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Discovery of novel phenylpyridone derivatives as potent and selective MCH1R antagonists

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ABSTRACT

The design, synthesis and structure–activity relationships of a novel class of *N*-phenylpyridone MCH1R antagonists are described. The core part of the *N*-phenylpyridone structure was newly designed and the side chain moieties that were attached to the core part were extensively explored. As a result of optimization of the *N*-phenylpyridone leads, we successfully developed the orally available, and brain-penetrable MCH1R selective antagonist **7c**, exhibiting excellent anti-obese effect in diet-induced obese (DIO) mice.

1. Introduction

Obesity is recently increasing in the developed countries and is becoming recognized as an associated risk factor for type 2 diabetes, stroke, hyperlipemia and cardiovascular disease. Consequently, pharmaceutical companies have made a concerted effort to develop anti-obesity agents. There are several potential biological targets for treatment of obesity,[1] in particular central nervous system including the neuropeptide-Y Y5 receptor, serotonin 5-HT2c receptor, cannabinoid 1 (CB1) receptor and melanin-concentrating hormone receptor 1 (MCH1R).

MCH is a cyclic 19-amino acid neuropeptide expressed throughout the brain, predominantly in mammalian neurons in the lateral hypothalamus and zona incerta region of the brain. Recent publications suggested that the MCH peptide plays a major role in the regulation of food intake and energy homeostasis.[2,3] Chronic intracerebroventricular (icv) infusion of MCH stimulates food intake, causing obesity with hyperphagia.[4,5] MCH gene knock-out mice are lean due to hypophagia and maintain elevated metabolic rate.[6] In contrast, transgenic mice in which MCH is overexpressed are susceptible to insulin resistance and prone to obesity.[7] Furthermore, chronic administration of MCH1R antagonists suppresses food intake and body weight gain in diet-induced obesity (DIO) rats and mice.[8,9] These findings suggest that the MCH1 receptor could be an attractive therapeutic target for the treatment of obesity.

There are a number of literature disclosures and patent applications describing potent small molecule MCH1R antagonists in a variety of structure classes.[10,11] T-226296 (**1**), which was first disclosed as a potent MCH1R antagonist by Takeda, suppressed MCH-induced food intake at 30 mpk in rats (Fig. 1).[12] GSK reported the biphenylcarboxamide analog **2** was discovered with good binding affinity for MCH1R and moderate brain penetrability in rats (brain–blood ratio: 1).[13] Abbott established that the indazole **3** exhibited significant in vitro and in vivo potency.[14] From a viewpoint of molecular profiling of current MCH1R lead structures, compounds with potent binding activity for MCH1R had common pharmacophore which consisted of three essential components as follows: a distal hydrophobic aryl group (A), a central *N*-aryl carboxamide core connecting the distal aryl group with a pendant basic amine (B) and a basic amine substituent coupled through a linker (C).

In order to discover structurally diverse molecules possessing potent MCH1R antagonist activity, we focused our attention on replacement of the central carboxamide moiety with a pyridone scaffold as shown in Figure 2 in hopes of further improving in vitro and in vivo potency. In this paper, we describe our efforts on the design, synthesis and structure–activity relationships (SAR) of a series of *N*-phenylpyridone derivatives and identification of potent and selective MCH1R antagonists for the treatment of obesity.

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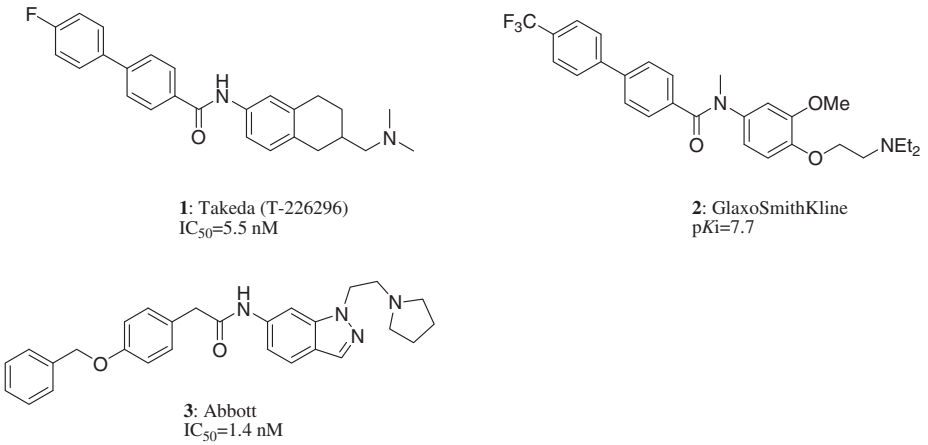


Figure 1. Structures of MCH1R antagonists.

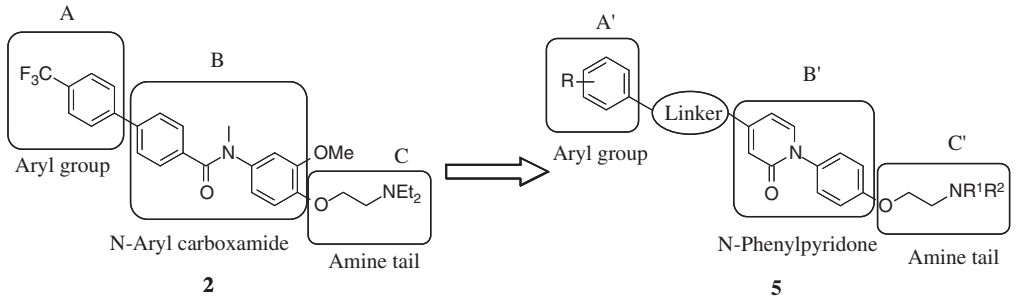
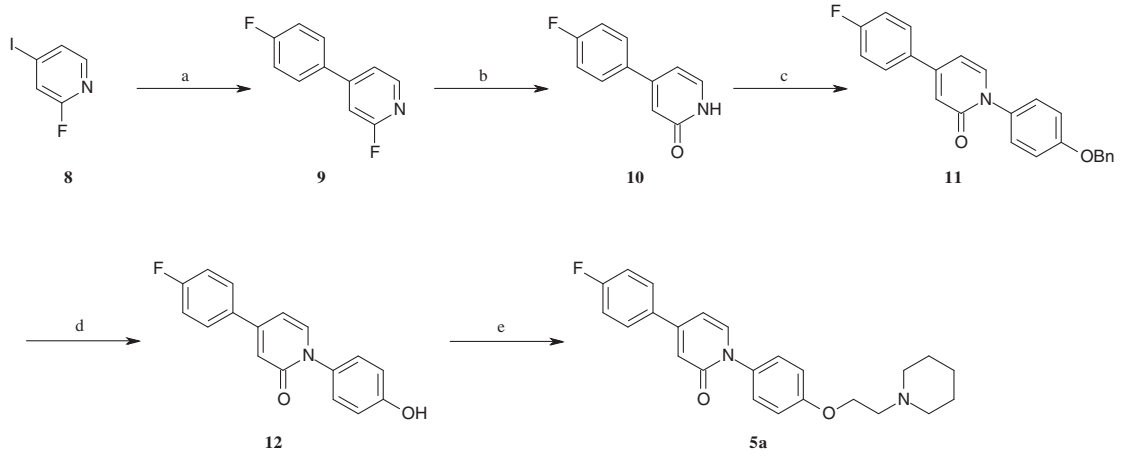


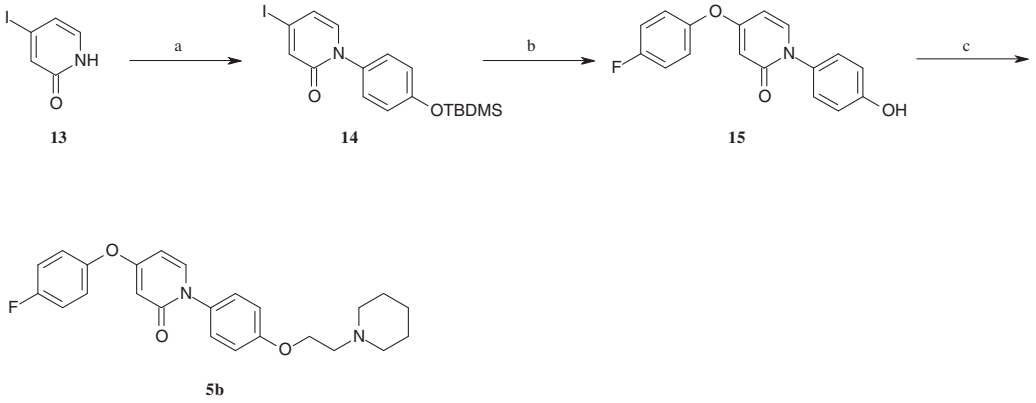
Figure 2. Design of the *N*-phenylpyridone scaffold.

