Total Synthesis of Ageliferin via Acyl N-amidinyliminium Ion Rearrangement

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Supporting Information

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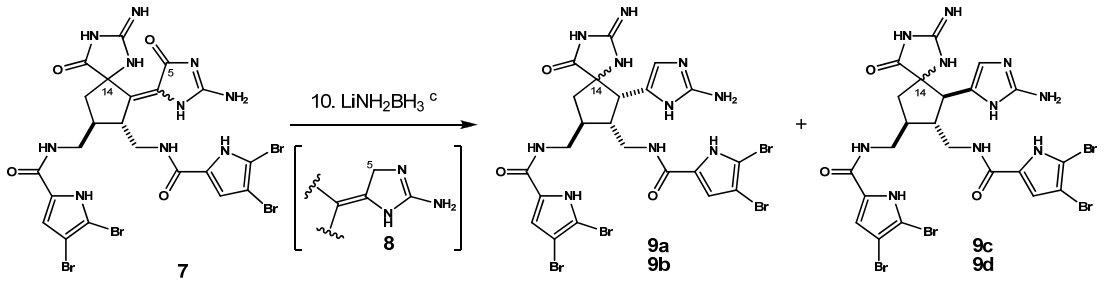
Materials and Methods

Unless stated otherwise, reactions were performed under an argon (Ar) atmosphere in flame-dried glassware. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), dimethoxyethane (DME), dimethyl formamide (DMF) and acetonitrile (CH_3CN) were dried and deoxygenated through activated alumina solvent drying systems or distilled prior to use. Column chromatography was performed on silica gel 60 (SiliCycle, 240-400 mesh). Thin layer chromatography (TLC) and preparative thin layer chromatography (pTLC) utilized pre-coated plates (silica gel 60 PF254, 0.25 mm or 0.5 mm). Purification of advanced intermediates employed an Agilent 1200 Preparative HPLC (pHPLC) system equipped with an Agilent Quadrupole 6130 ESI-MS detector and an automated fraction collector. Mobile phases (Mobile phase A: H_2O, Mobile Phase B: CH_3CN) were prepared with 0.1% or 1% trifluoroacetic acid (TFA) or 0.1% formic acid as indicated. Advanced intermediates isolated and characterized as trifluoroacetate salts are denoted as (X CF_3CO_2H) in tabulated data. The trifluoroacetate salt is omitted from some structures in schemes for clarity. NMR spectra were recorded on Bruker Avance spectrometers (500 MHz, 600 MHz). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration) at 298K, unless stated otherwise, and are referenced to a residual solvent peak. Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm) and are referenced to residual solvent peak.

Compounds **3** to **8** have been reported in our previous work.[1]

Reduction of glycocyamidine diastereomers 7 to provide a mixture of 2-aminoimidazoles 9



Preparation of LAB solution: To a suspension of $BH_3{\cdot}NH_3$ (0.57 g, 16.5 mmol, 90% purity) in THF (3.6 mL) cooled to –20 °C was added a solution of *n*-BuLi (2.5 M in hexanes, 6.4 mL, 16.0 mmol) dropwise. The mixture was warmed to RT, stirred for 1 h and used directly (~1.6 M) for the reduction reaction.

A portion of the above LAB solution (3.8 mL, 1.6 M, 6.1 mmol) was added to a solution of **9** (207 mg, 0.20 mmol) in THF (6.8 mL) at RT. Gentle gas evolution was observed. The mixture was stirred in a pre-heated oil-bath (60 °C) for 4 h. A second portion of the LAB solution (1.9 mL, 3.0 mmol) was added and the cloudy mixture was stirred at 60 °C for another 4 h. After cooled –40 °C, the reaction was quenched with slow addition of 10% TFA in H_2O (10 mL) (Note: gas evolution could be vigorous if the addition is too fast). The mixture was warmed to RT and stirred at 60 °C for 4 h, then purified by HPLC to give **9a**/**9b** (46 mg, 22.5%; t_R = 10.1 min), **9c** (21.0 mg, 11%; t_R = 10.6 min), **9d** (19 mg, 9.3%; t_R = 10.2 min), and recovered **7** (9.0 mg, 4.3%; t_R = 10.4 min).

HPLC conditions: Waters Sunfire C18 column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 1% TFA; B: acetonitrile, w/ 1% TFA; increase of B from 10% to 30%, 0-2 min; then to 60%, 12 min; flow rate: 20 mL/min.

Compounds **9a** and **9c** have been reported in our previous work.[1a]

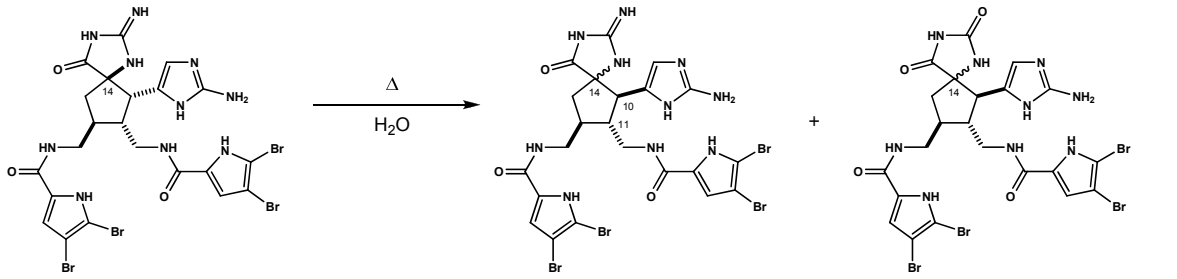
For characterization purposes, a portion of the **9a**/**9b** mixture was further purified by HPLC to give pure **9b** (t_R = 11.6 min).

HPLC conditions: Waters XSelect Fluoro-phenyl column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 1% TFA; B: acetonitrile, w/ 1% TFA; increase of B from 10% to 22%, 0-2 min; then to 26.5%, 14 min; flow rate: 30 mL/min.

Compound **9b**: ^{1}H NMR (MeOH-d_4): δ (ppm) 6.82 (s, 1H), 6.77 (s, 1H), 6.61 (s, 1H), 3.55 (d, J = 8.6 Hz, 1H), 3.47 (d, J = 5.9 Hz, 2H), 3.34-3.27 (m, partially overlapped with MeOH residue peak), 2.78 (dd, J = 15.8, 7.9 Hz, 1H), 2.56-2.46 (m, 1H), 2.27-2.21 (m, 1H), 2.12-2.05 (m, 1H); ^{13}C NMR (MeOH-d_4) δ (ppm): 162.2, 161.7, 148.5, 128.6, 128.4, 122.8, 114.54, 114.48, 112.3, 106.34, 106.29, 100.1, 100.0, 73.6, 47.2, 44.4, 43.7, 43.4, 41.9, 39.7; HRMS-ESI *m/z* calcd for $[C_{22}H_{22}Br_4N_{10}O_3+H]^+$: 794.8649; found: 794.8619.

Compound **9d**: ^{1}H NMR (MeOH-d_4): δ (ppm) 6.90 (s, 1H), 6.77 (s, 1H), 6.61 (s, 1H), 3.64 (dd, J = 13.7, 4.9 Hz, 1H), 3.51-3.45 (m, 3H), 3.25 (d, J = 12.5 Hz, 1H), 2.69-2.59 (m, 1H), 2.47-2.39 (m, 1H), 2.33-2.18 (m, 2H); ^{13}C NMR (MeOH-d_4) δ (ppm): 162.2, 162.1, 149.0, 128.6, 128.3, 123.5, 114.6, 114.4, 112.7, 106.5, 106.3, 100.06, 100.02, 73.1, 50.0, 45.9, 43.0, 41.0, 40.7, 38.2; HRMS-ESI *m/z* calcd for $[C_{22}H_{22}Br_4N_{10}O_3+H]^+$: 794.8649; found: 794.8666.

Preparation of 9c from 9a (Thermolysis in a microwave reactor)

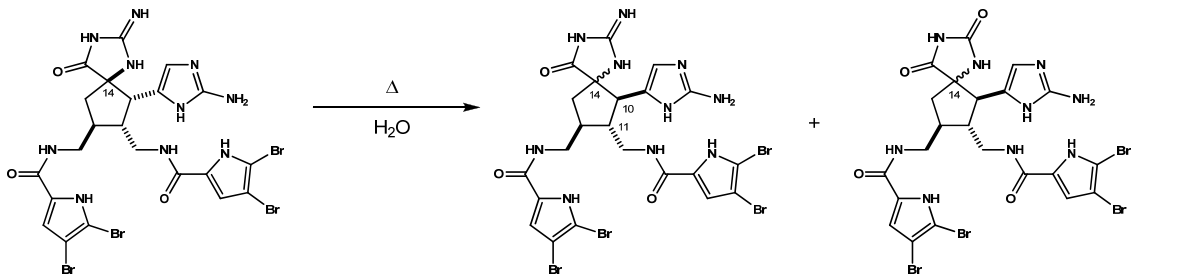


9a **9c/9d** **9c-1** (~10%, tentatively assigned by ms)

Pure **9a** (8.0 mg, 0.0078 mmol) was dissolved in MeOH (3 mL) and evenly distributed into three 10-mL microwave reaction vials. Each sample was concentrated, dissolved in DI-water and stirred at 180 °C for 15 min in a CEM microwave reactor. The mixtures were combined, diluted with MeOH and purified by pHPLC. Two *trans*-C10, C11 compounds were obtained (**9c**, 3.4 mg, 42%, t_R = 13.1 min; **9d**, 1.9 mg, 23%; t_R = 11.6 min), along with two epimeric compounds tentatively assigned as hydantoin compounds (**9c-1**; t_R = 15.3, 16.4 min) (LCMS analysis LRMS-ESI *m/z* for $[C_{22}H_{21}Br_4N_9O_4+H]^+$: 795.9; Found: 795.6; ~ 1 mg total, 10%).

HPLC conditions: Waters XBridge RP-18 column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 0.1% TFA; B: acetonitrile, w/ 0.1% TFA; increase of B from 10% to 33%, 0-2 min; then to 36%, 15 min; flow rate: 20 mL/min.

Preparation of 9c from (9a + 9b + 9d) (Thermolysis in a microwave reactor)

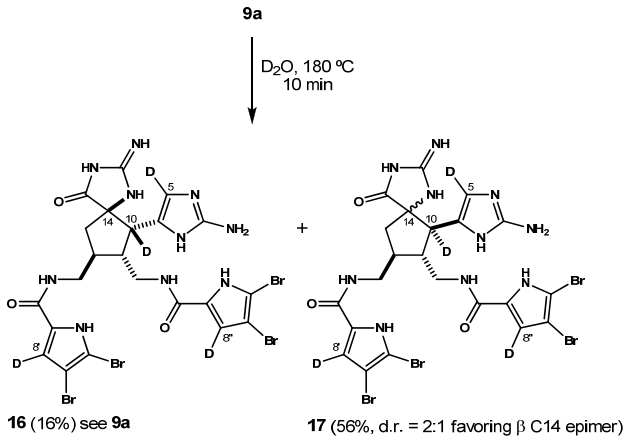


9a **9c/9d** **9c-1** (~10%, tentatively assigned by ms)

A mixture of (**9a** + **9b** + **9d**) (16.5 mg, 0.016 mmol, ~4:1:1.5) was dissolved in MeOH (3 mL) and evenly distributed into three 10-mL microwave reaction vials. Each sample was concentrated, dissolved in DI-water (4.5 mL each) and stirred at 180 °C for 18 min in a CEM microwave reactor. The mixtures were combined, diluted with MeOH and purified by pHPLC. Two *trans*-C10, C11 compounds were obtained (**9c**, 2.4 mg, 16%; **9d**, 2.2 mg, 14%), along with two epimeric compounds tentatively assigned as hydantoin compounds (**9c-1**) (LCMS analysis LRMS-ESI *m/z* for $[C_{22}H_{21}Br_4N_9O_4+H]^+$: 795.9; Found: 795.6; ~ 3 mg total, 18%).

HPLC conditions: Waters XBridge RP-18 column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 0.1% TFA; B: acetonitrile, w/ 0.1% TFA; increase of B from 10% to 33%, 0-2 min; then to 36%, 15 min; flow rate: 20 mL/min.

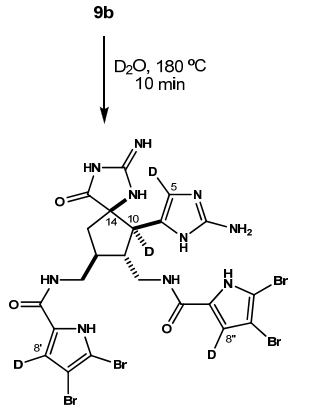
Thermolysis of 9a in D_2O by heating in a microwave reactor.



Pure **9a** (4.0 mg, 0.004 mmol) was dissolved in D_2O (3 mL) and evenly distributed into two 10-mL microwave reaction vials and stirred at 180 °C for 10 min in a CEM microwave reactor. The mixtures were combined, diluted with MeOH and purified by pHPLC. Two fractions were collected. The first fraction contains **16** and α-C14-**17** (1.4 mg, 1:1.1, 34%; t_R = 12.0 min) and the second fraction is β-C14-**17** (1.6 mg, 38%; t_R = 13.8 min).

HPLC conditions: Waters XBridge RP-18 column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 0.1% TFA; B: acetonitrile, w/ 0.1% TFA; increase of B from 10% to 32%, 0-2 min; then to 36%, 15 min; flow rate: 20 mL/min.

Thermolysis of 9c in D_2O by heating in a microwave reactor.

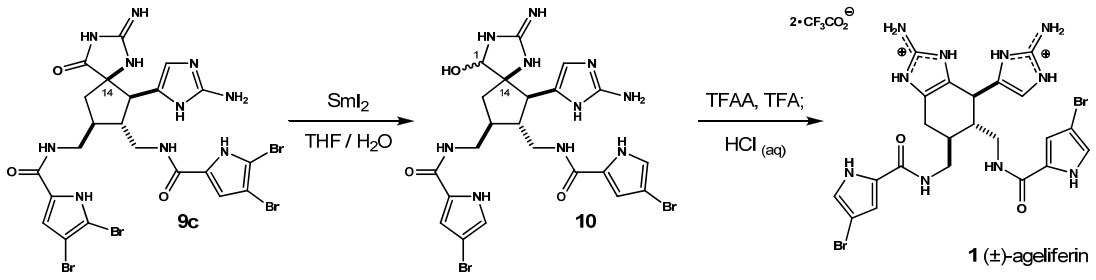


17 (70%, d.r. ≅ 2:1 favoring β C14 epimer)

Pure **9c** (4.2 mg, 0.0042 mmol) was dissolved in D_2O (5 mL) and evenly distributed into two 10-mL microwave reaction vials and stirred at 180 °C for 10 min in a CEM microwave reactor. The mixtures were combined, diluted with MeOH and purified by pHPLC. Two *trans*-C10,C11 compounds were obtained (α-C14-**17**, 0.9 mg, 21%; β-C14-**17**, 2.1 mg, 49%).

