Amide-Containing α-Hydroxytropolones as Inhibitors of Hepatitis B Virus Replication

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Supporting Information

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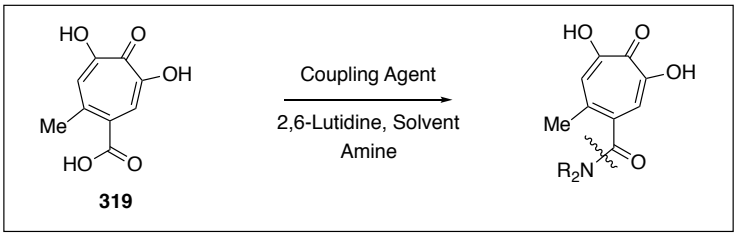
I. General Information

All starting materials and reagents were purchased from commercially available sources and used without further purification, with exception of THF and CH_2Cl_2, which were purified on a solvent purification system prior to the reaction. ^{1}H NMR shifts are measured using the solvent residual peak as the internal standard ($CDCl_3$ δ 7.26, Methanol-d_4 δ 3.31, Acetone-d_6 δ 2.05), and reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, p = pentet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, q = quartet, ABq = AB quartet, m = multiplet), coupling constant (Hz), and integration. Microwave reactions were performed via the Biotage Initiator 2.5. Purification via column chromatography was

performed on the Biotage Isolera Prime, with Biotage SNAP 12g C_{18} cartridges, in a solvent system of acetonitrile (MeCN) and water (H_2O), with each containing .05% trifluoroacetic acid (TFA). Column gradients are measured in terms of column volumes (CV). Other abbreviations used: THF = tetrahydrofuran; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; HATU = 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate; HBTU = 3-[Bis(dimethylamino)methyliumyl]-3H-benzotriazol-1-oxide hexafluorophosphate; PyBOP = (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate.

II. Synthesis and characterization of α-hydroxyamidotropolones

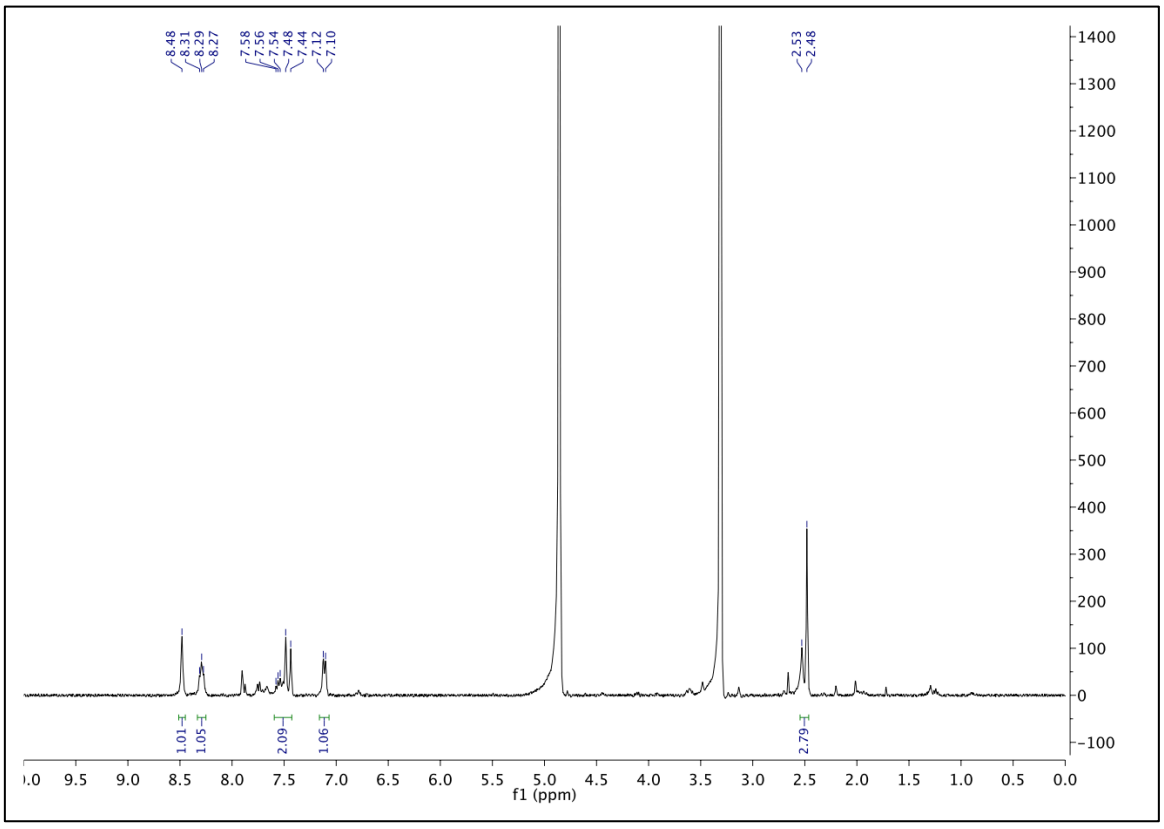


General Procedure.[1] To a solution of α-hydroxytropolone (αHT) carboxylic acid **319**[2] in solvent (THF, ethyl acetate, or DMF, .04M) was added 2,6-lutidine (2.2 equiv.) and a coupling agent (HATU, HBTU, or PyBOP, 1.1 equiv.). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. The amine (1-2.2 equiv.) was then added to the solution, at which point the reaction mixture was either subjected to microwave irradiation (85 °C for 15 min, or 95 °C for 30 min) or allowed to stir at rt for 4 days. For reactions ran in DMF, the reaction mixture was then directly loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions. For reactions ran in THF and ethyl acetate, the reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions. Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the corresponding amidotropolone. If further purification was required, the amidotropolone was dissolved in 5 mL methanol, washed with hexane (3 x 5 mL), and concentrated *in vacuo* to yield the purified amidotropolone.

[1]Berkowitz, A. J.; Abdelmessih, R. A.; Murelli, R. P. *Tetrahedron Lett.*, 2018, **59**, 3026–3028.
[2]Donlin, M. J.; Zunica, A.; Lipnicky, A; Garimallaprabhakaran, A. K.; Berkowitz, A. J.; Grigoryan, A.; Meyers, M. J.; Tavis, J. E.; Murelli, R. P. *Antimicrob. Agents Chemother.*, 2017, **61**, e02574-16.

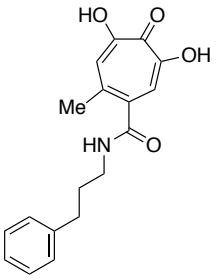
***N*-(6-fluoropyridin-3-yl)-4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carboxamide (707).**

To a solution of αHT carboxylic acid **319** (25 mg, .127 mmol) in THF (3.1 mL, .04M) was added 2,6-lutidine (32.5 µL, .280 mmol) and PyBOP (72.9 mg, .140 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 6-fluoropyridin-3-amine (15.7 mg, 0.127 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 85 °C for 15 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **707** as a yellow oil (2.8 mg, 8% yield). **^{1}H NMR (400 MHz, Methanol-*d*$_4$)** δ 8.48 (s, 1H), 8.29 (t, *J* = 7.4 Hz, 1H), 7.59 – 7.43 (m, 2H), 7.11 (d, *J* = 8.8 Hz, 1H), 2.55 – 2.46 (m, 3H).

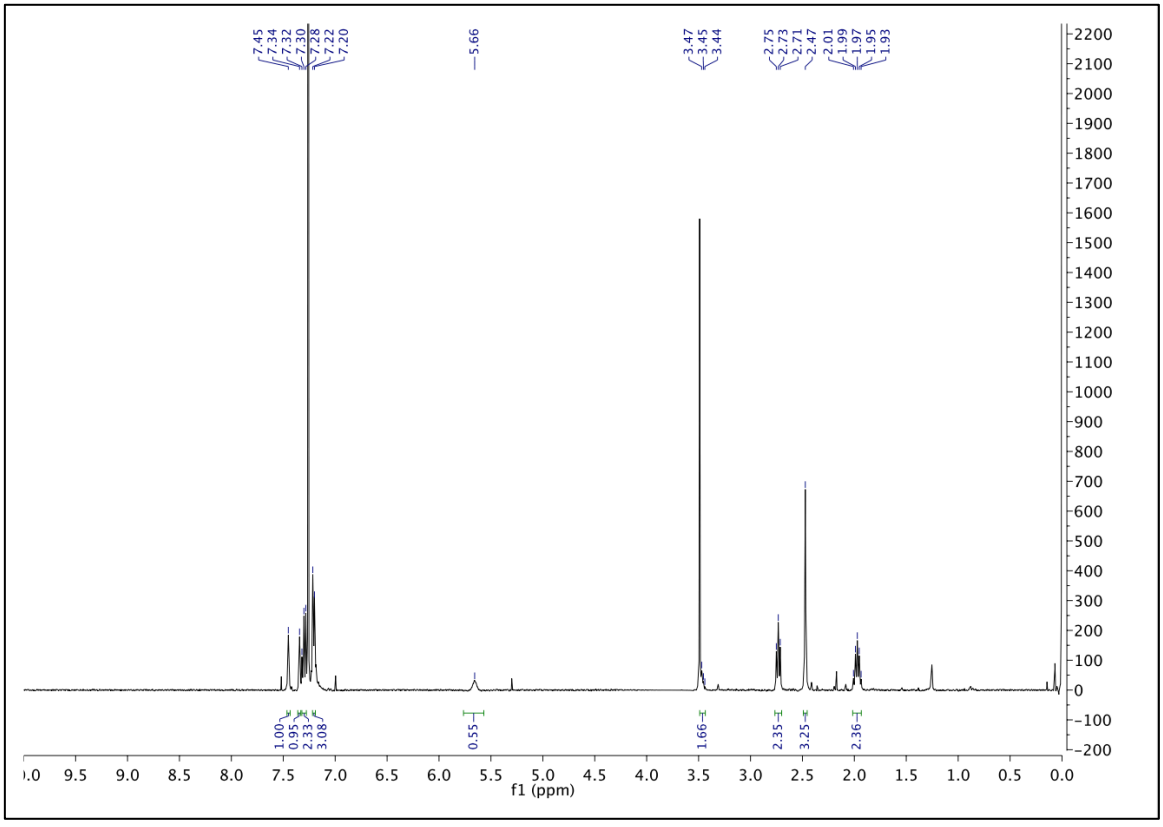


4,6-dihydroxy-2-methyl-5-oxo-*N*-(3-phenylpropyl)cyclohepta-1,3,6-triene-1-carboxamide (708).

To a solution of αHT carboxylic acid **319** (14.8 mg, .075 mmol) in ethyl acetate (1.9 mL, .04M) was added

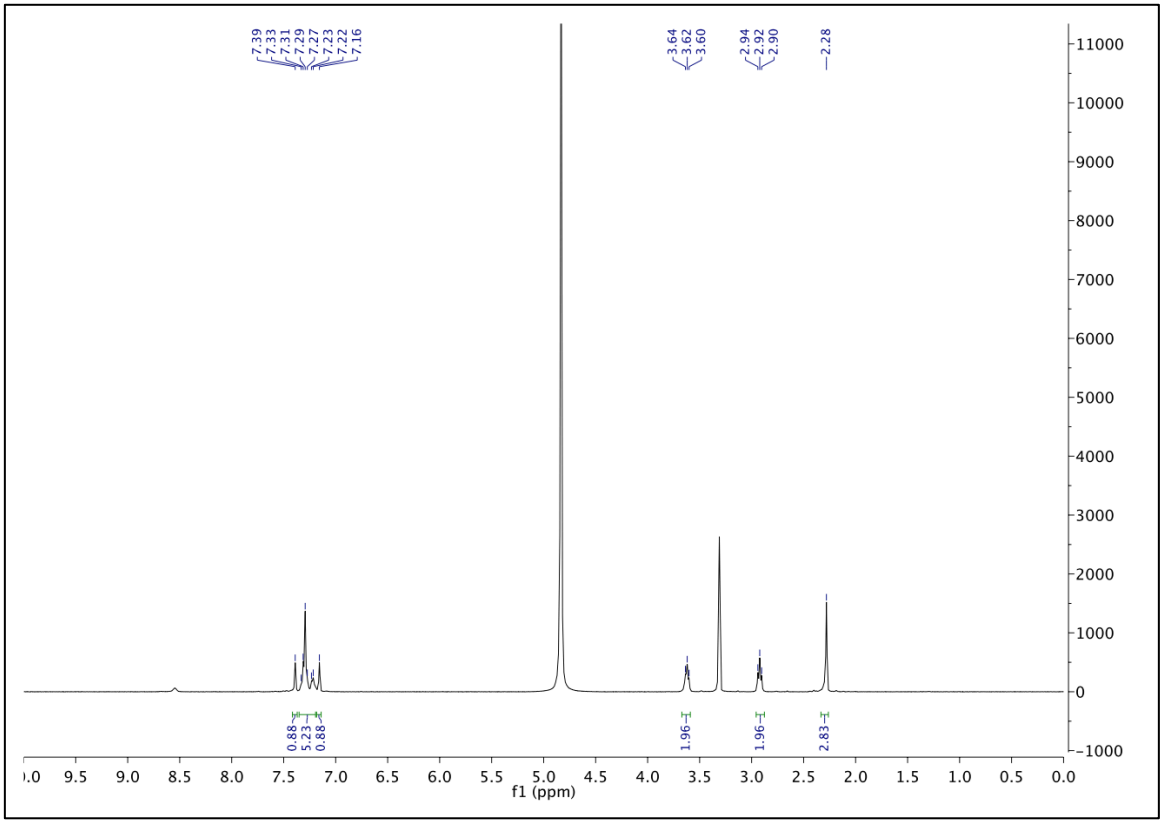


2,6-lutidine (19.2 µL, .166 mmol) and HBTU (31.5 mg, .083 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 3-phenylpropylamine (11.8 µL, 0.083 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 85 °C for 15 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **708** as a yellow oil (14.2 mg, 60% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.45 (s, 1H), 7.34 (s, 1H), 7.32 – 7.28 (m, 2H), 7.22 – 7.19 (m, 3H), 5.66 (br s, 1H), 3.49 – 3.44 (m, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.47 (s, 3H), 1.97 (p, *J* = 7.3 Hz, 2H).



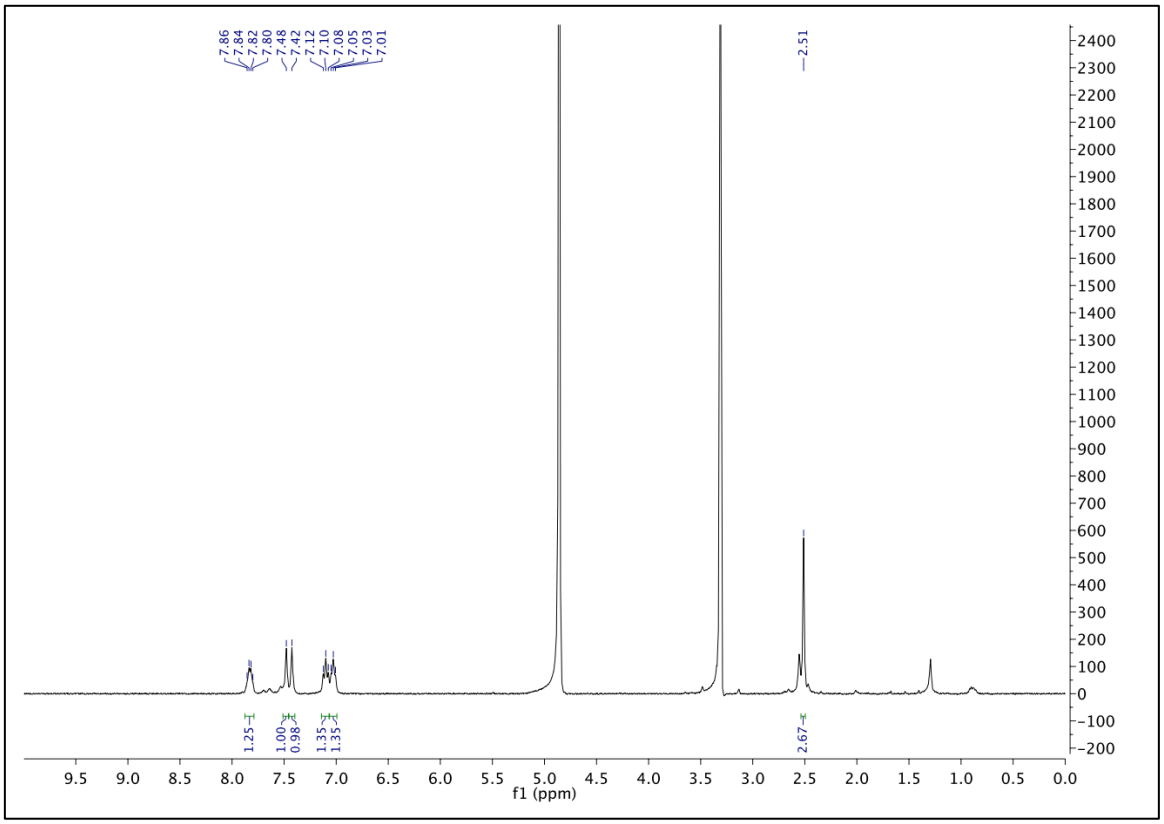
4,6-dihydroxy-2-methyl-5-oxo-*N*-phenethylcyclohepta-1,3,6-triene-1-carboxamide (710).

To a solution of αHT carboxylic acid **319** (10 mg, .051 mmol) in THF (1.3 mL, .04M) was added 2,6-lutidine (11.8 µL, .102 mmol) and PyBOP (29.2 mg, .056 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. Phenethylamine (12.8 µL, 0.102 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 85 °C for 15 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **710** as a yellow oil (5.6 mg, 37% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.39 (s, 1H), 7.35 – 7.19 (m, 5H), 7.16 (s, 1H), 3.62 (t, J = 7.0 Hz, 2H), 2.92 (t, J = 7.3 Hz, 2H), 2.28 (s, 3H).



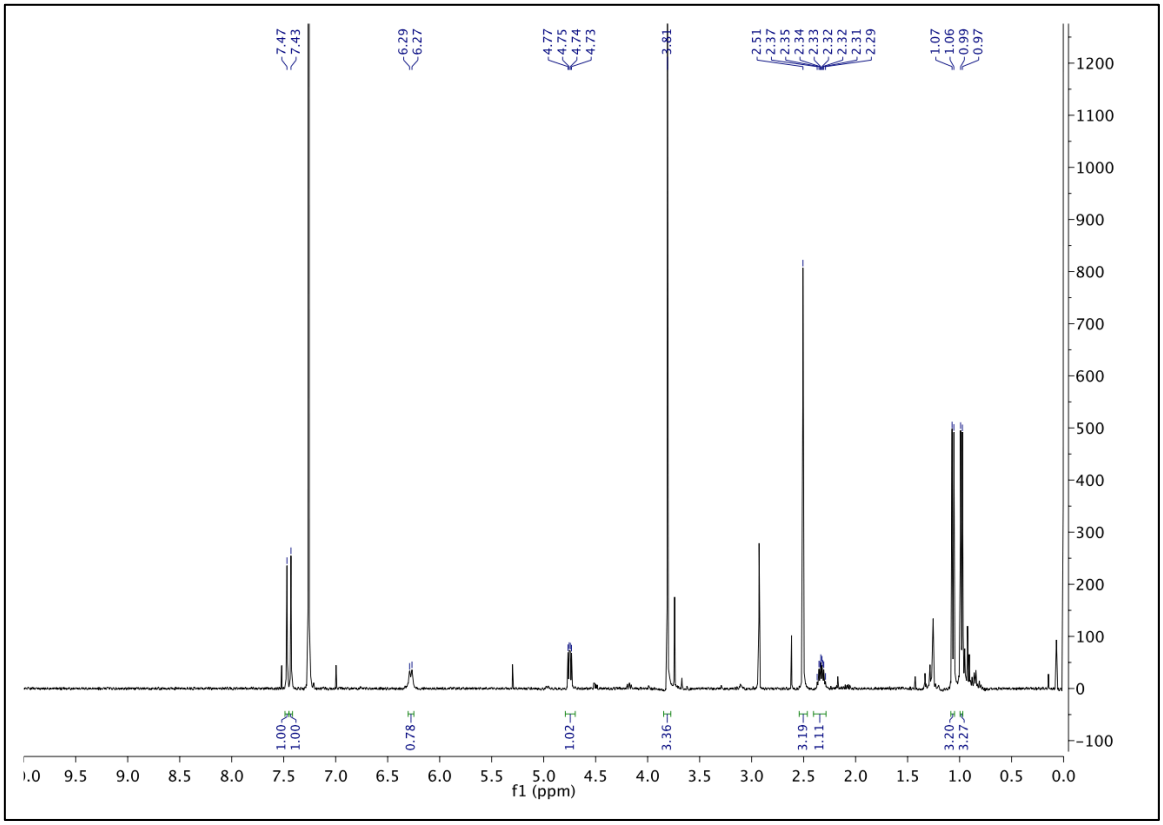
***N*-(2,4-difluorophenyl)-4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carboxamide (711).**

To a solution of αHT carboxylic acid **319** (15 mg, .0765 mmol) in THF (1.5 mL, .04M) was added 2,6-lutidine (19.5 µL, .168 mmol) and PyBOP (43.8 mg, .084 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 2,4-difluoroaniline (8.6 µL, 0.084 mmol) was then added to the solutionat which point the reaction mixture was allowed to stir at rt for 7 days . The reaction mixture was then concentrated in vacuo, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C18 silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **711** as a yellow oil (2.3 mg, 10% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.83 (q, J = 7.8 Hz, 1H), 7.48 (s, 1H), 7.42 (s, 1H), 7.10 (t, J = 9.5 Hz, 1H), 7.03 (t, J = 8.6 Hz, 1H), 2.51 (s, 3H).



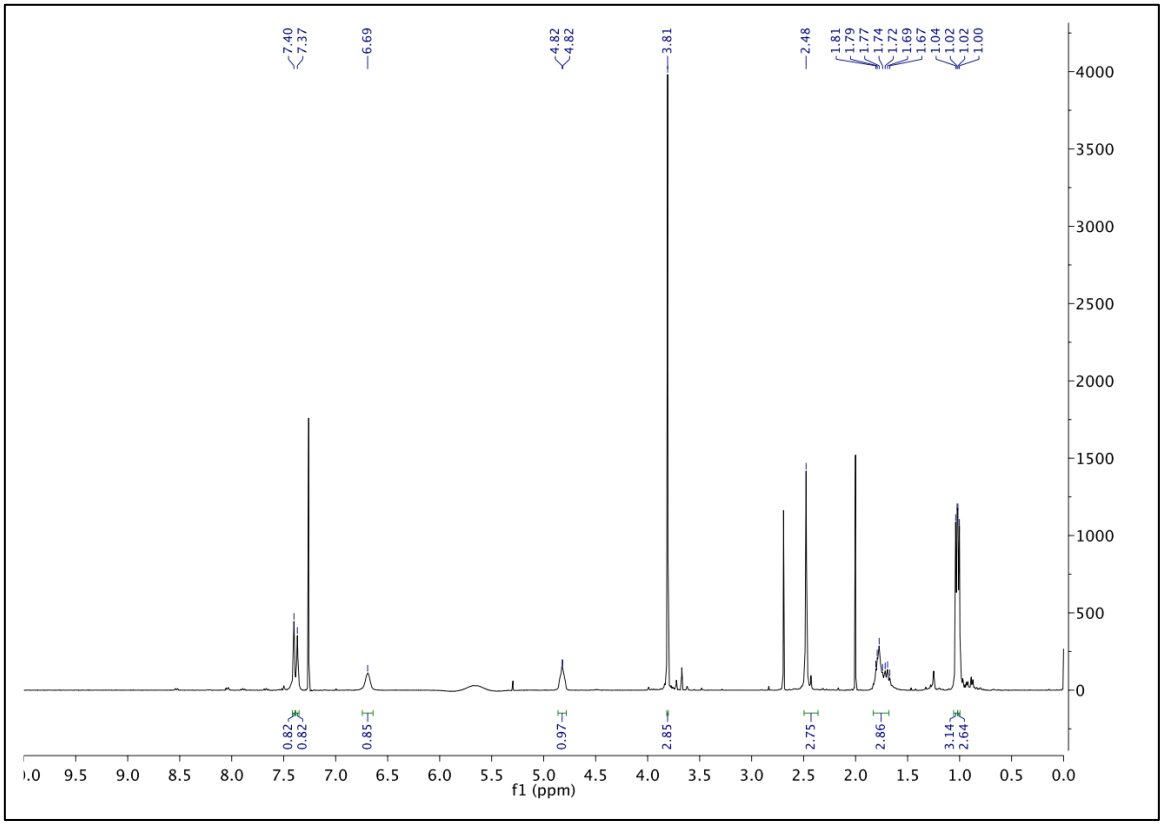
Methyl (4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carbonyl)-*L*-valinate (793).

