Electronic Supplementary Material (ESI) for MedChemComm.

Synthesis and Pharmacological Characterization of the Selective GluK1 Radioligand (*S*)-2-Amino-3-(6-[^{3}H]-2,4-dioxo-3,4-dihydrothieno[3,2-*d*]pyrimidin-1(2*H*)-yl)propanoic acid ([^{3}H]-NF608)

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SUPPORTING INFORMATION

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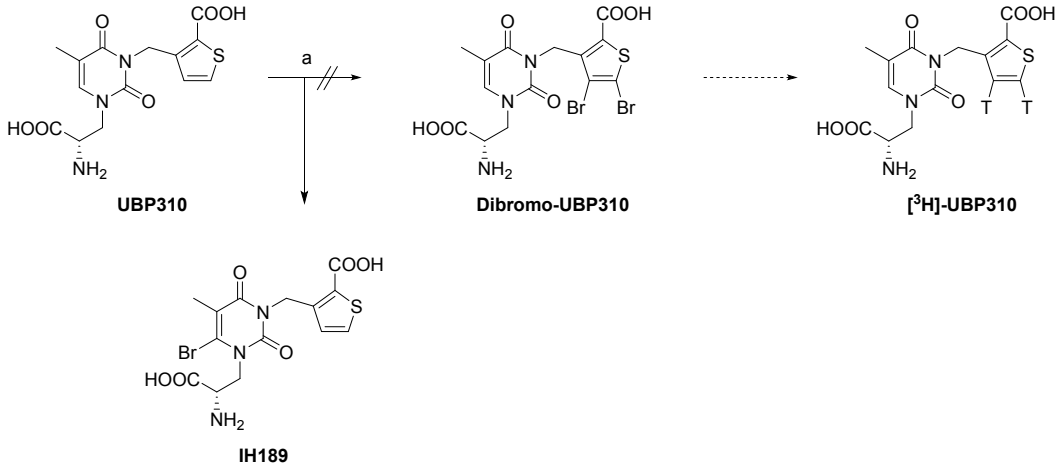
Attempted syntheses of [3H]-UBP310 from UBP310

Bromination of commercially available UBP310 (Scheme S1, step a) was attempted using the reported conditions by Atlason *et al*.[1] Despite the 3 to 4-fold excess of bromine only monobromination was observed after 3 days at rt. Increasing of reaction temperature, reaction time or concentration did not lead to a dibrominated product. From the crude reaction mixture two monobrominated products were isolated, and identified by LC-MS and ^{1}H-NMR to be rotamers where the bromination had taken place at the uracil ring, compound **IH189,** rather than on the thiophene ring.

Scheme S1. Failed attempt for the one-step synthesis of dibromo-UBP310 from commercially available UBP310.



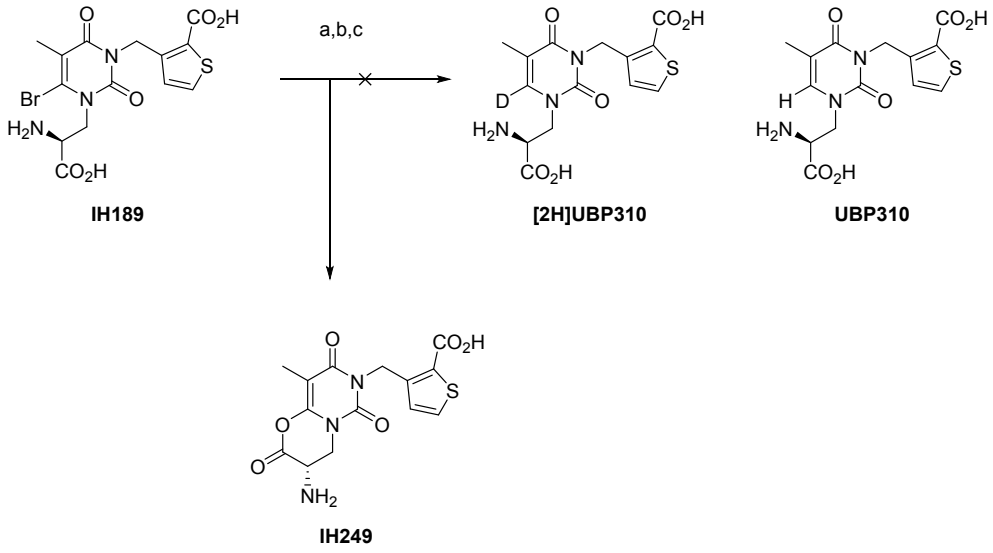
Reagents and conditions: a) 3 equiv. Br_2, AcOH, rt, 3-4 days.

With this unexpected brominated analog of UBP310 in hand, compound **IH189,** we decided to explore and establish optimal conditions for incorporation of deuterium prior to the eventual tritiation reaction. Thus, **IH189** was dissolved in H_2O with a catalytic amount of Pd/C and stirred at rt under a D_2 atmosphere. HPLC showed full conversion of **IH189**, however, ^{1}H-NMR and LC-MS analysis confirmed full incorporation of hydrogen. We believed that the carboxylic acid

[1] Atlason, P. T.; Scholefield, C. L.; Eaves, R. J.; Mayo-Martin, M. B.; Jane, D. E.; Molnár, E. "Mapping the ligand binding sites of kainate receptors: molecular determinants of subunit-selective binding of the antagonist [3H]UBP310" *Mol. Pharmacol*. **2010**, *78*, 1036-1045.

functionalities were the source of proton donation and consequently prepared the disodium salt of **IH189** and repeated the reaction. After 2.5 h at 40 °C full consumption of **IH189** was observed, however, the ^{1}H-NMR spectrum of the crude product did not confirm deuterium or hydrogen incorporation. The molecular mass [M+1] was determined by LC-MS to 352, two protons less than the calculated molecular mass [M+1= 354] of **UBP310**. Based on these data, we concluded that an intramolecular cyclization had taken place to give lactone **IH249** (Scheme S2).

Scheme S2: Attempted deuteration of **IH189** provided lactone **IH249** instead of deuterium incorporation



Reagents and conditions: a) Pd/C, H_2O, D_2 atm., rt; b) Pd/C, NaOH in D_2O, D_2 atm., rt; c) Pd/C, DMF, NEt_3, D_2 atm., rt.