2. Chemistry

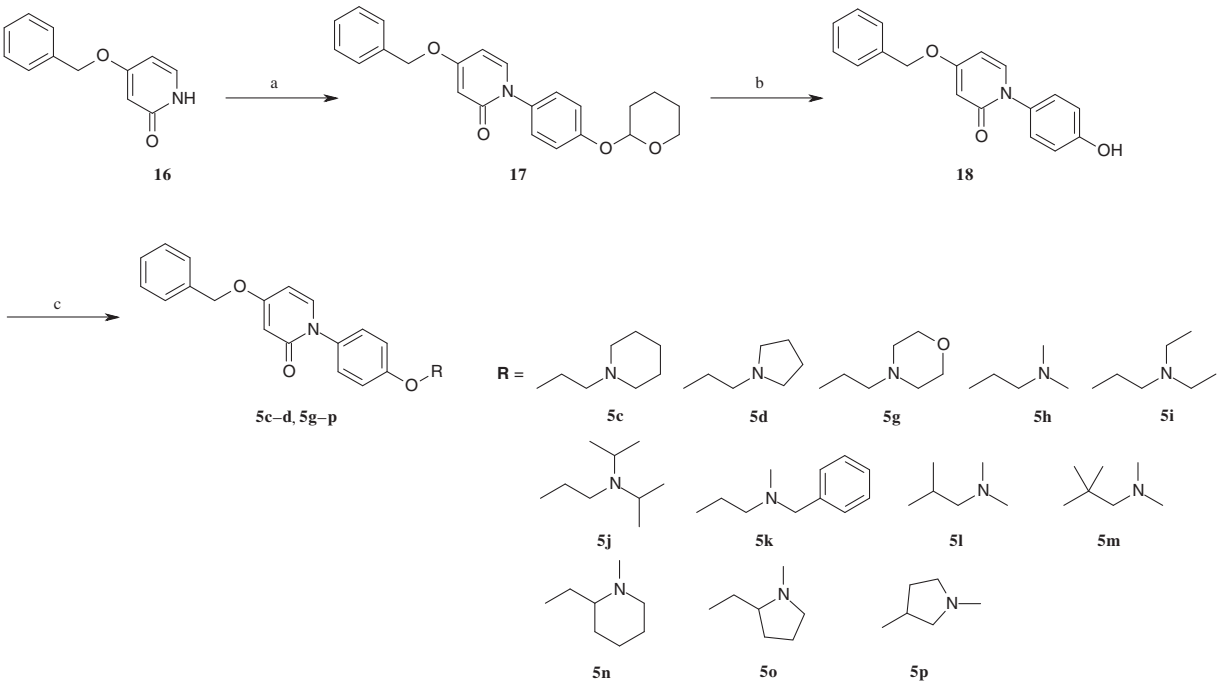
The synthesis of *N*-phenylpyridone MCH1R antagonists reported herein is outlined in Schemes 1–5. Compound **5a** was prepared from commercially available 2-fluoro-4-iodopyridine (**8**). Suzuki coupling reaction of (**8**) with 4-fluorophenylboronic acid formed compound **9**, followed by hydrolysis under acidic conditions to afford pyridone derivative **10**. Treatment of **10** with 1-benzyloxy-4-bromobenzene under Ullman coupling conditions gave *N*-phenylpyridone derivative **11**. Deprotection of the benzyl group under acidic conditions produced phenol analog **12**, followed by Mitsunobu reaction with 2-(piperidin-1-yl)ethanol to afford compound **5a** in good yield (Scheme 1). Preparation of **5b** is shown in Scheme 2. Coupling reaction of 4-iodo-2-pyridone (**13**) with 4-(*tert*-butyldimethylsilyloxy)phenylboronic acid in the presence of copper(II) acetate produced *N*-phenylpyridone derivative **14**. Subsequent treatment of **14** with 4-fluorophenol under Ullman coupling conditions gave the deprotected phenol derivative **15** in moderate yield. Phenol derivative **15** was alkylated with 2-(piperidin-1-yl)ethanol under Mitsunobu conditions to afford compound **5b**. Derivatives at the right-hand amine part were prepared as outlined in Scheme 3. Coupling of commercially available pyridone



Scheme 1. Reagents and conditions: (a) 4-Fluorophenylboronic acid, $Pd(PPh_3)_4$, 2 M Na_2CO_3, dimethoxyethane; (b) aq HCl; (c) 1-benzyloxy-4-bromobenzene, CuI, K_2CO_3, DMF, 150 °C; (d) concd HCl, water–MeOH, reflux; (e) diethyl azodicarboxylate, PPh_3, 2-(piperidin-1-yl)ethanol, THF.



Scheme 2. Reagents and conditions: (a) 4-(*tert*-Butyldimethylsilyloxy)phenylboronic acid, $Cu(OAc)_2$, molecular sieves 4A, pyridine, CH_2Cl_2; (b) 4-fluorophenol, CuI, K_2CO_3, DMF, 150 °C; (c) diethyl azodicarboxylate, PPh_3, 2-(piperidin-1-yl)ethanol, THF.



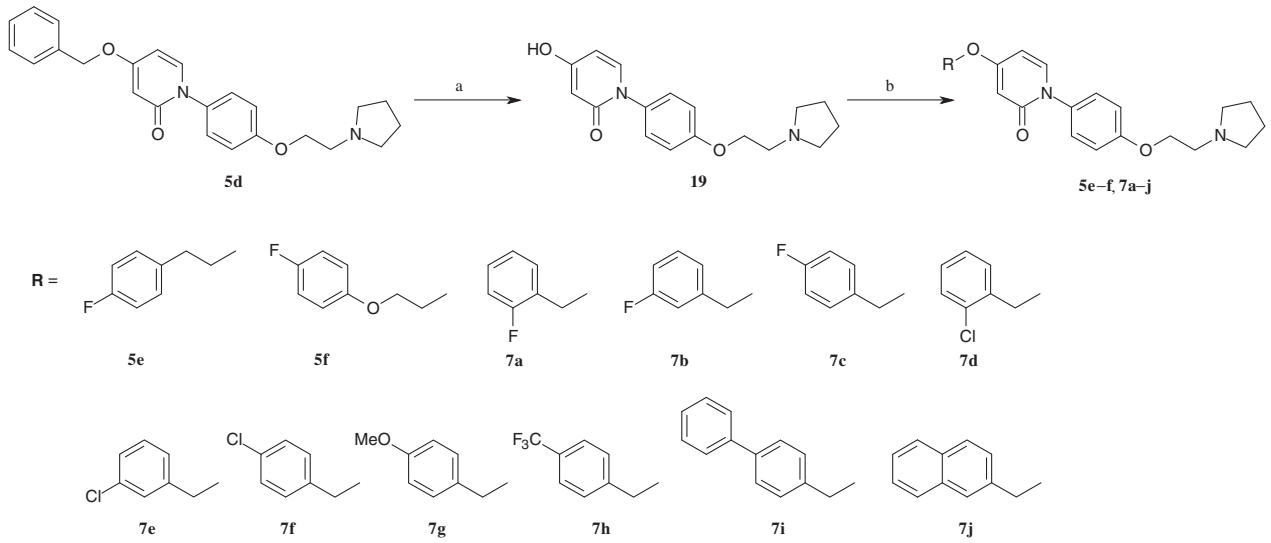
Scheme 3. Reagents and conditions: (a) 2-(4-Iodophenoxy)tetrahydro-2*H*-pyran, CuI, K_2CO_3, DMF, 150 °C; (b) pyridinium *p*-toluenesulfonate, EtOH, reflux; (c) diethyl azodicarboxylate, PPh_3, ROH, THF.

(**16**) with 2-(4-iodophenoxy)tetrahydro-2*H*-pyran in the catalytic amount of copper(I) iodide afforded the key intermediate *N*-phenylpyridone derivative **17** in moderate yield. Compound **17** was treated with a catalytic amount of pyridinium *p*-toluenesulfonate in EtOH, followed by Mitsunobu reaction with 2-aminoethanol derivatives to afford compounds **5c**–**d** and **5g**–**p** in moderate to good yield. Compounds which have related substituents in lieu of the left-hand benzyl group, different length linkers or other aryl groups were synthesized as described in Scheme 4. Catalytic hydrogenolysis of compound **5d** under hydrogen atmosphere produced the phenol derivative **19**, followed by Mitsunobu reaction to give compounds **5e**–**f** and **7a**–**j**. Ullman coupling reaction of (**16**) with 4-(methoxycarbonyl)phenylboronic acid produced compound **20**, which was hydrolyzed to form carboxylic acid **21**. Treatment of **21** with diphenylphosphoryl azide in MeOH–THF afforded carbamate derivative **22**, followed by alkylation with 2-(diethylamino)ethyl bromide to give compound **6c**. Removal of methoxycarbonyl group with lithium aluminum hydride afforded compound **6a**. Subsequent reductive amination with paraformaldehyde gave the N-methylated compound **6b**.

