- Electronic Supplementary Information (ESI) -

# New tetramethylthiepinium (TMTI) for Copper-Free Click Chemistry

Mathias King, Rachid Baati* and Alain Wagner*

Faculté de Pharmacie
Université de Strasbourg
74 route du Rhin
CS 60024
67401 ILLKIRCH CEDEX
Email: alwag@unistra.fr

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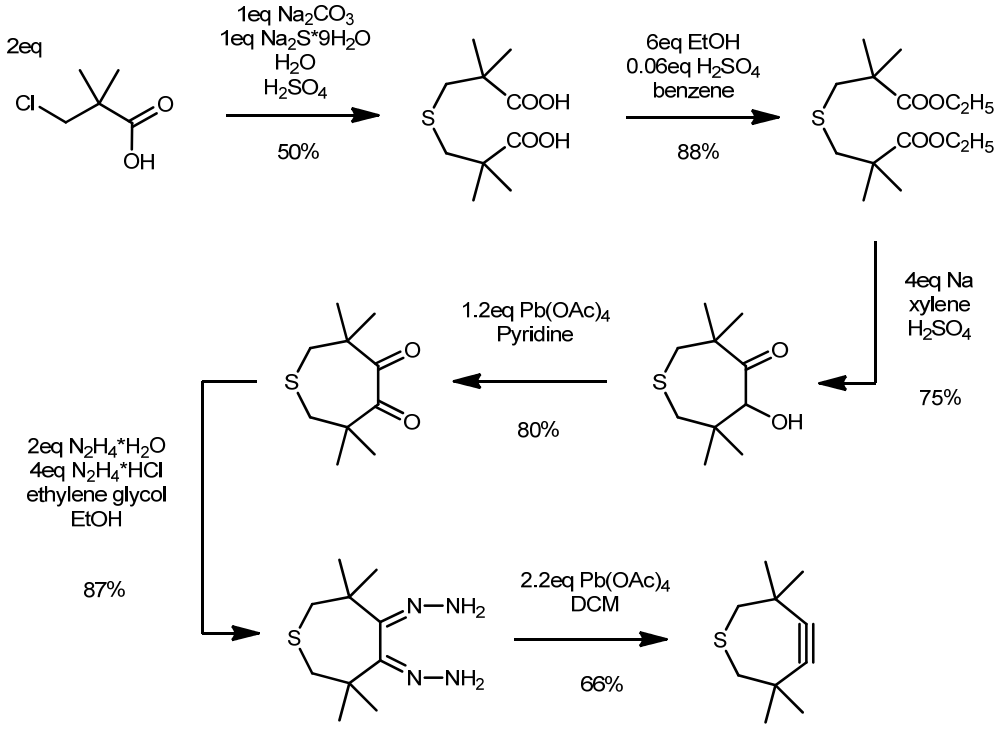
# 1. General

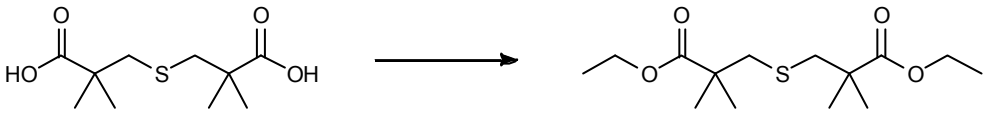
All chemical reagents and solvents were purchased from Sigma-Adrich, Acros, TCI or Alfa-Aesar and were used without further purification unless stated otherwise. $Na_2SO_4$ was used as a drying agent in all cases and solvent was evaporated with a Büchi Rotavapor R-114 equipped with a vacuubrand PC 101 NT.
Analytical thin layer chromatography (TLC) was performed using plates 60F-254 purchased from Merck. $^{1}H$ and $^{13}C$ NMR spectra were recorded at 23°C on Bruker 400 and 500 spectrometers. Recorded shifts are reported in parts per million (δ) and calibrated using residual undeuterated solvent. Data are represented as follows: Chemical shift, mutiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad), coupling constant (*J*, Hz) and integration. High resolution mass spectra (HRMS) were obtained using a Agilent Q-TOF (time of flight) 6520 and low resolution mass spectra using an Agilent MSD 1200 SL (ESI/APCI) with an Agilent HPLC1200 SL.

# 2. TMTH Synthesis reported by Krebs and Kimling[1]



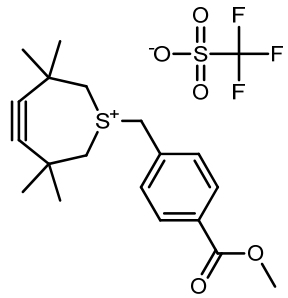
# 3. Experimental Procedures

**Synthesis of Ethyl 3-(3-ethoxy-2,2-dimethyl-3-oxopropyl)sulfanyl-2,2-dimethylpropanoate.**



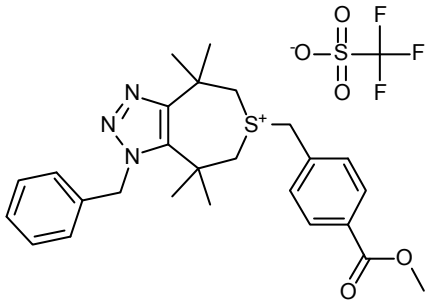

3-(2-carboxy-2-methylpropyl)sulfanyl-2,2-dimethylpropanoic acid (1g, 4.27mmol, 1eq) was suspended in 1,1,1-triethoxyethane (2.35ml, 12.80mmol, 3eq) and ethanol (0.50ml, 8.57mmol, 2eq) was added to increase solubility. The suspension was heated in a microwave oven to 140°C for 10min. Addition of brine (10ml) and extraction with Ethyl acetate (3 x 10ml). The combined organic phases were dried over $Na_2SO_4$, decanted and evaporated to dryness. The crude product was purified via silica gel column chromatography ($CH_2Cl_2$/MeOH 100:0 to 95:5) to yield the desired product as colorless oil (1.08g, 3.72mmol, 87%). $R_f$ = 0.88 in 98:2 $CH_2Cl_2$/MeOH.
Recorded NMR data is in agreement with reported spectral data[2].

