

Supporting Information for:

**Inhibitors of nicotinamide N-methyltransferase designed to mimic the
methylation reaction transition state**

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Richard B. Parsons,^b Davide Sartini^c, Monica Emanuelli^c and Nathaniel I. Martin^{a*}

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^c Department of Clinical Sciences, Università Politecnica delle Marche, Ancona, Italy

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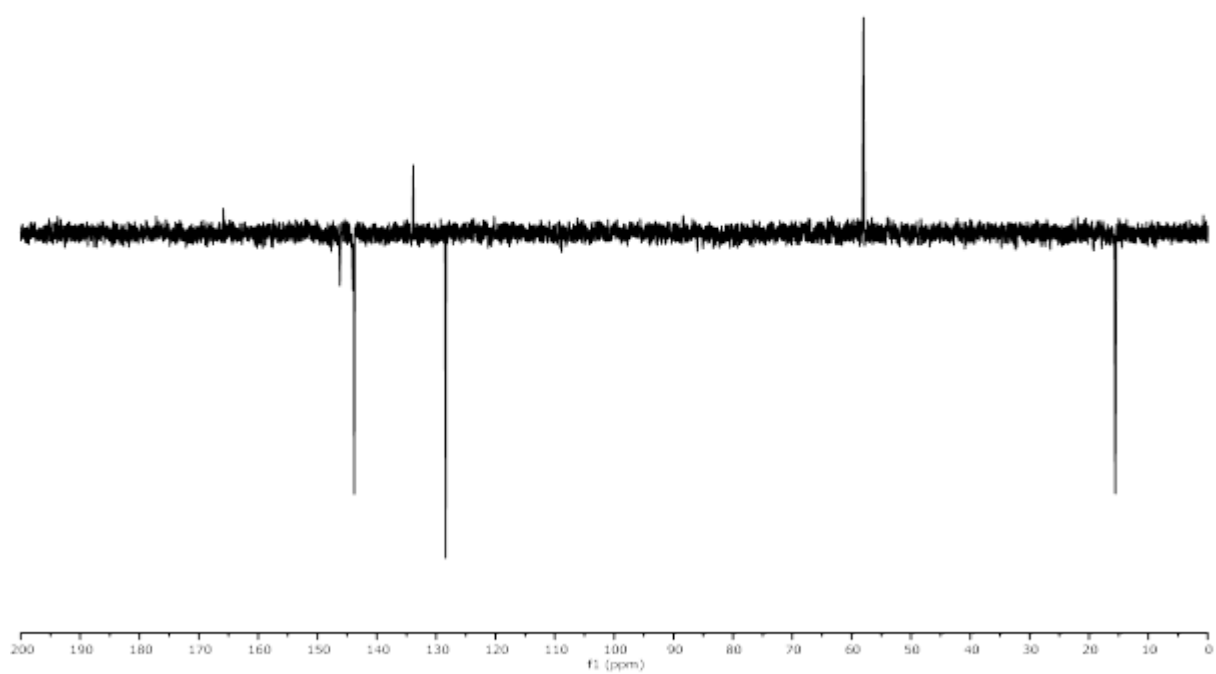
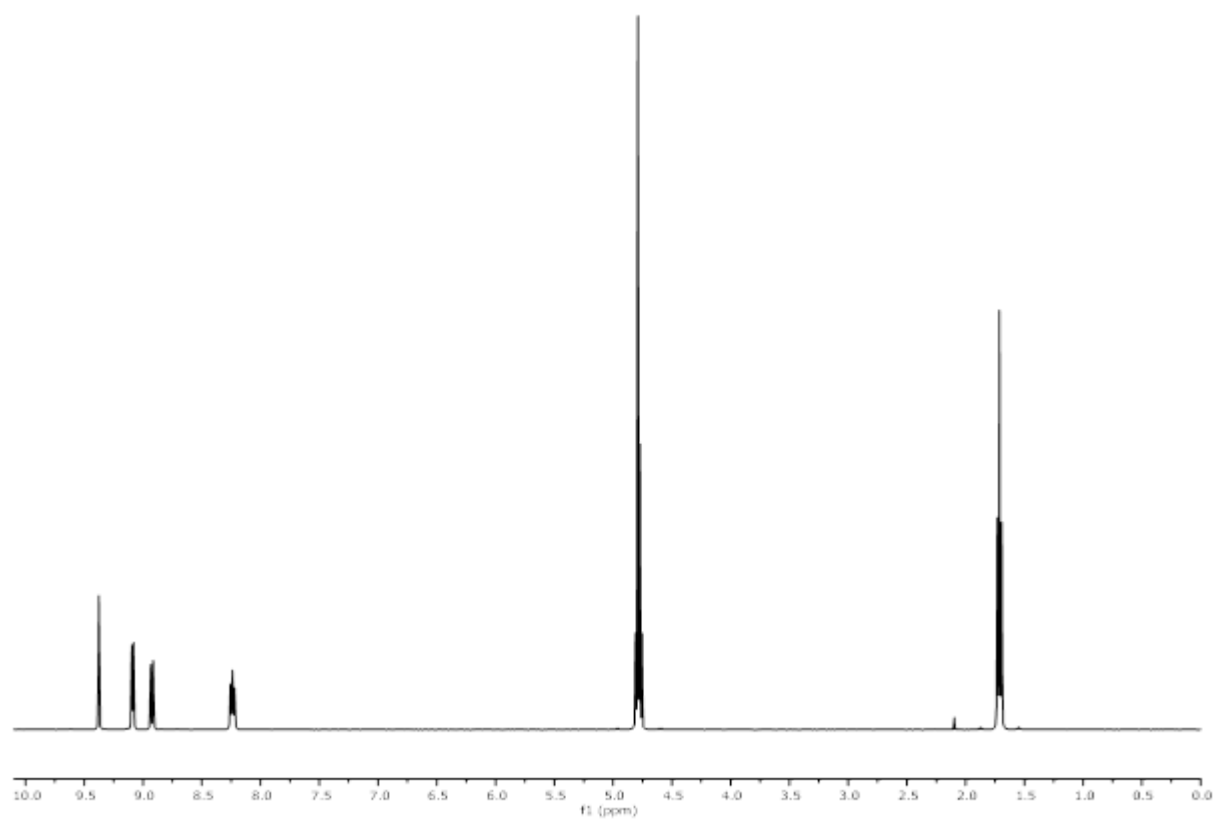
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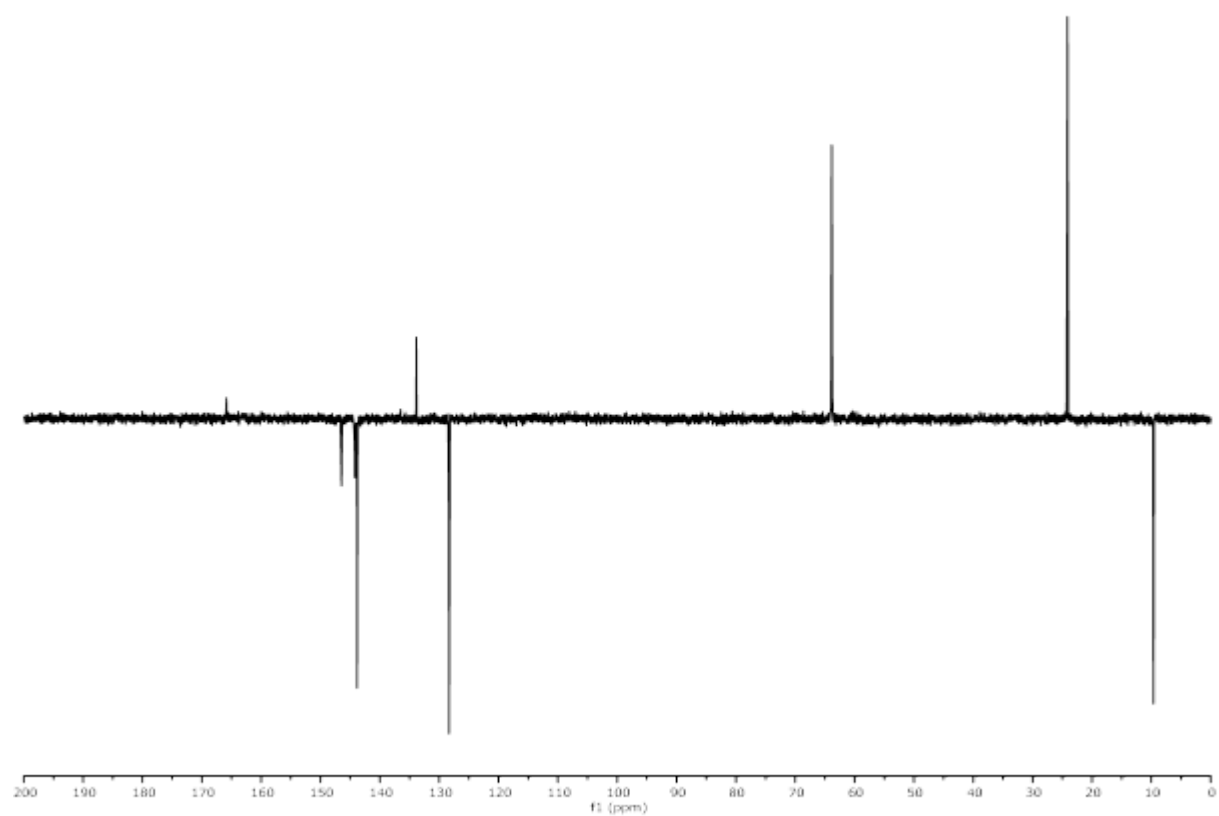
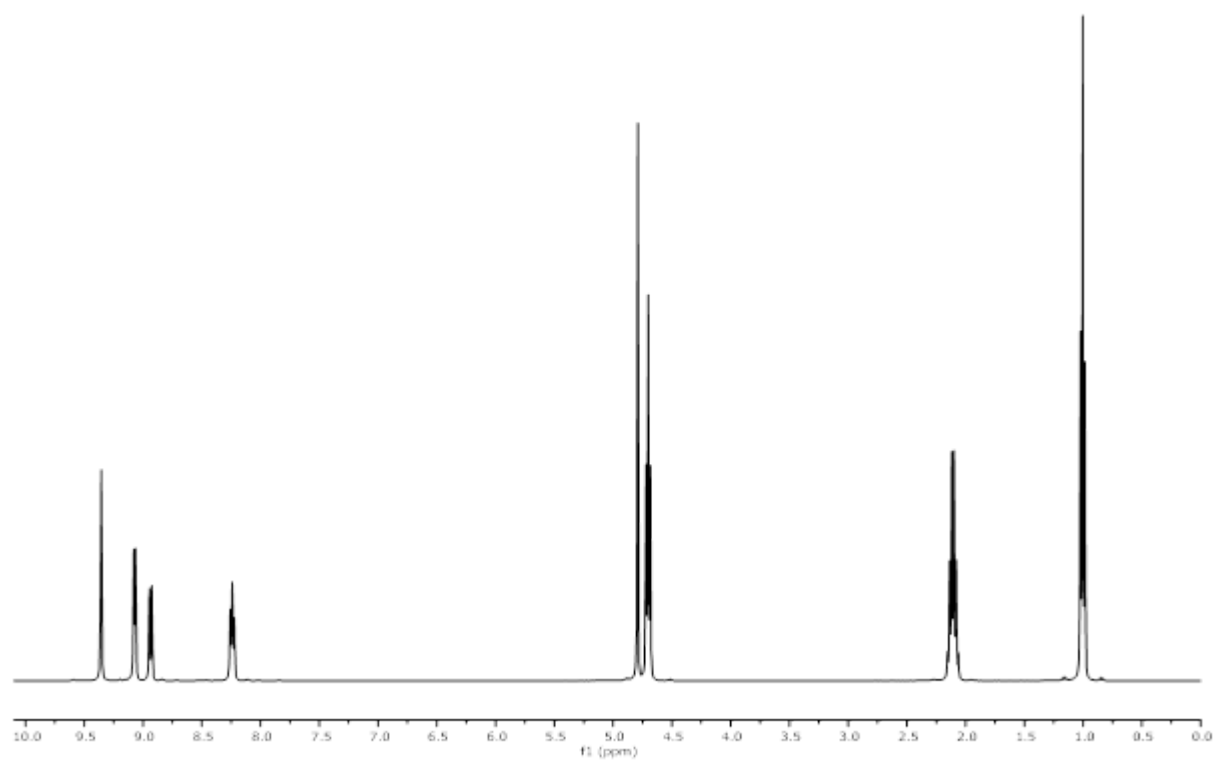
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NMR spectra

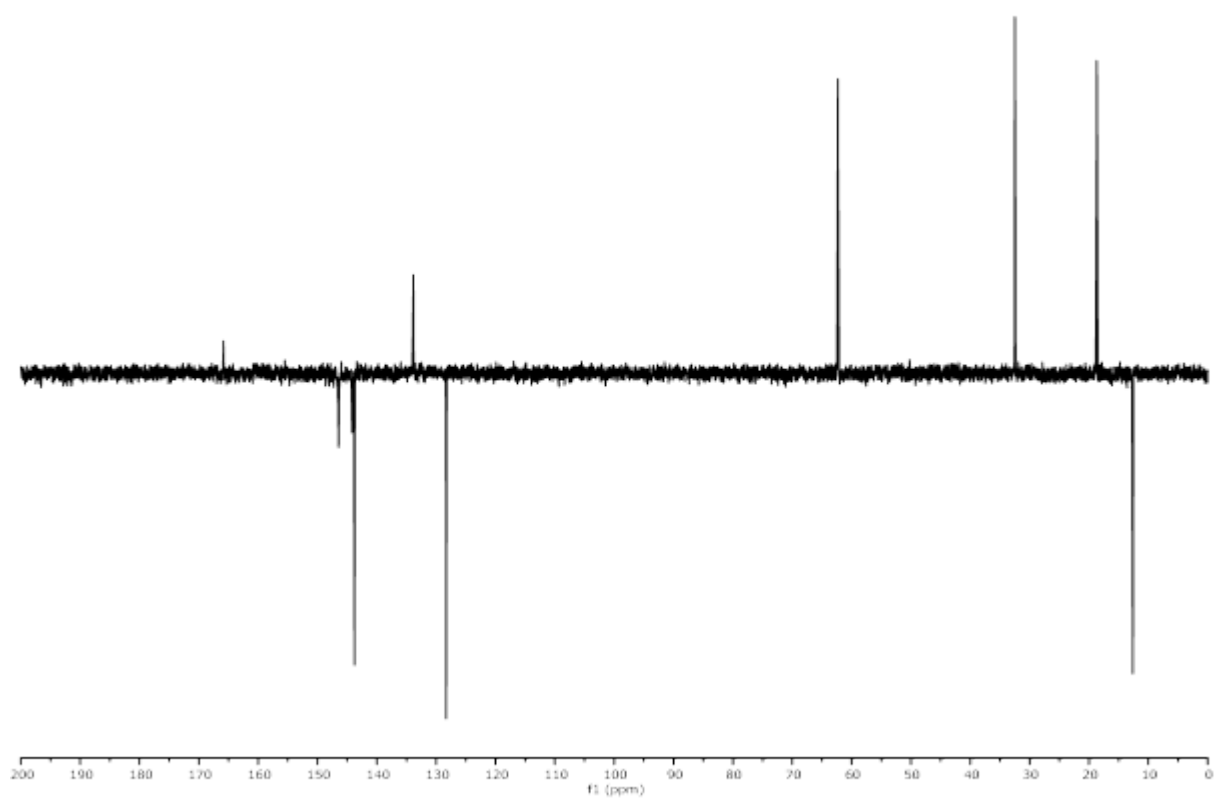
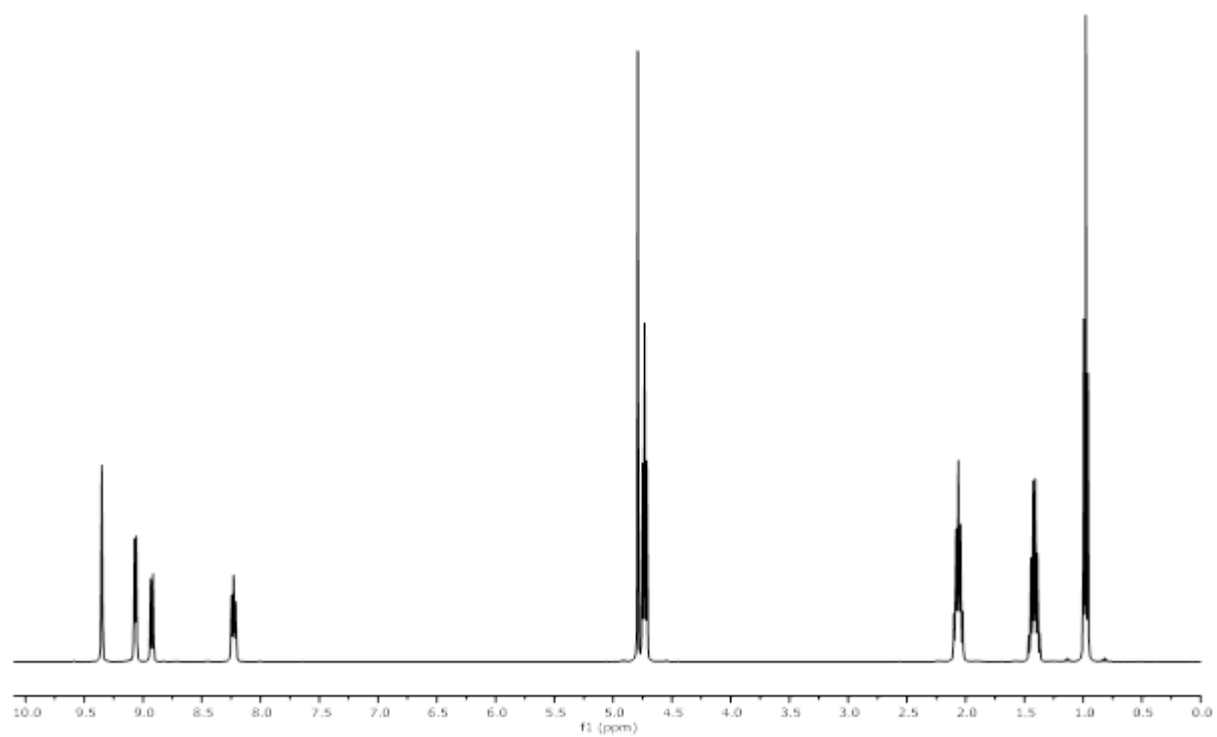
1-Ethyl-3-carbamoyl-pyridin-1-ium iodide (2a)



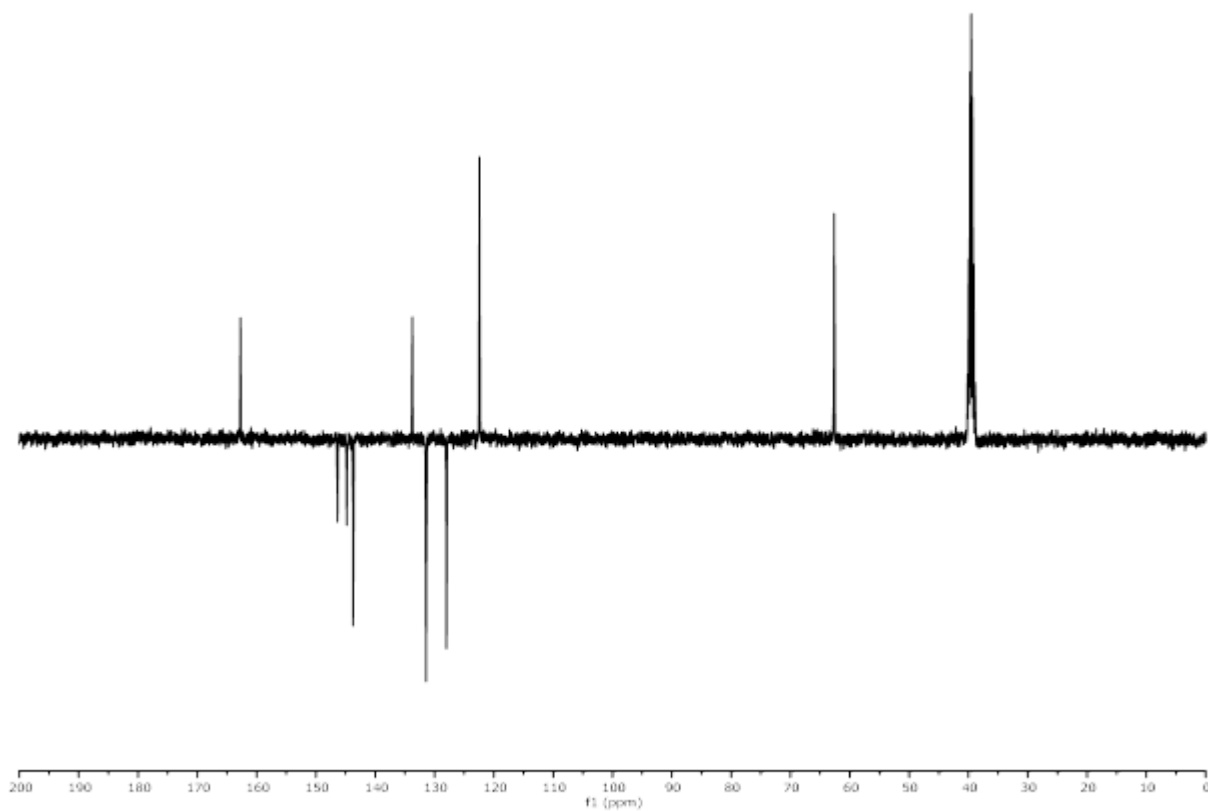
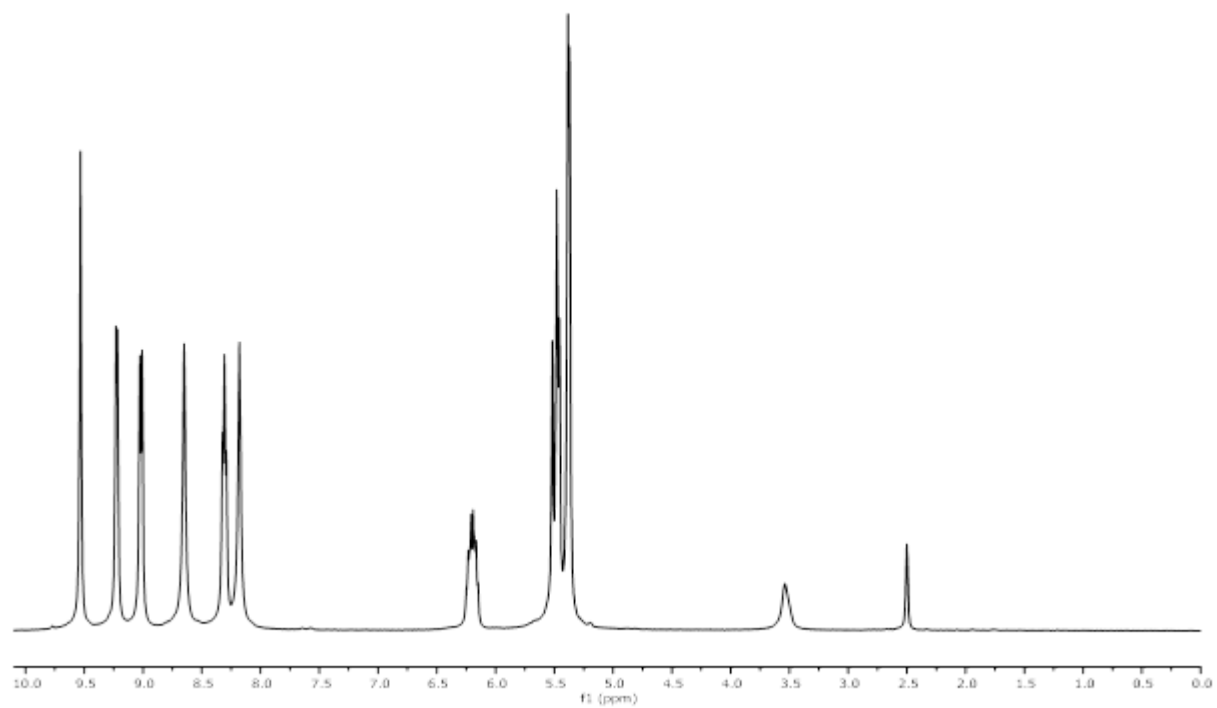
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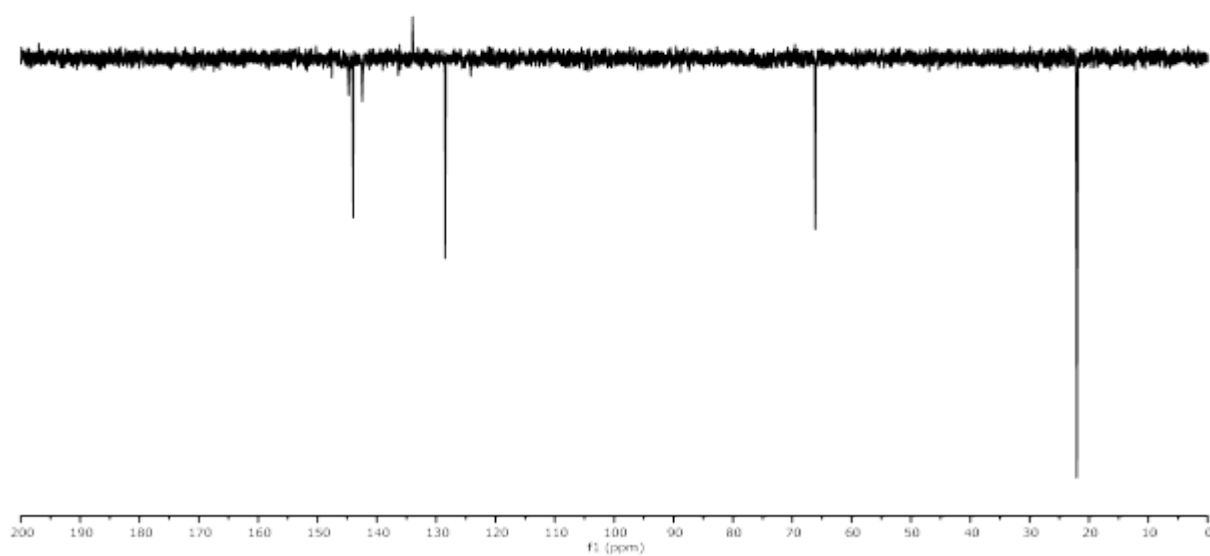
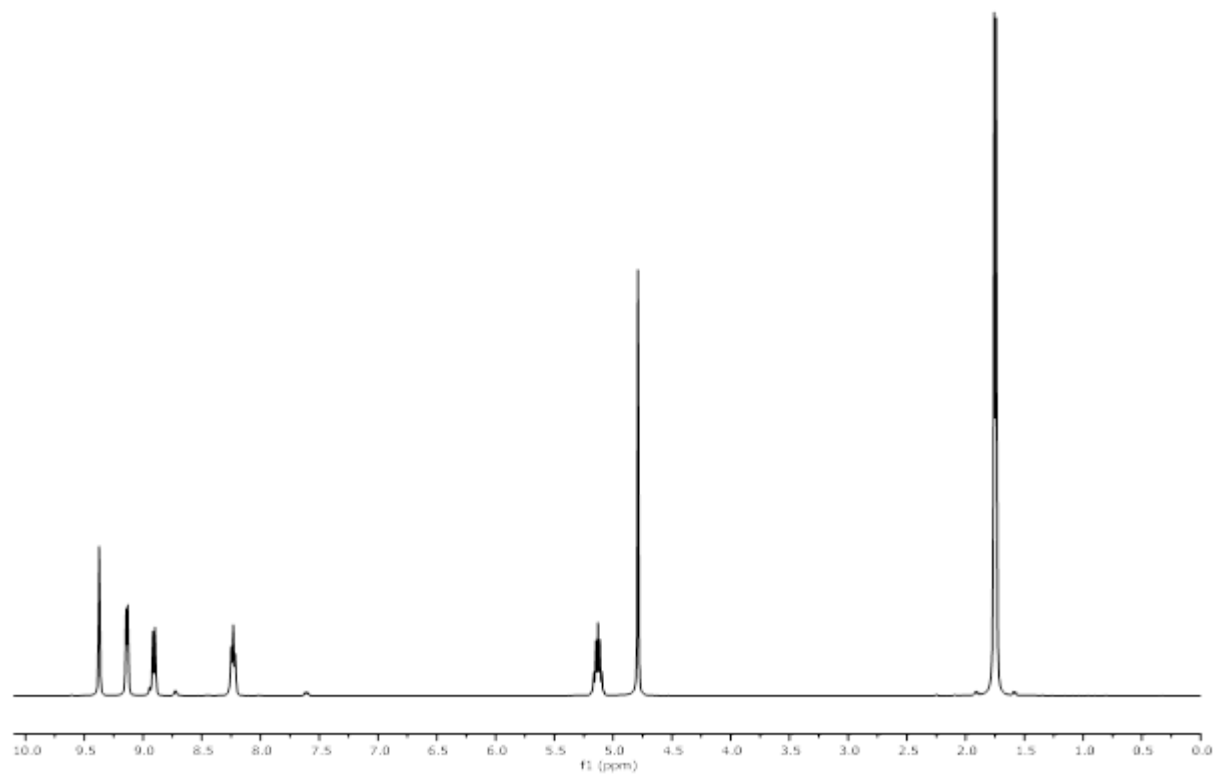
1-Butyl-3-carbamoyl-pyridin-1-ium bromide (2c)



