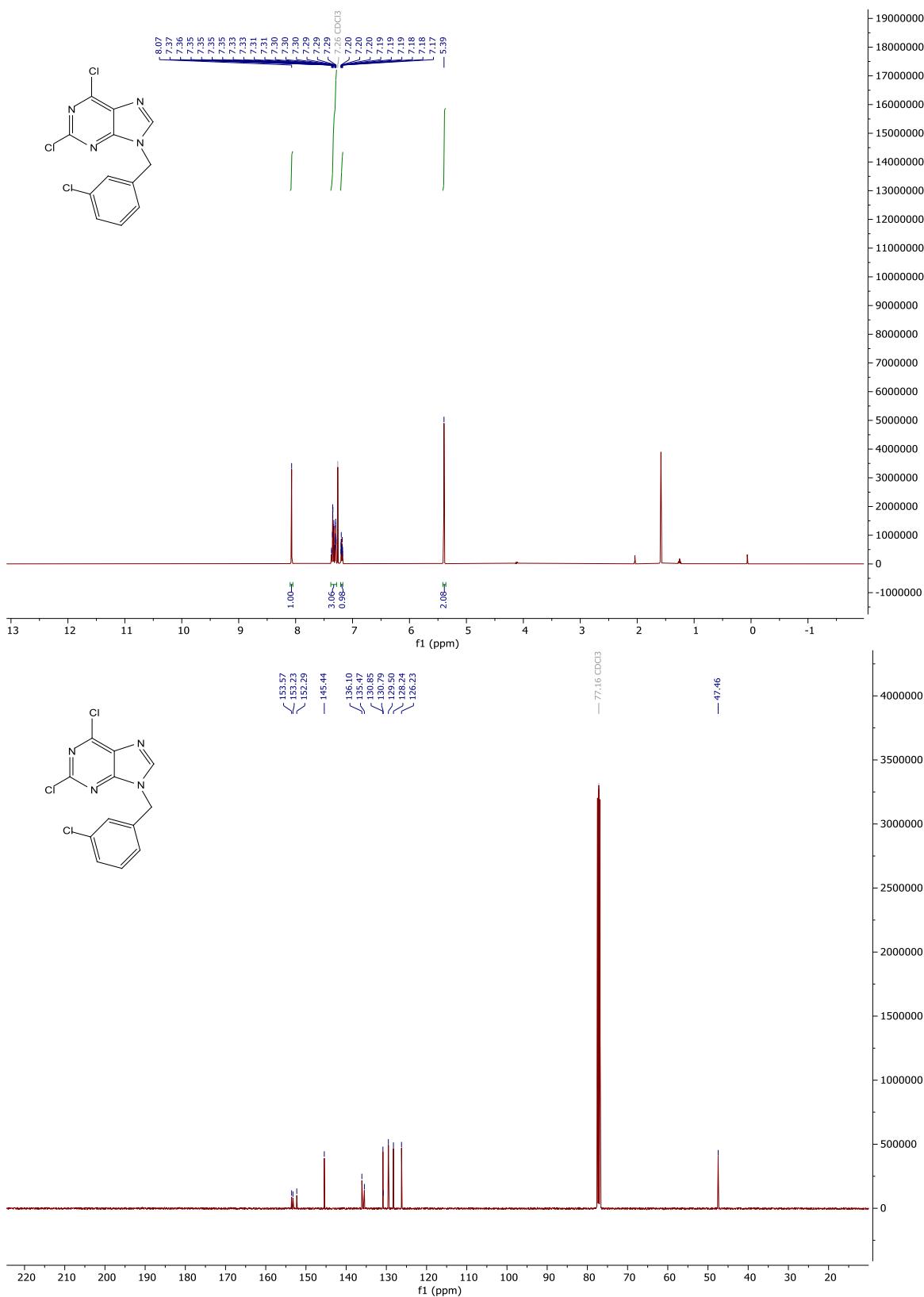
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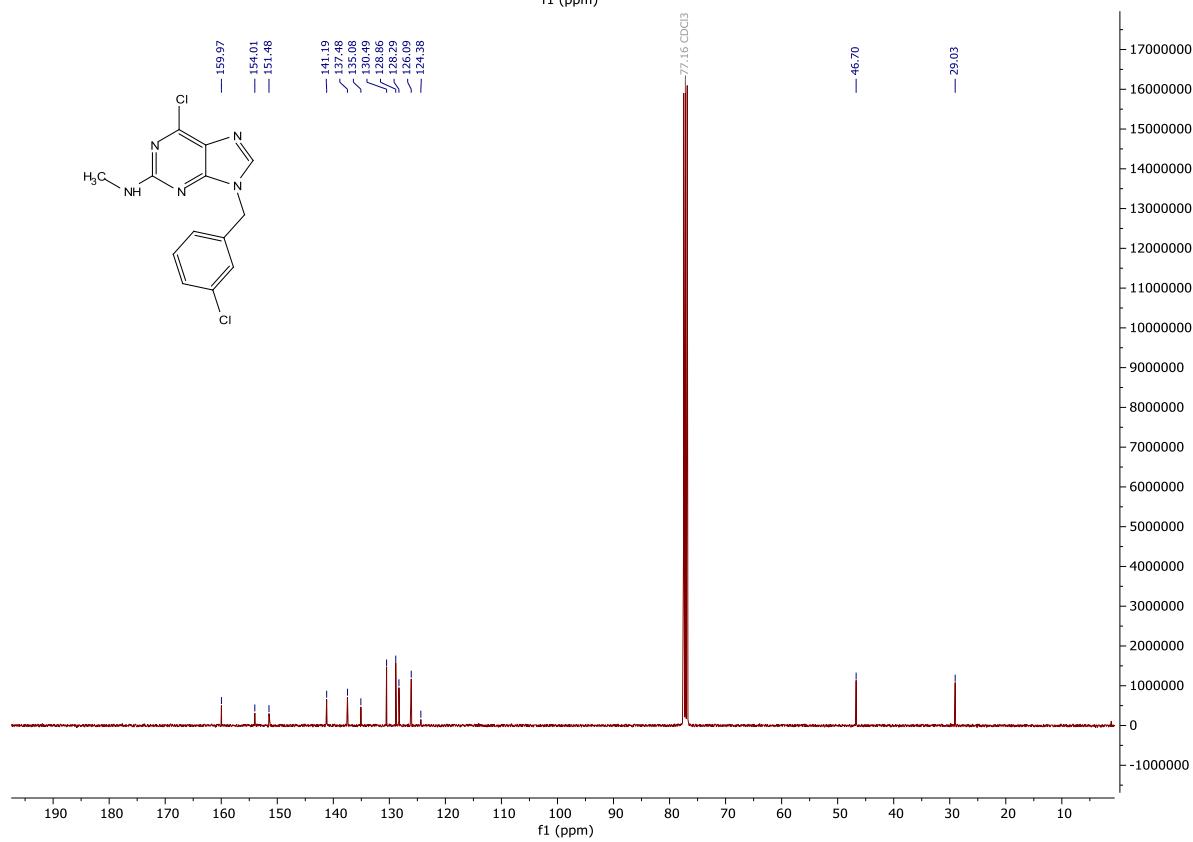
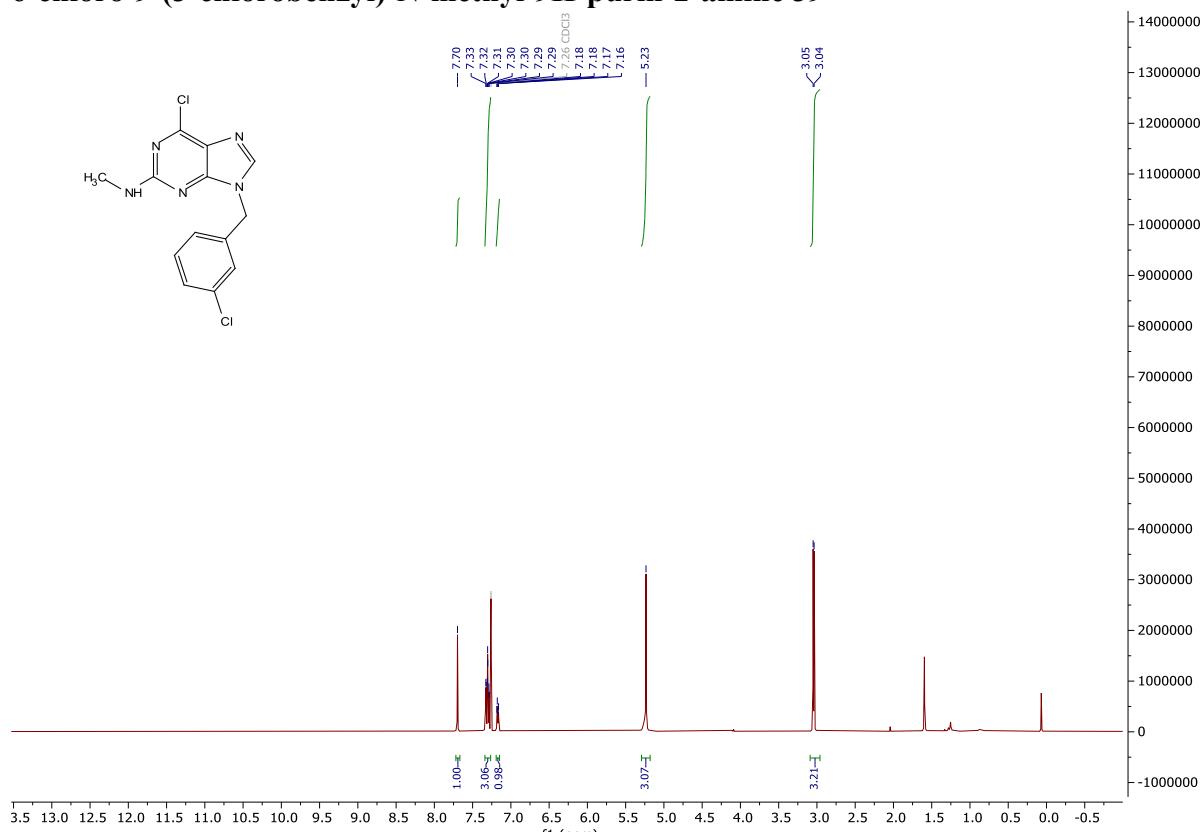
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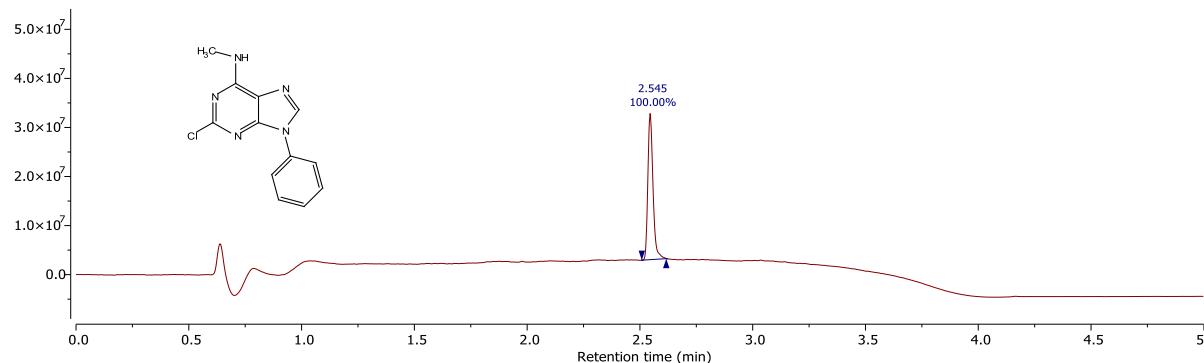


