Inhibition of human CYP3A4 by rationally designed ritonavir-like compounds: Impact and interplay of the side group functionalities

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SUPPORTING INFORMATION

Synthesis of CYP3A4 inhibitors, mass spectrometry and NMR data

^{1}H NMR spectra were recorded on Bruker DRX 400 MHz or DRX 500 MHz spectrometer. Chemical shifts (δ) are reported in ppm and J-values in hertz for the compound's solution in D_2O or deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as internal reference. All NMR data were processed using TopSpin 3.5 software. High resolution mass spectrometry data (HRMS) were obtained via ESI LC-TOF on a Waters (Micromass) LCT Premier spectrometer (Waters), with PEG as the calibrant. Thin layer chromatography (TLC) was performed using EMD Millipore silica gel 60 F_{254} aluminum plates. Separation by column chromatography was performed using Fisher silica gel 60 (230-400 mesh). Where applicable, optical rotation was measured with a JASCO P-1010 polarimeter. All reactions were conducted with commercially available reagents (Aldrich, Thermo-Fisher, Alfa Aesar, Acros, Oakwood, Millipore). Anhydrous solvents were acquired through a solvent purification system (Inert PureSolv and JC Meyer systems) or purified according to standard procedures.

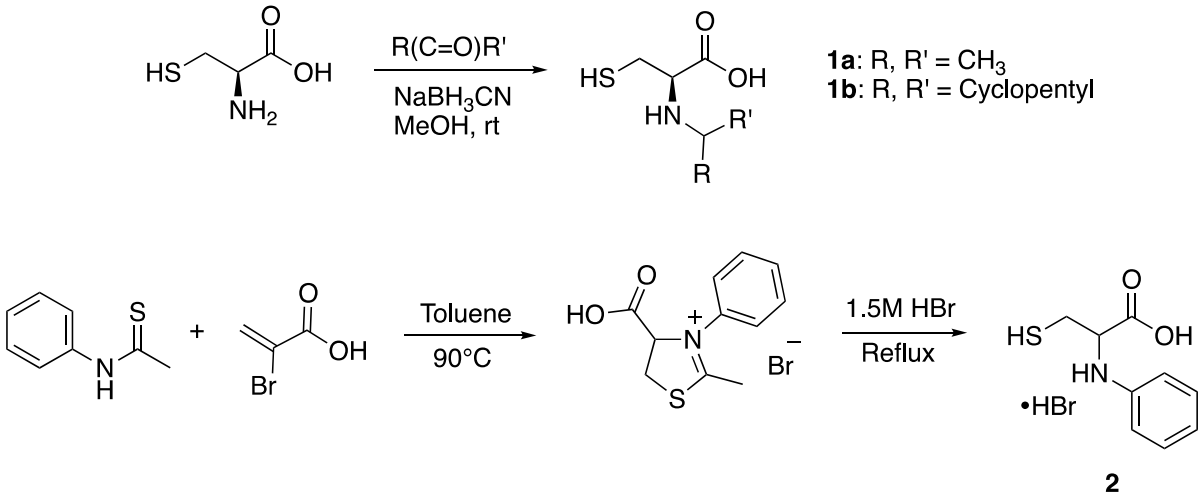
Synthesis of Analogs

*General Procedure for Synthesis of Compounds **1a,b***

Reference: Park, J. D., and Kim, D. H. (2002) *J Med Chem* **45**, 911-918

L-cysteine (10.0g, 82.5 mmol) was dissolved in methanol (MeOH; 150 ml). Sodium cyanoborohydride (5.18g, 82.5 mmol, 1 eq) was slowly added, followed by acetone (47.9g, 825 mmol, 10 eq), and the solution was stirred at room temperature overnight. On completion, the white precipitate was filtered, washed with MeOH, and dried to afford the pure product **1a** as a white powder (3.5g, 27%). ^{1}H NMR (400 MHz, D_2O) δ 3.98 (t, *J* = 4.5 Hz, 1H), 3.52 (quint, *J* = 6.6 Hz, 1H), 3.15 (dd, *J* = 4.8, 14.7 Hz, 1H) 3.04 (dd, *J* = 4.5, 14.8 Hz, 1H), 1.37 (d, *J* = 6.5 Hz, 6H). HRMS *m/z* calculated for $C_6H_{13}NO_2S$ $[M + Na]^+$: 186.0565. Found: 186.0569. The pure product **1b** was obtained as a white powder (3.55g, 22.5%). ^{1}H NMR (400 MHz, D_2O) δ 3.89 (t, *J* = 4.4 Hz, 1H), 3.63 (quint, *J* = 7.2 Hz, 1H), 3.12 (dd, *J* = 4.1, 14.9 Hz, 1H) 3.01 (dd, *J* = 4.6, 15.1 Hz, 1H), 2.08 (bs, 2H), 1.75-1.63 (bd, 6H). HRMS *m/z* calculated for $C_8H_{15}NO_2S$ $[M + H]^+$: 190.0902. Found: 190.0899.

Scheme 1: Synthesis of Cysteine Derivatives



*Synthesis of Compound **2***

References:

Park, J. D., and Kim, D. H. (2002) *J Med Chem* **45**, 911-918

Lee, G. H., Park, C. S., and Lee, H. W. (1988) *Bull. Korean Chem. Soc.* **9**, 25-27

2-Bromoacrylic acid (1.1g, 7.3 mmol, 1.1 eq) was added to a solution of thioacetanilide (1.0g, 6.6 mmol) in dry toluene (20 ml). The mixture was stirred at 90°C for 1 h and then cooled to room temperature. The formed precipitate was filtered, washed with acetone, and recrystallized from MeOH:ethyl acetate (EtOAc):hexane (1:1:2) to afford the thiazolinium bromide intermediate. The intermediate was refluxed with 1.5 M HBr (30 ml) for 3 hours and then cooled to room temperature. The residue was concentrated under reduced pressure, dissolved in 48% HBr, and evaporated to obtain a crude, viscous material, which was recrystallized from 1-propanol:benzene (1:8) to obtain the racemic pure product (hydrobromide salt) **2** as a light tan solid (1.1g, 84.5%) ^{1}H NMR (400 MHz, D_2O) δ 7.54-7.26 (m, 5H), 4.43 (q, *J* = 4.5 Hz, 1H), 3.14 (dd, *J* = 3.6, 14.8 Hz, 1H) 2.90 (dd, *J* = 4.8, 14.8 Hz, 1H). HRMS *m/z* calculated for $C_9H_{11}NO_2S$ $[M + Na]^+$: 220.0408. Found: 220.0405. Optical rotation (in MeOH): 0.053±0.003.

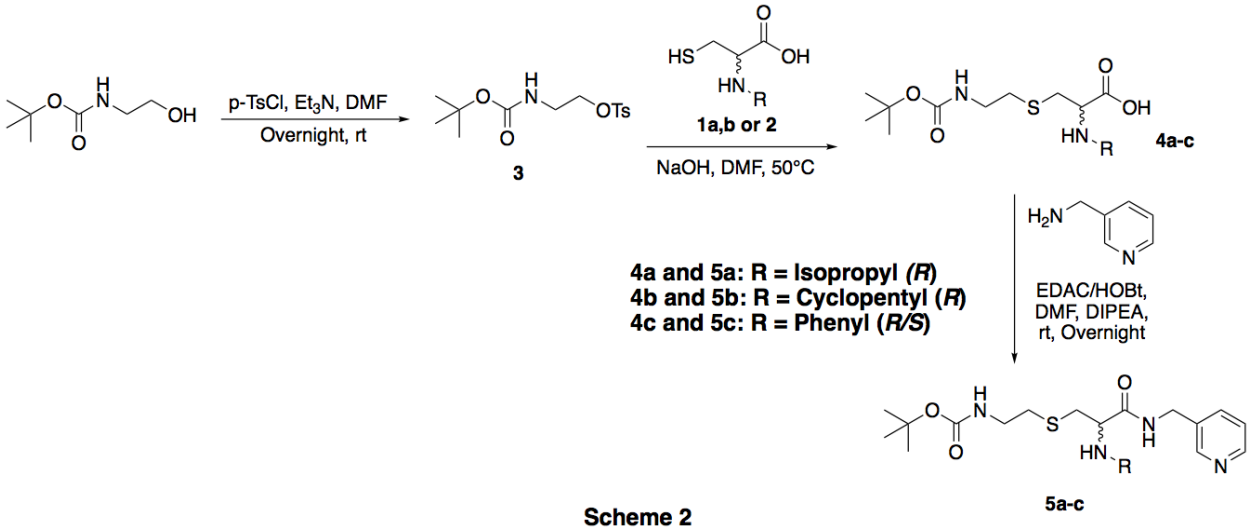
*Synthesis of Compound **3***

N-tert-butyloxycarbonyl *(Boc)*-ethanolamine (2.0g, 12.4 mmol) was added to dry dichloromethane (DCM; 25 ml). To this solution, *p*-toluenesulfonyl chloride (3.55g, 18.6 mmol, 1.5 eq) and triethylamine (3.76g, 37.2 mmol, 3 eq) were slowly added at 0°C. The reaction was allowed to slowly come to room temperature overnight. When the reaction was completed,

DCM was evaporated and the crude mixture was purified using column chromatography (1:1 hexane:EtOAc), affording the pure product **3** as a viscous, opaque oil (3.46g, 88%) TLC: hexane/EtOAc 1:1 (Rf. 0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 4.83 (bs, 1H (NH)), 4.12 (t, *J* = 5.0 Hz, 2H), 3.43 (q, *J* = 5.1 Hz, 2H), 2.46 (s, 3H), 1.41 (s, 9H). HRMS *m/z* calculated for $C_{14}H_{21}NO_5S$ [M + Na]$^+$: 338.1038. Found: 338.1031.

General Procedure for Synthesis of Compounds **4a-c**

To a DMF solution of compound **3** (0.5g, 1.6 mmol; 7 ml), compound **1a** (0.32g, 1.9 mmol, 1.23 eq) was added. To this mixture, 1 N NaOH (2 ml) was added, and the reaction was allowed to stir at 50°C overnight, where a white precipitate was formed. The precipitate was filtered, washed with ether, and dried, affording **4a** as a white crystalline powder (0.30g, 61%). HRMS *m/z* calculated for $C_{13}H_{26}N_2O_4S$ [M + Na]$^+$: 329.1511. Found: 329.1508. The product **4b** was obtained as a white powder (0.22g, 41%). HRMS *m/z* calculated for $C_{15}H_{28}N_2O_4S$ [M + Na]$^+$: 355.1667. Found: 355.1670. For **4c**, no precipitate formed. Therefore, the crude product was obtained by evaporating the solvent and was used in the next step without any further purification. HRMS *m/z* calculated for $C_{16}H_{24}N_2O_4S$ [M + Na]$^+$: 363.1354. Found: 363.1360



Scheme 2

General Procedure for Synthesis of Compounds ***5a-c***

Compound 4a (0.2g, 0.65 mmol) was dissolved in DMF (5 ml). To this solution, 1-ethyl-3-(3-Dimethylaminopropyl)carbodiimide (EDAC; 0.19g, 0.98 mmol, 1.5 eq) and hydroxybenzotriazole (HOBt; 0.15g, 0.98 mmol, 1.5 eq) were added, followed by the addition of 3-(aminomethyl)pyridine (0.11g, 0.98 mmol, 1.5 eq) and N,N-diisopropylethylamine (DIPEA; 0.25g, 1.95 mmol, 3 eq). The reaction was stirred at room temperature overnight. Upon completion, the solvent was evaporated and the reaction mixture was diluted with ethyl

acetate. The organic layer was then washed with saturated $NaHCO_3$, water, and brine. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product, which was purified via column chromatography (95:5 EtOAc:MeOH). The pure product **5a** was obtained as an opaque oil (0.091g, 35%). TLC: EtOAc/MeOH 90:10 (Rf. 0.32). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (m, 2H), 8.01 (t, *J* = 5.7 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 4.92 (bs, 1H (NH)), 4.48 (d, *J* = 6.0 Hz, 2H), 3.33-3.30 (m, 3H), 3.04 (dd, *J* = 3.9, 13.4 Hz, 1H), 2.77 (m, 2H), 2.64 (t, *J* = 6.1 Hz, 2H), 1.45 (bs, 9H), 1.04 (dd, *J* = 6.2, 33.2 Hz, 6H). HRMS *m/z* calculated for $C_{19}H_{32}N_4O_3S$ $[M + H]^+$: 397.2273. Found: 397.2289. The pure product **5b** was acquired as a clear oil (0.055g, 43%). TLC: EtOAc/MeOH 90:10 (Rf. 0.42). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (m, 2H), 7.97 (t, *J* = 6.5 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 4.92 (bs, 1H (NH)), 4.48 (d, *J* = 6.2 Hz, 2H), 3.32-3.29 (m, 3H), 3.04 (m, 1H), 2.77 (dd, *J* = 5.4, 8.0 Hz, 2H), 2.64 (t, *J* = 6.3 Hz, 2H) 1.71-1.53 (bm, 8H), 1.45 (bs, 9H). HRMS *m/z* calculated for $C_{21}H_{34}N_4O_3S$ $[M + H]^+$: 423.2430. Found: 423.2426. The pure product **5c** was obtained as a white fluffy solid (0.08g, 58%). TLC: EtOAc/MeOH 90:10 (Rf. 0.55). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (m, 2H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 5.6 Hz, 1H), 7.28-7.23 (m, 2H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 2H), 4.97 (bs, 1H (NH)), 4.66 (bs, 1H), 4.57 (dd, *J* = 6.3, 15.1 Hz, 1H), 4.46 (dd, *J* = 6.1, 15.1 Hz, 1H), 3.99 (bs, 1H (NH)), 3.35 (m, 2H), 3.22 (dd, *J* = 4.3, 13.6 Hz, 1H), 3.06 (q, *J* = 7.1 Hz, 1H), 2.67 (t, *J* = 6.3 Hz, 2H), 1.95 (bs, 1H (NH)), 1.48 (bs, 9H). HRMS *m/z* calculated for $C_{22}H_{30}N_4O_3S$ $[M + Na]^+$: 453.1936. Found: 453.1947.

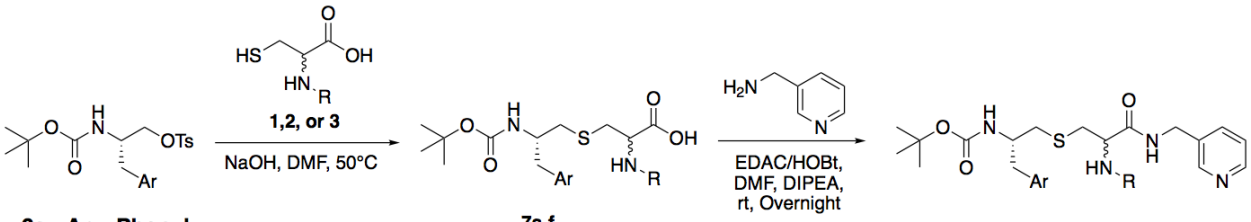
*General Procedure for Synthesis of Compounds **6a,b***

N-Boc-phenylalaninol (1.6g, 6.4 mmol) was added to dry DCM (15 ml). To this solution, *p*-toluenesulfonyl chloride (1.82g, 9.5 mmol, 1.5 eq) and triethylamine (1.93g, 19.1 mmol, 3 eq) were slowly added at 0°C. The reaction was allowed to slowly come to room temperature overnight. After the reaction completion, DCM was evaporated and the crude mixture was purified using column chromatography (1:1 hexane:EtOAc), affording the pure product **6a** as an off white powder (2.05g, 79%). TLC: hexane/EtOAc 1:1 (Rf. 0.64). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0 Hz, 2H), 7.46-7.25 (m, 5H), 7.14 (d, *J* = 7.2 Hz, 2H), 4.78 (bs, 1H (NH)), 4.07 (t, *J* = 9.8 Hz, 2H), 3.95 (d, *J* = 7.8 Hz, 1H), 2.96 (m, 1H), 2.84 (m, 1H), 2.52 (s, 3H), 1.45 (s, 9H). HRMS *m/z* calculated for $C_{21}H_{27}NO_5S$ $[M + Na]^+$: 428.1508. Found: 428.1527. The pure product **6b** was acquired as off white crystals (1.76g, 72%). TLC: hexane/EtOAc 1:1 (Rf. 0.46). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (bs, 1H (NH)), 7.76 (d, *J* = 8.1 Hz, 2H), 7.60 (t, *J* = 6.5 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.11 (t, *J* = 7.4 Hz, 2H), 7.00 (s, 1H), 4.76 (bs, 1H (NH)), 4.20-4.12 (m, 1H), 4.00 (s, 2H), 3.02 (m, 2H), 2.45 (s, 3H), 1.41 (s, 9H). HRMS *m/z* calculated for $C_{23}H_{28}N_2O_5S$ $[M + Na]^+$: 467.1617. Found: 467.1633.

General Procedure for Synthesis of Compounds **7a-f**

To a solution of compound **6a** (0.23g, 0.56 mmol) in DMF (5 ml), compound **1a** (0.11g, 0.68 mmol, 1.23 eq) was added. To this mixture, 1 N NaOH (2 ml) was added, and the reaction was allowed to stir at 50°C overnight. The crude product **7a** was obtained by evaporating the

solvent and used in the next step without any further purification. HRMS *m/z* calculated for $C_{20}H_{32}N_2O_4S$ $[M + Na]^+$: 419.1981. Found: 419.1986. **7b** formed a white precipitate, which was collected, washed with H_2O, and dried (0.14g, 55%). HRMS *m/z* calculated for $C_{22}H_{34}N_2O_4S$ $[M + Na]^+$: 445.2137. Found: 445.2130. **7c** HRMS *m/z* calculated for $C_{23}H_{30}N_2O_4S$ $[M + H]^+$: 431.2004. Found: 431.1992. **7d** HRMS *m/z* calculated for $C_{22}H_{33}N_3O_4S$ $[M + Na]^+$: 458.2090. Found: 458.2098. **7e** HRMS *m/z* calculated for $C_{24}H_{35}N_3O_4S$ $[M + Na]^+$: 484.2246. Found: 484.2244. **7f** HRMS *m/z* calculated for $C_{25}H_{31}N_2O_4S$ $[M + H]^+$: 470.2114. Found: 470.2111.



7a and 8a: Ar = Phenyl; R = Isopropyl (*R*)
7b and 8b: Ar = Phenyl; R = Cyclopentyl (*R*)
7c and 8c: Ar = Phenyl; R = Phenyl (*R/S*)
7d and 8d: Ar = Indole; R = Isopropyl (*R*)
7e and 8e: Ar = Indole; R = Cyclopentyl (*R*)
7f and 8f: Ar = Indole; R = Phenyl (*R/S*)

Scheme 3

*General Procedure for Synthesis of Compounds **8a-f***

Crude **7a** (0.3g, 0.75 mmol) was dissolved in DMF (5 ml). To this solution, EDAC (0.22g, 1.13 mmol, 1.5 eq) and HOBt (0.17g, 1.13 mmol, 1.5 eq) were added, followed by the addition of 3-(aminomethyl)pyridine (0.12g, 1.13 mmol, 1.5 eq) and DIPEA (0.29g, 2.25 mmol, 3 eq). The reaction was stirred at room temperature overnight. Upon completion, the solvent was evaporated and the reaction mixture was diluted with ethyl acetate. The organic layer was then washed with saturated $NaHCO_3$, water, and brine. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product, which was purified via column chromatography (95:5 EtOAc:MeOH). The pure product **8a** was obtained as yellow gum (0.054g, 20%). TLC: EtOAc/MeOH 90:10 (Rf. 0.48). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (m, 2H), 7.98 (t, *J* = 5.5 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.33-7.19 (m, 5H), 4.66 (bs, 1H (NH)), 4.45 (d, *J* = 6.3 Hz, 2H), 3.99 (bs, 1H (NH)), 3.31 (q, *J* = 4.0 Hz, 1H), 3.04 (dd, *J* = 4.0, 13.4 Hz, 1H), 2.86 (d, *J* = 6.4 Hz, 2H), 2.81-2.72 (m, 2H), 2.64 (m, 2H), 1.40 (bs, 9H), 1.02 (dd, *J* = 6.2, 25.8 Hz, 6H). HRMS *m/z* calculated for $C_{26}H_{38}N_4O_3S$ $[M + H]^+$: 487.2743. Found: 487.2752. The pure product **8b** was acquired as an opaque oil (0.09g, 57%). TLC: EtOAc/MeOH 90:10 (Rf. 0.53). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (m, 2H), 7.95 (t, *J* = 5.4 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.32-7.19 (m, 5H), 4.67 (bs, 1H (NH)), 4.45 (d, *J* = 6.2 Hz, 2H), 3.98 (bs, 1H (NH)), 3.30 (q, *J* = 3.8 Hz, 1H), 3.06 (m, 2H), 2.86

(d, *J* = 6.0 Hz, 2H), 2.78 (q, *J* = 7.2 Hz, 1H), 2.64 (m, 2H), 2.17 (bs, 2H), 1.81-1.50 (bs, 6H), 1.40 (bs, 9H). HRMS *m/z* calculated for $C_{28}H_{40}N_4O_3S$ $[M + H]^+$: 513.2899. Found: 513.2916. The pure product **8c** was obtained as a white fluffy solid (0.03g, 19%). TLC: EtOAc/MeOH 90:10 (Rf. 0.62). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (m, 2H), 7.59 (t, *J* = 4.0 Hz, 1H), 7.42 (m, 1H), 7.34-7.19 (m, 7H), 6.89 (m, 1H), 6.70 (q, *J* = 7.1 Hz, 2H), 4.77 (bd, *J* = 26.3 Hz, 1H). 4.67 (bs, 1H (NH)), 4.53 (td, *J* = 6.2, 15.7 Hz, 1H), 4.45 (td, *J* = 6.0, 15.7 Hz, 1H), 4.05 (bs, 1H (NH)), 3.97 (bs, 1H), 3.26-3.05 (m, 2H), 2.88 (m, 2H) 2.65 (m, 2H), 1.85 (bs, 1H (NH)), 1.46 (d, *J* = 9.7 Hz, 9H). HRMS *m/z* calculated for $C_{29}H_{36}N_4O_3S$ $[M + Na]^+$: 543.2406. Found: 543.2408. The pure product **8d** was acquired as a white fluffy solid (0.07g, 30%). TLC: EtOAc/MeOH 90:10 (Rf. 0.42). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (m, 2H), 8.44 (bs, 1H (NH)), 8.03 (t, *J* = 6.1 Hz, 1H), 7.68 (dd, *J* = 7.6, 24.2 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.32-7.23 (m, 1H), 7.17 (t, *J* = 7.1 Hz, 1H), 7.10 (s, 1H), 4.83 (bs, 1H (NH)), 4.47 (d, *J* = 5.7 Hz, 2H), 4.14 (bs, 1H (NH)), 3.36 (m, 1H), 3.10 (m, 2H), 2.84 (m, 1H), 2.78 (m, 1H), 2.69 (dd, *J* = 5.4, 16.2 Hz, 2H), 1.91 (bs, 2H), 1.46 (s, 9H), 1.05 (dd, *J* = 6.0, 26.3 Hz, 6H). HRMS *m/z* calculated for $C_{28}H_{39}N_5O_3S$ $[M + Na]^+$: 548.2672. Found: 548.2670. The pure product **8e** was obtained as a white fluffy solid (0.09g, 36%). TLC: EtOAc/MeOH 90:10 (Rf. 0.5). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (bs, 1H (NH)), 8.58 (m, 2H), 8.00 (t, *J* = 6.0 Hz, 1H), 7.67 (dd, *J* = 7.8, 21.5 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.09 (s, 1H), 4.83 (bs, 1H (NH)), 4.47 (d, *J* = 6.2 Hz, 2H), 4.14 (bs, 1H (NH)), 3.34 (q, *J* = 4.0 Hz, 1H), 3.10-3.04 (m, 2H), 3.04 (m, 1H), 2.82 (q, *J* = 7.1 Hz, 1H), 2.78 (m, 1H), 2.71 (dd, *J* = 6.0, 13.1 Hz, 1H), 2.65 (dd, *J* = 5.4, 13.2 Hz, 1H), 2.08 (bs, 2H), 1.83-1.52, 1.31 (m, 8H), 1.47 (s, 9H). HRMS *m/z* calculated for $C_{30}H_{41}N_5O_3S$ $[M + H]^+$: 552.3008. Found: 552.3007. The pure product **8f** was acquired as a white fluffy solid (0.032g, 17%). TLC: EtOAc/MeOH 90:10 (Rf. 0.6). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (m, 2H), 8.37 (bs, 1H (NH)), 7.66 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 6.9 Hz, 1H), 7.46-7.39 (m, 2H), 7.28-7.19 (m, 3H), 7.16 (q, *J* = 6.7 Hz, 1H), 7.03 (d, *J*= 5.5 Hz, 1H), 6.99 (m, 1H), 6.69 (dd, *J* = 7.8, 18.1 Hz, 2H), 4.82 (bs, 1H (NH)), 4.73 (bd, *J* = 35.8 Hz, 1H), 4.50 (td, *J* = 6.2, 15.3 Hz, 1H), 4.40 (dt, *J* = 5.0, 15.1 Hz, 1H), 4.17 (bs, 1H (NH)), 3.99 (bd, *J* = 54 Hz, 1H), 3.24-2.99 (m, 4H), 2.68 (m, 2H), 1.91 (bs, 1H (NH)), 1.48 (d, *J* = 15.4 Hz, 9H). HRMS *m/z* calculated for $C_{31}H_{37}N_5O_3S$ $[M + Na]^+$: 582.2515. Found: 582.2527.

