Supporting Information

Synthesis, and Biological Evaluation of 5-Benzylidenepyrimidine-2,4,6(1H,3H,5H)-trione Derivatives for the Treatment of Obesity-related Nonalcoholic Fatty Liver Disease

Liang Ma [1§], Caifeng Xie [2§], Yan Ran [1§], Xiaolin Liang [1], Li Huang [2], Heying Pei [2], Jinying Chen [3], Juan Liu [4], Yun Sang [1], Huijun Lai [4], Aihua Peng [2], Mingli Xiang [3], Yuquan Wei [2], Lijuan Chen [1,2]*

[1] Department of Medicinal Chemistry; [2] Department of Pharmacology; [3] Department of Computer Aided Drug Design; [4] Department of Pharmacokinetics, State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University, Keyuan Road 4, Gaopeng Street, Chengdu 610041, China

§ These authors contributed equally.

***Corresponding author**

State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University, Keyuan Road 4, Gaopeng Street, Chengdu, 610041, China

Tel: +86-28-85164063, Fax: +86-28-85164060.

E-mail address: lijuan17@hotmail.com (L-j. Chen).

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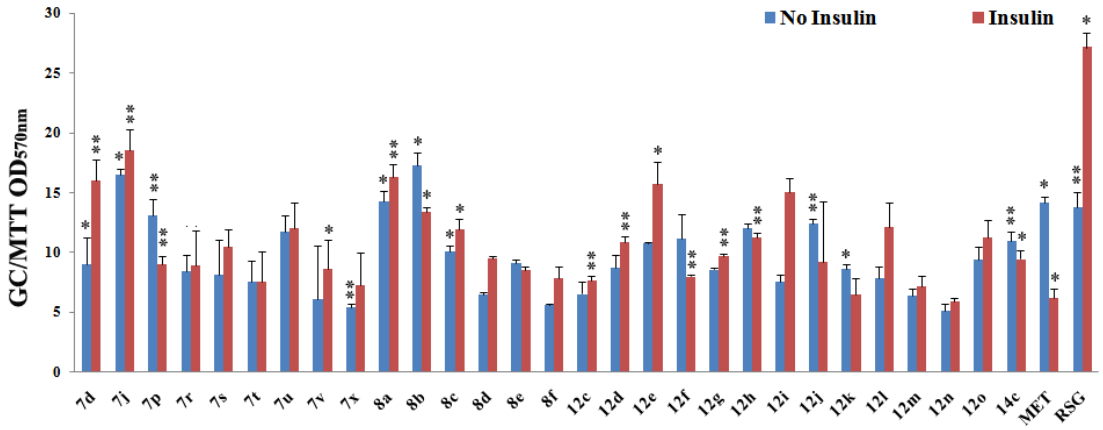


Figure S1 Effects of metformin, rosiglitazone, and synthesized derivatives on glucose consumption (GC)/MTT in insulin-resistant HepG2 cells. 1.0 mM metformin (Met), 10 μM rosiglitazone (RSG) and synthesized derivatives (**7a-z**, **8a-g**, **12a-p**, **14a-c**, and **17a-b** at 10 μM) were tested in the absence/presence of insulin (0.1 μM) by the glucose oxidase method (GENMED SCIENTIFICS, USA). Results were recorded from three independent experiments. *$P < 0.05$; **$P < 0.01$; and ***$P < 0.001$ vs. the corresponding control group;

Table S1 Biochemical characteristics of untreated and treated NAFLD rats (n=10).

Parameters	HFD	Metformin	7h	7q
TP (g/L)	59.3±0.9	58.5±1.1	56.3±0.9	56.6±0.7
ALB (mg/L)	42.4±0.4	42.3±0.6	41.2±0.4	41.2±0.2
ALP (U/L)	122.0±4.1	120.0±2.3	107±6.0	118.7±4.6

TP: total protein; ALB: serum albumin; ALP: serum alkaline phosphatase; Results are means ± SD. *P<0.05; **P<0.01 vs. model.

Table S2 Parameters of serum biochemical markers from DIO mice (n=10).

Parameters	Normal	HFD	HFD+7h	HFD+Met
AST (U/L)	80.0±9.1	141.7±48.2	121.7±22.5	118.3±18.6
H_bA_{1c} (%)	4.6±0.1	4.9±0.3	4.8±0.1	4.9±0.2

Table S3 Pharmacokinetic Profiles of **7h** in Sprague-Dawley rats (n=5).

	C_{max} (μg/L)	T_{max} (h)	$AUC_{0\text{-}t\ h}$ (μg·h/L)	$t_{1/2}$ (h)	F (%)
po	31.3	8.0	405.54	5.30	13.9
iv	148.13	0.083	582.31	2.23	

Dose: 50 mg/kg, po; 10 mg/kg, iv.

Synthesis and Analytical Data of All Intermediates

Chemical reagents of analytical grade were purchased from Chengdu Changzheng Chemical Factory (Sichuan, P. R. China). TLC was performed on 0.20 mm silical gel 60 F_{254} plates (Qingdao Ocean Chemical Factory, Shangdong, China). Hydrogen Nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz on a Varian spectrometer (Varian, Palo Alto, CA, USA) model Gemini 400 and reported in parts per million. Chemical shifts (δ) are quoted in ppm relative to tetramethylsilane (TMS) as an internal standard, where (δ) TMS = 0.00 ppm. The multiplicity of the signal is indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, defined as all multipeak signals where overlap or complex coupling of signals makes definitive descriptions of peaks difficult. Mass Spectra (MS) were measured by Q-TOF Priemier mass spectrometer utilizing electrospray ionization (ESI) (Micromass, Manchester, UK). Room temperature (RT) is within the range 20-25 °C.

General Procedure for the Synthesis of Compounds 4

A mixture of **2** (1.78 g, 5.0 mmol), appropriate 4-hydroxybenzaldehydes **3** (5.5 mmol), and K_2CO_3 (1.38 g, 10.0 mmol) in 15 mL of DMF was heated to 100 °C for 10h. And then, the K_2CO_3 was removed by filtration. The filtrate was poured into ice water, and extracted with CH_2Cl_2, saturated $NaHCO_3$, and brine, and the combined organic layer was dried over $MgSO_4$. Finally, the solvent was removed under reduced pressure to give the crude **4** without further purification.

***Tert*-butyl 4-(4-formylphenoxy)piperidine-1-carboxylate (4a, R_1 = H).** Yield 75.4%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.84 (d, 2H, *J* = 8.8 Hz), 7.02 (d, 2H, *J* = 8.4 Hz), 4.63 (m, 1H), 3.73 - 3.67 (m, 2H), 3.41 - 3.35 (m, 2H), 1.99 - 1.93 (m, 2H), 1.83 - 1.76 (m, 2H), 1.46 (s, 9H); MS (ESI), m/z: 328.26 $[M + Na]^+$.

***Tert*-butyl 4-(2-fluoro-4-formylphenoxy)piperidine-1-carboxylate (4b, R_1 = 3-F).** Yield 73.8%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.64 (d, 2H, *J* = 9.6 Hz), 7.11 (t, 1H, *J* = 8.0 Hz), 4.66 - 4.64 (m, 1H), 3.75 - 3.68 (m, 2H), 3.43 - 3.37 (m, 2H), 1.96 - 1.94 (m, 2H), 1.86 - 1.84 (m,2H), 1.47 (s, 9H); MS (ESI), m/z: 346.11 $[M + Na]^+$.

***Tert*-butyl 4-(2-ethoxy-4-formylphenoxy)piperidine-1-carboxylate (4c, R_1 = 3-OEt).** Yield 75.2%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.42 (s, 1H), 7.40 (s, 1H), 7.02 (d, 1H, *J* = 8.0 Hz), 4.63 - 4.56 (m, 1H), 4.14 (q, 2H, *J* = 8.0 Hz), 3.74 - 3.68 (m, 2H), 3.41 – 3.35 (m, 2H), 1.96 - 1.91 (m, 2H), 1.87 - 1.78 (m, 2H), 1.47 (s, 9H), 1.46 (t, 3H, *J* = 8.0 Hz); MS (ESI), m/z: 350.27 $[M + H]^+$.

***Tert*-butyl 4-(4-formyl-2,6-dimethoxyphenoxy)piperidine-1-carboxylate (4d, R_1 = 3,4-diOMe).** Yield 70.4%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.13 (s, 2H), 4.46 - 4.38 (m, 1H), 3.91 (s, 6H), 3.83 - 3.75 (m, 2H), 3.29 - 3.21 (m, 2H), 1.88 - 1.75 (m, 4H), 1.47 (s, 9H); MS (ESI), m/z: 366.23 $[M + H]^+$.

General Procedure for the Synthesis of Compounds 5

A solution of **4** (1.0 mmol) in 1 mL of TFA/CH_2Cl_2 (*v*/*v* = 1/1) at 0 °C was stirred for 3h and allowed to warm up to room temperature. After the reaction was completed,

the solvent was removed under reduced pressure. The residue was basified with 2 N NaOH and the solid was formed. The precipitate was collected by filtration and washed with water to afford the crude products **5** without further purification.