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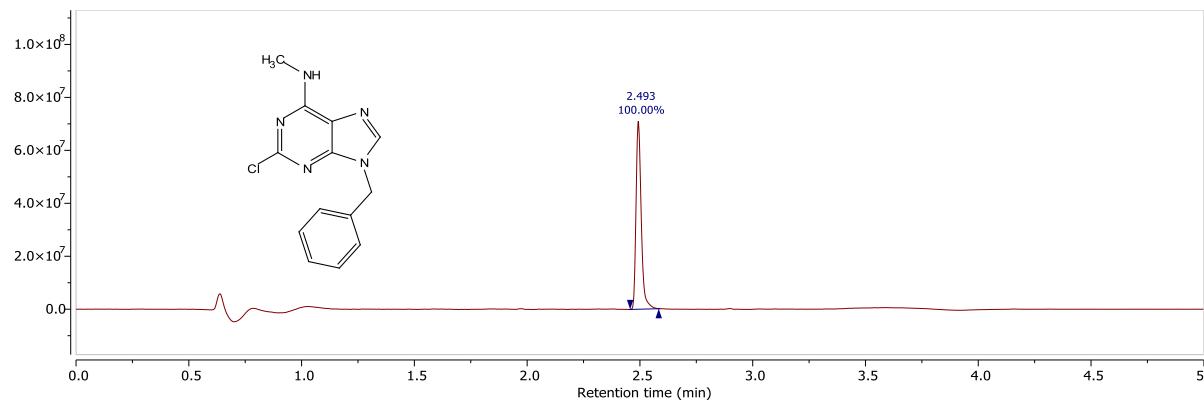


