Supplementary information

Synthesis and biological evaluation of pentanedioic acid derivatives as farnesyltransferase inhibitors

Liuqing Yang[a, #], Wei Liu[a, #], Hanbing Mei[a, #], Yuan Zhang[a], Xiaojuan Yu[a], Yufang Xu[a], Honglin Li[a]*, Jin Huang[a]*, Zhenjiang Zhao[a]*

[a] *Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China*
** Corresponding author. Zhenjiang Zhao, Tel: +86 10 64253962; Jin Huang, Tel: +86 10 64255689; Honglin Li, Tel: +86 10 64250213.*
E-mail address: zhjzhao@ecust.edu.cn (Z. Zhao); huangjin@ ecust.edu.cn (J. Huang); hlli@ ecust.edu.cn (H, Li).

Molecular Docking

Molecular docking of compound 13b on hFTase was performed by Maestro software package (Schrödinger Inc, version 9.0) using a crystal structure from the Protein Data Bank (PDB code 1LD8). All water and solvent molecules were removed from the complexed structure, hydrogen atoms and charges were added using the Protein Preparation wizard. Then, the grid-enclosing box was centered on the centroid of the bound ligand and defined so as to enclose residues located within 14 Å around from the ligand, and a scaling factor of 1.0 was set to van der Waals (VDW) radii of those receptor atoms with the partial atomic charge less than 0.25. Because of important chelate interaction between the zinc ion of the crystal structure and carboxyl groups of compound 13b, we added metal constraint by picking the zinc ion of 1LD8. Moreover, compound 13b was prepared using LigPrep module with default parameters. Finally, standard-Precision(SP) mode was used to perform the molecular docking simulations with constraint of the zinc ion. And the top 80 docked poses of compound 13b ranked by GlideScore were remained for further analysis.

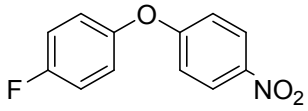
Synthetic Procedures and Characterizations of Compounds

General. All reagents were purchased from commercial suppliers and used without further purification. Melting points were determined using a WRS-1B digital melting

point apparatus. ^{1}H NMR spectra were recorded on a Brucker AM-400(400 Hz) spectrometer with $CDCl_3$ or DMSO-d_6 as the solvent. ^{13}C NMR spectra are recorded at 100 MHz. All coupling constants are measured in Hz and the chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm) relative to TMS (δ_0), which was used as the internal standard. Thin layer chromatography was performed to monitor the process of reactions using silica gel. Purification of compounds was achieved by column chromatography with silica gel (HaiYang, Qingdao) 300−400 mesh. The mass spectra were measured at The Institute of Fine Chemistry of ECUST. Analytical HPLC was performed on a Hewlett-Packard 1100 chromatography system equipped with photodiode array detector, and a Zorbax XDB-C18 column (250 mm × 4.6 mm) was used to determine the purity of the products. The mobile phase A was 10 mM NH_4OAc in water (pH 6.0) and mobile phase B was acetonitrile. A gradient of 10−100% B over 20 min was run at a flow rate of 1.0 mL/min.

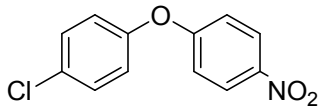
Compound **31** (HPLC: 95.04%, t_R 12.73 min), **32** (HPLC: 97.04%, t_R 12.74 min), **33** (HPLC: 95.58%, t_R 9.88 min) were purchased from SPECS datebase.

1-fluoro-4-(4-nitrophenoxy)benzene (8a)



To a solution of 1-fluoro-4-nitrobenzene (705 mg, 5.0 mmol, 1.0 equiv) and K_2CO_3 (2.07 g, 15.0 mmol, 3.0 equiv) in DMSO (5 mL) was added 4-fluorophenol (560 mg, 5.0 mmol, 1.0 equiv). The reaction mixture was stirred at 70°C overnight. The crude reaction mixture was dissolved in EtOAc and washed with water and brine. The organic layer was separated and dried over Na_2SO_4, filtered, and evaporated. A light yellow solid was obtained (990 mg, 85%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, 2 H, J = 8.8 Hz), 7.37-7.11 (m, 4 H), 7.12 (d, 2 H, J = 9.2 Hz).

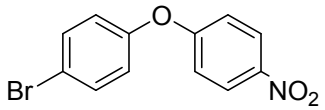
1-chloro-4-(4-nitrophenoxy)benzene (8b)



Synthesized from 1-fluoro-4-nitrobenzene (1.41 g, 10.0 mmol, 1.0 equiv) and 4-

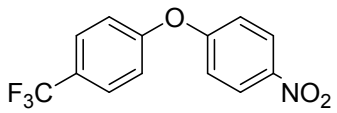
chlorophenol (1.28 g, 10.0 mmol, 1.0 equiv) in a manner similar to **8a**. A light yellow solid was obtained (2.3 g, 92%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, 2 H, J = 9.2 Hz), 7.55 (d, 2 H, J = 8.8 Hz),7.24 (d, 2 H, J = 8.4 Hz), 7.17 (d, 2 H, J = 8.4 Hz).

1-bromo-4-(4-nitrophenoxy)benzene (8c).



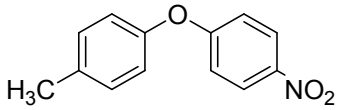
Synthesized from 1-fluoro-4-nitrobenzene (705 mg, 5.0 mmol, 1.0 equiv) and 4-bromophenol (860 mg, 5.0 mmol, 1.0 equiv) in a manner similar to **8a**. A light yellow solid was obtained (1.29 g, 88%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, 2 H, J = 9.2 Hz), 7.68 (d, 2 H, J = 8.8 Hz), 7.19 (d, 2 H, J = 8.8 Hz), 7.18 (d, 2 H, J = 9.6 Hz).

1-nitro-4-(4-(trifluoromethyl)phenoxy)benzene (8d).



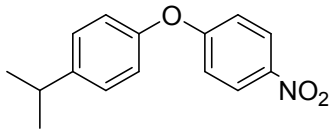
Synthesized from 1-fluoro-4-nitrobenzene (705 mg, 5.0 mmol, 1.0 equiv) and 4-(trifluoromethyl)phenol (972 mg, 6.0 mmol, 1.2 equiv) in a manner similar to **8a**.

1-methyl-4-(4-nitrophenoxy)benzene (8e)



Synthesized from 1-fluoro-4-nitrobenzene (705 mg, 5.0 mmol, 1.0 equiv) and p-cresol (541 mg, 5.0 mmol, 1.0 equiv) in a manner similar to **8a**. A light yellow solid was obtained (1.07 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (d, 2 H, J = 9.2 Hz), 7.31 (d, 2 H, J = 8.0 Hz), 7.09 (d, 4 H, J = 7.6 Hz), 2.35 (s, 3 H).

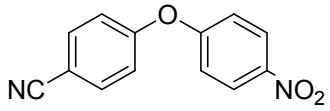
1-isopropyl-4-(4-nitrophenoxy)benzene (8f)



Synthesized from 1-fluoro-4-nitrobenzene (705 mg, 5.0 mmol, 1.0 equiv) and 4-isopropylphenol (680 mg, 5.0 mmol, 1.0 equiv) in a manner similar to **8a**. A maroon oil was obtained (1.17 g, 91%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (d, 2 H, J = 8.8 Hz), 7.37 (d, 2 H, J = 8.4 Hz), 7.13-7.10 (m, 4 H), 2.98-2.91 (m, 1 H), 1.23 (d, 6

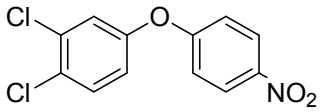
H, J = 6.8 Hz).

4-(4-nitrophenoxy)benzonitrile (8g)



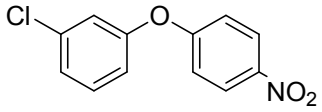
Synthesized from 1-fluoro-4-nitrobenzene (423 mg, 3.0 mmol, 1 equiv) and 4-hydroxybenzonitrile (357 mg, 3.0 mmol, 1 equiv) in a manner similar to **8a**. A light yellow solid was obtained (650 mg, 90%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (d, 2 H, J = 9.2 Hz), 7.96 (d, 2 H, J = 8.8 Hz), 7.34 (d, 2 H, J = 8.8 Hz), 7.30 (d,2 H, J = 9.2 Hz).

1,2-dichloro-4-(4-nitrophenoxy)benzene (8h)



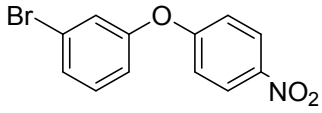
Synthesized from 1-fluoro-4-nitrobenzene (705 mg, 5.0 mmol, 1.0 equiv) and 3,4-dichlorophenol (810 mg, 5.0 mmol, 1.0 equiv) in a manner similar to **8a**. A light yellow solid was obtained (1.30 g, 92%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (d, 2 H, J = 8.8 Hz), 7.75 (d, 1 H, J = 8.8 Hz), 7.60 (s, 1 H), 7.23-7.22 (m, 3 H).

1-chloro-3-(4-nitrophenoxy)benzene (8i)



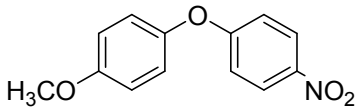
Synthesized from 1-fluoro-4-nitrobenzene (705 mg, 5.0 mmol, 1.0 equiv) and 3-chlorophenol (640 mg, 5.0 mmol, 1.0 equiv) in a manner similar to **8a**. A light yellow solid was obtained (1.15 g, 92%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (d, 2 H, J = 9.6 Hz), 7.55-7.50 (m, 1 H), 7.39-7.34 (m, 2 H), 7.22-7.17 (m, 3 H).

1-bromo-3-(4-nitrophenoxy)benzene (8j)



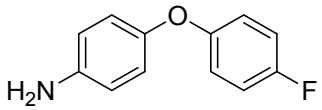
Synthesized from 1-fluoro-4-nitrobenzene (705 mg, 5.0 mmol, 1.0 equiv) and 3-bromophenol (860 mg, 5.0 mmol, 1.0 equiv) in a manner similar to **8a**. A light yellow solid was obtained (1.31 g, 89%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (d, 2 H, J = 9.2 Hz), 7.54-7.50 (m, 1 H), 7.39-7.35 (m, 2 H), 7.22-7.17 (m, 3 H).

1-methoxy-4-(4-nitrophenoxy)benzene (8k)



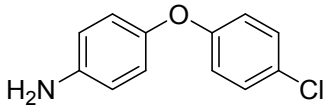
Synthesized from 1-fluoro-4-nitrobenzene (705 mg, 5.0 mmol, 1.0 equiv) and 4-methoxyphenol (621 mg, 5.0 mmol, 1.0 equiv) in a manner similar to **8a**. A light yellow solid was obtained (1.16 g, 82%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (d, 2 H, J = 9.2 Hz), 7.15 (d, 2 H, J = 9.2 Hz), 7.07 (d, 2 H, J = 9.2 Hz), 7.05 (d, 2 H, J = 9.2 Hz), 3.79 (s, 3 H).