4-(Piperidin-4-yloxy)benzaldehyde (5a, R_1 = 3-H). Yield 85.8%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.38 (d, 2H, *J* = 8.4 Hz), 7.00 (d, 2H, *J* = 8.4 Hz), 4.52 - 4.48 (m, 1H), 3.18 - 3.12 (m, 2H), 2.79 - 2.73 (m, 2H), 2.06 - 2.02 (m, 2H), 1.75 - 1.67 (m, 2H), 0.89 - 0.85 (m, 1H); MS (ESI), m/z: 206.03 $[M + H]^+$.
3-Fluoro-4-(piperidin-4-yloxy)benzaldehyde (5b, R_1 = 3-F). Yield 86.2%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.64 (dd, 2H, *J* = 2.0 Hz, *J* = 8.0 Hz), 7.11 (t, 1H, *J* = 8.4 Hz) , 4.62 - 4.58 (m, 1H), 3.25 - 3.19 (m, 2H), 2.90 - 2.84 (m, 2H), 2.14 - 2.09 (m, 2H), 1.89 - 1.80 (m, 2H); MS (ESI), m/z: 224.00 $[M + H]^+$.
3-Ethoxy-4-(piperidin-4-yloxy)benzaldehyde (5c, R_1 = 3-OEt). Yield 80.3%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.42 (s, 1H), 7.40 (s, 1H), 7.02 (d, 1H, *J* = 8.0 Hz), 4.56 - 4.49 (m, 1H), 4.15 (q, 2H, *J* = 8.0 Hz), 3.24 - 3.14 (m, 2H), 2.84 - 2.72 (m, 2H), 2.14 - 1.72 (m, 4H), 1.45 (t, 3H, *J* = 8.0 Hz); MS (ESI), m/z: 250.17 $[M + H]^+$.
3,5-Dimethoxy-4-(piperidin-4-yloxy)benzaldehyde (5d, R_1 = 3,4-diOMe). Yield 82.5%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.13 (s, 2H), 4.37 - 4.24 (m, 1H), 3.91 (s, 6H), 3.21 - 3.11 (m, 2H), 2.67 - 2.56 (m, 2H), 1.96 - 1.89 (m, 2H), 1.74 – 1.60 (m, 2H); MS (ESI), m/z: 266.05 $[M + H]^+$.

General Procedure for the Synthesis of Compounds 6
Method A for the synthesis of amide: The intermediates **5** (1.0 mmol), appropriate benzoic acid (1.2 mmol), EDCI (219.2 mg, 1.22 mmol), and DMAP (13.5 mg, 0.11 mmol) were dissolved in 5 mL of CH_2Cl_2. The mixture was stirred at room temperature overnight. After the reaction was completed, water was added into the solution. The solution was extracted with CH_2Cl_2, washed with water and brine, and dried with anhydrous Na_2SO_4. Then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the target compounds.

Method B for the synthesis of N-substituted compounds: To a solution of intermediates **5** (5.0 mmol), R_1X (5.0 mmol) in DMF (15 mL) was added K_2CO_3 (2.07 g, 15.0 mmol). The mixture was heated to 100 °C for 5 - 18h. After cooling to room temperature, the K_2CO_3 was removed by filtration. The filtrate was poured into water, extracted with EtOAc, washed with water and brine, and dried over $MgSO_4$. Then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the target compounds.

4-(1-Isonicotinoylpiperidin-4-yloxy)benzaldehyde (6a). Yield 80.2%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (s, 1H), 8.67 (s, 2H), 7.82 (d, 2H, *J* = 8.8 Hz), 7.28 (d, 1H, *J* = 3.6 Hz), 6.99 (d, 2H, *J* = 8.4 Hz), 4.75 - 4.71 (m, 1H), 3.88 - 3.80 (m, 2H), 3.60 - 3.56 (m, 1H), 3.38 - 3.31 (m, 1H), 2.09 - 1.82 (m, 4H); MS (ESI), m/z: 311.11 $[M + H]^+$.
4-(1-Nicotinoylpiperidin-4-yloxy)benzaldehyde (6b). Yield 74.2%; White solid; ^{1}H

NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 8.56 (d, 1H, *J* = 5.2 Hz), 7.81 (d, 2H, *J* = 8.4 Hz), 7.78 (dd, 1H, *J* = 1.6 Hz, *J* = 7.6 Hz), 7.62 (d, 1H, *J* =7.6 Hz), 7.34 (td, 1H, *J* = 0.8 Hz, *J* =7.2 Hz), 7.00 (d, 2H, *J* = 8.8 Hz), 4.74 - 4.70 (m, 1H), 3.90 (t, 2H, *J* = 6.0 Hz), 3.78 - 3.71 (m, 1H), 3.56 - 3.50 (m, 1H), 2.09 - 1.93 (m, 3H), 1.89 - 1.83 (m, 1H); MS (ESI), m/z: 333.14 $[M + Na]^+$.

4-(1-Picolinoylpiperidin-4-yloxy)benzaldehyde (6c). Yield 76.1%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 8.60 (d, 1H, *J* = 4.0 Hz), 7.86 (d, 2H, *J* = 8.4 Hz), 7.82 (dd, 1H, *J* = 2.0 Hz, *J* = 7.6 Hz), 7.67 (d, 1H, *J* = 8.0 Hz), 7.38 (td, 1H, *J* = 1.2 Hz, *J* = 6.8 Hz), 7.04 (d, 2H, *J* = 8.4 Hz), 4.78 - 4.74 (m, 1H), 3.95 (t, 2H, *J* = 5.6 Hz), 3.82 - 3.76 (m, 1H), 3.61 - 3.55 (m, 1H), 2.14 - 1.98 (m, 3H), 1.92 - 1.89 (m, 1H); MS (ESI), m/z: 333.15 $[M + Na]^+$.

4-(1-(5-Chloropicolinoyl)piperidin-4-yloxy)benzaldehyde (6d). Yield 82.3%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 8.50 (d, 1H, *J* = 6.4 Hz), 7.86 (d, 2H, *J* = 8.8 Hz), 7.69 (d, 1H, *J* = 1.2 Hz), 7.38 (dd, 1H, *J* = 2.0 Hz, *J* = 6.4 Hz), 7.04 (d, 2H, *J* = 8.8 Hz), 4.78 - 4.75 (m, 1H), 3.97 - 3.87 (m, 2H), 3.81 - 3.74 (m, 1H), 3.61 - 3.55 (m, 1H), 2.13 - 2.03 (m, 3H), 1.95 - 1.89 (m, 1H); MS (ESI), m/z: 367.15 $[M + Na]^+$.

4-(1-(2-Chloroisonicotinoyl)piperidin-4-yloxy)benzaldehyde (6e). Yield 82.3%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (s, 1H), 8.49 (d, 1H, *J* = 5.2 Hz), 7.86 (d, 2H, *J* = 8.4 Hz), 7.35 (s, 1H), 7.24 (d, 1H, *J* = 4.8 Hz), 7.03 (d, 2H, *J* = 8.8 Hz), 4.78 - 4.76 (m, 1H), 3.98 - 3.94 (m, 1H), 3.85 - 3.83 (m, 1H), 3.64 - 3.60 (m, 1H), 3.38 - 3.35 (m, 1H), 2.13 - 1.90 (m, 4H); MS (ESI), m/z: 367.14 $[M + Na]^+$.

4-(1-(3-(Trifluoromethyl)benzoyl)piperidin-4-yloxy)benzaldehyde (6f). Yield 84.3 %; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 7.86 (d, 2H, *J* = 8.8 Hz), 7.70 (s, 2H), 7.63 (d, 1H, *J* = 7.6 Hz), 7.59 (t, 1H , *J* = 7.6 Hz), 7.04 (d, 2H, *J* = 8.4 Hz), 4.78 - 4.73 (m, 1H), 3.92 - 3.90 (m, 2H), 3.67 - 3.65 (m, 1H), 3.43 - 3.41 (m, 1H), 2.08 - 1.89 (m, 4H); MS (ESI), m/z: 400.09 $[M + Na]^+$.

4-(1-(3-Fluoro-4-(trifluoromethyl)benzoyl)piperidin-4-yloxy)benzaldehyde (6g). Yield 84.3%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 7.86 (d, 2H, *J* = 8.4 Hz), 7.70 (t, 1H, *J* = 7.2 Hz), 7.31 (t, 2H, *J* = 8.0 Hz), 7.03 (d, 2H, *J* = 8.4 Hz), 4.77 - 4.75 (m, 1H), 3.93 - 3.86 (m, 2H), 3.69 - 3.63 (m, 1H), 3.41 - 2.99 (m, 1H), 2.07 - 1.90 (m, 4H); MS (ESI), m/z: 396.07 $[M + H]^+$.

4-(1-(4-(Difluoromethoxy)benzoyl)piperidin-4-yloxy)benzaldehyde (6h). Yield 82.5%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 7.86 (d, 2H, *J* = 8.8 Hz), 7.46 (d, 2H, *J* = 8.8 Hz), 7.18 (d, 2H, *J* = 8.4 Hz), 7.03 (d, 2H, *J* = 8.4 Hz), 6.73 (t, 1H, *J* = 73.6 Hz), 4.75 - 4.72 (m, 1H), 3.87 - 3.65 (m, 4H), 2.04 - 1.81 (m, 4H); MS (ESI), m/z: 398.22 $[M + Na]^+$.