To a solution of αHT carboxylic acid **319** (20 mg, .102 mmol) in THF (2.5 mL, .04M) was added 2,6-lutidine (26 µL, .224 mmol) and HBTU (42.5 mg, .112 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. Methyl *L*-valinate hydrochloride (18.8 mg, .112 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **793** as a yellow oil (6.5 mg, 21% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (s, 1H), 7.43 (s, 1H), 6.28 (br d, *J* = 9.2 Hz, 1H), 4.75 (dd, *J* = 8.8, 4.6 Hz, 1H), 3.81 (s, 3H), 2.51 (s, 3H), 2.41 – 2.28 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H).



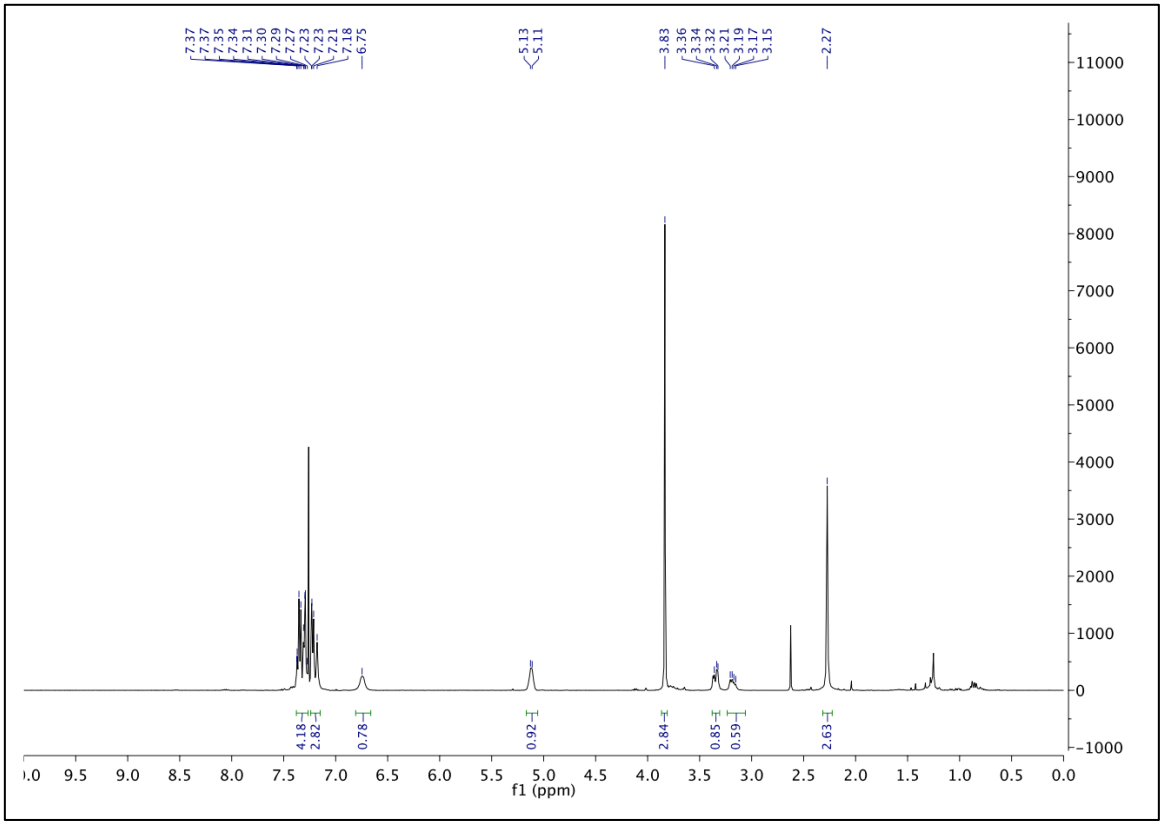
Methyl (4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carbonyl)-*L*-leucinate (794).

To a solution of αHT carboxylic acid **319** (20 mg, .102 mmol) in THF (2.5 mL, .04M) was added 2,6-lutidine (26 µL, .224 mmol) and HBTU (42.5 mg, .112 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. Methyl *L*-leucinate hydrochloride (20.4 mg, .112 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **794** as a brown oily solid (20.7 mg, 63% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 (s, 1H), 7.37 (s, 1H), 6.69 (br s, 1H), 4.86 – 4.78 (m, 1H), 3.81 (s, 3H), 2.48 (s, 3H), 1.83 – 1.67 (m, 3H), 1.03 (d, J = 5.5 Hz, 3H), 1.01 (d, J = 5.5 Hz, 3H).



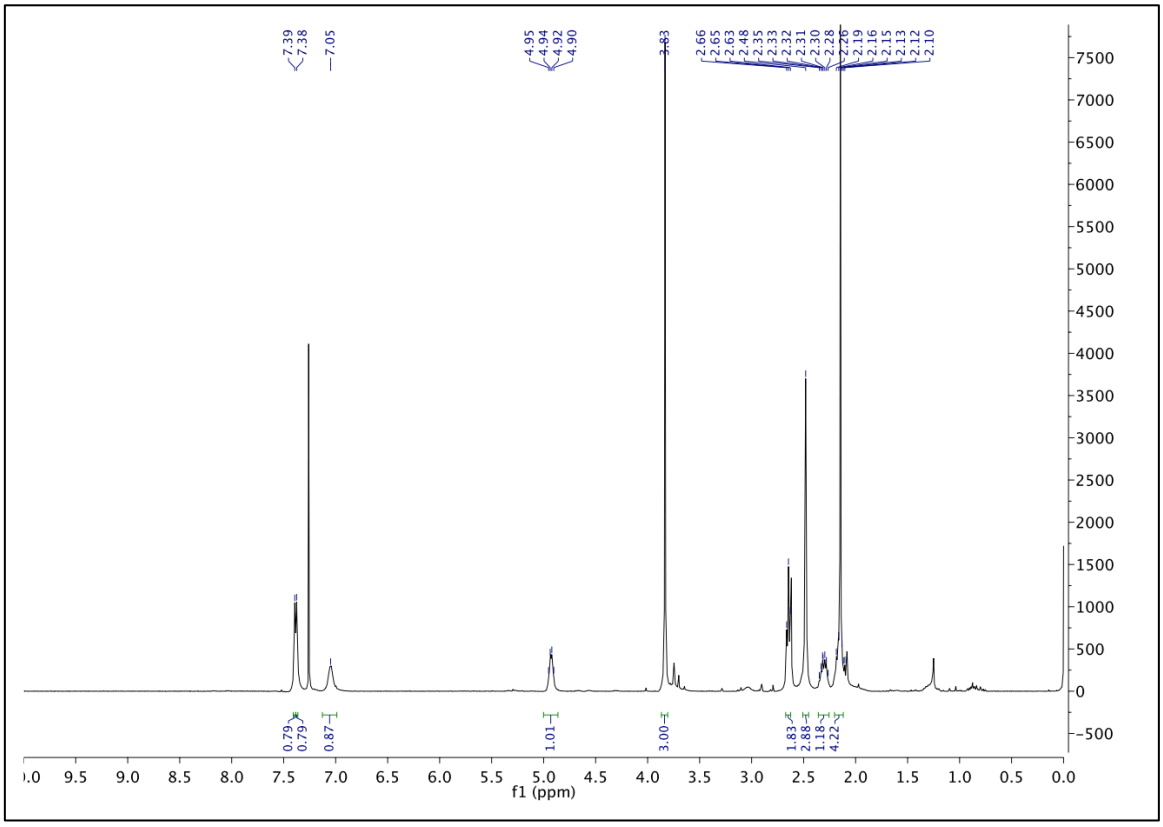
Methyl (4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carbonyl)-*L*-phenylalaninate (795).

To a solution of αHT carboxylic acid **319** (20 mg, .102 mmol) in THF (2.5 mL, .04M) was added 2,6-lutidine (26 µL, .224 mmol) and HBTU (42.5 mg, .112 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. Methyl *L*-phenylalaninate hydrochloride (24.2 mg, .112 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **795** as a brown oily solid (17.4 mg, 48% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.27 (m, 4H), 7.24 – 7.15 (m, 3H), 6.75 (br s, 1H), 5.17 – 5.06 (m, 1H), 3.83 (s, 3H), 3.38 – 3.31 (m, 1H), 3.18 (dd, *J* = 13.9, 7.3 Hz, 1H), 2.27 (s, 3H).



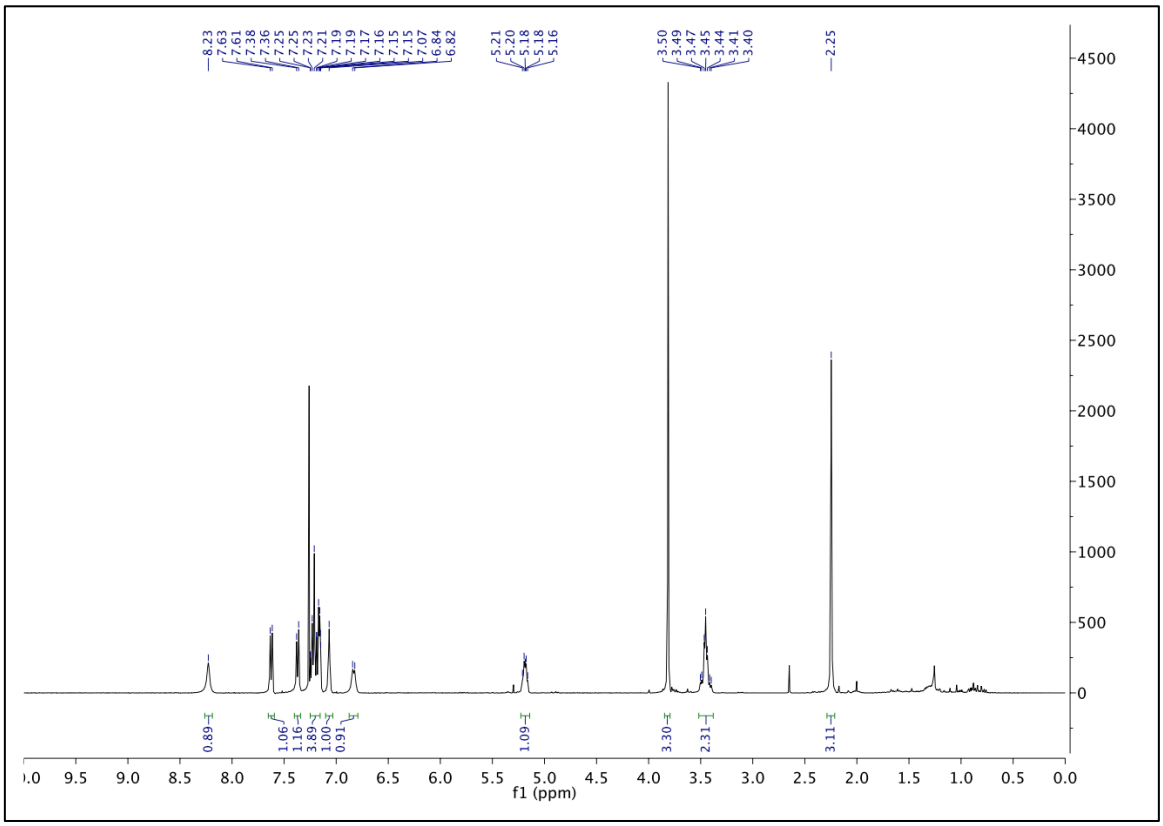
Methyl (4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carbonyl)-*L*-methioninate (796).

To a solution of αHT carboxylic acid **319** (20 mg, .102 mmol) in THF (2.5 mL, .04M) was added 2,6-lutidine (29.6 µL, .255 mmol) and HBTU (42.5 mg, .112 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. Methyl *L*-methioninate hydrochloride (30.5 mg, .153 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **796** as a tan solid (20.4 mg, 59% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.39 (s, 1H), 7.38 (s, 1H), 7.05 (br s, 1H), 5.00 – 4.86 (m, 1H), 3.83 (s, 3H), 2.65 (t, *J* = 7.3 Hz, 2H), 2.48 (s, 3H), 2.36 – 2.26 (m, 1H), 2.20 – 2.12 (m, 4H).



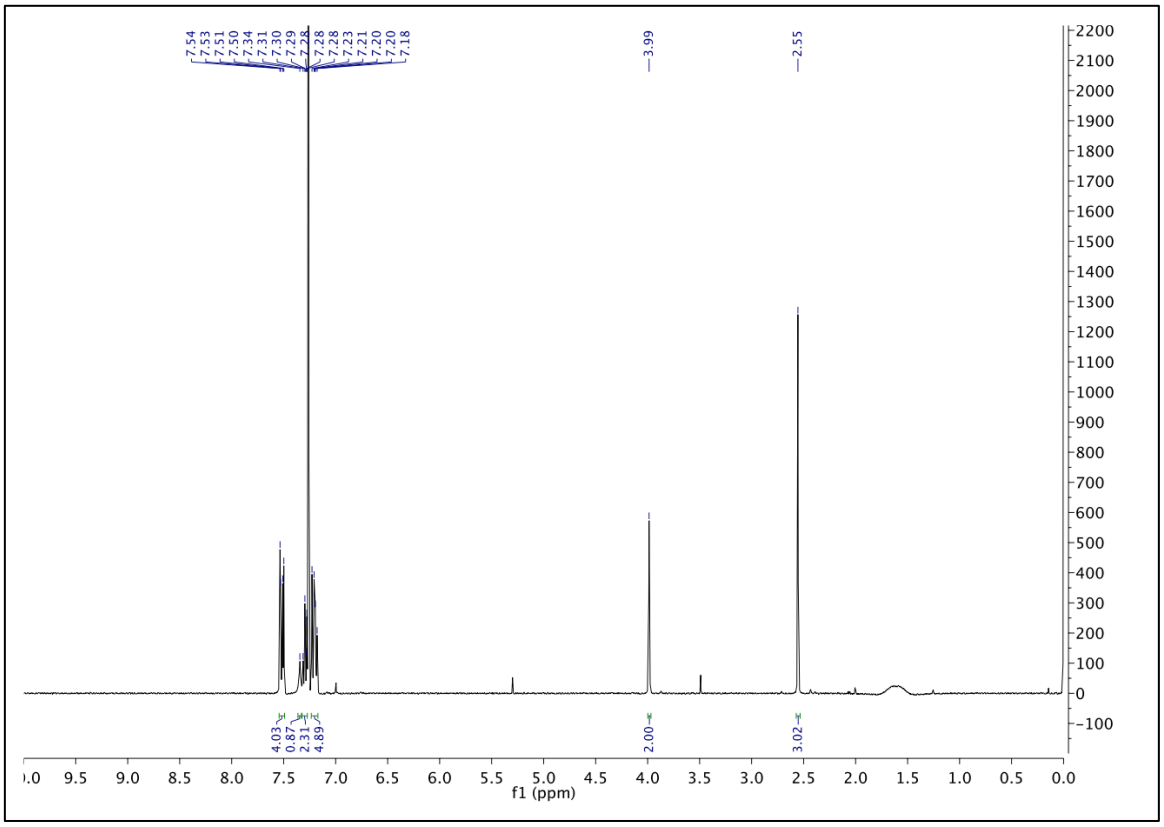
Methyl (4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carbonyl)-*L*-tryptophanate (797).

To a solution of αHT carboxylic acid **319** (20 mg, .102 mmol) in THF (2.5 mL, .04M) was added 2,6-lutidine (29.6 µL, .255 mmol) and HBTU (42.5 mg, .112 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. Methyl *L*-tryptophanate hydrochloride (39 mg, .153 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **797** as a tan solid (18.6 mg, 46% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.23 (br s, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.15 (m, 4H), 7.07 (s, 1H), 6.83 (br d, *J* = 8.4 Hz, 1H), 5.23 – 5.14 (m, 1H), 3.81 (s, 3H), 3.52 – 3.38 (m, 2H), 2.25 (s, 3H).



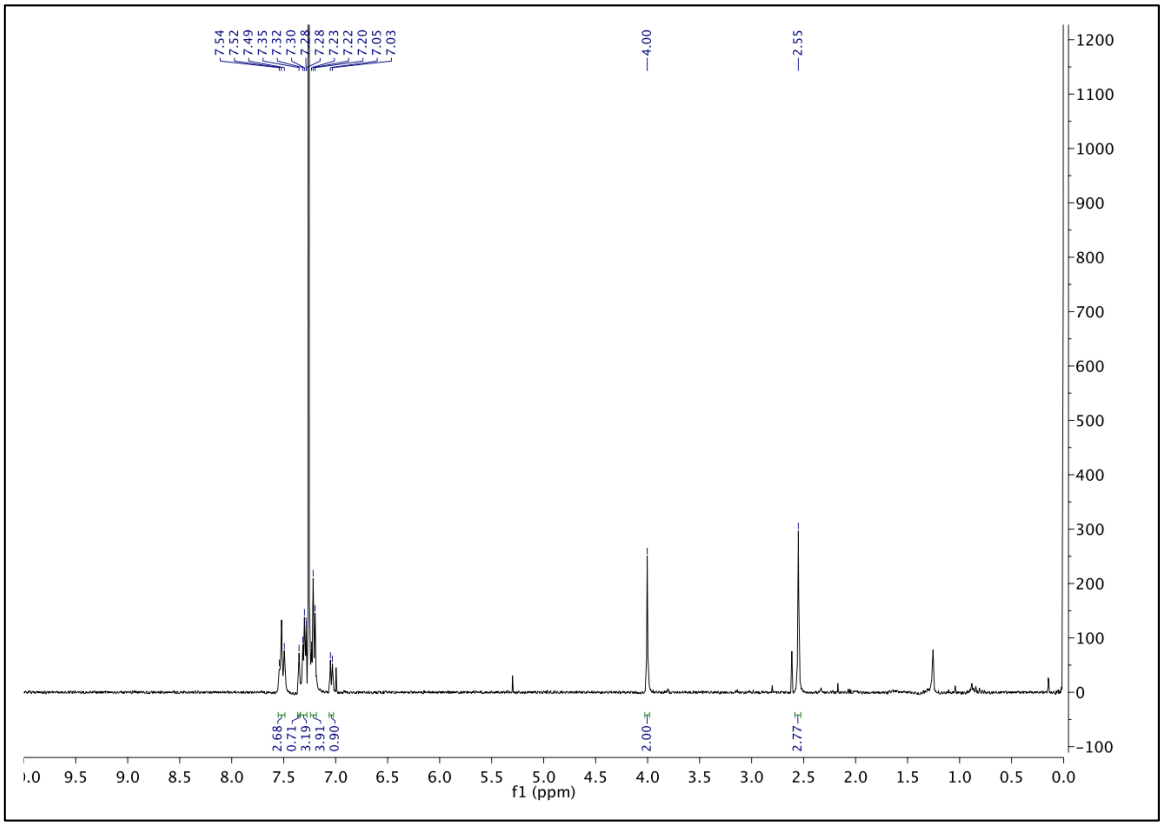
***N*-(4-benzylphenyl)-4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carboxamide (798).**

To a solution of αHT carboxylic acid **319** (15 mg, .076 mmol) in THF (1.9 mL, .04M) was added 2,6-lutidine (19.5 µL, .168 mmol) and PyBOP (43.8 mg, .084 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 4-benzylaniline (15.4 mg, .084 mmol) was then added to the solution, at which point the reaction mixture was allowed to stir at rt for 4 days. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **798** as a brown oil (1.7 mg, 6% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 – 7.49 (m, 4H), 7.34 (br s, 1H), 7.32 – 7.27 (m, 2H), 7.23 – 7.17 (m, 5H), 3.99 (s, 2H), 2.55 (s, 3H).



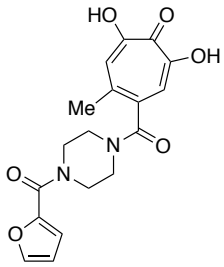
***N*-(3-benzylphenyl)-4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carboxamide (799).**

To a solution of αHT carboxylic acid **319** (15 mg, .076 mmol) in THF (1.9 mL, .04M) was added 2,6-lutidine (19.5 µL, .168 mmol) and HBTU (31.9 mg, .084 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 3-benzylaniline (15.4 mg, .084 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 85 °C for 15 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **799** as a brown oil (4.4 mg, 16% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.55 – 7.49 (m, 3H), 7.35 (s, 1H), 7.34 – 7.28 (m, 3H), 7.24 – 7.19 (m, 4H), 7.04 (d, J = 7.6 Hz, 1H), 4.00 (s, 2H), 2.55 (s, 3H).

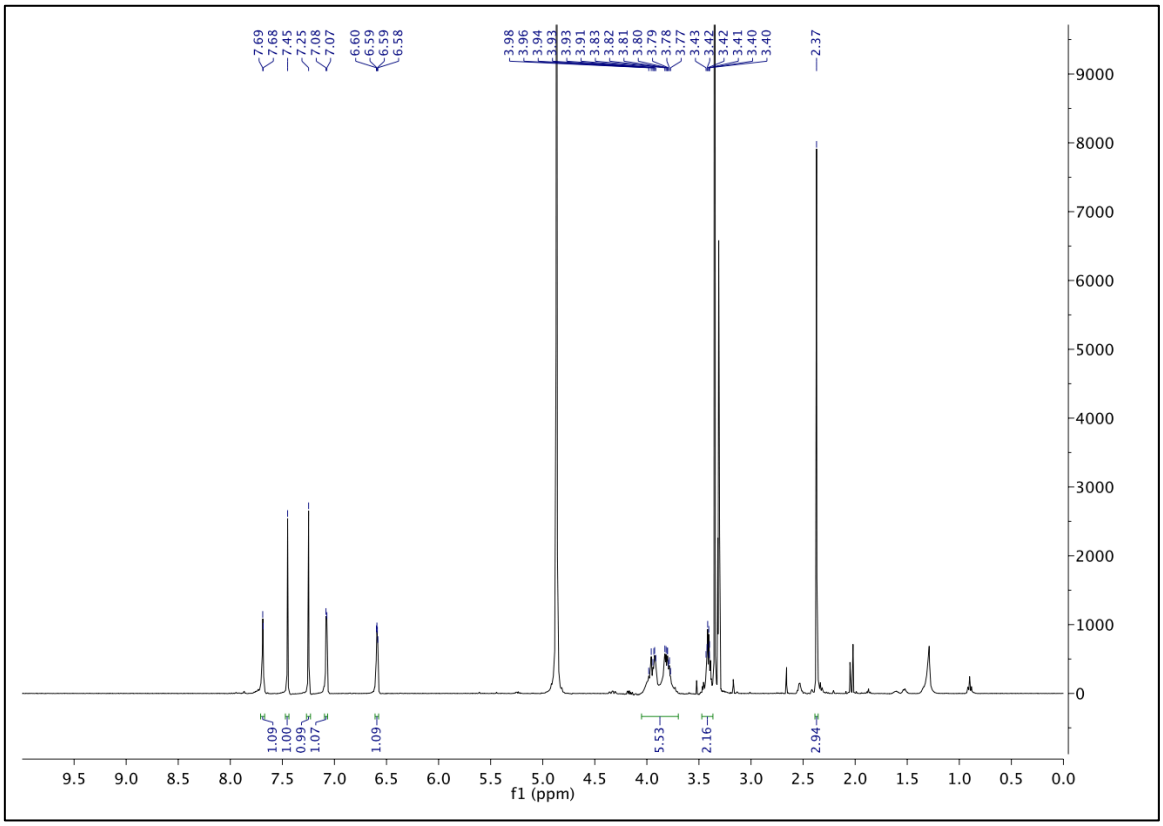


4-(4-(furan-2-carbonyl)piperazine-1-carbonyl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trien-1-one (800).