4-(4-fluorophenoxy)aniline (9a)



To a solution of **8a** (700 mg, 3.0 mmol) in EtOH (30 mL) was added 10% palladium on carbon (100 mg). The reaction mixture was stirred under H_2 at rt for 6 h. Upon completion of the reaction, Pd was removed by filtration and the filtrate was evaporated to dryness under reduced pressure to afford **9a** as a grey solid.

4-(4-chlorophenoxy)aniline (9b)

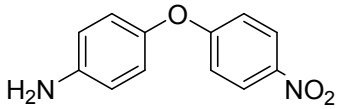


To a stirred solution of $SnCl_2{\cdot}H_2O$ (2.25 g, 10 mmol, 10.0 equiv) in HCl (10 mL) was added **8b** (249 mg, 1 mmol, 1.0 equiv). The reaction mixture was heated at reflux for 6 h. The pH was adjusted to 10 by cautious addition of concentrated aqueous NaOH. The reaction was partitioned between EtOAc and water. The organic layer was separated, washed repeatedly with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The product was obtained as a brownish solid.

4-(4-bromophenoxy)aniline (9c-9k)

Compound **9c-9k** were synthesized in a manner similar to **9b**.

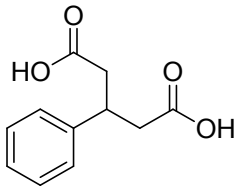
4-(4-nitrophenoxy)aniline (9l)



Synthesized from 1-fluoro-4-nitrobenzene (283 mg, 2.0 mmol, 1 equiv) and 4-

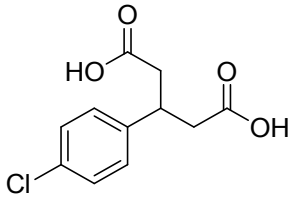
aminophenol (219 mg, 2.0 mmol, 1 equiv)) in a manner similar to **8a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (1:4) to give a yellow solid (310 mg, 67%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (d, 2 H, J = 9.2 Hz), 7.01 (d, 2 H, J = 9.2 Hz), 6.85 (d, 2 H, J = 8.8 Hz), 6.64 (d, 2 H, J = 8.8 Hz), 3.33 (s, 2 H).

3-Phenylpentanedioic Acid (11a*)*



Ethyl acetoacetate (20.8 g, 100 mmol, 2.0 equiv) was added to benzaldehyde (5.3 g, 50 mmol, 1.0 equiv) at 0 ^{o}C, and piperidine (1.0 mL) was added dropwise with stirring. The mixture was left at room temperature for 3 days. The resulting solid was recrystallized from ethanol (100 mL) to give a white solid (the bis-adduct of acetoacetate to benzaldehyde). The white solid was added stepwise to an aqueous solution of KOH (20 M, 60 mL), and the mixture was stirred at 80 ^{o}C for 2 h. Ice (50 mL) and ethyl acetate (50 mL) were added. The aqueous phase was separated, and the pH was adjusted to 1 by cautious addition of concentrated aqueous HCl. The mixture was extracted with ethyl acetate. The organic layer was separated, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate: hexanes (1:1) to give **11a** as a white solid (4.89 g, 47%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.05 (s, 2 H), 7.30-7.25 (m, 4 H), 7.21-7.16 (m, 1 H), 3.45-3.39 (m, 1 H), 2.64 (dd, 2 H, J_1 = 6.4 Hz, J_2 = 16.0 Hz), 2.55-2.49 (m, 2 H).

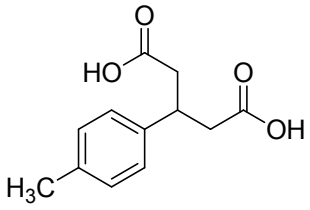
3-(4-Chlorophenyl)pentanedioic Acid (11b)



Synthesized from 4-chlorobenzaldehyde and ethyl acetoacetate in a manner similar to **11a** and purified by chromatography on silica gel using ethyl acetate: hexanes (1:1). Yield, 57%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (s, 2 H), 7.33 (d, 2 H, J = 8.8

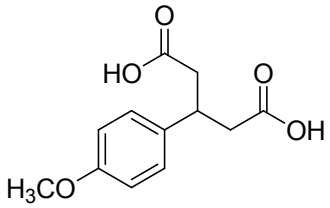
Hz), 7.30 (d, 2 H, J = 8.8 Hz), 3.45-3.37 (m, 1 H), 2.65 (dd, 2 H, J_1 = 6.4 Hz, J_2 = 16.0 Hz), 2.55-2.49 (m, 2 H).

3-(p-tolyl)pentanedioic acid (11c)



Synthesized from 4-methylbenzaldehyde and ethyl acetoacetate in a manner similar to **11a** and purified by column chromatography on silica gel using ethyl acetate: hexanes (1:1). Yield, 59%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.04 (s, 2 H), 7.14 (d, 2 H, J = 8.0 Hz), 7.07 (d, 2 H, J = 8.0 Hz), 3.42-3.37 (m, 1 H), 2.61 (dd, 2 H, J_1 = 6.4 Hz, J_2 = 16.0 Hz), 2.51-2.45 (m, 2 H), 2.25 (s, 3 H).

3-(4-methoxyphenyl)pentanedioic acid (11d)

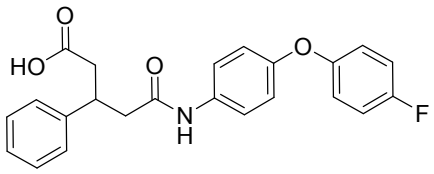


Synthesized from 4-methoxybenzaldehyde and ethyl acetoacetate in a manner similar to **11a** and purified by column chromatography on silica gel using ethyl acetate: hexanes (1:1). Yield, 53%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.00 (s, 2 H), 7.15 (d, 2 H, J = 8.4 Hz), 6.81 (d, 2 H, J = 8.4 Hz), 3.70 (s, 3 H), 3.38-3.31 (m, 1 H), 2.59 (dd, 2 H, J_1 = 6.4 Hz, J_2 = 15.6 Hz), 2.50-2.41 (m, 2 H).

General procedure for the preparation of 3-arylglutaricanhydride (12a-d)

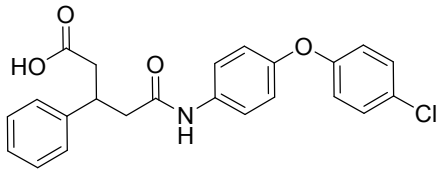
The suspension of 3-arylglutaricacid (1.00 g) in acetyl chloride (2.0 mL) was heated to reflux with stirring for 2 h. Then precipitation of the product is completed by addition of petrol ether (20 mL) and cooling to rt. The precipitate is isolated by suction filtration, washed with petrol ether, and dried in vacuo to give 3-arylglutaricanhydride as white crystals (76%~97%).

5-((4-(4-fluorophenoxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (13a)



To a solution of 3-phenyglutaric anhydride (**12a**, 190 mg, 1.0 mmol, 1.0 equiv) in dioxane (2 mL) was added **9a** (203 mg, 1.0 mmol, 1.0 equiv) and triethylamine (0.1 mL). The mixture was stirred at room temperature for 3 h. The mixture was then poured into water and extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate: hexanes (2:3) to give **13a** as a white solid (195 mg, 50%), mp 193.8-194.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (s, 1 H), 9.88 (s, 1 H), 7.52 (d, 2 H, J = 8.8 Hz), 7.29-7.28 (m, 4 H), 7.21-7.17 (m, 3 H), 7.01-6.98 (m, 2 H), 6.98 (d, 2 H, J = 8.8 Hz), 3.63-3.56 (m, 1 H), 2.72-2.55 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.4, 169.7, 158.4 (d, J = 237.6 Hz, C-F), 153.8, 152.6, 144.1, 135.4, 128.7, 127.9, 126.9, 121.3, 120.2 (d, J = 8.4 Hz, CH), 119.4, 116.9 (d, J = 23.2 Hz, CH), 43.2, 40.6, 38.7. HRMS (ESI) calcd for $C_{23}H_{20}FNO_4Na$ $[M+Na]^+$ 416.1274, found 416.1248. Purity: 98.79% (t_R 11.47 min).

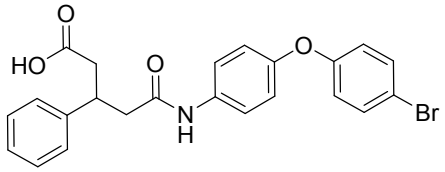
5-((4-(4-chlorophenoxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (13b)



Synthesized from **12a** (190 mg, 1.0 mmol, 1.0 equiv) and **8b** (219 mg, 1.0 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (2:3) to give a white solid (54%), mp 144.7-145.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (s, 1 H), 9.91 (s, 1 H), 7.54 (d, 2 H, J = 8.8 Hz), 7.39 (d, 2 H, J = 8.4 Hz), 7.29-7.28 (m, 4 H), 7.19-7.18 (m, 1 H), 6.99-6.95 (m, 4 H), 3.62-3.55 (m, 1 H), 2.72-2.55 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 169.7, 159.9, 151.6, 144.0, 135.9, 130.2, 128.7, 127.9, 127.0, 126.8, 121.3, 120.1, 119.9, 43.1, 38.7. HRMS (ESI) calcd for $C_{23}H_{20}ClNO_4Na$

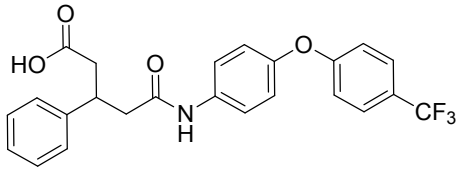
[M+Na]$^+$ 432.0979, found 432.0949. Purity: 99.78% (t_R 12.56 min).