HPLC conditions: Waters XBridge RP-18 column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 0.1% TFA; B: acetonitrile, w/ 0.1% TFA; increase of B from 10% to 32%, 0-2 min; then to 36%, 15 min; flow rate: 20 mL/min.

Synthesis of ageliferin (1).



To a solution of **9c** (20.0 mg, 0.019 mmol) in THF / H_2O (100 µL) was added a freshly-prepared solution of SmI_2 (700 µL, 0.196 mmol, 0.28M in THF) at –40 °C. The initially blue mixture became purple after degassed water (100 µL) was added. It turned to pale yellow after a few minutes. LCMS analysis indicated partial debromination occurred to give partially debrominated intermediates (LRMS-ESI *m/z* calcd for $[C_{22}H_{24}Br_2N_{10}O_4+H]^+$: 653.04; found: 653.1). The solvent volume was reduced by a stream of Ar and the mixture was cooled to –40°C. Another portion of SmI_2 (750 µL, 0.21 mmol, 0.28 M in THF) was added and the mixture was warmed to RT. The reaction

was quenched with degassed THF and water (1.2 mL each) under Argon. The crude solution was diluted with 10% TFA in water and purified by pHPLC. The desired C1-hemiaminal compounds **10** (LRMS-ESI *m/z* calcd for $[C_{22}H_{27}Br_2N_{10}O_3+H]^+$: 639.06; found: 639.1) were obtained (6.2 mg, ~37%, ~1:1 d.r.; t_R = 6.4 min). Compounds **10** in solution are prone to autooxidation so no further purification was performed.

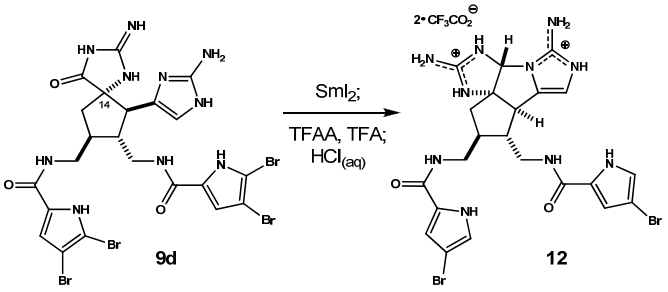
HPLC conditions: Waters XSelect Fluoro-phenyl column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 0.1% TFA; B: acetonitrile, w/ 0.1% TFA; increase of B from 10% to 25%, 0-2 min; then to 28%, 8 min; flow rate: 20 mL/min.

The above mixture **10** (6.2 mg) was dissolved in anhydrous THF (0.24 mL). TFAA (100 µL, 0.71 mmol) was added, followed by TFA (50 µL, 0.78 mmol). The vial was sealed and stirred at 70°C for 27 h. The reaction mixture was concentrated and dissolved in DME (0.3 mL), then treated with 2M HCl in water (0.4 mL, 0.8 mmol) at 45 °C for 14h. It was diluted with water and purified by HPLC to afford ageliferin **1** (2.2 mg, 38% from **10**; t_R = 10.6 min).

HPLC conditions: Waters XBridge RP-18 column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 0.1% TFA; B: acetonitrile, w/ 0.1% TFA; increase of B from 10% to 28%, 0-2 min; then to 34%, 25 min; flow rate: 20 mL/min.

Ageliferin (**1**): ^{1}H NMR (MeOH-d_4): δ (ppm) 6.97 (d, *J* = 1.5 Hz, 1H), 6.94 (d, *J* = 1.5 Hz, 1H), 6.91 (d, *J* = 1.5 Hz, 1H), 6.81 (d, *J* = 1.5 Hz, 1H), 6.77 (brs, 1H), 3.80 (d, *J* = 7.0 Hz, 1H), 3.76 (dd, *J* = 14.6, 4.4 Hz, 1H), 3.64 (dd, *J* = 14.0, 3.5 Hz, 1H), 3.49 (dd, *J* = 14.5, 4.9 Hz, 1H), 3.33 (m, partially overlapped with MeOH residue), 2.76 (ddd, *J* = 16.5, 5.7, 1.1 Hz, 1H), 2.45 (ddd, *J* = 16.6, 8.1, 1.9 Hz, 1H), 2.28-2.22 (m, 1H), 2.14-2.09 (m, 1H); ^{13}C NMR (MeOH-d_4) δ (ppm): 163.3, 163.0, 149.26, 149.19, 127.6, 127.2, 127.1, 123.3, 123.1, 122.8, 119.1, 114.2, 113.6, 113.0, 97.7, 97.6, 44.1, 42.8, 40.0, 37.2, 33.3, 23.7; HRMS-ESI *m/z* calcd for $[C_{22}H_{24}Br_2N_{10}O_2+H]^+$: 621.0510; found: 621.0500.

Synthesis of aminal 12.



To a solution of **9d** (16.7 mg, 0.016 mmol) in THF (100 µL) was added a freshly-prepared solution of SmI_2 (290 µL, 0.0667 mmol, 0.23 M in THF) at RT. The initially blue mixture became purple after degassed water (80 µL) was added. It turned to pale yellow after a few minutes. LCMS analysis indicated partial debromination occurred to give partially debrominated intermediates **A** (LRMS-ESI *m/z* calcd for $[C_{22}H_{24}Br_2N_{10}O_4+H]^+$: 653.04; found: 653.1). The solvent volume was reduced by a

stream of Ar. A solution of SmI_2 (750 µL, 0.21 mmol, 0.28 M in THF) was added at RT. The solvent was removed by a stream of argon and more SmI_2 in THF (290 µL, 0.23 M, 0.0667 mmol) was added at RT. This concentration-addition procedure was repeated 4 more times and LC shows >60% conversion of the debrominated compounds **A** to the desired product. The reaction was quenched with THF and water (1.2 mL each) under Argon. The crude solution was diluted with 10% TFA in water and purified by pHPLC. The desired C1-hemi-aminal compounds (LRMS-ESI *m/z* calcd for $[C_{22}H_{27}Br_2N_{10}O_3+H]^+$: 639.06; found: 639.0) were obtained (5.5 mg, ~39%, ~1:1 d.r; t_R = 6.2 min). These compounds in solution are prone to autooxidation so no further purification was performed.

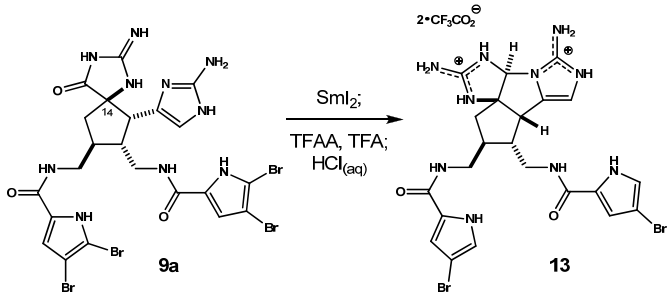
HPLC conditions: Waters XBridge RP-18 column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 0.1% TFA; B: acetonitrile, w/ 0.1% TFA; increase of B from 10% to 32%, 0-2 min; then to 33.5%, 7 min; flow rate: 20 mL/min.

The above mixture (5.5 mg) was dissolved in anhydrous THF (0.28 mL). TFAA (45 µL, 0.32 mmol) was added, followed by TFA (50 µL, 0.65 mmol). The vial was sealed and stirred at 60°C for 80 min. The reaction mixture was concentrated and dissolved in MeOH (50 µL), then treated with 2M HCl in water (0.25 mL, 0.5 mmol) at 60°C for 4h. It was diluted with water and purified by HPLC to afford **12** (3.0 mg, 22% from **9d**; t_R = 8.8 min).

HPLC conditions: Waters XBridge RP18 column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 1% TFA; B: acetonitrile, w/ 1% TFA; increase of B from 10% to 28%, 0-2 min; then to 32.5%, 10 min; flow rate: 20 mL/min.

Aminal **12**: ^{1}H NMR (MeOH-d_4): δ (ppm) 6.96 (d, J = 1.5 Hz, 1H), 6.92 (d, J = 1.5 Hz, 1H), 6.88 (d, J = 1.5 Hz, 1H), 6.80 (d, J = 1.5 Hz, 1H), 6.51 (d, J = 1.2 Hz, 1H), 6.00 (s, 1H), 3.76 (dd, J = 14.0, 4.2 Hz, 1H), 3.57 (dd, J = 14.0, 4.2 Hz, 1H), 3.51 (dd, J = 13.0, 6.5 Hz, 1H), 3.44 (d, J = 9.3 Hz, 1H), 3.34 (m, partially overlapped with MeOH residue), 2.48-2.37 (m, 1H), 2.34-2.17 (m, 2H), 1.94-1.89 (m, 1H); ^{13}C NMR (MeOH-d_4) δ (ppm): 163.0, 162.9, 158.6, 144.3, 133.1, 127.25, 127.21, 123.3, 123.0, 113.4, 106.8, 97.7, 97.5, 85.0, 77.0, 53.3, 51.4, 44.9, 42.6, 41.5, 40.1; HRMS-ESI *m/z* calcd for $[C_{22}H_{24}Br_2N_{10}O_2+H]^+$: 621.0510; found: 621.0500.

Synthesis of aminal 13.



To a solution of **9a** (23.0 mg, 0.022 mmol) in THF (110 μL) was added a freshly-prepared solution of SmI_2 (800 μL, 0.224 mmol, 0.28M in THF) at –40°C. The initially blue mixture became purple after degassed water (100 μL) was added. It turned to pale yellow after a few minutes. LCMS analysis indicated partial debromination occurred to give partially debrominated intermediate **B** (LRMS-ESI *m/z* calcd for $[C_{22}H_{24}Br_2N_{10}O_4+H]^+$: 653.04; found: 653.1). The solvent volume was reduced by a stream of Ar. A solution of SmI_2 (750 μL, 0.21 mmol, 0.28 M in THF) was added at RT. The solvent was removed by a stream of argon and more SmI_2 in THF (800 μL, 0.28 M, 0.224 mmol) was added at RT. This concentration-addition procedure was repeated two more times and LC shows >60% conversion of the partially debrominated compounds **B** to the desired product. The reaction was quenched with degassed THF and water (1.2 mL each) under Argon. The crude solution was diluted with 10% TFA in water and purified by pHPLC. The desired aminal compounds (LRMS-ESI *m/z* calcd for $[C_{22}H_{27}Br_2N_{10}O_3+H]^+$: 639.06; found: 639.0) were obtained (8.2 mg, ~42%, as a mixture of ~1:1 diastereomers; t_R = 7.0 min). These compounds in solution are prone to autooxidation so no further purification was performed.

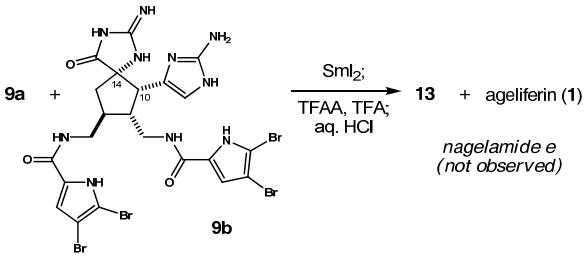
HPLC conditions: Waters XSelect Fluoro-phenyl column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 0.1% TFA; B: acetonitrile, w/ 0.1% TFA; increase of B from 10% to 25%, 0-2 min; then to 28%, 8 min; flow rate: 20 mL/min.

The above mixture (8.2 mg) was dissolved in anhydrous THF (0.28 mL). TFAA (100 μL, 0.71 mmol) was added, followed by TFA (120 μL, 1.57 mmol). The vial was sealed and stirred at 60°C for 7 h. The reaction mixture was concentrated and dissolved in THF (0.1 mL), then treated with 2M HCl in water (0.2 mL, 0.4 mmol) at 60°C for 4h. It was diluted with water and purified by HPLC to afford **13** (2.4 mg, 13% from **9a**; t_R = 8.9 min).

HPLC conditions: Waters XBridge RP-18 column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 0.1% TFA; B: acetonitrile, w/ 0.1% TFA; increase of B from 10% to 28%, 0-2 min; then to 33.3%, 11 min; flow rate: 20 mL/min.

Aminal **13**: ^{1}H NMR (MeOH-d_4): δ (ppm) 6.94 (d, J = 1.2 Hz, 1H), 6.93 (d, J = 1.2 Hz, 1H), 6.88 (d, J = 1.2 Hz, 1H), 6.83 (d, J = 1.2 Hz, 1H), 6.66 (s, 1H), 5.95 (s, 1H), 3.83 (d, J = 9.3 Hz, 1H), 3.56-3.36 (m, 4H), 2.51-2.38 (m, 2H), 2.03-1.96 (m, 2H); ^{13}C NMR (MeOH-d_4) δ (ppm): 163.1, 162.9, 158.9, 144.6, 129.4, 127.29, 127.23, 123.11, 123.06, 113.7, 113.6, 108.8, 97.7, 97.5, 84.8, 76.9, 50.8, 43.9, 43.6, 41.5, 40.8, 40.5; HRMS-ESI *m/z* calcd for $[C_{22}H_{24}Br_2N_{10}O_2+H]^+$: 621.0510; found: 621.0519.

Synthesis of aminal 13 and ageliferin (1) from a mixture of 9a and 9b.



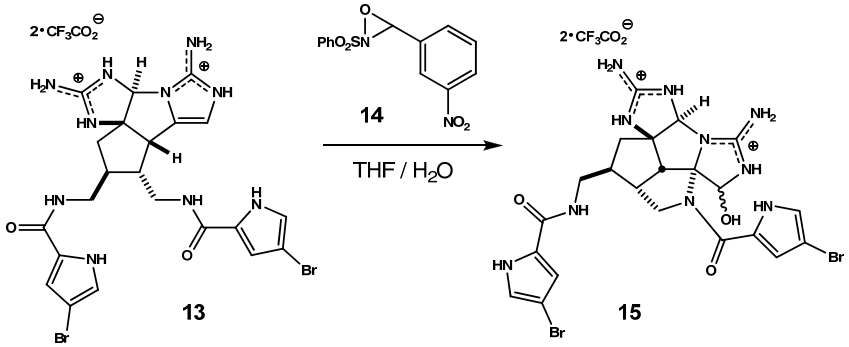
To a solution of **9a** and **9b** (57 mg, 0.056 mmol; ~4:1) in THF (200 µL) was added a freshly-prepared solution of SmI_2 (2.0 mL, 0.56 mmol, 0.28M in THF) at –40°C. The initially blue mixture became purple after degassed water (200 µL) was added. It turned to pale yellow after a few minutes. LCMS analysis indicated partial debromination occurred to give debrominated intermediates **C** (LRMS-ESI *m/z* calcd for $[C_{22}H_{24}Br_2N_{10}O_4+H]^+$: 653.04; found: 653.1). The solvent volume was reduced by a stream of Ar. A solution of SmI_2 (1.8 mL, 0.50 mmol, 0.28 M in THF) was added at RT. The reaction was quenched with degassed THF and water (2.0 mL each) under Argon. The crude solution was diluted with 10% TFA in water and purified by pHPLC. The desired *C1*-hemi-aminal compounds were obtained (23.5 mg, ~41%; t_R = 6.3 min) as a mixture of diastereomers.

