Synthesis

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Supporting Information

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SUPPORTING INFORMATION

for

The Synthesis of New 7-(R-benzyl)-4,5-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-6(7H)-ones via Ugi-Huisgen Sequence Reactions

Nazariy Pokhodylo, Mykola Tupychak, Evgeny Goreshnik, Mykola D. Obushak

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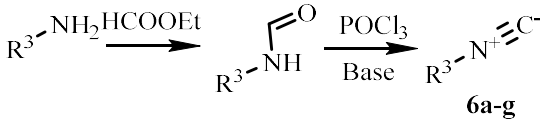
Synthesis of isonitriles 6

The starting isonitriles **6a-g** were obtained by reacting formamides with $POCl_3$ (Scheme S1). Formamides were prepared by reacting ethyl methanoate with the corresponding amines without solvent.



Scheme S1. Synthesis of isonitriles **6**

Pyridine/ petroleum ether system was used for the synthesis of liquid isonitriles 6a-e and whole products were cleaned by vacuum distillation.[1]

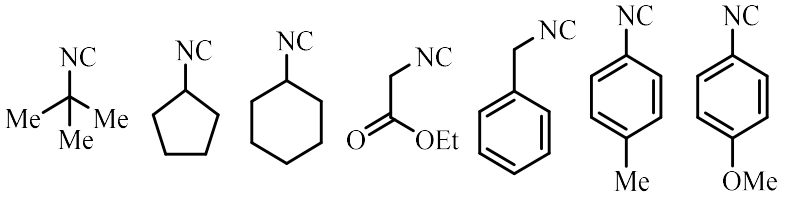
In the case of solid isonitriles **6f,g**, the triethylamine / dichloromethane system was effective, followed by purification of the products by flash chromatography according to the method [2]. This approach allowed to obtain the necessary isonitriles highly pure.

General protocol for the synthesis of isonitriles 6a-e

A solution consisting of 0.5 mole of formamide, 250 ml (245 g, 3.1 moles) of pyridine, and 150 ml of petroleum ether (is charged into a 1-l three-necked round-bottomed flask equipped with a stirrer, dropping funnel, reflux condenser, and thermometer. The flask is immersed in an ice bath, and 46 g. (0.30 mole) of phosphorous oxychloride is added from the dropping funnel to the stirred mixture in the course of 30–40 minutes. The mixture is stirred under reflux for 10 minutes after all the phosphorus oxychloride is added. The mixture is then cooled to 0–5°; this converts it to a heavy slurry. Ice water (800 ml.) is gradually added with stirring, and stirring of the cold mixture is continued until all solid material has dissolved. The organic phase is separated in a separatory funnel. The aqueous phase is extracted with three 30-ml portions of petroleum ether, and the extracts are combined with the organic phase, which is then extracted with three 50-ml portions of water, dried over 10 g of magnesium sulfate, and distilled.

General protocol for the synthesis of isonitriles 6f,g

To a solution of formamide (0.5 mol) in dichloromethane (2 M), triethylamine(5.0 equiv.) was added at room temperature. Subsequently, phosphorus oxychloride (1.0 equiv.) was added at 0 °C. The reaction mixture was stirred for 10 min. After completion of the reaction as indicated by TLC, the compound was purified using column chromatography. The crude reaction mixture was loaded directly on a column (20×9 cm) dry-packed with 600 g 100–200 mesh size silica. Diethyl ether was used as the mobile phase and fractions of 250 ml were collected. The compound was eluted within the first four fractions. The solvent was evaporated under reduced pressure to afford the pure product as a solid.



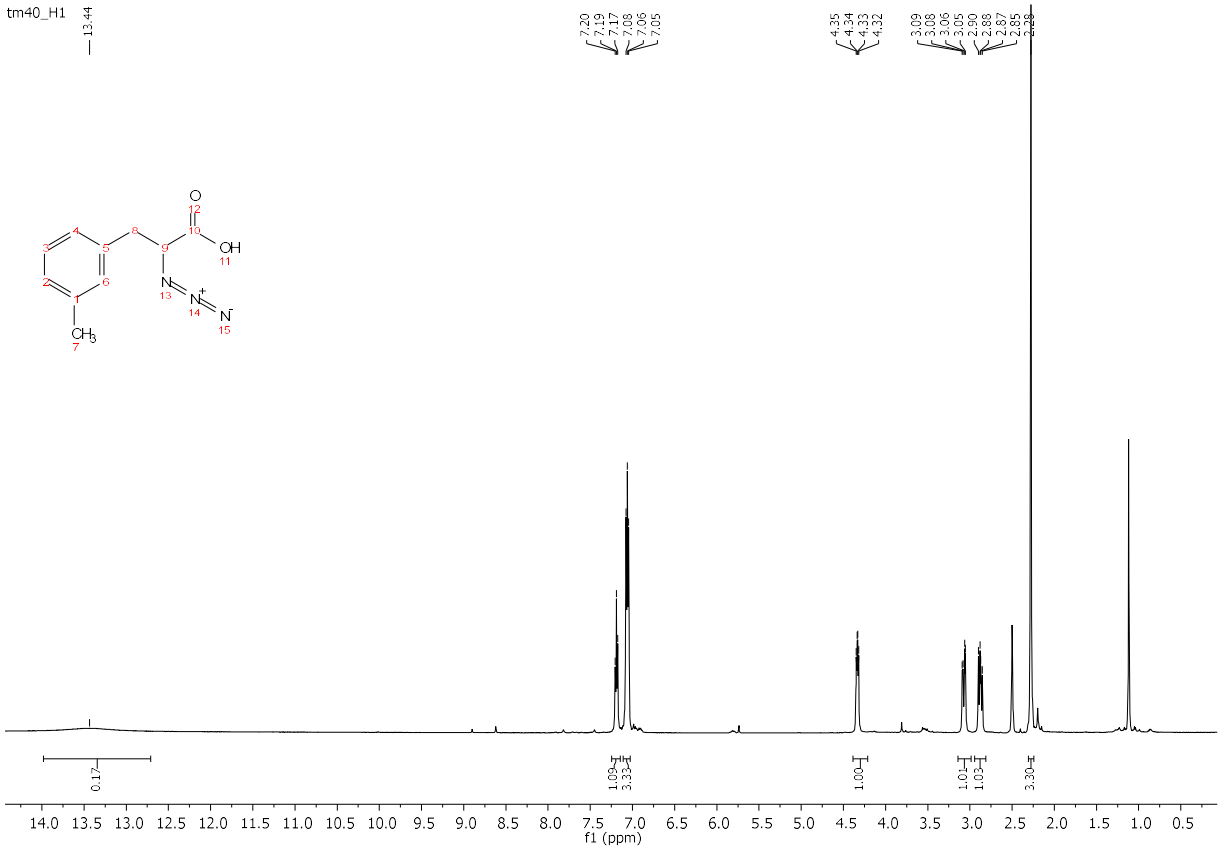
6a [3] **6b** [4] **6c** [2] **6d** [2] **6e** [2] **9f** [2] **6g** [2]

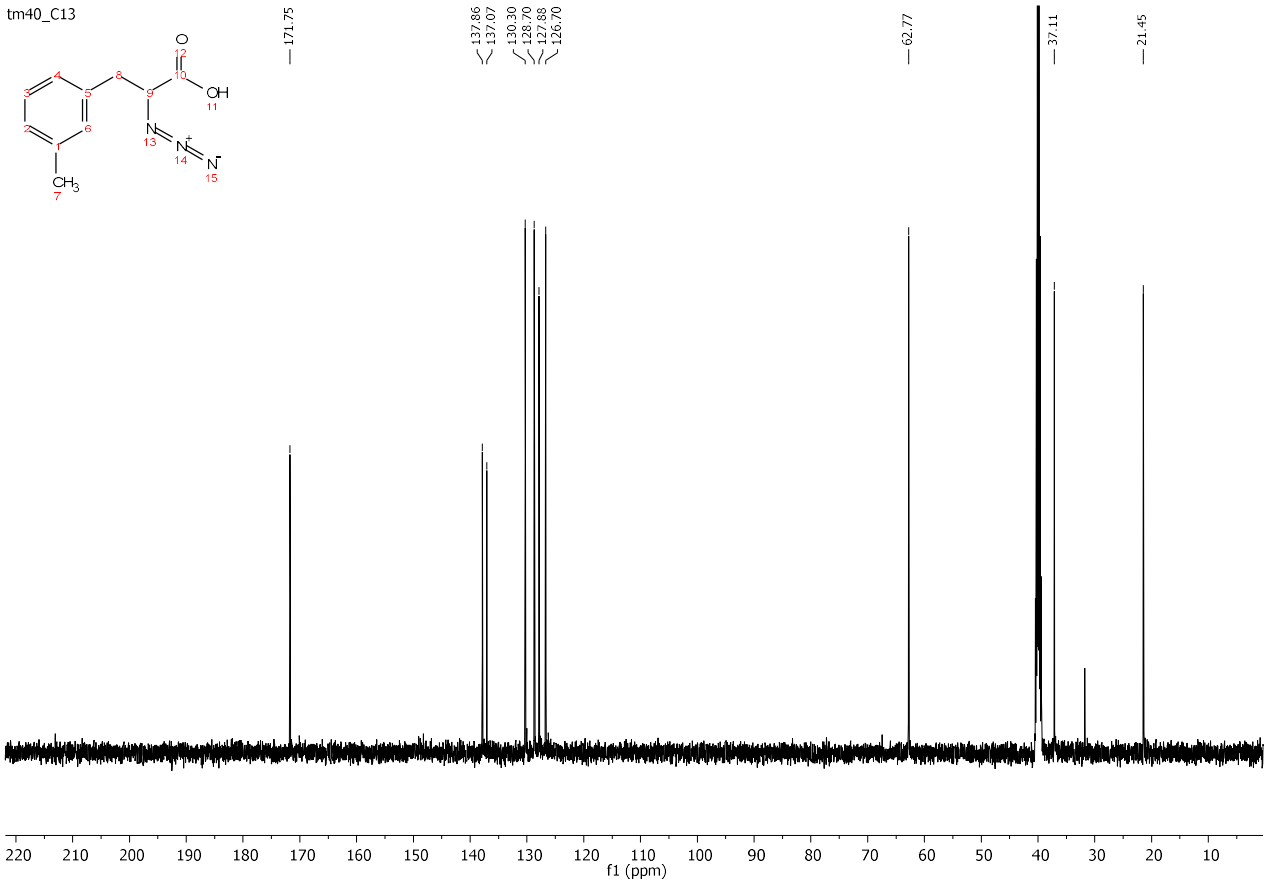
Scheme 2. Synthesis of isonitriles 9a-g

1. Ugi, R. Meyr, M. Lipinski, F. Bodesheim, F. Rosendahl, *Organic Syntheses,* **2003**, *41*, 13. https://doi.org/10.1002/0471264180.os041.04
2. P. Patil, M. Ahmadian-Moghaddam, A. Dömling, *Green Chem*. **2020**, *22*, 6902-6911. https://doi.org/10.1039/D0GC02722G
3. M. Suginome, Y. Ito, Science of Synthesis **2004**, *19*, 445-530 https://doi.org/10.1055/sos-sd-019-00308
4. L. Zeng, H. Sajiki, S. Cui, *Organic Lett.*, **2019**, *21*, 5269-5272. https://doi.org/10.1021/acs.orglett.9b01871

Spectra Images

NMR 2-Azido-3-(m-tolyl)propanoic acid 3a:





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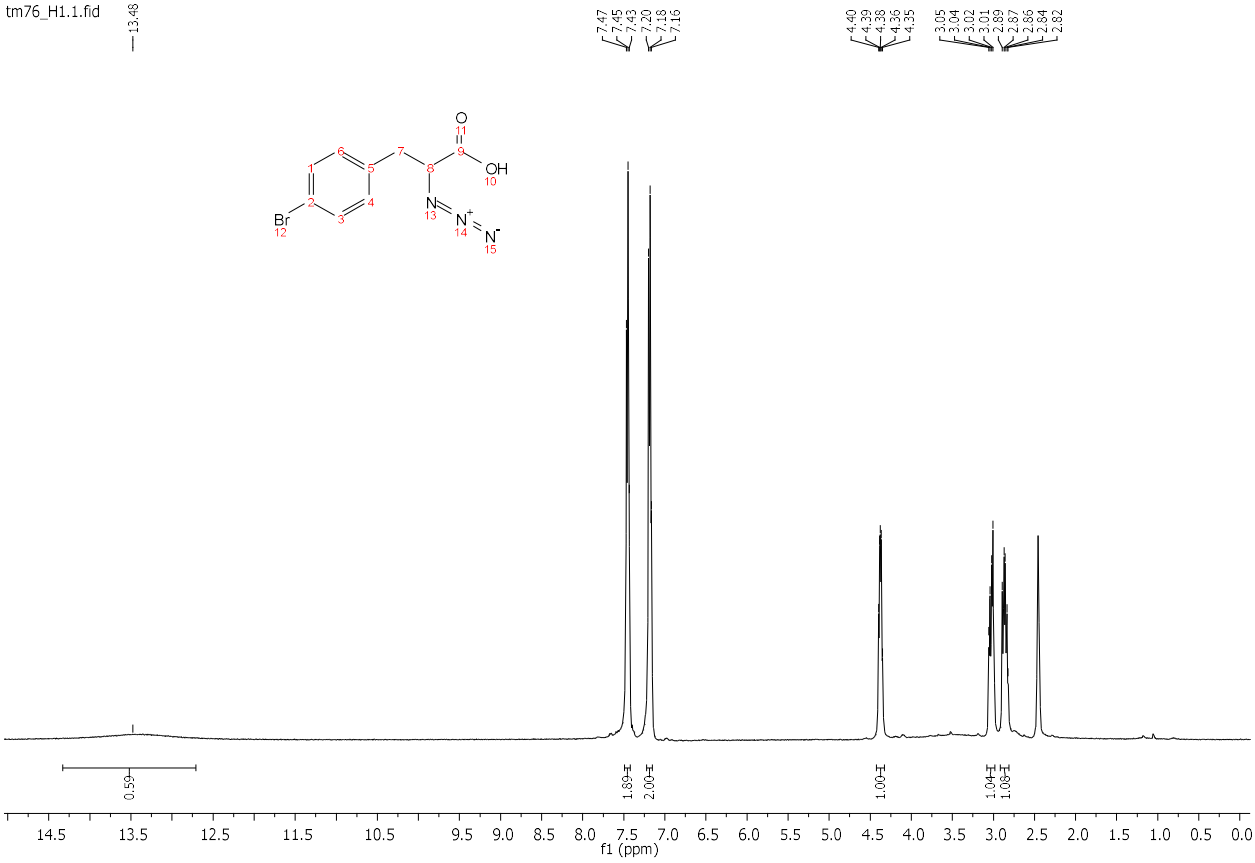

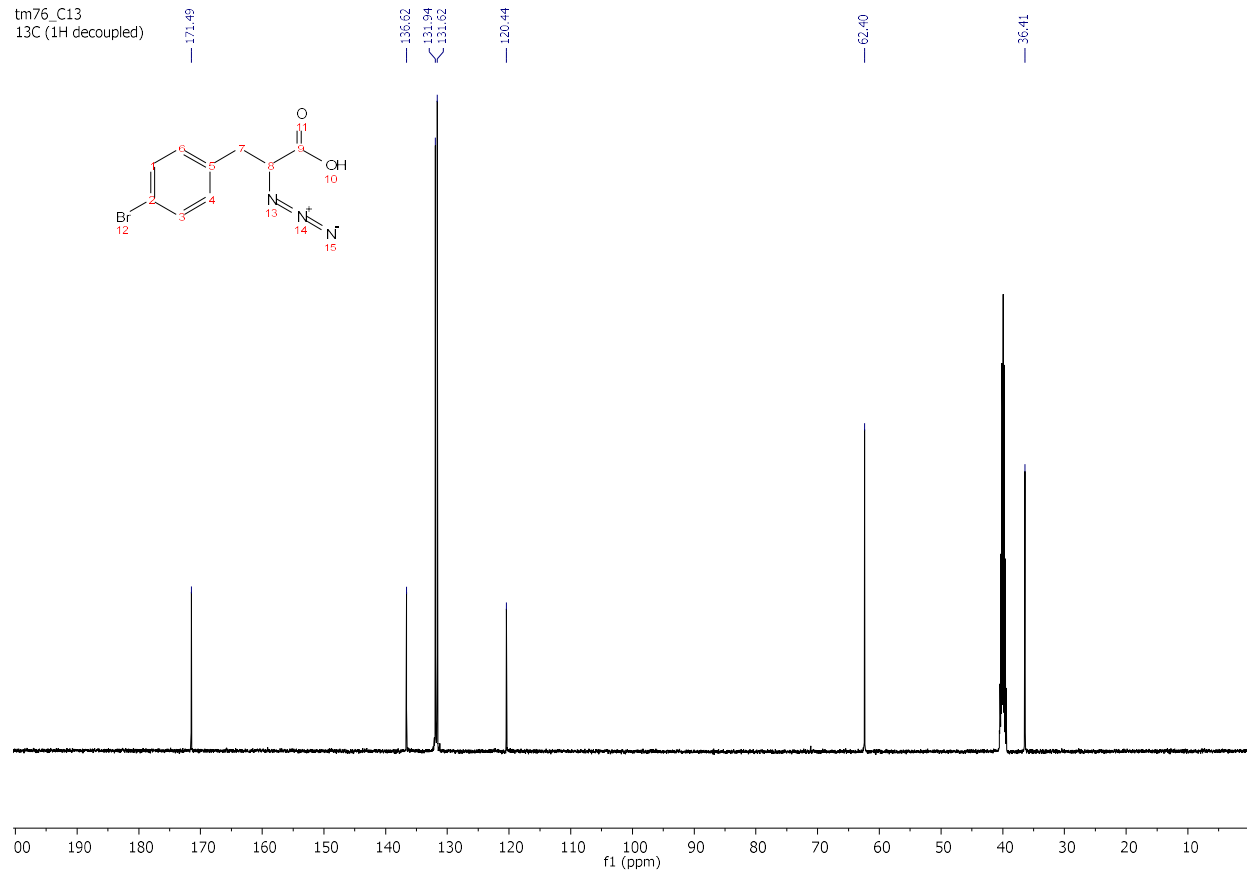

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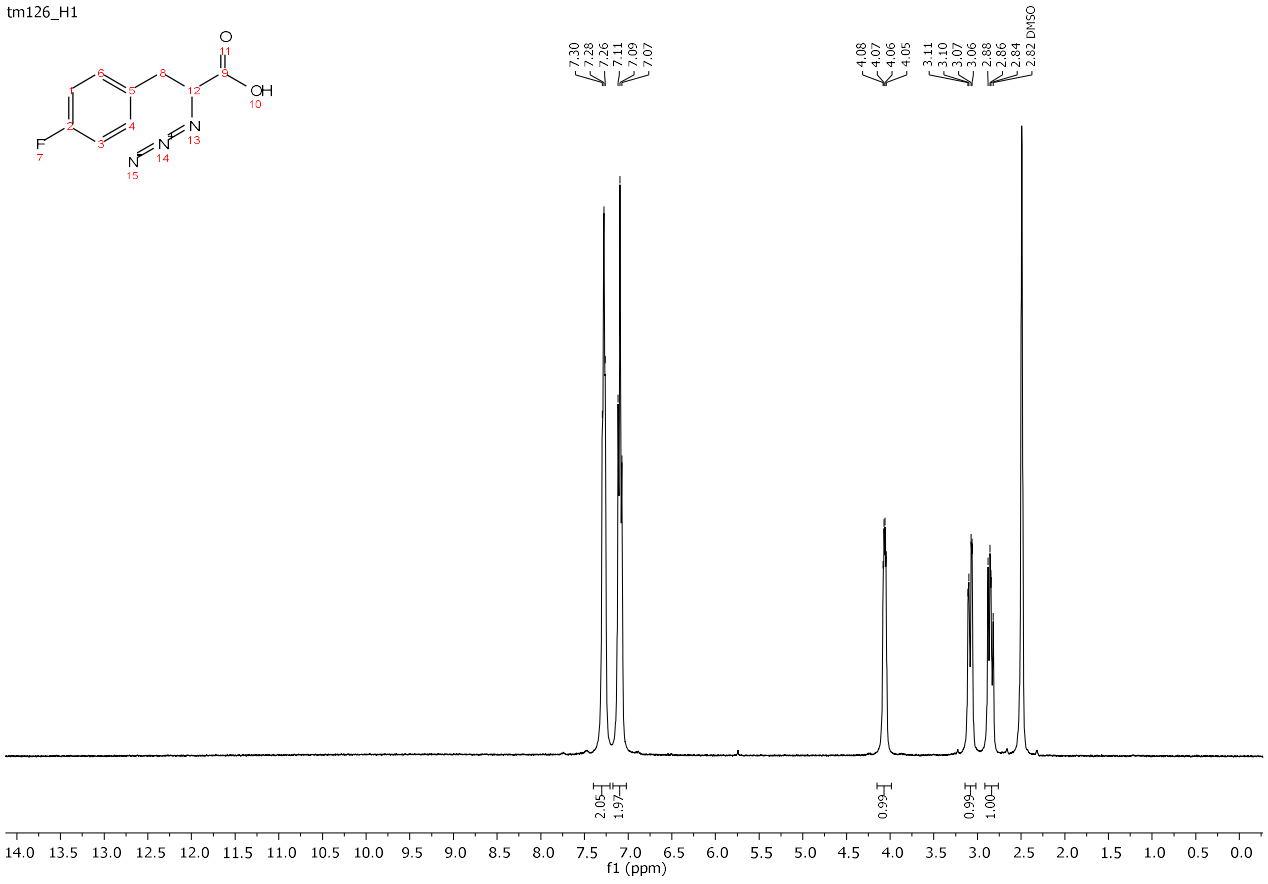

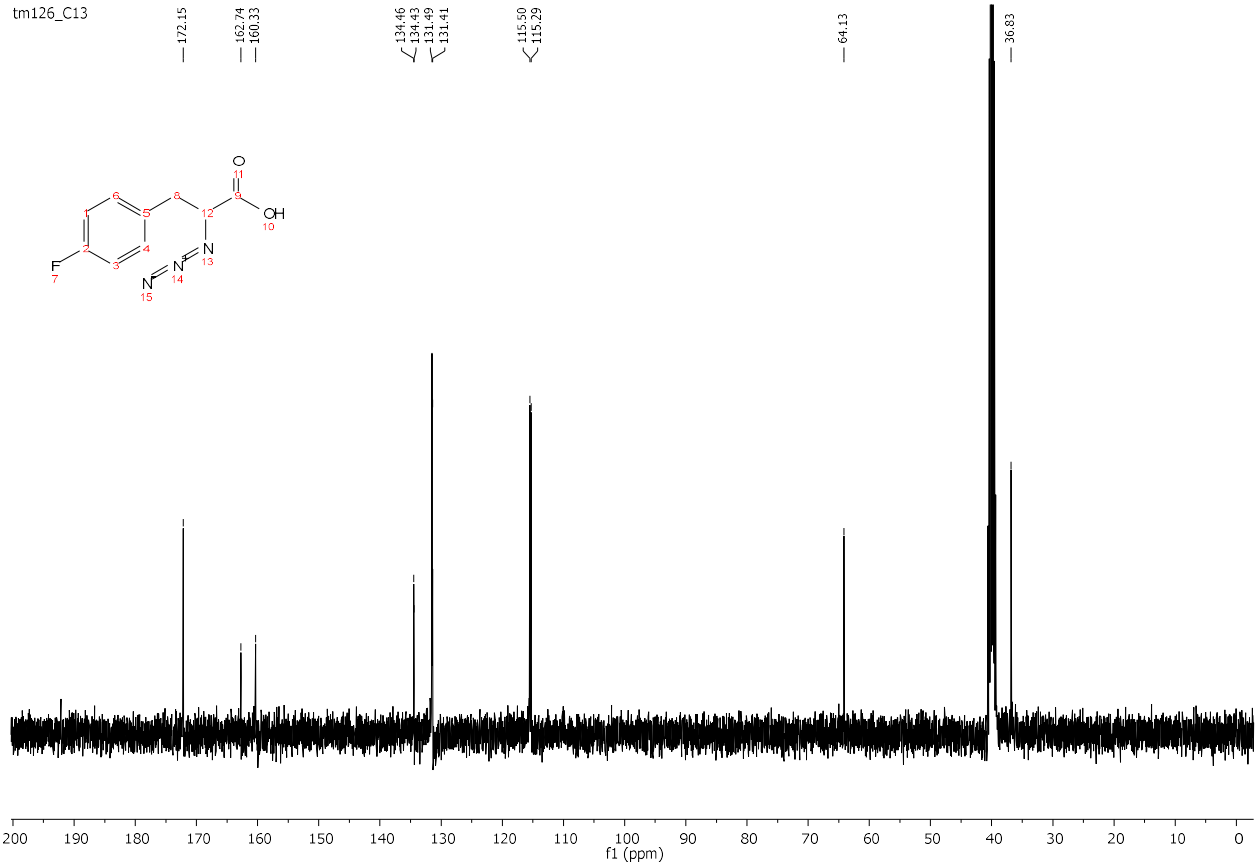

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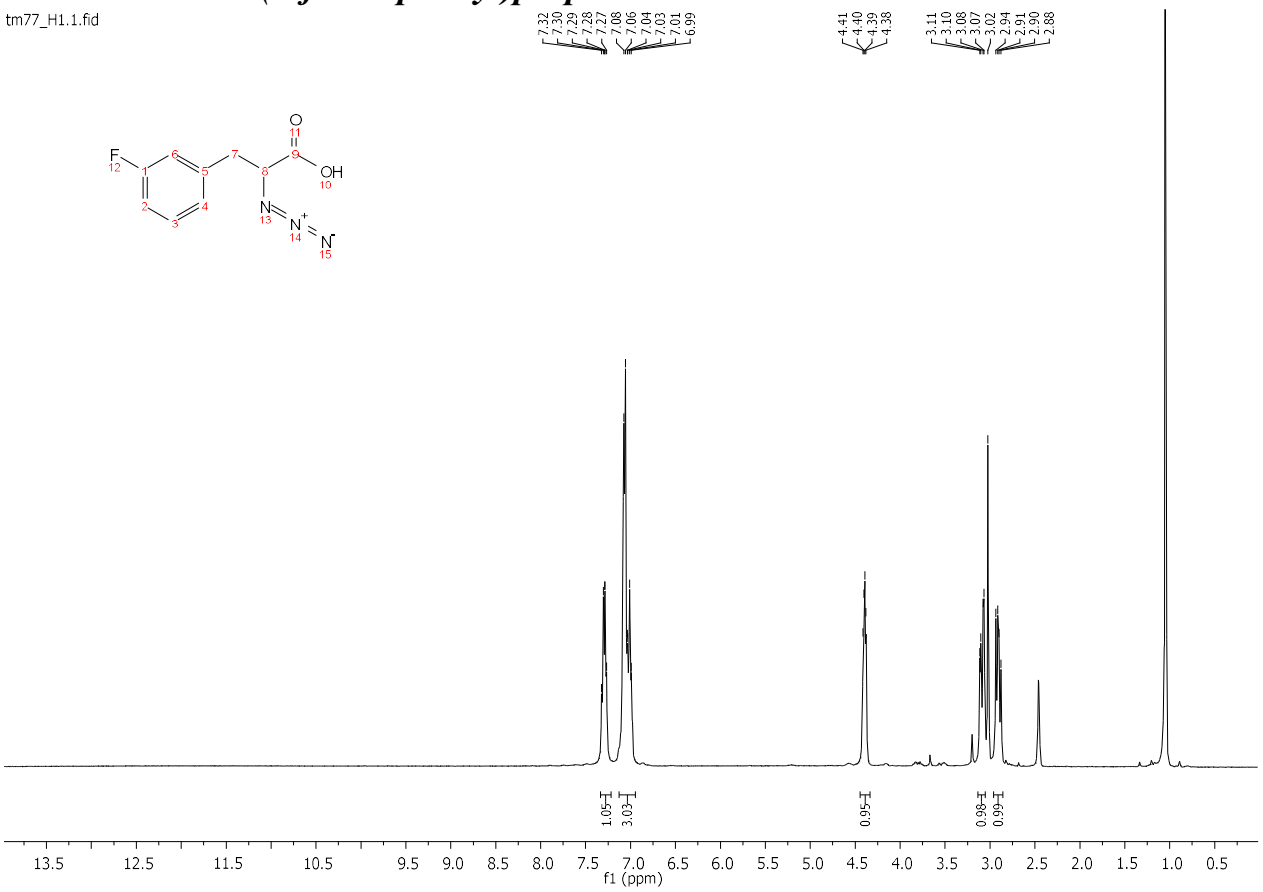