The purity of compounds **5a**-**c** and **8a**-**f** was >95% as determined by NMR, with the exception of occasional residual solvent (noted on spectra where applicable). HRMS and NMR spectra for all compounds are shown after Table S2.

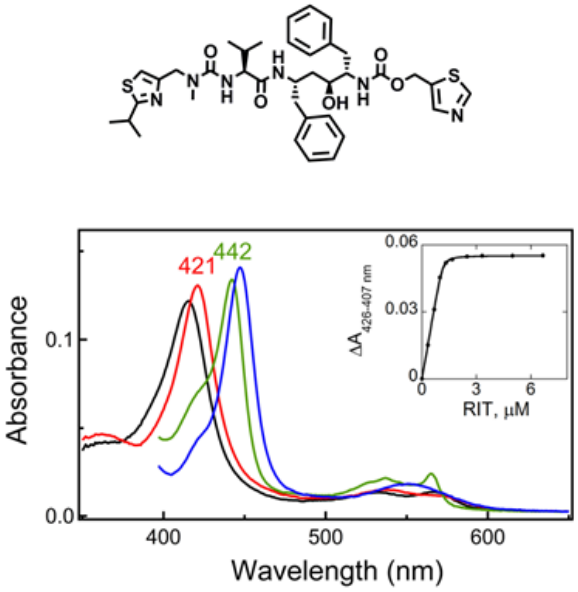


Figure S1. Chemical structure and spectral changes induced by ritonavir in CYP3A4. Spectra of the ferric ligand-free and ritonavir-bound CYP3A4 are shown in black and red, respectively. Spectra of the ferrous and ferrous CO-bound forms are in green and blue, respectively. *Inset* is a titration plot and quadratic fit, which gives the K_s value of 17 nM.

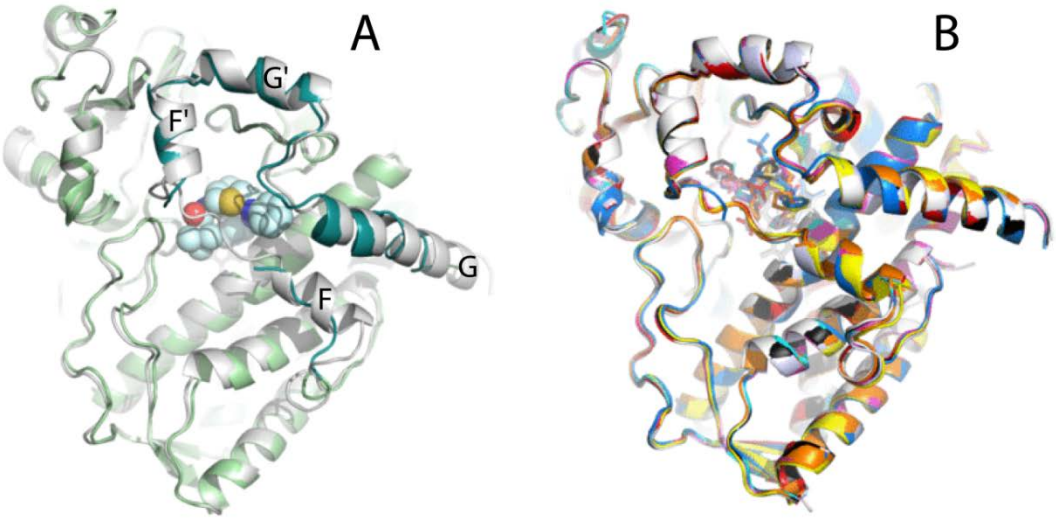


Figure S2. ***A***, Structural overlay of the ligand-free (PDB ID 5VCC; in gray) and **8c**-bound CYP3A4 (in shades of green). **8c** is in cpk representation. The F, F', G' and G helices are labeled to show that binding of **8c** leads to disorder of the F-F' loop, unwinding of the F-helix, and positional shift of the G-helix. No major alterations were observed in other ligand-bound structures (panel ***B***): **5a** - cyan, **5b** - magenta, **5c** - yellow, **8a** - pale blue, **8b** - orange, **8c** - blue, **8d** - red, **8e** - black, and **8f** – green.

Table S1. Data collection and refinement statistics

Ligand	**5a**	**5b**	**5c**	**8a**	**8b**
PDB ID	**6BCZ**	**6BD5**	**6BD6**	**6BD7**	**6BD8**
Data statistics					
Space group	I222	I222	I222	I222	I222
Unit cell parameters	*a* = 77 Å, *b* = 101 Å, *c* = 128 Å; α, β, γ = 90°	*a* = 77 Å, *b* = 102 Å, *c* = 129 Å; α, β, γ = 90°	*a* = 77 Å, *b* = 101 Å, *c* = 127 Å; α, β, γ = 90°	*a* = 78 Å, *b* = 103 Å, *c* = 129 Å; α, β, γ = 90°	*a* = 76 Å, *b* = 101 Å, *c* = 124 Å; α, β, γ = 90°
Molecules per asymmetric unit	1	1	1	1	1
Resolution range (Å)	79.39-2.23 (2.35-2.23) [a]	80.03-2.50 (2.64-2.50)	79.38-2.45 (2.58-2.45)	80.29-2.42 (2.55-2.42)	78.35-2.38 (2.51-2.38)
Total reflections	139,233	62,649	55,487	93,759	69,992
Unique reflections	24,881	17,153	17,706	19,640	18,695
Redundancy	5.6 (5.4)	3.7 (3.3)	3.1 (3.2)	4.8 (5.0)	3.7 (3.6)
Completeness	99.9 (99.9)	95.5 (93.4)	95.1 (97.7)	98.7 (99.2)	96.7 (95.5)
Average $I/\sigma I$	11.2 (0.9)	7.6 (0.2)	9.1 (0.5)	9.4 (0.6)	8.7 (0.4)
R_{merge}	0.049 (1.813)	0.057 (3.494)	0.049 (1.933)	0.056 (1.971)	0.052 (2.453)
R_{pim}	0.023 (0.858)	0.032 (2.125)	0.032 (1.270)	0.029 (0.951)	0.030 (1.408)
CC ½	0.999 (0.300)	0.997 (0.371)	0.997 (0.399)	0.998 (0.309)	0.994 (0.341)
Refinement statistics					
R/R_{free} [b]	20.0 (26.1)	20.9 (27.5)	20.4/26.7	19.3/26.4	21.2/26.9
Number of atoms:					
Protein	3815	3780	3693	3806	3753
Solvent	11	0	0	0	4
R.m.s. deviations:					
Bond lengths, Å	0.009	0.010	0.009	0.009	0.009
Bond angles, °	1.224	1.276	1.117	1.142	1.290

[a] Values in brackets are for the highest resolution shell.

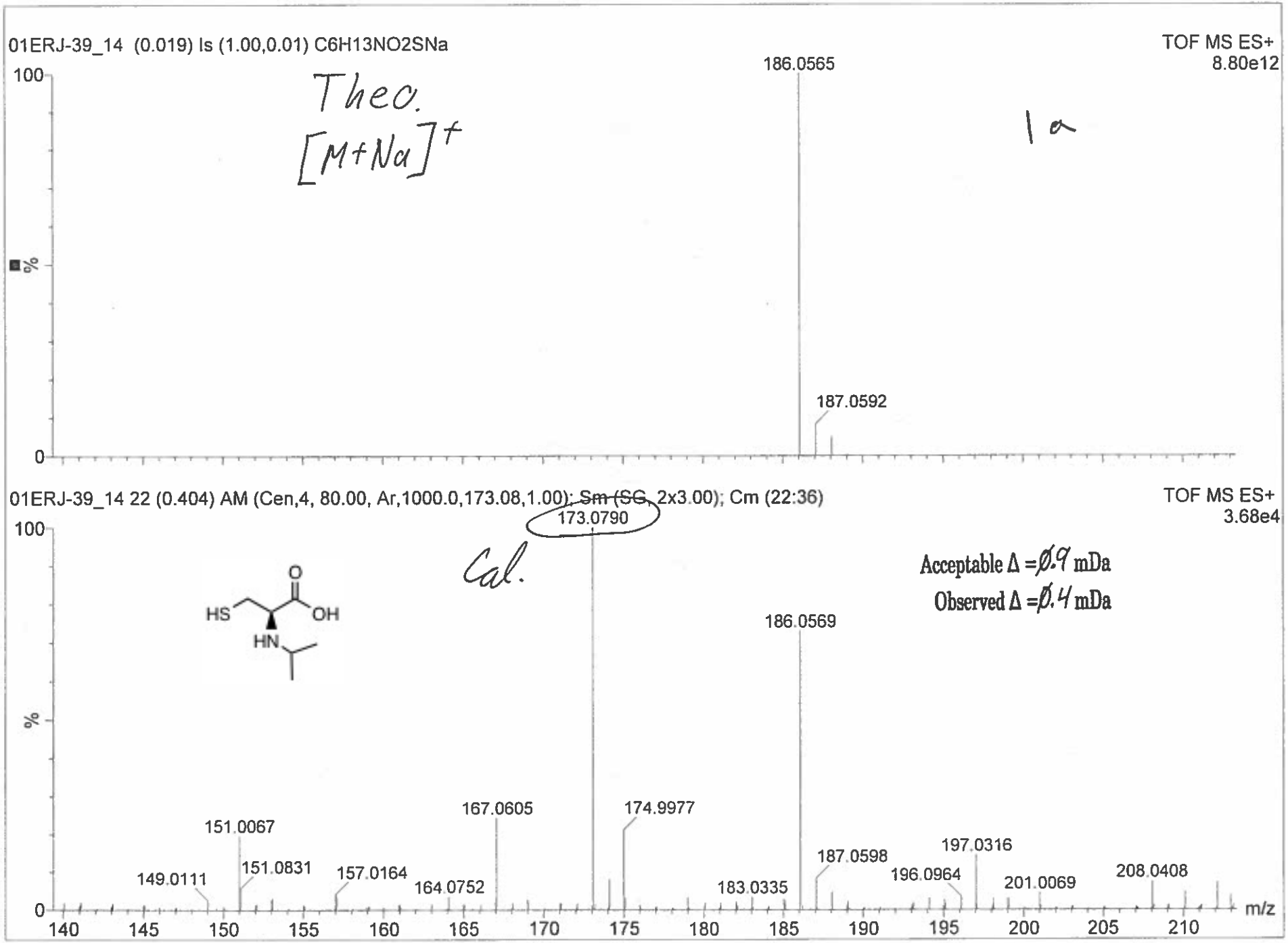
[b] R_{free} was calculated from a subset of 5% of the data that were excluded during refinement.

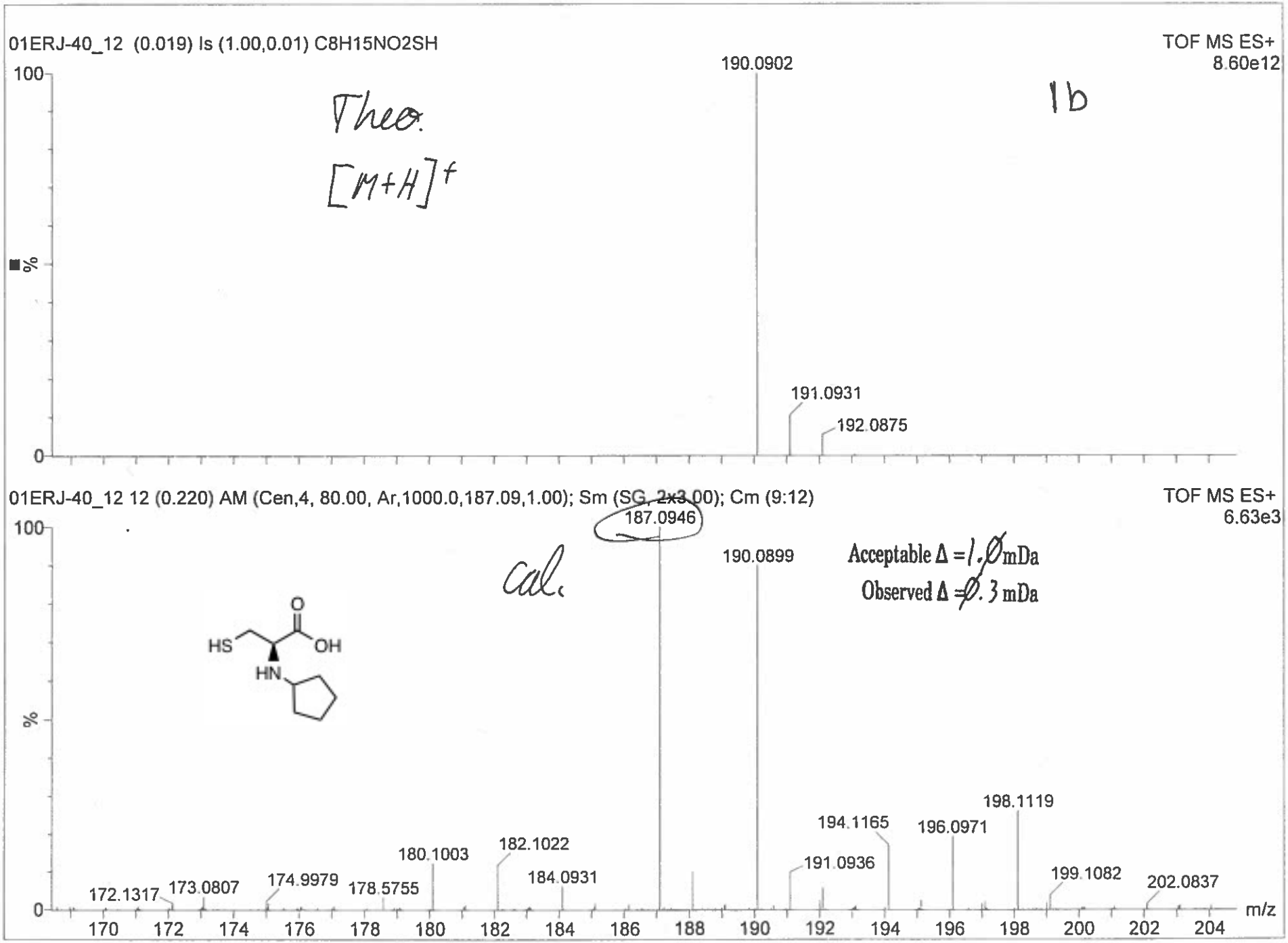
Table S2. Data collection and refinement statistics

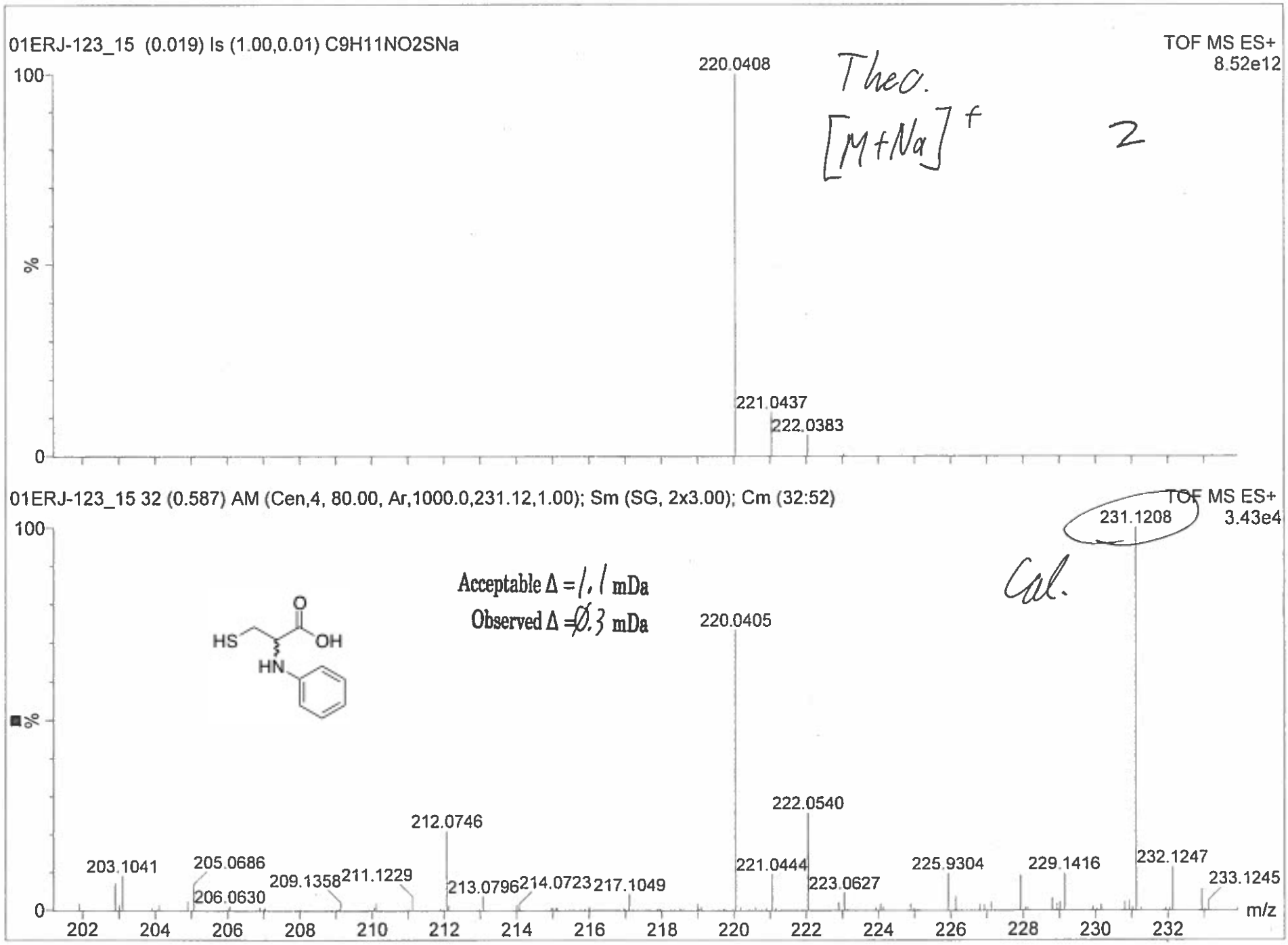
Ligand	**8c**	**8d**	**8e**	**8f**
PDB ID	6BDH	6BDI	6BDK	6BDM
Data statistics				
Space group	I222	I222	I222	I222
Unit cell parameters	*a* = 76 Å, *b* = 100 Å, *c* = 126 Å; α, β, γ = 90°	*a* = 78 Å, *b* = 102 Å, *c* = 128 Å; α, β, γ = 90°	*a* = 77 Å, *b* = 102 Å, *c* = 128 Å; α, β, γ = 90°	*a* = 77 Å, *b* = 101 Å, *c* = 127 Å; α, β, γ = 90°
Molecules per asymmetric unit	1	1	1	1
Resolution range (Å)	78.25-2.25 (2.37-2.25) [a]	79.92-2.57 (2.71-2.57)	79.90-2.67 (2.81-2.67)	79.33-2.60 (2.74-2.60)
Total reflections	89,557	77,790	53,812	70,890
Unique reflections	22,571	16,151	14,250	15,756
Redundancy	4.0 (4.0)	4.8 (4.8)	3.8 (3.5)	4.5 (4.6)
Completeness	97.5 (98.1)	97.8 (97.6)	96.9 (95.5)	99.9 (100.0)
Average $I/\sigma I$	7.6 (0.4)	9,4 (0.9)	8.0 (0.8)	7.6 (0.4)
R_{merge}	0.065 (2.814)	0.060 (1.817)	0.069 (1.522)	0.079 (3.396)
R_{pim}	0.035 (1.540)	0.030 (0.897)	0.039 (0.914)	0.042 (1.767)
CC ½	0.997 (0.488)	0.999 (0.315)	0.998 (0.355)	0.999 (0.303)
Refinement statistics				
R/R_{free} [b]	20.7 (28.0)	19.2 (24.5)	20.6/27.2	20.1/27.5
Number of atoms:				
Protein	3552	3785	3778	3712
Solvent	30	2	0	0
R.m.s. deviations:				
Bond lengths, Å	0.009	0.010	0.009	0.010
Bond angles, °	1.096	1.202	1.138	1.198

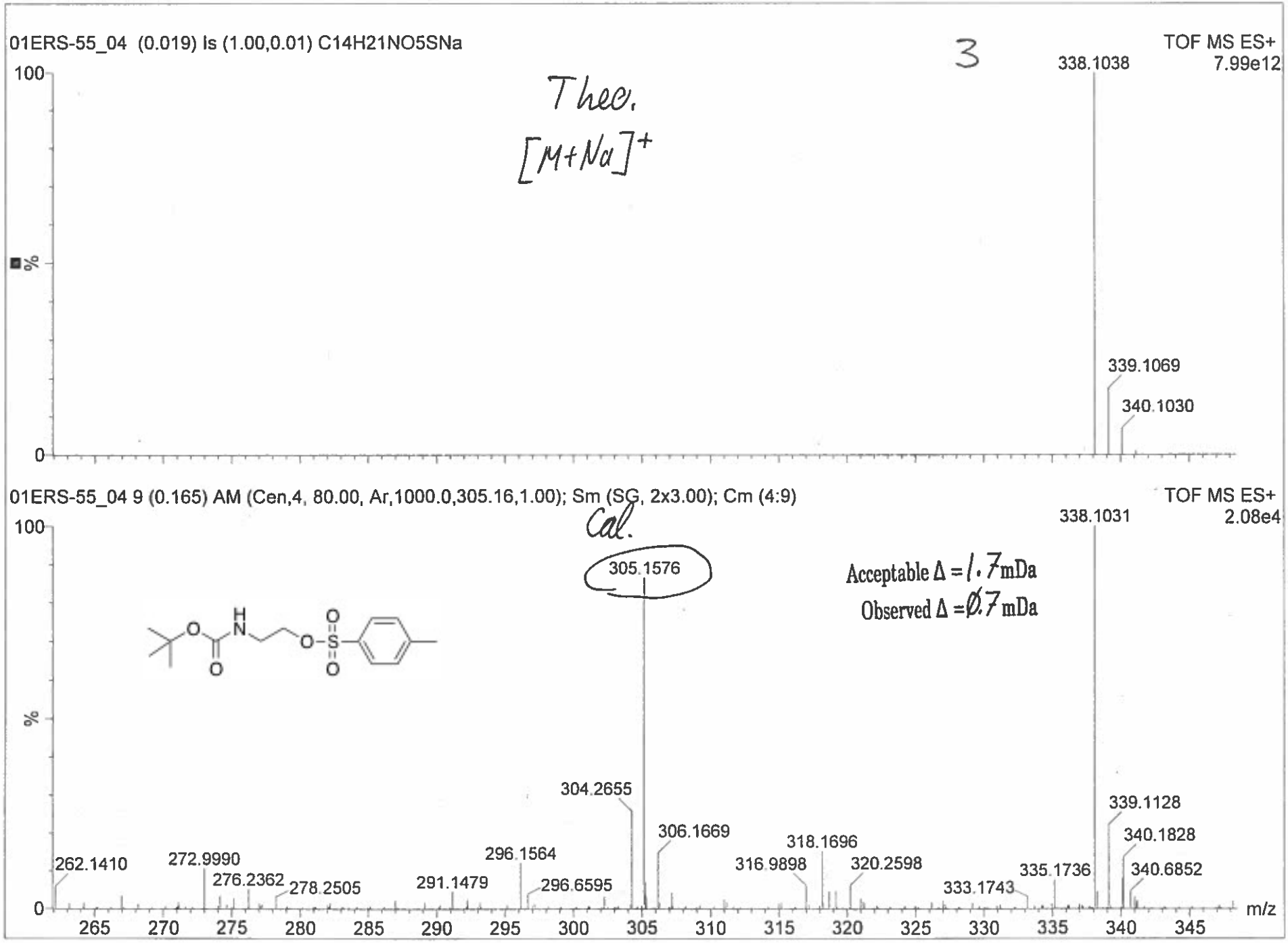
[a] Values in brackets are for the highest resolution shell.

