Supporting Information

Hantzsch Synthesis of Pyrazolo[1',2':1,2]pyrazolo[3,4-*b*]pyridines: Partial Agonists of the Calcitonin Receptor

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General. All yields are unoptimized. Proton NMR spectra were recorded at 400 MHz and coupling constants are reported in Hz. Chemical shifts are reported in ppm relative to the residual protonated solvent resonance at 7.24 ppm (deuteriochloroform) or 2.49 ppm (dimethylsulfoxide-d_6). Electrospray (ES) mass spectral data (ms) are reported in the form m/z (molecular ion, relative intensity).

Method for human calcitonin receptor reporter cell system. Human calcitonin receptor (hCT2R) was cloned[14] as a HindIII fragment into plasmid 15 BS SKII. Chinese hamster ovary cells were co-transfected with a 6CRE-luciferase reporter system and hCTR2. Cells were cultured at 37°C in an atmosphere of 5% CO_2 in commercially available media supplemented with 2 mM L-glutamine and 5% fetal bovine serum (FBS). Structure activity studies with compounds were performed on CHO-6CRE-luciferase cells with or without co-transfected hCT2R. Cells were removed from culture flasks with trypsin 48 h hours before each assay and plated in 96-well microtiter plates at 100,000 cells/well. Media containing FBS was removed 16 h before each assay and replaced with media lacking FBS. Compounds were added and incubated for 4 h at 37° C. After incubation, media was aspirated and 50 microliters of LucLite (Perkin Elmer, Inc.) in PBS (1:1) containing 1 mM $CaCl_2$ and lmM $MgCl_2$ were added to each well. Plates were sealed and incubated for 20 minutes in the dark before quantification of luminescence on a Packard TopCount. Concentration-response curves were calculated and plotted as a percentage of the maximal human calcitonin response. Potencies were reported as the concentration of compounds producing half-maximal responses (EC_{50}).

General Procedure for Synthesis of β-Keto Esters 7a-b from Hydrocinnamic Acids 5a-b. A solution of **5** (60 mmol), Meldrum's acid (60 mmol), DMAP (60 mmol)

and DCC (60 mmol) in CH_2Cl_2 (150 mL) was stirred at rt overnight. Precipitated DCU was removed by filtration and the filtrate was concentrated at reduced pressure. All remaining material was reconstituted in EtOAc, and additional DCU was collected by filtration. The final filtrate was washed with 1N HCl and brine, dried, filtered and concentrated to yield **6** as an oil which solidified on standing. This material was dissolved in ethanol (150 mL) and the solution was heated at reflux for 3 h. Concentration *in vacuo* afforded **7** as an oil. This material was used without further purification.

Ethyl 5-(4-fluorophenyl)-3-oxopentanoate (7a). This compound was prepared from **5a** (pale yellow oil, 54% yield): ^{1}H NMR ($CDCl_3$): δ7.15 (dd, 2H, J = 8, 6), 6.95 (t, 2H, J = 8), 4.17 (q, 2H, J = 7), 4.42 (s, 2H), 2.88 (m, 4H), 1.26 (t, 3H, J = 7).

Ethyl 3-oxo-5-(4-trifluoromethylphenyl)pentanoate (7b). This compound was prepared from **5b** (pale yellow oil, 99% yield): ^{1}H NMR ($CDCl_3$): δ7.52 (d, 2H, J = 8), 7.29 (d, 2H, J = 8), 4.15 (m, 2H), 3.42 (s, 2H), 2.96 (m, 2H), 2.90 (m, 2H), 1.24 (t, 3H, J = 7).

General Procedure for Synthesis of Knoevenagel Adducts 9a-c from β-Keto Esters 7a-b. A mixture of **7** (14 mmol), **8** (14 mmol) and piperidine (0.25 mL, 2.6 mmol) in benzene (60 mL) was heated at reflux overnight under Dean-Stark conditions. The mixture was concentrated and the resulting solid was triturated with EtOAc/hexanes to afford **9** as a mixture of *E* and *Z* isomers. This material was used without further purification.