To a solution of αHT carboxylic acid **319** (23.3 mg, .119 mmol) in ethyl acetate (1.8 mL, .04M) was added

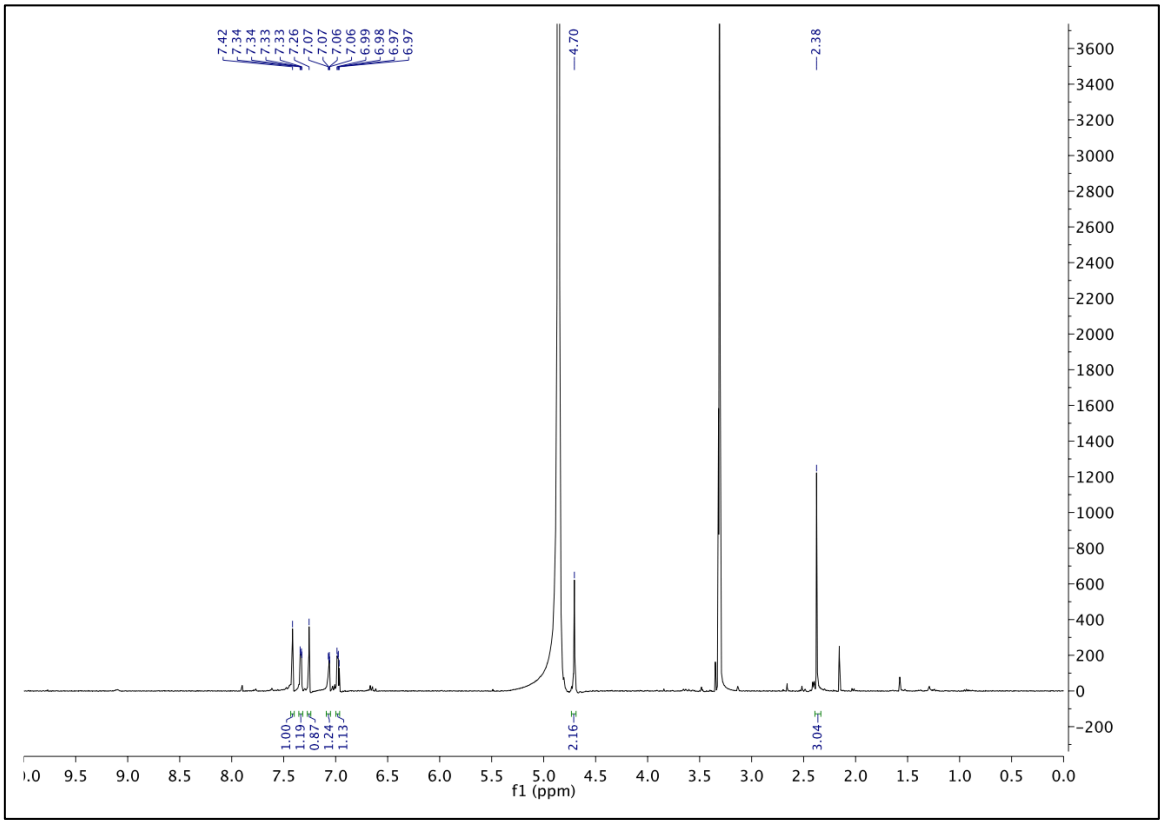


2,6-lutidine (30.3 µL, .261 mmol) and PyBOP (68 mg, .131 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. Furan-2-yl(piperazin-1-yl)methanone (23.6 mg, 0.131 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 85 °C for 15 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **800** as a yellow-brown solid (20.2 mg, 47% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.69 (d, J = 1.7 Hz, 1H), 7.45 (s, 1H), 7.25 (s, 1H), 7.08 (d, J = 3.6 Hz, 1H), 6.59 (dd, J = 3.5, 1.8 Hz, 1H), 4.05 – 3.70 (m, 6H), 3.47 – 3.37 (m, 2H), 2.37 (s, 3H).



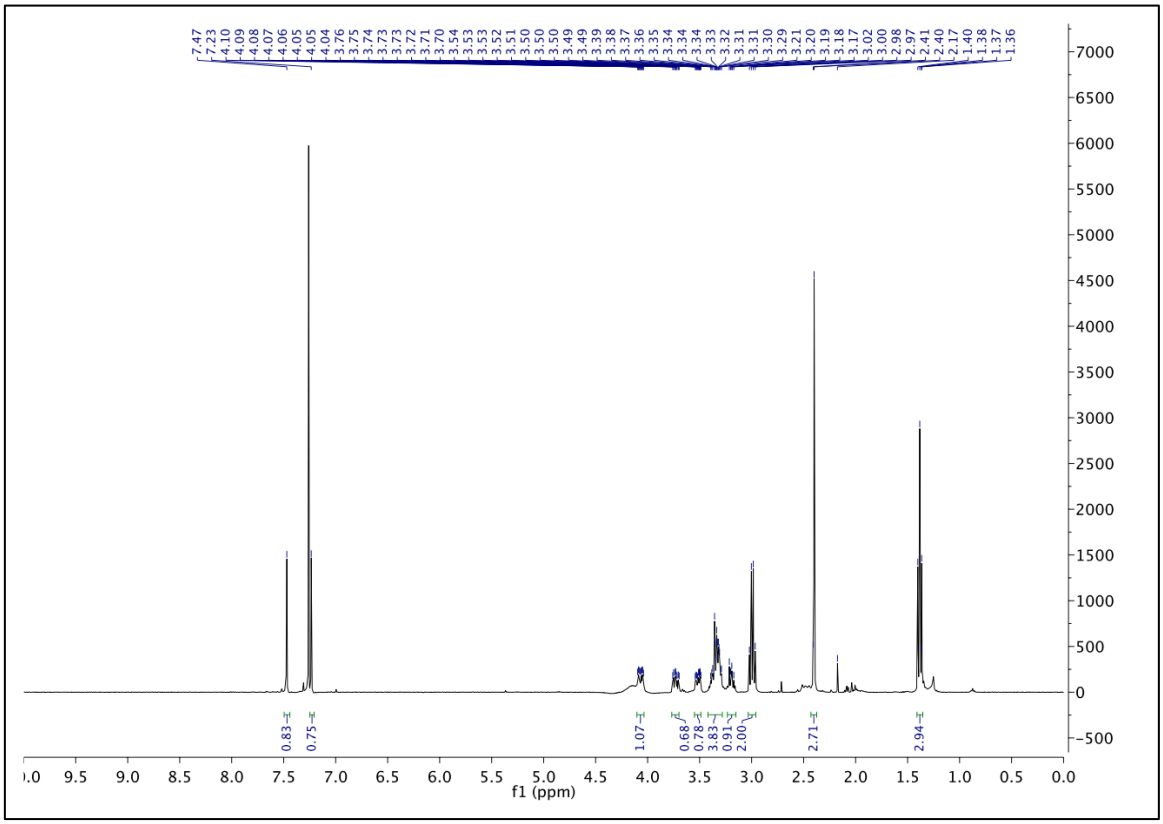
4,6-dihydroxy-2-methyl-5-oxo-*N*-(thiophene-2-ylmethyl)cyclohepta-1,3,6-triene-1-carboxamide (801).

To a solution of αHT carboxylic acid **319** (15 mg, .0765 mmol) in THF (2 mL, .04M) was added 2,6-lutidine (19.6 µL, .168 mmol) and PyBOP (43.8 mg, .084 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. Thiophen-2-ylmethanamine (8.6 µL, 0.084 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **801** as a yellow solid (9.9 mg, 44% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.42 (s, 1H), 7.33 (dd, J = 5.1, 1.3 Hz, 1H), 7.26 (s, 1H), 7.06 (dd, J = 3.5, 1.1 Hz, 1H), 6.98 (dd, J = 5.2, 3.4 Hz, 1H), 4.70 (s, 2H), 2.38 (s, 3H).



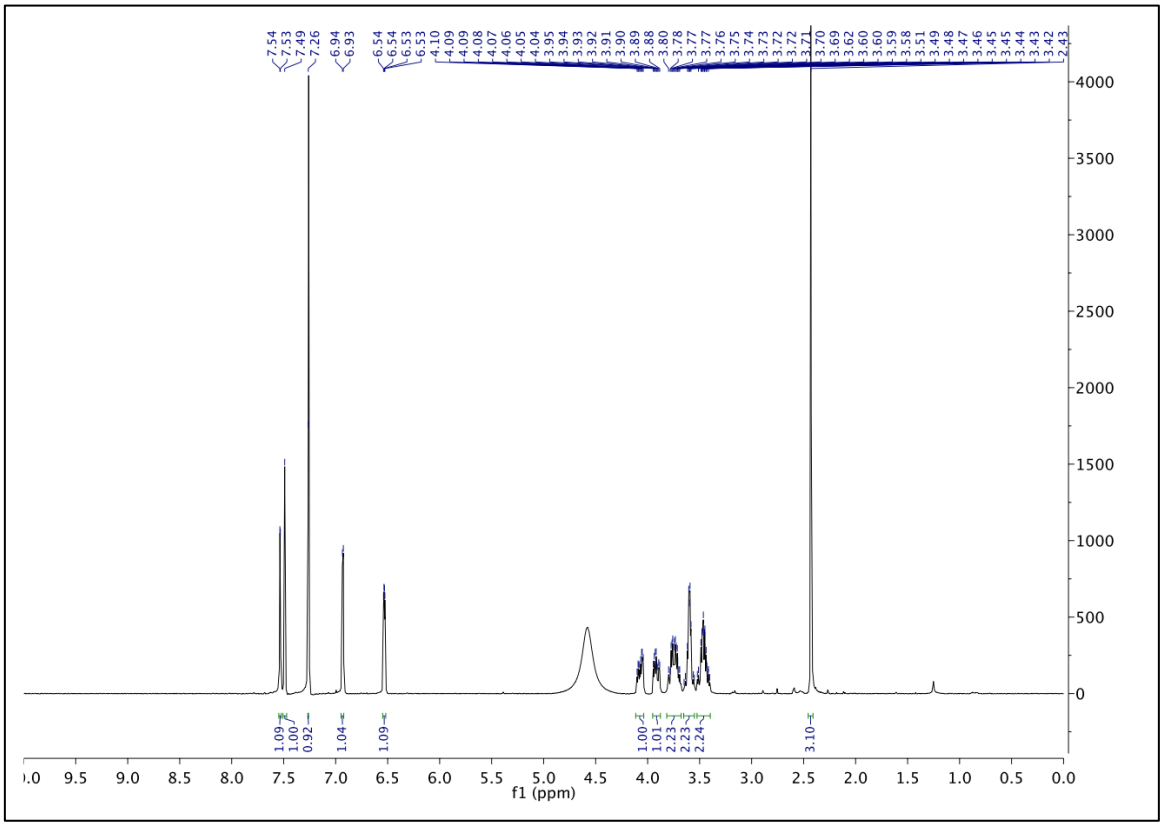
4-(4-(ethylsulfonyl)piperazine-1-carbonyl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trien-1-one (802).

To a solution of αHT carboxylic acid **319** (11.1 mg, .057 mmol) in THF (1.4 mL, .04M) was added 2,6-lutidine (14.5 µL, .125 mmol) and PyBOP (32.4 mg, .062 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 1-(ethylsulfonyl)piperazine (11.1 mg, 0.062 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 85 °C for 15 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **802** as a yellow solid (8.9 mg, 44% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (s, 1H), 7.23 (s, 1H), 4.07 (ddd, *J* = 13.4, 5.9, 3.3 Hz, 1H), 3.77 – 3.70 (m, 1H), 3.55 – 3.49 (m, 1H), 3.42 – 3.28 (m, 4H), 3.23 – 3.15 (m, 1H), 2.99 (q, *J* = 7.4 Hz, 2H), 2.40 (s, 3H), 1.38 (t, *J* = 7.4 Hz, 3H).



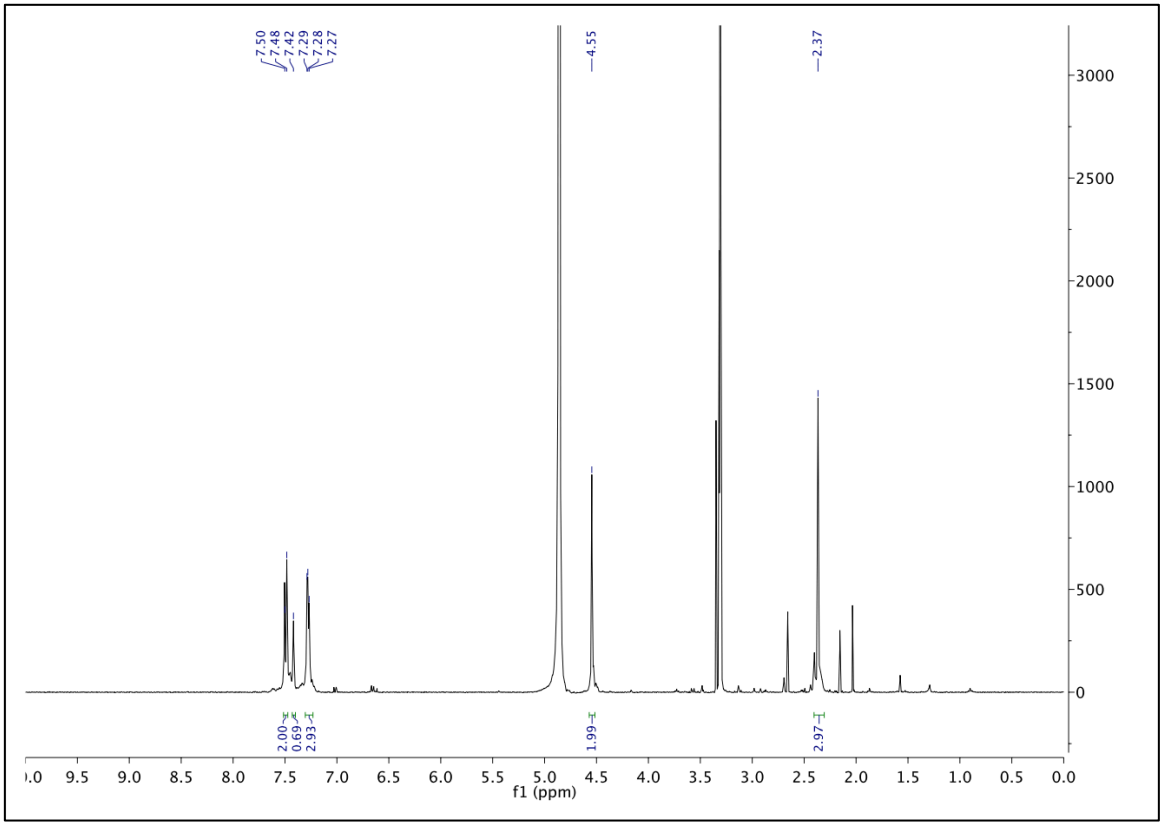
5-(4-(4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carbonyl)piperazin-1-yl)-2-(furan-2-yl)oxazole-4-carbonitrile (803).

To a solution of αHT carboxylic acid **319** (15.6 mg, .0795 mmol) in THF (2 mL, .04M) was added 2,6-lutidine (20.3 µL, .175 mmol) and HBTU (33.2 mg, .0875 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 2-(furan-2-yl)-5-(piperazin-1-yl)oxazole-4-carbonitrile (25.3 mg, 0.103 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **803** as a yellow solid (11 mg, 33% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.53 (d, *J* = 1.7 Hz, 1H), 7.49 (s, 1H), 7.26 (s, 1H), 6.93 (d, *J* = 3.5 Hz, 1H), 6.53 (dd, *J* = 3.5, 1.8 Hz, 1H), 4.07 (ddd, *J* = 13.5, 6.3, 3.8 Hz, 1H), 3.91 (ddd, *J* = 13.6, 7.3, 3.7 Hz, 1H), 3.82 – 3.68 (m, 2H), 3.65 – 3.55 (m, 2H), 3.53 – 3.40 (m, 2H), 2.43 (s, 3H).



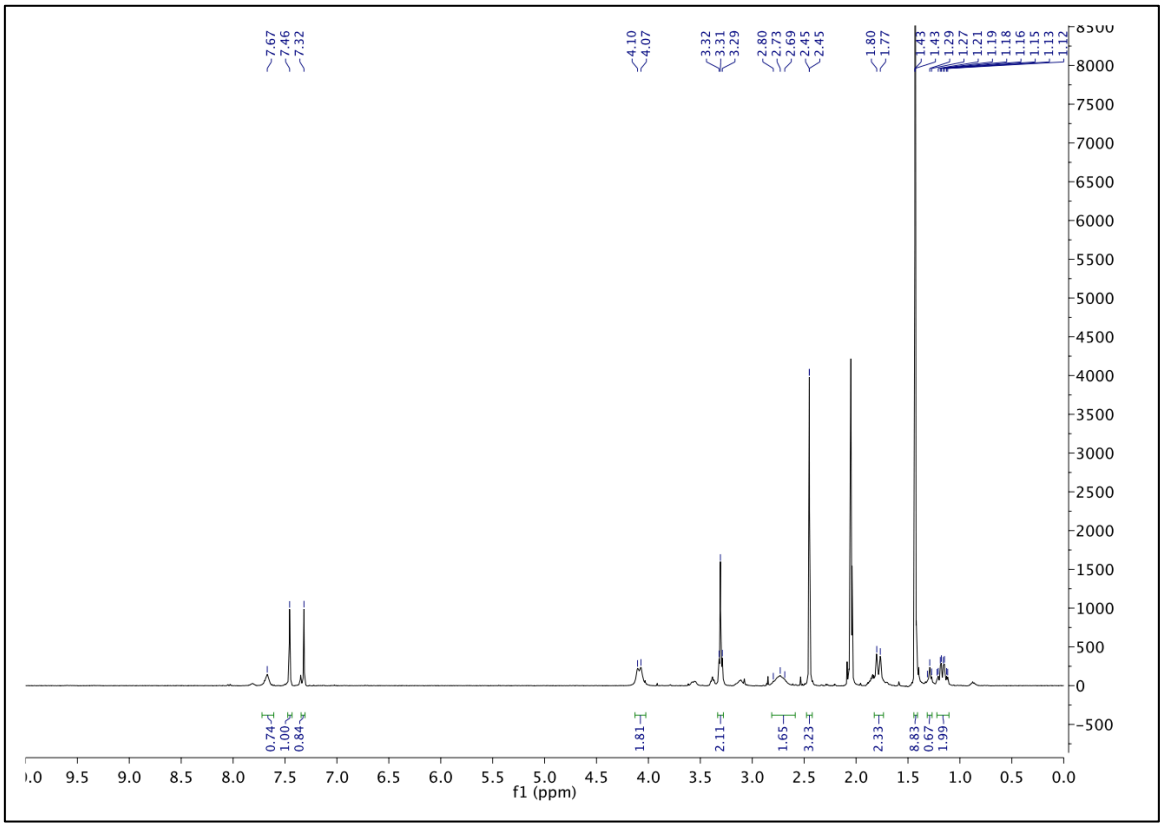
4,6-dihydroxy-2-methyl-5-oxo-*N*-(4-(trifluoromethoxy)benzyl)cyclohepta-1,3,6-triene-1-carboxamide (804).

To a solution of αHT carboxylic acid **319** (50 mg, .255 mmol) in THF (6.5 mL, .04M) was added 2,6-lutidine (65 µL, .562 mmol) and HBTU (106 mg, .280 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 4-(trifluoromethoxy)benzylamine (42.7 µL, .280 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **804** as a brown solid (28.7 mg, 31% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.49 (d, J = 7.6 Hz, 2H), 7.42 (s, 1H), 7.30 – 7.26 (m, 3H), 4.55 (s, 2H), 2.37 (s, 3H).



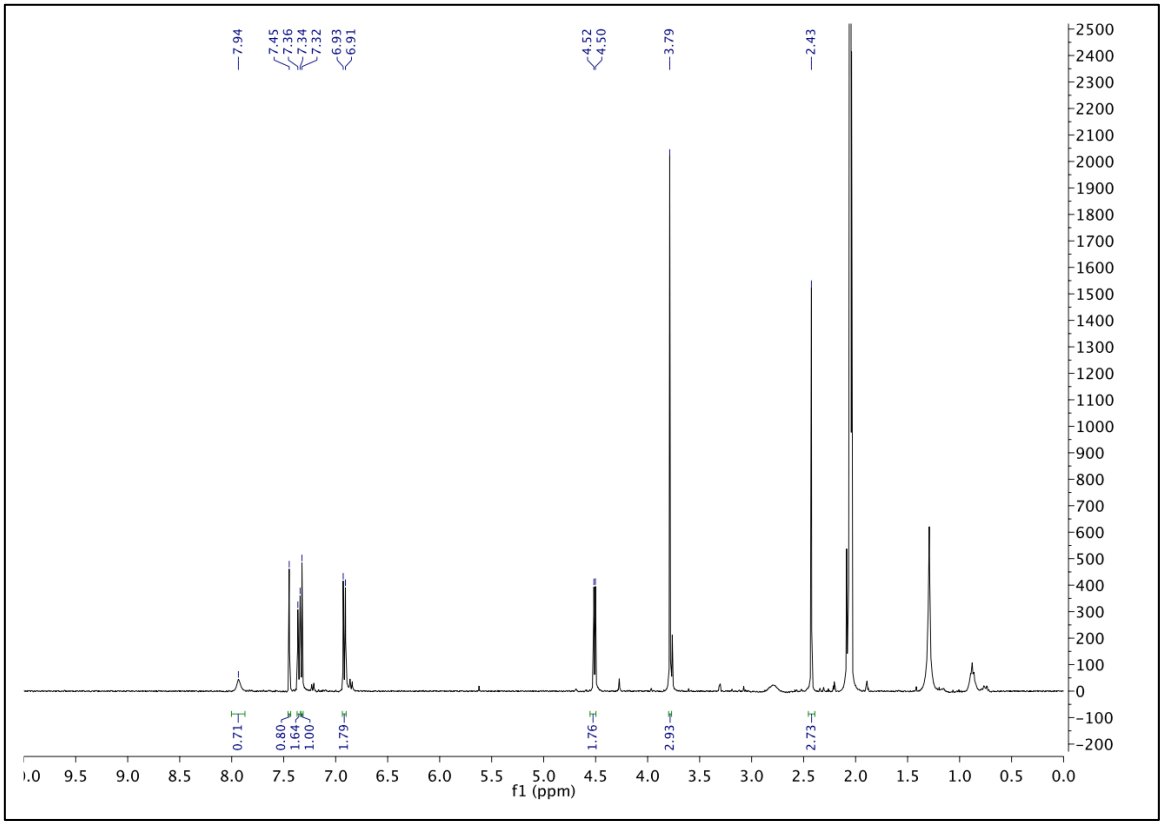
***tert*-butyl 4-((4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carboxamido)methyl)piperidine-1-carboxylate (805).**

To a solution of αHT carboxylic acid **319** (35 mg, .178 mmol) in THF (4.6 mL, .04M) was added 2,6-lutidine (45.4 µL, .392 mmol) and HBTU (73.5 mg, .190 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 1-Boc-4-(aminomethyl)piperidine (41.5 µL, .196 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **805** as a yellow solid (15.1 mg, 16% yield). **^{1}H NMR (400 MHz, Acetone-d_6)** δ 7.67 (br s, 1H), 7.46 (s, 1H), 7.32 (s, 1H), 4.09 (d, J = 13.2 Hz, 2H), 3.33 – 3.28 (m, 2H), 2.81 – 2.59 (m, 2H), 2.45 (s, 3H), 1.78 (d, J = 13.7 Hz, 2H), 1.43 (s, 9H), 1.29 (t, J = 8.0 Hz, 1H), 1.17 (m, 2H).



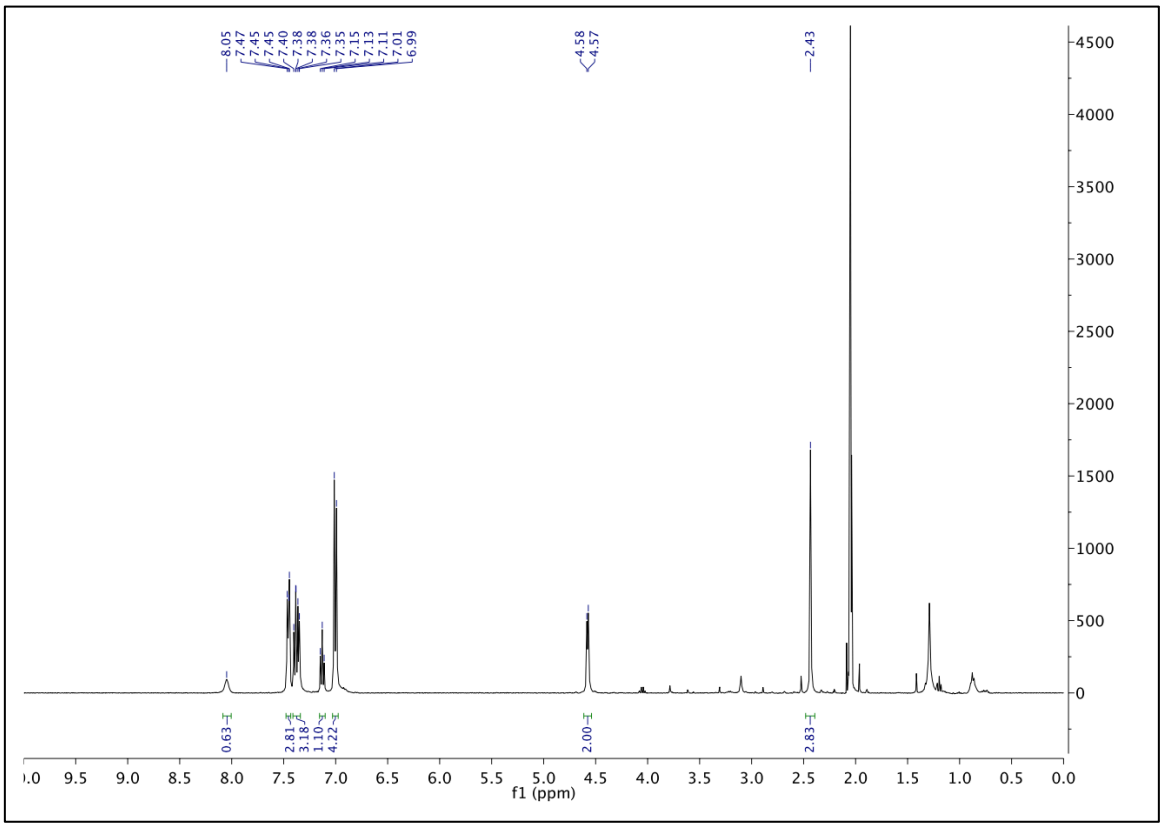
4,6-dihydroxy-*N*-(4-methoxybenzyl)-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carboxamide (806).