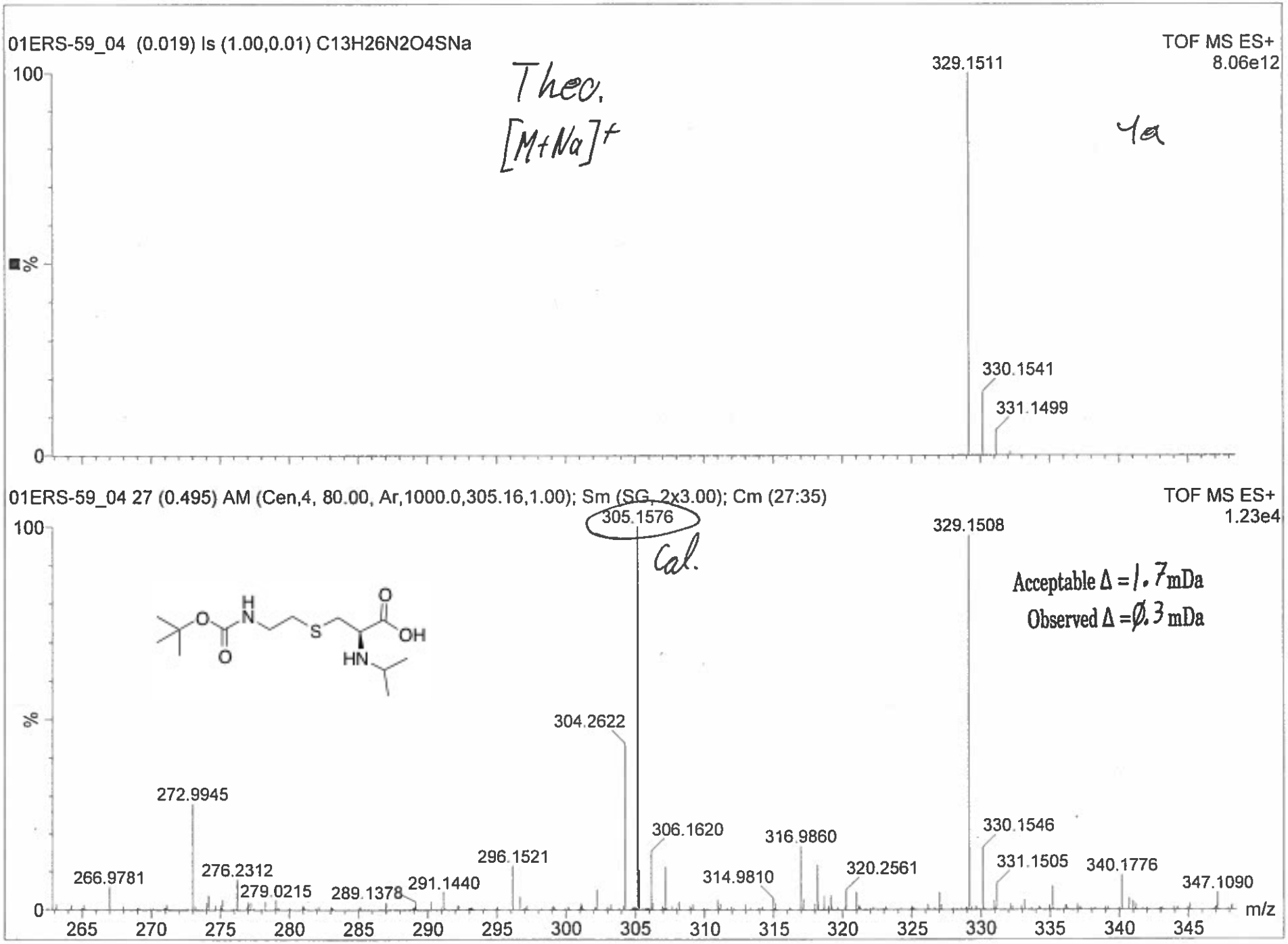
[b] R_{free} was calculated from a subset of 5% of the data that were excluded during refinement.

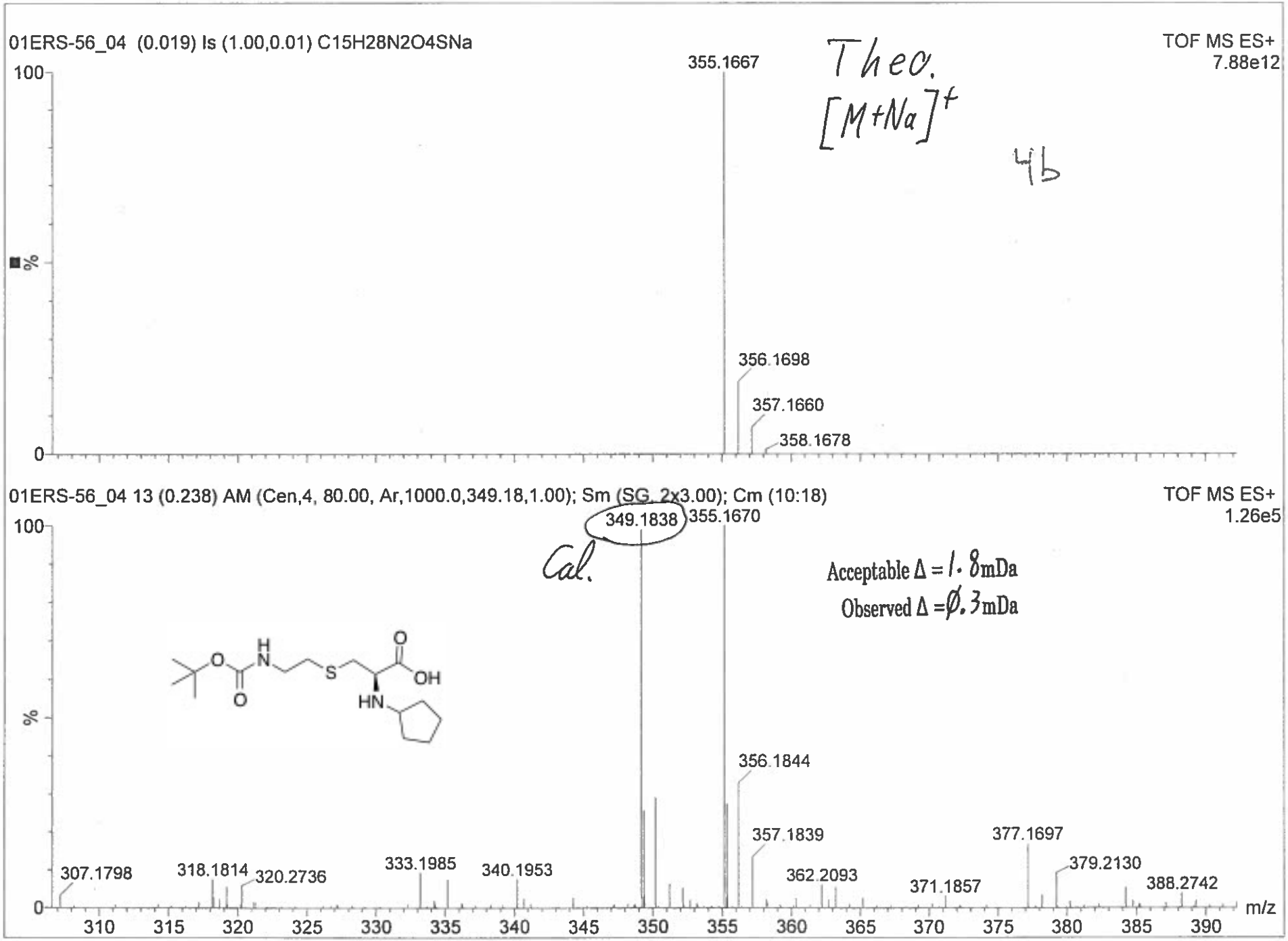

01ERJ-39_14 (0.019) Is (1.00,0.01) C6H13NO2SNa
TOF MS ES+
8.80e12
100
%
0
186.0565
187.0592
Theo.
[M+Na]+
1a
01ERJ-39_14 22 (0.404) AM (Cen,4, 80.00, Ar,1000.0,173.08,1.00); Sm (SG, 2x3.00); Cm (22:36)
TOF MS ES+
3.68e4
100
%
0
173.0790
Cal.
Acceptable Δ = 0.9 mDa
Observed Δ = 0.4 mDa
186.0569
167.0605
174.9977
151.0067
151.0831
149.0111
157.0164
164.0752
183.0335
187.0598
196.0964
197.0316
201.0069
208.0408
m/z
140
145
150
155
160
165
170
175
180
185
190
195
200
205
210

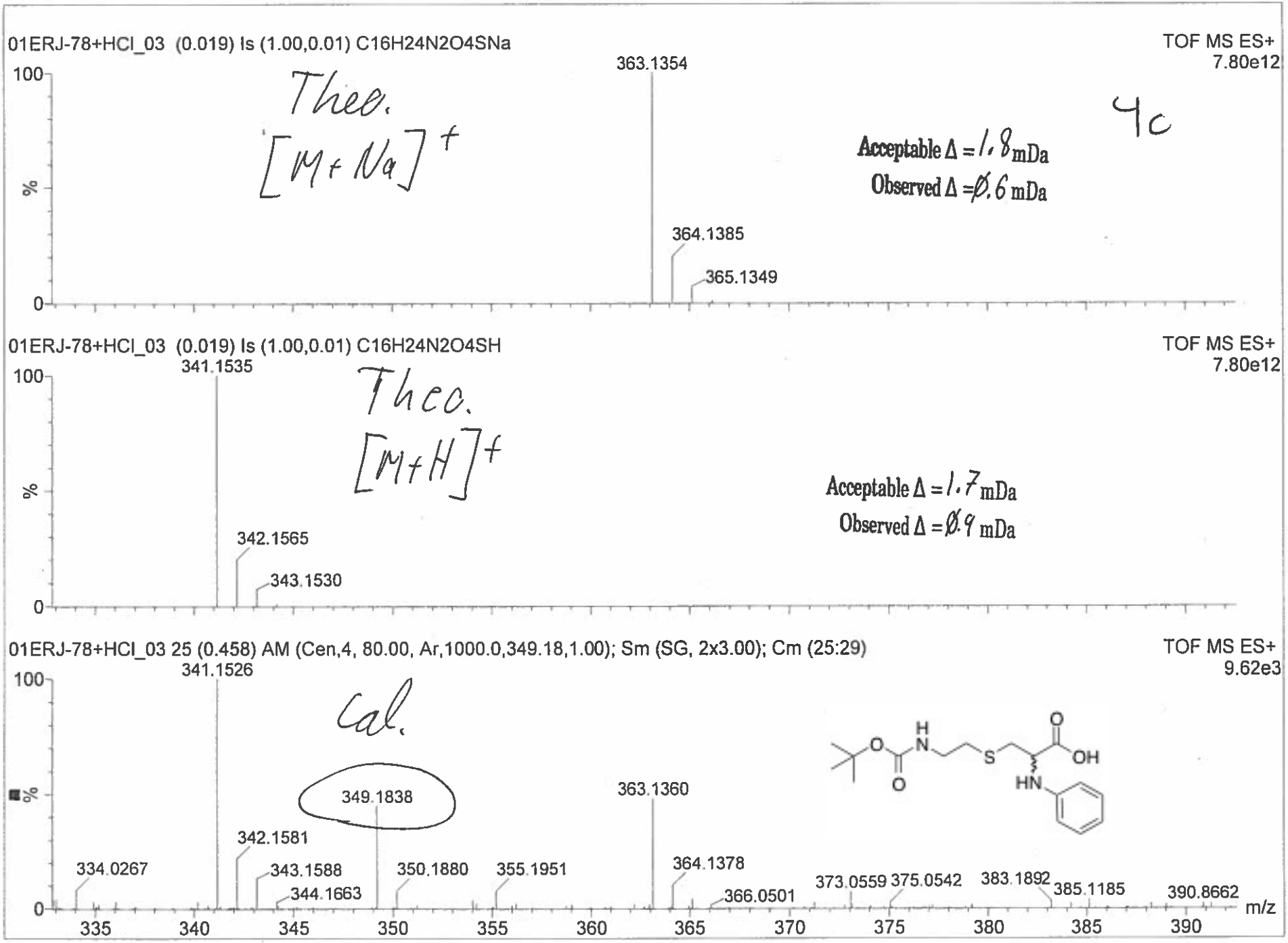

01ERJ-40_12 (0.019) Is (1.00,0.01) C8H15NO2SH
TOF MS ES+
8.60e12
100
%
0
190.0902
191.0931
192.0875
Theo.
[M+H]+
1b
01ERJ-40_12 12 (0.220) AM (Cen,4, 80.00, Ar,1000.0,187.09,1.00); Sm (SG, 2x3.00); Cm (9:12)
TOF MS ES+
6.63e3
187.0946
190.0899
cal.
Acceptable Δ = 1.0 mDa
Observed Δ = 0.3 mDa
HS
O
OH
HN
172.1317
173.0807
174.9979
178.5755
180.1003
182.1022
184.0931
191.0936
194.1165
196.0971
198.1119
199.1082
202.0837
m/z
170
172
174
176
178
180
182
184
186
188
190
192
194
196
198
200
202
204

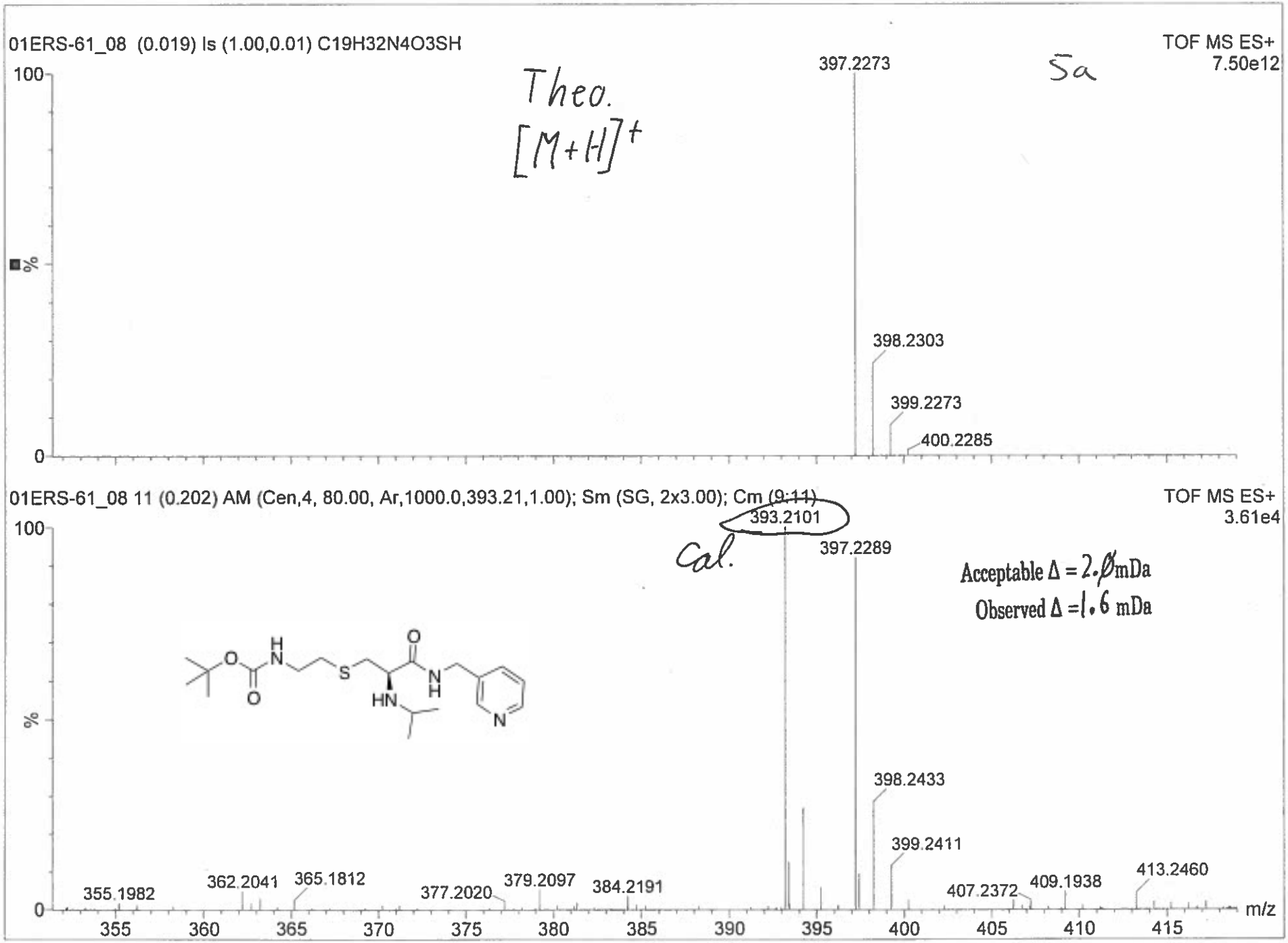

01ERJ-123_15 (0.019) Is (1.00,0.01) C9H11NO2SNa
TOF MS ES+
8.52e12
100
%
0
220.0408
221.0437
222.0383
Theo.
[M+Na]+
2
01ERJ-123_15 32 (0.587) AM (Cen,4, 80.00, Ar,1000.0,231.12,1.00); Sm (SG, 2x3.00); Cm (32:52)
TOF MS ES+
3.43e4
231.1208
Cal.
Acceptable Δ = 1.1 mDa
Observed Δ = 0.3 mDa
HS
OH
HN
O
220.0405
222.0540
212.0746
203.1041
205.0686
206.0630
209.1358
211.1229
213.0796
214.0723
217.1049
221.0444
223.0627
225.9304
229.1416
232.1247
233.1245
m/z
202
204
206
208
210
212
214
216
218
220
222
224
226
228
230
232

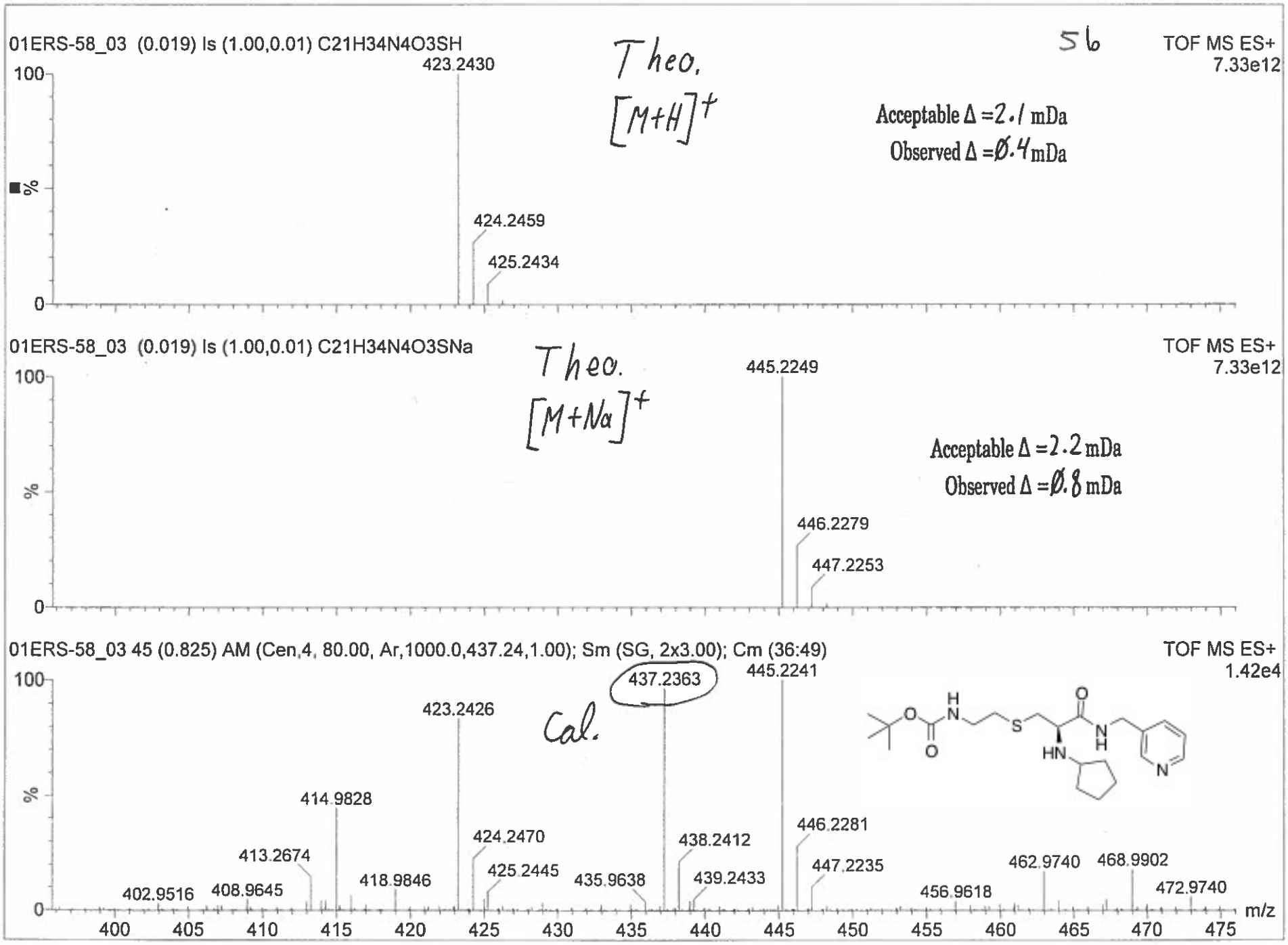

01ERS-55_04 (0.019) Is (1.00,0.01) C14H21NO5SNa
3
TOF MS ES+
7.99e12
Thec.
[M+Na]+
100
%
0
338.1038
339.1069
340.1030
01ERS-55_04 9 (0.165) AM (Cen,4, 80.00, Ar,1000.0,305.16,1.00); Sm (SG, 2x3.00); Cm (4:9)
TOF MS ES+
2.08e4
Cal.
305.1576
Acceptable Δ = 1.7 mDa
Observed Δ = 0.7 mDa
338.1031
304.2655
306.1669
339.1128
340.1828
340.6852
318.1696
320.2598
316.9898
335.1736
333.1743
296.1564
296.6595
291.1479
272.9990
276.2362
278.2505
262.1410
m/z
265
270
275
280
285
290
295
300
305
310
315
320
325
330
335
340
345

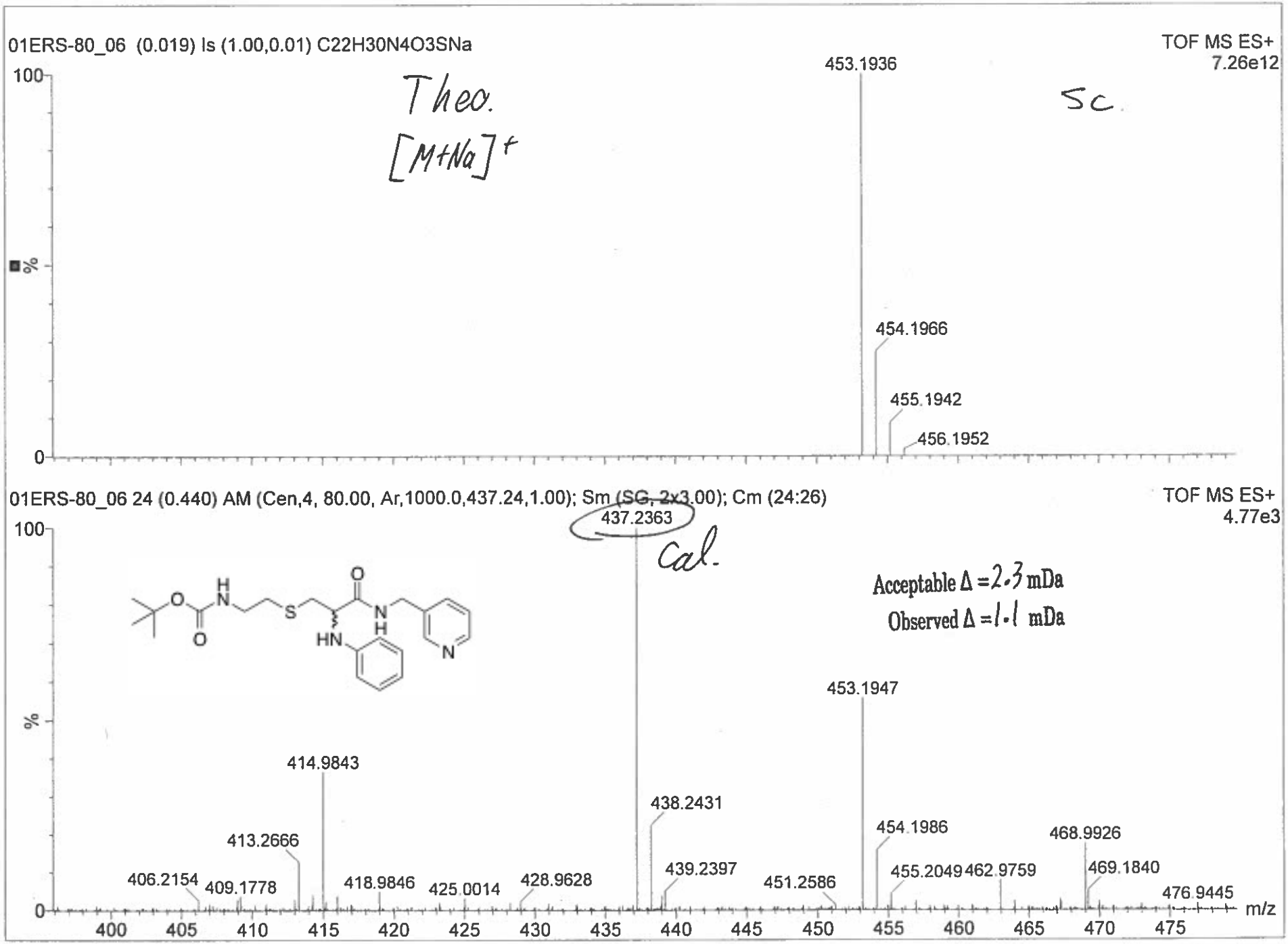

01ERS-59_04 (0.019) Is (1.00,0.01) C13H26N2O4SNa
TOF MS ES+
8.06e12
Theo.
[M+Na]+
4a
329.1511
330.1541
331.1499
01ERS-59_04 27 (0.495) AM (Cen,4, 80.00, Ar,1000.0,305.16,1.00); Sm (SG, 2x3.00); Cm (27:35)
TOF MS ES+
1.23e4
305.1576
Cal.
329.1508
Acceptable Δ = 1.7 mDa
Observed Δ = 0.3 mDa
304.2622
272.9945
306.1620
316.9860
330.1546
296.1521
331.1505
340.1776
266.9781
276.2312
320.2561
279.0215
314.9810
347.1090
289.1378
291.1440
m/z