4-(1-(2-Chloronicotinoyl)piperidin-4-yloxy)benzaldehyde (6i). Yield 82.5%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 8.47 (dd, 1H, *J* = 1.6 Hz, *J* = 4.4 Hz), 7.86 (d, 2H, *J* = 8.8 Hz), 7.70 (td, 1H, *J* = 2.0 Hz, *J* = 8.8 Hz), 7.36 (q, 1H, *J* = 5.2 Hz), 7.04 (q, 2H, *J* = 5.6 Hz), 4.78 - 4.76 (m, 1H), 3.99 - 3.90 (m, 1H), 3.66 - 3.58 (m, 1H), 3.36 - 3.17 (m, 2H), 2.14 - 1.95 (m, 2H), 1.91 - 1.83 (m, 1), 1.60 - 1.54 (m, 1H); MS (ESI), m/z: 367.03 $[M + Na]^+$.

4-(1-(4-Nitropyridin-2-yl)piperidin-4-yloxy)benzaldehyde (6j). Yield 84.2%;

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (s, 1H), 8.04 (d, 1H , *J* = 6.0 Hz), 7.87 (d, 2H, *J* = 8.8 Hz), 7.04 (d, 2H, *J* = 8.8 Hz), 6.70 (d, 1H, *J* = 2.0 Hz), 6.63 (dd, 1H, *J* = 2.0 Hz, *J* = 6.0 Hz), 4.74 - 4.72 (m, 1H), 3.66 - 3.60 (m, 2H), 3.44 - 3.38 (m, 2H), 2.11 - 2.05 (m, 2H), 1.98 - 1.94 (m, 2H); MS (ESI), m/z: 328.15 $[M + H]^+$.

4-(1-(5-Nitropyridin-2-yl)piperidin-4-yloxy)benzaldehyde (6k). Yield 86.1%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (s, 1H), 9.06 (s, 1H), 8.24 (dd, 1H, *J* = 3.2 Hz , *J* = 9.2 Hz), 7.88 (d, 2H, *J* = 9.2 Hz), 7.06 (d, 2H, *J* = 8.8 Hz), 6.64 (d, 1H, *J* = 9.6 Hz), 4.80 - 4.77 (m, 1H), 4.00 - 3.94 (m, 2H), 3.91 - 3.85 (m, 2H), 2.11 - 2.04 (m, 2H), 2.01 - 1.96 (m, 2H); MS (ESI), m/z: 328.07 $[M + H]^+$.

2-(4-(4-Formylphenoxy)piperidin-1-yl)nicotinonitrile (6l). Yield 83.8%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 8.36 (dd, 1H, *J* = 1.6 Hz, *J* = 4.8 Hz), 7.86 (d, 2H, *J* = 8.8 Hz), 7.80 (dd, 2H, *J* = 2.0 Hz, *J* = 7.6 Hz), 7.05 (d, 2H, *J* = 8.4 Hz), 6.79 (q, 1H, *J* = 4.8 Hz), 4.76 - 4.71 (m, 1H), 3.98 - 3.92 (m, 2H), 3.74 - 3.68 (m, 2H), 2.19 - 2.12 (m, 2H), 2.04 - 1.97 (m, 2H); MS (ESI), m/z: 330.11 $[M + Na]^+$.

4-(1-(3-(Trifluoromethyl)pyridin-2-yl)piperidin-4-yloxy)benzaldehyde (6m). Yield 84.2%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 8.45 (d, 1H, *J* = 3.6 Hz), 7.89 (d, 1H, *J* = 8.0 Hz), 7.86 (d, 2H, *J* = 8.8 Hz), 7.05 (d, 2H, *J* = 8.8 Hz), 7.02 (d, 1H, *J* = 4.8 Hz), 4.68 - 4.63 (m, 1H), 3.57 - 3.51 (m, 2H), 3.25 - 3.20 (m, 2H), 2.18 - 2.11 (m, 2H), 2.03 - 1.89 (m, 2H); MS (ESI), m/z: 351.15 $[M + H]^+$.

4-(1-(5-(Trifluoromethyl)pyridin-2-yl)piperidin-4-yloxy)benzaldehyde (6n). Yield 84.8%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 8.41 (s, 1H), 7.86 (dd, 2H, *J* = 2.0 Hz, *J* = 6.8 Hz), 7.66 (dd, 1H, *J* = 2.0 Hz, *J* = 9.2 Hz), 7.04 (d, 2H, *J* = 8.8 Hz), 6.72 (d, 1H, *J* = 9.2 Hz), 4.75 - 4.71 (m, 1H), 3.97 - 3.91 (m, 2H), 3.71 - 3.69 (m, 2H), 2.11 - 2.06 (m, 2H), 1.96 - 1.89 (m, 2H); MS (ESI), m/z: 351.14 $[M + H]^+$.

3-Fluoro-4-(1-nicotinoylpiperidin-4-yloxy)benzaldehyde (6o). Yield 83.2%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 8.60 (d, 2H, *J* = 4.0 Hz), 7.84 (t, 1H, *J* = 7.2 Hz), 7.67 (t, 3H, *J* = 8.4 Hz), 7.38 (q, 1H, *J* = 4.2 Hz) , 7.14 (t, 1H, *J* = 8.0 Hz), 4.80 - 4.79 (m, 1H), 3.98 - 3.91 (m, 2H), 3.83 - 3.78 (m, 1H), 3.61 - 3.57 (m, 1H), 2.14 - 2.04 (m, 2H), 2.01 - 1.91 (m, 2H); MS (ESI), m/z: 329.17 $[M + H]^+$.

3-Fluoro-4-(1-isonicotinoylpiperidin-4-yloxy)benzaldehyde (6p). Yield 84.6%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.79 - 8.77 (m, 2H), 7.65 (d, 2H, *J* = 9.6 Hz), 7.49 (s, 1H), 7.11 (s, 1H), 4.82 - 4.80 (m, 1H), 4.03 - 4.01 (m, 1H), 3.84 - 3.82 (m, 1H), 3.71 - 3.69 (m,1H), 3.49 - 3.37 (m, 1H), 2.07 - 2.01 (m, 2H), 1.96 - 1.94 (m, 2H); MS (ESI), m/z: 329.31 $[M + H]^+$.

4-(1-(2-Chloronicotinoyl)piperidin-4-yloxy)-3-fluorobenzaldehyde (6q). Yield 84.6%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.47 (dd, 1H, *J* = 2.0 Hz, *J* = 5.6 Hz), 7.70 (t, 1H, *J* = 7.6 Hz), 7.65 (d, 2H, *J* = 8.4 Hz), 7.37 (td, 1H, *J* = 2.8 Hz, *J* = 4.8 Hz), 7.13 (t, 1H, *J* = 7.6 Hz), 4.83 - 4.75 (m, 1H), 4.18 - 4.13 (m, 1H), 3.98 - 3.81 (m, 1H), 3.80 - 3.75 (m, 1H), 3.56 - 3.49(m, 1H), 2.11 - 1.99 (m, 3H), 1.92 - 1.86 (m, 1H); MS (ESI), m/z: 363.53 $[M + H]^+$.

3-Fluoro-4-(1-(3-(trifluoromethyl)benzoyl)piperidin-4-yloxy)benzaldehyde (6r). Yield 82.5%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.69 (s, 2H), 7.65 (t, 1H, *J* = 2.0 Hz), 7.62 (d, 2H, *J* = 6.0 Hz), 7.58 (t, 1H, *J* = 8.0 Hz), 7.12 (t, 1H,

J = 8.4 Hz), 4.79 - 4.78 (m, 1H), 3.95 - 3.87 (m, 2H), 3.69 - 3.67 (m,1H), 3.44 - 3.42 (m, 1H), 2.04 - 1.91 (m, 3H), 1.64 - 1.62 (m, 1H); MS (ESI), m/z: 396.11 $[M + H]^+$.

3-Fluoro-4-(1-(3-fluoro-4-(trifluoromethyl)benzoyl)piperidin-4-yloxy)benzaldehyde (6s). Yield 80.4%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.71 (t, 1H, *J* = 7.2 Hz), 7.66 (d, 2H, *J* = 9.6 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 7.13 (t, 1H, *J* = 8.0 Hz), 4.81 - 4.79 (m, 1H), 3.99 - 3.97 (m, 1H), 3.86 - 3.84 (m,1H), 3.73 - 3.67 (m, 1H), 3.43 - 3.41 (m, 1H), 2.06 - 2.04 (m, 2H), 1.93 - 1.91 (m, 2H); MS (ESI), m/z: 414.25 $[M + H]^+$.

4-(1-(4-(Difluoromethoxy)benzoyl)piperidin-4-yloxy)-3-fluorobenzaldehyde (6t). Yield 87.4%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.64 (t, 1H, *J* = 2.0 Hz), 7.61 (s, 1H), 7.46 (d, 2H, *J* = 8.8 Hz), 7.17 (d, 2H, *J* = 8.4 Hz), 7.12 (t, 1H, *J* = 8.0 Hz), 6.73 (t, 1H, *J* = 73.2 Hz), 4.77 - 4.75 (m, 1H), 3.87 - 3.73 (m, 3H), 3.47 - 3.45 (m, 1H), 1.94 - 1.65 (m, 3H), 1.64 - 1.63 (m, 1H); MS (ESI), m/z: 416.10 $[M + Na]^+$.

