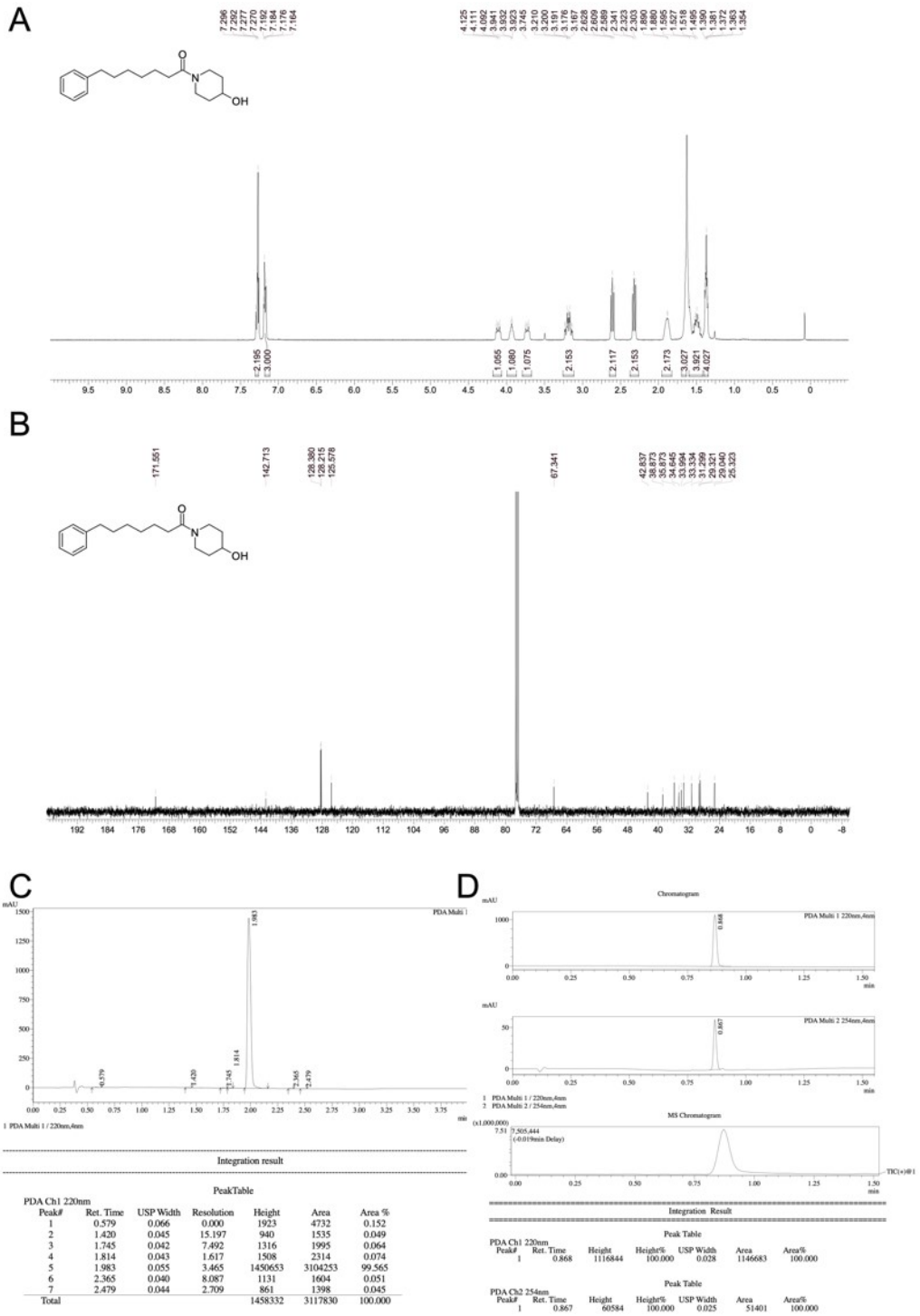
SUPPLEMENTARY MATERIALS

Detailed synthetic methods and characterization of ***compounds 3–13****.*

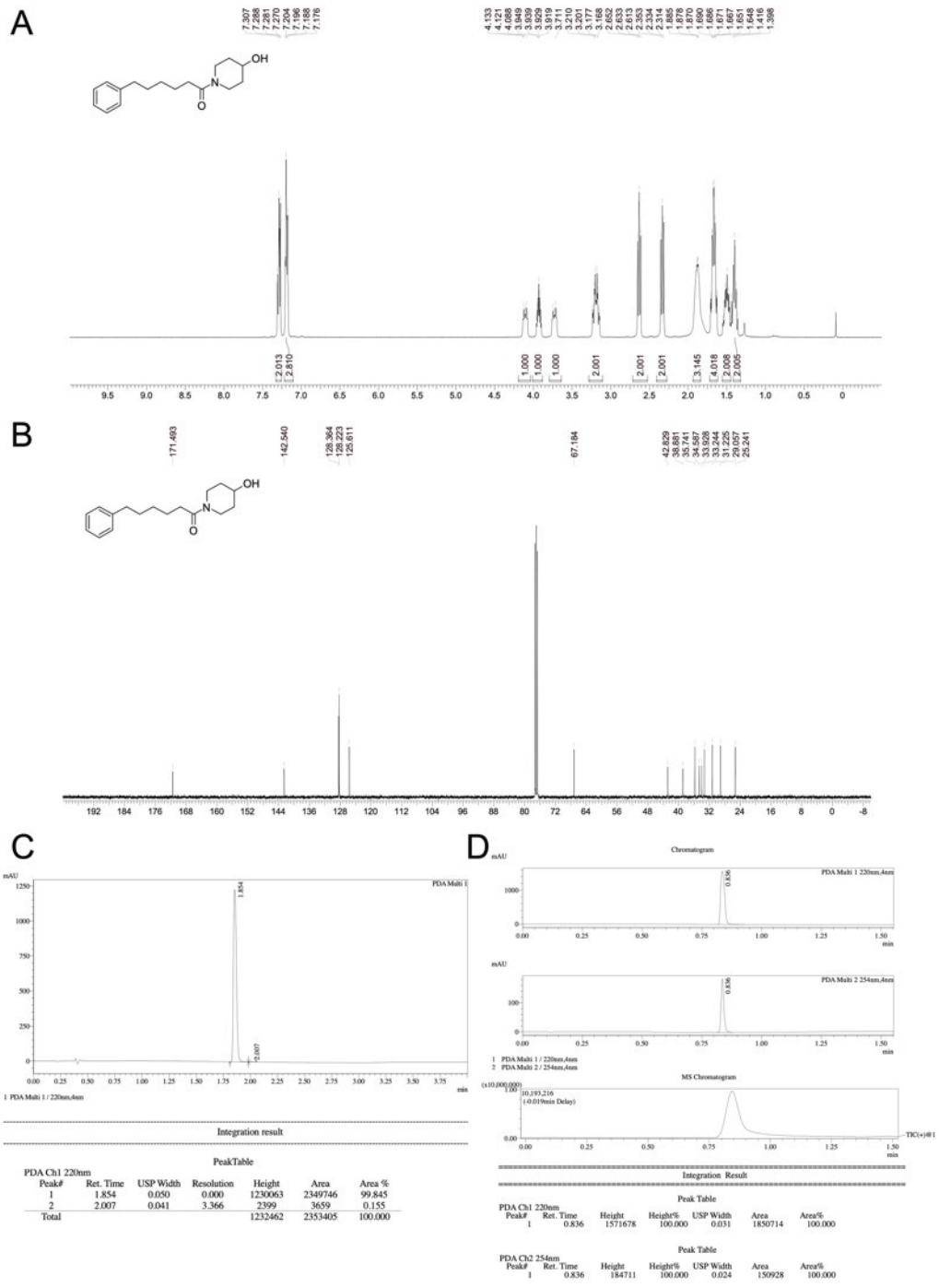
Compounds were synthesized at WuXi Apptec Co. Ltd. Starting materials whose preparation is not reported in this Experimental Section are known compounds purchased by WuXi Apptec Co. Ltd. from third party suppliers. The methods of NMR, analytical HPLC and LC-MS and the synthesis procedure for compound **2** were reported previously [15].

*1-(4-hydroxypiperidin-1-yl)-7-phenylheptan-1-one (****compound 3****).* To a solution of 7phenylheptanoic acid (**3a**, 100 mg, 484 μmol) in DMF (1.00 mL) was added HOBt (78.6 mg, 581 μmol), EDCI (139 mg, 727 μmol) and DIEA (125 mg, 969 μmol, 168 μL). Then we added piperidin-4-ol (**3b**, 53.9 mg, 533 mol) and stirred at 25 °C for 16 h. The mixture was purified by Pre-HPLC (column: Phenomenex Gemini-NX C18 75 * 30 mm * 3 μm; mobile phase: [water (0.1% TFA) - ACN]; B%: 45%-55%, 7 min). After pre-HPLC purification, the residue was adjusted to pH 7 with saturated sodium bicarbonate solution and extracted with EtOAc (20.0 mL * 2). The combined organic layers were dried over Na_2SO_4 and then concentrated under vacuum at 40 °C and the residue was added with H_2O (20.0 mL) and ACN (2.50 mL). The mixture was lyophilized to obtain **3** (31.1 mg, 106 μmol, 22.1% yield, 99.5% purity) as a yellow oil. LC-MS: Rt = 0.868 min, m/z = 290.1(M+H). HPLC: Rt = 1.983 min, 99.5% purity under 220 nm. ^{1}H NMR: 400 MHz $CDCl_3$ δ: 7.26 - 7.30 (m, 2H), 7.16 - 7.19 (m, 3H), 4.08 - 4.14 (m, 1H), 3.92 - 3.94 (m, 1H), 3.70 - 3.76 (m, 1H), 3.14 – 3.23 (m, 2H), 2.59 - 2.63 (m, 2H), 2.30 - 2.34 (m, 2H), 1.86 - 1.89 (m, 2H), 1.55 – 1.62 (m, 4H), 1.46 - 1.53 (m, 2H),
1.35 – 1.39 (m, 4H). ^{13}C NMR: 400 MHz $CDCl_3$ δ: (171, 142, 128, 125, 77.3, 77.2, 76.7, 67.3, 42.8, 38.8, 35.8, 34.6, 34.0, 33.3, 31.3, 29.3, 29.0, 25.3) ppm.