5-((4-(4-bromophenoxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (13c)



Synthesized from **12a** (190 mg, 1.0 mmol, 1.0 equiv) and **8c** (263 mg, 1.0 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (2:3) to give a white solid (37%), mp 156.1-157.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (s, 1 H), 9.91 (s, 1 H), 7.55-7.50 (m, 4 H), 7.29-7.28 (m, 4 H), 7.19-7.18 (m, 1 H), 6.98 (d, 2 H, J = 8.4 Hz), 6.90 (d, 2 H, J = 8.0 Hz), 3.63-3.55 (m, 1 H), 2.72-2.55 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 169.7, 157.4, 151.4, 144.0, 135.9, 133.1, 128.7, 127.9, 126.9, 121.3, 120.23, 120.20, 114.9, 43.2, 38.7. HRMS (ESI) calcd for $C_{23}H_{20}BrNO_4Na$ [M+Na]$^+$ 476.0473, found 476.0443. Purity: 98.50% (t_R 12.69 min)

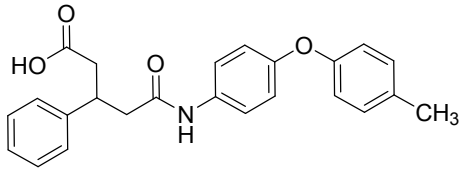
5-oxo-3-phenyl-5-((4-(4-(trifluoromethyl)phenoxy)phenyl)amino)pentanoic acid (13d)



Synthesized from **12a** (190 mg, 1.0 mmol, 1.0 equiv) and **8d** (253 mg, 1.0 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using AcOEt/petroleum ether (2:3) to give a white solid (36%), mp 156.4-157.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (s, 1 H), 9.97 (s, 1 H), 7.70 (d, 2 H, J = 8.4 Hz), 7.60 (d, 2 H, J = 8.4 Hz), 7.30-7.27 (m, 4 H), 7.20-7.19 (m, 1 H), 7.09-7.06 (m, 4 H), 3.63-3.56 (m, 1 H), 2.73-2.56 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.4, 169.8, 161.5, 150.3, 144.0, 136.6, 128.7, 127.9, 127.8 (q, J = 3.7 Hz, CH), 126.9, 124.8 (q, J = 269.7 Hz, C-F), 123.4 (q, J = 31.9 Hz, CH), 121.3, 121.1, 117.7, 43.2, 40.6, 38.7. HRMS (ESI) calcd for $C_{24}H_{20}F_3NO_4Na$ [M+Na]$^+$

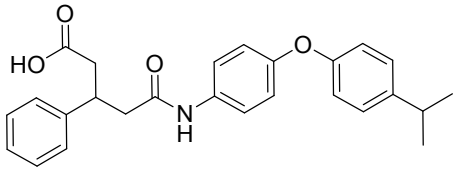
466.1242, found 466.1214. Purity: 99.63% (t_R 13.04 min)

5-oxo-3-phenyl-5-((4-(p-tolyloxy)phenyl)amino)pentanoic acid (13e)



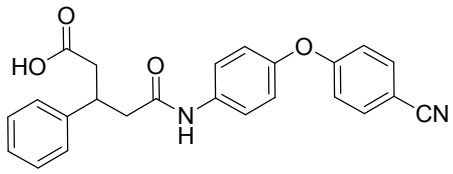
Synthesized from **12a** (190 mg, 1.0 mmol, 1.0 equiv) and **8e** (199 mg, 1.0 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (2:3) to give a white solid (41%), mp 135.5-137.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.08 (s, 1 H), 9.87 (s, 1 H), 7.49 (d, 2 H, J = 9.2 Hz), 7.29-7.28 (m, 4 H), 7.20-7.14 (m, 3 H), 6.89 (d, 2 H, J = 9.2 Hz), 6.85 (d, 2 H, J = 9.2 Hz), 3.61-3.53 (m, 1 H), 2.71-2.54 (m, 4 H), 2.27 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 169.6, 155.4, 152.7, 144.1, 135.1, 132.5, 130.7, 128.7, 127.9, 126.8, 121.2, 119.3, 118.5, 43.1, 38.7, 20.7. HRMS (ESI) calcd for $C_{24}H_{24}NO_4$ $[M+H]^+$ 390.1705, found 390.1683. Purity: 97.21% (t_R 12.24 min).

5-((4-(4-isopropylphenoxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (13f)



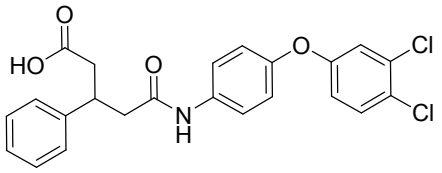
Synthesized from **12a** (190 mg, 1.0 mmol, 1.0 equiv) and **8f** (227 mg, 1.0 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (2:3) to give a white solid (45%), mp 139.0-141.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.08 (s, 1 H), 9.88 (s, 1 H), 7.51 (d, 2 H, J = 8.4 Hz), 7.29-7.28 (m, 4 H), 7.23-7.18 (m, 3 H), 6.92 (d, 2 H, J = 8.4 Hz), 6.87 (d, 2 H, J = 8.0 Hz), 3.62-3.55 (m, 1 H), 2.90-2.81 (m, 1 H), 2.72-2.55 (m, 4 H), 1.19 (d, 6 H, J = 7.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 169.6, 155.7, 152.5, 144.1, 143.5, 135.2, 128.7, 128.1, 127.9, 126.8, 121.2, 119.5, 118.3, 43.1, 38.7, 20.7. HRMS (ESI) calcd for $C_{26}H_{28}NO_4$ $[M+H]^+$ 418.2018, found 418.2014. Purity: 99.61% (t_R 13.83 min).

5-((4-(4-cyanophenoxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (13g)



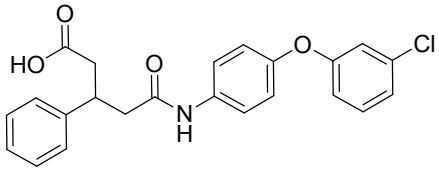
Synthesized from **12a** (95 mg, 0.5 mmol, 1.0 equiv) and **8g** (105 mg, 0.5 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (2:3) to give a white solid (42%), mp 136.1-136.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (s, 1 H), 10.00 (s, 1 H), 7.81 (d, 2 H, J = 8.8 Hz), 7.60 (d, 2 H, J = 7.60 Hz), 7.30-7.29 (m, 4 H), 7.21-7.16 (m, 1 H), 7.07 (d, 2 H, J = 9.2 Hz), 7.04 (d, 2 H, J = 8.8 Hz), 3.62-3.55 (m, 1 H), 2.72-2.55 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 169.8, 162.1, 149.8, 144.0, 136.8, 135.0, 128.7, 127.9, 126.9, 121.4, 121.3, 119.2, 117.9, 105.1, 43.2, 38.7. HRMS (ESI) calcd for $C_{24}H_{20}N_2O_4Na$ $[M+Na]^+$ 423.1321, found 423.1351. Purity: 97.62% (t_R 12.19 min).

5-((4-(3,4-dichlorophenoxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (13h)



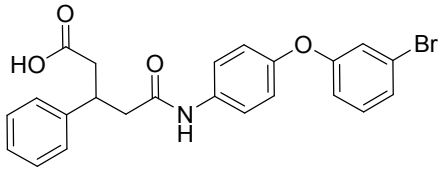
Synthesized from **12a** (380 mg, 2.0 mmol, 1.0 equiv) and **8h** (506 mg, 2.0 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (2:3) to give a white solid (45%), mp 163.9-165.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (s, 1 H), 9.95 (s, 1 H), 7.60-7.56 (m, 3 H), 7.30-7.29 (m, 4 H), 7.21-7.19 (m, 2 H), 7.03 (d, 2 H, J = 8.8 Hz), 6.94 (d, 1 H, J = 8.4 Hz), 3.65-3.55 (m, 1 H), 2.73-2.55 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 169.8, 157.7, 150.8, 144.0, 136.4, 132.4, 131.9, 128.7, 127.9, 126.9, 125.2, 121.3, 120.5, 119.8, 118.3, 43.2, 38.7. HRMS (ESI) calcd for $C_{23}H_{20}Cl_2NO_4$ $[M+H]^+$ 444.0769, found 444.0778. Purity: 99.37% (t_R 13.64 min).

5-((4-(3-chlorophenoxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (13i)



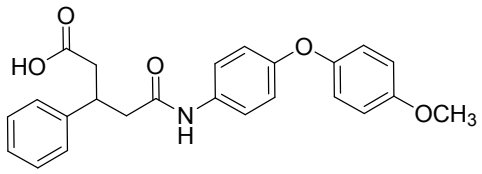
Synthesized from **12a** (190 mg, 1.0 mmol, 1.0 equiv) and **8i** (219 mg, 1.0 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (2:3) to give a white solid (51%), mp 160.7-161.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.08 (s, 1 H), 9.94 (s, 1 H), 7.56 (d, 2 H, J = 8.4 Hz), 7.37 (t, 1 H, J = 8.4 Hz), 7.30-7.27 (m, 4 H), 7.20-7.14 (m, 2 H), 7.01 (d, 2 H, J = 8.4 Hz), 6.97 (s, 1 H), 6.90 (d, 1 H, J= 8.0 Hz), 3.60-3.57 (m, 1 H), 2.71-2.55 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 169.7, 159.1, 151.0, 144.0, 136.2, 134.4, 131.8, 128.7, 127.9, 126.9, 123.2, 121.3, 120.5, 117.8, 116.6, 43.2, 38.7. HRMS (ESI) calcd for $C_{23}H_{20}ClNO_4Na$ $[M+Na]^+$ 432.0979, found 432.0938. Purity: 95.19% (t_R 12.53 min).

5-((4-(3-bromophenoxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (13j)



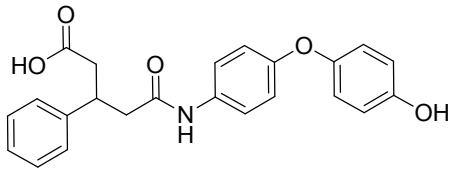
Synthesized from **12a** (190 mg, 1.0 mmol, 1.0 equiv) and **8j** (263 mg, 1.0 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (2:3) to give a white solid (29%), mp 168.3-168.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (s, 1 H), 9.94 (s, 1 H), 7.56 (d, 2 H, J = 8.8 Hz), 7.33-7.29 (m, 6 H), 7.20-7.19 (m, 1 H), 7.10 (s, 1 H), 7.01 (d, 2 H, J = 8.4 Hz),7.95 (d, 1 H, J = 7.2 Hz), 3.62-3.55 (m, 1 H), 2.73-2.55 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 169.7, 159.2, 151.0, 144.1, 136.2, 132.1, 128.7, 127.9, 126.9, 126.1, 122.6, 121.3, 120.6, 120.5, 117.0, 43.2, 38.7. HRMS (ESI) calcd for $C_{23}H_{20}BrNO_4Na$ $[M+Na]^+$ 476.0473, found 476.0490. Purity: 99.74% (t_R 12.72 min).

5-((4-(4-methoxyphenoxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (13k)



Synthesized from **12a** (480 mg, 2.5 mmol, 1.0 equiv) and **8k** (508 mg, 2.5 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (2:3) to give a white solid (61%), mp 148.2-149.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.05 (s, 1 H), 9.82 (s, 1 H), 7.47 (d, 2 H, J = 8.8 Hz), 7.29-7.27 (m, 4 H), 7.21-7.15 (m, 1 H), 6.93 (s, 4 H), 6.85 (d, 2 H, J = 9.2 Hz), 3.73 (s, 3 H), 3.61-3.53 (m, 1 H), 2.71-2.54 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 169.6, 155.8, 153.6, 150.7, 144.1, 134.7, 128.7, 127.9, 126.8, 121.3, 120.4, 118.4, 115.5, 55.9, 43.2, 40.6, 38.7. HRMS (ESI) calcd for $C_{24}H_{22}NO_5$ $[M-H]^+$ 404.1498, found 404.1502. Purity: 99.52% (t_R 11.14 min).