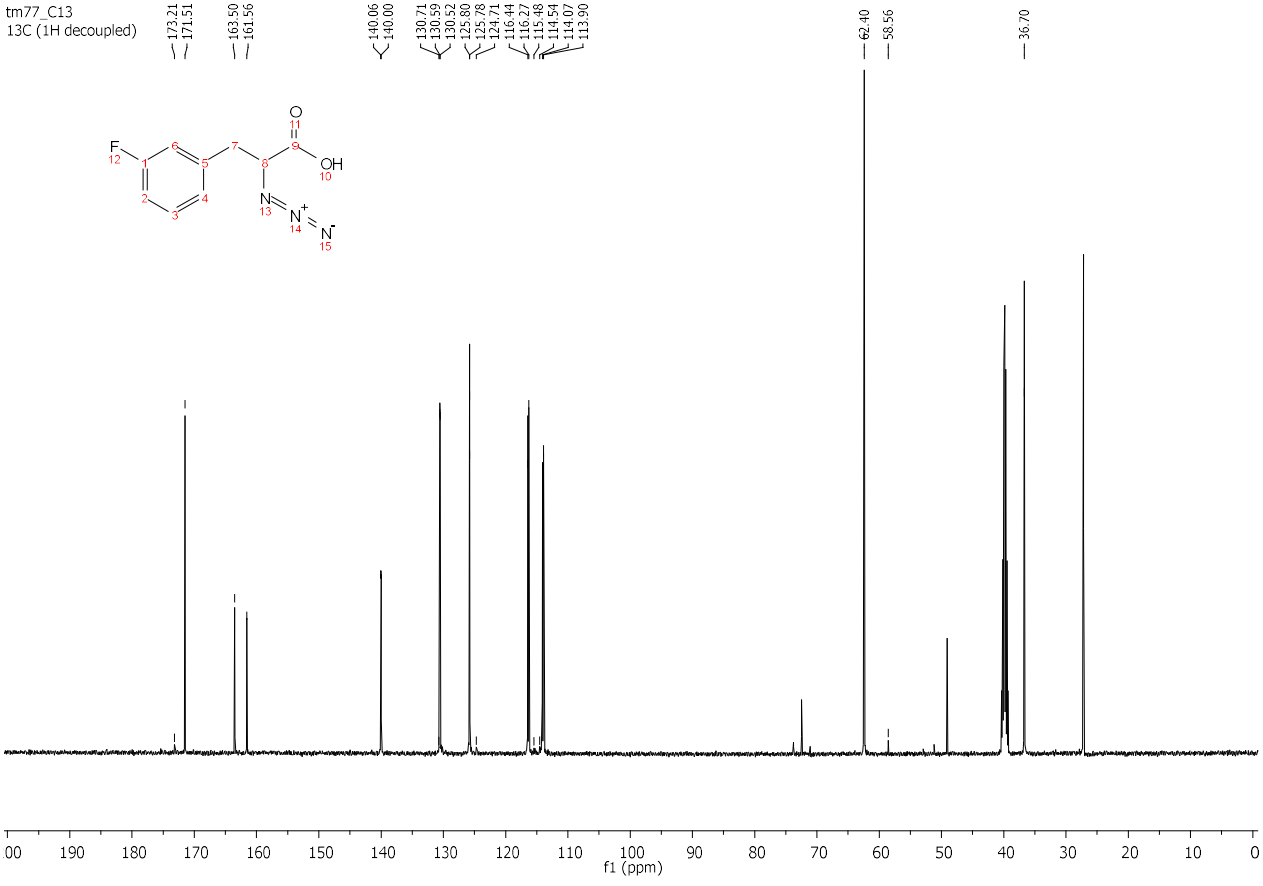

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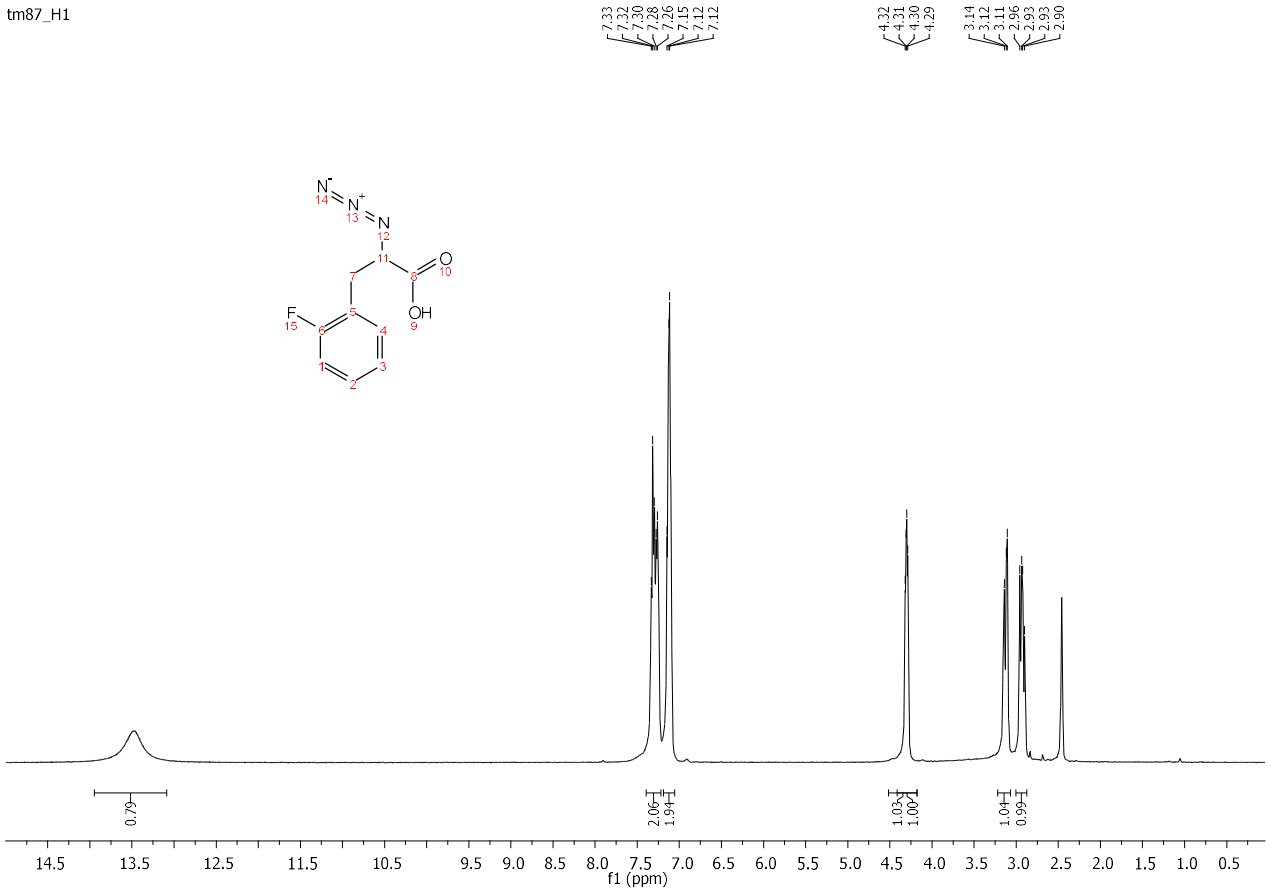

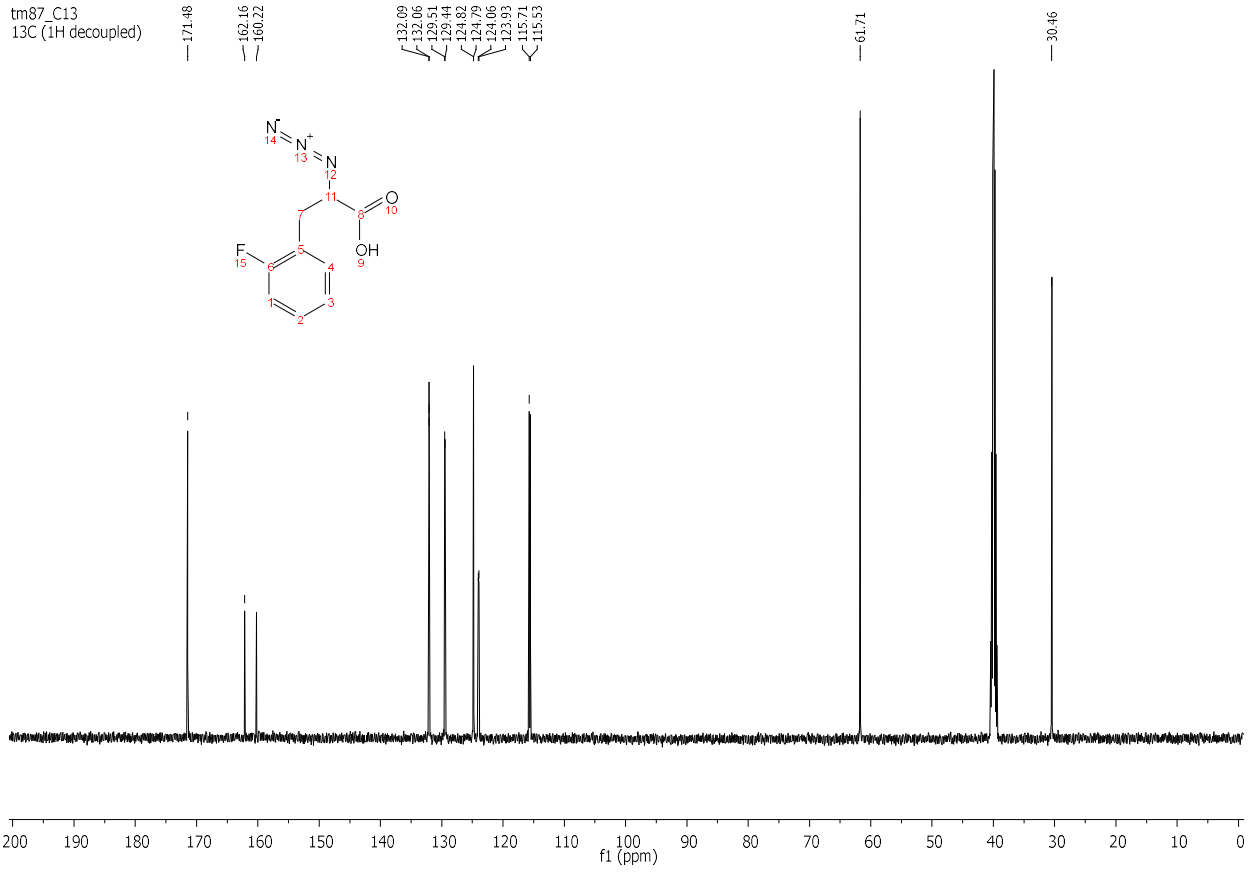

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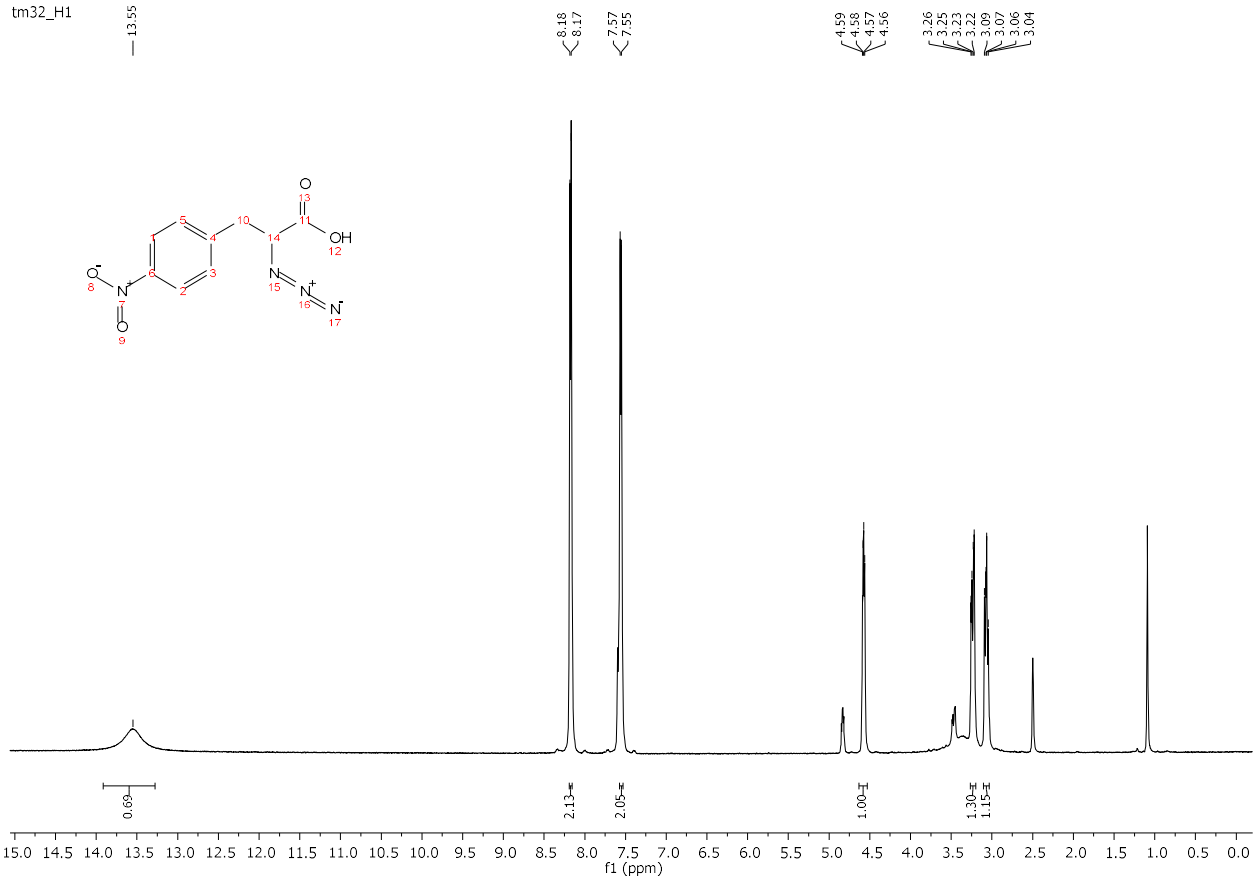
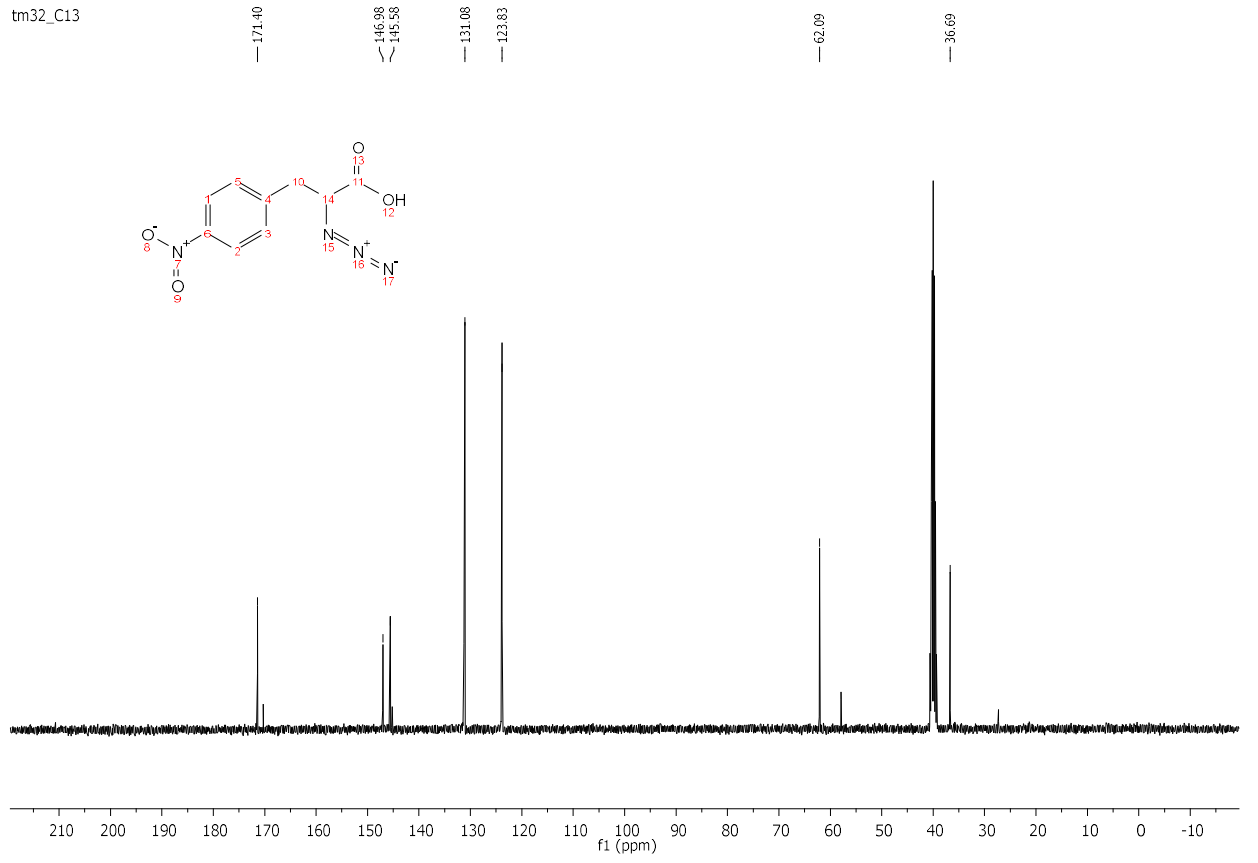
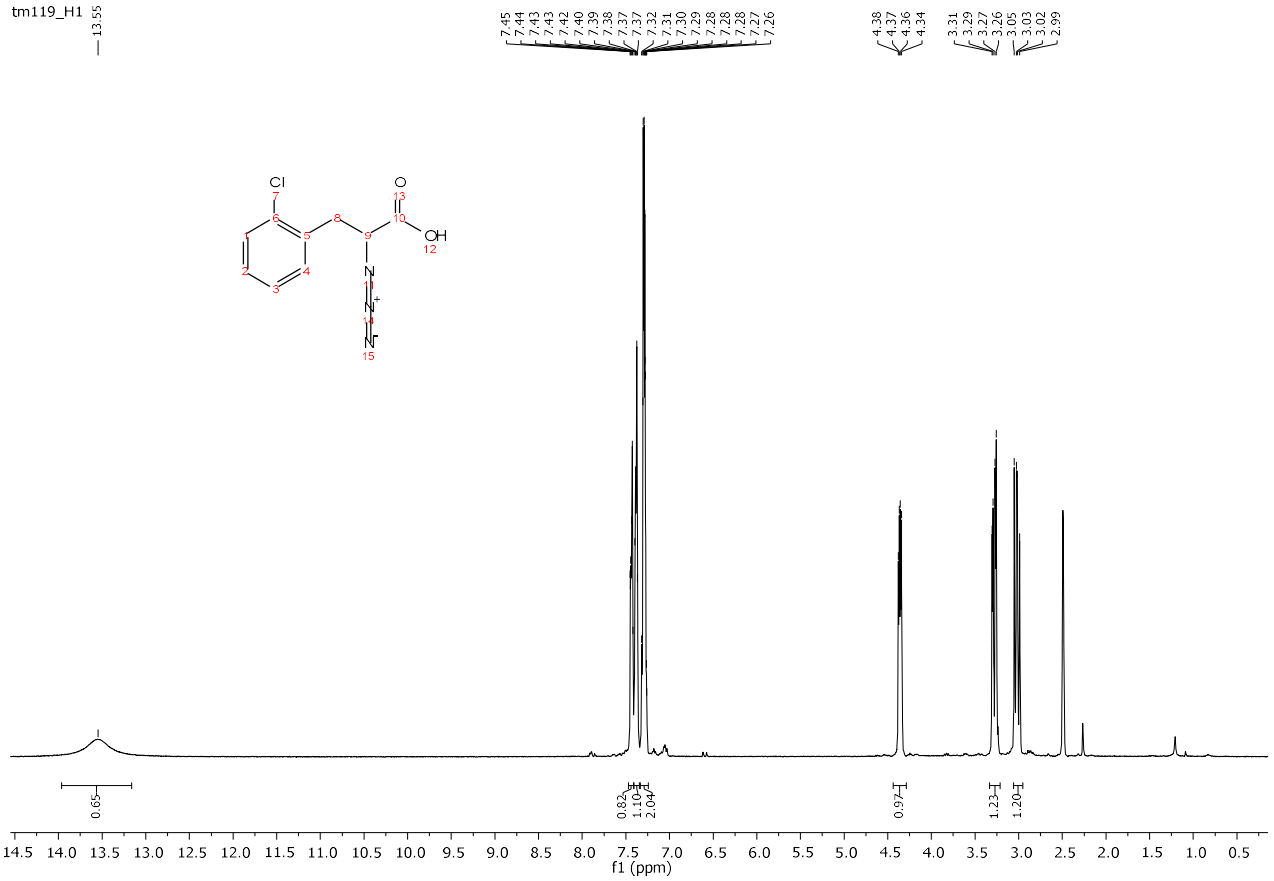
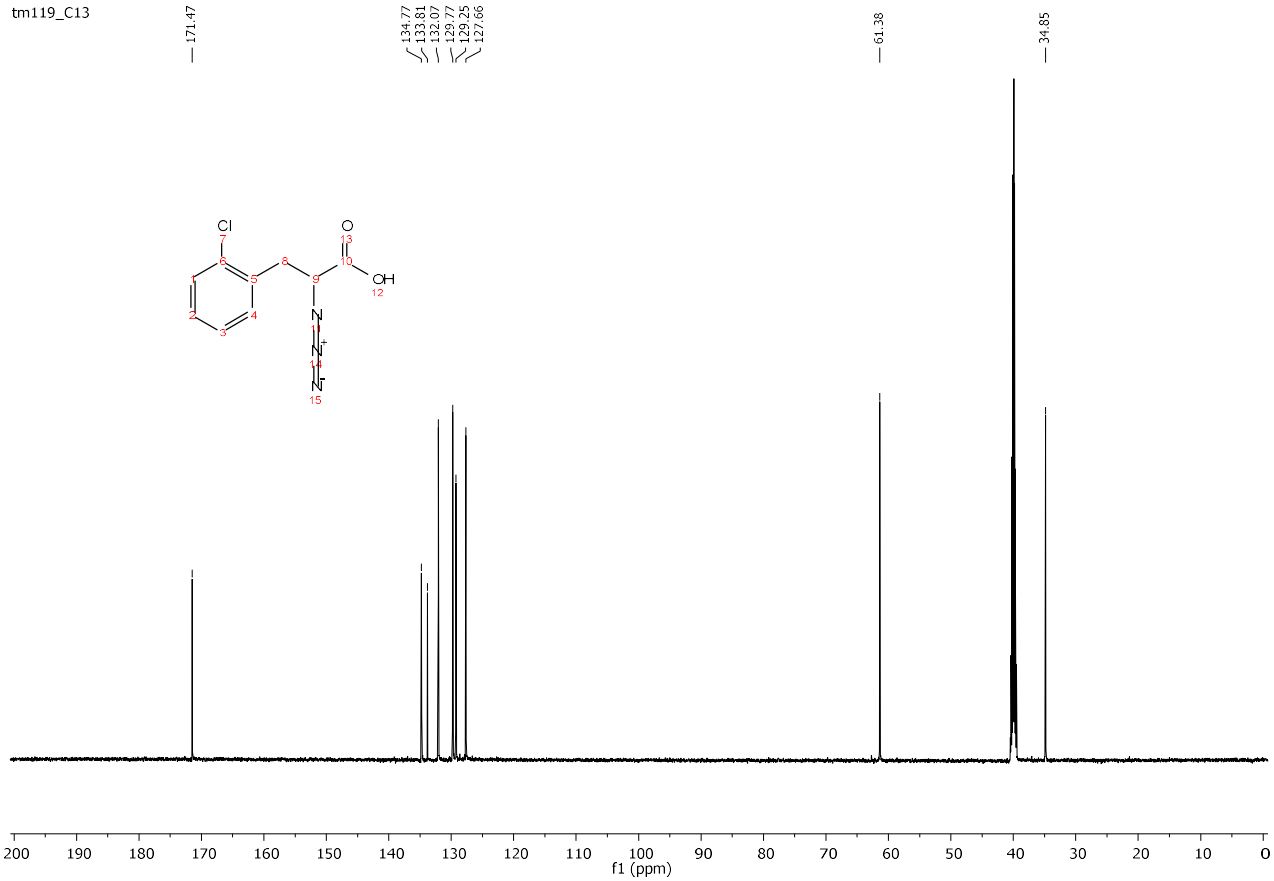


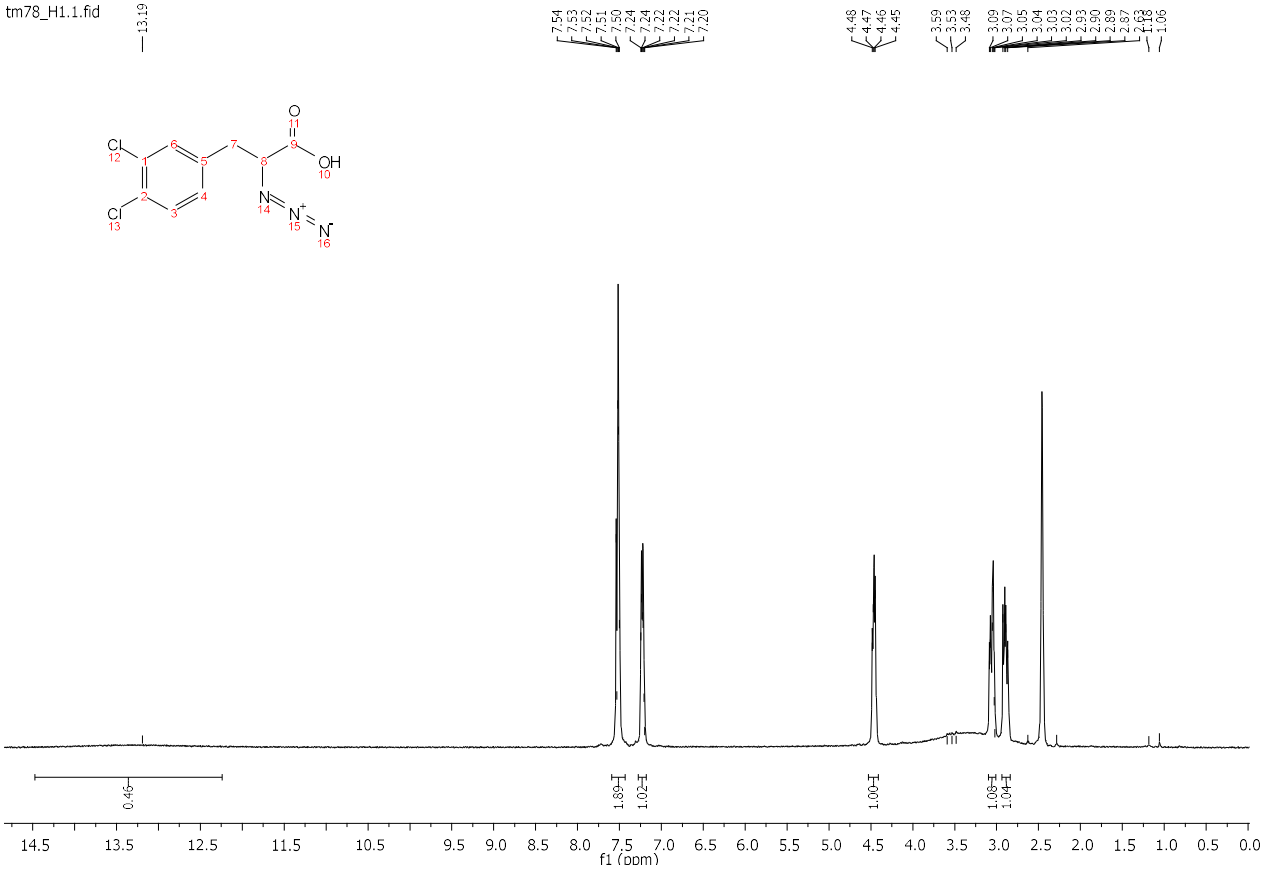


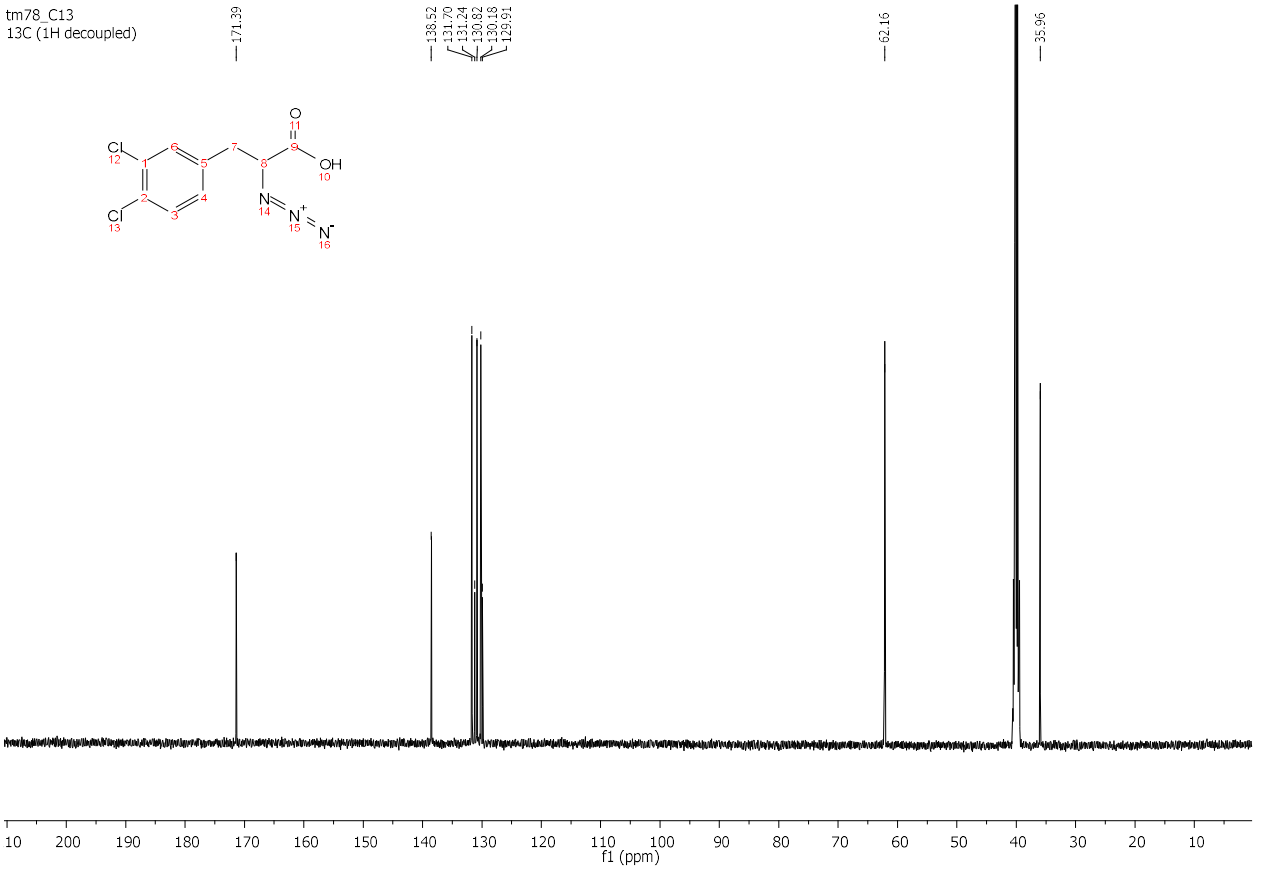
NMR 2-Azido-3-(2-chlorophenyl)propanoic acid 3g