Supplemental Figure S1. *^{1}H NMR, ^{13}C NMR, HPLC and LC-MS chromatography of* ***compound 3***. **A.** ^{1}H NMR: 400 MHz $CDCl_3$ δ: 7.26 - 7.30 (m, 2H), 7.16 - 7.19 (m, 3H), 4.08 - 4.14 (m, 1H), 3.92 - 3.94 (m, 1H), 3.70 - 3.76 (m, 1H), 3.14 – 3.23 (m, 2H), 2.59 - 2.63 (m, 2H), 2.30 - 2.34 (m, 2H), 1.86 - 1.89 (m, 2H), 1.55 – 1.62 (m, 4H), 1.46 - 1.53 (m, 2H), 1.35 – 1.39 (m, 4H). **B.** ^{13}C NMR: 400 MHz $CDCl_3$ δ: (171, 142, 128, 125, 77.3, 77.2, 76.7, 67.3, 42.8, 38.8, 35.8, 34.6, 34.0, 33.3, 31.3, 29.3, 29.0, 25.3) ppm. **C.** HPLC: Rt = 1.983 min, 99.5% purity under 220 nm. **D.** LC-MS: Rt = 0.868 min, m/z = 290.1(M+H).

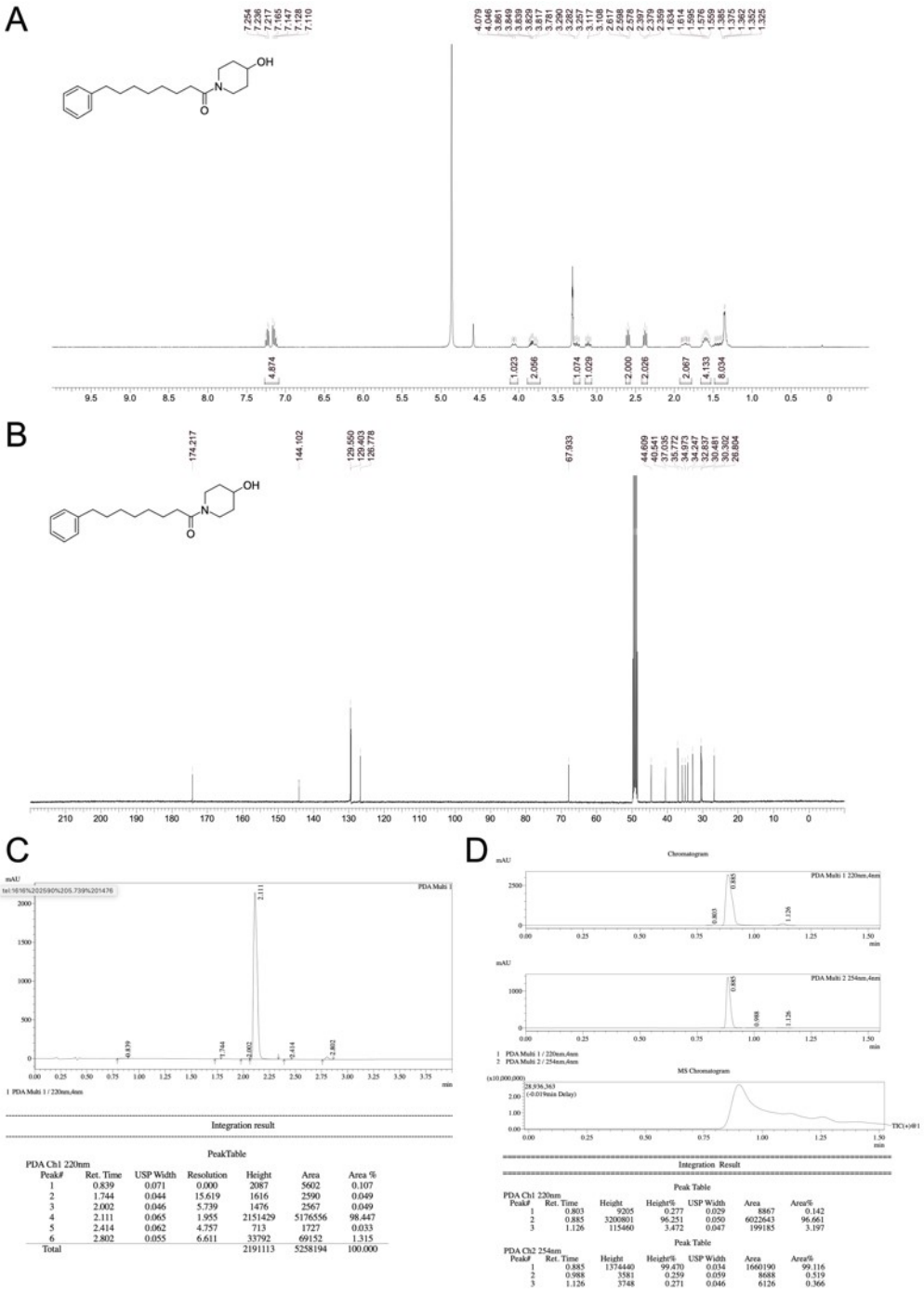
1-(4-hydroxypiperidin-1-yl)-6- phenylhexan-1-one (***compound 4***). HOBt (84.3 mg, 624 μmol) was added to a solution of 6-phenylhexanoic acid (**4a**, 100 mg, 520 μmol, 98.0 μL) in DMF (1.00 mL), DIEA (134 mg, 1.04 mmol, 181 μL), EDCI (150 mg, 780 μmol) and **3b** (57.9 mg, 572 μmol). The mixture was stirred at 30 °C for 16 h and was purified by PreHPLC (column: Phenomenex Gemini-NX C18 75 * 30mm * 3μm; mobile phase: [water (0.1%TFA) - ACN]; B%: 38% - 48%, 7 min). The residue was adjusted to pH 7 with saturated sodium bicarbonate solution and extracted with EtOAc (20.0 mL * 3). The combined organic layers were dried over Na_2SO_4, and then concentrated under reduced pressure to give a residue, and we added H_2O (15 mL) and ACN (5.0 mL). Then, the mixture was lyophilized to obtain **4** (49.2 mg, 178 μmol, 34.3% yield, 99.8% purity) as a white solid. LCMS: Rt = 0.836 min, m/z = 276.1(M+H). HPLC: Rt = 1.854 min, 99.8% purity under 220 nm. ^{1}H NMR: 400 MHz $CDCl_3$ δ: 7.27 - 7.31 (m, 2H), 7.18 - 7.20 (m, 3H), 4.09 - 4.13 (m, 1H), 3.92 - 3.95 (m, 1H), 3.71 - 3.91 (m, 1H), 3.17 – 3.21 (m, 2H), 2.61 - 2.65 (m, 2H), 2.31 - 2.35 (m, 2H), 1.87 - 1.89 (m, 3H), 1.67 – 1.69 (m, 4H), 1.64 - 1.65 (m, 2H), 1.40 – 1.42 (m, 2H). ^{13}C NMR: 400 MHz $CDCl_3$ δ: (171, 143, 128, 126, 67.2, 42.8, 38.9, 35.7, 34.6, 33.9, 33.2, 31.2, 29.1, 25.2) ppm.



Supplemental Figure S2. *[1]H NMR, [13]C NMR, HPLC and LC-MS chromatography of* ***compound 4***. **A.** [1]H NMR: 400 MHz $CDCl_3$ δ: 7.27 - 7.31 (m, 2H), 7.18 - 7.20 (m, 3H), 4.09 - 4.13 (m, 1H), 3.92 - 3.95 (m, 1H), 3.71 - 3.91 (m, 1H), 3.17 – 3.21 (m, 2H), 2.61 - 2.65 (m, 2H), 2.31 - 2.35 (m, 2H), 1.87 - 1.89 (m, 3H), 1.67 – 1.69 (m, 4H), 1.64 - 1.65 (m, 2H), 1.40 – 1.42 (m, 2H). **B.** [13]C NMR: 400 MHz $CDCl_3$ δ: (171, 143, 128, 126, 67.2, 42.8, 38.9, 35.7, 34.6, 33.9, 33.2, 31.2, 29.1, 25.2) ppm. **C.** HPLC: Rt = 1.854 min, 99.8% purity under 220 nm. **D.** LC-MS: Rt = 0.836 min, m/z = 276.1(M+H).

*1-(4-hydroxypiperidin-1-yl)-8-phenyloctan-1-one (****compound 5****).* HOBt (73.6 mg, 544.6 μmol), EDCI (130 mg, 680 μmol), DIEA (117 mg, 907 μmol, 158 μL) and **3a** (53.9 mg, 533 μmol) were added

to a solution of 9phenylnonan-2-one (**5a**, 100 mg, 453 μmol) in DMF (1.00 mL). The mixture was stirred at 30 °C for 3.5 h and purified by Pre-HPLC (column: Phenomenex Gemini-NX C18 75 * 30 mm * 3 μm; mobile phase: [water (0.1%TFA) - ACN]; B%: 52%-62%, 7 min). The residue was adjusted to pH 7 with saturated sodium bicarbonate solution and extracted with EtOAc (20 mL * 3). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure to give a residue, and we added H_2O (10 mL) and ACN (1.00 mL) before the mixture was lyophilized to give **5** (45.2 mg, 146 μmol, 32.3% yield, 98.4% purity) as an off-white solid. LC-MS: Rt = 0.885 min, m/z = 304.2 (M+H)+. HPLC: Rt = 2.111 min, 98.4% purity under 220 nm. ^{1}H NMR: 400 MHz MeOD δ: 7.2 - 7.25 (m, 2H), 7.11 - 7.17 (m, 3H), 4.05 - 4.08 (m, 1H), 3.78 - 3.86 (m, 2H), 3.26 - 3.29 (m, 1H), 3.11 - 3.12 (m, 1H), 2.58 - 2.62 (m, 2H), 2.36 - 2.40 (m, 2H), 1.56 - 1.63 (m, 2H),1.38-1.39
(m, 4H),1.33-1.36(m, 8H). ^{13}C NMR: 400 MHz MeOD δ: 174, 144, 130, 127, 67.9, 44.6, 40.5, 37.0, 35.8, 35.0, 34.2, 32.8, 30.5, 30.3, 26.8) ppm.