5-[(1*E*/1*Z*)-2-[(Ethoxy)carbonyl]-5-(4-fluorophenyl)-3-oxo-1-penten-1-yl] thiophene-2-carboxylic acid (9a). This compound was prepared from **7a** and **8a** as a *ca.*

3:2 ratio of isomers (off-white solid, 34% yield): ^{1}H NMR ($CDCl_3$): δ 7.78 (d, 1H, J = 4), 7.71 (d, 1H, J = 4, minor isomer), 7.68 (s, 1H, minor isomer), 7.62 (s, 1H), 7.33 (d, 1H, J = 4), 7.14 (m, 5H), 6.96 (m, 4H), 4.43 (q, 2H, J = 7), 4.26 (q, 2H, J = 7, minor isomer), 3.03-2.93 (m, 8H), 1.36 (t, 3H, J = 7), 1.28 (t, 3H, J = 7, minor isomer).

5-[(1*E*/1*Z*)-2-[(Ethoxy)carbonyl]-5-(4-fluorophenyl)-3-oxo-1-penten-1-yl] furan-2-carboxylic acid (9b). This compound was prepared from **7a** and **8b** as a *ca.* 4:1 ratio of isomers (beige solid, 51% yield): ^{1}H NMR ($CDCl_3$): δ 7.37 (s, 1H), 7.30 (s, 1H, minor isomer), 7.24 (m, 2H), 6.93 (m, 2H), 6.83 (s, 1H, minor isomer), 6.67 (s, 1H), 4.44 (q, 2H, J = 7, minor isomer), 4.25 (q, 2H, J = 7), 3.07 (s, 4H), 2.96 (s, 4H, minor isomer), 1.32 (t, 3H, J = 7, minor isomer), 1.27 (t, 3H, J = 7).

4-[(1*E*/1*Z*)-2-[(Ethoxy)carbonyl]-5-(4-fluorophenyl)-3-oxo-1-penten-1-yl]benzoic acid (9c). This compound was prepared from **7a** and **8c** as a *ca.* 1:1 mixture of isomers (yellow solid, 25% yield): ^{1}H NMR ($CDCl_3$): δ 8.10 (d, 2H, J = 8), 7.98 (d, 2H, J = 8), 7.70 (s, 1H), 7.60 (s, 1H), 7.50 (d, 2H, J = 8), 7.32 (d, 2H, J = 8), 7.17 (dd, 2H, J = 8, 6), 7.07 (dd, 2H, J = 8, 6), 6.97 (t, 2H, J ~ 9), 6.91 (t, 2H, J ~ 9), 4.29 (q, 2H, J = 7), 4.27 (q, 2H, J = 7), 3.03 (m, 2H), 2.98 (m, 2H), 2.91 (m, 2H), 2.84 (m, 2H), 1.29 (t, 3H, J = 7), 1.23 (t, 3H, J = 7).

5-{3-[(Ethoxy)carbonyl]-2-[2-(4-fluorophenyl)ethyl]-5-oxo-1,5,8,9-tetrahydro-4*H*,7*H*-pyrazolo[1',2':1,2]pyrazolo[3,4-*b*]pyridin-4-yl}furan-2-carboxylic acid (10b). This compound was prepared from **9b** (64% yield): ^{1}H NMR (d_6-DMSO) δ 12.72 (br s, 1H), 9.81 (s, 1H), 7.24 (dd, 2H, J = 9, 6), 7.08 (t, 2H, J = 9), 7.03 (d, 1H, J = 3.4), 6.10 (d, 1H, J = 3.4), 4.86 (s, 1H), 3.96 (m, 2H), 3.44 (2H, m), 3.18-3.40 (m, 2H),

2.93 (m, 2H), 2.78 (t, 2H, *J* = 8), 2.28 (m, 2H, *J* = 7), 1.06 (t, 3H, *J* = 7); ES^+ MS: 370 (100), 482 ($M + H^+$, 80).

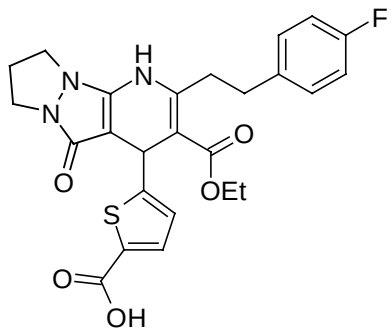
4-{3-[(Ethoxy)carbonyl]-2-[2-(4-fluorophenyl)ethyl]-5-oxo-1,5,8,9-tetrahydro-4*H*,7*H*-pyrazolo[1',2':1,2]pyrazolo[3,4-*b*]pyridin-4-yl}benzoic acid (10c). This compound was prepared from **9c** (41% yield): ^{1}H NMR (d_6-DMSO) δ 9.76 (s, 1H), 7.77 (d, 2H, *J* = 8), 7.27 (dd, 2H, *J* = 8, 6), 7.20 (d, 2H, *J* = 8), 7.11 (t, 2H, *J* = 9), 4.76 (s, 1H), 3.87 (q, 2H, *J* = 7), 3.43 (m, 2H), 3.27 (m, 2H), 2.96 (m, 2H), 2.85 (m, 2H), 2.26 (m, 2H), 0.96 (t, 3H, *J* = 7); ES^+ MS: 492 ($M + H^+$, 100).