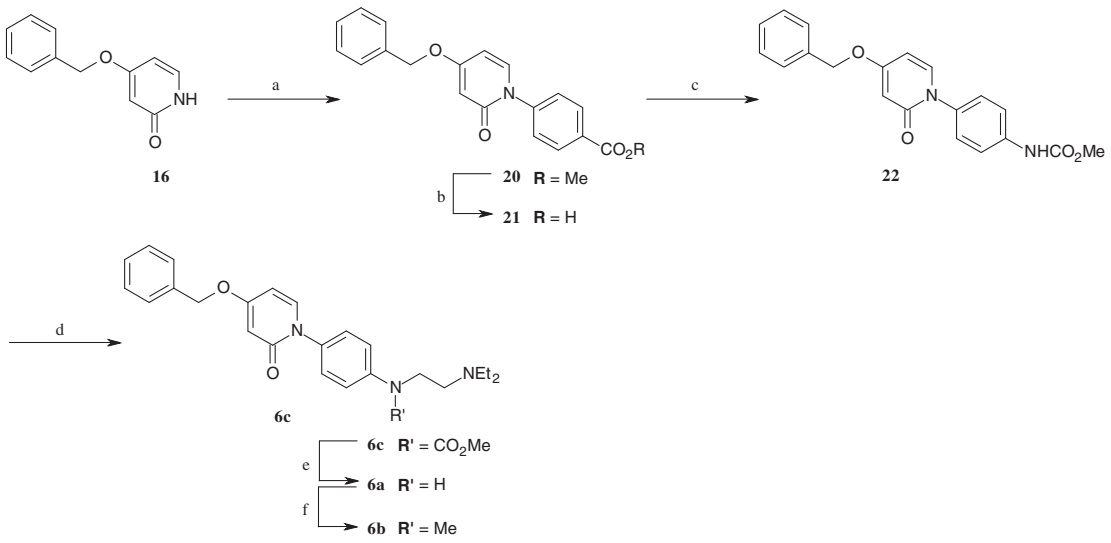
3. Results and discussion

3.1. In vitro evaluation

The primary screening of compounds were evaluated for their binding affinity to the membranes of CHO cells expressing human MCH1R in a competition binding assay with [^{125}I]-MCH as the radioligand. Subsequently, antagonistic activity was estimated by the inhibitory effect of compounds on intracellular calcium release induced by MCH using FLIPR in CHO cells expressing human MCH1R.[9] Furthermore, selected compounds were evaluated for hERG K^+ channel inhibitory activity using the [^{35}S]*N*-[(4R)-1′-[(2*R*)-6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl]-3,4-dihydro-4-hydroxyspiro-[2*H*-1-benzopyran-2,4′-piperidin]-6-yl]methanesulfonamide binding assay to assess QTc prolongation liability.[15]



Scheme 4. Reagents and conditions: (a) Pd on carbon, H_2, MeOH, THF; (b) 1,1′-(azodicarbonyl)dipiperidine, PBu_3, ROH, THF.

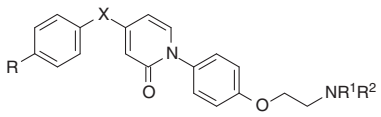


Scheme 5. Reagents and conditions: (a) 4-(Methoxycarbonyl)phenylboronic acid, $Cu(OAc)_2$, molecular sieves 4A, pyridine, CH_2Cl_2; (b) 4 N NaOH, MeOH, THF; (c) diphenylphosphoryl azide, triethylamine, MeOH, THF; (d) 2-(diethylamino)ethyl bromide hydrobromide, potassium *tert*-butoxide, THF; (e) $LiAlH_4$, THF; (f) paraformaldehyde, $ZnCl_2$, $NaB(CN)H_3$, MeOH.

Our initial modification of the length of linker which connected the *N*-phenylpyridone analog and the distal aryl group is outlined in Table 1. Direct attachment of the terminal phenyl group to the pyridone analog as in **5a** was detrimental to MCH1R potency. Introduction of oxygen atom between distal phenyl group and pyridone analog as in **5b** resulted in no improvement in potency. Interestingly, incorporation of a methyleneoxy spacer as a linker provided compounds with good binding affinities for MCH1R receptor (IC_{50} values of 4.4 and 5.8 nM for **5c** and **5d**, respectively). In addition, both compounds **5c** and **5d** exhibited good functional activities with IC_{50} values of 19 and 27 nM, respectively. However, further elongation of the spacer, as exemplified by **5e** and **5f**, led to decreases in potency with IC_{50} values of 650 and 150 nM, respectively. These results suggest that compounds with good binding affinity for MCH1R in the *N*-phenylpyridone series require a methyleneoxy spacer which probably arranges the distal aryl group and the pyridone moiety to an appropriate spatial region in MCH1R pharmacophore.

Based on the observation that compounds with a methyleneoxy spacer as a linker significantly exhibited MCH1R potency, further optimization at the right-hand amine part was explored using 4-benzyloxy-*N*-phenylpyridone scaffold as a template. Table 2 outlines the SAR of *N*-phenylpyridone derivatives with a variety of amine moieties with regard to MCH1R and hERG inhibitory activities. Replacement of piperidine with morpholine (as in **5g**) decreased hERG inhibitory activity (IC_{50} >10 μM), however this change resulted in 5-fold less potent MCH1R binding affinity than **5c**. Compounds with acyclic amines such as dimethylamine (**5h**), diethylamine (**5i**) and di-isopropylamine (**5j**) showed comparable MCH1R binding affinity to **5c** and **5d** (IC_{50} values of 9.5, 6.6 and 5.1 nM for **5h**, **5i** and **5j**, respectively). Furthermore, the smallest dimethyl amine moiety as in **5h** led to a decrease in hERG inhibitory activity. Incorporation of bulky benzyl group on the nitrogen atom as in **5k** was also well tolerated but increased in hERG inhibitory activity significantly (IC_{50} = 0.81 μM). Introduction of methyl or dimethyl groups into the ethylene spacer provided compounds

Table 1
hMCHIR binding affinity of compounds **5a–5f**



Compd	R	X (Linker)	NR^1R^2	IC_{50}[a] (nM)	FLIPR IC_{50}[a] (nM)
5a	F	Null		>1000	nt
5b	F	O		>1000	nt
5c	H	CH_2O		4.4	19
5d	H	CH_2O		5.8	27
5e	F	CH_2CH_2O		650	nt
5f	F	OCH_2CH_2O		150	nt

[a] Values are means of two experiments. Compounds competed with [^{125}I]-MCH for binding at the human MCH1 receptor. nt = not tested.

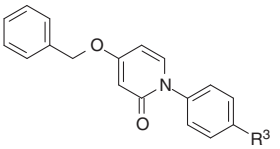
5l and **5m**, but with a drop in intrinsic MCH1R potency (IC_{50} values of 51 and 180 nM for **5l** and **5m**, respectively). Immobilization of the amine side chain onto the ethylene spacer via cyclization provided piperidinyl (**5n**) and pyrrolidinyl analogs (**5o** and **5p**) with a slight decrease in MCH1R potency. Replacement of the oxygen atom, which had connected the *N*-phenylpyridone analog and the amine tail, with a nitrogen atom, led to compound **6a** with comparable MCH1R binding affinity and hERG inhibitory activity to **5d**. Subsequently, methyl substitution on the proximal nitrogen atom of **6a** provided compound **6b** with a slight loss in MCH1R potency with IC_{50} values of 16 nM and increase in hERG inhibitory activity with IC_{50} values of 1.7 μM. Moreover, the methyl carbamate **6c** was devoid of MCH1R activity.

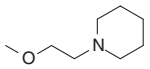
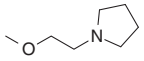
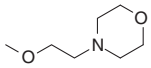
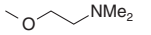
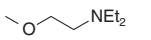
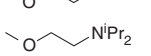
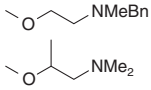
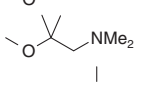
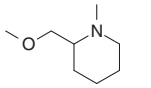
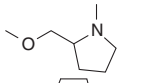
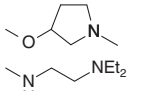
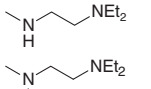
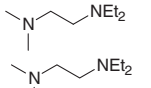
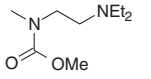
In an attempt to further enhance the MCH1R in vitro profiles, we investigated the development of SAR of the distal phenyl group as outlined in Table 3. Substitution with fluorine or chlorine atom on the distal phenyl ring provided compounds (**7a–7f**) with good MCH1R binding activities. Among these compounds, substitution at the *para*-position exhibited significantly excellent potency (IC_{50} values of 5.6 and 1.4 nM for fluoro **7c** and chloro **7f**, respectively). In addition, **7c** and **7f** were comparable functional activity to **5d**. The relatively small fluoro derivative **7c** showed less potent hERG inhibitory activity than **7f** (hERG inhibitory IC_{50} values of 9.0 and 1.7 μM for **7c** and **7f**, respectively). Incorporation of electron donating methoxy (**7g**) and electron withdrawing trifluoromethyl (**7h**) at the *para*-position were also tolerated but both resulted in increase in hERG inhibitory activities as compared to fluoro compound **7c**. Incorporation of a biphenyl moiety (**7i**) led to a significant drop in potency, whereas the naphthyl derivative **7j** retained MCH1R binding affinity but without improving hERG inhibitory activity.

3.2. In vivo evaluation

The representative compounds **5c**, **7c** and **7f** were evaluated for their ability to penetrate the CNS in rats. The brain and cerebrospinal fluid (CSF) levels in SD rats were examined (2 h after 10 mg/kg oral administration of these compounds) as compiled in Table 4. All compounds in the *N*-phenylpyridone series exhibited good brain penetrability with brain/plasma ratios of 3.8, 2.4 and 3.6 for **5c**, **7c** and **7f**, respectively. The relatively low plasma level of **5c** is probably attributable to its metabolical unstability in rats relative to **7c** (data was not shown). Compound **7c** exhibited excellent brain penetrability with brain concentration of 2.4 μM and besides CSF exposure of **7c** is much higher than that of **7f**. In addition, compound **7c** was confirmed to have excellent selectivity over not only hERG inhibitory activity but also a panel of 150 diverse, unrelated binding sites (500-fold less affinity than MCH 1R binding affinity).