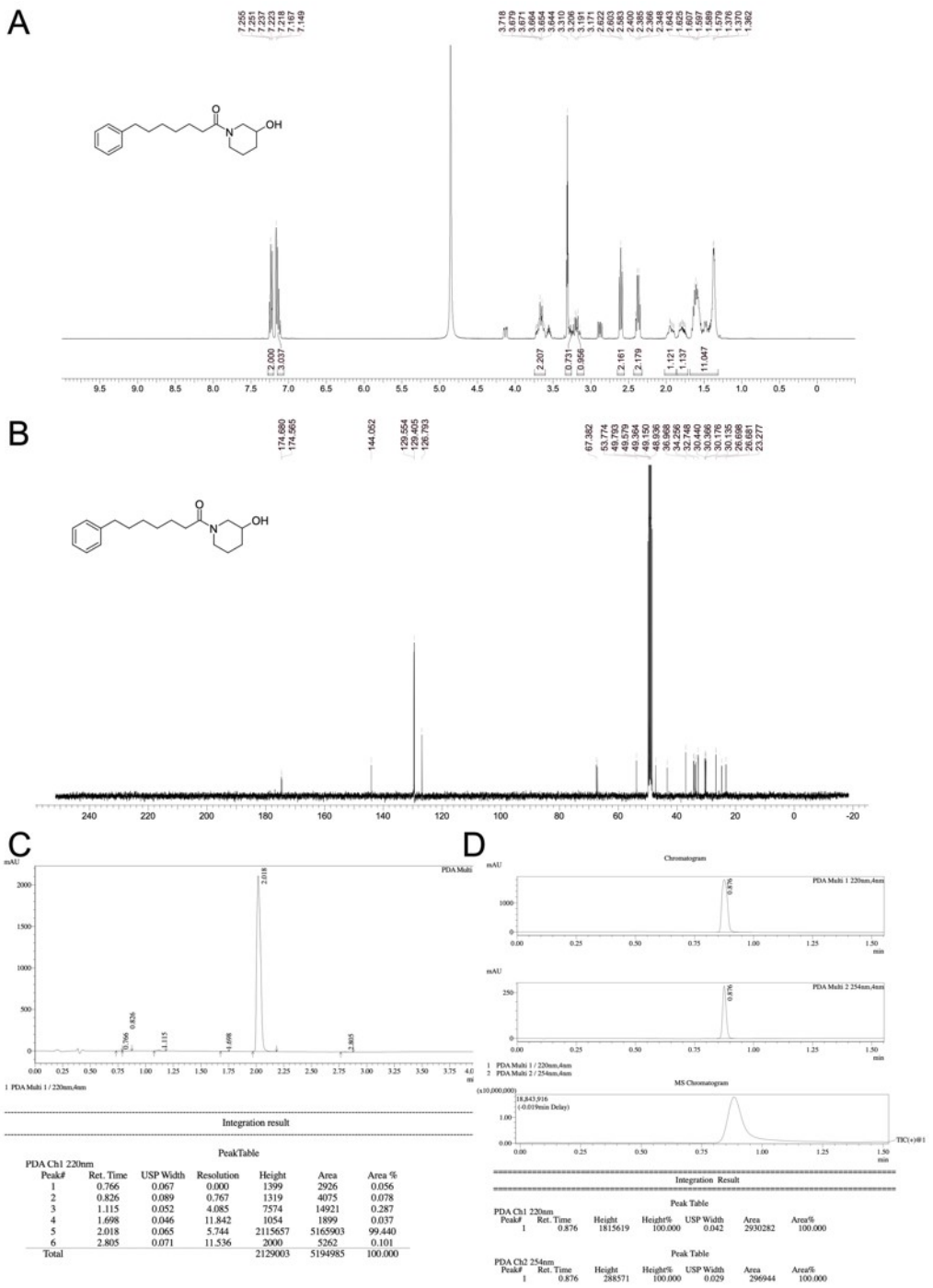


Supplemental Figure S3. *[1]H NMR, [13]C NMR, HPLC and LC-MS chromatography of* ***compound 5***. **A.** [1]H NMR: 400 MHz MeOD δ: 7.2 - 7.25 (m, 2H), 7.11 - 7.17 (m, 3H), 4.05 - 4.08 (m, 1H), 3.78 - 3.86 (m, 2H), 3.26 - 3.29 (m, 1H), 3.11 - 3.12 (m, 1H), 2.58 - 2.62 (m, 2H), 2.36 - 2.40 (m, 2H), 1.56 - 1.63 (m, 2H),1.38-1.39 (m, 4H),1.33-1.36(m, 8H). **B.** [13]C NMR: 400 MHz MeOD δ: 174, 144, 130, 127, 67.9, 44.6, 40.5, 37.0, 35.8, 35.0, 34.2, 32.8, 30.5, 30.3, 26.8) ppm. **C.** HPLC: Rt = 2.111 min, 98.4% purity under 220 nm. **D.** LC-MS: Rt = 0.885 min, m/z = 304.2 (M+H)+.

*1-(3-hydroxypiperidin-1-yl)-7-phenylheptan-1-one (****compound 6****).* HOBt (78.6 mg, 581 μmol), EDCI (139 mg, 727 μmol) and DIEA (125 mg, 969 μmol, 168 μL) were added to a solution of 7phenylheptanoic acid (**6a**, 100 mg, 484 μmol) in DMF (1.00 mL). Then, piperidin-3-ol (**6b**, 53.9 mg,

533 μmol) was added to the mixture and stirred at 25 °C for 16 h. The mixture was then purified by Pre-HPLC (column: Phenomenex Gemini-NX C18 75 * 30mm * 3um; mobile phase: [water (0.1% TFA) - ACN]; B%: 48% - 58%, 7 min). The residue was adjusted to pH 7 with saturated sodium bicarbonate solution and extracted with EtOAc (20.0 mL * 3). The combined organic layers were dried over Na_2SO_4 and then concentrated under vacuum at 45°C. Then, the residue was added with H_2O (20.0mL) and ACN (2.50mL). The mixture was lyophilized to give **6** (35.5 mg, 121 μmol, 25.2% yield, 99.4% purity) as a light-yellow oil. LC-MS: Rt = 0.876 min, m/z = 290.2 (M+H)-. HPLC: Rt = 2.018 min, 99.4% purity under 220 nm. ^{1}H NMR: 400 MHz MeOD-d4 δ: 7.20 - 7.28 (m, 2H), 7.10 - 7.18 (m, 3H), 3.62 - 3.70 (m, 2H), 3.23 – 3.29 (m, 1H), 3.15 - 3.21 (m, 1H), 2.60 (t, J = 7.6 Hz, 2H), 2.35 - 2.40 (m, 2H), 1.90 - 1.95 (m, 1H), 1.75 – 1.83 (m, 1H), 1.36 - 1.64

(m, 11H).^{13}C NMR: 400 MHz MeOD-d4 δ: (174, 144, 129, 126, 67.3, 53.7, 47.3, 43.3, 36.9, 34.3, 33.8, 33.5, 32.7, 30.4, 30.2, 26.6, 24.7, 23.3) ppm.

