Supplementary Data

Synthesis of Bis-(arylsulfonamide) hydroxamate-Based Selective MMP Inhibitors

Rajesh Subramaniam,[a] Manas K. Haldar,[a] Shakila Tobwala,[b] Bratati Ganguly,[b] D. K. Srivastava,[b*] and Sanku Mallik[a*]

[a]Department of Pharmaceutical Sciences and [b]Department of Chemistry, Biochemistry and Molecular Biology, North Dakota State University, Fargo, ND 58105

General procedure for the synthesis of bis-(arylsulfonamide) carboxylic acids:

Commercially available diamino carboxylic acid (5 mmol for 2,3-diamino propanoic acid hydrobromide salt and 12 mmol for ornithine hydrochloride salt and lysine hydrate) was dissolved in 5 mL water at room temperature. The pH of the solution was adjusted to 10-11 with 2 N NaOH solution and then 2.1 eqiv. of the aryl sulfonyl chloride was added. The pH of the reaction mixture was maintained between 10-11 until no pH change with time was observed. Excess solid sulfonyl chlorides were filtered off. The filtrate (reaction mixture, in the case of liquid sulfonyl chlorides) was then acidified to pH 2-3 with 1 N HCl and the mixture cooled to 0 ^{o}C overnight. The precipitated solid collected by filtration, washed with cold water and lyophilized.

General procedure for the synthesis of *O*-benzyl hydroxamates:

The bis-(arylsulfonamide) carboxylic acid (0.5 mmol), *O*-benzyl hydroxyl amine (1 eqiv.) and HOAt (1 eqiv.) taken in 3 mL anhydrous DMF. HATU added followed by the addition of 2 eqiv. of diisopropylethylamine (DIPEA). The reaction mixture was stirred at room temperature overnight. DMF was distilled out. To the residual oil, water and ethyl acetate were added. The extracted organic layer was successively washed with 15% citric acid, 4% $NaHCO_3$ solution and then dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure produced the crude products which were purified by flash chromatography (silica gel, EtOAc/hexane as the eluants).

General procedure for the synthesis of hydroxamates:

The *O*-benzyl hydroxamate (0.25 mmol) was dissolved in 5 mL dry THF and 30 wt% of 5% Pd-C added. The reaction mixture stirred with constant H_2 bubbling at room temperature until TLC indicated no starting material (usually 3 h). Subsequently, the solid catalyst was filtered and the solvent was evaporated under reduced pressure to give the crude products. The crude products were purified by preparatory TLC (70% EtOAc/hexane).

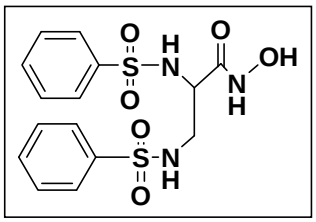
The bromo- and iodoaryl sulfonamide *O*-benzyl hydroxamate derivatives were debenzylated using methanesulfonic acid (MsOH). The *O*-benzyl hydroxamate derivative (100 mg) was dissolved in 1 mL of $CHCl_3$ and 40 eqiv. of MsOH added. After stirring overnight at room temperature, the reaction was quenched by pouring over crushed ice. The precipitated solid was collected by filtration and purified by preparatory TLC (70% EtOAC/hexane).

For the lysine derivatives, the organics were extracted using EtOAc, washed with 4% $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated to get the crude products. The crude products were purified by preparatory TLC (70% EtOAC/hexane).

Sample characterization:

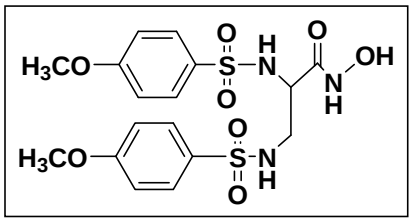
The samples were characterized by ^{1}H and ^{13}C NMR taken using a 300 or 400 MHz Varian NMR Spectrometer. Melting points were measured using an Electrothermal Mel-Temp® melting point apparatus.

All the hydroxamate derivatives of 2,3-diamino propanoic acid and (L)-ornithine synthesized were found to be decomposing above 170 ^{o}C, while those of (L)-lysine were semi-solids or oil at RT.