3-Fluoro-4-(1-(3-(1,1,2,2-tetrafluoroethoxy)benzoyl)piperidin-4-yloxy)benzaldehyde (6u). Yield 83.6%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.66 (d, 2H, *J* = 10.0 Hz), 7.48 (td, 1H, *J* = 1.2 Hz, *J* = 8.0 Hz), 7.36 (d, 1H, *J* = 7.6 Hz), 7.30 (d, 2H, *J* = 6.4 Hz), 7.13 (t, 1H, *J* = 8.4 Hz), 6.07 (tt, 1H, *J* = 2.4 Hz, *J* = 52.8 Hz), 4.79 - 4.78 (m, 1H), 3.90 - 3.83 (m, 2H), 3.70 - 3.68 (m, 1H), 3.45 - 3.43 (m, 1H), 2.03 - 1.92 (m, 3H), 1.63 - 1.61 (m, 1H); MS (ESI), m/z: 466.08 $[M + Na]^+$.

4-(1-(2,2-Difluorobenzo[d][1,3]dioxole-4-carbonyl)piperidin-4-yloxy)-3-fluorobenzaldehyde (6v). Yield 82.8%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.65 (d, 2H, *J* = 9.2 Hz), 7.23 (dd, 1H, *J* = 2.0 Hz, *J* = 7.2 Hz), 7.19 (d, 1H, *J* = 8.0 Hz), 7.15 (s, 1H), 7.12 (d, 1H, *J* = 8.0 Hz), 4.81 - 4.79 (m, 1H), 4.03 - 3.99 (m, 1H), 3.88 - 3.83 (m, 1H), 3.70 - 3.65 (m, 1H), 3.42 - 3.39 (m, 1H), 2.10 - 1.97 (m, 4H); MS (ESI), m/z: 430.23 $[M + Na]^+$.

2-(4-(2-Fluoro-4-formylphenoxy)piperidin-1-yl)nicotinonitrile (6w). Yield 80.5%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.37 (dd, 1H, *J* = 2.0 Hz, *J* = 4.8 Hz), 7.80 (dd, 1H, *J* = 7.6 Hz, *J* = 2.0 Hz), 7.65 (td, 2H, *J* = 6.4 Hz, *J* = 2.0 Hz), 7.16 (t, 1H, *J* = 8.4 Hz), 6.80 (q, 1H, *J* = 4.8 Hz), 4.80 - 4.75 (m, 1H), 3.99 - 3.93 (m, 2H), 3.76 - 3.70 (m, 2H), 2.02 - 2.13 (m, 2H), 2.08 - 2.01 (m, 2H); MS (ESI), m/z: 326.27 $[M + H]^+$.

3-Fluoro-4-(1-(3-(trifluoromethyl)pyridin-2-yl)piperidin-4-yloxy)benzaldehyde (6x). Yield 83.5%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.45 (dd, 1H, *J* = 1.2 Hz, *J* = 4.8 Hz), 7.89 (dd, 1H, *J* = 1.6 Hz, *J* = 7.6 Hz), 7.65 (s, 1H), 7.63 (d, 1H, *J* = 2.4 Hz), 7.15 (t, 1H, *J* = 8.0 Hz), 7.03 (q, 1H, *J* = 4.2 Hz), 4.71 - 4.66 (m, 1H), 3.60 - 3.54 (m, 2H), 3.27 - 3.21 (m, 2H), 2.21 - 2.14 (m, 2H), 2.08 - 2.00 (m, 2H); MS (ESI), m/z: 369.25 $[M + H]^+$.

3-Fluoro-4-(1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yloxy)benzaldehyde (6y). Yield 82.7%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.40 (s, 1H), 7.65 (s, 2H), 7.63 (d, 1H, *J* = 2.0 Hz), 7.14 (t, 1H, *J* = 8.4 Hz), 6.71 (d, 1H, *J* = 9.2 Hz), 4.77 - 4.74 (m, 1H), 3.98 - 3.92 (m, 2H), 3.71 - 3.65 (m, 2H), 2.17 - 2.05 (m, 2H), 1.99 - 1.91 (m, 2H); MS (ESI), m/z: 369.26 $[M + H]^+$.

Methyl4-(4-(2-fluoro-4-formylphenoxy)piperidin-1-ylsulfonyl)thiophene-3-carbo

xylate (6z). Yield 80.5%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.62 (d, 2H, *J* = 1.6 Hz), 7.52 (q, 2H, *J* = 5.2 Hz), 7.08 (t, 2H, *J* = 8.0 Hz), 4.67 - 4.65 (m, 1H), 3.88 (s, 3H), 3.54 - 3.49 (m, 2H), 3.14 - 3.11(m, 2H), 2.05-1.96(m, 2H), 1.43 - 1.40 (m, 2H); MS (ESI), m/z: 450.03 $[M + Na]^+$.

4-(1-(5-Methylpyrazine-2-carbonyl)piperidin-4-yloxy)benzaldehyde (6i-a). Yield 75.2%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.83 (s, 1H), 8.41 (s, 1H), 7.84 (d, 2H, *J* = 8.8 Hz), 7.03 (d, 2H, *J* = 8.8 Hz), 4.77 - 4.74 (m, 1H), 3.98 - 3.77 (m, 3H), 3.65 - 3.59 (m, 1H), 2.62 (s, 3H), 2.28 - 2.24 (m, 1H), 2.09 - 1.88 (m, 3H); MS (ESI), m/z: 326.13 $[M + H]^+$.

4-(1-(4-Chloro-2-methoxybenzoyl)piperidin-4-yloxy)benzaldehyde (6i-b). Yield 73.2%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 7.86 (d, 2H, *J* = 8.0 Hz), 7.33 (dd, 1H, *J* = 2.4 Hz, *J* = 8.8 Hz), 7.25 (t, 1H, *J* = 2.8 Hz), 7.03 (dd, 2H, *J* = 2.4 Hz, *J* = 8.0 Hz), 6.87 (d, 1H, *J* = 8.4Hz), 4.72 - 4.70 (m, 1H), 3.96 - 3.87 (m, 1H), 3.84 (s, 3H), 3.73 - 3.68 (m, 1H), 3.55 - 3.46 (m, 1H), 3.24 - 3.19 (m, 1H), 2.12 - 1.80 (m, 4H); MS (ESI), m/z: 374.24 $[M + H]^+$.

4-(1-(4-Fluorophenylsulfonyl)piperidin-4-yloxy)benzaldehyde (6i-c). Yield 76.4%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.81 (s, 2H), 7.79 (s, 2H), 7.25 (d, 2H, *J* = 8.8 Hz), 6.92 (d, 2H, *J* = 8.4 Hz), 4.56 - 4.54 (m, 1H), 3.25 - 3.21 (m, 2H), 3.16 - 3.11 (m, 2H), 2.08 - 1.97 (m, 4H); MS (ESI), m/z: 386.14 $[M + Na]^+$.

3-Ethoxy-4-(1-(3-fluoro-4-(trifluoromethyl)benzoyl)piperidin-4-yloxy)benzaldehyde (6i-d). Yield 73.7%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.70 (t, 1H, *J* = 7.2 Hz), 7.43 (d, 2H, *J* = 6.0 Hz) ,7.31 (d, 2H, *J* = 8.4 Hz), 7.04 (d, 1H, *J* = 8.8 Hz), 4.75 - 4.73 (m, 1H), 4.17 (q, 2H, *J* = 6.8 Hz), 3.96 - 3.94 (m, 1H), 3.88 - 3.86 (m, 1H), 3.72 - 3.70 (m, 1H), 3.40 - 3.38 (m, 1H), 1.91 - 1.89 (m, 2H), 1.63 - 1.61 (m, 2H), 1.49 (t, 3H, *J* = 7.2 Hz); MS (ESI), m/z: 440.22 $[M + H]^+$.

2-(4-(2-Ethoxy-4-formylphenoxy)piperidin-1-yl)nicotinonitrile (6i-e). Yield 76.2%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 8.36 (dd, 1H, *J* = 1.6 Hz, *J* = 4.8 Hz), 7.80 (dd, 1H, *J* = 1.6 Hz, *J* = 7.6 Hz), 7.44 - 7.43 (m, 2H), 7.06 (d, 1H, *J* = 8.8 Hz), 6.78 (q, 1H, *J* = 4.8 Hz), 4.74 - 4.72 (m, 1H), 4.17 (q, 2H, *J* = 6.4 Hz), 4.02 - 3.96 (m, 2H), 3.75 - 3.70 (m, 2H), 2.13 - 2.11 (m, 2H), 2.09 - 2.02 (m, 2H), 1.49 (t, 3H, *J* = 7.2 Hz); MS (ESI), m/z: 352.33 $[M + H]^+$.

2-(4-(4-Formyl-2,6-dimethoxyphenoxy)piperidin-1-yl)nicotinonitrile (6i-f). Yield 71.8%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 8.35 (dd, 1H, *J* = 2.0 Hz , *J* = 4.4 Hz), 7.78 (dd, 1H, *J* = 2.0 Hz, *J* = 7.6 Hz), 7.14 (s, 2H), 6.74 (q, 1H, *J* = 5.2 Hz), 4.57 - 4.54 (m, 1H), 4.12 - 4.06 (m, 2H), 3.92 (s, 6H), 3.67 - 3.61 (m, 2H), 2.05 - 1.97 (m, 4H); MS (ESI), m/z: 368.26 $[M + H]^+$.

General Procedure for the Synthesis of Compounds 9

Method A for the synthesis of amide: *Tert*-butyl piperidin-4-ylcarbamate (401 mg, 2.0 mmol) was added to a solution of appriotiate benzoic acid (2.0 mmol), EDCI (573 mg, 3.0 mmol), and DMAP (122 mg, 1.0 mmol) in 10 mL of CH_2Cl_2 and stirred at room temperature overnight. The mixture was extracted with CH_2Cl_2 and water. And then, the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the target compounds.