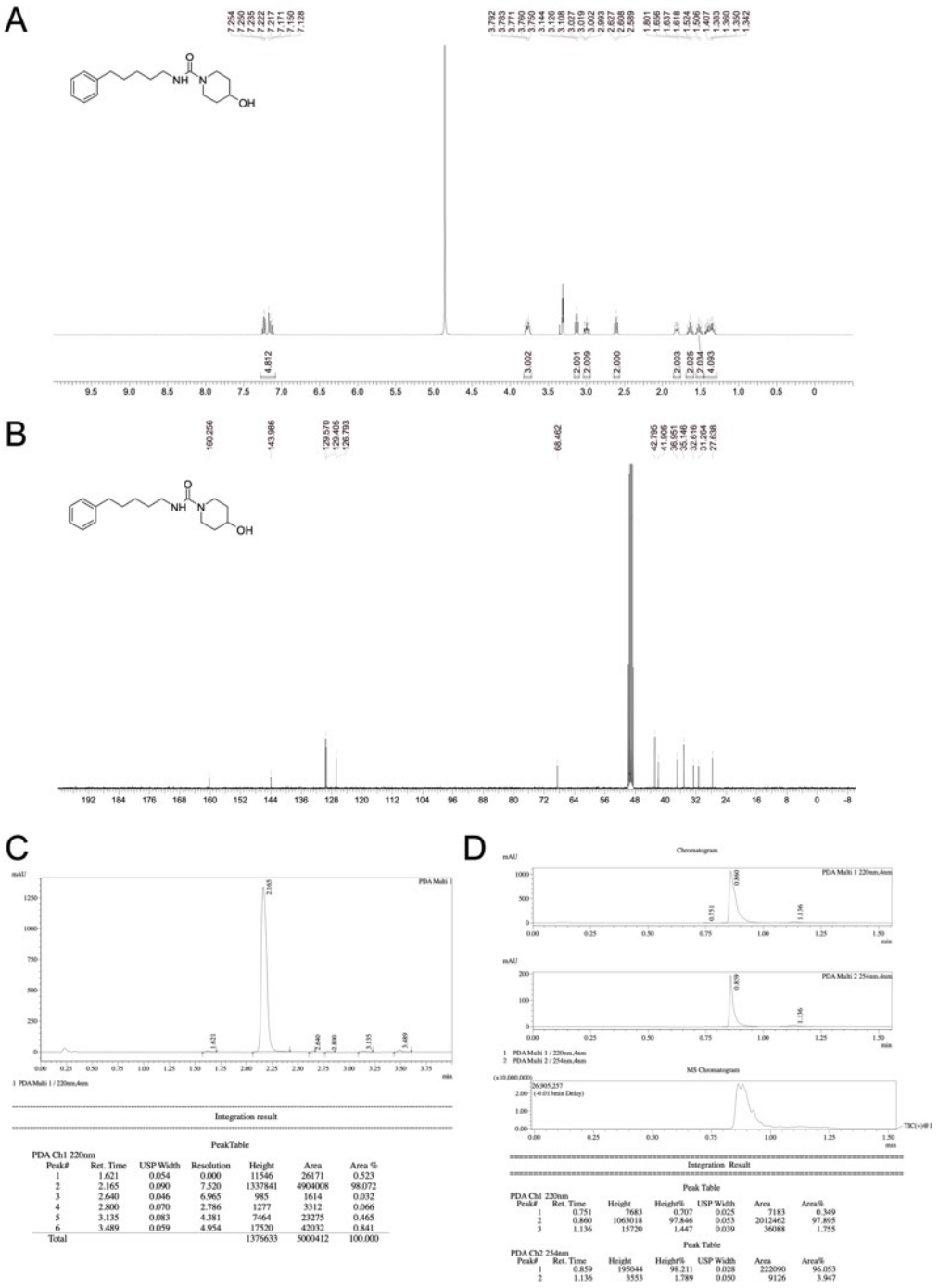


Supplemental Figure S4. *^{1}H NMR, ^{13}C NMR, HPLC and LC-MS chromatography of* ***compound 6***. **A.** ^{1}H NMR: 400 MHz MeOD-d4 δ: 7.20 - 7.28 (m, 2H), 7.10 - 7.18 (m, 3H), 3.62 - 3.70 (m, 2H), 3.23 – 3.29 (m, 1H), 3.15 - 3.21 (m, 1H), 2.60 (t, J = 7.6 Hz, 2H), 2.35 - 2.40 (m, 2H), 1.90 - 1.95 (m, 1H), 1.75 – 1.83 (m, 1H), 1.36 - 1.64 (m, 11H). **B.** ^{13}C NMR: 400 MHz MeOD-d4 δ: (174, 144, 129, 126, 67.3, 53.7, 47.3, 43.3, 36.9, 34.3, 33.8, 33.5, 32.7, 30.4, 30.2, 26.6, 24.7, 23.3) ppm. **C.** HPLC: Rt = 2.018 min, 99.4% purity under 220 nm. **D.** LC-MS: Rt = 0.876 min, m/z = 290.2 (M+H)-.

*4-hydroxy-N-(5-phenylpentyl)piperidine-1-carboxamide (**compound 7**).* To a solution of 5-phenylpentan-1-amine (**7a**, 100 mg, 500 μmol, HCl) in DMF (1.0 mL), CDI (97.4 mg, 600 μmol) and

TEA (152 mg, 1.50 mmol, 209 μL) were added. The mixture was degassed and purged with N_2 3 times and stirred at 30 °C for 0.5 h under N_2. Then, we added

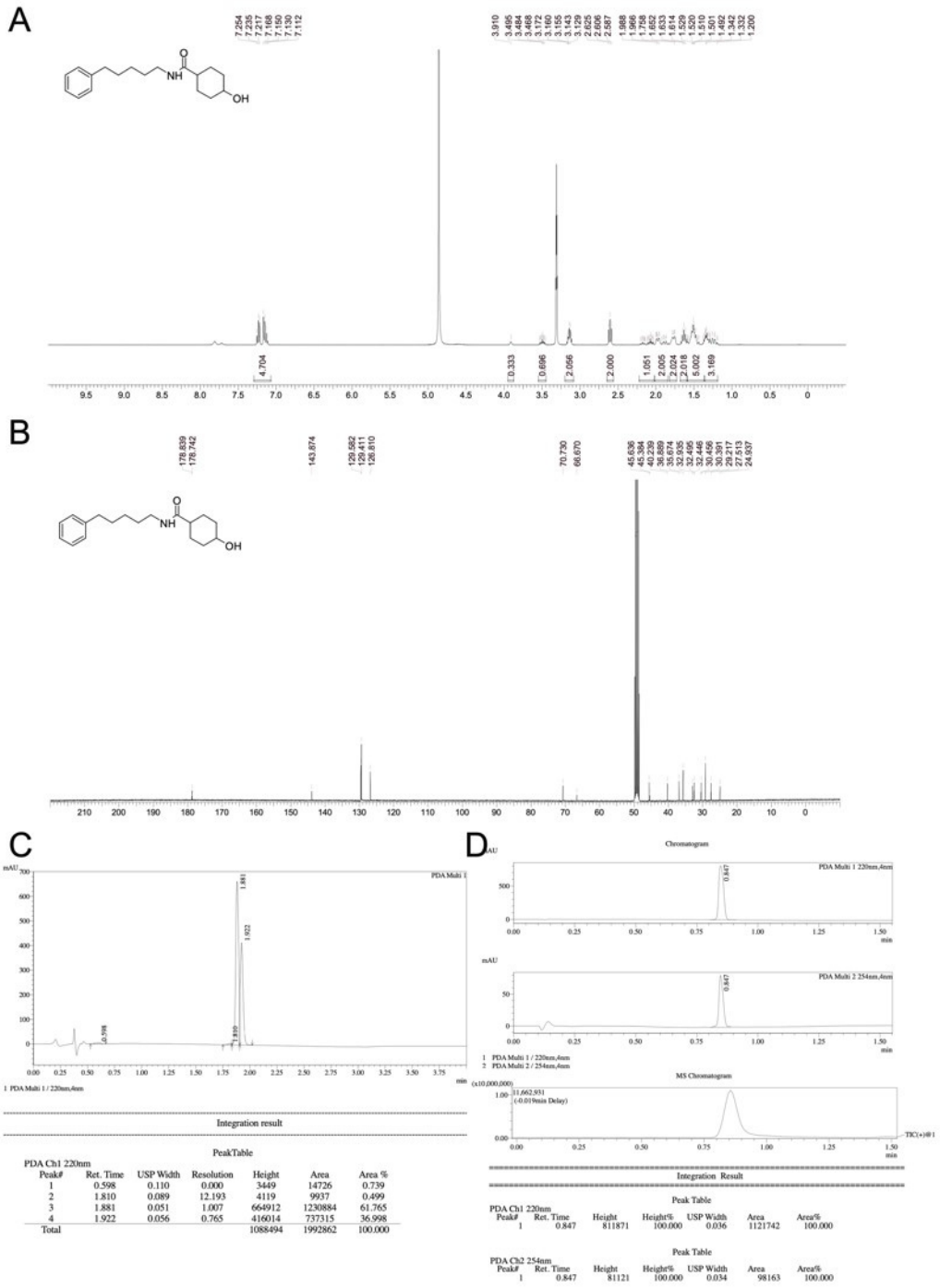
3a (60.7 mg, 600 μmol) and stirred at 30 °C for 16 h under N_2. The mixture was diluted with H_2O (15 mL) and extracted with EtOAc (15 mL * 3). The combined organic layers were washed with brine (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, and purified by Pre-HPLC (column: Waters Xbridge C18 150 * 50 mm * 10 μm; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 20% - 50%,10 min) to obtain **7** (44.8 mg, 151 μmol, 30.2% yield, 98.0% purity) as an off-white solid. LCMS: Rt = 0.860 min, m/z = 291.3 (M+H)+. HPLC: Rt = 2.165 min, 98.1% purity under 220 nm. ^{1}H NMR: 400 MHz MeOD-d4 δ: 7.25 - 7.13 (m, 5H), 3.79 - 3.75 (m, 3H), 3.14 - 3.11 (m, 2H), 3.03 - 2.99 (m, 2H), 2.63 - 2.59 (m, 2H), 1.80 – 1.66 (m, 2H), 1.64 - 1.62 (m, 2H), 1.52 - 1.41 (m, 2H), 1.38 - 1.34 (m, 4H). ^{13}C NMR: 400 MHz MeOD-d4 δ: 160, 143, 130, 129, 127, 68.4, 42.8, 41.9, 36.9, 35.1, 32.6, 31.3, 27.6) ppm.



Supplemental Figure S5. *[1]H NMR, [13]C NMR, HPLC and LC-MS chromatography of* ***compound 7****.* **A.** [1]H NMR: 400 MHz MeOD-d4 δ: 7.25 - 7.13 (m, 5H), 3.79 - 3.75 (m, 3H), 3.14 - 3.11 (m, 2H), 3.03 - 2.99 (m, 2H), 2.63 - 2.59 (m, 2H), 1.80 – 1.66 (m, 2H), 1.64 - 1.62 (m, 2H), 1.52 - 1.41 (m, 2H), 1.38 - 1.34 (m, 4H). **B.** [13]C NMR: 400 MHz MeOD-d4 δ: 160, 143, 130, 129, 127, 68.4, 42.8, 41.9, 36.9, 35.1, 32.6, 31.3, 27.6) ppm. **C.** HPLC: Rt = 2.165 min, 98.1% purity under 220 nm. **D.** LCMS: Rt = 0.860 min, m/z = 291.3 (M+H)+.