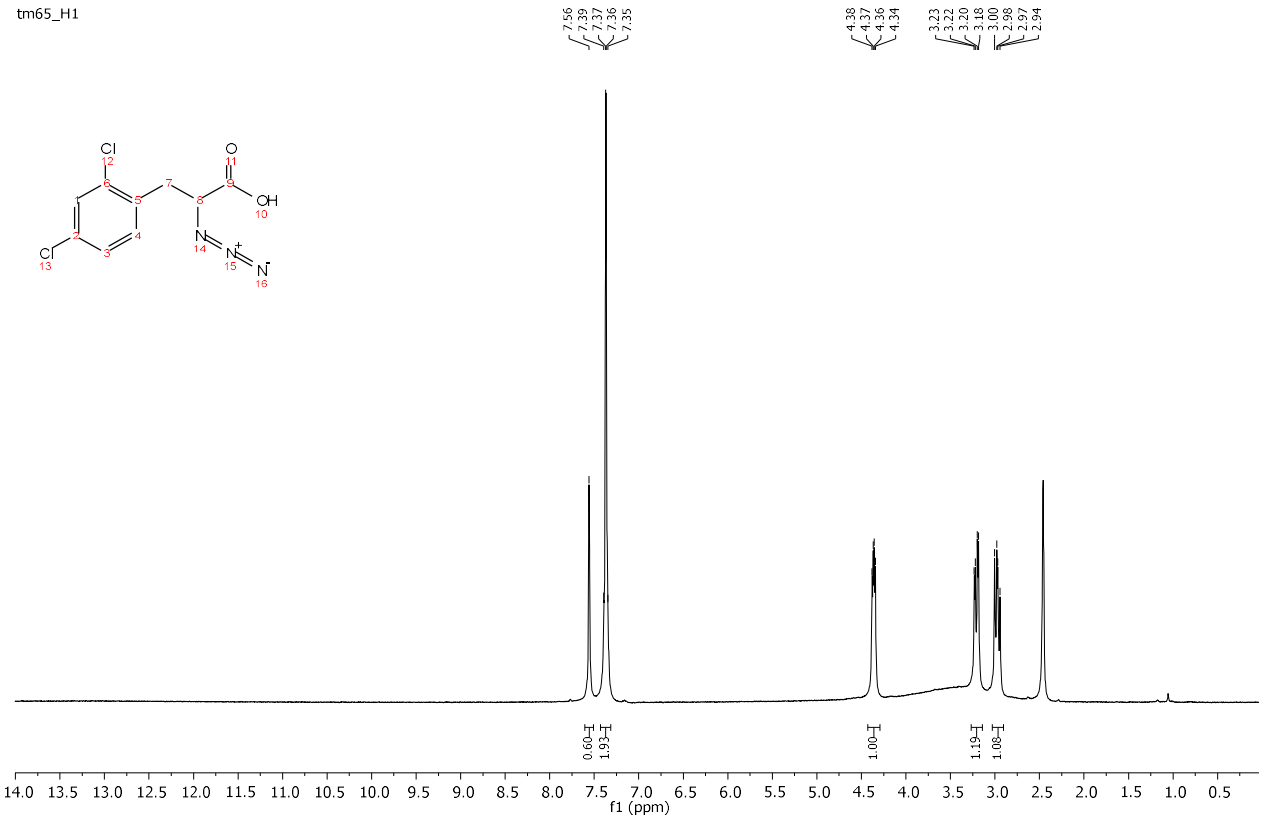


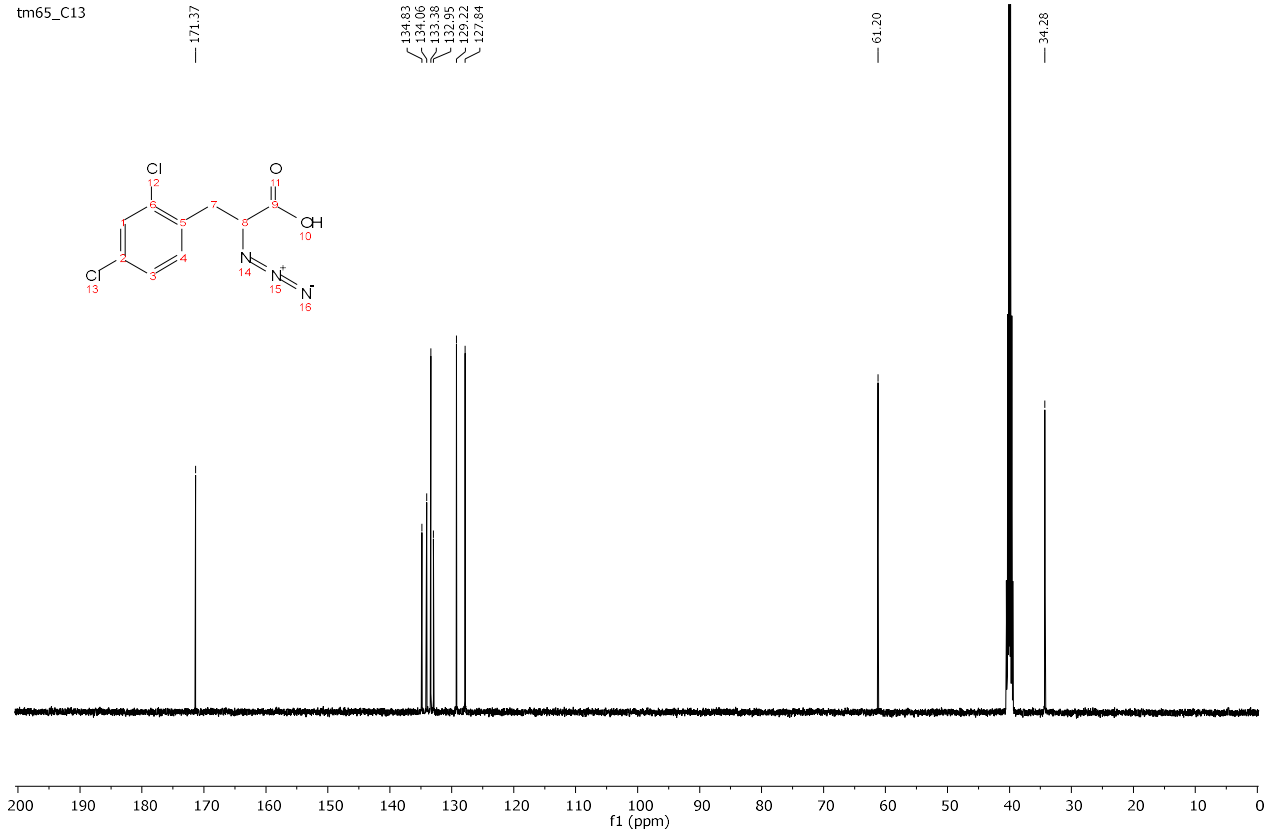
NMR 2-Azido-3-(3,4-dichlorophenyl)propanoic acid 3h





NMR 2-Azido-3-(2,4-dichlorophenyl)propanoic acid 3i





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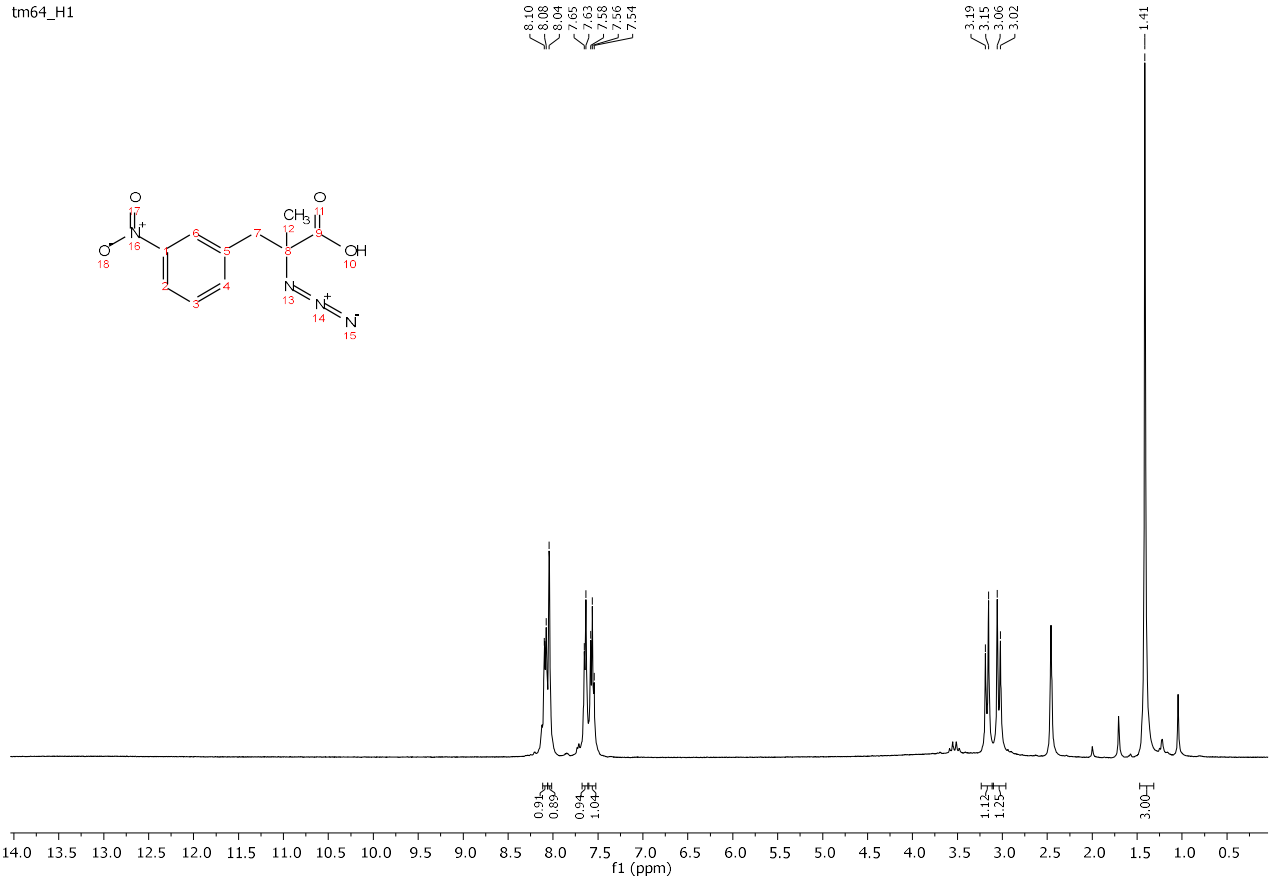

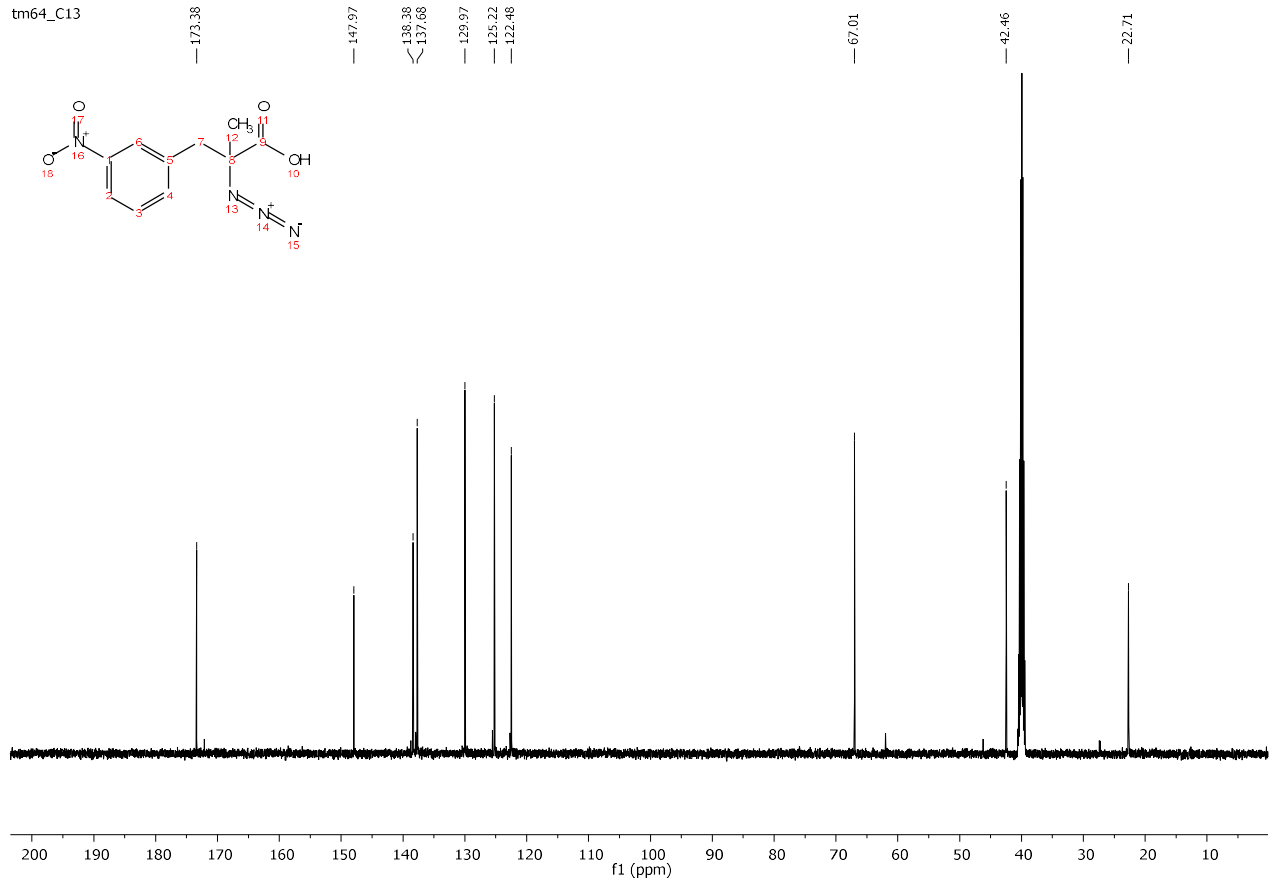

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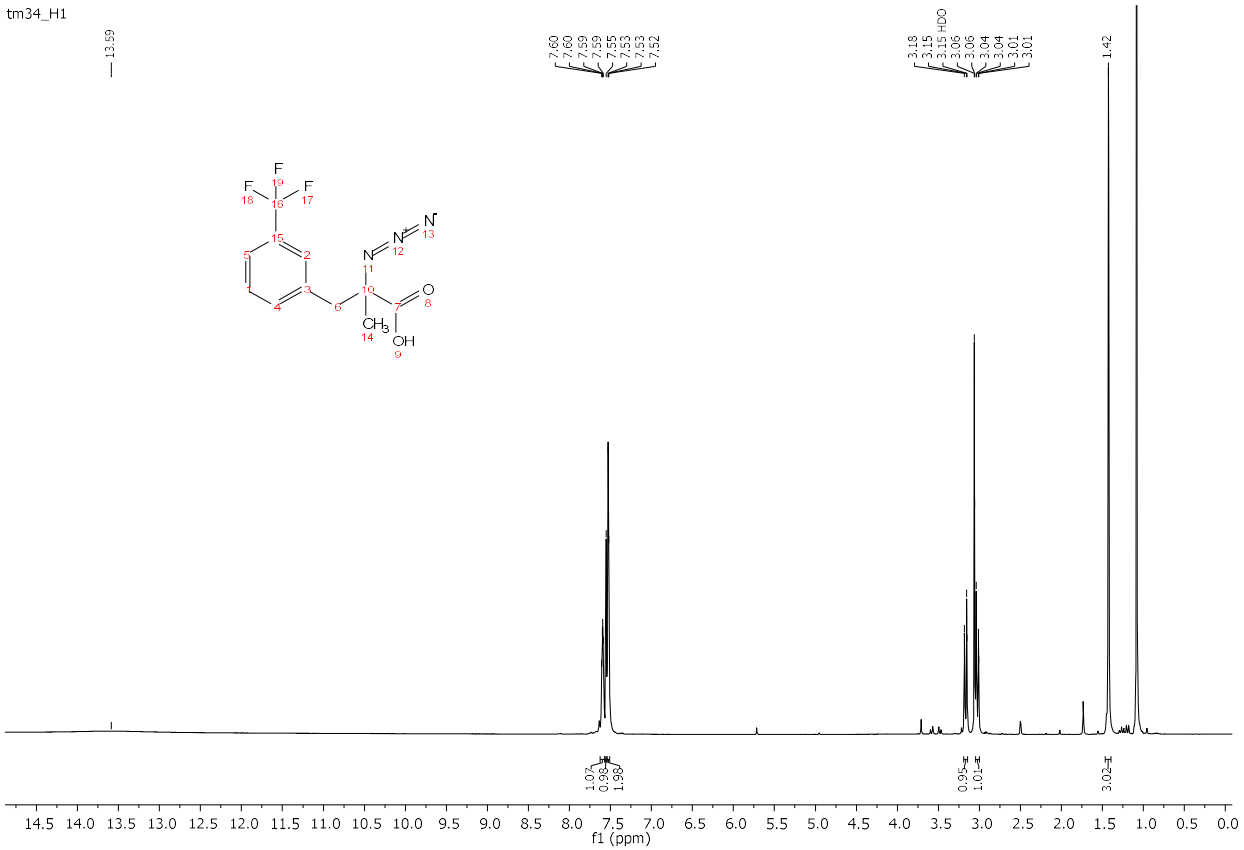
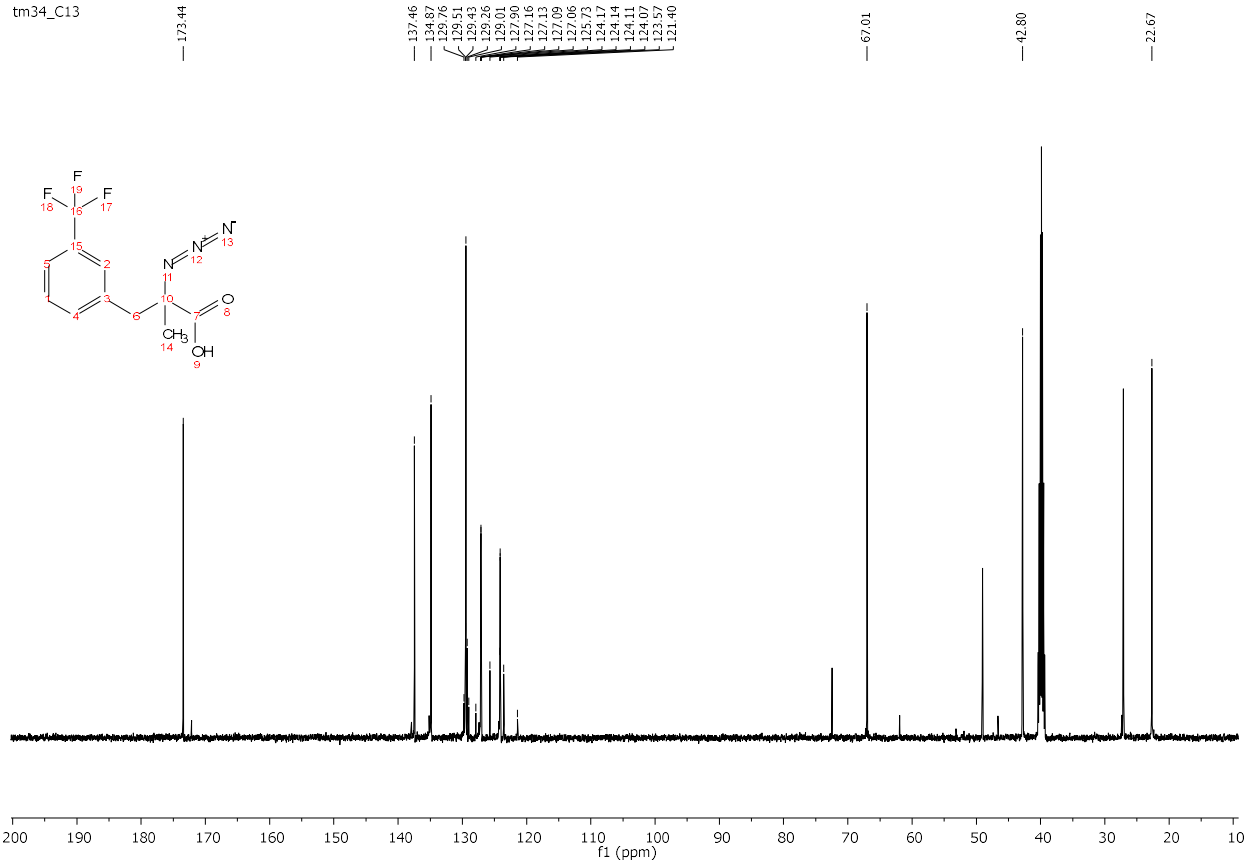
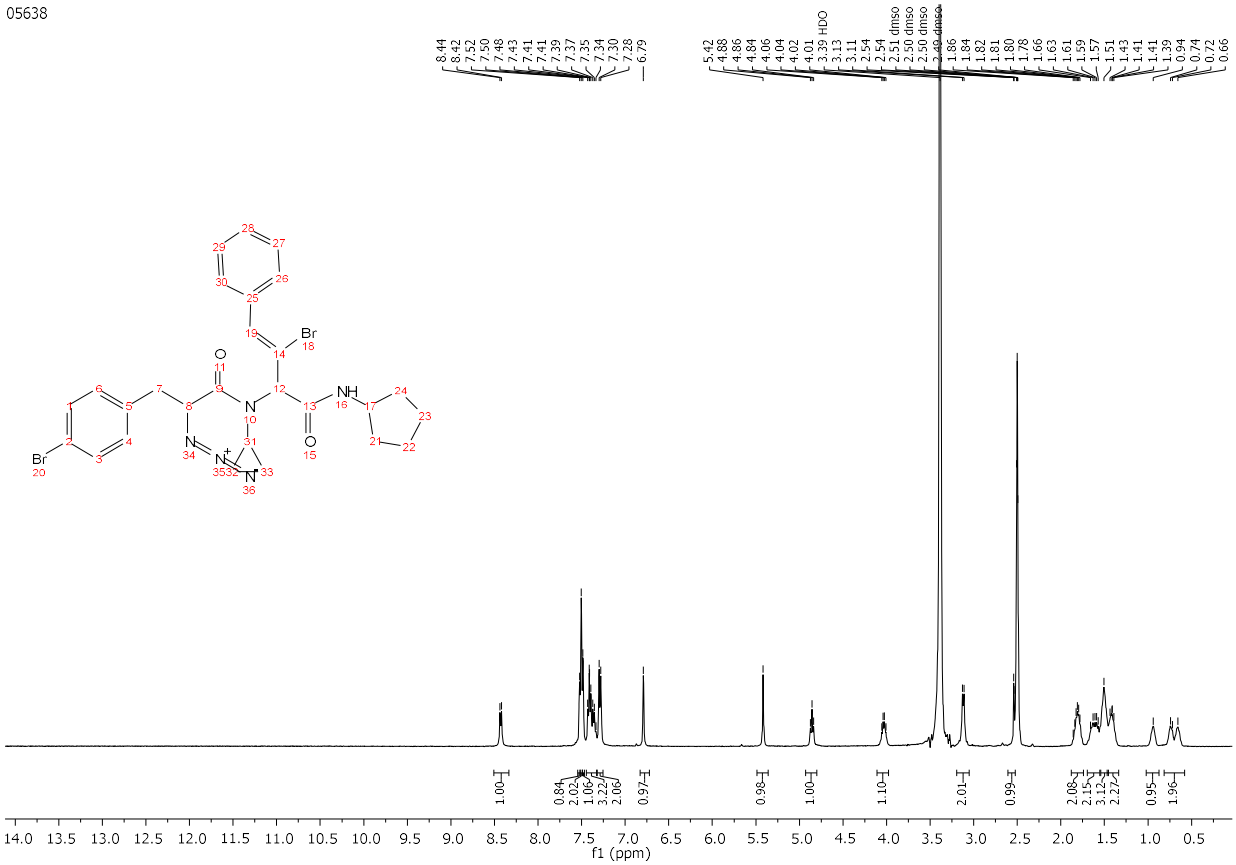
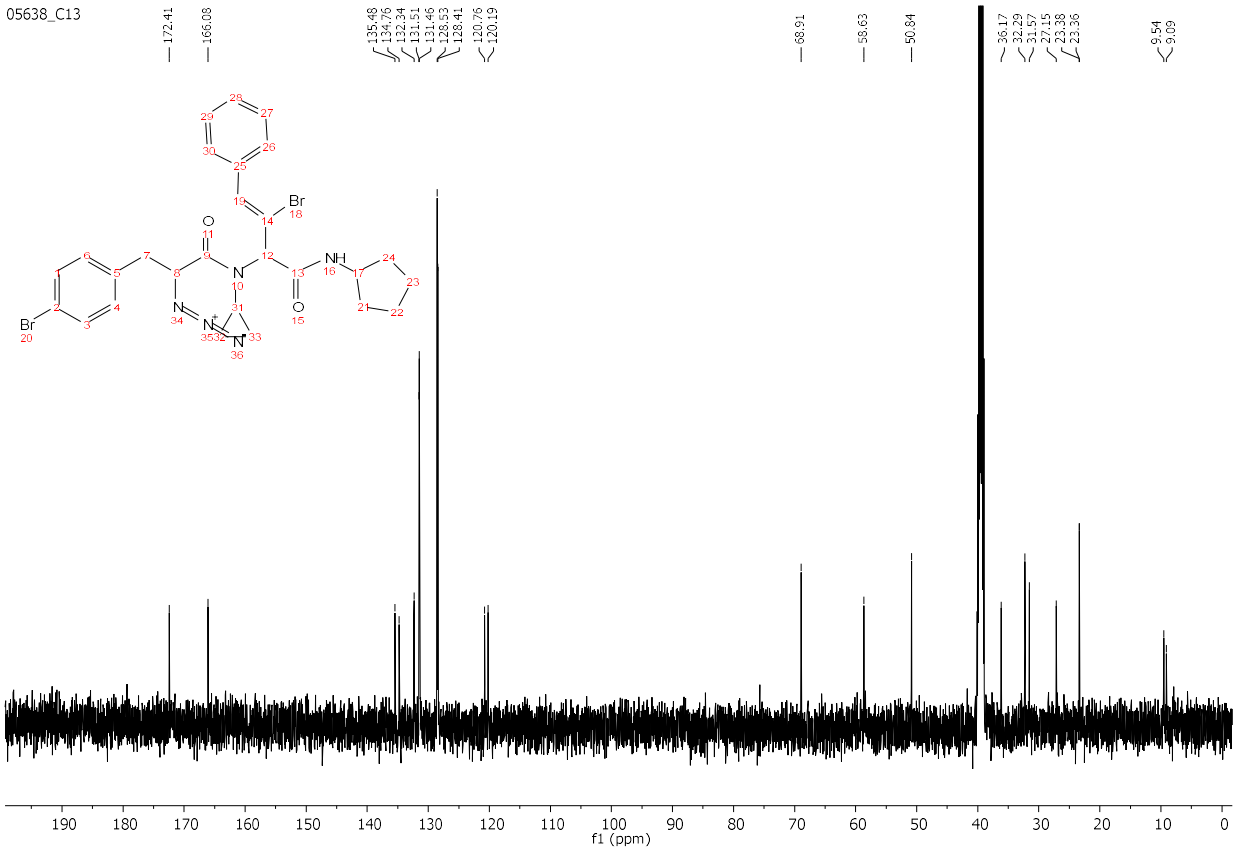