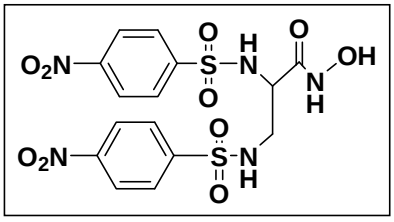


Compound 1: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 2.75 (dd, J = 13.8, 5.8 Hz, 1 H) 2.91 (dd, J = 13.8, 7.7 Hz, 1 H) 3.84 (dd, J = 7.7, 5.8 Hz, 1 H) 7.48 - 7.56 (m, 4 H) 7.56 - 7.64 (m, 2 H) 7.67 - 7.71 (m, 2 H) 7.83 - 7.87 (m, 2 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 168.0, 142.2, 141.2, 134.1, 134.0, 130.5, 128.3, 128.2, 56.0, 45.4

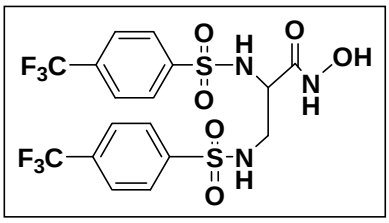
Compound 2: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 2.72 (dd, J = 13.7, 6 Hz, 1 H) 2.86 (dd, J = 13.7, 7.7 Hz, 1 H) 3.80 (dd, J = 7.7, 6 Hz, 1 H) 3.84 (s, 3 H) 3.86 (s, 3 H) 6.97 - 7.05 (m, 4 H) 7.59 - 7.63 (m, 2 H) 7.73 - 7.79 (m, 2 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 168.2, 164.8, 164.7, 133.5, 132.5, 130.5, 130.4, 130.0, 115.6, 115.5, 56.4, 56.0, 45.3.



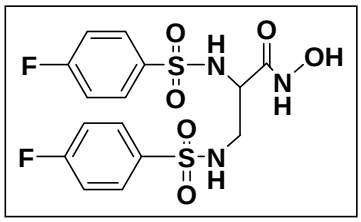
Compound 3: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 3.20 (dd, J = 6.5 Hz, 1 H) 3.28 (d, J = 5.4 Hz, 1 H) 4.04 (t, J = 5.8 Hz, 1 H) 8.06 (d, J = 8.5 Hz, 4 H) 8.37 (dd, J = 13.5, 9.0 Hz 4 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ ppm 168.9, 151.7, 151.6, 148.0, 147.8, 129.8, 129.6, 125.6, 125.4, 57.7, 46.4.



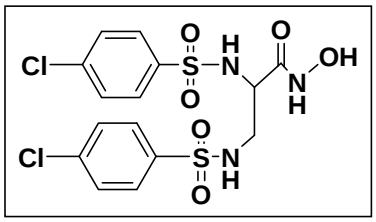
Compound 4: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 2.87 (dd, *J* = 13.8, 6.4 Hz, 1 H) 3.05 (dd, *J* = 13.8, 7.4 Hz, 1 H) 3.92 (t, *J* = 7 Hz, 1 H) 7.83 - 7.89 (m, 4 H) 7.95 (d, *J* = 8.3 Hz, 2 H) 8.05 (d, *J* = 8.3 Hz, 2 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 167.5, 146.2, 145.4, 135.5, 135.4, 129.1, 128.9, 127.6, 127.5, 126.5, 123.7, 56.2, 45.6.



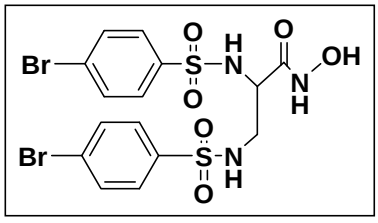
Compound 5: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 2.82 (dd, *J* = 13.5, 6.4 Hz, 1 H) 2.99 (dd, *J* = 13.5, 6.4 Hz, 1 H) 3.85 (t, *J* = 6.7 Hz, 1 H) 7.27 (t, *J* = 8.7 Hz, 4 H) 7.80 (dd, *J* = 8.7, 5 Hz, 2 H) 7.90 (dd, *J* = 8.7, 5 Hz, 2 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 167.9, 165.4, 131.3, 131.2, 131.1, 131.0, 126.3, 117.5, 117.3, 56.0, 45.5.