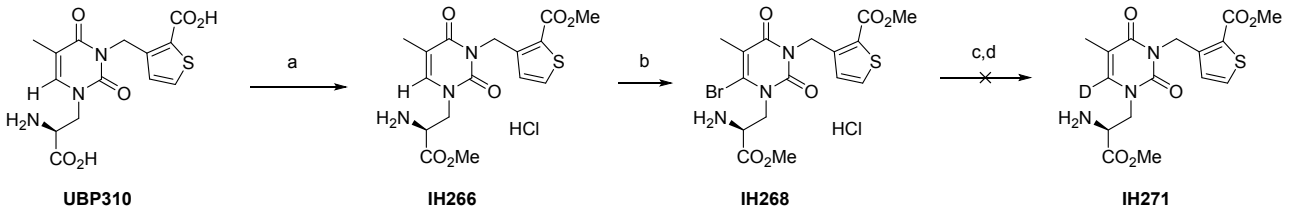
*Synthesis of bromo precursors dimethyl ester **IH268** and dimethyl ester carbamate **IH274***

To circumvent the basic conditions during the deuterium incorporation, we prepared the dimethyl ester of **IH189** (Scheme S3). Thus, **UBP310** was subjected to standard Fisher-esterification affording dimethyl ester **IH266** in quantitative yield. Bromination using excess bromine in AcOH at

rt afforded one monobrominated product which was confirmed by ^{1}H-NMR and LCMS to be **IH268**.

Finally, **IH268** was dissolved in MeOD and in the presence of Pd/C stirred under a D_2 atmosphere for 5 h. HPLC analysis showed full consumption of bromine **IH268**, however LC-MS and ^{1}H-NMR showed incorporation of hydrogen rather than deuterium.

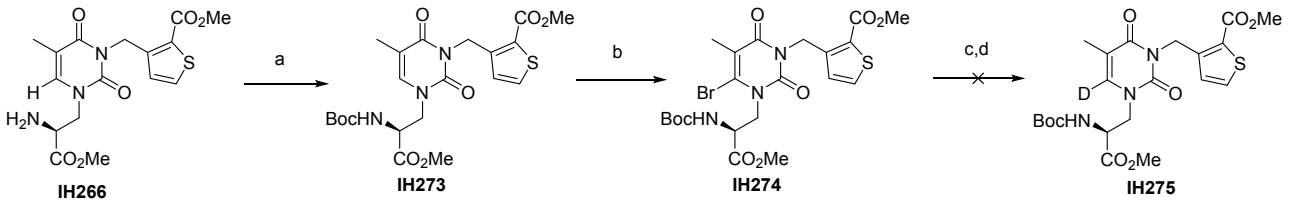
Scheme S3: Synthesis of dimethyl ester **IH268** and attempted deuterium experiments



Reagents and conditions: a) MeOH, $SOCl_2$, 40 °C, 16 h, quant.; b) Br_2, AcOH, rt, 4d; c) Pd/C, MeOD, D_2, rt, 5h; d) Pd/C, DMF, NEt_3 (pH6-7), D_2, rt, 4h.

This was presumably due to the slightly acidic ammonium functionality (from the HCl salt) for which reason we next decided to protect the amine as its BOC carbamate (Scheme S4). Thus, dimethyl ester **IH268** was treated with BOC_2O in the presence of DMAP to give **IH273** in high yield. Bromination of **IH273** by use of excess NBS in $CDCl_3$/AcOH (1:1) afforded a single monobrominated product, which was determined by ^{1}H-NMR to be the uracil brominated analog **IH274**. Subsequently, **IH274** was dissolved in THF with a catalytic amount of Pd/C and stirred at rt under a D_2 atmosphere. HPLC showed full consumption of **IH274** after 3.5 h, however, again LC-MS and ^{1}H-NMR analysis confirmed incorporation of hydrogen only.

Scheme S4: Synthesis of dimethyl ester carbamate **IH274** and attempted incorporation of deuterium



Reagents and conditions: a) Boc_2O, DMAP, NEt_3, rt, 2d, 87% (crude); b) NBS, AcOH/$CDCl_3$ (1:1), rt, 3h, 39%; c) Pd/C, THF, D_2, rt, 3.5h; d) NaOMe or Cs_2CO_3, MeOD, rt, 30 min.

Conclusion

In summary, deuteration of bromo analog **IH189** without the use of base resulted in full hydrogen incorporation while addition of base resulted in an intramolecular cyclization to give the corresponding lactone **IH249**. To avoid basic conditions, dimethyl ester and carbamate protected analogs **IH268** and **IH274** were prepared. Unfortunately, these were also unsuccessful as starting points for incorporation of deuterium on the uracil ring. Regrettably, we conclude that uracil brominated UBP310 analogs are not feasible intermediates for deuterium incorporation and thus not a viable strategy for the synthesis of a tritium labeled analog of UBP310.

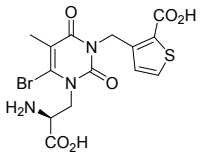
Experimental data

General remarks

All reactions involving dry solvents or sensitive agents were performed under a nitrogen or argon atmosphere, and glassware was dried prior to use. Commercially available chemicals were used without further purification. Solvents were dried prior to use with an SG water solvent purification system or dried by standard methods. Reactions were monitored by analytical thin-layer chromatography (TLC, Merck silica gel 60 F254 aluminum sheets), analytical HPLC or UPLC. Flash chromatography was carried out using the Merck silica gel 60 (15–40 μm) or Merck silica gel 60 (40–63 μm). ^{1}H NMR spectra were recorded on a 400 MHz Bruker Avance III or 600 MHz Bruker Avance III HD, and ^{13}C NMR spectra on a 101 MHz Bruker Avance III or 151 MHz Bruker Avance III HD. Chemical shifts are reported in δ (ppm) relative to the singlet at δ = 7.26 ppm of $CDCl_3$, the quintet at 2.50 ppm of DMSO-d6, and the singlet at 4.79 ppm of D_2O for ^{1}H NMR, and to the centre line of the triplet at δ = 77.16 ppm of $CDCl_3$, the heptuplet at 39.52 ppm of DMSO-d6 for ^{13}C-NMR. Analytical HPLC was performed using a Dionex UltiMate 3000 pump and Dionex Ultimate 3000 Diode Array Detector (200, 210, 225 and 254 nm) installed with a Phenomenex Gemini-NX 3μ C18 110A, 250 × 4.60 mm column. Solvent A: H_2O + 0.1% TFA; Solvent B: MeCN-H_2O 9:1 + 0.1% TFA. For HPLC control, data collection and data handling, Chromeleon software v. 6.80 was used. Preparative HPLC was carried out on an Ultimate 3000 Thermo SCIENTIFIC system with a Dionex Ultimate 3000 series pump, a Dionex Ultimate 3000 Diode Array Detector (200, 210, 225 and 254 nm), and a Phenomenex Gemini-NX 5μ C18 110A, 250 × 21.20 mm column for preparative purifications or a Phenomenex Gemini-NX 5μ C18 110A, 250 × 10.00 mm column for semi-preparative purifications. Solvent A: H_2O + 0.1% TFA; Solvent B: MeCN-H_2O 9:1 + 0.1% TFA. For HPLC control, data collection and data handling, Chromeleon software v. 6.80 was used. UPLC-MS spectra were recorded using an Acquity UPLC H-Class Waters series solvent delivery system equipped with an autoinjector coupled to an Acquity QDa and