To a solution of αHT carboxylic acid **319** (25 mg, .128 mmol) in THF (3.25 mL, .04M) was added 2,6-lutidine (32.6 µL, .282 mmol) and HBTU (53.1 mg, .140 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 4-methoxybenzylamine (18.3 µL, 0.140 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **806** as a yellow solid (22.5 mg, 28% yield). **^{1}H NMR (400 MHz, Acetone-d_6)** δ 7.94 (br s, 1H), 7.45 (s, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.32 (s, 1H), 6.92 (d, J = 8.7 Hz, 2H), 4.51 (d, J = 6.0 Hz, 2H), 3.79 (s, 3H), 2.43 (s, 3H).



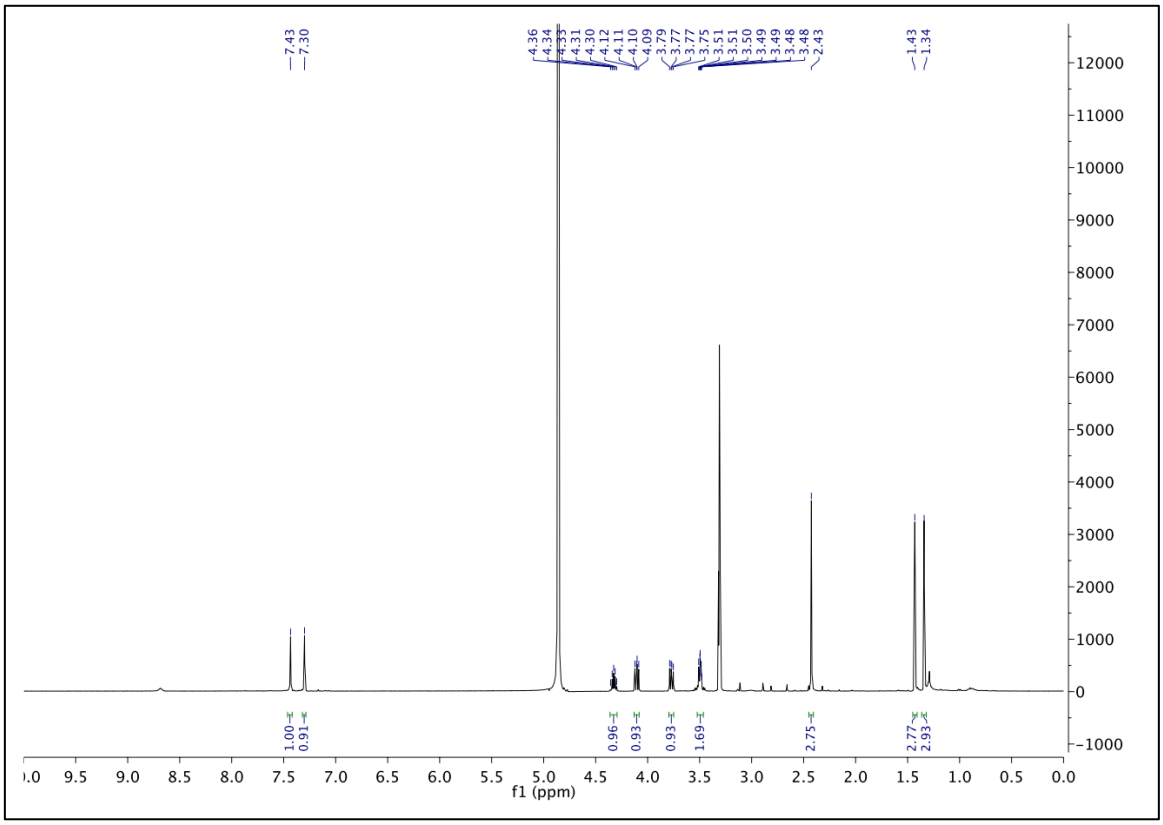
4,6-dihydroxy-2-methyl-5-oxo-*N*-(4-phenoxybenzyl)cyclohepta-1,3,6-triene-1-carboxamide (807).

To a solution of αHT carboxylic acid **319** (25 mg, .128 mmol) in THF (3.25 mL, .04M) was added 2,6-lutidine (32.6 µL, .282 mmol) and HBTU (53.1 mg, .140 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. (4-phenoxyphenyl)methanamine (27.9 mg, 0.140 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **807** as a yellow solid (6.6 mg, 14% yield). **^{1}H NMR (400 MHz, Acetone-d_6)** δ 8.05 (br s, 1H), 7.48 – 7.43 (m, 3H), 7.41 – 7.34 (m, 3H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 4H), 4.58 (d, *J* = 5.6 Hz, 2H), 2.43 (s, 3H).



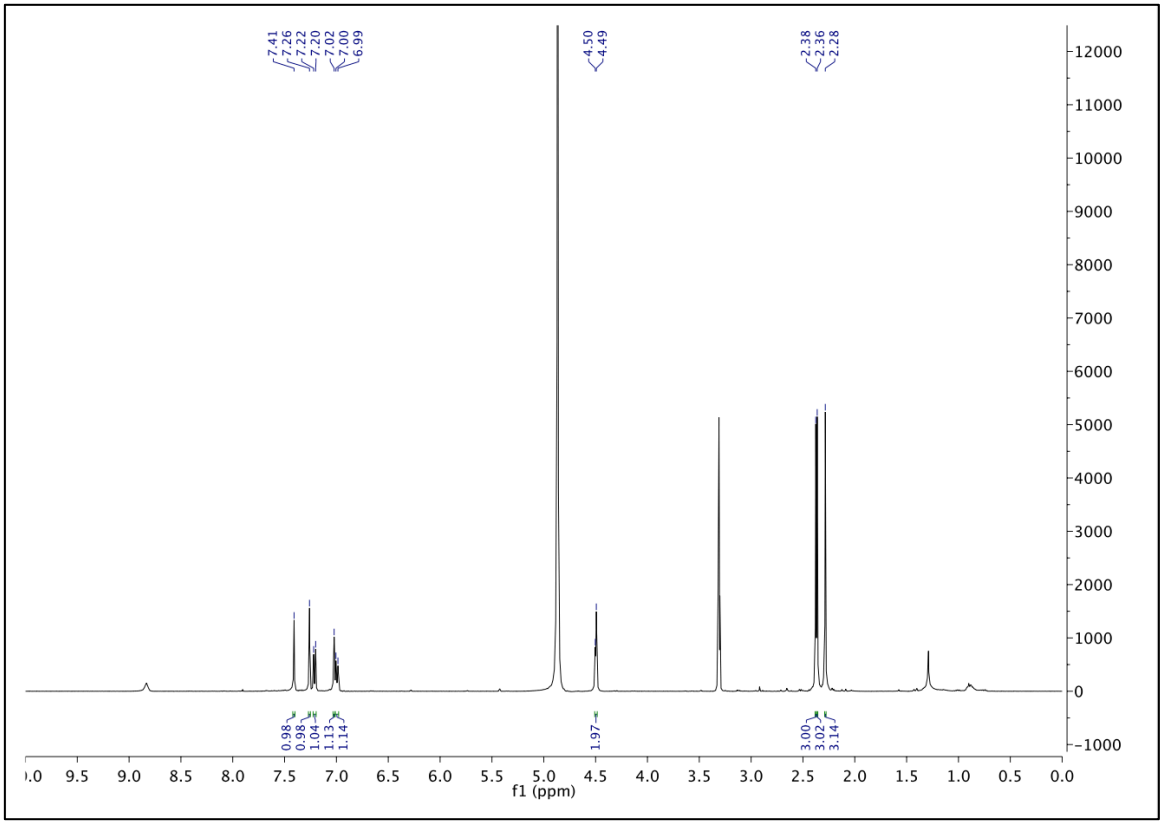
***N*-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carboxamide (808).**

To a solution of αHT carboxylic acid **319** (25 mg, .128 mmol) in THF (3.25 mL, .04M) was added 2,6-lutidine (32.6 µL, .282 mmol) and HBTU (53.1 mg, .140 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. (2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (18.2 µL, 0.140 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **808** as a yellow oil (5 mg, 13% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.43 (s, 1H), 7.30 (s, 1H), 4.33 (p, *J* = 5.9 Hz, 1H), 4.10 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.77 (dd, *J* = 8.4, 5.8 Hz, 1H), 3.52 – 3.46 (m, 2H), 2.43 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H).

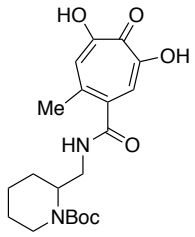


***N*-(2,4-dimethylbenzyl)-4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carboxamide (809).**

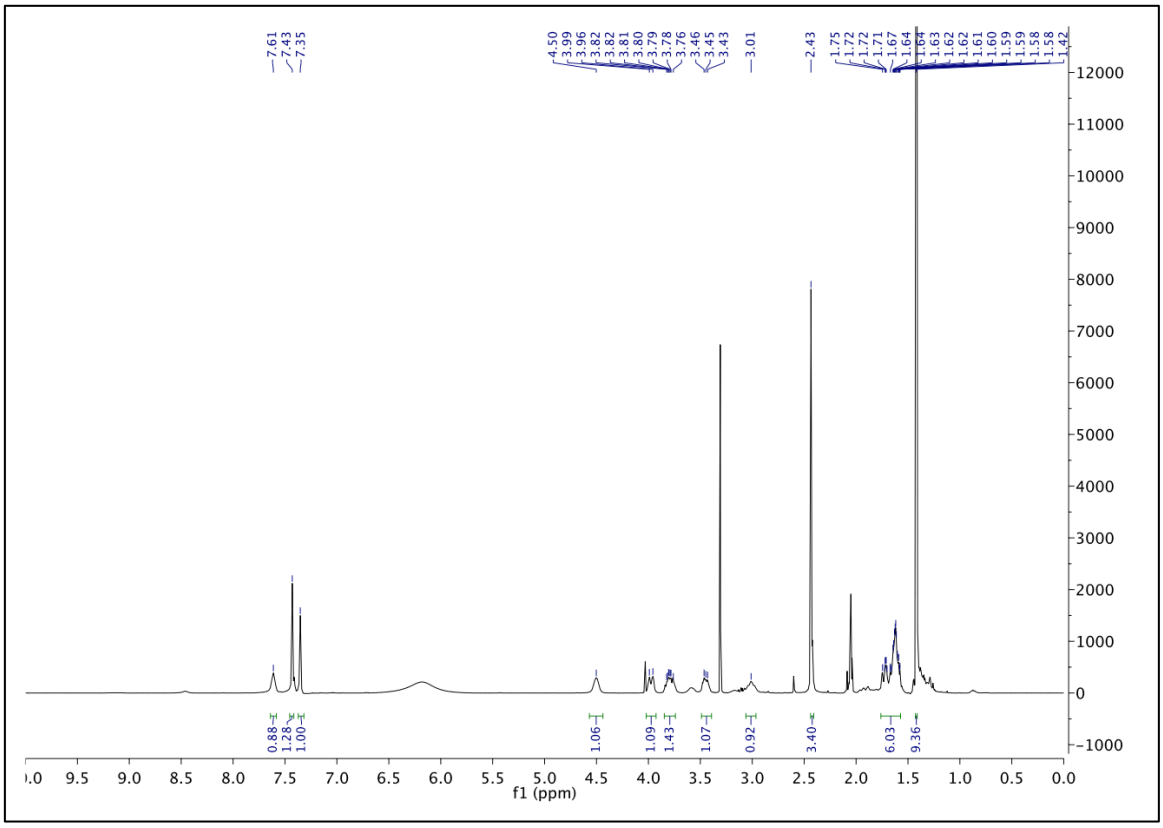
To a solution of αHT carboxylic acid **319** (25 mg, .128 mmol) in THF (3.25 mL, .04M) was added 2,6-lutidine (32.6 µL, .282 mmol) and HBTU (53.1 mg, .140 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 2,4-dimethylbenzylamine (18.2 µL, 0.140 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **809** as a brown solid (12.4 mg, 31% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.41 (s, 1H), 7.26 (s, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.02 (s, 1H), 7.00 (d, J = 7.7 Hz, 1H), 4.51 – 4.48 (m, 2H), 2.38 (s, 3H), 2.36 (s, 3H), 2.28 (s, 3H).



***tert*-butyl 2-((4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carboxamido)methyl)piperidine-1-carboxylate (810).**

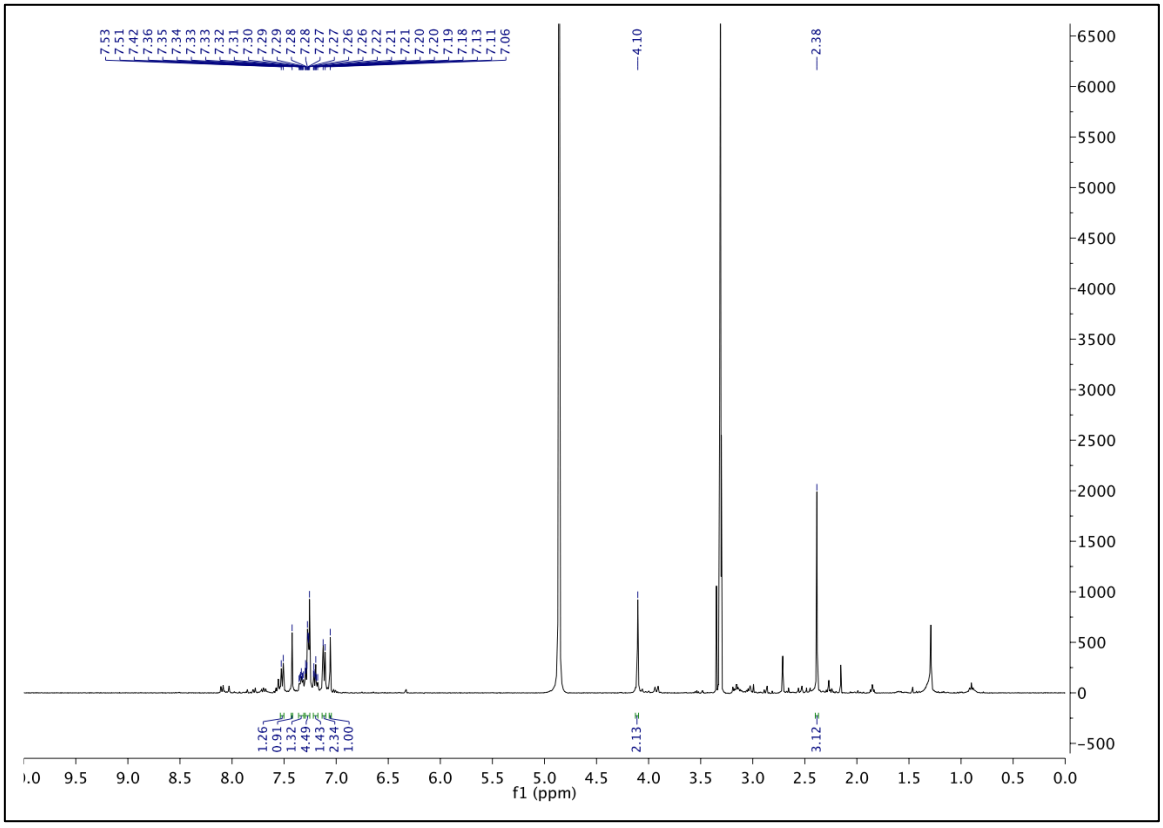


To a solution of αHT carboxylic acid **319** (25 mg, .128 mmol) in THF (3.25 mL, .04M) was added 2,6-lutidine (32.6 µL, .282 mmol) and HBTU (53.1 mg, .140 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 1-Boc-2-(aminomethyl)piperidine (29.6 µL, 0.140 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **810** as a brown oil (35.1 mg, 70% yield). **^{1}H NMR (400 MHz, Acetone-d_6)** δ 7.61 (br s, 1H), 7.43 (s, 1H), 7.35 (s, 1H), 4.50 (s, 1H), 3.97 (d, J = 13.7 Hz, 1H), 3.85 – 3.74 (m, 1H), 3.49 – 3.39 (m, 1H), 3.01 (s, 1H), 2.43 (s, 3H), 1.76 – 1.57 (m, 6H), 1.42 (s, 9H).



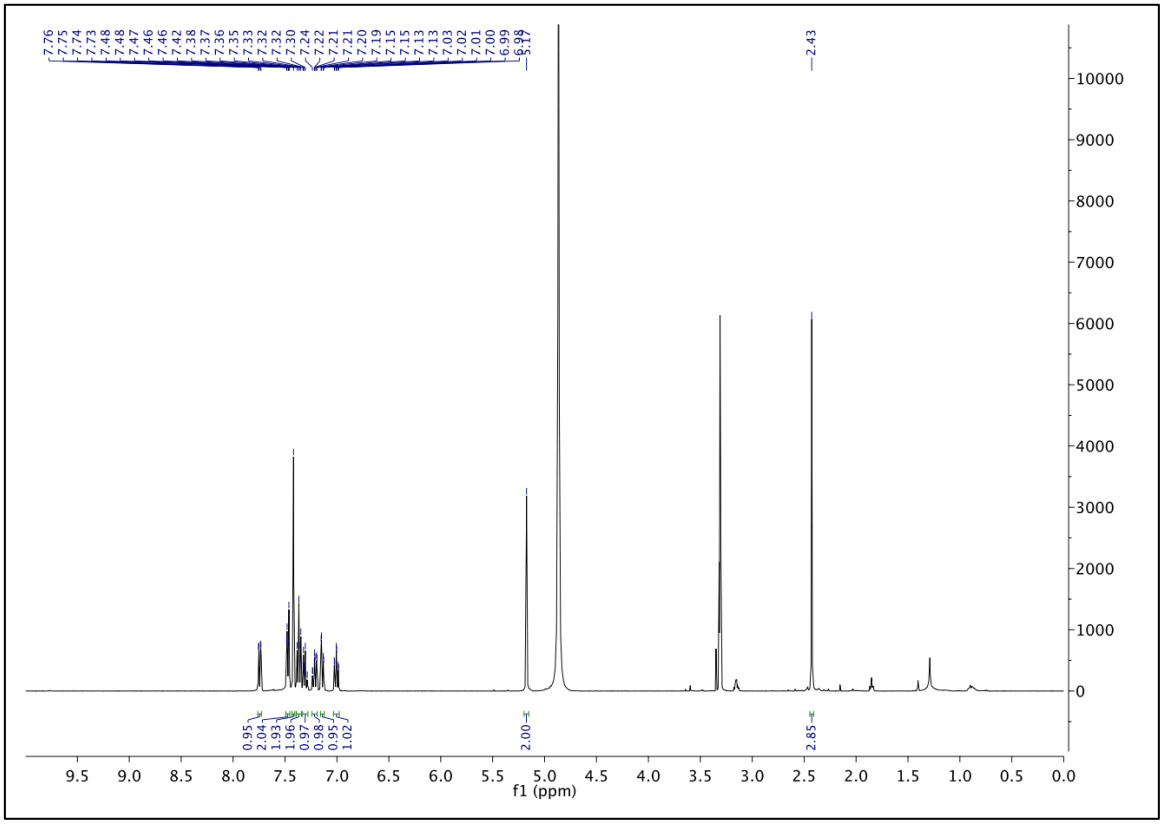
***N*-(2-benzylphenyl)-4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carboxamide (834).**

To a solution of αHT carboxylic acid **319** (14.2 mg, .072 mmol) in DMF (1.8 mL, .04M) was added 2,6-lutidine (18.3 µL, .158 mmol) and HBTU (30 mg, .079 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 2-benzylaniline (13.2 mg, .072 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 85 °C for 15 min. The reaction mixture was then directly loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **834** as a yellow oily solid (3 mg, 12% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.52 (d, J = 7.8 Hz, 1H), 7.42 (s, 1H), 7.36 – 7.31 (m, 1H), 7.30 – 7.24 (m, 4H), 7.22 – 7.17 (m, 1H), 7.11 (d, J = 7.8 Hz, 2H), 7.06 (s, 1H), 4.10 (s, 2H), 2.38 (s, 3H).



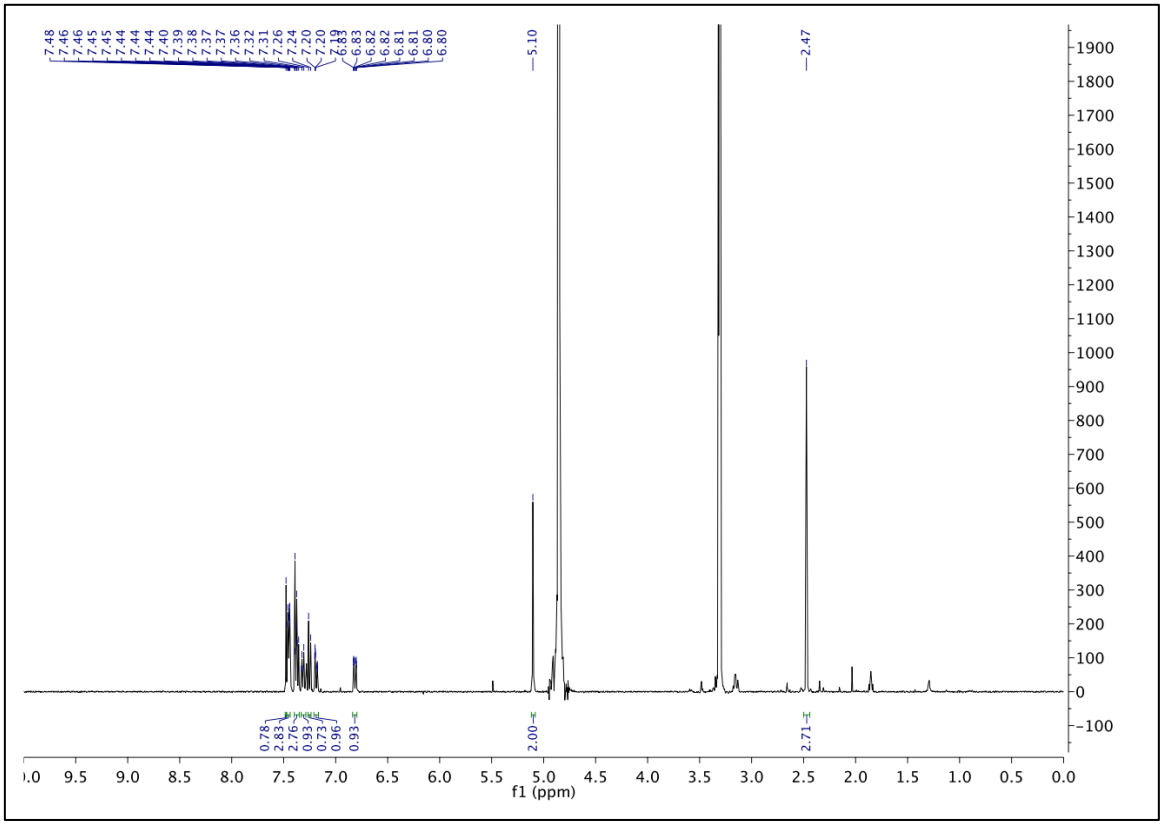
***N*-(2-(benzyloxy)phenyl)-4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carboxamide (835).**

To a solution of αHT carboxylic acid **319** (25 mg, .128 mmol) in THF (3.25 mL, .04M) was added 2,6-lutidine (32.6 µL, .282 mmol) and PyBOP (72.9 mg, .140 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 2-(benzyloxy)aniline (27.9 mg, 0.140 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **835** as a tan solid (21.1 mg, 40% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.74 (dd, J = 7.9, 1.6 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.42 (s, 2H), 7.39 – 7.34 (m, 2H), 7.33 – 7.28 (m, 1H), 7.24 – 7.19 (m, 1H), 7.16 – 7.12 (m, 1H), 7.00 (td, J = 7.6, 1.4 Hz, 1H), 5.17 (s, 2H), 2.43 (s, 3H).