HPLC conditions: Waters XSelect Fluoro-phenyl column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 0.1% TFA; B: acetonitrile, w/ 0.1% TFA; increase of B from 10% to 25%, 0-2 min; then to 28%, 8 min; flow rate: 20 mL/min.

Part of the above mixture (22.0 mg, ~0.025 mmol) was dissolved in anhydrous THF (0.9 mL). TFAA (360 µL, 2.59 mmol) was added, followed by TFA (360 µL, 4.7 mmol). The vial was sealed and stirred at 60°C for 5 h. The reaction mixture was concentrated and dissolved in DME (0.6 mL), then treated with 2M HCl in water (1.0 mL, 2.0 mmol) at 60°C for 14 h. It was diluted with water and purified by HPLC to afford **13** (6.3 mg, 18% from **9a**; t_R = 8.9 min) and ageliferin **1** (2.0 mg, 22% from **9b**; t_R = 10.7 min).

HPLC conditions: Waters XBridge RP-18 column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 0.1% TFA; B: acetonitrile, w/ 0.1% TFA; increase of B from 10% to 31%, 0-2 min; then to 33%, 12 min; flow rate: 20 mL/min.

Synthesis of aminals 15



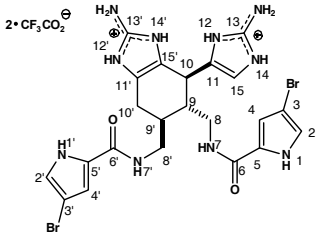
To a solution of **13** (4.3 mg, 0.0051 mmol) in THF-H_2O (5:1, 360 µL) was added 3-(3-nitrophenyl)-2-(phenylperoxythio)-1, 2-oxaziridine **14** (3.2 mg, 0.010 mmol) at RT. The mixture was stirred at 55°C for 2h. The mixture was diluted with 10% TFA in water and purified by pHPLC to give **15a** (1.7 mg, 39%; t_R = 6.9 min) and **15b** (1.2 mg, 27%; t_R = 7.8 min).

HPLC conditions: Waters XBridge RP18 column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 0.1% TFA; B: acetonitrile, w/ 0.1% TFA; increase of B from 10% to 28%, 0-2 min; then to 30%, 10 min; flow rate: 20 mL/min.

Aminal **15a**: ^{1}H NMR (MeOH-d_4): δ (ppm) 7.03 (d, J = 1.4 Hz, 1H), 6.91 (d, J = 1.5 Hz, 1H), 6.77 (d, J = 1.5 Hz, 1H), 6.76 (d, J = 1.4 Hz, 1H), 5.99 (s, 1H), 5.62 (s, 1H), 4.49 (dd, J = 14.4, 8.1 Hz, 1H), 3.50-3.35 (m, 2H), 2.79 (d, J = 12.2 Hz, 1H), 2.74-2.65 (m, 1H), 2.46 (dd, J = 14.0, 14.0 Hz, 1H), 2.35-2.28 (m, 1H), 1.99-1.94 (m, 2H); ^{1}H NMR (DMSO-d_6): δ (ppm) 12.04 (s, 1H), 11.76 (s, 1H), 9.84 (s, 1H), 8.97 (s, 1H), 8.90 (brs, 2H), 8.36 (s, 1H), 8.25 (dd, J = 6.0, 6.0 Hz, 1H), 8.17 (brs, 2H), 7.30 (s, 1H), 7.16 (s, 1H), 6.96 (s, 1H), 6.83 (s, 1H), 6.78 (s, 1H), 5.82 (s, 1H), 5.53 (s, 1H), 4.35 (dd, J = 14.5, 9.0 Hz, 1H), 3.50 (m, 2H, overlapped with water residue; refer to data in MeOH-d_4), 2.63-2.60 (m, 1H), 2.52 (m, 1H, overlapped with DMSO residue), 2.29-2.24 (m, 1H), 2.18-2.15 (m, 1H), 1.99-1.93 (m, 1H), 1.84-1.78 (m, 1H); ^{13}C NMR (MeOH-d_4) δ (ppm): 163.0, 158.6, 157.5, 127.2, 124.5, 124.4, 123.1, 115.9, 113.4, 99.2, 97.9, 97.6, 84.8, 77.6, 72.4 (weak), 54.0, 44.7, 42.8, 40.0, 38.1; HRMS-ESI *m/z* calcd for $[C_{22}H_{24}Br_2N_{10}O_3+H]^+$: 637.0459; found: 637. 0442.

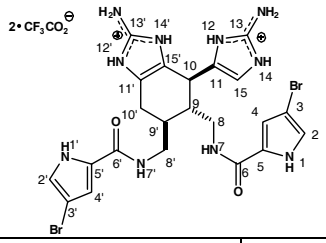
Aminal **15b**: ^{1}H NMR (MeOH-d_4): δ (ppm) 6.97 (d, J = 1.4 Hz, 1H), 6.93 (d, J = 1.5 Hz, 1H), 6.77 (d, J = 1.5 Hz, 1H), 6.62 (d, J = 1.4 Hz, 1H), 5.41 (s, 1H), 5.22 (s, 1H), 4.11 (d, J = 10.6 Hz, 1H), 4.01(d, J = 10.4 Hz, 1H), 3.92 (dd, J = 10.6, 7.0 Hz, 1H), 3.56-3.44 (m, 2H), 2.80-2.75 (m, 1H), 2.49-2.46 (m, 1H), 2.21-2.15 (m, 1H), 1.90 (dd, J = 12.5, 12.5 Hz, 1H); ^{1}H NMR (DMSO-d_6): δ (ppm) 11.97 (s, 1H), 11.81 (s, 1H), 9.89 (s, 1H), 9.04 (s, 1H), 8.88 (s, 1H), 8.68 (s, 1H), 8.42 (brs, 2H), 8.22 (dd, J = 6.0, 6.0 Hz, 1H), 7.18 (d, J = 5.2 Hz, 1H), 7.10 (dd, J = 3.2, 1.6 Hz, 1H), 6.96 (dd, J = 2.8, 1.5 Hz, 1H), 6.83 (s 1H), 6.65 (s 1H), 5.30 (s 1H), 5.07 (dd, J = 5.3, 2.1 Hz, 1H), 3.94 (d, J = 10.6 Hz, 1H), 3.81 (dd, J = 10.6, 6.8 Hz, 1H), 3.78 (d, J = 10.4 Hz, 1H), 3.42-3.38 (m, 2H), 2.60-2.57 (m, 1H), 2.15 (dd, J = 13.0, 5.4 Hz, 1H), 2.05-1.93 (m, 1H), 1.75 (dd, J = 12.9, 12.9 Hz, 1H); ^{13}C NMR (MeOH-d_4) δ (ppm): 162.9, 162.1, 158.7, 158.6, 127.1, 126.8, 123.9, 116.6, 113.3, 99.9, 98.0, 97.7, 84.6, 83.4, 81.4, 57.1, 54.2, 45.1, 44.6, 42.1, 41.3.; HRMS-ESI *m/z* calcd for $[C_{22}H_{24}Br_2N_{10}O_3+H]^+$: 637.0459; found: 637.0449.

Ageliferin (500 MHz, MeOH-d_4)



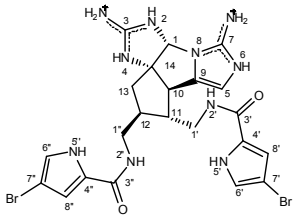
Position	1H NMR, d (mult, *J* in Hz)	1H NMR, d (mult, *J* in Hz)	1H NMR, d (mult, *J* in Hz)
	TFA salt (this work)	TFA salt (Chen)	natural HCl salt
1			
1'			
2	6.94 (d, *J*= 1.5)	6.94 (dd, *J*= 1.5, 0.7)	6.96 (d, *J*= 1.5)
2'	6.97 (d, *J*= 1.5)	6.97 (dd, *J*= 1.5, 0.7)	6.97 (d, *J*= 1.5)
3			
3'			
4	6.81 (d, *J*= 1.5)	6.83 (dd, *J*= 1.5, 0.7)	6.85 (d, *J*= 1.5)
4'	6.91 (d, *J*= 1.5)	6.93 (dd, *J*= 1.5, 0.7)	6.94 (d, *J*= 1.5)
5			
5'			
6			
6'			
7			
7'			
8a	3.49 (dd, *J*= 14.5, 4.9)	3.50 (dd, *J*= 14.6, 4.9)	3.50 (dd, *J*= 14, 5)
8b	3.76 (dd, *J*= 14.6, 4.4)	3.78 (dd, *J*= 14.6, 4.2)	3.77 (dd, *J*= 14, 4.5)
8'a	3.33 (dd, *J*= 14.3, 9.5)*	3.32 (dd, *J*= 14.0, 9.1)	3.33 (dd, *J*= 14, 4.5)
8'b	3.64 (dd, *J*= 14.0,3.5)	3.67 (dd, *J*= 14.0,3.4)	3.64 (dd, *J*= 14, 3)
9	2.14-2.09 (m)	2.15-2.11 (m)	2.16 (m)
9'	2.28-2.22 (m)	2.28-2.23 (m)	2.27 (m)
10	3.80 (d, *J*= 7.0)	3.82 (d, *J*= 7.3)	3.83 (brd, *J*= 7)
10'a	2.45 (ddd, *J*= 16.6, 8.1, 1.9)	2.47 (ddd, *J*= 16.4, 8.0, 2.4)	2.48 (ddd, *J*= 16, 8, 2.5)
10'b	2.76 (ddd, *J*= 16.5, 5.7, 1.1)	2.77 (ddd, *J*= 16.4, 5.4, 1.2)	2.78 (ddd, *J*= 16, 5.5, 1.5)
11			
11'			
12			
12'			
13			
13'			
14			
14'			
15	6.77(brs)	6.78 (s)	6.79 (brs)
15'			
	* partially overlapped with methanol residue peak		

Ageliferin (125 MHz, MeOH-d_4)



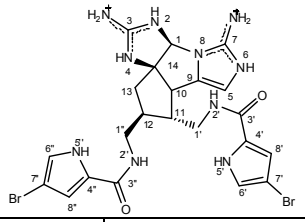
Position	13C NMR	13C NMR (Chen)	13C NMR (Baran)	13C NMR (natural)
	TFA salt	TFA salt	TFA salt	HOAc salt
1				
1'				
2	123.3	123.3	123.3	123.2
2'	123.1	123.1	123.1	123.0
3	97.7	97.7	97.7	97.7
3'	97.6	97.6	97.6	97.6
4	114.2	114.2	114.3	114.2
4'	113.6	113.6	113.8	113.6
5	127.2	127.2	127.3	127.3
5'	127.1	127.1	127.2	127.3
6	163.3	163.2	163.2	163.1
6'	163.0	162.9	163.0	162.9
7				
7'				
8a	40.0	40.0	40.0	40.6
8b				
8'a	42.8	42.8	42.9	43.0
8'b				
9	44.1	44.1	44.0	43.8
9'	37.2	37.2	37.3	37.4
10	33.3	33.3	33.4	34.3
10'a	23.7	23.7	23.9	23.8
10'b				
11	127.6	127.5	127.6	131.4
11'	122.8	122.8	122.8	123.0
12				
12'				
13	149.26	149.24	149.4	150.2
13'	149.19	149.18	149.3	149.4
14				
14'				
15	113.0	113.0	113.1	112.4
15'	119.1	119.1	119.3	122.3

12 (MeOH-d_4)



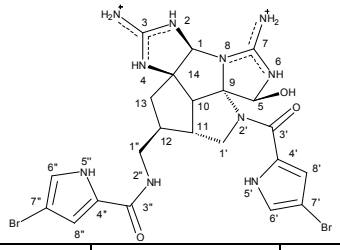
Position	13C NMR	1H NMR	COSY	HMBC (C no.)	TROESY
1	77.0	6.00 (s)		C3, C9, C13	H13b
2					
3	158.6				
4					
5	106.8	6.51 (d, *J* = 1.2 Hz)		C7, C9	
6					
7	144.3				
8					
9	133.1				
10	53.3	3.44 (d, *J*= 9.3 Hz)	H11	C9, C12, C14, C1'	
11	44.9	1.94-1.89 (m)	H10, H12, H1', H1'b		
12	51.4	2.48-2.37 (m)	H11, H13, H13b, H1", H1"b		
13	42.6	2.34-2.17 (m)	H12, H13b		
13b		2.34-2.17 (m)	H12, H13	C12, C14	
14	85.0				
1'	40.1	3.76 (dd, *J* = 14.0, 4.2 Hz)	H11, H1'b	C3'	H1'b
1'b		3.57 (dd, *J* = 14.0, 4.2 Hz)	H11, H1'	C3'	H1'
2'	N-amide				
3'	163.0				
4'	127.21				
5'	N-pyr				
6'	113.4	6.80 (d, *J* = 1.5 Hz)		C4', C8'	
7'	97.7				
8'	123.3	6.96 (d, *J* = 1.5Hz)		C4', C6', C7'	
1"	41.50	3.51 (dd, *J* = 13.0, 6.5 Hz)			H1'
1"b		3.34 (m)			
2"	N-amide				
3"	162.9				
4"	127.25				
5"	N-pyr				
6"	113.4	6.88 (d, *J* = 1.5 Hz)		C4", C8"	
7"	97.5				
8"	123.0	6.92 (d, *J* = 1.5 Hz)		C4", C6", C7"	

13 (MeOH-d_4)



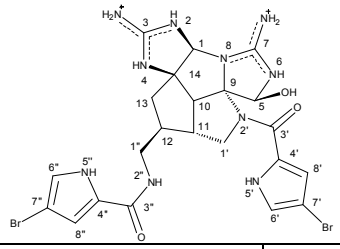
Position	13C NMR	1H NMR, d (mult, *J* in Hz)	COSY	HMBC (C no.)
1	76.9	5.95 (s)		C3, C9, C10, C13
2				
3	158.9			
4				
5	108.8	6.66 (s)		C7, C9
6				
7	144.6			
8				
9	129.4			
10	50.8	3.83 (d, *J*= 9.3 Hz)	H11	C9, C11, C12, C14
11	43.9	2.51 (m)	H10, H1', H1'b	
12	43.6	2.03-1.96 (m)	H11, H13, H13b, H1"	C1, C14, C1'
13	41.5	2.38 (m)	H12, H13b	C1, C10, C14,
13b		2.03-1.96 (m)	H12, H13	C1, C10, C11, C14
14	84.8			
1'	40.8	3.56-3.36 (m)	H11, H1'b	C10, C11, C12, C3'
1'b		3.56-3.36 (m)	H11, H1'	
2'	N-amide			
3'	162.9			
4'	127.23			
5'	N-pyr			
6'	113.7	6.83 (d, *J* = 1.2 Hz)		C4', C8'
7'	97.7			
8'	123.11	6.94 (d, *J* = 1.2 Hz)		C4', C6', C7'
1"	40.5	3.56-3.36 (m)		
2"	N-amide			
3"	163.1			
4"	127.29			
5"	N-pyr			
6"	113.6	6.88 (d, *J* = 1.2 Hz)		C4", C8"
7"	97.5			
8"	123.06	6.93 (d, *J* = 1.2 Hz)		C4", C6", C7"