Method B for the synthesis of N-substituted compounds:: *Tert*-butyl piperidin-4-ylcarbamate (2.11 g, 10.5 mmol), R_1Cl (10.0 mmol), and potassium carbonate (4.14 g, 30.0 mmol) in 60 mL of DMF were stirred at 80 °C for 4 h. The mixture was poured into 100 mL ice water and the formed solid was collected by filtration, washed with water, and dried *in vacuo* without further purification.

***Tert*-butyl (1-(4-nitropyridin-2-yl)piperidin-4-yl)carbamate (9a)**. Yield 35.7%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, 1H, *J* = 6.0 Hz), 6.63 (s, 1H), 6.56 - 6.54 (m, 1H), 3.79 - 3.76 (m, 3H), 3.01 - 2.95 (m, 2H), 2.04 - 2.02 (m, 2H), 1.43 - 1.36 (m, 11H); MS (ESI), m/z: 323.16 $[M - H]^-$.

***Tert*-butyl (1-(5-nitropyridin-2-yl)piperidin-4-yl)carbamate (9b)**. Yield 35.7%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (s, 1H), 8.21 (dd, 1H, *J* = 6.4 Hz, *J* = 2.8 Hz), 6.61 (d, 1H, *J* = 9.6 Hz), 4.46 (d, 2H, *J* = 12.4 Hz), 3.79 (s, 1H), 3.18 (t, 2H, *J* = 12.0 Hz), 2.10 (d, 2H, *J* = 12.0 Hz), 1.46 - 1.38 (m, 11H); MS (ESI), m/z: 323.16 $[M - H]^-$.

***Tert*-butyl (1-(3-cyanopyridin-2-yl)piperidin-4-yl)carbamate (9c)**. Yield 94.5%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 - 8.35 (m, 1H), 7.76 (dd, 1H, *J* = 7.6 Hz, *J* = 1.6 Hz), 6.80 - 6.77 (m, 1H), 4.46 (d, 2H, *J* = 12.4 Hz), 3.79 (s, 1H), 3.18 (t, 2H, *J* = 12.0 Hz), 2.10 (d, 2H, *J* = 12.0 Hz), 1.46 - 1.38 (m, 11H); MS (ESI), m/z: 303.16 $[M - H]^-$.

***Tert*-butyl (1-(4-(difluoromethoxy)benzoyl)piperidin-4-yl)carbamate (9n)**. Yield 57.8%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, 2H, *J* = 8.0 Hz), 7.18 (d, 2H, *J* = 8.0 Hz), 6.54 - 6.35 (m, 1H), 4.48 (m, 2H), 3.64 (m, 1H), 3.05 (t, 2H, *J* = 12.4 Hz), 2.10 - 2.08 (m, 2H), 1.46 - 1.38 (m, 11H); m/z: 371.14 $[M - H]^-$.

***Tert*-butyl (1-(3-fluoro-4-(trifluoromethyl)benzoyl)piperidin-4-yl)carbamate (9o)**. Yield 59.0%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, 1H, *J* = 8.4 Hz), 7.59 - 7.57 (m, 1H), 7.18 - 7.17 (m, 1H), 3.78 - 3.75 (m, 3H), 3.01 (t, 2H, *J* = 13.2 Hz), 2.04 - 2.02 (m, 2H), 1.50 - 1.46 (m, 11H); MS (ESI), m/z: 391.16 $[M - H]^-$.

***Tert*-butyl (1-(3-(1,1,2,2-tetrafluoroethoxy)benzoyl)piperidin-4-yl)carbamate (9p)**. Yield 49.9%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (t, 1H, *J* = 7.6 Hz), 7.35 (m, 1H), 7.18 (d, 1H *J* = 8.0 Hz), 7.57 - 7.56 (m, 1H), 6.73 - 6.65 (m, 1H), 4.41 (d, 2H, *J* = 13.2 Hz), 3.79 - 3.77 (m, 1H), 3.01 - 2.95 (m, 2H), 2.12 - 2.09 (m, 2H), 1.49 - 1.40 (m, 11H); MS (ESI), m/z: 421.17 $[M - H]^-$.

General Procedure for the Synthesis of Compounds 11

Procedure C for 11a-k, and 11n-p: R_2COCl or R_2SO_2Cl (2.0 mmol) was added to a solution of **10** (2.0 mmol), and Et_3N (834 μL, 6.0 mmol) in CH_2Cl_2 (10 mL), and stirred at room temperature overnight. Then the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the target compounds.

4-(((1-(5-Nitropyridin-2-yl)piperidin-4-yl)amino)methyl)benzaldehydes (11a). Yield 69.4%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 9.02 (s, 1H), 8.18 (d, 2H, *J* = 9.2 Hz), 7.86 (d, 2H, *J* = 7.6 Hz), 7.54 (d, 2H, *J* = 6.8 Hz), 6.58 (d, 1H, *J* = 9.6 Hz), 4.41 (d, 2H, *J* = 12.0 Hz), 3.96 (s, 2H), 3.16 (t, 2H, *J* = 12.0 Hz), 2.89 (d, 2H, *J* = 12.0 Hz), 1.48 - 1.46 (m, 2H); MS (ESI), m/z: 341.15 $[M - H]^-$.

N-(4-Formylbenzyl)-N-(1-(5-nitropyridin-2-yl)piperidin-4-yl)methanesulfonamide (11b). Yield 69.4%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 9.02 (s, 1H), 8.18 (m, 1H), 7.86 (d, 2H, *J* = 8.0 Hz), 7.54 (d, 2H, *J* = 8.0 Hz), 6.58 (d, 1H, *J* = 9.6 Hz), 4.56 (s, 2H), 4.38 (d, 2H, *J* = 13.2 Hz), 4.08 - 4.02 (m, 1H), 3.02 (t, 2H, *J* = 12.0 Hz), 2.92 (s, 3H), 1.90 - 1.78 (m, 4H); MS (ESI), m/z: 419.13 $[M - H]^-$.

Methyl 3-(N-(4-formylbenzyl)-N-(1-(5-nitropyridin-2-yl)piperidin-4-yl)sulfamoyl)thiophene-2-carboxylate (11c). Yield 65.0%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 8.32 - 8.30 (m, 1H), 8.99 (m, 1H), 8.18 (d, 1H, *J* = 8.0 Hz), 7.76 (d, 2H, *J* = 8.0 Hz), 7.47 (d, 2H, *J* = 8.0 Hz), 7.42 (m, 2H), 6.54 (d, 1H, *J* = 9.6 Hz), 4.66 (s, 2H), 4.57 - 4.49 (m, 3H), 3.95 (s, 3H), 3.03 (t, 2H, *J* = 12.0 Hz), 4.11 (m, 1H), 3.25 - 3.18 (m, 2H), 3.08 (t, 2H, *J* = 12.0 Hz), 1.84 - 1.53 (m, 4H); MS (ESI), m/z: 545.11 $[M - H]^-$.

2-(4-((4-Formylbenzyl)amino)piperidin-1-yl)nicotinonitrile (11d). Yield 72.5%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 8.32 (dd, 1H, *J* = 4.8 Hz, *J* = 2.0 Hz), 7.86 (d, 2H, *J* = 8.0 Hz), 7.76 (dd, 1H, *J* = 7.6 Hz, *J* = 2.0 Hz), 7.53 (d, 2H, *J* = 8.0 Hz), 6.74 - 6.71 (m, 1H), 4.32 (d, 2H, *J* = 13.6 Hz), 3.95 (s, 2H), 3.17 - 3.10 (m, 2H), 2.84 - 2.78 (m, 1H), 2.07 - 2.04 (m, 2H), 1.58 - 1.50 (m, 2H); MS (ESI), m/z: 321.16 $[M - H]^-$.

N-(1-(3-Cyanopyridin-2-yl)piperidin-4-yl)-N-(4-formylbenzyl)methanesulfonamide (11e). Yield 60.4%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 8.32 (dd, 1H, *J* = 4.8 Hz, *J* = 2.0 Hz), 7.86 (d, 2H, *J* = 8.0 Hz), 7.78 - 7.76 (m,1H), 7.58 (d, 2H, *J* = 8.0 Hz), 6.80 - 6.76 (m, 1H), 4.49 (s, 2H), 4.38 (d, 2H, *J* = 13.2 Hz), 4.09 - 4.03 (m, 1H), 3.02 (t, 2H, *J* = 12.0 Hz), 2.92 (s, 3H), 1.90 – 1.78 (m, 4H) ; MS (ESI), m/z: 399.14 $[M - H]^-$.

Methyl 3-(N-(1-(3-cyanopyridin-2-yl)piperidin-4-yl)-N-(4-formylbenzyl)sulfamoyl)thiophene-2-carboxylate (11f). Yield 70.4%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 8.29 - 8.28 (m, 1H), 7.78 (d, 2H, *J* = 8.0 Hz), 7.74 - 7.72 (m, 1H), 7.51 (d, 2H, *J* = 8.0 Hz), 7.41 (dd, 2H, *J* = 12.8 Hz, *J* = 5.6 Hz), 6.76 - 6.72 (m, 1H), 4.74 (s, 2H), 4.32 (d, 2H, *J* = 12.0 Hz), 3.94 (s, 3H), 3.01 - 2.95 (m, 2H), 1.75 - 1.62 (m, 4H); MS (ESI), m/z: 525.12 $[M - H]^-$.