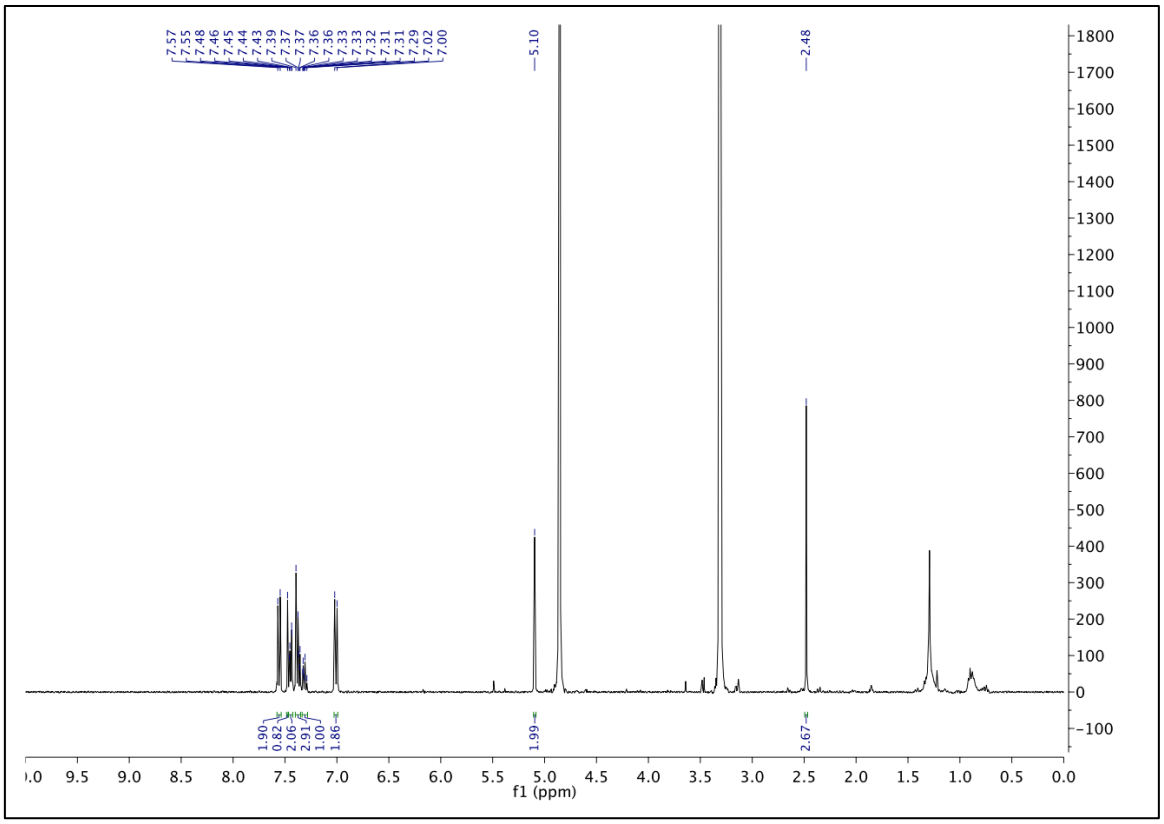
***N*-(3-(benzyloxy)phenyl)-4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carboxamide (836).**

To a solution of αHT carboxylic acid **319** (25 mg, .128 mmol) in THF (3.25 mL, .04M) was added 2,6-lutidine (32.6 µL, .282 mmol) and PyBOP (72.9 mg, .140 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 3-(benzyloxy)aniline (27.9 mg, 0.140 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **836** as a yellow solid (6.9 mg, 13% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.48 (s, 1H), 7.47 – 7.44 (m, 3H), 7.40 – 7.35 (m, 3H), 7.33 – 7.29 (m, 1H), 7.27 – 7.24 (m, 1H), 7.19 (ddd, J = 8.0, 1.9, 1.0 Hz, 1H), 6.81 (ddd, J = 8.2, 2.5, 1.0 Hz, 1H), 5.10 (s, 2H), 2.47 (s, 3H).



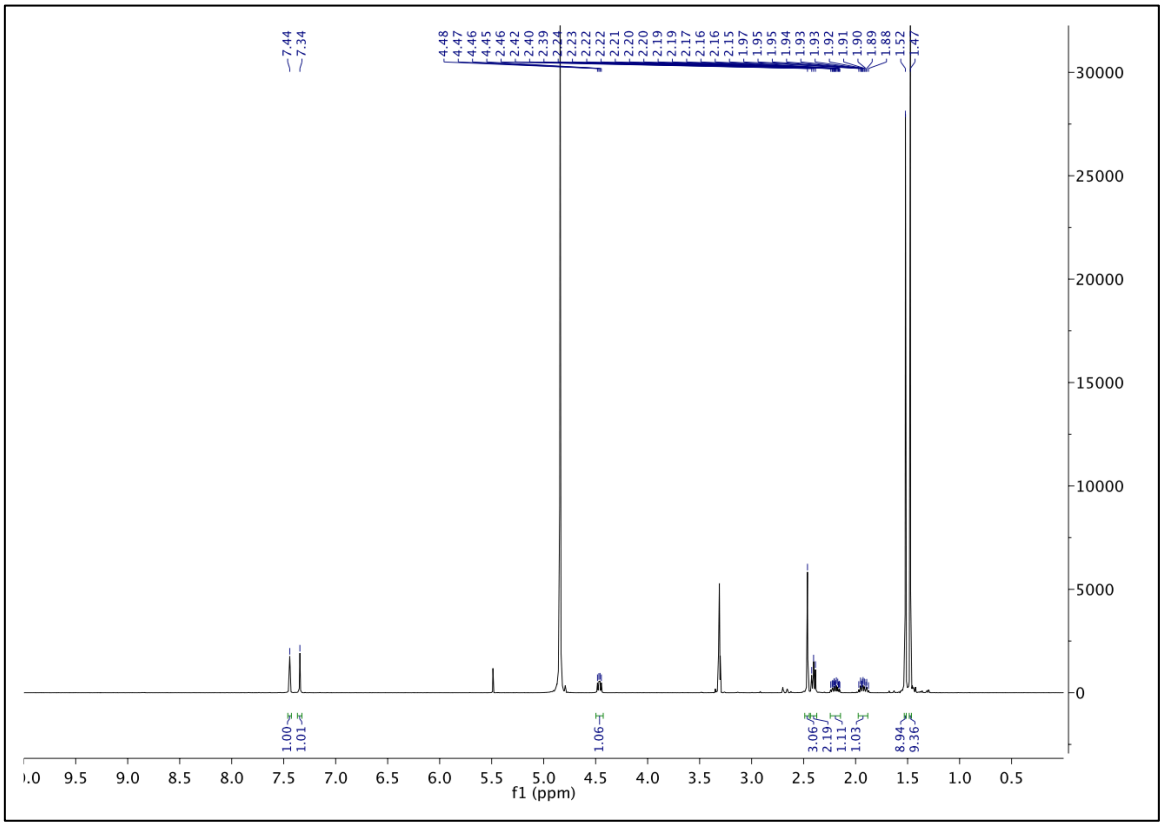
***N*-(4-(benzyloxy)phenyl)-4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carboxamide (837).**

To a solution of αHT carboxylic acid **319** (25 mg, .128 mmol) in THF (3.25 mL, .04M) was added 2,6-lutidine (32.6 µL, .282 mmol) and PyBOP (72.9 mg, .140 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 4-(benzyloxy)aniline (27.9 mg, 0.140 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **837** as a tan solid (29.7 mg, 56% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.56 (d, J = 9.1 Hz, 2H), 7.48 (s, 1H), 7.47 – 7.42 (m, 2H), 7.40 – 7.35 (m, 3H), 7.34 – 7.28 (m, 1H), 7.01 (d, J = 9.1 Hz, 2H), 5.10 (s, 2H), 2.48 (s, 3H).



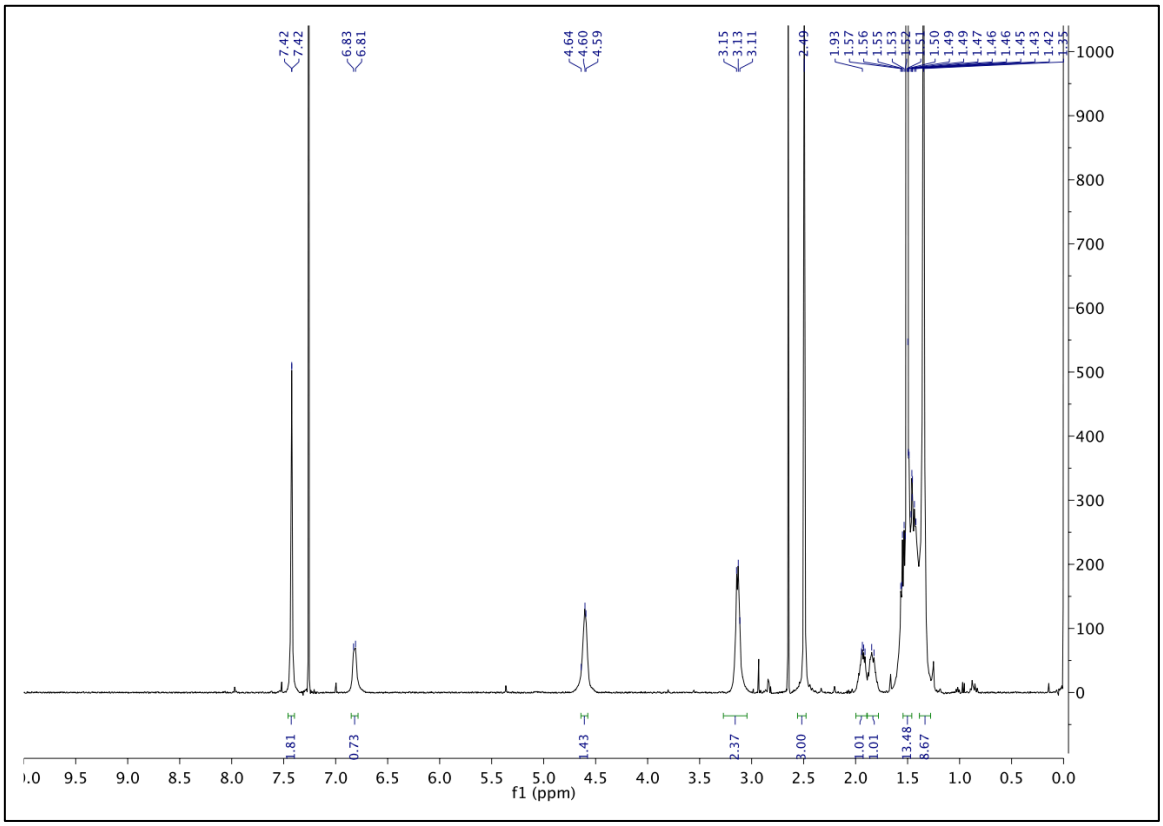
Di-*tert*-butyl (4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carbonyl)-*L*-glutamate (867).

To a solution of αHT carboxylic acid **319** (17 mg, .087 mmol) in THF (2 mL, .04M) was added 2,6-lutidine (22.2 µL, .191 mmol) and HBTU (38.7 mg, .096 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. Di-*tert*-butyl *L*-glutamate hydrochloride (25 mg, 0.087 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 85 °C for 15 min. The reaction mixture was then diluted with 10 mL CH_2Cl_2, and washed with NH_4Cl (aq) (2 x 15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **867** as a yellow oil (30 mg, 79% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.44 (s, 1H), 7.34 (s, 1H), 4.46 (dd, J = 9.6, 5.2 Hz, 1H), 2.46 (s, 3H), 2.40 (t, J = 7.3 Hz, 2H), 2.24 – 2.15 (m, 1H), 1.98 – 1.88 (m, 1H), 1.52 (s, 9H), 1.47 (s, 9H).



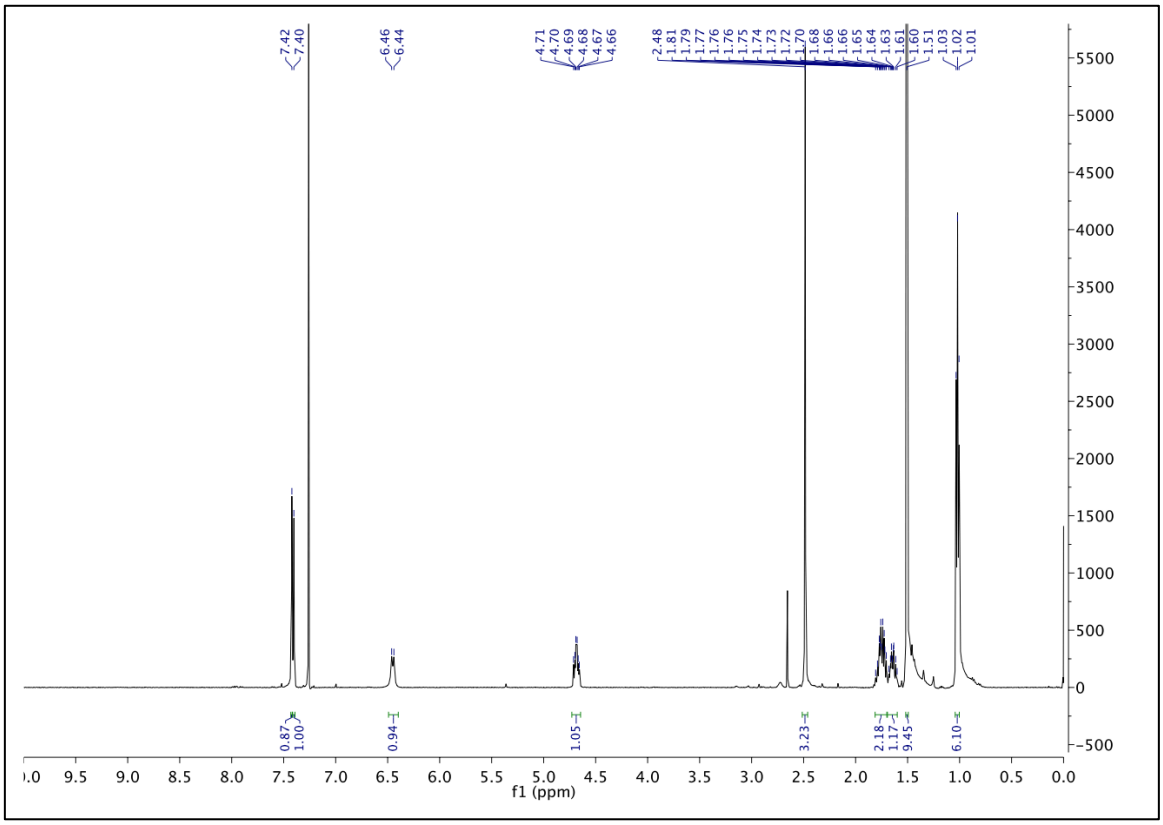
***tert*-butyl N^6-(*tert*-butoxycarbonyl)-N^2-(4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carbonyl)-*L*-lysinate (869).**

To a solution of αHT carboxylic acid **319** (10 mg, .051 mmol) in THF (1.3 mL, .04M) was added 2,6-lutidine (13 µL, .112 mmol) and HBTU (21.3 mg, .056 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. (S)-*tert*-butyl 2-amino-6-((*tert*-butoxycarbonyl)amino)hexanoate hydrochloride (19 mg, 0.056 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 85 °C for 15 min. The reaction mixture was then diluted with 10 mL CH_2Cl_2, and washed with NH_4Cl (aq) (2 x 15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo.* The residue was dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **869** as a yellow oil (20.1 mg, 85% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 – 7.40 (m, 2H), 6.82 (br d, *J* = 7.7 Hz, 1H), 4.64 – 4.58 (m, 1H), 3.27 – 3.04 (m, 2H), 2.49 (s, 3H), 2.00 – 1.89 (m, 1H), 1.89 – 1.78 (m, 1H), 1.54 – 1.46 (m, 13H), 1.35 (s, 9H).



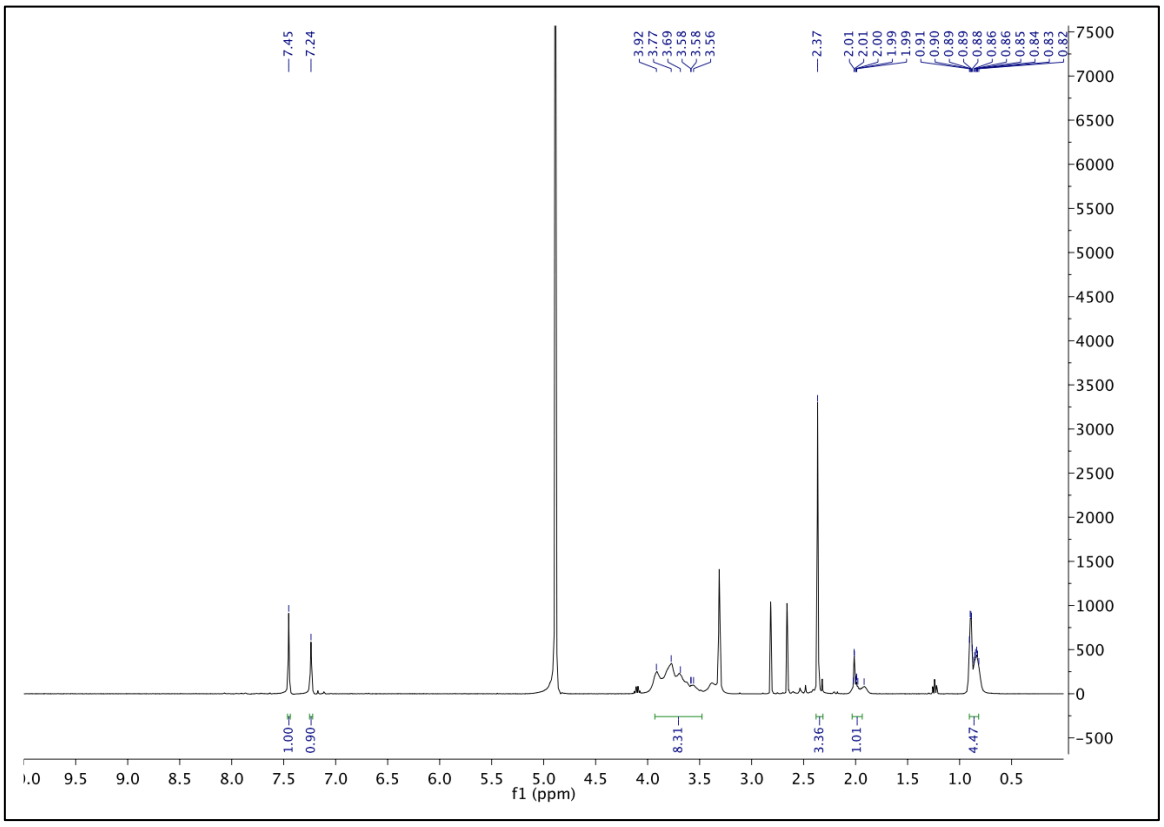
***tert*-butyl (4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carbonyl)-*L*-leucinate (870).**

To a solution of αHT carboxylic acid **319** (10 mg, .051 mmol) in THF (1.3 mL, .04M) was added 2,6-lutidine (13 µL, .112 mmol) and HBTU (21.3 mg, .056 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. *tert*-butyl *L*-leucinate hydrochloride (12.6 mg, 0.056 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 85 °C for 15 min. The reaction mixture was then diluted with 10 mL CH_2Cl_2, and washed with NH_4Cl (aq) (2 x 15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **870** as a yellow oil (11.9 mg, 64% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42 (s, 1H), 7.40 (s, 1H), 6.45 (br d, *J* = 8.6 Hz, 1H), 4.68 (td, *J* = 8.7, 4.9 Hz, 1H), 2.48 (s, 3H), 1.81 – 1.70 (m, 2H), 1.69 – 1.60 (m, 1H), 1.51 (s, 9H), 1.02 (t, *J* = 5.7 Hz, 6H).



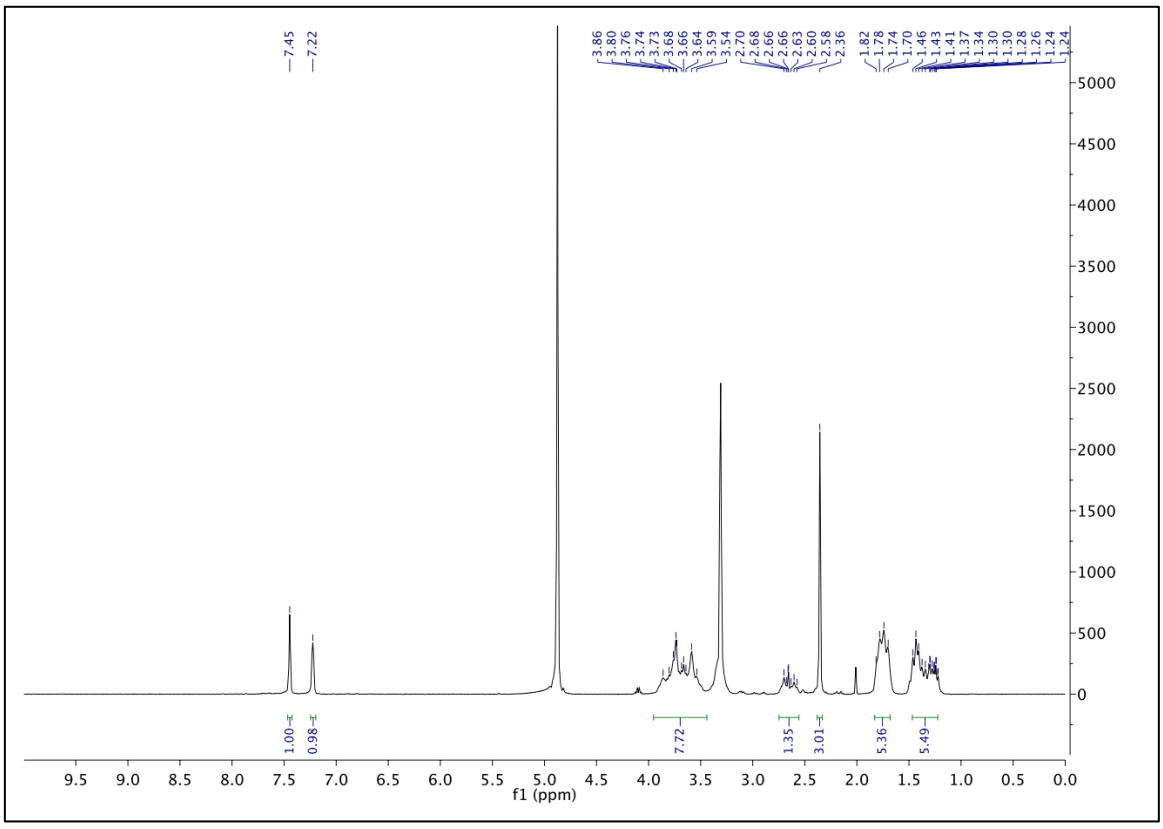
4-(4-cyclopropylpiperazine-1-carbonyl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trien-1-one (871).

To a solution of αHT carboxylic acid **319** (10 mg, .051 mmol) in THF (1.3 mL, .04M) was added 2,6-lutidine (12 µL, .112 mmol) and HBTU (21.2 mg, .056 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 1-cyclopropylpiperazine (8 µL, 0.056 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **871** as a yellow oil (4 mg, 26% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.45 (s, 1H), 7.24 (s, 1H), 3.93 – 3.48 (m, 8H), 2.37 (s, 3H), 2.03 – 1.94 (m, 1H), 0.91 – 0.82 (m, 4H).