6. HPLC traces of final compounds

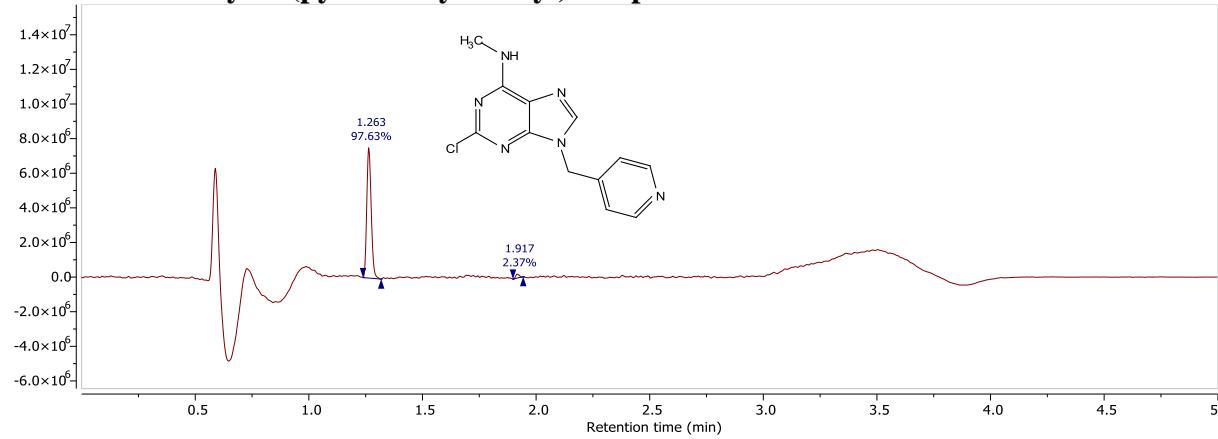
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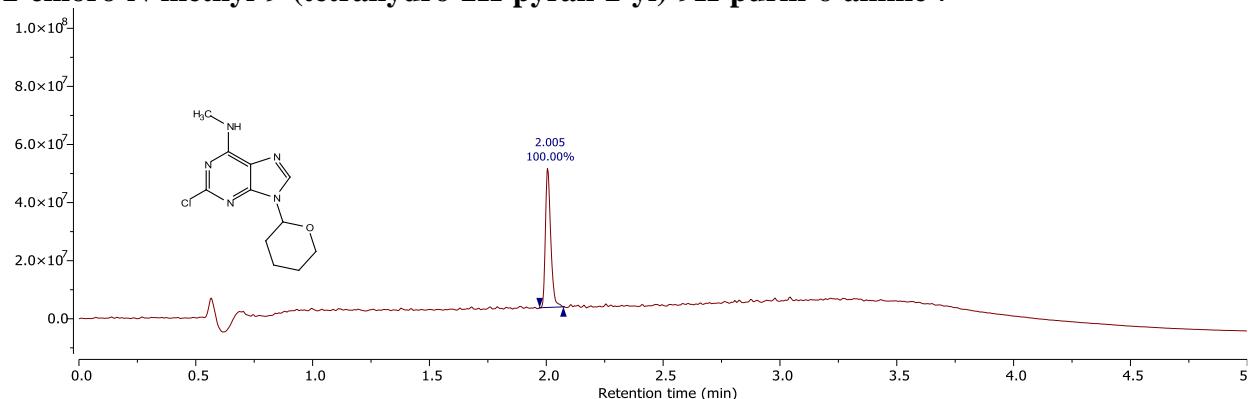
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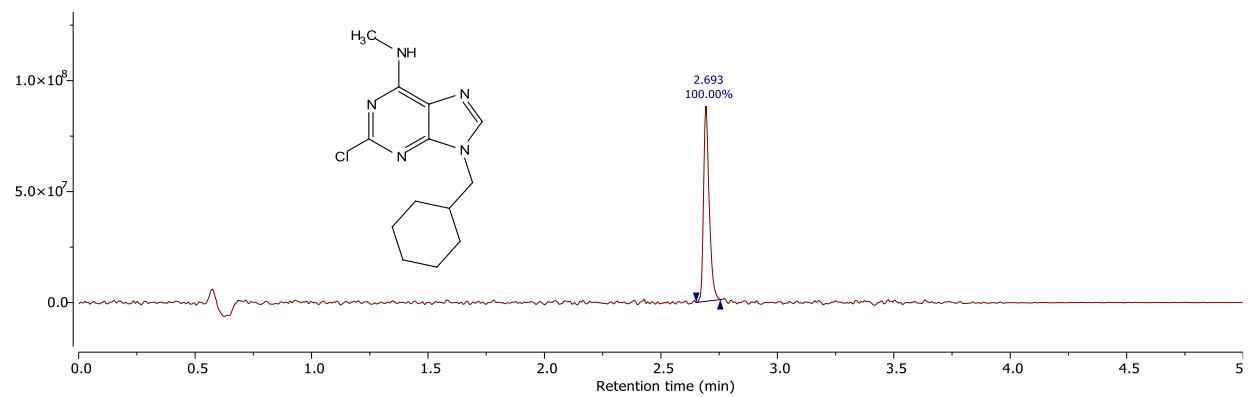
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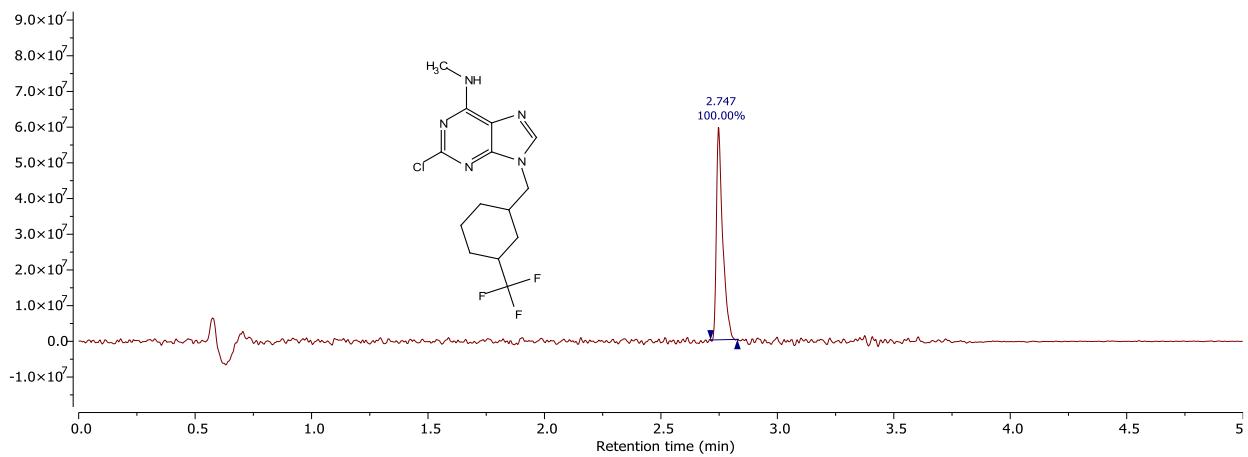
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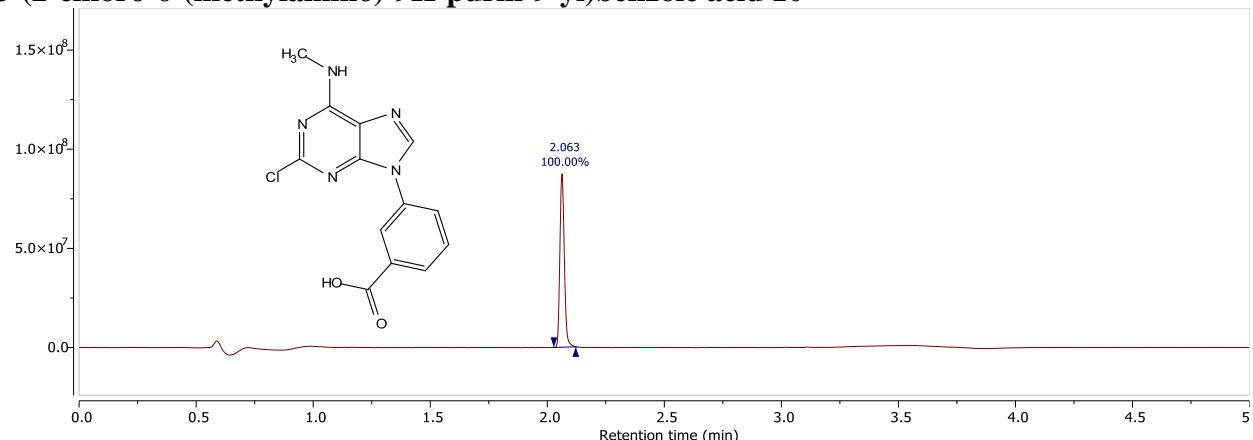
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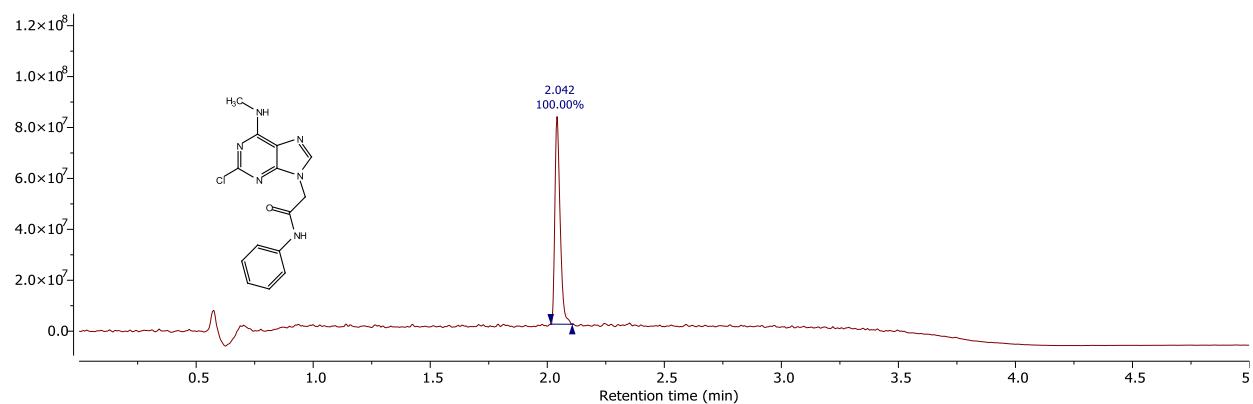
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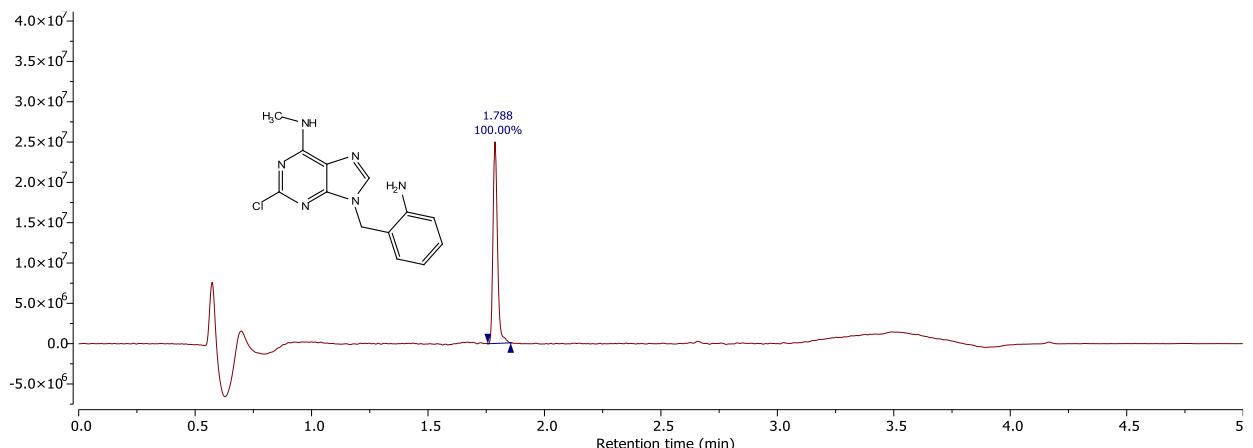
3-(2-chloro-6-(methylamino)-9H-purin-9-yl)benzoic acid 10



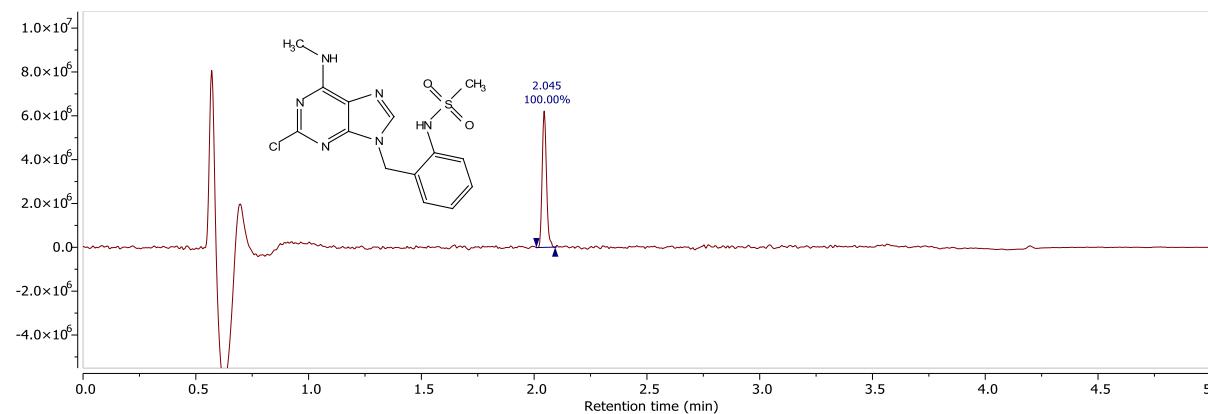
2-(2-chloro-6-(methylamino)-9H-purin-9-yl)-N-phenylacetamide 11