**Synthesis of 1-[4-(methoxycarbonyl)benzyl]-3,3,6,6-tetramethyl-4,5-didehydro-2,3,6,7-tetrahydrothiepinium trifluoromethanesulfonate**




3, 3, 6, 6- tetramethylthiacycloheptyne (10 mg, 0.06 mmol, 1 eq) and methyl 4-(bromomethyl)benzoate (27.2 mg, 0.12 mmol, 2 eq) were dissolved in dichloromethane (0.4 ml) and placed under argon atmosphere. Lithium trifluoromethanesulfonate (92.7 mg, 0.59 mmol, 10 eq) was added in water (0.2 ml) and the reaction mixture was stirred at room temperature for 24 h. Water (1.8 ml) was added and the reaction mixture was extracted with dichloromethane (3 x 5 ml). The combined organic phases were dried with $Na_2SO_4$, decanted and evaporated to dryness. The crude product was purified via silica gel column chromatography ($CH_2Cl_2$/MeOH 100:0 to 9:1) to yield the desired product (17.8 mg, 0.04 mmol, 64%). $R_f$ = 0.18 in 95:5 $CH_2Cl_2$/MeOH.
$^1$H NMR ($CDCl_3$, 400MHz): δ 8.10 - 7.98 (m, *J* = 8.0 Hz, 2 H), 7.66 - 7.55 (m, *J* = 8.3 Hz, 2 H), 4.97 (s, 2 H), 4.15 (d, *J* = 12.5 Hz, 2 H), 3.93 (s, 3 H), 3.63 (d, *J* = 12.3 Hz, 2 H), 1.34 (s, 6 H), 1.27 (s, 6 H). $^{13}$C NMR $CDCl_3$, 101MHz): δ 166.0, 132.6, 131.7, 130.8, 130.7, 106.0, 61.5, 52.4, 34.5, 29.7, 26.2, 25.3. HRMS (ESI) calc for $C_{19}H_{25}O_2S^+$ $[M]^+$, 317.15761; found 317.15814.

**Synthesis of 1-benzyl-6-[4-(methoxycarbonyl)benzyl]-4,4,8,8-tetramethyl-4,5,7,8-tetrahydro-1H-thiepino[4,5-d][1,2,3]triazol-6-ium trifluoromethane-sulfonate**

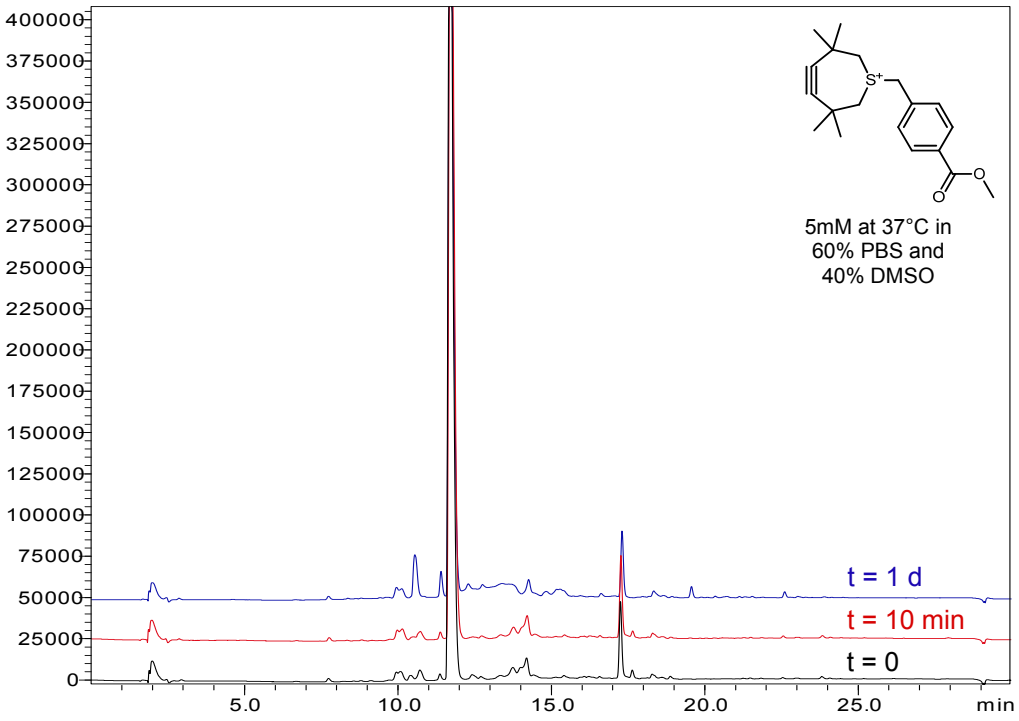


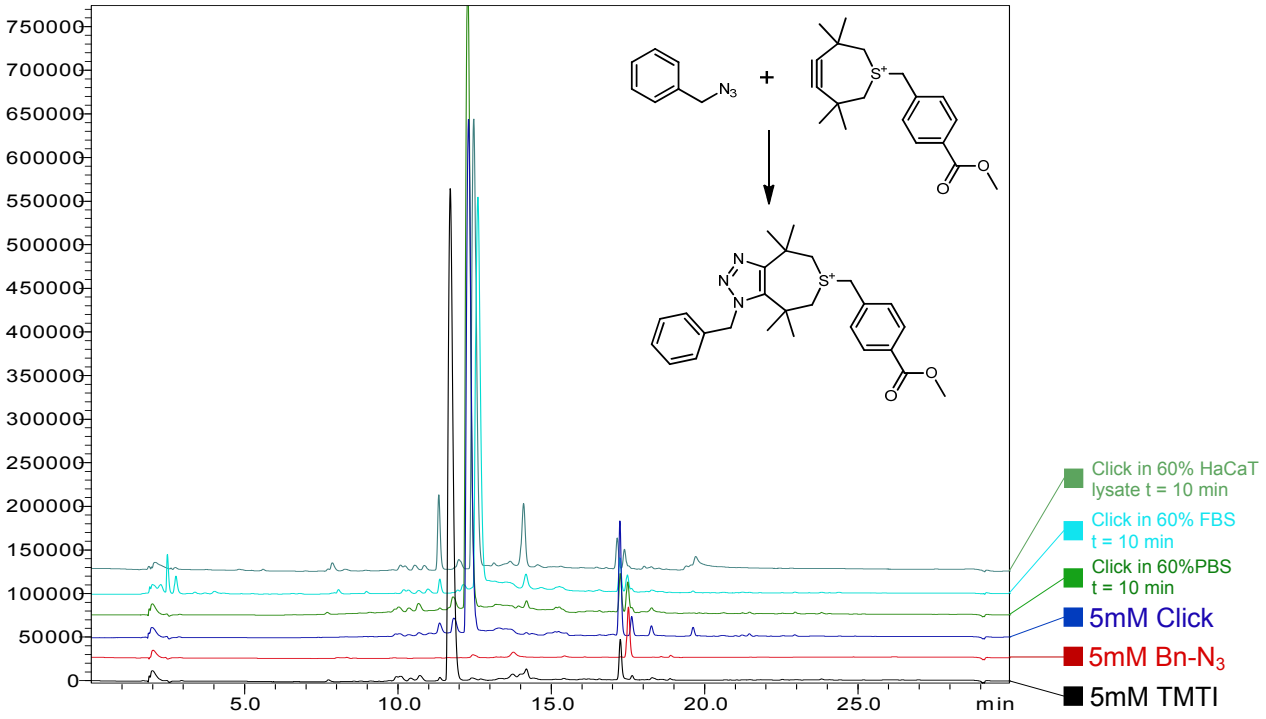
1-[4-(methoxycarbonyl)benzyl]-3,3,6,6-tetramethyl-4,5-didehydro-2,3,6,7-tetrahydro-thiepinium trifluoromethanesulfonate (3.5 mg, 7.5 µmol, 1 eq) is dissolved in acetonitrile (0.25 ml) under argon atmosphere. Benzyl azide (6.0 mg, 45.0 µmol, 6 eq) is added and the reaction mixture is stirred at room temperature for 2 h. The solvent is evaporated under reduced pressure. The crude product is purified via silica gel column chromatography ($CH_2Cl_2$/MeOH 100:0 to 9:1) to yield the desired product (3.3 mg, 5.5 µmol, 37%). $R_f$ = 0.22 in 95:5 $CH_2Cl_2$/MeOH.
$^1$H NMR ($CDCl_3$, 400MHz): δ 8.07 - 7.95 (m, 2 H), 7.59 - 7.46 (m, 2 H), 7.32 - 7.21 (m, 3 H), 6.87 (d, *J* = 6.5 Hz, 2 H), 5.70 (d, *J* = 16.6 Hz, 1 H), 5.61 (d, *J* = 16.6 Hz, 1 H), 5.11 (d, *J* = 13.1 Hz, 1 H), 4.99 (d, *J* = 12.8 Hz, 1 H), 3.87 (s, 3 H), 3.67 (d, *J* = 12.8 Hz, 1 H), 3.43 (d, *J* = 13.1 Hz, 1 H), 3.33 (s, 2 H), 1.73 (s, 3 H), 1.50 (s, 3 H), 1.32 (s, 3 H), 1.12 (s, 3 H). $^{13}$C NMR $CDCl_3$, 101MHz): δ 166.0, 147.4, 136.4, 135.2, 132.3, 131.2, 131.0, 130.9, 129.2, 128.5, 126.3, 55.3, 53.4, 52.6, 50.9, 46.1, 36.3, 35.1, 31.2, 30.5, 29.3, 27.5. HRMS (ESI) calc for $C_{26}H_{32}N_3O_2S^+$ $[M]^+$, 450.22103; found 450.2205.