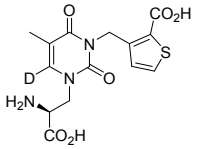
TUV detectors installed with an Acquity UPLC®BECH C18 1.7 µm column. Solvent A: 5% aq MeCN + 0.1% HCO_2H: Solvent B: MeCN + 0.1% HCO_2H. Usually, gradients from A:B 1:0 to 0:1 (5 min) or A:B 1:0 to 0:50 (5 min), were performed depending on the polarity of the compounds. For data collection and data handling, MassLynx software was used. Compounds were dried under high vacuum or freeze dried using a ScanVac Cool Safe Freeze Drier.

(*S*)-3-((3-(2-Amino-2-carboxyethyl)-4-bromo-5-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)methyl)-thiophene-2-carboxylic acid (IH189).



Commercially available **UBP310** (10.0 mg, 28.0 µmol) was stirred in glacial AcOH (2 mL) until dissolved. Then Br_2 in AcOH (1M solution, 85 µl, 85.0 µmol) was added and the reaction was stirred at r.t. for 3 d. The solvent was evaporated *in vacuo* and prep. HPLC (R_t = 13.38 and 13.81 min; Gradient run: A:B 100:0 to A:B 20:80 in 25 min) afforded the *title compound* as a mixture of rotamers as white solid (7.41 mg, 17.14 µmol, 61%). Rotamer 1: ^{1}H NMR (600 MHz, TFA-d) δ: 7.97 (d, J = 5.1 Hz, 1H), 7.36 (d, J = 5.1 Hz, 1H), 5.90 (d, J = 17.3 Hz, 1H), 5.72 (t, J = 8.6 Hz, 2H), 5.26 (s, 1H), 4.82 (dd, J = 15.9, 5.6 Hz, 1H), 4.73 (d, J = 15.6 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, TFA-d) δ: 170.3, 169.2, 168.1, 155.9, 145.6, 134.3, 127.2, 125.7, 87.2, 54.4, 51.9, 48.9, 42.0, 21.9. HPLC: R_t = 1.37 min. Rotamer 2: ^{1}H NMR (600 MHz, TFA-d) δ: 7.84 (d, J = 5.1 Hz, 1H), 7.26 (d, J = 5.1 Hz, 1H), 5.77 (d, J = 17.2 Hz, 1H), 5.57 – 5.50 (m, 2H), 5.10 (s, 1H), 4.95 (dd, J = 15.9, 2.7 Hz, 1H), 4.41 (dd, J = 15.9, 6.3 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (150 MHz, TFA-d) δ: 170.3, 169.1, 168.0, 154.8, 145.5, 134.3, 127.4, 125.7, 87.1, 54.1, 52.2, 49.7, 42.0, 21.7. HPLC: R_t = 1.41 min. LC-MS *(m/z)* calcd for $C_{14}H_{15}BrN_3O_6S$ [M + H^+]: 432.0, 434.0; found: 431.9, 433.9.

Deuterium experiments (IH249):



1. Bromine **IH189** (2.2 mg, 5.09 μmol) was dissolved in deionized H_2O (0.1 mL) and Pd/C (0.6 mg, 0.51 μmol) was added. The flask was evacuated and backfilled with argon gas (2x) and evacuated and backfilled with D_2 gas. The reaction was stirred under a D_2 atmosphere at 40 °C for 7 h. The reaction mixture was filtered through a PVD 0.45 μm filter, washed with deionized H_2O and the solvent was removed on the freeze-dryer. ^{1}H-NMR analysis of the crude reaction mixture only showed **UBP310**.

2. Bromine **IH189** (0.57 mg, 1.18 μmol) was dissolved in dry DMSO (0.05 mL) and Pd/C (0.2 mg, 0.2 μmol) was added. The flask was evacuated and backfilled with argon gas (x2) and evacuated and backfilled with D_2 gas. The reaction was stirred under a D_2 atmosphere at 40 °C for 2.5 h. The reaction mixture was filtered through a PVD 0.45 μm filter, washed and the solvent was removed on the freeze-dryer. ^{1}H-NMR analysis of the crude reaction mixture only showed **UBP310**.

3. Bromine **IH189** (0.3 mg, 0.69 μmol) was dissolved in a 0.1 M NaOH in D_2O sol. (14 μL, 1.39 μmol) and Pd/C (0.07 mg, 0.07 μmol) was added. The disodium salt was stirred under a D_2 atmosphere (1 atm.) at 40 °C for 2.5 h. The solution was cooled to r.t., filtered through a PVD 0.45 μm filter, washed with D_2O (0.1 ml) and the solvent was evaporated via freeze drying.

4. Bromine **IH189** (1.94 mg, 3.55 μmol) was dissolved in 0.1 M NaOH in D_2O solution until the solution reached pH = 8. Pd/C (0.07 mg, 0.07 μmol) was added and the flask was evaporated

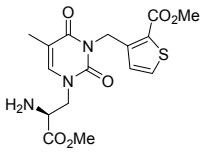
and backfilled with D_2 gas (x3). The reaction mixture was stirred under D_2 atmosphere at r.t. for 2 h then filtered through a PVD 0.45 µm filter and the solvent was removed on the freeze-dryer.