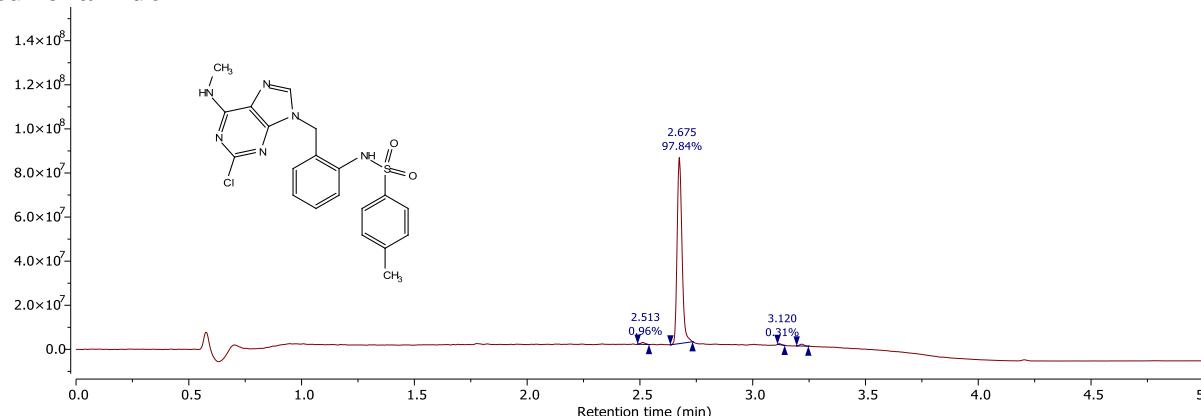
9-(2-aminobenzyl)-2-chloro-N-methyl-9H-purin-6-amine 12



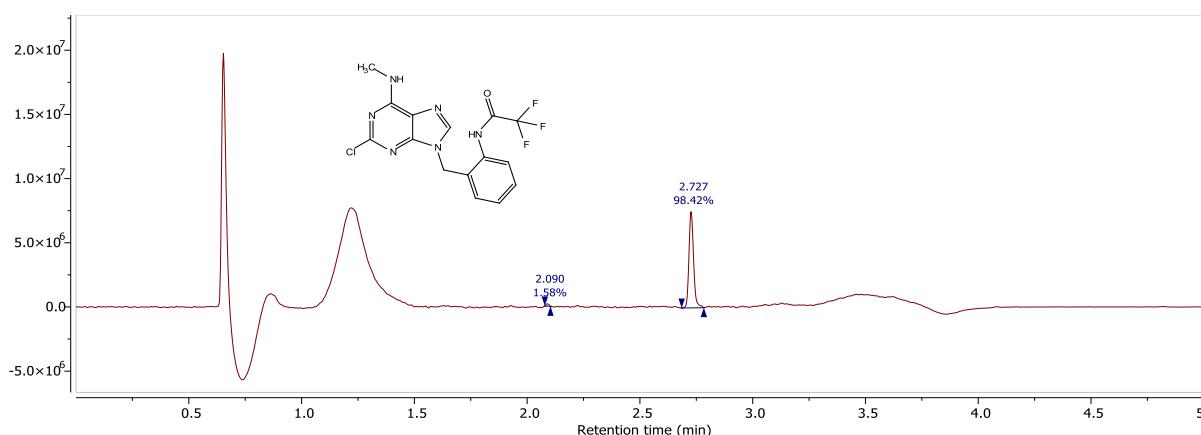
N-(2-((2-chloro-6-(methylamino)-9H-purin-9-yl) methyl)phenyl) methanesulfonamide 13



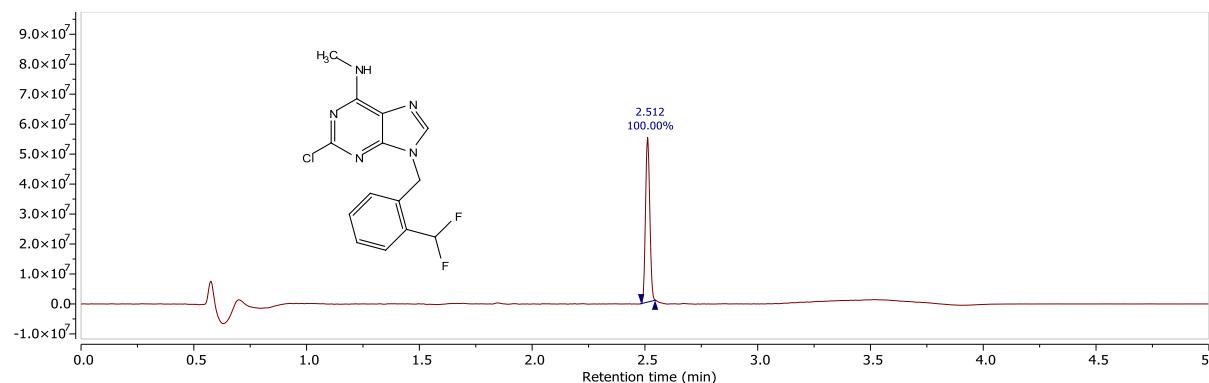
N-(2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)-4-methylbenzenesulfonamide 14



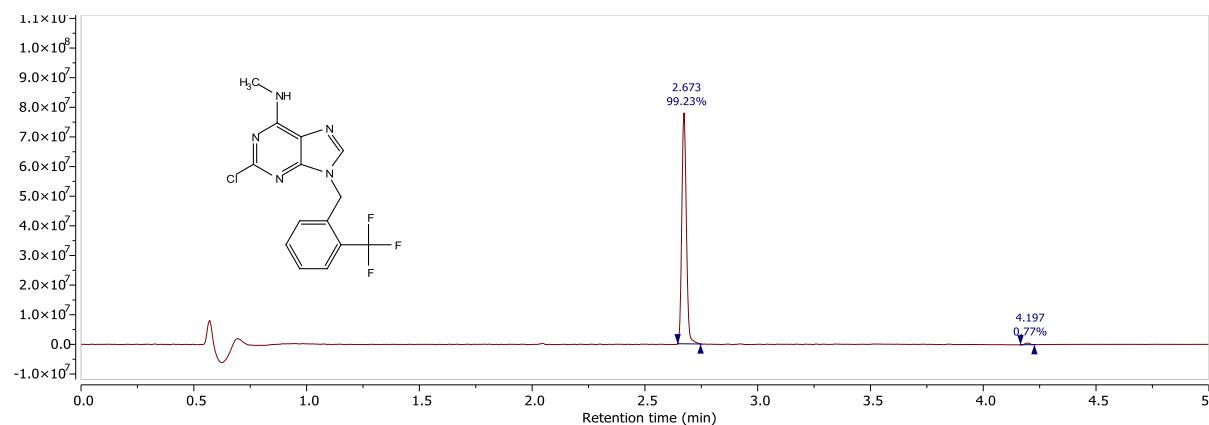
N-(2-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)phenyl)-2,2,2-trifluoroacetamide 15



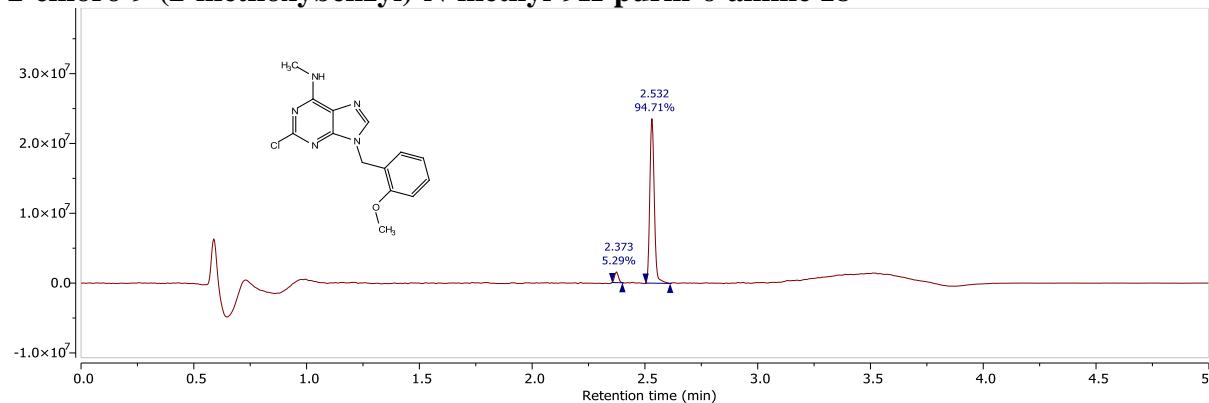
2-chloro-9-(2-(difluoromethyl)benzyl)-N-methyl-9H-purin-6-amine 16