15a NMR (MeOH-d_4)



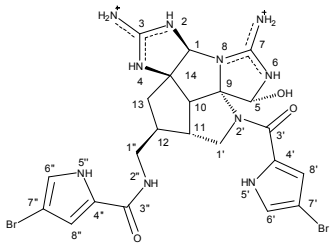
Position	13C NMR	1H NMR, d (mult, *J* in Hz)	COSY	HMBC (C no.)	TROESY
1	77.6	5.62 (s)		C3, C7, C9, C10, C13, C14	2-NH,7-NH, H13, H13b,
2					H1
3	158.6				H10
4					
5	72.4	5.99 (s)		C7, C9, C1', C3'	H6, 5-OH, H6'
6					H5
7	157.5				H1
8					
9	99.2				
10	54.0	2.79 (d, *J*= 12.2 Hz)	H11	C1, C9, C11, C12, C14	H3, 5-OH
11	38.1	2.74-2.65 (m)	H10, H1', H1'b		
12	44.7	1.99-1.94 (m)	H11, H1", H1"b		
13	40.0	2.35-2.28 (m)	H12, H13b	C1, C10, C11, C14	H1, H13b
13b		1.99-1.94 (m)	H12, H13	C1, C12, C14	H1, H13
14	84.8				
1'	42.8	4.49 (dd, *J*= 14.8, 8.1 Hz)	H11, H1"b	C5, C10, C11	H6'
1'b		2.46 (dd, *J* = 14.0, 14.0 Hz)	H11, H1"		
2'	N-amide				
3'	163.0				
4'	124.4				
5'	N-pyr				H8'
6'	115.9	6.76 (d, *J* = 1.4 Hz)		C4'	H5, H1'
7'	97.9				
8'	124.5	7.03 (d, *J* = 1.4 Hz)		C4', C6', C7'	H5'
1"	42.8	3.50-3.35 (m)	H12		
2"	N-amide				H6"
3"	163.0				
4"	127.1				
5"	N-pyr				H8"
6"	113.4	6.77 (d, *J* = 1.5 Hz)		C4"	
7"	97.6				
8"	123.1	6.91 (d, *J* = 1.5 Hz)		C4", C6", C7"	H5"

15a NMR (DMSO-d_6)



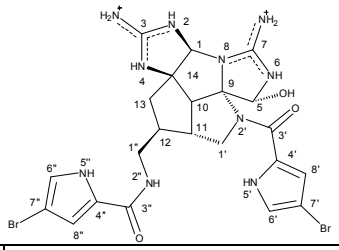
Position	1H NMR, d (mult, *J* in Hz) MeOH-*d4*	1H NMR, d (mult, *J* in Hz) DMSO-*d6*	COSY DMSO-*d6*	TROESY DMSO-*d6*
1	5.62 (s)	5.53 (s)	H2	2-NH,7-NH, H13, H13b,
2		8.36 (s)	H1, H3	H1
3		8.97 (s)	H2	H10
4		8.17 (s)		
5	5.99 (s)	5.82 (s)	H6	H6, 5-OH, H6'
5-OH		7.30 (s)		
6		9.84 (s)	H5	H5
7		8.90 (brs, 2H)		H1
8				
9				
10	2.79 (d, *J*= 12.2 Hz)	2.63-2.60 (m)	H11	H3, 5-OH
11	2.74-2.65 (m)	2.52 (m)	H10	
12	1.99-1.94 (m)	1.99-1.93 (m)		
13	2.35-2.28 (m)	2.18-2.15 (m)	H13b	H1, H13b
13b	1.99-1.94 (m)	1.84-1.78 (m)	H13	H1, H13
14				
1'	4.49 (dd, *J*= 14.8, 8.1 Hz)	4..35 (dd, *J*= 14.5, 9.0 Hz)	H1'b	H6'
1'b	2.46 (dd, *J* = 14.0, 14.0 Hz)	2.29-2.24 (m)	H1'	
2'				
3'				
4'				
5'		12.04 (s, 1H)	H8'	H8'
6'	6.76 (d, *J* = 1.4 Hz)	6.78 (s)		H5, H1'
7'				
8'	7.03 (d, *J* = 1.4 Hz)	7.30 (s)	H5'	H5'
1"	3.50-3.35 (m)	3.50 (m)		
2"		8.25 (dd, *J*= 6.0, 6.0 Hz)		H6"
3"				
4"				
5"			H8"	H8"
6"	6.77 (d, *J* = 1.5 Hz)	6.83 (s)		
7"				
8"	6.91 (d, *J* = 1.5 Hz)	6.96 (s)	H5"	H5"

15b NMR (MeOH-d_4)



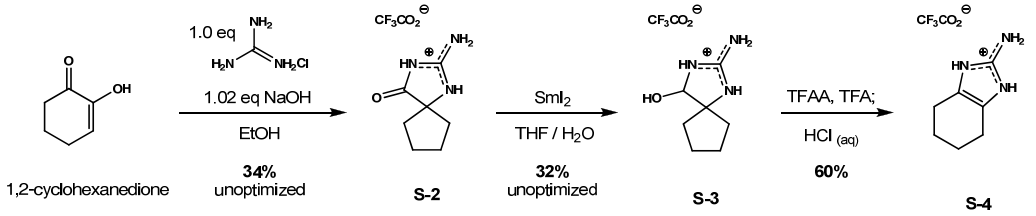
Position	13C NMR	1H NMR, d (mult, *J* in Hz)	COSY	HMBC (C no.)
1	81.4	5.41 (s)		C3, C9, C10, C13, C14
2				
3	158.7			
4				
5	83.4	5.22 (s)		C1, C7, C9
6				
7	158.6			
8				
9	99.9			
10	57.1	4.11 (d, *J*= 10.6 Hz)	H11	C1, C9, C12, C14
11	44.6	2.80-2.75 (m)	H10, H1', H1'b	C9, C12, C13
12	45.1	2.21-2.15 (m)	H11, H13b, H1"	
13	41.3	2.49-2.46 (m)	H12, H13b	C1, C10, C11, C14
13b		1.90 (dd, *J*= 12.5, 12.5 Hz)	H12, H13	C1, C1", C12, C14
14	84.5			
1'	54.2	4.01 (d, *J*= 10.4 Hz)	H11, H1'b	C9, C10, C12
1'b		3.92 (dd, *J* = 10.6, 7.0 Hz)	H11, H1'	C12
2'	N-amide			
3'	162.1			
4'	126.8			
5'	N-pyr			
6'	116.6	6.62 (d, *J* = 1.4 Hz)		C4', C8'
7'	98.0			
8'	123.9	6.97 (d, *J* = 1.4 Hz)		C4', C6', C7'
1"	42.0	3.56-3.44 (m)	H12	C11, C13, C3'
2"	N-amide			
3"	162.9			
4"	127.1			
5"	N-pyr			
6"	113.3	6.78 (d, *J* = 1.5 Hz)		C4", C8"
7"	97.7			
8"	123.3	6.94 (d, *J* = 1.5 Hz)		C4", C6", C7"

15b NMR (DMSO-d_6)

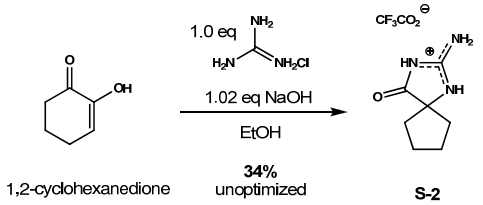


Position	1H NMR, d (mult, *J* in Hz) MeOH-*d4*	1H NMR, d (mult, *J* in Hz) DMSO-*d6*	COSY DMSO-*d6*	TROSEY DMSO-*d6*
1	5.41 (s)	5.30 (s)	2-NH	
2		8.68 (s)	H1, 3-NH	
3		9.04 (s)	2-NH	
4		8.42 (s)		
5	5.22 (s)	5.07 (s)	5-OH, 6-NH	5-OH, 6-NH
5-OH		7.18 (d, *J*= 5.2 Hz)		H5
6		9.89 (s)		H5
7		8.88 (s)		
8				
9				
10	4.11 (d, *J*= 10.6 Hz)	3.78 (d, *J*= 10.4 Hz)	H11	H11, H8’
11	2.80-2.75 (m)	2.60-2.57 (m)	H12, H1'	H10, H12
12	2.21-2.15 (m)	2.05-1.93 (m)	H13, H13b	H11
13	2.29-2.26 (m)	2.15 (dd, *J*= 13.0, 5.4 Hz)	H12, H13b	H13b
13b	1.90 (dd, *J*= 12.5, 12.5 Hz)	1.75 (dd, *J*= 12.9, 12.9 Hz)	H12, H13	H13
14				
1'	4.01 (d, *J*= 10.4 Hz)	3.94 (d, *J*= 10.6 Hz)	H11	H1’b
1'b	3.92 (dd, *J* = 10.6, 7.0 Hz)	3.81 (dd, *J* = 10.6, 6.8 Hz)		H1’
2'				
3'				
4'				
5'		11.97 (s)		H8’
6'	6.62 (d, *J* = 1.4 Hz)	6.65 (s)	5'-NH	
7'				
8'	6.97 (d, *J* = 1.4 Hz)	7.10 (dd, *J* = 3.2, 1.6 Hz)	5'-NH	H5’
1"	3.56-3.44 (m)	3.42-3.38 (m)		
2"		8.22 (dd, *J* = 6.0, 6.0 Hz)	H1"	
3"				
4"				
5"				H8’’
6"	6.78 (d, *J* = 1.5 Hz)	6.83 (s)	5"-NH	
7"				
8"	6.94 (d, *J* = 1.5 Hz)	6.96 (dd, *J* =2.8, 1.5 Hz)	5"-NH	H5’’

Procedures for the synthesis of model system 2-amino-1,3-diazaspiro[4.4]non-1-en-4-ol (S-3) and ring-expansive rearrangement to provide 4,5,6,7-tetrahydro-1H-benzo[d]imidazol-2-amine (S-4).



1,2-Cyclohexanedione was prepared from cyclohexanone according to literature procedures.[2]



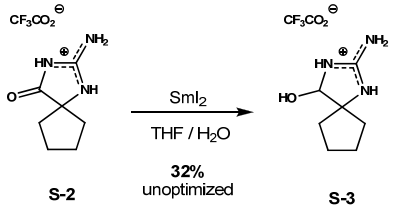
2-Imino-1,3-diazaspiro[4.4]nonan-4-one **(S-2)**.

Guanidine hydrochloride (6.81 g, 71 mmol) was stirred with granulated sodium hydroxide (2.92 g, 73 mmol, 1.02 eq) in EtOH (355-mL, 0.2 M) at RT for 5 min. 1,2-cyclohexanedione (8.25 g, 71 mmol) was added to the opaque white solution and the reaction was heated to reflux. The solution became light yellow and clear and was heated for 2.5h until judged complete by TLC analysis. The reaction was cooled to RT and concentrated in vacuo to provide a crude brown foam. The crude free base was dissolved in 10-mL MeOH, filtered to remove salts and loaded onto a dry silica gel column. Purification by flash chromatography (isocratic 90:9:1 CH_2Cl_2 / MeOH / conc. NH_4OH for 8 CV followed by column flush with isocratic 50:49:1 CH_2Cl_2 / MeOH / conc. NH_4OH) gave **S-2** as a tan solid (3.70 g, 34%). This material showed spectroscopic data consistent with literature. [3]

(**S-2**) Freebase: ^{1}H NMR (500 MHz, MeOH-d_4): δ (ppm) 2.04-1.95 (m, 2H), 1.89-1.71 (m, 6H); ^{13}C NMR (125 MHz, MeOH-d_4): δ (ppm) 195.8, 170.9, 73.3, 38.4, 26.5.

The isolated free base (S-2) can be readily converted to the trifluoroacetate salt by dissolution in MeOH and addition of ~1.2 eq TFA followed by concentration *in vacuo*.

(**S-2**) CF_3CO_2H: ^{1}H NMR (500 MHz, MeOH-d_4): δ (ppm) 2.16-2.08 (m, 2H), 1.98-1.85 (m, 6H); ^{13}C NMR (125 MHz, MeOH-d_4): δ (ppm) 179.5, 158.5, 71.6, 38.4, 26.2; HRMS-ESI (m/z) calcd for $[C_7H_{11}N_3O+H]^+$: 154.0980; found: 154.0986.

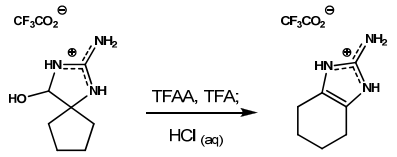


S-2 S-3

2-Amino-1,3-diazaspiro[4.4]non-1-en-4-ol (**S-3**).

To a solution of **S-2** (14 mg, 0.052 mmol) in degassed THF (0.2 mL) was added a freshly prepared solution of SmI_2 (2.0 mL, 0.56 mmol, 0. 28 M in THF) at –40 °C. The initially blue mixture became purple after degassed water (0.2 mL) was added. The reaction turned to pale yellow after a few minutes. The solvent volume was reduced by a stream of Ar. A solution of SmI_2 (2.0 mL, 0.56 mmol, 0.28 M in THF) was added at RT. This concentration-addition procedure was repeated two more times. The reaction was diluted with 10% TFA in water and purifed by pHPLC. The desired C-4 hemiaminal **S-3** was obtained (4.5 mg, 32%). This material showed spectroscopic data consistent with literature. [4]

HPLC conditions: Waters Sunfire C18 column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 1% TFA; B: acetonitrile, w/ 1% TFA; increase of B from 10% to 25%, 0-2 min; then to 28.8%, 9 min; flow rate: 20 mL/min.



S-3 S-4

4,5,6,7-Tetrahydro-1H-benzo[d]imidazol-2-amine (**S-4**).

2-Amino-1,3-diazaspiro[4.4]non-1-en-4-ol (**S-3**) (4.5 mg, 0.0167 mmol, TFA salt) was dissolved in anyhydrous THF (0.8 mL). TFAA (120 µL, 0.86 mmol) was added followed by TFA (120 µL, 1.57 mmol). The reaction vial was sealed and stirred at 70 °C for 6 h. The reaction mixture was concentrated and treated with 2M HCl in water (0.6 mL, 1.2 mmol) at RT for 2 h. The resultant solution was diluted with water and purified by HPLC to afford **S-4 (**2.7 mg, 64%). This material showed spectroscopic data consistent with literature[5] and an authentic sample which was prepared from the condensation reaction of 2-aminocyclohexanone[6] and cyanamide (5 eq) in H_2O (0.1 M, pH = 4.3 adjusted with 10% NaOH) at 100 °C for 3h.