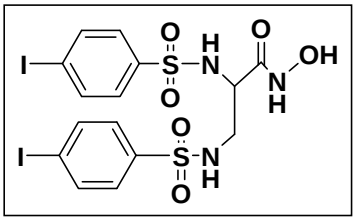
Compound 6: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 2.60 (dd, *J* = 13.3, 5.8 Hz, 1 H) 2.89 (dd, *J* = 13.3, 6.2 Hz, 1 H) 3.81 (t, *J* = 6.2 Hz, 1 H) 7.50 - 7.59 (m, 4 H) 7.77 - 7.83 (m, 4 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 166.3, 140.7, 140.0, 130.6, 130.4, 130.1, 130.0, 57.8, 46.7.



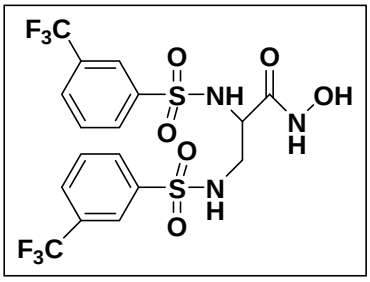
Compound 7: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 2.46 (dd, *J* = 13.0, 6.0 Hz, 1 H) 2.82 (dd, *J* = 13.0, 6.0 Hz, 1 H) 3.78 (t, *J* = 6.0 Hz, 1 H) 7.66 - 7.75 (m, 8 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 165.7, 140.9, 140.5, 133.3, 133.1, 129.5, 128.1, 56.9, 45.9.



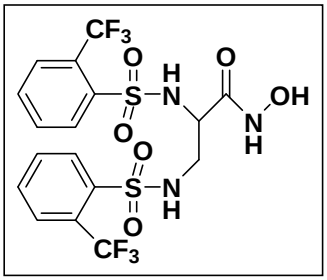
Compound 8: ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.36 (dd, *J* = 13.9, 5.6 Hz, 1 H) 2.77 (dd, *J* = 13.9, 8.7 Hz, 1 H) 3.74 (dd, *J* = 8.7, 5.6 Hz, 1 H) 7.35 - 7.44 (m, 2 H) 7.49 - 7.54 (m, 2 H) 7.92 - 8.00 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.6, 141.0, 139.2, 138.1, 138.0, 128.2, 128.1, 100.6, 100.5, 54.0, 43.3.



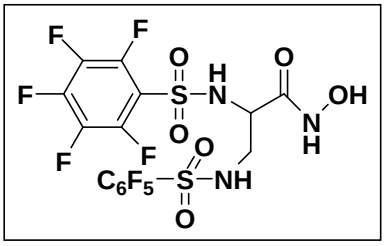
Compound 9: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 2.87 (dd, *J* = 13.7, 6.4 Hz, 1 H) 3.03 (dd, *J* = 13.7, 7.1 Hz, 1 H) 3.89 (t, *J* = 6.7 Hz, 1 H) 7.71 - 7.78 (m, 2 H) 7.90 (d, *J* = 7.7 Hz, 2 H) 7.97 - 8.05 (m, 2 H) 8.07 - 8.16 (m, 3 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 167.2, 143.3, 142.5, 138.7, 131.5, 131.3, 131.2, 130.2, 126.0, 124.8, 55.8, 45.3.



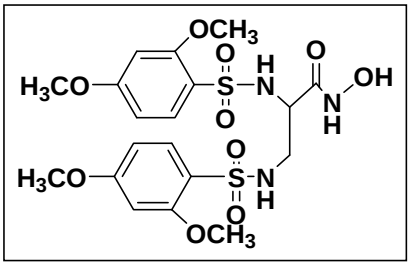
Compound 10: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 3.01 (dd, *J* = 13.5, 6.7 Hz, 1 H) 3.20 (dd, *J* = 13.5, 6.7 Hz, 1 H) 3.97 (t, *J* = 6.3 Hz, 1 H) 7.79 (dd, *J* = 5.7, 3.4 Hz, 4 H) 7.89 - 7.96 (m, 2 H) 8.05 (dd, *J* = 5.4, 3.7 Hz, 1 H) 8.20 (dd, *J* = 5.0, 3.0 Hz, 1 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 164.7, 140.5, 140.1, 134.3, 134.0, 132.4, 132.1, 129.82, 129.76, 129.72, 129.65, 129.0, 128.6, 123.14, 123.11, 49.4, 46.0.