5. Bromine **IH189** (0.70 mg, 1.49 µmol) was dissolved in dry, degassed DMF (30 µL) and NEt_3 (1 µl, 7.45 µmol) was added followed by Pd/C (0.01 mg, 0.15 µmol). The flask was evaporated and backfilled with D_2 gas (3 x) and the reaction was stirred under D_2 atmosphere at r.t. for 2 h. The mixture was diluted with H_2O (0.5 ml), filtered through a PVD 0.45 µm filter and the filtrate washed with H_2O (0.5 ml). The solution was frozen and evaporated on the freeze-dryer.

^{1}H NMR (600 MHz, TFA-d) δ: 7.60 (d, J = 5.1 Hz, 1H), 6.90 (d, J = 5.1 Hz, 1H), 5.57 (d, J = 17.3 Hz, 1H), 5.33-5.35 (m, 2H), 4.77-4.80 (m, 1H), 4.29 (dd, J = 10.8, 7.3 Hz, 1H), 1.80 (s, 3H).

HPLC: R_t = 1.14min; LC-MS *(m/z)* calcd for $C_{14}H_{14}N_3O_6S$ [M + H^+]: 352.2; found: 352.1.

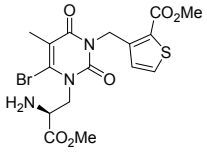
Methyl 3-((3-(2-amino-3-methoxy-3-oxopropyl)-5-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)methyl)thiophene-2-carboxylate (IH266).



Commercially available **UBP310** (2.44 mg, 6.90 µmol) was added to a cooled solution of $SOCl_2$ in MeOH (10%, 0.2 mL) and then stirred at 40 °C for 16 h. The reaction was cooled to r.t., the solvent evaporated and the residue taken up in H_2O and evaporated on the freeze dryer to afford the *title compound* as a crude yellow solid (HCl salt, 3.05 mg, 7.30 µmol, quant.); ^{1}H NMR (600 MHz, MeOD) δ: 7.56 (d, J = 3.7 Hz, 1H), 7.45 (s, 1H), 6.80 (d, J = 3.6 Hz, 1H), 5.53 – 5.39 (m, 2H), 4.47 (s, 1H), 4.32 (s, 1H), 4.28 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.5, 165.2, 164.1, 153.7, 146.3, 141.3, 132.3, 128.9, 128.1, 111.5, 54.2, 53.4, 52.5,

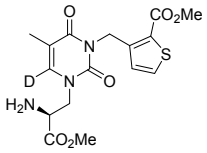
50.0, 41.7, 13.0; HPLC: R_t = 1.36 min; LC-MS (*m/z*) calcd for $C_{16}H_{20}N_3O_6S$ [M + H^+], 382.1; found; 382.1.

Methyl (*S*)-3-((3-(2-amino-3-methoxy-3-oxopropyl)-4-bromo-5-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)methyl)thiophene-2-carboxylate (IH268).



Dimethyl ester **IH266** (3.05 mg, 7.30 µmol) was dissolved in AcOH (0.2 ml), Br_2 (1M in AcOH, 22 µl, 22 µmol) was added and the reaction stirred at r.t. for 4 d. The mixture was diluted with H_2O, frozen and the solvent was evaporated on the freeze-dryer. HPLC: R_t = 1.55 and 1.61 min; ^{1}H NMR (600 MHz, MeOD) δ: 7.58 (d, J = 4.5 Hz, 1H), 6.96 (d, J = 4.9 Hz, 1H), 5.42 – 5.38 (m, 1H), 5.25 – 5.19 (m, 1H), 4.41 (s, 1H), 4.16-4.12 (m, 1H), 4.06 – 3.99 (m, 1H), 3.88 (s, 6H), 3.86 (s, 3H). LC-MS (m/z) calcd for $C_{16}H_{19}BrN_3O_6S$ [M + H+]: 460.0, 462.0; found: 460.0, 462.0.

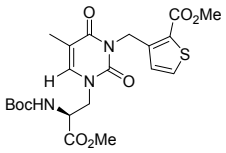
Deuterium experiments with bromine IH268:



1. Bromine **IH268** (1.0 mg, 2.17 µmol) was dissolved in MeOD (0.4 ml), Pd/C (0.1 mg, 0.1 µmol) was added and the flask was evaporated and backfilled with D_2 gas (3x). The reaction mixture was stirred under D_2 atmosphere at r.t. for 5 h then filtered through a PVD 0.45 µm filter and the solvent was removed on the freeze-dryer. Crude ^{1}H-NMR was identical with **IH266**.
2. Bromine **IH268** (1.0 mg, 2.17 µmol) was dissolved in degassed DMF (0.5 ml) and the solution was neutralized to pH=7 with NEt_3. Pd/C (0.1 mg, 0.1 µmol) was added and the flask was

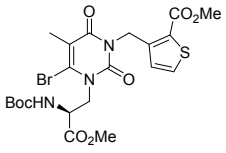
evaporated and backfilled with D_2 gas (3x). The reaction mixture was stirred under D_2 atmosphere at r.t. for 4 h then filtered through a PVD 0.45 µm filter and the solvent was removed on the freeze-dryer. Compound could not be identified as **IH266** or the lactone. LC-MS found: 398.1.

Methyl (*S*)-3-((3-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-5-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)methyl)thiophene-2-carboxylate (IH273).



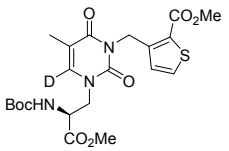
IH266 (10.0 mg, 23.93 µmol) was dissolved in MeOH (0.5 mL) and cooled to 0 °C. NEt_3 (3.3 µL, 23.93 µmol) followed by BOC_2O (5.8 mg, 26.57 µmol) were added and the reaction was stirred at r.t. for 2 d. The solvent was evaporated and the residue dissolved in EtOAC (1 mL) and washed with H_2O (2 x 0.5 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to afford the *title compound* as a crude off-white solid (10 mg, 20.77 µmol, 87%); R_f = 0.50 (DCM/EtOAc 2:1); ^{1}H NMR (600 MHz, MeOD) δ: 7.54 (d, J = 5.2 Hz, 1H), 7.38 (s, 1H), 6.94 (d, J = 5.1 Hz, 1H), 5.50 (d, J = 16.4 Hz, 1H), 5.41 (d, J = 16.5 Hz, 1H), 4.67 (dd, J = 9.6, 4.5 Hz, 1H), 4.45 (dd, J = 13.8, 4.6 Hz, 1H), 3.89 (s, 3H), 3.74 (s, 3H), 3.69 (d, J = 9.9 Hz, 1H), 1.90 (s, 3H), 1.39 (s, 9H). LC-MS (*m/z*) calcd for $C_{21}H_{28}N_3O_8S$ [M + H^+], 482.1; found; 482.1.