5-{3-[(Ethoxy)carbonyl]-2-[2-(4-fluorophenyl)ethyl]-5-oxo-8,9-dihydro-5*H*,7*H*-pyrazolo[1',2':1,2]pyrazolo[3,4-*b*]pyridin-4-yl}furan-2-carboxylic acid data (11b). This compound was prepared from **10b** (56% yield): ^{1}H NMR (d_6-DMSO) δ 13.36 (br s, 1H), 8.14 (d, 1H, *J* = 3.7), 7.37 (d, 1H, *J* = 3.7), 7.21 (m, 2H), 7.06 (t, 2H, *J* = 9), 4.29 (q, 2H, *J* = 7), 3.87 (t, 2H, *J* = 6.5), 3.86 (t, 2H, *J* = 6.5), 2.99 (m, 4H), 2.56 (m, 2H, *J* = 7), 1.10 (t, 3H, *J* = 7).

4-{3-[(Ethoxy)carbonyl]-2-[2-(4-fluorophenyl)ethyl]-5-oxo-8,9-dihydro-5*H*,7*H*-pyrazolo[1',2':1,2]pyrazolo[3,4-*b*]pyridin-4-yl}benzoic acid (11c). This compound was prepared from **10c** (77% yield): ^{1}H NMR (d_6-DMSO) δ 13.10 (br s, 1H), 7.95 (d, 2H, *J* = 8), 7.41 (d, 2H, *J* = 8), 7.22 (dd, 2H, *J* = 8, 6), 7.07 (t, 2H, *J* = 9), 3.87 (m, 4H), 3.77 (t, 2H, *J* = 7), 3.06 (m, 2H), 2.99 (m, 2H), 2.54 (m, 2H), 0.75 (t, 3H, *J* = 7).

4-(3-[(Ethoxy)carbonyl]-5-oxo-2-{2-[4-(trifluoromethyl)phenyl]ethyl}-8,9-dihydro-5*H*,7*H*-pyrazolo[1',2':1,2]pyrazolo[3,4-*b*]pyridin-4-yl)benzoic acid (11d). This compound was prepared from **10d** (77% yield): ^{1}H NMR (d_6-DMSO) δ 13.05 (br s,

1H), 7.94 (d, 2H, *J* = 8), 7.61 (d, 2H, *J* = 8), 7.42 (d, 2H, *J* = 8), 7.40 (t, 2H, *J* = 8), 3.87 (m, 4H), 3.77 (t, 2H, *J* = 7), 3.11 (s, 4H), 2.53 (m, 2H, *J* = 7), 0.73 (t, 3H, *J* = 7).