5-Chloro-N-(1-(3-cyanopyridin-2-yl)piperidin-4-yl)-N-(4-formylbenzyl)thiophene-2-carboxamide (11g). Yield 56.1%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.01 (s, 1H), 8.33 - 8.31 (m, 1H), 7.89 (d, 2H, *J* = 8.0 Hz), 7.78 - 7.75 (m,1H), 7.46 (d, 2H, *J* = 8.0 Hz), 7.02 (s, 1H), 6.79 - 6.76 (m, 2H), 4.83 (s, 2H), 4.66 (m, 1H), 4.40 (d, 2H, *J* = 12.8 Hz), 3.07 - 3.01 (m, 2H), 1.90 - 1.85 (m, 4H); MS (ESI), m/z: 465.11 $[M - H]^-$.

N-(1-(3-Cyanopyridin-2-yl)piperidin-4-yl)-N-(4-formylbenzyl)-3-morpholinopropane-1-sulfonamide (11h). Yield 53.9%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ10.00 (s, 1H), 8.31 (dd, 1H, *J* = 4.8 Hz, *J* = 2.0 Hz), 7.86 (d, 2H, *J* = 8.0 Hz), 7.76 (dd, 1H, *J* = 7.6 Hz, *J* = 2.0 Hz), 7.58 (d, 2H, *J* = 8.0 Hz), 6.79 - 6.76 (m, 1H), 4.50 (s, 2H), 4.37 (d, 2H, *J* = 13.2 Hz), 4.04 - 3.98 (m, 1H), 3.69 (t, 4H, *J* = 4.4 Hz), 3.04 - 2.97 (m, 4H), 2.45 - 2.42 (m, 6H), 2.03 - 1.75 (m, 4H); MS (ESI), m/z: 512.22 [M -

H]⁻.

5-Bromo-N-(1-(3-cyanopyridin-2-yl)piperidin-4-yl)-N-(4-formylbenzyl)thiophene-2-carboxamide (11i). Yield 45.2%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 8.33 (dd, 1H, *J* = 4.8 Hz, *J* = 2.0 Hz), 7.89 (d, 2H, *J* = 8.0 Hz), 7.78 - 7.76 (m,1H), 7.47 (d, 2H, *J* = 8.0 Hz), 6.80 - 6.77 (m, 1H), 4.84 (s, 2H), 4.66 (m, 1H), 4.40 (d, 2H, *J* = 13.2 Hz), 3.08 - 3.02 (m, 2H), 1.91 - 1.86 (m, 4H); MS (ESI), m/z: 509.06 [M - H]⁻.

(3r,5r,7r)-N-(1-(3-Cyanopyridin-2-yl)piperidin-4-yl)-N-(4-formylbenzyl)adamantane-1-carboxamide (11j). Yield 52.8%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (s, 1H), 8.31 (dd, 1H, *J* = 4.8 Hz, *J* = 2.0 Hz), 7.78 (d, 2H, *J* = 8.4 Hz), 7.76 (dd, 1H, *J* = 7.6 Hz, *J* = 2.0 Hz), 7.29 (d, 2H, *J* = 8.0 Hz), 6.78 – 6.75 (m, 1H), 4.57 (s, 3H), 4.40 (d, 2H, *J* = 12.6 Hz), 3.06 – 3.00 (m, 2H), 2.06 – 1.70 (m, 19H); MS (ESI), m/z: 482.27 [M - H]⁻.

N-(1-(3-Cyanopyridin-2-yl)piperidin-4-yl)-N-(4-formylbenzyl)pentanamide (11k). White 61.4%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 8.32 (s, 1H), 7.89 (d, 2H, *J* = 7.6 Hz), 7.75 (d, 1H, *J* = 7.6 Hz), 7.46 (d, 2H, *J* = 7.6 Hz), 6.76 - 6.73 (m, 1H), 4.89 (m,1H), 4.78 (s, 2H), 4.37 (d, 2H, *J* = 12.6 Hz), 3.09 - 3.03 (m, 2H), 1.88 - 1.80 (m, 4H), 1.73 - 0.69 (m, 11H); MS (ESI), m/z: 405.22 [M - H]⁻.

N-(1-(4-(Difluoromethoxy)benzoyl)piperidin-4-yl)-N-(4-formylbenzyl)methanesulfonamide (11n). Yield 55.1%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 7.88 (d, 2H, *J* = 8.4 Hz), 7.57 (d, 2H, *J* = 8.0 Hz), 7.35 (d, 2H, *J* = 8.0 Hz), 7.18 (d, 2H, *J* = 8.0 Hz), 6.54 - 6.35 (m, 1H), 4.48 (s, 2H), 4.01 (m, 2H), 2.91 (s, 3H); MS (ESI), m/z: 467.14 [M - H]⁻.

N-(1-(3-Fluoro-4-(trifluoromethyl)benzoyl)piperidin-4-yl)-N-(4-formylbenzyl)methanesulfonamide (11o). Yield 50.1%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 7.89 (d, 2H, *J* = 6.4 Hz), 7.64 - 7.57 (m, 3H), 7.18 - 7.15 (m, 2H), 4.80 (s, 1H), 4.48 (m, 3H), 4.02 (s, 1H), 3.65 - 3.64 (m, 1H), 3.08 (s, 1H), 2.92 (s, 3H); MS (ESI), m/z: 487.12 [M - H]⁻.

N-(4-Formylbenzyl)-N-(1-(3-(1,1,2,2-tetrafluoroethoxy)benzoyl)piperidin-4-yl)methanesulfonamide (11p). Yield 40.4%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.01 (s, 1H), 7.87 (d, 2H, *J* = 6.4 Hz), 7.64 - 7.57 (m, 3H), 7.35 (d, 2H, *J* = 8.0 Hz), 7.18 (d, 1H, *J* = 8.0 Hz), 6.73 - 6.65 (m, 1H),4.80 (s, 2H), 4.48 (m, 3H), 3.65 - 3.64 (m, 1H), 3.08 (s, 1H), 2.92 (s, 3H); MS (ESI), m/z: 517.13 [M - H]⁻.

Procedure D for 11l, and 11m: Iso(thio)cyanate (2.0 mmol), or $(R_2CO)_2O$ (24 mmol) was added to a solution of **10** (2.0 mmol) in pyridine (10 mL) and stirred at room temperature overnight. Then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the target compounds.

1-(1-(3-Cyanopyridin-2-yl)piperidin-4-yl)-3-ethyl-1-(4-formylbenzyl)urea (11l). Yield 48.7%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 8.32 - 8.31 (m, 1H), 7.90 (d, 2H, *J* = 8.0 Hz), 7.76 (dd, 1H, *J* = 7.6 Hz, *J* = 1.6 Hz), 7.40 (d, 2H, *J* = 8.0 Hz), 6.78 - 6.74 (m, 1H), 5.76 - 5.73 (m, 1H), 5.36 (d, 1H, *J* = 4.0 Hz), 4.70 (s, 2H), 4.41 (d, 2H, *J* = 13.2 Hz), 3.14 (t, 2H, *J* = 13.2 Hz), 3.08 (d, 3H, *J* = 4.4 Hz),

2.05 (d, 2H, *J* = 14.4 Hz), 1.75 - 1.70 (m, 2H); MS (ESI), m/z: 392.20 $[M - H]^-$.

1-(1-(3-Cyanopyridin-2-yl)piperidin-4-yl)-1-(4-formylbenzyl)-3-methylthiourea (11m). Yield 47.8%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 8.32 - 8.30 (m, 1H), 7.88 (d, 2H, *J* = 8.4 Hz), 7.75 - 7.73 (m, 1H), 7.44 (d, 2H, *J* = 8.4 Hz), 6.76 - 6.72 (m, 1H), 4.67 - 4.61 (m, 1H), 4.44 (s, 2H), 4.39 (d, 2H, *J* = 13.2 Hz), 4.11 (m, 1H), 3.25 - 3.18 (m, 2H), 3.08 (t, 2H, *J* = 12.0 Hz), 1.91 - 1.88 (m, 2H), 1.75 - 1.64 (m, 2H) 1.00 (t, 3H, *J* = 7.2 Hz); MS (ESI), m/z: 394.16 $[M - H]^-$.

General Procedure for the Synthesis of Compounds 13, and 16

To a solution of 4-formylbenzoic acid (2.0 mmol), EDCI (573 mg, 3.0 mmol) and DMAP (122 mg, 1.0 mmol) in 10 mL CH_2Cl_2, the substituted 4-aminopiperidine (2.0 mmol) was added and stirred at room temperature overnight. The mixture was treated according to Procedure A.

4-Formyl-N-(1-(4-nitropyridin-2-yl)piperidin-4-yl)benzamide (13a). Yield 46.2%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.13 (d, 1H, *J* = 6.0 Hz), 7.96 (d, 2H, *J* = 8.0 Hz), 7.91 (d, 2H, *J* = 8.4 Hz), 6.69 - 6.68 (m, 1H), 6.62 - 6.60 (m, 1H), 6.08 (d, 1H, *J* = 7.2 Hz), 4,31 - 4.27 (m, 1H), 3.91 (d, 2H, *J* = 13.2 Hz), 4.37 (s, 1H), 3.13 - 3.07 (m, 2H), 2.20 - 2.18 (m, 2H), 1.63 - 1.56 (m, 2H); MS (ESI), m/z: 355.13 $[M - H]^-$.