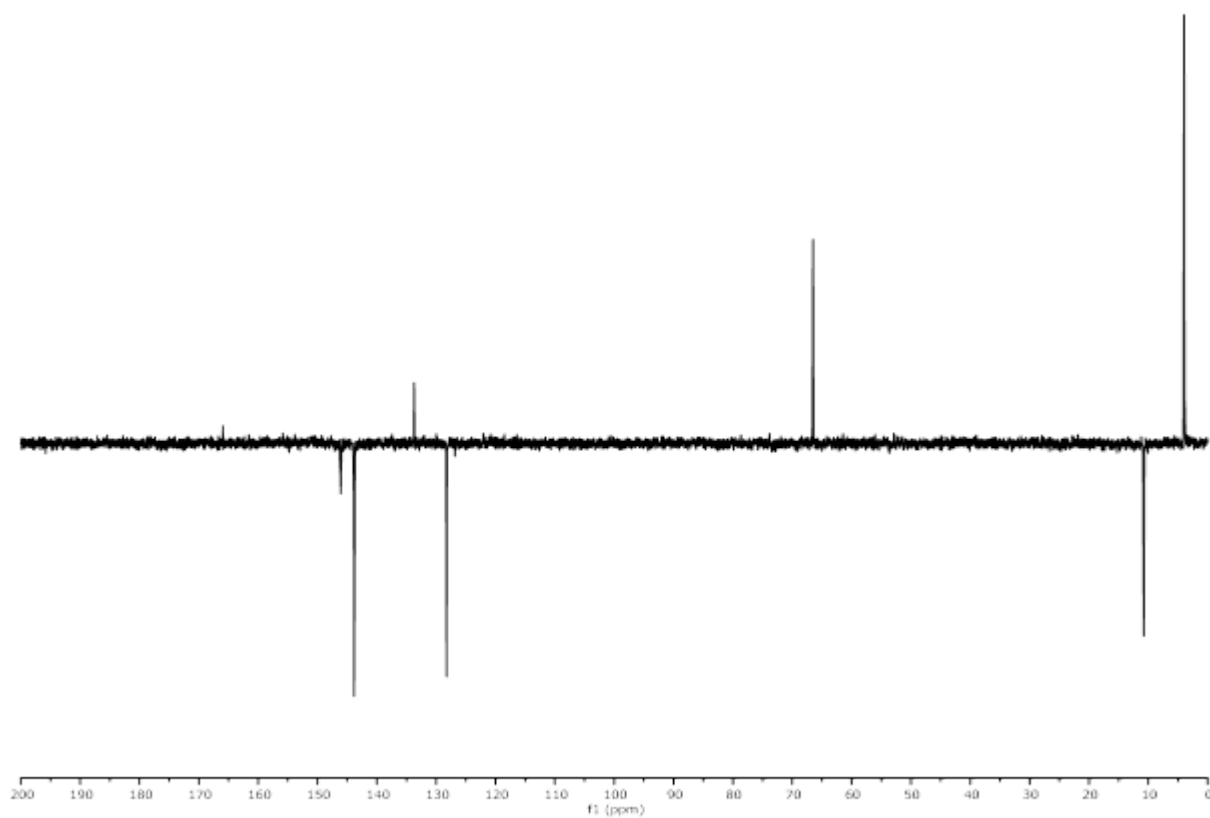
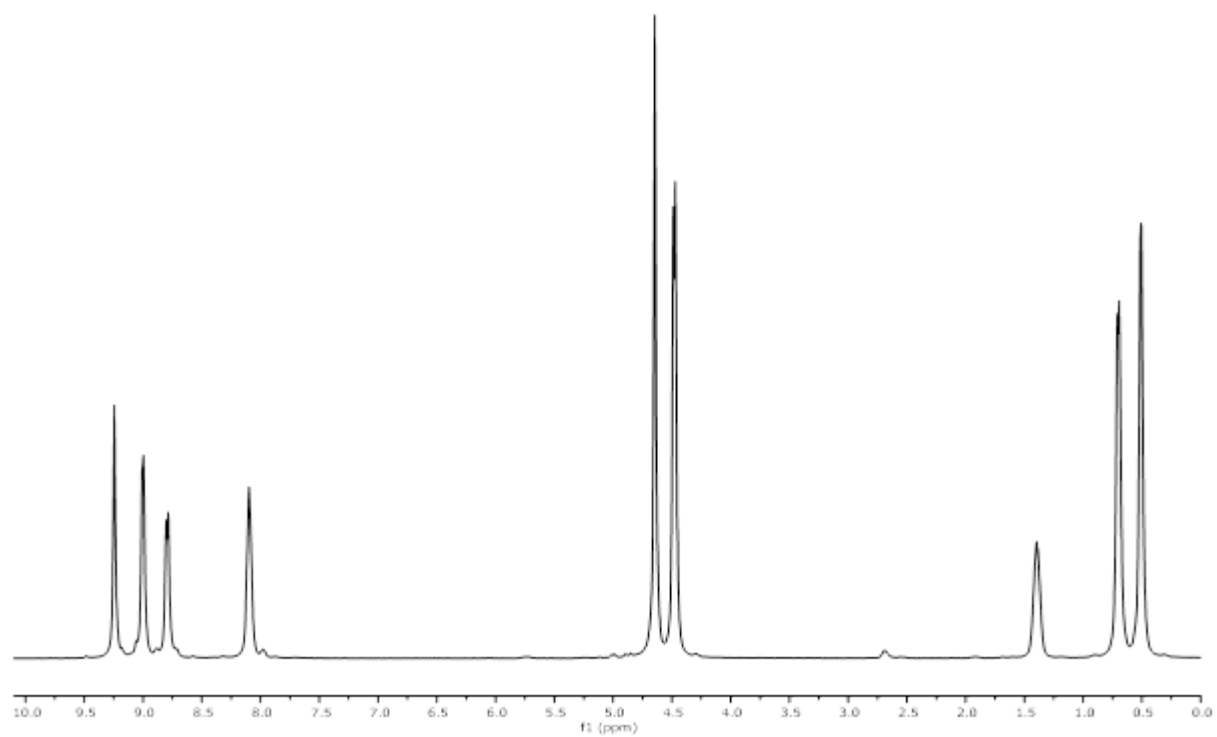
1-Allyl-3-carbamoyl-pyridin-1-ium bromide (2d)



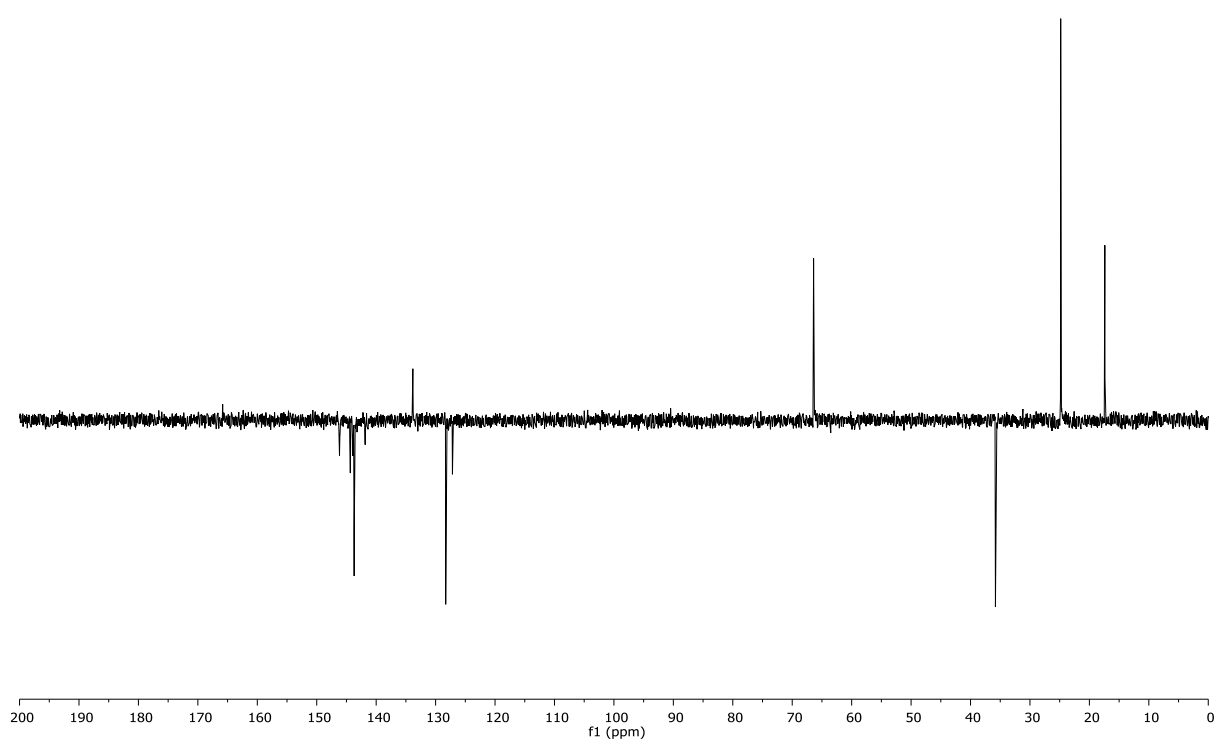
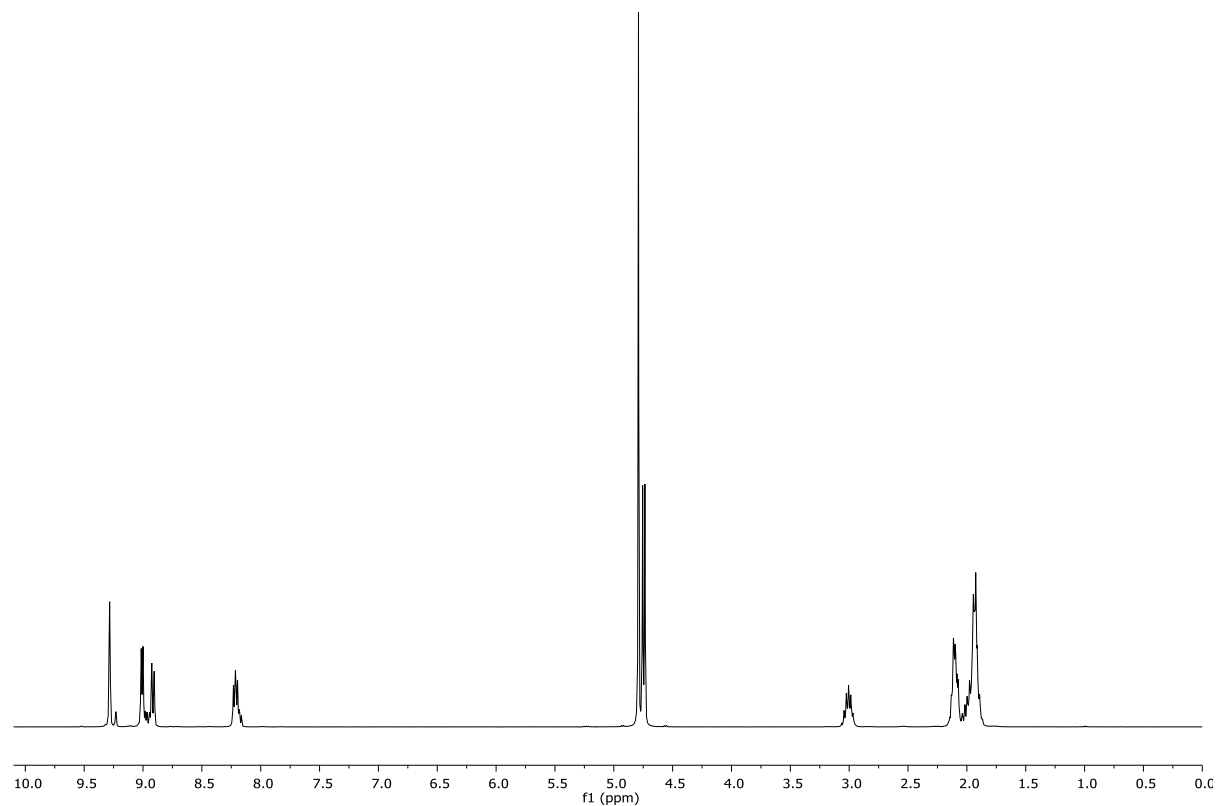
1-Isopropyl-3-carbamoyl-pyridin-1-ium iodide (2e)



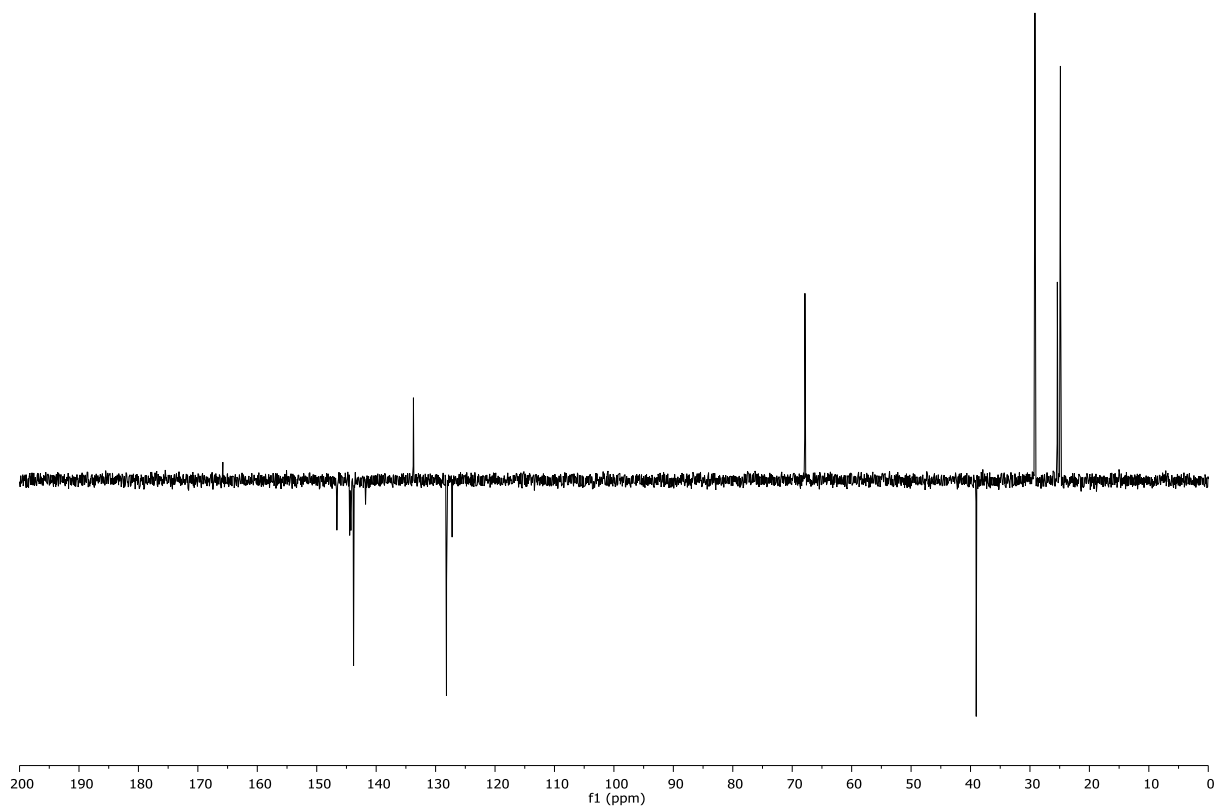
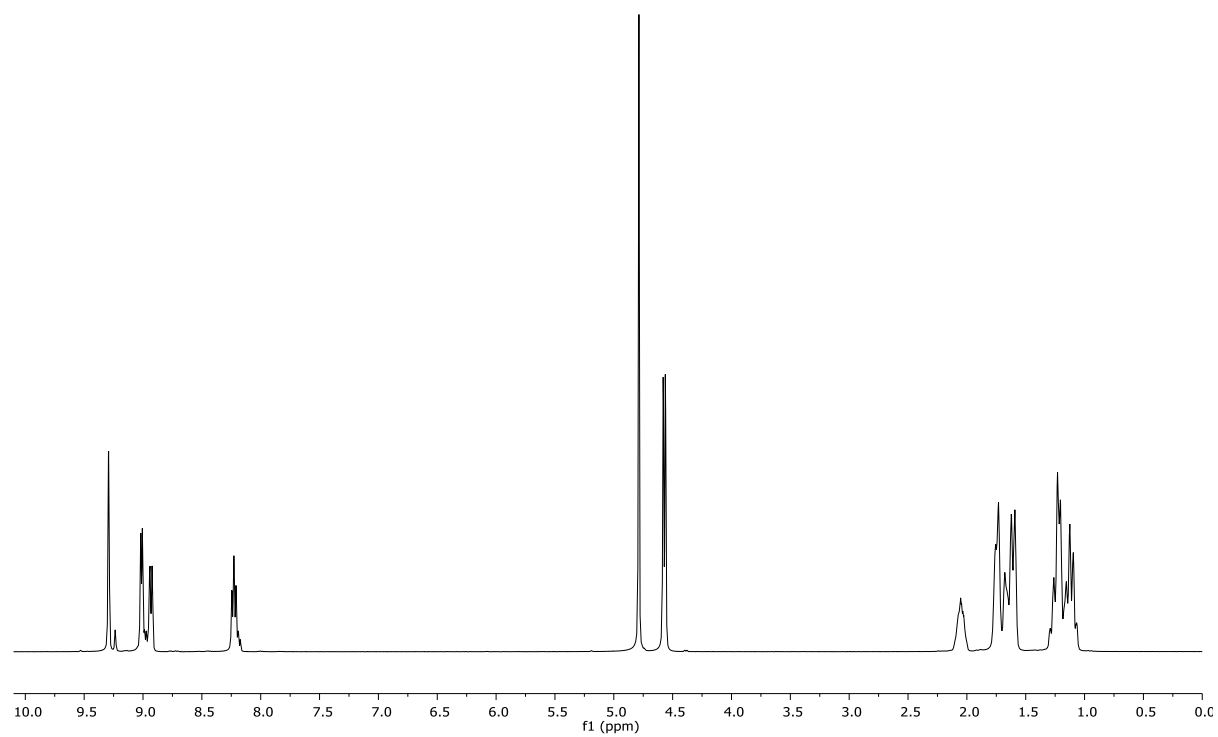
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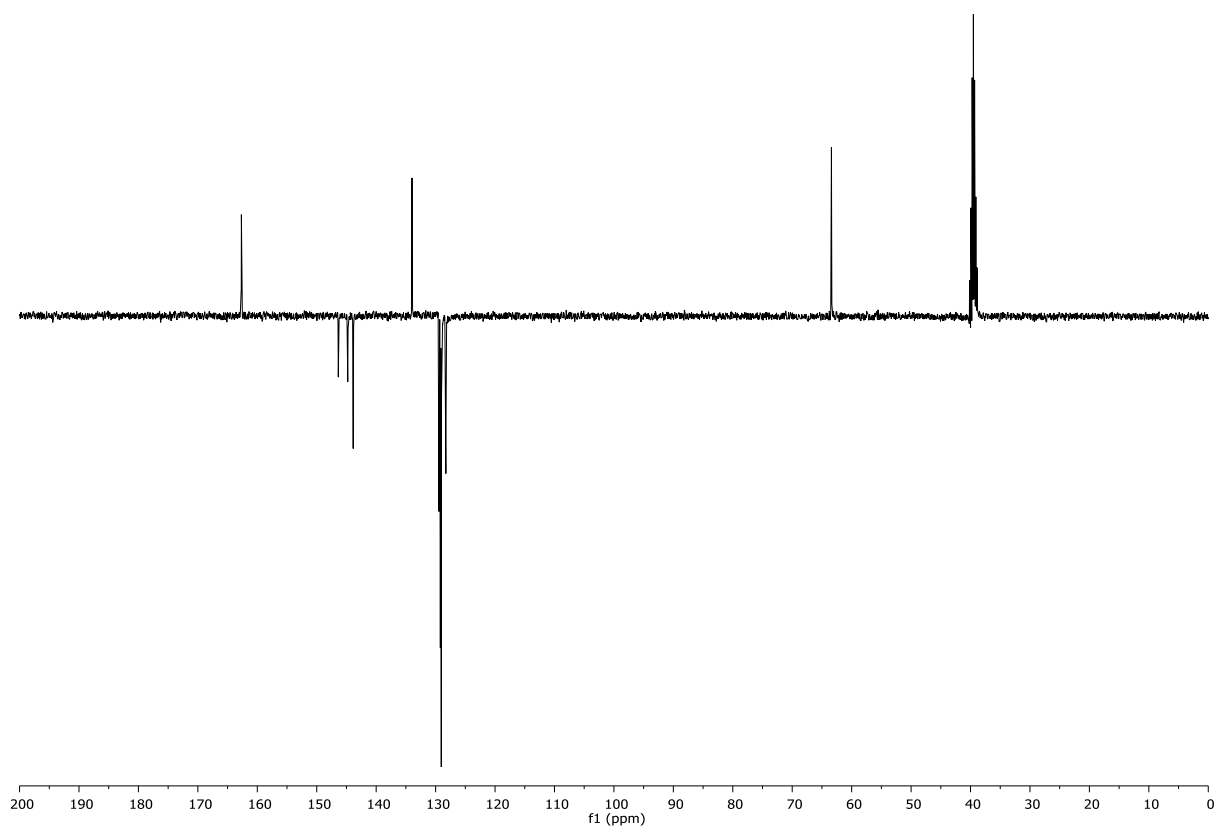
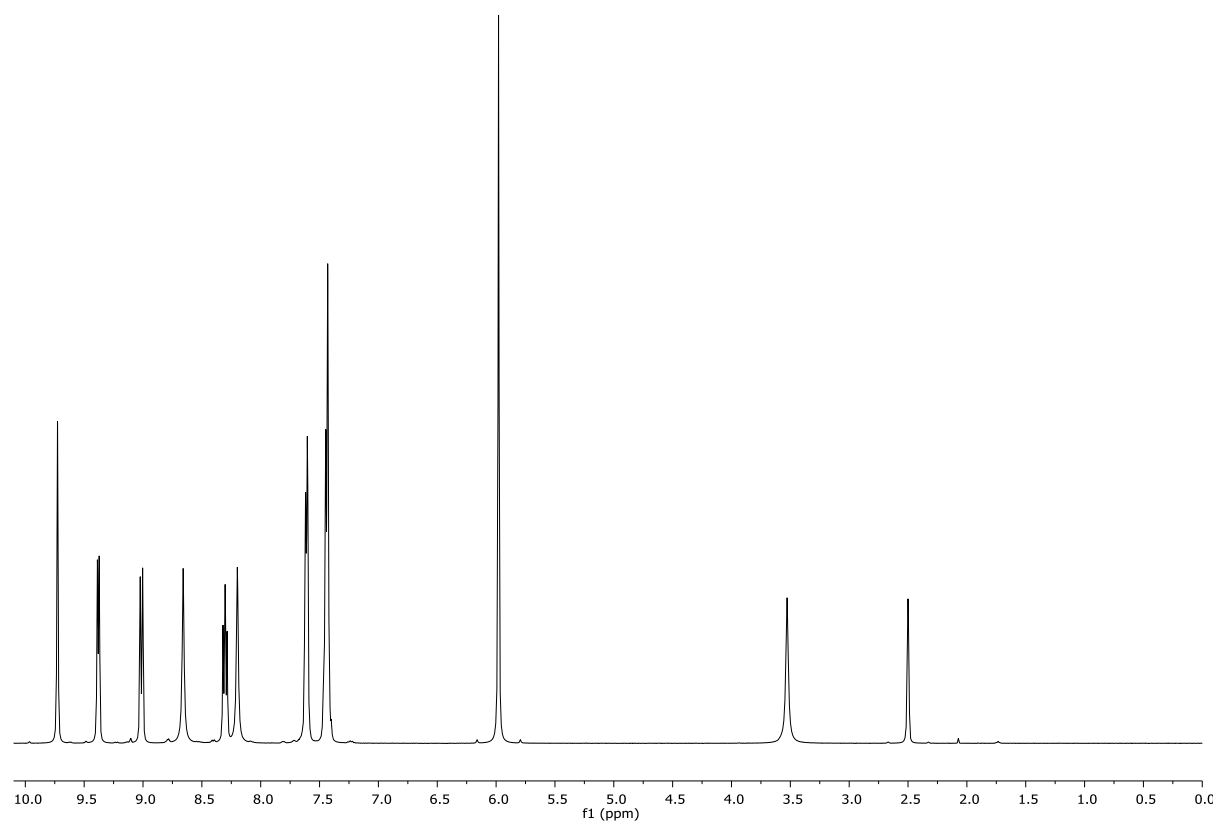
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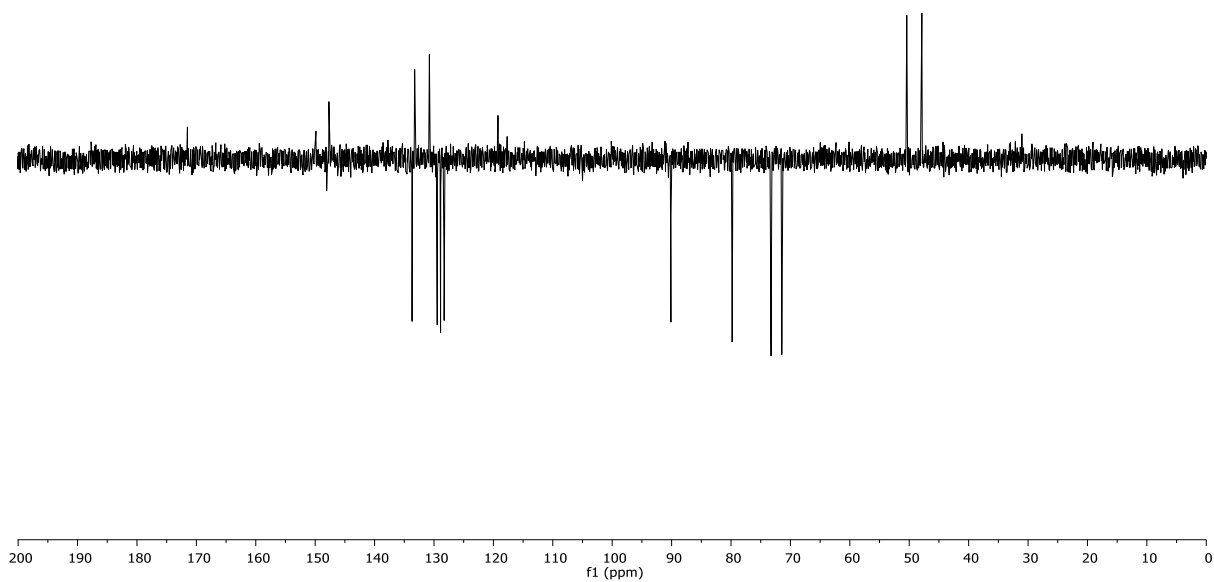
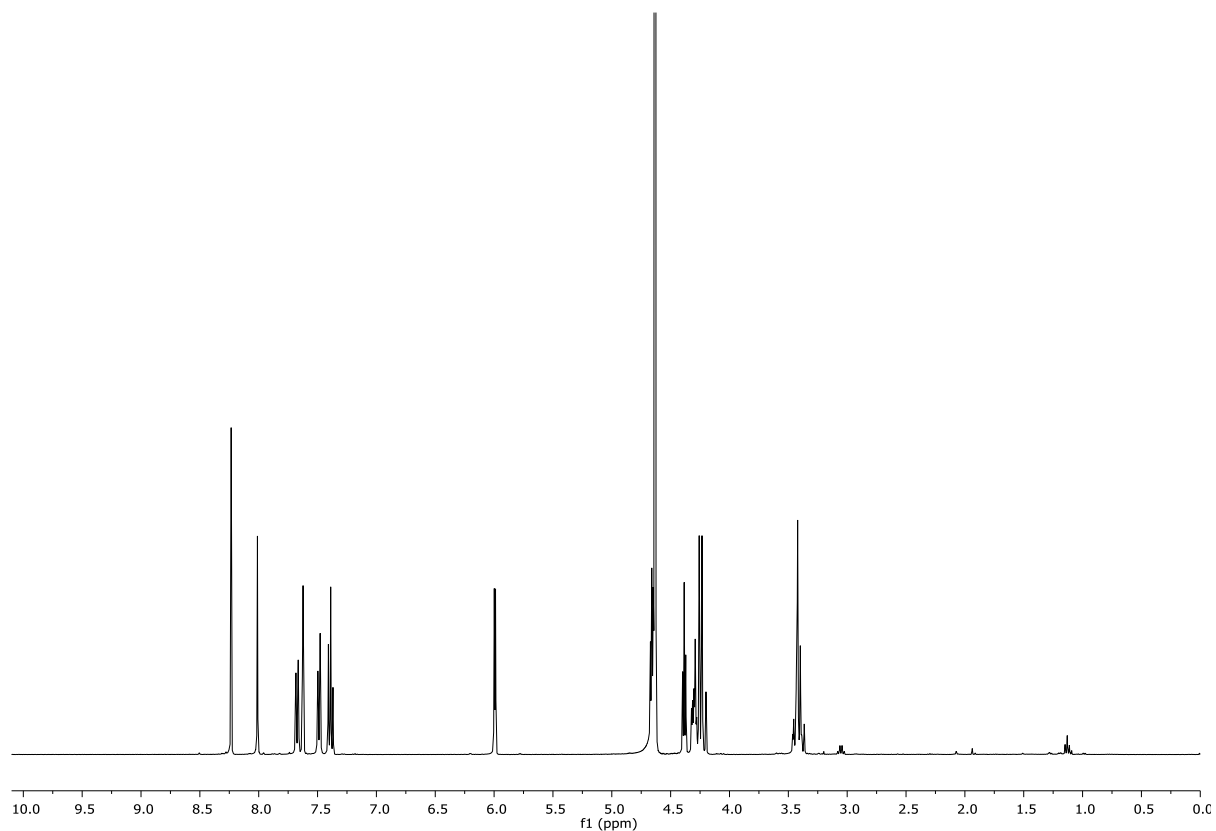
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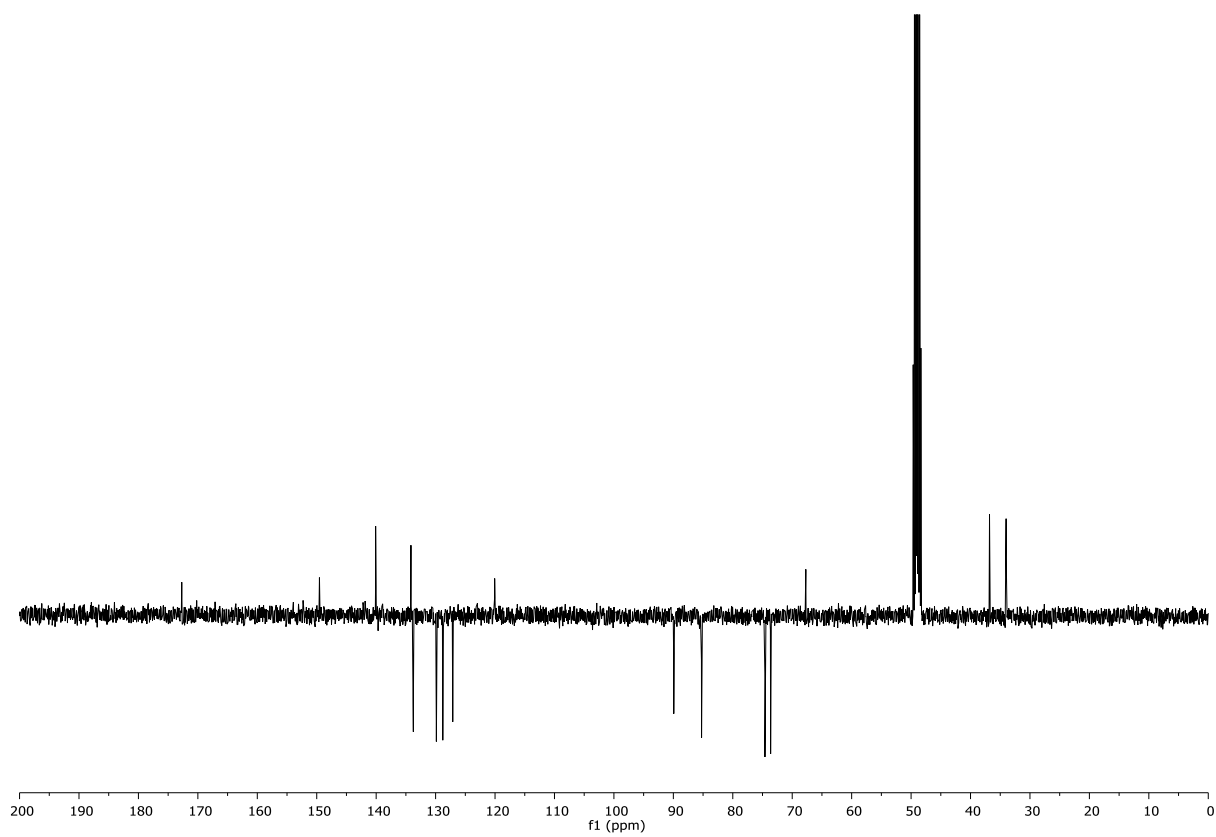
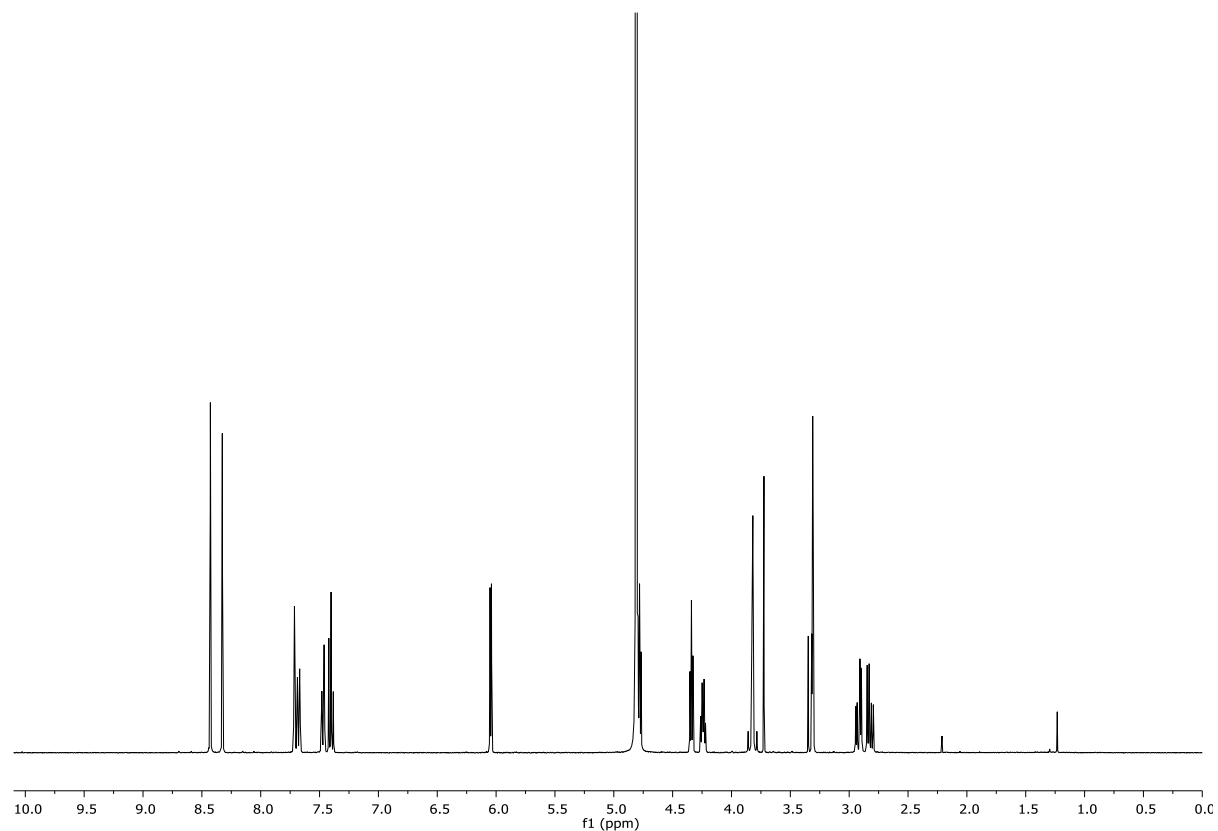
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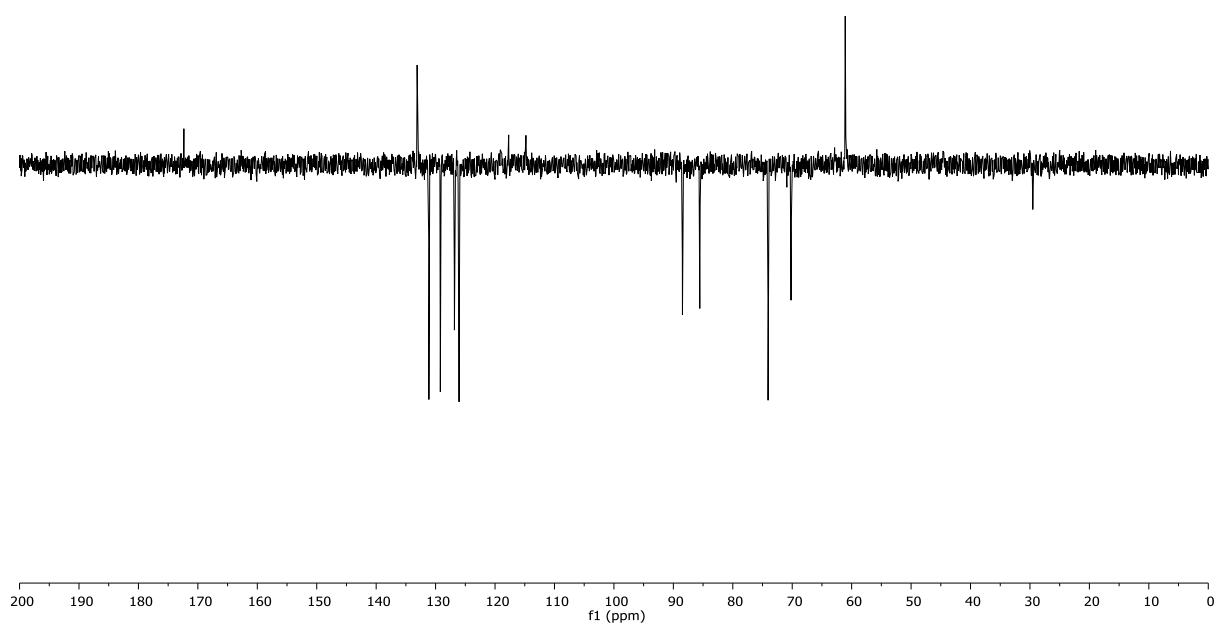
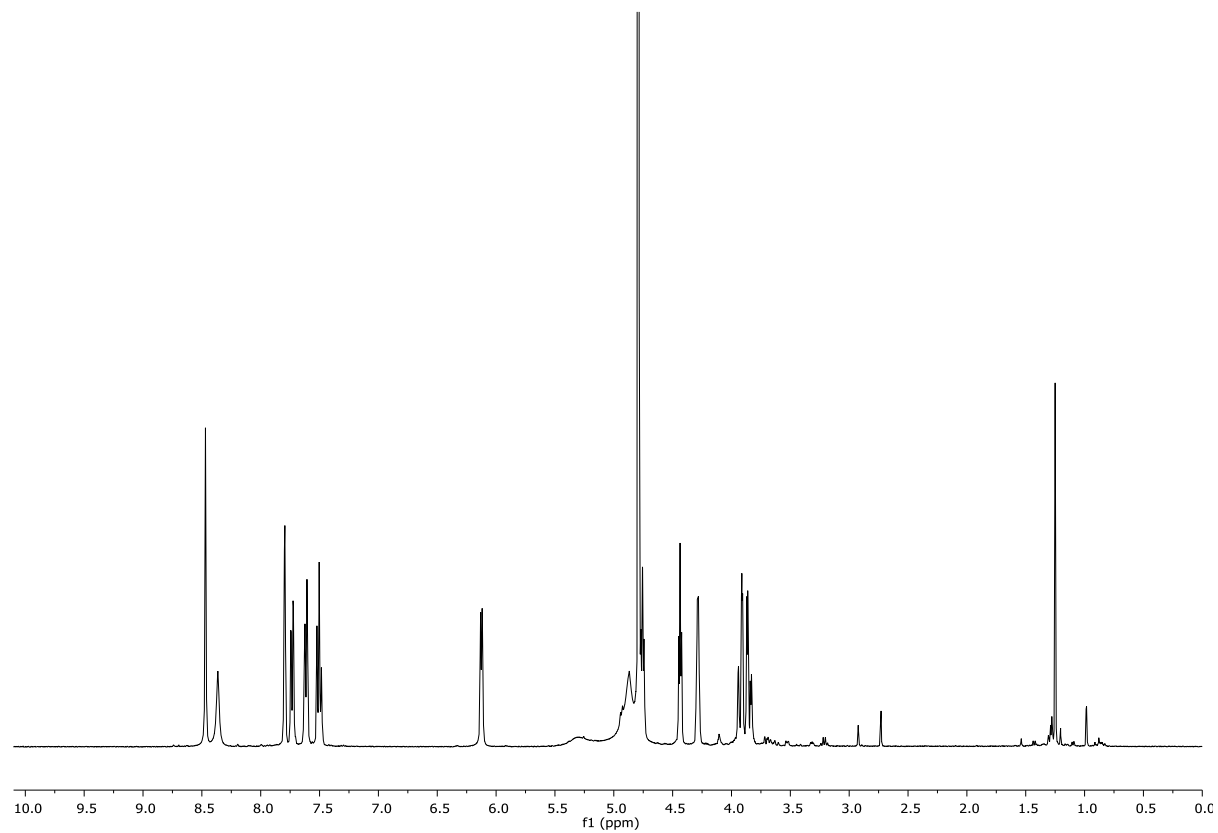
3-((((2R,3S,4R,5R)-5-(6-Amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)amino)-methyl) benzamide (9)