Methyl (*S*)-3-((4-bromo-3-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-5-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)methyl)thiophene-2-carboxylate (IH274).



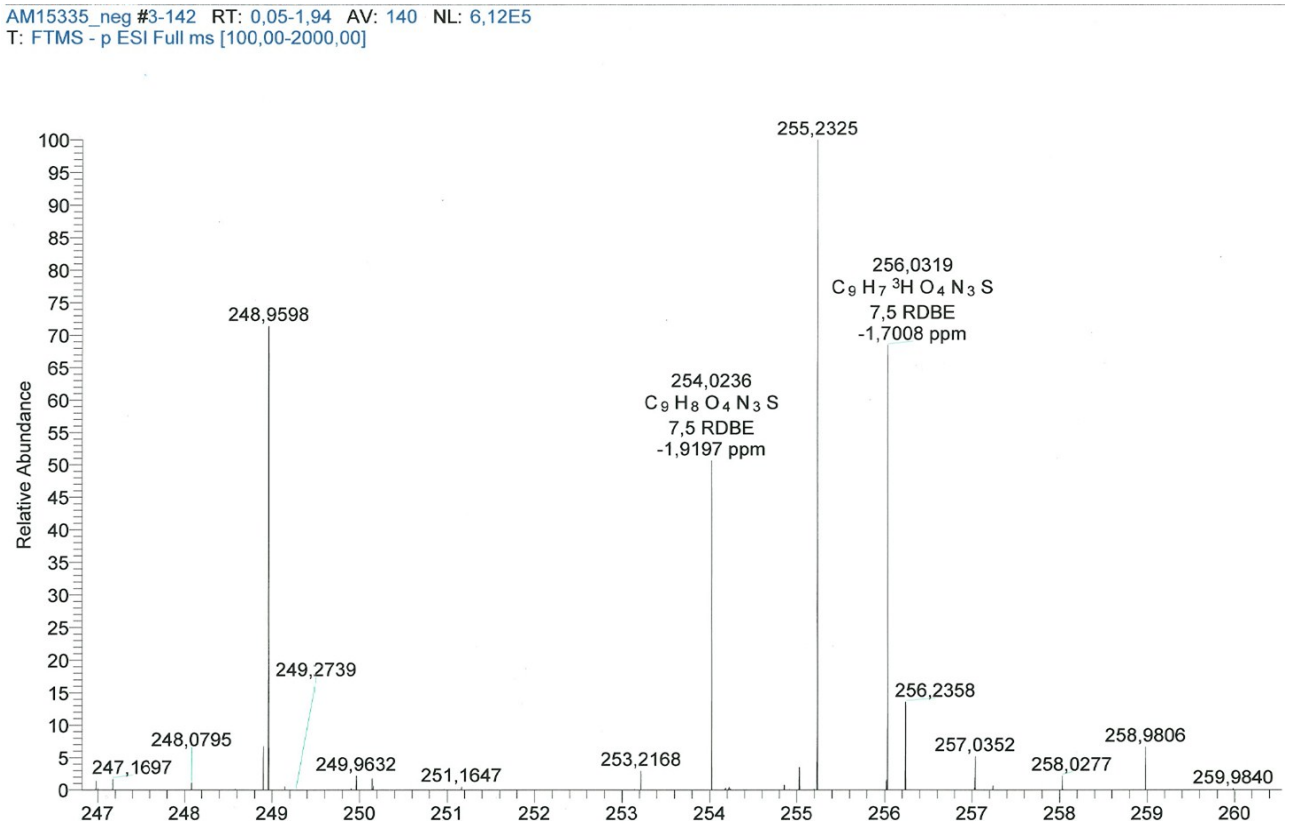
Dimethyl ester carbamate **IH273** (34.58 mg, 71.82 µmol) was dissolved in $CDCl_3$/AcOH (1:1, 1 mL) and NBS (33.4 mg, 187.66 µmol) was added. The reaction was stirred at r.t. under N_2 atmosphere for 3 h. The reaction was diluted with H_2O (1 ml) and the phases were separated. The organic phase was washed with H_2O (1 ml), dried over $MgSO_4$, filtered and evaporated. Prep. TLC (heptane/EtOAc 1:1) afforded the *title compound* as a clear oil (15.68 mg, 27.98 µmol, 39%); R_f = 0.16 (heptane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (d, J = 5.1 Hz, 1H), 6.93 (d, J = 5.1 Hz, 1H), 6.13 (s, 1H), 5.50 (d, J = 16.9 Hz, 1H), 5.19 (d, J = 16.9 Hz, 1H), 4.67 (t, J = 8.1 Hz, 1H), 4.32 (dd, J = 14.4, 10.7 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.49 (dd, J = 14.4, 3.6 Hz, 1H), 2.04 (s, 3H), 1.39 (s, 9H). LC-MS *(m/z)* calcd. for $C_{21}H_{27}BrN_3O_8S$ [M + H$^+$]: 560.1, 562.1; found: 460.1, 462.1 [M + H$^+$ – Boc].

Deuterium experiments with bromine IH274:

