

SUPPLEMENTARY MATERIAL

Hari, A.; Miller, B. L.

Rapid and Efficient Synthesis of 2-Amino-4*H* Benzothiazines

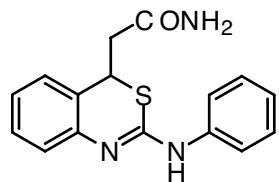
Representative experimental procedure:

4,5-dimethoxy 2-nitrocinnamate was loaded onto 50 mg of Wang resin (Advanced Chemtech, 1.2 mmol/g) and reduced using catalytic CrCl_2 in the presence of Mn metal and TMSCl as reported previously. After separation of the resin from Mn and transfer to a second reaction vessel (Bio-Rad Bio-Spin 1.5 ml polyethylene chromatography column fitted with a porous polymer frit), it was treated with 1.0 ml 50% aqueous DMF for 12 hours at room temperature. The aqueous DMF solution was then removed, and the resin washed with DMF and CH_2Cl_2 . After drying the resin thoroughly on an aspirator, 29 μl (0.24 mmol, 4 equivalents) phenyl isothiocyanate (Aldrich) was then shaken with the resin in 1.0 ml DMF for 12 hours. The resin was then thoroughly washed with DMF, CH_3OH , and CH_2Cl_2 . Cyclization and product release was accomplished by treatment of the resin with 1.0 ml 50% trifluoroacetic acid in CH_2Cl_2 for 30 minutes. This solution was drained off, and the resin washed with 1 ml CH_2Cl_2 . The CH_2Cl_2 solutions were combined, and solvent removed *in vacuo*. Purification of the crude sample by preparative reverse-phase HPLC (C18 column, 10-100% 0.1% TFA/ CH_3CN in 0.1% TFA/ H_2O) provided the desired benzothiazine essentially pure as a white solid (14 mg, 65%).

Spectral data for selected compounds:

NMR spectra were recorded on Bruker AMX-400 or Avance-400 instruments operating at a field strength of 400 MHz for ^1H and 100 MHz for ^{13}C . Infrared spectra were recorded on a Perkin-Elmer model 1600 FTIR as thin films. High resolution mass spectra were obtained by the mass spectral facility at the University of California, Riverside, using a VG-7070 instrument with electron impact ionization.

1) 2-Anilino-4H-benzothiazineacetamide:



^1H NMR (400MHz, CDCl₃+ CD₃OD):

δ (ppm) 7.35 (m, 4H); 7.22 (m, 5H); 4.68 (dd, J = 6.8, 2 Hz, 1H); 2.64 (m, 2H).

^{13}C NMR (100MHz, CD₃OD):

δ (ppm) 171.9, 135.6, 134.8, 129.6, 129.1, 127.1, 126.6, 124.6, 123.3, 119.8, 41.3, 39.9.