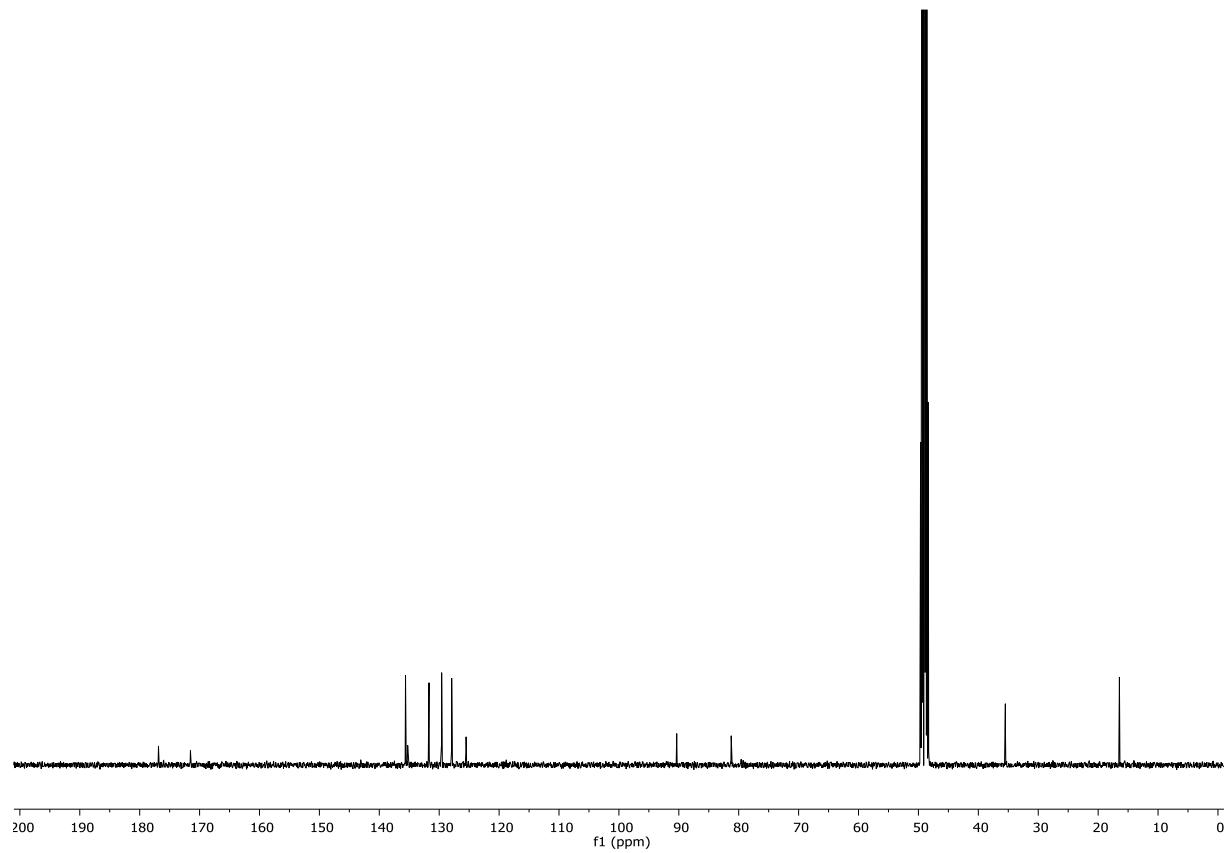
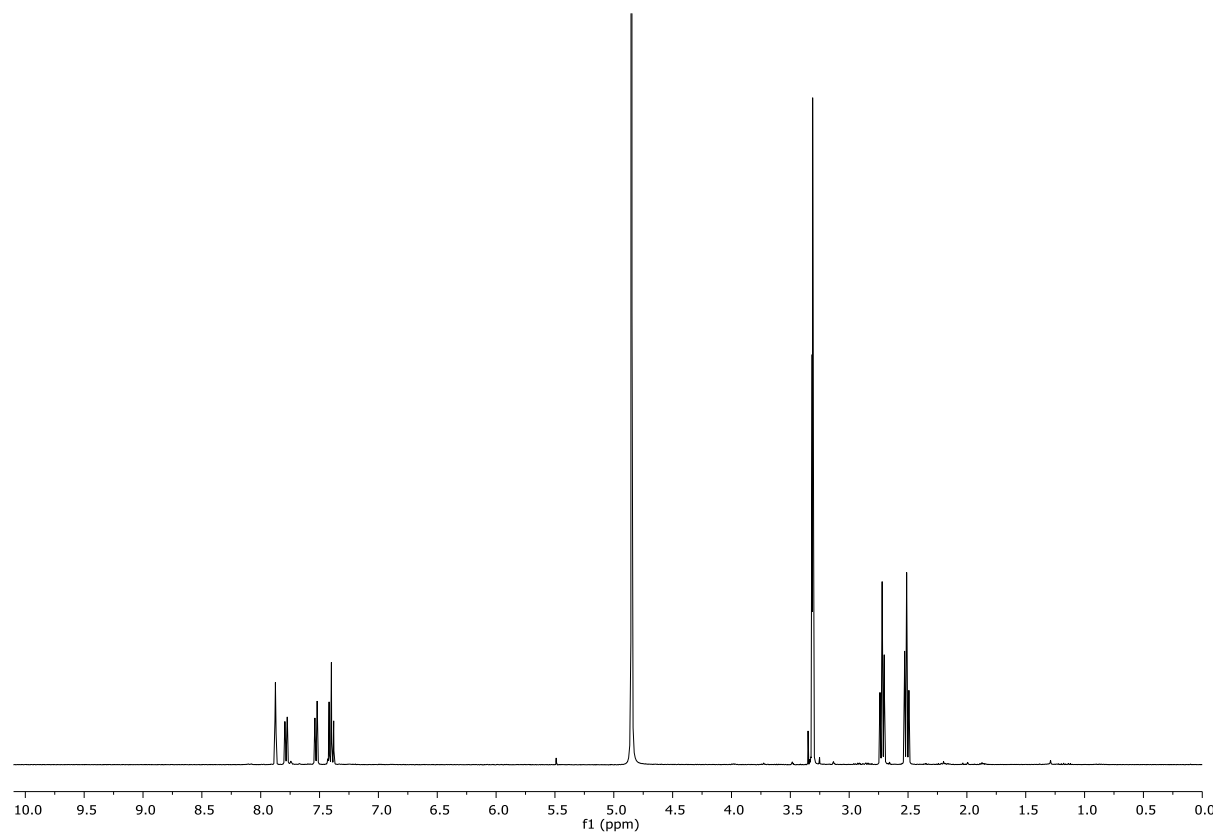
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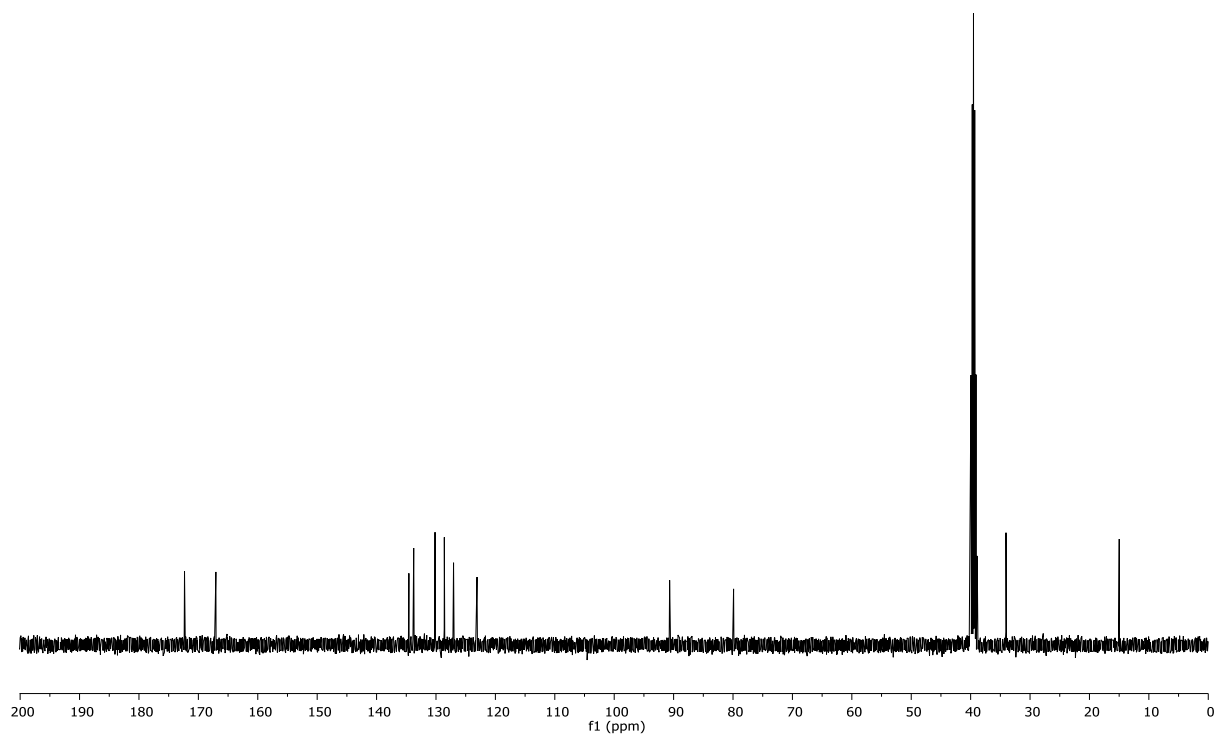
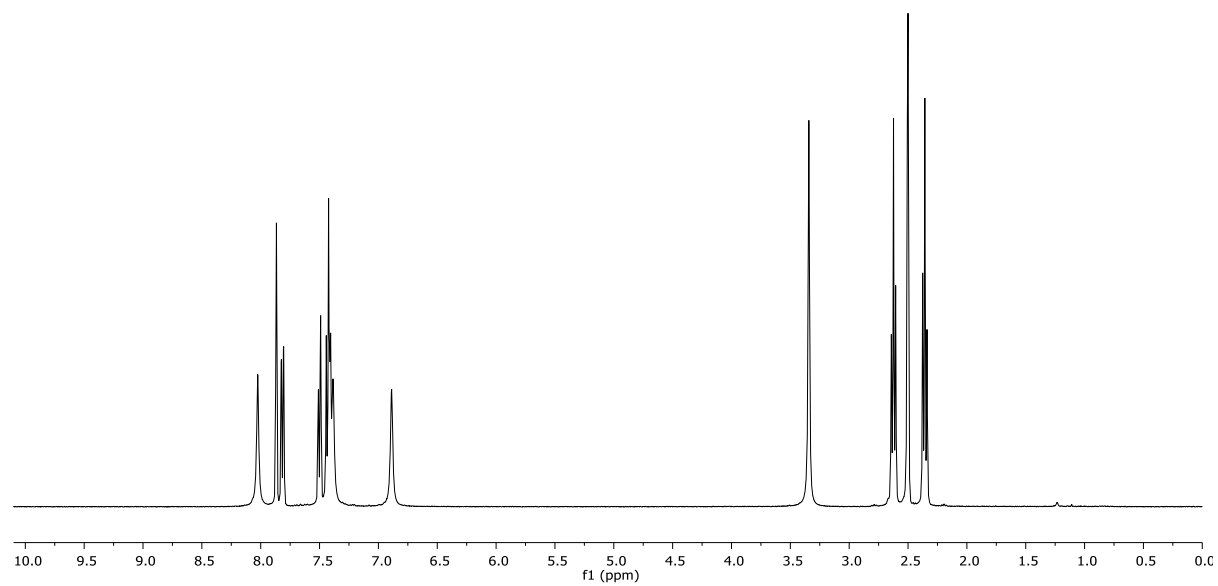
3-((((2S,3S,4R,5R)-5-(6-Amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)methyl)benzamide (11)



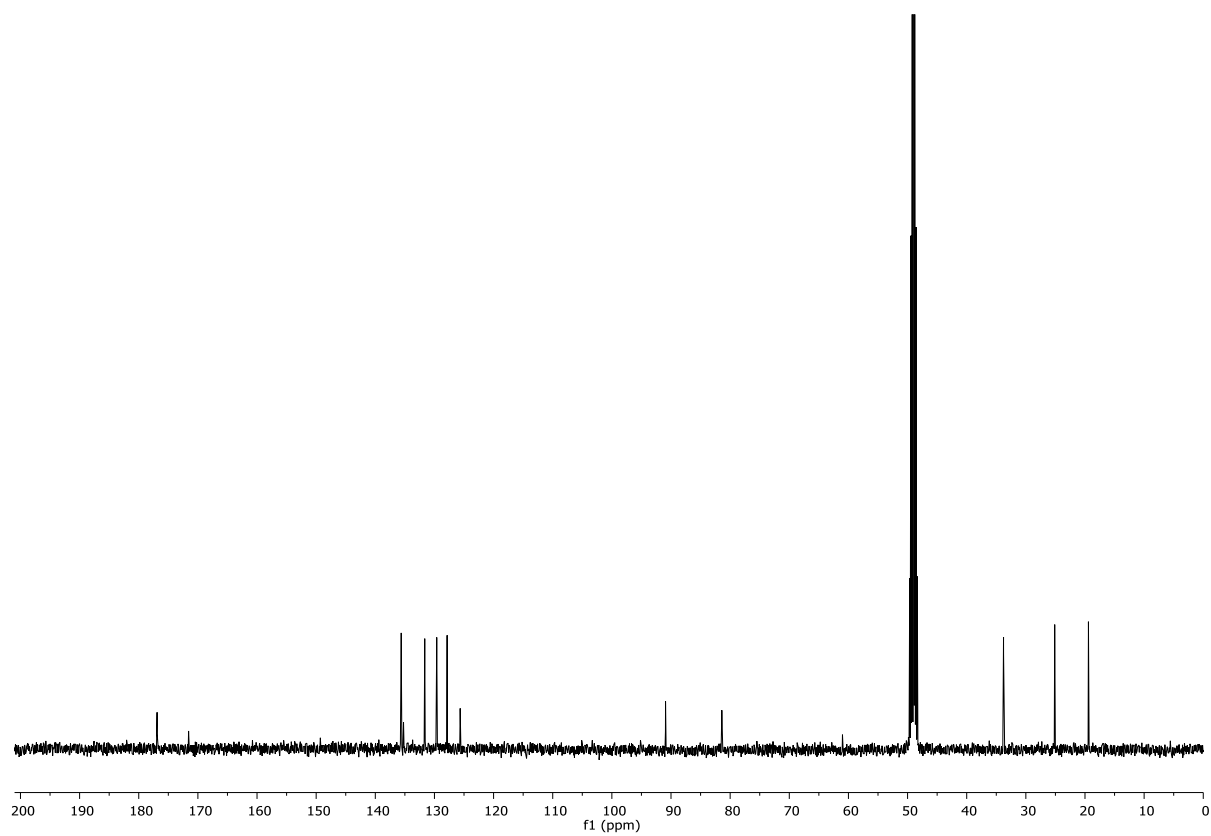
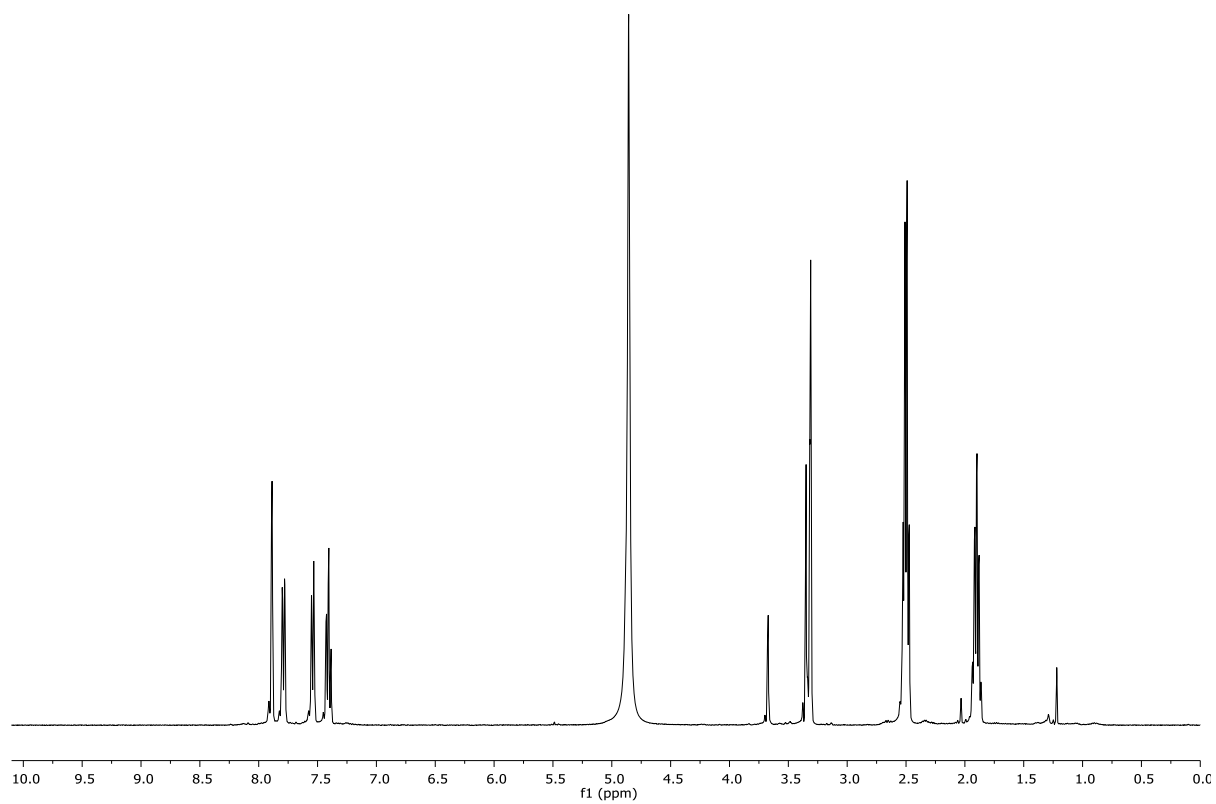
5-(3-Carbamoylphenyl)pent-4-ynoic acid (12)