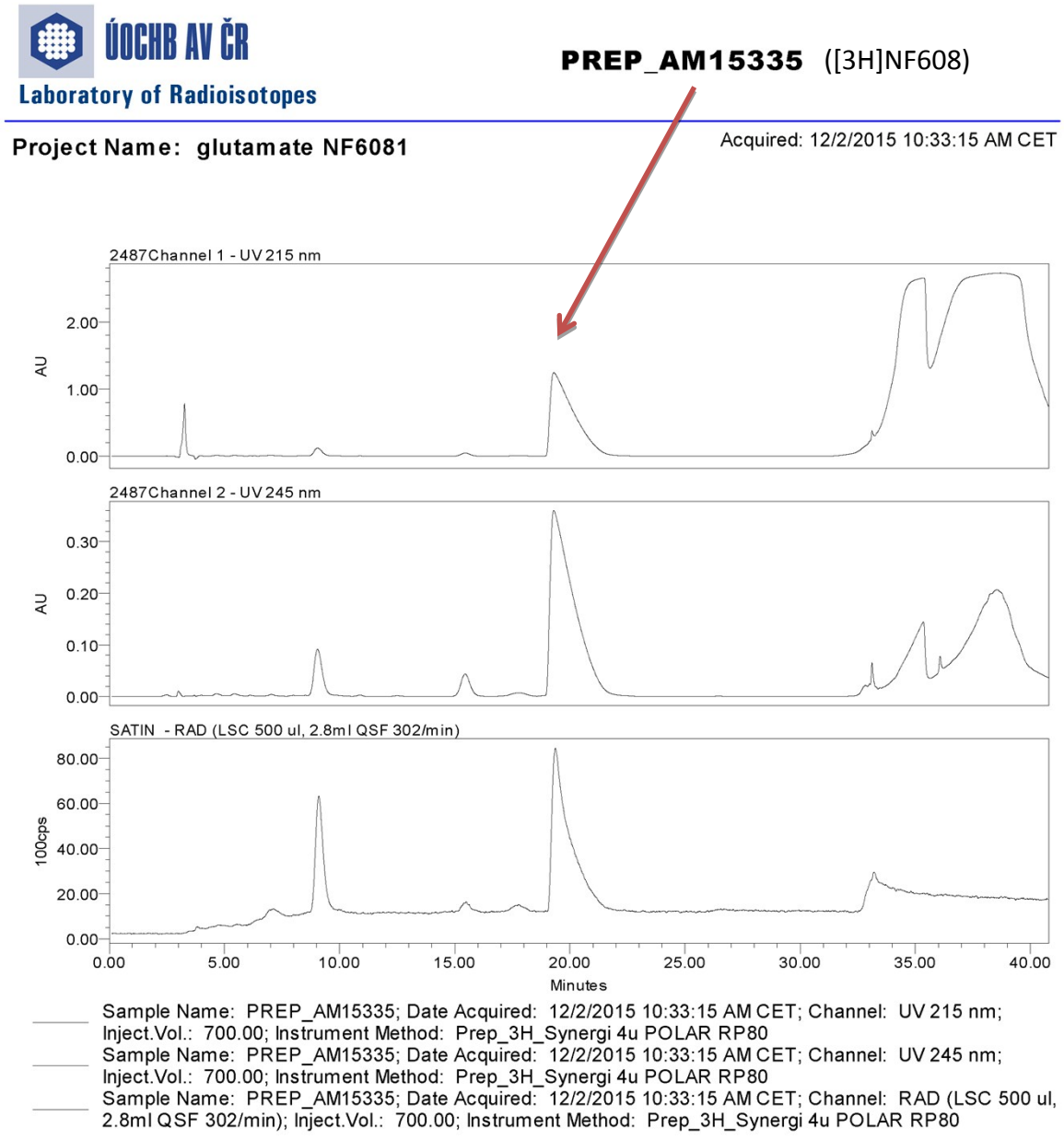


1. Bromine **IH274** (1.36 mg, 2.43 µmol) was dissolved in dry THF (0.1 mL) and Pd/C (0.3 mg, 0.28 µmol) was added. The vial was evacuated and backfilled with D_2 gas. The reaction was stirred at r.t. for 20 h. The reaction was filtered and the solvent was evaporated to afford a crude residue; R_f = 0.29 (heptane/EtOAc 1:1); LC-MS *(m/z)* calcd for $C_{21}H_{28}N_3O_8S$ [M + H$^+$], 482.1; found: 482.2.
2. An oven-dried vial was evacuated and backfilled with N_2 (3x) and then filled with Pd/C (10 wt%, 0.2 mg, 0.19 µmol). The vial was again evacuated and backfilled with N_2 (2x) before evacuated and backfilled with D_2. Bromine **IH274** (0.4 mg, 0. 17 µmol), dissolved in dry THF (0.05 mL), was added via a syringe and the reaction mixture was stirred at r.t. for 3.5 h. LC-MS *(m/z)* calcd for $C_{21}H_{28}N_3O_8S$ [M + H$^+$], 482.1; found: 482.2.

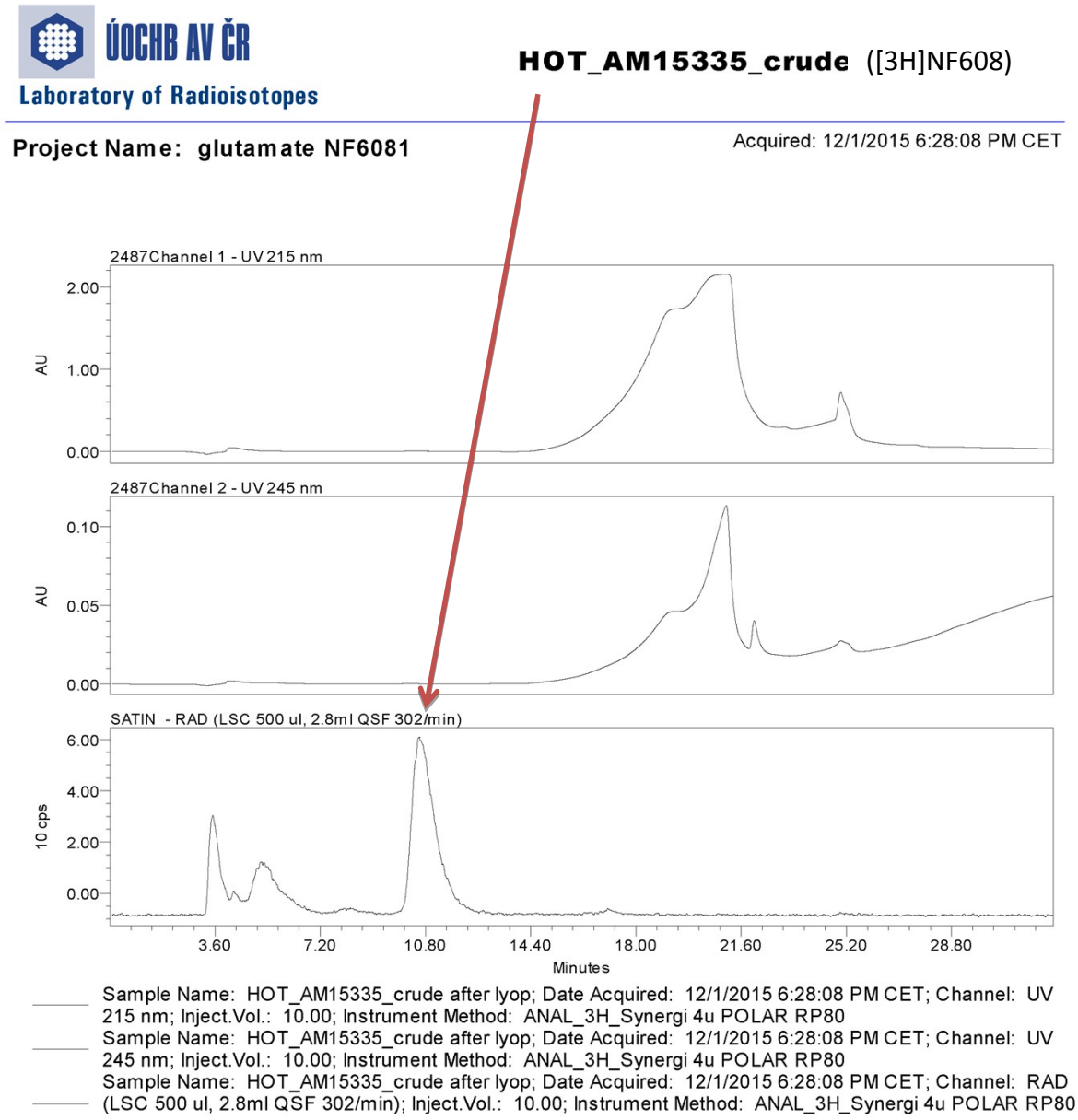
HRMS spectrum (negative mode) of ^{3}H-NF608



