Electronic Supplementary Material (ESI) for MedChemComm.

Synthesis, biological evaluation, and structure activity relationship (SAR) study of pyrrolidine derivatives as N-acylethanolamine Acid Amidase (NAAA) inhibitors

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Supplemental Experimental Procedures

1. Materials and methods

1.1 Materials and instruments

The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 400 spectrometer. ^{1}H-NMR spectra were registered in $CDCl_3$, d_6-DMSO, or CD_3OD, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet Avatar 360 RT-IR spectrophotometer. Mass spectra were recorded on an Applied Biosystems MDS SCIEX 3200Q TRAP mass spectrometry (MS) system with electrospray ionization (ESI) and direct injection. The HRFABMS spectra were recorded on a Bruker APEX-FTMS apparatus.

All reagents used in the present study were purchased from Sigma-Aldrich (Shanghai, China), seeking the highest grade commercially available unless otherwise indicated. Tetrahydrofuran (THF) was distilled prior to use from sodium benzophenone ketyl. Methylene chloride (CH_2Cl_2) was distilled from phosphorus pentoxide. Dimethylformamide (DMF) was distilled from calcium hydride. Silica gel (300–400 mesh) from Yantai Athy Chemical Technology Co. Ltd. (Zhifu, China) was used for column chromatography, and compounds were eluted with ethyl acetate (EtOAc) /petroleum ether (PE) (60–90°C) mixture (unless otherwise stated). HPLC analysis was run on Agilent-1200 series HPLC system equipped with a photodiode array detector, using a Hypersil Gold C18 column (dimensions 250 × 4.6 mm, particle size 5 mm). Photodiode array (PDA) detector range was set as 210–600 nm.

1.2 Synthesis of pyrrolidine inhibitors

1.2.1 Synthesis of acids 1l-1~1t-1, 3e-1~3j-1, 4d-1 and 4g-1 (Scheme 1)

A solution of Na_2CO_3 (1.06 g, 10 mmol) in H_2O (5 mL) was added dropwise to a mixture of aryl halide (1.5 mmol), $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol) and 3-(4-boronophenyl) propanoic acid (3 mmol) in toluene (10 mL) and EtOH (5 mL) under a nitrogen atmosphere. The resulting solution was stirred under 80 ºC for 2 h, then quenched with 5% aqueous HCl, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel and **1l-1~1t-1**, **3e-1~3j-1, 4d-1 and 4g-1** were then obtained.

1.2.2 Synthesis of acids 1c-1~1k-1, 2c-1, 2d-1, 2g-1~2j-1, 3a-1~3d-1 and 3i-1 (Scheme 2)

To a solution of (5-carboxypentyl)triphenylphosphonium bromide (457 mg, 1.5 mmol) in THF (15 mL) was added slowly a solution of 2 M LiHMDS (2.5 mmol, 1.25 mL THF) under nitrogen atmosphere at –78°C. The reaction mixture was stirred at –78°C

for 15 min, and allowed to warm slowly to 0°C in 0.5 hour. After being stirred at 0°C for 1 hour, a solution of appropriate aldehyde (1.55 mmol) in THF (2 mL) was slowly added at –78°C. The reaction mixture was allowed to warm slowly to 0°C and stirred at the same temperature for 18 hour. The reaction was quenched with 15 mL aqueous 4 M HCl and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue in EtOAc (10 mL) was treated with 10% Pd/C (200 mg) and purged with H_2. After stirring for 2 hours at room temperature, the reaction mixture was filtered through celite and concentrated under reduced pressure to afford the acids **1c-1~1k-1**, **2c-1, 2d-1, 2g-1~2j-1**, **3a-1~3d-1**, and **3i-1**.

1.2.3 Synthesis of amides 1c~1t, 2c, 2d, 2g~2j, 3a~3j, 4d and 4g (Scheme 3)

Pyrrolidine (0.03 mL, 0.4 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a mixture of appropriate acid (0.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (115 mg, 0.6 mmol) and Et_3N (0.08 mL, 0.6 mmol) in anhydrous CH_2Cl_2 (5 mL) under a nitrogen atmosphere. The resulting solution was stirred at 50°C for 4 h, then quenched with saturated aqueous ammonium chloride, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel and **1c~1t**, **2c, 2d, 2g~2j**, **3a~3j, 4d** and **4g** were then obtained.

1.2.4 Synthesis of compounds 2a and 2b (Scheme 4)

To a solution of (5-carboxypentyl)triphenylphosphonium bromide (1368 mg, 3 mmol) in THF (30 mL) was added slowly a solution of 2 M LiHMDS (2.5 mmol, 2.5 mL THF) under nitrogen atmosphere at –78°C. The reaction mixture was stirred at –78°C for 15 min, and allowed to warm slowly to 0°C in 0.5 hour. After being stirred at 0°C for 1 hour, a solution of appropriate aldehyde (3.1 mmol) in THF (2 mL) was slowly added at –78°C. The reaction mixture was allowed to warm slowly to 0°C and stirred at the same temperature for 18 hours. The reaction was quenched with 15 mL aqueous 4 M HCl and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 1: 5) to afford the crude product **2a-1** and **2b-1**.

To a stirred solution of crude acid (~200 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (115 mg, 0.6 mmol) and Et_3N (0.08 mL, 0.6 mmol) in anhydrous CH_2Cl_2 (5 mL), was added a mixture of pyrrolidine (0.03 mL, 0.4 mmol) in CH_2Cl_2 (5 mL). The resulting solution was stirred at 50°C for 4 h, then

quenched with saturated aqueous ammonium chloride, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue in EtOAc (10 mL) was treated with 10% Pd/C (200 mg) and purged with H_2. After stirring for 2 hours at room temperature, the reaction mixture was filtered through celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 1: 5) to afford amides **2a** and **2b**.

1.2.5 Synthesis of amides 2e and 2f (Scheme 5)

A solution of **2g** or **2h** (0.05 mmol) in EtOH (5 mL) was added dropwise to a solution of lithium hydroxide (LiOH) (0.3 mmol) in H_2O (15 mL). The resulting solution was stirred at 0°C for 4 hour, then quenched with 5% aqueous HCl, and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel and **2e** and **2f** were then obtained.

1.2.6 Synthesis of amides 4a (Scheme 6)

To a solution of (2-carboxymethyl) triphenylphosphonium bromide (1200 mg, 3 mmol) in THF (30 mL) was added slowly a solution of 2 M LiHMDS (2.5 mmol, 2.5 mL THF) under nitrogen atmosphere at –78°C. The reaction mixture was stirred at –78°C for 15 min, and allowed to warm slowly to 0°C in 0.5 hour. After being stirred at 0°C for 1 hour, a solution of 4-phenylcyclohexanecarbaldehyde (564 mg, 3 mmol) in THF (2 mL) was slowly added at –78°C. The reaction mixture was allowed to warm slowly to 0°C and stirred at the same temperature for 18 hours. The reaction was quenched with 15 mL aqueous 4 M HCl and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 1: 5) to afford the crude product **4a-1**. Pyrrolidine (0.03 mL, 0.4 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a mixture of crude **4a-1** (~150 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (115 mg, 0.6 mmol) and Et_3N (0.08 mL, 0.6 mmol) in anhydrous CH_2Cl_2 (5 mL) under a nitrogen atmosphere. The resulting solution was stirred at 50°C for 4 h, then quenched with saturated aqueous ammonium chloride, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel and **4a** was then obtained.

1.2.7 Synthesis of amides 4b (Scheme 7)

A solution of the 3-(4-hydroxyphenyl)propanoic acid (166 mg, 1 mmol) in CH_3OH (10 mL) at 0 °C was treated with 0.2 mL of $SOCl_2$. After stirring for 1 h at 0 °C, the reaction mixture was concentrated. The residue was added dropwise to a mixture of 1-iodobenzene (204 mg, 1 mmol) and NaH (48 mg, 2 mmol) in anhydrous DMSO (5 mL) under a nitrogen atmosphere. The resulting solution was stirred at 50°C for 4 h, then quenched with saturated aqueous ammonium chloride (50 mL), and extracted with EtOAc (5 × 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 1: 5) and **4b-1** was then obtained.

To a stirred solution of crude **4b-1** (50 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (115 mg, 0.6 mmol) and Et_3N (0.08 mL, 0.6 mmol) in anhydrous CH_2Cl_2 (5 mL), was added a mixture of pyrrolidine (0.03 mL, 0.4 mmol) in CH_2Cl_2 (5 mL). The resulting solution was stirred at 50°C for 4 h, then quenched with saturated aqueous ammonium chloride, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue in EtOAc (10 mL) was treated with 10% Pd/C (200 mg) and purged with H_2. After stirring for 2 hours at room temperature, the reaction mixture was filtered through celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 1: 5) to afford amides **4b**.