Table 2
Profiles of compounds **5c–d**, **5g–p** and **6a–c**

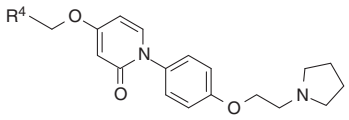


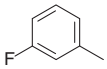
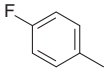
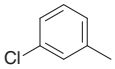
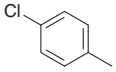
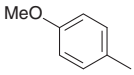
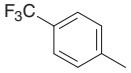
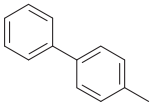
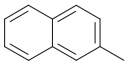
Compd	R^3	hMCH1R IC_{50}[a] (nM)	FLIPR IC_{50}[a] (nM)	hERG IC_{50}[b] (μM)
5c		4.4	19	5.8
5d		5.8	27	8.1
5g		24	34	>10
5h		9.5	18	>10
5i		6.6	24	9.8
5j		5.1	22	4.3
5k		3.8	nt	0.81
5l		51	nt	nt
5m		180	nt	nt
5n		18	nt	5.8
5o		12	23	9.3
5p		18	nt	>10
6a		6.8	nt	7.0
6b		16	nt	1.7
6c		>1000	nt	nt

[a] Values are means of two experiments. Compounds competed with [^{125}I]-MCH for binding at the human MCH1 receptor.
[b] Inhibition of [^{35}S]*N*-[(4*R*)-1′-[(2*R*)-6-cyano-1,2,3,4-tetrahydro-2-naphthyl]-3,4-dihydro-4-hydroxyspiro[2*H*-1-benzopyran-2,4′-piperidin]-6-yl]methanesulfonamide binding to hERG in HEK293 cells. nt = not tested.

Encouraged by its good potency, selectivity and excellent brain penetrability, further evaluation of compound **7c** in an acute food intake model was investigated. The food intake efficacy of **7c** was evaluated in established DIO mice fed a high-fat diet. Acute oral administration of **7c** dose-dependently suppressed spontaneous food intake for 24 h in DIO mice as outlined in Figure 3 (6%, 13% and 19% at 3, 10 and 30 mg/kg, respectively).[16] The excellent in vivo efficacy of **7c** in the food intake model stimulated us to further evaluate this antagonist in a chronic efficacy model. Chronic oral administration of **7c** at 3, 10 and 30 mg/kg once-daily for 1.5 months dose-dependently reduced the food intake and body weight of established DIO mice. The reduction of the body weight at the end of treatment was 4%, 11% and 21% loss in body weight at 3, 10 and 30 mpk, q.d., respectively (Fig. 4).[17]

Table 3
Profiles of compounds **7a–7j**



Compd	R	hMCH1R IC_{50}[a] (nM)	FLIPR IC_{50}[a] (nM)	hERG IC_{50}[b] (μM)
7a		8.7	30	4.3
7b		5.9	22	2.9
7c		5.6	23	9.0
7d		12	nt	nt
7e		4.2	nt	1.9
7f		1.4	17	1.7
7g		7.0	11	1.2
7h		6.7	49	2.4
7i		640	nt	nt
7j		7.7	175	0.67

[a] Values are means of two experiments. Compounds competed with [^{125}I]-MCH for binding at the human MCH1 receptor.

[b] Inhibition of [^{35}S]*N*-[(4*R*)-1′-[(2*R*)-6-cyano-1,2,3,4-tetrahydro-2-naphthyl]-3,4-dihydro-4-hydroxyspiro[2*H*-1-benzopyran-2,4′-piperidin]-6-yl]methanesulfonamide binding to hERG in HEK293 cells. nt = not tested.

Table 4
Biological properties of the representative phenylpyridone compounds

Compd	Brain penetration in SD rats 2 h @10 mpk			
	Plasma (μM)	Brain (nmol/g)	CSF (μM)	Brain/plasma ratio
5c	0.2	0.76	nd	3.8
7c	1.0	2.4	0.055	2.4
7f	0.47	1.67	0.01	3.6

nd = Not detected.

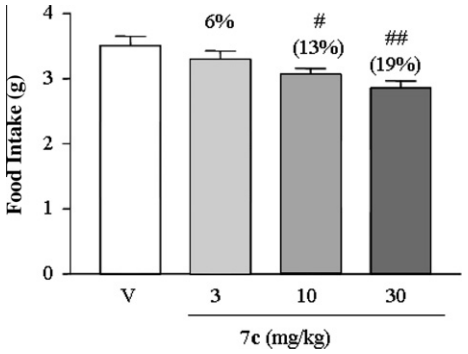


Figure 3. Effect of **7c** on spontaneous food intake in DIO mice. Food intake was measured 24 h after **7c** was orally administrated. $^{\#}P$ <0.05 versus vehicle treated control group. $^{\#\#}P$ <0.01 versus vehicle treated control group.

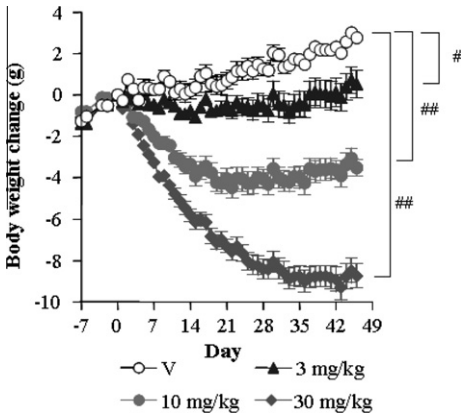


Figure 4. Body weight change in DIO mice with administration of compound **7c** for 1.5 months (q.d). Data are mean ± SEM. $^{\#}P$ <0.05 versus vehicle treated control group. $^{\#\#}P$ <0.01 versus vehicle treated control group.

4. Conclusion

In conclusion, we designed the novel *N*-phenylpyridone structure as a central core, and explored the side chain moieties that were attached to this core, aiming at identifying a potent MCH1R antagonist. The structure–activity relationship and the subsequent characterization of the selected compounds revealed that **7c** was a potent and selective MCH1R antagonist with excellent brain penetrability. Compound **7c** exhibited excellent body weight reduction in a dose-dependent manner in DIO mice model. Further development of the *N*-phenylpyridone class is ongoing to evaluate their potential as a clinical development candidate for the treatment of obesity.

5. Experimental

5.1. Chemistry

5.1.1. General procedures

In general, all reagents and solvents were obtained from commercial suppliers and used without further purification. The ^{1}H NMR spectra were obtained at 300 MHz on a Gemini-300, 400 MHz on a Mercury-400 (Varian) or 400 MHz on a JMN-AL400 (JEOL) spectrometer, with chemical shifts (δ, ppm) expressed relative to TMS as an internal standard. Mass spectra were recorded with electron-spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Waters micromass ZQ, micromass Quattro II or micromass Q-TOF-2 instrument. TLC was performed with Merck Silica Gel 60 F254 pre-coated plates. Flash chromatography was carried out with Wakogel C-300 (mesh 45–75 μm) or prepacked silica gel columns (KP-Sil silica) from Biotage. Preparative thin-layer chromatography (TLC) was performed with TLC Silica Gel 60 F (Merck KGaA). Preparative HPLC purification was carried out on a YMC-Pack *Pro* C18 (YMC, 50 × 30 mm i.d.), eluting with a gradient of CH_3CN/aqueous CF_3CO_2H (0.1%) 10:90 to 50:50 over 8 min at a flow rate of 40 mL/min. High-resolution mass spectra were recorded with electron-spray ionization on a micromass Q-TOF-2 instrument. Melting points were determined on a Yanaco MP-S3 melting point apparatus and are uncorrected.

5.1.2. 1-[4-(Benzyloxy)phenyl]-4-(4-fluorophenyl)pyridin-2(1*H*)-one (11)

A mixture of 2-fluoro-4-iodopyridine (**8**, 2.0 g, 8.97 mmol), (4-fluorophenyl)boronic acid (1.4 g, 10.0 mmol), tetrakis(triphenylphosphine)palladium (270 mg, 0.234 mmol), 2 M Na_2CO_3 (10 mL) in DME (20 mL) was stirred at 80 °C overnight. The mixture was cooled and diluted with EtOAc (20 mL), then washed with water (20 mL) and brine (20 mL). The organic fraction was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexane) to give compound **9** (1.70 g, 99%) as a white solid. A mixture of 2-fluoro-4-(4-fluorophenyl)pyridine (**9**, 1.70 g, 8.97 mmol) in concd HCl (5 mL) and water (10 mL) was refluxed for 4hr and stirred at room temperature overnight. The precipitate was collected and washed with water and acetone to afford compound **10** (1.46 g, 87%) as a white solid. Compound **10** was used without further purifications. A mixture of 4-(4-fluorophenyl)pyridin-2(1*H*)-one (**10**, 300 mg, 1.58 mmol), 1-(benzyloxy)-4-bromobenzene (500 mg, 1.90 mmol), CuI (90 mg, 0.48 mmol), K_2CO_3 (440 mg, 3.17 mmol) in DMF (6 mL) was stirred at 150 °C overnight. Furthermore, 1-(benzyloxy)-4-bromobenzene (180 mg, 0.684 mmol) and CuI (150 mg, 0.80 mmol) were added to the mixture and stirred at 150 °C for 6 h and then cooled. The mixture was diluted with $CHCl_3$ (200 mL), then washed with water (200 mL) and brine (100 mL). The organic fraction was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexane) and crystallized (EtOAc/hexane) to provide compound **11** (458 mg, 78%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.18 (s, 2H), 6.64 (dd, J = 7.2, 2.0 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H), 7.12 (d, J = 8.9 Hz, 2H), 7.28–7.51 (m, 9H), 7.69 (d, J = 7.2 Hz, 1H), 7.83 (dd, J = 8.9, 5.4 Hz, 2H).