HPLC prep trace of [3H]NF608



HPLC analytical trace of [3H]NF608



Error Log
All Peaks Table group contains information that doesn't match the data being reported.

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HPLC analytical trace of NF608 (cold)

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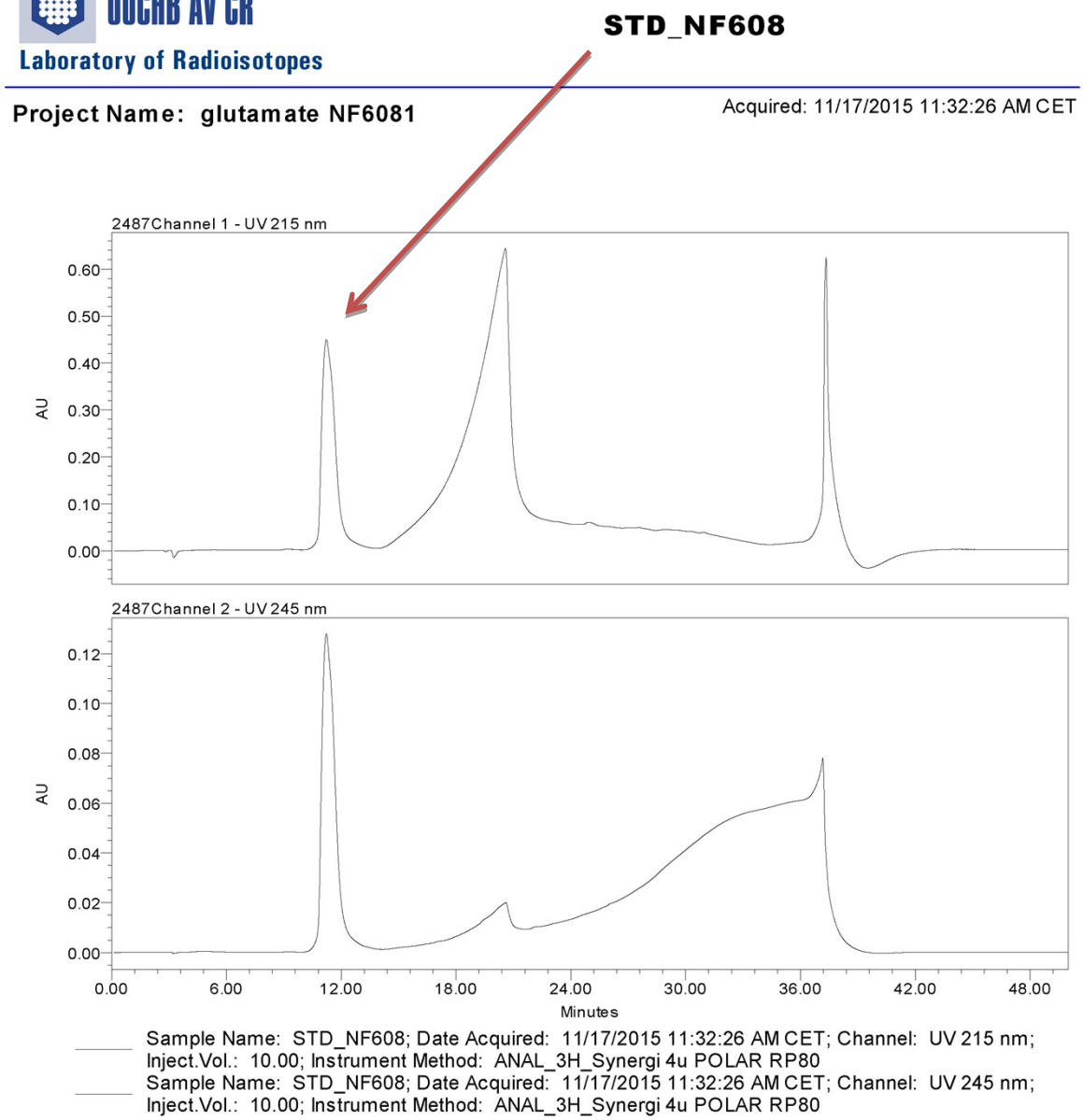