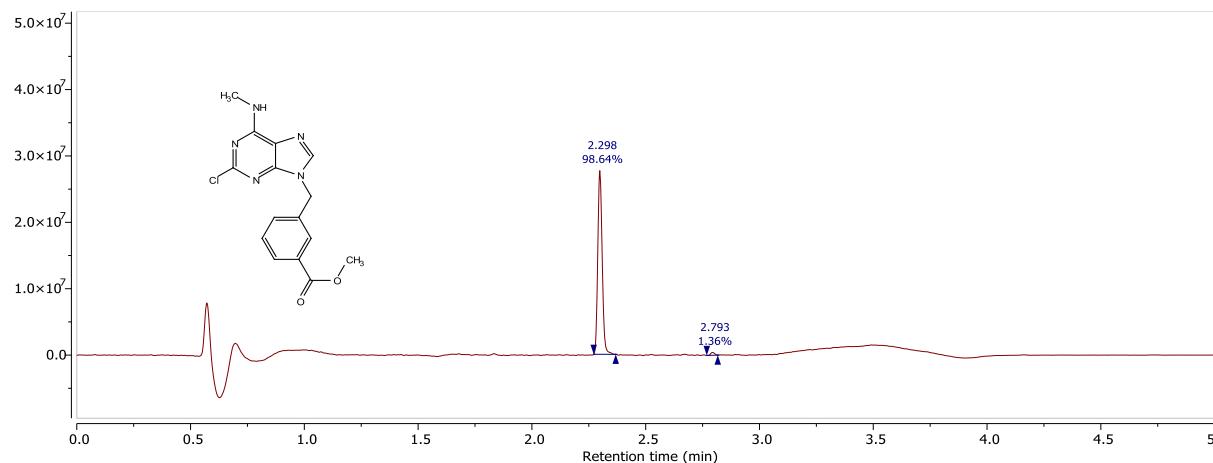
2-chloro-N-methyl-9-(2-(trifluoromethyl)benzyl)-9H-purin-6-amine 17



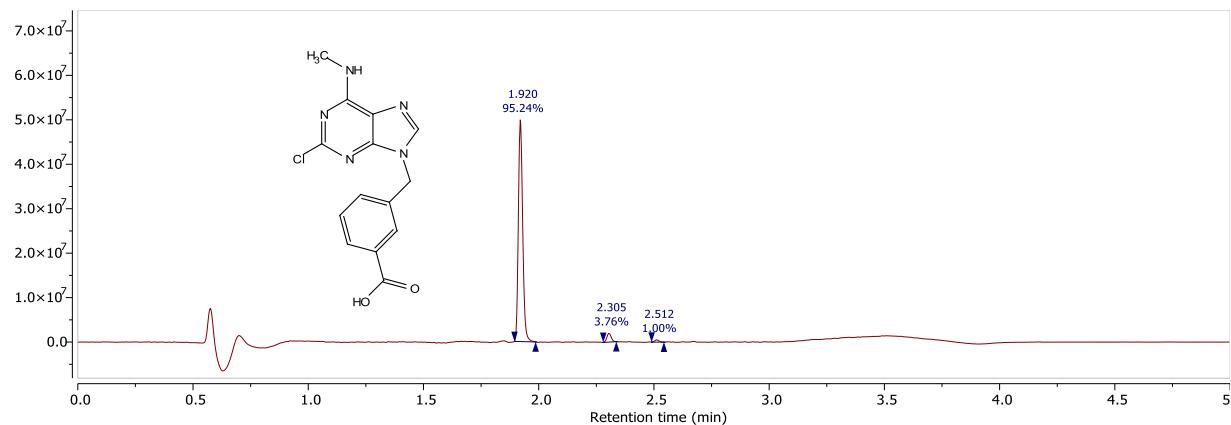
2-chloro-9-(2-methoxybenzyl)-N-methyl-9H-purin-6-amine 18



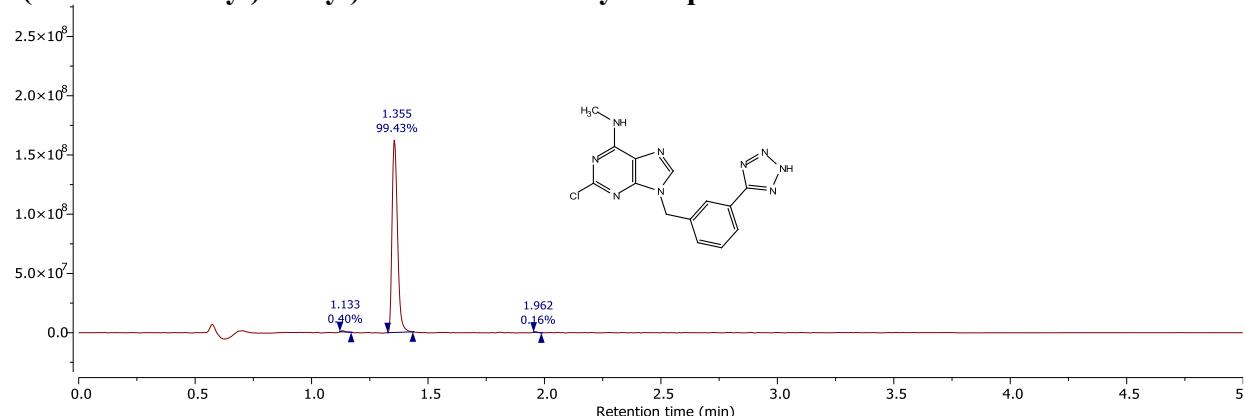
methyl 3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoate 19



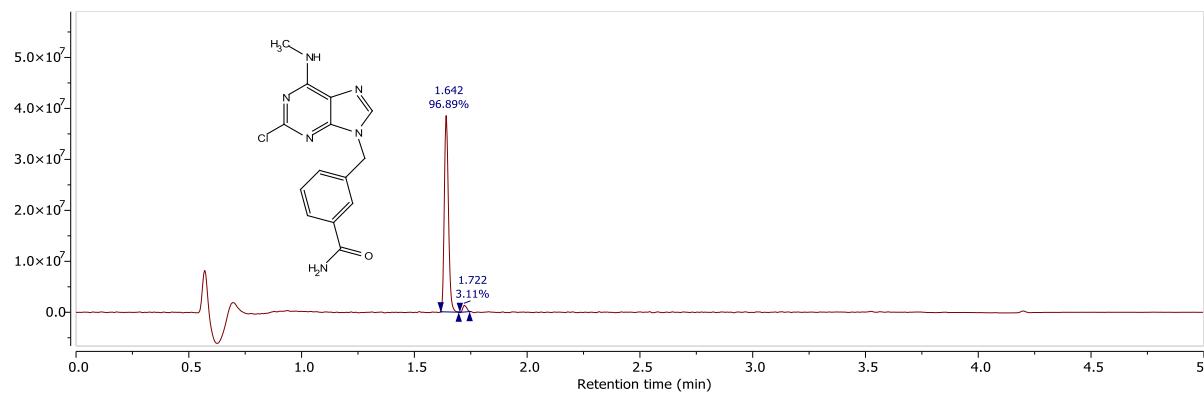
3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid 20



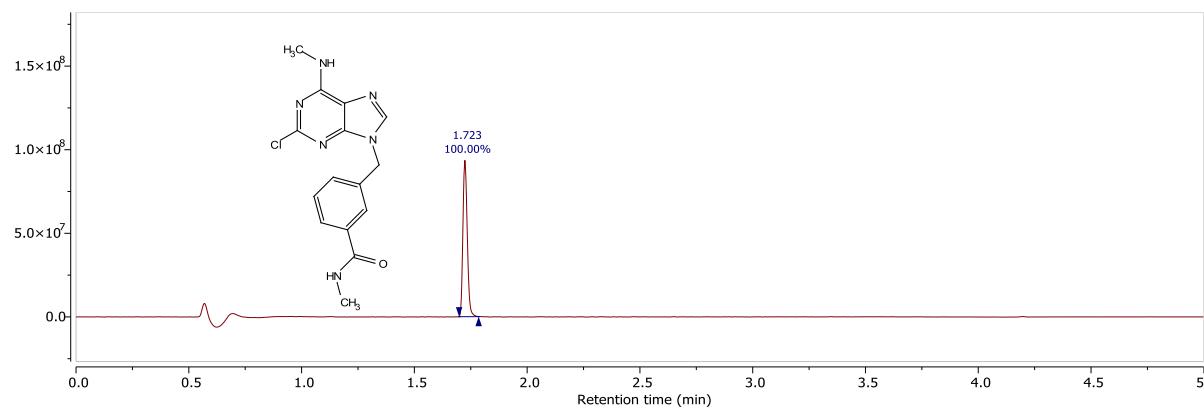
3-(2H-tetrazol-5-yl)benzyl-2-chloro-N-methyl-9H-purin-6-amine 21



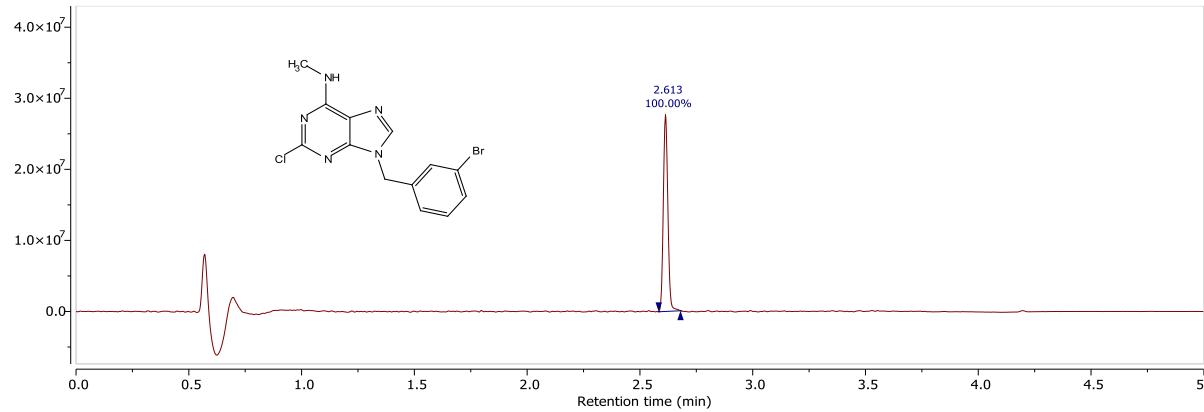
3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzamide 22