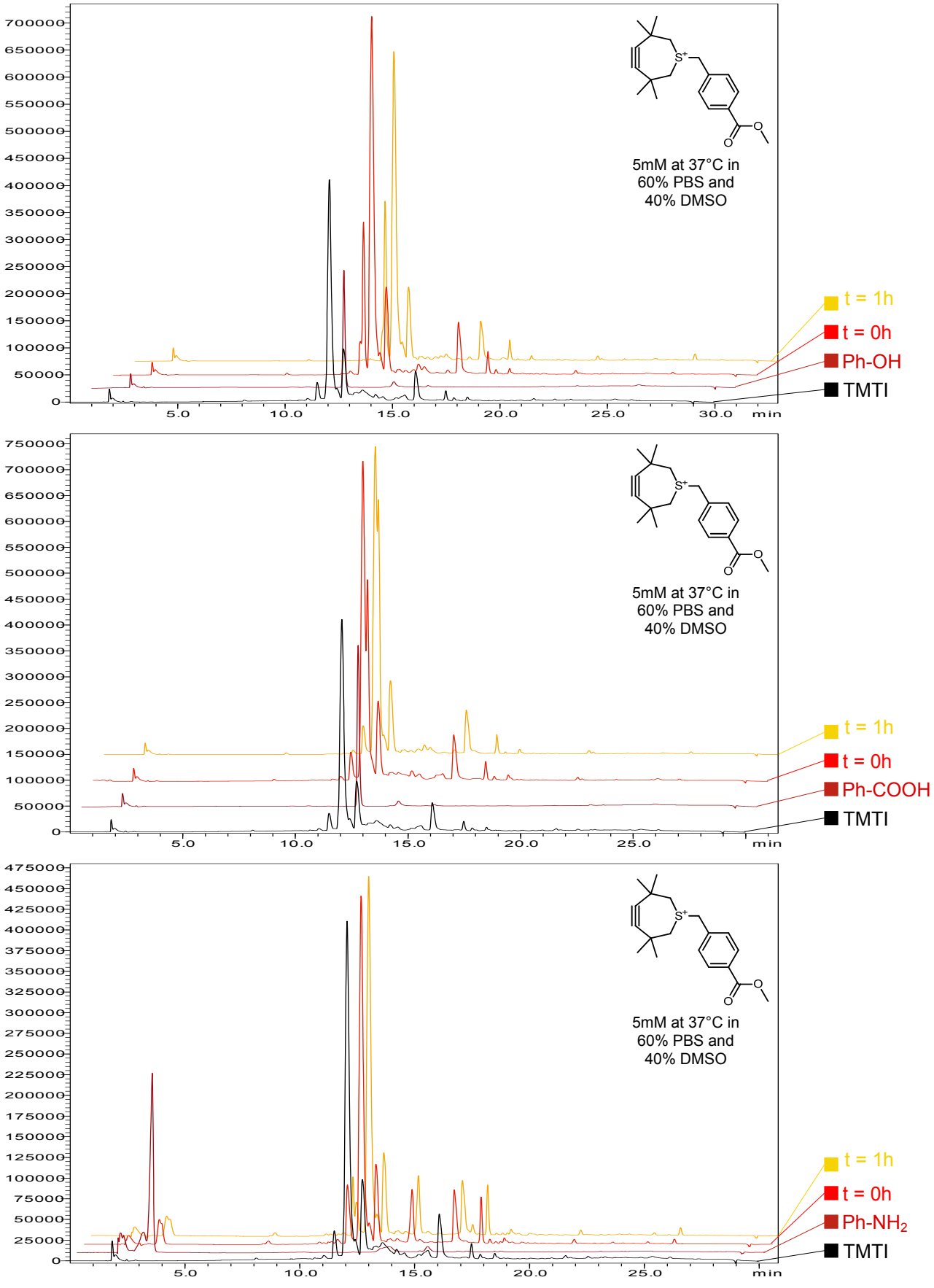
(1) Krebs, A.; Kimling, H. *Tetrahedron Letters* **1970**, 761-764.

(2) Feeder, N.; Ginnelly, M. J.; Jones, R. V. H.; O'Sullivan, S.; Warren, S. *Tetrahedron Letters* **1994**, *35*, 9095-9098.