1.2.8 Synthesis of amides 4c (Scheme 8)

The methyl 3-(4-oxocyclohexyl)propanoate (184 mg, 1 mmol) was added to a mixture of $NaBH_4$ (76 mg, 2 mmol) in THF (25 mL) at 0°C. The resulting solution was stirred at room temperature for 4 h, then quenched with saturated aqueous ammonium chloride (50 mL), and extracted with EtOAc (5 × 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was added to a solution of tosyl chloride (190 mg, 1 mmol) and NaH (24 mg, 1 mmol) in DMSO (10 mL) at room temperature. After stirring for 1 h, phenol (94 mg, 1 mmol) in DMSO (1 mL) was added dropwise. The reaction mixture was allowed to warm at 120 °C and was stirred for 24 h. The reaction was quenched with 4M HCl (50 mL) and extracted with EtOAc (5 × 10 mL). The combined organic phases were washed with brine, filtered, and concentrated under reduced pressure. The residue was added to a solution of NaOH (41 mg, 1 mmol) in EtOH/H_2O (5 + 5 mL) at room temperature. After stirring for 2 h, the reaction was quenched with 4M HCl (10 mL) and extracted with EtOAc. The

combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 1: 3) and **4c-1** was then obtained.

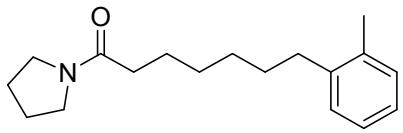
Pyrrolidine (0.03 mL, 0.4 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a mixture of crude **4c-1** (62 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (115 mg, 0.6 mmol) and Et_3N (0.08 mL, 0.6 mmol) in anhydrous CH_2Cl_2 (5 mL) under a nitrogen atmosphere. The resulting solution was stirred at 50°C for 4 h, then quenched with saturated aqueous ammonium chloride, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel and **4c** was then obtained.

1.2.9 Synthesis of amides 4e and 4f (Scheme 9)

Pyrrolidine (0.03 mL, 0.4 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a mixture of crude **4f-1** (65 mg, 0.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (115 mg, 0.6 mmol) and Et_3N (0.08 mL, 0.6 mmol) in anhydrous CH_2Cl_2 (5 mL) under a nitrogen atmosphere. The resulting solution was stirred at 50°C for 4 h, then quenched with saturated aqueous ammonium chloride, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 1: 3) and **4f** was then obtained.

4f (10 mg) in EtOAc (10 mL) was treated with 10% Pd/C (100 mg) and purged with H_2. After stirring for 2 hours at room temperature, the reaction mixture was filtered through celite and concentrated under reduced pressure to afford the compound **4e**.

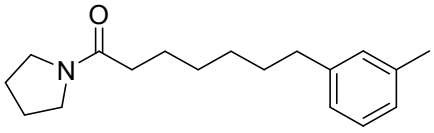
1-(pyrrolidin-1-yl)-7-o-tolylheptan-1-one (1c)



Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1c-1** with pyrrolidine afford **1c** as white solid; 26 mg, yield 32%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.58–1.68 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 8.0 Hz, 2 H), 2.32 (s, 3 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 7.04–7.11 (m, 4 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 24.3, 24.7, 26.0, 29.0, 29.2, 31.2, 33.2, 34.0, 45.5, 46.5, 125.7, 125.8, 128.2, 130.1, 135.0, 139.4, 171.6 ppm; MS (ESI, m/z): 274 (M +

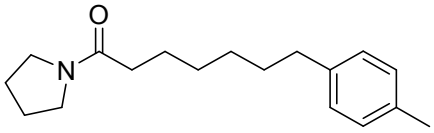
H)$^+$.

1-(pyrrolidin-1-yl)-7-m-tolylheptan-1-one (1d)



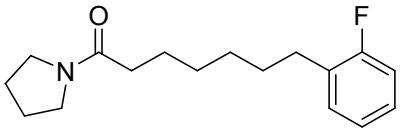
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1d-1** with pyrrolidine afford **1d** as white solid; 37 mg, yield 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.58–1.68 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 8.0 Hz, 2 H), 2.32 (s, 3 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 6.96-7.01 (m, 3 H), 7.22 (t, J = 3.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 24.3, 24.7, 26.0, 29.0, 29.2, 31.2, 33.2, 34.0, 45.5, 46.5, 125.8, 126.5, 128.0, 129.5, 137.8, 142.3, 178.9, 171.6 ppm; MS (ESI, m/z): 274 (M + H)$^+$.

1-(pyrrolidin-1-yl)-7-p-tolylheptan-1-one (1e)



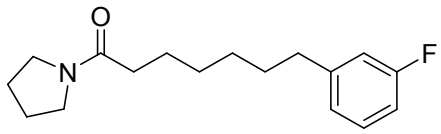
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1e-1** with pyrrolidine afford **1e** as white solid; 31 mg, yield 38%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.58–1.68 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.32 (s, 3 H), 2.60 (t, J = 7.8 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 7.10-7.14 (m, 4 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 24.3, 24.7, 26.0, 29.0, 29.2, 31.2, 33.2, 34.0, 45.5, 46.5, 128.5, 128.8, 135.0, 141.0, 171.6 ppm; MS (ESI, m/z): 274 (M + H)$^+$.

7-(2-fluorophenyl)-1-(pyrrolidin-1-yl)heptan-1-one (1f)



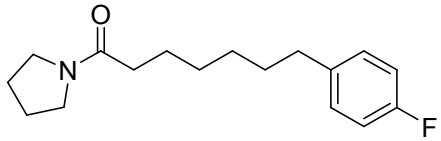
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1f-1** with pyrrolidine afford **1f** as white solid; 57 mg, yield 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.45 (t, J = 7.9 Hz, 2 H), 2.60 (t, J = 7.9 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 7.11 (td, J = 7.5, 1.2 Hz, 1 H), 7.14-7.19 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.7, 26.0, 29.0, 29.2, 31.2, 33.8, 34.5, 45.5, 46.5, 115.6 (d, J = 22.5 Hz), 124.0 (d, J = 3.8 Hz), 128.4 (d, J = 32.0 Hz), 130.6 (d, J = 18.0 Hz), 130.9 (d, J = 5.8 Hz), 172.3 ppm; MS (ESI, m/z): 278 (M + H)$^+$.

7-(3-fluorophenyl)-1-(pyrrolidin-1-yl)heptan-1-one (1g)



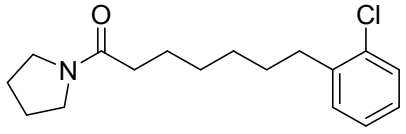
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1g-1** with pyrrolidine afford **1g** as white solid; 44 mg, yield 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.45 (t, J = 8.0 Hz, 2 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 6.87–6.92 (m, 2 H), 6.95 (d, J = 8.0 Hz, 1 H), 7.20–7.24 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.7, 26.0, 29.0, 29.2, 31.2, 33.8, 34.5, 45.5, 46.5, 112.5 (d, J = 21.3 Hz), 116.1 (d, J = 22.0 Hz), 120.0 (d, J = 2.5 Hz), 130.2 (d, J = 7.8 Hz), 146.0 (d, J = 7.0 Hz), 164.0 (d, J = 248.0 Hz), 172.5 ppm; MS (ESI, m/z): 278 $(M + H)^+$.

7-(4-fluorophenyl)-1-(pyrrolidin-1-yl)heptan-1-one (1h)



Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1h-1** with pyrrolidine afford **1h** as white solid; 60 mg, yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 6.95–7.00 (m, 2 H), 7.10–7.14 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.7, 26.0, 29.0, 29.2, 31.2, 33.8, 34.5, 45.5, 46.5, 115.5 (d, J = 22.5 Hz), 129.2 (d, J = 8.0 Hz), 140.0 (d, J = 2.5 Hz), 162.0 (d, J = 245.0 Hz), 172.5 ppm; MS (ESI, m/z): 278 $(M + H)^+$.

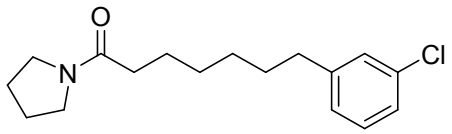
7-(2-chlorophenyl)-1-(pyrrolidin-1-yl)heptan-1-one (1i)



Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1i-1** with pyrrolidine afford **1i** as white solid; 18 mg, yield 21%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 7.12–7.15 (m, 1 H), 7.15–7.21 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.7, 26.0, 29.0, 29.2, 31.2, 33.6, 34.0, 45.5,

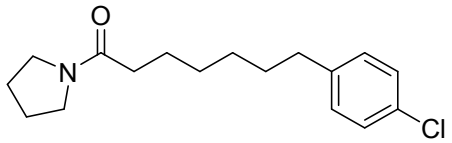
46.5, 127.0, 127.2, 130.1, 130.2, 134.5, 140.1, 172.5 ppm; MS (ESI, m/z): 292 (M − H)⁻.

7-(3-chlorophenyl)-1-(pyrrolidin-1-yl)heptan-1-one (1j)



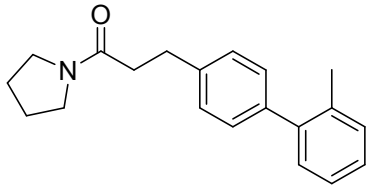
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1j-1** with pyrrolidine afford **1j** as white solid; 9 mg, yield 10%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 7.08 (d, J = 7.5 Hz, 1 H), 7.15–7.18 (m, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.7, 26.0, 29.0, 29.2, 31.2, 33.6, 34.5, 45.5, 46.5, 127.0, 128.5, 129.8, 134.3, 145.2, 172.5 ppm; MS (ESI, m/z): 292 (M − H)⁻.