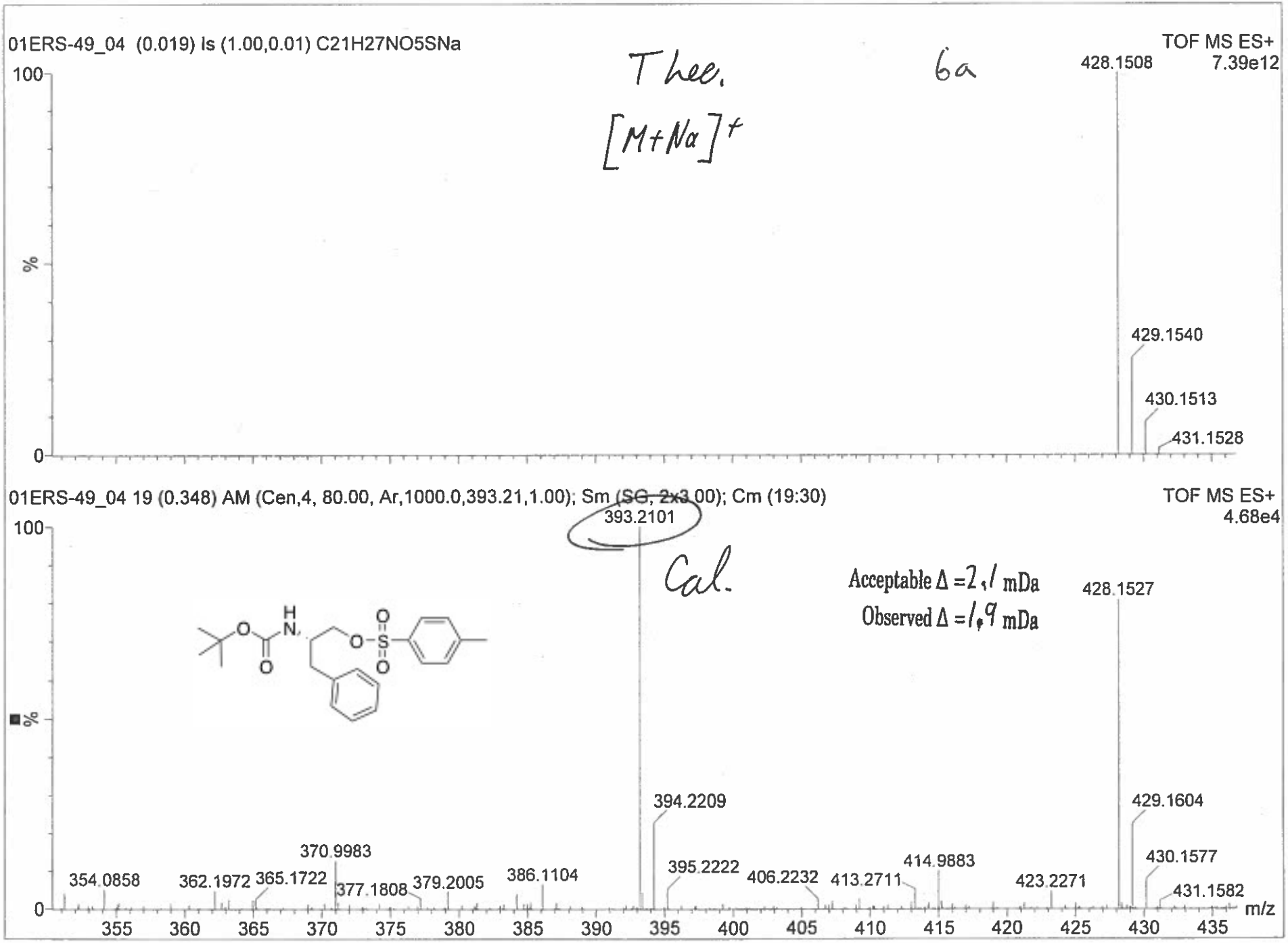

01ERS-56_04 (0.019) Is (1.00,0.01) C15H28N2O4SNa
TOF MS ES+
7.88e12
100
%
0
355.1667
356.1698
357.1660
358.1678
Theo.
[M+Na]+
4b
01ERS-56_04 13 (0.238) AM (Cen,4, 80.00, Ar,1000.0,349.18,1.00); Sm (SG, 2x3.00); Cm (10:18)
TOF MS ES+
1.26e5
349.1838
355.1670
Cal.
Acceptable Δ = 1.8mDa
Observed Δ = 0.3mDa
356.1844
357.1839
377.1697
379.2130
388.2742
307.1798
318.1814
320.2736
333.1985
340.1953
362.2093
371.1857
m/z
310
315
320
325
330
335
340
345
350
355
360
365
370
375
380
385
390

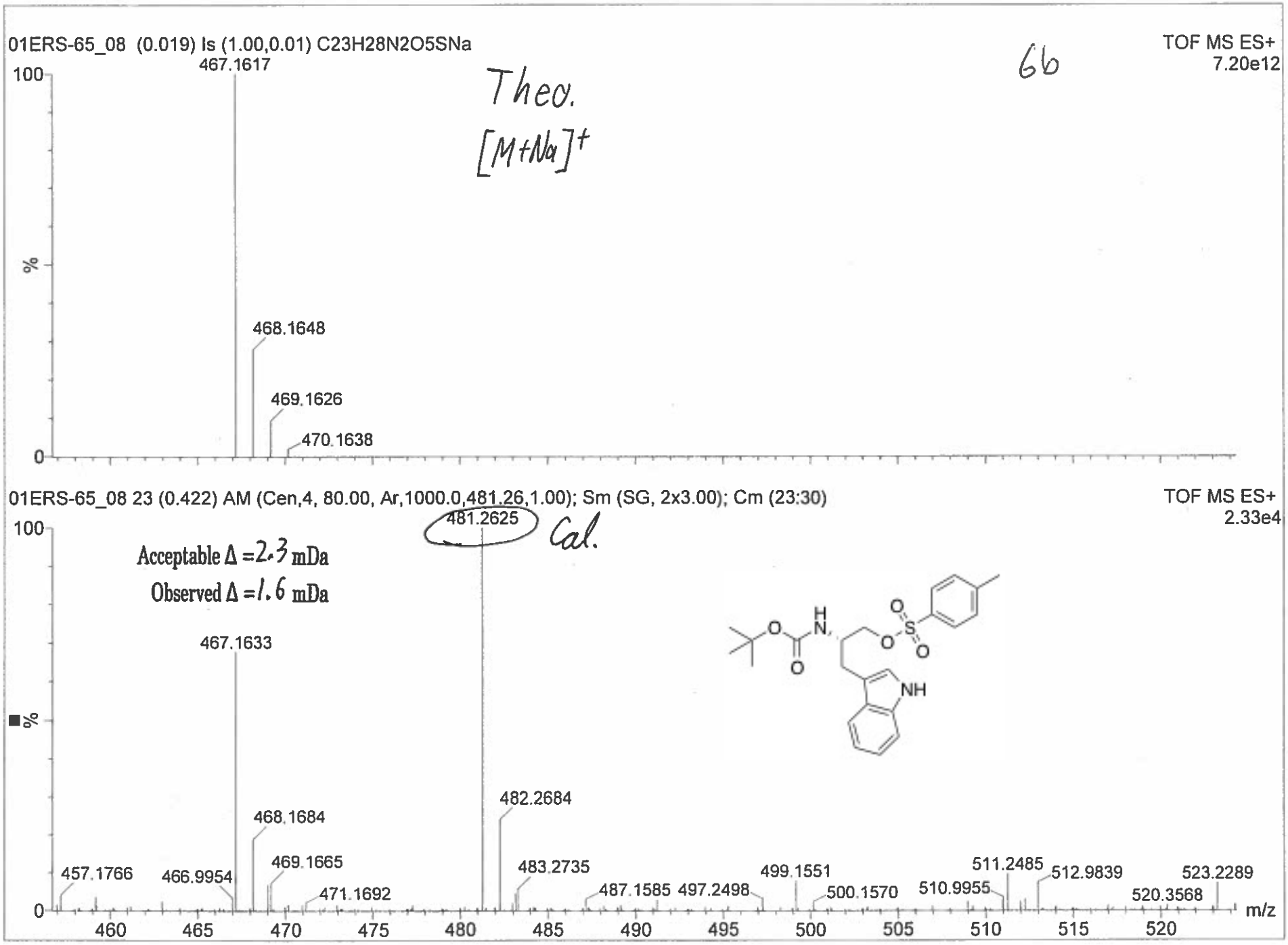

01ERJ-78+HCl_03 (0.019) Is (1.00,0.01) C16H24N2O4SNa
TOF MS ES+
7.80e12
Theo.
[M+Na]+
4c
363.1354
364.1385
365.1349
Acceptable Δ = 1.8 mDa
Observed Δ = 0.6 mDa
01ERJ-78+HCl_03 (0.019) Is (1.00,0.01) C16H24N2O4SH
TOF MS ES+
7.80e12
Theo.
[M+H]+
341.1535
342.1565
343.1530
Acceptable Δ = 1.7 mDa
Observed Δ = 0.9 mDa
01ERJ-78+HCl_03 25 (0.458) AM (Cen,4, 80.00, Ar,1000.0,349.18,1.00); Sm (SG, 2x3.00); Cm (25:29)
TOF MS ES+
9.62e3
Cal.
341.1526
349.1838
363.1360
342.1581
334.0267
343.1588
344.1663
350.1880
355.1951
364.1378
366.0501
373.0559
375.0542
383.1892
385.1185
390.8662
m/z

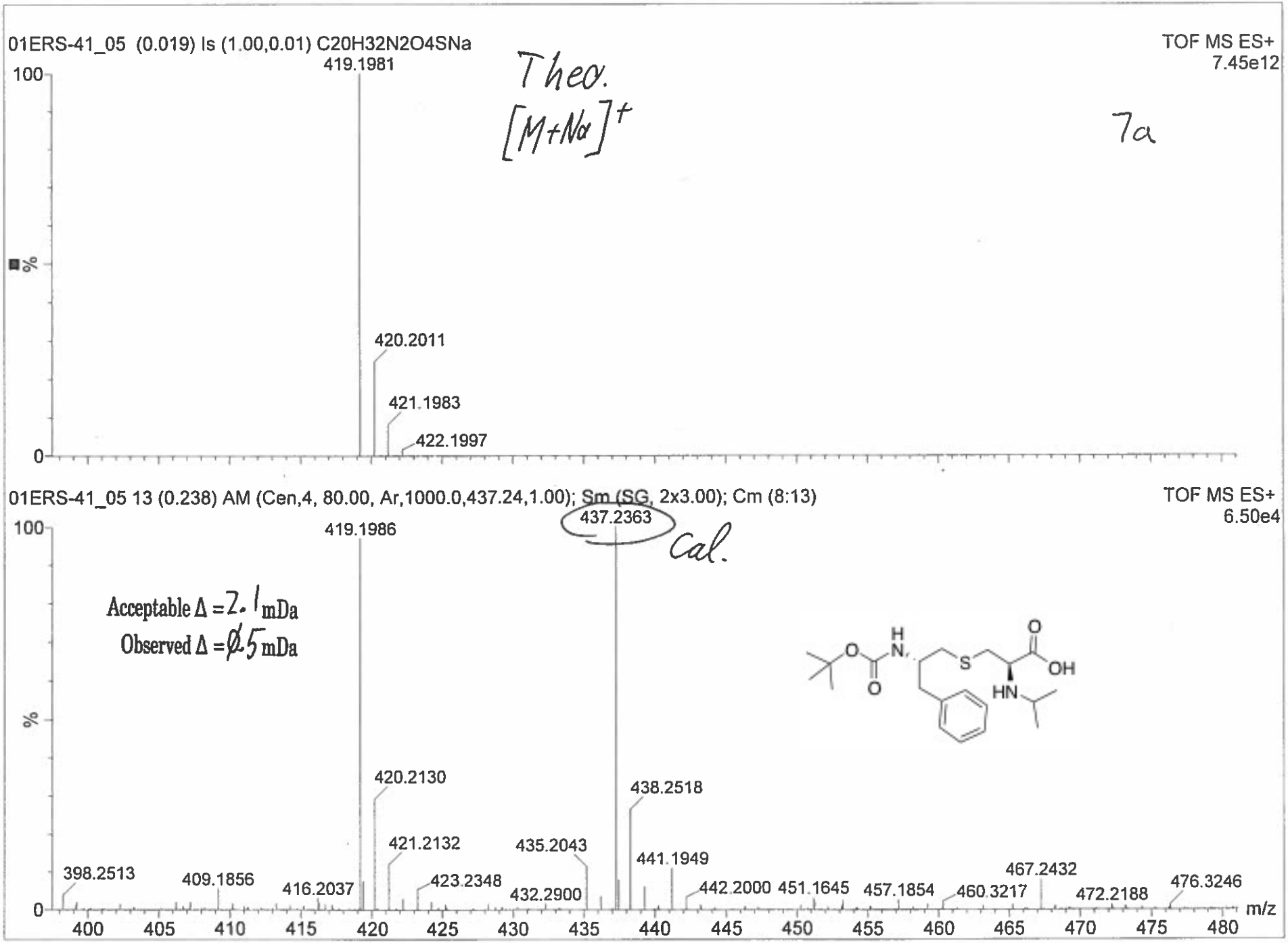

01ERS-61_08 (0.019) Is (1.00,0.01) C19H32N4O3SH
TOF MS ES+
7.50e12
Theo.
[M+H]+
5a
100
%
0
397.2273
398.2303
399.2273
400.2285
01ERS-61_08 11 (0.202) AM (Cen,4, 80.00, Ar,1000.0,393.21,1.00); Sm (SG, 2x3.00); Cm (9:11)
TOF MS ES+
3.61e4
393.2101
Cal.
397.2289
Acceptable Δ = 2.0 mDa
Observed Δ = 1.6 mDa
398.2433
399.2411
355.1982
362.2041
365.1812
377.2020
379.2097
384.2191
407.2372
409.1938
413.2460
m/z
355
360
365
370
375
380
385
390
395
400
405
410
415


01ERS-58_03 (0.019) Is (1.00,0.01) C21H34N4O3SH
TOF MS ES+
7.33e12
Theo.
[M+H]+
56
Acceptable Δ = 2.1 mDa
Observed Δ = 0.4 mDa
423.2430
424.2459
425.2434
01ERS-58_03 (0.019) Is (1.00,0.01) C21H34N4O3SNa
TOF MS ES+
7.33e12
Theo.
[M+Na]+
Acceptable Δ = 2.2 mDa
Observed Δ = 0.8 mDa
445.2249
446.2279
447.2253
01ERS-58_03 45 (0.825) AM (Cen,4, 80.00, Ar,1000.0,437.24,1.00); Sm (SG, 2x3.00); Cm (36:49)
TOF MS ES+
1.42e4
Cal.
437.2363
445.2241
423.2426
414.9828
424.2470
438.2412
446.2281
413.2674
425.2445
439.2433
447.2235
462.9740
468.9902
402.9516
408.9645
418.9846
435.9638
456.9618
472.9740
m/z


01ERS-80_06 (0.019) Is (1.00,0.01) C22H30N4O3SNa
TOF MS ES+
7.26e12
Theo.
[M+Na]+
5c
100
%
0
453.1936
454.1966
455.1942
456.1952
01ERS-80_06 24 (0.440) AM (Cen,4, 80.00, Ar,1000.0,437.24,1.00); Sm (SG, 2x3.00); Cm (24:26)
TOF MS ES+
4.77e3
437.2363
Cal.
Acceptable Δ = 2.3 mDa
Observed Δ = 1.1 mDa
453.1947
414.9843
438.2431
454.1986
413.2666
468.9926
439.2397
406.2154
409.1778
418.9846
425.0014
428.9628
451.2586
455.2049
462.9759
469.1840
476.9445
m/z
400
405
410
415
420
425
430
435
440
445
450
455
460
465
470
475


01ERS-49_04 (0.019) Is (1.00,0.01) C21H27NO5SNa
TOF MS ES+
7.39e12
Thee.
6a
[M+Na]+
428.1508
429.1540
430.1513
431.1528
01ERS-49_04 19 (0.348) AM (Cen,4, 80.00, Ar,1000.0,393.21,1.00); Sm (SG, 2x3.00); Cm (19:30)
TOF MS ES+
4.68e4
393.2101
Cal.
Acceptable Δ = 2.1 mDa
Observed Δ = 1.9 mDa
428.1527
394.2209
429.1604
370.9983
354.0858
362.1972
365.1722
377.1808
379.2005
386.1104
395.2222
406.2232
413.2711
414.9883
423.2271
430.1577
431.1582
m/z


01ERS-65_08 (0.019) Is (1.00,0.01) C23H28N2O5SNa
TOF MS ES+
7.20e12
100
%
0
467.1617
468.1648
469.1626
470.1638
Theo.
[M+Na]+
66
01ERS-65_08 23 (0.422) AM (Cen,4, 80.00, Ar,1000.0,481.26,1.00); Sm (SG, 2x3.00); Cm (23:30)
TOF MS ES+
2.33e4
481.2625
Cal.
Acceptable Δ = 2.3 mDa
Observed Δ = 1.6 mDa
467.1633
468.1684
469.1665
457.1766
466.9954
471.1692
482.2684
483.2735
487.1585
497.2498
499.1551
500.1570
510.9955
511.2485
512.9839
520.3568
523.2289
m/z
460
465
470
475
480
485
490
495
500
505
510
515
520
O
H
N
O
O
S
O
O
O
NH


01ERS-41_05 (0.019) Is (1.00,0.01) C20H32N2O4SNa
TOF MS ES+
7.45e12
Theo.
[M+Na]+
7a
419.1981
420.2011
421.1983
422.1997
01ERS-41_05 13 (0.238) AM (Cen,4, 80.00, Ar,1000.0,437.24,1.00); Sm (SG, 2x3.00); Cm (8:13)
TOF MS ES+
6.50e4
437.2363
Cal.
419.1986
Acceptable Δ = 2.1 mDa
Observed Δ = 0.5 mDa
420.2130
438.2518
421.2132
435.2043
441.1949
398.2513
409.1856
416.2037
423.2348
432.2900
442.2000
451.1645
457.1854
460.3217
467.2432
472.2188
476.3246
m/z

01ERS-36_06 (0.019) Is (1.00,0.01) C22H34N2O4SNa

TOF MS ES+
7.29e12

445.2137

Theo.
$[M+Na]^+$

7b

446.2168

447.2144

448.2156

01ERS-36_06 20 (0.367) AM (Cen,4, 80.00, Ar,1000.0,437.24,1.00); Sm (SG, 2x3.00); Cm (20:29)

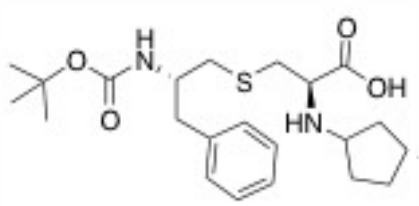
TOF MS ES+
4.02e4

437.2363

445.2130

Cal.

Acceptable Δ = 2.2 mDa
Observed Δ = 0.7 mDa



446.2234

467.2046

438.2443

447.2199

468.2088

394.2223

414.9901

439.2466

448.2204

461.2053

473.2135

395.2226

406.2255

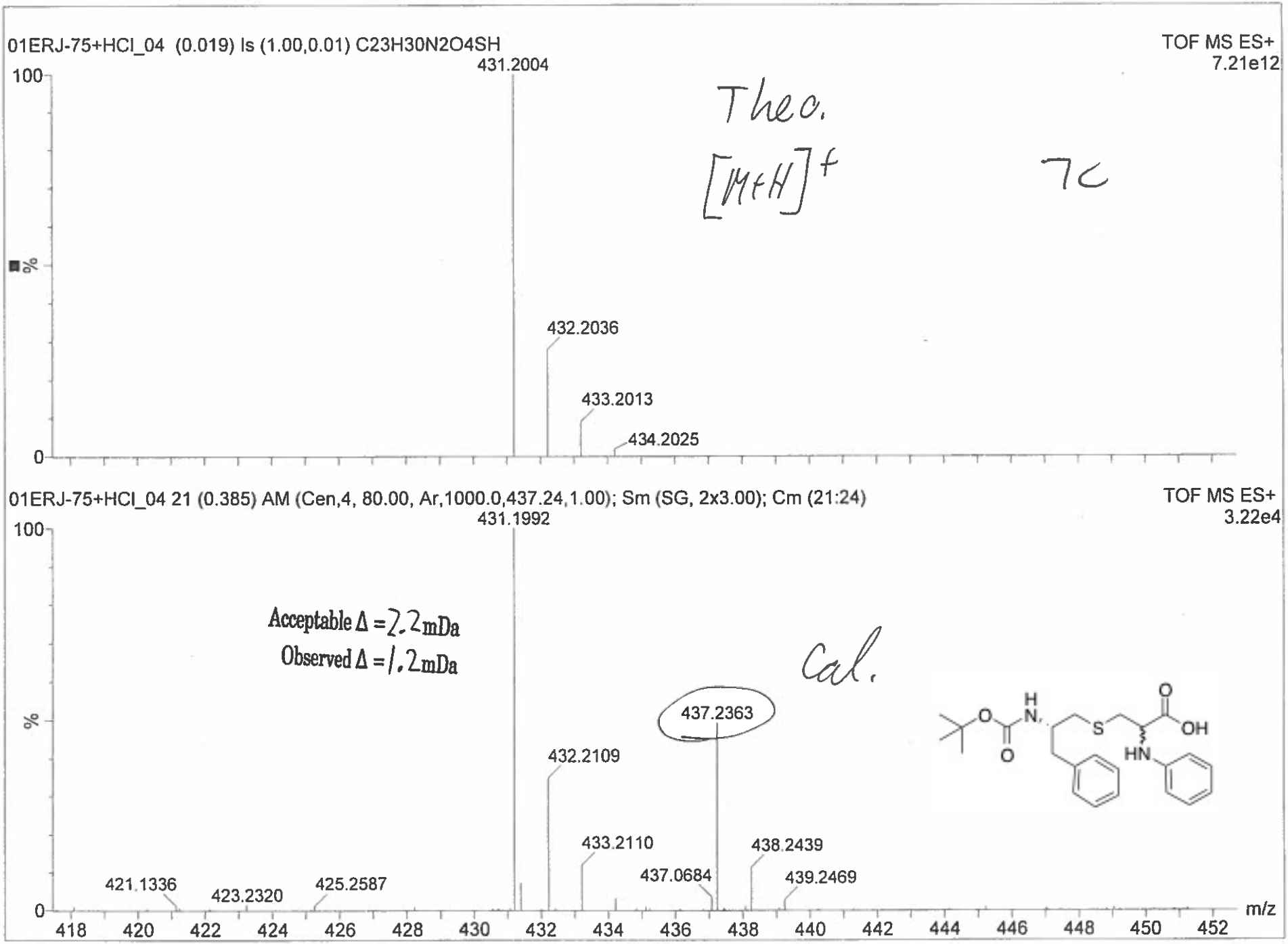
413.2751

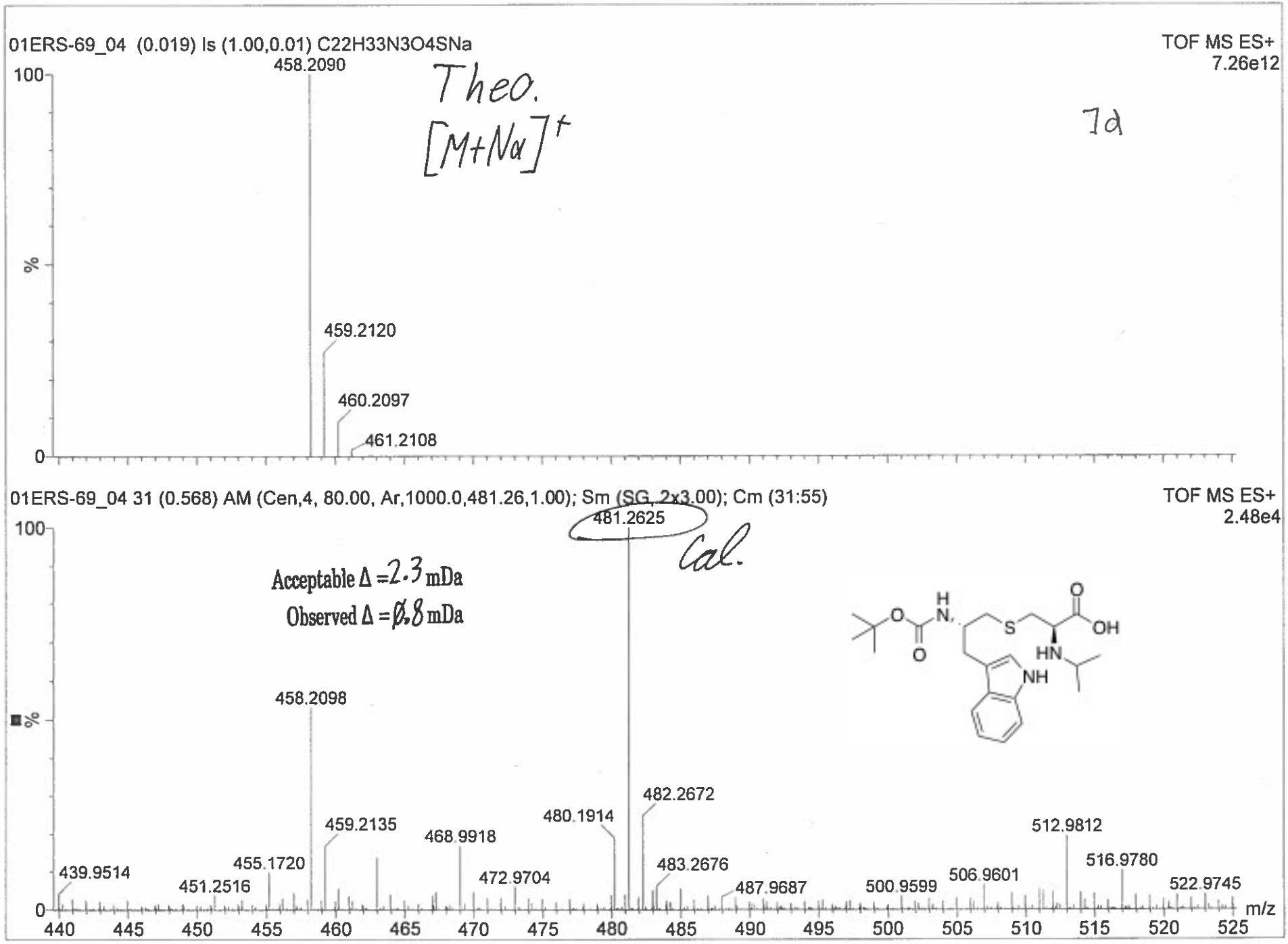
415.2035

423.2331

428.2346

m/z


01ERJ-75+HCl_04 (0.019) Is (1.00,0.01) C23H30N2O4SH
TOF MS ES+
7.21e12
100
%
0
431.2004
432.2036
433.2013
434.2025
Theo.
[M+H]+
7C
01ERJ-75+HCl_04 21 (0.385) AM (Cen,4, 80.00, Ar,1000.0,437.24,1.00); Sm (SG, 2x3.00); Cm (21:24)
TOF MS ES+
3.22e4
431.1992
Acceptable Δ = 2.2mDa
Observed Δ = 1.2mDa
Cal.
437.2363
432.2109
433.2110
438.2439
437.0684
439.2469
421.1336
423.2320
425.2587
m/z
418
420
422
424
426
428
430
432
434
436
438
440
442
444
446
448
450
452