HPLC conditions: Waters XBridge RP18 column (19×250 mm) with UV detection at 280 nm; solution A: water, w/ 0.1% TFA; B: acetonitrile, w/ 0.1% TFA; increase of B from 10% to 32%, 0-2 min; then to 33.5%, 6 min; flow rate: 20 mL/min.

(**S-4**) CF_3CO_2H:
^1H NMR (500 MHz, MeOH-d_4): δ (ppm) 2.43-2.41 (m, 4H), 1.82-1.80 (m, 4H); ^{13}C NMR (125 MHz, MeOH-d_4): δ (ppm) 148.0, 121.9, 23.23, 21.06; HRMS-ESI (m/z) calcd for $[C_7H_{11}N_3+H]^+$: 138.1031; found: 138.1044.

Supporting Information References

[1] (a) Ding, H.; Roberts, A. G.; Harran, P. G. *Angew. Chem., Int. Ed.* **2012**, 51, 4340–4343. (b) Li, Q.; Hurley, P.; Ding, H.; Roberts, A. G.; Akella, R.; Harran, P. G. *J. Org. Chem.* **2009**, 74, 5909–5919.

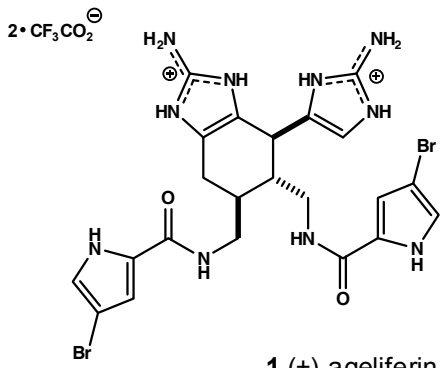
[2] For the preparation of 1,2-cyclohexanedione (CAS Registry Number: 765-87-7): Hach, C. C.; Banks, C. V.; Diehl, H. *Org. Syn.*, **1963** *Col l. Vol. 4*, 229; **1952** Vol. *32*, 35.

[3] The conversion of 1,2-cyclohexanedione to **S-2** via an α-diketone rearrangement with guanidines has been reported previously. The reported procedure was modified to provide adequate quantities of model substrate **S-2**. Anzai, K. *Bull. Chem. Soc. Jap.* **1969**, *42*, 3314–3317. (Compound **VIII** in text)

[4] Su, S.; Sieple, I. B.; Young, I. S.; Baran, P. S. *J. Am. Chem. Soc.*, **2008**, *130*, 16490–16491. (Compound **11** in text).

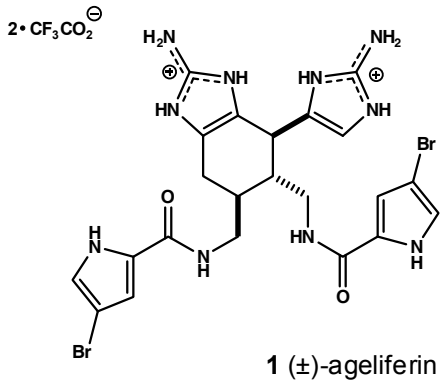
[5] 4,5,6,7-Tetrahydro-1H-benzo[d]imidazol-2-amine (**S-4**) was previously prepared and characterized as the ethyl sulfate salt. Little, T. L.; Webber, S. E. *J. Org. Chem.* **1994**, *59*, 7299–7305.

[6] For the preparation of 2-aminocyclohexanone (CAS Registry Number: 22374-48-7): (a) Baumgarten, H. E.; Peterson, J. M. J. Am. Chem. Soc. **1960,** *82*, 459–463. (b) Alt, G. H; Knowles, W. S. *Org. Syn.*, **1973** *Col l. Vol. 5*, 208; **1965** Vol. *45*, 16.