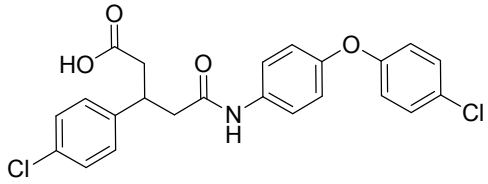
5-((4-(4-hydroxyphenoxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (13l)



To a stirred solution of **13k** (500 mg, 1.23 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was at 0°C was added dropwise BBr_3 (6 mL, 1.0 M in CH_2Cl_2, 6.0 equiv). The temperature was allowed to room temperature for 30 min. Then water (10 mL) was added to quench the reaction and CH_2Cl_2 was removed under vacuum. The resulting mixture was extracted with ethyl acetate. The organic was separated and concentrated under vacuum, the residue was purified by chromatography on silica gel using ethyl acetate: hexanes (1:1-2:1) to give a white solid (58%), mp 172.9-173.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.04 (s, 1 H), 9.80 (s, 1 H), 9.27 (s, 1 H), 7.44 (d, 2 H, J = 8.8 Hz), 7.28-7.27 (m, 4 H), 7.21-7.15 (m, 1 H), 6.83-6.81 (m, 4 H), 6.75 (d, 2 H, 8.8 Hz), 3.60-3.53 (m, 1 H), 2.71-2.53 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 169.5, 154.1, 154.0, 149.1, 144.1, 134.4, 128.7, 127.9, 126.9, 121.2, 120.7, 118.0, 116.6, 43.1, 40.6, 38.7. HRMS (ESI) calcd for $C_{23}H_{20}NO_5$ $[M-H]^+$ 390.1341, found

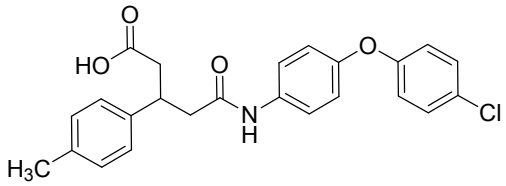
390.1341. Purity: 98.91% (t_R 9.07 min).

5-((4-(4-chlorophenoxy)phenyl)amino)-3-(4-chlorophenyl)-5-oxopentanoic acid (13m)



Synthesized from **12b** (168 mg, 0.75 mmol, 1.0 equiv) and **9b** (165 mg, 0.75 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (2:1) to give a white solid (54%), mp 174.3-174.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.12 (s, 1 H), 9.93 (s, 1 H), 7.54 (d, 2 H, J = 8.8 Hz), 7.39 (d, 2 H, J = 8.4 Hz), 7.34-7.30 (m, 4 H), 6.99-6.95 (m, 4 H), 3.62-3.54 (m, 1 H), 2.73-2.55 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.2, 169.5, 156.9, 151.6, 143.0, 135.8, 131.4, 130.2, 129.9, 128.6, 127.0, 121.3, 120.1, 119.8，42.9，39.2. HRMS (ESI) calcd for $C_{23}H_{20}NO_4Cl_2$ $[M+H]^+$ 444.0769, found 444.0771. Purity: 99.5% (t_R 13.21 min).

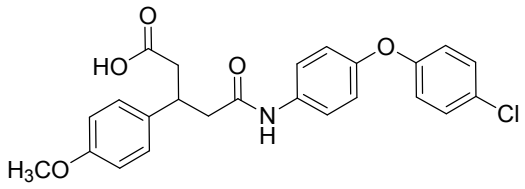
5-((4-(4-chlorophenoxy)phenyl)amino)-5-oxo-3-(p-tolyl)pentanoic acid (13n)



Synthesized from **12c** (153 mg, 0.75 mmol, 1.0 equiv) and **9b** (165 mg, 0.75 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (2:1) to give a white solid (50%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.04 (s, 1 H), 9.91 (s, 1 H), 7.55 (d, 2 H, J = 9.2 Hz), 7.39 (d, 2 H, J = 8.8 Hz), 7.17 (d, 2 H, J = 8.0 Hz), 7.08 (d, 2 H, J = 8.0 Hz), 6.97-6.95 (m, 4 H), 3.58- 3.51 (m, 1 H), 2.69-2.53 (m, 4 H), 2.25 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.4, 169.7, 156.9, 151.5, 141.0, 135.9, 135.8, 130.2, 129.3, 127.7, 127.0, 121.2, 120.1, 119.8, 43.2, 38.3, 21.1. HRMS (ESI) calcd for $C_{24}H_{23}NO_4Cl$ $[M+H]^+$ 424.1316, found 424.1315. Purity: 96.31% (t_R 12.77 min).

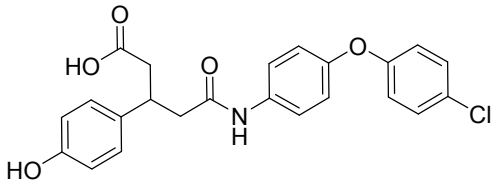
5-((4-(4-chlorophenoxy)phenyl)amino)-3-(4-methoxyphenyl)-5-oxopentanoic acid

(13o)



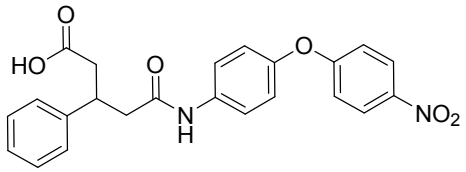
Synthesized from **12d** (220 mg, 1.0 mmol, 1.0 equiv) and **9b** (219 mg, 1.0 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (2:1) to give a white solid (49%), mp 167.1-169.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (1 H), 9.90 (1 H), 7.55 (d, 2 H, J = 8.8 Hz), 7.39 (d, 2 H, J = 8.8 Hz), 7.20 (d, 2 H, J = 8.4 Hz), 6.99-6.95 (m, 4 H), 6.84 (d, 2 H, J = 8.4 Hz), 3.71 (s, 3 H), 3.57-3.50 (m, 1 H), 2.68-2.53 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.4, 169.8, 158.2, 156.9, 151.5, 135.94, 135.87, 130.2, 128.8, 127.0, 121.3, 120.1, 119.8, 114.1, 55.4, 43.4, 40.9, 37.9. HRMS (ESI) calcd for $C_{24}H_{23}ClNO_5$ $[M+H]^+$ 440.1265, found 440.1263. Purity: 99.2% (t_R 12.41 min).

5-((4-(4-chlorophenoxy)phenyl)amino)-3-(4-hydroxyphenyl)-5-oxopentanoic acid (13p)



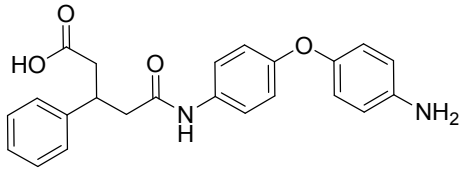
Synthesized from **13o** in a manner similar to **13l**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (1:1) to give a white solid (58%), mp 177.4-179.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.00 (s, 1 H), 9.87 (s, 1 H), 9.17 (s, 1 H), 7.54 (d, 2 H, J = 9.2 Hz), 7.39 (d, 2 H, J = 9.2 Hz), 7.07 (d, 2 H, J = 8.8 Hz), 6.98-6.95 (s, 4 H), 6.66 (d, 2 H, J = 8.8 Hz), 3.51-3.44 (m, 1 H), 2.65-2.50 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.5, 169.9, 156.9, 156.2, 151.5, 135.9, 134.1, 130.2, 128.7, 127.0, 121.3, 120.1, 119.8, 115.4, 43.5, 41.0, 40.0. HRMS (ESI) calcd for $C_{23}H_{19}ClNO_5$ $[M-H]^+$ 424.0952, found 424.0952. Purity: 97.92% (t_R 10.94 min).

5-((4-(4-nitrophenoxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (13q)



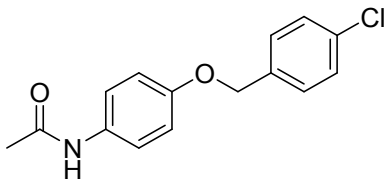
Synthesized from **12a** (240 mg, 1.25 mmol, 1.0 equiv) and **9l** (290 mg, 1.25 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (1:3) to give a yellow solid (59%), mp 195.3-196.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (s, 1 H), 10.00 (s, 1 H), 8.22 (d, 2 H, J = 9.2 Hz), 7.63 (d, 2 H, J = 8.8 Hz), 7.30-7.29 (m, 4 H), 7.21-7.17 (m, 1 H), 7.11 (d, 2 H, J = 8.8 Hz), 7.08 (d, 2 H, J = 9.2 Hz), 3.63-3.56 (m, 1 H), 2.73-2.55 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 169.9, 163.8, 149.7, 144.0, 142.5, 137.1, 128.7, 127.9, 126.9, 126.6, 121.4, 117.3, 43.2, 40.7, 38.7. HRMS (ESI) calcd for $C_{23}H_{21}N_2O_6$ $[M+H]^+$ 421.1400, found 421.1402. Purity: 99.29% (t_R 11.48 min).

5-((4-(4-aminophenoxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (13r)



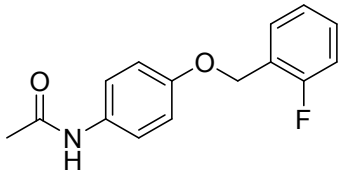
Synthesized from **13q** (500 mg, 1.19 mmol) in a manner similar to **9a**. The residue was purified by chromatography on silica gel using CH_2Cl_2/CH_3OH (15:1) to give a yellow solid (64%), mp 165.7-167.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.76 (s, 1 H), 7.41 (d, 2 H, J = 9.2 Hz), 7.28-7.27 (m, 4 H), 7.19-7.16 (m, 1 H), 6.77 (d, 2 H, J = 9.2 Hz), 6.70 (d, 2 H, J = 8.8 Hz), 6.70 (d, 2 H, J = 8.8 Hz), 3.60-3.52 (m, 1 H), 2.70-2.53 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.4, 169.5, 154.8, 146.9, 145.6, 144.1, 134.0, 128.7, 127.9, 126.9, 121.3, 120.9, 117.5, 115.4, 43.2, 40.6, 38.8. HRMS (ESI) calcd for $C_{23}H_{21}N_2O_4$ $[M-H]^+$ 389.1501, found 389.1505. Purity: 98.14% (t_R 8.76 min).

N-(4-((4-chlorobenzyl)oxy)phenyl)acetamide (15a)



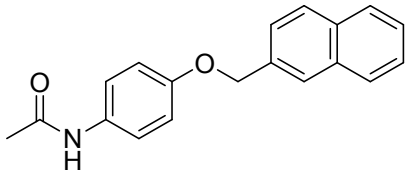
Synthesized from N-(4-hydroxyphenyl)acetamide (300 mg, 2.0 mmol, 1.0 equiv) and 1-(bromomethyl)-4-chlorobenzene (411 mg, 2.0 mmol, 1.0 equiv) in a manner similar to **8a**. A white solid was obtained (85%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.78 (s, 1 H), 7.49-7.45 (m, 6 H), 6.94 (d, 2 H, J = 8.8 Hz), 5.06 (s, 2 H), 2.00 (s, 3 H).