*4-hydroxy-N-(5-phenylpentyl)cyclohexane-1-carboxamide (****compound 8****).* To a solution of 4-hydroxycyclohexane-1-carboxylic acid (**8a**, 32.8 mg, 227 μmol) in DMF (1.0 mL), HOBt (36.9 mg, 273 μmol), EDCI (65.4 mg, 341 μmol), DIEA (88.2 mg, 682 μmol, 118 μL) and **7a** (50.0 mg, 250 μmol, HCl)

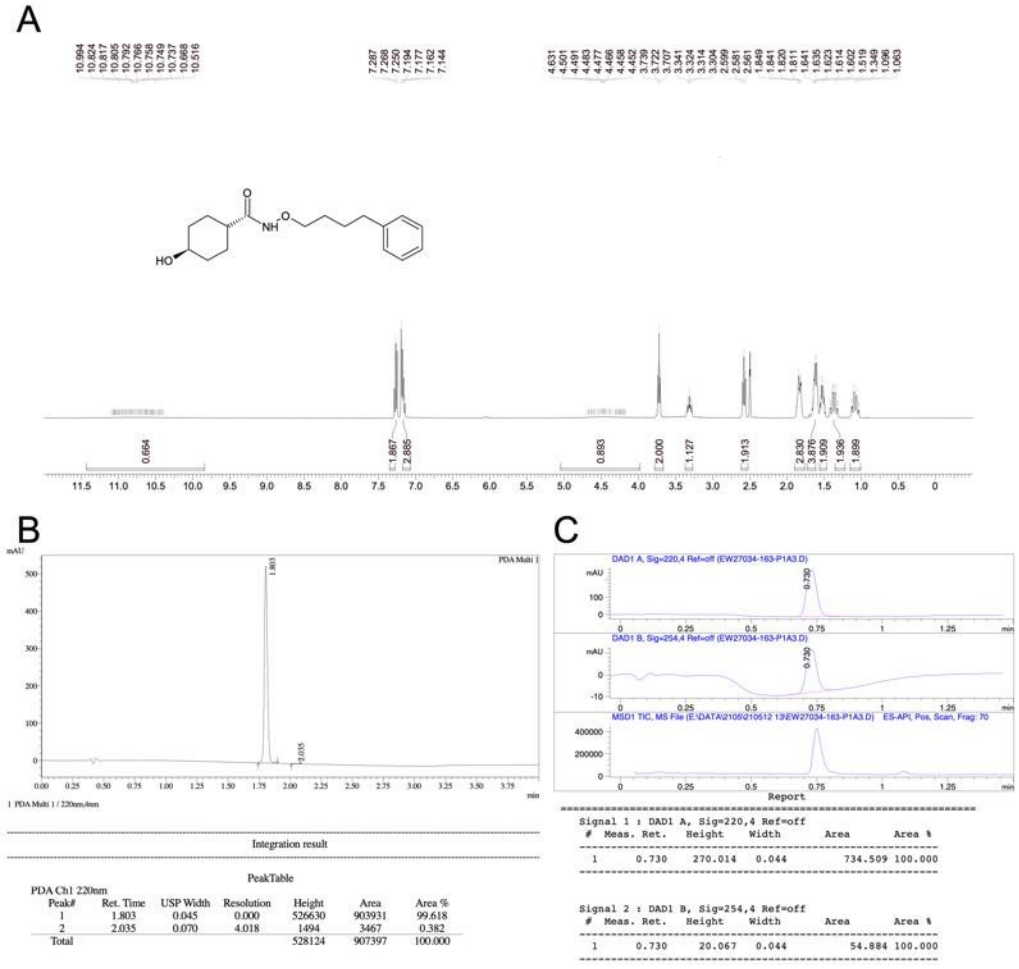
were added. The mixture was stirred at 30 °C for 16 h. The mixture was purified by Pre-HPLC (column: Phenomenex Gemini-NX C18 75 * 30 mm * 3 μm; mobile phase: [water (0.1%TFA) - ACN]; B%: 40% - 50%, 7min). **8** (44.0 mg, 150 μmol, 66.0% yield, 98.7% purity) was obtained as an off-white solid. LC-MS: Rt = 0.847 min, m/z = 290.1 (M+H)-. HPLC: Rt = 1.881 min, Rt = 1.922 min, 98.7% purity under 220 nm. ^{1}H NMR: 400 MHz MeOD-d4 δ: 7.25 - 7.11 (m, 5H), 3.91 - 3.47 (m, 1H), 3.17 - 3.13 (m, 2H), 2.62 – 2.59 (m, 2H), 1.99 - 1.97 (m, 1H), 1.76 - 1.65 (m, 2H), 1.63 - 1.61 (m, 2H), 1.53 - 1.50 (m, 2H), 1.49 – 1.34 (m, 5H), 1.33 - 1.20 (m, 3H).^{13}C NMR: 400 MHz MeODd4 δ: (179, 178, 143, 130, 129, 126, 70.7, 66.6, 45.6, 45.4, 40.2, 36.9, 35.7, 32.9, 32.5, 32.4, 30.4, 30.3, 29.2, 27.5, 24.9) ppm.



Supplemental Figure S6. *^{1}H NMR, ^{13}C NMR, HPLC and LC-MS chromatography of* ***compound 8***. **A.** ^{1}H NMR: 400 MHz MeOD-d4 δ: 7.25 - 7.11 (m, 5H), 3.91 - 3.47 (m, 1H), 3.17 - 3.13 (m, 2H), 2.62 – 2.59 (m, 2H), 1.99 - 1.97 (m, 1H), 1.76 - 1.65 (m, 2H), 1.63 - 1.61 (m, 2H), 1.53 - 1.50 (m, 2H), 1.49 – 1.34 (m, 5H), 1.33 - 1.20 (m, 3H). **B.** ^{13}C NMR: 400 MHz MeOD-d4 δ: (179, 178, 143, 130, 129, 126, 70.7, 66.6, 45.6, 45.4, 40.2, 36.9, 35.7, 32.9, 32.5, 32.4, 30.4, 30.3, 29.2, 27.5, 24.9) ppm. **C.** HPLC: Rt = 1.881 min, Rt = 1.922 min, 98.7% purity under 220 nm. **D.** LC-MS: Rt = 0.847 min, m/z = 290.1 (M+H)-.

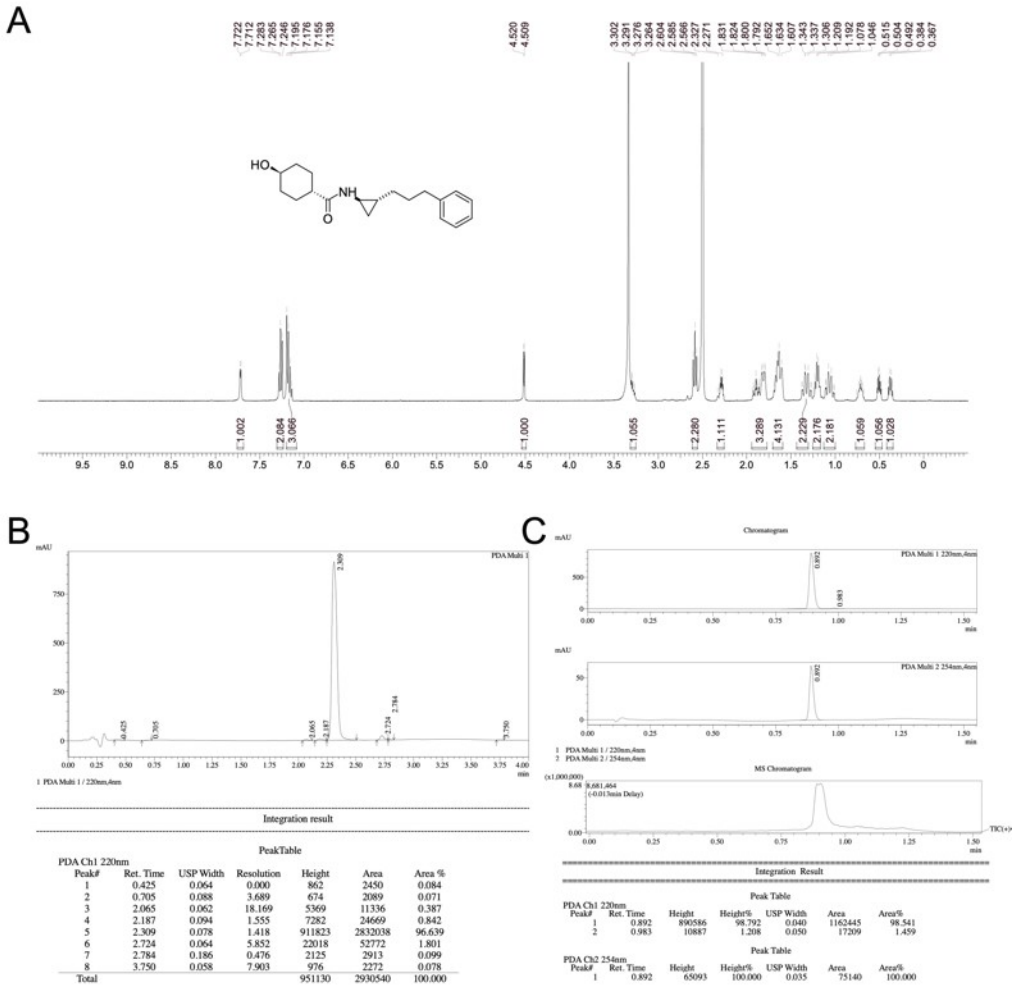
*(1r,4r)-4-hydroxy-N-(4-phenylbutoxy)cyclohexane-1-carboxamide (****compound 9****).* To a mixture of (4-bromobutyl)benzene (300 mg, 1.41 mmol) and 2-hydroxyisoindoline-1,3dione (275 mg, 1.69 mmol)