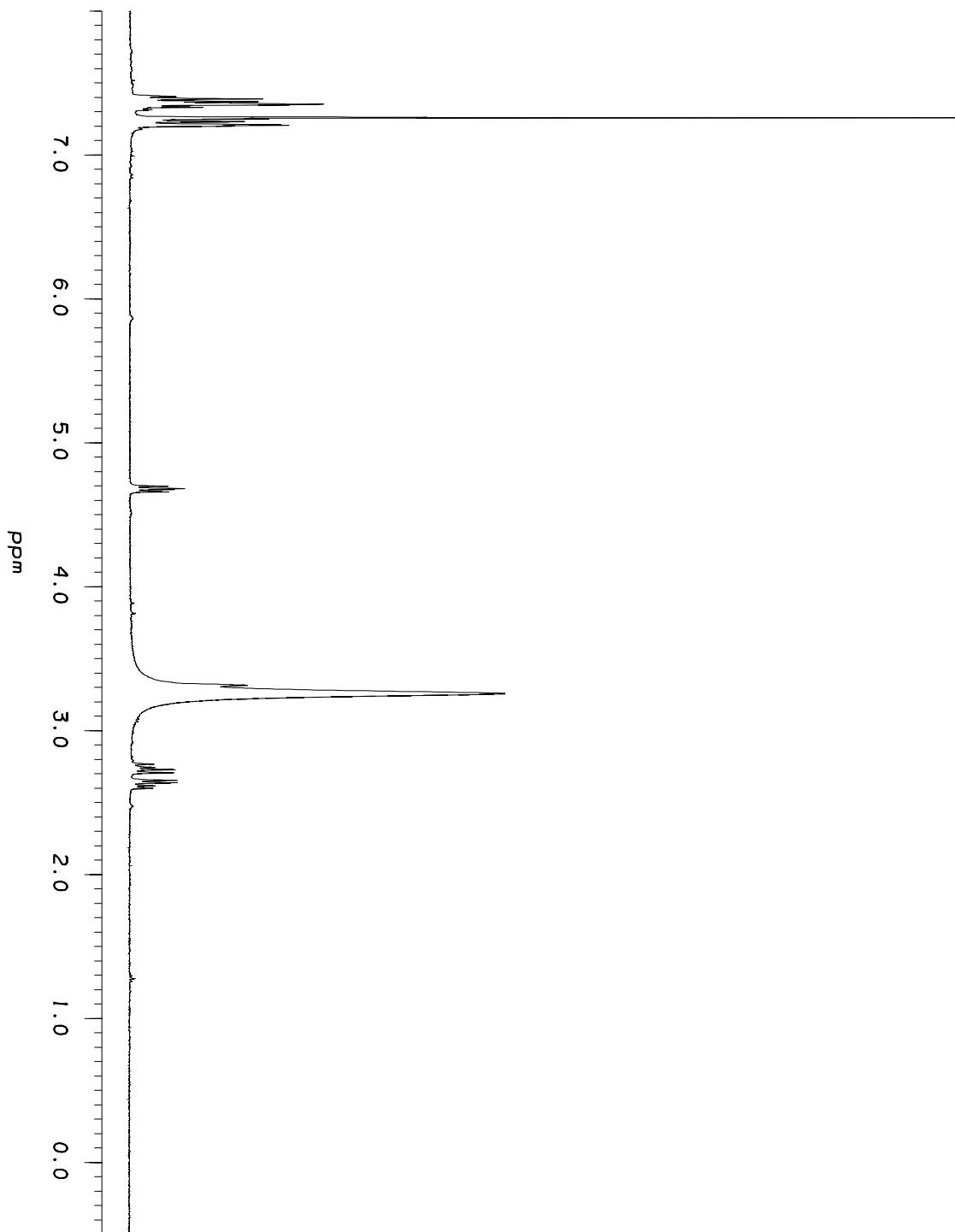
FTIR (thin film):

3193, 1667, 1576, 1495, 1409, 1200, 1137, 832, 798, 761, 722 cm⁻¹.