7-(4-chlorophenyl)-1-(pyrrolidin-1-yl)heptan-1-one (1k)



Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1k-1** with pyrrolidine afford **1k** as white solid; 4 mg, yield 5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 7.08 (d, J = 8.0 Hz, 2 H), 7.21 (d, J = 8.0 Hz, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.7, 26.0, 29.0, 29.2, 31.2, 33.6, 34.5, 45.5, 46.5, 128.5, 130.2, 132.1, 140.3, 178.5 ppm; MS (ESI, m/z): 292 (M − H)⁻.

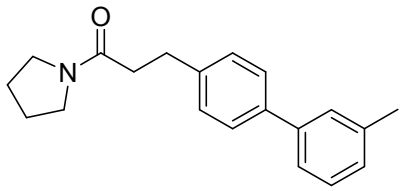
3-(4-(2-methylphenyl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (1l)



Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1l-1** with pyrrolidine afford **1l** as white solid; 56 mg, yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79-1.92 (m, 4 H), 2.20 (s, 3 H), 2.59 (t, J = 8.0 Hz, 2 H), 3.02 (t, J = 8.0 Hz, 2 H), 3.31 (t, J = 6.8 Hz, 2 H), 3.47 (t, J = 6.8 Hz, 2 H), 7.04 (m, 1 H), 7.13–7.19

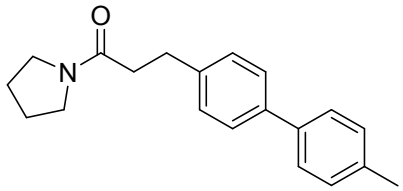
(m, 6 H), 7.32–7.37 (m, 1 H) ppm; MS (ESI, m/z): 294 $(M + H)^+$.

3-(4-(3-methylphenyl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (1m)



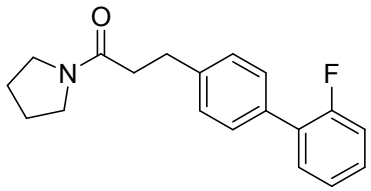
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1m-1** with pyrrolidine afford **1m** as white solid; 29 mg, yield 32%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79-1.92 (m, 4 H), 2.39 (s, 3 H), 2.59 (t, J = 8.0 Hz, 2 H), 3.02 (t, J = 8.0 Hz, 2 H), 3.31 (t, J = 6.8 Hz, 2 H), 3.47 (t, J = 6.8 Hz, 2 H), 7.15 (m, 2 H), 7.31 (m, 3 H), 7.33 (d, J = 7.6 Hz, 2 H), 7.51 (d, J = 7.8 Hz, 2 H) ppm; MS (ESI, m/z): 294 $(M + H)^+$.

3-(4-(4-methylphenyl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (1n)



Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1n-1** with pyrrolidine afford **1n** as white solid; 11 mg, yield 12%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79-1.92 (m, 4 H), 2.39 (s, 3 H), 2.59 (t, J = 8.0 Hz, 2 H), 3.02 (t, J = 8.0 Hz, 2 H), 3.31 (t, J = 6.8 Hz, 2 H), 3.47 (t, J = 6.8 Hz, 2 H), 7.23 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.46-7.51 (m, 4 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 24.4, 26.0, 30.8, 36.7, 45.6, 46.5, 126.8, 126.9, 128.8, 129.4, 136.8, 138.1, 138.9, 140.3, 170.7 ppm; MS (ESI, m/z): 294 $(M + H)^+$.

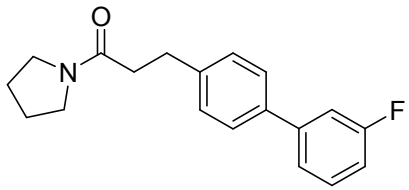
3-(4-(2-fulorophenyl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (1o)



Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1o-1** with pyrrolidine afford **1o** as white solid; 17 mg, yield 19%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79-1.92 (m, 4 H), 2.59 (t, J = 8.0 Hz, 2 H), 3.02 (t, J = 8.0 Hz, 2 H), 3.31 (t, J = 6.8 Hz, 2 H), 3.47 (t, J = 6.8 Hz, 2 H), 7.10–7.15 (m, 2 H), 7.25–7.30 (m, 1 H), 7.33 (d, J = 7.8 Hz, 2 H), 7.39 (t, J = 7.6 Hz, 1 H), 7.48 (d, J = 7.6 Hz, 2 H) ppm; MS

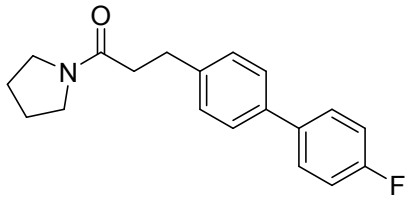
(ESI, m/z): 298 $(M + H)^+$.

3-(4-(3-fulorophenyl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (1p)



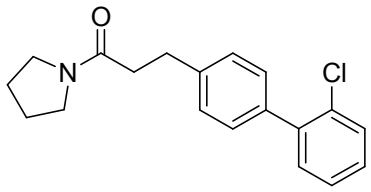
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1p-1** with pyrrolidine afford **1p** as white solid; 6 mg, yield 7%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79-1.92 (m, 4 H), 2.59 (t, J = 8.0 Hz, 2 H), 3.02 (t, J = 8.0 Hz, 2 H), 3.31 (t, J = 6.8 Hz, 2 H), 3.47 (t, J = 6.8 Hz, 2 H), 6.98–7.02 (m, 1 H), 7.24–7.27 (m, 1 H), 7.32–7.38 (m, 4 H), 7.51 (d, J = 8.0 Hz, 2 H) ppm; MS (ESI, m/z): 298 $(M + H)^+$.

3-(4-(4-fulorophenyl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (1q)



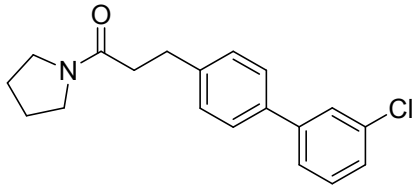
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1q-1** with pyrrolidine afford **1q** as white solid; 16 mg, yield 17%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79-1.92 (m, 4 H), 2.59 (t, J = 8.0 Hz, 2 H), 3.02 (t, J = 8.0 Hz, 2 H), 3.31 (t, J = 6.8 Hz, 2 H), 3.47 (t, J = 6.8 Hz, 2 H), 7.11–7.15 (m, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 7.50 (d, J = 8.0 Hz, 2 H), 7.53–7.57 (m, 2 H) ppm; MS (ESI, m/z): 298 $(M + H)^+$.

3-(4-(2-chlorophenyl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (1r)



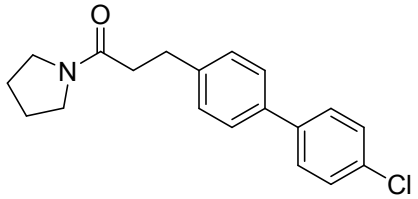
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1r-1** with pyrrolidine afford **1r** as white solid; 31 mg, yield 33%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79-1.92 (m, 4 H), 2.59 (t, J = 8.0 Hz, 2 H), 3.02 (t, J = 8.0 Hz, 2 H), 3.31 (t, J = 6.8 Hz, 2 H), 3.47 (t, J = 6.8 Hz, 2 H), 7.19–7.28 (m, 3 H), 7.45 (t, J = 7.8 Hz, 1 H), 7.30 (d, J = 8.2 Hz, 2 H), 7.35 (d, J = 8.0 Hz, 2 H) ppm; MS (ESI, m/z): 312 $(M - H)^-$.

3-(4-(3-chlorophenyl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (1s)



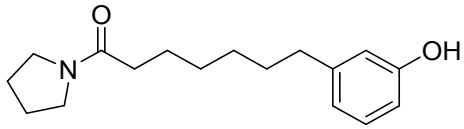
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1s-1** with pyrrolidine afford **1s** as white solid; 23 mg, yield 24%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79-1.92 (m, 4 H), 2.59 (t, J = 8.0 Hz, 2 H), 3.02 (t, J = 8.0 Hz, 2 H), 3.31 (t, J = 6.8 Hz, 2 H), 3.47 (t, J = 6.8 Hz, 2 H), 7.31-7.38 (m, 4 H), 7.49-7.56 (m, 4 H) ppm; MS (ESI, m/z): 312 $(M - H)^-$.

3-(4-(4-chlorophenyl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (1t)



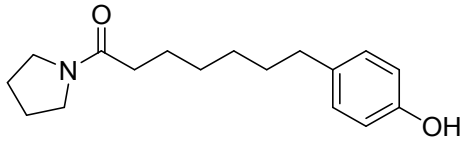
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **1t-1** with pyrrolidine afford **1t** as white solid; 68 mg, yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79-1.92 (m, 4 H), 2.59 (t, J = 8.0 Hz, 2 H), 3.02 (t, J = 8.0 Hz, 2 H), 3.31 (t, J = 6.8 Hz, 2 H), 3.47 (t, J = 6.8 Hz, 2 H), 7.33 (d, J = 8.2 Hz, 2 H) , 7.40 (d, J = 8.2 Hz, 2 H), 7.46–7.48 (m, 4 H) ppm; MS (ESI, m/z): 312 $(M - H)^-$.