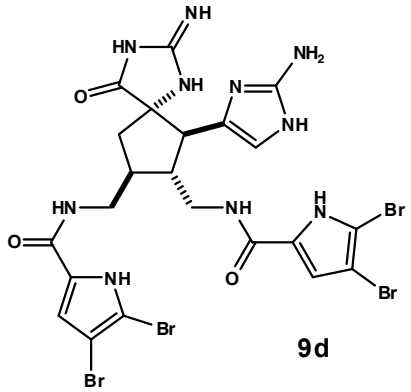
1 (±)-ageliferin

500 MHz, MeOH-d_4



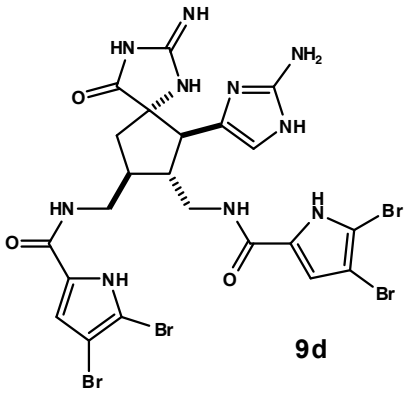
1 (±)-ageliferin

125 MHz, MeOH-d_4



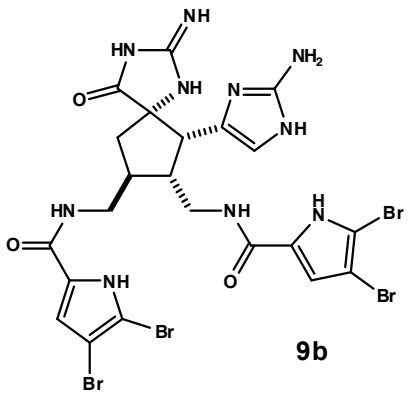
9d

500 MHz, MeOH-d_4



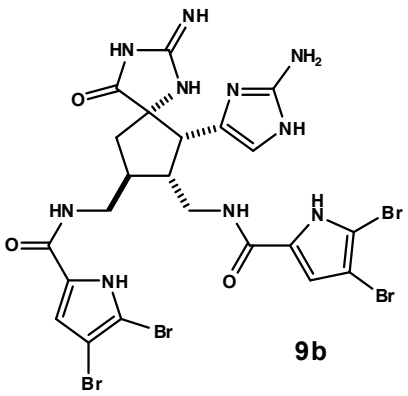
9d

125 MHz, MeOH-d_4



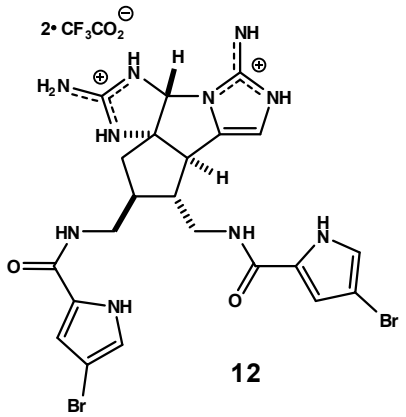
9b

500 MHz, MeOH-d_4



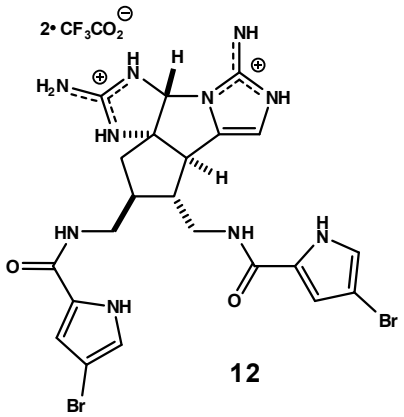
9b

125 MHz, MeOH-d_4



12

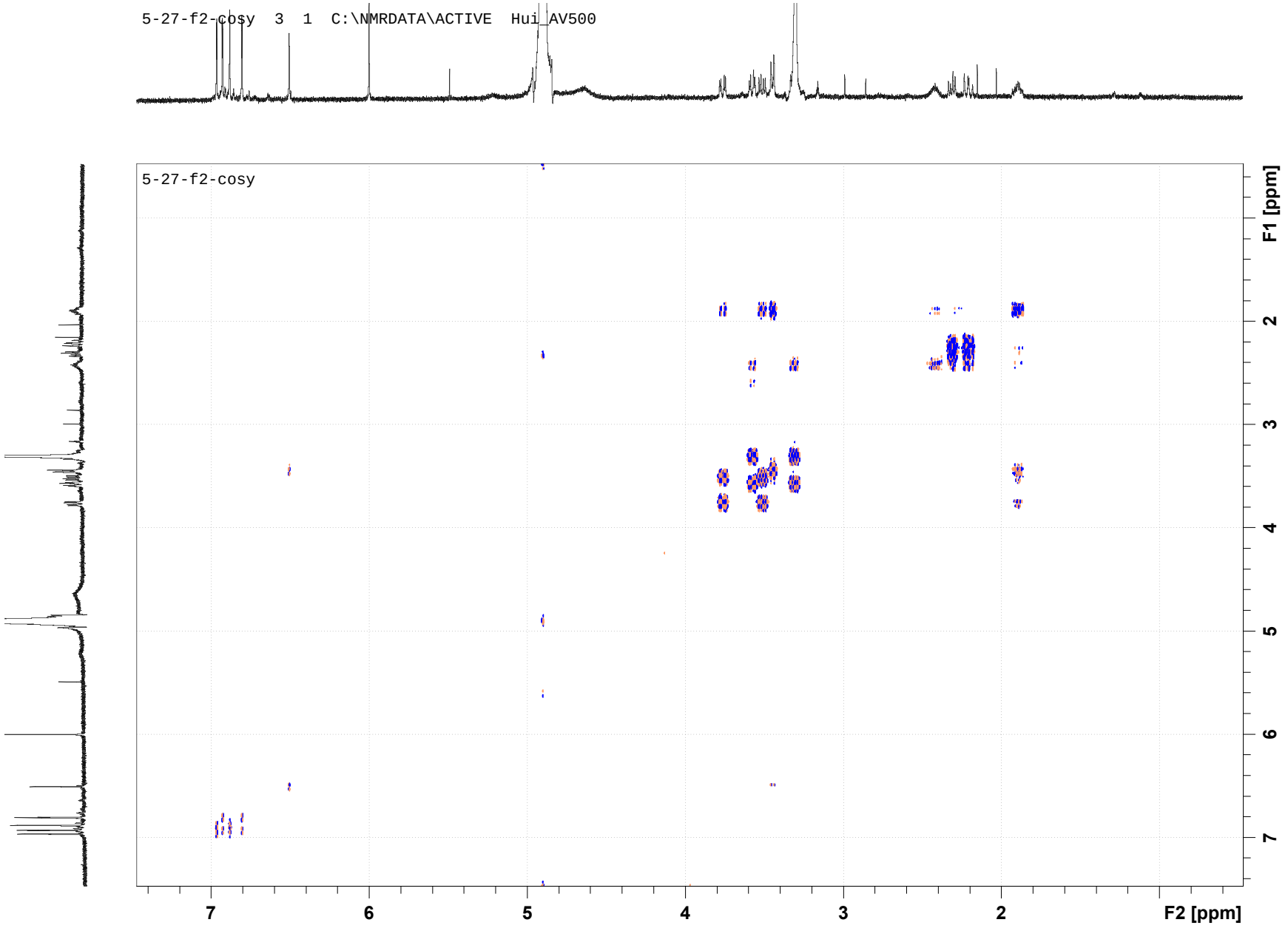
500 MHz, MeOH-d_4



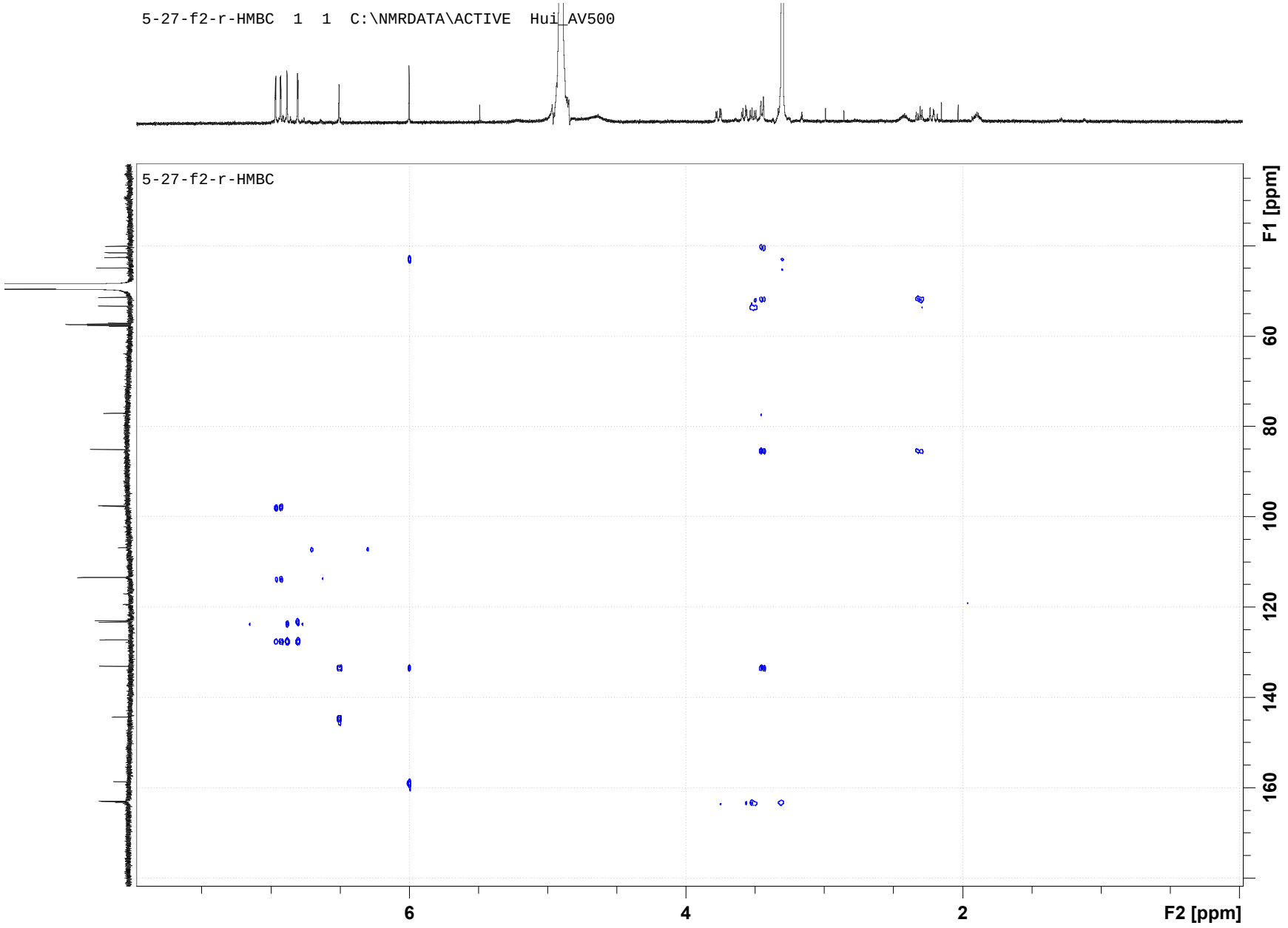
12

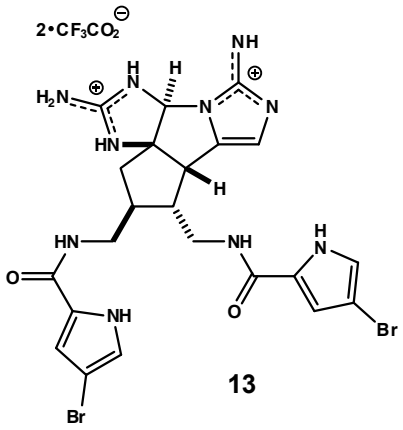
125 MHz, MeOH-d_4

12 COSY



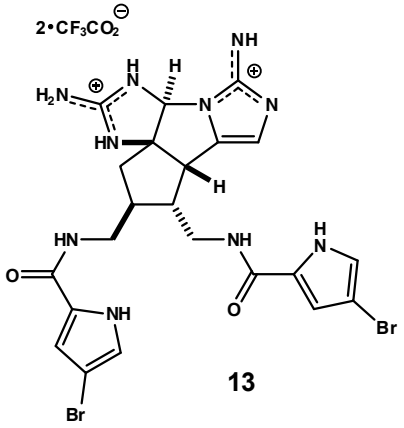
12 HMBC