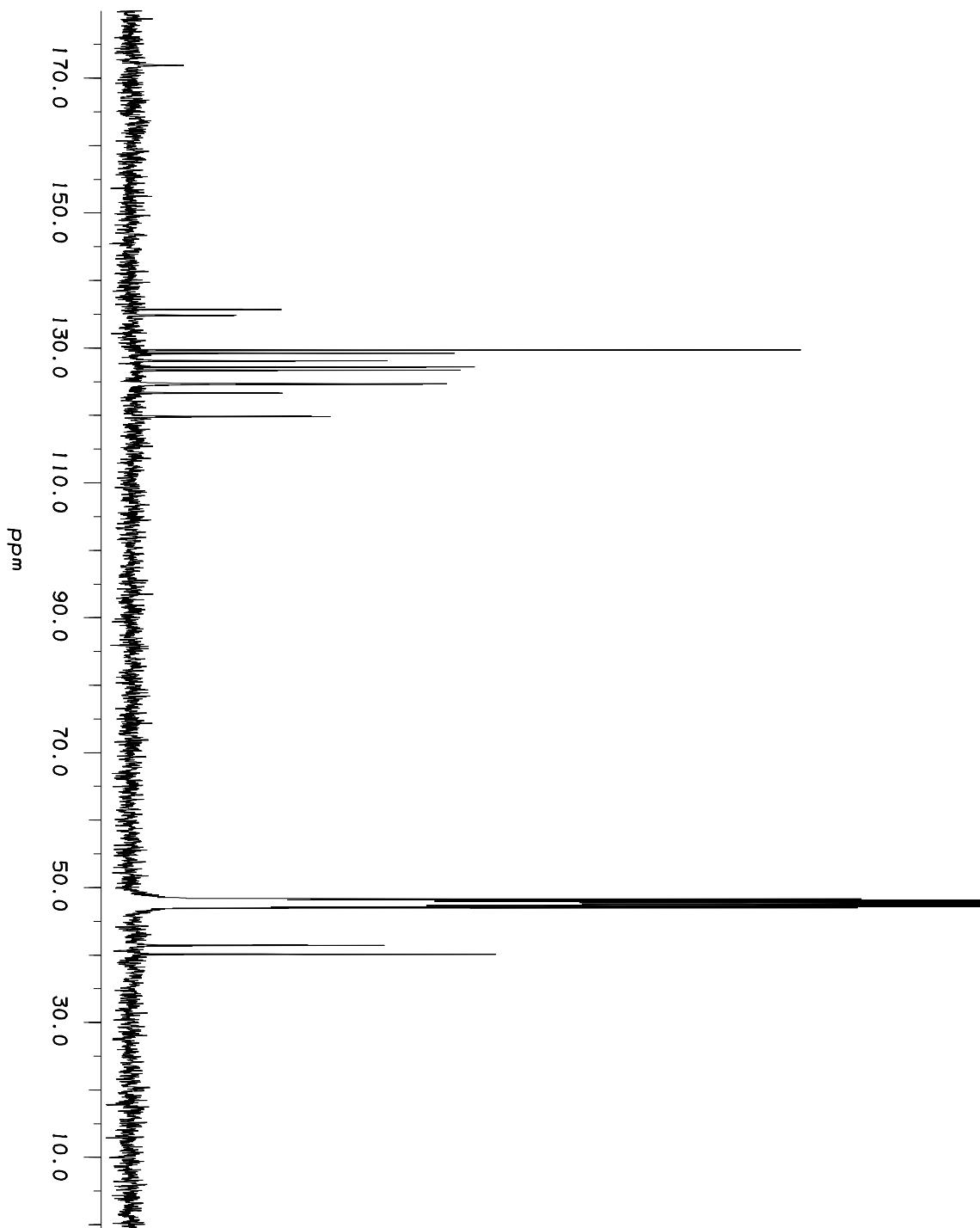
HRMS:

Calculated for C₁₆H₁₅N₃OS (M+) 297.0935 found 297.0927.

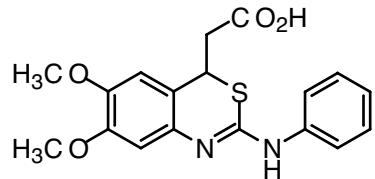
2-Anilino-4*H*-benzothiazineacetamide, ^1H NMR (400MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$):



2-Anilino-4H-benzothiazineacetamide, ^{13}C NMR (100MHz, CD_3OD):



2) 2-Anilino-6,7-dimethoxy-4*H*-benzothiazineacetic acid:



¹H NMR (400MHz, CDCl₃ + CD₃OD):

δ (ppm) 7.29 (m, 5H); 6.94 (s, 1H); 6.71 (s, 1H); 4.52 (dd, J = 6.5, 1.8 Hz, 1H); 3.92 (s, 3H); 3.85 (s, 3H); 2.74 (m, 2H).

¹³C NMR (100MHz, CDCl₃ + CD₃OD):

δ (ppm) 171.3, 149.9, 147.3, 135.3, 129.5, 128.3, 128.0, 125.3, 112.8, 109.3, 103.3, 56.2, 56.1, 41.8, 39.7.