in DMF (10.00 mL), K_2CO_3 (389 mg, 2.82 mmol) was added at 20 °C and stirred at 80 °C for 1 hr to obtain intermediate 2-(4-phenylbutoxy)isoindoline-1,3dione (**9a**, 191 mg, 646 μmol, 45.9% yield). To a solution of **9a** (190 mg, 643 μmol) in DCM (10.0 mL) NH_2-NH_2.H_2O (322 mg, 6.43 mmol) was added at 25 °C and stirred for 2 hrs to obtain O-(4-phenylbutyl)hydroxylamine (**9b**, 95.0 mg, 574 μmol, 89.3% yield). Then, (1r,4r)-4hydroxycyclohexane-1-carboxylic acid (**9c**, 124 mg, 862 μmol) in THF (10.0 mL) was added in HATU (327 mg, 862 μmol) and Et3N (174 mg, 1.72 mmol, 3.00 mL) at 25 °C. The mixture was stirred at 25 °C for 2 hrs. The reaction mixture was concentrated under reduced pressure to produce a residue. The reside was purified by preparative HPLC (neutral condition, column: Waters Xbridge 150 * 25 mm * 5 μm; mobile phase: [water (10 mM NH4HCO3) - ACN]; B%: 26% - 56%, 10 min). **9** (83.72 mg, 286 μmol, 49.7% yield, 99.6% purity) was obtained as an off-white solid. LCMS: RT = 0.730 min, m/z = 292.2 (M+H)+. HPLC: RT = 1.803 mins, 99.6% purity under 220 nm. ^{1}H NMR: 400 MHz, DMSO-d6 δ: 10.9-10.5 (m, 1H), 7.28-7.25 (m, 2H), 7.19-7.14 (m, 3H), 4.63-4.52 (m, 1H), 3.73-3.70 (m, 2H), 3.34-3.30 (m, 1H), 2.59 – 2.56 (m, 2H), 1.84-1.81 (m, 3H), 1.64-1.62 (m, 4H), 1.60-1.51 (m, 2H), 1.431.28 (m, 2H), 1.09-1.06 (m, 2H).



Supplemental Figure S7. *^{1}H NMR, HPLC and LC-MS chromatography of* ***compound 9***. **A.** ^{1}H NMR: 400 MHz, DMSO-d6 δ: 10.9-10.5 (m, 1H), 7.28-7.25 (m, 2H), 7.19-7.14 (m, 3H), 4.63-4.52 (m, 1H), 3.73-3.70 (m, 2H), 3.34-3.30 (m, 1H), 2.59 – 2.56 (m, 2H), 1.84-1.81 (m, 3H), 1.64-1.62 (m, 4H), 1.60-1.51 (m, 2H), 1.43-1.28 (m, 2H), 1.09-1.06 (m, 2H). **B.** HPLC: RT = 1.803 mins, 99.6% purity under 220 nm. **C.** LCMS: RT = 0.730 min, m/z = 292.2 (M+H)+.

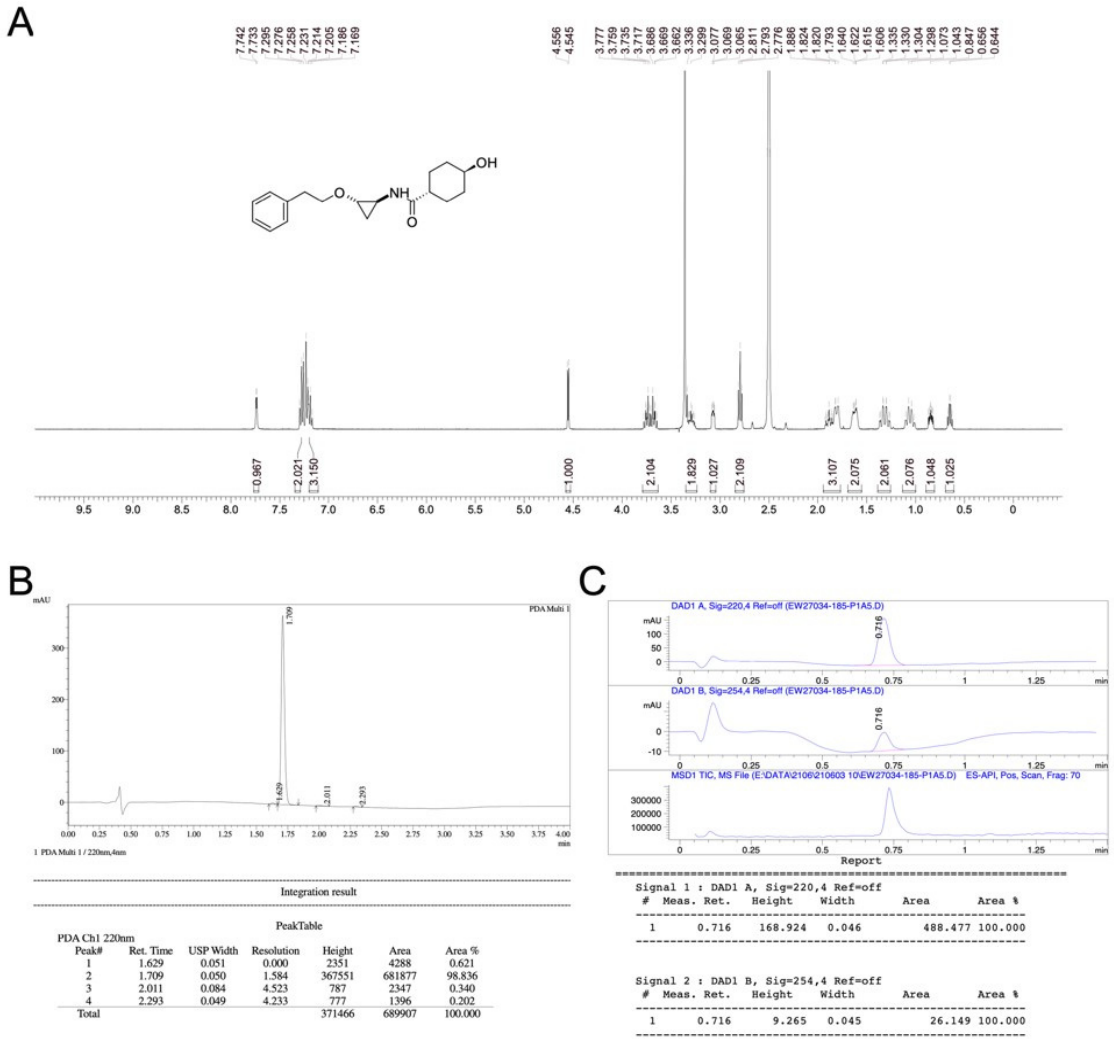
(1r,4R)-4-hydroxy-N-((1R,2R)-2-(3-phenylpropyl)cyclopropyl)cyclohexane-1carboxamide (***compound 10***). To a solution of 4-phenylbutanal (3.34 g, 22.5 mmol) tert-butyl 2-(triphenyl-l5-phosphaneylidene)acetate (10.1 g, 27.0 mmol) under N_2 was added at 25 °C and stirred for 12 hrs to obtain intermediate tert-butyl (E)-6-phenylhex-2-enoate (**10a**, 3.54 g, 14.3 mol, 63.7% yield). To a mixture of BLAHmethane iodide (1.61 g, 7.31 mmol) in DMSO (10.0 mL) NaH (292 mg, 7.31 mmol) was added at 25 °C under N_2 and stirred at 25 °C for 1 hr, then we added **10a** (1.50 g, 6.09 mmol) and stirred for another 1 hr to obtain tertbutyl (1S,2S)-2-(3-phenylpropyl)cyclopropane-1-carboxylate (**10b**, 790 mg, 3.03 mmol, 49.8% yield). To a mixture of **10b** (790 mg, 3.03 mmol) in DCM (10.0 mL) TFA (14.1 g, 124 mmol, 9.19 mL) was added at 25 °C and stirred for 1 hr to obtain (1S,2S)-2-(3phenylpropyl)cyclopropane-1-carboxylic acid (**10c**, 576 mg, 2.82 mmol, 92.9% yield). To a mixture of **10c** (576 mg, 2.82 mmol) in toluene (10.0 mL) DPPA (776 mg, 2.82 mmol) and TFA (428 mg, 4.23 mmol) were added at 25 °C under N_2, and the mixture was heated to 105 °C and stirred for 2 hrs to obtain (1S,2S)-2-(3-phenylpropyl)cyclopropan-1-amine (**10d**, 73.0 mg, 416 μmol, 14.7% yield). To a mixture of **10d** (73.0 mg, 416 μmol) and **9c** (72.1 mg, 500 μmol) in THF (10.0 mL) HATU (237 mg, 625 μmol) and Et3N (361 mg, 3.57 mmol, 0.50 mL) were added at 25 °C and stirred for 12 hrs. The reaction mixture was concentrated under reduced pressure to give a residue, and purified by preparative HPLC (TFA condition, column: Phenomenex Synergi Polar-RP 100 * 25 mm * 4 μm; mobile phase: [water (TFA) - ACN]; B%: 43%-63%, 7 min) to obtain **10** (8.29 mg, 26.6 μmol, 6.38% yield, 96.6% purity) as a white solid. LCMS: RT = 0.892 min, m/z = 302.2 (M+H)+. HPLC: RT = 2.309 mins, 96.6% purity under 220 nm. ^{1}H NMR: 400 MHz, DMSO-d6 δ: 7.72 (d, J = 4.0, 1H), 7.28-7.24 (m, 2H), 7.19-7.13 (m, 3H), 4.51 (d, J = 4.4, 1H), 3.30-3.26 (m, 1H), 2.60-2.56 (m, 2H), 2.32– 2.27 (m, 1H), 1.83-1.79 (m, 3H), 1.65-1.60 (m, 4H), 1.34-1.30 (m, 2H), 1.20-1.19 (m, 2H), 1.07–1.04 (m, 2H), 0.75–0.70 (m, 1H), 0.51–0.49 (m, 1H), 0.38–0.36 (m, 1H).