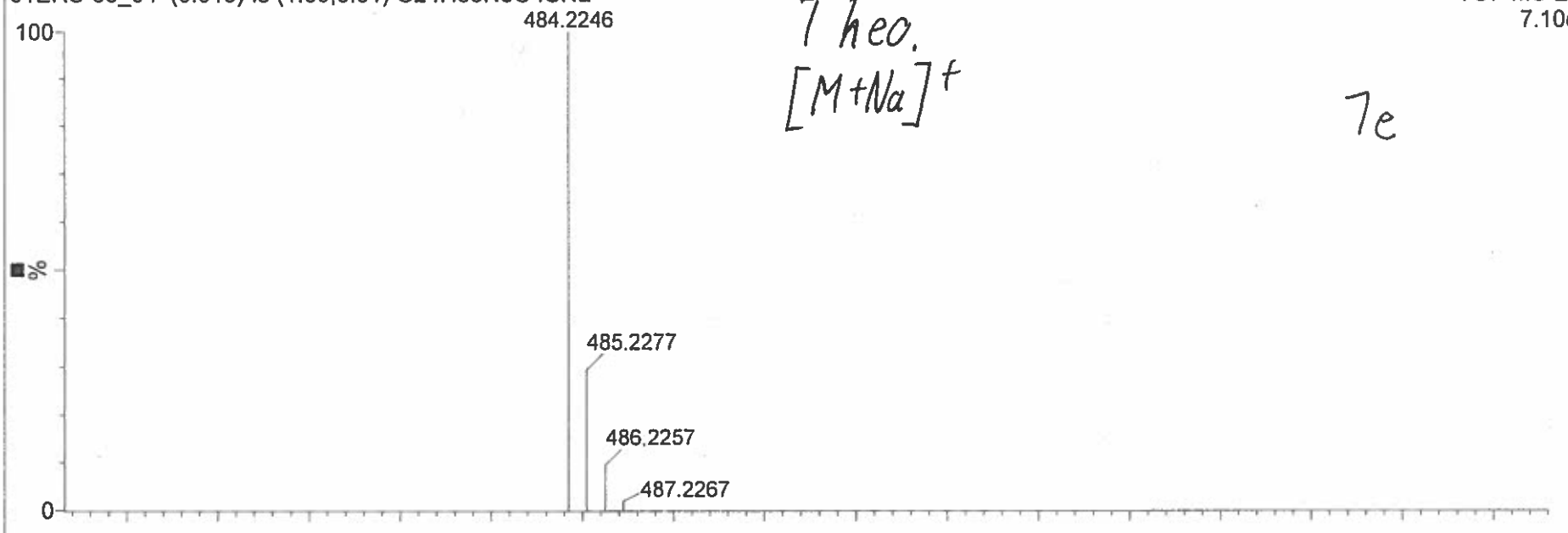

01ERS-69_04 (0.019) Is (1.00,0.01) C22H33N3O4SNa
TOF MS ES+
7.26e12
100
%
0
458.2090
459.2120
460.2097
461.2108
Theo.
[M+Na]+
7d
01ERS-69_04 31 (0.568) AM (Cen,4, 80.00, Ar,1000.0,481.26,1.00); Sm (SG, 2x3.00); Cm (31:55)
TOF MS ES+
2.48e4
481.2625
Cal.
Acceptable Δ = 2.3 mDa
Observed Δ = 0.8 mDa
458.2098
459.2135
439.9514
451.2516
455.1720
468.9918
472.9704
480.1914
482.2672
483.2676
487.9687
500.9599
506.9601
512.9812
516.9780
522.9745
m/z
440
445
450
455
460
465
470
475
480
485
490
495
500
505
510
515
520
525

01ERS-66_04 (0.019) Is (1.00,0.01) C24H35N3O4SNa

TOF MS ES+
7.10e12

Theo.
$[M+Na]^+$

7e

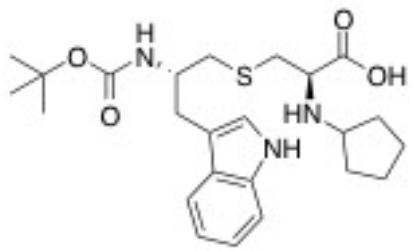


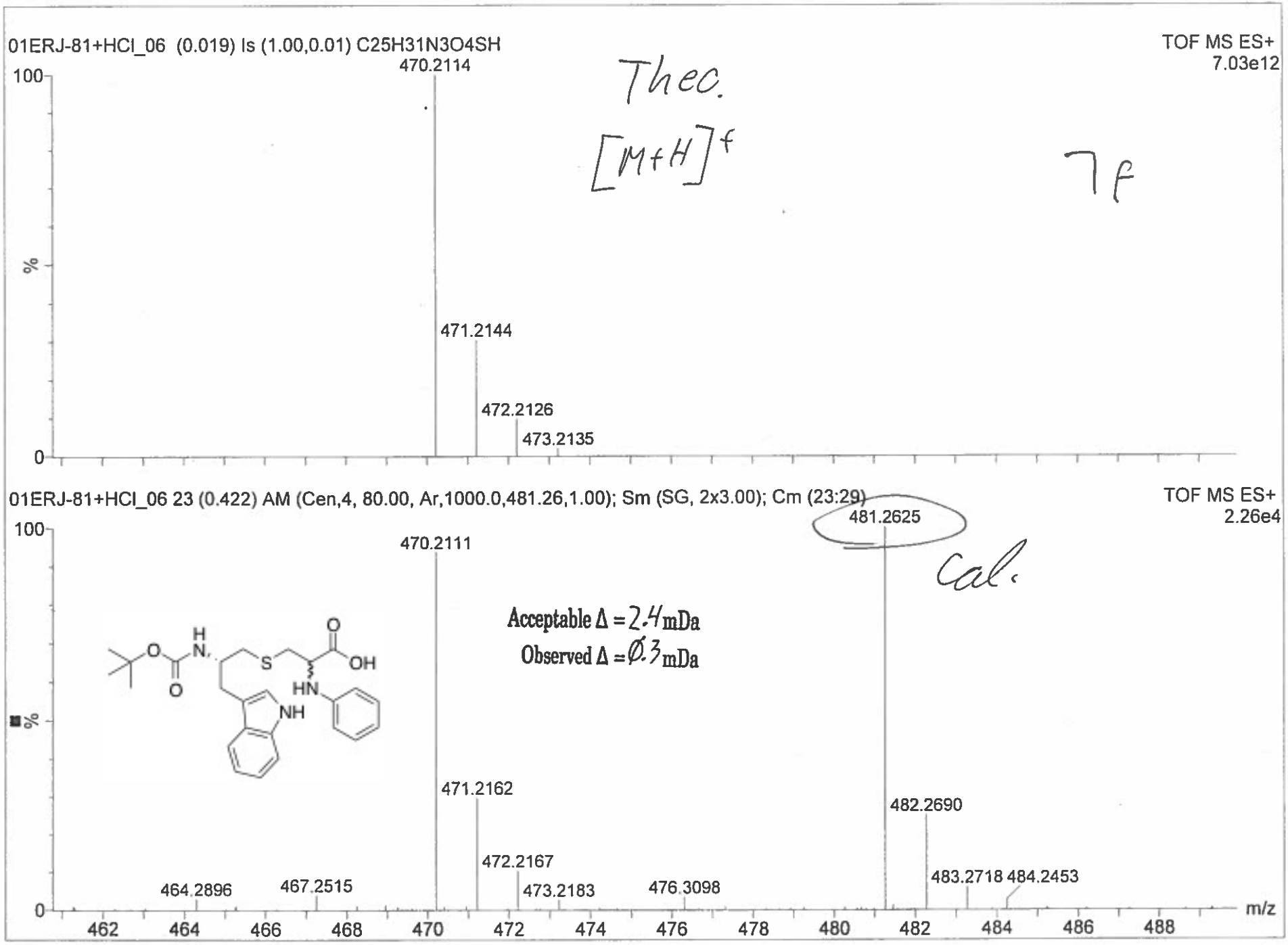
01ERS-66_04 15 (0.275) AM (Cen,4, 80.00, Ar,1000.0,495.28,1.00); Sm (SG, 2x3.00); Cm (13:21)

TOF MS ES+
1.32e5

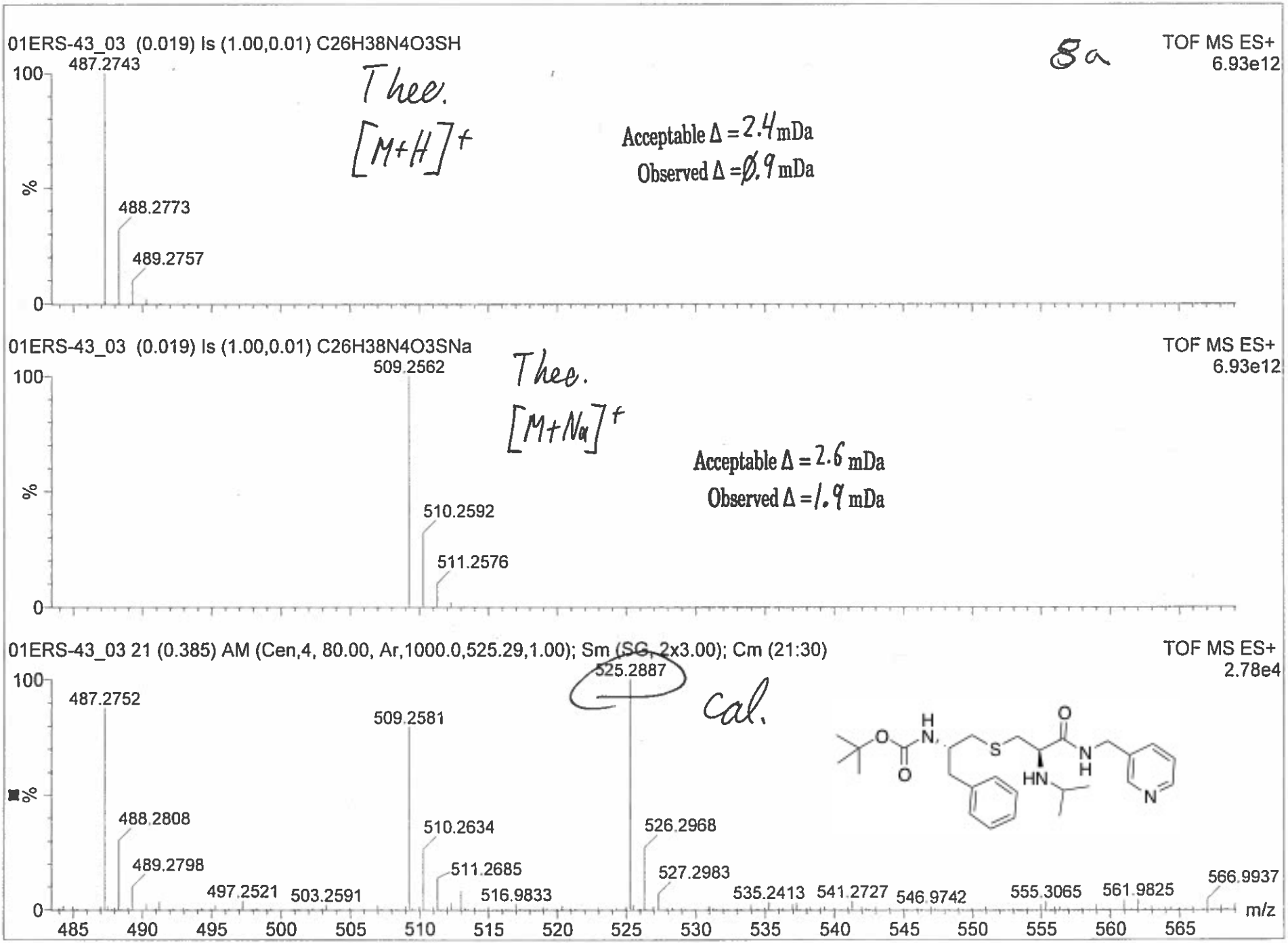
Cal.

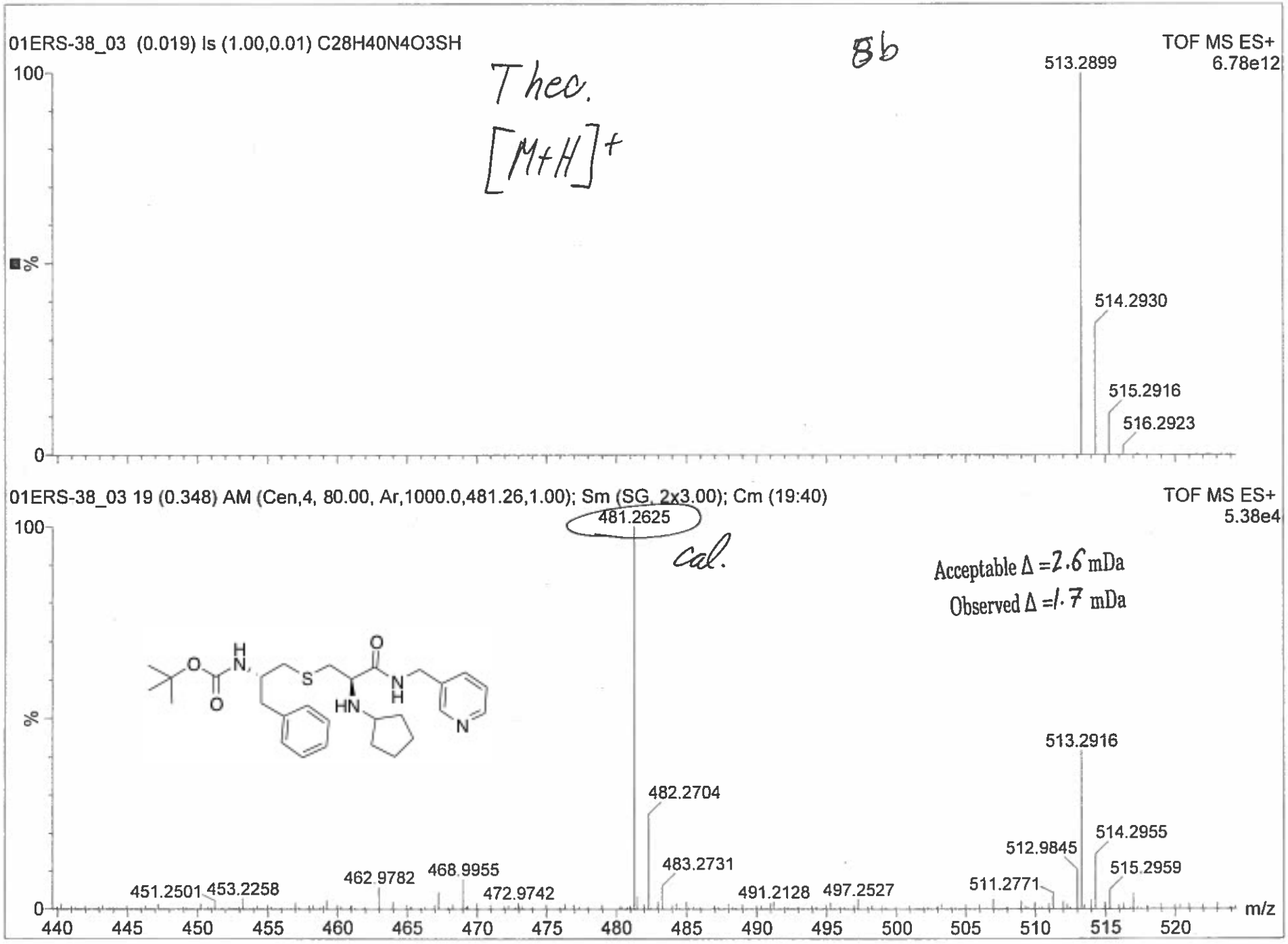
Acceptable Δ = 2.4 mDa
Observed Δ = 0.2 mDa

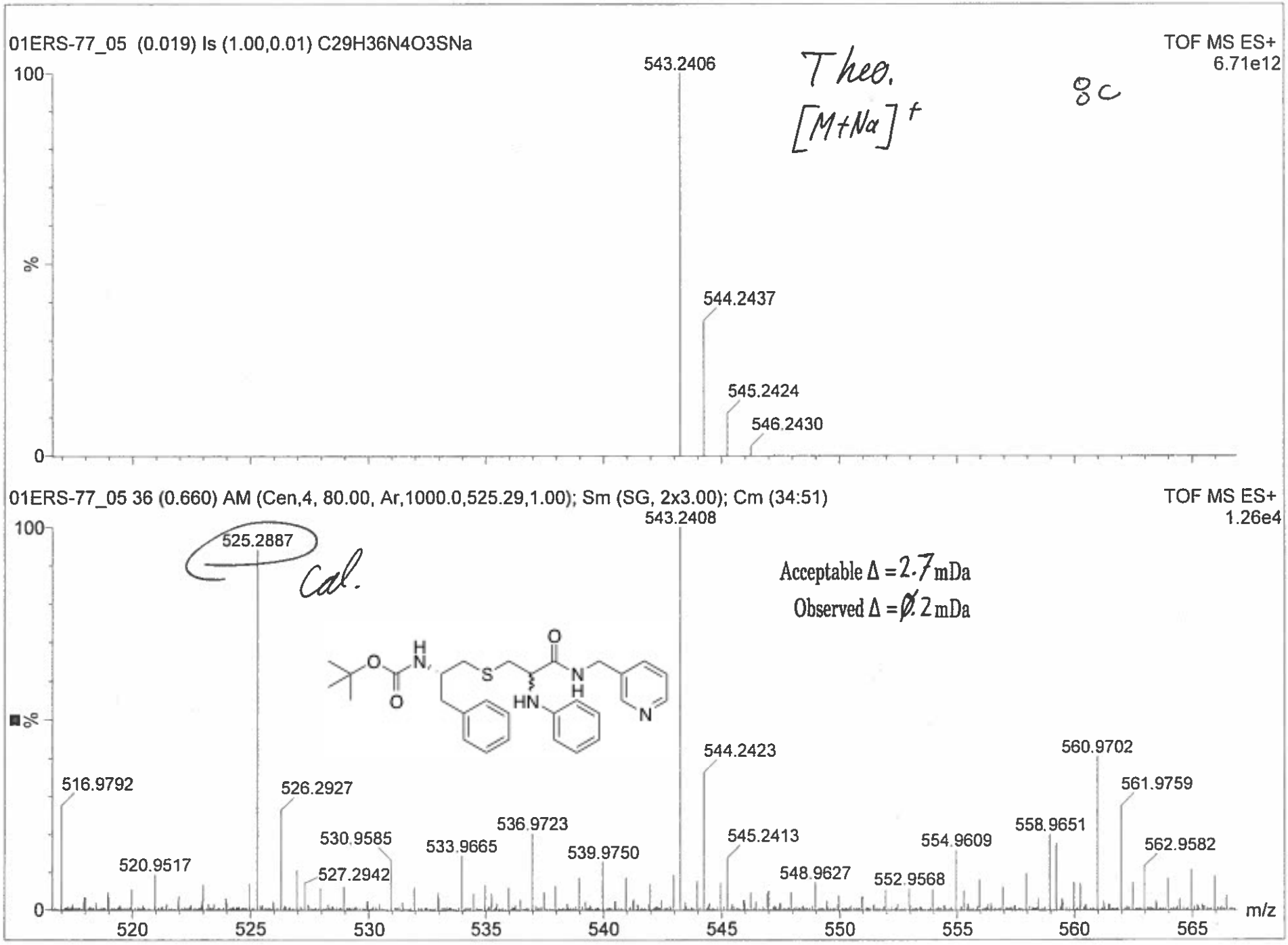


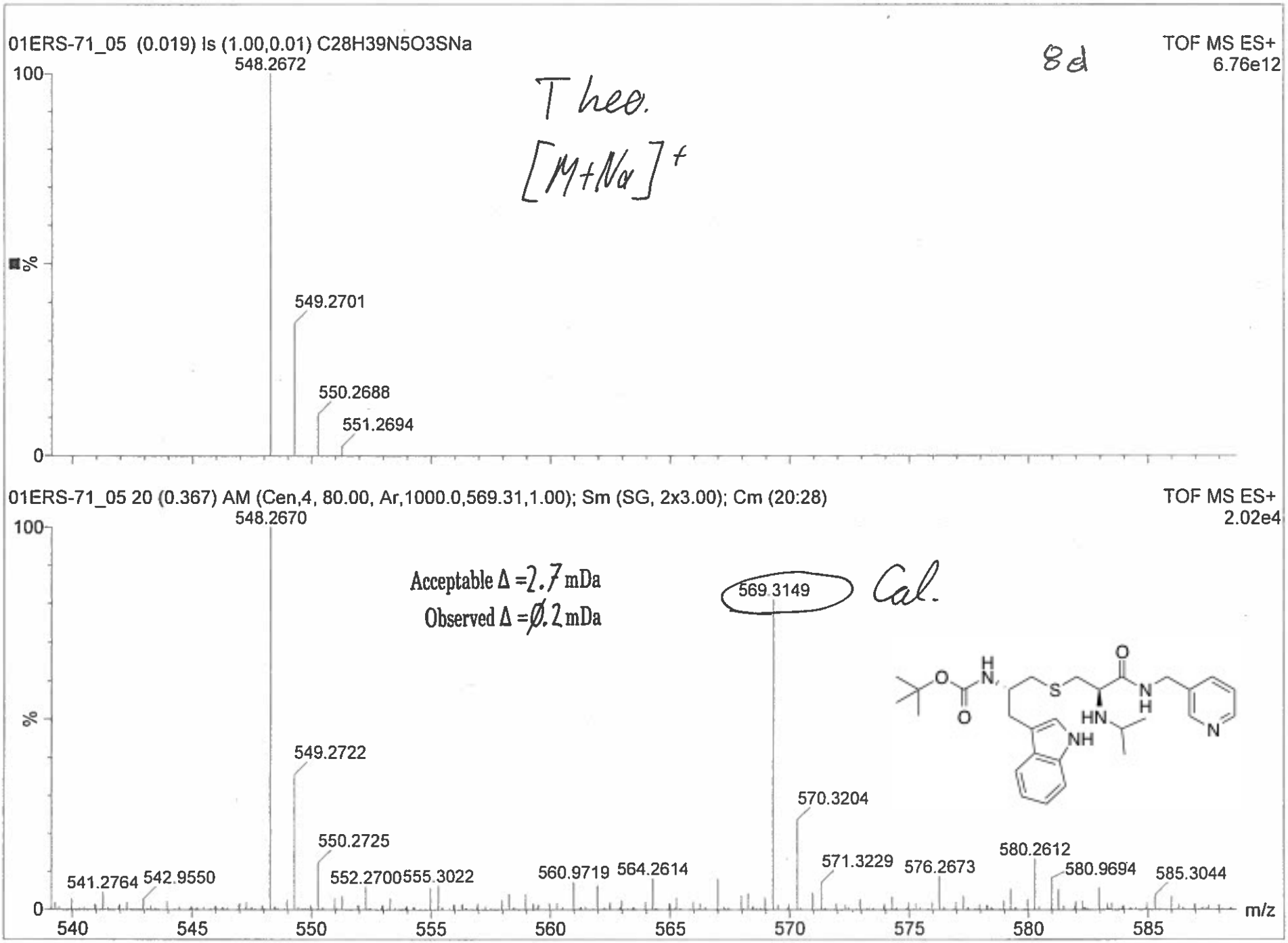

01ERJ-81+HCl_06 (0.019) Is (1.00,0.01) C25H31N3O4SH
TOF MS ES+
7.03e12
100
%
0
470.2114
471.2144
472.2126
473.2135
Thec.
[M+H]+
7f
01ERJ-81+HCl_06 23 (0.422) AM (Cen,4, 80.00, Ar,1000.0,481.26,1.00); Sm (SG, 2x3.00); Cm (23:29)
TOF MS ES+
2.26e4
481.2625
Cal.
470.2111
Acceptable Δ = 2.4 mDa
Observed Δ = 0.3 mDa
471.2162
482.2690
472.2167
483.2718
484.2453
464.2896
467.2515
473.2183
476.3098
m/z
462
464
466
468
470
472
474
476
478
480
482
484
486
488