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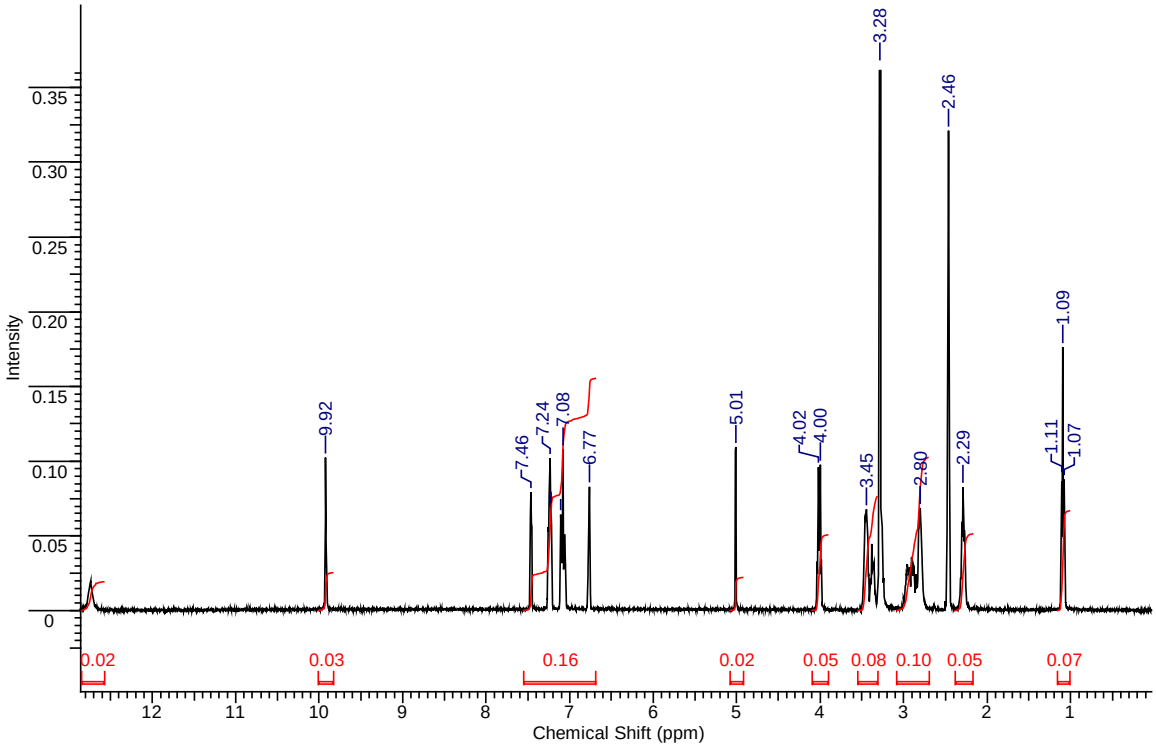

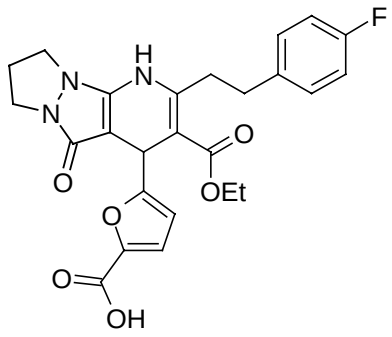

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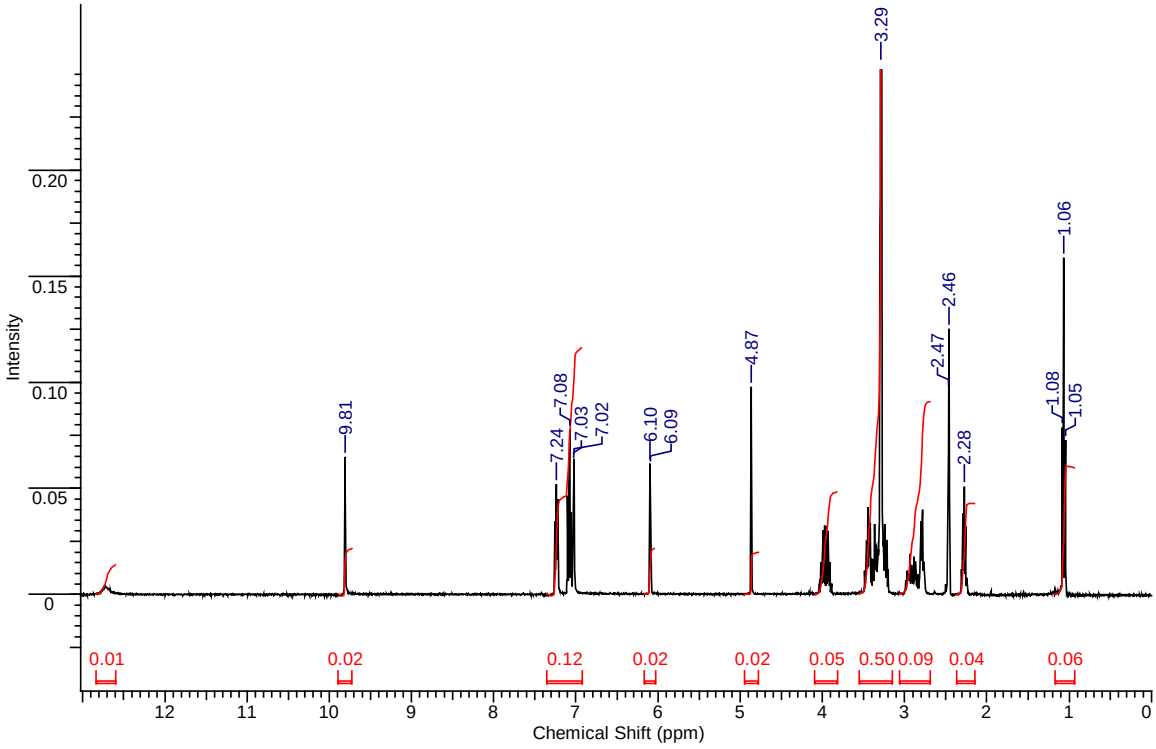