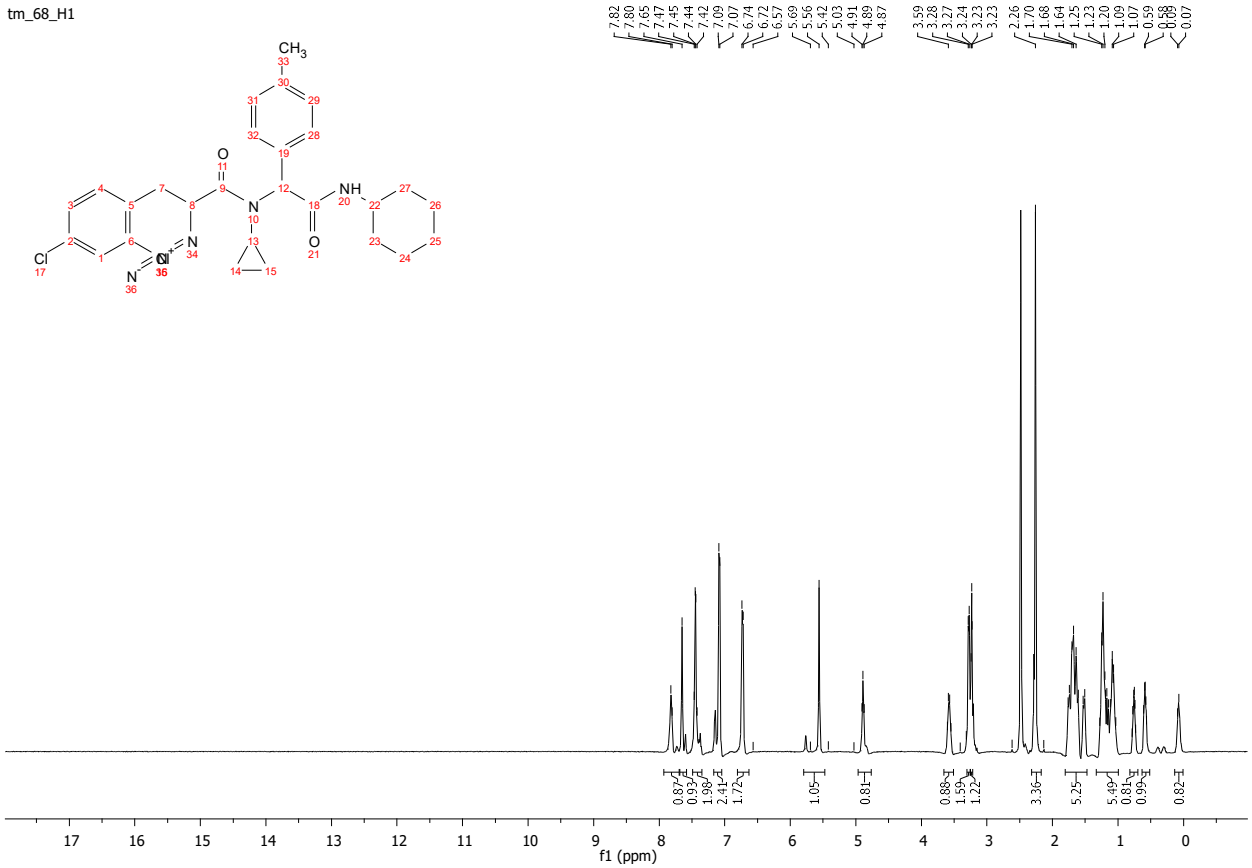


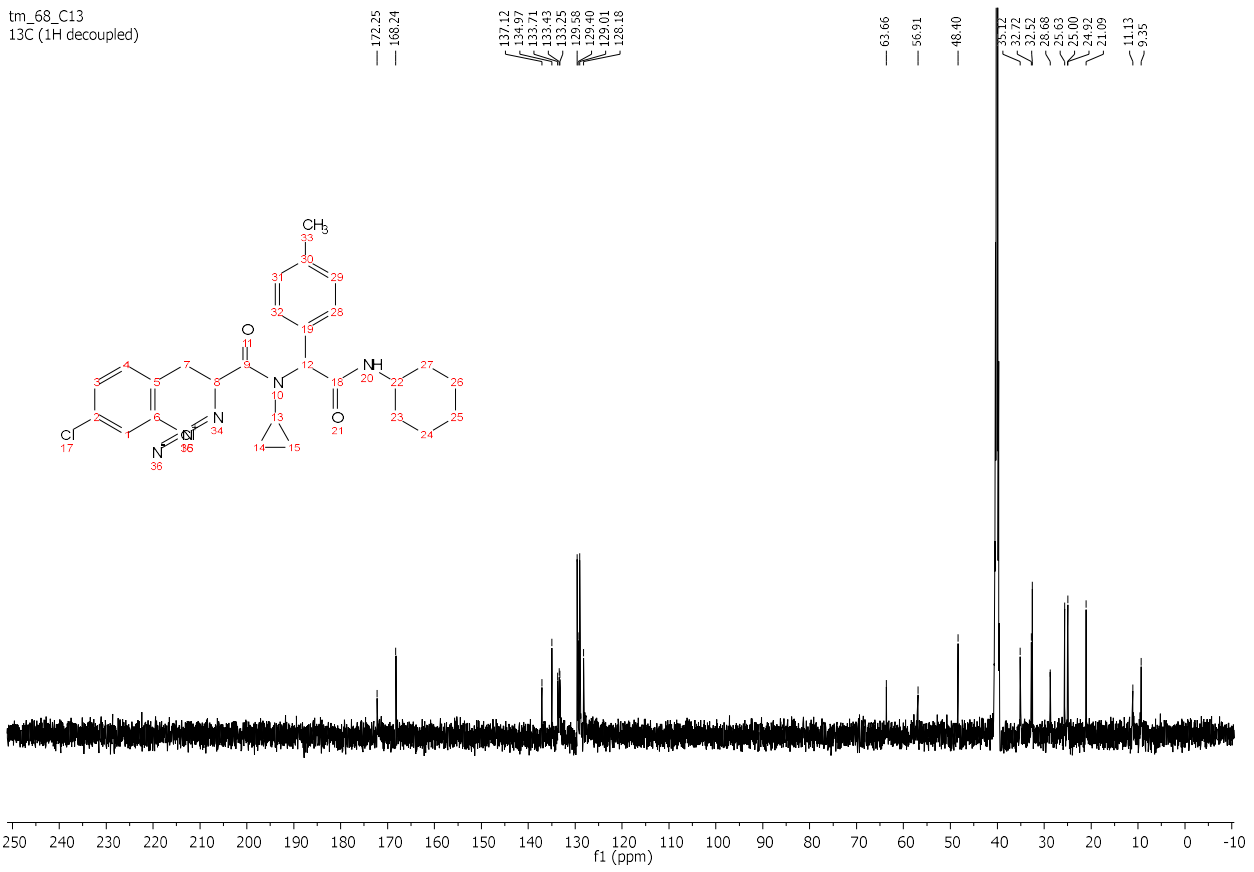
NMR (Z)-2-(2-azido-3-(4-bromophenyl)-N-cyclopropylpropanamido)-3-bromo-N-cyclopentyl-4-phenylbut-3-enamide 7a



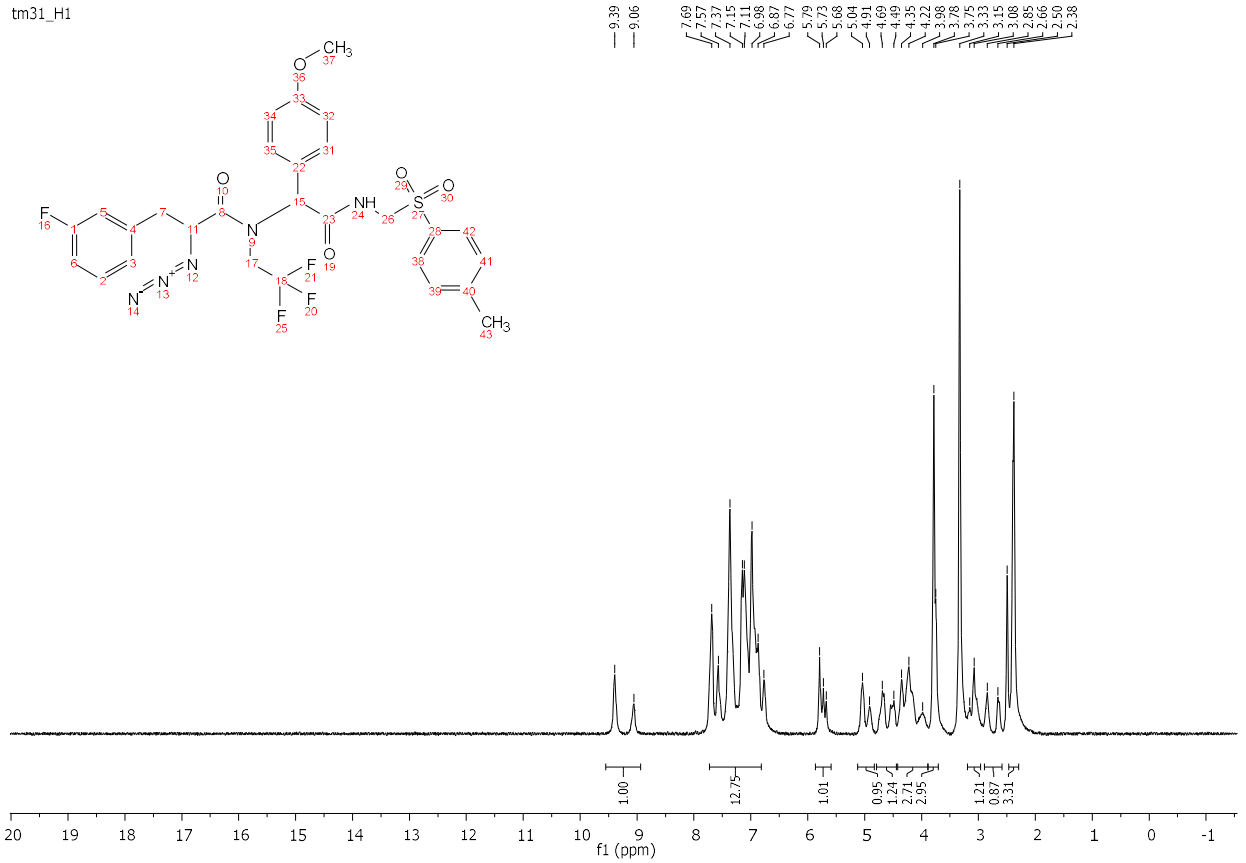


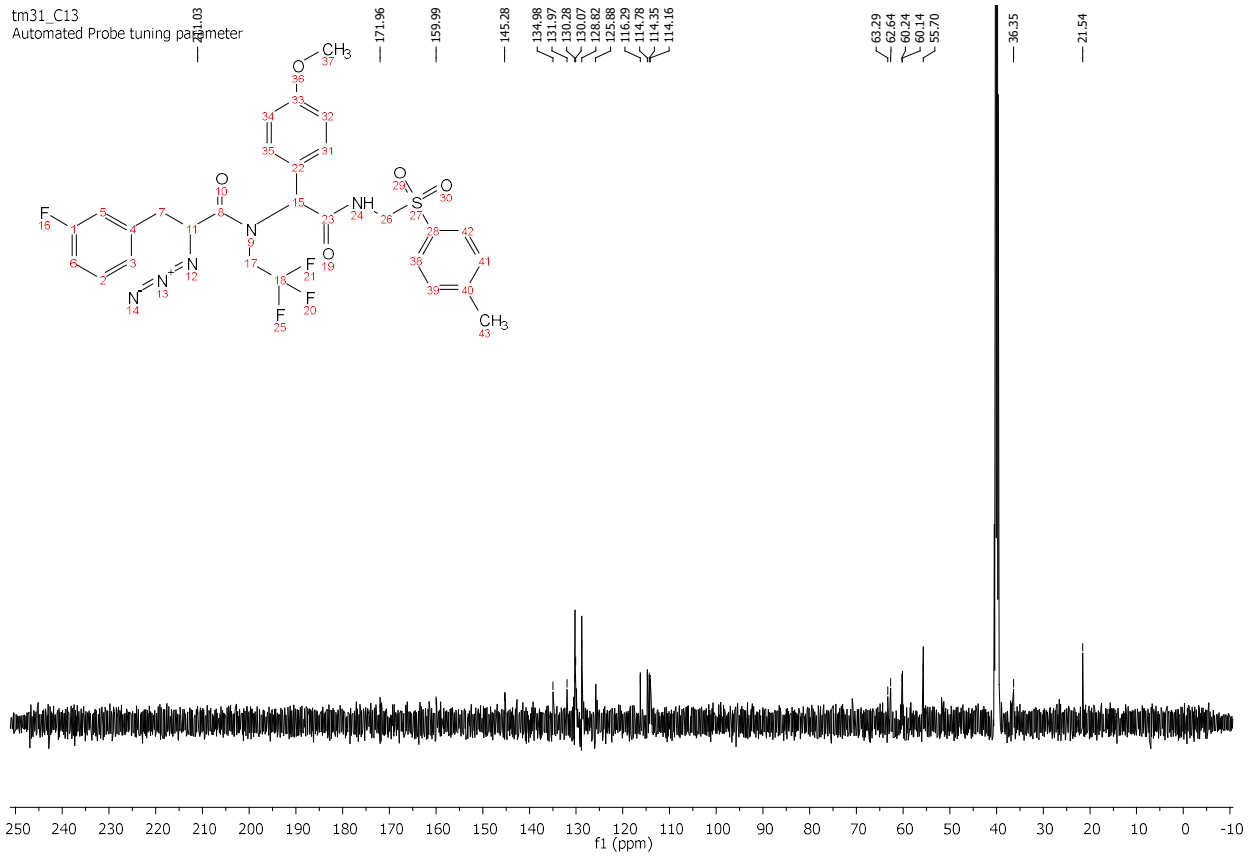
NMR 2-Azido-N-(2-(cyclohexylamino)-2-oxo-1-(p-tolyl)ethyl)-N-cyclopropyl-3-(2,4-dichlorophenyl)propanamide 7b





NMR 2-Azido-3-(3-fluorophenyl)-N-(1-(4-methoxyphenyl)-2-oxo-2-((tosylmethyl)amino)ethyl)-N-(2,2,2-trifluoroethyl)propanamide 7c





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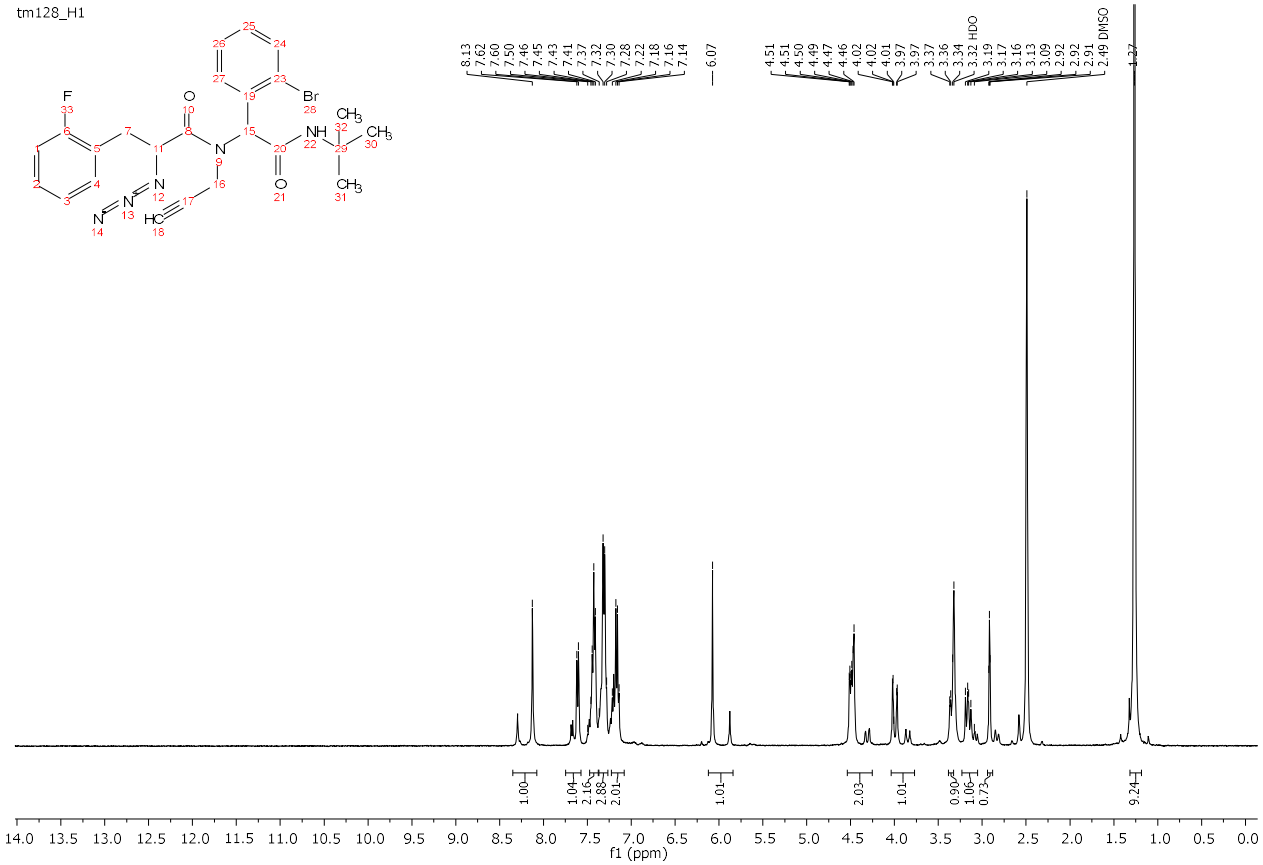

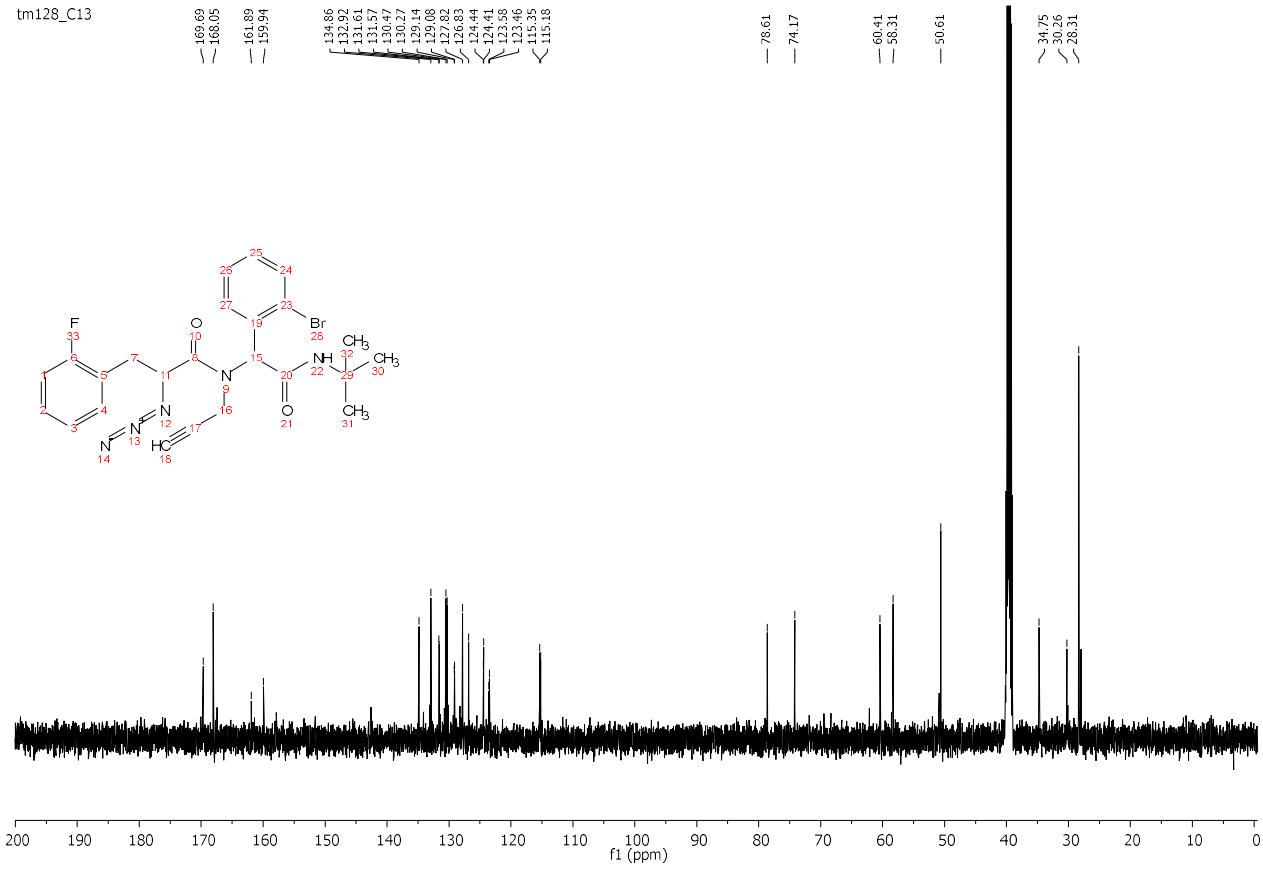

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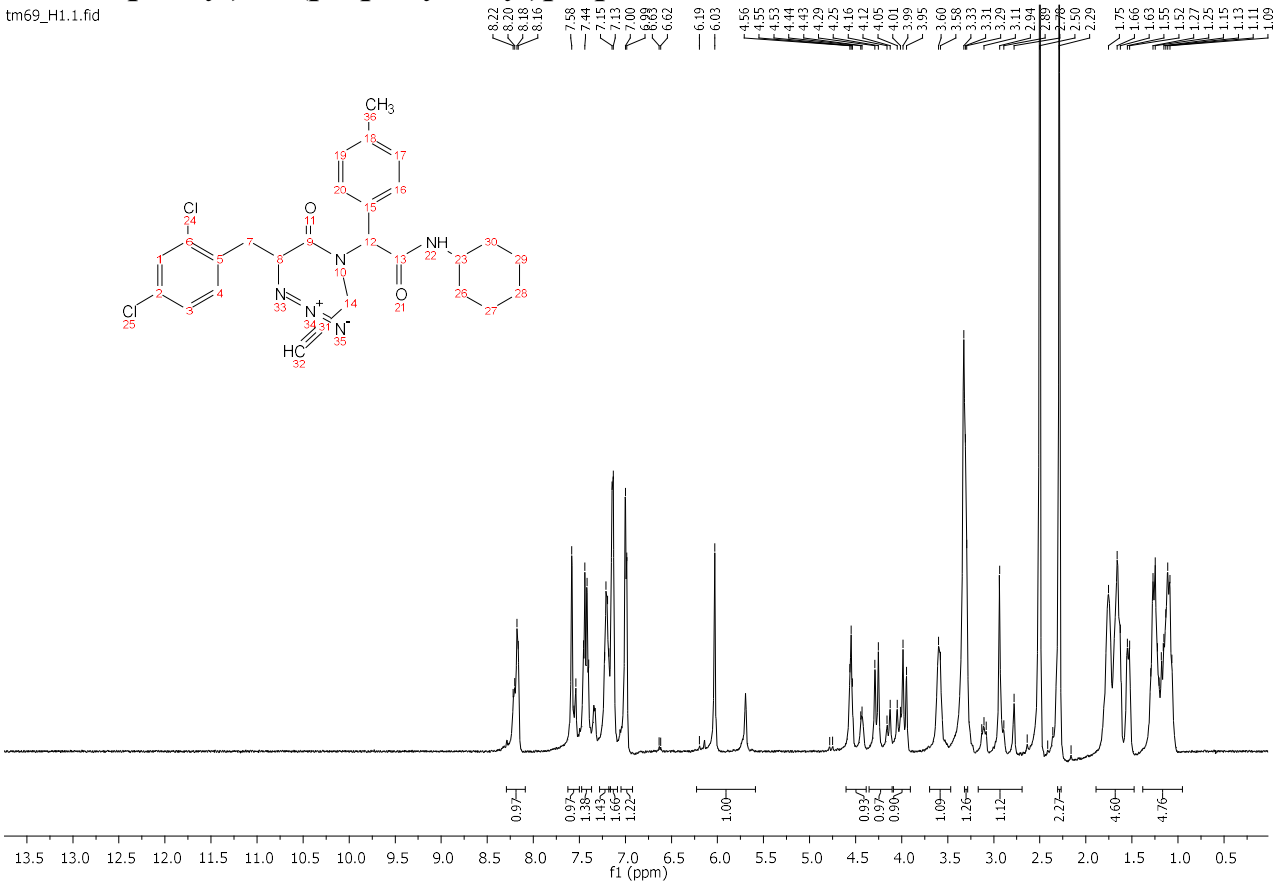

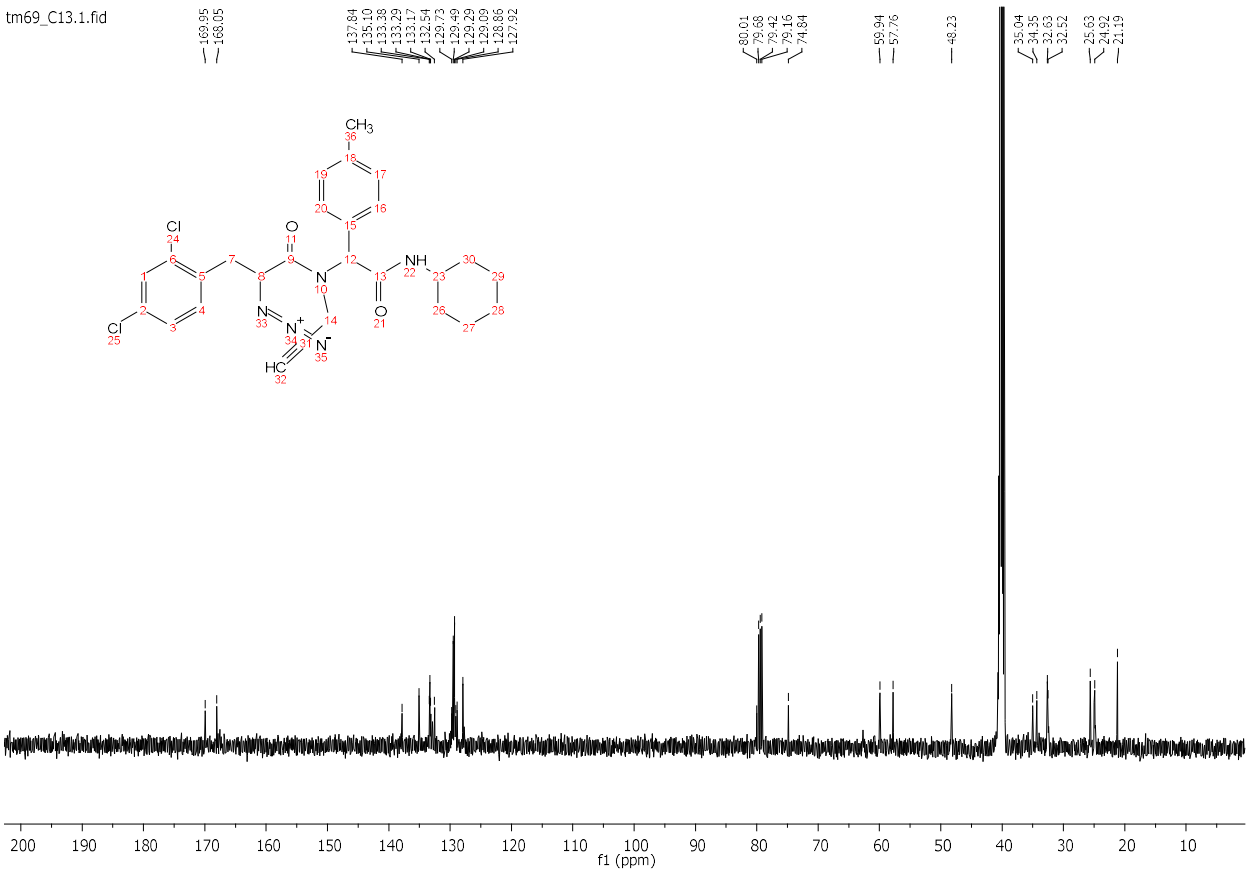

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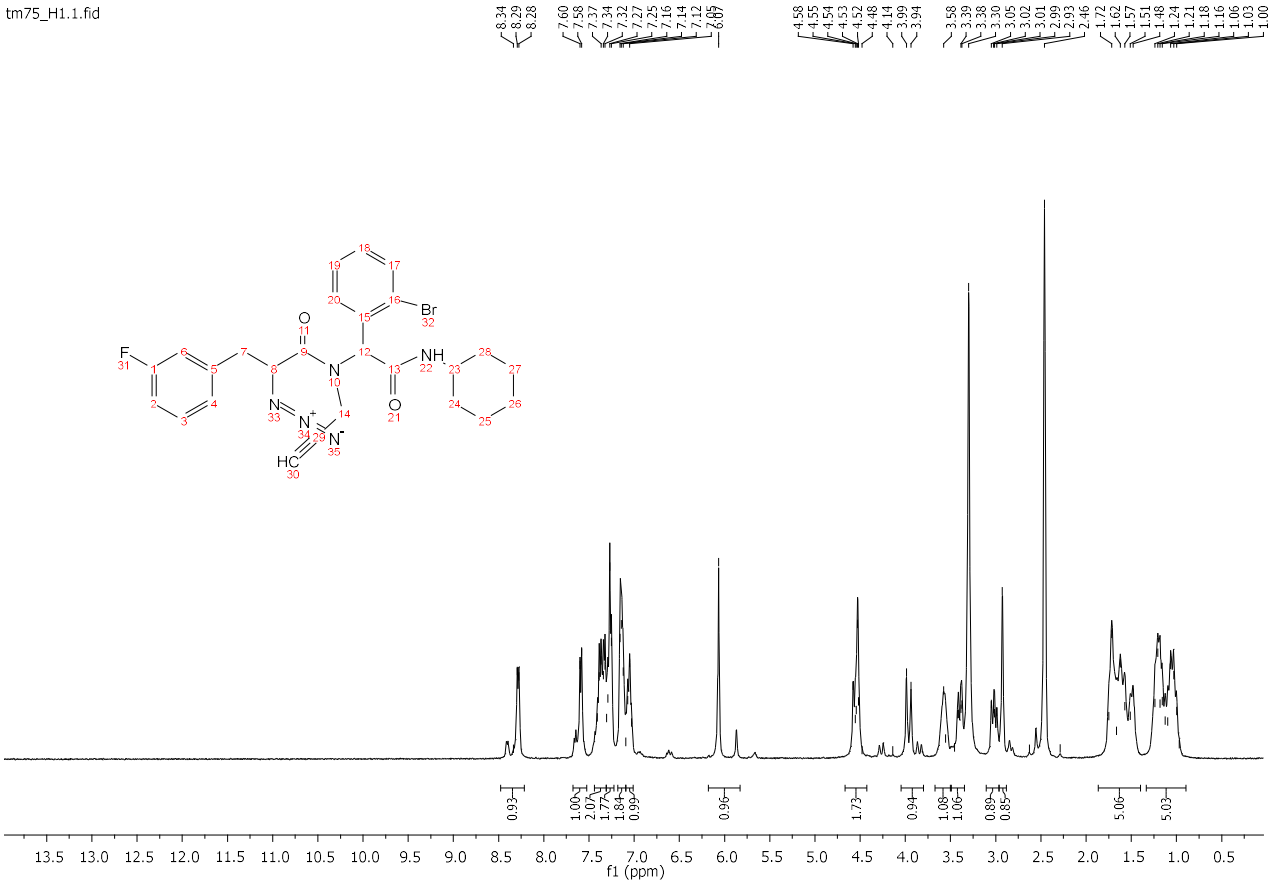