7-(3-hydroxyphenyl)-1-(pyrrolidin-1-yl)heptan-1-one (2a)



The reaction afford **2a** as yellow solid; 57 mg, yield 7%; ^{1}H NMR (400 MHz, $CDCl_3/D_2O$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 6.61-6.66 (m, 2 H), 6.76 (d, J = 7.6 Hz, 1 H), 7.10-7.15 (m, 1 H) ppm; MS (ESI, m/z): 276 $(M + H)^+$.

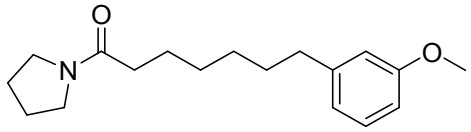
7-(4-hydroxyphenyl)-1-(pyrrolidin-1-yl)heptan-1-one (2b)



The reaction afford **2b** as yellow solid; 33 mg, yield 4%; ^{1}H NMR (400 MHz,

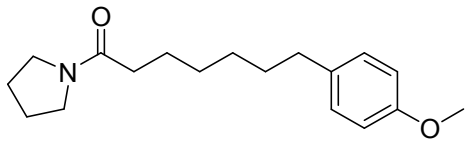
$CDCl_3/D_2O$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 6.83 (d, 2 H, J = 8.1 Hz), 7.10 (d, 2 H, J = 8.2 Hz) ppm; MS (ESI, m/z): 276 $(M + H)^+$.

7-(3-methoxyphenyl)-1-(pyrrolidin-1-yl)heptan-1-one (2c)



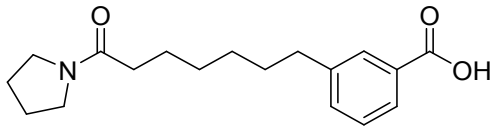
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **2c-1** with pyrrolidine afford **2c** as white solid; 34 mg, yield 39%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 3.81 (s, 3 H), 6.73–6.75 (m, 2 H), 6.75 (d, J = 7.8 Hz, 1H), 7.15-7.20 (m, 1 H) ppm; MS (ESI, m/z): 290 $(M + H)^+$.

7-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)heptan-1-one (2d)



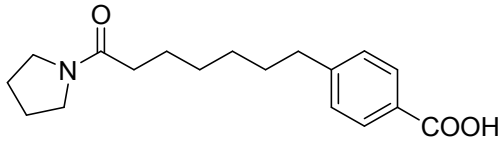
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **2d-1** with pyrrolidine afford **2d** s white solid; 68 mg, yield 78%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 3.81 (s, 3 H), 6.82 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H) ppm; MS (ESI, m/z): 290 $(M + H)^+$.

3-(7-oxo-7-(pyrrolidin-1-yl)heptyl)benzoic acid (2e)



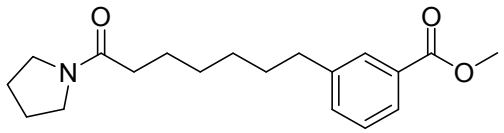
Following the **General Procedure 1.2.4** (eluent: EtOAc/PE 1: 2), the reaction of **2g** with pyrrolidine afford **2e** as yellow oil; 13 mg, yield 87%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H) 2.60 (t, J = 8.0 Hz, 2 H), 2.62 (t, J = 7.6 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 7.34 (m, 1 H), 7.35-7.42 (m, 1 H), 7.86-7.93 (m, 2 H) ppm; MS (ESI, m/z): 304 $(M + H)^+$.

4-(7-oxo-7-(pyrrolidin-1-yl)heptyl)benzoic acid (2f)



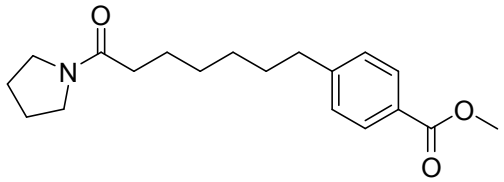
Following the **General Procedure 1.2.4** (eluent: EtOAc/PE 1: 2), the reaction of **2h** with pyrrolidine afford **2f** as yellow oil; 8 mg, yield 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.62 (t, J = 7.6 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 7.26-7.28 (m, 2 H), 8.01 (d, J = 7.8 Hz, 2 H) ppm; MS (ESI, m/z): 304 $(M + H)^+$.

methyl 3-(7-oxo-7-(pyrrolidin-1-yl)heptyl)benzoate (2g)



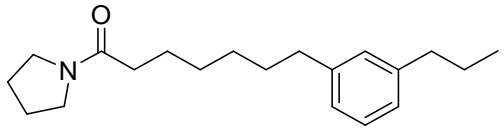
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **2g-1** with pyrrolidine afford **2g** as white solid; 23 mg, yield 24%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H) 2.60 (t, J = 8.0 Hz, 2 H), 2.62 (t, J = 7.6 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 3.95 (s, 3 H), 7.33–7.36 (m, 1 H), 7.81 (s, 1 H), 7.84–7.85 (m, 1 H) ppm; MS (ESI, m/z): 318 $(M + H)^+$.

methyl 4-(7-oxo-7-(pyrrolidin-1-yl)heptyl)benzoate (2h)



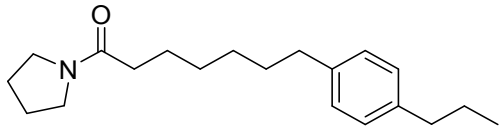
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **2h-1** with pyrrolidine afford **2h** as white solid; 36 mg, yield 38%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.62 (t, J = 7.6 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 3.92 (s, 3 H), 7.22 (d, J = 8.0 Hz, 2 H), 8.00 (d, J = 8.0 Hz, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.7, 26.0, 29.0, 29.2, 31.2, 33.6, 34.5, 45.5, 46.5, 51.9, 127.5, 128.6, 129.7, 148.8, 167.5, 178.5 ppm; MS (ESI, m/z): 318 $(M + H)^+$.

7-(3-propylphenyl)-1-(pyrrolidin-1-yl)heptan-1-one (2j)



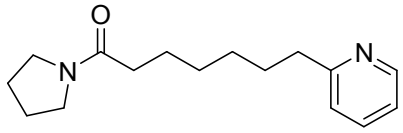
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **2i-1** with pyrrolidine afford **2i** as white solid; 42 mg, yield 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3 H), 1.36–1.40 (m, 6 H), 1.58–1.68 (m, 6 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 8.0 Hz, 2 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 6.96-7.01 (m, 3 H), 7.22 (t, J = 3.6 Hz, 1H) ppm; MS (ESI, m/z): 302 $(M + H)^+$.

7-(4-propylphenyl)-1-(pyrrolidin-1-yl)heptan-1-one (2k)



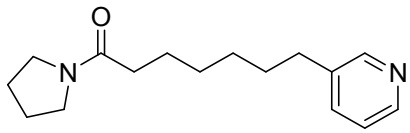
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **2k-1** with pyrrolidine afford **2k** as white solid; 21 mg, yield 23%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3 H), 1.36–1.40 (m, 6 H), 1.58–1.68 (m, 6 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 8.0 Hz, 2 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 7.09-7.10 (m, 4 H) ppm; MS (ESI, m/z): 302 $(M + H)^+$.

7-(pyridin-2-yl)-1-(pyrrolidin-1-yl)heptan-1-one (3a)



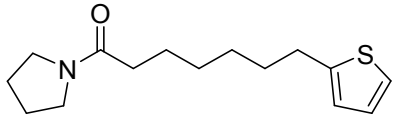
Following the **General Procedure 1.2.3** (eluent: EtOAc), the amidation of **3a-1** with pyrrolidine afford **3a** as white solid; 61 mg, yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.56 (t, J = 8.0 Hz, 2 H), 2.70 (t, J = 7.8 Hz, 2 H) , 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 7.30–7.32 (m, 1 H), 7.79–7.82 (m, 1 H), 7.82–7.88 (m, 1 H), 8.67 (d, J = 4.7 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.7, 26.0, 29.0, 29.2, 31.2, 34.2, 34.5, 45.5, 46.5, 120.5, 123.1, 136.5, 150.0, 163.3, 178.5 ppm; MS (ESI, m/z): 261 $(M + H)^+$.

7-(pyridin-3-yl)-1-(pyrrolidin-1-yl)heptan-1-one (3b)



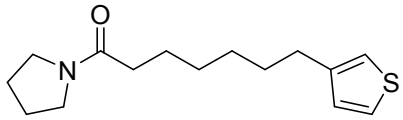
Following the **General Procedure 1.2.3** (eluent: EtOAc), the amidation of **3b-1** with pyrrolidine afford **3b** as white solid; 45 mg, yield 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.56 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 7.20–7.22 (m, 1 H), 7.48–7.51 (m, 1 H), 8.40–8.43 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.7, 26.0, 29.0, 29.2, 31.2, 34.2, 34.9, 45.5, 46.5, 120.5, 123.1, 136.5, 150.0, 163.3, 178.5 ppm; MS (ESI, m/z): 261 $(M + H)^+$.