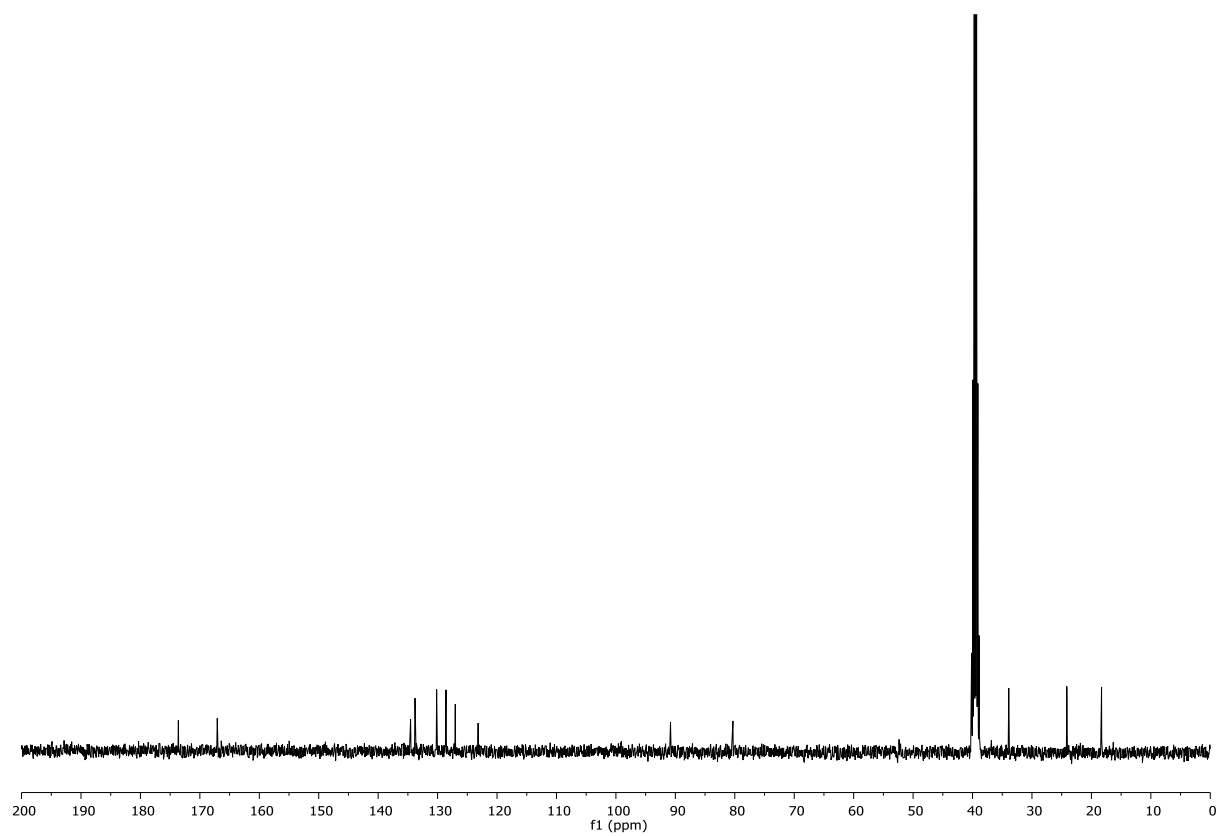
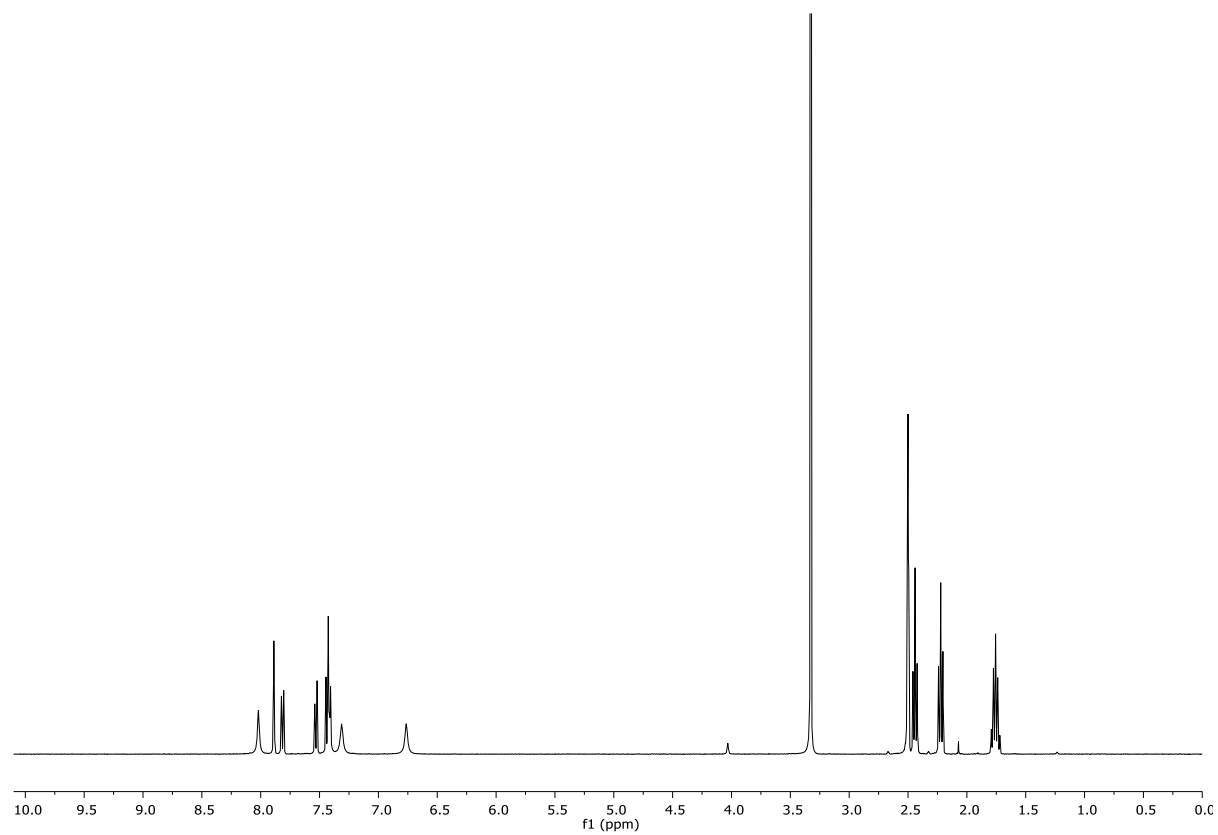
5-(3-Carbamoylphenyl)pent-4-ynoic amide (13)



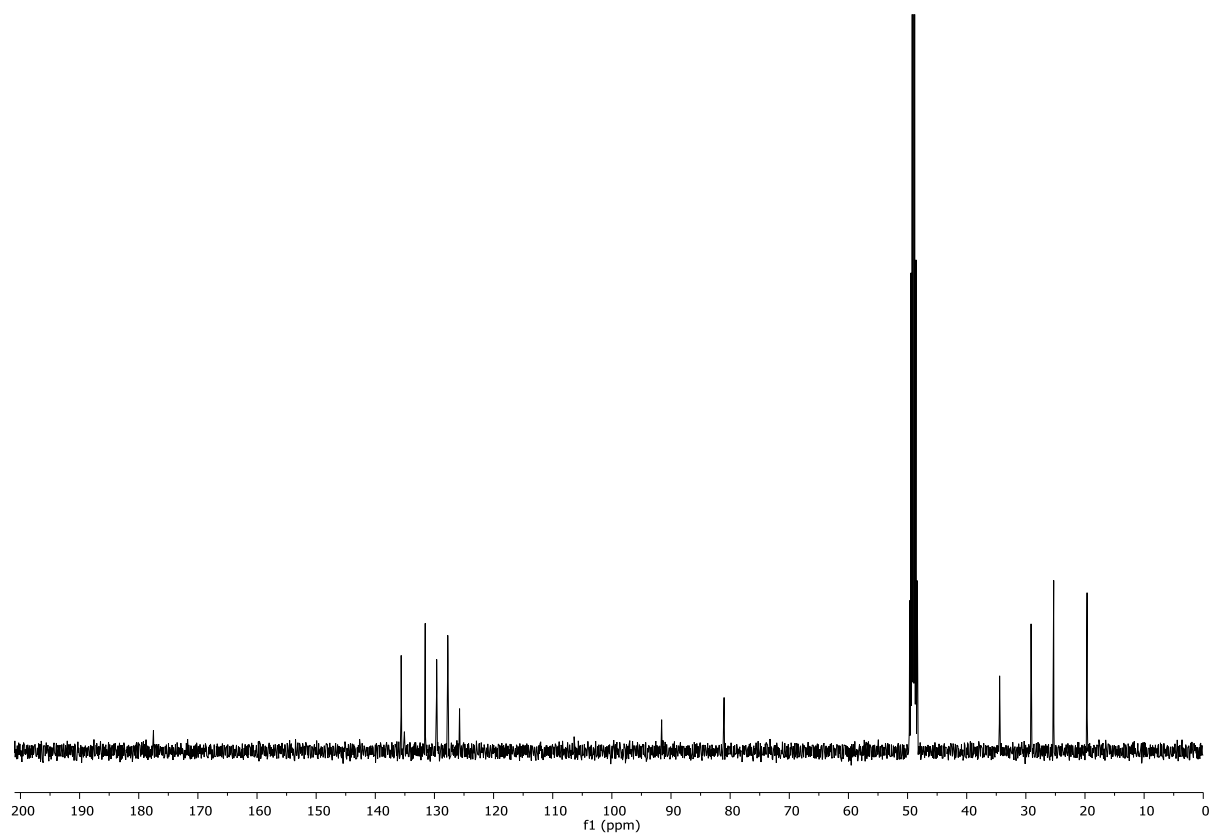
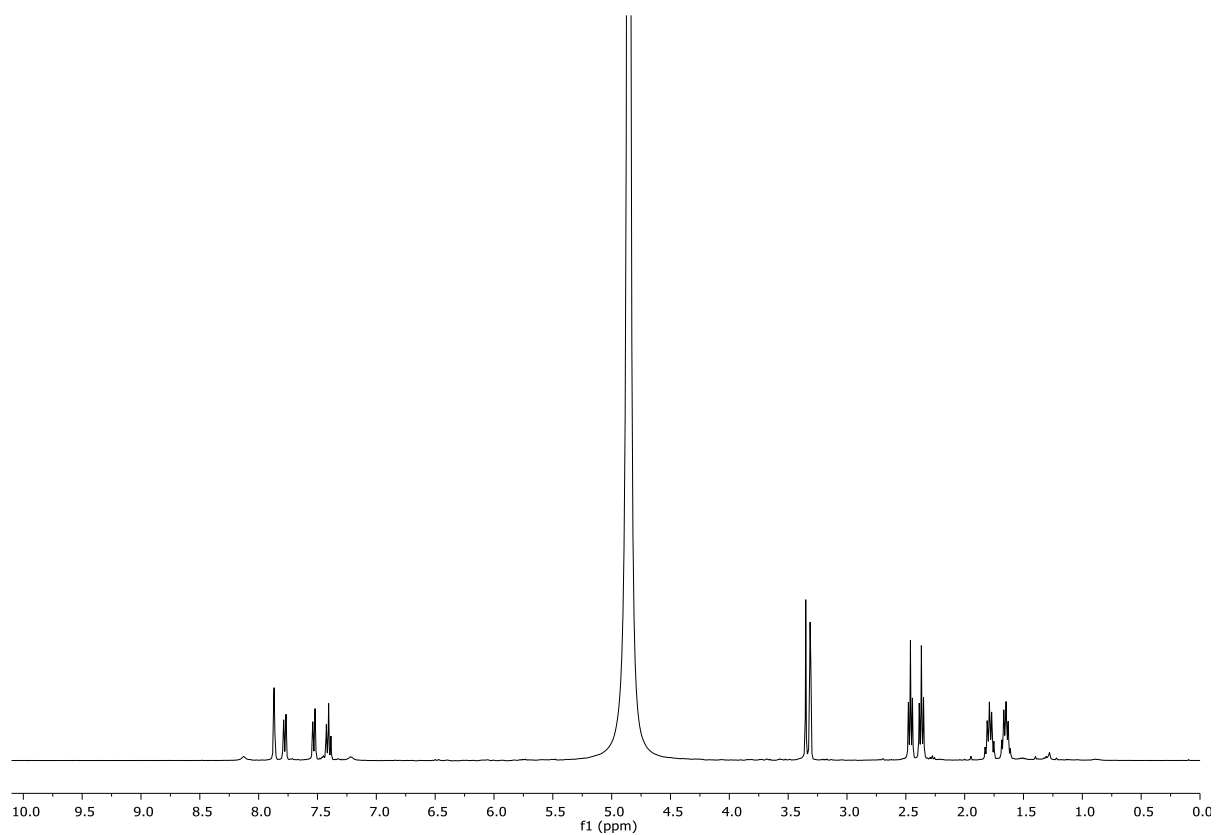
6-(3-Carbamoylphenyl)hex-5-ynoic acid (14)



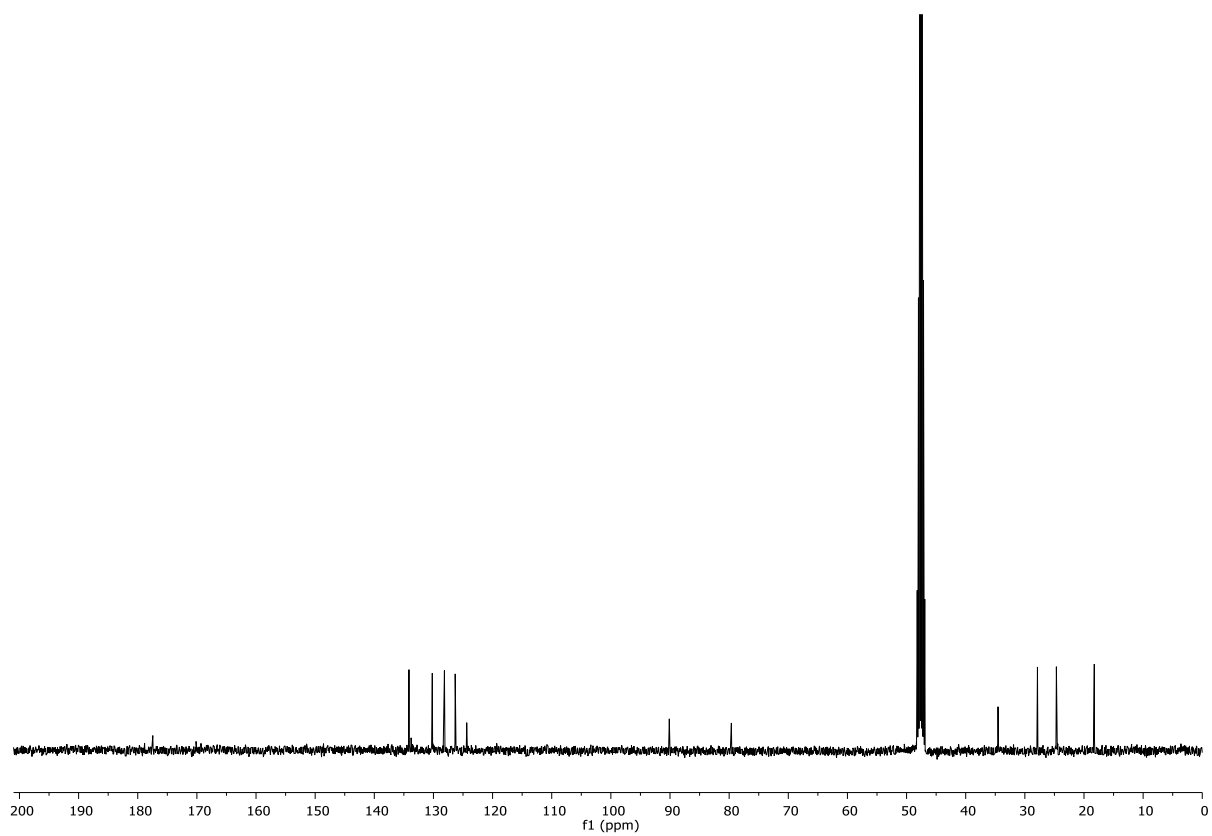
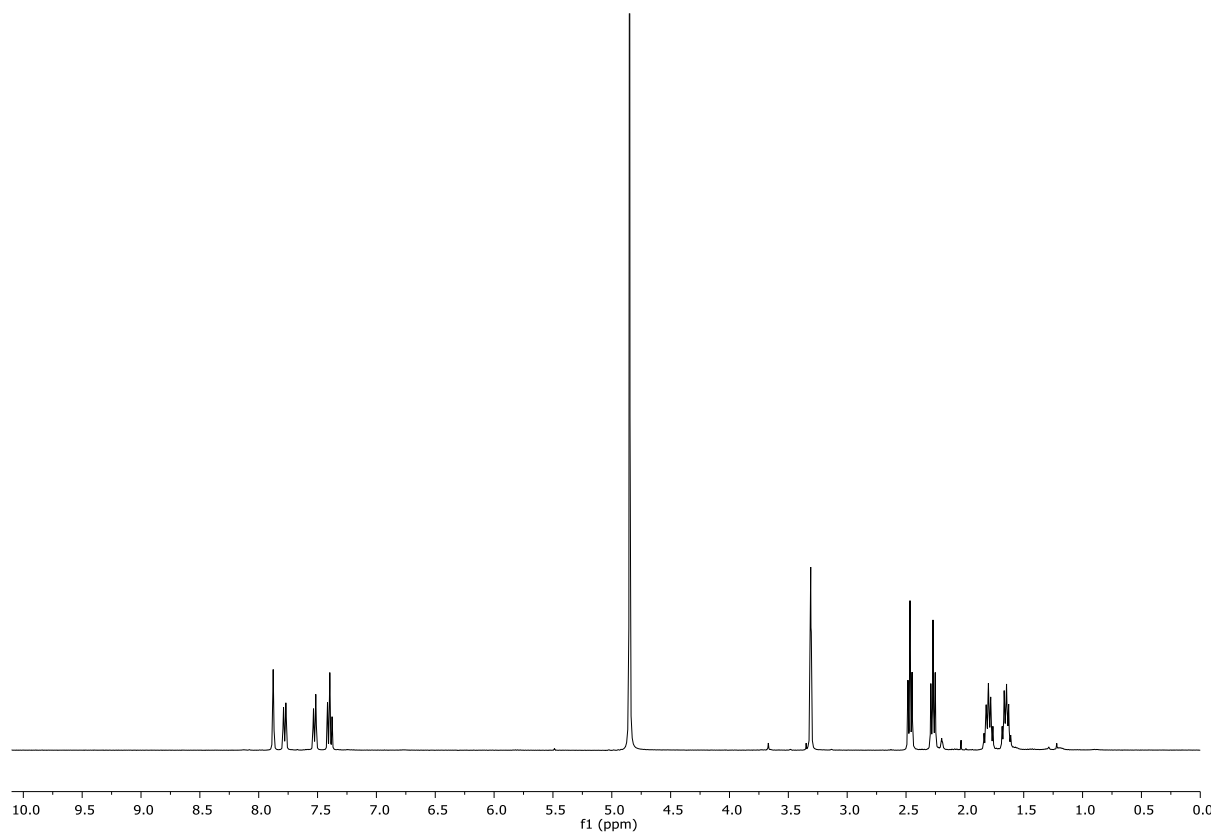
6-(3-Carbamoylphenyl)hex-5-ynoic amide (15)



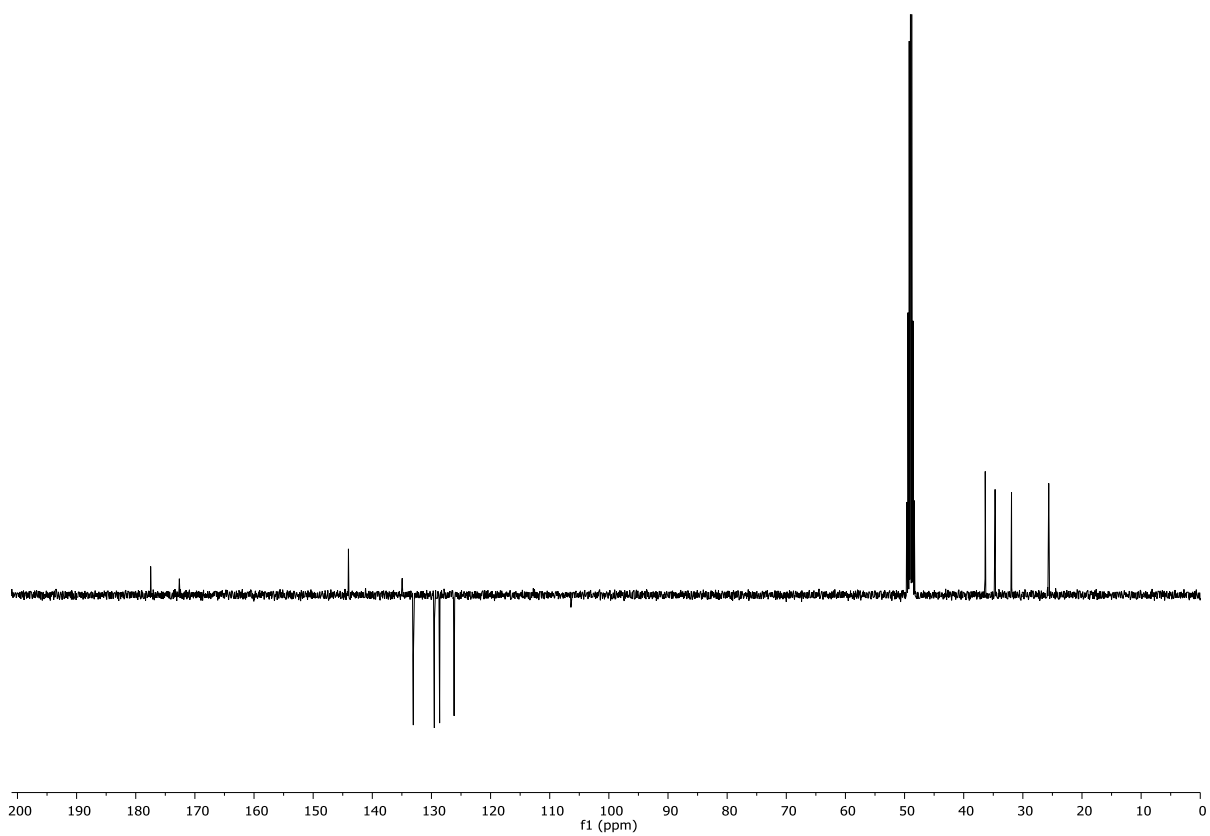
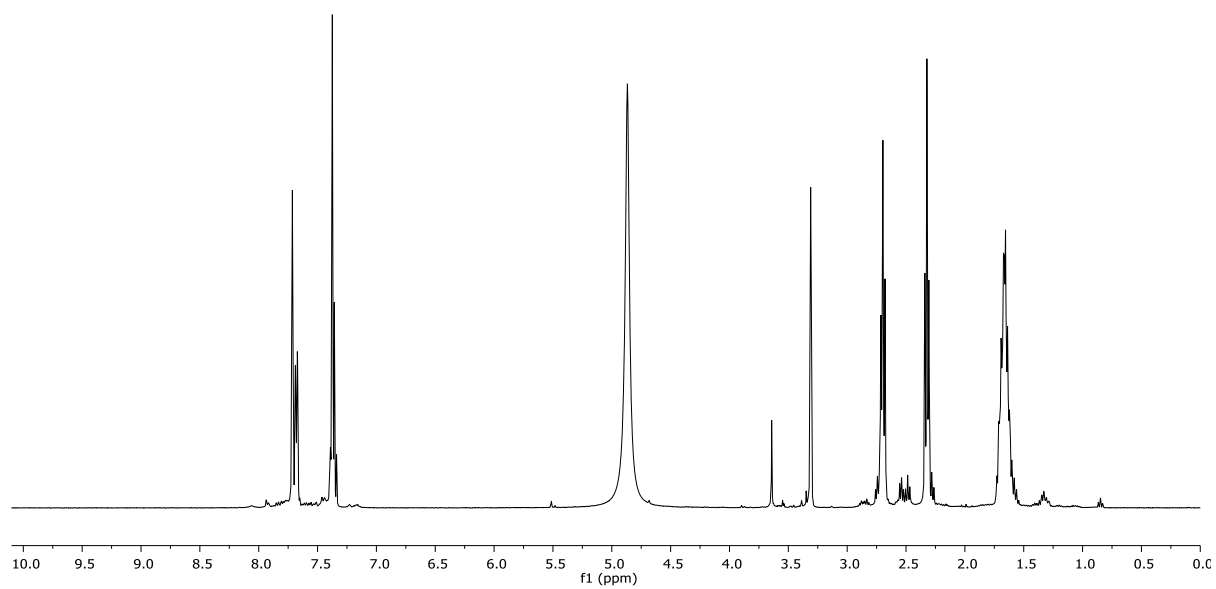
7-(3-Carbamoylphenyl)hept-6-ynoic acid (16)



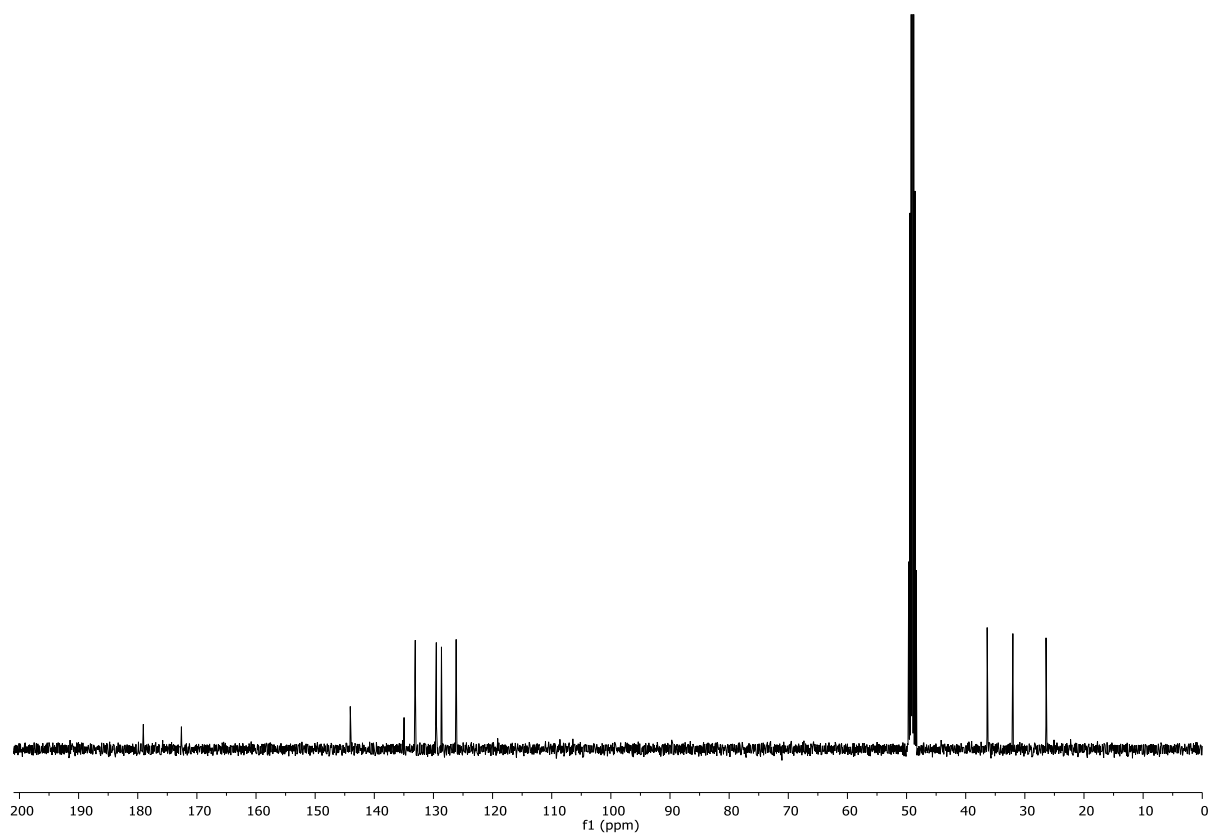
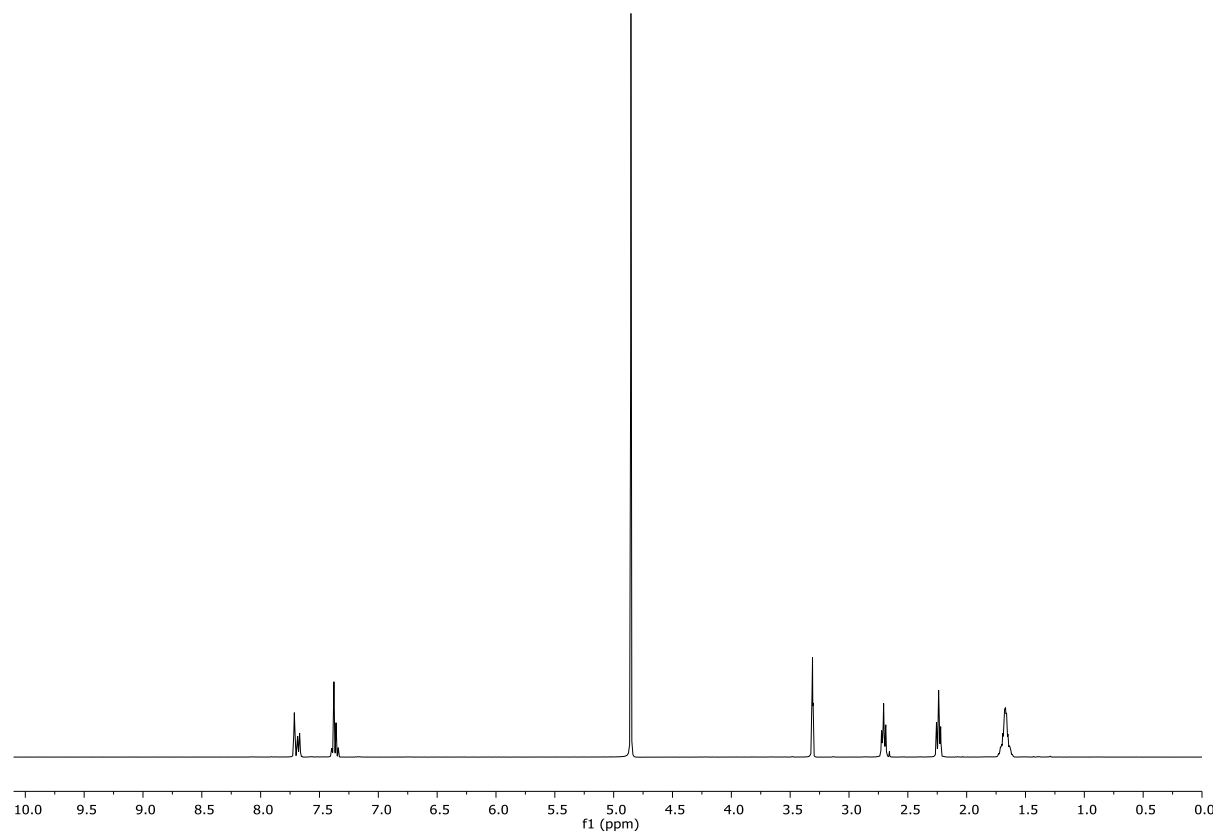
7-(3-Carbamoylphenyl)hept-6-ynoic amide (17)