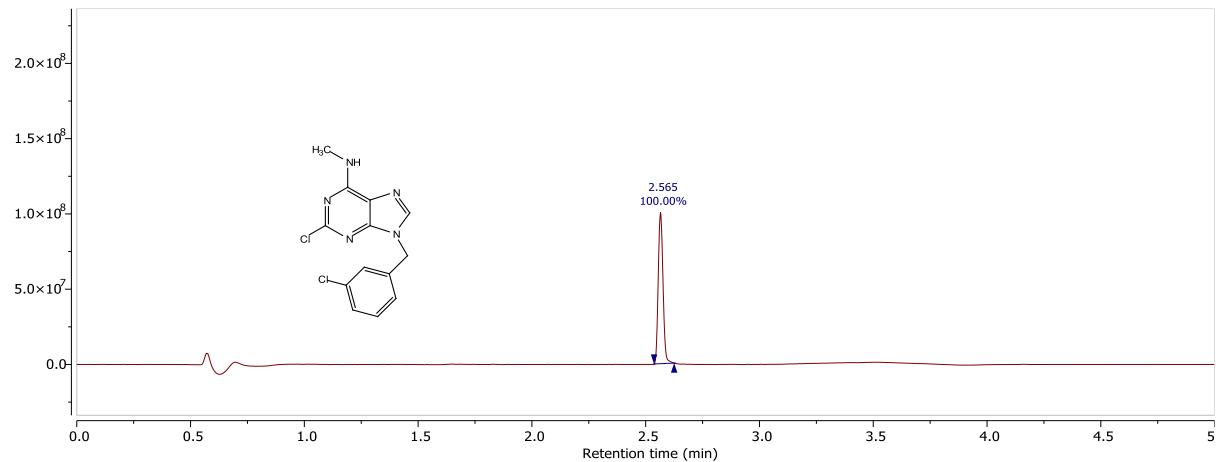
3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)-N-methyl benzamide 23



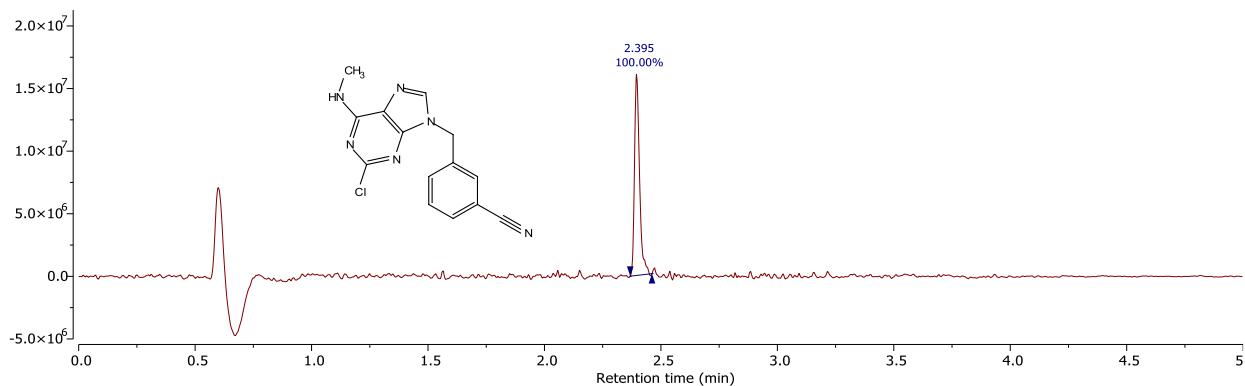
9-(3-bromobenzyl)-2-chloro-N-methyl-9H-purin-6-amine 24



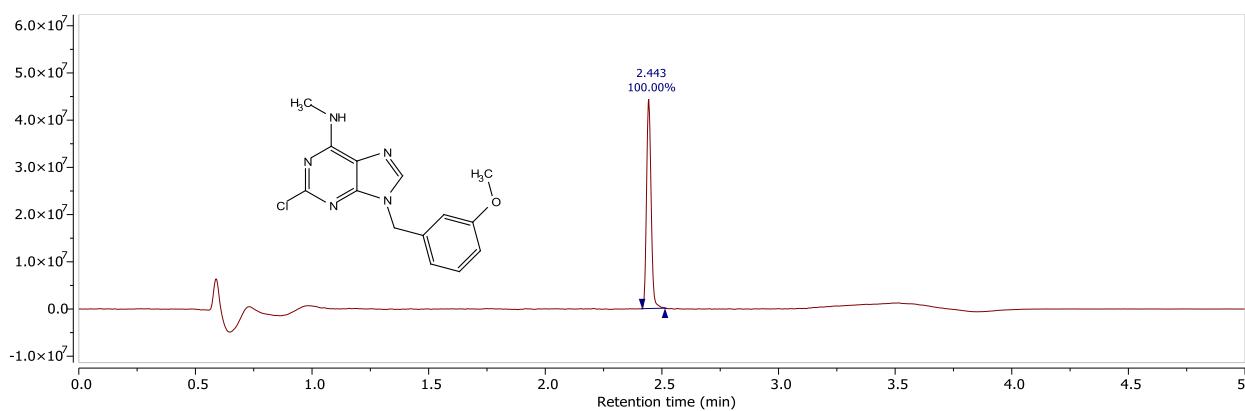
2-chloro-9-(3-chlorobenzyl)-N-methyl-9H-purin-6-amine 25



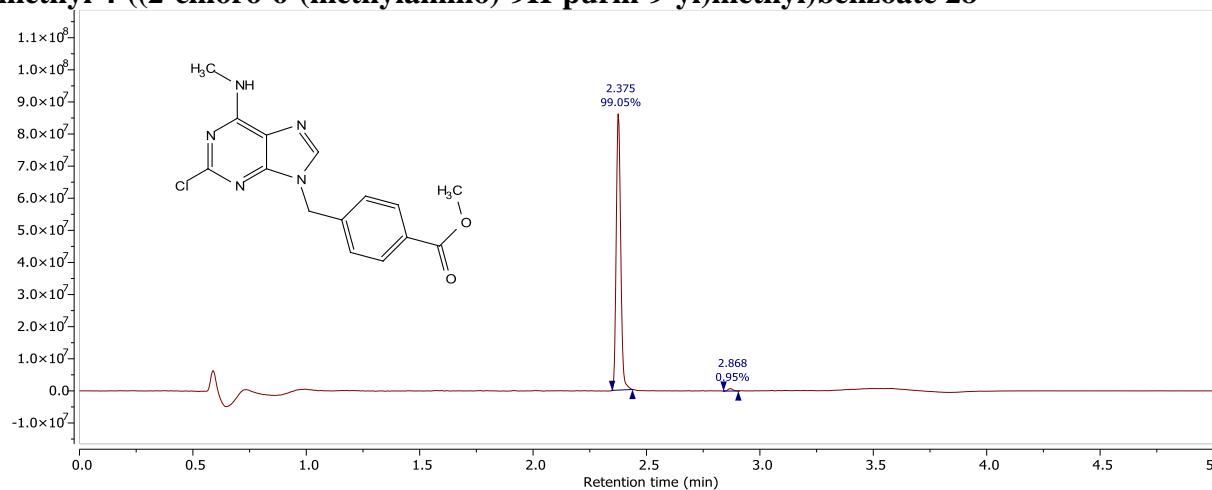
3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzonitrile 26



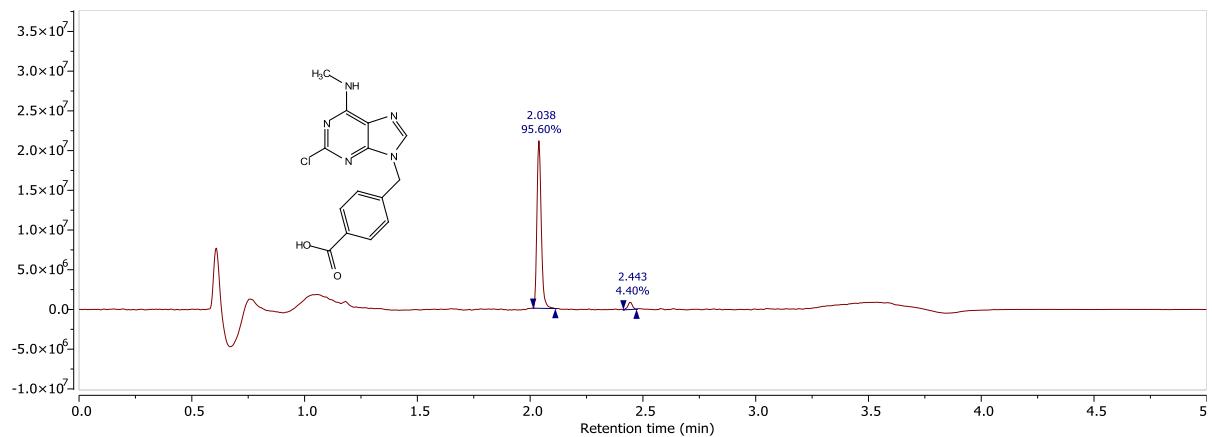
2-chloro-9-(3-methoxybenzyl)-N-methyl-9H-purin-6-amine 27