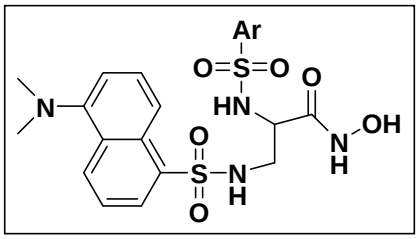
Compound 11: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 3.28 (dd, *J* = 14.6, 8.8 Hz, 1 H) 3.40 (dd, *J* = 14.6, 4.4 Hz, 1 H) 4.00 (dd, *J* = 8.7, 4.3 Hz, 1 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 166.6, 147.2, 146.7, 144.7, 140.9, 140.7, 138.2, 138.1, 56.3, 45.5.



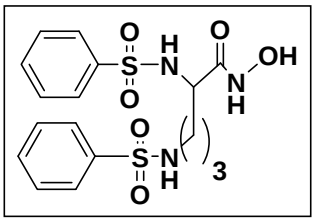
Compound 12: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 3.08 (dd, J = 5.8, 1.6 Hz, 2 H) 3.71 (t, J = 5.8 Hz, 1 H) 3.85 (s, 3 H) 3.88 (s, 3 H) 3.89 (s, 3 H) 3.93 (s, 3 H) 6.55 - 6.67 (m, 4 H) 7.68 (dd, J = 18.4, 8.7 Hz, 2 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 170.1, 166.9, 166.8, 159.9, 159.7, 133.0, 132.8, 120.3, 120.1, 106.0, 105.8, 100.3, 57.1, 57.0, 56.8, 56.5, 56.4, 47.0.



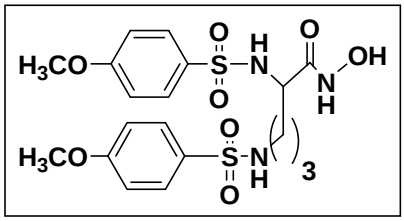
Compound 13: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 2.79 (dd, J = 14.6, 5.4 Hz, 1 H) 2.84 (s, 6 H) 2.88 (s, 6 H) 3.72 (dd, J = 14.6, 8.4 Hz, 1 H) 3.80 (dd, J = 8.4, 5.4 Hz, 1 H) 7.22 (dd, J = 7.3, 5.8 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.47 - 7.60 (m, 3 H) 7.64 (d, J = 8 Hz, 1 H) 8.09 (d, J = 8.5 Hz, 1 H) 8.24 (dd, J = 7.4, 3.7 Hz, 3 H) 8.47 (d, J = 8.5 Hz, 1 H) 8.58 (d, J = 8.5 Hz, 1 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 153.3, 136.4, 135.5, 131.8, 131.4, 131.3, 131.2, 131.0, 130.8, 130.7, 130.4, 129.42, 129.36, 124.4, 124.2, 120.3, 120.2, 116.54, 116.48, 55.8, 46.0, 45.9, 45.0.



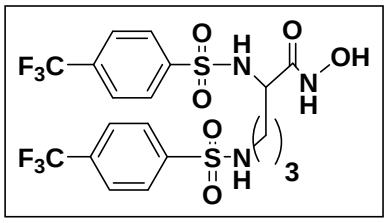
Compound 14: ^{1}H NMR (300 MHz, METHANOL-d_4) δ 1.3-1.7 (m, 4 H), 2.72 (dd, J = 6.6, 4.2 Hz, 2 H), 3.59 (dd, J = 6.6, 6.0 Hz, 1 H), 7.49-7.61 (m, 6 H), 7.79-7.84 (m, 4 H). ^{13}C NMR (75 MHz, METHANOL-d_4) δ 170.0, 142.0, 141.7, 133.8, 133.6, 130.23, 130.19, 128.0, 127.9, 55.4, 43.4, 31.5, 26.9.