# 4. HPLC Chromatograms and NMR Results

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40% DMSO
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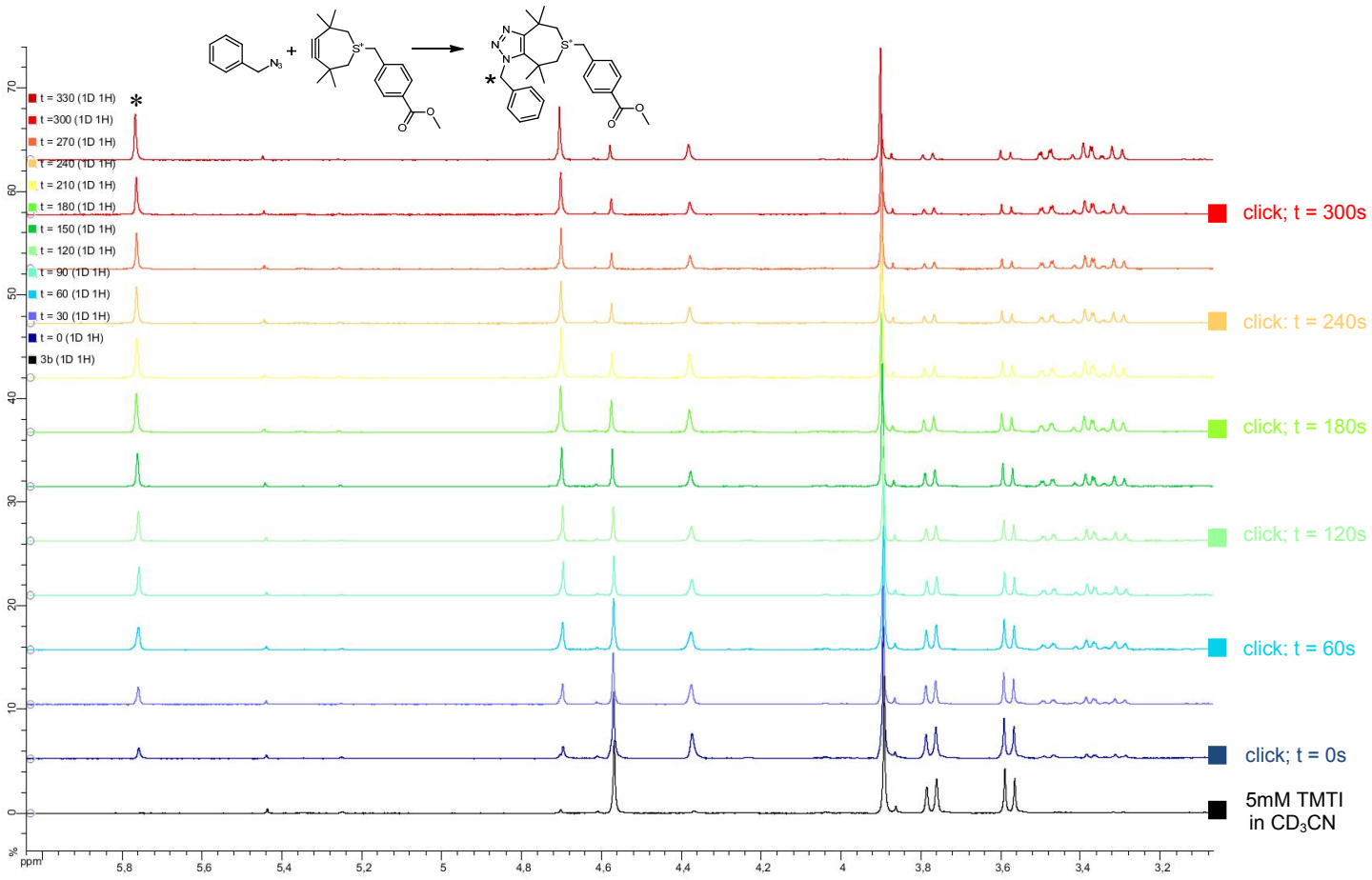
t = 0h
Ph-OH
TMTI
min
5mM at 37°C in
60% PBS and
40% DMSO
t = 1h
t = 0h
Ph-COOH
TMTI
min
5mM at 37°C in
60% PBS and
40% DMSO
t = 1h
t = 0h
Ph-NH2
TMTI
min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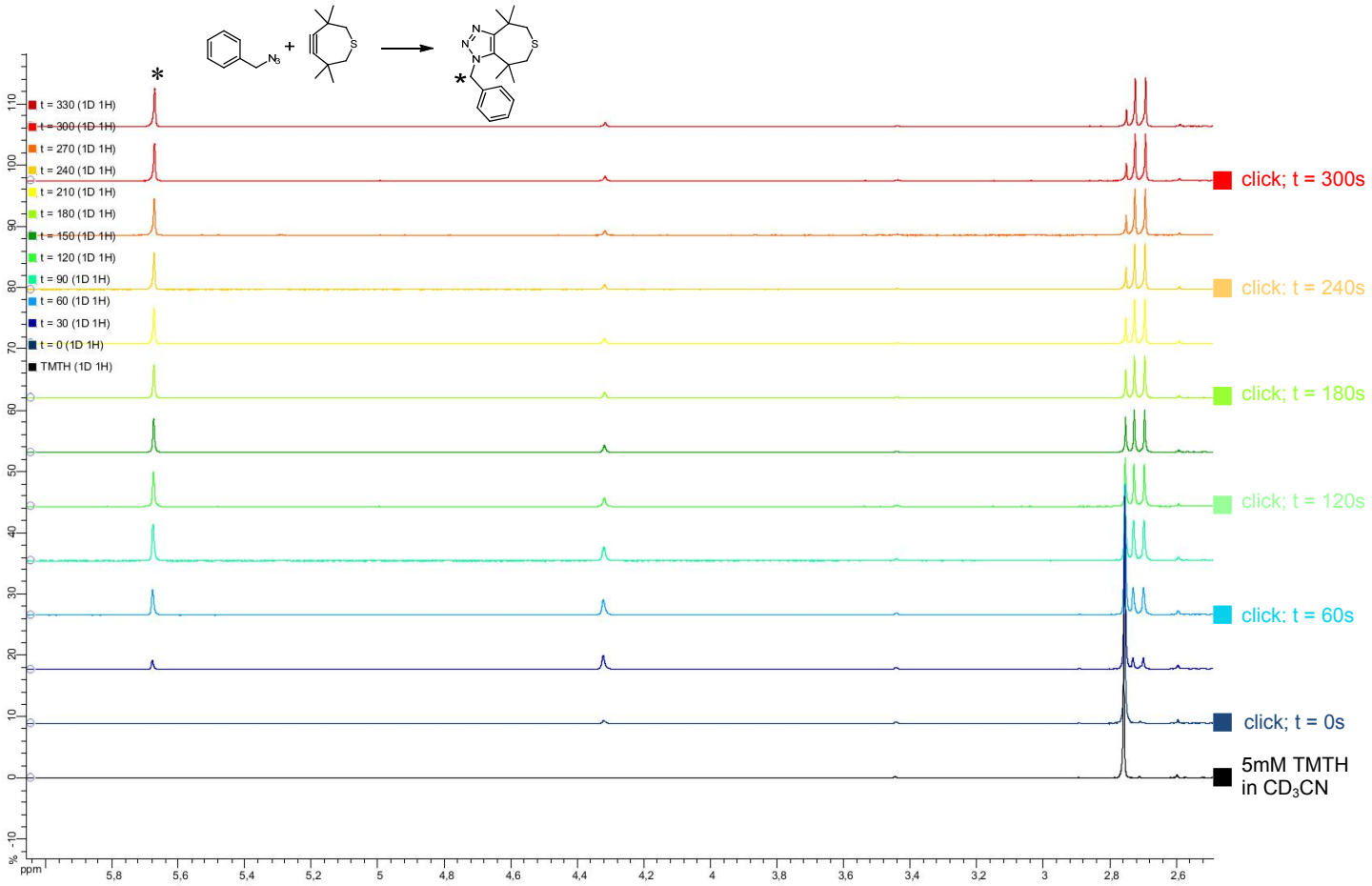
t =300 (1D 1H)
t = 270 (1D 1H)
t = 240 (1D 1H)
t = 210 (1D 1H)
t = 180 (1D 1H)
t = 150 (1D 1H)
t = 120 (1D 1H)
t = 90 (1D 1H)
t = 60 (1D 1H)
t = 30 (1D 1H)
t = 0 (1D 1H)