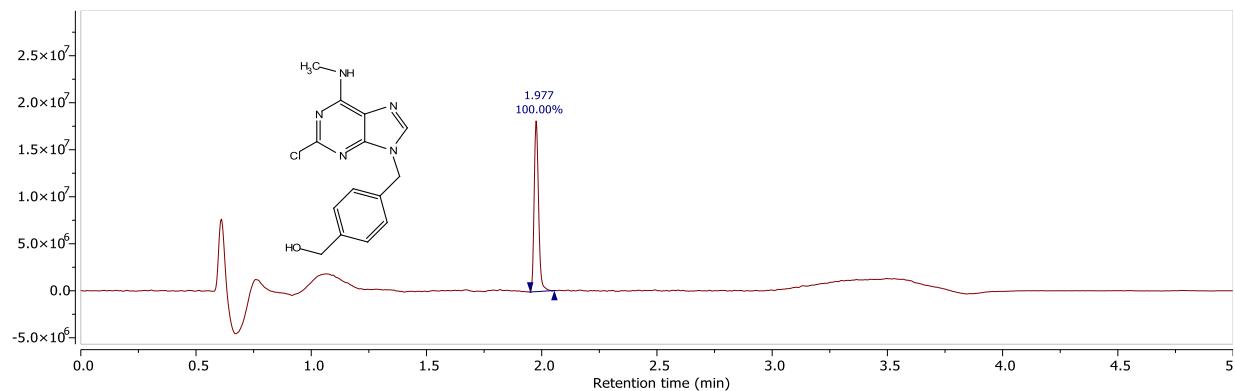
methyl 4-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoate 28



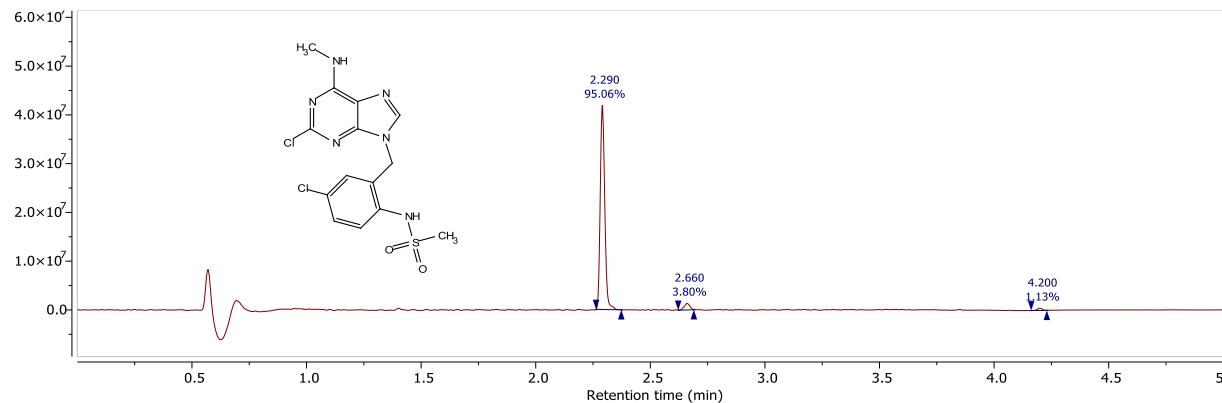
3-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid 29



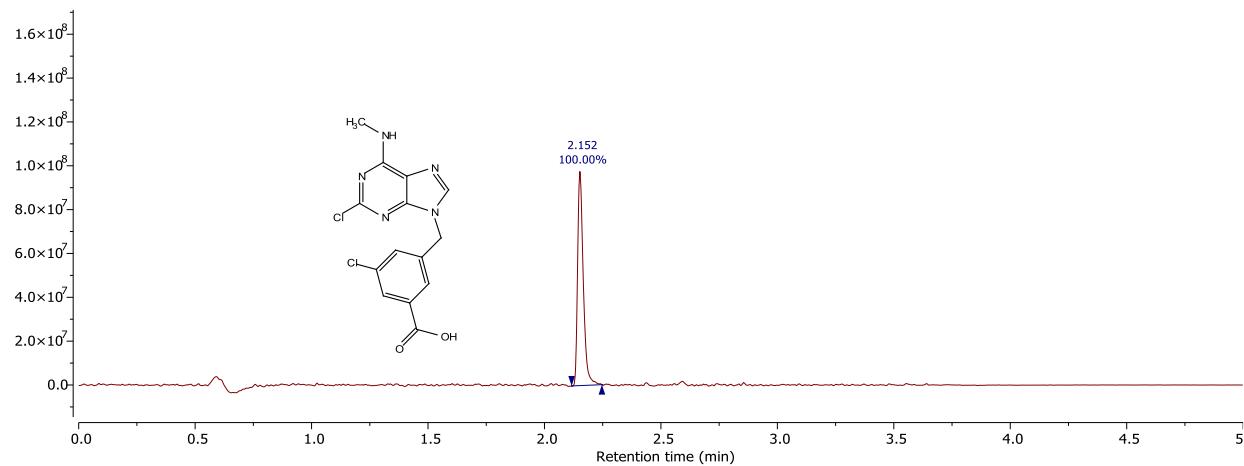
(4-((2,6-dichloro-9H-purin-9-yl)methyl)phenyl)methanol 30



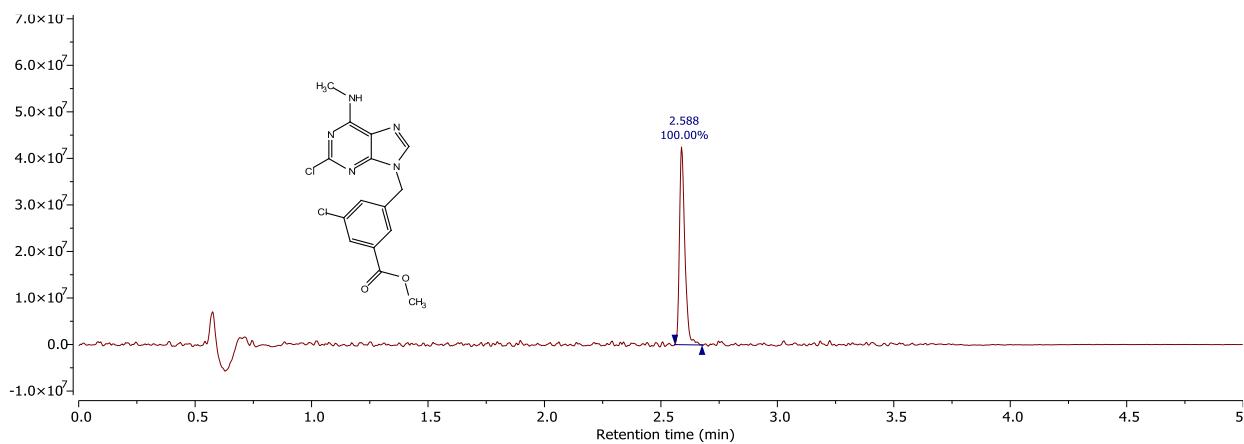
N-(4-chloro-2-((2-chloro-6-(methylamino)-9H-purin-9-yl) methyl)phenyl) methanesulfonamide 31



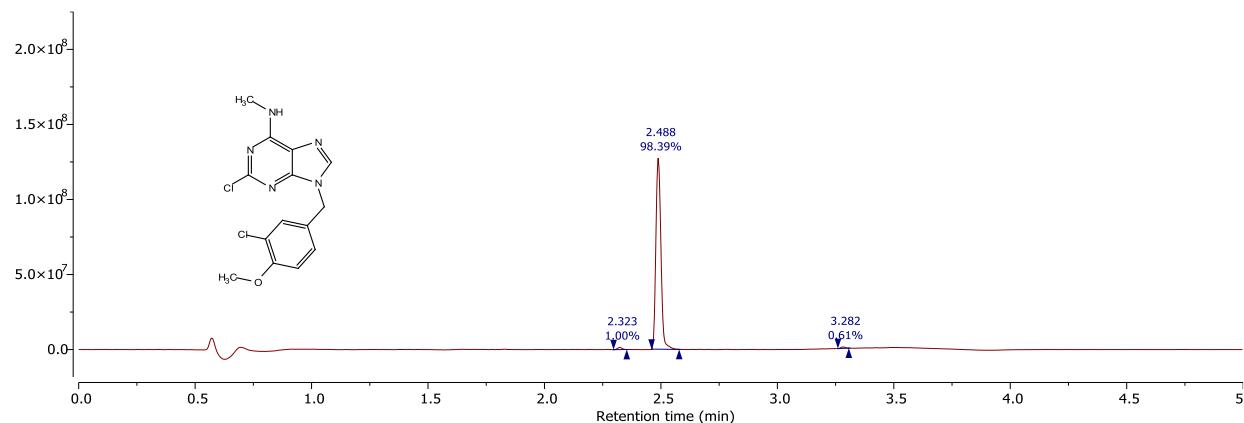
3-chloro-5-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoic acid 32