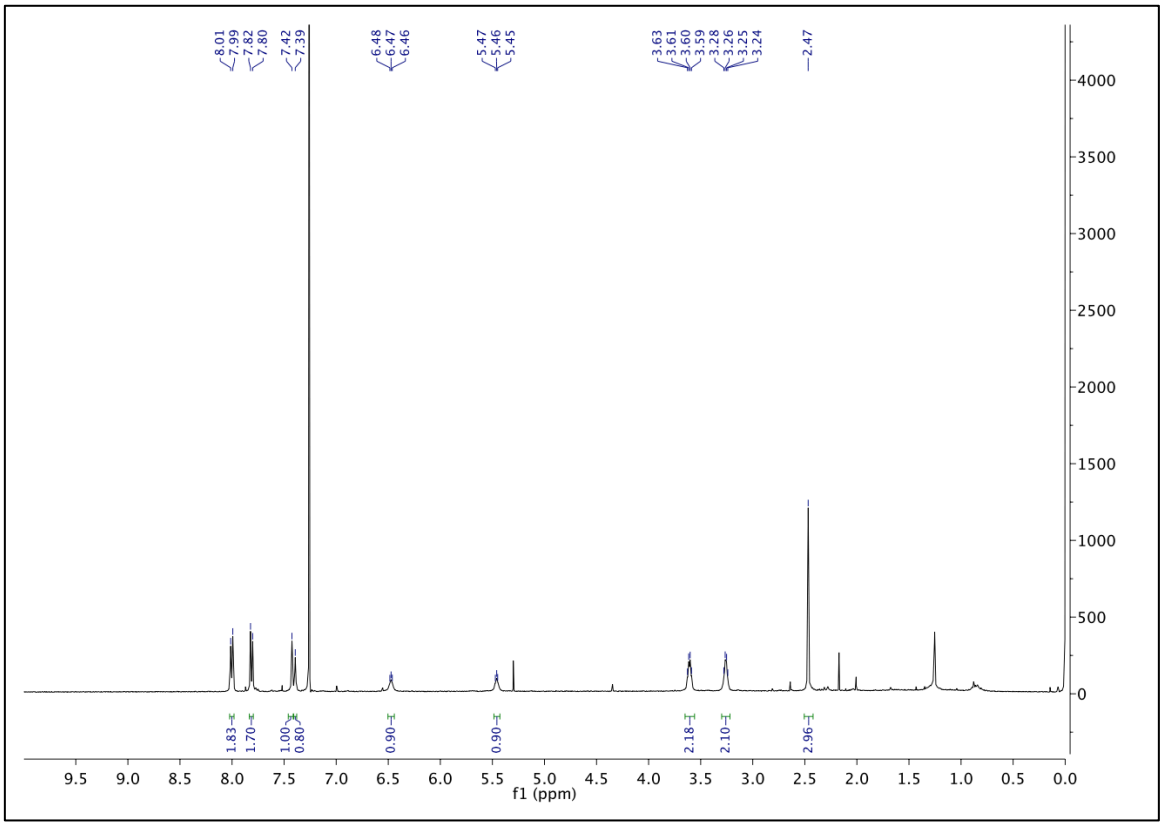
4-(4-(cyclohexanecarbonyl)piperazine-1-carbonyl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trien-1-one (872).

To a solution of αHT carboxylic acid **319** (10 mg, .051 mmol) in THF (1.3 mL, .04M) was added 2,6-lutidine (12 µL, .112 mmol) and HBTU (21.2 mg, .056 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. Cyclohexyl(piperazin-1-yl)methanone (11 mg, 0.056 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **872** as a yellow oil (6.4 mg, 34% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.45 (s, 1H), 7.22 (s, 1H), 3.95 – 3.44 (m, 8H), 2.75 – 2.56 (m, 1H), 2.36 (s, 3H), 1.83 – 1.68 (m, 5H), 1.47 – 1.22 (m, 5H).



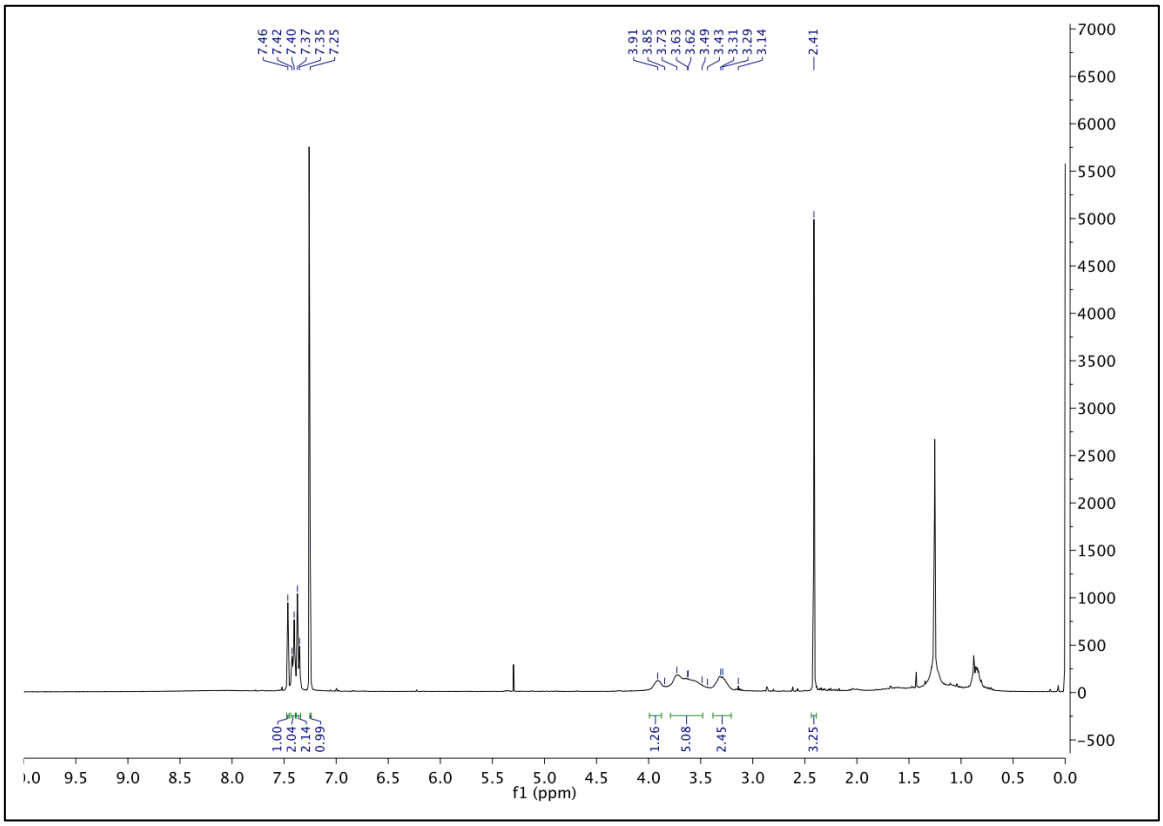
4,6-dihydroxy-2-methyl-5-oxo-*N*-(2-((4-(trifluoromethyl)phenyl)sulfonamido)ethyl)cyclohepta-1,3,6-triene-1-carboxamide (874).

To a solution of αHT carboxylic acid **319** (12.8 mg, .065 mmol) in THF (1.5 mL, .04M) was added 2,6-lutidine (16.7 µL, .144 mmol) and PyBOP (37.4 mg, .072 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. *N*-(2-aminoethyl)-4-(trifluoromethyl)benzenesulfonamide (22.8 mg, 0.085 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **874** as a yellow solid (14.8 mg, 51% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00 (d, *J* = 8.1 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.42 (s, 1H), 7.39 (s, 1H), 6.47 (br s, 1H), 5.46 (br s, 1H), 3.65 – 3.56 (m, 2H), 3.30 – 3.22 (m, 2H), 2.47 (s, 3H).



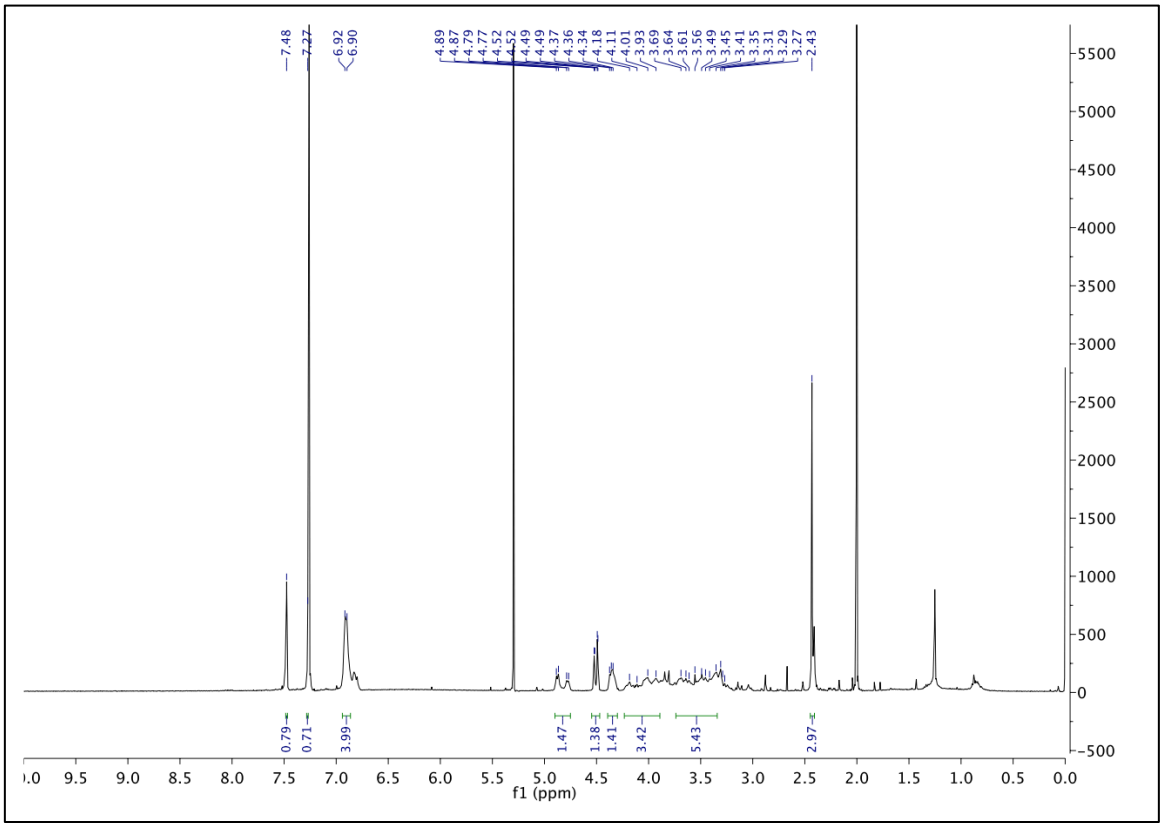
4-(4-(4-chlorobenzoyl)piperazine-1-carbonyl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trien-1-one (875).

To a solution of αHT carboxylic acid **319** (12.7 mg, .065 mmol) in THF (1.6 mL, .04M) was added 2,6-lutidine (16.5 µL, .142 mmol) and HBTU (27 mg, .071 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. (4-chlorophenyl)(piperazin-1-yl)methanone (18.9 mg, 0.084 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **875** as a yellow solid (4.6 mg, 18% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 (s, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.25 (s, 1H), 3.99 – 3.88 (m, 1H), 3.79 – 3.48 (m, 5H), 3.38 – 3.21 (m, 2H), 2.41 (s, 3H).



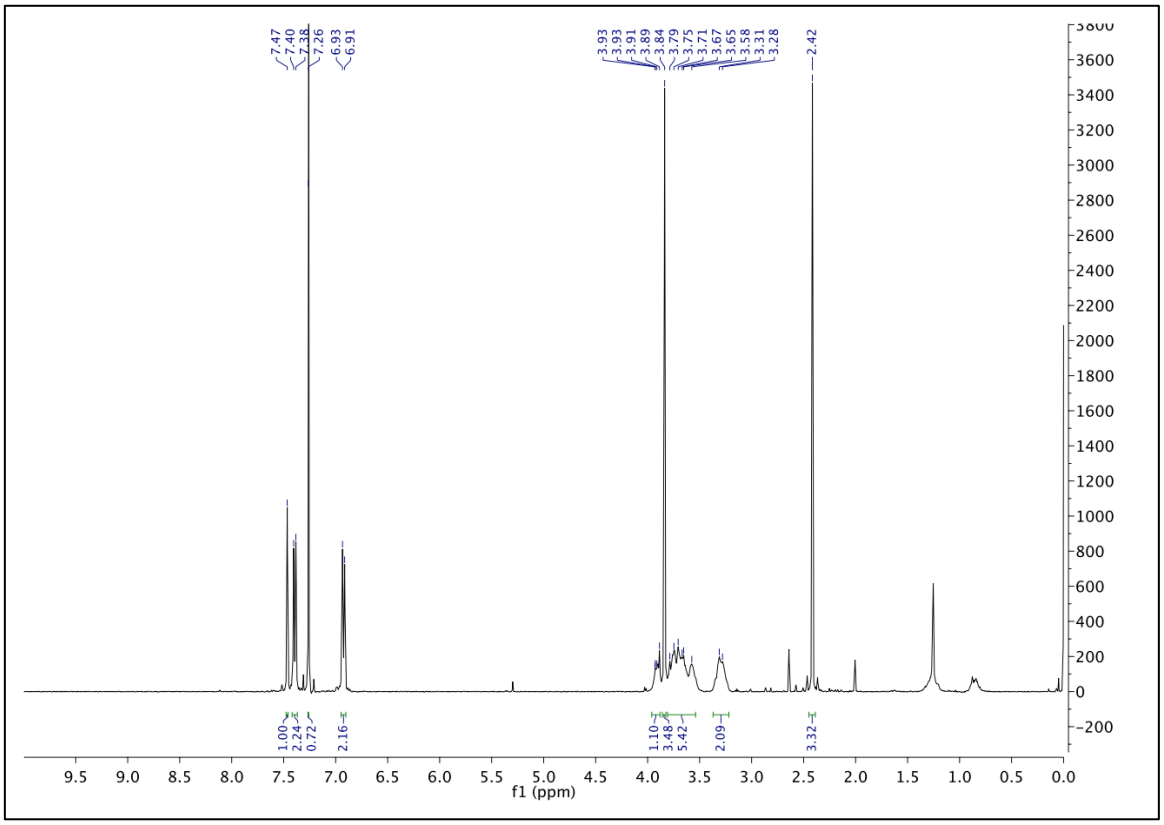
4-(4-(2,3-dihydrobenzo[*b*][1,4]dioxine-2-carbonyl)piperazine-1-carbonyl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trien-1-one (876).

To a solution of αHT carboxylic acid **319** (14 mg, .0765 mmol) in THF (1.9 mL, .04M) was added 2,6-lutidine (19.6 µL, .168 mmol) and HBTU (31.9 mg, .084 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. (2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)(piperazin-1-yl)methanone (24.7 mg, 0.099 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **876** as a brown oil (9.1 mg, 28% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.48 (s, 1H), 7.27 (s, 1H), 6.94 – 6.86 (m, 4H), 4.90 – 4.75 (m, 1H), 4.50 (dd, J = 12.0, 2.5 Hz, 1H), 4.39 – 4.30 (m, 1H), 4.23 – 3.89 (m, 3H), 3.74 – 3.34 (m, 5H), 2.43 (s, 3H).



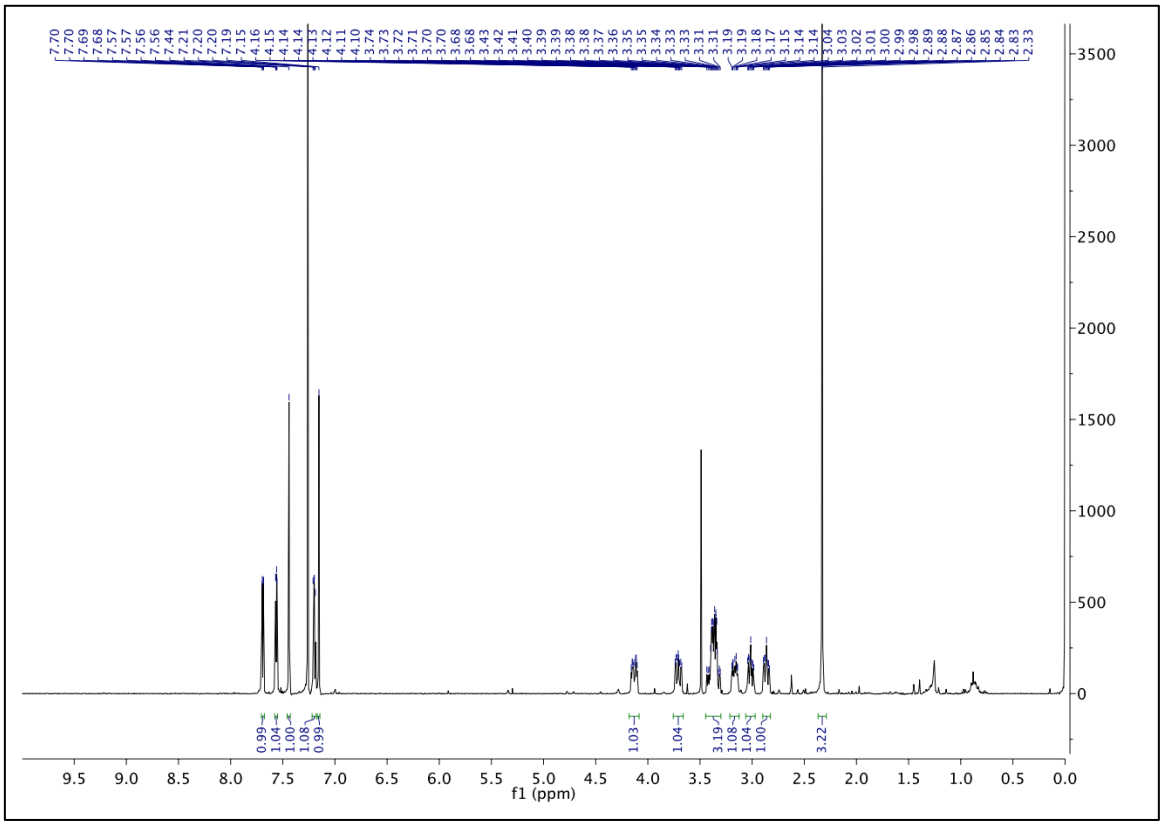
2,7-dihydroxy-4-(4-(4-methoxybenzoyl)piperazine-1-carbonyl)-5-methylcyclohepta-2,4,6-trien-1-one (877).

To a solution of αHT carboxylic acid **319** (13.7 mg, .0698 mmol) in THF (1.7 mL, .04M) was added 2,6-lutidine (17.8 µL, .154 mmol) and HBTU (28.8 mg, .077 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. (4-methoxyphenyl)(piperazin-1-yl)methanone (20 mg, 0.091 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **877** as a yellow oil (6 mg, 22% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.26 (s, 1H), 6.92 (d, *J* = 8.3 Hz, 2H), 3.96 – 3.88 (m, 1H), 3.84 (s, 3H), 3.81 – 3.54 (m, 5H), 3.37 – 3.22 (m, 2H), 2.42 (s, 3H).



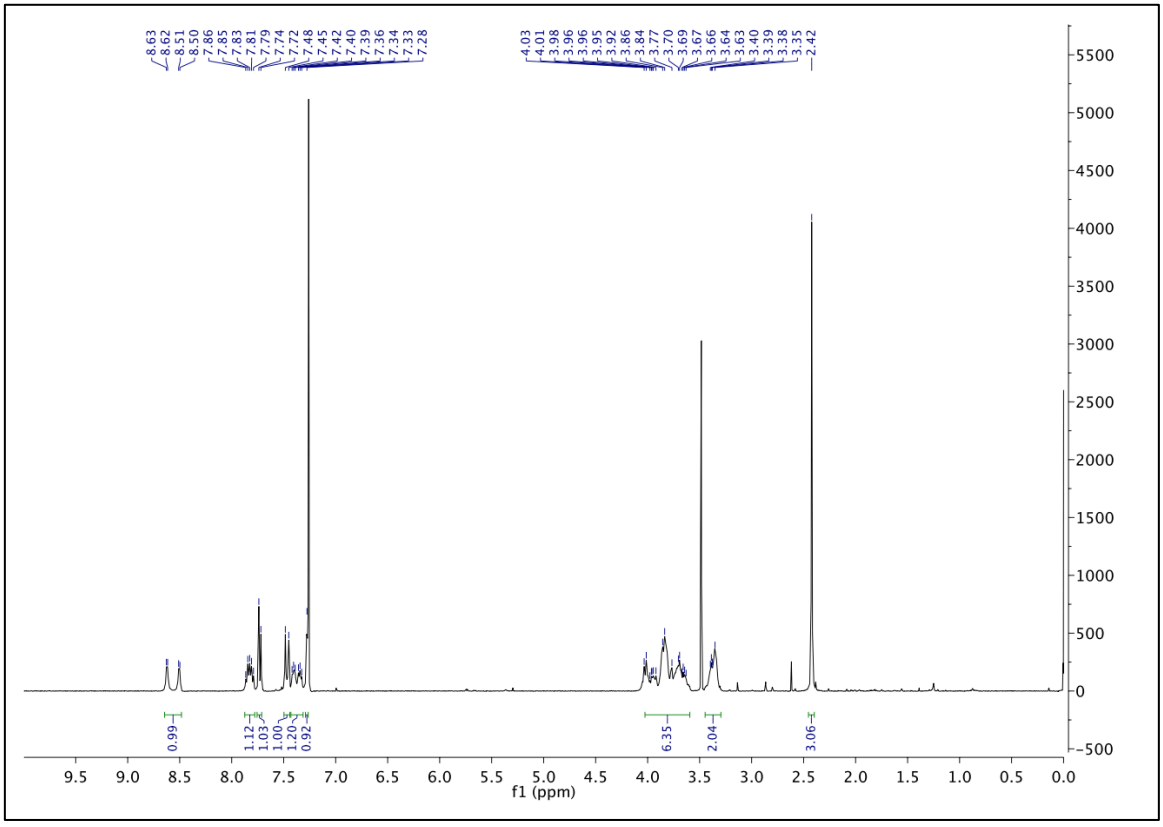
2,7-dihydroxy-4-methyl-5-(4-(thiophen-2-ylsulfonyl)piperazine-1-carbonyl)cyclohepta-2,4,6-trien-1-one (917).

To a solution of αHT carboxylic acid **319** (10 mg, .051 mmol) in DMF (1.3 mL, .04M) was added 2,6-lutidine (13 µL, .112 mmol) and HATU (21.3 mg, .056 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 1-(thiophen-2-ylsulfonyl)piperazine (28.3 mg, 0.122 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 85 °C for 15 min. The reaction mixture was then directly loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **917** as a yellow oil (6 mg, 29% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.69 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.56 (dd, *J* = 3.8, 1.3 Hz, 1H), 7.44 (s, 1H), 7.20 (dd, *J* = 5.0, 3.7 Hz, 1H), 7.15 (s, 1H), 4.13 (ddd, *J* = 13.4, 5.8, 3.5 Hz, 1H), 3.71 (ddd, *J* = 13.4, 8.2, 3.4 Hz, 1H), 3.45 – 3.30 (m, 3H), 3.21 – 3.12 (m, 1H), 3.01 (ddd, *J* = 11.7, 8.3, 3.4 Hz, 1H), 2.86 (ddd, *J* = 11.6, 7.8, 3.6 Hz, 1H), 2.33 (s, 3H).



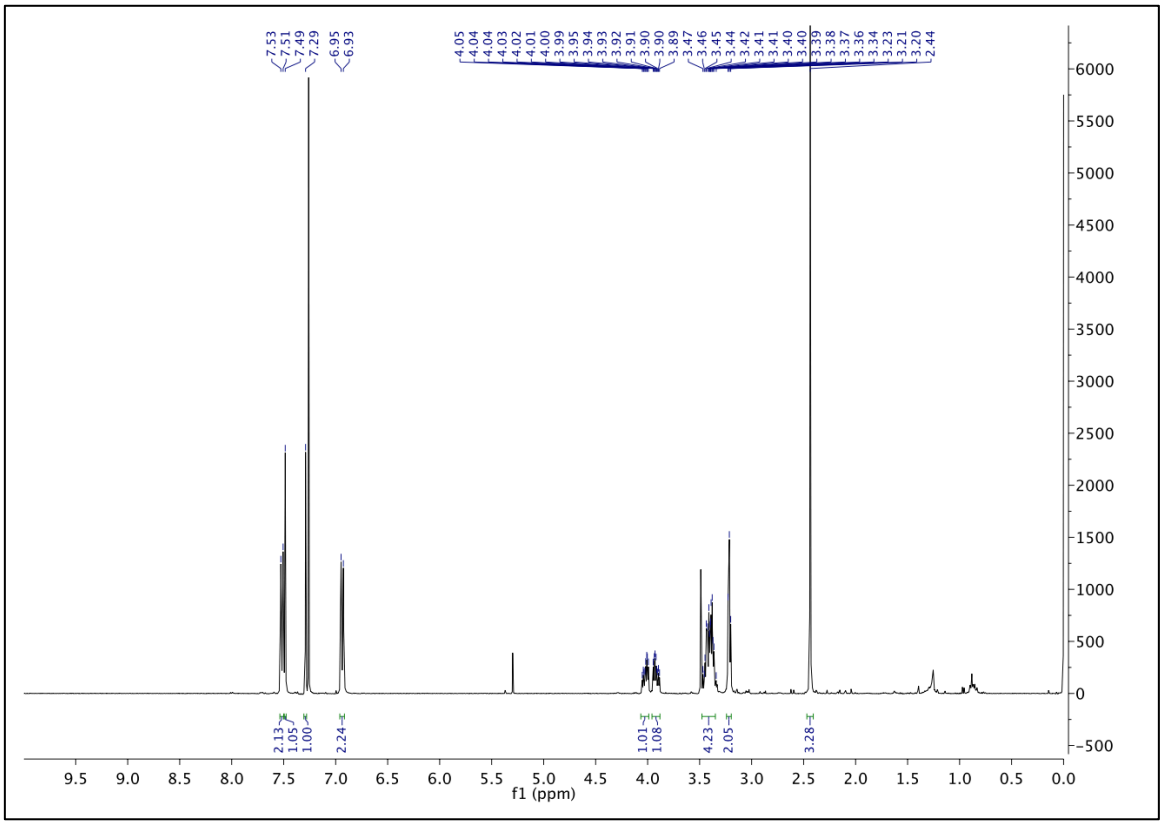
2,7-dihydroxy-4-methyl-5-(4-picolinoylpiperazine-1-carbonyl)cyclohepta-2,4,6-trien-1-one (918).