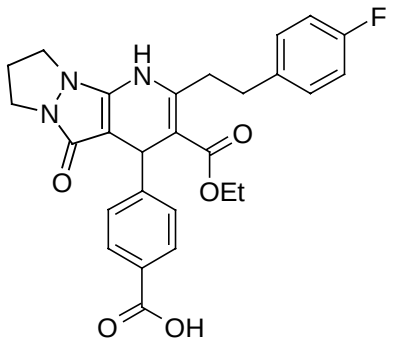

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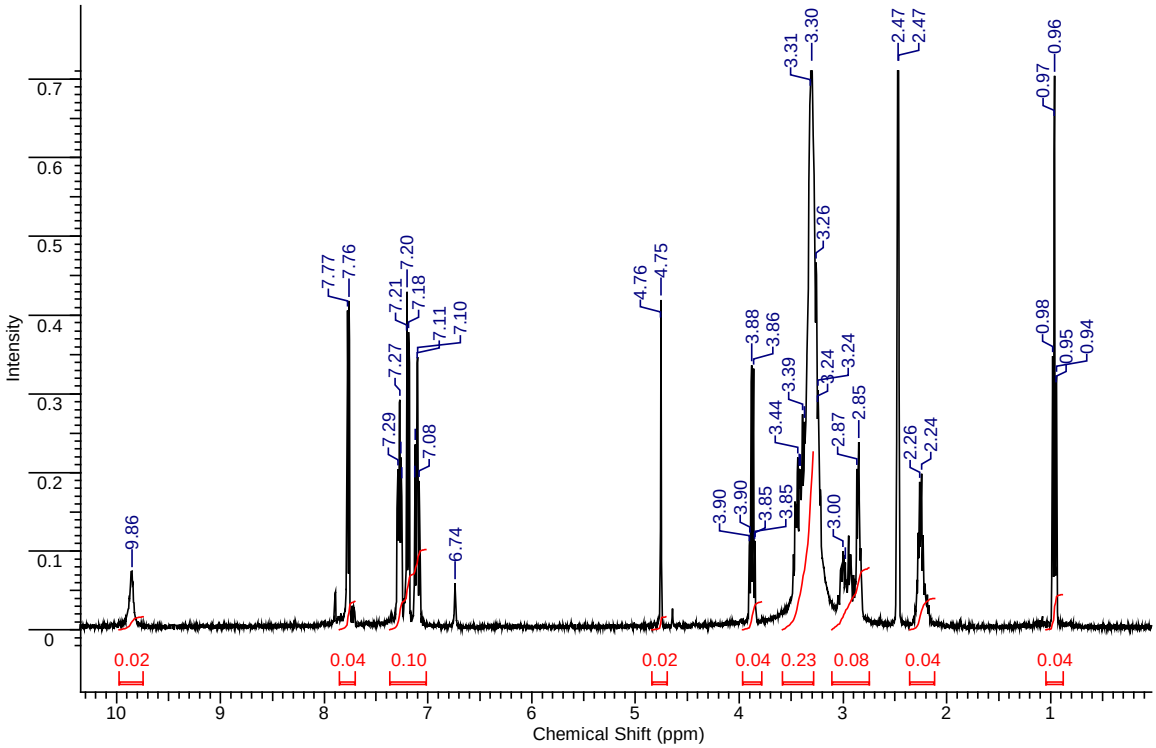