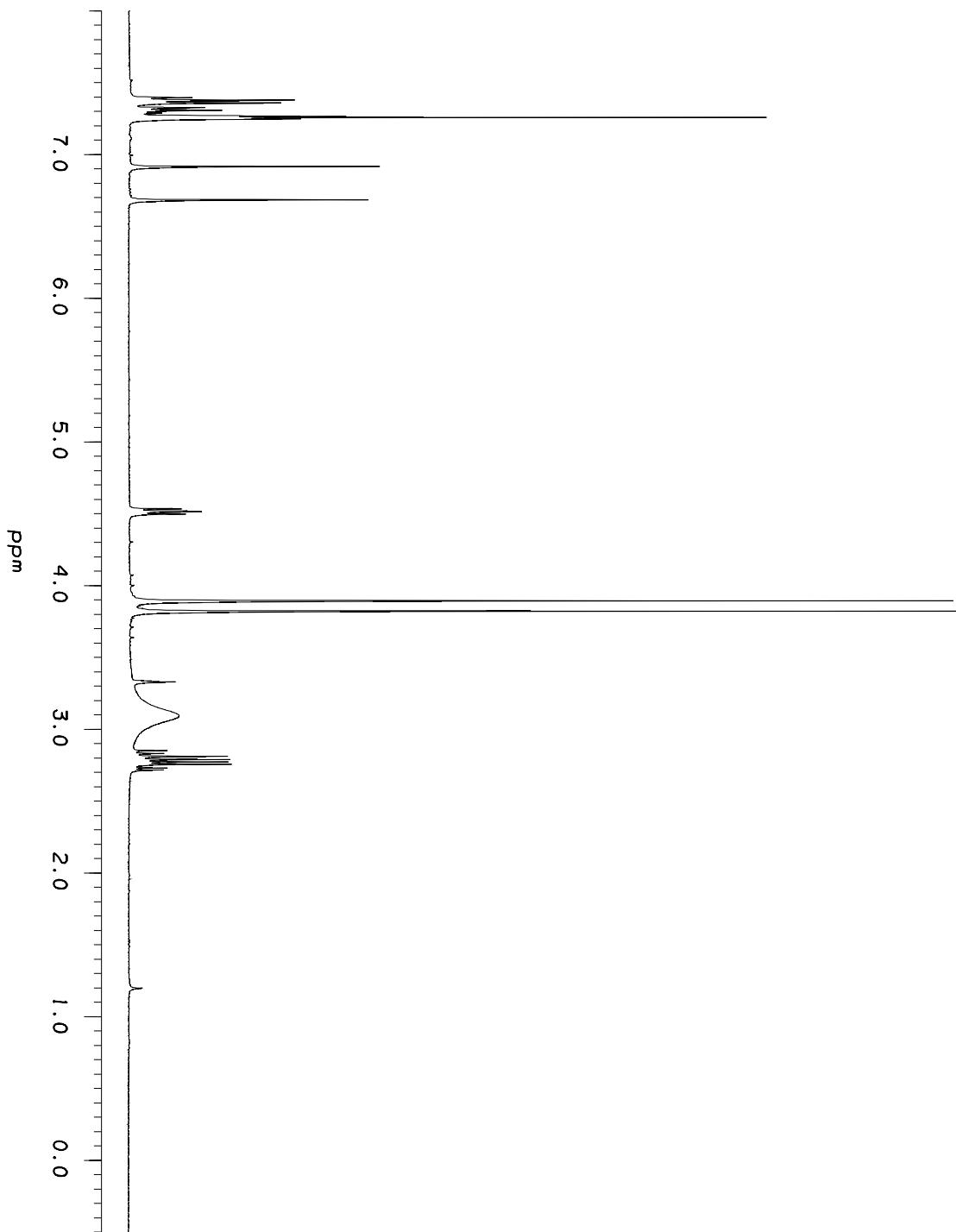
FTIR (thin film):

2928, 1671, 1583, 1517, 1441, 1365, 1266, 1200, 1133, 1004, 911, 845, 799, 724, 693 cm^{-1} .