To a solution of αHT carboxylic acid **319** (15 mg, .0765 mmol) in THF (1.9 mL, .04M) was added 2,6-lutidine (19.5 µL, .168 mmol) and HBTU (31.9 mg, .084 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. Piperazin-1-yl(pyridin-2-yl)methanone (19 mg, 0.099 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **918** as a yellow oil (12.8 mg, 45% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.65 – 8.48 (m, 1H), 7.87 – 7.78 (m, 1H), 7.76 – 7.71 (m, 1H), 7.50 – 7.44 (m, 1H), 7.43 – 7.31 (m, 1H), 7.28 (s, 1H), 4.03 – 3.59 (m, 6H), 3.45 – 3.30 (m, 2H), 2.42 (s, 3H).



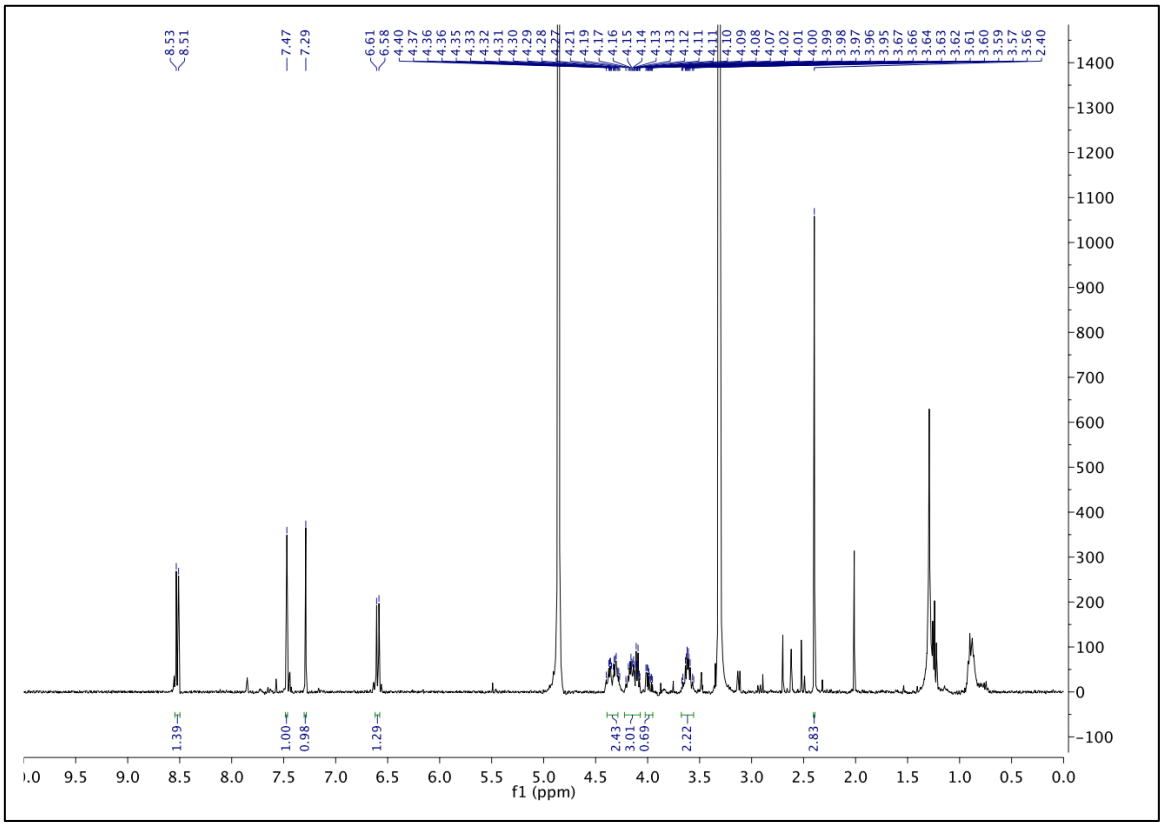
2,7-dihydroxy-4-methyl-5-(4-(4-(trifluoromethyl)phenyl)piperazine-1-carbonyl)cyclohepta-2,4,6-trien-1-one (919).

To a solution of αHT carboxylic acid **319** (10 mg, .051 mmol) in DMF (1.3 mL, .04M) was added 2,6-lutidine (13 µL, .112 mmol) and HATU (21.3 mg, .056 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 1-(4-(trifluoromethyl)phenyl)piperazine (25.8 mg, 0.112 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 85 °C for 15 min. The reaction mixture was then directly loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **919** as a yellow oil (7.5 mg, 36% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.52 (d, *J* = 8.6 Hz, 2H), 7.49 (s, 1H), 7.29 (s, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 4.02 (ddd, *J* = 13.3, 6.3, 4.0 Hz, 1H), 3.92 (ddd, *J* = 13.3, 6.9, 4.0 Hz, 1H), 3.48 – 3.35 (m, 4H), 3.21 (t, *J* = 5.2 Hz, 2H), 2.44 (s, 3H).



2,7-dihydroxy-4-methyl-5-(4-(7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)piperazine-1-carbonyl)cyclohepta-2,4,6-trien-1-one (920).

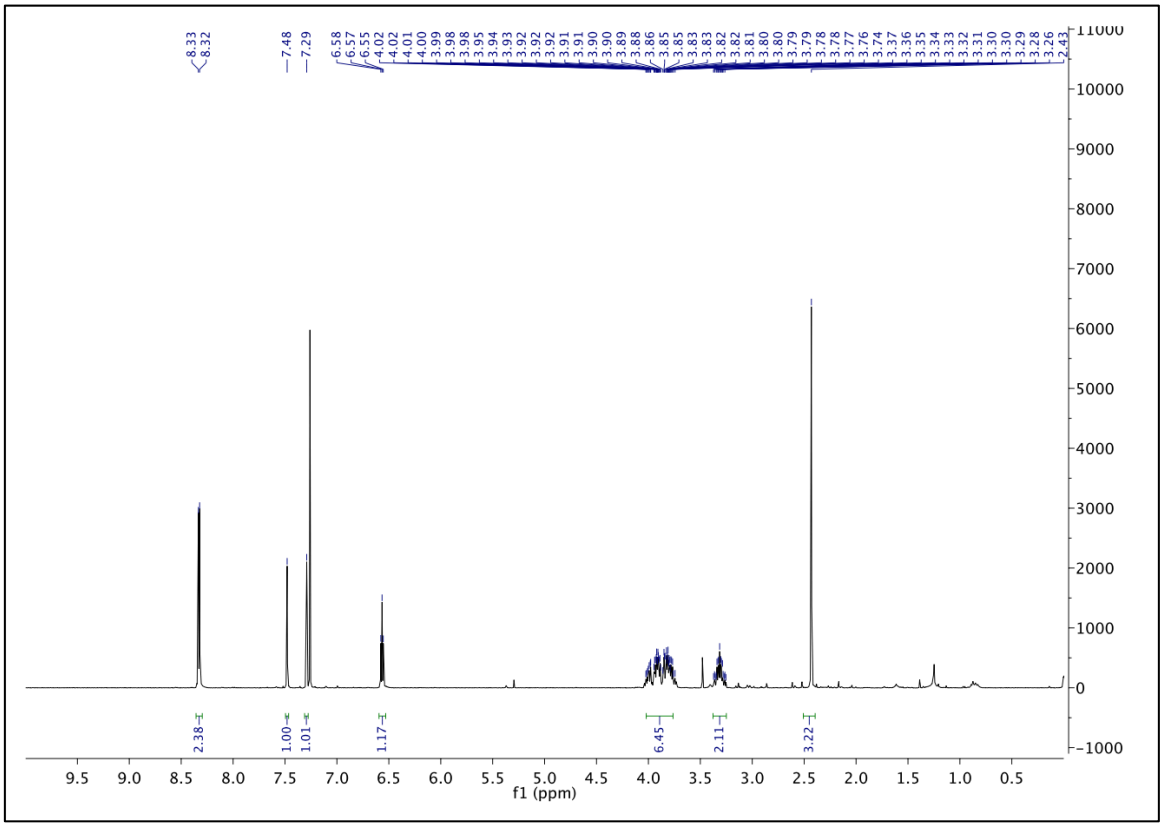
To a solution of αHT carboxylic acid **319** (10 mg, .051 mmol) in THF (1.3 mL, .04M) was added 2,6-lutidine (12 µL, .112 mmol) and HBTU (21.2 mg, .056 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 4-nitro-7-(piperazin-1-yl)benzo[*c*][1,2,5]oxadiazole (20.3 mg, 0.056 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **920** as a red/orange solid (4 mg, 18% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 8.52 (d, J = 9.0 Hz, 1H), 7.47 (s, 1H), 7.29 (s, 1H), 6.60 (d, J = 9.0 Hz, 1H), 4.39 – 4.29 (m, 2H), 4.22 – 4.07 (m, 3H), 4.02 – 3.95 (m, 1H), 3.68 – 3.56 (m, 2H), 2.40 (s, 3H).



2,7-dihydroxy-4-methyl-5-(4-(pyrimidin-2-yl)piperazine-1-carbonyl)cyclohepta-2,4,6-trien-1-one (1016).

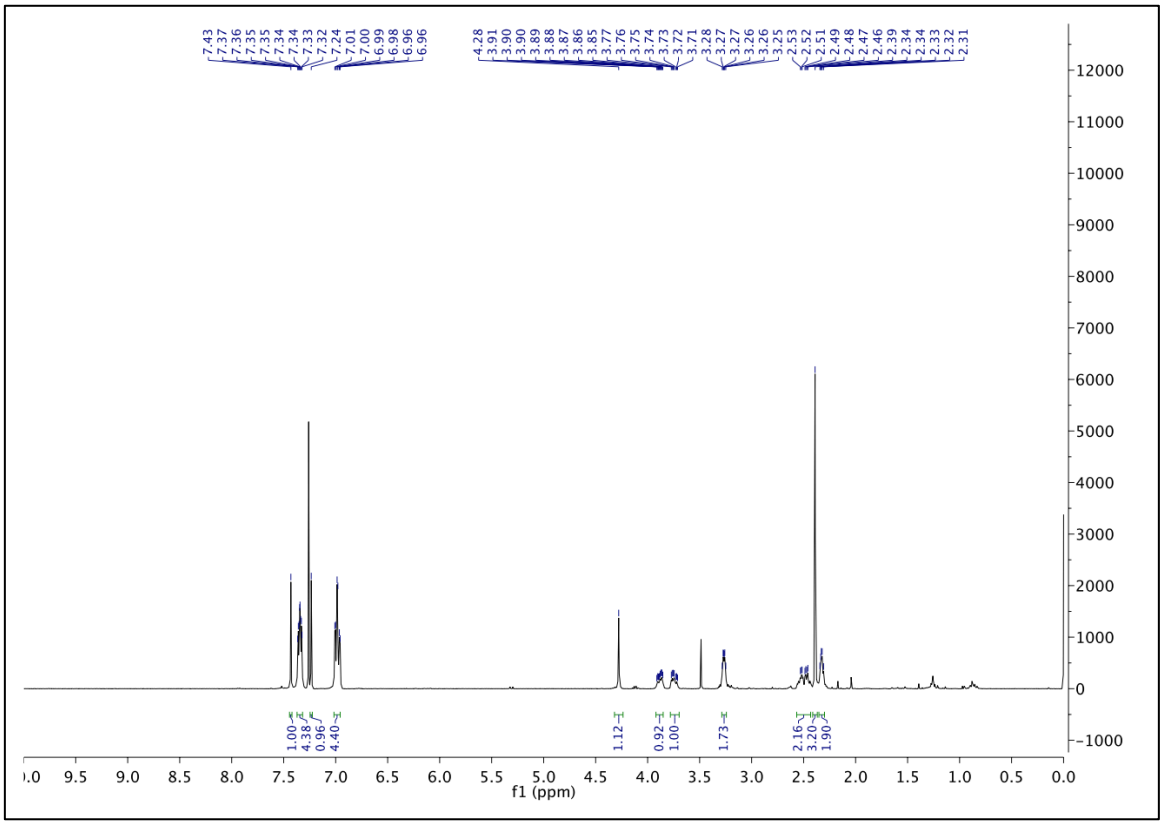
To a solution of αHT carboxylic acid **319** (15.1 mg, .077 mmol) in THF (1.9 mL, .04M) was added 2,6-lutidine (19.6 µL, .169 mmol) and HBTU (31.5 mg, .085 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 2-(piperazin-1-yl)pyrimidine (14.2 µL, 0.100 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **1016** as a yellow oily solid (5.4 mg, 21% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 4.8 Hz, 2H), 7.48 (s, 1H), 7.29 (s, 1H), 6.57 (t, *J* = 4.7 Hz, 1H), 4.02 – 3.76 (m, 6H), 3.38 – 3.25 (m, 2H), 2.43 (s, 3H).



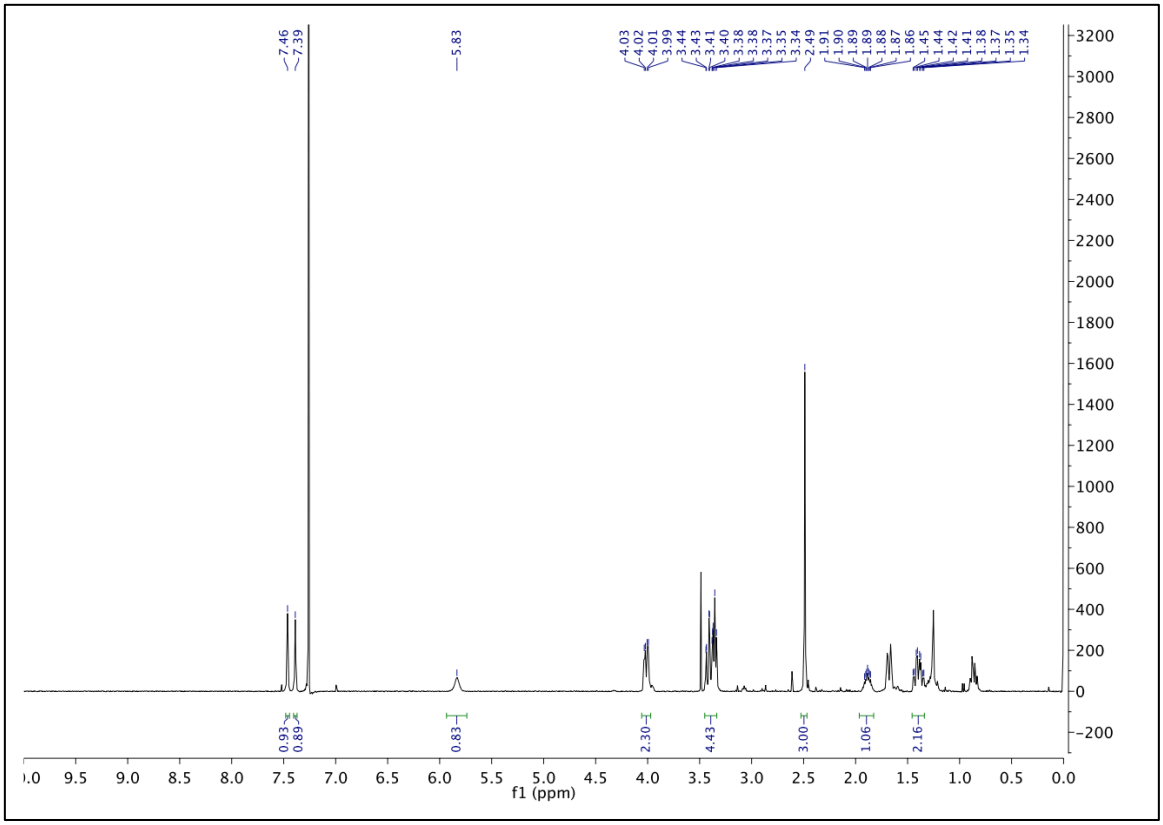
4-(4-(bis(4-fluorophenyl)methyl)piperazine-1-carbonyl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trien-1-one (1017).

To a solution of αHT carboxylic acid **319** (15.8 mg, .081 mmol) in THF (2.0 mL, .04M) was added 2,6-lutidine (20.5 µL, .177 mmol) and HBTU (33.0 mg, .089 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 1-(bis(4-fluorophenyl)methyl)piperazine (30.2 mg, 0.105 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **1017** as a yellow solid (8.4 mg, 22% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43 (s, 1H), 7.34 (ddd, *J* = 8.9, 5.3, 2.4 Hz, 4H), 7.24 (s, 1H), 6.98 (td, *J* = 8.6, 2.9 Hz, 4H), 4.28 (s, 1H), 3.92 – 3.85 (m, 1H), 3.78 – 3.70 (m, 1H), 3.29 – 3.24 (m, 2H), 2.57 – 2.43 (m, 2H), 2.39 (s, 3H), 2.35 – 2.30 (m, 2H).



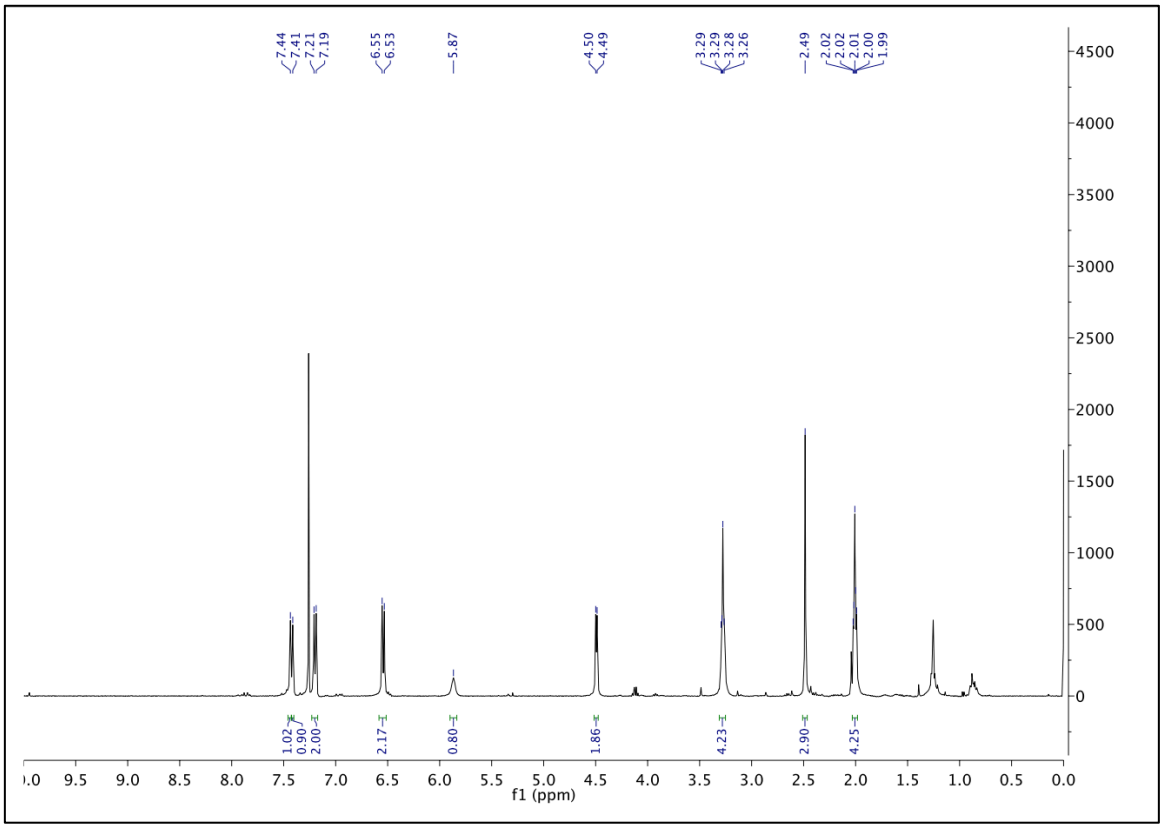
4,6-dihydroxy-2-methyl-5-oxo-*N*-((tetrahydrofuran-3-yl)methyl)cyclohepta-1,3,6-triene-1-carboxamide (1018).

To a solution of αHT carboxylic acid **319** (15.4 mg, .079 mmol) in THF (2.0 mL, .04M) was added 2,6-lutidine (20 µL, .173 mmol) and HBTU (32.8 mg, .086 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. (Tetrahydrofuran-3-yl)methanamine (11.4 µL, .102 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **1018** as a yellow solid (3.7 mg, 17% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 (s, 1H), 7.39 (s, 1H), 5.83 (br s, 1H), 4.01 (dd, *J* = 11.3, 4.8 Hz, 2H), 3.45 – 3.33 (m, 4H), 2.49 (s, 3H), 1.97 – 1.83 (m, 1H), 1.40 (qd, *J* = 12.1, 4.5 Hz, 2H).



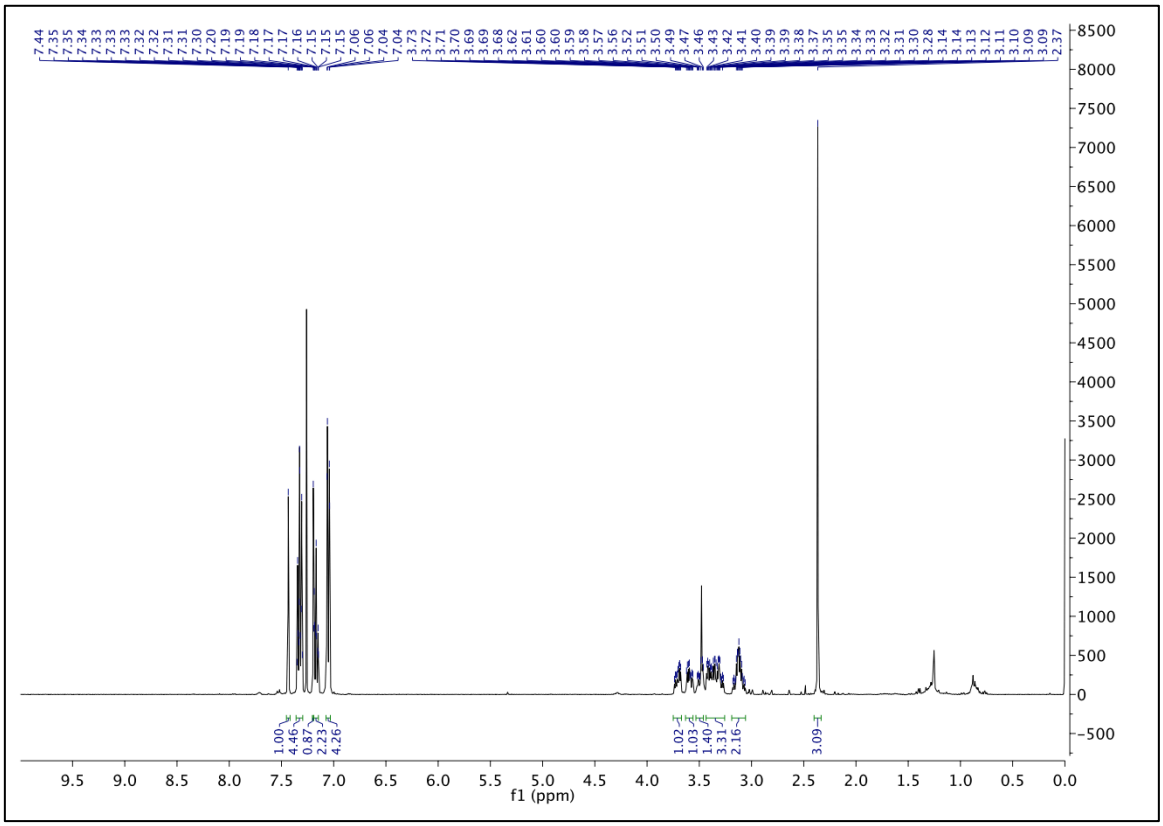
4,6-dihydroxy-2-methyl-5-oxo-*N*-(4-(pyrrolidin-1-yl)benzyl)cyclohepta-1,3,6-triene-1-carboxamide (1019).