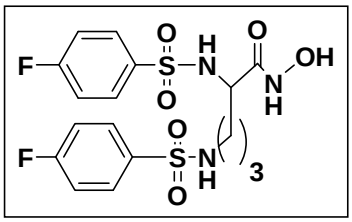
Compound 15: ^{1}H NMR (300 MHz, METHANOL-d_4) δ 1.2-1.7 (m, 4 H), 2.70 (dd, J = 6.9, 6.3 Hz, 2 H), 3.55 (dd, J = 7.8, 6.0 Hz, 1 H), 3.87 (s, 3 H), 3.88 (s, 3 H), 7.01-7.07 (m, 4 H), 7.72-7.76 (m, 4 H). 170.2, 164.4, 164.3, 133.4, 133.1, 130.2, 130.1, 115.3, 56.3, 55.3, 43.3, 31.5, 26.9



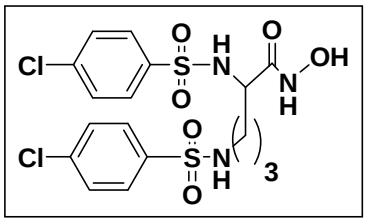
Compound 16: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 1.37 - 1.73 (m, 4 H) 2.84 (t, J = 6.8 Hz, 2 H) 3.68 (dd, J = 8.4, 6.4 Hz, 1 H) 7.86 (dd, J = 16.8, 8.3 Hz, 4 H) 8.01 (dd, J = 8.4, 1.3 Hz, 4 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 169.8, 146.3, 146.0, 128.9, 127.6, 127.52, 127.47, 127.43, 123.7, 55.4, 43.4, 31.5, 27.0.



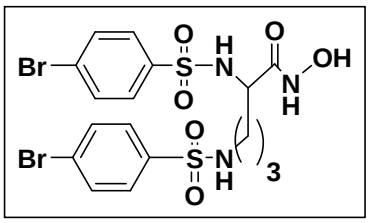
Compound 17: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 1.35-1.68 (m, 4 H) 2.79 (t, J = 6.8 Hz, 2 H) 3.60 (dd, J = 8.3, 6.3 Hz, 1 H) 7.22 - 7.33 (m, 4 H) 7.84 - 7.91 (m, 4 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 170.0, 167.8, 167.7, 165.3, 165.2, 138.3, 131.1, 131.0, 130.9, 117.5, 117.4, 117.3, 117.2, 55.4, 43.4, 31.5, 26.9.



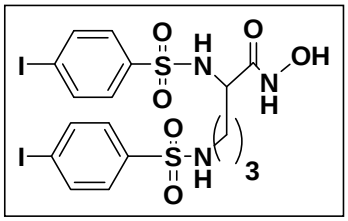
Compound 18: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 1.34 - 1.69 (m, 4 H) 2.79 (td, J = 6.8, 2.9 Hz, 2 H) 3.59 (dd, J = 7.8, 6.4 Hz, 1 H) 7.52 - 7.57 (m, 2 H) 7.59 - 7.63 (m, 2 H) 7.79 - 7.85 (m, 4 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 169.0, 161.5, 153.5, 141.7, 139.7, 130.6, 130.4, 129.9, 56.0, 43.5, 31.9, 27.0.



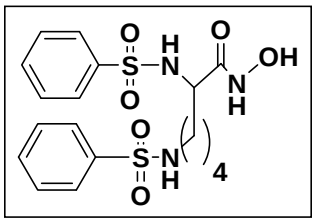
Compound 19: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 1.36 - 1.71 (m, 4 H) 2.79 (t, J = 6.7 Hz, 2 H) 3.62 (dd, J = 8.1, 6.1 Hz, 1 H) 7.66 - 7.75 (m, 8 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 169.8, 165.2, 141.3, 141.0, 133.5, 133.4, 129.7, 128.4, 128.2, 55.2, 43.2, 31.3, 26.7.