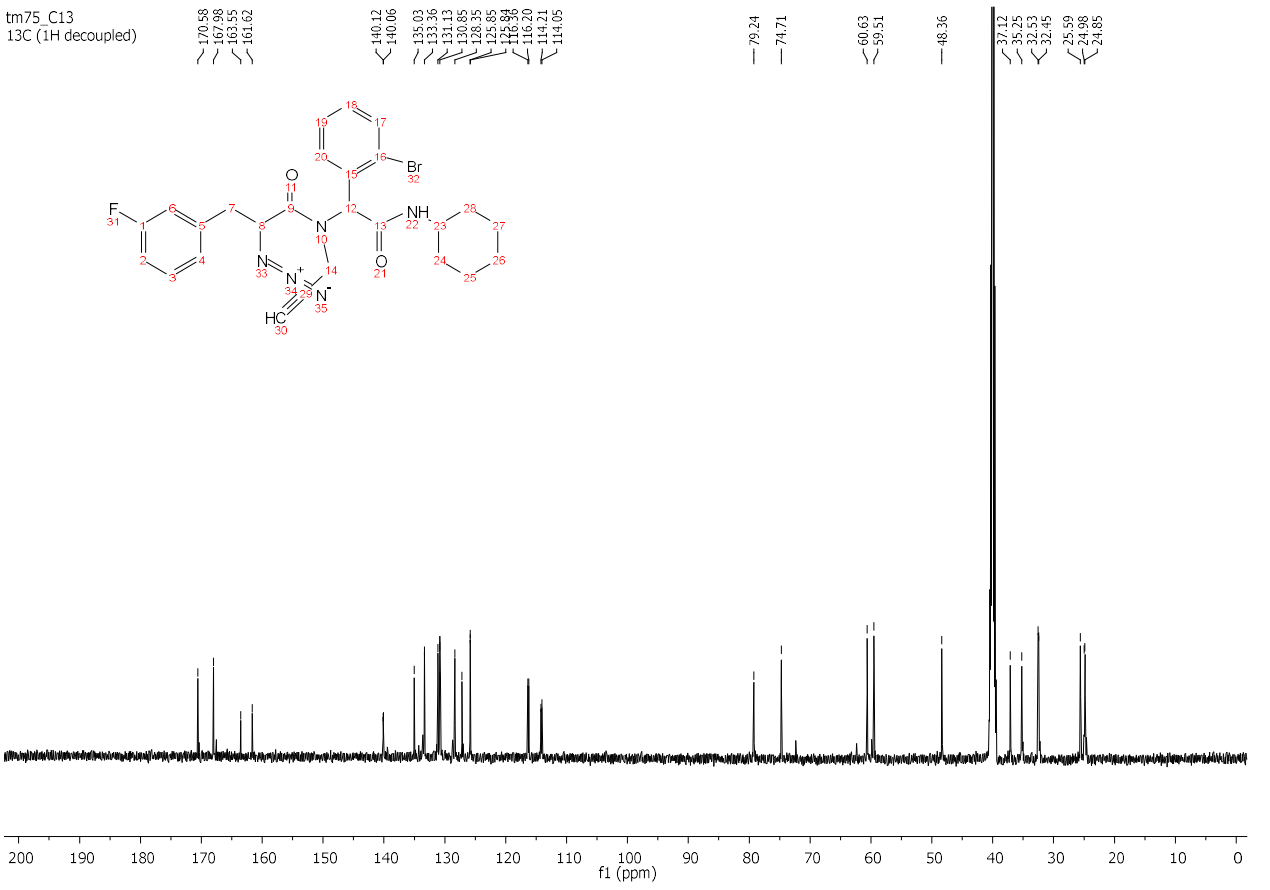

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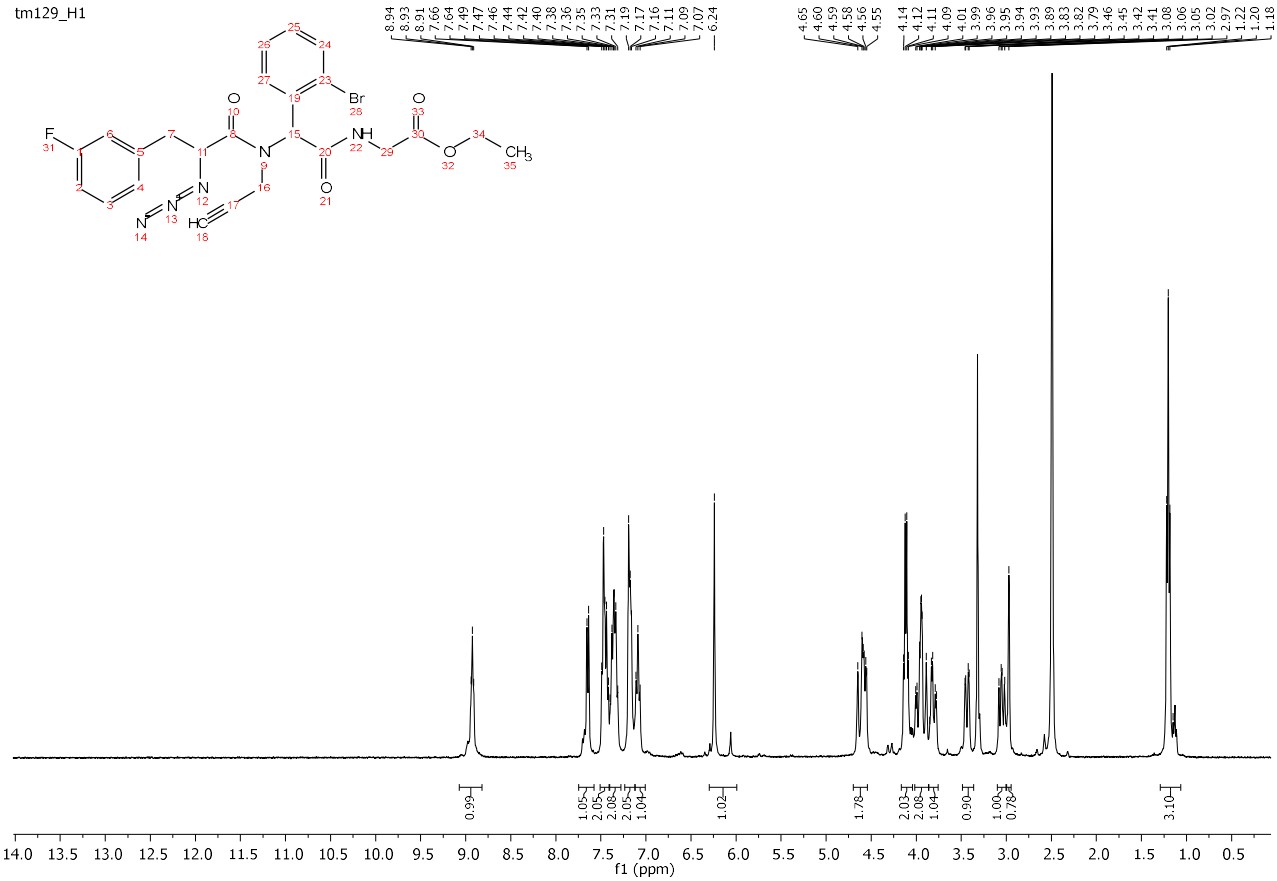

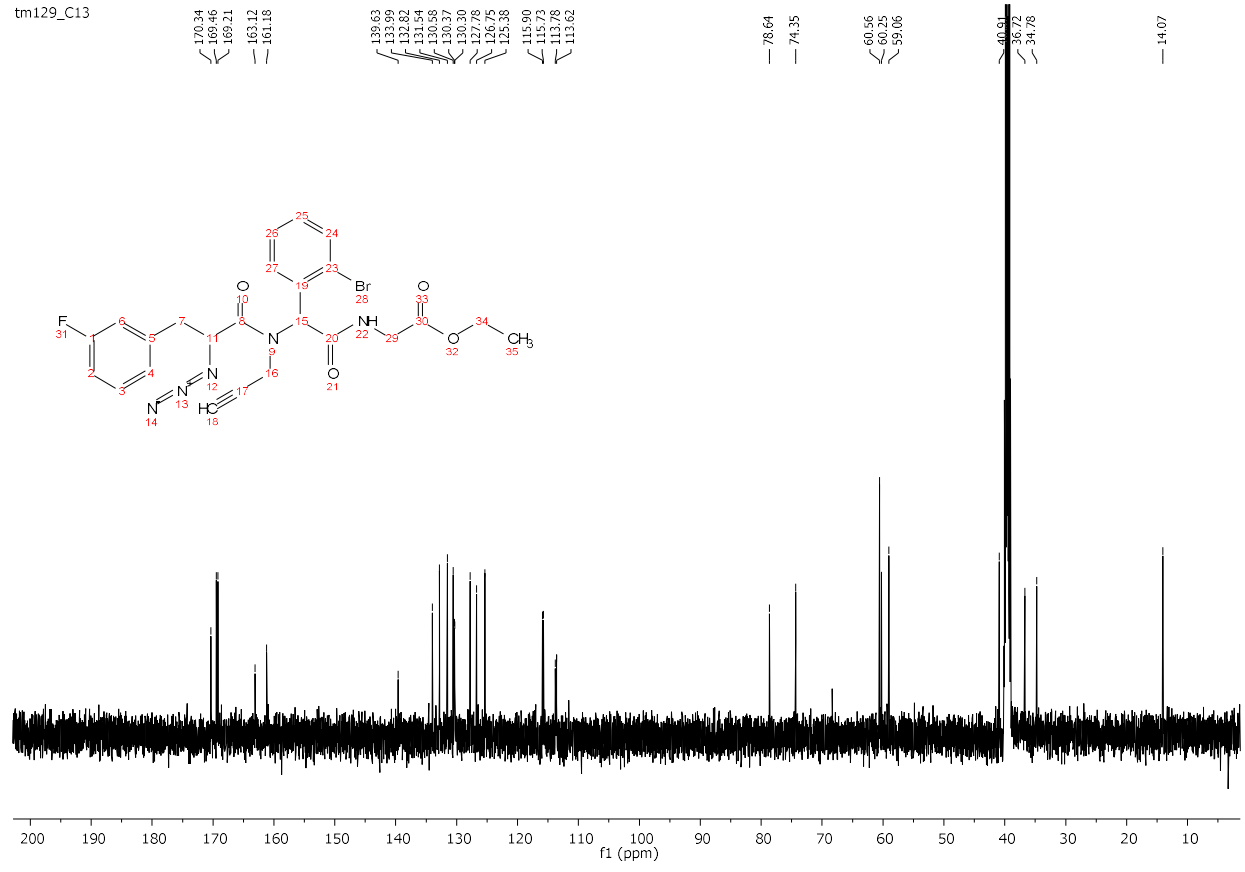

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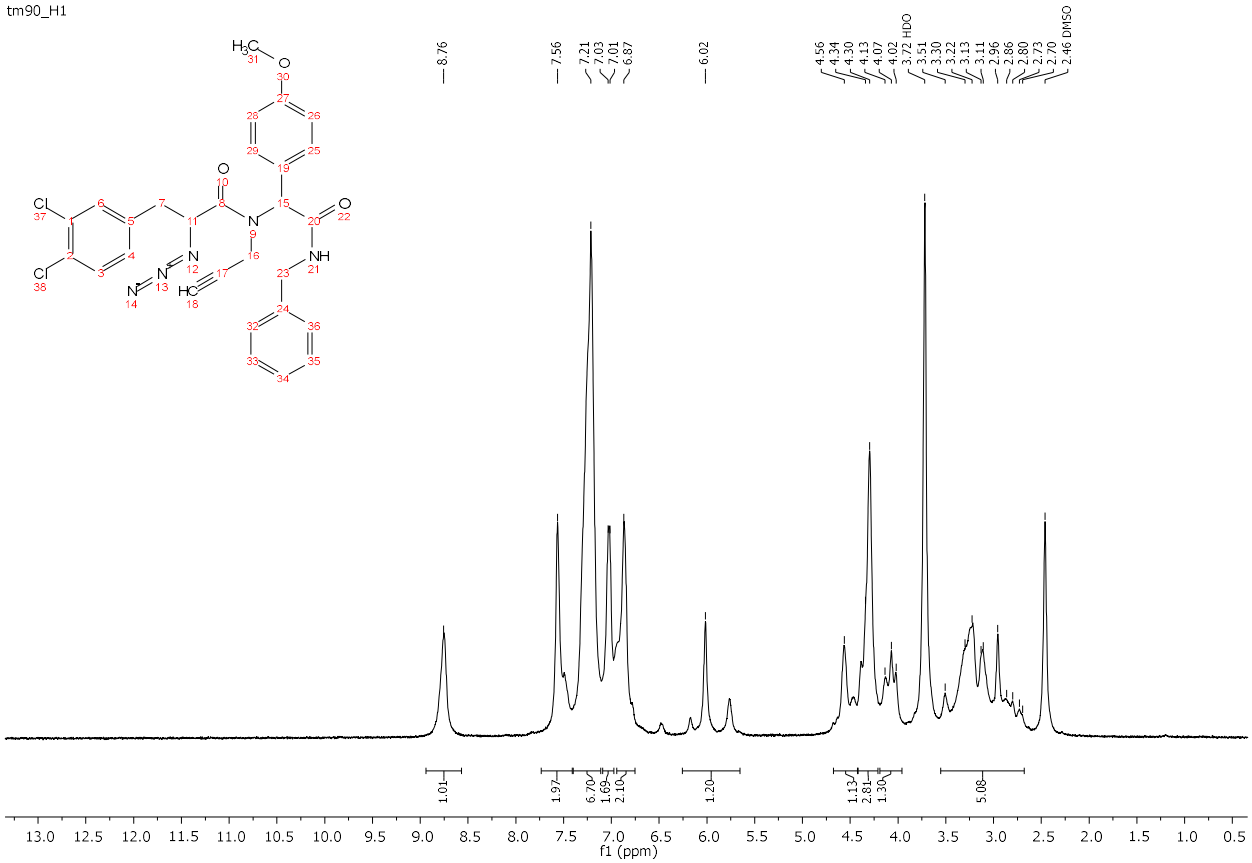

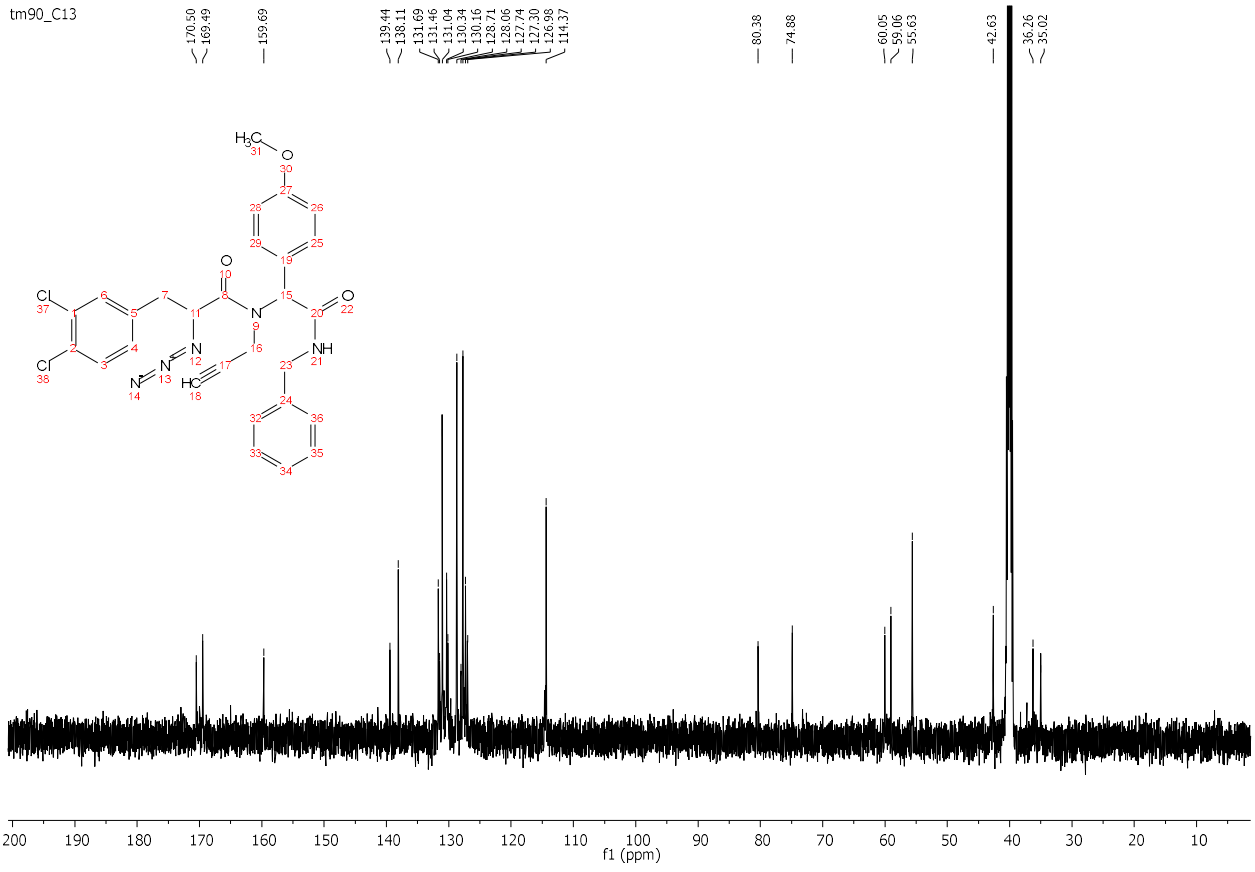

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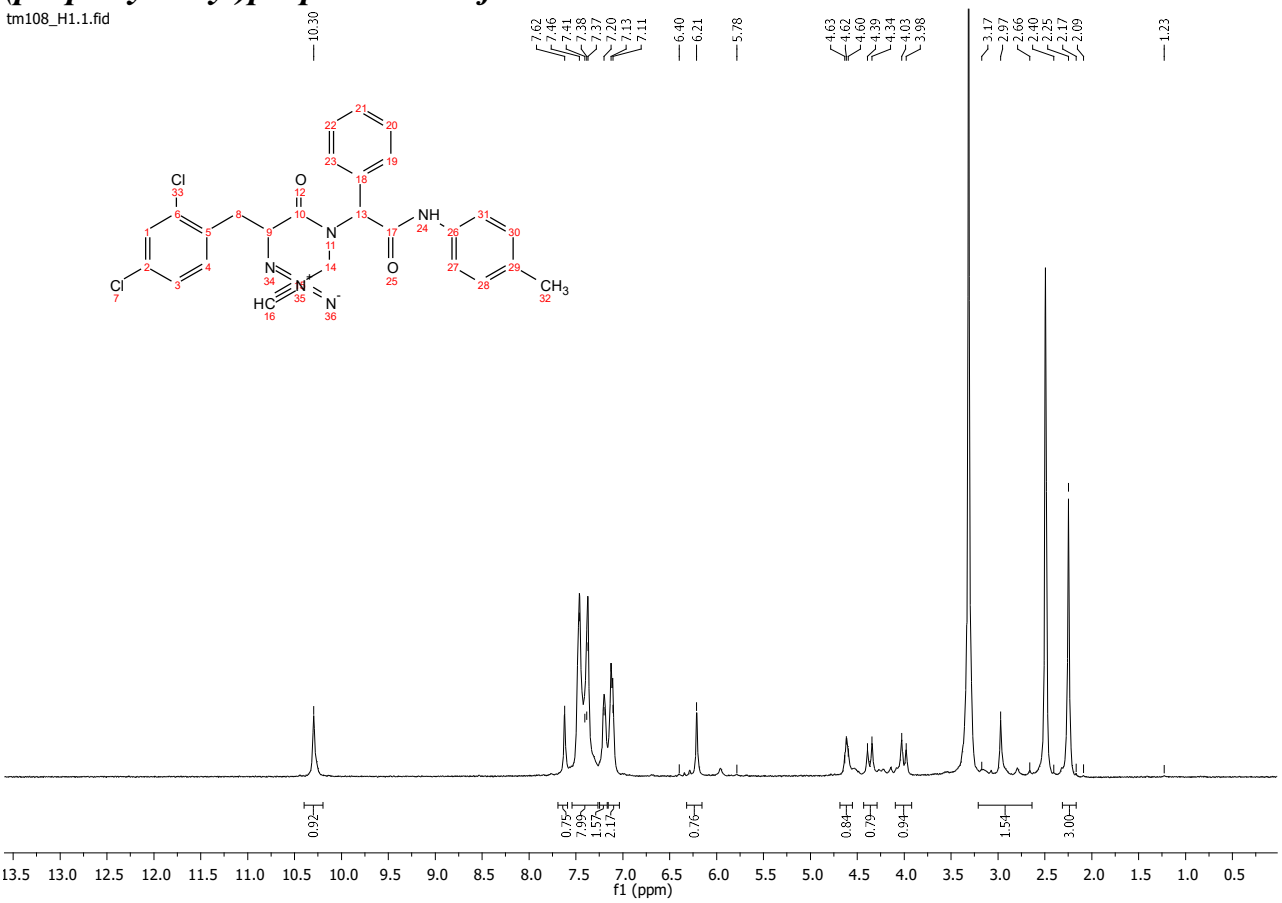

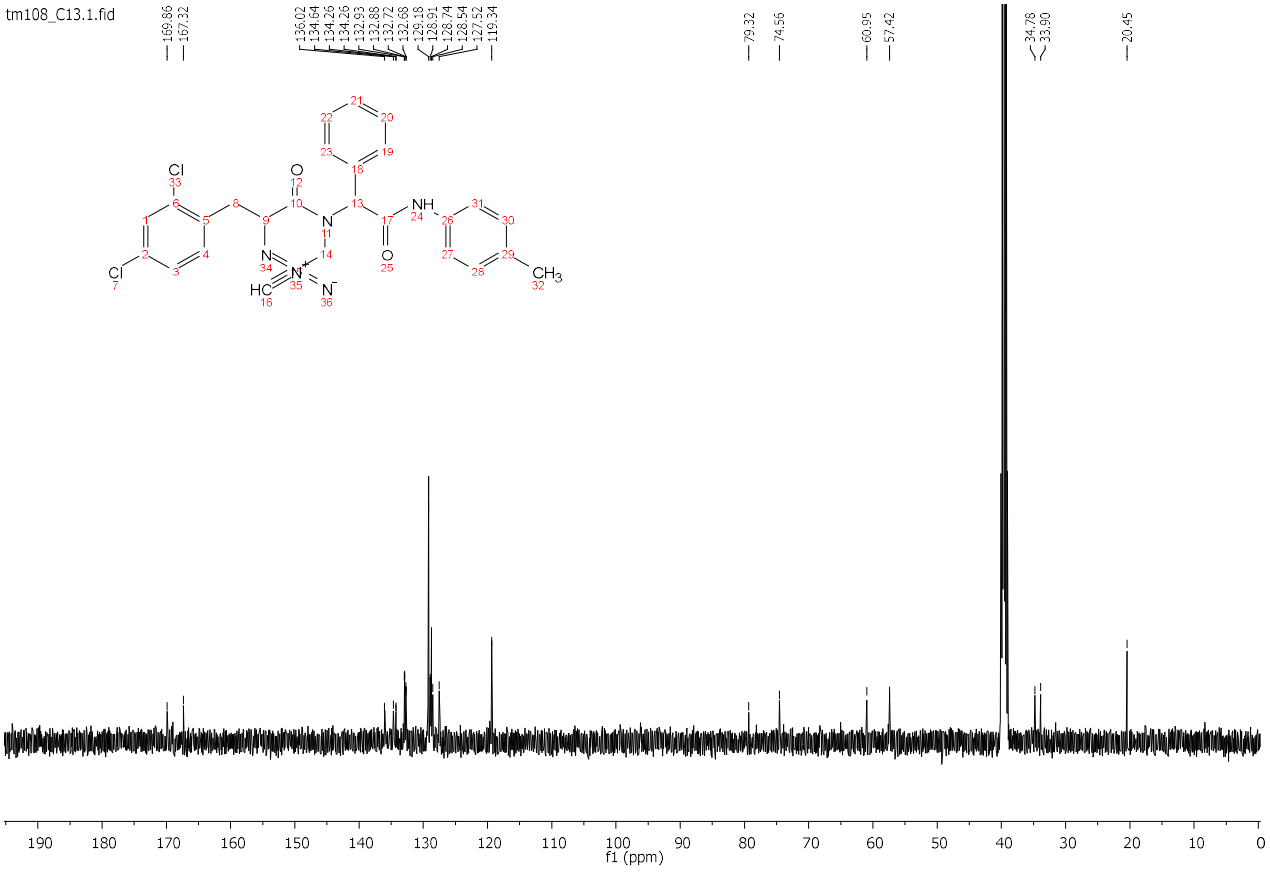

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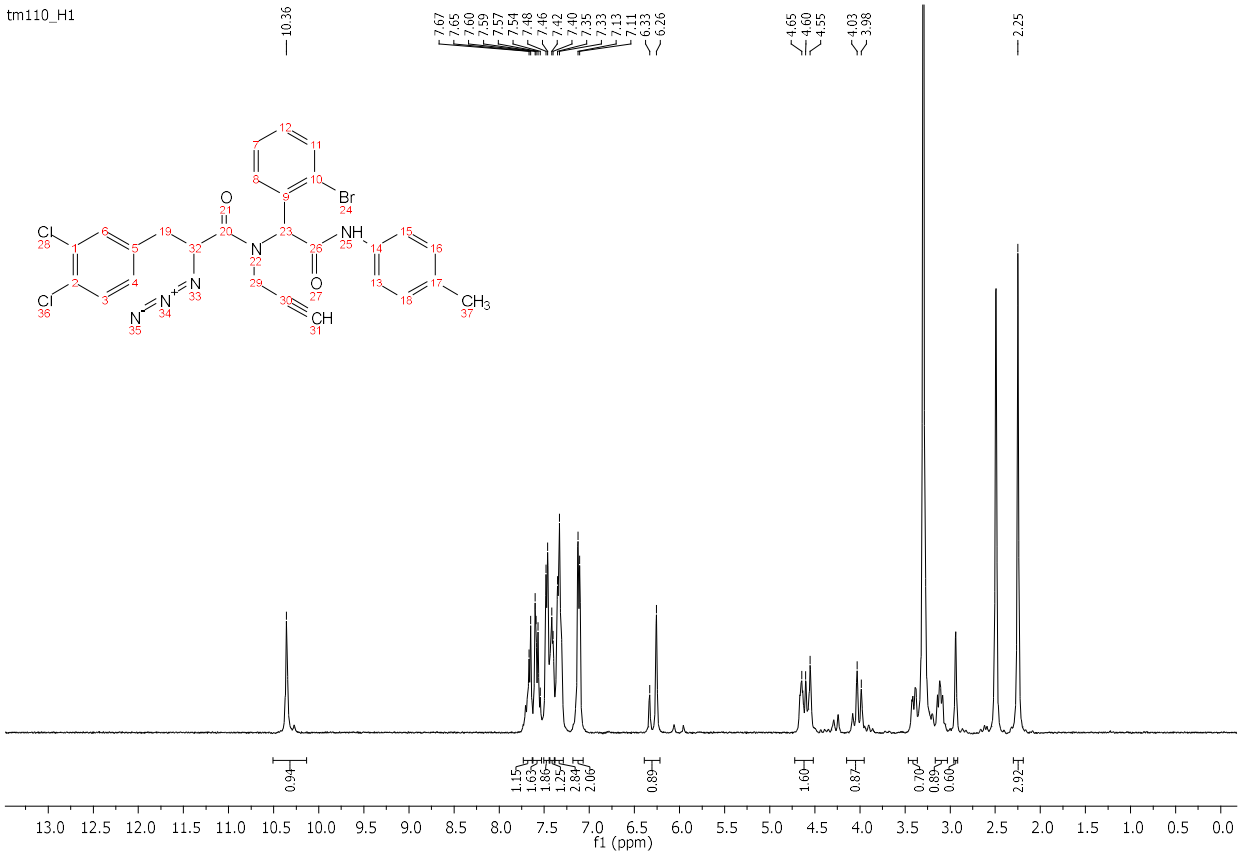