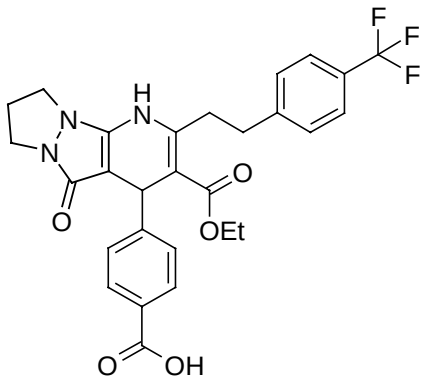

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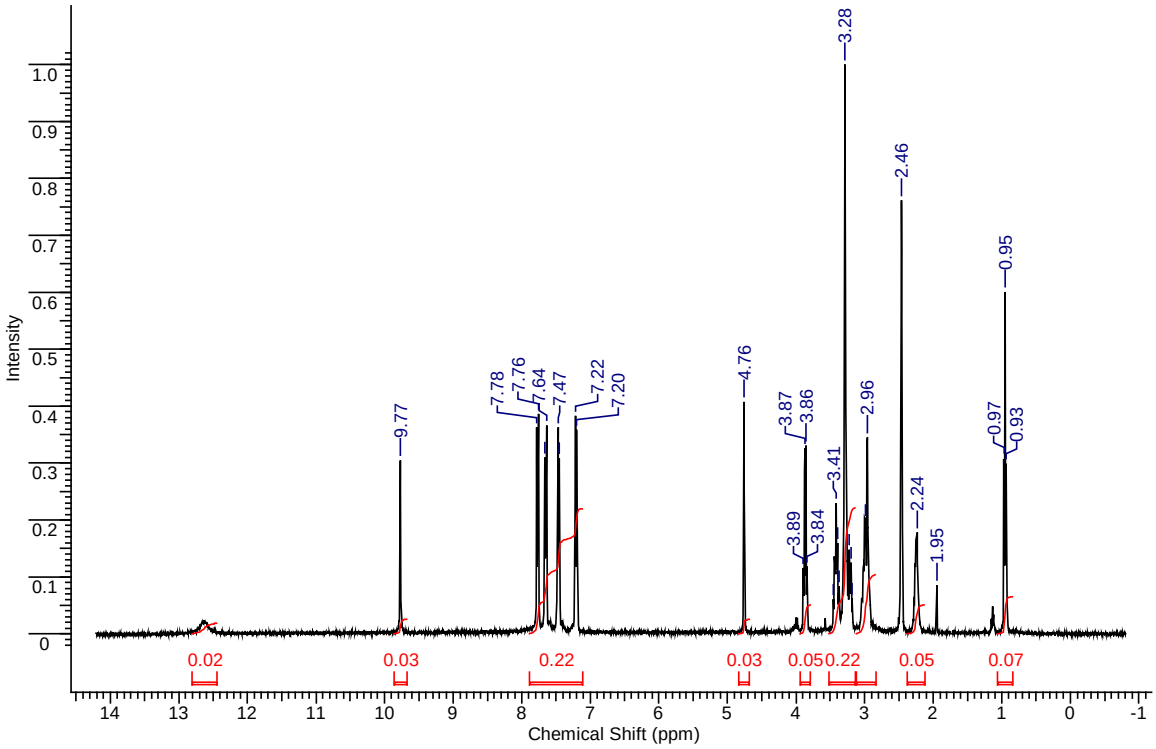