3b (1D 1H)
click; t = 300s
click; t = 240s
click; t = 180s
click; t = 120s
click; t = 60s
click; t = 0s
5mM TMTI in CD3CN
ppm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t = 270 (1D 1H)
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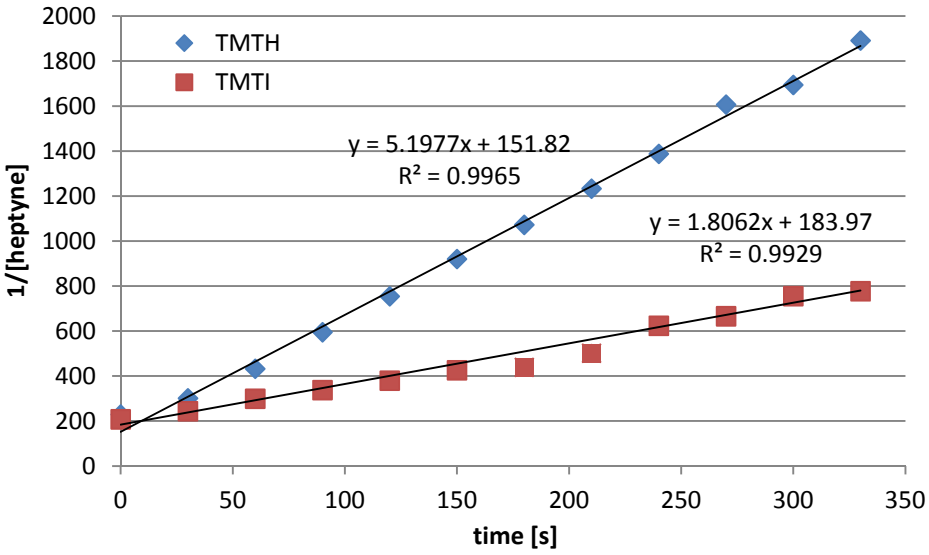
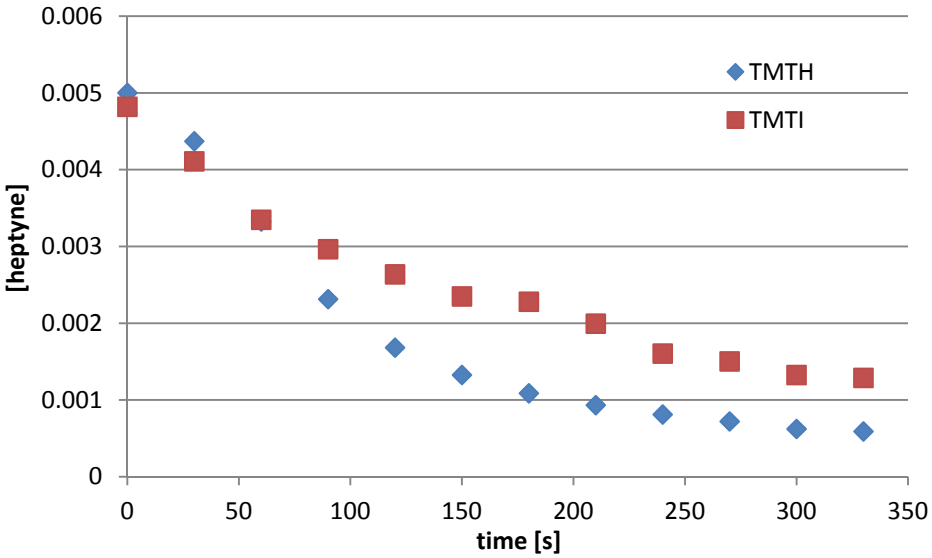
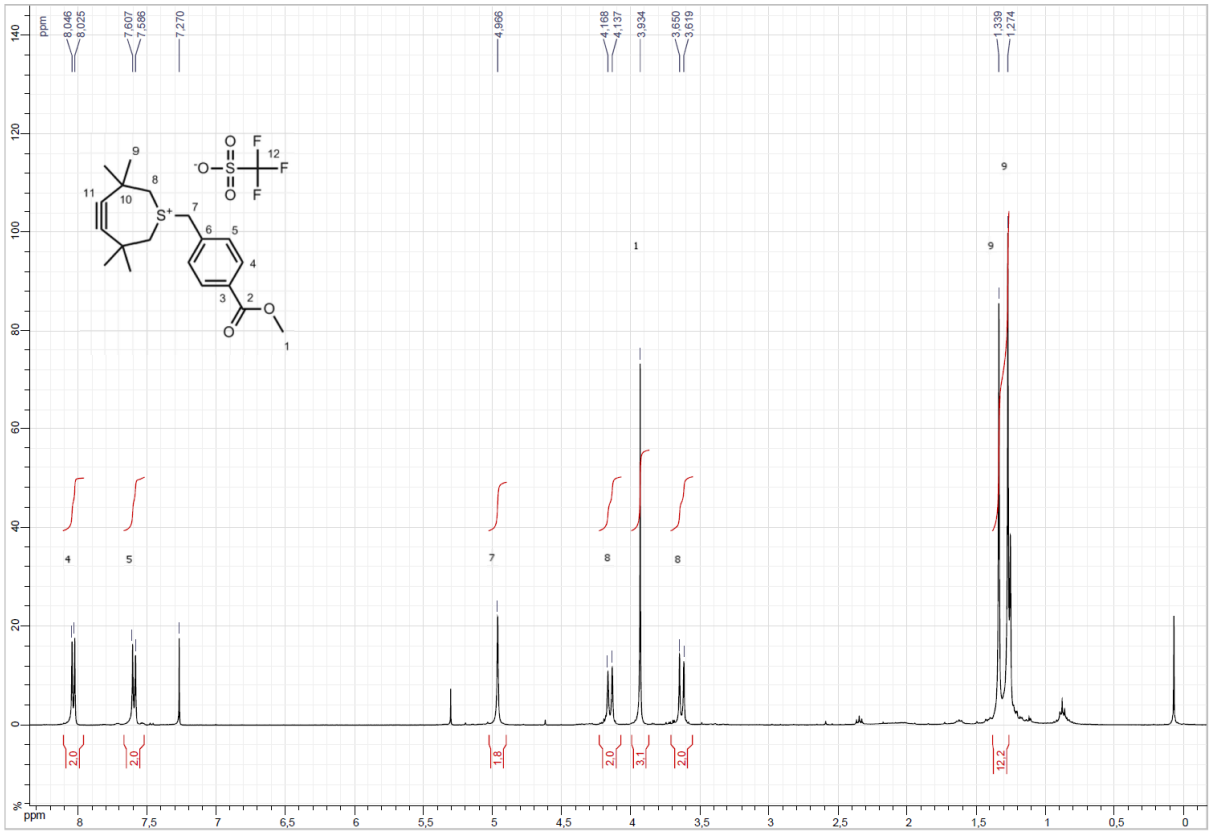
t = 180 (1D 1H)
t = 150 (1D 1H)
t = 120 (1D 1H)
t = 90 (1D 1H)
t = 60 (1D 1H)
t = 30 (1D 1H)
t = 0 (1D 1H)
TMTH (1D 1H)
click; t = 300s
click; t = 240s
click; t = 180s
click; t = 120s
click; t = 60s
click; t = 0s
5mM TMTH in CD3CN
ppm