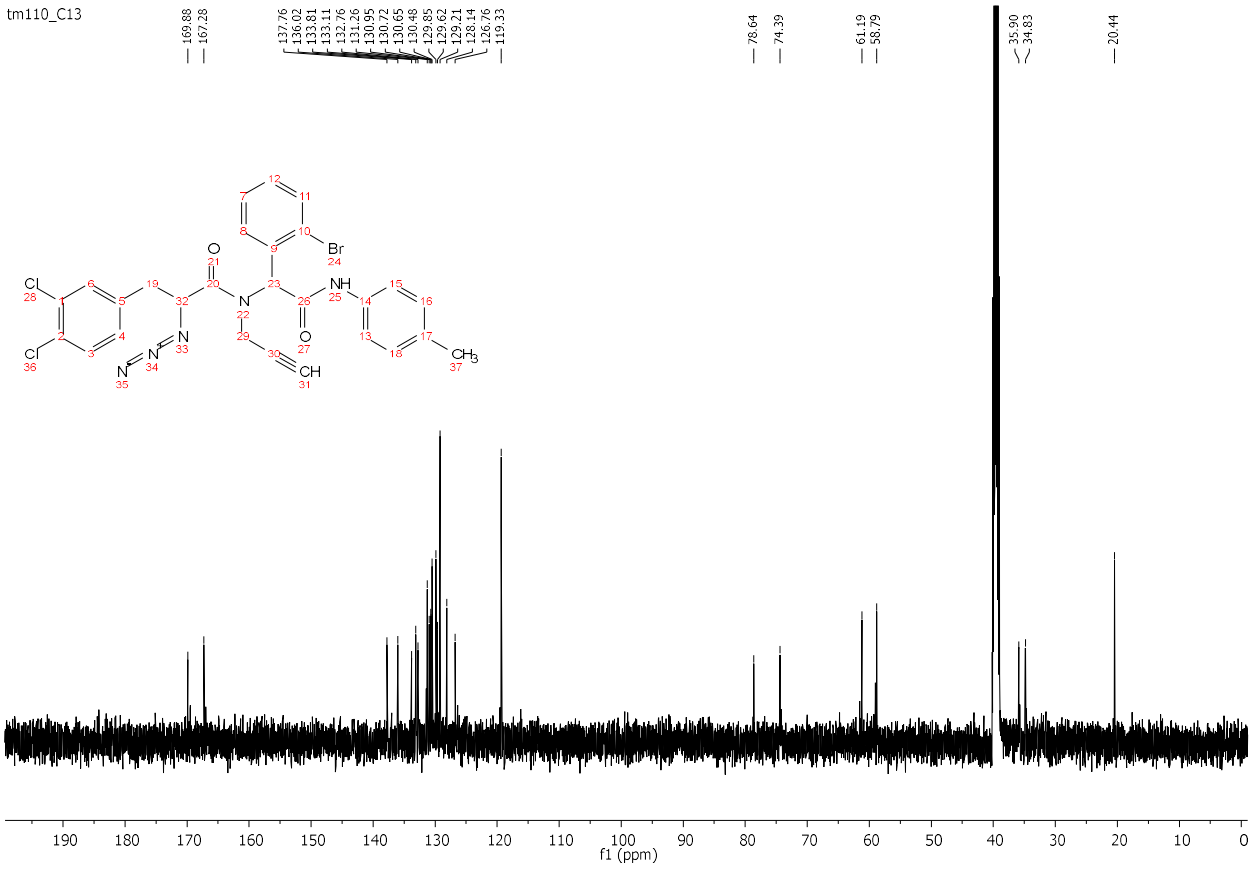

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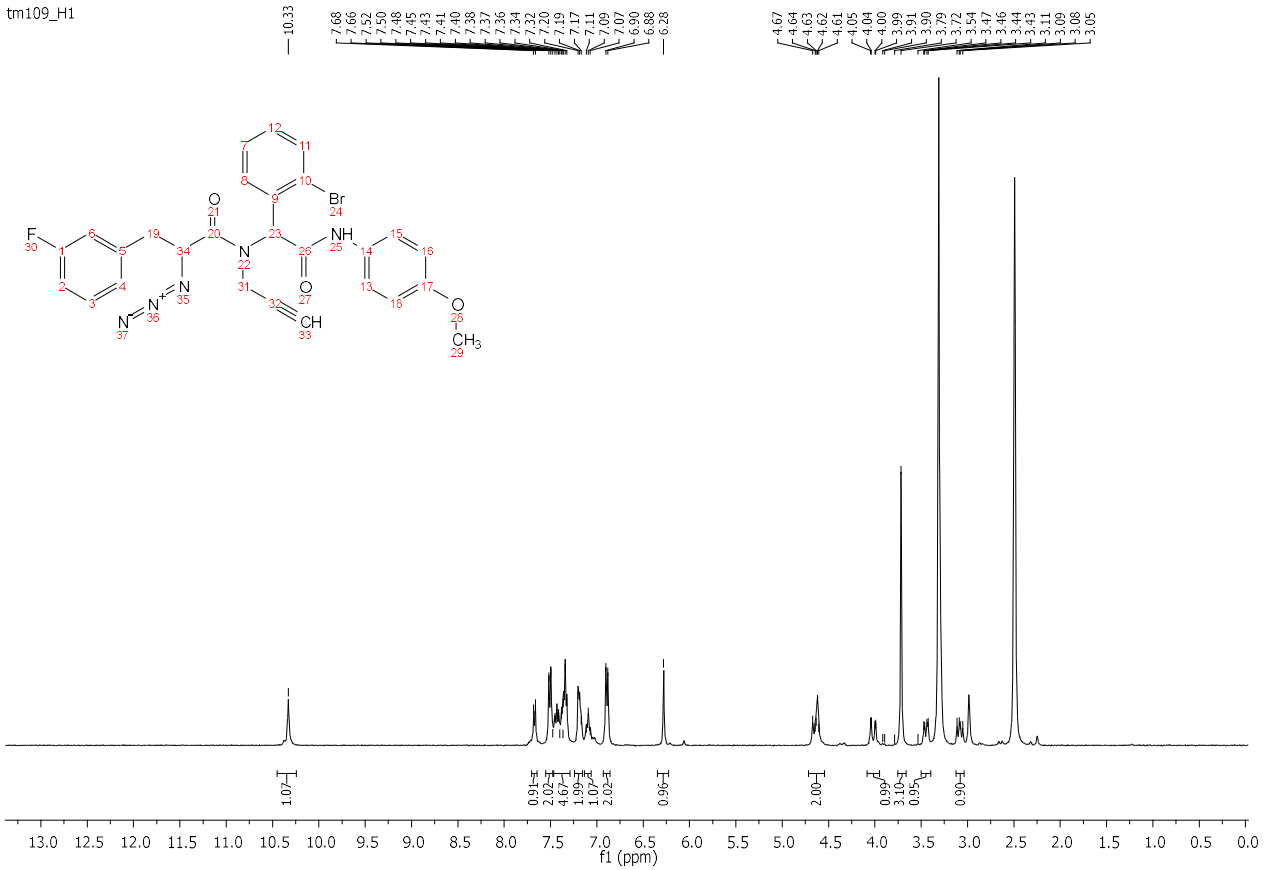
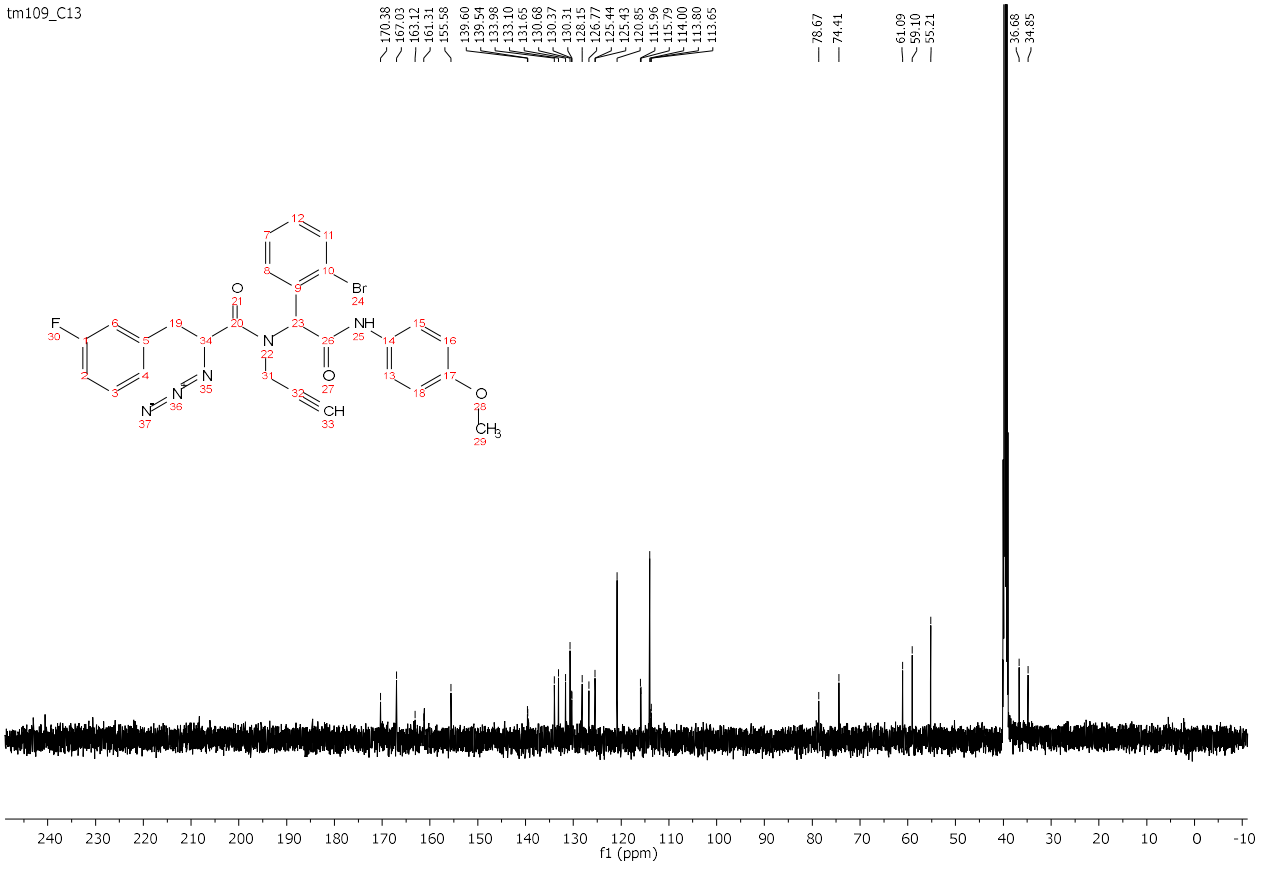
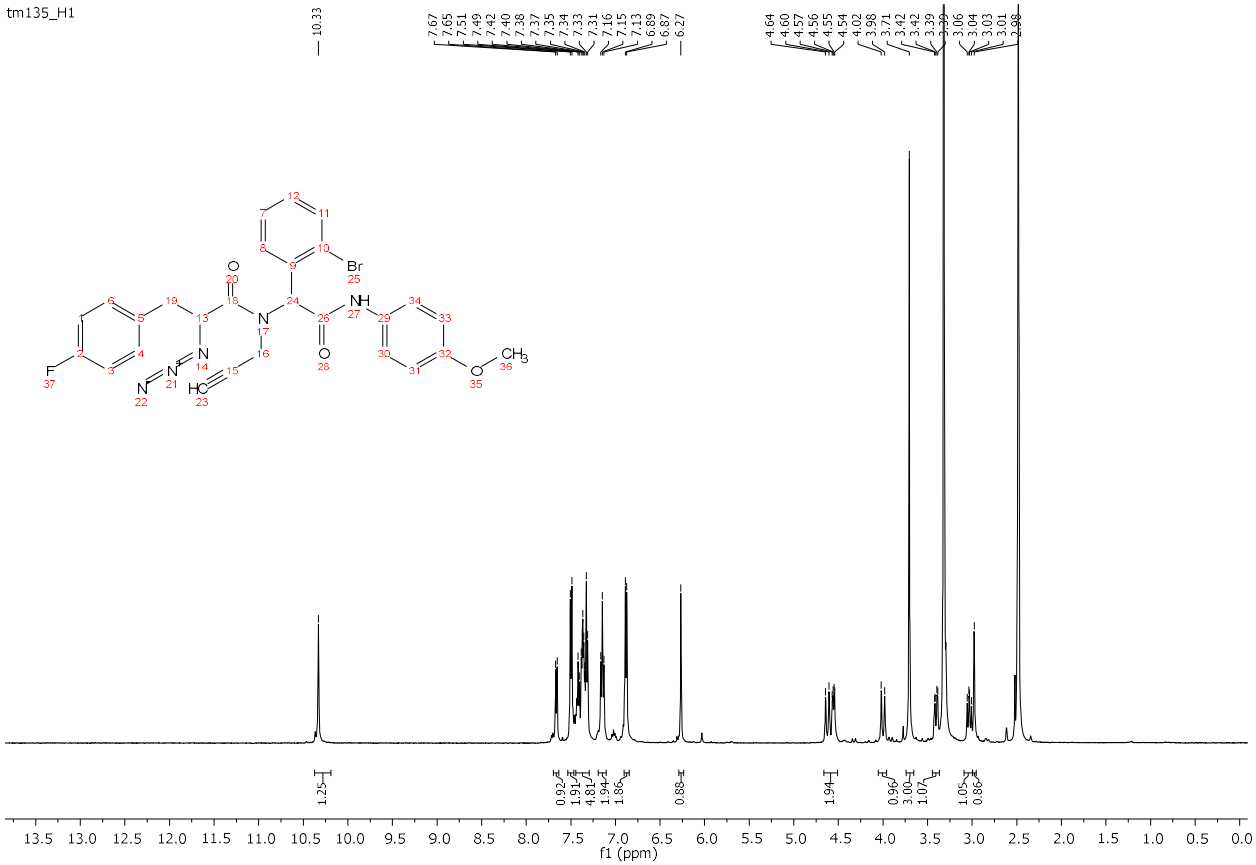
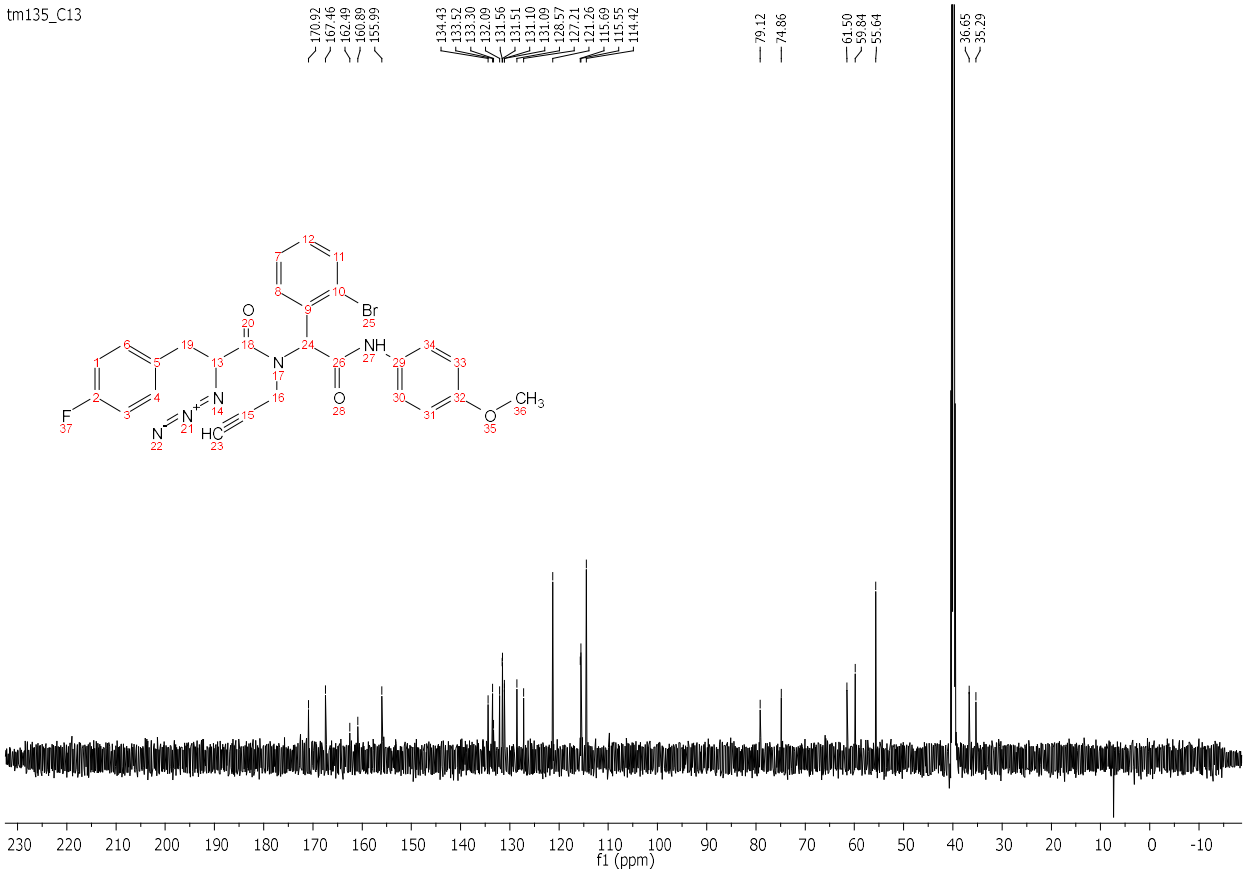


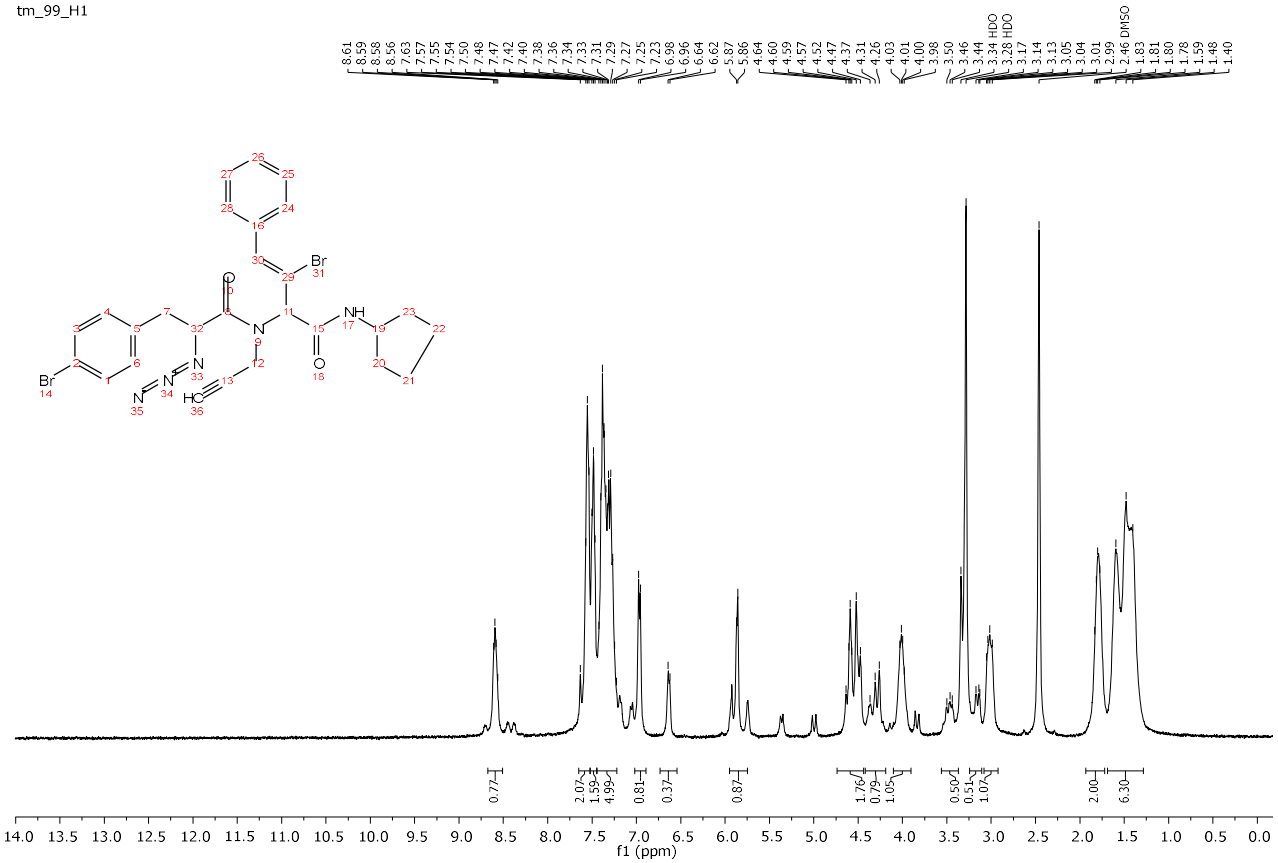


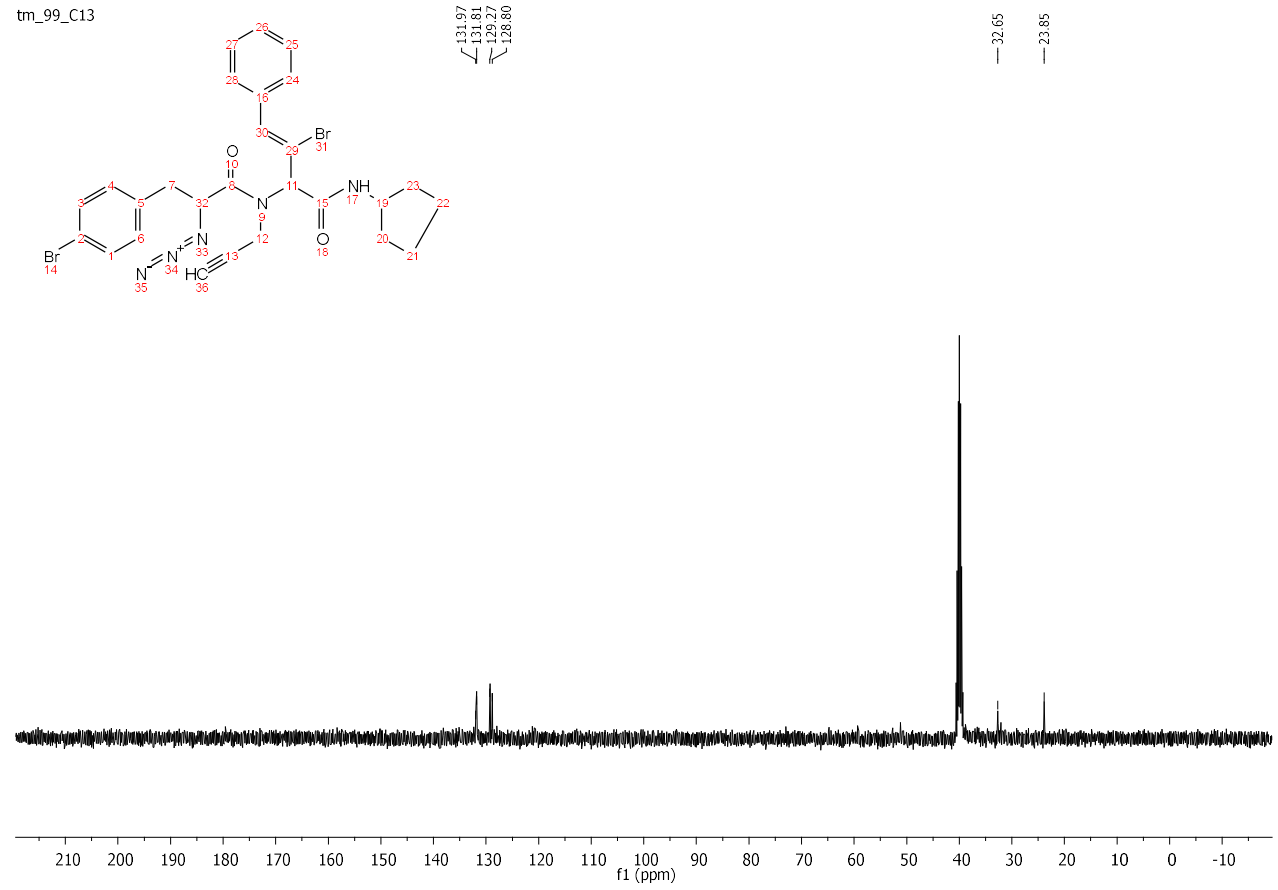
NMR 2-Azido-N-(1-(2-bromophenyl)-2-((4-methoxyphenyl)amino)-2-oxoethyl)-3-(4-fluorophenyl)-N-(prop-2-yn-1-yl)propanamide 8i



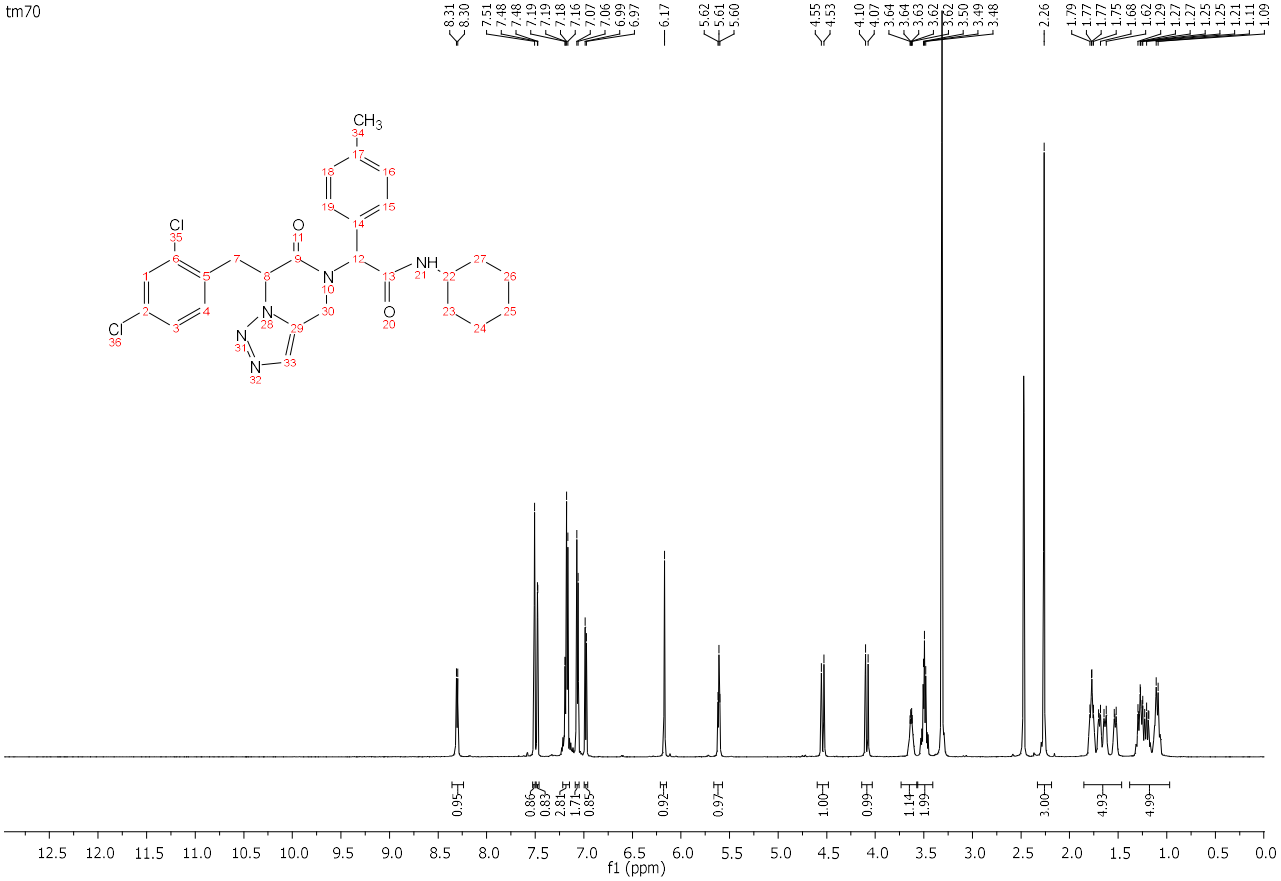


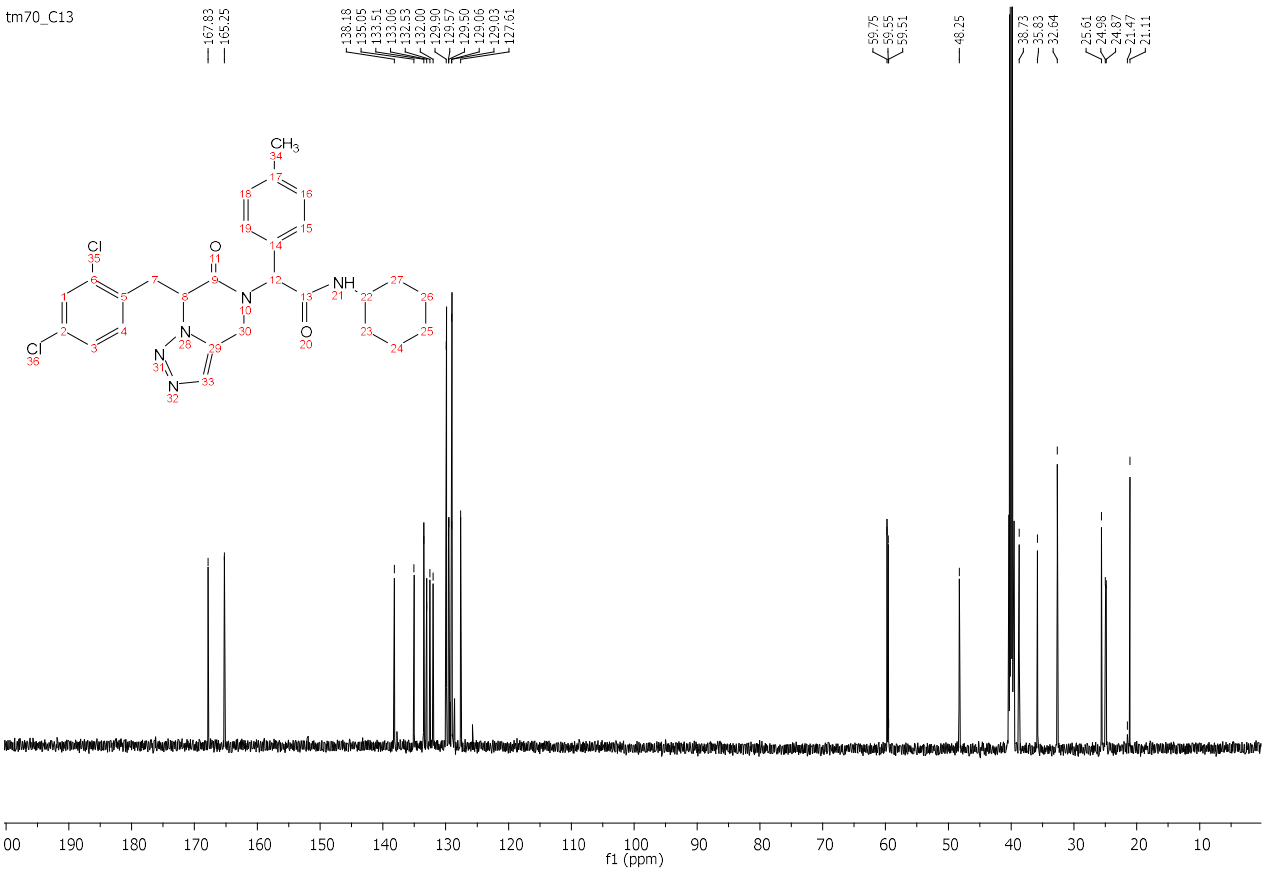
NMR (Z)-2-(2-azido-3-(4-bromophenyl)-N-(prop-2-yn-1-yl)propanamido)-3-bromo-N-cyclopentyl-4-phenylbut-3-enamide 8j