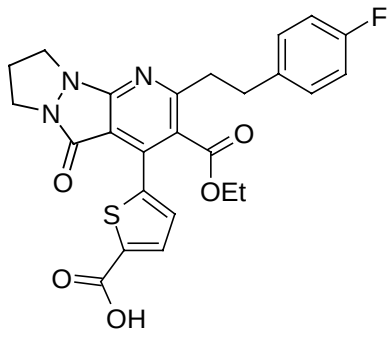

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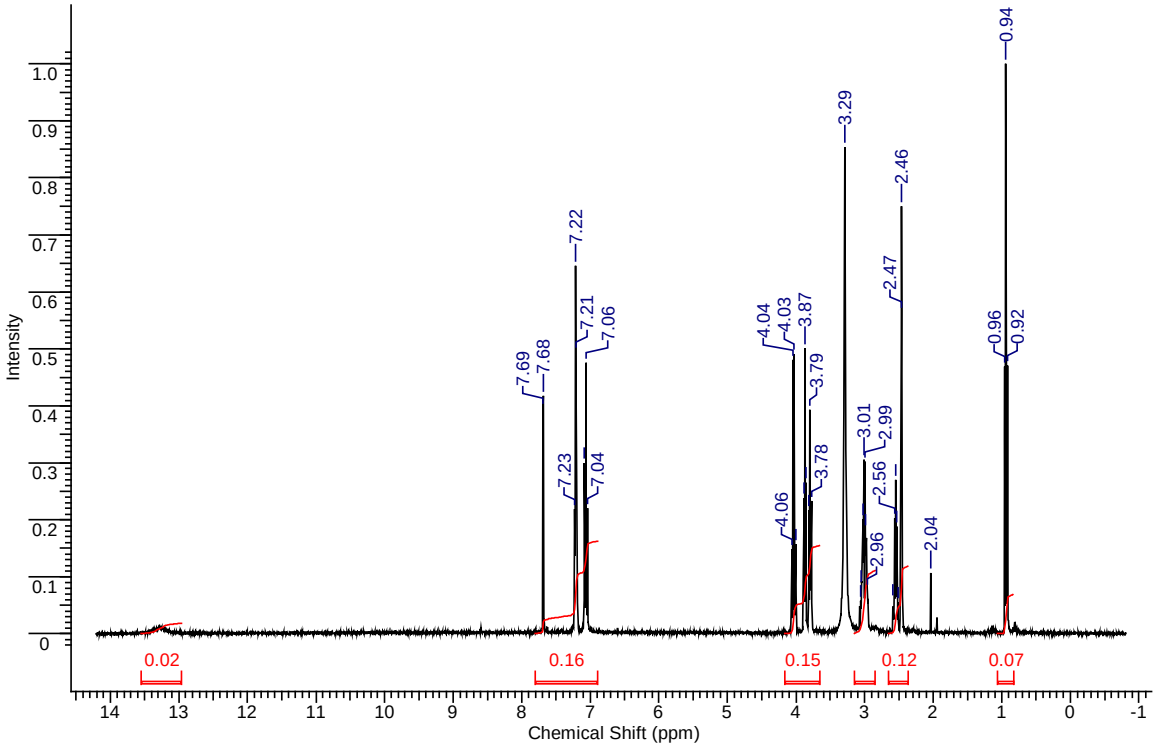

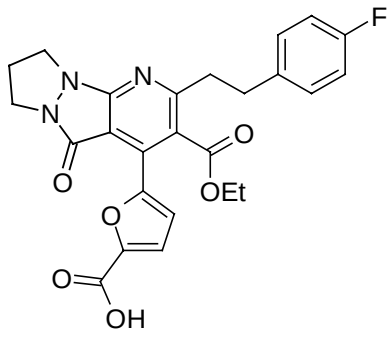

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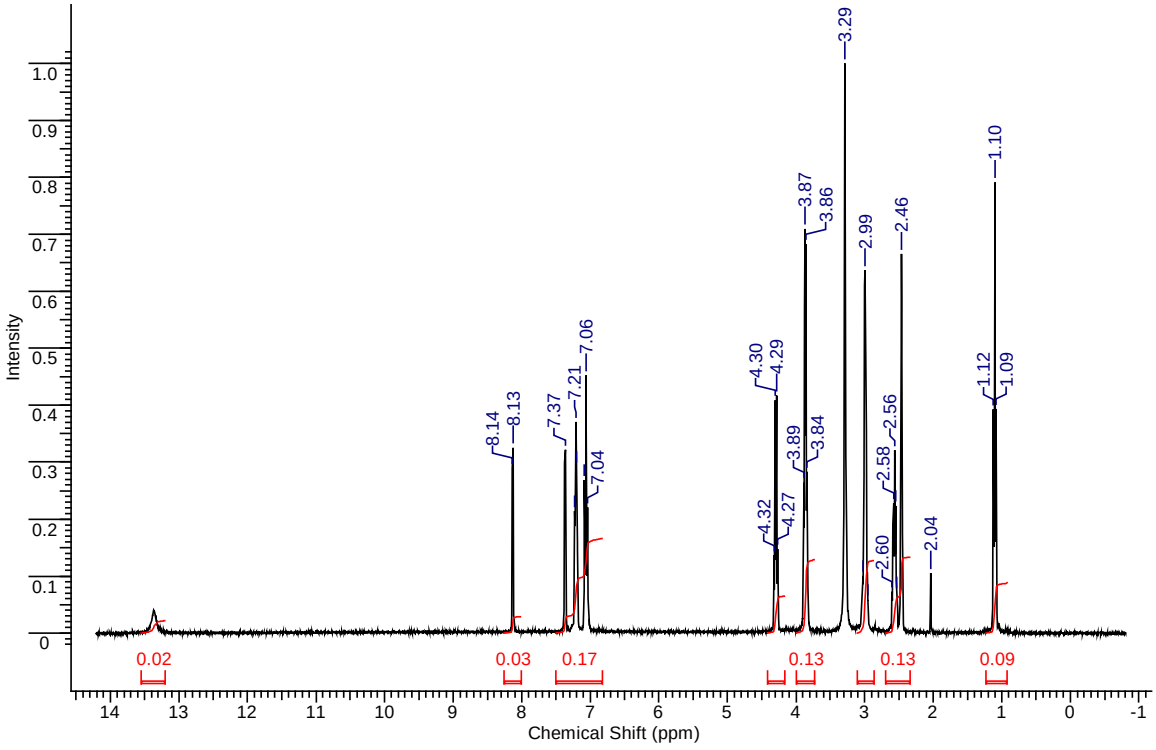