5.1.3. 4-(4-Fluorophenyl)-1-(4-hydroxyphenyl)pyridin-2(1*H*)-one (12)

A mixture of 1-[4-(benzyloxy)phenyl]-4-(4-fluorophenyl)pyridin-2(1*H*)-one (**11**, 200 mg, 0.539 mmol) in concd HCl (2 mL)–water (2 mL)–MeOH (2 mL) was refluxed for 1 h. Concd H_2SO_4 (0.5 mL) was added to the mixture and the mixture was refluxed for 3 h. The mixture was diluted with water (5 mL) and cooled to room temperature with stirring. The precipitate was collected and washed with water and MeOH to afford compound **12** (141 mg, 93%) as a pale yellow solid. The solid was used without further purifications.

5.1.4. 4-(4-Fluorophenyl)-1-{4-[2-(piperidin-1-yl)ethoxy]phenyl}pyridin-2(1*H*)-one (5a)

To a solution of 4-(4-fluorophenyl)-1-(4-hydroxyphenyl)pyridin-2(1*H*)-one (**12**, 40 mg, 0.142 mmol), PPh_3 (56 mg, 0.213 mmol), 2-(piperidin-1-yl)ethanol (0.025 mL, 0.170 mmol) in THF (2 mL) was added diethyl azodicarboxylate (37 mg, 0.213 mmol). The mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (MeOH/$CHCl_3$) and crystallized (EtOAc/hexane) to give compound **5a** (41 mg, 73%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.32–1.42 (m, 2H), 1.43–1.54 (m, 4H), 2.38–2.46 (m, 4H), 2.66 (t, J = 5.9 Hz, 2H), 4.11 (t, J = 5.9 Hz, 2H), 6.63 (dd, J = 7.2, 2.0 Hz, 1H), 6.74 (d, J = 2.0 Hz, 1H), 7.05 (d, J = 8.9 Hz, 2H), 7.29–7.37 (m, 4H), 7.68 (d, J = 7.2 Hz, 1H), 7.83 (dd, J = 8.9, 5.5 Hz, 2H); MS (ESI) m/z = 393 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{26}FN_2O_2$ 393.1978; found 393.1977 $[M+H]^+$.

5.1.5. 1-[4-(*tert*-Butyldimethylsilyloxy)phenyl]-4-iodopyridin-2(1*H*)-one (14)

A mixture of 4-iodepyridin-2(1*H*)-one (**13**, 2.0 g, 9.05 mmol), 4-(*tert*-butyldimethylsilyloxy)phenylboronic acid (6.8 g, 27.1 mmol), $Cu(OAc)_2$ (2.46 g, 13.6 mmol), pyridine (0.73 mL, 27.1 mmol), molecular sieves 4A (2.0 g) in CH_2Cl_2 (40 mL) was stirred at room temperature for 2.5 days. The mixture was filtrated and washed with brine (100 mL). The organic fraction was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexane) and crystallized (hexane) to give compound **14** (439 mg, 11%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.22 (s, 6H), 0.96 (s, 9H), 6.60 (dd, J = 7.0, 1.8 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 1.8 Hz, 1H) , 7.26 (d, J = 8.8 Hz, 2H) , 7.38 (d, J = 7.0 Hz, 1H).

5.1.6. 4-(4-Fluorophenoxy)-1-(4-hydroxyphenyl)pyridin-2(1*H*)-one (15)

A mixture of 1-[4-(*tert*-butyldimethylsilyloxy)phenyl]-4-iodopyridin-2(1*H*)-one (**14**, 100 mg, 0.23 mmol), 4-fluorophenol (29 mg, 0.26 mmol), CuI (50 mg, 0.26 mmol), K_2CO_3 (65 mg, 0.27 mmol) in DMF (1 mL) was stirred at 150 °C for 1.5 h. $CHCl_3$ (20 mL) and water (20 mL) were added to the mixture, and then the mixture was filtrated. The organic layer was washed with brine (10 mL). The organic fraction was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexane) and crystallized (EtOAc/hexane) to provide compound **15** (18 mg, 26%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.84 (d, J = 2.6 Hz, 1H), 6.19 (dd, J = 7.5, 2.6 Hz, 1H), 6.61 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 7.07–7.15 (m, 4H), 7.32 (d, J = 7.6 Hz, 1H); MS (ESI) m/z = 298 $[M+H]^+$.

5.1.7. 4-(4-Fluorophenoxy)-1-{4-[2-(piperidin-1-yl)ethoxy]phenyl}pyridin-2(1*H*)-one (5b)

Compound **5b** was prepared from **15** and 2-(piperidin-1-yl)ethanol using the procedure described for **5a** with 55% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.31–1.40 (m, 2H), 1.42–1.52 (m, 4H), 2.36–2.43 (m, 4H), 2.65 (t, J = 6.0 Hz, 2H), 4.09 (t, J = 6.0 Hz, 2H), 5.45 (d, J = 2.9 Hz, 1H), 6.14 (dd, J = 7.6, 2.9 Hz, 1H), 7.01 (d, J = 8.9 Hz, 2H), 7.24 (d, J = 8.9 Hz, 2H), 7.27–7.37 (m, 4H), 7.65 (d, J = 7.6 Hz, 1H); MS (ESI) m/z = 409 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{26}FN_2O_3$ 409.1927; found 409.1922 $[M+H]^+$.

5.1.8. 4-(Benzyloxy)-1-[4-(tetrahydro-2*H*-pyran-2-yloxy)-phenyl]pyridin-2(1*H*)-one (17)

A mixture of 4-(benzyloxy)pyridin-2(1*H*)-one (**16**, 26.06 g, 129.5 mmol), 2-(4-iodophenoxy)tetrahydro-2*H*-pyran (50.3 g, 165.4 mmol), CuI (7.78 g, 40.85 mmol), K_2CO_3 (38.12 g, 275.8 mmol) in DMF (500 mL) was stirred at 150 °C for 24 h. The mixture was cooled and poured into water (3.0 L) to appear a precipitate. The precipitate was collected and then the precipitate was dissolved in $CHCl_3$ (1 L). The organic layer was washed with brine (500 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was crystallized (EtOAc) to give compound **17** (28.12 g, 60%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.46–1.58 (m, 3H), 1.58–1.93 (m, 3H), 3.50–3.60 (m, 1H), 3.70–3.81 (m, 1H), 5.12 (s, 2H), 5.52 (s, 1H), 5.95 (d, J = 2.7 Hz, 1H), 6.06 (dd, J = 7.7, 2.7 Hz, 1H), 7.09 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.32–7.49 (m, 5H), 7.53 (d, J = 7.7 Hz, 1H); MS (ESI) m/z = 378 $[M+H]^+$.

5.1.9. 4-(Benzyloxy)-1-(4-hydroxyphenyl)pyridin-2(1*H*)-one (18)

A mixture of 4-(benzyloxy)-1-[4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl]pyridin-2(1*H*)-one (**17**, 982 mg, 2.60 mmol), pyridinium *p*-toluenesulfonate (65 mg, 0.26 mmol) in EtOH (16 mL) was refluxed for 1 h. The mixture was cooled and water (60 mL) was added to the mixture to appear a precipitate. The precipitate was collected and washed with water and EtOAc to afford compound **18** (746 mg, 98%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.06 (s, 2H), 6.08–6.15 (m, 2H), 6.73 (d, J = 8.8 Hz, 2H), 7.07 (d,

J = 8.8 Hz, 2H), 7.23 (d, J = 7.5 Hz, 1H), 7.38–7.44 (m, 5H); MS (ESI) m/z = 294 $[M+H]^+$.

5.1.10. 4-(Benzyloxy)-1-{4-[2-(piperidin-1-yl)ethoxy]phenyl}-pyridin-2(1*H*)-one (5c)

Compound **5c** was prepared from **18** and 2-(piperidin-1-yl)ethanol using the procedure described for **5a** with 72% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.32–1.42 (m, 2H), 1.43–1.55 (m, 4H), 2.38–2.47 (m, 4H), 2.66 (t, J = 5.5 Hz, 2H), 4.09 (t, J = 5.9 Hz, 2H), 5.12 (s, 2H), 5.94 (d, J = 2.6 Hz, 1H), 6.05 (dd, J = 7.7, 2.6 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 7.23 (d, J = 8.9 Hz, 2H), 7.32–7.47 (m, 5H), 7.50 (d, J = 7.6 Hz, 1H); MS (ESI) m/z = 405 $[M+H]^+$; HRMS (ESI) calcd for $C_{25}H_{29}N_2O_3$ 405.2178; found 405.2177 $[M+H]^+$.

5.1.11. 4-(Benzyloxy)-1-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}-pyridin-2(1*H*)-one (5d)

Compound **5d** was prepared from **18** and 2-(pyrrolidin-1-yl)ethanol using the procedure described for **5a** with 85% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.80–1.85 (m, 4H), 2.62–2.67 (m, 4H), 2.93 (t, J = 6.3 Hz, 2H), 4.15 (t, J = 6.3 Hz,2H), 5.03 (s, 2H), 6.03 (dd, J = 7.8, 2.4 Hz, 1H), 6.06 (d, J = 2.4 Hz, 1H), 6.99 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 8.6 Hz, 2H), 7.40 (dd, J = 13.7, 4. 3 Hz, 5H); MS (ESI) m/z = 391 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{27}N_2O_3$ 391.2022; found 391.2021 $[M+H]^+$; mp 109–111 °C.