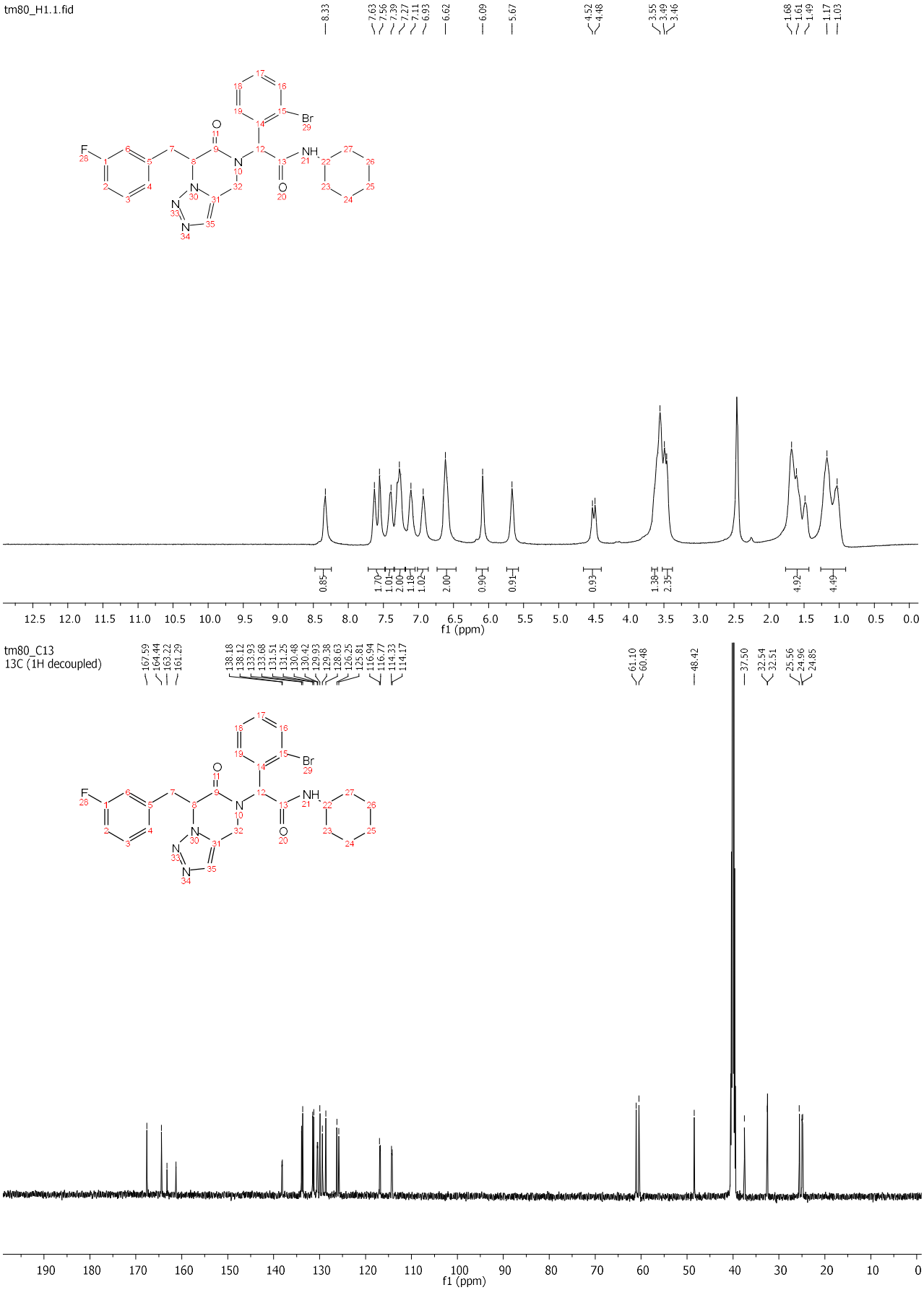


NMR N-cyclohexyl-2-(7-(2,4-dichlorobenzyl)-6-oxo-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)-2-(p-tolyl)acetamide 9a

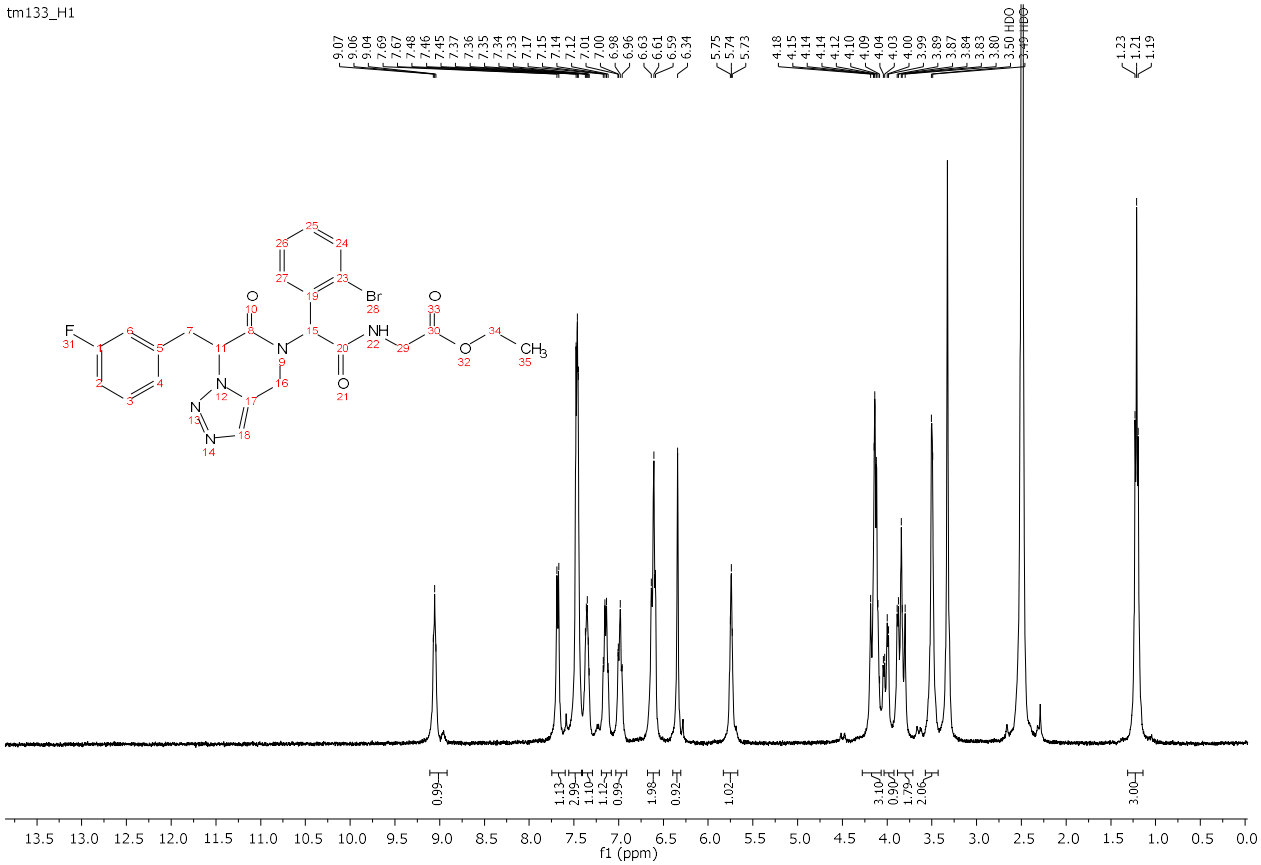


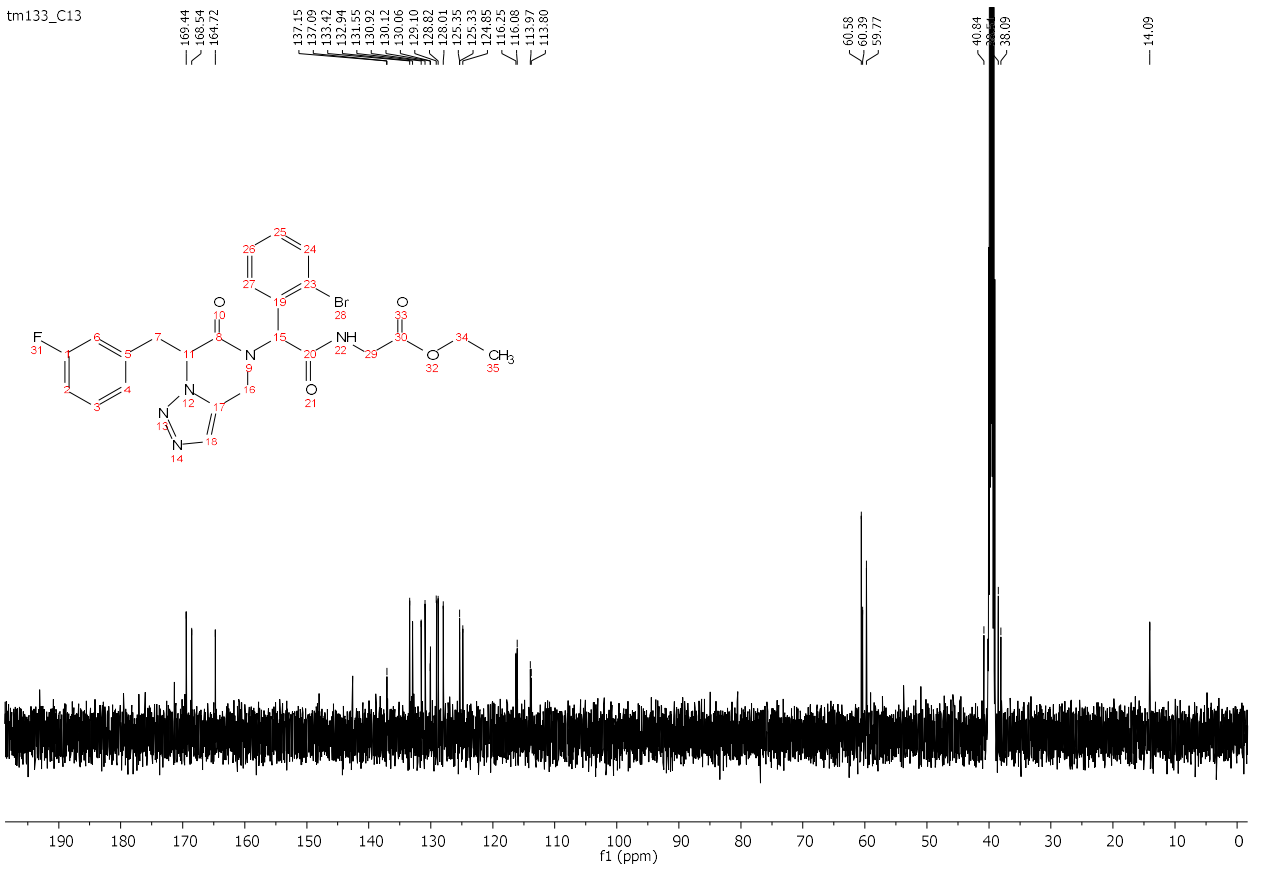


NMR 2-(2-Bromophenyl)-N-cyclohexyl-2-(7-(3-fluorobenzyl)-6-oxo-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)acetamide 9b

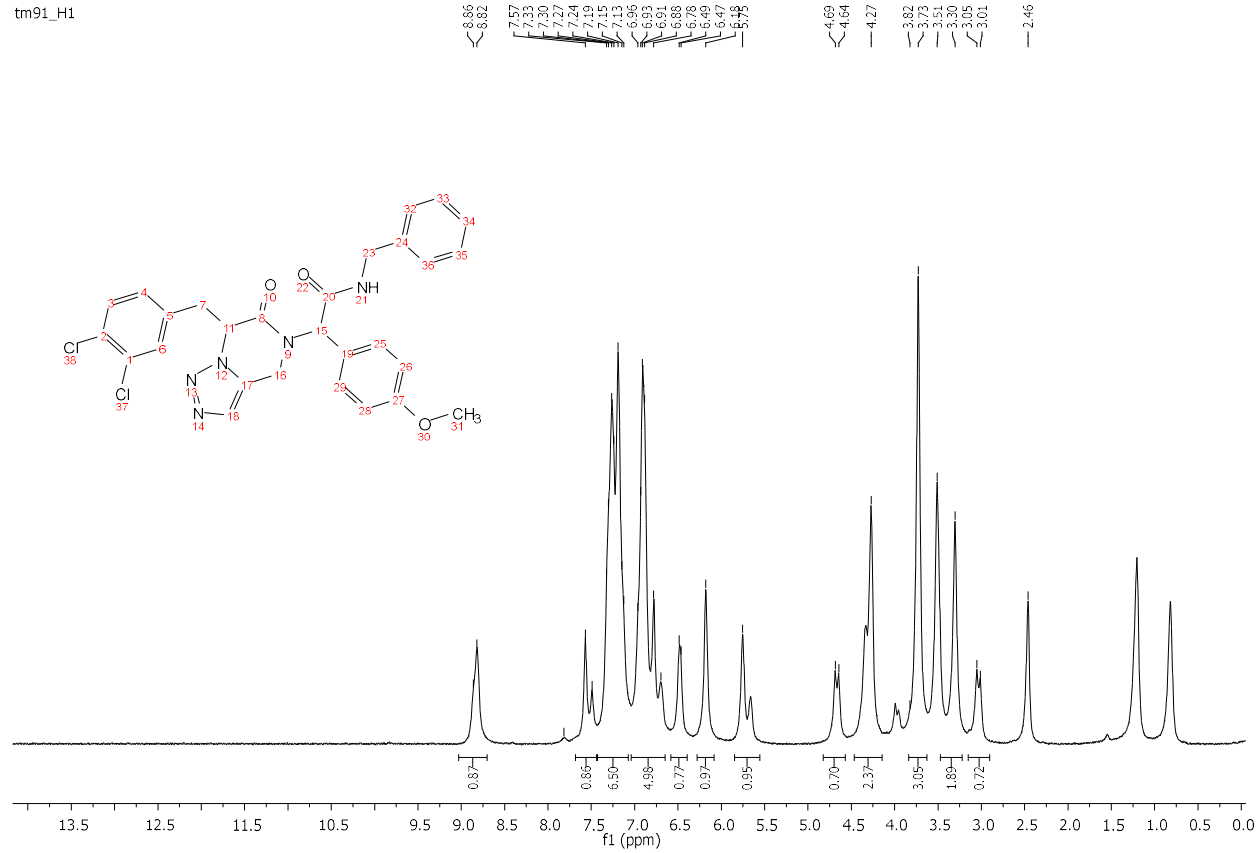


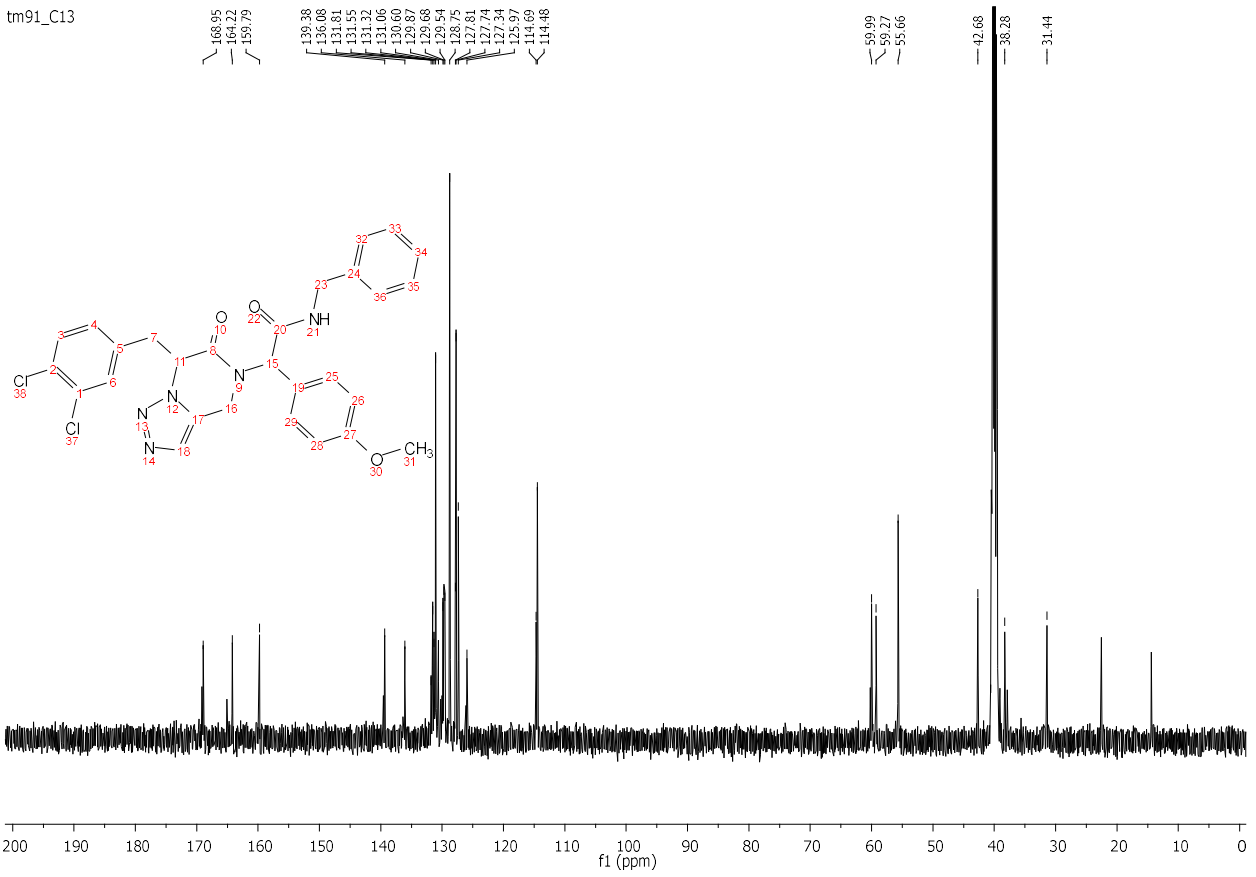
NMR Ethyl (2-(2-bromophenyl)-2-(7-(3-fluorobenzyl)-6-oxo-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)acetyl)glycinate 9c



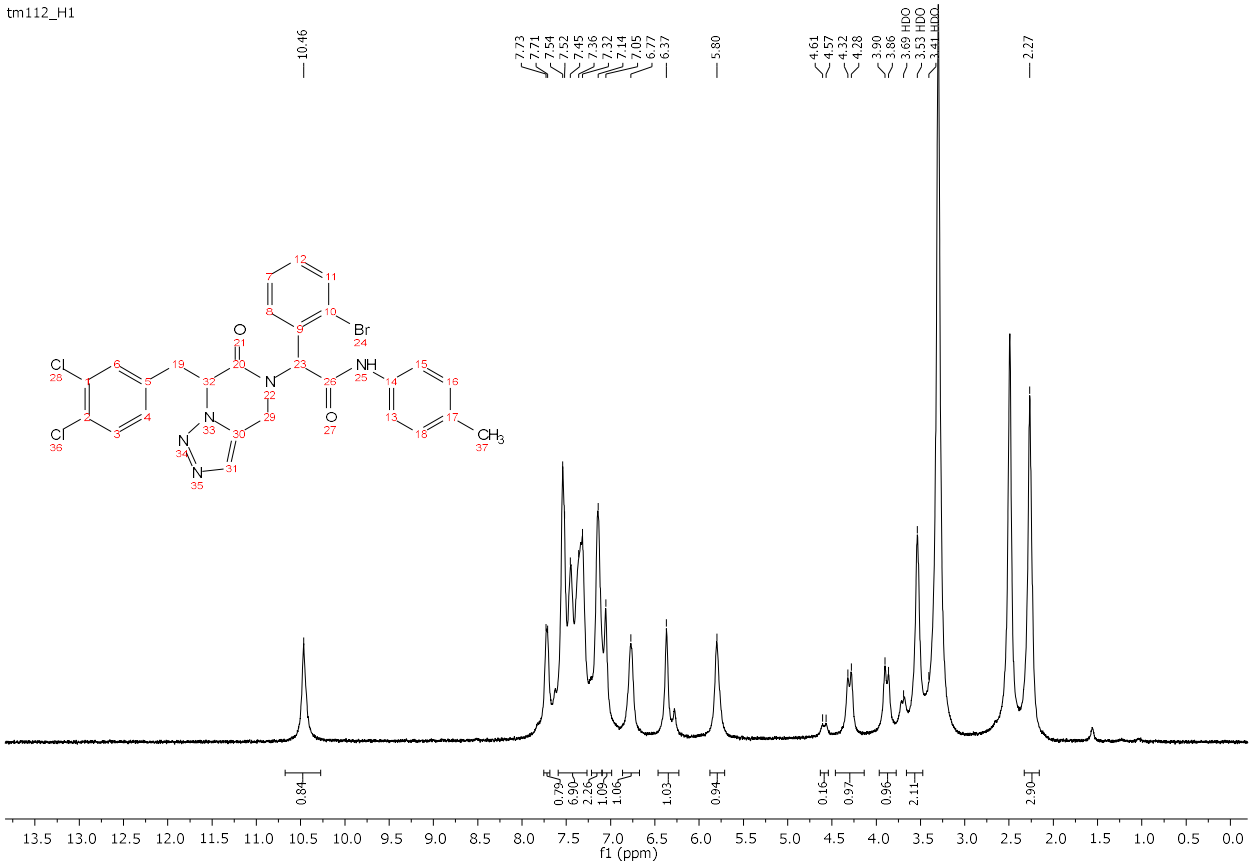


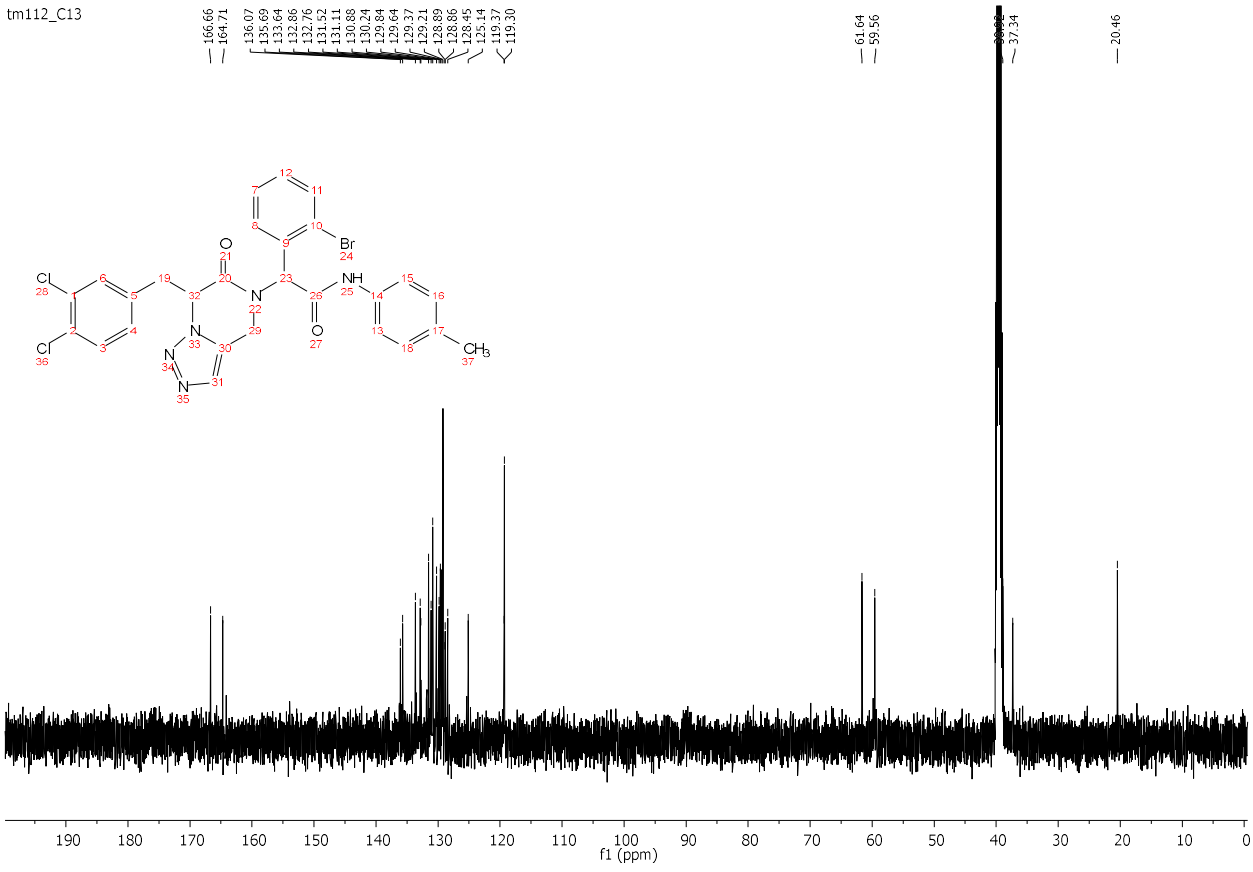
NMR N-Benzyl-2-(7-(3,4-dichlorobenzyl)-6-oxo-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)-2-(4-methoxyphenyl)acetamide 9d



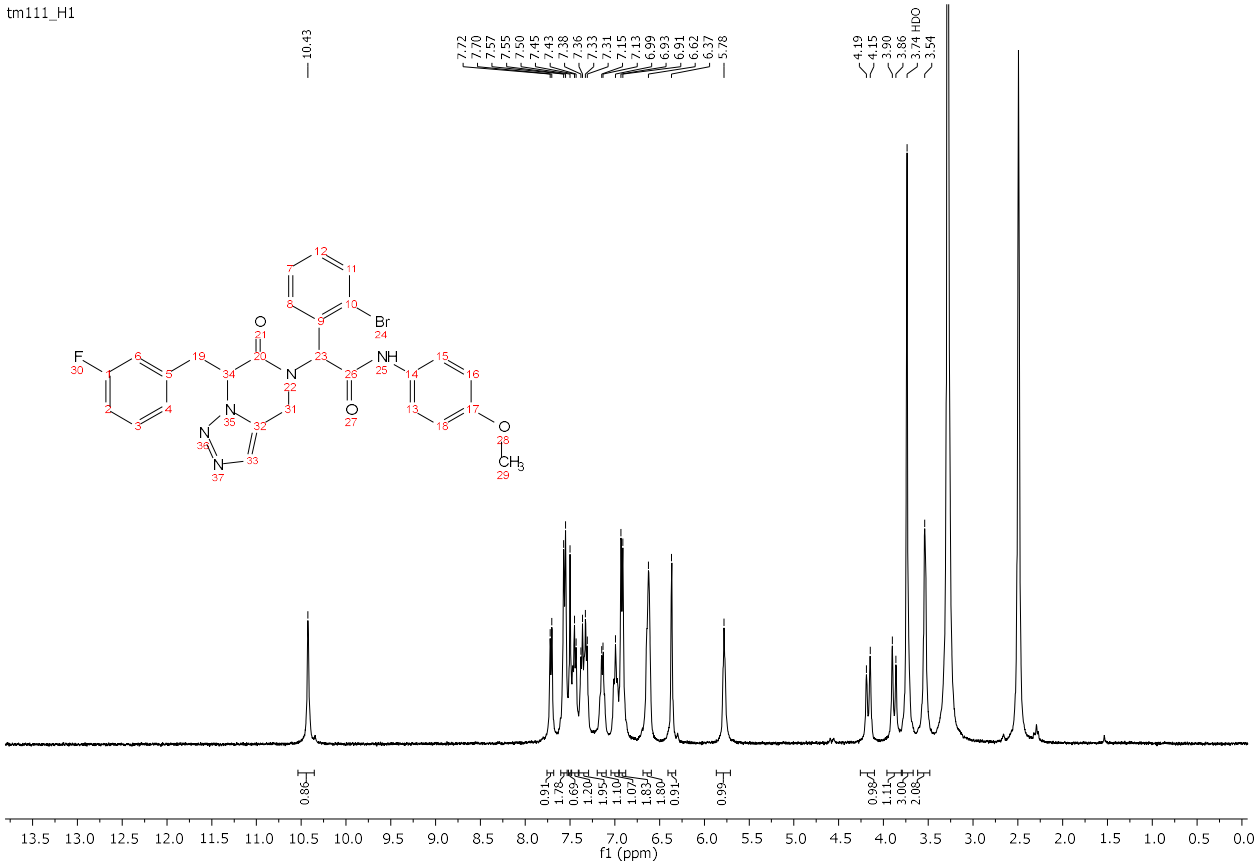


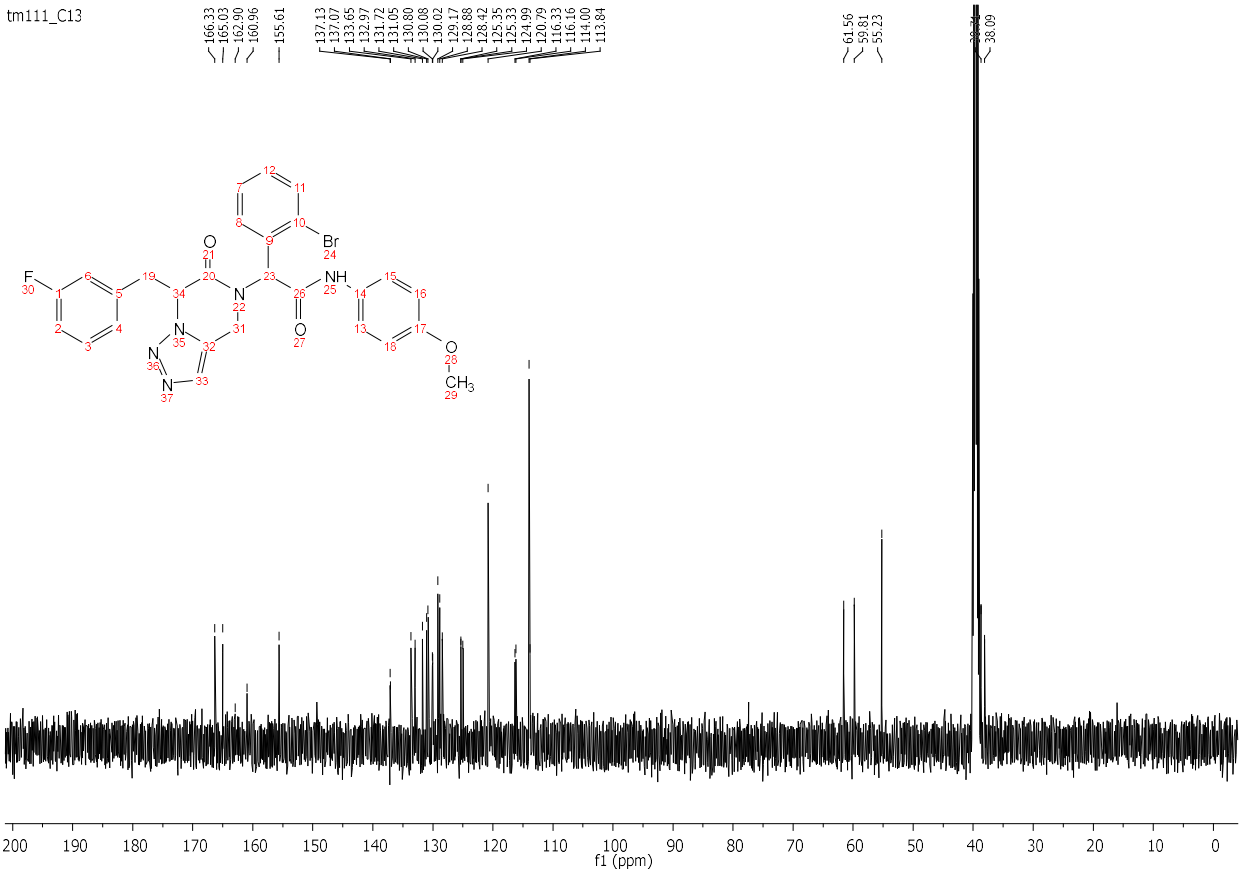
NMR 2-(2-Bromophenyl)-2-(7-(3,4-dichlorobenzyl)-6-oxo-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)-N-(p-tolyl)acetamide 9e