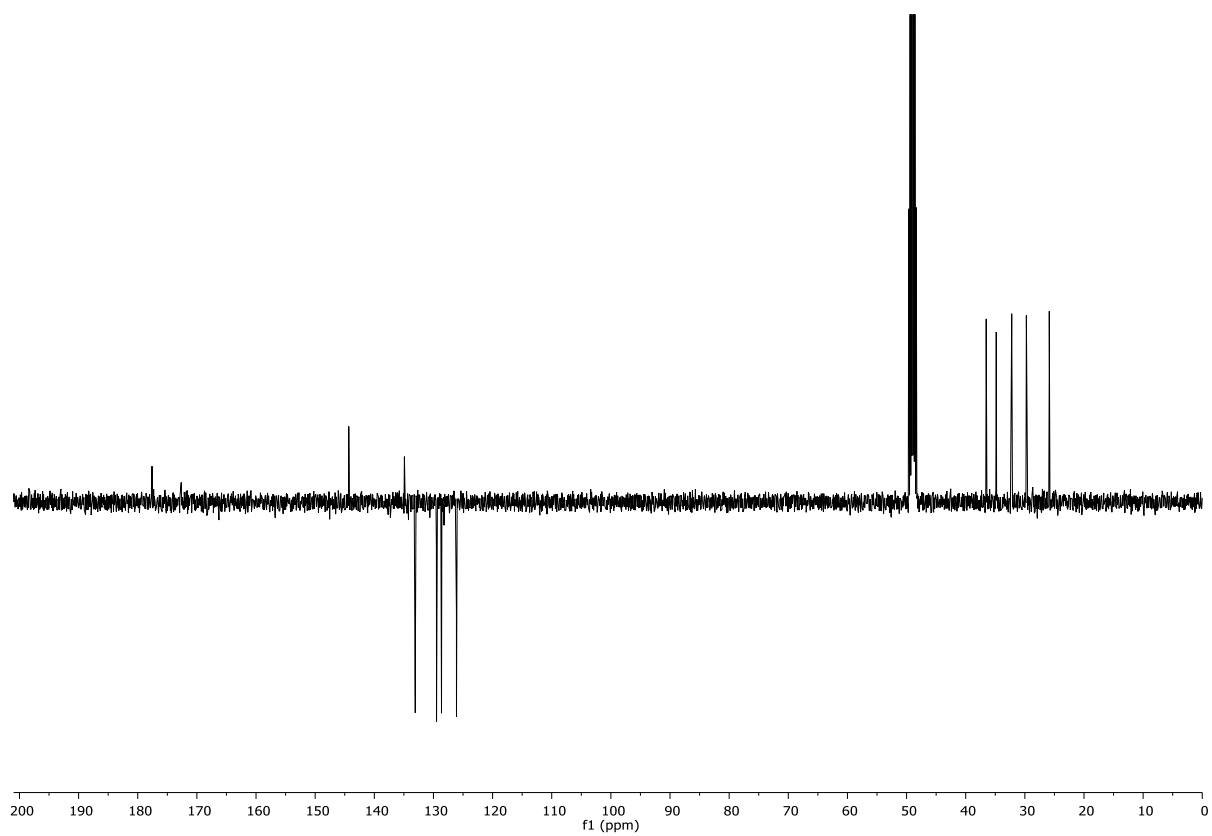
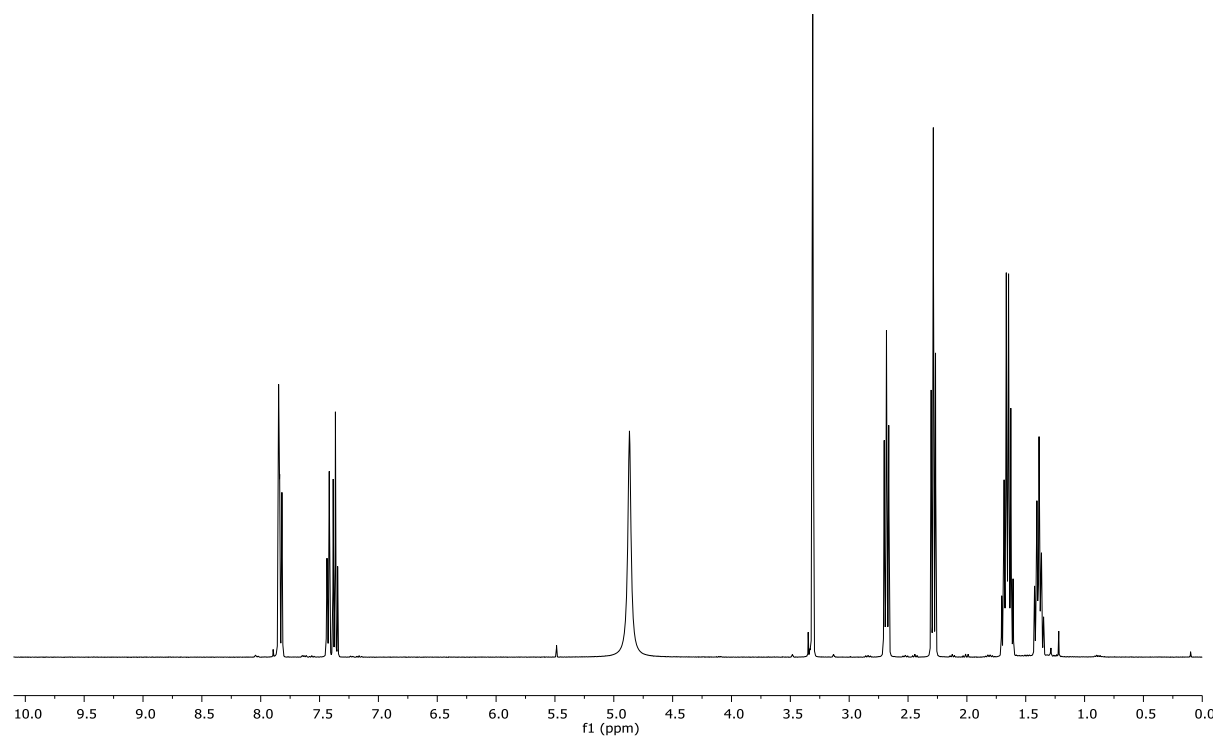
5-(3-Carbamoylphenyl)pentanoic acid (18)



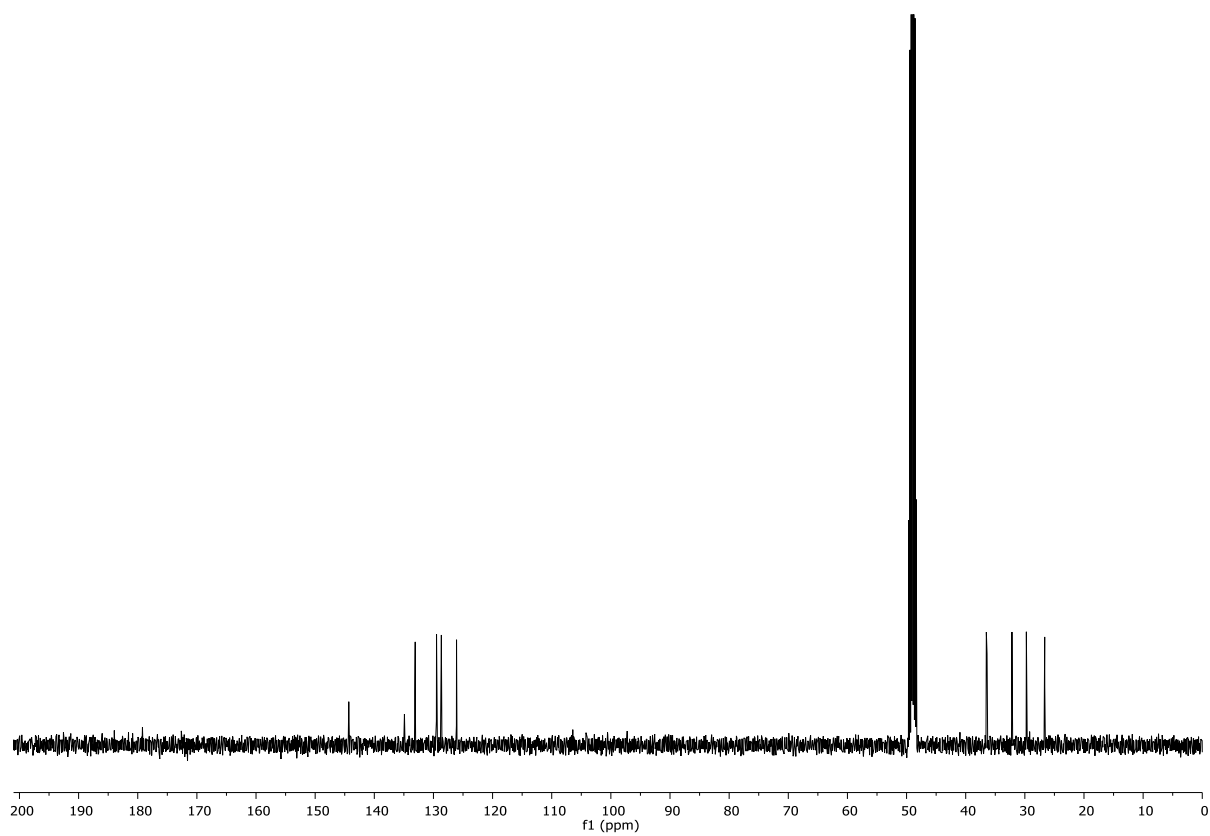
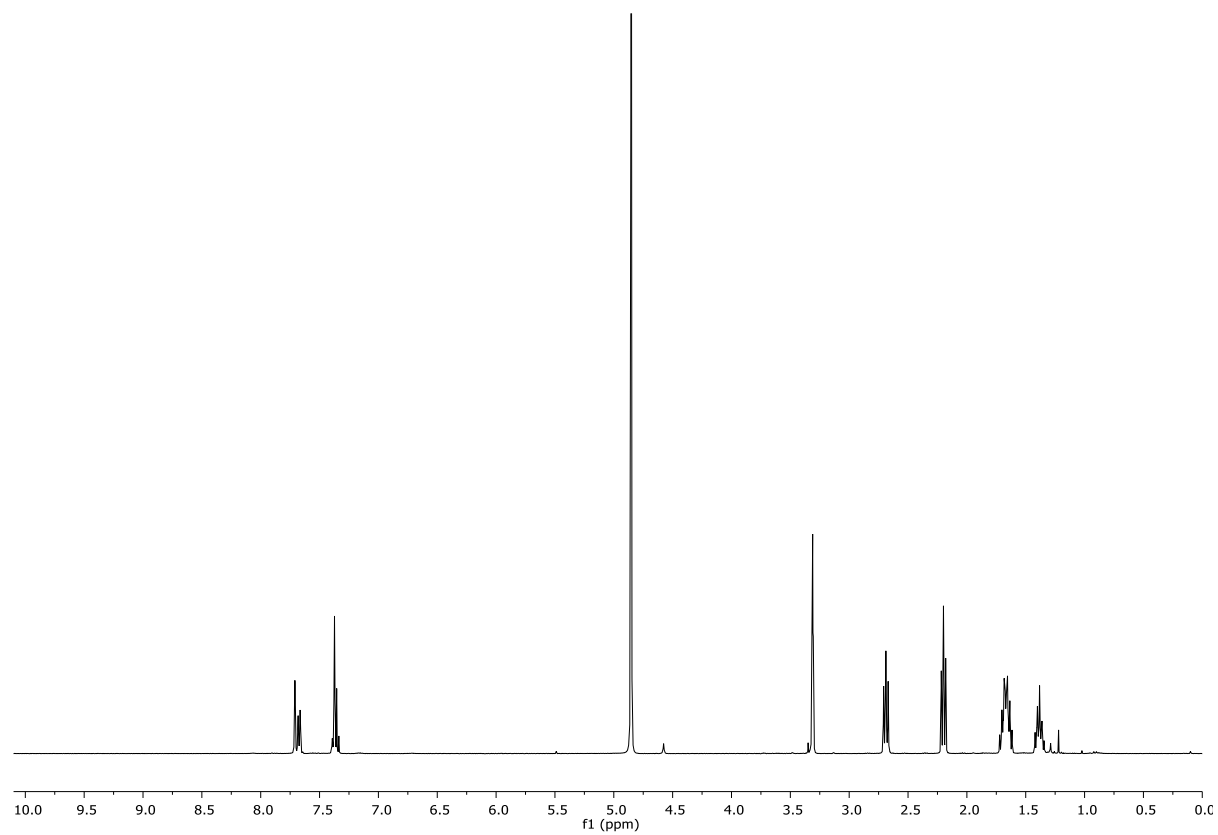
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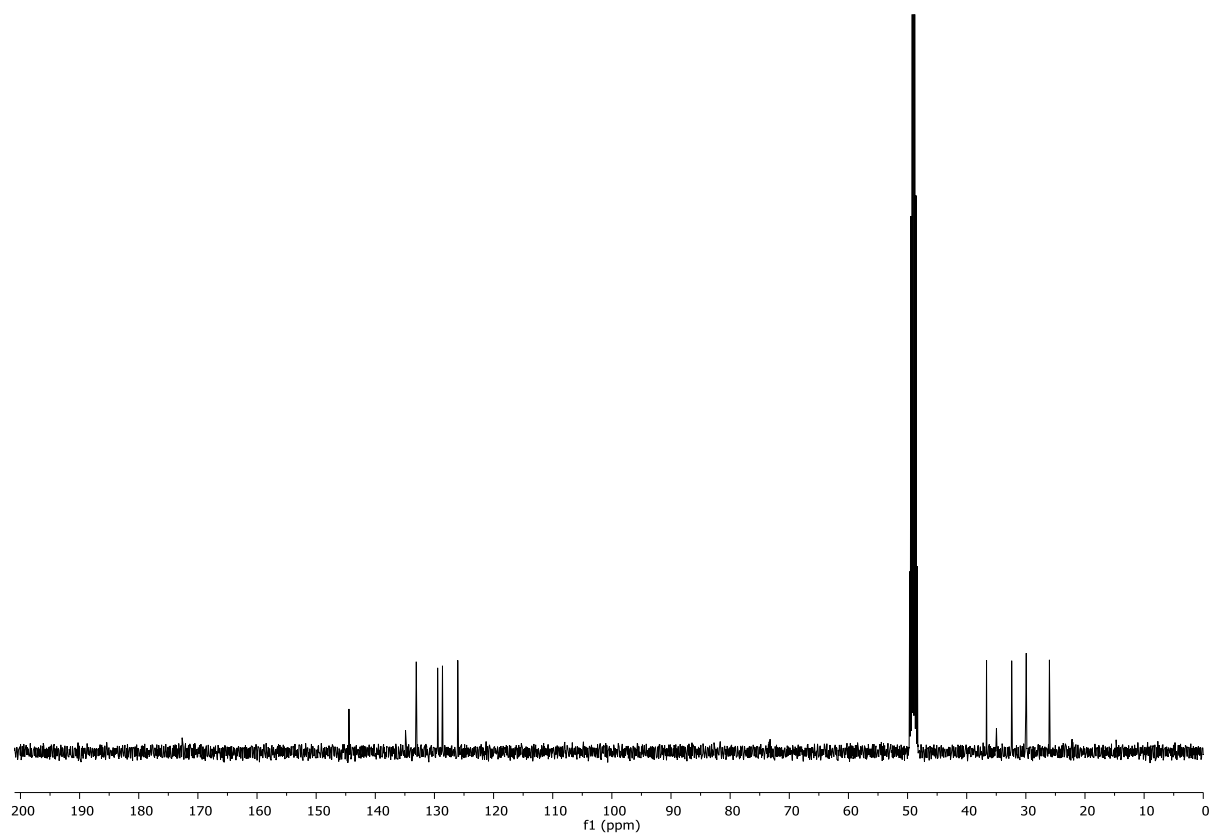
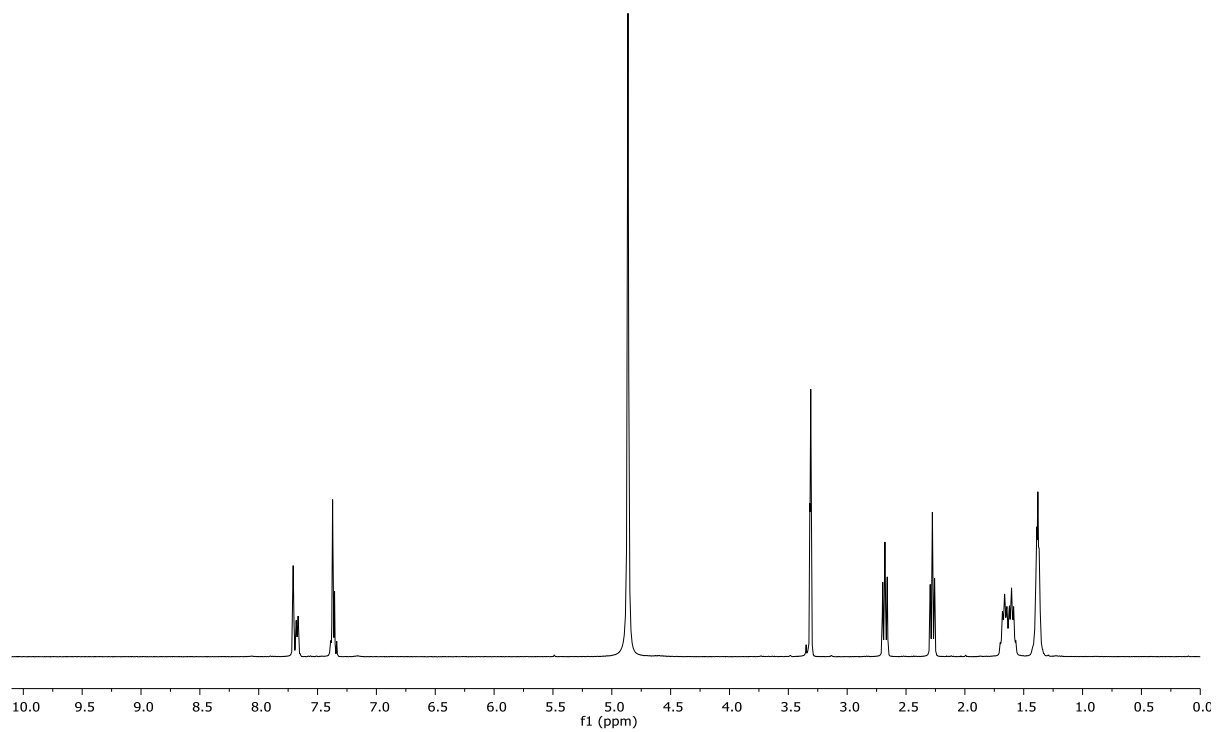
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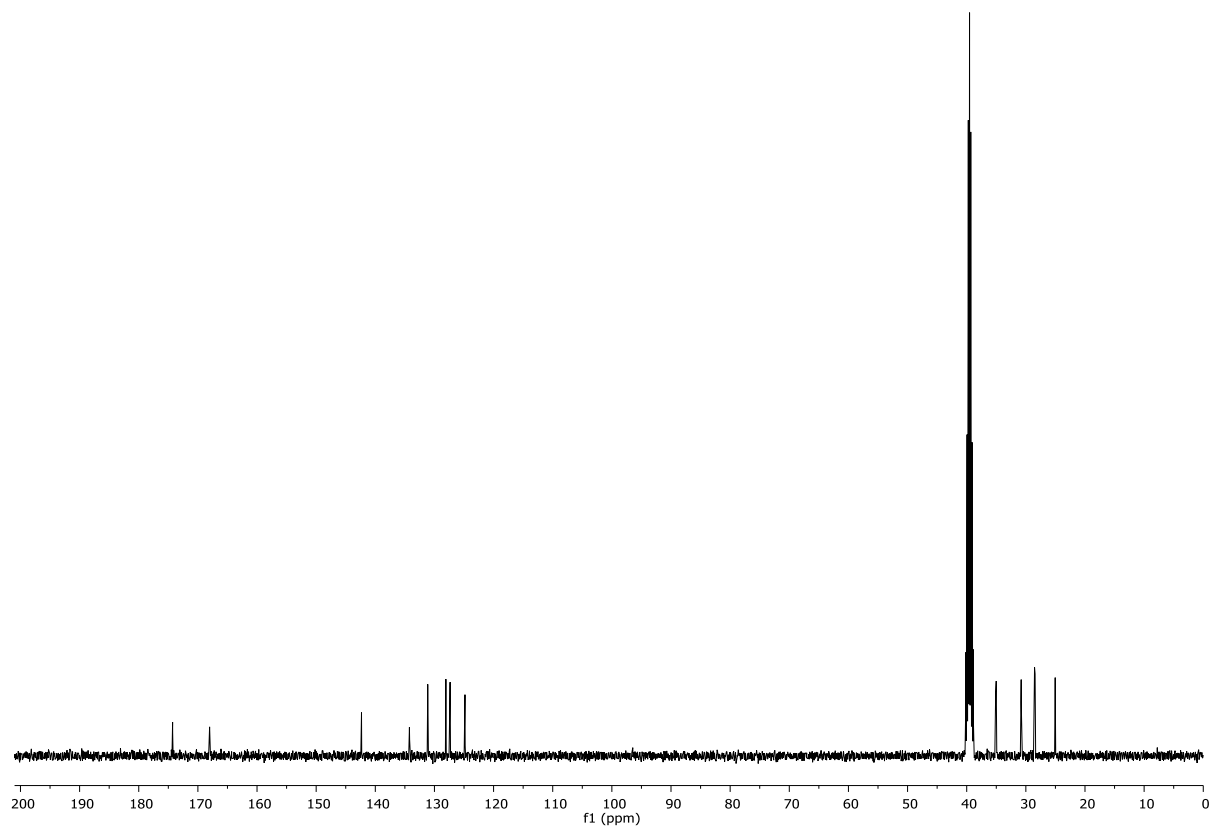
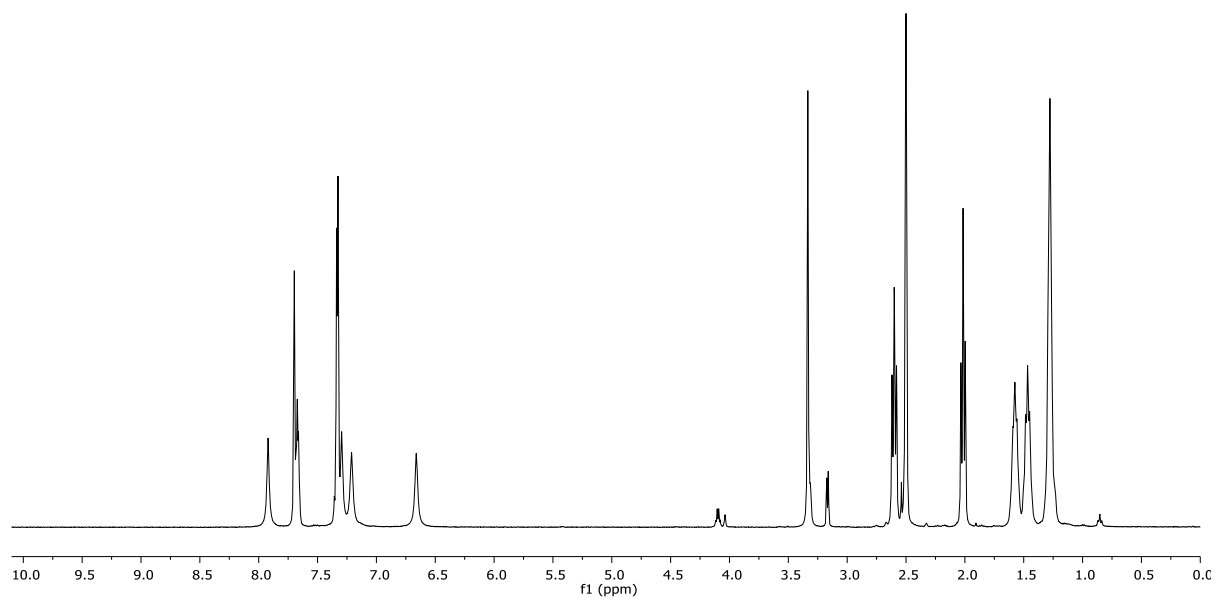
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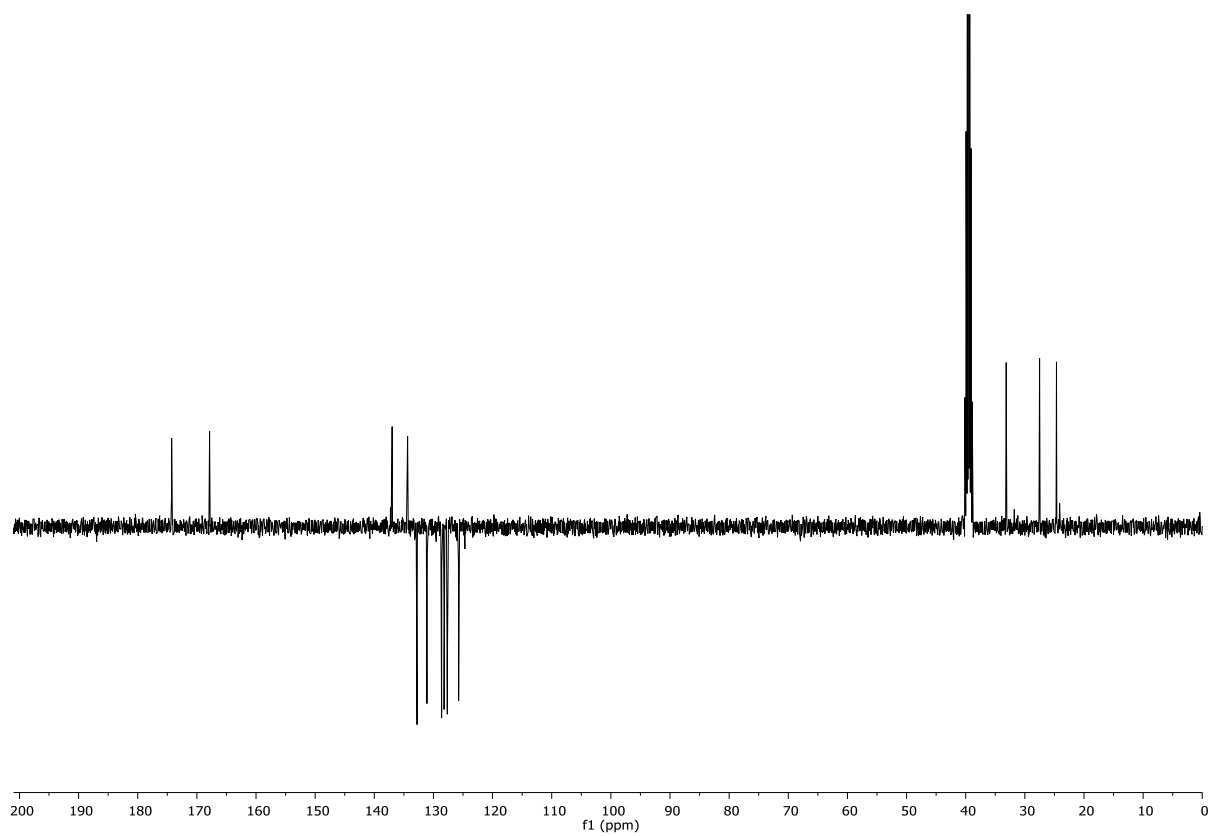
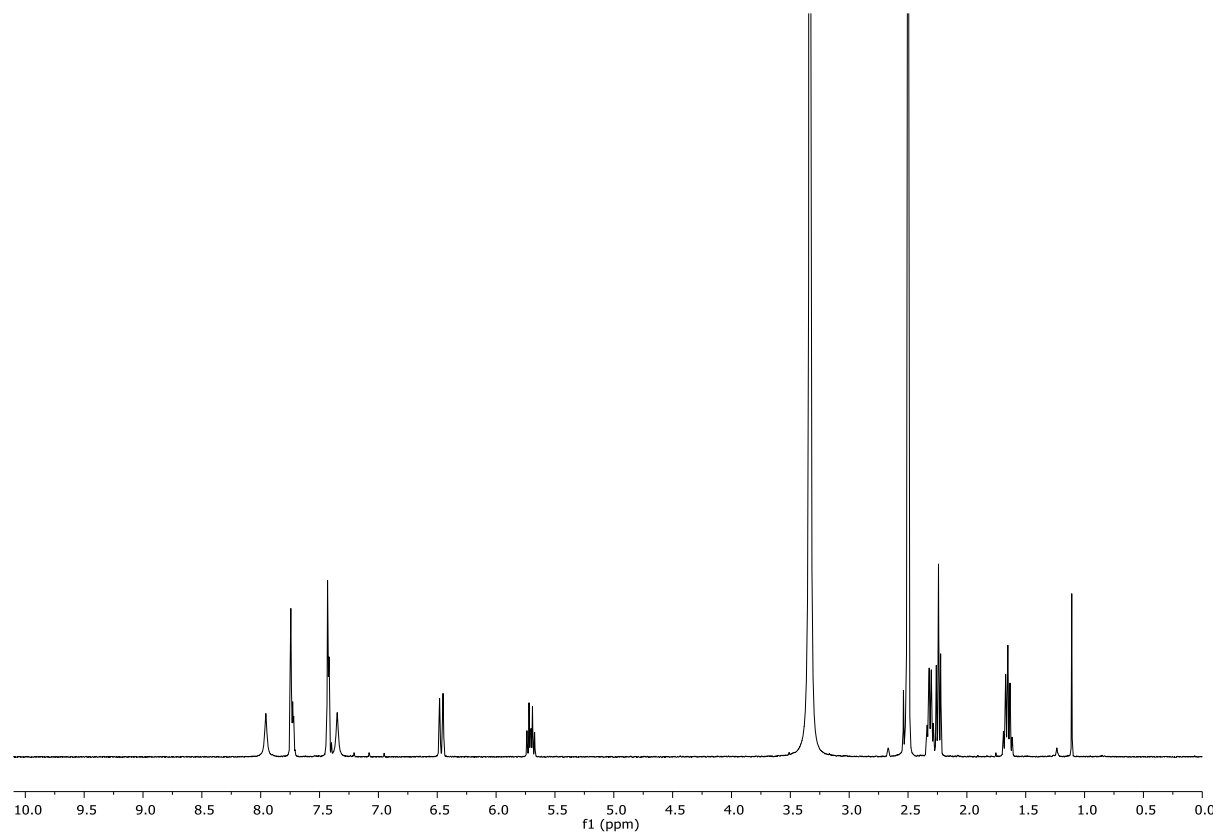
7-(3-Carbamoylphenyl)heptanoic acid (22)