8a


01ERS-43_03 (0.019) Is (1.00,0.01) C26H38N4O3SH
TOF MS ES+
6.93e12
Thee.
[M+H]+
Acceptable Δ = 2.4 mDa
Observed Δ = 0.9 mDa
487.2743
488.2773
489.2757
01ERS-43_03 (0.019) Is (1.00,0.01) C26H38N4O3SNa
TOF MS ES+
6.93e12
Thee.
[M+Na]+
Acceptable Δ = 2.6 mDa
Observed Δ = 1.9 mDa
509.2562
510.2592
511.2576
01ERS-43_03 21 (0.385) AM (Cen,4, 80.00, Ar,1000.0,525.29,1.00); Sm (SG, 2x3.00); Cm (21:30)
TOF MS ES+
2.78e4
cal.
525.2887
487.2752
509.2581
488.2808
510.2634
526.2968
489.2798
511.2685
527.2983
497.2521
503.2591
516.9833
535.2413
541.2727
546.9742
555.3065
561.9825
566.9937
%
m/z


01ERS-38_03 (0.019) Is (1.00,0.01) C28H40N4O3SH
8b
Theo.
[M+H]+
TOF MS ES+
6.78e12
100
%
0
513.2899
514.2930
515.2916
516.2923
01ERS-38_03 19 (0.348) AM (Cen,4, 80.00, Ar,1000.0,481.26,1.00); Sm (SG, 2x3.00); Cm (19:40)
TOF MS ES+
5.38e4
481.2625
cal.
Acceptable Δ = 2.6 mDa
Observed Δ = 1.7 mDa
513.2916
482.2704
514.2955
512.9845
483.2731
515.2959
511.2771
451.2501
453.2258
462.9782
468.9955
472.9742
491.2128
497.2527
m/z
440
445
450
455
460
465
470
475
480
485
490
495
500
505
510
515
520


01ERS-77_05 (0.019) Is (1.00,0.01) C29H36N4O3SNa
TOF MS ES+
6.71e12
100
%
0
543.2406
544.2437
545.2424
546.2430
Theo.
[M+Na]+
8c
01ERS-77_05 36 (0.660) AM (Cen,4, 80.00, Ar,1000.0,525.29,1.00); Sm (SG, 2x3.00); Cm (34:51)
TOF MS ES+
1.26e4
100
%
0
543.2408
525.2887
Cal.
Acceptable Δ = 2.7 mDa
Observed Δ = 0.2 mDa
544.2423
560.9702
561.9759
516.9792
526.2927
530.9585
536.9723
533.9665
539.9750
545.2413
558.9651
554.9609
562.9582
520.9517
527.2942
548.9627
552.9568
m/z
520
525
530
535
540
545
550
555
560
565

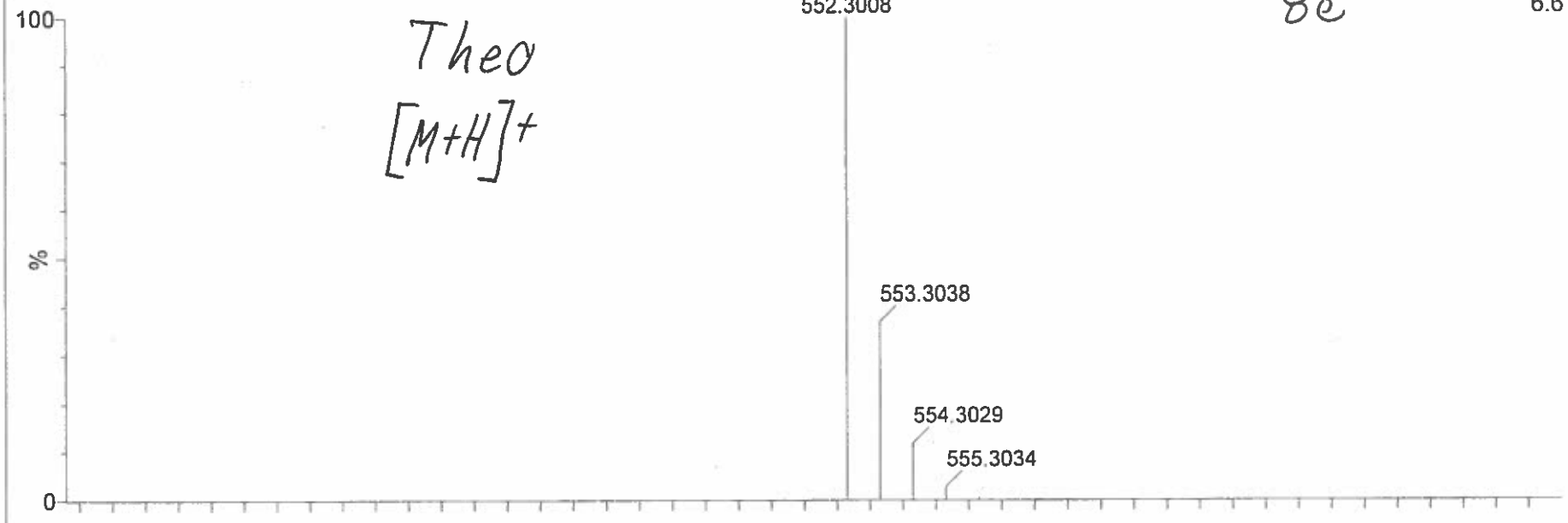

01ERS-71_05 (0.019) Is (1.00,0.01) C28H39N5O3SNa
TOF MS ES+
6.76e12
8d
Theo.
[M+Na]+
548.2672
549.2701
550.2688
551.2694
01ERS-71_05 20 (0.367) AM (Cen,4, 80.00, Ar,1000.0,569.31,1.00); Sm (SG, 2x3.00); Cm (20:28)
TOF MS ES+
2.02e4
548.2670
Acceptable Δ = 2.7 mDa
Observed Δ = 0.2 mDa
569.3149
Cal.
549.2722
550.2725
570.3204
541.2764
542.9550
552.2700
555.3022
560.9719
564.2614
571.3229
576.2673
580.2612
580.9694
585.3044
%
m/z
100
0
540
545
550
555
560
565
570
575
580
585

01ERS-68_07 (0.019) Is (1.00,0.01) C30H41N5O3SH

TOF MS ES+
6.61e12

8e

Theo
[M+H]+

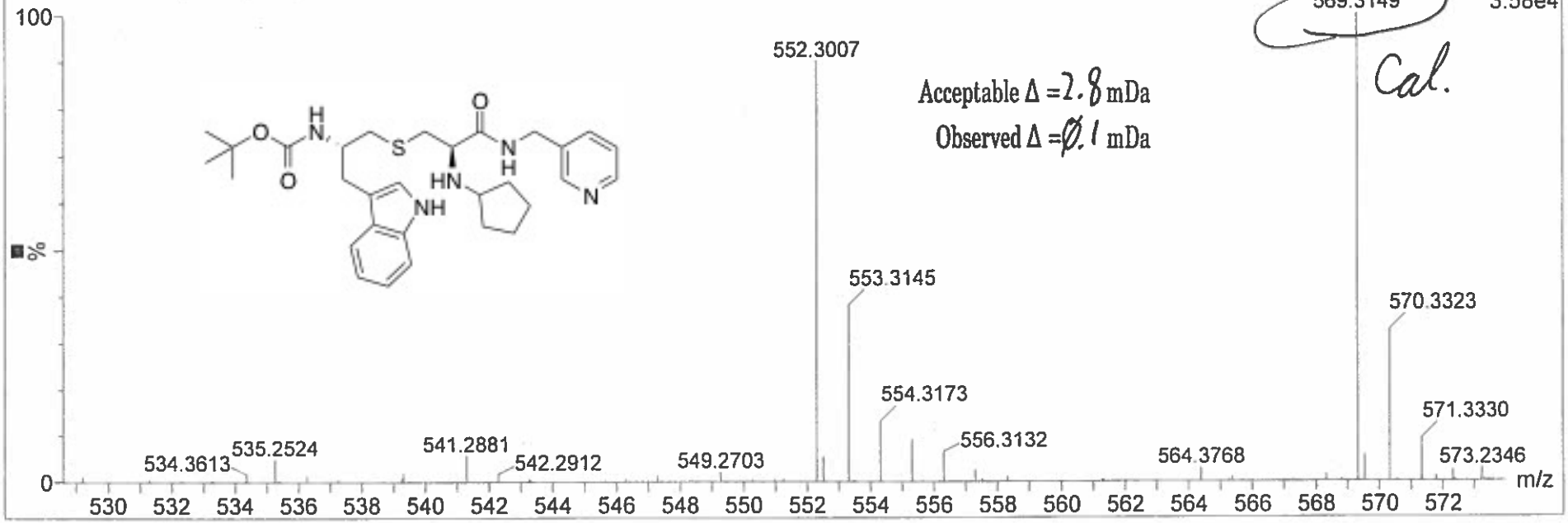


01ERS-68_07 9 (0.165) AM (Cen,4, 80.00, Ar,1000.0,569.31,1.00); Sm (SG, 2x3.00); Cm (7:9)

TOF MS ES+
3.58e4

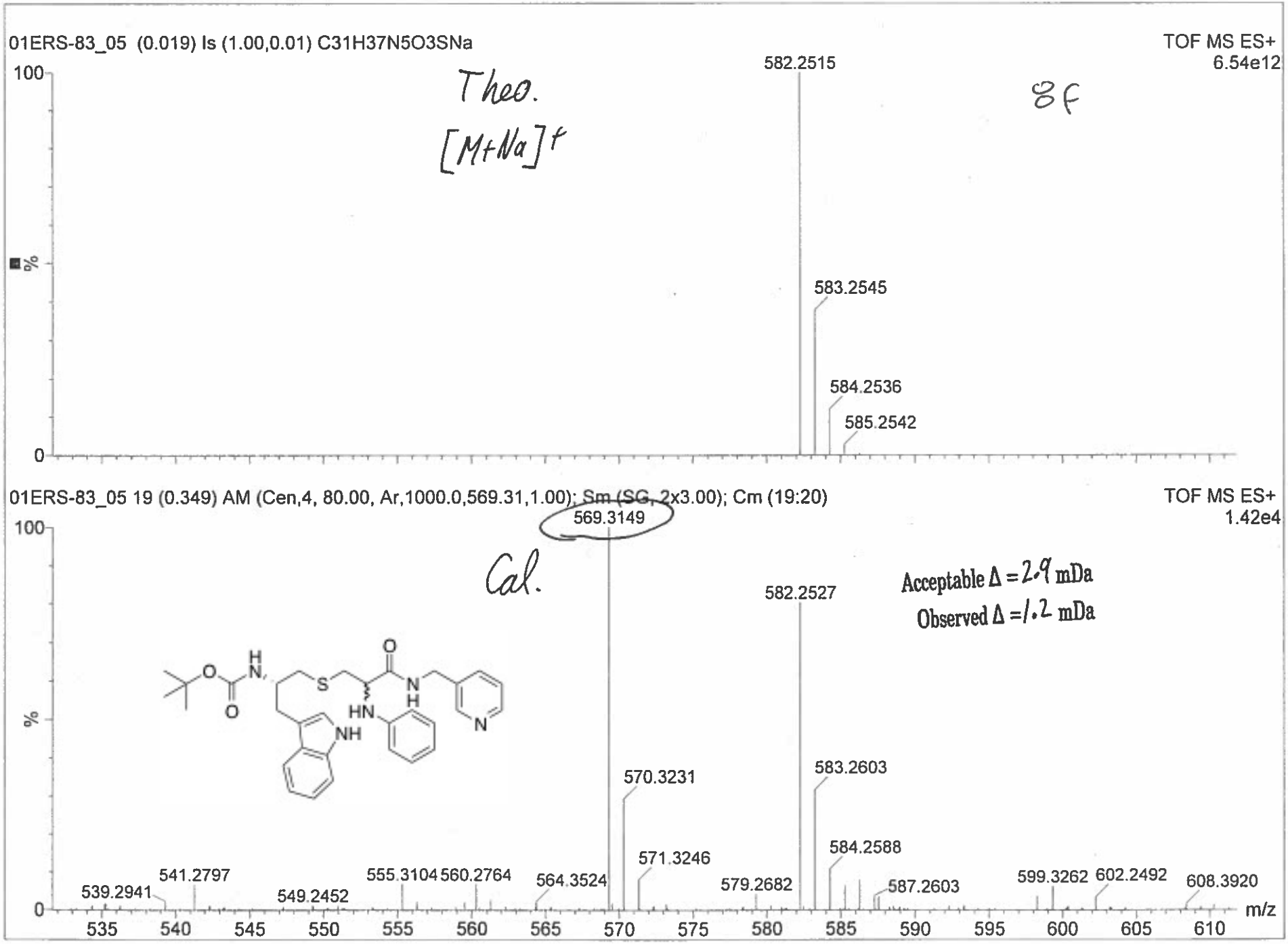
569.3149

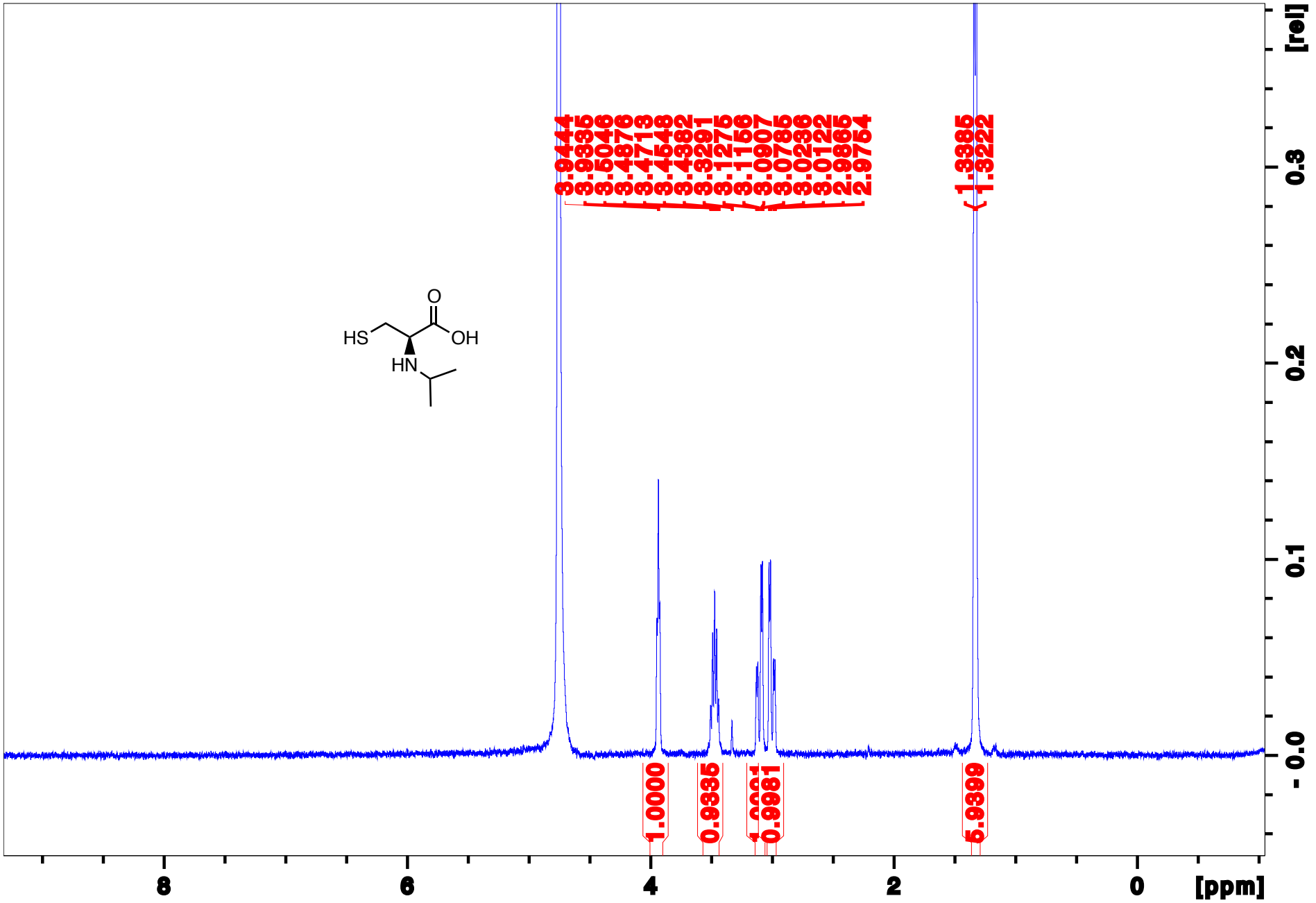
Cal.