5.1.12. 4-(Benzyloxy)-1-{4-[2-(morpholin-4-yl)ethoxy]phenyl}-pyridin-2(1*H*)-one (5g)

Compound **5g** was prepared from **18** and 2-(morpholin-4-yl)ethanol using the procedure described for **5a** with 82% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.40–2.55 (m, 4H), 2.70 (t, J = 5.6 Hz, 2H), 3.53–3.60 (m, 4H), 4.12 (t, J = 5.6 Hz, 2H), 5.12 (s, 2H), 5.94 (d, J = 2.6 Hz, 1H), 6.06 (dd, J = 7.6, 2.6 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.32–7.48 (m, 5H), 7.50 (d, J = 7.6 Hz, 1H); MS (ESI) m/z = 407 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{27}N_2O_4$ 407.1971; found 407.1974 $[M+H]^+$.

5.1.13. 4-(Benzyloxy)-1-{4-[2-(dimethylamino)ethoxy]phenyl}-pyridin-2(1*H*)-one (5h)

Compound **5h** was prepared from **18** and 2-(dimethylamino)ethanol using the procedure described for **5a** with 60% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.21 (s, 6H), 2.63 (t, J = 5.8 Hz, 2H), 4.08 (t, J = 5.8 Hz, 2H), 5.12 (s, 2H), 5.94 (d, J = 2.6 Hz, 1H), 6.06 (dd, J = 7.6, 2.6 Hz, 1H), 7.01 (d, J = 8.9 Hz, 2H), 7.23 (d, J = 8.9 Hz, 2H), 7.32–7.48 (m, 5H), 7.51 (d, J = 7.6 Hz, 1H); MS (ESI) m/z = 365 $[M+H]^+$; HRMS (ESI) calcd for $C_{22}H_{25}N_2O_3$ 365.1865; found 365.1863 $[M+H]^+$.

5.1.14. 4-(Benzyloxy)-1-{4-[2-(diethylamino)ethoxy]phenyl}-pyridin-2(1*H*)-one (5i)

Compound **5i** was prepared from **18** and 2-(diethylamino)ethanol using the procedure described for **5a** with 73% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.97 (t, J = 7.1 Hz, 6H), 2.54 (q, J = 7.1 Hz, 4H), 2.78 (t, J = 5.9 Hz, 2H), 4.04 (t, J = 5.9 Hz, 2H), 5.12 (s, 2H), 5.94 (d, J = 2.7 Hz, 1H), 6.05 (dd, J = 7.6, 2.6 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 7.23 (d, J = 8.9 Hz, 2H), 7.32–7.48 (m, 5H), 7.51 (d, J = 7.6 Hz, 1H); MS (ESI) m/z = 393 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{29}N_2O_3$ 393.2178; found 393.2171 $[M+H]^+$.

5.1.15. 4-(Benzyloxy)-1-{4-[2-(diisopropylamino)ethoxy]-phenyl}pyridin-2(1*H*)-one (5j)

Compound **5j** was prepared from **18** and 2-(diisopropylamino)ethanol using the procedure described for **5a** with 73% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.98 (d, J = 6.5 Hz, 12H), 2.79 (t, J = 6.9 Hz, 2H), 3.01 (h, J = 6.5 Hz, 2H), 3.90 (t, J = 5.9 Hz, 2H), 5.12 (s, 2H), 5.94 (d, J = 2.7 Hz, 1H), 6.05 (dd, J = 7.6, 2.7 Hz, 1H), 6.98 (d, J = 8.9 Hz, 2H), 7.23 (d, J = 8.9 Hz, 2H), 7.32–7.48 (m, 5H), 7.50 (d, J = 7.6 Hz, 1H); MS (ESI) m/z = 421 $[M+H]^+$; HRMS (ESI) calcd for $C_{26}H_{33}N_2O_3$ 421.2491; found 421.2490 $[M+H]^+$.

5.1.16. 1-(4-{2-[Benzyl(methyl)amino]ethoxy}phenyl)-4-(benzyloxy)pyridin-2(1*H*)-one (5k)

Compound **5k** was prepared from **18** and 2-[benzyl(methyl)-amino]ethanol using the procedure described for **5a** with 70% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.23 (s, 3H), 2.75 (t, J = 5.9 Hz, 2H), 3.57 (s, 2H), 4.13 (t, J = 5.9 Hz, 2H), 5.12 (s, 2H), 5.94 (d, J = 2.8 Hz, 1H), 6.06 (dd, J = 7.6, 2.8 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 7.23 (d, J = 8.9 Hz, 2H), 7.20–7.48 (m, 10H), 7.51 (d, J = 7.6 Hz, 1H); MS (ESI) m/z = 441 $[M+H]^+$; HRMS (ESI) calcd for $C_{28}H_{29}N_2O_3$ 441.2178; found 441.2180 $[M+H]^+$.

5.1.17. 4-(Benzyloxy)-1-(4-{[1-(dimethylamino)propan-2-yl]-oxy}phenyl)pyridin-2(1*H*)-one (5l)

Compound **5l** was prepared from **18** and 1-(dimethylamino)propan-2-ol (racemate) using the procedure described for **5a** with 9% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.24 (d, J = 6.0 Hz, 3H), 2.19 (s, 6H), 2.36 (dd, J = 12.7, 5.5 Hz, 1H), 2.45–2.55 (m, 1H), 4.61 (m, 1H), 5.12 (s, 2H), 5.95 (d, J = 2.7 Hz, 1H), 6.05 (dd, J = 7.5, 2.7 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 7.22 (d, J = 8.9 Hz, 2H), 7.32–7.48 (m, 5H), 7.52 (d, J = 7.5 Hz, 1H); MS (ESI) m/z = 379 $[M+H]^+$; HRMS (ESI) calcd for $C_{23}H_{27}N_2O_3$ 379.2022; found 379.2031 $[M+H]^+$.

5.1.18. 4-(Benzyloxy)-1-(4-{[1-(dimethylamino)-2-methylpropan-2-yl]oxy}phenyl)pyridin-2(1*H*)-one (5m)

Compound **5m** was prepared from **18** and 2-(dimethylamino)-2-methylpropan-1-ol using the procedure described for **5a** with 61% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.27 (s, 6H), 2.29 (s, 6H), 2.47 (s, 2H), 5.12 (s, 2H), 5.96 (d, J = 2.8 Hz, 1H), 6.06 (dd, J = 7.6, 2.8 Hz, 1H), 7.04 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.32–7.48 (m, 5H), 7.54 (d, J = 7.6 Hz, 1H); MS (ESI) m/z = 393 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{29}N_2O_3$ 393.2178; found 393.2181 $[M+H]^+$.

5.1.19. 4-(Benzyloxy)-1-{4-[(1-methylpiperidin-2-yl)methoxy]-phenyl}pyridin-2(1*H*)-one (5n)

Compound **5n** was prepared from **18** and (1-methylpiperidin-2-yl)methanol (racemate) using the procedure described for **5a** with 16% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.10–1.85 (m, 6H), 2.00–2.90 (m, 6H), 3.90–4.15 (m, 2H), 5.12 (s, 2H), 5.94 (d, J = 2.7 Hz, 1H), 6.06 (dd, J = 7.6, 2.6 Hz, 1H), 7.01 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.7 Hz, 2H), 7.32–7.48 (m, 5H), 7.51 (d, J = 7.6 Hz, 1H); MS (ESI) m/z = 405 $[M+H]^+$; HRMS (ESI) calcd for $C_{25}H_{29}N_2O_3$ 405.2178; found 405.2177 $[M+H]^+$.

5.1.20. 4-(Benzyloxy)-1-{4-[(1-methylpyrrolidin-2-yl)methoxy]-phenyl}pyridin-2(1*H*)-one (5o)

Compound **5o** was prepared from **18** and (1-methylpyrrolidin-2-yl)methanol (racemate) using the procedure described for **5a** with 17% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.50–1.75 (m, 3H), 1.90–2.05 (m, 1H), 2.13–2.28 (m, 1H), 2.37 (s, 3H), 2.53–2.63 (m, 1H), 2.92–3.00 (m, 1H), 3.82–3.90 (m, 1H), 3.97–4.05 (m, 1H), 5.12 (s, 2H), 5.94 (d, J = 2.9 Hz, 1H), 6.06 (dd, J = 7.6, 2.9 Hz, 1H), 7.01 (d, J = 8.9 Hz, 2H), 7.23 (d, J = 8.9 Hz, 2H), 7.32–7.48 (m, 5H), 7.51 (d, J = 7.6 Hz, 1H); MS (ESI) m/z = 391 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{27}N_2O_3$ 391.2022; found 391.2022 $[M+H]^+$.

5.1.21. 4-(Benzyloxy)-1-{4-[(1-methylpyrrolidin-3-yl)oxy]-phenyl}pyridin-2(1*H*)-one (5p)

Compound **5p** was prepared from **18** and 1-methylpyrrolidin-3-ol (racemate) using the procedure described for **5a** with 28% as a

white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.70–1.85 (m, 1H), 2.25 (s, 3H), 2.25–2.40 (m, 2H), 2.53–2.81 (m, 3H), 4.85–4.95 (m, 1H), 5.12 (s, 2H), 5.94 (d, J = 2.7 Hz, 1H), 6.05 (dd, J = 7.6, 2.7 Hz, 1H), 6.94 (d, J = 8.9 Hz, 2H), 7.22 (d, J = 8.9 Hz, 2H), 7.32–7.48 (m, 5H), 7.51 (d, J = 7.6 Hz, 1H); MS (ESI) m/z = 377 $[M+H]^+$; HRMS (ESI) calcd for $C_{23}H_{25}N_2O_3$ 377.1865; found 377.1866 $[M+H]^+$.