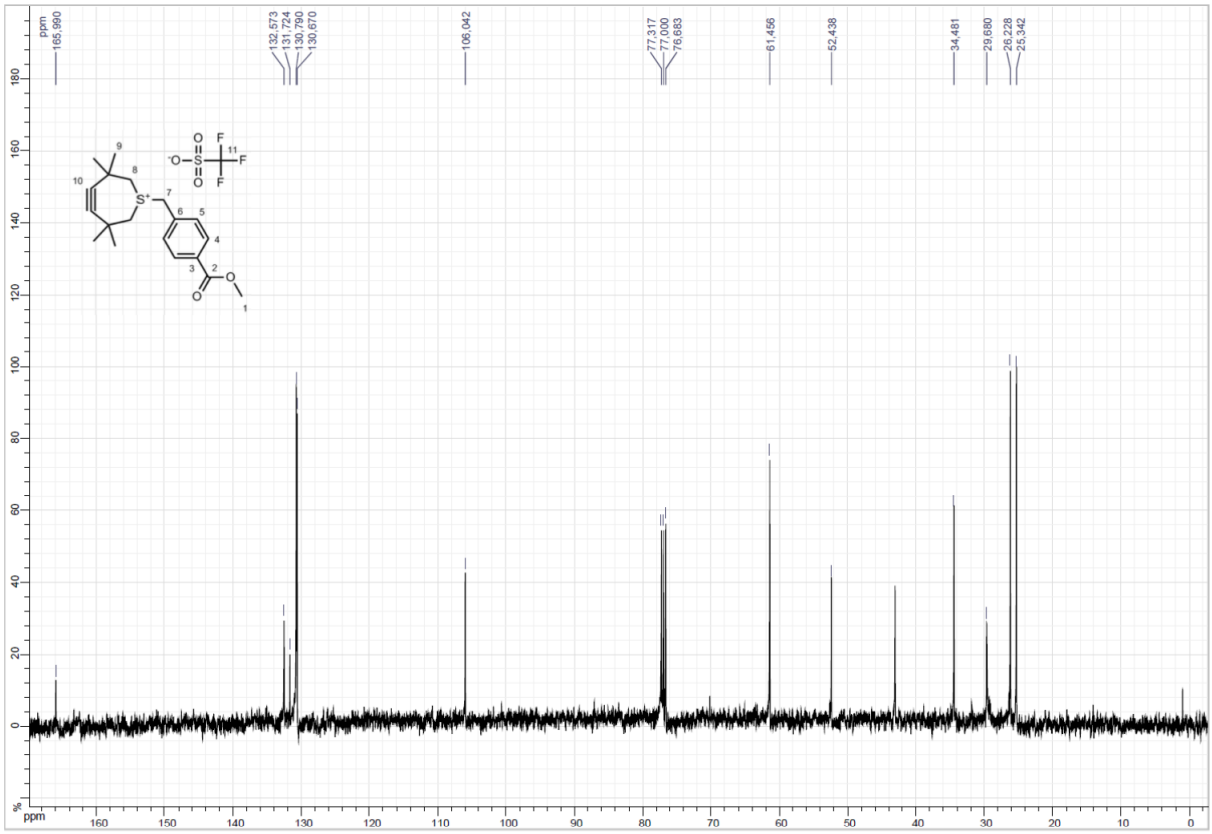
Kinetic recorded with benzyl azide via NMR and integration of the benzyl signal