1-(pyrrolidin-1-yl)-7-(thiophen-2-yl)heptan-1-one (3c)



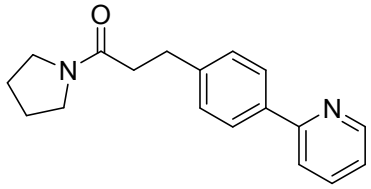
Following the **General Procedure 1.2.3** (eluent: EtOAc), the amidation of **3c-1** with pyrrolidine afford **3c** as white solid; 65 mg, yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.56 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 6.75–6.80 (m, 1 H), 6.88 (d, J = 5.1, 3.0 Hz, 1 H), 7.02 (d, J = 5.1 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.7, 26.0, 29.0, 29.2, 31.2, 34.2, 34.9, 45.5, 46.5, 122.8, 124.5, 127.3, 145.6, 178.5 ppm; MS (ESI, m/z): 266 $(M + H)^+$.

1-(pyrrolidin-1-yl)-7-(thiophen-3-yl)heptan-1-one (3d)



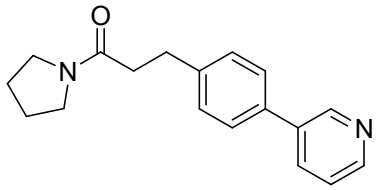
Following the **General Procedure 1.2.3** (eluent: EtOAc), the amidation of **3d-1** with pyrrolidine afford **3d** as white solid; 60 mg, yield 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.56 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 6.95–7.00 (m, 2 H), 7.23 (d, J = 5.0 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.7, 26.0, 29.0, 29.2, 31.2, 34.2, 34.9, 45.5, 46.5, 120.3, 125.5, 129.3, 143.3, 178.5 ppm; MS (ESI, m/z): 266 $(M + H)^+$.

3-(4-(pyridin-2-yl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (3e)



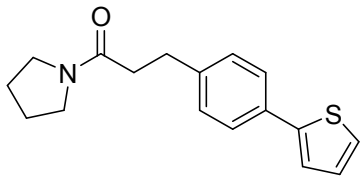
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **3e-1** with pyrrolidine afford **3e** as white solid; 9 mg, yield 11%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.87 (m, 4 H), 2.58 (t, J = 8.0 Hz, 2 H), 2.88 (t, J = 8.0 Hz, 2 H), 3.28 (t, J = 6.8 Hz, 2 H), 3.36 (t, J = 6.8 Hz, 2 H), 7.40 (d, J = 8.4 Hz, 2 H), 7.68-7.73 (m, 4 H), 8.62 (dd, J = 4.4, 1.6 Hz, 2 H) ppm; ^{13}C NMR (100 MHz, DMSO) δ 24.4, 26.1, 30.5, 35.8, 45.7, 46.2, 121.4, 127.1, 129.7, 135.2, 143.6, 147.3, 150.7, 169.9 ppm; MS (ESI, m/z): 281 $(M + H)^+$.

3-(4-(pyridin-3-yl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (3f)



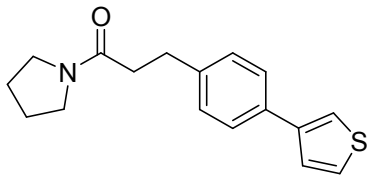
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **3f-1** with pyrrolidine afford **3f** as white solid; 7 mg, yield 8.3%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.87 (m, 4 H), 2.58 (t, J = 8.0 Hz, 2 H), 2.88 (t, J = 8.0 Hz, 2 H), 3.28 (t, J = 6.8 Hz, 2 H), 3.36 (t, J = 6.8 Hz, 2 H), 7.40 (d, J = 8.4 Hz, 2 H), 7.68-7.73 (m, 4 H), 8.62 (dd, J = 4.4, 1.6 Hz, 2 H) ppm; ^{13}C NMR (100 MHz, DMSO) δ 24.4, 26.1, 30.5, 35.8, 45.7, 46.2, 121.4, 127.1, 129.7, 135.2, 143.6, 147.3, 150.7, 169.9 ppm; MS (ESI, m/z): 281 $(M + H)^+$.

3-(4-(thiophen-2-yl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (3g)



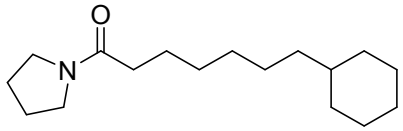
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **3g-1** with pyrrolidine afford **3g** as white solid; 55 mg, yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 6.50-6.80 (m, 1 H), 7.0-7.7 (m, 6 H) ppm; MS (ESI, m/z): 281 $(M + H)^+$.

3-(4-(thiophen-3-yl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (3h)



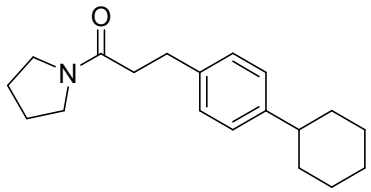
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **3h-1** with pyrrolidine afford **3h** as white solid; 62 mg, yield 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.40 (m, 4 H), 1.59–1.70 (m, 4 H), 1.83 (tt, J = 6.4, 7.0 Hz, 2 H), 1.93 (tt, J = 6.4, 7.0 Hz, 2 H), 2.23 (t, J = 7.8 Hz, 2 H), 2.60 (t, J = 8.0 Hz, 2 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 5.15-5.20 (m, 1 H), 7.40 (d, J = 8.4 Hz, 2 H), 7.52-7.57 (m, 1 H), 7.61 (d, J = 5.0 Hz, 1 H), 7.65-7.70 (m, 2 H) ppm; MS (ESI, m/z): 281 $(M + H)^+$.

7-cyclohexyl-1-(pyrrolidin-1-yl)heptan-1-one (3i)



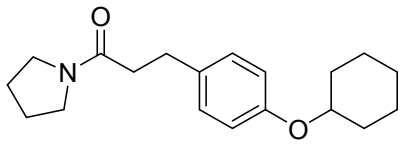
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **3i-1** with pyrrolidine afford **3i** as white solid; 54 mg, yield 67.4%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83–0.93 (m, 2 H), 1.15–1.35 (m, 12 H), 1.65–1.72 (m, 7 H), 1.81–1.88 (m, 2 H), 1.91–1.98 (m, 2 H), 2.25 (t, *J* = 8 Hz, 2 H), 3.39–3.47 (m, 4 H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 26.0, 24.5, 26.5, 26.6, 26.7, 29.4, 29.5, 33.4, 34.1, 37.2, 37.6, 45.5, 46.5, 125.8, 126.5, 128.0, 129.5, 137.8, 142.3, 178.9, 171.6 ppm; MS (ESI, m/z): 267 $(M + H)^+$.

3-(4-cyclohexylphenyl)-1-(pyrrolidin-1-yl)propan-1-one (3j)



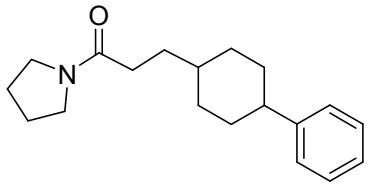
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **3j-1** with pyrrolidine afford **3j** as white solid; 12 mg, yield 14%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30-1.55 (m, 6 H), 1.8-2.01 (m, 9 H), 2.39 (s, 3 H), 2.48-3.00 (m, 3 H), 3.02 (t, J = 8.0 Hz, 2 H), 3.31 (t, J = 6.8 Hz, 2 H), 3.47 (t, J = 6.8 Hz, 2 H), 7.10-7.15 (m, 4 H) ppm; MS (ESI, m/z): 286 $(M + H)^+$.

3-(4-(cyclohexyloxy)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (3k)



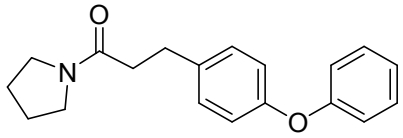
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **3k-1** with pyrrolidine afford **3k** as white solid; 66 mg, yield 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30-1.50 (m, 5H), 1.50-1.60 (m, 1 H), 1.60-2.00 (m, 8H), 2.58 (t, J = 8.0 Hz, 2 H), 2.88 (t, J = 8.0 Hz, 2 H), 3.28 (t, J = 6.8 Hz, 2 H), 3.36 (t, J = 6.8 Hz, 2 H), 4.40–4.50 (m, 1H), 6.85 (d, J = 8.0 Hz, 2 H), 7.10 (d, J = 8.0 Hz, 2 H) ppm; MS (ESI, m/z): 302 $(M + H)^+$.

3-(4-phenylcyclohexyl)-1-(pyrrolidin-1-yl)propan-1-one (4a)



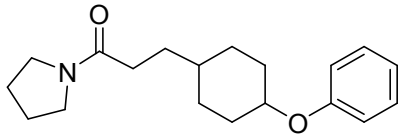
Following the **General Procedure 1.2.6** (eluent: EtOAc/PE 1: 5), the amidation of **4a-1** with pyrrolidine afford **4a** as white solid; 111 mg, yield 13%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13-2.0 (m, 13 H), 2.38-2.58 (m, 2 H), 2.88 (t, J = 8.0 Hz, 2 H), 3.28 (t, J = 6.8 Hz, 2 H), 3.36 (t, J = 6.8 Hz, 2 H), 6.8-7.5 (m, 5 H) ppm; MS (ESI, m/z): 286 $(M + H)^+$.