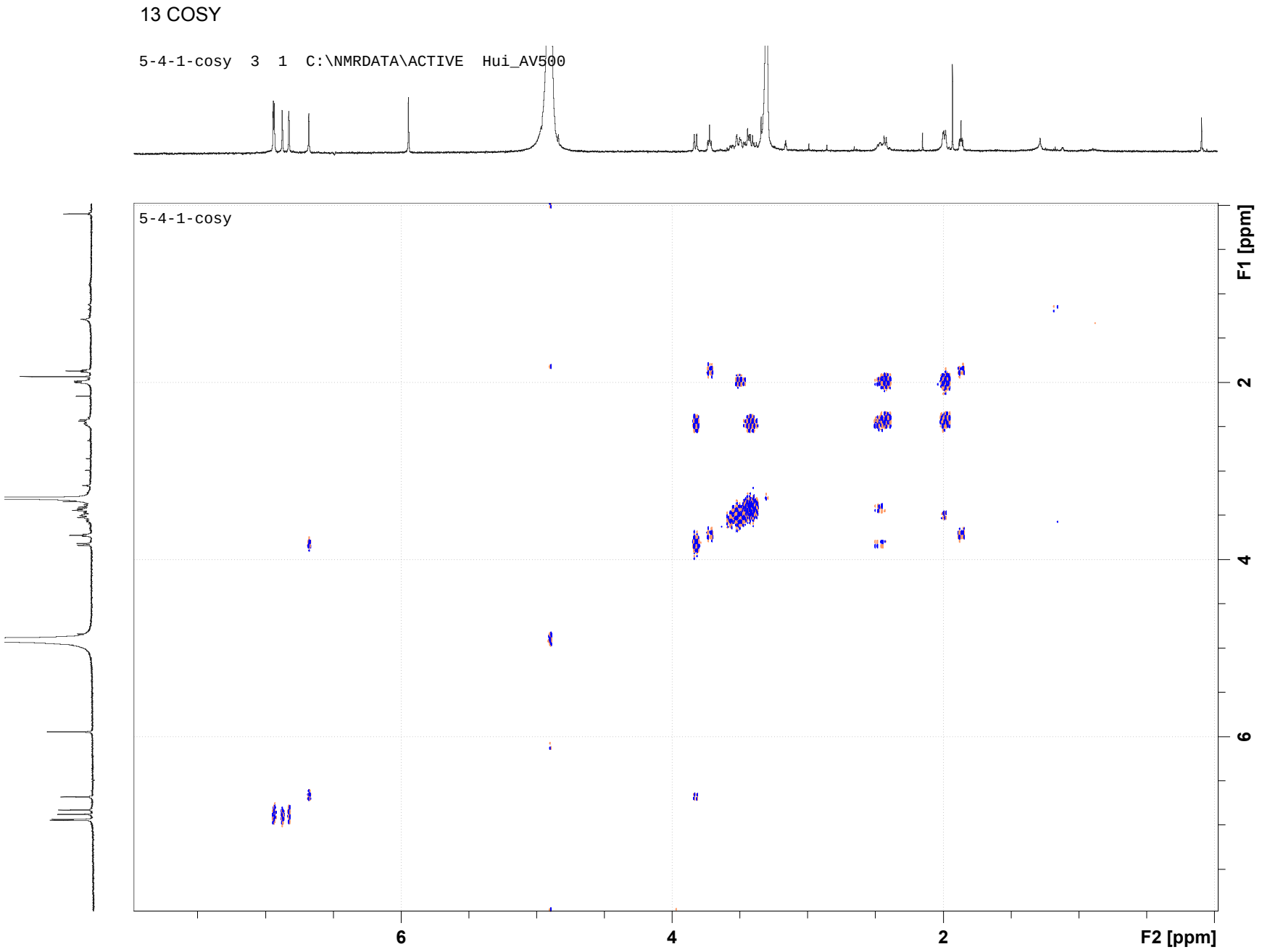
13

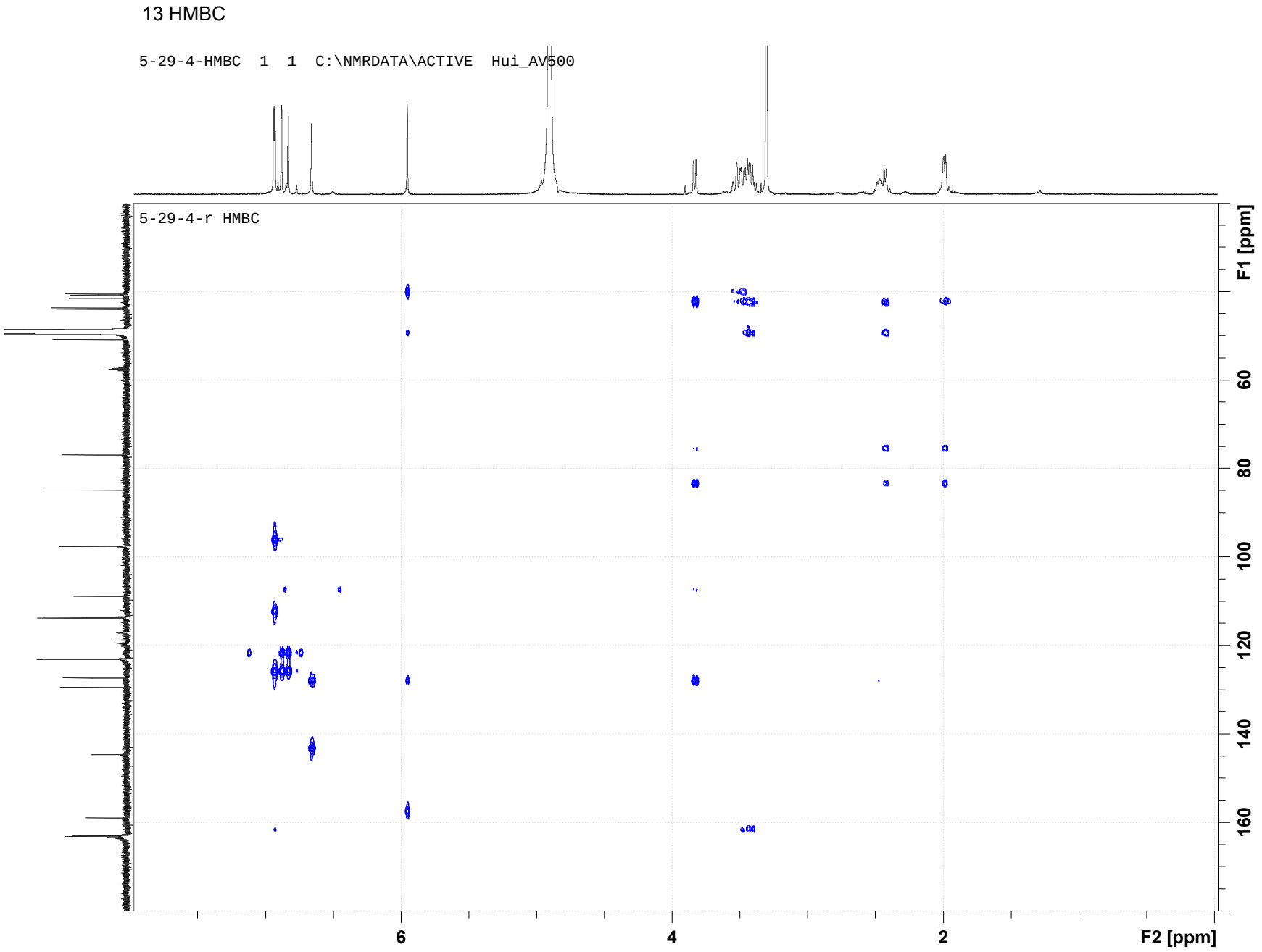
500 MHz, MeOH-d_4

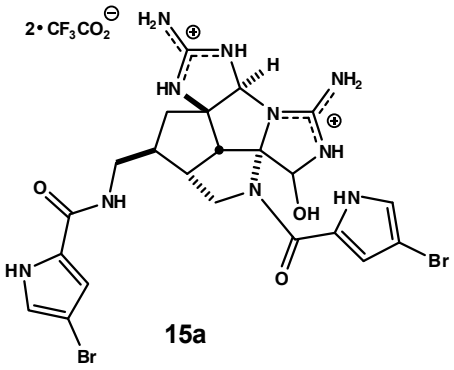


13

125 MHz, MeOH-d_4

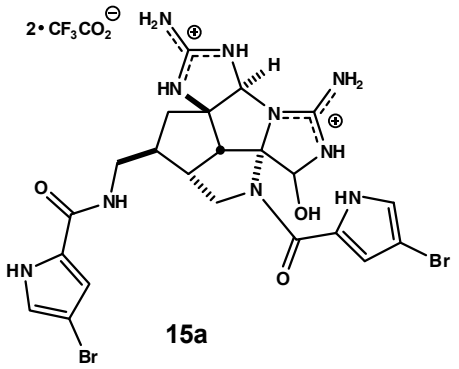






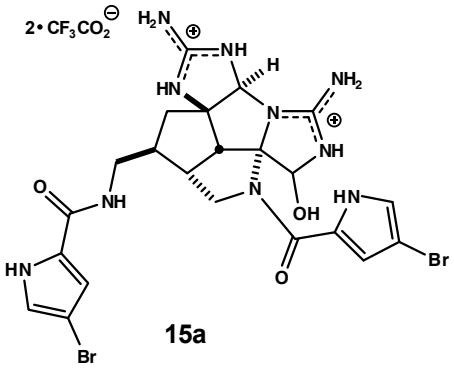
15a

500 MHz, MeOH-d_4



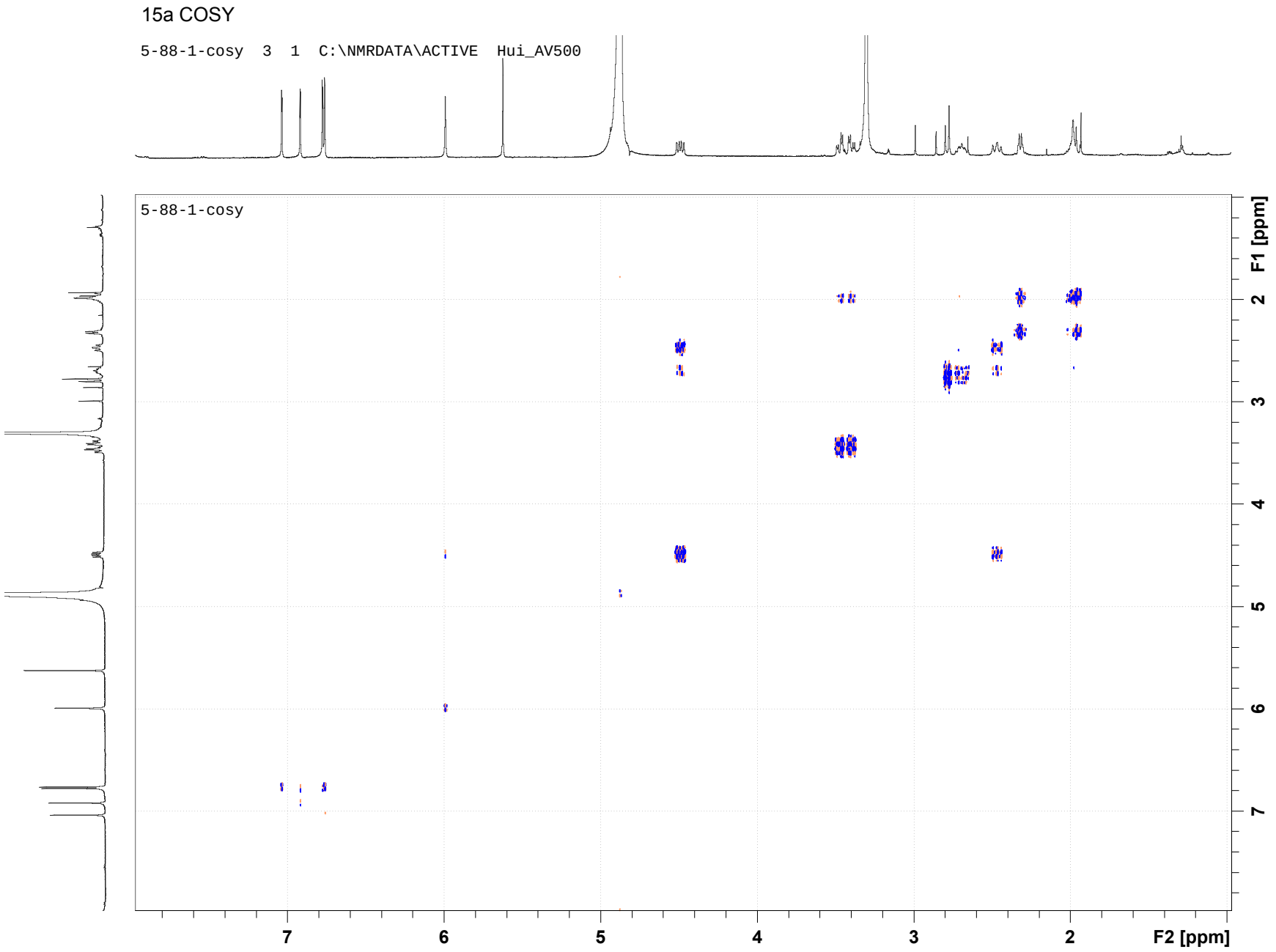
15a

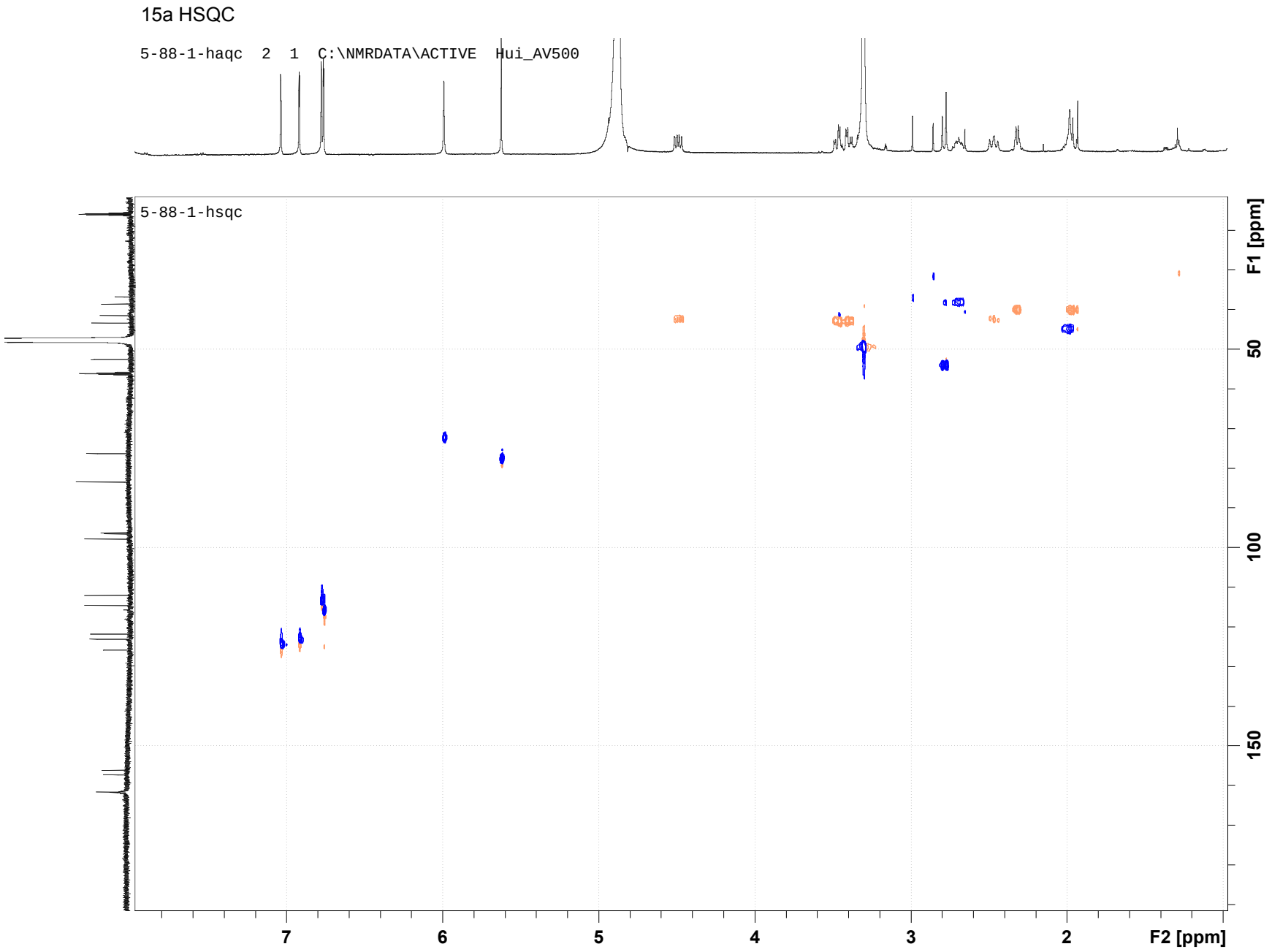
125 MHz, MeOH-d_4

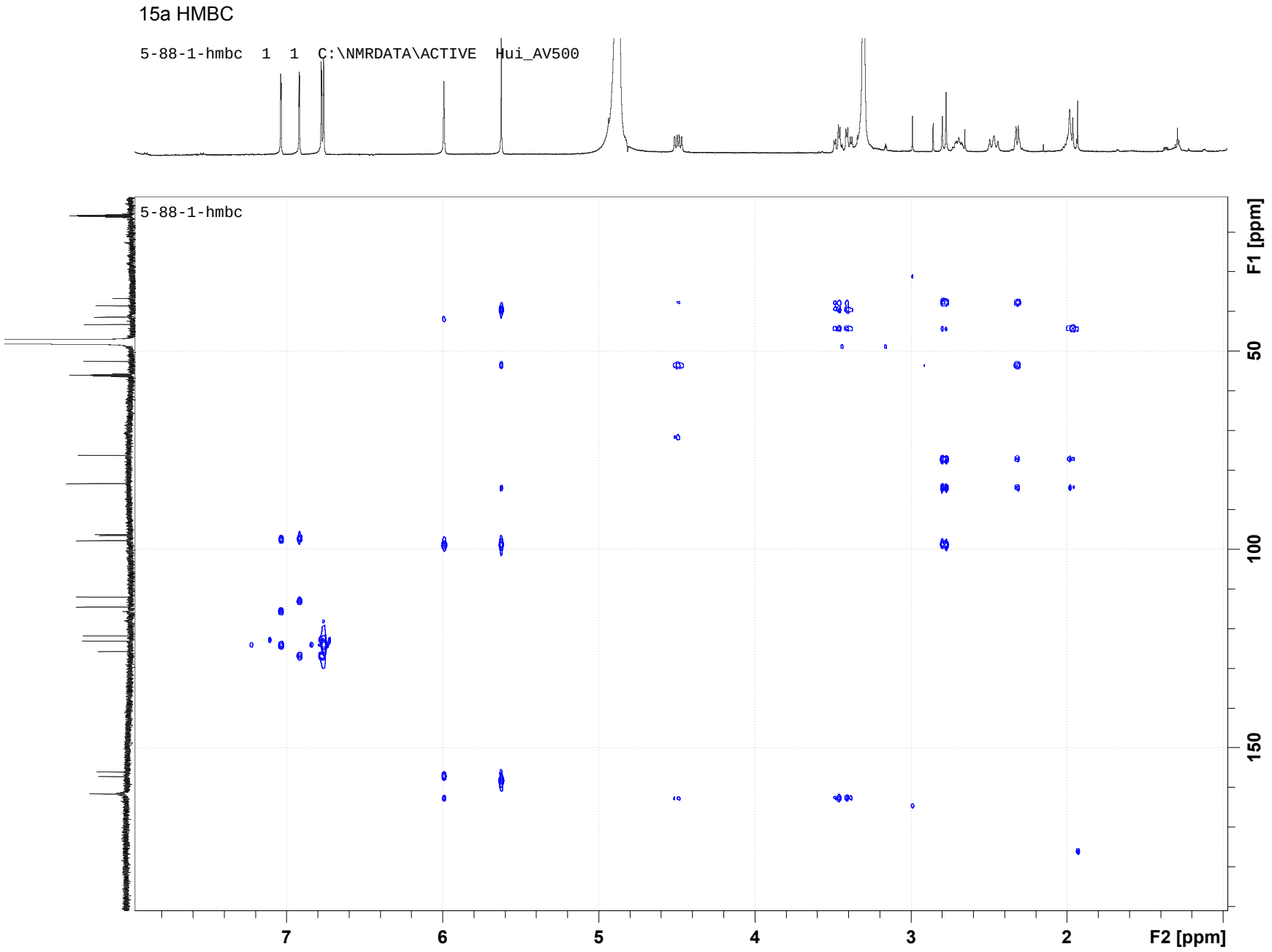


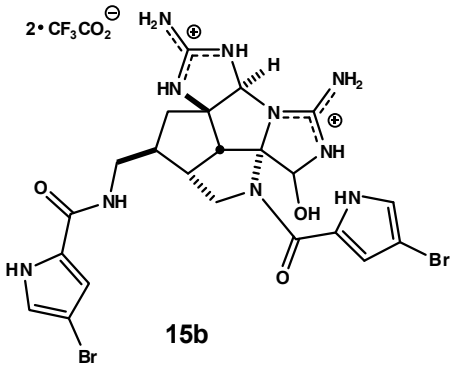
15a

500 MHz, DMSO-d_6



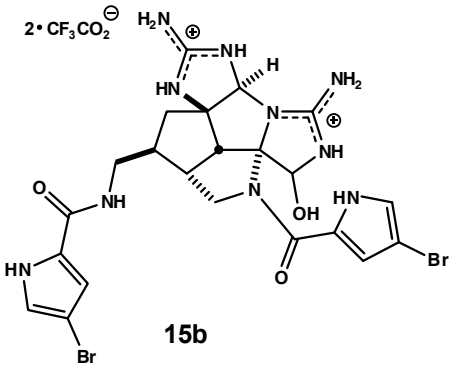






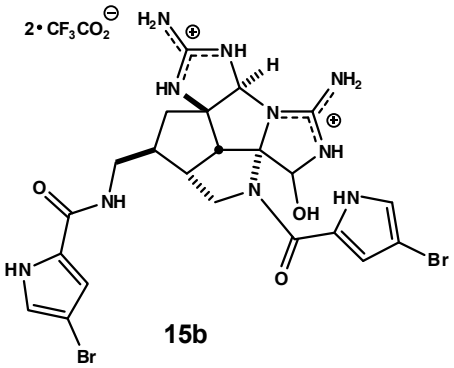
15b

500 MHz, MeOH-d_4



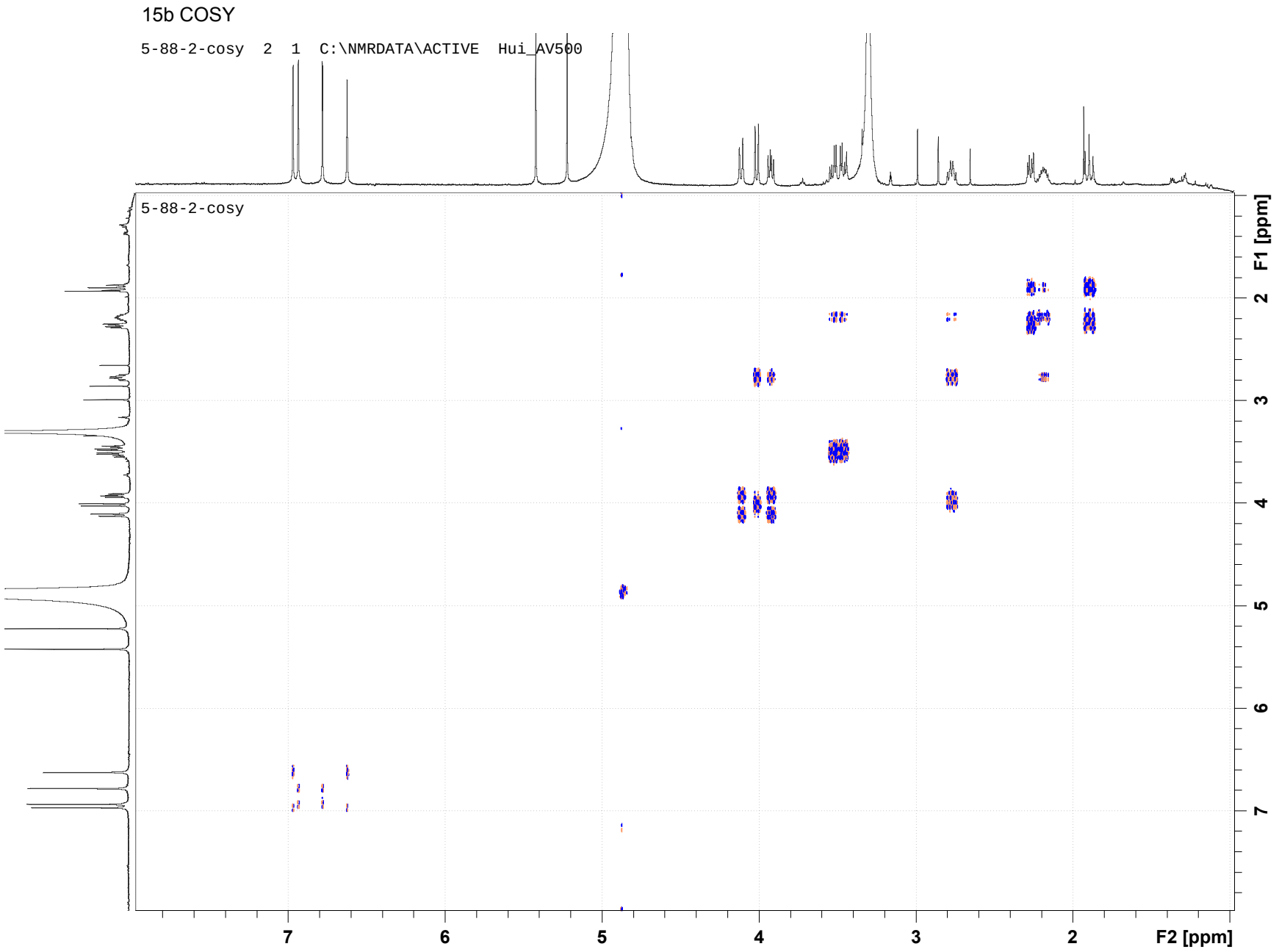
15b