N-(4-((2-fluorobenzyl)oxy)phenyl)acetamide (15b)



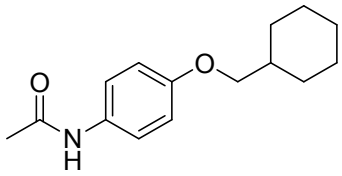
Synthesized from N-(4-hydroxyphenyl)acetamide (300 mg, 2.0 mmol, 1.0 equiv) and 4-chlorobenzyl bromide (375 mg, 2.0 mmol, 1.0 equiv) in a manner similar to **8a**. A white solid was obtained (87%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.79 (s, 1 H), 7.56 (m, 1 H), 7.49 (d, 2 H, J = 8.8 Hz), 7.45-7.39 (m, 1 H), 7.27-7.22 (m, 2 H), 6.96 (d, 2 H, J = 9.2 Hz), 5.09 (s, 2 H), 2.01 (s, 3 H). Purity:

N-(4-(naphthalen-2-ylmethoxy)phenyl)acetamide (15c)



Synthesized from N-(4-hydroxyphenyl)acetamide (755 mg, 5.0 mmol, 1.0 equiv) and 2-(bromomethyl)naphthalene (1.11 g, 5.0 mmol, 1.0 equiv) in a manner similar to **8a**. The rude product was purified by column chromatography on silica gel using ethyl acetate: hexanes (2:1) to give **15c** as a white solid (82%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.73 (s, 1 H), 7.97-7.91 (m, 4 H), 7.58-7.48 (m, 5 H), 7.00 (d, 2 H, J = 8.8 Hz), 5.23 (s, 2 H), 2.00 (s, 3 H). Purity:

N-(4-(cyclohexylmethoxy)phenyl)acetamide (15d)



To a stirred solution of N-(4-hydroxyphenyl)acetamide (755 mg, 5.0 mmol, 1.0 equiv) and bromomethyl cyclohexane (885 mg, 5.0 mmol, 1.0 equiv) in DMF (5 mL) was added K_2CO_3 (848 mg, 6.0 mmol, 1.2 equiv) and KI (83 mg, 0.5 mmol, 0.1 equiv.). The solution was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum, and the residue partitioned between water and ethyl acetate. The organic layer separated, dried over Na_2SO_4, concentrated, and the crude product was purified by column chromatography on silica gel using ethyl acetate: hexanes (1:1) to give **15d** as a white solid (26%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.76 (s, 1 H), 7.45 (d, 2 H, J = 8.8 Hz), 6.84 (d, 2 H, J = 8.8 Hz), 3.72 (d, 2 H, J = 6.0 Hz), 2.00-1.64 (m, 6 H), 1.26-1.15 (m, 3 H), 1.07-0.98 (m, 2 H). Purity:

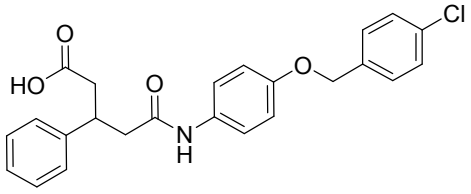
4-((4-Chlorobenzyl)oxy)aniline (16a)

To a stirred solution of **15a** (300 mg, 1.03 mmol) in CH_3OH (5 mL) was added a solution of KOH (2 N). The mixture was heated to reflux with stirring overnight. The reaction mixture was concentrated under vacuum, and the residue partitioned between water and ethyl acetate. The organic layer separated, dried over Na_2SO_4, concentrated, and the crude product was used without further purification.

Aniline derivates (16b-d)

Synthesized from **15b-d** in a manner similar to **16a**, and the crude product was used without further purification.

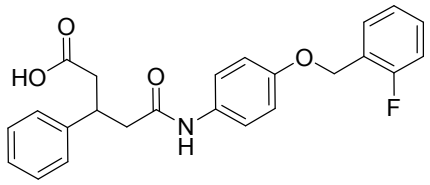
5-((4-((4-Chlorobenzyl)oxy)phenyl)amino)-5-oxo-3-phenylpentanoic Acid (17a)



Synthesized from **12a** (190 mg, 1.0 mmol, 1.0 equiv) and **16a** (233 mg, 1.0 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (2:3) to give a white solid (60%), mp 167.4-

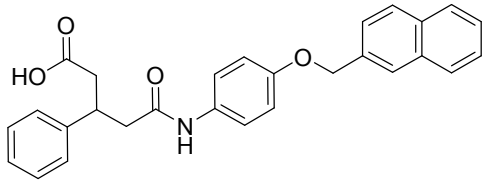
168.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.02 (s, 1 H), 9.69 (s, 1 H), 7.47-7.45 (m, 4 H), 7.41 (d, 2 H, J = 8.8 Hz), 7.28 (d, 4 H, J = 4.4 Hz), 7.20-7.17 (m, 1 H), 6.91 (d, 2 H, J = 8.8 Hz), 5.05 (s, 2 H), 3.61-3.31 (m, 1 H), 2.72-2.56 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 169.3, 154.4, 144.1, 136.7, 133.0, 132.8, 129.9, 128.9, 128.7, 127.9, 126.8, 121.1, 115.3, 68.9, 43.1, 38.7. HRMS (ESI) calcd for $C_{24}H_{23}NO_4Cl$ $[M+H]^+$ 424.1316, found 424.1315. Purity: 99.66% (t_R 12.41 min).

5-((4-((2-fluorobenzyl)oxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (17b)



Synthesized from **12a** (280 mg, 1.47 mmol, 1.0 equiv) and **16b** (323 mg, 1.47 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (2:1) to give a white solid (55%), mp 178.7-179.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.02 (s, 1 H), 9.69 (s, 1 H), 7.51-7.47 (m, 1 H), 7.38-7.34 (m, 3 H), 7.24-7.11 (m, 7 H), 6.89 (d, 2 H, J = 8.8 Hz), 5.03 (s, 2 H), 3.56-3.48 (m, 1 H), 2.67-2.49 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.4, 169.4, 160.8 (d, J = 244.4 Hz, C-F), 154.4, 144.1, 133.1, 131.1 (d, J = 4.1 Hz, CH), 130.8 (d, J = 8.2 Hz, C), 128.7, 127.9, 126.8, 125.0 (d, J = 3.3 Hz, CH), 124.3 (d, J = 4.5 Hz, CH), 121.1, 115.8 (d, J = 20.7 Hz, CH), 115.2, 64.12 (d, J = 3.6 Hz, CH_2), 43.2, 38.7. HRMS (ESI) calcd for $C_{24}H_{22}FNO_4$ $[M-H]^+$ 406.1455, found 406.1454. Purity: 98.77% (t_R 11.31 min).

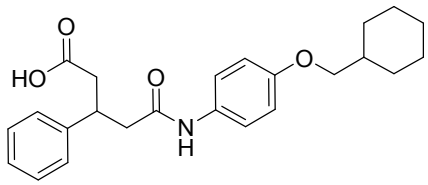
5-((4-(naphthalen-2-ylmethoxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (17c)



Synthesized from **12a** (133 mg, 0.7 mmol, 1.0 equiv) and **16c** (174 mg, 0.7 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on

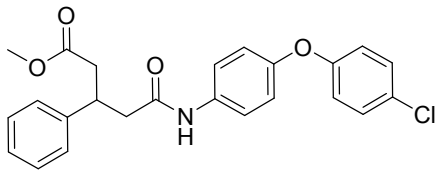
silica gel using ethyl acetate: hexanes (2:1) to give a white solid (62%), mp 163.8-164.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.05 (s, 1 H), 9.72 (s, 1 H), 7.96-7.91 (m, 4 H), 7.59-7.51 (m, 3 H), 7.41 (d, 2 H, J = 8.0 Hz), 7.28-7.27 (m, 4 H), 7.19-7.16 (m, 1 H), 6.96 (d, 2 H, J = 8.4 Hz), 5.21 (s, 2 H), 3.58- 3.54 (m, 1 H), 2.71-2.53 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.4, 169.3, 154.6, 144.1, 135.3, 133.3, 132.99, 132.97, 128.7, 128.5, 128.3, 128.1, 127.9, 126.9, 126.8, 126.64, 126.56, 126.1, 121.1, 115.3, 70.0, 43.2, 38.7. HRMS (ESI) calcd for $C_{28}H_{24}NO_4$ $[M-H]^+$ 438.1705, found 438.1706. Purity: 99.24% (t_R 12.79 min).

5-((4-(cyclohexylmethoxy)phenyl)amino)-5-oxo-3-phenylpentanoic acid (17d)



Synthesized from **12a** (231 mg, 01.2 mmol, 1.0 equiv) and **16d** (246 mg, 1.2 mmol, 1.0 equiv) in a manner similar to **13a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (1:1) to give a white solid (54%), mp 168.2-168.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (s, 1 H), 9.61 (s, 1 H), 7.39 (d, 2 H, J = 8.4 Hz), 7.29-7.28 (m, 4 H), 7.20-7.17 (m, 1 H), 6.82 (d, 2 H, J = 8.8 Hz), 3.71 (d, 2 H, 6.4 Hz), 3.61-3.54 (m, 1 H), 2.72-2.55 (m, 4 H), 1.80-1.63 (m, 6 H), 1.29-0.97 (m, 5 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.4, 169.3, 155.2, 144.1, 132.6, 128.7, 127.9, 126.8, 121.2, 114.8, 73.4, 43.2, 38.7, 37.6, 29.8, 26.5, 25.8. HRMS (ESI) calcd for $C_{24}H_{28}NO_4$ $[M-H]^+$ 394.2018, found 394.2026. Purity: 97.80% (t_R 13.58 min).

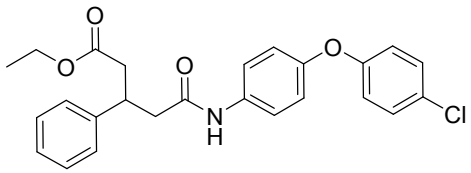
Methyl 5-((4-(4-chlorophenoxy)phenyl)amino)-5-oxo-3-phenylpentanoate (18a)



$SOCl_2$ (1 mL) was added to CH_3OH (1 mL) in 0°C. Then **13b** (41 mg, 0.1 mmol) was added to the mixture dropwise. The mixture was allowed to room temperature for 1 h.

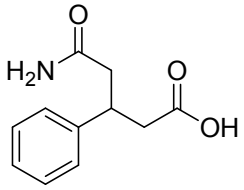
Water was added to quench the reaction and CH_3OH was removed under vacuum. The resulting mixture was extracted with ethyl acetate. The organic was separated and concentrated under vacuum, the residue was purified by chromatography on silica gel using ethyl acetate: hexanes (1:3) to give a white solid (58%), mp 130.0-130.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.93 (s, 1 H), 7.55 (dd, 2 H, J = 8.8 Hz), 7.39 (dd, 2 H, J = 8.4 Hz), 7.31-7.28 (m, 4 H), 7.20-7.19 (m, 1 H), 6.99-6.95 (m, 4 H), 3.64-3.54 (m, 1 H), 3.49 (s, 3 H), 2.83-2.62 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.2, 169.6, 156.9, 151.6, 143.7, 135.9, 130.2, 128.8, 127.8, 127.1, 127.0, 121.3, 120.1, 119.8, 51.7, 42.9, 38.7. HRMS (ESI) calcd for $C_{24}H_{23}NO_4Cl$ $[M+H]^+$ 424.1316, found 424.1316. Purity: 99.55% (t_R 18.91 min).