Supplement Figure S8. *[1]H NMR, HPLC and LC-MS chromatography of* ***compound 10****.* **A.** [1]H NMR: 400 MHz, DMSO-d6 δ: 7.72 (d, J = 4.0, 1H), 7.28-7.24 (m, 2H), 7.19-7.13 (m, 3H), 4.51 (d, J = 4.4, 1H), 3.30-3.26 (m, 1H), 2.60-2.56 (m, 2H), 2.32–2.27 (m, 1H), 1.83-1.79 (m, 3H), 1.65-1.60 (m, 4H), 1.34-1.30 (m, 2H), 1.20-1.19 (m, 2H), 1.07–1.04 (m, 2H), 0.75–0.70 (m, 1H), 0.51–0.49 (m, 1H), 0.38–0.36 (m, 1H). **B.** HPLC: RT = 2.309 mins, 96.6% purity under 220 nm. **C.** LCMS: RT = 0.892 min, m/z = 302.2 (M+H)+.

*(1r,4S)-4-hydroxy-N-((1S,2S)-2-phenethoxycyclopropyl)cyclohexane-1carboxamide (****compound 11****).* To a mixture of ethyl (1S,2S)-2-phenethoxycyclopropane-1carboxylate (**11a**, 440 mg, 1.88 mmol) in MeOH (5.00 mL), THF (5.00 mL) and H_2O (2.00 mL) were added LiOH·H2O (157 mg, 3.76 mmol) at 25 °C. The mixture was heated to 70 °C and stirred for 2 hrs to obtain (1S,2S)-2-phenethoxycyclopropane-1-carboxylic acid (**11b**, 284 mg, 1.38 mmol, 73.3% yield). To a mixture of **11b** (264 mg, 1.28 mmol) in toluene (10.0 mL) DPPA (352 mg, 1.28 mmol) and TFA (194 mg, 1.92 mmol, 1.50 eq) were added at 25 °C under N_2, the mixture was heated to 105 °C and stirred for 2 hrs to obtain (1S,2S)-2phenethoxycyclopropan-1-amine (**11c**, 54.0 mg, 304 μmol, 23.8% yield). To a mixture of **11c** (47.0 mg, 265 μmol) and **9c** (45.8 mg, 318 μmol) in THF (10.0 mL) HATU (151 mg, 397 μmol) and Et3N (727 mg, 7.18 mmol, 1.00 mL) were added at 25 °C and stirred for 12 hrs. The reaction mixture was concentrated under reduced pressure to give a residue, and was

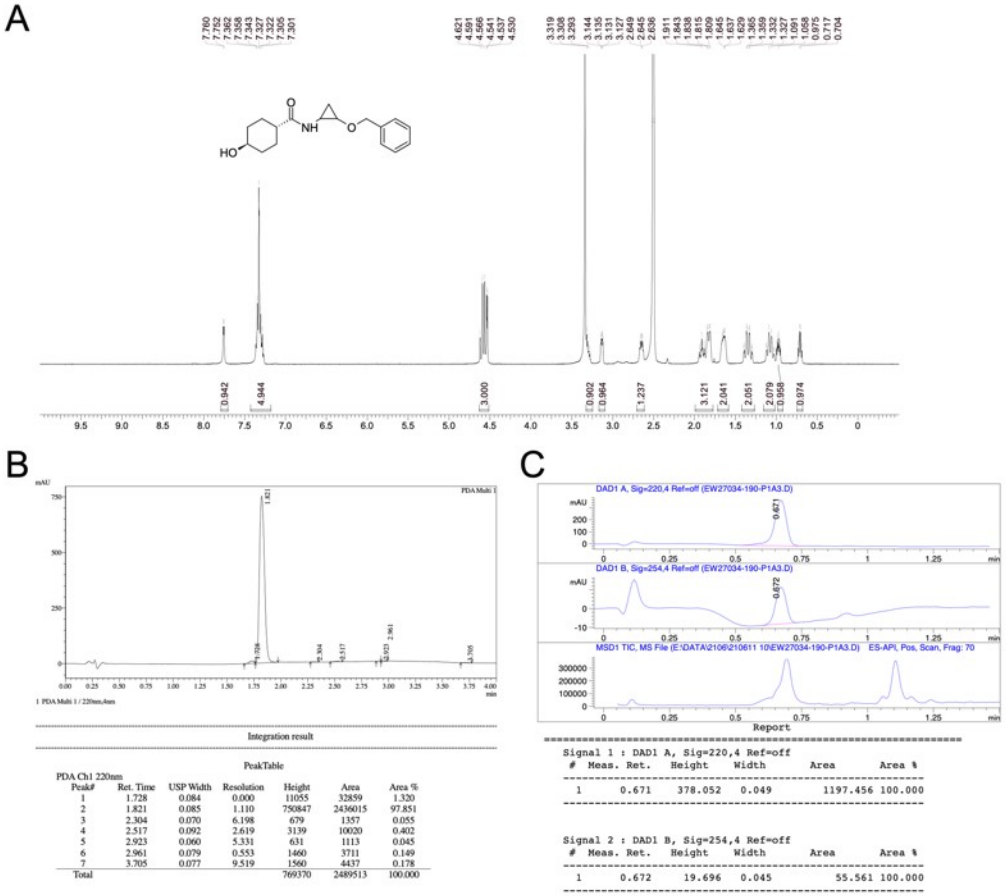
purified by preparative HPLC (neutral condition, column: Waters Xbridge 150 * 25 mm * 5 μm; mobile phase: [water (NH_4HCO_3) - ACN]; B%: 25% - 55%, 10 min and TFA condition, column: Phenomenex Synergi Polar-RP 100 * 25 mm * 4 μm; mobile phase: [water (TFA) - ACN]; B%: 36% - 56%, 7 min) to obtain **11** (7.89 mg, 25.7 μmol, 9.69% yield, 98.8% purity) as a white solid. LCMS: RT = 0.716 min, m/z = 304.2 (M+H)+. HPLC: RT = 1.709 mins, 98.8% purity under 220 nm. ^{1}H NMR: 400 MHz, DMSO-d6 δ: 7.74 (d, J = 3.6, 1H), 7.297.25 (m, 2H), 7.23-7.16 (m, 3H), 4.55 (d, J = 4.4, 1H), 3.77-3.66 (m, 2H), 3.33-3.29 (m, 2H), 3.07 – 3.06 (m, 1H), 2.81-2.77 (m, 2H), 1.88-1.79 (m, 3H), 1.64-1.60 (m, 2H), 1.33-1.30 (m, 2H), 1.13-1.07 (m, 2H), 0.84-0.82 (m, 1H), 0.65-0.64 (m, 2H).



Supplement Figure S9. *^{1}H NMR, HPLC and LC-MS chromatography of* ***compound 11***. **A.** ^{1}H NMR: 400 MHz, DMSO-d6 δ: 7.74 (d, J = 3.6, 1H), 7.29-7.25 (m, 2H), 7.23-7.16 (m, 3H), 4.55 (d, J = 4.4, 1H), 3.77-3.66 (m, 2H), 3.33-3.29 (m, 2H), 3.07 – 3.06 (m, 1H), 2.81-2.77 (m, 2H), 1.88-1.79 (m, 3H), 1.64-1.60 (m, 2H), 1.33-1.30 (m, 2H), 1.13-1.07 (m, 2H), 0.84-0.82 (m, 1H), 0.65-0.64 (m, 2H).
B. HPLC: RT = 1.709 mins, 98.8% purity under 220 nm. **C.** LCMS: RT = 0.716 min, m/z = 304.2 (M+H)+.