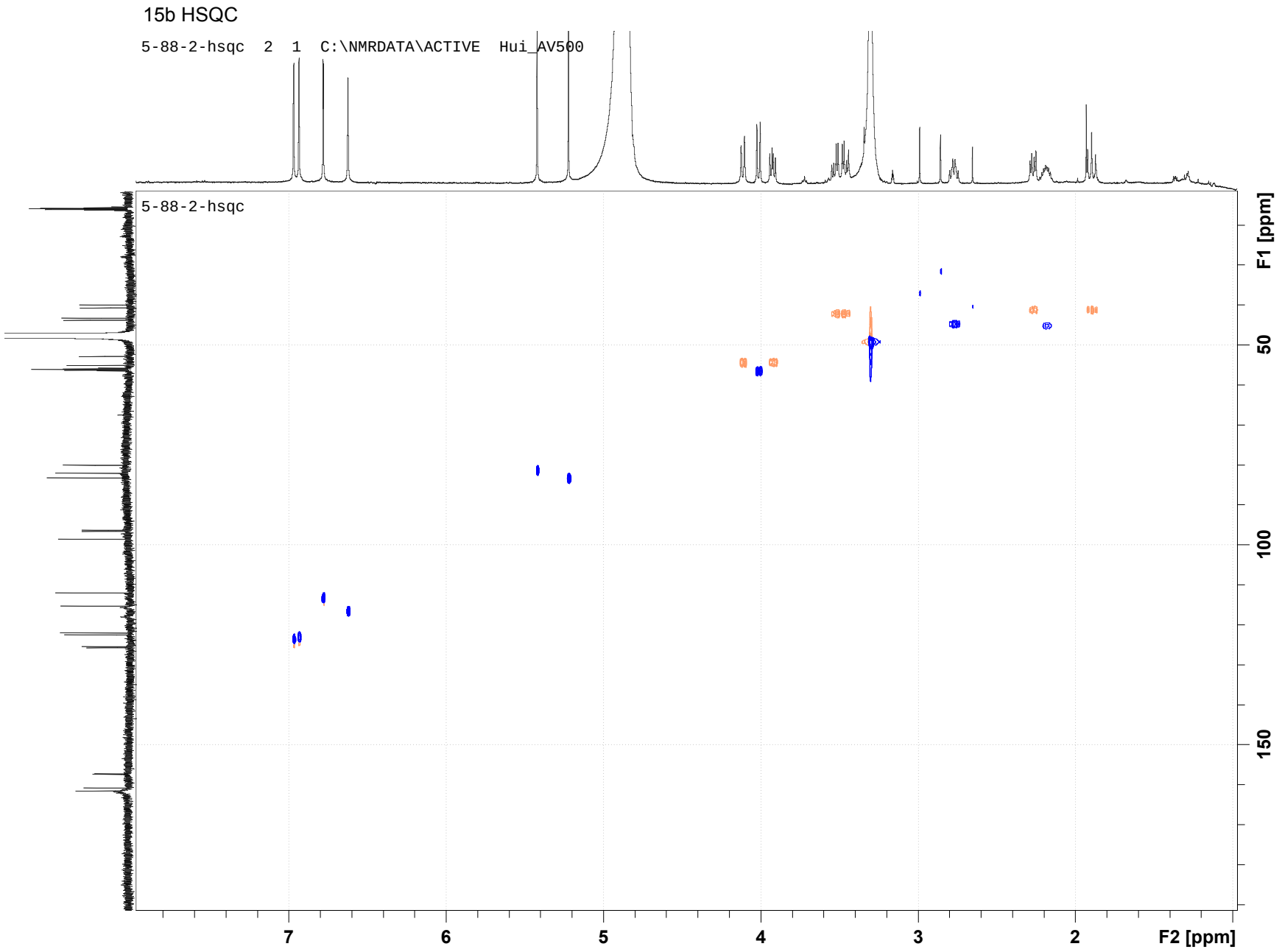
125 MHz, MeOH-d_4

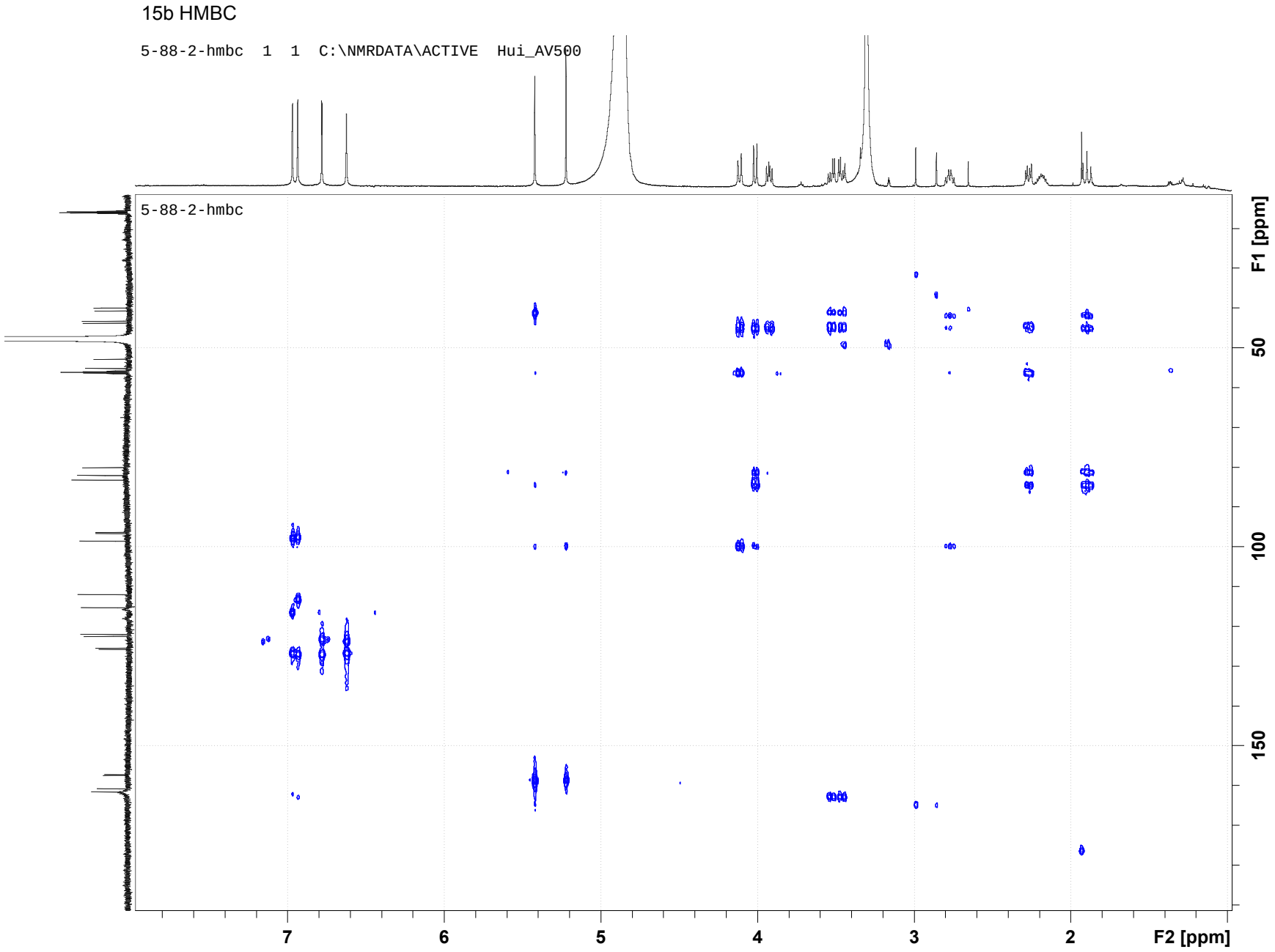


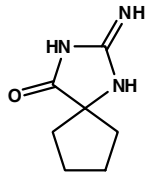
15b

500 MHz, DMSO-d_6

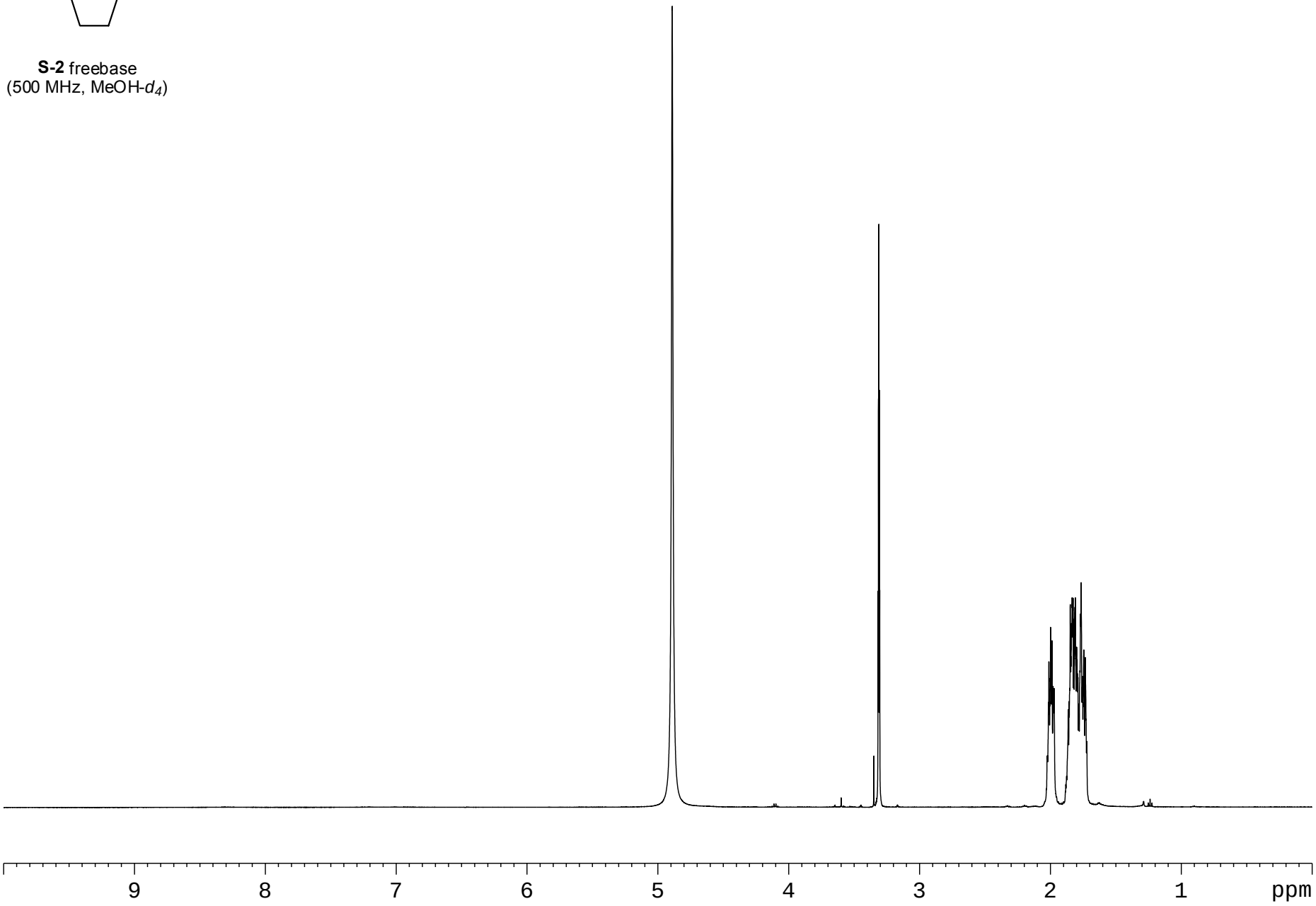


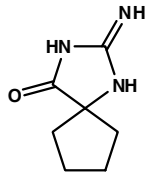




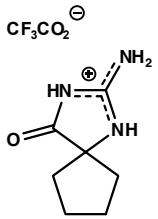


S-2 freebase
(500 MHz, MeOH-d_4)

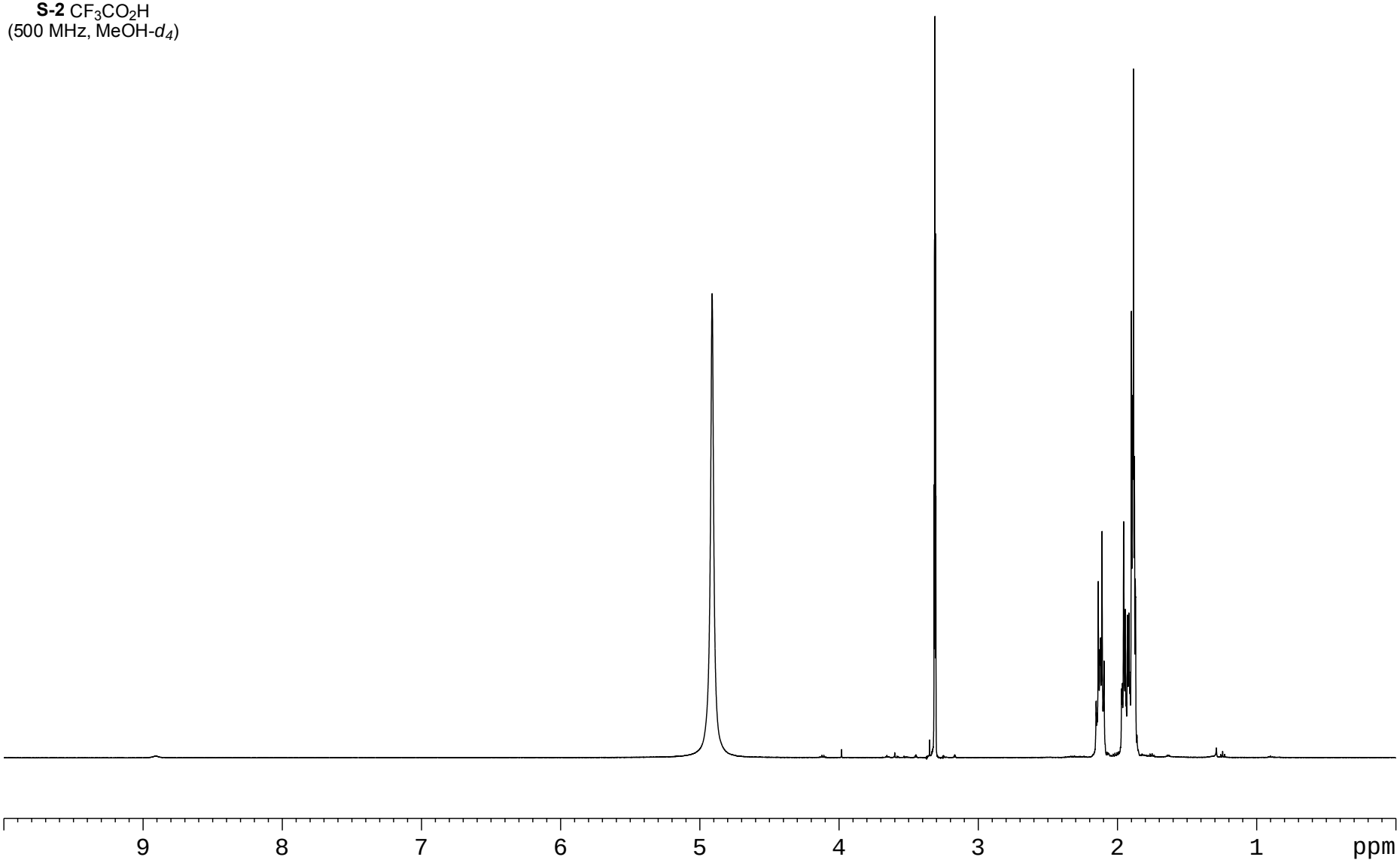


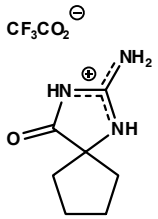


S-2 freebase
(125 MHz, MeOH-d_4)

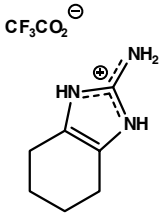


S-2 CF_3CO_2H
(500 MHz, MeOH-d_4)

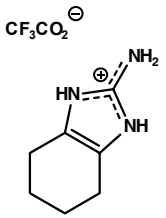




S-2 CF_3CO_2H
(125 MHz, MeOH-d_4)



S-4 CF_3CO_2H
(500 MHz, MeOH-d_4)



S-4 CF_3CO_2H
(125 MHz, MeOH-d_4)