To a solution of αHT carboxylic acid **319** (15.7 mg, .080 mmol) in THF (2.0 mL, .04M) was added 2,6-lutidine (20.3 µL, .175 mmol) and HBTU (32.6 mg, .087 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. (4-(pyrrolidin-1-yl)phenyl)methanamine (18.2 mg, .103 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **1019** as a tan solid (2.3 mg, 8% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 (s, 1H), 7.41 (s, 1H), 7.20 (d, J = 8.4 Hz, 2H), 6.54 (d, J = 8.3 Hz, 2H), 5.87 (br s, 1H), 4.49 (d, J = 5.3 Hz, 2H), 3.31 – 3.25 (m, 4H), 2.49 (s, 3H), 2.03 – 1.98 (m, 4H).



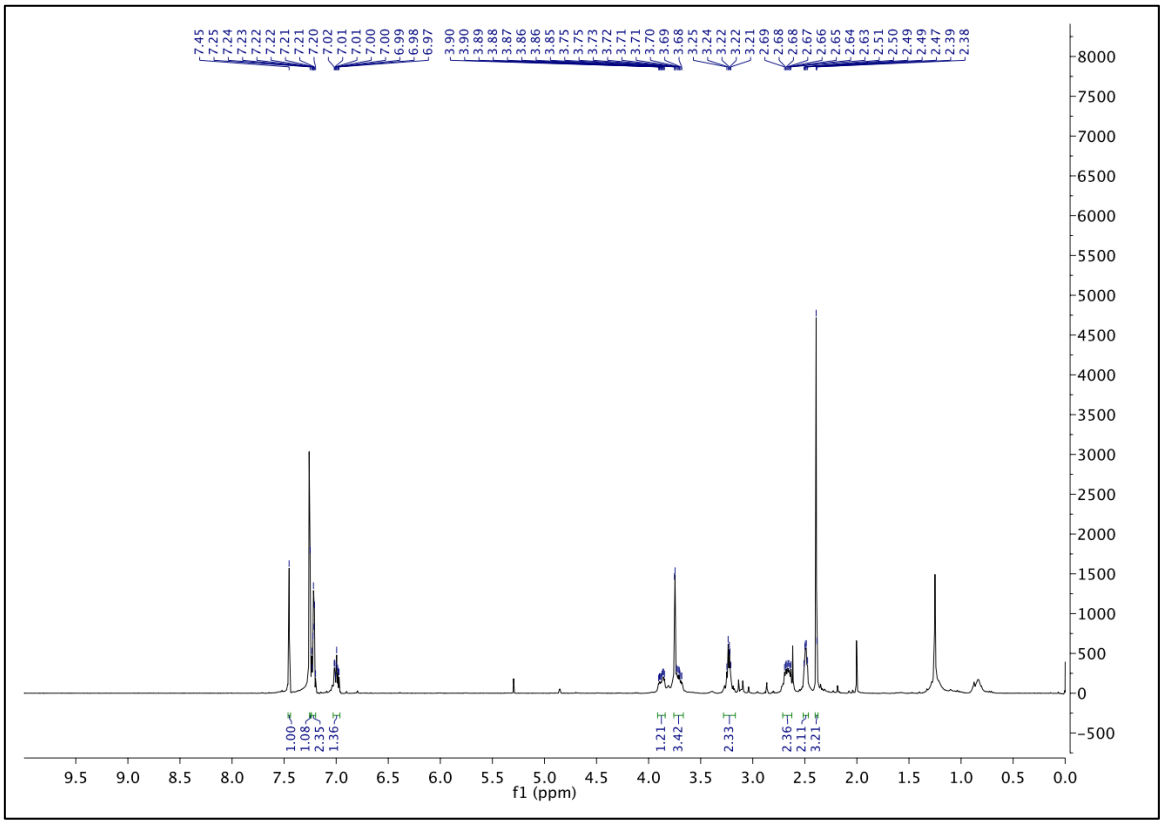
4-(4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carbonyl)-*N*,*N*-diphenylpiperazine-1-carboxamide (1020).

To a solution of αHT carboxylic acid **319** (12.9 mg, .066 mmol) in THF (1.6 mL, .04M) was added 2,6-lutidine (16.8 µL, .145 mmol) and HBTU (27.4 mg, .072 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. *N*,*N*-diphenylpiperazine-1-carboxamide (24.1 mg, 0.085 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **1020** as a brown oil (16.3 mg, 54% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 (s, 1H), 7.36 – 7.30 (m, 4H), 7.20 (s, 1H), 7.19 – 7.15 (m, 2H), 7.05 (dd, *J* = 8.5, 1.2 Hz, 4H), 3.71 (ddd, *J* = 13.3, 6.5, 3.6 Hz, 1H), 3.59 (ddd, *J* = 13.3, 7.3, 3.5 Hz, 1H), 3.53 – 3.46 (m, 1H), 3.44 – 3.26 (m, 3H), 3.19 – 3.06 (m, 2H), 2.37 (s, 3H).



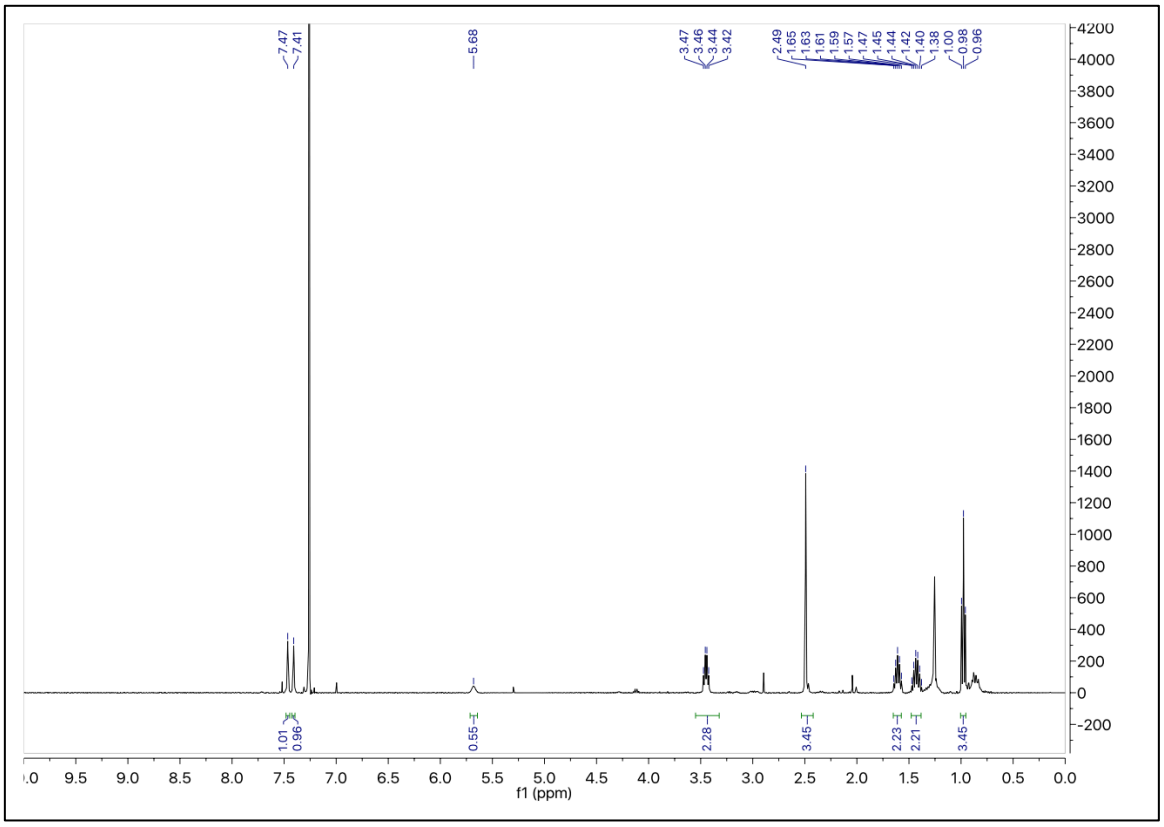
4-(4-(2-chloro-6-fluorobenzyl)piperazine-1-carbonyl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trien-1-one (1021).

To a solution of αHT carboxylic acid **319** (16.4 mg, .084 mmol) in THF (2 mL, .04M) was added 2,6-lutidine (19.7 µL, .184 mmol) and HBTU (34.9 mg, .092 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. 1-(2-chloro-6-fluorobenzyl)piperazine (20.7 µL, 0.109 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 95 °C for 30 min. The reaction mixture was then concentrated *in vacuo*, dissolved in 800 µL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **1021** as a brown oil (8.3 mg, 24% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.45 (s, 1H), 7.25 (s, 1H), 7.24 – 7.20 (m, 2H), 7.03 – 6.96 (m, 1H), 3.88 (ddd, *J* = 13.0, 6.0, 3.4 Hz, 1H), 3.76 – 3.67 (m, 3H), 3.28 – 3.17 (m, 2H), 2.71 – 2.63 (m, 2H), 2.52 – 2.47 (m, 2H), 2.39 (s, 3H).

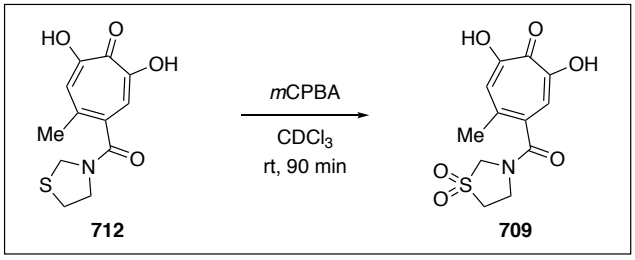


***N*-butyl-4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carboxamide (1039).**

To a solution of αHT carboxylic acid **319** (12 mg, .061 mmol) in DMF (1.5 mL, .04M) was added 2,6-lutidine (15.6 µL, .135 mmol) and HATU (25.6 mg, .067 mmol). The mixture was allowed to stir for 15 min at rt under an atmosphere of Ar gas. Butylamine (13.3 µL, .135 mmol) was then added to the solution, at which point the reaction mixture was subjected to microwave irradiation at 85 °C for 15 min. The reaction mixture was then directly loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 0-35% MeCN in H_2O (30 CV); 35-60% MeCN in H_2O (15 CV); 60-100% MeCN in H_2O (5 CV); 100% MeCN (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **1039** as a brown oil (6.5 mg, 42% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (s, 1H), 7.41 (s, 1H), 5.68 (br s, 1H), 3.45 (q, J = 6.9 Hz, 2H), 2.49 (s, 3H), 1.65 – 1.57 (m, 2H), 1.47 – 1.38 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H).



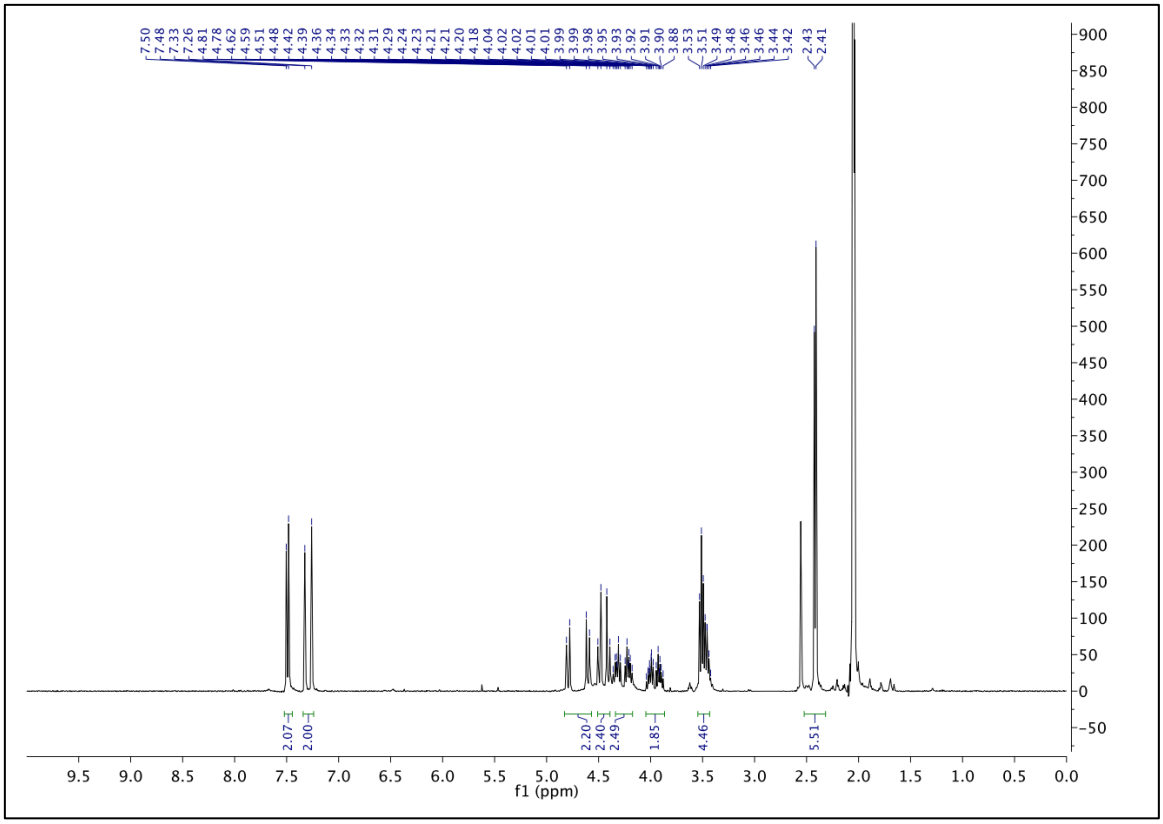
III. Synthesis and characterization of α-hydroxyamidotropolone 709



4-(1,1-dioxidothiazolidine-3-carbonyl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trien-1-one (709).

General Procedure.[3] To a solution of 2,7-dihydroxy-4-methyl-5-(thiazolidine-3-carbonyl)cyclohepta-2,4,6-trien-1-one **712**[4] (11.1 mg, .042 mmol) in $CDCl_3$ (1 mL) was added *meta*-chloroperoxybenzoic acid (70-75% balance 3-chlorobenzoic acid and water, 28.7 mg, .166 mmol). The reaction mixture was allowed to stir for 90 min at rt, at which point the mixture was quenched via the addition of sat. Na_2SO_3 (aq, 15 mL). This mixture was then extracted with CH_2Cl_2 (3 x 10 mL), and the combined organics were concentrated *in vacuo*. They were then redissolved in 1 mL of DMSO, loaded onto a SNAP 12g C_{18} silica gel column, and subjected to reverse-phase column chromatography conditions (Biotage Isolera Prime, solvent gradient: 10-90% MeCN in H_2O (15 CV); 90-100% MeCN in H_2O (5 CV); MeCN and H_2O each contained 0.05% TFA). Product fractions were concentrated *in vacuo* to remove MeCN, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **709** as a yellow solid (2.9 mg, 23% yield). **^{1}H NMR (400 MHz, Acetone-d_6)** δ 7.52 – 7.45 (m, 2H), 7.34 – 7.24 (m, 2H), 4.69 (ABq, J_{AB} = 12.3 Hz, 2H), 4.45 (ABq, J_{AB} = 11.9 Hz, 2H), 4.35 – 4.17 (m, 2H), 4.05 – 3.87 (m, 2H), 3.55 – 3.43 (m, 4H), 2.52 – 2.32 (m, 6H).[5]

[3]Agyemang, N. B.; Kukla, C. R.; Edwards, T. C.; Li, Q.; Langen, M. K.; Schaal, A.; Franson, A. D.; Casals, A. G.; Donald, K. A.; Yu, A. J.; Donlin, M. J.; Morrison, L. A.; Tavis, J. E.; Murelli, R. P. *RSC Adv.*, 2019, **9**, 34227–34234.
[4]Hirsch, D. R.; Metrano, A. J.; Stone, E. A.; Storch, G.; Miller, S. J.; Murelli R. P. *Org. Lett.*, 2019, **21**, 2412–2415.
[5]Complex splitting arises from the molecule's atropdiastereotopicity. This is due to hindered rotation about the Ar-C(O) bond combined with the presence of inequivalent E and Z amide rotamers. A more thorough discussion on a similar phenomenon observed with starting material **712** can be found in reference 4.


7.50
7.48
7.33
7.26
4.81
4.78
4.62
4.59
4.51
4.48
4.42
4.39
4.36
4.34
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4.32
4.31
4.29
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4.23
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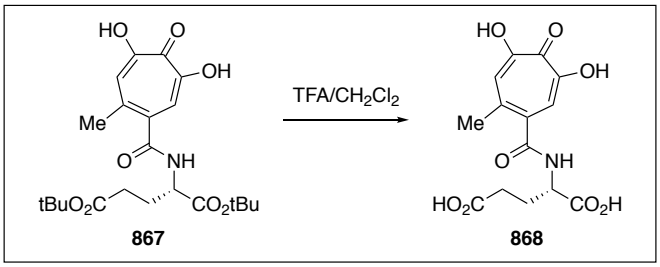
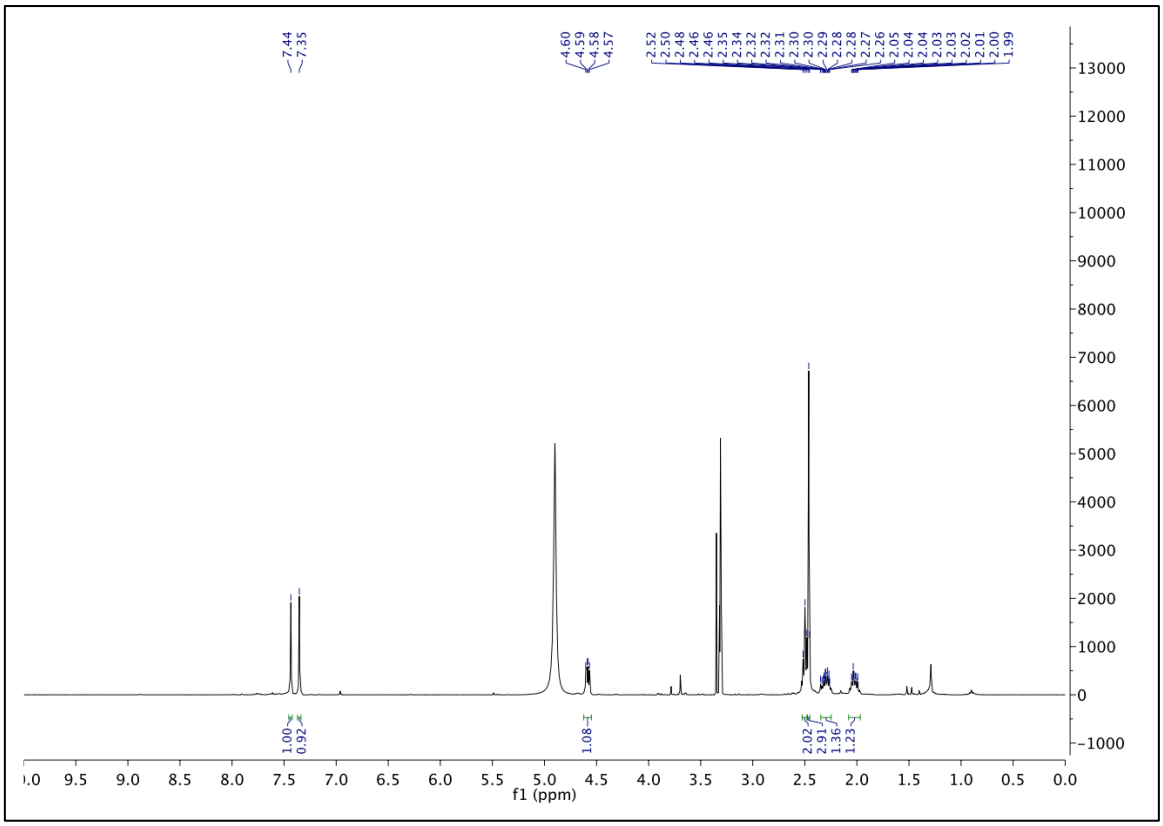
2.43
2.41
2.07
2.00
2.20
2.40
2.49
1.85
4.46
5.51
f1 (ppm)

IV. Synthesis and characterization of α-hydroxyamidotropolone 868

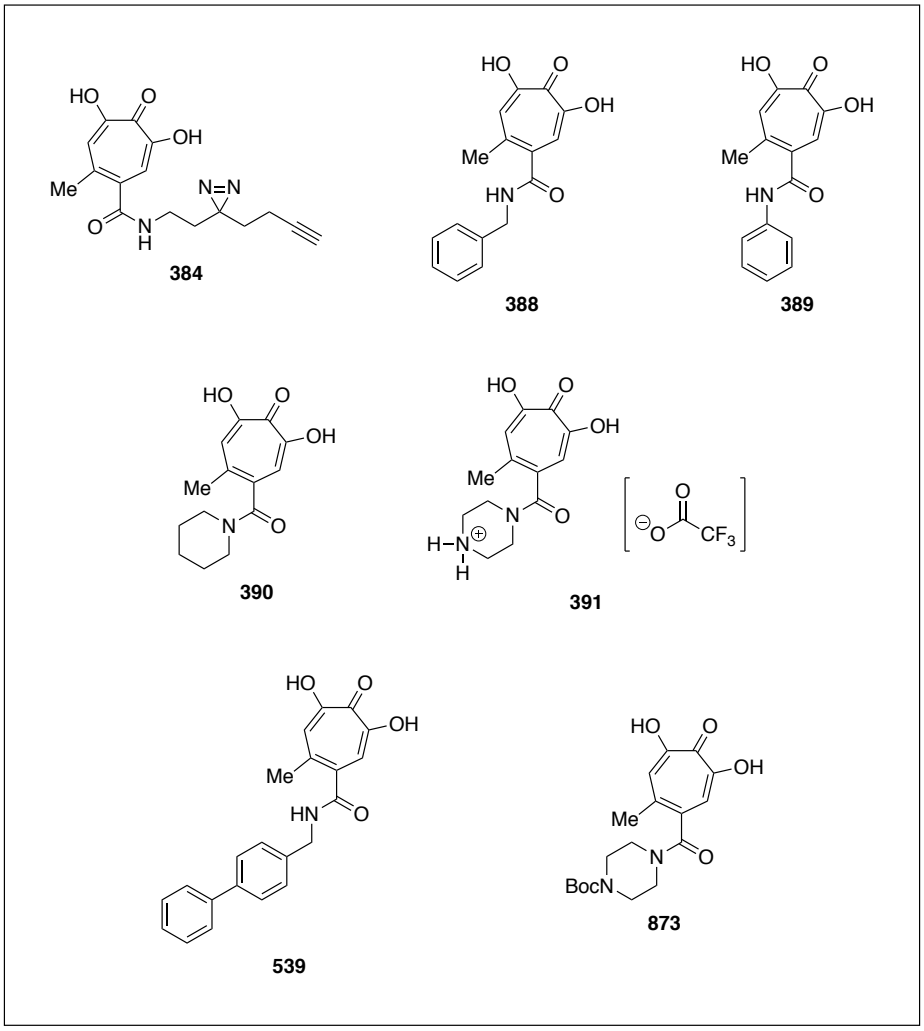


(4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carbonyl)-*L*-glutamic acid (868).

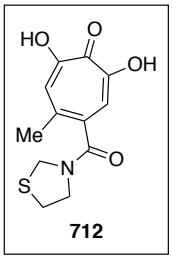
General Procedure. A solution of di-*tert*-butyl (4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-triene-1-carbonyl)-*L*-glutamate **867** (20.5 mg, .047 mmol) and 50% trifluoroacetic acid in CH_2Cl_2 (500 µL) was subjected to microwave irradiation at 70 °C for 4 min. The organic layer was concentrated *in vacuo* and then subjected to azeotropic removal with $CHCl_3$ (5 × 2 mL) to yield **868** as a yellow oil (9.1 mg, 60% yield). **^{1}H NMR (400 MHz, Methanol-d_4)** δ 7.44 (s, 1H), 7.35 (s, 1H), 4.59 (dd, J = 9.5, 4.9 Hz, 1H), 2.50 (t, J = 7.3 Hz, 2H), 2.46 (s, 3H), 2.35 – 2.25 (m, 1H), 2.08 – 1.97 (m, 1H).



V. Previously characterized α-hydroxyamidotropolones



General Information. α-Hydroxyamidotropolones **384**, **388**, **389**, **390**, **391**, **539**, and **873** have been previously synthesized and characterized in reference 1 (Berkowitz, et al., *Tetrahedron Lett.*, 2018, **59**, 3026).



α-Hydroxyamidotropolone **712** has been previously synthesized and characterized in reference 4 (Hirsch, et al., *Org. Lett.*, 2019, **21**, 2412).