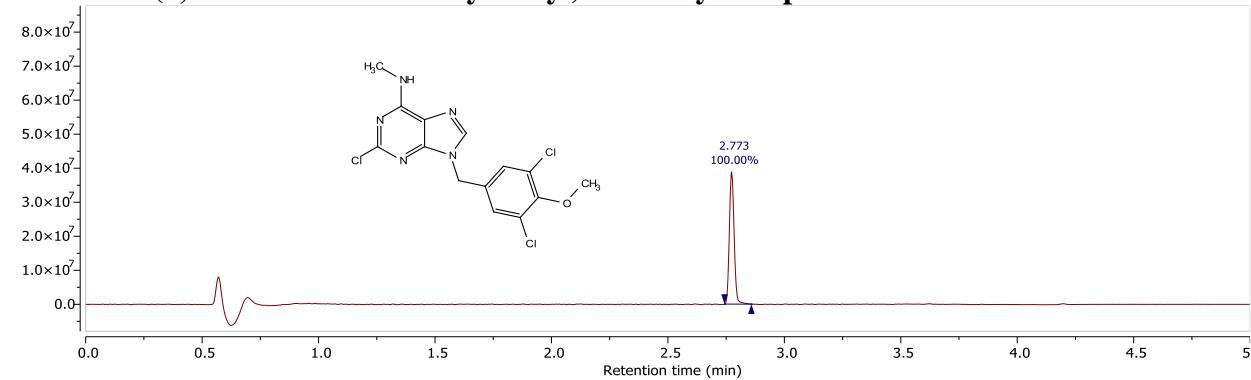
methyl 3-chloro-5-((2-chloro-6-(methylamino)-9H-purin-9-yl)methyl)benzoate 33



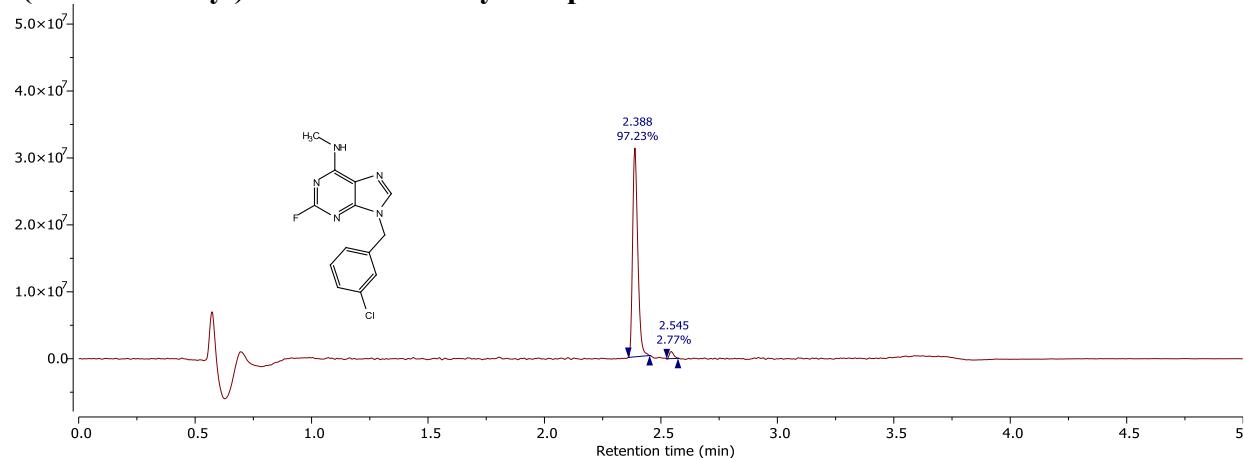
2-chloro-9-(3-chloro-4-methoxybenzyl)-N-methyl-9H-purin-6-amine 34



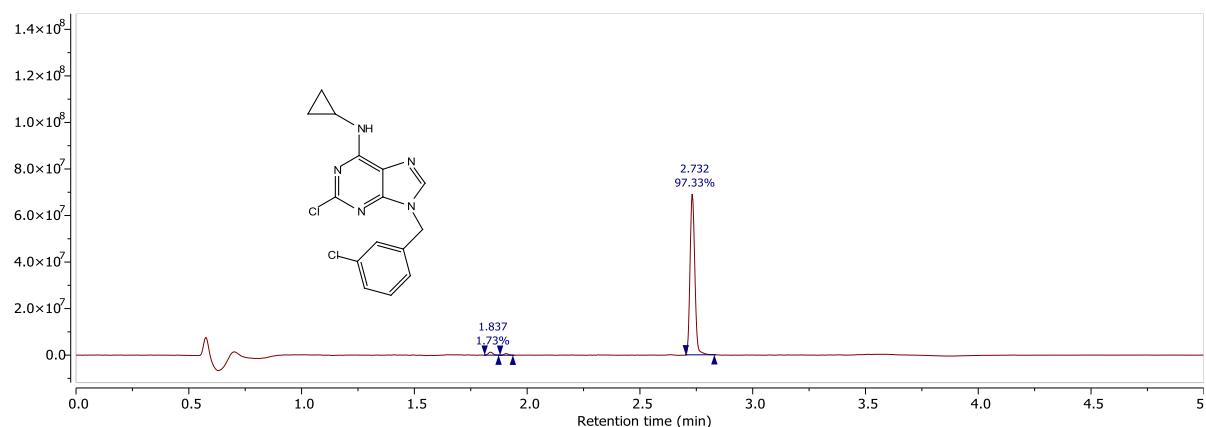
2-chloro-9-(3,5-dichloro-4-methoxybenzyl)-N-methyl-9H-purin-6-amine 35



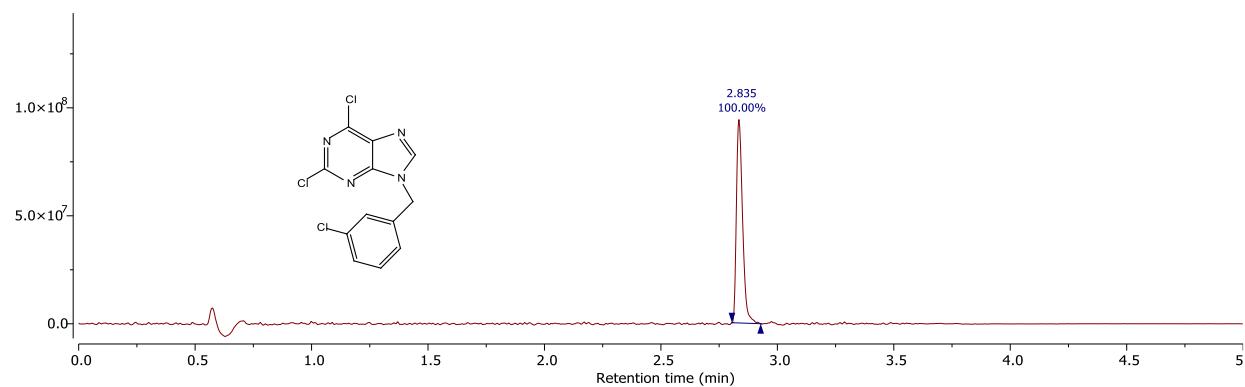
9-(3-chlorobenzyl)-2-fluoro-N-methyl-9H-purin-6-amine 36



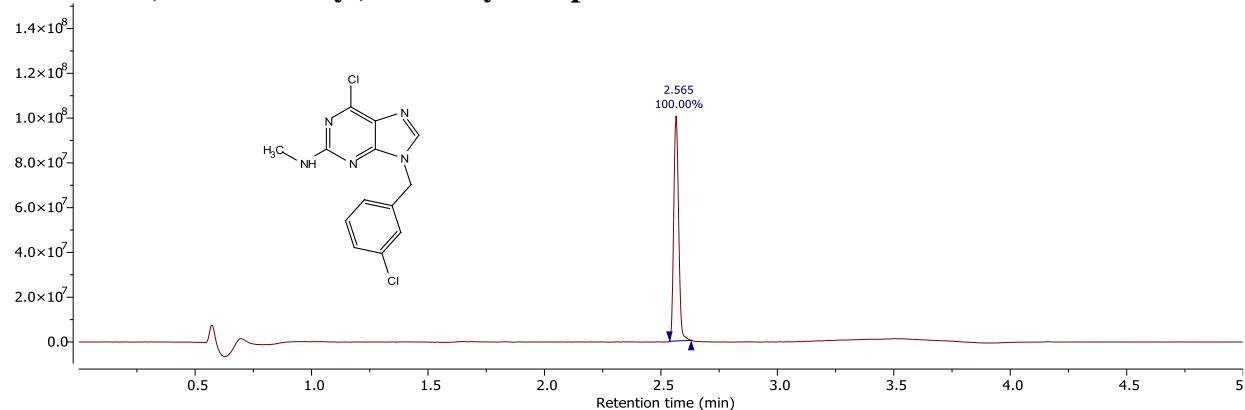
2-chloro-9-(3-chlorobenzyl)-N-cyclopropyl-9H-purin-6-amine 37



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