3-(4-phenoxyphenyl)-1-(pyrrolidin-1-yl)propan-1-one (4b)



Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **4b-1** with pyrrolidine afford **4b** as white solid; 48 mg, yield 54%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76–1.89 (m, 4 H), 2.51 (t, J = 7.2 Hz, 2 H), 2.92 (t, J = 7.2 Hz, 2 H), 3,26 (t, J = 6.8 Hz, 2 H), 3.44 (t, J = 6.8 Hz, 2 H), 5.02 (s, 2 H), 6.89 (d, J = 6.6 Hz, 2 H), 7.13 (d, J = 8.4 Hz, 2 H), 7.29–7.42 (m, 5 H) ppm; MS (ESI, m/z): 296 $(M + H)^+$.

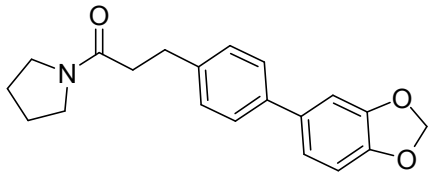
3-(4-phenoxycyclohexyl)-1-(pyrrolidin-1-yl)propan-1-one (4c)



Following the **General Procedure 1.2.8** (eluent: EtOAc/PE 1: 5), the amidation of

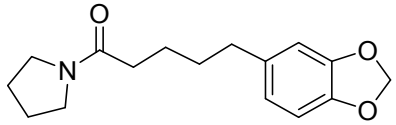
4c-1 with pyrrolidine afford **4c** as white solid; 105 mg, yield 35%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23-2.0 (m, 13 H), 2.51 (t, J = 7.2 Hz, 2 H), 2.92 (t, J = 7.2 Hz, 2 H), 3,26 (t, J = 6.8 Hz, 2 H), 3.44 (t, J = 6.8 Hz, 2 H), 4.27-4.38 (m, 1H), 6.8–7.4 (m, 5 H) ppm; MS (ESI, m/z): 302 $(M + H)^+$.

3-(4-(benzo[d][1,3]dioxol-5-yl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (4d)



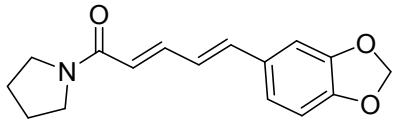
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 10), the amidation of **4d-1** with pyrrolidine afford **4d** as white solid; 56 mg, yield 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.87 (m, 4 H), 2.58 (t, J = 8.0 Hz, 2 H), 2.88 (t, J = 8.0 Hz, 2 H), 3.28 (t, J = 6.8 Hz, 2 H), 3.36 (t, J = 6.8 Hz, 2 H), 5.99 (s, 2 H), 6.5-7.3 (m, 7 H) ppm; MS (ESI, m/z): 324 $(M + H)^+$.

5-(benzo[d][1,3]dioxol-5-yl)-1-(pyrrolidin-1-yl)pentan-1-one (4e)



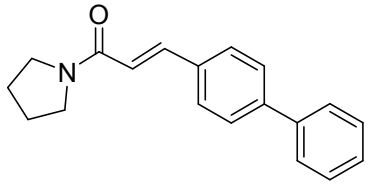
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **4e-1** with pyrrolidine afford **4e** as white solid; 26 mg, yield 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64–1.79 (m, 4 H), 1.83 (tt, J = 6.4, 6.8 Hz, 2 H), 1.88 (tt, J = 6.4, 6.8 Hz, 2 H), 2.27 (t, J = 7.2 Hz, 2 H), 2.64 (t, J = 7.2 Hz, 2 H), 3.37 (t, J = 6.8 Hz, 2 H), 3.45 (t, J = 6.8 Hz, 2 H), 5.99 (s, 2 H), 6.80-7.00 (m, 3 H) ppm; MS (ESI, m/z): 276 $(M + H)^+$.

(2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)-1-(pyrrolidin-1-yl)penta-2,4-dien-1-one (4f)



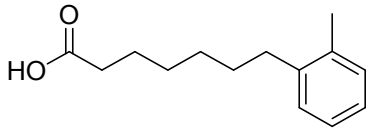
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **4f-1** with pyrrolidine afford **4f** as white solid; 27 mg, yield 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.87 (m, 4 H), 2.58 (t, J = 8.0 Hz, 2 H), 2.88 (t, J = 8.0 Hz, 2 H), 3.28 (t, J = 6.8 Hz, 2 H), 3.36 (t, J = 6.8 Hz, 2 H), 5.99 (s, 2 H), 6.45 (d, J = 15 Hz, 1 H), 6.75-6.82 (m, 3 H), 6.91 (d, J = 8.0 Hz, 1 H), 7.00 (s, 1 H), 7.33-7.45 (m, 1 H) ppm; MS (ESI, m/z): 272 $(M + H)^+$.

(E)-3-(4-phenylphenyl)-1-(pyrrolidin-1-yl)prop-2-en-1-one (4g)



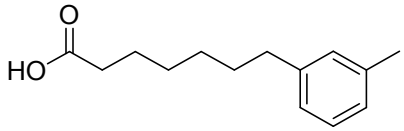
Following the **General Procedure 1.2.3** (eluent: EtOAc/PE 1: 5), the amidation of **4g-1** with pyrrolidine afford **4g** as white solid; 29 mg, yield 34%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91–1.98 (m, 4 2), 2.01–2.08 (m, 2 H), 3.62-3.70 (m, 4 H), 6.80 (d, J = 15.6 Hz, 1 H), 7.39 (t, J = 7.2 Hz, 1 H), 7.48 (t, J = 7.2 Hz, 2 H), 7.76 (d, J = 15.6 Hz, 1 H) ppm; MS (ESI, m/z): 284 $(M + H)^+$.

7-o-tolylheptanoic acid (1c-1)



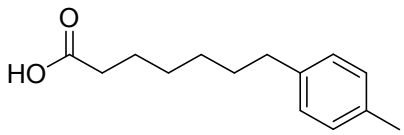
Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the Wittig reaction afforded **1c-1** as oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 4 H), 1.59–1.70 (m, 4 H), 2.32 (s, 3 H), 2.40 (t, J = 8.0 Hz, 2 H), 2.57 (t, J = 8.0 Hz, 2 H), 7.04–7.11 (m, 4 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 24.0, 28.9, 29.2, 30.0, 33.2, 34.0, 125.7, 125.8, 128.2, 130.1, 135.0, 139.4, 180.0 ppm;

7-m-tolylheptanoic acid (1d-1)



Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the Wittig reaction afforded **1d-1** as oil; 148 mg, yield 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 4 H), 1.59–1.70 (m, 4 H), 2.32 (s, 3H), 2.41 (t, J = 8.0 Hz, 2 H), 2.58 (t, J = 8.0 Hz, 2 H), 6.95-7.00 (m, 3 H), 7.21 (t, J = 3.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 24.2, 28.8, 28.9, 30.9, 34.0, 35.8, 125.8, 126.5, 128.0, 129.5, 137.8, 142.3, 178.9 ppm;

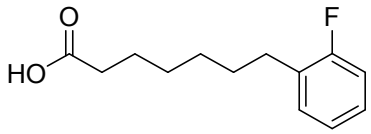
7-p-tolylheptanoic acid (1e-1)



Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the Wittig reaction afforded **1e-1** as oil; 183 mg, yield 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 4 H), 1.59–1.70 (m, 4 H), 2.32 (s, 3H), 2.41 (t, J = 7.8 Hz, 2 H), 2.58 (t, J = 7.8 Hz, 2

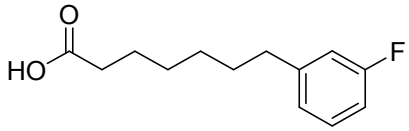
H), 7.10-7.14 (m, 4 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 24.2, 28.8, 28.9, 30.9, 34.0, 35.8, 128.5, 128.8, 135.0, 141.0, 180.0 ppm.

7-(2-fluorophenyl)heptanoic acid (1f-1)



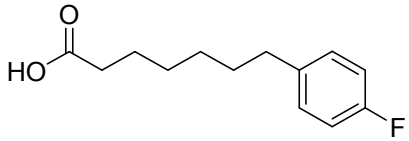
Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the Wittig reaction afforded **1f-1** as oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 4 H), 1.59–1.70 (m, 4 H), 2.41 (t, J = 7.8 Hz, 2 H), 2.65 (t, J = 7.8 Hz, 2 H), 6.95-7.00 (m, 1 H), 7.11 (td, J = 7.5, 1.2 Hz, 1 H), 7.14-7.19 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 28.8, 28.9, 29.9, 34.0, 35.8, 115.6 (d, J = 22.5 Hz), 124.0 (d, J = 3.8 Hz), 128.4 (d, J = 32.0 Hz), 130.6 (d, J = 18.0 Hz), 130.9 (d, J = 5.8 Hz), 179.5 ppm

7-(3-fluorophenyl)heptanoic acid (1g-1)