(1r,4r)-N-(2-(benzyloxy)cyclopropyl)-4-hydroxycyclohexane-1-carboxamide

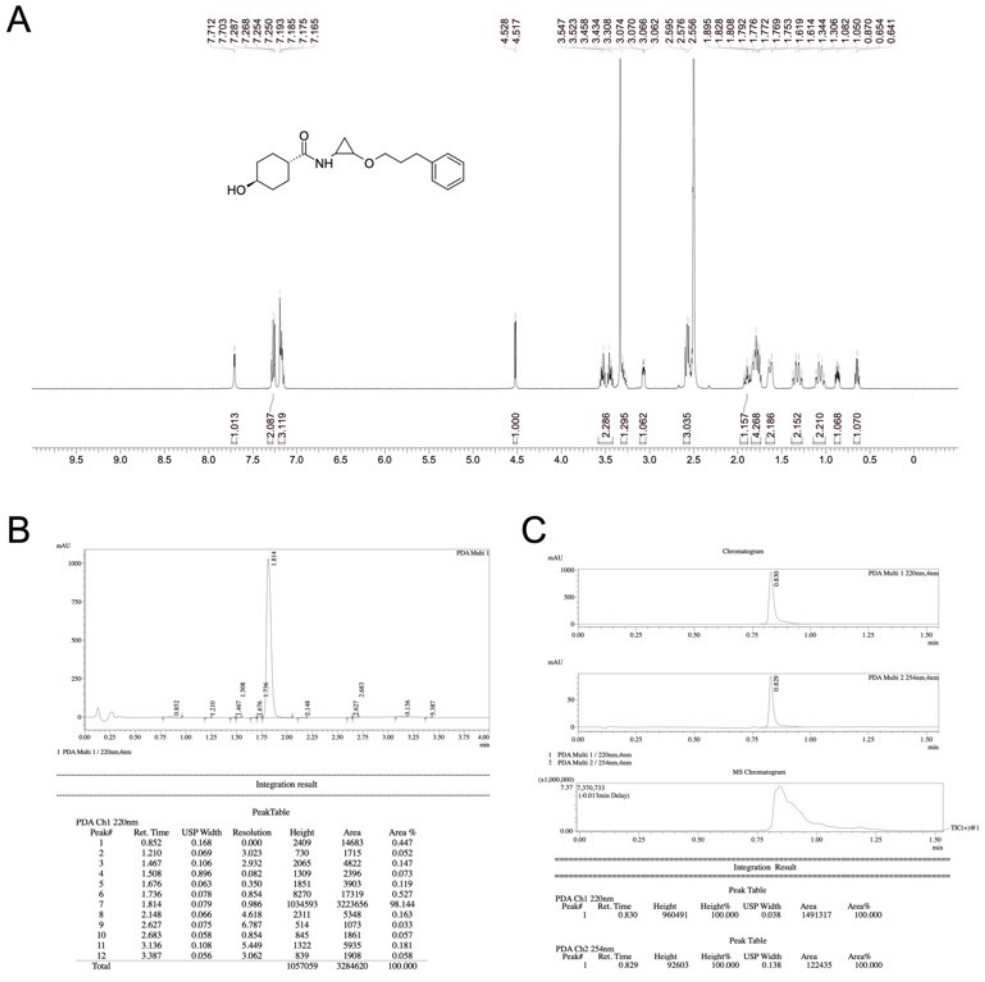
(***compound 12***). To a mixture of ethyl 2-(benzyloxy)cyclopropane-1-carboxylate (**12a**, 750 mg, 3.41 mmol) in MeOH (5.00 mL), THF (5.00 mL) and H_2O (2.00 mL) were added LiOH·H_2O (285 mg, 6.81 mmol) at 25 °C. The mixture was heated to 70 °C and stirred for 2 hrs to obtain 2-(benzyloxy)cyclopropane-1-carboxylic acid (**12b**, 485 mg, 2.52 mmol, 74.1% yield). To a mixture of **12b** (485 mg, 2.52 mmol) in toluene (10.0 mL) DPPA (694 mg, 2.52 mmol) and TFA (382 mg, 3.78 mmol) were added at 25 °C under N_2, the mixture was heated to 105 °C and stirred for 2 hrs to obtain 2-(benzyloxy)cyclopropan-1-amine (**12c**, 108 mg, 661 μmol, 26.2% yield). To a mixture of **12c** (108 mg, 661 μmol) and **9c** (114 mg, 794 μmol) in THF (10.0 mL) was added HATU (377 mg, 992 μmol) and Et3N (1.81 g, 17.9 mmol, 2.50 mL) at 25 °C and it was stirred for 12 hrs. The reaction mixture was concentrated under reduced pressure to give a residue and was purified by preparative HPLC (TFA condition column: Phenomenex Synergi Polar-RP 100 * 25 mm * 4 μm; mobile phase: [water (TFA) - ACN]; B%: 32% - 52%, 7 min) and preparative HPLC (neutral condition, column: Waters Xbridge 150 * 25 mm * 5 μm; mobile phase: [water (NH_4HCO_3) - ACN]; B%: 21% - 51%, 9 min) to obtain **12** (5.97 mg, 20.1 μmol, 3.05% yield, 97.8% purity) as a white solid. LCMS: RT = 0.671 min, m/z = 290.1 (M+H)+. HPLC: RT = 1.821 mins, 97.8% purity under 220 nm. ^{1}H NMR: 400 MHz, DMSO-d6 δ: 7.76 (d, J = 3.2, 1H), 7.26-7.30 (m, 5H), 4.62-4.53 (m, 3H), 3.31-3.29 (m, 1H), 3.14-3.12 (m, 1H), 2.64-2.63 (m, 1H), 1.91 – 1.80 (m, 3H), 1.64-1.62 (m, 2H), 1.36-1.33 (m, 2H), 1.09-1.05 (m, 2H), 1.01-0.97 (m, 1H), 0.71-0.70 (m, 1H).



Supplement Figure S10. *^{1}H NMR, HPLC and LC-MS chromatography of* ***compound 12***. **A.** ^{1}H NMR: 400 MHz, DMSO-d6 δ: 7.76 (d, J = 3.2, 1H), 7.26-7.30 (m, 5H), 4.62-4.53 (m, 3H), 3.31-3.29 (m, 1H), 3.14-3.12 (m, 1H), 2.64-2.63 (m, 1H), 1.91 – 1.80 (m, 3H), 1.64-1.62 (m, 2H), 1.36-1.33 (m, 2H), 1.09-1.05 (m,

2H), 1.01-0.97 (m, 1H), 0.71-0.70 (m, 1H). **B.** HPLC: RT = 1.821 mins, 97.8% purity under 220 nm. **C.** LCMS: RT = 0.671 min, m/z = 290.1 (M+H)+.

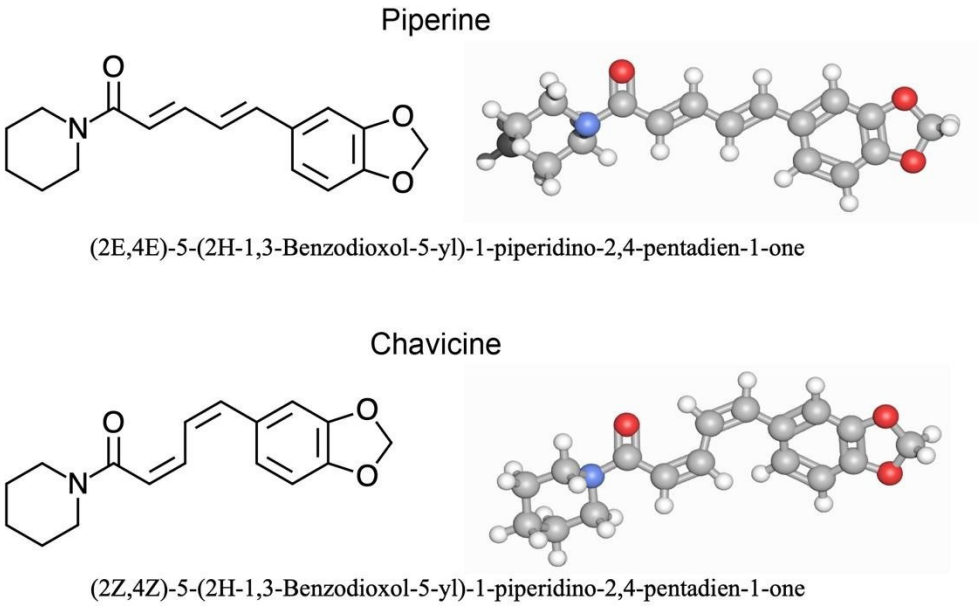
(1r,4r)-4-hydroxy-N-(2-(3-phenylpropoxy)cyclopropyl)cyclohexane-1-carboxamide (***compound 13***). To a mixture of ethyl 2-(3-phenylpropoxy)cyclopropane-1-carboxylate (**13a**, 870 mg, 3.50 mmol) in MeOH (5.00 mL), THF (5.00 mL) and H_2O (2.00 mL) were added $LiOH·H_2O$ (294 mg, 7.01 mmol) at 25 °C. The mixture was heated to 70 °C and stirred for 2 hrs to obtain 2-(3-phenylpropoxy)cyclopropane-1-carboxylic acid (**13b**, 690 mg, 3.13 mmol, 89.4% yield). To a mixture of **13b** (690 mg, 3.13 mmol) in toluene (10.0 mL) DPPA (862 mg, 3.13 mmol) and TFA (475 mg, 4.70 mmol) were added at 25 °C under N_2, the mixture was heated to 105 °C and stirred for 2 hrs to obtain 2-(3-phenylpropoxy)cyclopropan-1-amine (**13c**, 154 mg, 805 μmol, 25.7% yield). To a mixture of **13c** (154 mg, 805 μmol) and **9c** (139 mg, 966 μmol) in THF (5.00 mL) was added HATU (459 mg, 1.21 mmol) and Et3N (727 mg, 7.18 mmol, 1.00 mL) at 25 °C and stirred for 12 hrs. The reaction mixture was concentrated under reduced pressure to give a residue and was purified by preparative HPLC (TFA condition column: Phenomenex Synergi Polar-RP 100 * 25 mm * 4 μm; mobile phase: [water (TFA) - ACN]; B%: 41%-61%, 7 min) and preparative HPLC (neutral condition, column: Waters Xbridge 150 * 25 mm * 5 μm; mobile phase: [water (NH4HCO3) - ACN]; B%: 31% - 61%, 10 min) to obtain **13** (7.29 mg, 22.5 μmol, 2.80% yield, 98.1% purity) as an off-white solid.



Supplement Figure S11. *^{1}H NMR, HPLC and LC-MS chromatography of* ***compound 13***. **A.** ^{1}H NMR:

400 MHz, DMSO-d6 δ: 7.71 (d, J = 3.6, 1H), 7.28-7.25 (m, 2H), 7.19-7.16 (m, 3H), 4.52 (d, J = 4.4, 1H), 3.54-3.45 (m, 2H), 3.43-3.30 (m, 1H), 3.07-3.06 (m, 1H), 2.59 – 2.55 (m, 3H), 1.89-1.82 (m, 1H), 1.80-1.76 (m, 4H), 1.73-1.61 (m, 2H), 1.34-1.30 (m, 2H), 1.08-1.05 (m, 2H), 0.90-0.87 (m, 1H), 0.65-0.64 (m, 1H). **B.** HPLC: RT = 1.814 mins, 98.1% purity under 220 nm. **C.** LCMS: RT = 0.830 min, m/z = 318.2 (M+H)+.

SUPPLEMENTAL INFORMATION



Supplemental Figure S12. *Piperine and chavicine structures.*