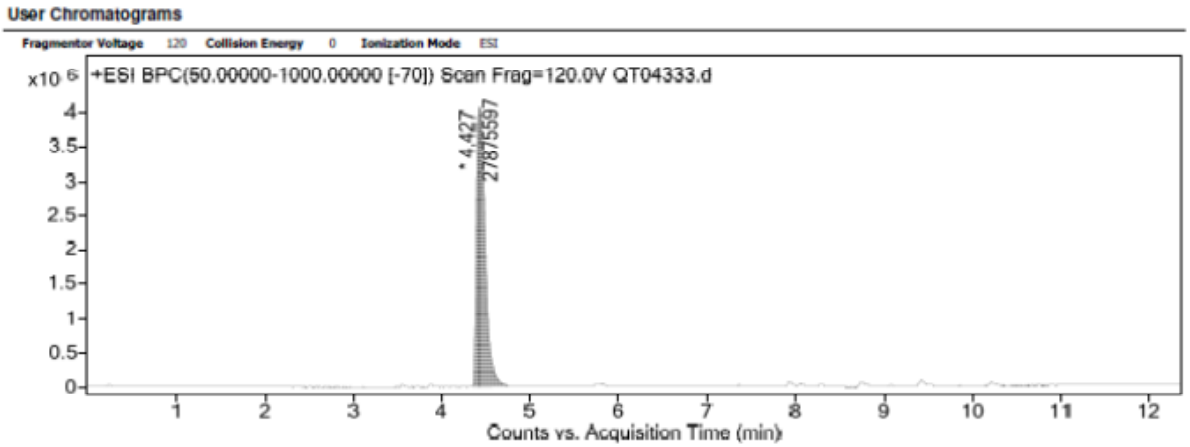


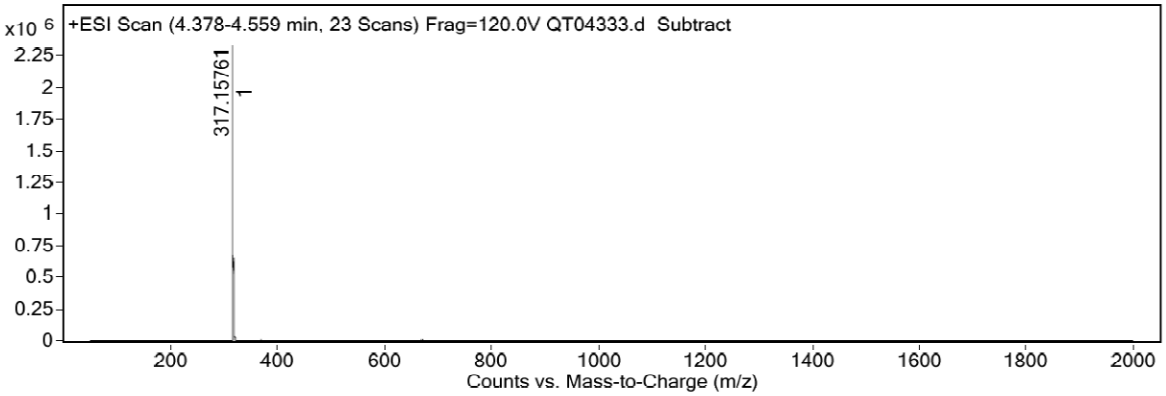



# 5. Analytical results



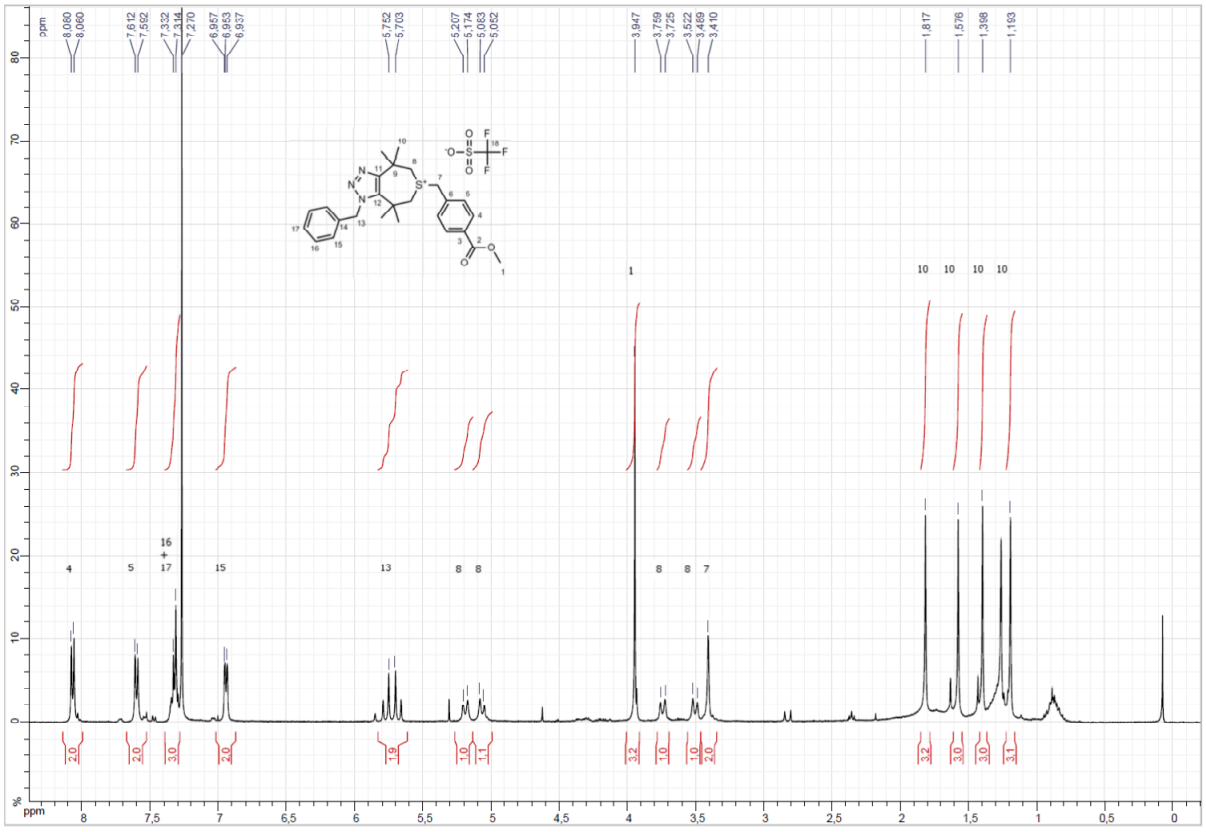



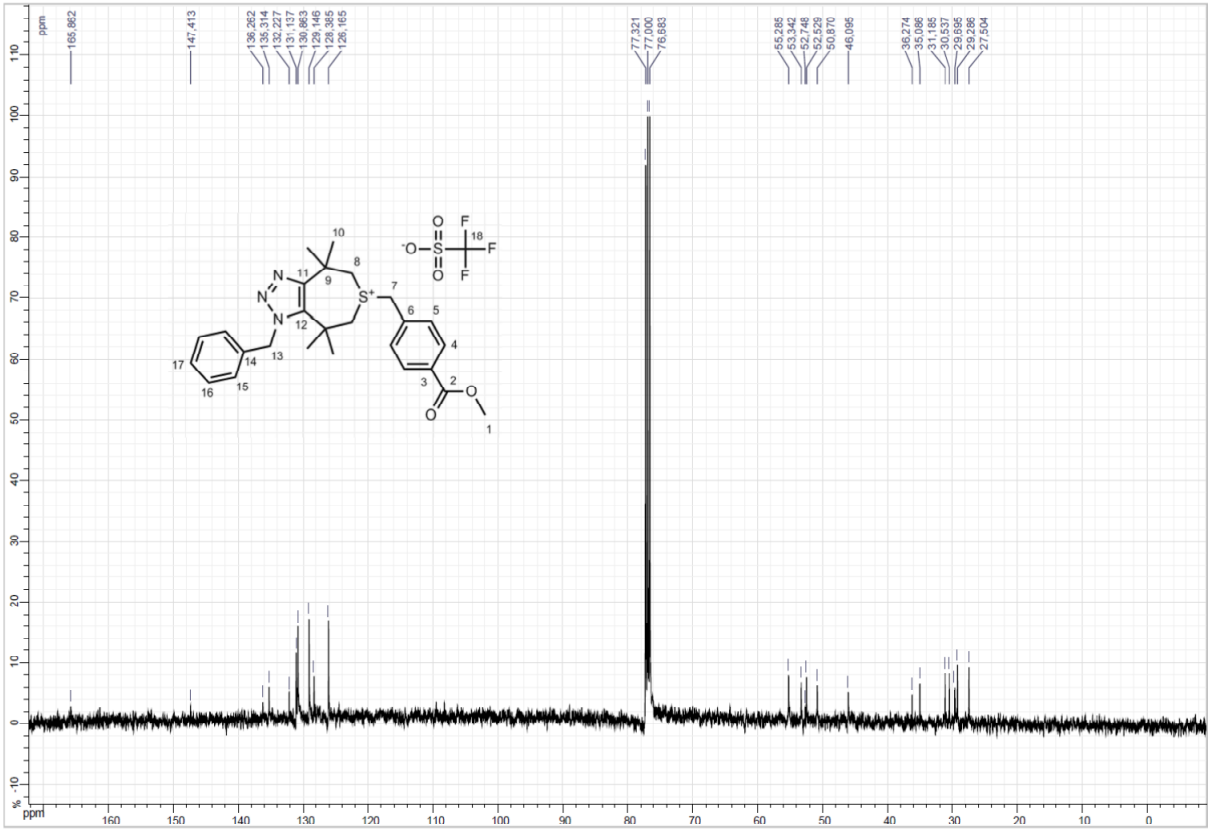


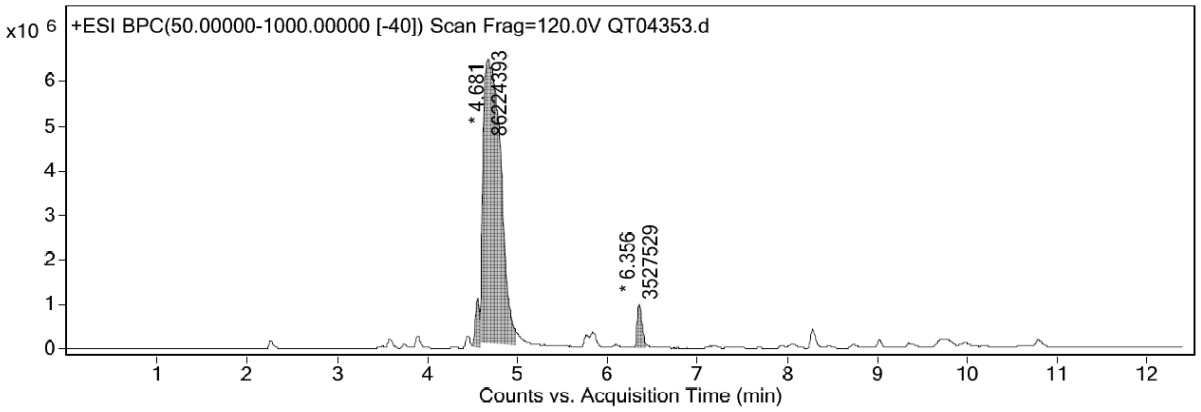



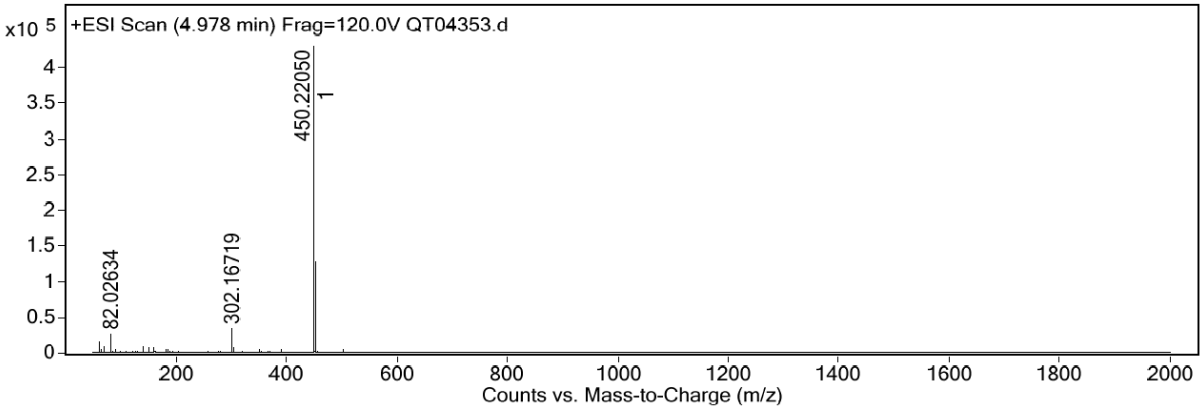

**Formula Calculator Results**

| Formula | Best | Mass | Tgt Mass | Diff (ppm) | Mz | Ion Species | Score |
|---|---|---|---|---|---|---|---|
| C19 H25 O2 S | TRUE | 317.15814 | 317.15753 | -1.95 | 317.15761 | C19 H25 O2 S | 92.48 |
| C12 H25 N6 S2 | | 317.15817 | 317.15821 | 0.14 | 317.15761 | C12 H25 N6 S2 | 82.31 |
| C12 H17 N10 O | | 317.15817 | 317.15868 | 1.62 | 317.15761 | C12 H17 N10 O | 81.06 |
| C11 H21 N6 O5 | | 317.15816 | 317.15734 | -2.56 | 317.15761 | C11 H21 N6 O5 | 76.46 |
| C15 H25 O7 | | 317.15813 | 317.16003 | 5.97 | 317.15761 | C15 H25 O7 | 68.77 |
| C16 H29 O2 S2 | | 317.15815 | 317.1609 | 8.66 | 317.15761 | C16 H29 O2 S2 | 66.8 |
| C15 H21 N6 S | | 317.15816 | 317.15484 | -10.47 | 317.15761 | C15 H21 N6 S | 63.49 |
| C10 H25 N2 O9 | | 317.15814 | 317.15601 | -6.74 | 317.15761 | C10 H25 N2 O9 | 61.95 |
| C8 H25 N6 O5 S | | 317.15817 | 317.16071 | 8.02 | 317.15761 | C8 H25 N6 O5 S | 59.46 |