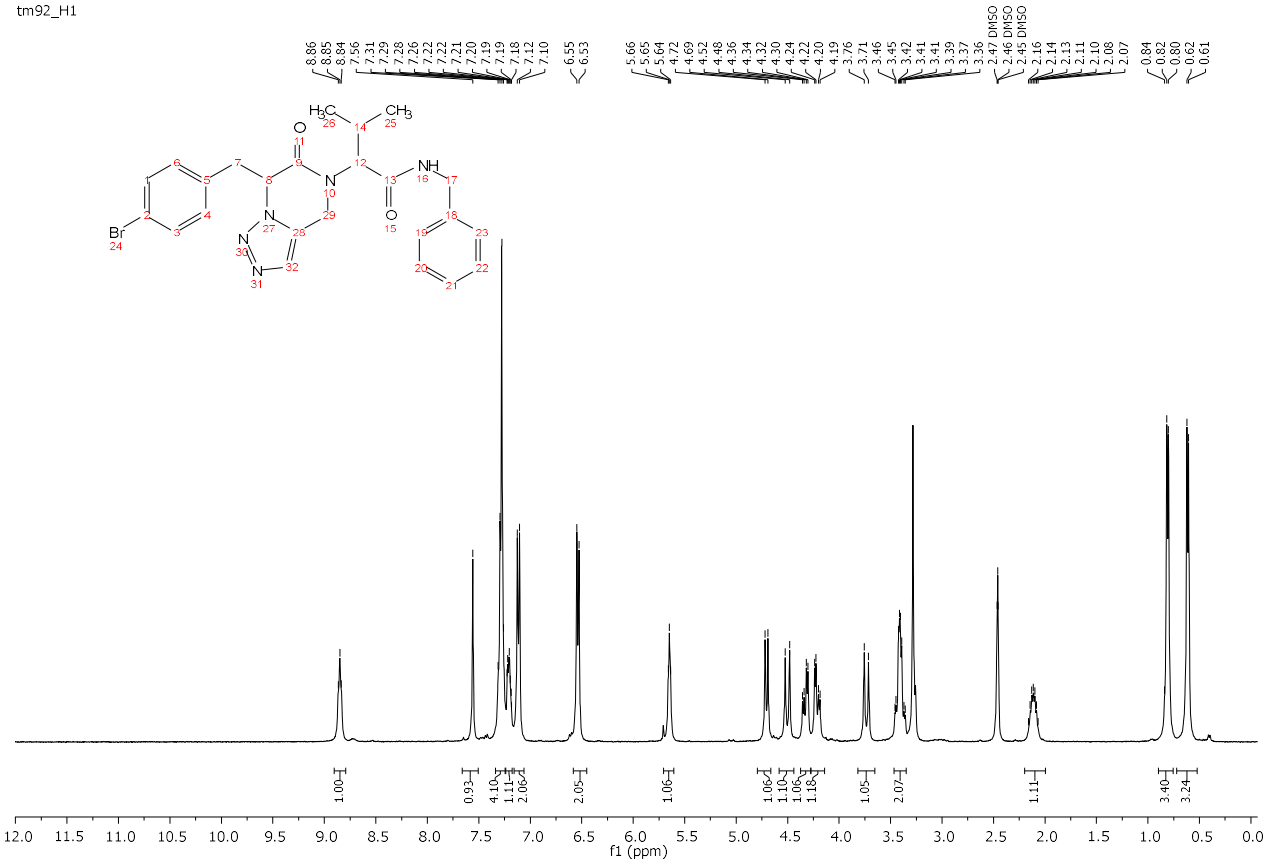


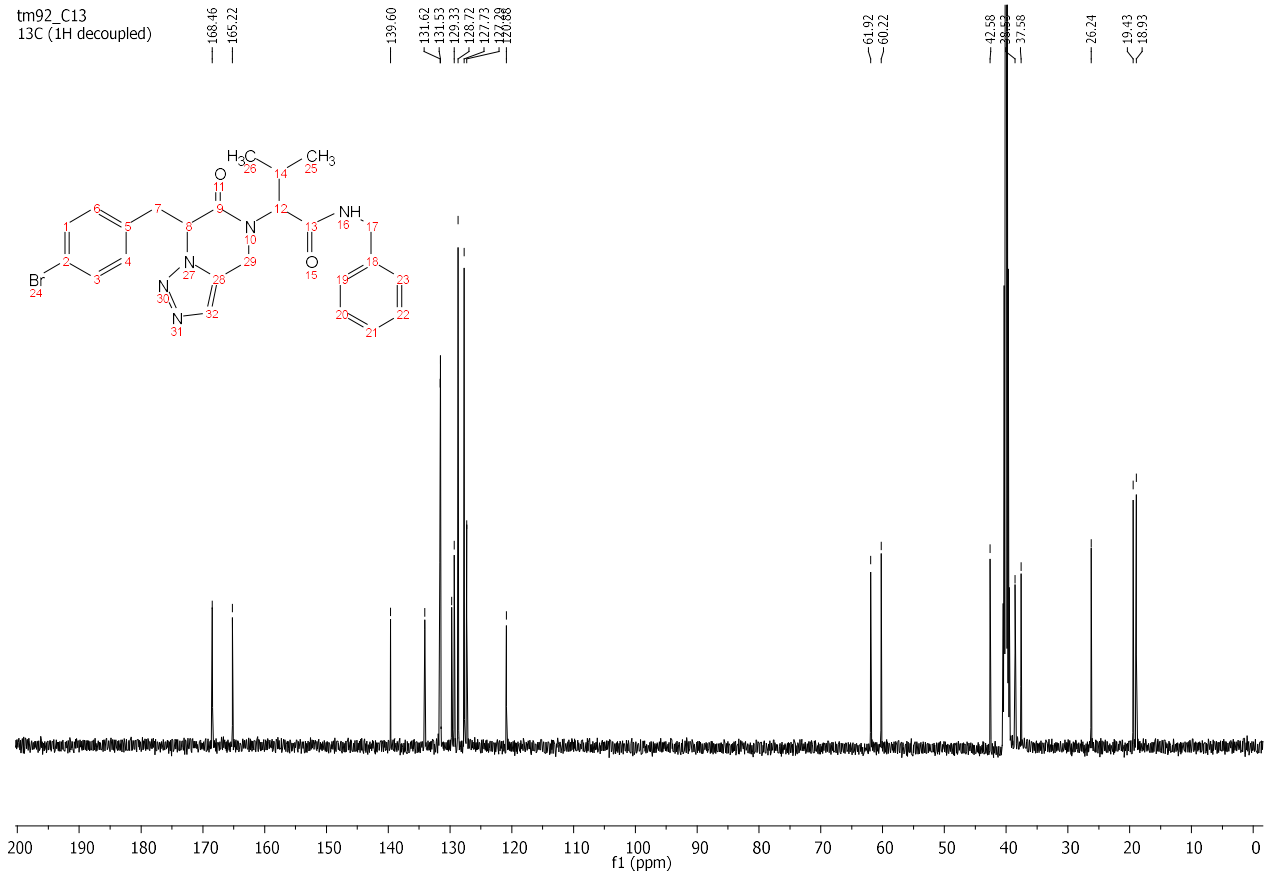
NMR 2-(2-Bromophenyl)-2-(7-(3-fluorobenzyl)-6-oxo-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)-N-(4-methoxyphenyl)acetamide 9f



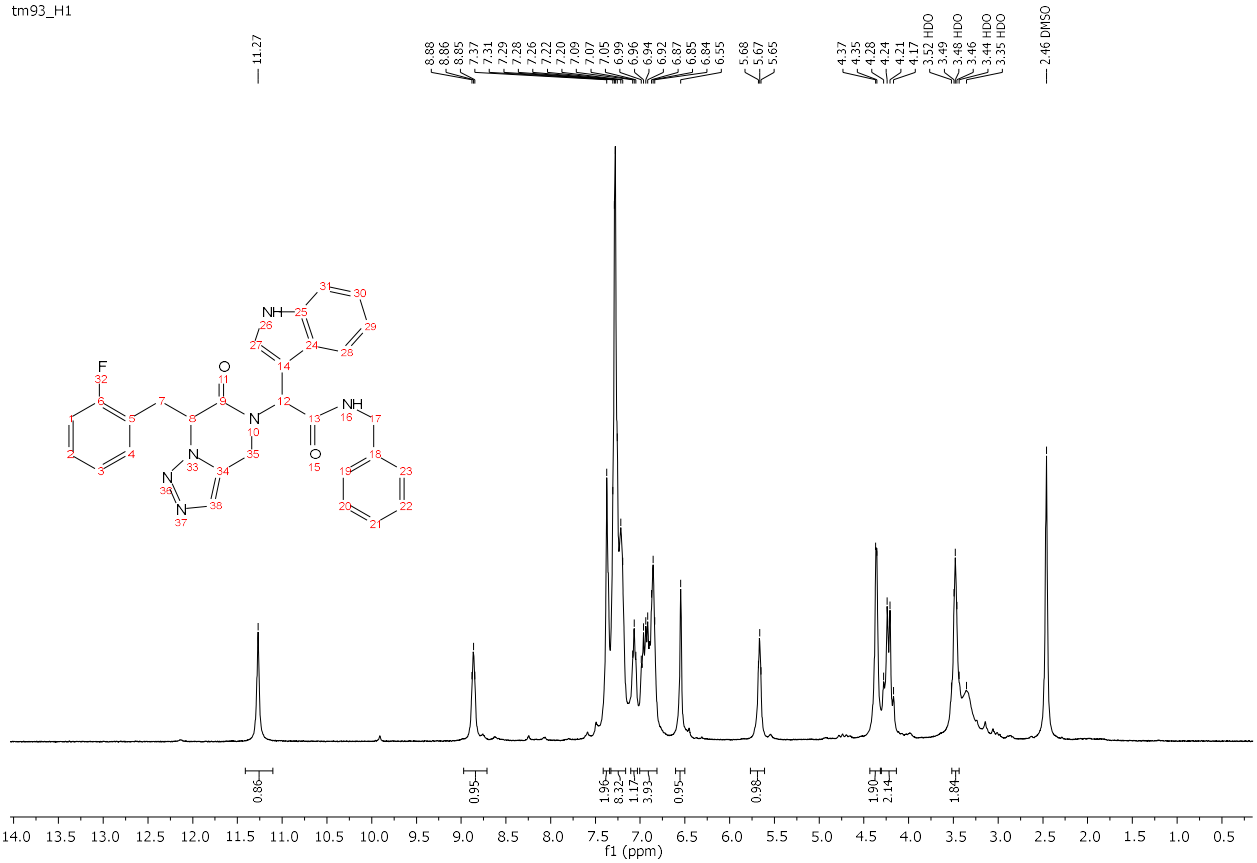


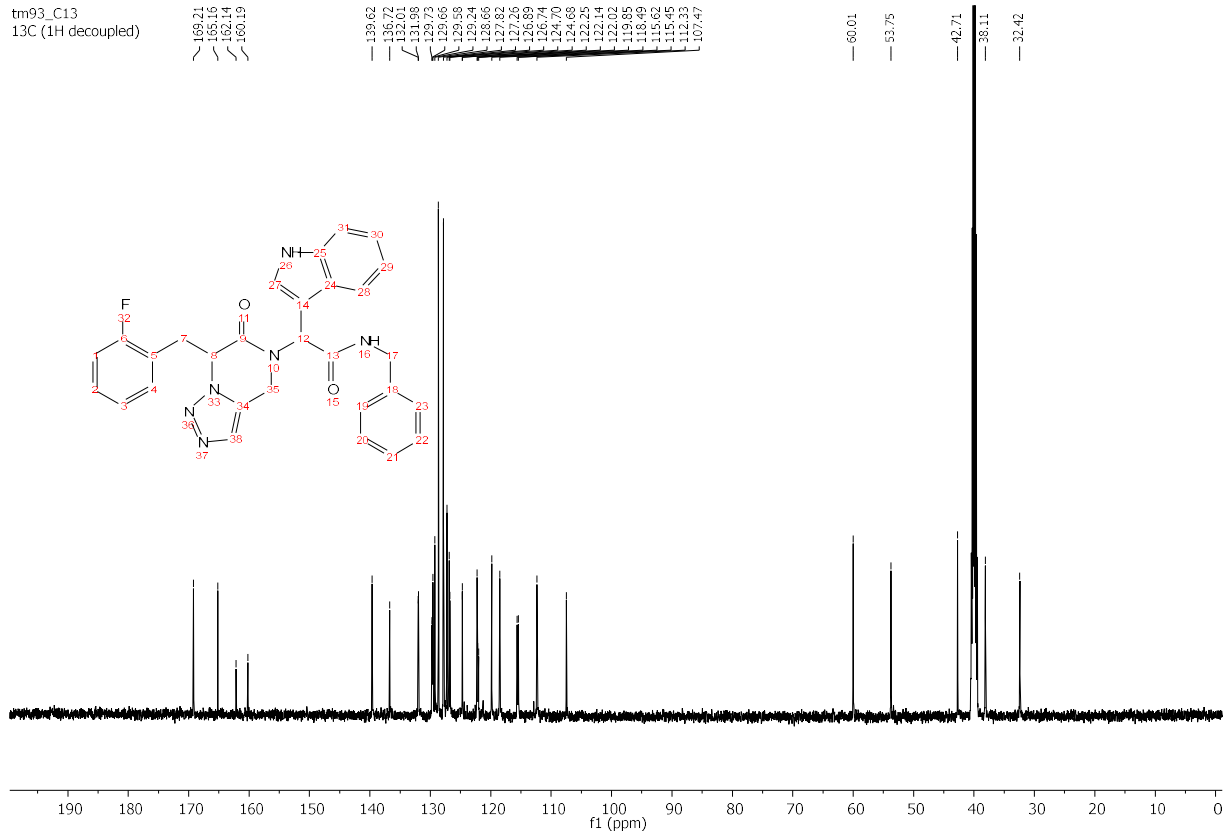
NMR N-benzyl-2-(7-(4-bromobenzyl)-6-oxo-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)-3-methylbutanamide 9g



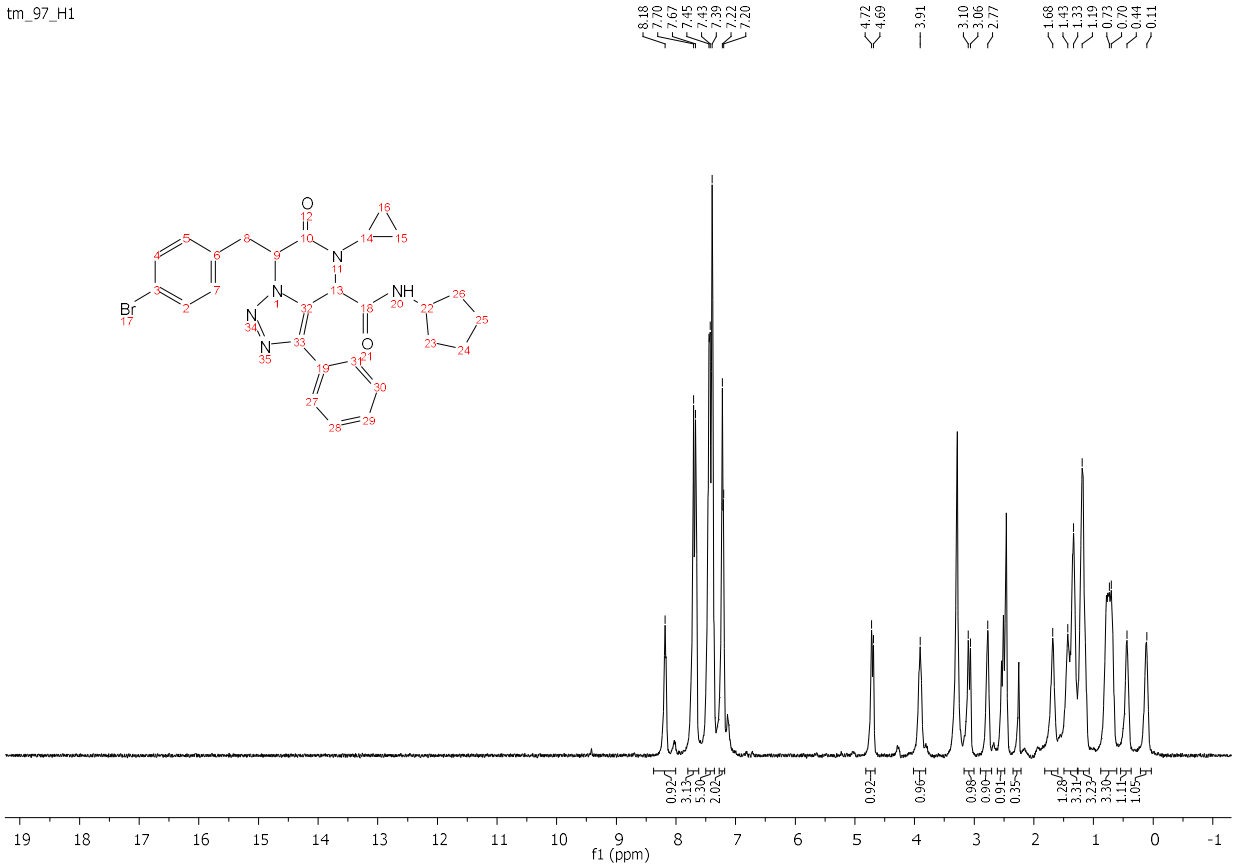


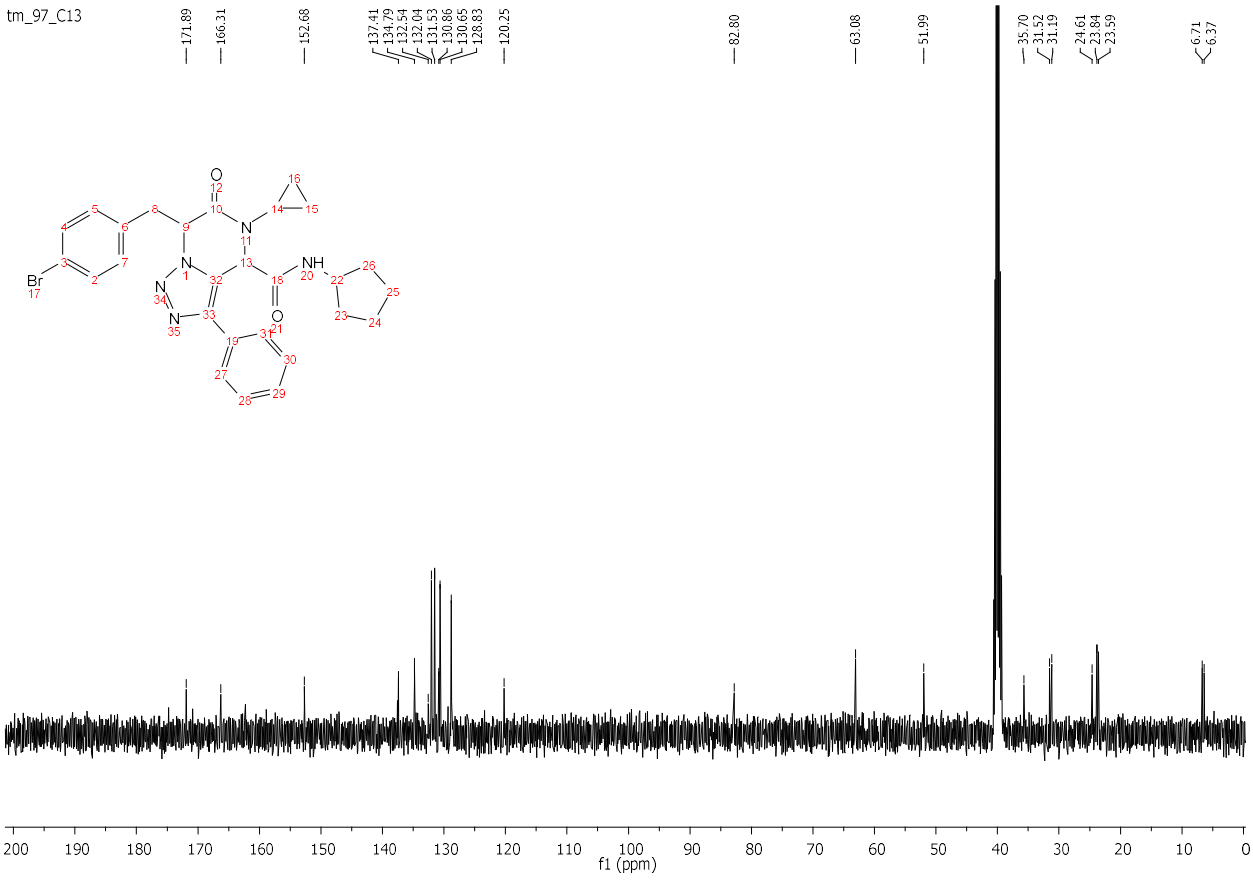
NMR N-benzyl-2-(7-(2-fluorobenzyl)-6-oxo-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)-2-(1H-indol-3-yl)acetamide 9h



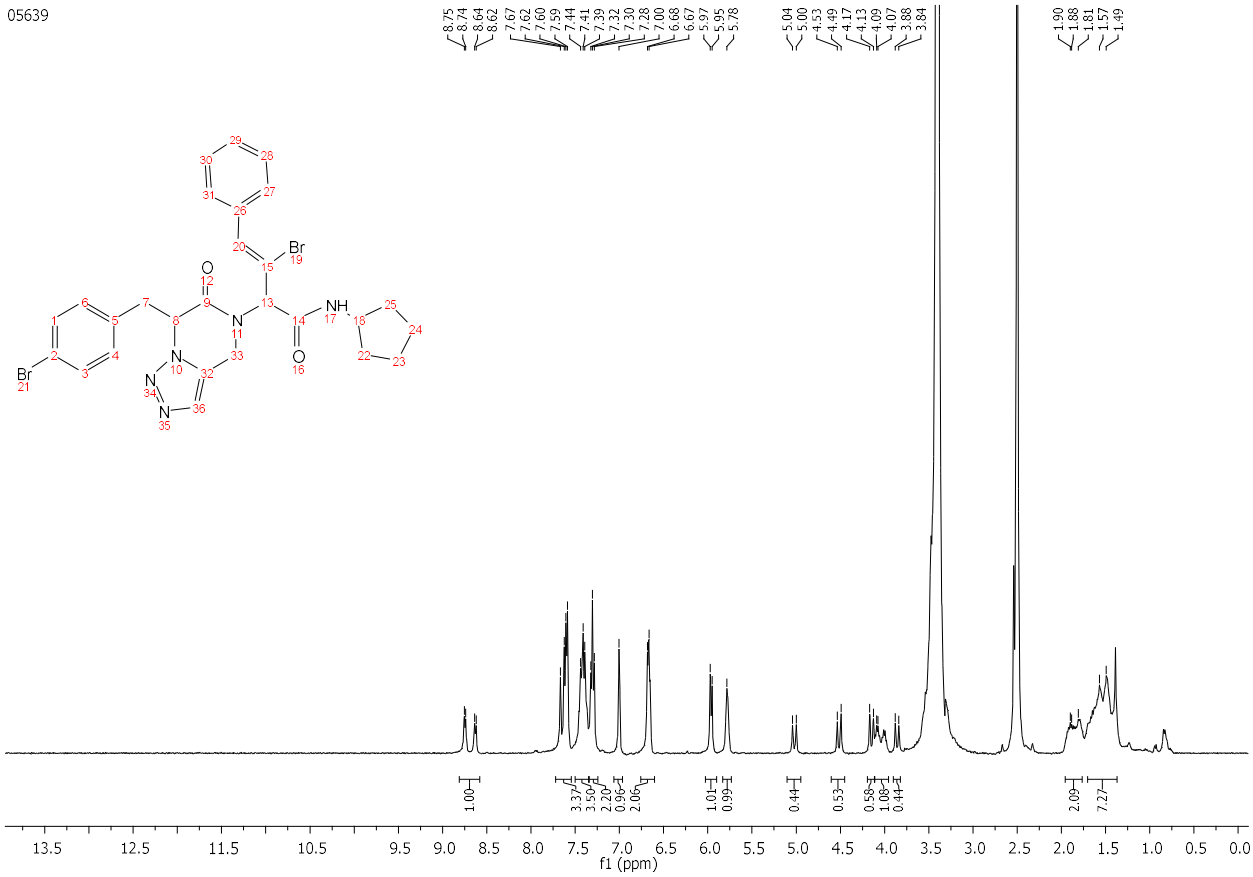


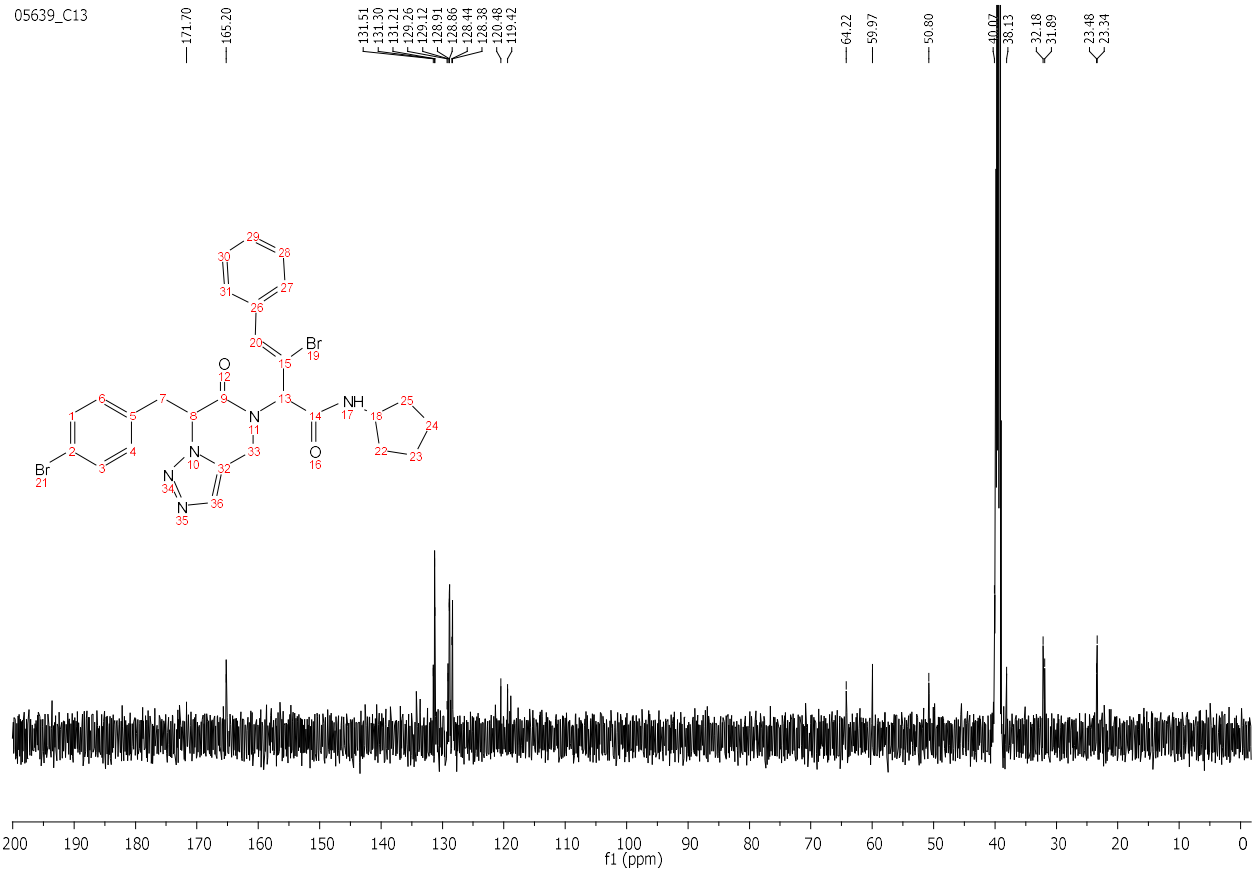
NMR 7-(4-Bromobenzyl)-N-cyclopentyl-5-cyclopropyl-6-oxo-3-phenyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyrazine-4-carboxamide 10





NMR (Z)-3-Bromo-2-(7-(4-bromobenzyl)-6-oxo-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)-N-cyclopentyl-4-phenylbut-3-enamide 11





Overlay of 9g (A) and 9g (B) enantiomers. Atoms of triazole rings are used for overlay fit