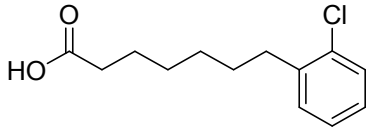
Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **1g-1** as oil; 23 mg, yield 7%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 4 H), 1.59–1.70 (m, 4 H), 2.41 (t, J = 7.8 Hz, 2 H), 2.60 (t, J = 7.8 Hz, 2 H), 6.85–6.90 (m, 2 H), 6.94 (d, J = 8.0 Hz, 1 H), 7.20–7.25 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 28.8, 28.9, 30.9, 34.0, 35.8, 112.5 (d, J = 21.3 Hz), 116.1 (d, J = 22.0 Hz), 120.0 (d, J = 2.5 Hz), 130.2 (d, J = 7.8 Hz), 146.0 (d, J = 7.0 Hz), 164.0 (d, J = 248.0 Hz), 180.1 ppm

7-(4-fluorophenyl)heptanoic acid (1h-1)



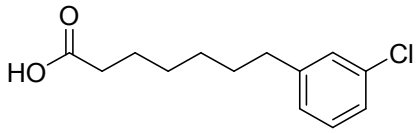
Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **1h-1** as oil; 47 mg, yield 14%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 4 H), 1.59–1.70 (m, 4 H), 2.41 (t, J = 7.8 Hz, 2 H), 2.58 (t, J = 7.8 Hz, 2 H), 6.95–7.00 (m, 2 H), 7.10–7.14 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 28.8, 28.9, 29.6, 34.0, 35.8, 115.5 (d, J = 22.5 Hz), 129.2 (d, J = 8.0 Hz), 140.0 (d, J = 2.5 Hz), 162.0 (d, J = 245.0 Hz), 180.0 ppm

7-(2-chlorophenyl)heptanoic acid (1i-1)



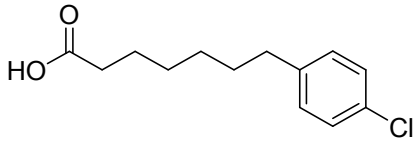
Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **1i-1** as oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 4 H), 1.59–1.70 (m, 4 H), 2.41 (t, J = 7.8 Hz, 2 H), 2.62 (t, J = 7.8 Hz, 2 H), 7.12–7.15 (m, 1 H), 7.15–7.21 (m, 2 H), 7.30–7.33 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 28.8, 28.9, 29.5, 34.0, 35.5, 127.0, 127.2, 130.1, 130.2, 134.5, 140.1, 180.1 ppm.

7-(3-chlorophenyl)heptanoic acid (1j-1)



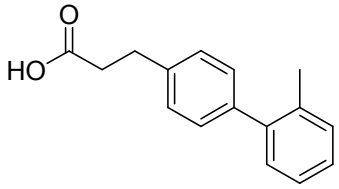
Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **1j-1** as oil; 31 mg, yield 8.6%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 4 H), 1.59–1.70 (m, 4 H), 2.41 (t, J = 7.8 Hz, 2 H), 2.58 (t, J = 7.8 Hz, 2 H), 7.08 (d, J = 7.5 Hz, 1 H), 7.15–7.18 (m, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 28.8, 28.8, 30.5, 34.1, 35.6, 127.0, 128.5, 129.8, 134.3, 145.2, 180.1 ppm.

7-(4-chlorophenyl)heptanoic acid (1k-1)



Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **1k-1** as oil; 16 mg, yield 4%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 4 H), 1.59–1.70 (m, 4 H), 2.41 (t, J = 7.8 Hz, 2 H), 2.58 (t, J = 7.8 Hz, 2 H), 7.08 (d, J = 8.0 Hz, 2 H), 7.21 (d, J = 8.0 Hz, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 28.8, 28.8, 30.5, 34.1, 35.6, 128.5, 130.2, 132.1, 140.3, 178.5 ppm.

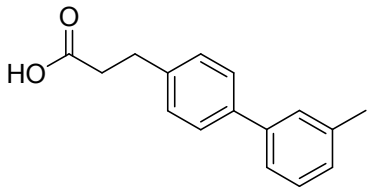
3-(4-(2-methylphenyl)phenyl)propanoic acid (1l-1)



Following the **General Procedure 1.2.1** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **1l-1** as oil; 18 mg, yield 5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3 H),

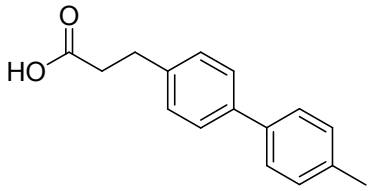
2.73 (t, J = 8.0 Hz, 2 H), 3.00 (t, J = 8.0 Hz, 2 H), 7.04 (m, 1 H), 7.13–7.19 (m, 6 H), 7.32–7.37 (m, 1 H) ppm.

3-(4-(3-methylphenyl)phenyl)propanoic acid (1m-1)



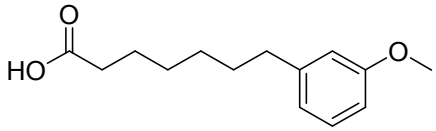
Following the **General Procedure 1.2.1** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **1m-1** as oil; 45 mg, yield 45 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 2.73 (t, J = 8.0 Hz, 2 H), 3.00 (t, J = 8.0 Hz, 2 H), 7.15 (m, 2 H), 7.31 (m, 3 H), 7.33 (d, J = 7.6 Hz, 2 H), 7.51 (d, J = 7.8 Hz, 2 H) ppm.

3-(4-(4-methylphenyl)phenyl)propanoic acid (1n-1)



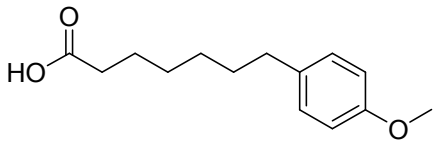
Following the **General Procedure 1.2.1** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **1n-1** as oil; 137 mg, yield 38%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 2.73 (t, J = 8.0 Hz, 2 H), 3.00 (t, J = 8.0 Hz, 2 H), 7.23-7.30 (m, 4 H), 7.47 (d, J = 8.0 Hz, 2 H), 7.51 (d, J = 8.0 Hz, 2 H) ppm.

7-(3-methoxyphenyl)heptanoic acid (2c-1)



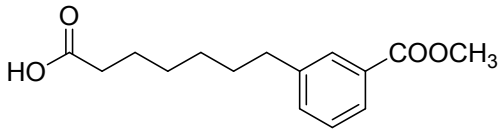
Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **2c-1** as oil; 36 mg, yield 10%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 4 H), 1.59–1.70 (m, 4 H), 2.41 (t, J = 7.8 Hz, 2 H), 2.58 (t, J = 7.8 Hz, 2 H), 3.81 (s, 3 H), 6.73–6.75 (m, 2 H), 6.75 (d, J = 7.8 Hz, 1H), 7.15-7.20 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 28.8, 28.9, 30.5, 34.1, 35.6, 56.3, 111.2, 113.8, 121.5, 128.5, 144.5, 160.2, 179.5 ppm.

7-(4-methoxyphenyl)heptanoic acid (2d-1)



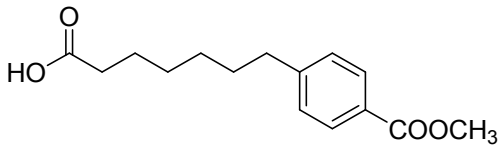
Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **2d-1** as oil; 64 mg, yield 18%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35–1.40 (m, 4 H), 1.60–1.70 (m, 4 H), 2.41 (t, J = 7.8 Hz, 2 H), 2.58 (t, J = 7.8 Hz, 2 H), 3.81 (s, 3 H), 6.82 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 28.8, 28.9, 31.5, 34.1, 35.0, 55.2, 113.8, 128.5, 134.5, 158.4, 180.0 ppm.

7-(3-(methoxycarbonyl)phenyl)heptanoic acid (2g-1)



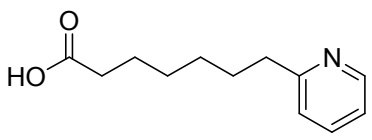
Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **2g-1** as oil; 33 mg, yield 8.3%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35–1.40 (m, 4 H), 1.60–1.72 (m, 4 H), 2.57 (t, J = 7.6 Hz, 2 H), 2.62 (t, J = 7.6 Hz, 2 H), 3.95 (s, 3 H), 7.33–7.36 (m, 1 H), 7.81 (s, 1 H), 7.84–7.85 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 28.8, 29.2, 31.1, 34.1, 35.0, 51.9, 127.1, 128.5, 130.1, 130.2, 133.2, 143.5, 170.4, 179.8 ppm.

7-(4-(methoxycarbonyl)phenyl)heptanoic acid (2h-1)



Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **2h-1** as oil; 91 mg, yield 23%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35–1.40 (m, 4 H), 1.60–1.72 (m, 4 H), 2.50 (t, J = 7.8 Hz, 2 H), 2.58 (t, J = 7.8 Hz, 2 H), 3.92 (s, 3 H), 7.22 (d, J = 8.0 Hz, 2 H), 8.00 (d, J = 8.0 Hz, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 28.8, 29.2, 31.1, 34.1, 35.0, 51.9, 127.5, 128.6, 129.7, 148.8, 167.5, 179.8 ppm.