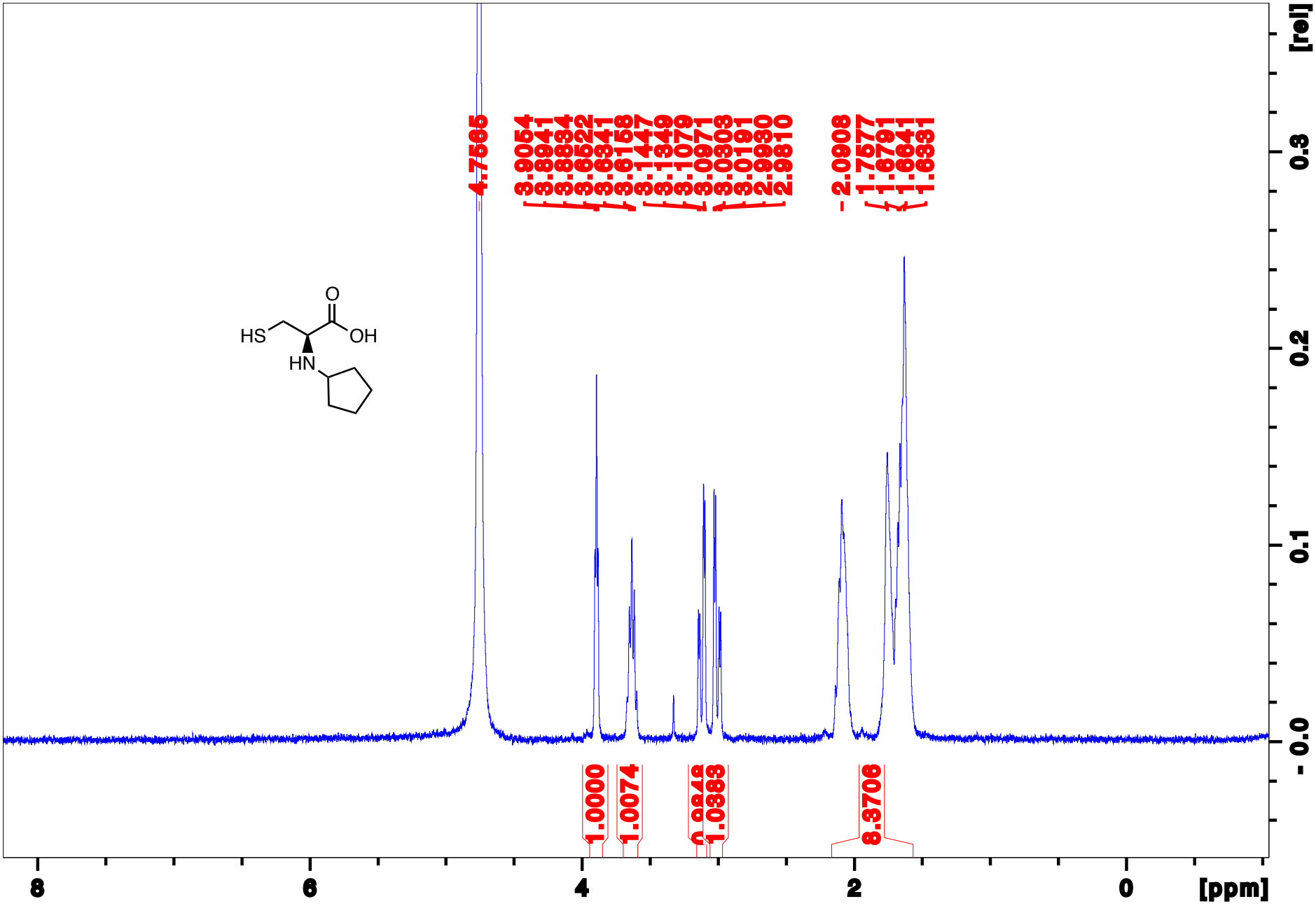


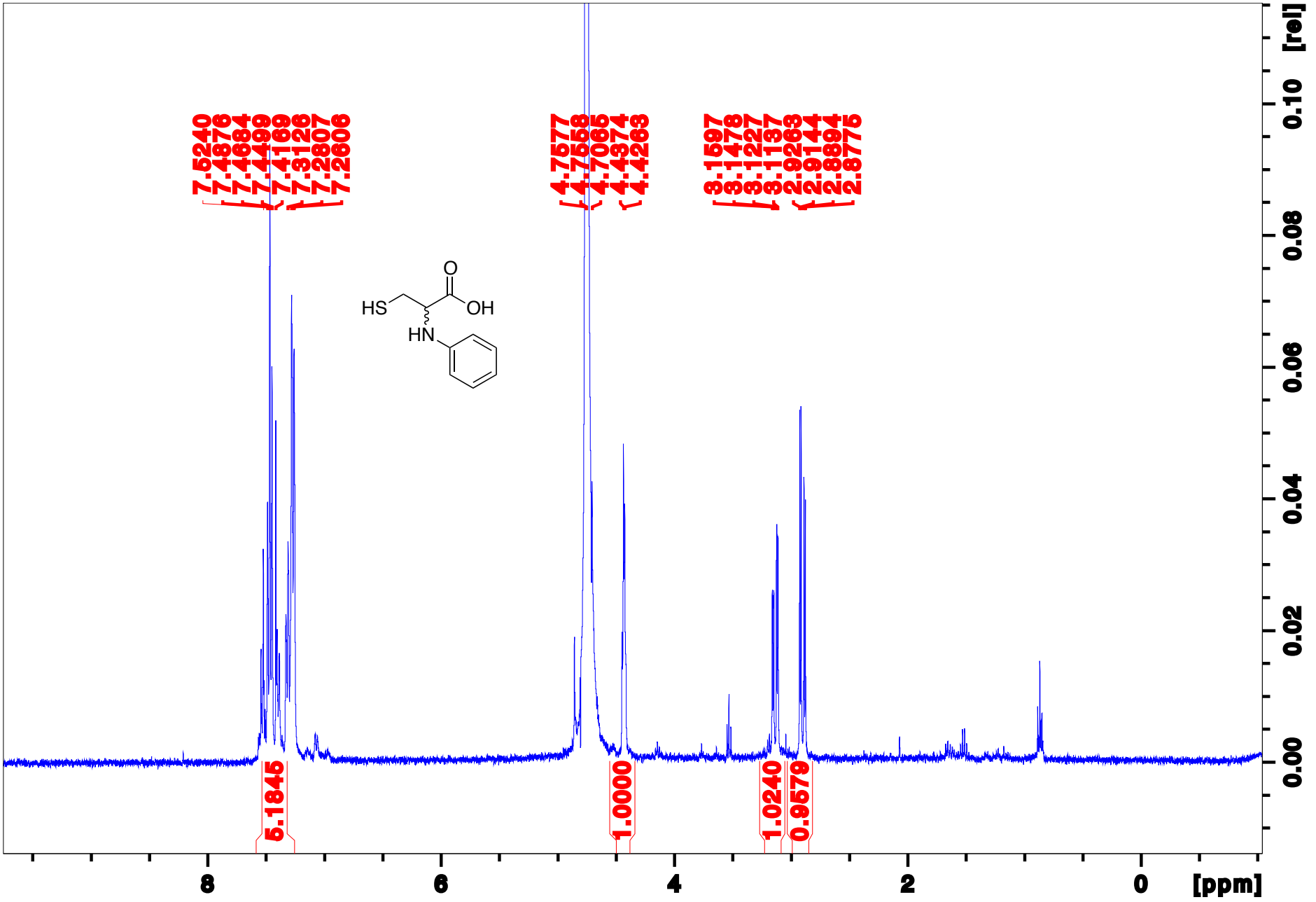
Acceptable Δ = 2.8 mDa

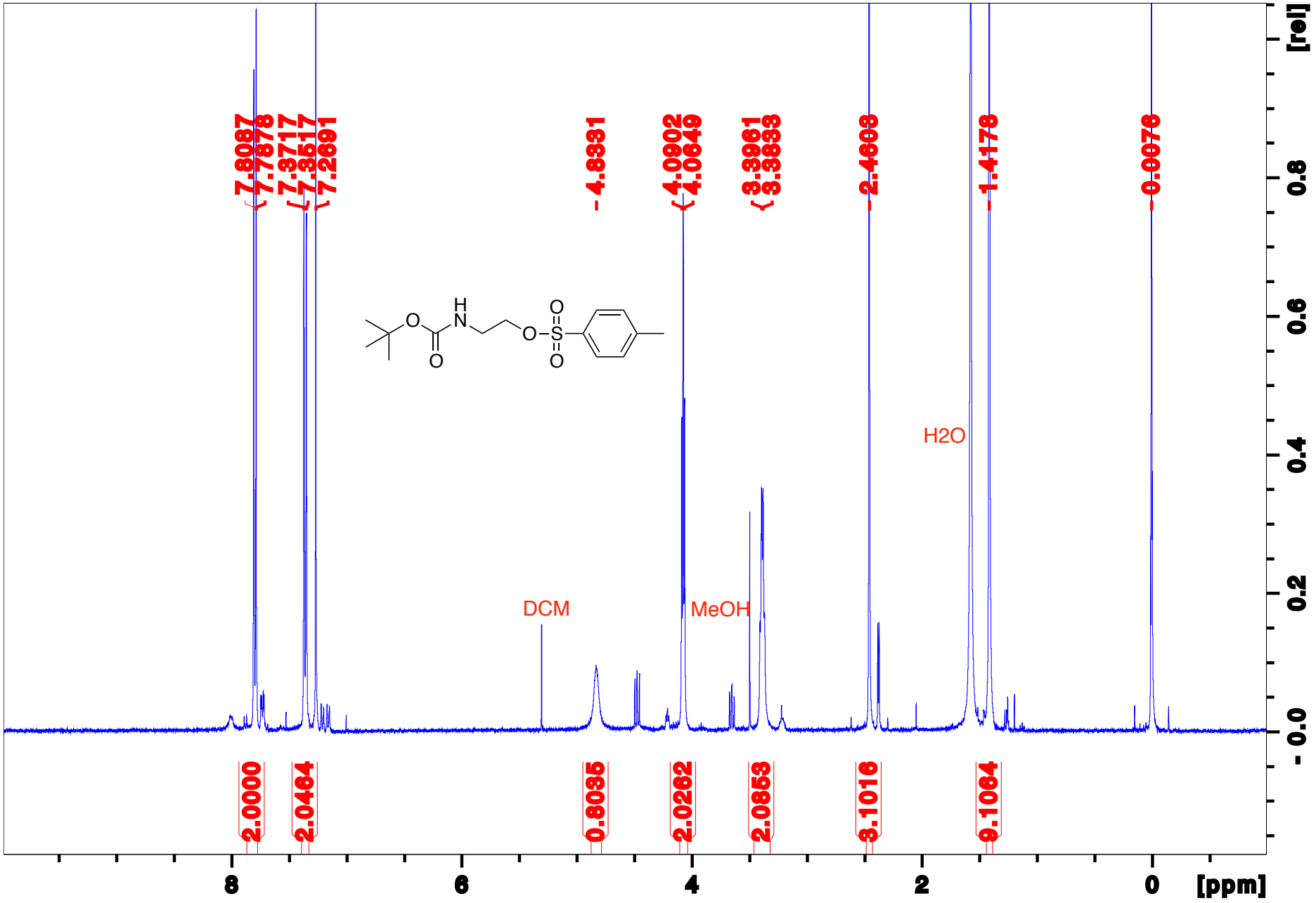
Observed Δ = 0.1 mDa


01ERS-83_05 (0.019) Is (1.00,0.01) C31H37N5O3SNa
TOF MS ES+
6.54e12
100
%
0
582.2515
583.2545
584.2536
585.2542
Theo.
[M+Na]+
8F
01ERS-83_05 19 (0.349) AM (Cen,4, 80.00, Ar,1000.0,569.31,1.00); Sm (SG, 2x3.00); Cm (19:20)
TOF MS ES+
1.42e4
569.3149
Cal.
582.2527
Acceptable Δ = 2.9 mDa
Observed Δ = 1.2 mDa
570.3231
583.2603
571.3246
584.2588
539.2941
541.2797
549.2452
555.3104
560.2764
564.3524
579.2682
587.2603
599.3262
602.2492
608.3920
m/z
535
540
545
550
555
560
565
570
575
580
585
590
595
600
605
610


3.9444
3.9335
3.5046
3.4876
3.4713
3.4548
3.4382
3.3291
3.1275
3.1156
3.0907
3.0765
3.0236
3.0122
2.9865
2.9754
1.3385
1.3222
HS
O
OH
HN
1.0000
0.9335
0.9981
5.9399
8
6
4
2
0
[ppm]
[rel]
0.3
0.2
0.1
- 0.0


4.7505
3.9054
3.8941
3.8834
3.6522
3.6341
3.6158
3.1447
3.1349
3.1079
3.0971
3.0303
3.0191
2.9930
2.9810
2.0908
1.7577
1.6791
1.6641
1.6331
1.0000
1.0074
0.9848
1.0383
8.3706
HS
O
OH
HN
8
6
4
2
0
[ppm]
[rel]
0.3
0.2
0.1
0.0


7.5240
7.4376
7.4084
7.4099
7.4169
7.3126
7.2807
7.2606
4.7577
4.7558
4.7065
4.4374
4.4263
3.1597
3.1478
3.1227
3.1137
2.9263
2.9144
2.8894
2.8775
HS
OH
HN
O
5.1845
1.0000
1.0240
0.9579
8
6
4
2
0
[ppm]
0.00
0.02
0.04
0.06
0.08
0.10
[rel]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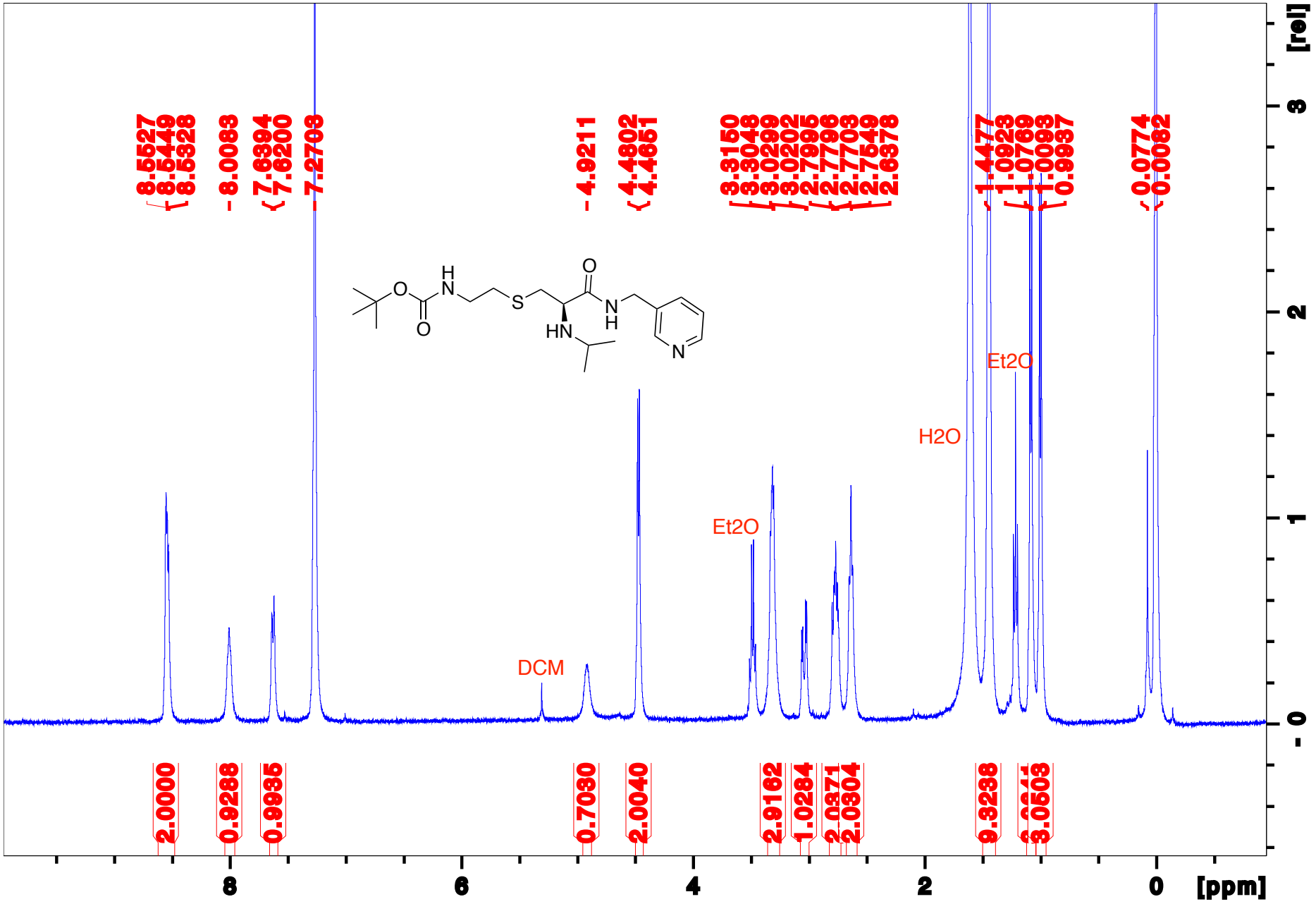
7.7878
7.3717
7.3517
7.2691
4.8331
4.0902
4.0849
3.9961
3.9833
2.4608
1.4178
0.0076
DCM
MeOH
H2O
2.0000
2.0464
0.8035
2.0262
2.0853
3.1016
9.1064
8
6
4
2
0
[ppm]
[rel]
0.8
0.6
0.4
0.2
0.0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8.5449
8.5328
8.0083
7.6394
7.6200
7.2703
4.9211
4.4802
4.4651
3.3150
3.3048
3.2999
3.2902
2.7995
2.7796
2.7703
2.7549
2.6378
1.4477
1.0923
1.0769
1.0093
0.9937
0.0774
0.0082
DCM
Et2O
H2O
Et2O
2.0000
0.9288
0.9935
0.7030
2.0040
2.9162
1.0284
2.0371
2.0304
9.3238
3.0641
3.0503
8
6
4
2
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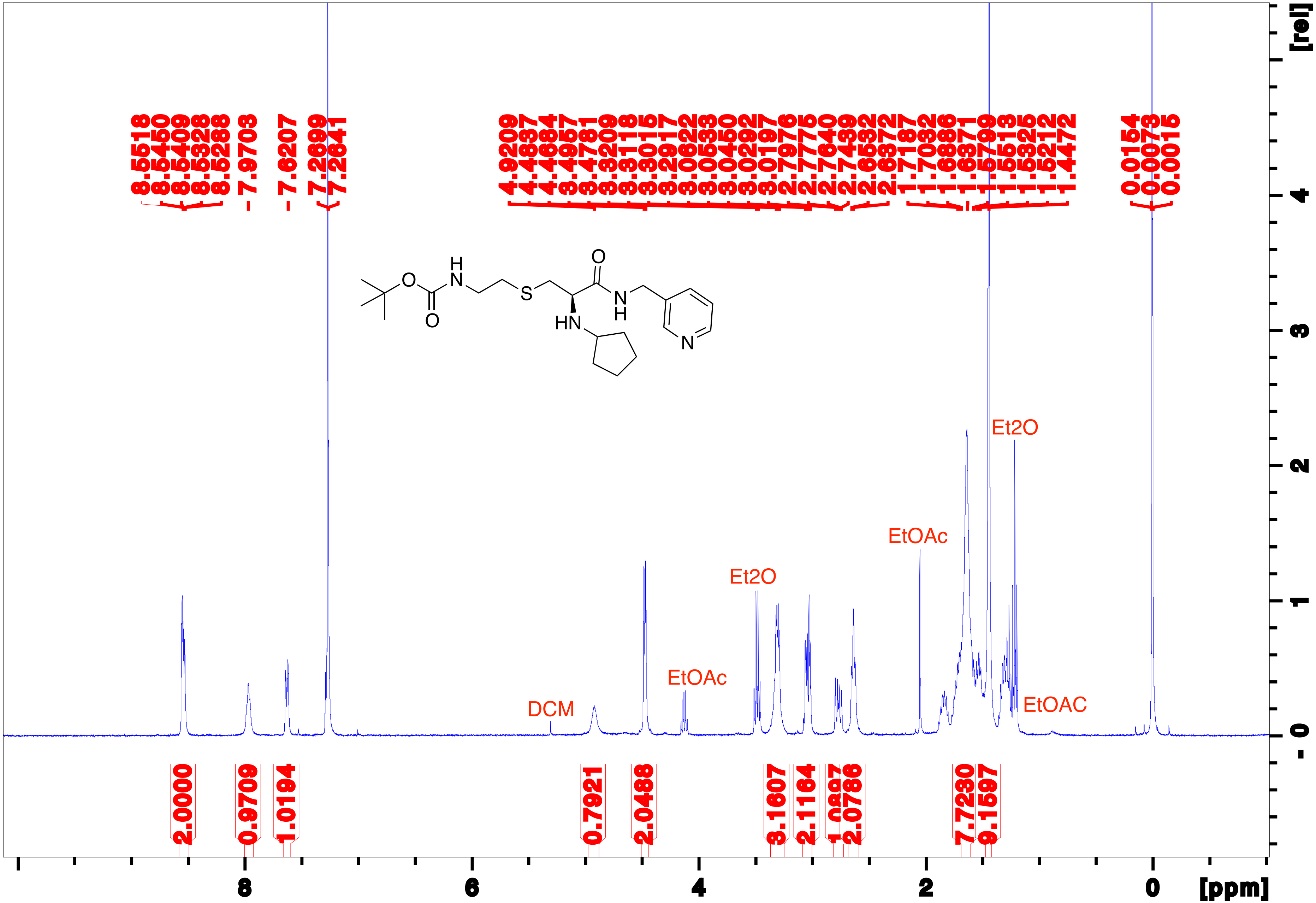
[rel]


8.5518
8.5450
8.5409
8.5328
8.5288
7.9703
7.6207
7.2699
7.2641
4.9209
4.4837
4.4684
3.4957
3.4781
3.3209
3.3118
3.3015
3.2917
3.0622
3.0533
3.0450
3.0292
3.0197
2.7976
2.7775
2.7640
2.7439
2.6532
2.6372
1.7187
1.7082
1.6886
1.6371
1.5799
1.5513
1.5325
1.5212
1.4472
0.0154
0.0073
0.0015
DCM
EtOAc
Et2O
EtOAc
Et2O
EtOAC
2.0000
0.9709
1.0194
0.7921
2.0488
3.1607
2.1164
1.0897
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7.7230
9.1597
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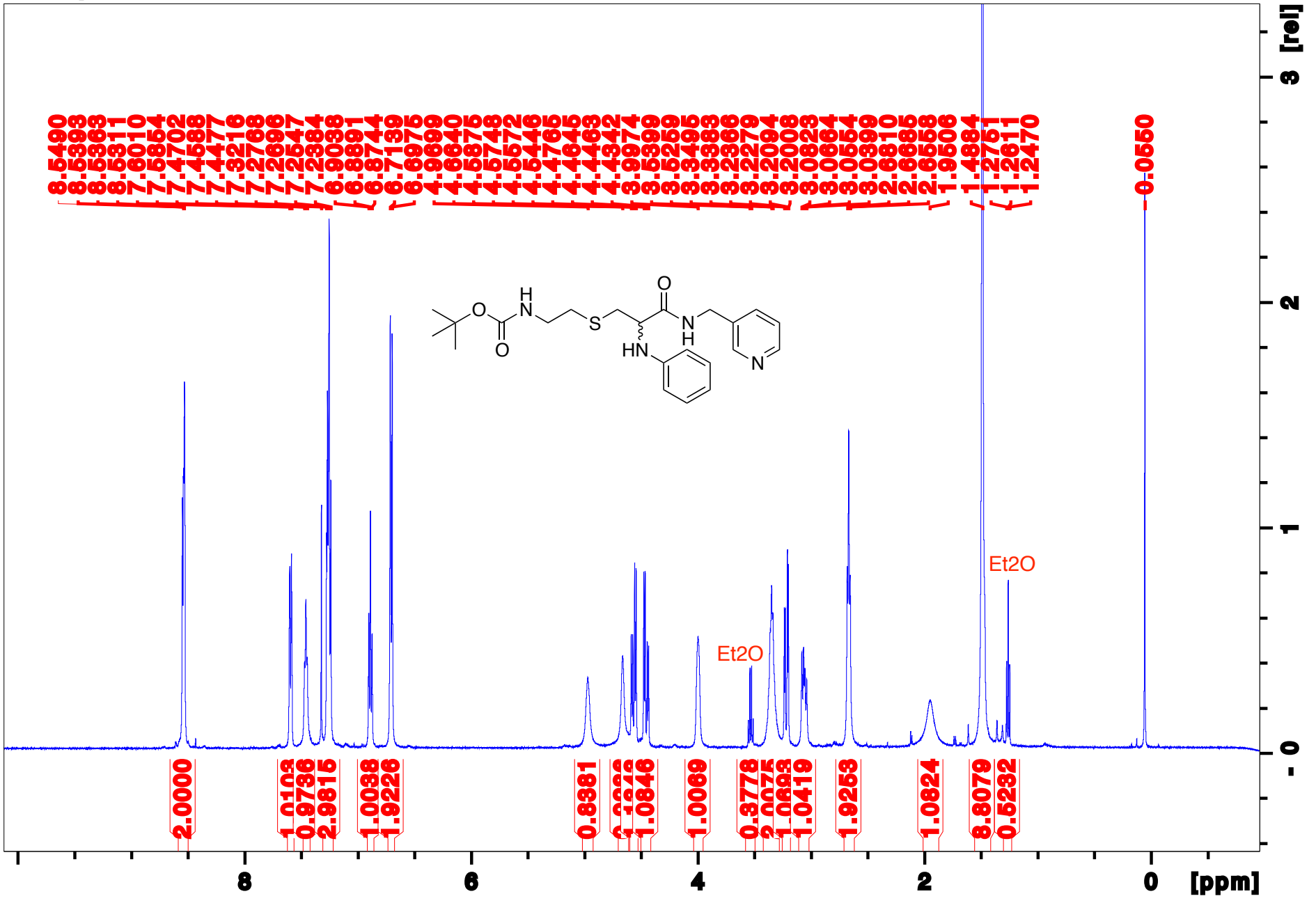
[ppm]