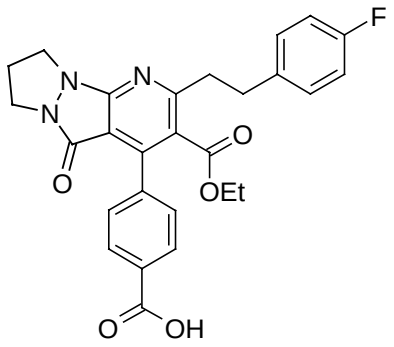

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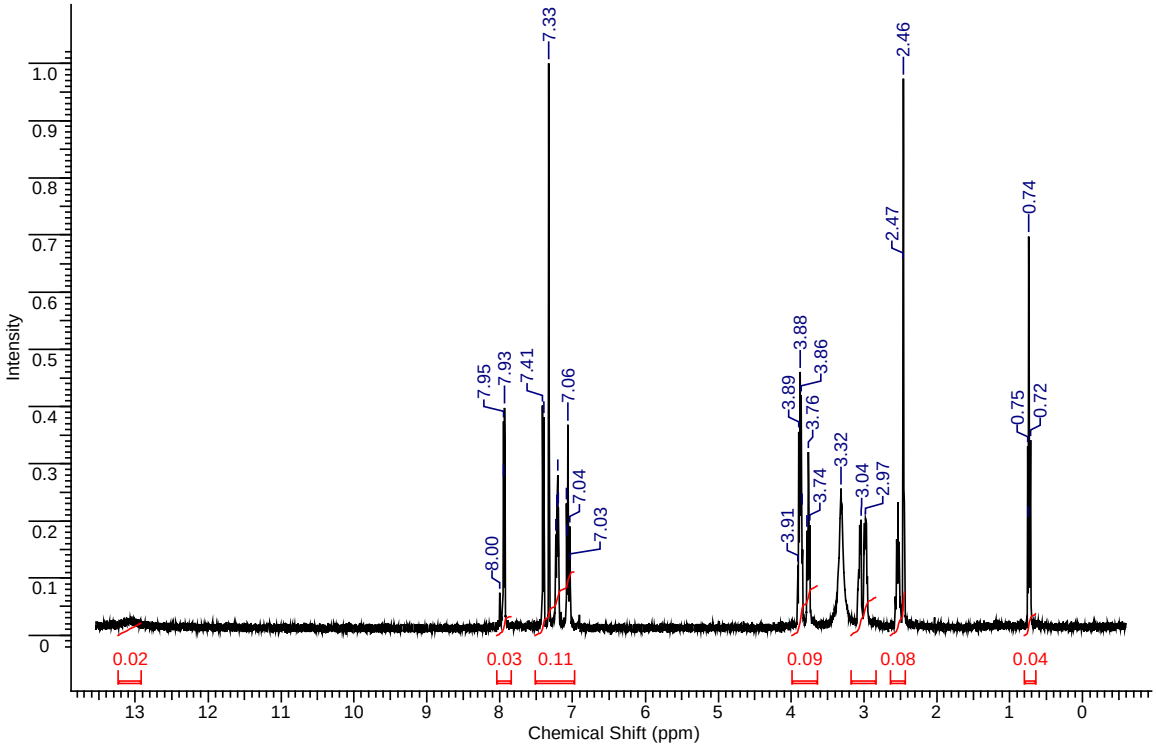

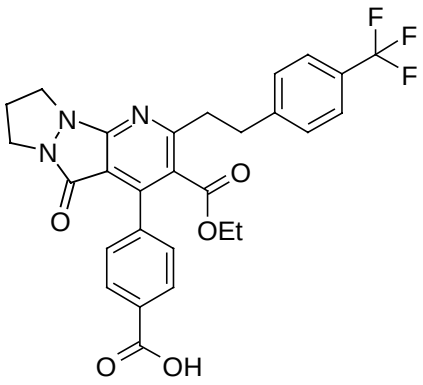

11d (crude) d_6-DMSO (400 MHz)