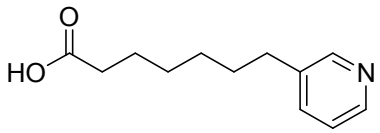
7-(pyridin-2-yl)heptanoic acid (3a-1)



Following the **General Procedure 1.2.2** (eluent: MeOH/$CHCl_3$ 1: 15), the wittig

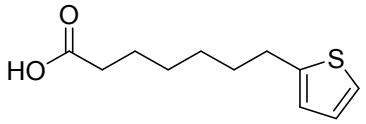
reaction afforded **3a-1** as oil; 11 mg, yield 3.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38–1.42 (m, 4 H), 1.60–1.68 (m, 4 H), 2.58 (t, J = 7.8 Hz, 2 H), 2.70 (t, J = 7.8 Hz, 2 H), 7.30–7.32 (m, 1 H), 7.79–7.82 (m, 1 H), 7.82–7.88 (m, 1 H), 8.67 (d, J = 4.7 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 28.8, 29.2, 30.5, 34.1, 35.0, 123.0, 136.1, 136.5, 147.6, 149.4, 179.8 ppm.

7-(pyridin-3-yl)heptanoic acid (3b-1)



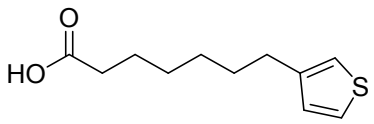
Following the **General Procedure 1.2.2** (eluent: MeOH/$CHCl_3$ 1: 15), the wittig reaction afforded **3b-1** as oil; 18 mg, yield 6%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38–1.48 (m, 4 H), 1.60–1.70 (m, 4 H), 2.60 (t, J = 8.0 Hz, 2 H), 2.62 (t, J = 8.0 Hz, 2 H), 7.20–7.22 (m, 1 H), 7.48–7.51 (m, 1 H), 8.40–8.43 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 28.8, 29.2, 30.5, 34.1, 35.0, 123.0, 136.1, 136.5, 147.6, 149.4, 180.0 ppm.

7-(thiophen-2-yl)heptanoic acid (3c-1)



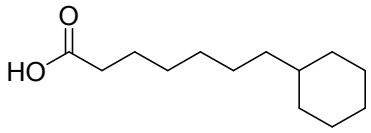
Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **3c-1** as oil; 125 mg, yield 39%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 4 H), 1.59–1.70 (m, 4 H), 2.41 (t, J = 8.0 Hz, 2 H), 2.65 (t, J = 8.0 Hz, 2 H), 6.75–6.80 (m, 1 H), 6.88 (d, J = 5.1, 3.0 Hz, 1 H), 7.02 (d, J = 5.1 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 28.8, 28.9, 30.5, 34.1, 35.6, 56.3, 122.8, 124.5, 127.3, 145.6, 182.1 ppm.

7-(thiophen-3-yl)heptanoic acid (3d-1)



Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **3d-1** as oil; 98 mg, yield 31%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 4 H), 1.59–1.70 (m, 4 H), 2.41 (t, J = 8.0 Hz, 2 H), 2.65 (t, J = 8.0 Hz, 2 H), 6.95–7.00 (m, 2 H), 7.23 (d, J = 5.0 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 28.8, 28.9, 29.2, 30.1, 34.1, 120.3, 125.5, 129.3, 143.3, 182.1 ppm.

7-cyclohexylheptanoic acid (3i-1)



Following the **General Procedure 1.2.2** (eluent: EtOAc/PE 1: 3), the wittig reaction afforded **3i-1** as oil; 157 mg, yield 49%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83–0.93 (m, 2 H), 1.15–1.35 (m, 12 H), 1.65–1.72 (m, 7 H), 2.35 (t, J = 7.8 Hz, 2 H) ppm;^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 26.5, 26.6, 26.7, 29.4, 29.5, 33.4, 34.1, 37.2, 37.6, 180.1 ppm;

1.3 HPLC-MS/MS Analysis

A HPLC-MS/MS method was developed and validated for free fatty acids (FFAs) quantification. An ABI 3200 Q-Trap mass spectrometer equipped with Agilent 1200-HPLC system was used. FFAs were eluted at 1.0 mL min^{-1} at 40°C with MeOH: water (95:5, v/v, each containing 0.25% acetic acid and 5 mmol/L ammonium acetate, pH = 7.4. The molecular ions were monitored by ESI negative mode at m/z = 267 for heptadecenoic acid, m/z 303 for arachidonic acid, and m/z 269 for heptadecanoic acid.

1.4 Protein preparation and enzymatic assay

HEK293 cells overexpressing rat NAAA (HEK293-rNAAA) [1] and rat FAAH (HEK293-rFAAH) [2] were kind gifts from Dr. Daniele Piomelli in University of California, Irvine. HEK293 cells overexpressing rat NAAA (HEK293–rNAAA) or rat FAAH (HEK293–rFAAH) were maintained in Dulbecco's modified Eagle medium (DMEM, Hyclone, Beijing, China) supplemented with 10% fetal bovine serum (FBS, Gibco®, Shanghai, China) containing 0.3 mg/mL geneticin G418. HEK293–rNAAA or HEK293–rFAAH cells were harvested, washed with PBS, sonicated in 20 mM Tris–HCl (pH = 7.5) containing 0.32 M sucrose, and centrifuged at 800 × g for 15 min at 4°C. The supernatants were collected, and the protein concentrations were measured by a BCA protein assay kit (Pierce, Shanghai, China). NAAA activity was measured by incubating 30 μg recombinant rNAAA protein with 25 μM heptadecenoylethanolamide at 37°C for 30 min in 0.2 mL of phosphate buffer (50 mM, pH = 4.5) containing 0.1% Triton X-100 and 3 mM dithiothreitol with or without the tested compounds. FAAH activity was measured by incubating 30 μg of protein derived from the HEK293–rFAAH cell extract at 37°C in Tris–HCl buffer (50 mM, pH = 8.0) containing fatty acid-free bovine serum albumin (0.05%). Anandamide (25 μM) was used as the substrate for FAAH. The reactions were

terminated by adding 200 μL of methanol containing 1 nmol heptadecanoic acid as internal standard, and the remaining substrates were analysed by HPLC-MS/MS. AC activity was measured by incubating 100 μg of recombinant rAC protein at 37 °C for 30 min in 0.2 mL of phosphate buffer (50 mM, pH 5.0) containing 0.1% Triton X-100 and 3 mM DTT, 100 μM N-lauroylceramide as the substrate, and the test compound. The reactions were terminated by adding 0.2 mL of methanol containing 1 nmol heptadecanoic acid, and the products were analyzed by LC/MS. IC_{50} of each compound was analysed by GraphPad Prism 5.

1.5 In Vitro chemical and rat plasma stability.

Chemical and rat plasma stability was investigated in basic Tris–HCl buffer (50 mM, pH = 7.4), acidic phosphate buffer (50 mM, pH = 5.0), and 80% rat plasma solution (fresh plasma was diluted to 80% (v/v) with PBS (pH = 7.4)). Solutions (5 μL) of compounds **4g** in DMSO were prepared and incubated with a buffer solution or plasma solution (final DMSO concentration ≤ 1%; final compounds concentration = 1 μM). The resulting mixture was maintained at 37 °C for 16 h and the remaining compound was analyzed by HPLC.

1.6 In vivo biological evaluation of 4g

All animal experiments were performed in accordance with Guide and Care and Use of Laboratory Animals from National Institutes of Health (NIH) and approved by the Animal Care and Use Committees of Xiamen University in China.

We used Lipopolysaccharides (LPS)-induced acute lung injury (ALI) model to test the anti-inflammatory effect of **4g**. 129s mice (20–22 g) were randomly grouped, with 6-8 animals for each group. Mice were anesthetized and instilled intratracheally with LPS (7 mg/kg) in 40–50 μL PBS. Oral administration of **4g** (30 mg/kg, dissolved in saline with 5% polyethylene glycol 400 and 5% tween 80) or its vehicle once daily with or without PPAR-α antagonist MK886 (2 mg/kg, *i.p.*) starting from the day of LPS application. Animals were sacrificed 5 days after LPS treatment.

1.7 H&E assay

The whole lungs of mice were harvested and fixed in paraformaldehyde at 4 °C, followed by embedding in paraffin and sectioning to 5 μm using a microtome. The slices were then stained with hematoxylin and eosin (H&E) after deparaffinized with xylene. Imaging of stained areas was performed with a light microscopy (Nikon, Shanghai, China) using 4 × objectives.

1.8 Docking

Molecular docking was performed on Surflex-Dock GeomX module of Sybyl 2.0. Crystal structure of human NAAA (PDB code: 6DY2) obtained from Protein Data Bank was used as the receptors for molecular docking study. Our compound Structure was drawn and optimized with SYBYL package. The docking procedure was started with the protocol generation. The protocol was created using a ligand-based approach (native ligand for NAAA structure). Proto threshold was set to 0.5 and proto bloat was left at 0 as a default parameter. For docking, max conformation and max rotation values were 20 and 100, respectively. Docking results were compared by the total score values. A higher total-score value represents better docking of the ligands in the receptor site.

Table S1. Inhibitory effects of compounds **3j**, **3k** and **4g** on rat FAAH and rat AC activities[a]

	IC_{50} (FAAH) (µM)	**AC Inhibition on 100 µM**
3j	33 ± 8.5	4%
3k	21 ± 3.3	8%
4g	550 ± 70	6%

[a]Data are presented as IC_{50} ± standard error of the mean. All experiments were performed in triplicate

References

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