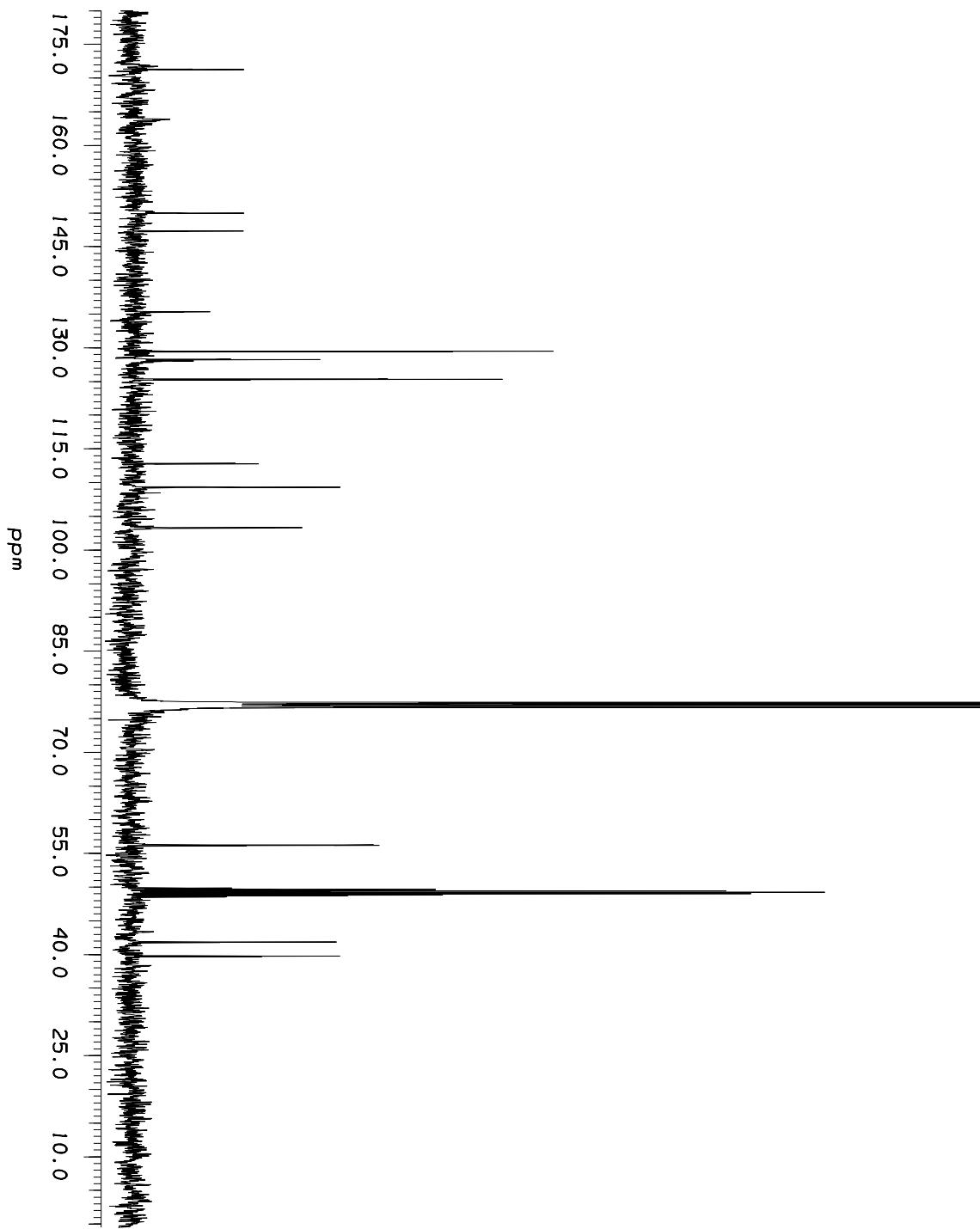
HRMS:

Calculated for C₁₈H₁₈N₂O₄S (M+) 358.0987 found 358.0977.

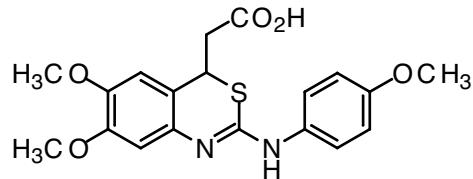
2-Anilino-6,7-dimethoxy-4*H*-benzothiazineacetic acid, ^1H NMR (400MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$):



2-Anilino-6,7-dimethoxy-4*H*-benzothiazineacetic acid, ^{13}C NMR (100MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$):



3) 2-*p*-Methoxyanilino-6,7-dimethoxy-4*H*-benzothiazineacetic acid:



¹H NMR (400MHz, CDCl₃ + CD₃OD):

δ (ppm) 7.15 (d, J = 8.8 Hz, 2H); 6.88 (m, 3H); 6.68 (s, 1H); 4.49 (t, J = 8.0 Hz, 1H); 3.91 (s, 3H); 3.84 (s, 3H); 3.80 (s, 3H); 2.73 (m, 2H).

¹³C NMR (100MHz, CDCl₃ + CD₃OD):

δ (ppm) 171.1, 159.6, 150.0, 147.3, 127.7, 127.3, 114.6, 112.6, 109.3, 103.0, 56.2, 56.1, 55.5, 41.8, 39.7.