4-Formyl-N-(1-(5-nitropyridin-2-yl)piperidin-4-yl)benzamide (13b). Yield 39.3%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (s, 1H), 9.06 (s, 1H), 8.23 (d, 2H, *J* = 8.4 Hz), 7.97 (d, 2H, *J* = 7.6 Hz), 7.92 (d, 2H, *J* = 7.6 Hz), 6.65 (d, 1H, *J* = 8.8 Hz), 6.05 (s, 1H), 4.59 (d, 2H, *J* = 12.6 Hz), 4.37 (s, 1H), 3.24 (m, 2H), 2.24 - 2.18 (m, 2H), 0.88 - 0.84 (m, 2H); MS (ESI), m/z: 355.13 $[M - H]^-$.

N-(1-(3-Cyanopyridin-2-yl)piperidin-4-yl)-4-formylbenzamide (13c). Yield 33.0%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.37 - 8.35 (m, 1H), 7.97 (d, 2H, *J* = 8.4 Hz), 7.92 (d, 2H, *J* = 8.4 Hz), 7.76 (m, 1H), 6.80 - 6.77 (m, 1H), 6.10 (d, 1H, *J* = 7.2 Hz), 4.35 (d, 2H, *J* = 13.6 Hz), 4.29 (m, 1H), 3.21 (t, 2H, *J* = 11.6 Hz), 2.22 (d, 2H, *J* = 12.0 Hz), 1.75 - 1.71 (m, 2H); MS (ESI), m/z: 335.14 $[M - H]^-$.

4-(4-((4-Nitropyridin-2-yl)amino)piperidine-1-carbonyl)benzaldehyde (16a). Yield 34.2%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.06 (s, 1H), 7.96 - 7.94 (m, 3H), 7.57 (d, 2H, *J* = 8.4 Hz), 6.53 (s, 1H), 6.43 (m, 1H), 6.77 - 6.66 (m, 2H), 3.71 - 3.61 (m, 2H), 1.78 - 1.23 (m, 4H); MS (ESI), m/z: 355.13 $[M - H]^-$.

4-(4-((5-Nitropyridin-2-yl)amino)piperidine-1-carbonyl)benzaldehyde (16b). Yield 35.7%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.06 (s, 1H), 9.00 (s, 1H), 8.23 (d, 2H, *J* = 8.4 Hz), 7.95 (d, 2H, *J* = 7.6 Hz), 7.57 (d, 2H, *J* = 7.6 Hz), 6.43 (d, 1H, *J* = 8.8 Hz), 5.42 (s,1H), 4.69 (s, 1H), 4.19 (s, 1H), 3.71 (s, 1H), 3.28 - 3.10 (m, 2H), 2.64 - 2.21 (m, 2H), 1.62 - 1.55 (m, 2H); MS (ESI), m/z: 355.13 $[M - H]^-$.

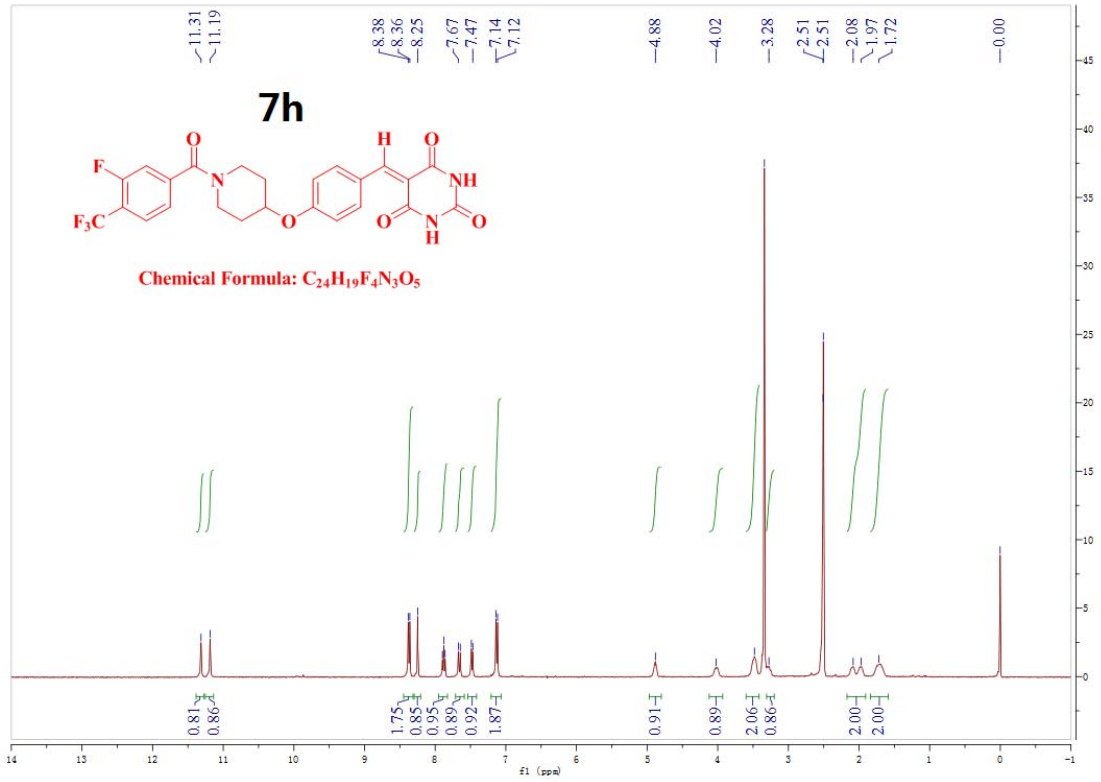
General Procedure for the Synthesis of Compounds 15

Tert-butyl 4-aminopiperidine-1-carboxylate (2.11 g, 10.5 mmol), R_1Cl (10.0 mmol), and anhydrous K_2CO_3 (4.14 g, 30.0 mmol) in 60 mL of acetonitrile were stirred at 80 ^oC for 24h. The solution was removed under reduced pressure. The residue was extracted with CH_2Cl_2 and water, and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Then the solvent was removed under reduced pressure

and the residue was purified by column chromatography on silica gel to afford the target compounds.

***Tert*-butyl 4-((4-nitropyridin-2-yl)amino)piperidine-1-carboxylate (15a)**. Yield 64.3%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, 1H, *J* = 6.0 Hz), 6.83 (s, 1H), 6.67 - 6.66 (m, 1H), 3.79 - 3.76 (m, 3H), 3.02 (t, 2H, *J* = 12.0 Hz), 2.04 - 2.02 (m, 2H), 1.43 - 1.36 (m, 11H); MS (ESI), m/z: 323.16 $[M - H]^-$.