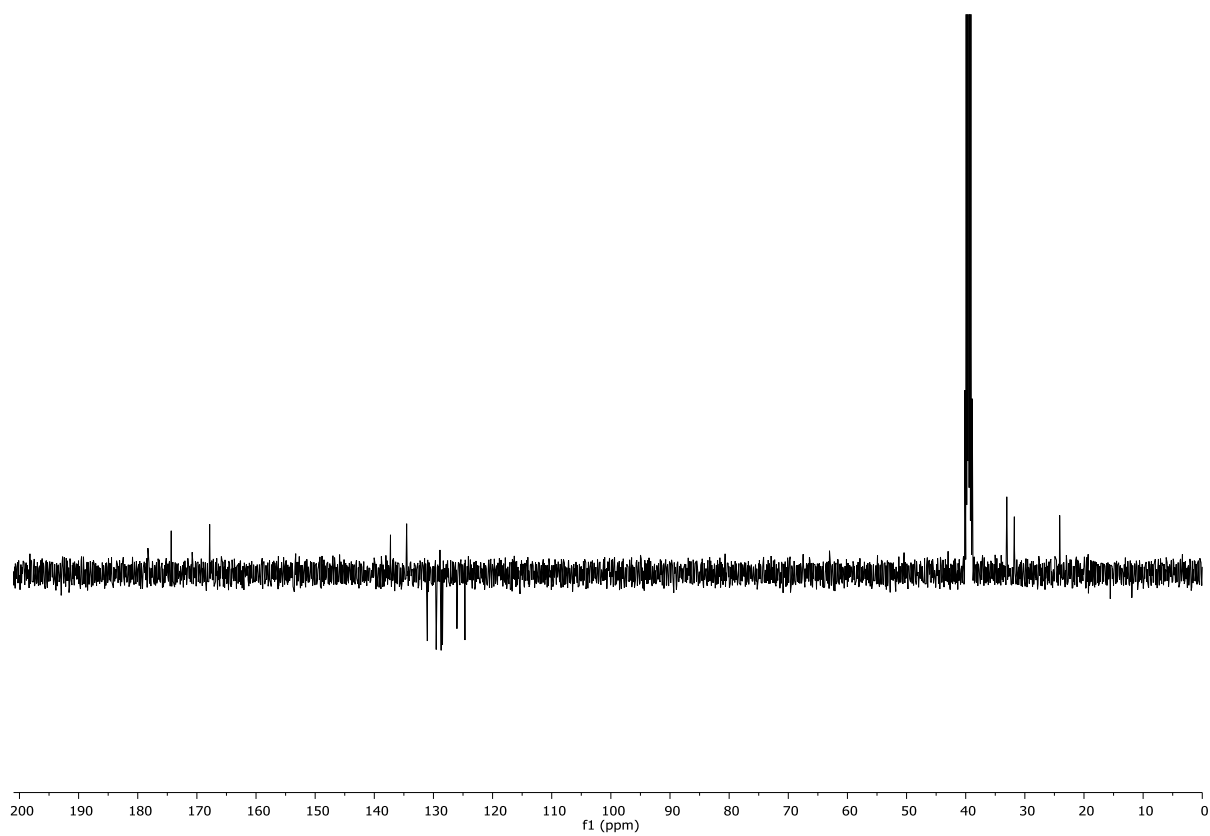
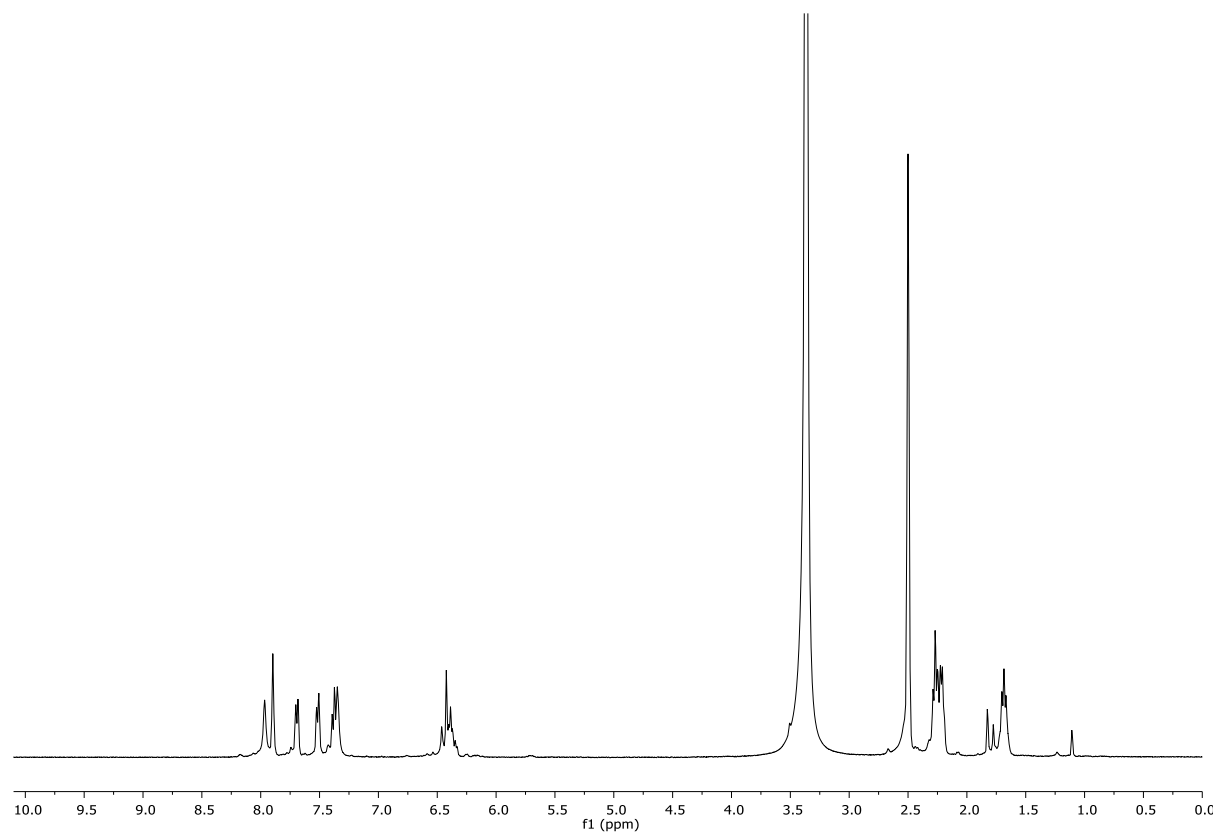
7-(3-Carbamoylphenyl)heptanoic amide (23)



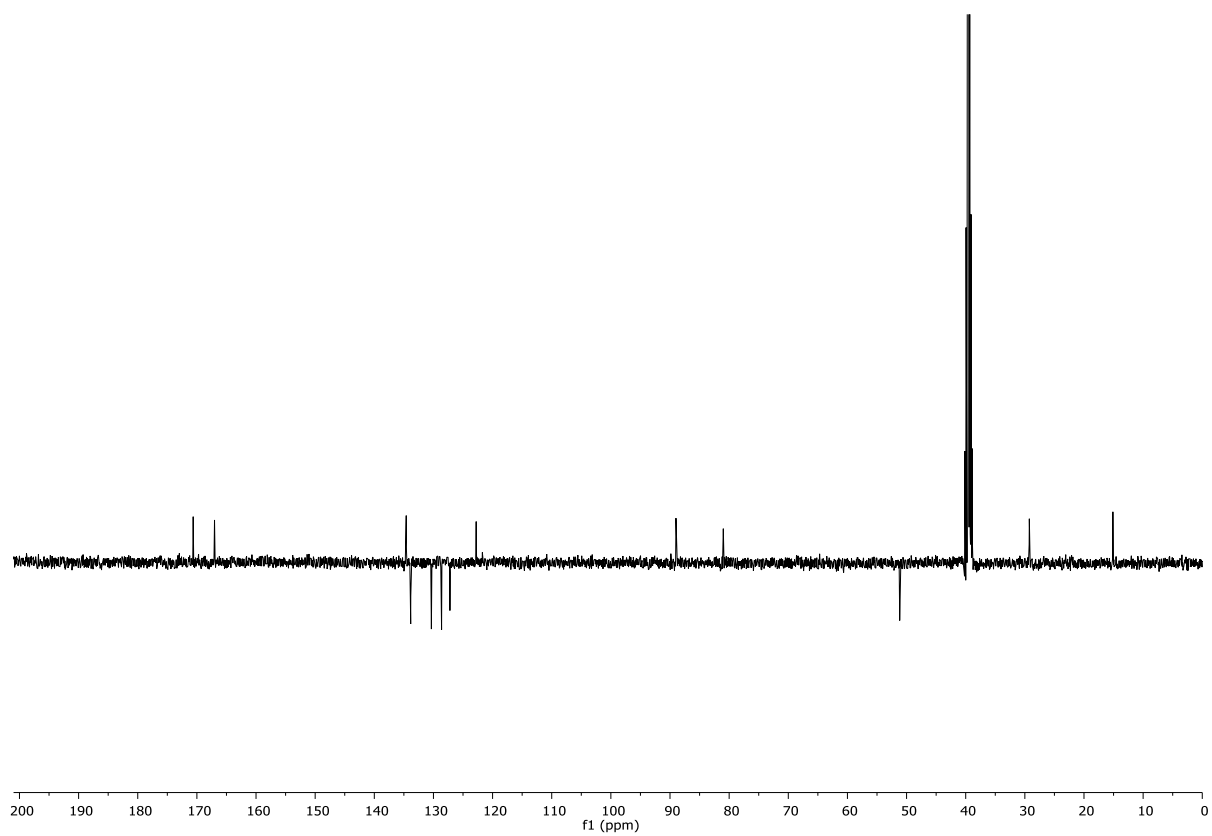
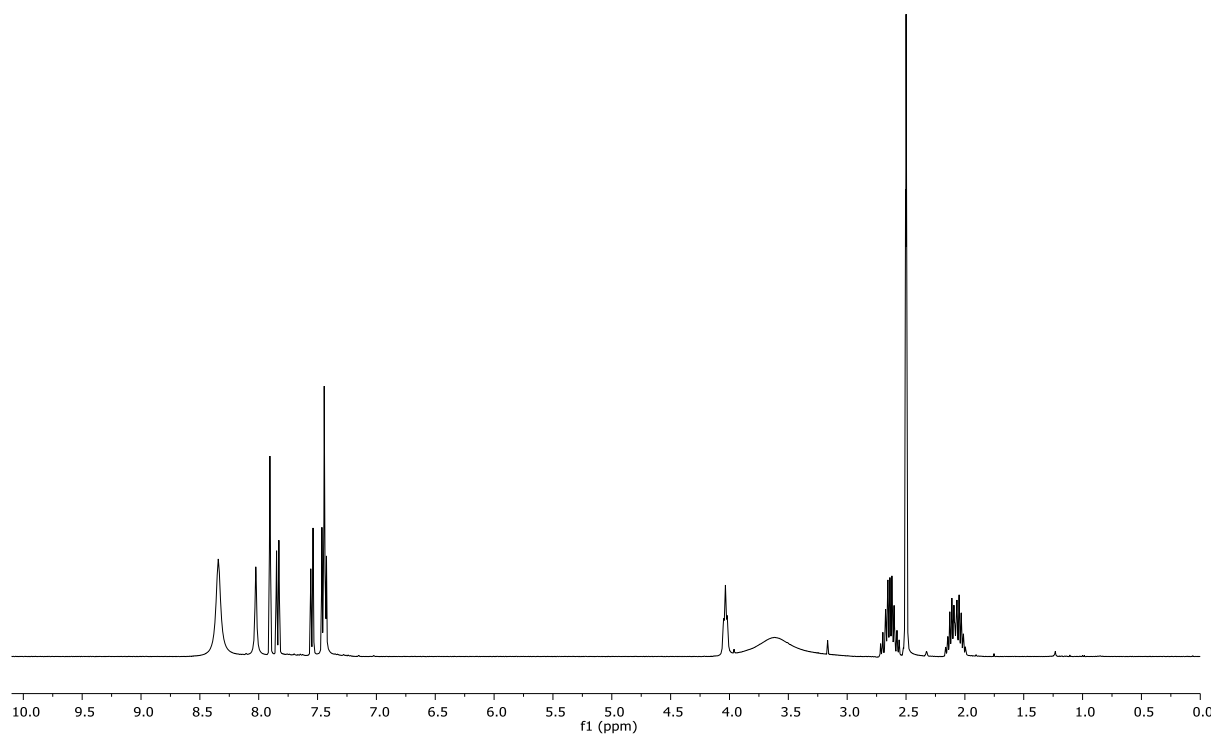
(Z)-6-(3-Carbamoylphenyl)hex-5-enoic acid (24)



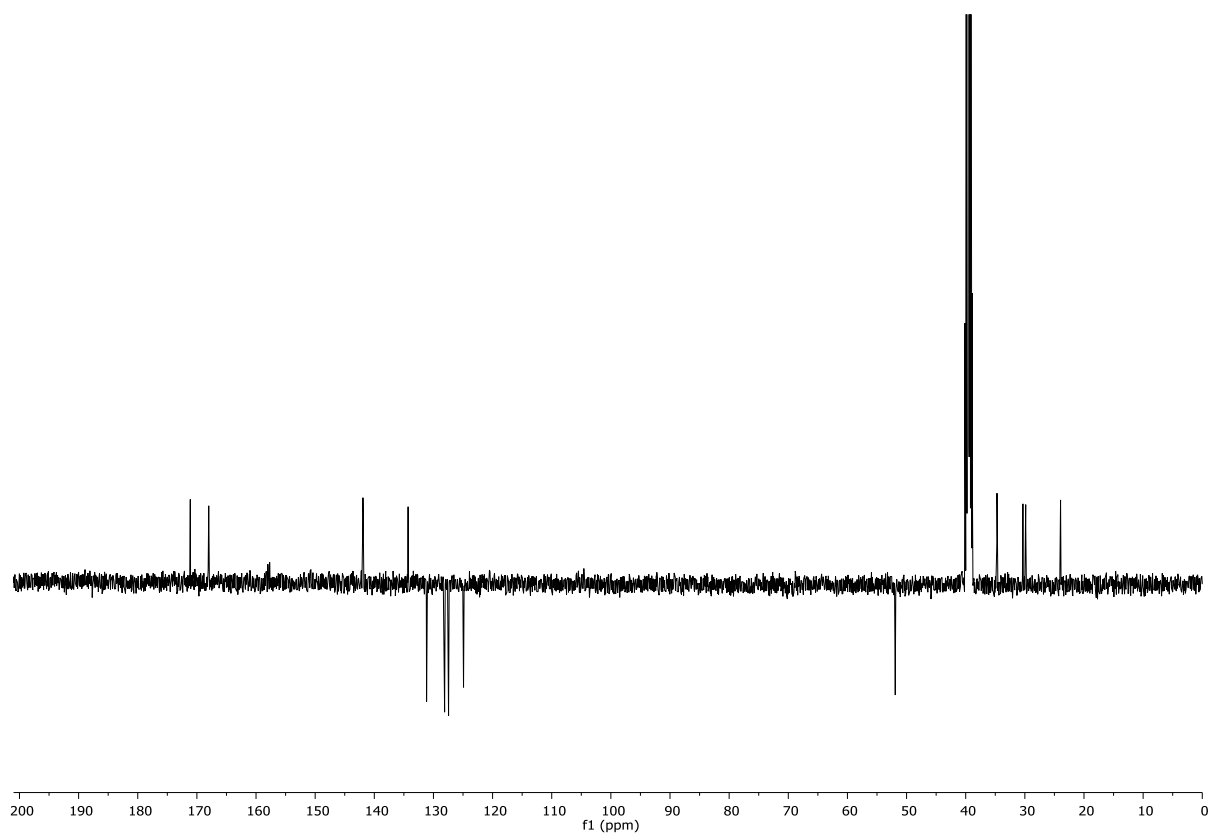
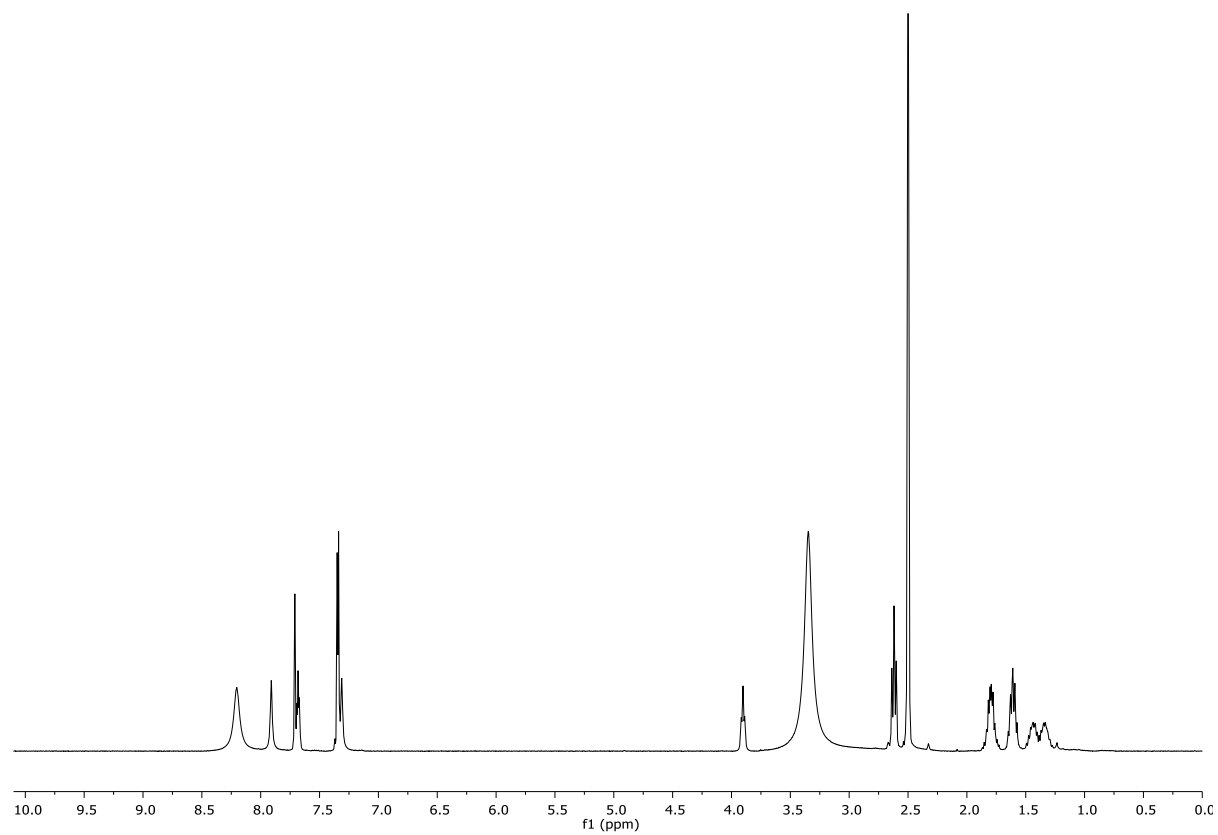
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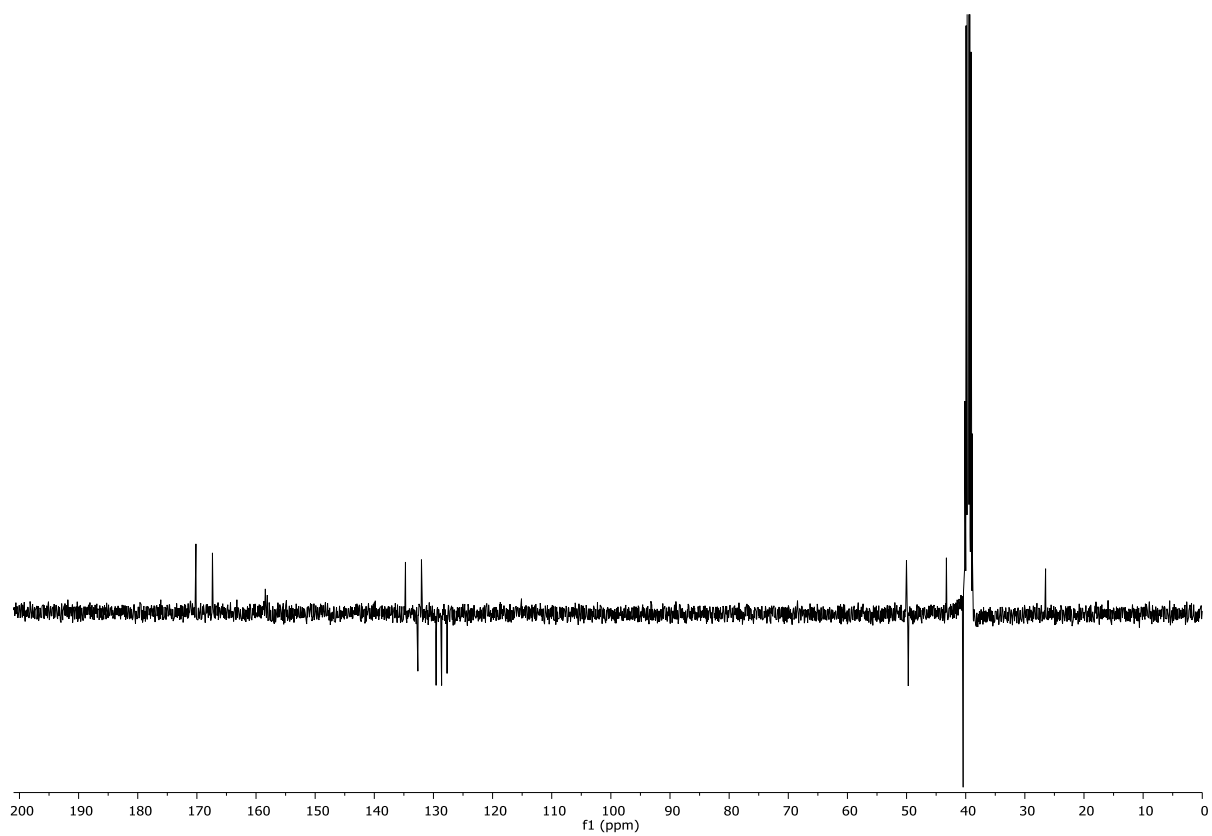
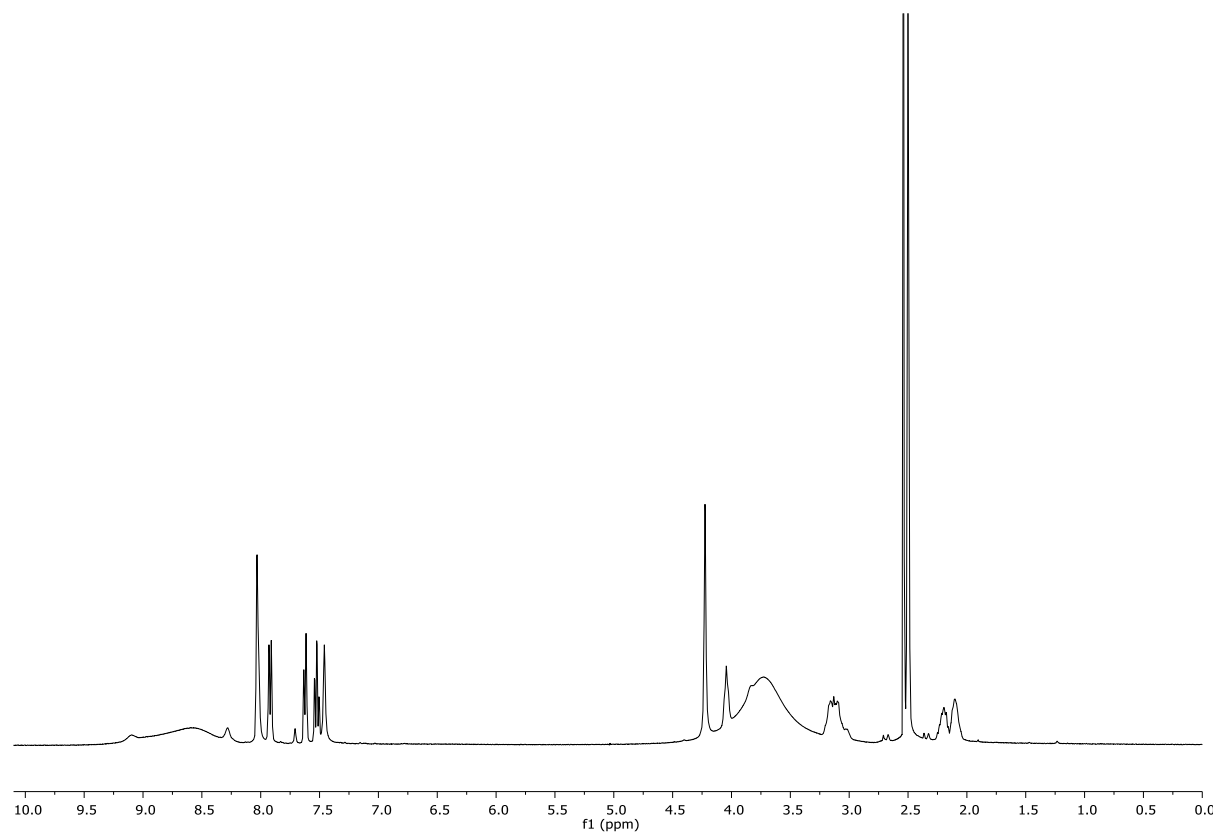
(S)-2-Amino-6-(3-carbamoylphenyl)hex-5-ynoic acid (27)



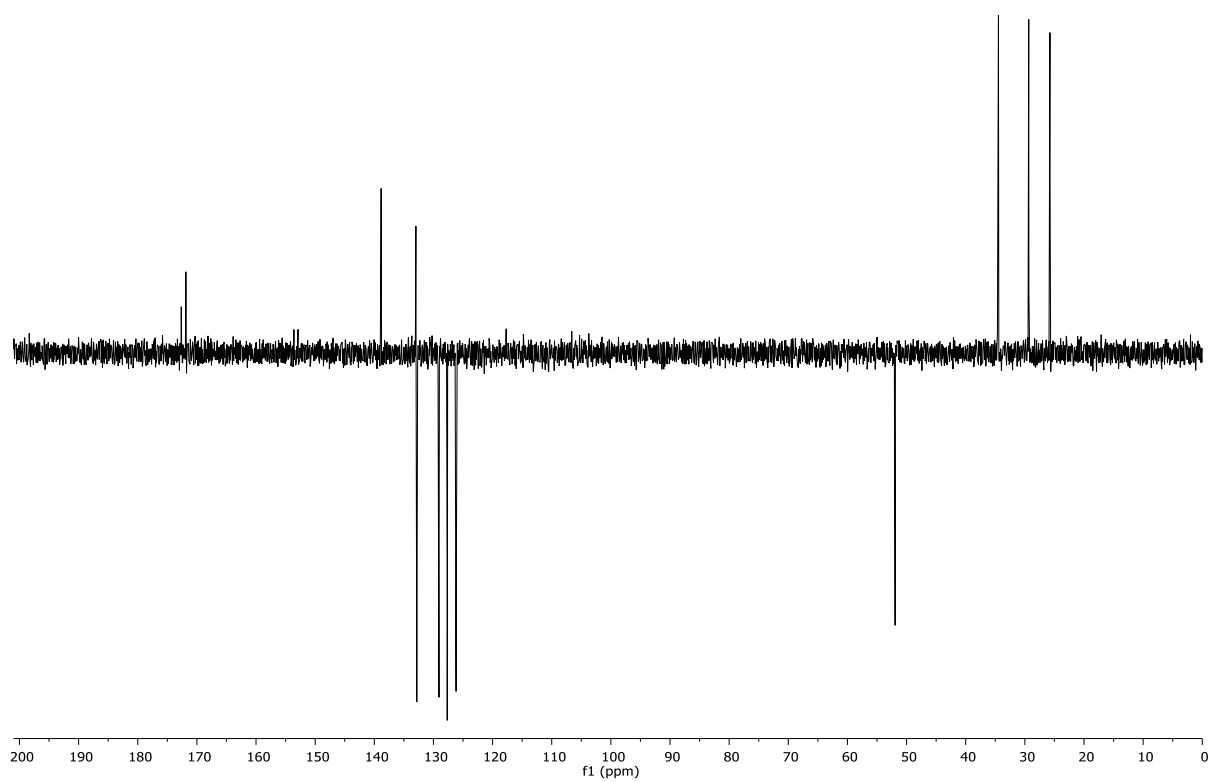
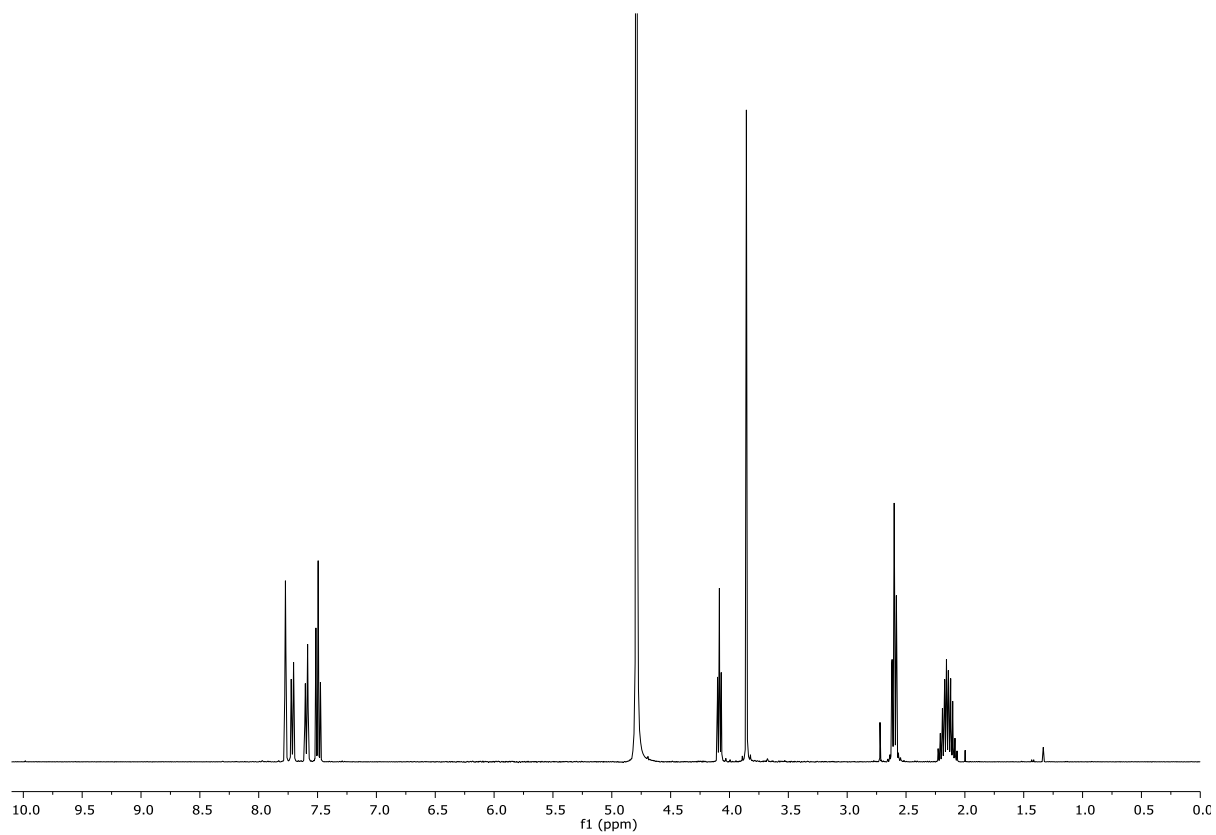
(S)-2-Amino-6-(3-carbamoylphenyl)hexanoic acid (28)