Ethyl 5-((4-(4-chlorophenoxy)phenyl)amino)-5-oxo-3-phenylpentanoate (18b)



Synthesized from **13b** (41 mg, 0.1 mmol) in a manner similar to **18a**. The residue was purified by chromatography on silica gel using ethyl acetate: hexanes (1:3) to give a yellow solid (64%), mp 113.7-114.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.94 (s, 1 H), 7.55 (d, 2 H, J = 8.0 Hz), 7.39 (d, 2 H, J = 7.6 Hz), 7.29-7.28 (m, 4 H), 7.21-7.18 (m, 1 H), 7.00-6.95 (m, 4 H), 3.96-3.91 (q, 2 H, J = 7.2 Hz), 3.64-3.56 (m, 1 H), 2.80-2.62 (m, 4 H), 1.04 (t, 3 H, J = 7.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.7, 169.6, 156.9, 151.6, 143.6, 135.9, 130.2, 128.7, 127.9, 127.04, 126.97, 121.2, 120.1, 119.8, 60.2, 43.0, 38.8, 14.4. HRMS (ESI) calcd for $C_{25}H_{25}NO_4Cl$ $[M+H]^+$ 438.1472, found 438.1472. Purity: 99.82% (t_R 19.55 min).

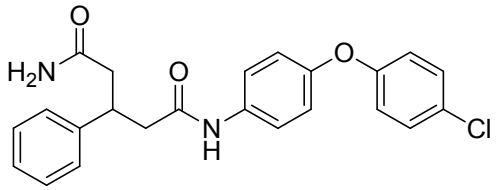
5-amino-5-oxo-3-phenylpentanoic acid (19)



To a stirred solution of **12a** (500 mg) in THF was added ammonium hydroxide (25

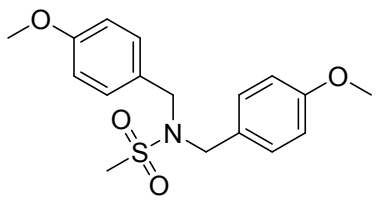
mL). The reaction mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum, and the residue was washed by ethyl acetate. The white solid obtained was acidized by HCl (5%), and then the other white solid was obtained by filtration. ^{1}H NMR (400 MHz，DMSO-d_6)：δ 7.28-7.15 (m, 6 H), 6.70 (s, 1 H), 3.49-3.42 (m, 1 H), 2.59-2.36 (m, 4 H).

N1-(4-(4-chlorophenoxy)phenyl)-3-phenylpentanediamide (20)



To a stirred solution of **19** (300 mg, 1.45 mmol, 1.0 equiv) and **9b** (317 mg, 1.45 mmol, 1.0 equiv) in DMF (3 mL) was added HBTU (956 mg, 1.74 mmol, 1.2 equiv) and DIPEA (225 mg, 1.74 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum, and the residue partitioned between water and ethyl acetate. The organic layer separated, dried over Na_2SO_4, concentrated, and the crude compound was purified by column chromatography on silica gel using ethyl acetate: hexanes (1:3) to give **20** as a brown solid (350 mg, 59%), mp 170.5-170.7 °C. ^{1}H NMR (400 MHz，$CDCl_3$)：δ 9.89 (s，1 H)，7.53 （d，2 H，J = 8.8 Hz)，7.39 (d, 2 H, J = 8.8 Hz), 7.27-7.26 (m，5 H)，7.18-7.17 (m，1 H)，6.98-6.95 (m，4 H)，6.72 (s，1 H)，3.63-3.57 (m，1 H)，2.65-2.60 (m，2 H)，2.44-2.42 (m，2 H)。^{13}C NMR (100 MHz，DMSO-d_6)：δ 173.0，169.8，156.9，151.5，144.4，135.9，130.2，128.6，127.9，127.0，126.7，121.3, 120.1，119.8，43.2，41.9，38.8。 HRMS (ESI) calcd for $C_{23}H_{21}ClN_2O_3Na$ $[M+Na]^+$ 431.1138，found 431.1142. Purity: 98.87% (t_R 14.85 min).

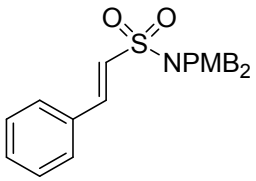
N,N-bis(4-methoxybenzyl)methanesulfonamide (23)



The mixture of 4-methoxybenzaldehyde (6.80 g, 50 mmol, 1.0 equiv) and 4-

methoxybenzylamine (6.85 g, 50 mmol, 1.0 equiv) was heated to reflux in EtOH (100 mL) under N_2 for 2 hours. Afterward, solvents were evaporated under reduced pressure, and the residual oil was redissolved in EtOH. The temperature was cool to 0°C. Sodium borohydride (2.8 g, 73.6 mmol) was added in small portions. The reaction was slowly heated to reflux for 2 hours. After the completion of reaction, the solvents were removed under vacuum. The residual oil was dissolved in ethyl acetate, washed with aqueous $NaHCO_3$, dried over $NaSO_4$, and filtered. Compound **15** (8.90 g) was obtained without further purification. Methanesulfonyl chloride (3.25 g, 28.5 mmol, 1.0 equiv) was added to the solution of bis(4-methoxybenzyl)amine (**15**, 7.32 g, 28.5 mmol, 1.0 equiv.) in CH_2Cl_2 (60 mL) in 0°C. Afterward, triethylamine (5.76 g, 57 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to warm up to room temperature for 5 hours. The mixture was then poured into water (100 mL) and extracted with CH_2Cl_2(100 mL). The organic layer was separated, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate: hexanes (1:4) to give **23** as a white solid (6.03 g, 63%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.19 (d, 4 H, J = 8.4 Hz), 6.89 (d, 4 H, J = 8.8 Hz), 4.19 (s, 4 H), 3.74 (s, 6 H), 2.89 (s, 3 H). LRMS (EI) m/z: 335 $[M]^+$.

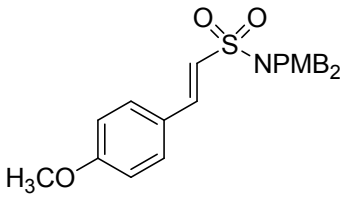
N,N-bis(4-methoxybenzyl)-2-phenylethenesulfonamide (25a)



Compound **23** (2.01 g, 15 mmol, 1.0 equiv) in an oven-dried 100 mL round-bottomed flask was cooled to -20 °C. A solution of LiHMDS (1 mol/1 L, 30 mL, 2.0 equiv) in THF was added dropwise. The mixture was stirred for 30 min at -20 °C and then diethyl chlorophosphate (2.60 g, 15 mmol, 1.0 equiv) was added. Benzaldehyde (1.59 g, 15 mmol, 1.0 equiv) was added after 1 h. The mixture was then warmed to room temperature for 1 h. Then, ice water (10 mL) was add to quench the reaction, and the THF was removed. The residual was poured into water (100 mL) and extracted with ethyl acetate (100 mL). The organic layer was separated, dried over Na_2SO_4,

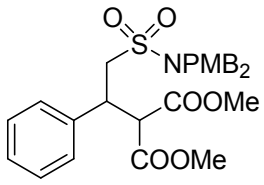
concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate: hexanes (1:10) to give **25a** as a white crystal (4.87 g, 77%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.64-7.50 (m, 5 H), 7.38 (d, 1 H, J = 15.8 Hz), 7.24-7.18 (m, 5 H), 6.86 (d, 4 H, J = 8.4 Hz), 4.21 (s, 4 H), 3.71 (s, 6 H). LRMS (EI) m/z: 423 $[M]^+$.

N,N-bis(4-methoxybenzyl)-2-(4-methoxyphenyl)ethenesulfonamide (25b)



Synthesized from 4-methoxybenzaldehyde and **23** in a manner similar to **25a**. Purification: column chromatography on silica gel using ethyl acetate: hexanes (1:10). Yield, 57%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60 (d, 2 H, J = 8.8 Hz), 7.32 (d, 1 H, J = 15.2 Hz), 7.17 (d, 4 H, J = 8.4 Hz), 7.04 (d, 1 H, J = 15.6 Hz), 6.99 (d, 2 H, J = 8.8 Hz), 6.85 (d, 4 H, J = 8.4 Hz), 4.18 (s, 4 H), 3.80 (s, 3 H), 3.71 (s, 6 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.7, 159.1, 140.6, 130.7, 130.2, 128.6, 125.8, 123.3, 114.8, 114.2, 55.8, 55.5, 49.9. LRMS (EI) m/z: 453 $[M]^+$.

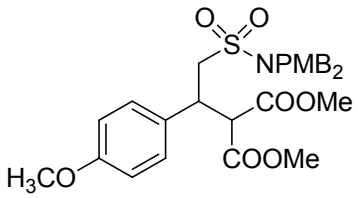
Dimethyl 2-(2-(N,N-bis(4-methoxybenzyl)sulfamoyl)-1-phenylethyl)malonate (26a)



To a stirred solution of **25a** (4.23 g, 10 mmol 1.0 equiv) in CH_3CN (20 mL), dimethyl malonate (2.65 g, 20 mmol, 2.0 equiv) was added followed by the addition of a solution of CH_3ONa (1.08 g, 20 mmol, 2.0 equiv) in CH_3OH(20 mL). The mixture was heated at reflux for 34 h. The reaction mixture was concentrated under vacuum, and the residue partitioned between water and ethyl acetate. The organic layer separated, dried over Na_2SO_4, concentrated, and the crude compound was purified by column chromatography on silica gel using ethyl acetate: hexanes (1:5) to give **26a** as a white crystal (3.14 g, 57%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.31-7.23 (m, 5 H),

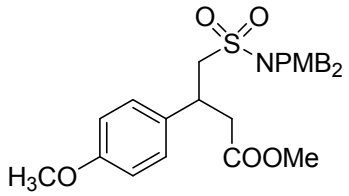
7.06 (d, 4 H, J = 8.0 Hz), 6.83 (d, 4 H, J = 8.4 Hz), 4.09 (d, 2 H, J = 15.2 Hz), 3.94 (d, 1 H, J = 9.2 Hz), 3.91 (d, 2 H, J = 15.2 Hz), 3.85-3.80 (m, 1 H), 3.72 (s, 6 H), 3.70-3.63 (m, 4 H), 3,46-3.42 (dd, 1 H, J_1 = 2.8 Hz, J_2 = 14.4 Hz), 3.36 (s, 3 H). LCMS (EI) m/ z: 555 $[M+H]^+$.