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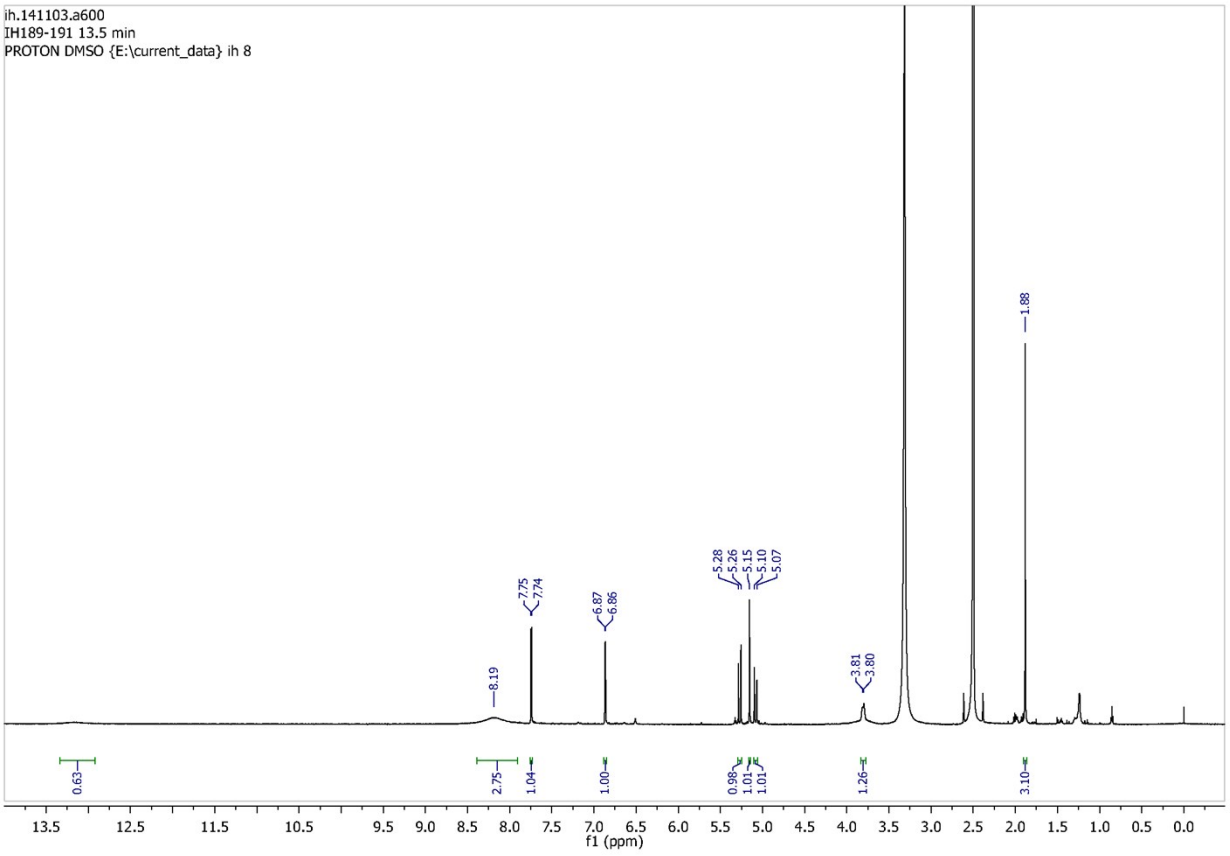
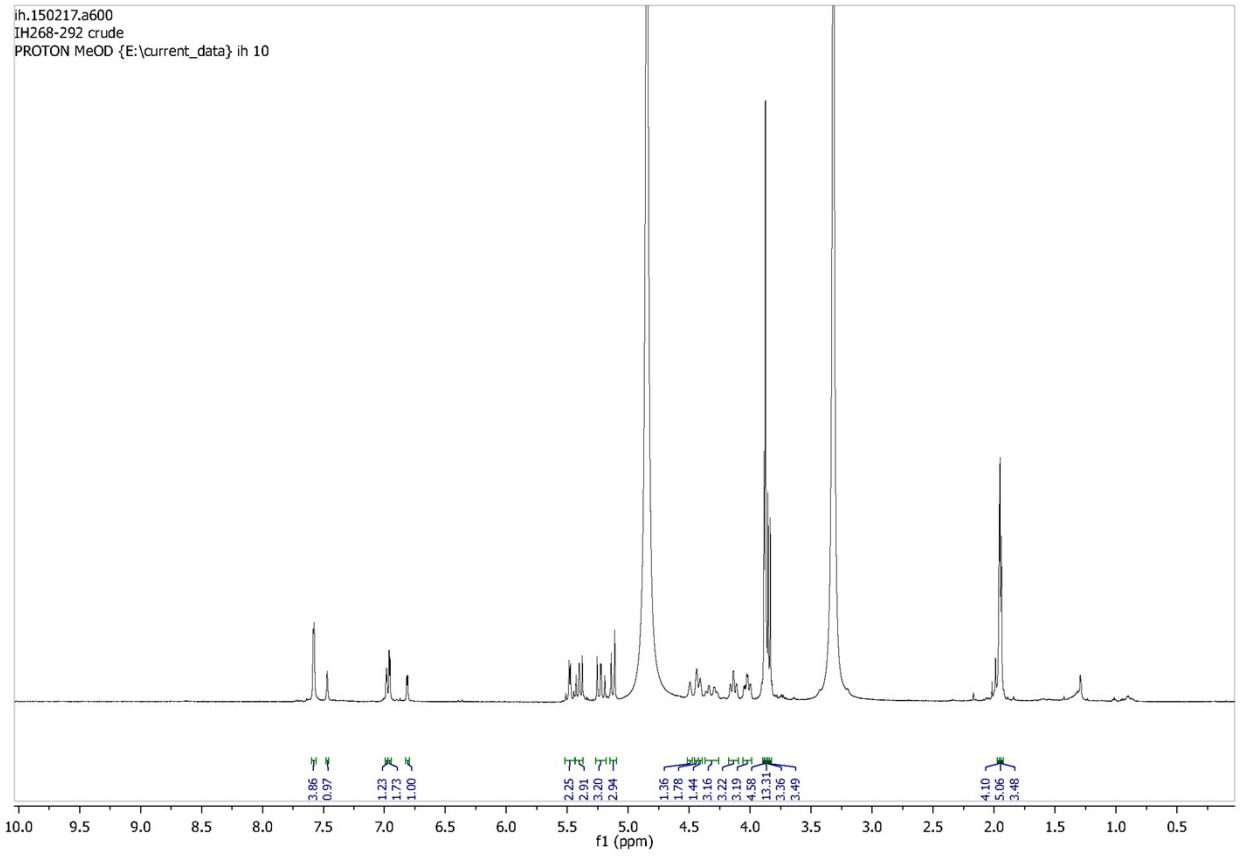
^{1}H NMR of **IH189**



^{1}H NMR of **IH268**



^{1}H NMR of **IH274**