Et2O
Et2O
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[ppm]
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1.0103
0.9736
2.9815
1.0038
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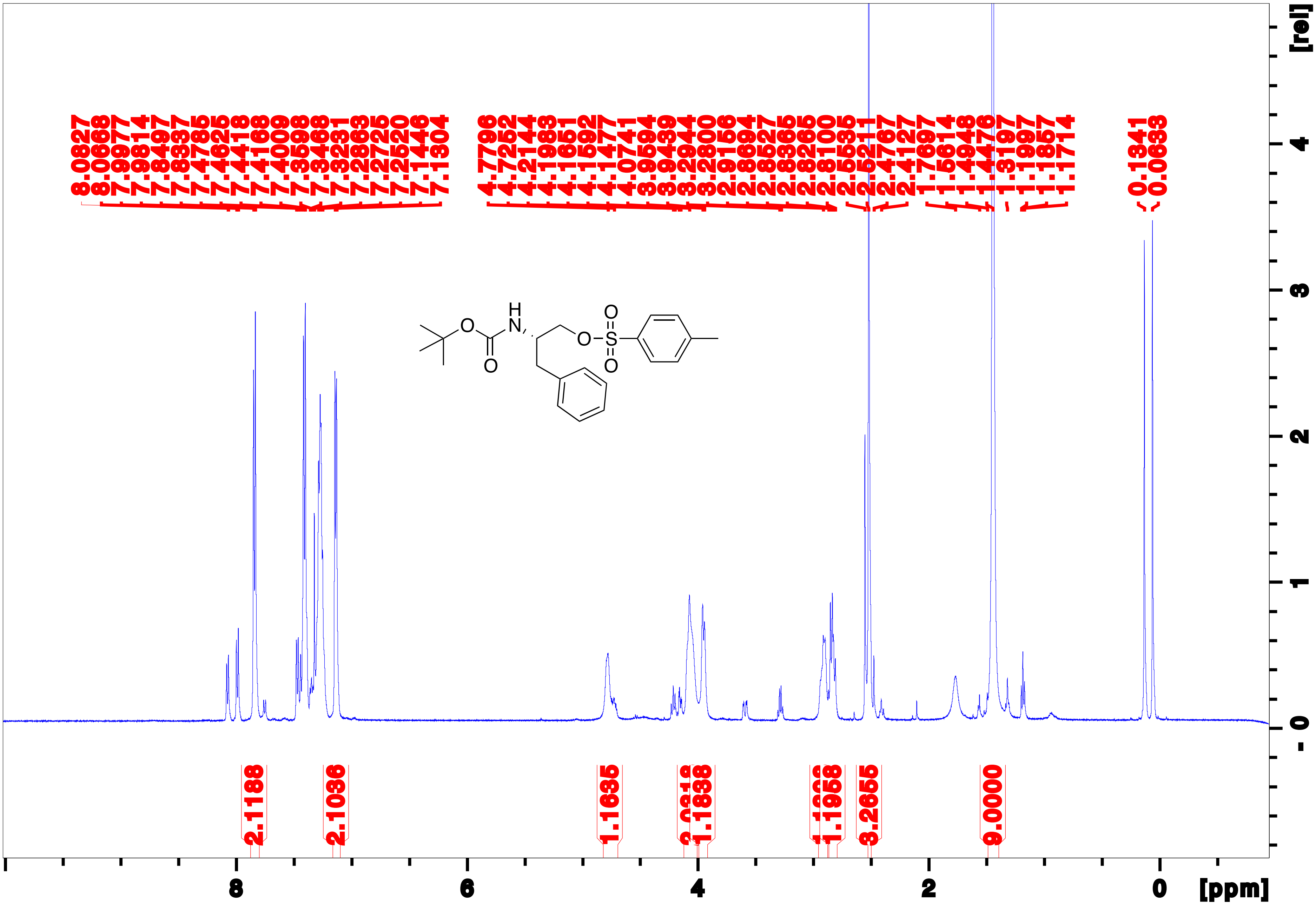
0.3778
2.0075
1.0693
1.0419
1.9253
1.0824
8.8079
0.5232
0.0550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7.9977
7.9814
7.8497
7.8337
7.4785
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7.4418
7.4168
7.4009
7.3598
7.3468
7.3231
7.2863
7.2725
7.2520
7.1446
7.1304
4.7796
4.7252
4.2144
4.1983
4.1651
4.1592
4.1477
4.0741
3.9594
3.9439
3.2944
3.2800
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2.8694
2.8527
2.8365
2.8260
2.8100
2.5535
2.5211
2.4767
2.4127
1.7697
1.5614
1.4948
1.4476
1.3197
1.1997
1.1857
1.1714
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2.1036
1.1635
1.1888
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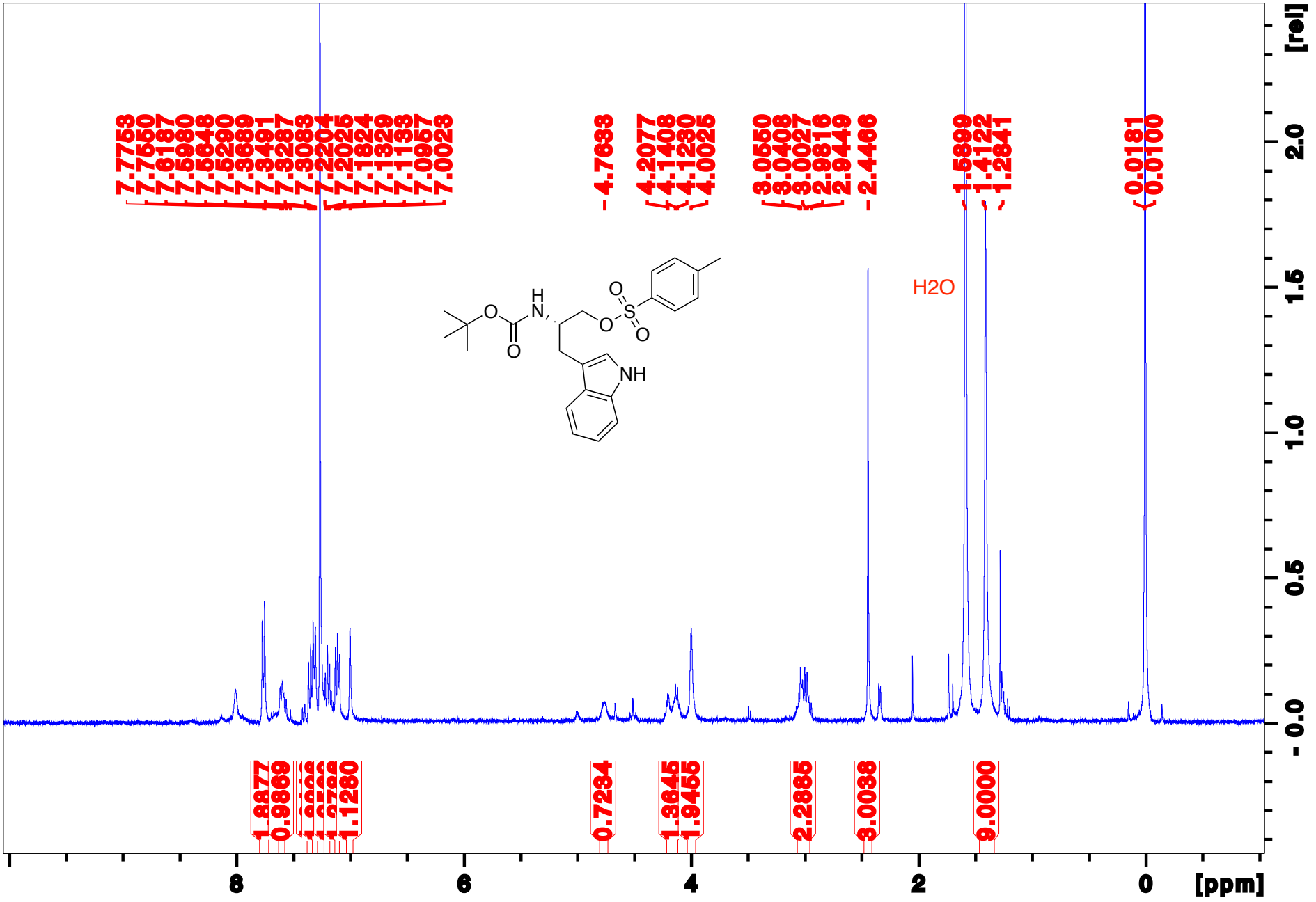
[ppm]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7.7550
7.6187
7.5980
7.5643
7.5290
7.3689
7.3491
7.3287
7.3083
7.3004
7.2025
7.2024
7.1329
7.1157
7.0957
7.0023
4.7633
4.2077
4.1408
4.1290
4.0025
3.0550
3.0403
3.0027
2.9816
2.9449
2.4466
1.5899
1.4122
1.2841
0.0181
0.0100
H2O
1.8877
0.9869
1.1280
0.7234
1.3645
1.9455
2.2885
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9.0000
8
6
4
2
0
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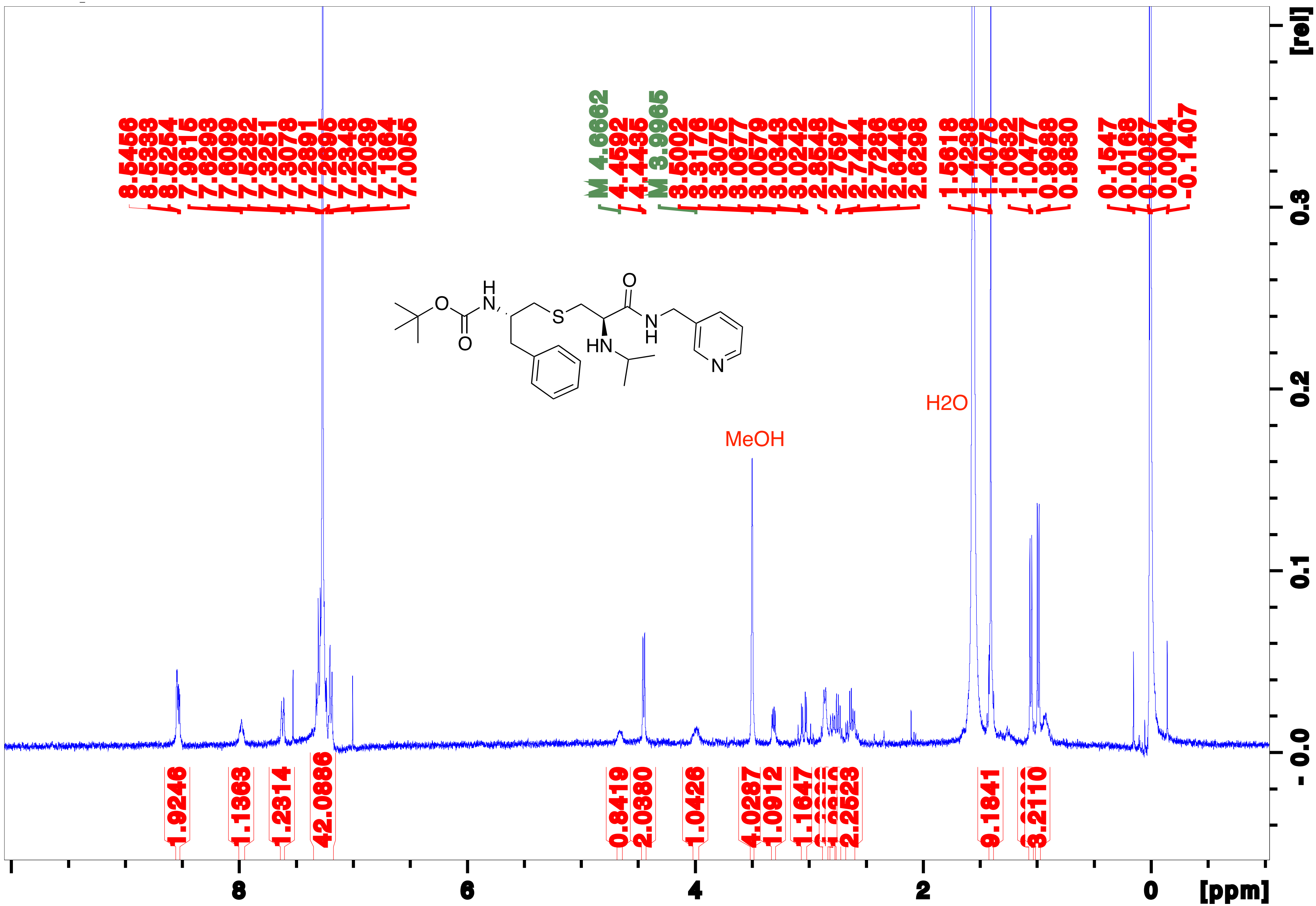
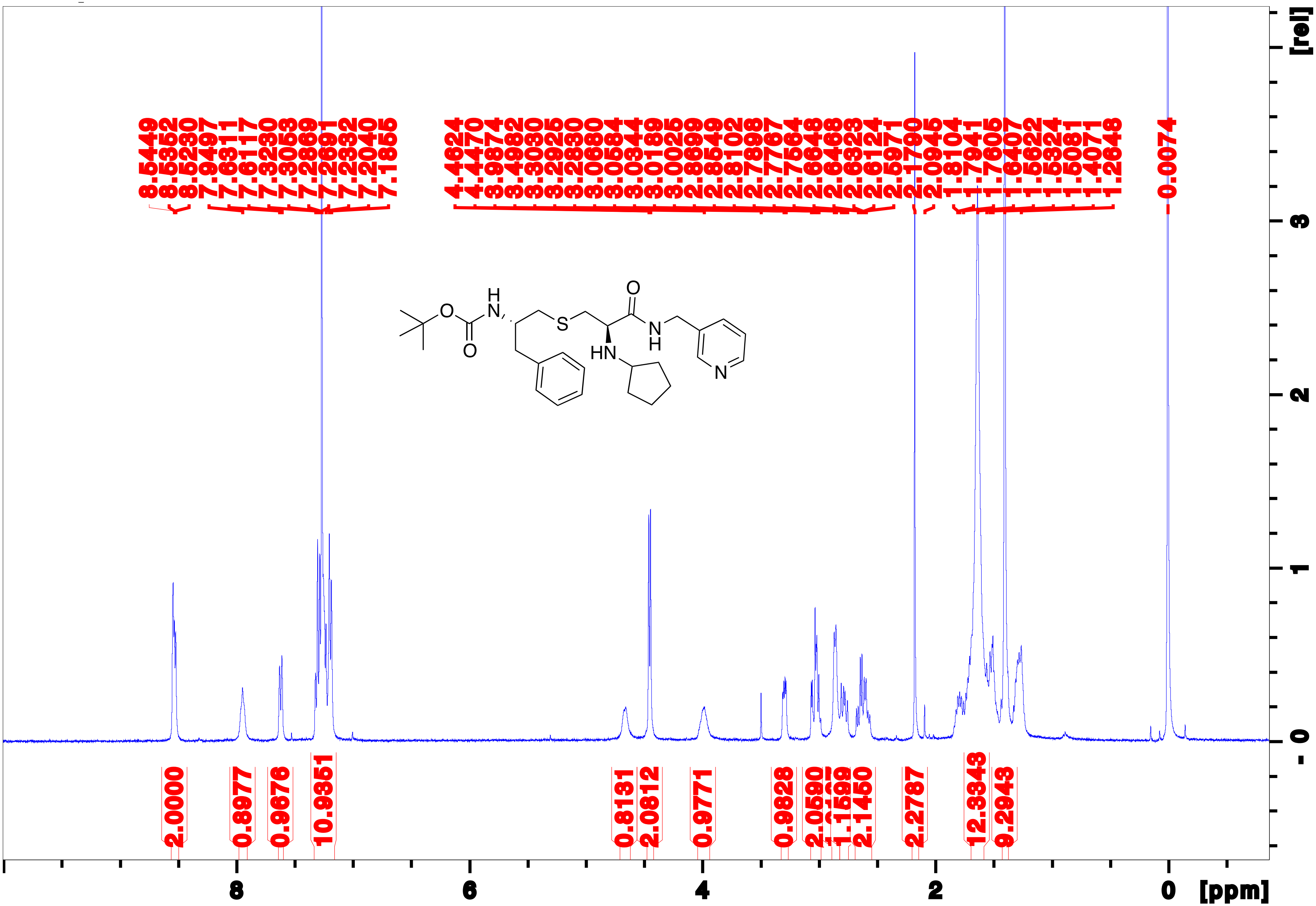
[rel]
2.0
1.5
1.0
0.5
0.0



8.5456
8.5333
8.5254
7.9815
7.6293
7.6099
7.5282
7.3251
7.3078
7.2891
7.2695
7.2348
7.2039
7.1864
7.0055
M 4.6662
4.4592
4.4435
M 3.9965
3.5002
3.3176
3.3075
3.0677
3.0579
3.0343
3.0242
2.8548
2.7597
2.7444
2.7286
2.6446
2.6298
1.5618
1.4238
1.4075
1.0632
1.0477
0.9988
0.9830
0.1547
0.0168
0.0087
0.0004
-0.1407
MeOH
H2O
1.9246
1.1363
1.2314
42.0886
0.8419
2.0380
1.0426
4.0287
1.0912
1.1647
2.2523
9.1841
3.2110
[rel]
0.3
0.2
0.1
0.0
8
6
4
2
0
[ppm]



8.5449
8.5352
8.5230
7.9497
7.6311
7.6117
7.3230
7.3053
7.2869
7.2691
7.2332
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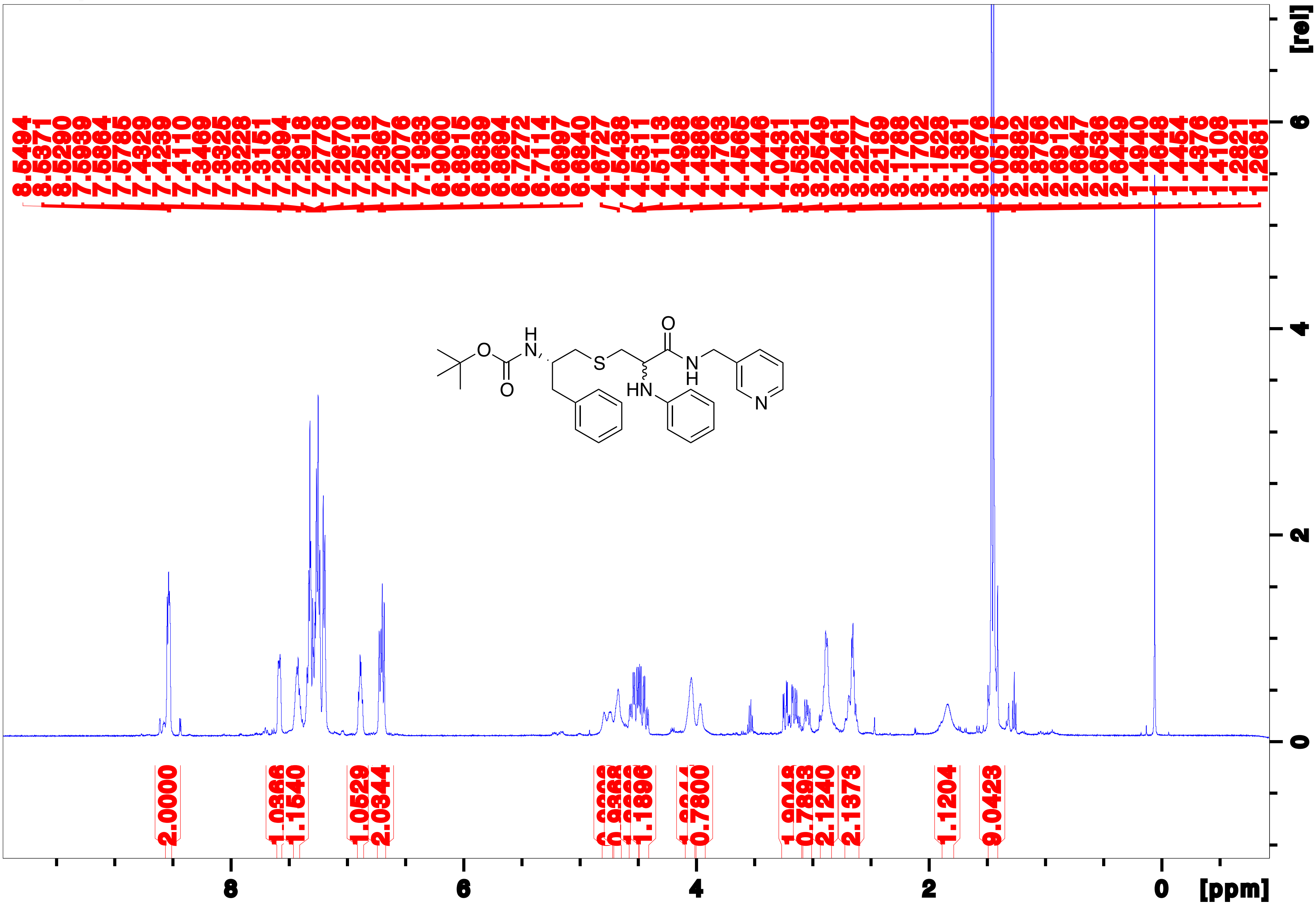
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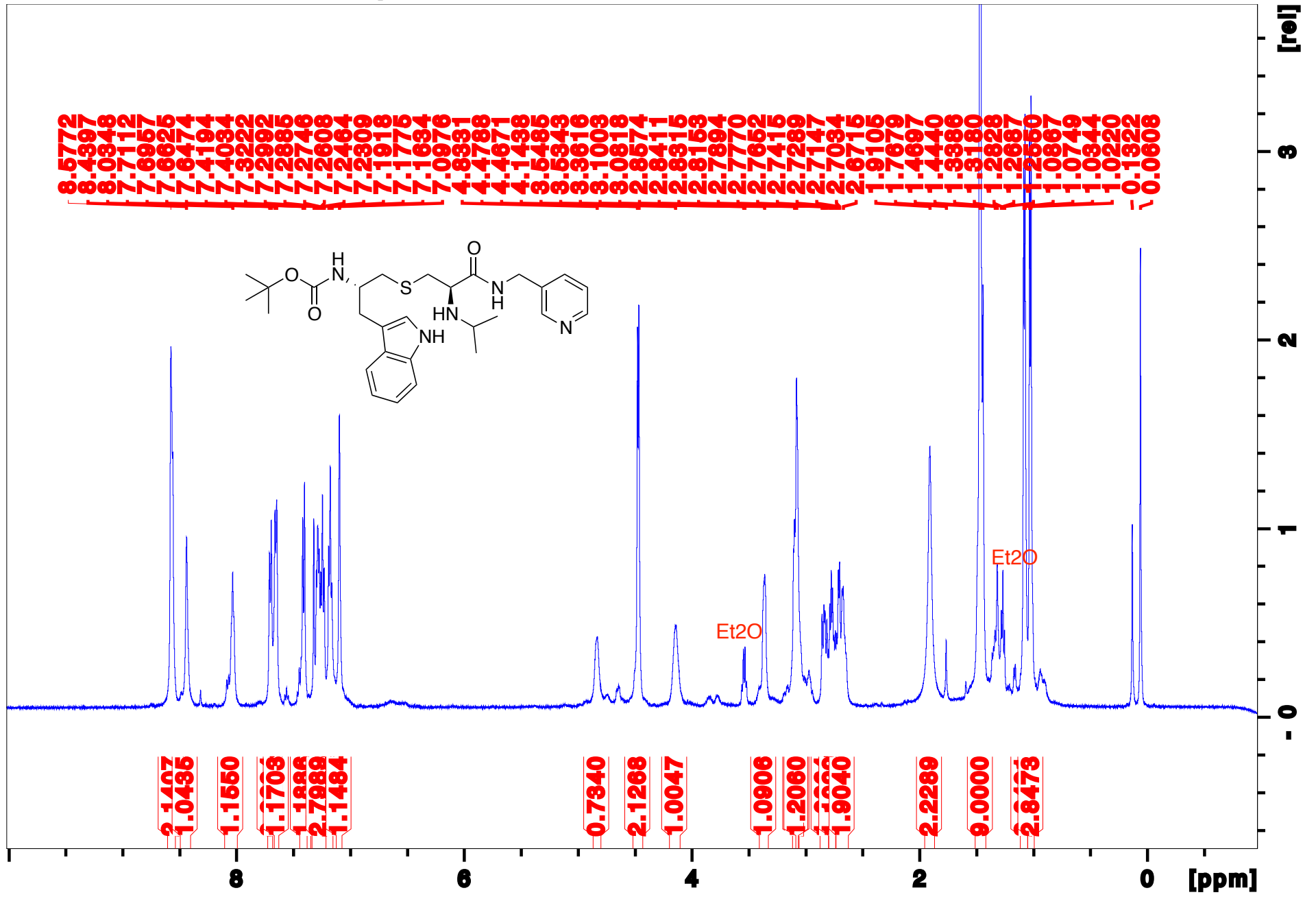
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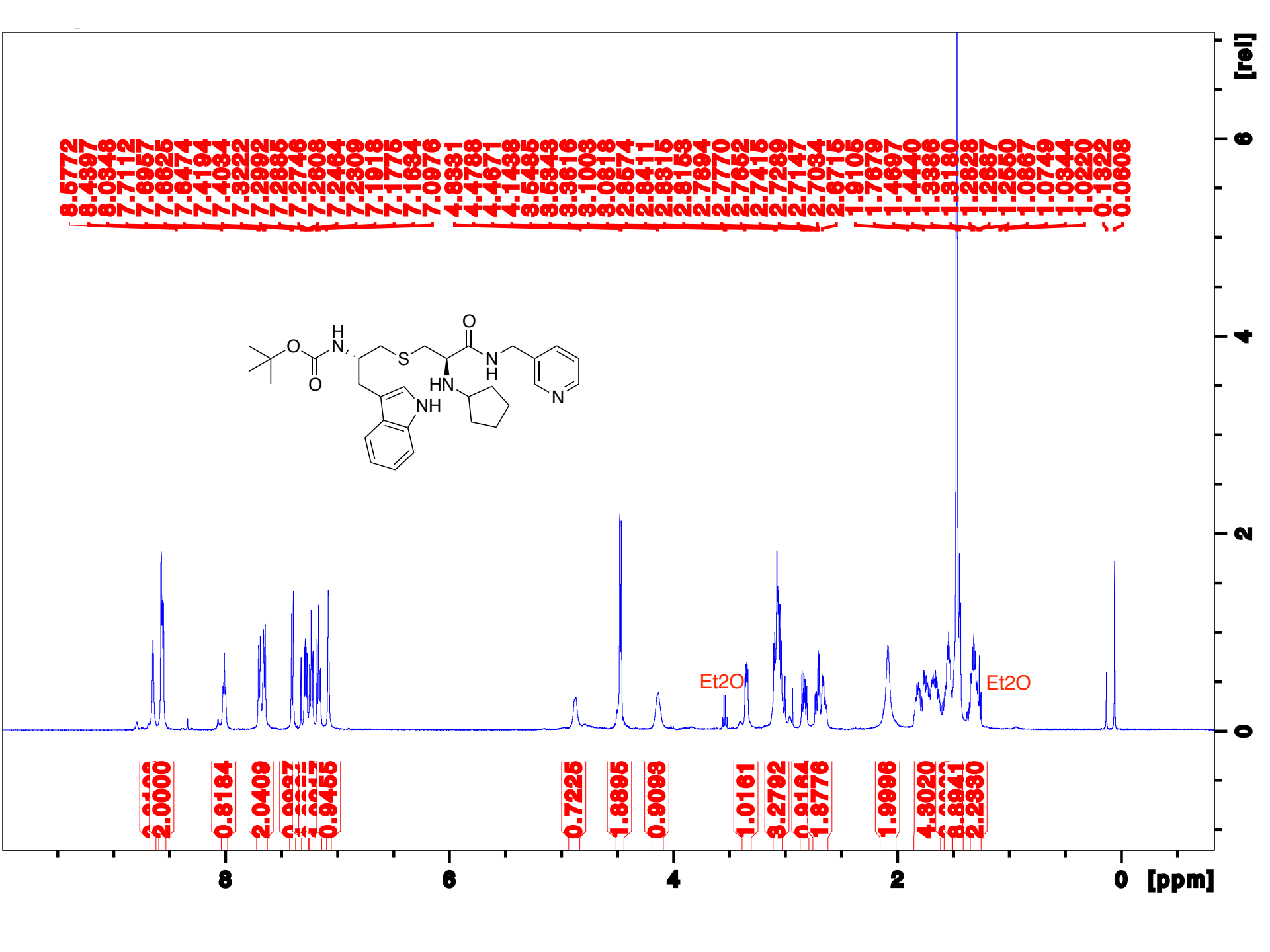
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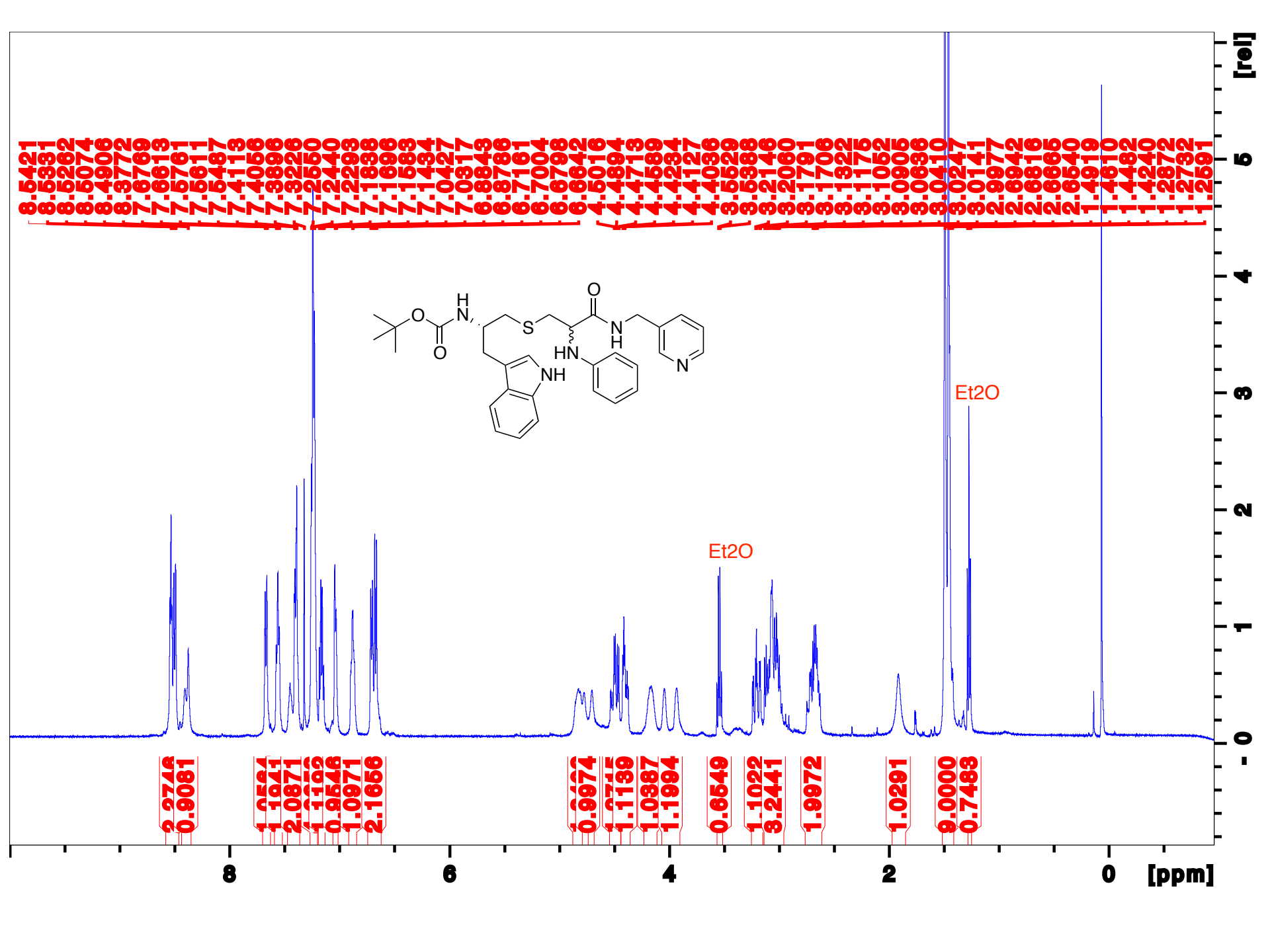
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