Dimethyl2-(2-(N,N-bis(4-methoxybenzyl)sulfamoyl)-1-(4-methoxyphenyl)ethyl)malonate (26b)



Synthesized from **25b** and DMM in a manner similar to **26a**. Purification: column chromatography on silica gel using ethyl acetate: hexanes (1:4). Yield, 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, 2 H, J = 8.8 Hz), 7.70 (d, 2 H, J = 8.4 Hz), 6.84 (d, 6 H, J = 8.8 Hz), 4.10 (d, 2 H, J = 15.6), 3.95-3.91 (m, 3 H), 3.81-3.76 (m, 1 H), 3.74 (s, 3 H), 3.73 (s, 6 H), 3.67 (s, 3 H), 3.64-3.58 (dd, 1 H, J_1 = 10.0 Hz, J_2 = 14.0 Hz), 3.43-3.40 (m, 4 H). LRMS (EI) m/z: 585 $[M]^+$.

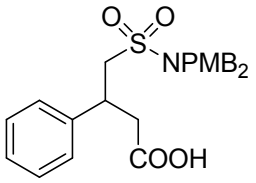
Methyl 4-(N,N-bis(4-methoxybenzyl)sulfamoyl)-3-(4-methoxyphenyl)butanoate (27b)



To a solution of **26b** (3.2 g, 5.47 mmol, 1.0 equiv) in DMF (10 mL) and water (2 drops) was added LiCl (1.67 g, 27.50 mmol, 5.0 equiv). The reaction mixture was heated at reflux for 5 h. The reaction mixture was concentrated under vacuum, and the residue partitioned between water and ethyl acetate. The organic layer separated, dried over Na_2SO_4, concentrated, and the crude compound was purified by column chromatography on silica gel using ethyl acetate: hexanes (1:4) to give **27b** as a Colorless oil (1.41 g, 49%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.15-7.12 (m, 6 H), 6.87-6.84 (m, 6 H), 4.18 (d, 2 H, J = 15.2 Hz), 4.09 (d, 2 H, J = 15.2 Hz), 3.73 (s, 3 H), 3.72 (s, 6 H), 3.50-3.47 (m, 5 H), 3.25-3.19 (dd, 1 H, J_1 = 8.8 Hz, J_2 = 17.2 Hz),

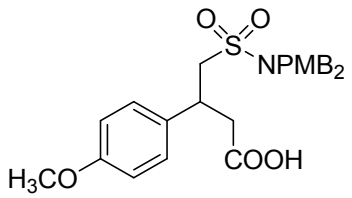
3.01-2.96 (dd, 1 H, J_1 = 4.4 Hz, J_2 = 16.0 Hz), 2.70-2.63 (dd, 1 H, J_1 = 8.8 Hz, J_2 = 15.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.8, 159.2, 158.6, 134.1, 130.3, 129.0, 128.5, 114.3, 114.2, 57.1, 55.5, 55.4, 51.7, 49.8, 40.2, 36.9. LRMS (EI) m/z: 527 $[M]^+$.

4-(N,N-bis(4-methoxybenzyl)sulfamoyl)-3-phenylbutanoic acid (28a)



To a solution of **26a** (360 mg, 0.65 mmol, 1.0 equiv) in DMF (2 mL) and water (2 drops) was added LiCl (196 mg, 3.25 mmol, 5.0 equiv). The reaction mixture was heated at reflux for 5 h. The reaction mixture was concentrated under vacuum, and the residue partitioned between water and ethyl acetate. The organic layer separated, dried over Na_2SO_4, concentrated, and the crude compound was dissolved in CH_3OH (5 mL). A solution of $LiOH{\cdot}H_2O$ (137 mg, 3.25 mmol 5.0 equiv) in water (2 mL) was added to the mixture. The reaction mixture was stirred at room temperature overnight. After that, the reaction mixture was concentrated under vacuum, and the residue partitioned between water and ethyl acetate. The organic layer separated, dried over Na_2SO_4, concentrated, and the crude compound was purified by column chromatography on silica gel using ethyl acetate: hexanes (1:2) to give **28a** as a white crystal (255 mg, 81%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.15 (s, 1 H), 7.32-7.20 (m, 5 H), 7.13 (d, 4 H, J = 8.8 Hz), 6.85 (d, 4 H, J = 8.8 Hz), 4.18 (d, 2 H, J = 15.2 Hz), 4.08 (d, 2 H, J = 14.8), 3.73 (s, 6 H), 3.54-3.48 (m, 2 H), 3.28-3.23 (dd, 1 H, J_1 = 4.8 Hz, J_2 = 12.8 Hz), 2.96-2.90 (dd, 1 H, J_1 = 4.4 Hz, J_2 = 16.0 Hz), 2.64-2.58 (dd, 1 H, J_1 = 9.2 Hz, J_2 = 16.0 Hz).

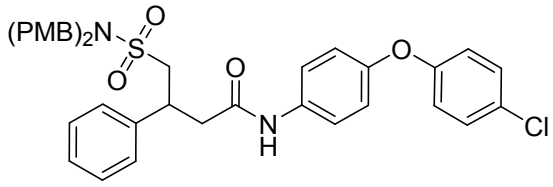
4-(N,N-bis(4-methoxybenzyl)sulfamoyl)-3-(4-methoxyphenyl)butanoic acid (28b)



To a stirred solution of **27b** (1.06 g, 2.0 mmol, 1.0 equiv) in CH_3OH (15 mL) was added a solution of $LiOH{\cdot}H_2O$ (420 mg, 10.0 mmol, 5.0 equiv) in water (6 mL). After

that, the reaction mixture was concentrated under vacuum, and the residue partitioned between water and ethyl acetate. The organic layer separated, dried over Na_2SO_4, concentrated, and the crude compound was purified by column chromatography on silica gel using ethyl acetate: hexanes (1:2 to 2:1) to give **28b** as a white solid (1.02 g, 99%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.11 (s, 1 H), 7.16-7.12 (m, 6 H), 6.87-6.84 (m, 6 H), 4.18 (d, 2 H, J = 15.2 Hz), 4.08 (d, 2 H, J = 15.2 Hz), 3.732 (s, 3 H), 3.727 (s, 6 H), 3.50-3.44 (m, 2 H), 3.24-3.18 (m, 1 H), 2.92-2.87 (dd, 1 H, J_1 = 4.0 Hz, J_2 = 15.6 Hz), 2.59-2.53 (dd, 1 H, J_1 = 9.2 Hz, J_2 = 15.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.9, 159.1, 158.5, 134.4, 130.2, 129.1, 128.5, 114.2, 57.2, 55.5, 55.4, 49.8, 40.5, 36.9. LRMS (EI) m/z: 513 $[M]^+$.

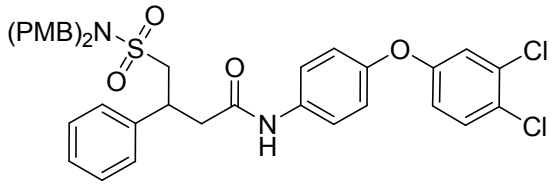
4-(N,N-bis(4-methoxybenzyl)sulfamoyl)-N-(4-(4-chlorophenoxy)phenyl)-3-phenylbutanamide (29a)



To a stirred solution of **28a** (97 mg, 0.20 mmol, 1.0 equiv) and **9b** (50 mg, 0.22 mmol, 1.1 equiv) in DMF (2 mL) was added HBTU (92 mg, 0.24 mmol, 1.2 equiv) and DIPEA (32 mg, 0.24 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum, and the residue partitioned between water and ethyl acetate. The organic layer separated, dried over Na_2SO_4, concentrated, and the crude compound was purified by column chromatography on silica gel using ethyl acetate: hexanes (1:3) to give **29a** as a white crystal (107 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1 H), 7.51 (d, 2 H, J = 8.8 Hz), 7.38 (d, 2 H, J = 8.8 Hz), 7.31-7.21 (m, 5 H), 7.13 (d, 4 H, J = 8.8 Hz), 6.96 (d, 2 H, J = 9.2 Hz), 6.95 (d, 2 H, J = 8.8 Hz), 6.84 (d, 4 H, J = 8.8 Hz), 4.19 (d, 2 H, J = 15.2 Hz), 4.07 (d, 2 H, J = 15.2), 3.74-3.69 (m, 7 H), 3.55 (dd, 1 H, J_1 = 6.8 Hz, J_2 = 14.4 Hz), 3.53-3.35 (m, 1 H), 2.93 (dd, 1 H, J_1 = 5.6 Hz, J_2 = 15.2 Hz), 2.71 (dd, 1 H, J_1 = 9.2 Hz, J_2 = 14.8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.1, 159.1, 156.9, 151.6, 142.6, 135.7, 130.3, 130.2, 128.7, 128.5, 128.2, 127.2, 127.1, 121.3, 120.1,

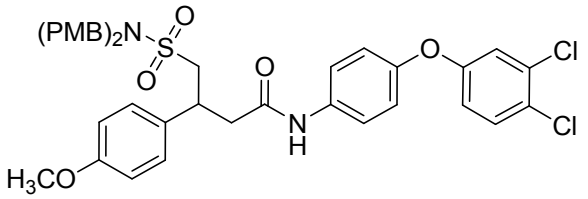
119.8, 114.2, 57.1, 55.5, 49.8 , 42.6, 37.7.

4-(N,N-bis(4-methoxybenzyl)sulfamoyl)-N-(4-(3,4-dichlorophenoxy)phenyl)-3-phenylbutanamide (29b)



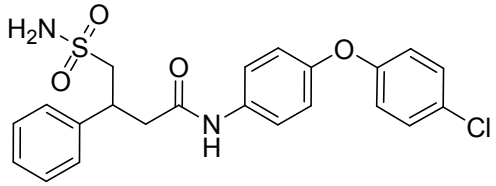
Synthesized from **28a** and **9i** in a manner similar to **29a**. Purification: column chromatography on silica gel using ethyl acetate: hexanes (1:3). Yield, 69%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.9 (s, 1 H), 7.59-7.53 (m, 3 H), 7.32-7.19 (m, 6 H), 7.13 (d, 4 H, J = 8.4 Hz), 7.02 (d, 2 H, J = 8.8 Hz), 6.94-6.91 (dd, 1 H, J_1 = 2.8 Hz, J_2 = 8.8 Hz), 6.84 (d, 4 H, J = 8.8 Hz), 4.19 (d, 2 H, J = 15.2 Hz), 4.07 (d, 2 H, J = 15.2 Hz), 3.75-3.69 (m, 7 H), 3.58-3.53 (dd, 1 H, J_1 = 6.8 Hz, J_2 = 17.0 Hz), 3.38-3.33 (dd, 1 H, J_1 = 7.2 Hz, J_2 = 14.4 Hz), 2.97-2.92 (dd, 1 H, J_1 = 5.6 Hz, J_2 = 15.2 Hz), 2.75-2.69 (dd, 1 H, J_1 = 9.2 Hz, J_2 = 14.8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.2, 159.2, 157.6, 150.9, 142.6, 136.2, 132.4, 132.0, 130.3, 128.8, 128.5, 128.2, 127.2, 125.2, 121.3, 120.5, 119.8, 118.3, 114.2, 57.1, 55.5,49.8, 42.6, 37.7. LRMS (EI) m/z: 718 $[M]^+$.