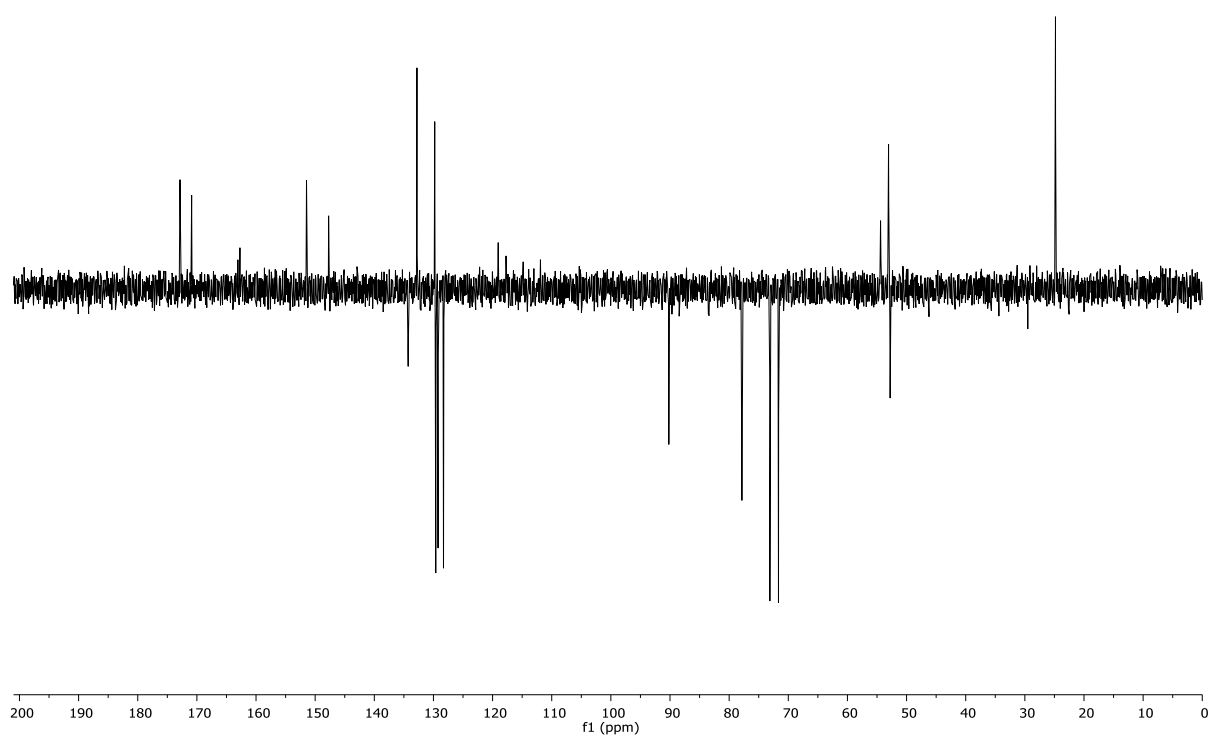
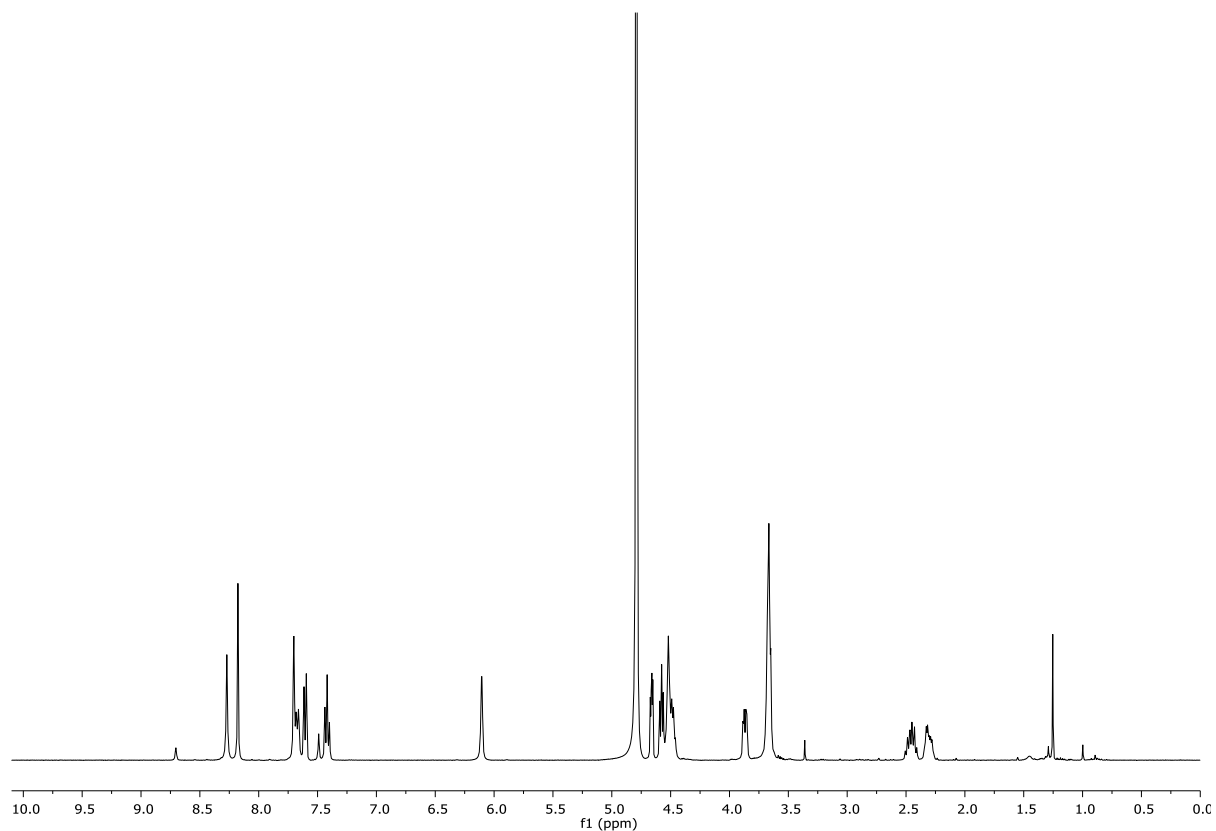
(S)-2-Amino-4-((3-carbamoylbenzyl)amino)butanoic acid (35)



(S)-2-Amino-4-((3-carbamoylbenzyl)thio)butanoic acid (41)

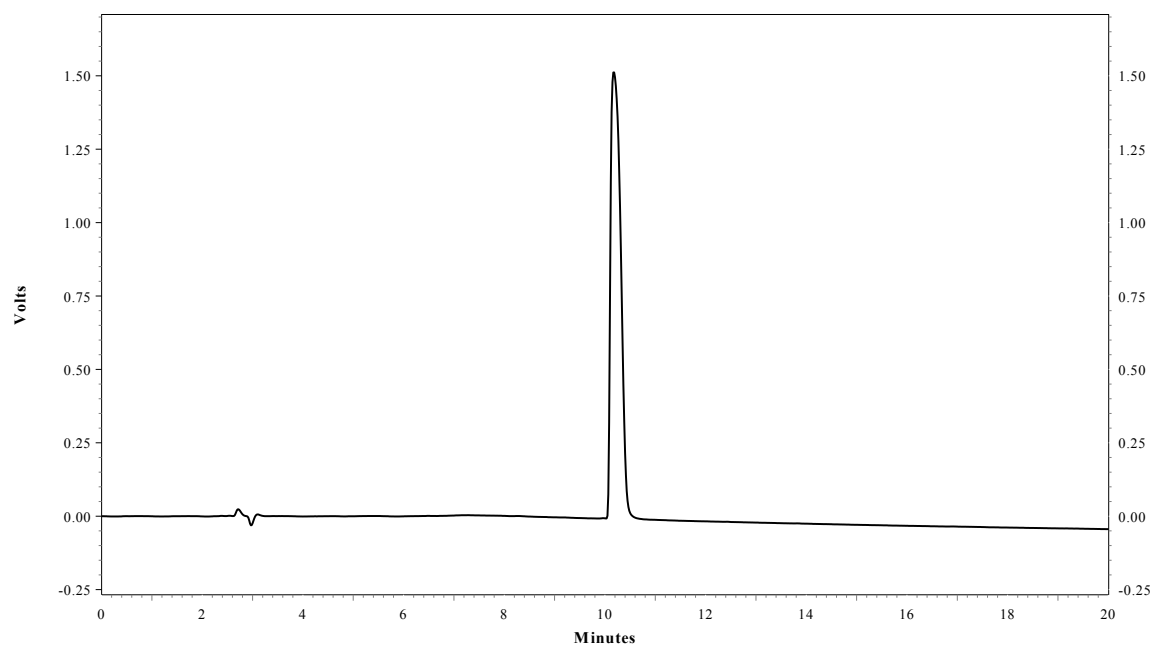


(S)-2-Amino-4-(((2R,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(3-carbamoylbenzyl)amino)butanoic acid (45)

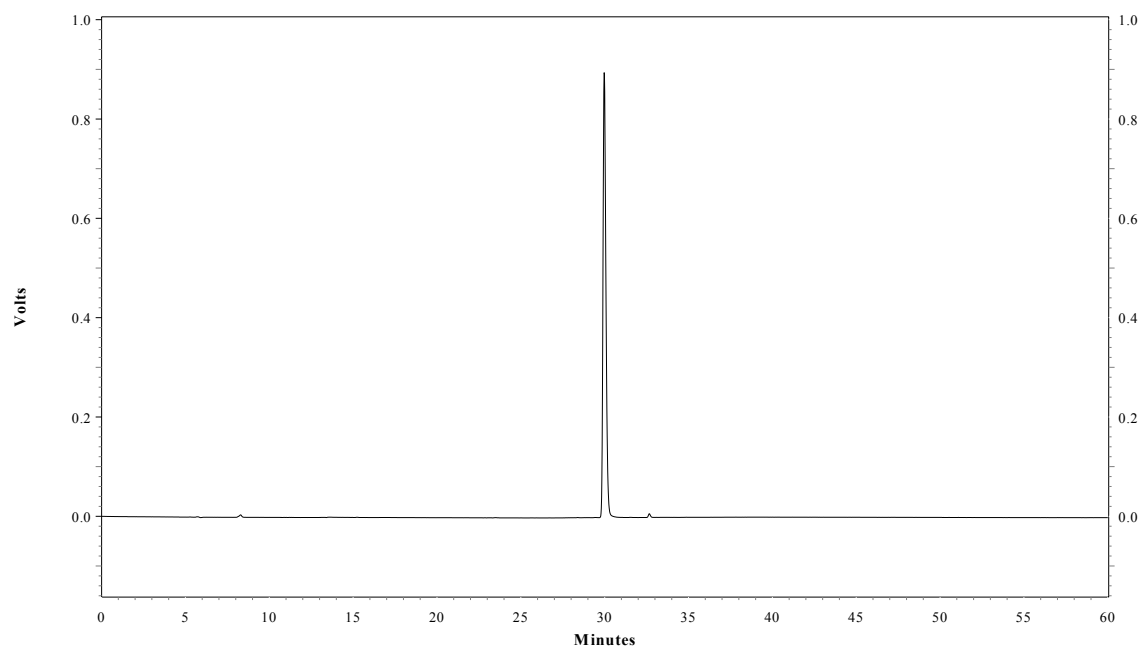


HPLC Traces

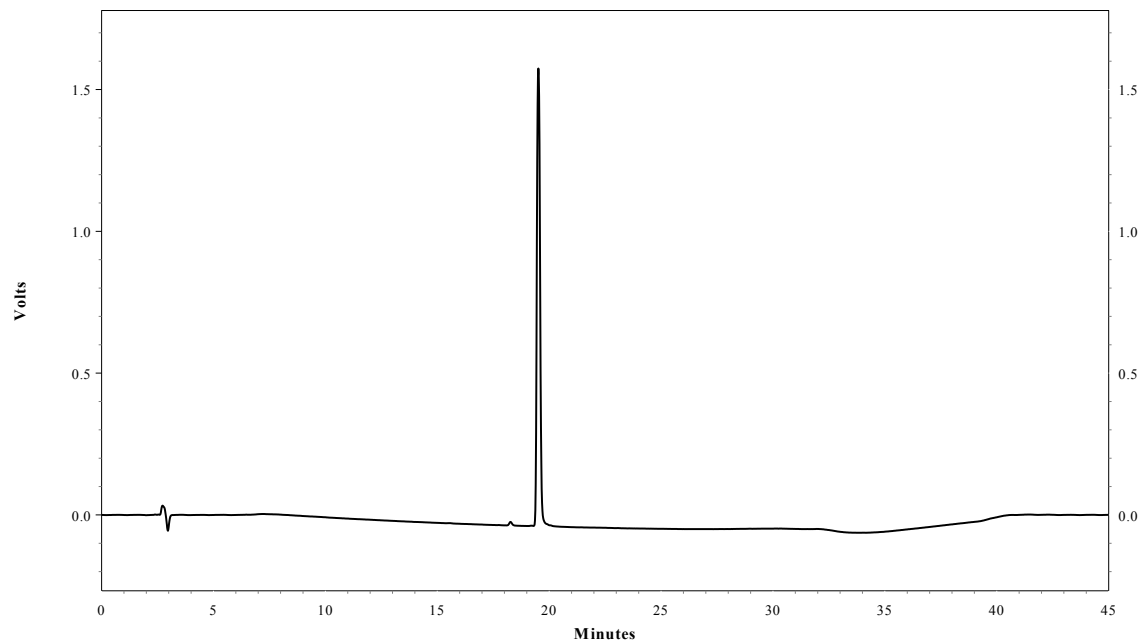
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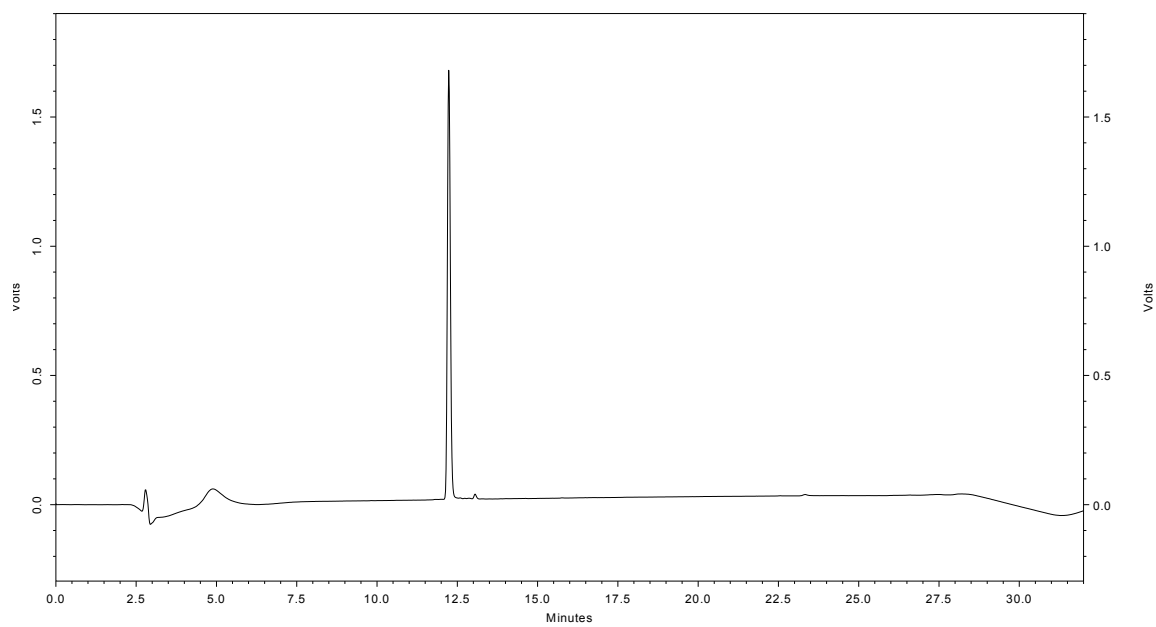
3-((((2S,3S,4R,5R)-5-(6-Amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)thio)methyl)benzamide (10)



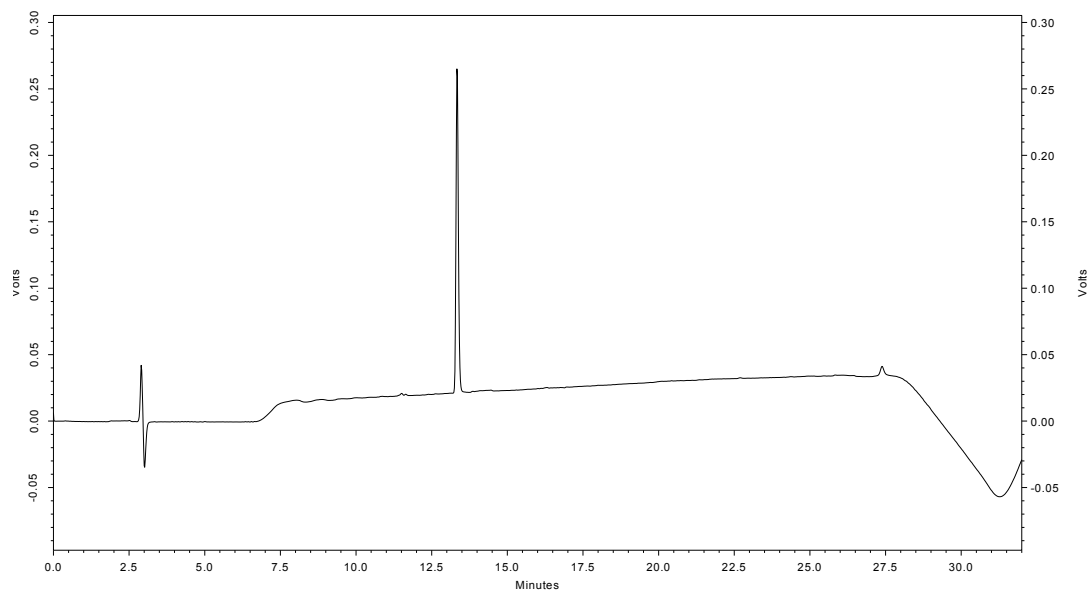
3-((((2S,3S,4R,5R)-5-(6-Amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)methyl)benzamide (11)



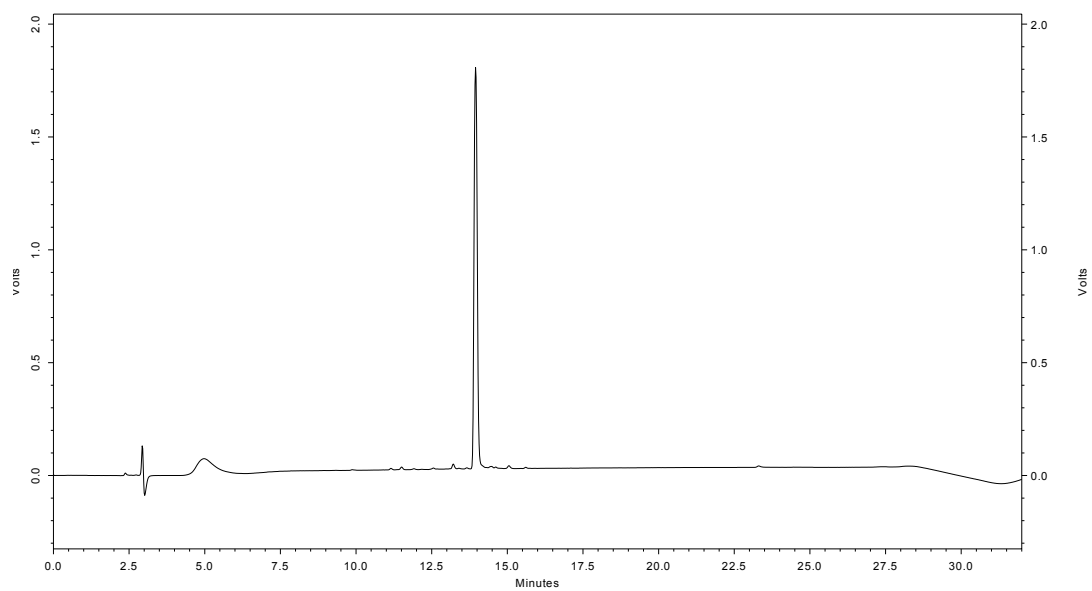
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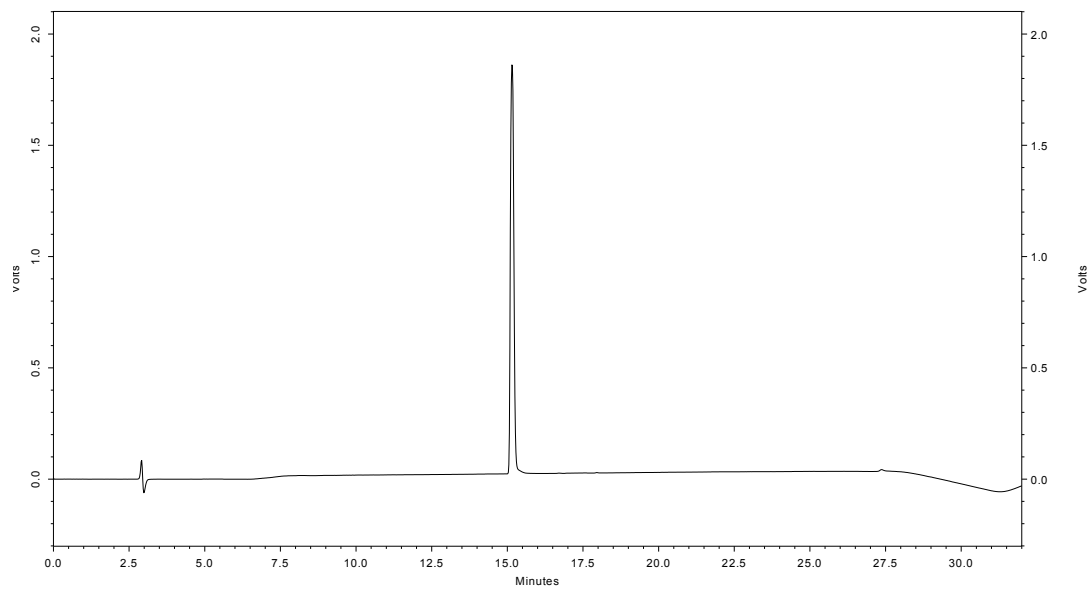
5-(3-Carbamoylphenyl)pent-4-ynoic amide (13)



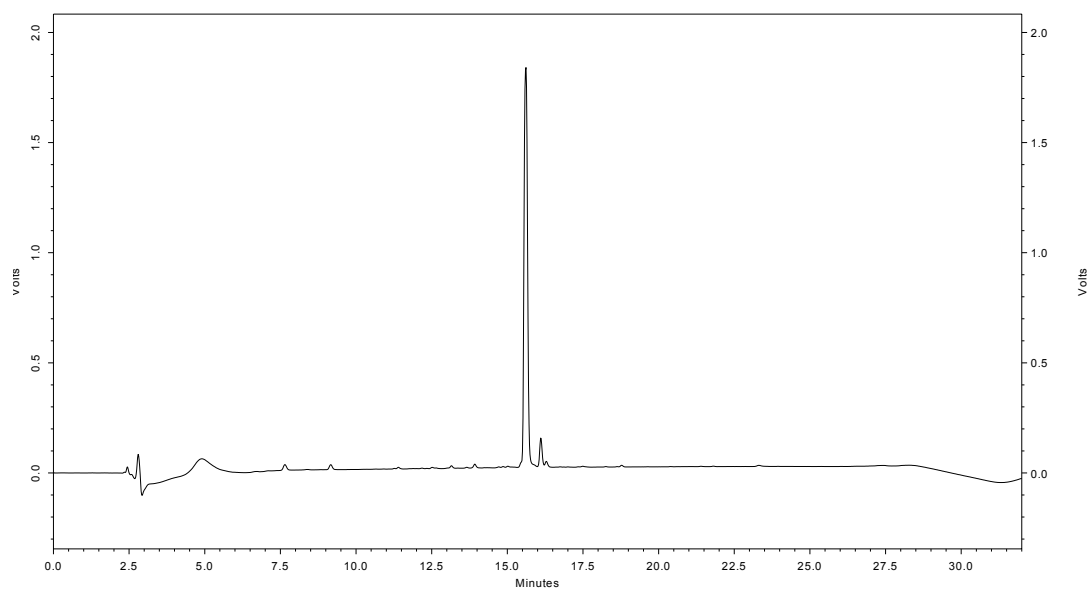
6-(3-Carbamoylphenyl)hex-5-ynoic acid (14)



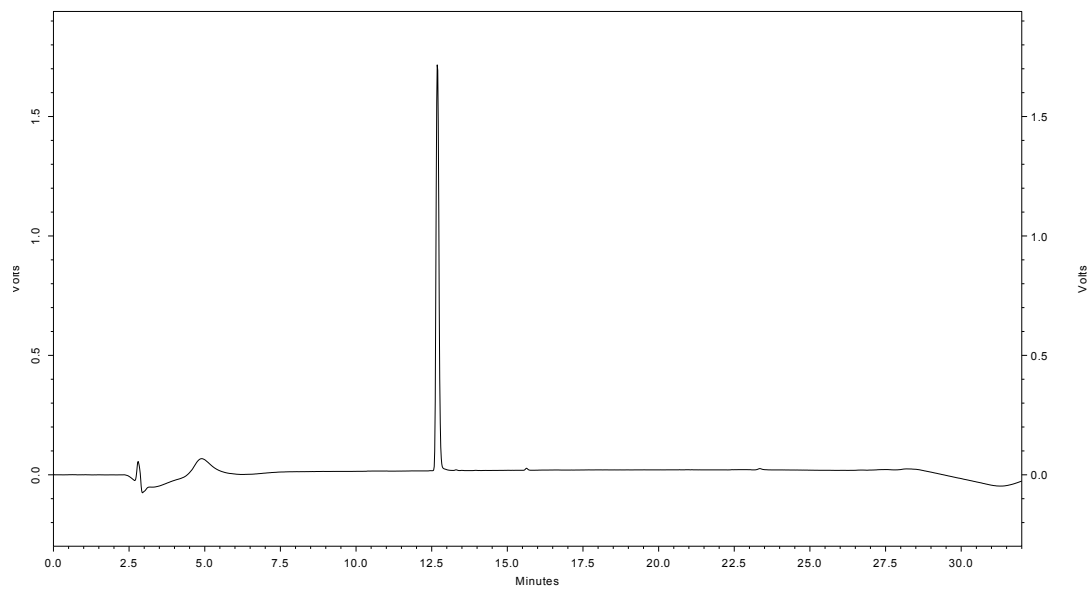
6-(3-Carbamoylphenyl)hex-5-ynoic amide (15)