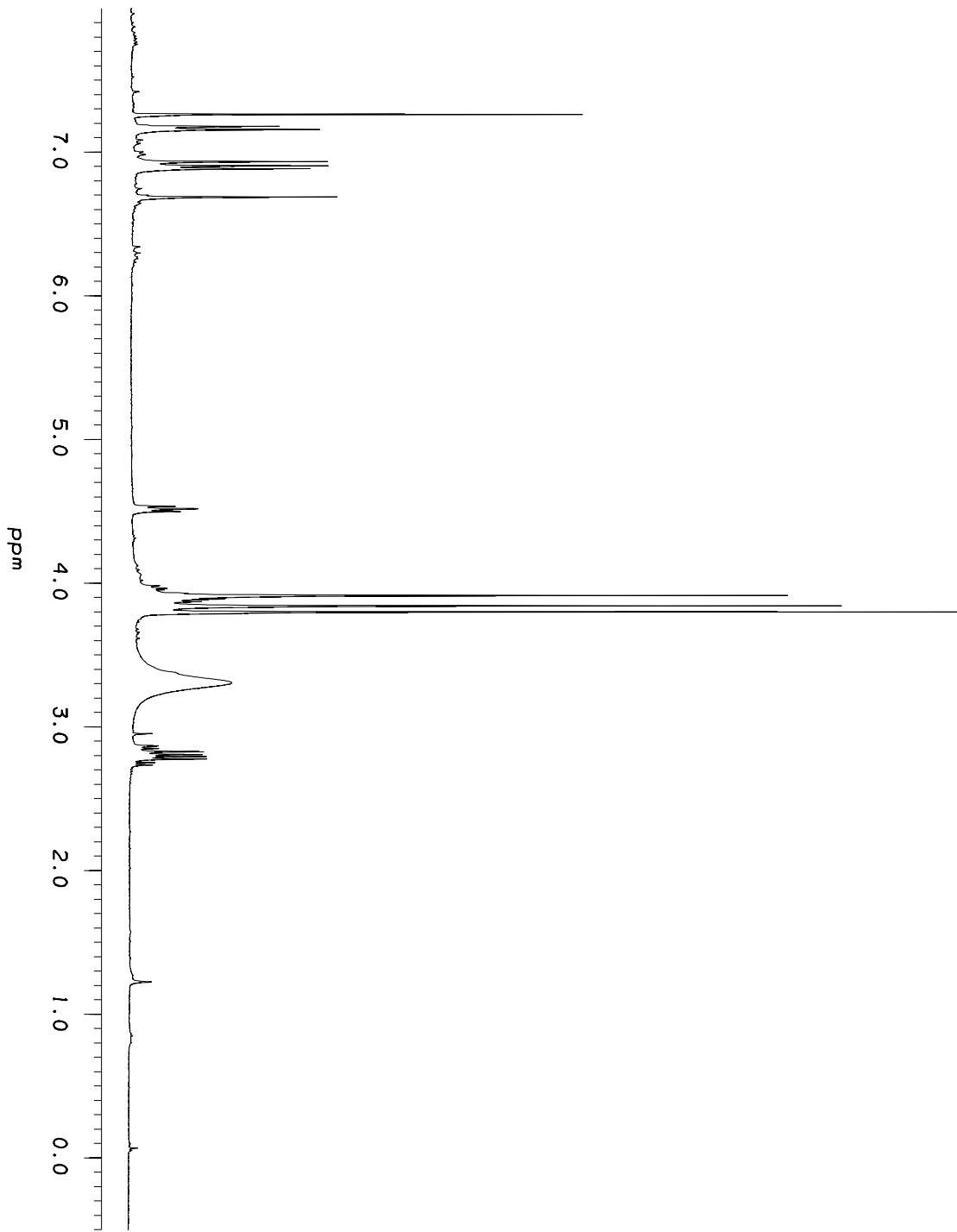
FTIR (thin film):

2977, 2940, 2842, 1781, 1728, 1667, 1633, 1588, 1511, 1466, 1444, 1401, 1367, 1253, 1202, 1029, 1004, 952, 836, 798, 723, 705 cm⁻¹.

HRMS:

Calculated for C₁₉H₂₀N₂O₅S (M+) 388.1092 found 388.1103.

2-*p*-Methoxyanilino-6,7-dimethoxy-4*H*-benzothiazineacetic acid, ^1H NMR (400MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$):



2-*p*-Methoxyanilino-6,7-dimethoxy-4*H*-benzothiazineacetic acid, ^{13}C NMR (100MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$):