| C16 H21 N4 O3 | | 317.15814 | 317.16137 | 10.16 | 317.15761 | C16 H21 N4 O3 | 58.11 |








**Formula Calculator Results**

| Formula | Best | Mass | Tgt Mass | Diff (ppm) | Mz | Ion Species | Score |
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| C26 H32 N3 O2 S | TRUE | 450.22103 | 450.22152 | 1.09 | 450.2205 | C26 H32 N3 O2 S | 98.88 |
| C19 H32 N9 S2 | | 450.22105 | 450.22221 | 2.57 | 450.2205 | C19 H32 N9 S2 | 93.75 |
| C18 H36 N5 O4 S2 | | 450.22104 | 450.22087 | -0.38 | 450.2205 | C18 H36 N5 O4 S2 | 93.42 |
| C22 H28 N9 S | | 450.22105 | 450.21884 | -4.9 | 450.2205 | C22 H28 N9 S | 92.4 |
| C18 H28 N9 O5 | | 450.22104 | 450.22134 | 0.66 | 450.2205 | C18 H28 N9 O5 | 90.49 |
| C17 H32 N5 O9 | | 450.22103 | 450.22 | -2.29 | 450.2205 | C17 H32 N5 O9 | 86.51 |
| C34 H28 N | | 450.22102 | 450.22217 | 2.56 | 450.2205 | C34 H28 N | 83.7 |
| C14 H36 N5 O9 S | | 450.22104 | 450.22337 | 5.18 | 450.2205 | C14 H36 N5 O9 S | 82.14 |
| C21 H32 N5 O4 S | | 450.22104 | 450.2175 | -7.86 | 450.2205 | C21 H32 N5 O4 S | 82.06 |
| C22 H32 N3 O7 | | 450.22103 | 450.22403 | 6.66 | 450.2205 | C22 H32 N3 O7 | 78.59 |