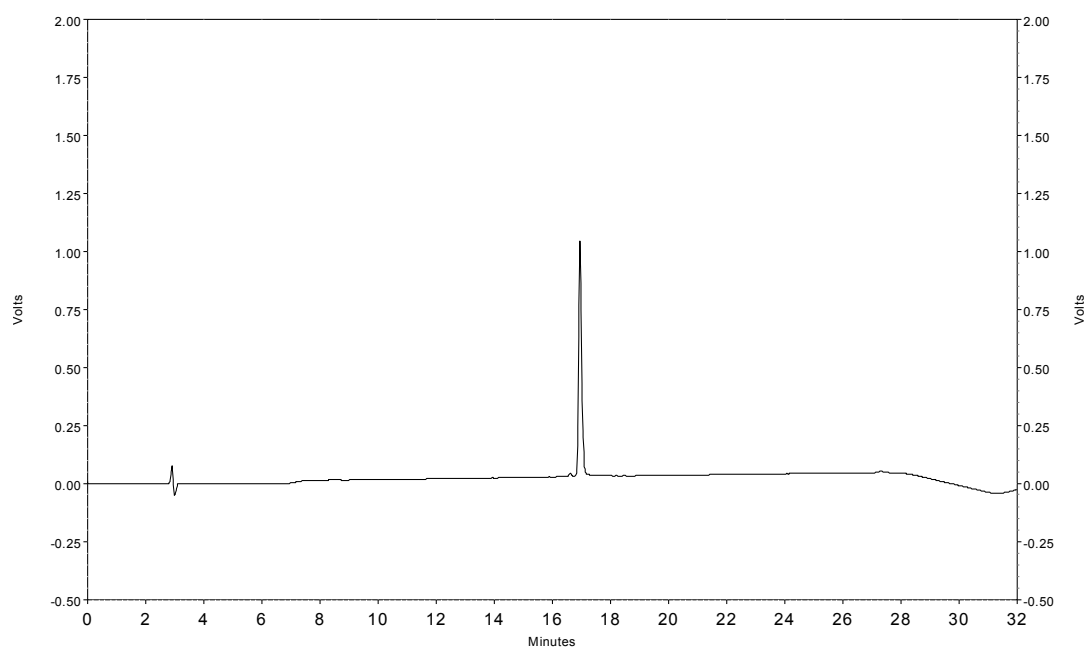
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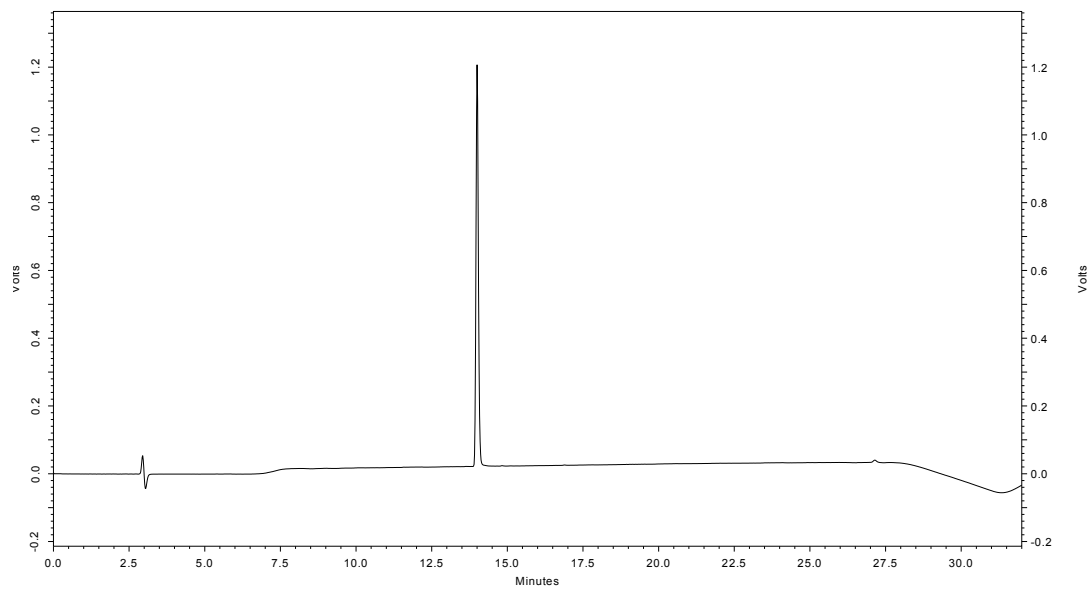
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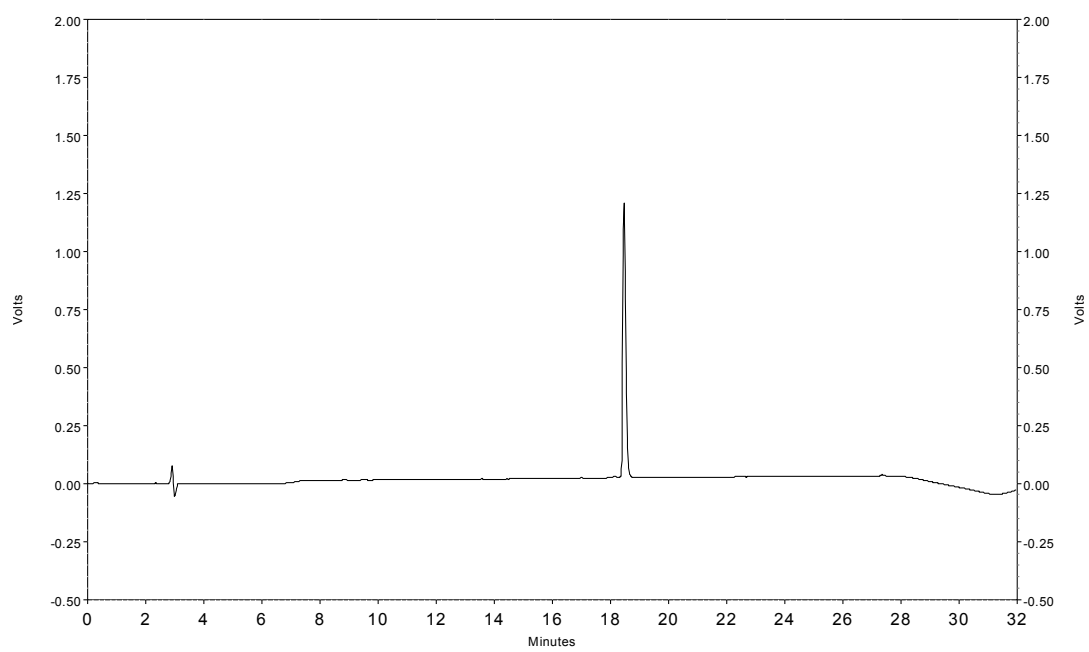
5-(3-Carbamoylphenyl)pentanoic acid (18)



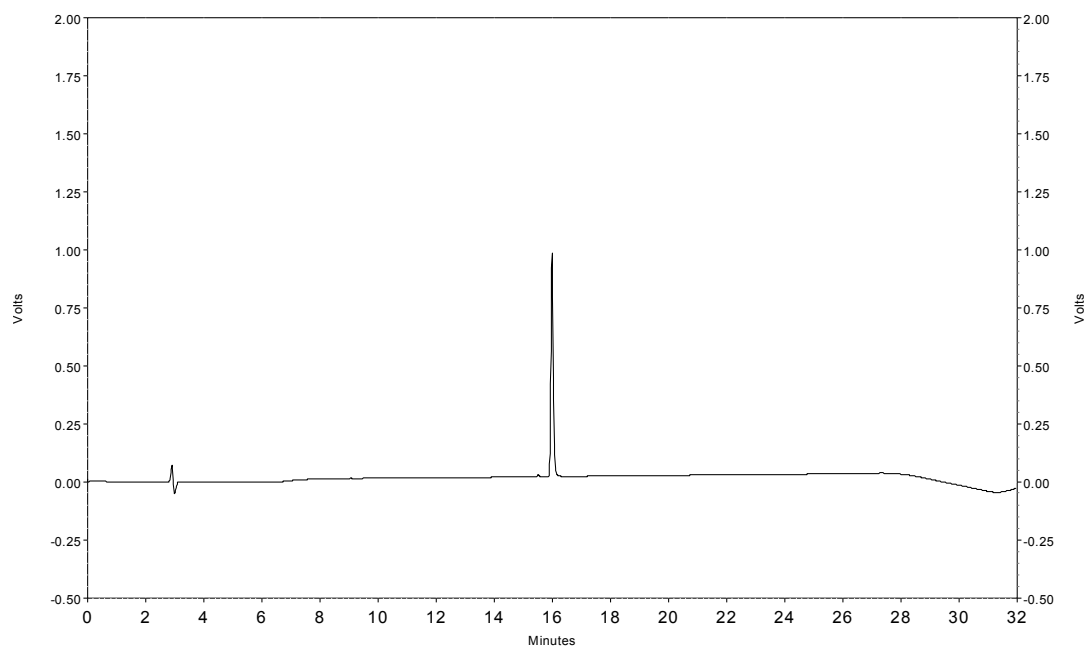
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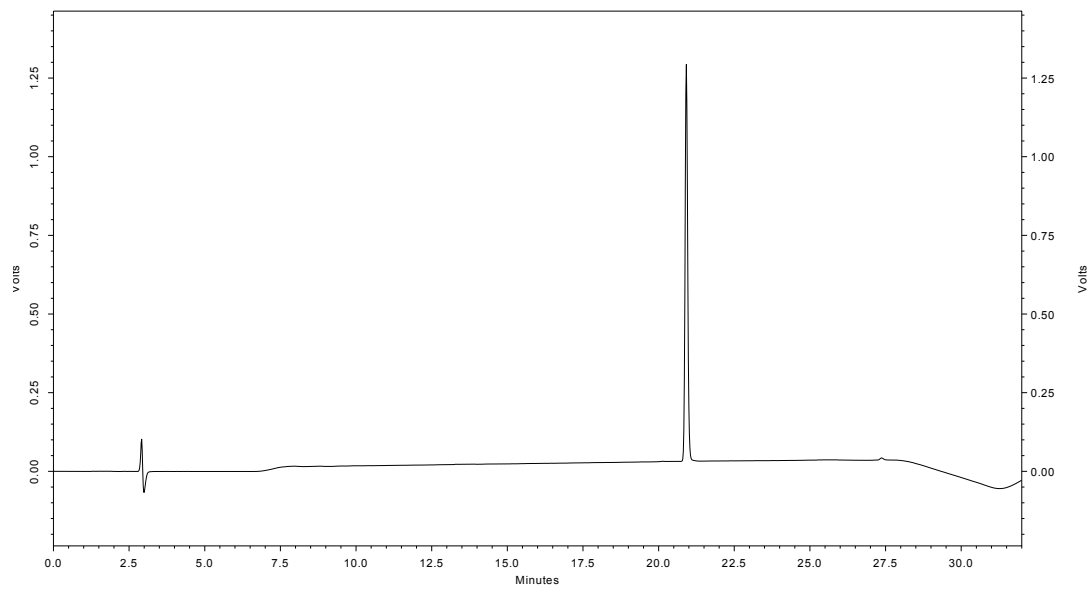
6-(3-Carbamoylphenyl)hexanoic acid (20)



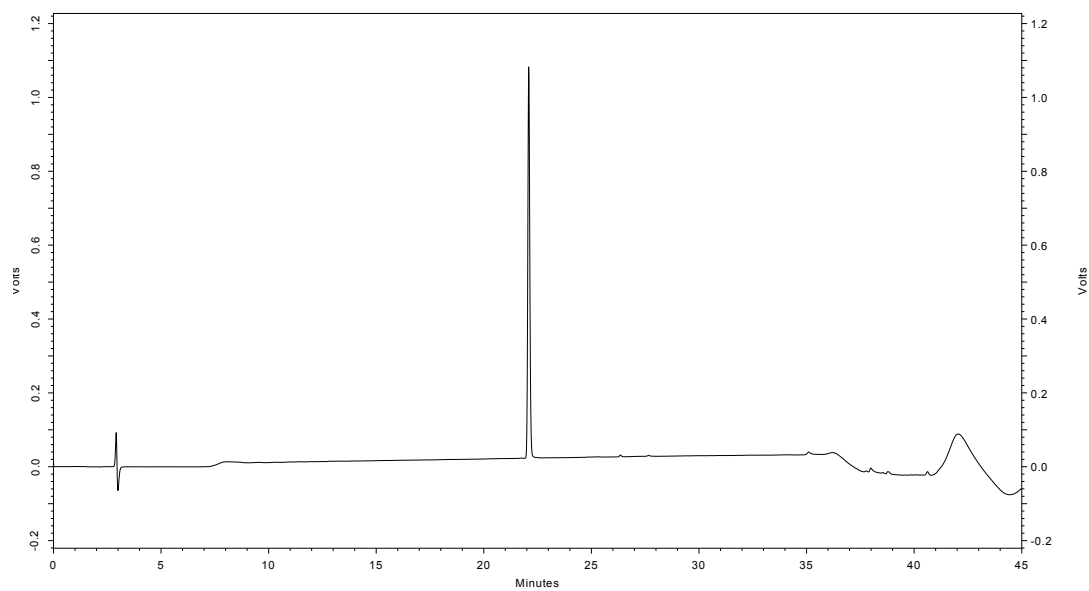
6-(3-Carbamoylphenyl)hexanoic amide (21)



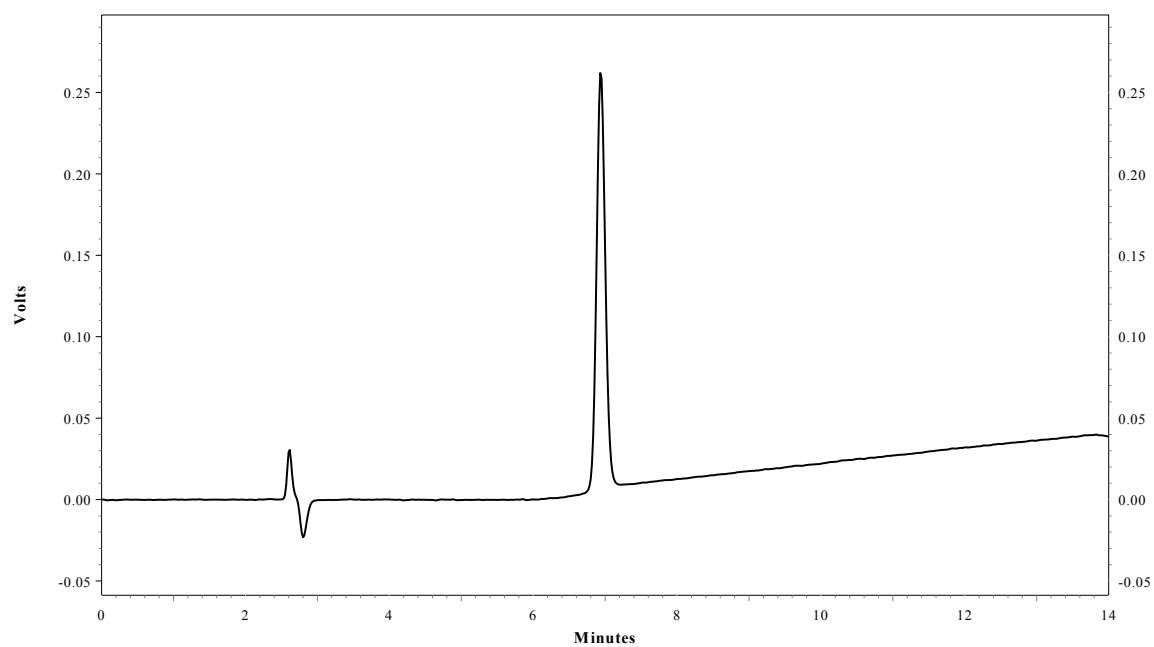
7-(3-Carbamoylphenyl)heptanoic acid (22)



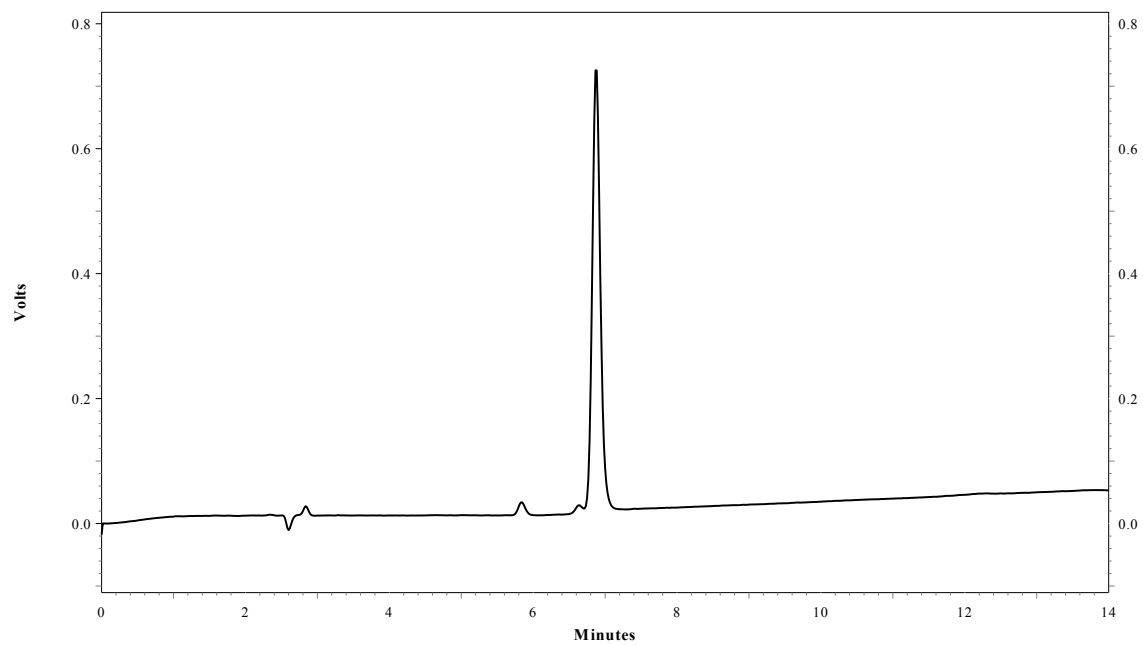
7-(3-Carbamoylphenyl)heptanoic amide (23)



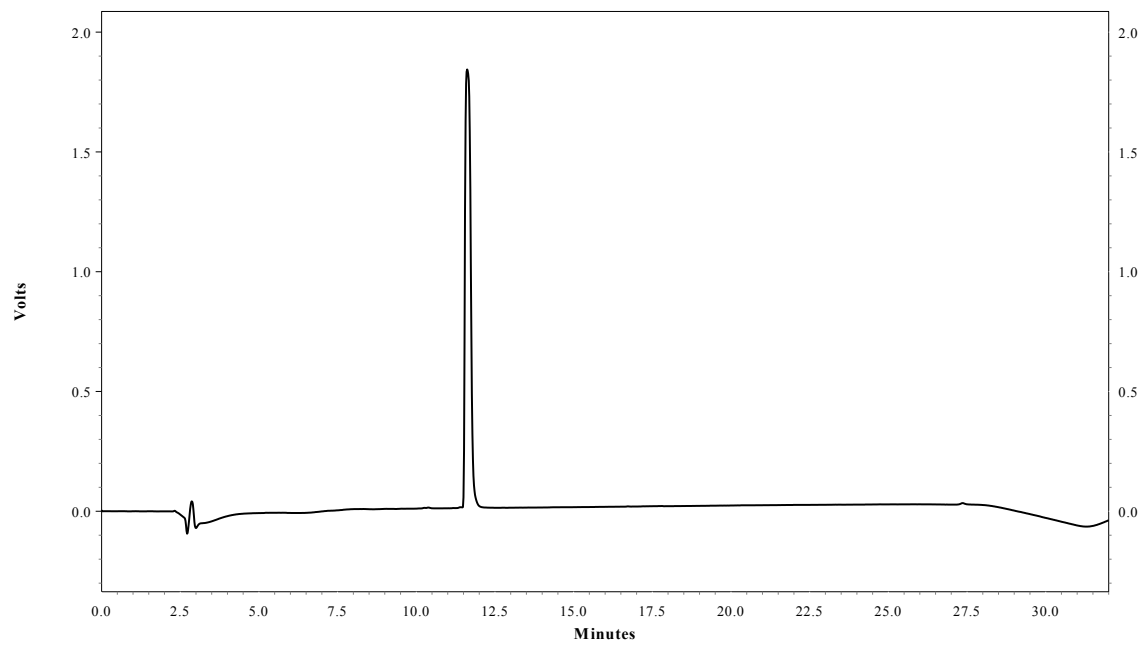
(Z)-6-(3-Carbamoylphenyl)hex-5-enoic acid (24)



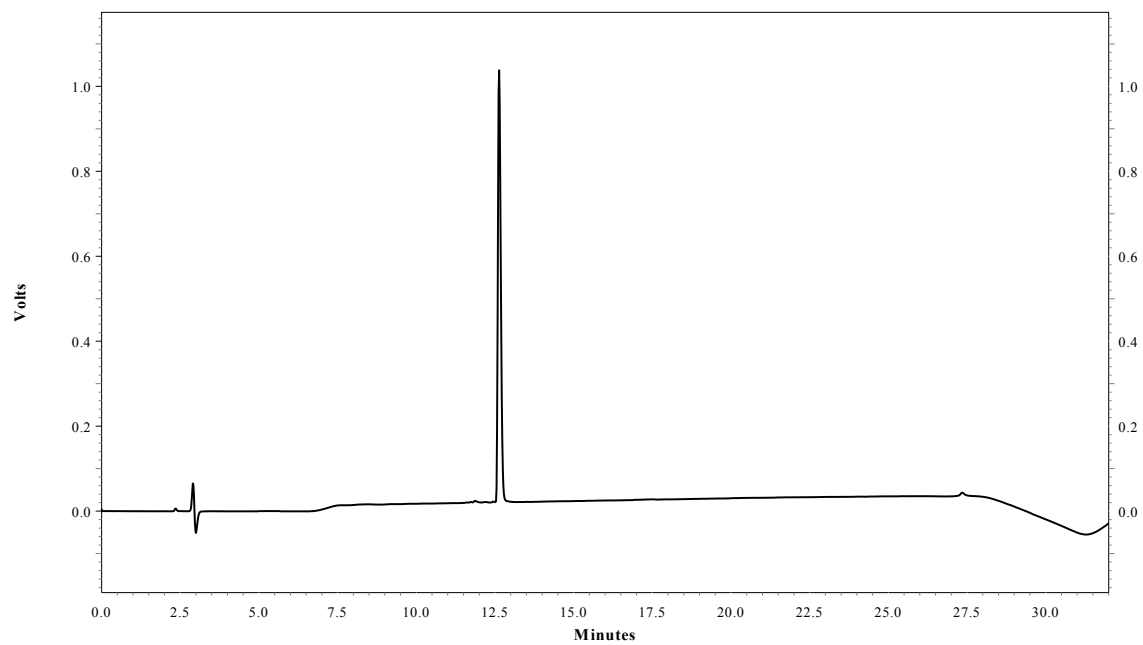
(E)-6-(3-Carbamoylphenyl)hex-5-enoic acid (25)



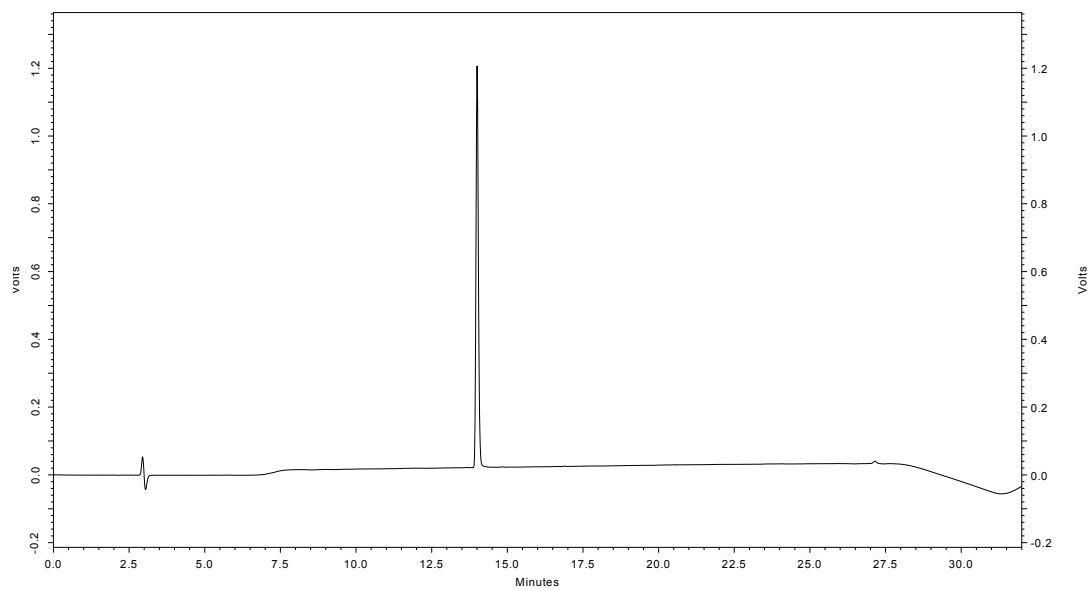
(S)-2-Amino-6-(3-carbamoylphenyl)hex-5-ynoic acid (27)



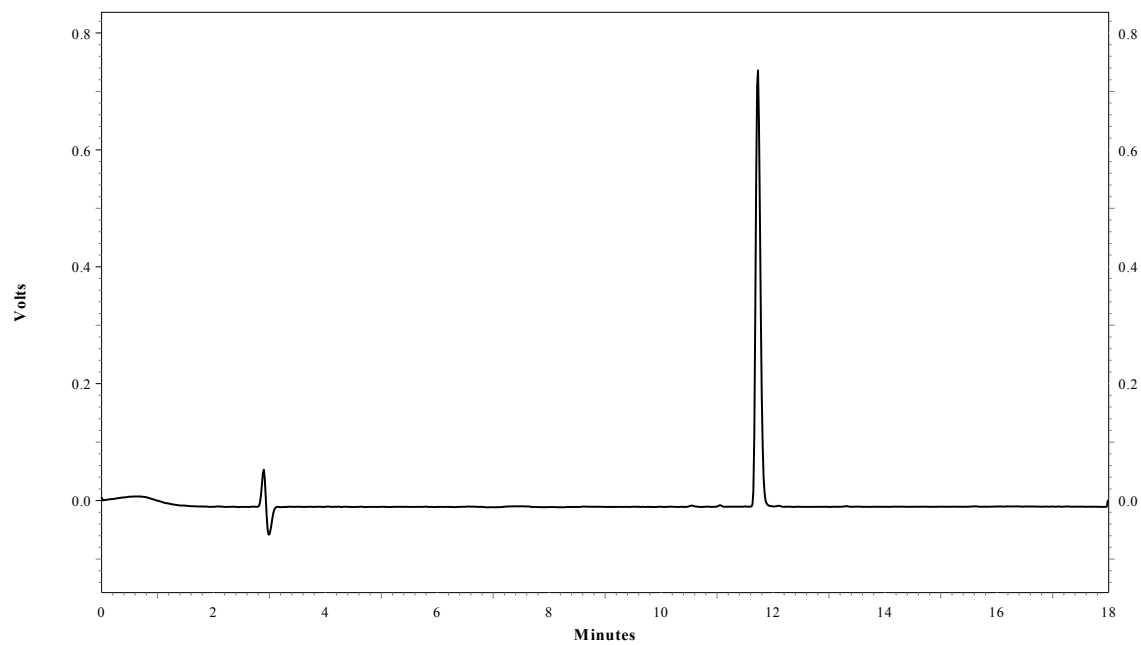
(S)-2-Amino-6-(3-carbamoylphenyl)hexanoic acid (28)



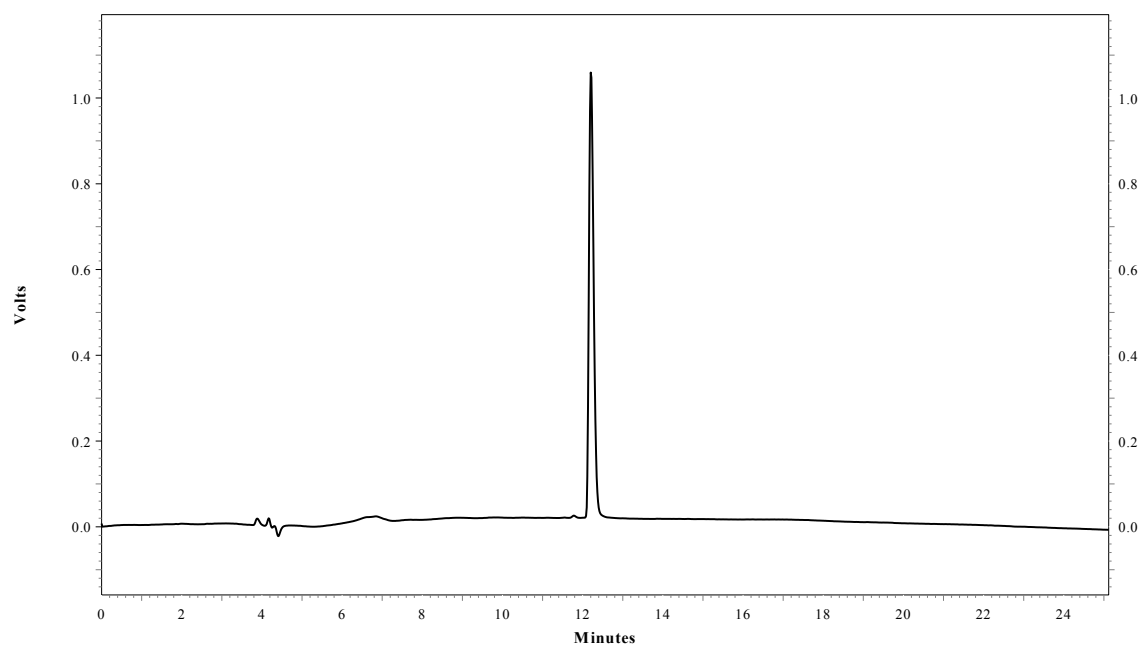
(S)-2-Amino-4-((3-carbamoylbenzyl)amino)butanoic acid (35)



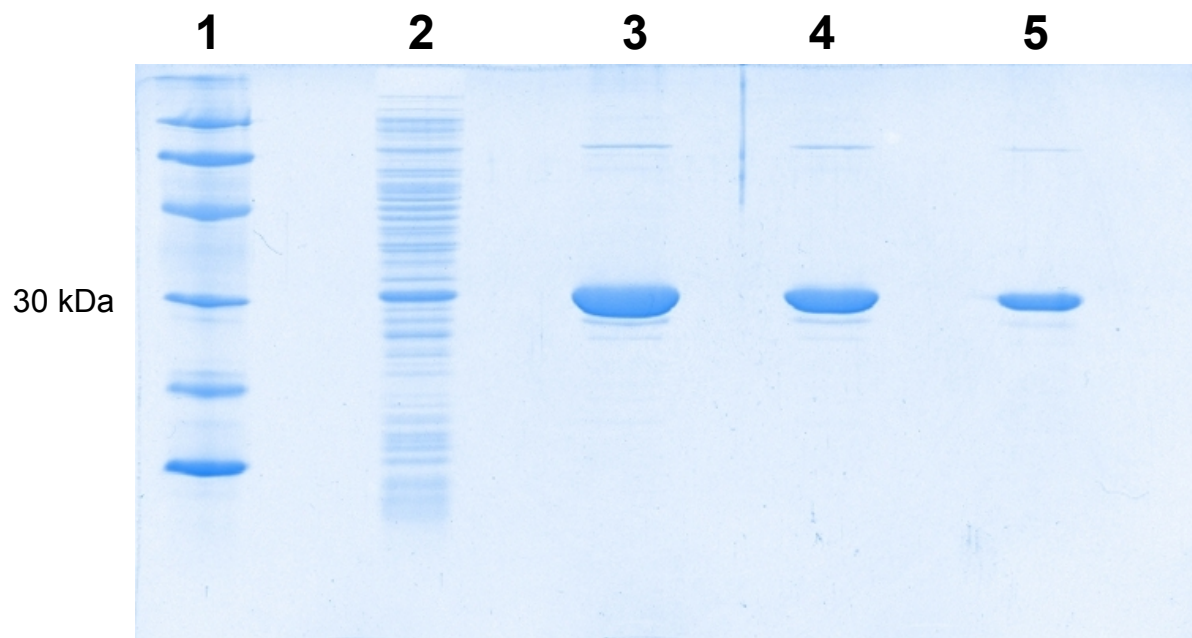
(S)-2-Amino-4-((3-carbamoylbenzyl)thio)butanoic acid (41)



(S)-2-Amino-4-(((2R,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(3-carbamoylbenzyl)amino)butanoic acid (45)



SDS-PAGE gel of wt-hNNMT



*Supplemental Figure 1. SDS-PAGE gel showing the purity of wild type human nicotinamide N-methyltransferase (wt-hNNMT). Proteins were stained with Coomassie Brilliant Blue. Lane 1 contains a molecular weight standard, lane 2 contains 10 μ g of the crude product in an extract of IPTG-induced *E.coli* BL21 (DE3) harbouring pET-28a-wt-hNNMT, lane 3 contains 10 μ g of the affinity purified recombinant wt-hNNMT, lane 4 contains 5 μ g of the affinity purified recombinant wt-hNNMT and lane 5 contains 2 μ g of the affinity purified recombinant wt-hNNMT*

IC₅₀ curves