5.1.22. 4-Hydroxy-1-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}-pyridin-2(1*H*)-one (19)

To a solution of 4-(benzyloxy)-1-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}pyridin-2(1*H*)-one (**5d**, 395 mg, 1.01 mmol) in THF (5 mL) and MeOH (5 mL) was added Pd (10 wt % on activated carbon, 200 mg). The mixture was stirred at room temperature under H_2 atmosphere for 2 h. The mixture was filtrated and washed with MeOH. The filtrate was concentrated to give compound **19** (303 mg, 99%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.82–1.87 (m, 4H), 2.68–2.74 (m, 4H), 2.96 (t, J = 5.8 Hz, 2H), 4.12 (t, J = 5.8 Hz, 2H), 5.84 (d, J = 2.4 Hz, 1H), 5.92 (dd, J = 7.8, 2.4 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 8.8 Hz, 2H); MS (ESI) m/z = 301 $[M+H]^+$.

5.1.23. 4-[2-(4-Fluorophenyl)ethoxy]-1-{4-[2-(pyrrolidin-1-yl)-ethoxy]phenyl}pyridin-2(1*H*)-one (5e)

To a solution of 4-hydroxy-1-{4-[2-(pyrrolidin-1-yl)ethoxy]-phenyl}pyridin-2(1*H*)-one (**19**, 30 mg, 0.10 mmol), PBu_3 (0.075 mL, 0.30 mmol), 2-(4-fluorophenyl)ethanol (0.025 mL, 0.20 mmol) in THF (1 mL) was added 1,1′-(azodicarbonyl)dipiperidine (76 mg, 0.30 mmol). The mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (MeOH/$CHCl_3$) to give compound **5e** (24 mg, 57%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.82–1.86 (m, 4H), 2.65–2.71 (m, 4H), 2.95 (t, J = 5.9 Hz, 2H), 3.07 (t, J = 6.7 Hz, 2H), 4.12–4.18 (m, 4H), 5.92–5.96 (m, 2H), 6.97–7.04 (m, 4H), 7.27–7.16 (m, 5H); MS (ESI) m/z = 423 $[M+H]^+$; HRMS (ESI) calcd for $C_{25}H_{28}FN_2O_3$ 423.2084; found 423.2081 $[M+H]^+$.

5.1.24. 4-[2-(4-Fluorophenoxy)ethoxy]-1-{4-[2-(pyrrolidin-1-yl)-ethoxy]phenyl}pyridin-2(1*H*)-one (5f)

Compound **5f** was prepared from **19** and 2-(4-fluorophenoxy)ethanol using the procedure described for **5e** with 7% as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32–1.43 (m, 2H), 1.44–1.55 (m, 4H), 1.82–1.93 (m, 2H), 2.28–2.47 (m, 6H), 4.05 (t, J = 6.3 Hz, 2H), 6.64 (dd, J = 7.2, 2.0 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H), 7.03 (d, J = 8.9 Hz, 2H), 7.29–7.37 (m, 4H), 7.69 (d, J = 7.2 Hz, 1H), 7.83 (dd, J = 7.8, 5.3 Hz, 2H); MS (ESI) m/z = 439 $[M+H]^+$; HRMS (ESI) calcd $C_{25}H_{28}FN_2O_4$ 439.2033; found 439.2025 $[M+H]^+$.

5.1.25. 4-[(2-Fluorobenzyl)oxy]-1-{4-[2-(pyrrolidin-1-yl)ethoxy]-phenyl}pyridin-2(1*H*)-one (7a)

Compound **7a** was prepared from **19** and 2-fluorophenylmethanol using the procedure described for **5e** with 41% as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.93–1.99 (m, 4H), 2.88–3.04 (m, 4H), 3.14–3.20 (m, 2H), 4.28–4.33 (m, 2H), 5.10 (s, 2H), 6.04 (dd, J = 7.8, 2.4 Hz, 1H), 6.08 (d, J = 2.4 Hz, 1H), 6.95–7.49 (m, 9H); MS (ESI) m/z = 409 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{26}FN_2O_3$ 409.1927; found 409.1932 $[M+H]^+$.

5.1.26. 4-[(3-Fluorobenzyl)oxy]-1-{4-[2-(pyrrolidin-1-yl)ethoxy]-phenyl}pyridin-2(1*H*)-one (7b)

Compound **7b** was prepared from **19** and 3-fluorophenylmethanol using the procedure described for **5e** with 29% as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.90–1.94 (m, 4H), 2.82–2.90 (m, 4H), 3.08 (t, J = 5.3 Hz, 2H), 4.26 (t, J = 5.3 Hz, 2H), 5.04 (s, 2H), 6.01 (d, J = 2.7 Hz, 1H), 6.05 (dd, J = 7.7, 2.7 Hz, 1H), 6.97–7.41 (m, 9H); MS (ESI) m/z = 409 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{26}FN_2O_3$ 409.1927; found 409.1931 $[M+H]^+$.

5.1.27. 4-[(4-Fluorobenzyl)oxy]-1-{4-[2-(pyrrolidin-1-yl)ethoxy]-phenyl}pyridin-2(1*H*)-one (7c)

Compound **7c** was prepared from **19** and 4-fluorophenylmethanol using the procedure described for **5e** with 48% as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.81–1.86 (m, 4H), 2.64–2.70 (m, 4H), 2.95 (t, J = 5.9 Hz, 2H), 4.16 (t, J = 5.9 Hz, 2H), 4.99 (s, 2H), 6.01 (dd, J = 7.4, 2.9 Hz, 1H), 6.04 (d, J = 2.9 Hz, 1H), 6.99 (d, J = 8.6 Hz, 2H), 7.10 (t, J = 8.6 Hz, 2H), 7.21 (d, J = 7.4 Hz, 1H), 7.25 (d, J = 8.6 Hz, 2H), 7.40 (dd, J = 8.6, 5.5 Hz, 2H); MS (ESI) m/z = 409 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{26}FN_2O_3$ 409.1927; found 409.1933 $[M+H]^+$; mp 124–126 °C.

5.1.28. 4-[(2-Chlorobenzyl)oxy]-1-{4-[2-(pyrrolidin-1-yl)ethoxy]-phenyl}pyridin-2(1*H*)-one (7d)

Compound **7d** was prepared from **19** and 2-chlorophenylmethanol using the procedure described for **5e** with 42% as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.66–1.69 (m, 4H), 2.45–2.55 (m, 4H), 2.79 (t, J = 5.9 Hz, 2H), 4.10 (t, J = 5.9 Hz, 2H), 5.17 (s, 2H), 5.98 (d, J = 2.6 Hz, 1H), 6.06 (dd, J = 7.6, 2.6 Hz, 1H), 7.01 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 9.0 Hz, 2H), 7.39–7.45 (m, 2H), 7.51–7.55 (m, 2H), 7.61 (d, J = 7.6 Hz, 1H); MS (ESI) m/z = 425 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{26}ClN_2O_3$ 425.1632; found 425.1628 $[M+H]^+$.

5.1.29. 4-[(3-Chlorobenzyl)oxy]-1-{4-[2-(pyrrolidin-1-yl)ethoxy]-phenyl}pyridin-2(1*H*)-one (7e)

Compound **7e** was prepared from **19** and 3-chlorophenylmethanol using the procedure described for **5e** with 45% as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.64–1.70 (m, 4H), 2.44–2.54 (m, 4H), 2.78 (t, J = 5.9 Hz, 2H), 4.09 (t, J = 5.9 Hz, 2H), 5.12 (s, 2H), 5.93 (d, J = 2.8 Hz, 1H), 6.05 (dd, J = 7.6, 2.8 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 7.23 (d, J = 8.9 Hz, 2H), 7.40–7.48 (m, 3H), 7.52 (m, 2H); MS (ESI) m/z = 425 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{26}ClN_2O_3$ 425.1632; found 425.1630 $[M+H]^+$.

5.1.30. 4-[(4-Chlorobenzyl)oxy]-1-{4-[2-(pyrrolidin-1-yl)ethoxy]-phenyl}pyridin-2(1*H*)-one (7f)

Compound **7f** was prepared from **19** and 4-chlorophenylmethanol using the procedure described for **5e** with 46% as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.62–1.73 (m, 4H), 2.45–2.55 (m, 4H), 2.78 (t, J = 6.0 Hz, 2H), 4.09 (t, J = 6.0 Hz, 2H), 5.14 (s, 2H), 5.94 (d, J = 2.9 Hz, 1H), 6.08 (dd, J = 7.8, 2.9 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 7.23 (d, J = 9.0 Hz, 2H), 7.39–7.48 (m, 3H), 7.50–7.56 (m, 2H); MS (ESI) m/z = 425 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{26}ClN_2O_3$ 425.1632; found 425.1630 $[M+H]^+$.

5.1.31. 4-[(4-Methoxybenzyl)oxy]-1-{4-[2-(pyrrolidin-1-yl)-ethoxy]phenyl}pyridin-2(1*H*)-one (7g)

Compound **7g** was prepared from **19** and 4-methoxyphenylmethanol using the procedure described for **5e** with 34% as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.64–1.70 (m, 4H), 2.44–2.54 (m, 4H), 2.78 (t, J = 5.9 Hz, 2H), 3.76 (s, 3H), 4.09 (t, J = 5.9 Hz, 2H), 5.03 (s, 2H), 5.94 (d, J = 2.8 Hz, 1H), 6.02 (dd, J = 7.8, 2.8 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 7.8 Hz, 1H); MS (ESI) m/z = 421 $[M+H]^+$; HRMS (ESI) calcd for $C_{25}H_{29}N_2O_4$ 421.2127; found 421.2130 $[M+H]^+$.