4-(N,N-bis(4-methoxybenzyl)sulfamoyl)-N-(4-(3,4-dichlorophenoxy)phenyl)-3-(4-methoxyphenyl)butanamide (29c)



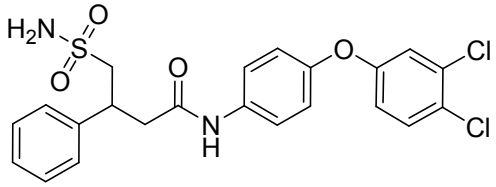
Synthesized from **28b** and **9i** in a manner similar to **29a**. Purification: column chromatography on silica gel using CH_2Cl_2:CH_3OH (100:1). Yield, 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (s, 1 H), 7.58 (d, 2 H, J = 8.8 Hz), 7.54 (s, 1 H), 7.20 (d, 1 H, J = 2.8 Hz), 7.18 (d, 2 H, J = 8.8 Hz), 7.13 (d, 4 H, J = 8.8 Hz), 7.02 (d, 2 H, J = 9.2 Hz), 6.94-6.91 (dd, 1 H, J_1 = 2.8 Hz, J_2 = 8.8 Hz), 6.85 (d, 6 H, J = 8.8 Hz), 4.20 (d, 2 H, J = 15.2 Hz), 4.08 (d, 2 H, J = 15.2 Hz), 3.72-3.65 (m, 10 H), 3.55-3.49 (dd, 1 H, J_1 = 6.8 Hz, J_2 = 14.0 Hz), 3.32-3.28 (m, 1 H), 2.94-2.89 (dd, 1 H, J_1 = 5.2 Hz, J_2 = 14.8 Hz), 2.71-2.65 (dd, 1 H, J_1 = 9.2 Hz, J_2 = 15.2 Hz). LRMS (EI) m/z: 748 $[M]^+$.

N-(4-(4-chlorophenoxy)phenyl)-3-phenyl-4-sulfamoylbutanamide (30a)



To a stirred solution of **29a** (50 mg, 0.073 mmol) in CH_2Cl_2 (1 mL)was added TFA (1 mL). And the reaction mixture was stirred at room temperature for 3 h. Solvents were removed under vacuum, and the residue partitioned between water and ethyl acetate. The organic layer separated, dried over Na_2SO_4, concentrated, and the crude compound was purified by column chromatography on silica gel using CH_2Cl_2:CH_3OH (50:1) to give **30a** as a white crystal (21 mg, 65%), mp 135.5-136.9 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.89 (s, 1 H), 7.50 (d, 2 H, J = 8.8 Hz), 7.38 (d, 2 H, J = 8.8 Hz), 7.33-7.27 (m, 4 H), 7.21-7.18 (m, 1 H), 6.96 (d, 2 H, J = 9.2 Hz), 6.95 (d, 2 H, J = 9.2 Hz), 6.86 (s, 2 H), 3.78-3.71 (m, 1 H), 3.54-3.49 (dd, 1 H, J_1 = 7.2 Hz, J_2 = 14.4 Hz), 3.31-3.26 (dd, 1 H, J_1 = 6.0 Hz, J_2 = 14.4 Hz), 3.02-2.97 (dd, 1 H, J_1 = 5.6 Hz, J_2 = 14.8 Hz), 2.76-2.70 (dd, 1 H, J_1 = 7.2 Hz, J_2 = 14.8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3, 156.9, 151.6, 143.3, 135.8, 130.2, 128.7, 127.1, 121.3, 120.1, 119.8, 60.1, 42.5, 37.9. HRMS (ESI) calcd for $C_{22}H_{21}ClN_2O_4S$ $[M+Na]^+$ 467.0808, found 467.0806. Purity: 99.46% (t_R 16.13 min).

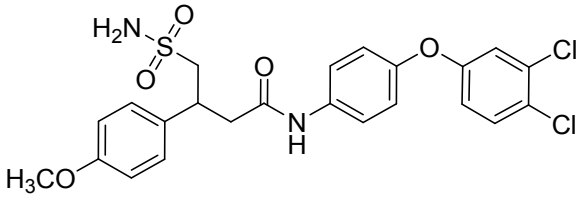
N-(4-(3,4-dichlorophenoxy)phenyl)-3-phenyl-4-sulfamoylbutanamide (30b)



Synthesized from **29b** in a manner similar to **30a**. Purification: column chromatography on silica gel using CH_2Cl_2:CH_3OH (50:1). Yield, 29%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (s, 1 H), 7.58 (d, 1 H, J = 9.2 Hz), 7.53 (d, 2 H, J = 9.2 Hz), 7.33-7.27 (m, 4 H), 7.21-7.19 (m, 2 H), 7.01 (d, 2 H, J = 9.2 Hz), 6.94-6.91 (dd, 1 H, J_1 = 5.2 Hz, J_2 = 9.2 Hz), 6.85 (s, 2 H), 3.78-3.71 (m, 1 H), 3.54-3.49 (dd, 1 H, J_1 = 7.6 Hz, J_2 = 15.2 Hz), 3.33-3.26 (dd, 1 H, J_1 = 6.0 Hz, J_2 = 14.0 Hz), 3.03-2.97 (dd, 1 H, J_1 = 5.6 Hz, J_2 = 15.2 Hz), 2.77-2.71 (dd, 1 H, J_1 = 9.2 Hz, J_2 = 14.8 Hz). ^{13}C

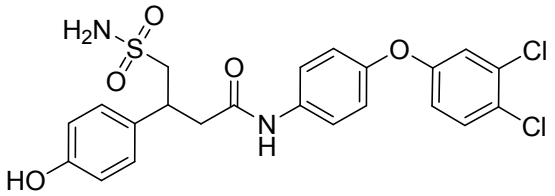
NMR (100 MHz, DMSO-d_6): δ 169.3, 157.6, 150.9, 143.3, 136.3, 132.4, 131.9, 128.7, 128.0, 127.1, 125.2, 121.3, 120.5, 119.8, 118.3, 60.1, 42.5, 37.9. HRMS (ESI) calcd for $C_{22}H_{20}N_2O_4NaSCl_2$ $[M+Na]^+$ 501.0419, found 501.0421. Purity: 99.41% (t_R 17.48 min).

N-(4-(3,4-dichlorophenoxy)phenyl)-3-(4-methoxyphenyl)-4-sulfamoylbutanamide (30c)



Synthesized from **29c** in a manner similar to **30a**. Purification: column chromatography on silica gel using CH_2Cl_2:CH_3OH (50:1). Yield, 77%. Mp 180.4-180.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1 H), 7.58 (d, 1 H, J = 8.8 Hz), 7.54 (d, 2 H, J = 9.2 Hz), 7.23 (d, 2 H, J = 8.8 Hz), 7.20 (d, 1 H, J = 2.8 Hz), 7.02 (d, 2 H, J = 8.8 Hz), 6.94-6.91 (dd, 1 H, J_1 = 2.8 Hz, J_2 = 8.8 Hz), 6.85 (d, 2 H, J = 8.8 Hz), 6.82 (s, 2 H), 3.71-3.66 (m, 4 H), 3.51-3.46 (dd, 1 H, J_1 = 3.46 Hz, J_2 = 14.4 Hz), 3.27-3.22 (dd, 1 H, J_1 = 5.2 Hz, J_2 = 14.8 Hz), 3.00-2.95 (dd, 1 H, J_1 = 5.2 Hz, J_2 = 14.8 Hz), 2.73-2.66 (dd, 1 H, J_1 = 9.2 Hz, J_2 = 14.8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.9, 157.8, 157.1, 150.3, 135.8, 134.7, 131.9, 131.4, 128.5, 124.7, 120.8, 120.0, 119.3, 117.8, 113.6, 59.9, 54.9, 42.2, 36.6. HRMS (ESI) calcd for $C_{23}H_{22}N_2O_5NaSCl_2$ $[M+Na]^+$ 531.0524, found 531.0522. Purity: 99.91% (t_R 17.14 min).

N-(4-(3,4-dichlorophenoxy)phenyl)-3-(4-hydroxyphenyl)-4-sulfamoylbutanamide (30d)



Synthesized from **30c** in a manner similar to **13l**. Purification: column chromatography on silica gel using ethyl acetate: hexanes (3:1). Yield, 77%. Mp

199.5-200.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1 H), 9.21 (s, 1 H), 7.57 (d, 1 H, J = 9.2 Hz), 7.54 (d, 2 H, J = 9.2 Hz), 7.20 (d, 1 H, J = 2.8 Hz), 7.09 (d, 2 H, J = 8.4 Hz), 7.01 (d, 2 H, J = 8.8 Hz), 6.94-6.91 (dd, 1 H, J_1 = 2.8 Hz, J_2 = 8.8 Hz), 6.79 (s, 2 H), 6.67 (d, 2 H, J = 8.4 Hz), 3.67-3.60 (m, 1 H), 3.48-3.43 (dd, 1 H, J_1 = 8.0 Hz, J_2 = 14.4 Hz), 3.24-3.19 (dd, 1 H, J_1 = 6.0 Hz, J_2 = 14.4 Hz), 2.98-2.93 (dd, 1 H, J_1 = 5.6 Hz, J_2 = 14.8 Hz), 2.69-2.63 (dd, 1 H, J_1 = 9.6 Hz, J_2 = 15.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5, 157.6, 156.4, 150.8, 136.3, 133.5, 132.4, 131.9, 128.9, 125.2, 121.3, 120.5, 119.8, 118.3, 115.5, 60.5, 42.7, 37.1. HRMS (ESI) calcd for $C_{22}H_{21}N_2O_5SCl_2$ $[M+H]^+$ 495.0548, found 495.0542. Purity: 96.71% (t_R 15.17 min).

Experimental Procedure about Enzymatic Activity Assay

The plasmid pRSF-Duet1-FTase (a kind gift from Professor Gerrit J. K. Praefcke) was purified from an E.coli expression system using NI-NTA affinity resin as previously described (1). The assay mixture contained 1.5 mg/ml hFTase, 50 mM Tris-HCl, 10 mM $MgCl_2$, 10 mM $ZnCl_2$, 5.0 mM DTT, 0.02% (w/v) N-octyl-D-glucopyranoside(pH 7.5). Stock solution of compounds were prepared in DMSO and were incubated with hFTase enzyme in assay buffer. The reaction was initiated by adding 2.0 mM N-dansyl-GCVLS and the reaction progress was monitored fluorometrically using a Synergy 2 multimode microplate reader (BioTek) with an excitation wavelength 340 nm and emission at 486 nm. Each sample was performed in triplicate.