***Tert*-butyl 4-((5-nitropyridin-2-yl)amino)piperidine-1-carboxylate (15b)**. Yield 89.5%; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (s, 1H), 8.21- 8.20 (m, 1H), 6.61 (d, 1H, *J* = 9.6 Hz), 4.44 (d, 2H, *J* = 12.4 Hz), 3.79 (m, 1H), 3.18 (t, 2H, *J* = 12.0 Hz), 2.10 (d, 2H, *J* = 12.0 Hz), 1.46 - 1.38 (m, 11H); MS (ESI), m/z: 323.16 $[M - H]^-$.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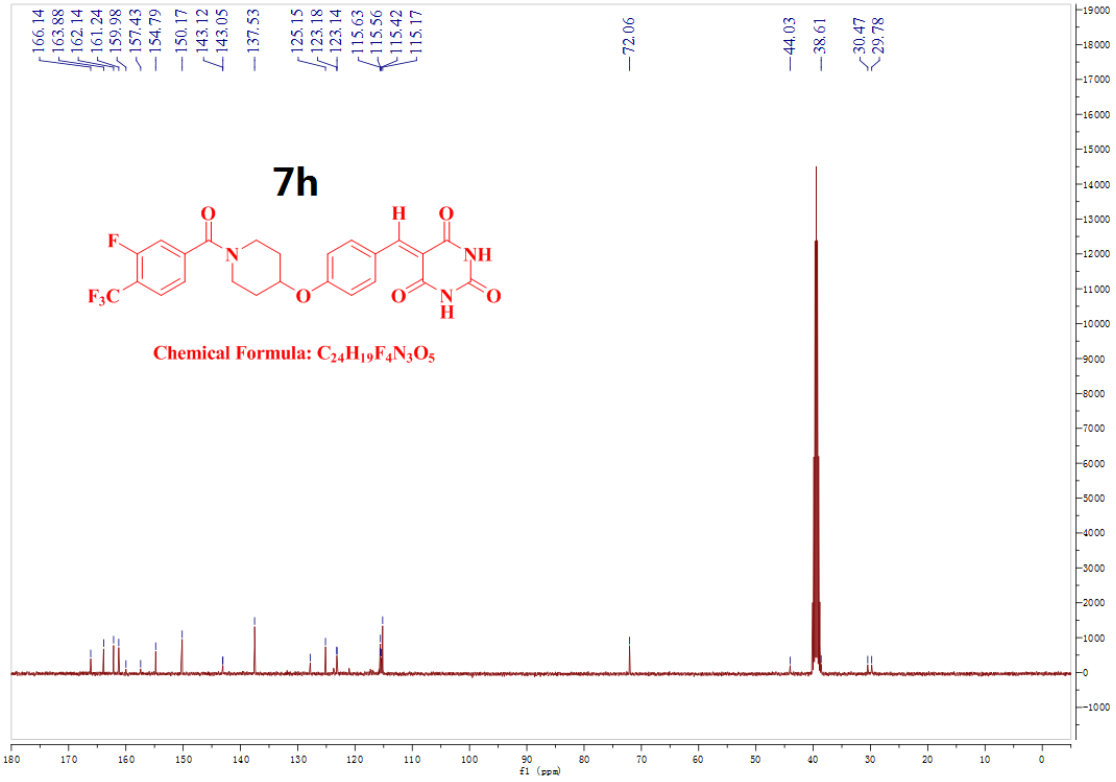
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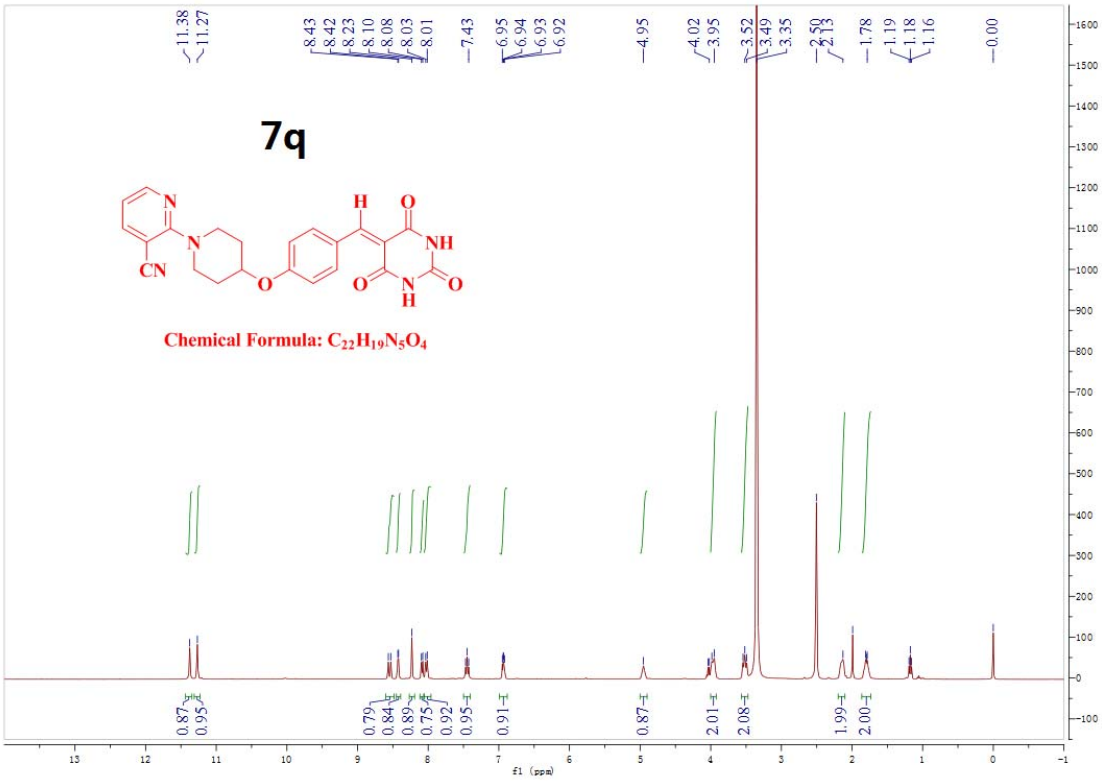
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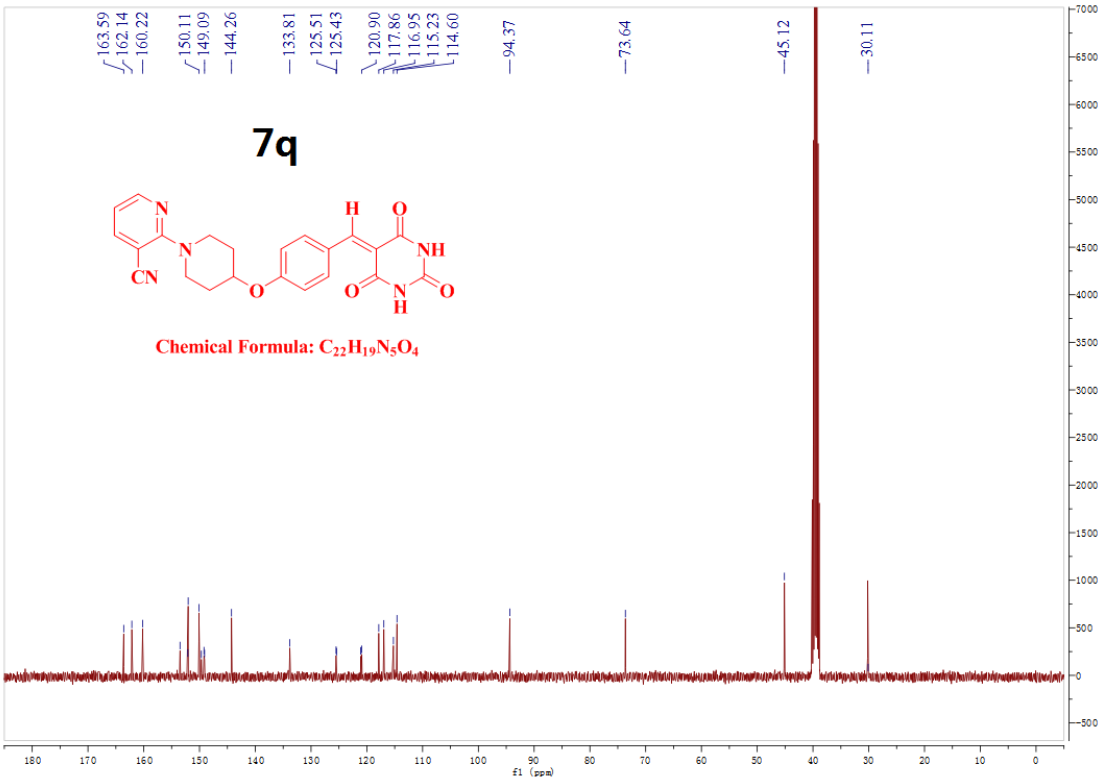
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HPLC Chromatograms of 7h

Empower 3 SOFTWARE

mutiple sample

SAMPLE INFORMATION

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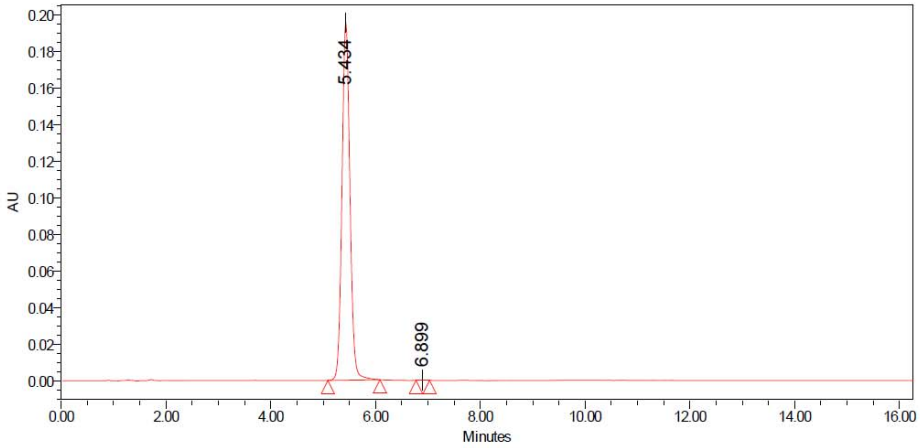

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Page: 1 of 1

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Date Printed:
9/13/2012
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HPLC Chromatograms of 7q

Empower 3 SOFTWARE

mutiple sample

SAMPLE INFORMATION

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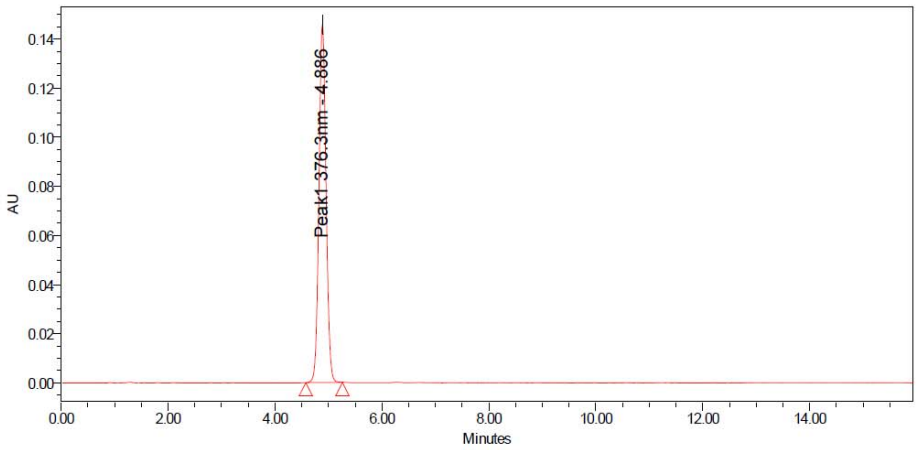

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