5.1.32. 1-{4-[2-(Pyrrolidin-1-yl)ethoxy]phenyl}-4-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one (7h)

Compound **7h** was prepared from **19** and 4-trifluoromethylphenylmethanol using the procedure described for **5e** with 54% as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.83–1.88 (m, 4H),

2.68–2.75 (m, 4H), 2.98 (t, J = 5.5 Hz, 2H), 4.18 (t, J = 5.5 Hz, 2H), 5.10 (s, 2H), 6.02 (d, J = 2.4 Hz, 1H), 6.05 (dd, J = 7.8, 2.4 Hz, 1H), 6.99 (d, J = 9.4 Hz, 2H), 7.22–7.27 (m, 3H), 7.54 (d, J = 7.8 Hz, 2H), 7.67 (d, J = 7.8 Hz, 2H); MS (ESI) m/z = 459 $[M+H]^+$; HRMS (ESI) calcd for $C_{25}H_{26}F_3N_2O_3$ 459.1896; found 459.1904 $[M+H]^+$.

5.1.33. 4-(Biphenyl-4-ylmethoxy)-1-{4-[2-(pyrrolidin-1-yl)-ethoxy]phenyl}pyridin-2(1*H*)-one (7i)

Compound **7i** was prepared from **19** and biphenyl-4-ylmethanol using the procedure described for **5e** with 38% as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.81–1.86 (m, 4H), 2.64–2.70 (m, 4H), 2.95 (t, J = 5.9 Hz, 2H), 4.16 (t, J = 5.9 Hz, 2H), 5.08 (s, 2H), 6.05 (dd, J = 7.8, 2.3 Hz, 1H), 6.09 (d, J = 2.3 Hz, 1H), 7.00 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 8.6 Hz, 2H), 7.35–7.40 (m, 1H), 7.43–7.51 (m, 4H), 7.65–7.59 (m, 4H); MS (ESI) m/z = 467 $[M+H]^+$; HRMS (ESI) calcd for $C_{30}H_{31}N_2O_3$ 467.2335; found 467.2326 $[M+H]^+$.

5.1.34. 4-(Naphthalen-2-ylmethoxy)-1-{4-[2-(pyrrolidin-1-yl)-ethoxy]phenyl}pyridin-2(1*H*)-one (7j)

Compound **7j** was prepared from **19** and naphthalen-2-ylmethanol using the procedure described for **5e** with 43% as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.66–1.69 (m, 4H), 2.47–2.53 (m, 4H), 2.78 (t, J = 6.1 Hz, 2H), 4.09 (t, J = 5.9 Hz, 2H), 5.30 (s, 2H), 6.01 (d, J = 2.6 Hz, 1H), 6.10 (dd, J = 7.6, 2.6 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 7.23 (d, J = 8.9 Hz, 2H), 7.51–7.58 (m, 4H), 7.91–8.01 (m, 4H); MS (ESI) m/z = 441 $[M+H]^+$; HRMS (ESI) calcd for $C_{28}H_{29}N_2O_3$ 441.2178; found 441.2170 $[M+H]^+$.

5.1.35. Methyl 4-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]benzoate (20)

Compound **20** was prepared from **16** using the procedure described for **14** with 80% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.93 (s, 3H), 5.05 (s, 2H),6.04–6.13 (m, 2H), 7.21–7.25 (m, 1H), 7.33–7.50 (m, 7H), 8.12–8.18 (m, 2H); MS (ESI) m/z = 336 $[M+H]^+$.

5.1.36. 4-[4-(Benzyloxy)-2-oxopyridin-1(2*H*)-yl]benzoic acid (21)

A mixture of methyl 4-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]-benzoate (**20**, 0.39 g, 1.16 mmol), 4 N NaOH (3.2 mL, 12.8 mmol), MeOH (20 mL) and THF (20 mL) was stirred at 90 °C for 5 h. The mixture was cooled and 1 N HCl was added until the mixture was adjusted to PH 2–3. The mixture was extracted with EtOAc (100 mL). The organic fractions were dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford compound **21** (0.31 g, 83%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ: 5.15 (s, 2H), 6.08–6.10 (m, 1H), 6.25–6.30 (m, 1H), 7.30–7.56 (m, 8H), 8.11–8.16 (m, 2H); MS (ESI) m/z = 322 $[M+H]^+$.

5.1.37. Methyl *N*-{4-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]-phenyl}carbamate (22)

A mixture of 4-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]benzoic acid (**21**, 0.31 g, 0.97 mmol), diphenylphosphoryl azide (0.11 mL, 1.15 mmol), triethylamine (0.16 mL, 1.15 mmol), MeOH (0.2 mL) and DMF (5 mL) was stirred at 100 °C overnight. The mixture was cooled and brine (20 mL) was added. The mixture was extracted with $CHCl_3$ (40 mL). The organic fractions were dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel ($MeOH/CHCl_3$) to provide compound **22** (203 mg, 60%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.99 (s, 3H), 5.05 (s, 2H),6.04–6.08 (m, 2H), 6.86 (brs, 1H), 7.17–7.50 (m, 10H); MS (ESI) m/z = 351 $[M+H]^+$.

5.1.38. Methyl *N*-{4-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]-phenyl}-*N*-[2-(diethylamino)ethyl]carbamate (6c)

To a solution of methyl *N*-{4-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]phenyl}carbamate (**22**, 90 mg, 0.257 mmol), potassium tert-butoxide (86 mg, 0.766 mmol) in THF (10 mL) was added 2-(diethylamino)ethyl bromide hydrobromide (135 mg, 0.517 mmol) and the mixture was stirred at room temperature for 1.5 h. The mixture was diluted with sat. $NaHCO_3$ (20 mL) and extracted with $CHCl_3$ (20 mL). The organic fraction was dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel ($MeOH/CHCl_3$) to give compound **6c** (107 mg, 93%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.00 (t, J = 7.1 Hz, 6H), 2.48–2.60 (m, 4H), 2.62–2.74 (m, 2H), 3.71 (s, 3H), 3.68–3.80 (m, 2H), 5.05 (s, 2H), 6.02–6.10 (m, 2H), 7.21–7.48 (m, 10H); MS (ESI) m/z = 450 $[M+H]^+$.

5.1.39. 4-(Benzyloxy)-1-(4-{[2-(diethylamino)ethyl]amino}-phenyl)pyridin-2(1*H*)-one (6a)

To a solution of methyl *N*-{4-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]phenyl}-*N*-[2-(diethylamino)ethyl]carbamate (**6c**, 100 mg, 0.222 mmol) in THF (10 mL) was added lithium aluminum hydride ($LiAlH_4$: 10 mg, 0.264 mmol), and the mixture was stirred at room temperature for 1 h. Additional $LiAlH_4$ (10 mg, 0.264 mmol) was added to the mixture and stirred for 1.5 h. The reaction mixture was quenched by $Na_2SO_4{\cdot}10H_2O$, EtOAc were added to the mixture and stirred overnight. The precipitate was removed by filtration and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC to give compound **6a** (8 mg, 9%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.03 (t, J = 7.1 Hz, 6H), 2.57 (q, J = 7.1 Hz, 4H), 2.71 (t, J = 5.9 Hz, 2H), 3.08–3.19 (m, 2H), 4.50–4.67 (m, 1H), 5.03 (s, 2H), 6.00 (dd, J = 7.6, 2.6 Hz, 1H), 6.06 (d, J = 2.6 Hz, 1H), 6.66 (d, J = 8.7 Hz, 2H), 7.13 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 7.6 Hz, 1H), 7.30–7.48 (m, 5H); MS (ESI) m/z = 392 $[M+H]^+$.

5.1.40. 4-(Benzyloxy)-1-(4-{[2-(diethylamino)ethyl](methyl)-amino}phenyl)pyridin-2(1*H*)-one (6b)

To a solution of 4-(benzyloxy)-1-(4-{[2-(diethylamino)ethyl]-amino}phenyl)pyridin-2(1*H*)-one (**6a**, 7 mg, 0.018 mmol) and paraformaldehyde (1 mg) in MeOH (1 mL) was added $ZnCl_2$ (41 mg, 0.3 mmol) and $NaB(CN)H_3$ (23 mg, 0.6 mmol). The mixture was stirred at room temperature for 1 h. The mixture was diluted with $CHCl_3$ (20 mL), washed with 1 N NaOH (10 mL) and brine (10 mL). The organic fraction was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give compound **6b** (2.8 mg, 39%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.06 (t, J = 7.1 Hz, 6H), 2.52–2.72 (m, 2H), 2.61 (q, J = 7.1 Hz, 4H), 3.42–3.52 (m, 2H), 2.99 (s, 3H), 5.03 (s, 2H), 6.00 (dd, J = 7.6, 2.7 Hz, 1H), 6.06 (d, J = 2.7 Hz, 1H), 6.72 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 9.0 Hz, 2H), 7.22 (d, J = 7.6 Hz, 1H), 7.32–7.45 (m, 5H); MS (ESI) m/z = 406 $[M+H]^+$.

5.2. Biology

5.2.1. In vivo efficacy in diet-induced obese mice

C57BL/6J mice were fed moderately high-fat diet for about 10 months before the experiment was initiated. The mice were then divided into three groups, and each group was orally administrated either vehicle (0.5% methylcellulose in water) or compound **7c** at doses of 3, 10 and 30 mg/kg once-daily for 1.5 month. Compound **7c** was administered after measurement of daily food intake and body weight, 1–2 h before the beginning of the dark period.

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