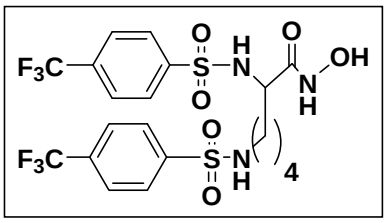
Compound 20: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 1.31 - 1.68 (m, 4 H) 2.75 (td, *J* = 6.7, 2.0 Hz, 2 H) 3.60 (dd, *J* = 8.3, 6.0 Hz, 1 H) 7.54 - 7.60 (m, 4 H) 7.89 - 7.98 (m, 4 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 169.8, 159.0, 154.7, 154.4, 142.2, 141.8, 139.8, 139.7, 129.9, 129.7, 100.9, 100.6, 55.4, 43.4, 31.5, 27.0.



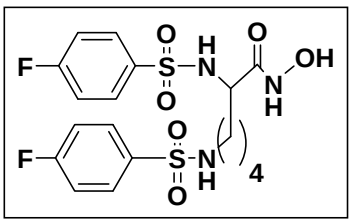
Compound 21: ^{1}H NMR (300 MHz, METHANOL-d_4) δ 1.01-1.60 (m, 6 H), 2.69 (t, *J* = 6.8 Hz, 2 H), 3.58 (dd, *J* = 8.0, 6.6 Hz, 1 H), 7.48-7.63 (m, 6 H), 7.80-7.84 (m, 4 H). ^{13}C NMR (75 MHz, METHANOL-d_4) δ 169.0, 140.8, 140.5, 132.7, 132.4, 129.1, 129.0, 126.82, 126.75, 78.4, 54.5, 42.7, 32.6, 28.9, 22.5.



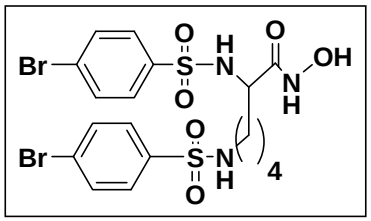
Compound 22: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 1.12 - 1.65 (m, 6 H) 2.80 (t, *J* = 6.8 Hz, 2 H) 3.65 (dd, *J* = 8.0, 6.5 Hz, 1 H) 7.86 (dd, *J* = 16.2, 8.8 Hz, 4 H) 8.01 (d, *J* = 8.3 Hz, 4 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 167.0, 146.3, 146.1, 138.9, 135.3, 135.0, 128.92, 128.88, 127.54, 127.5, 127.45, 127.41, 126.3, 55.8, 43.8, 31.0, 30.3, 23.7.



Compound 23: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 1.11 - 1.62 (m, 6 H) 2.76 (t, *J* = 6.8 Hz, 2 H) 3.58 (dd, *J* = 8.0, 6.5 Hz, 1 H) 7.22 - 7.33 (m, 4 H) 7.84 - 7.91 (m, 4 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 170.2, 167.8, 167.7, 165.3, 165.2, 138.5, 138.3, 131.2, 131.0, 130.9, 117.44, 117.41, 117.22, 117.18, 55.7, 43.8, 33.9, 30.1, 23.7.



Compound 24: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 1.11 - 1.61 (m, 6 H) 2.76 (t, J = 6.8 Hz, 2 H) 3.60 (t, J = 7.1 Hz, 1 H) 7.67 - 7.76 (m, 8 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 170.1, 159.8, 150.4, 143.2, 141.6, 141.3, 133.62, 133.55, 129.94, 129.91, 128.4, 128.2, 55.7, 43.8, 33.8, 30.2, 23.7.



Compound 25: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 1.11 - 1.63 (m, 6 H) 2.75 (t, J = 6.8 Hz, 2 H) 3.59 (dd, J = 8.0, 6.3 Hz, 1 H) 7.54 - 7.60 (m, 4 H) 7.88 - 7.96 (m, 4 H). ^{13}C NMR (100 MHz, METHANOL-d_4) δ 170.0, 141.9, 141.6, 139.8, 139.6, 139.5, 139.4, 129.5, 100.7, 100.4, 97.1, 79.5, 79.2, 78.9, 55.6, 43.7, 33.7, 30.0, 23.6.