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Bioorganic & Medicinal Chemistry 15 (2007) 2092–2105
Bioorganic & Medicinal Chemistry

The efficacy and cardiac evaluation of aminomethyl tetrahydronaphthalene ketopiperazines: A novel class of potent MCH-R1 antagonists

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Received 12 September 2006; revised 18 November 2006; accepted 15 December 2006
Available online 20 December 2006

Abstract—The design, synthesis, and biological studies of a novel class of MCH-R1 antagonists based on an aminotetrahydronaphthalene ketopiperazine scaffold is described. Compounds within this class promoted significant body weight reduction in mouse diet induced obesity studies. The potential for hERG blockage activity and QT interval studies in anesthetized dogs are discussed.

1. Introduction

The World Health Organization considers obesity a major health concern for many countries, especially the US. Estimates indicate that more than 30% of the US adult population is overweight, and that obesity-related health care cost is in the range of $100 billion per year.[1] These trends have promoted increased research activity in the pharmaceutical industry directed to find anti-obesity therapies.[2]

The G-protein-coupled melanin-concentrating hormone receptor 1 (MCH-R1) has received significant attention in recent years as a potential target for effective anti-obesity therapies.[3] It has been suggested that CNS-located MCH-R1 is involved in biological processes related to mammal feeding behaviors and energy expenditure.[4–6] Therefore, small molecule MCH-R1 antagonists are being heavily pursued by many laboratories trying to find an effective drug molecule for the treatment of obesity.[7,8]

Structures **1**, **2** and **3** (Fig. 1) exemplify classes of potent MCH-R1 antagonists that have been disclosed in recent patent literature.[9] All these compounds are similar in structure by having a biphenyl carboxy group and a tertiary amine linked via an aniline or aminotetralin unit. Aided by molecular modeling, we utilized putative key receptor contact points of these classes of compounds to design and synthesize additional lead classes of MCH-R1 antagonists.

1.1. Structure-based design of biphenyl carboxy group replacements

Extensive SAR developed in our laboratory suggests that the tertiary amine, the amide bond, and the terminal aromatic ring of the biphenylcarboxy group are key pharmacophoric points for biological activity, as also observed by others.[10] Docking experiments performed in our h-MCH-R1 homology model[11] suggest that compounds of the type shown in Figure 1 are embedded in the transmembrane region between helices 3, 6, and 7. Our model suggests that the basic amine

Keywords: Melanin-concentrating hormone; MCH R1 antagonists; Obesity; hERG; QT interval prolongation.
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doi:10.1016/j.bmc.2006.12.028

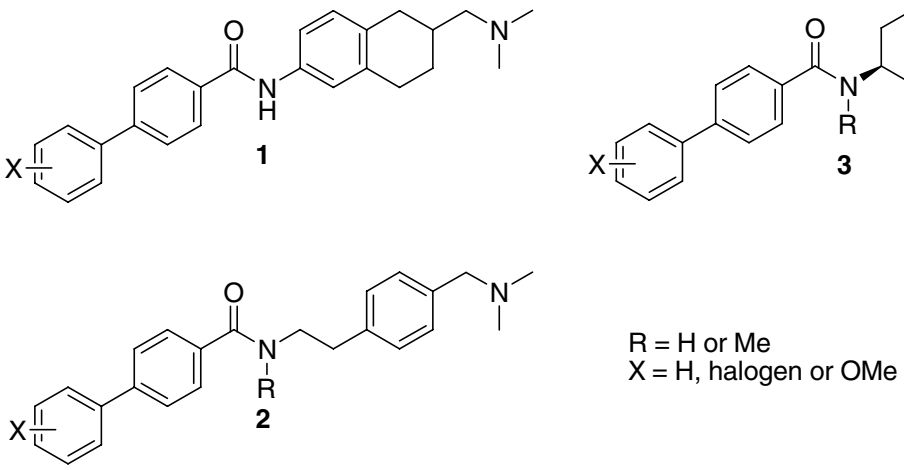


Figure 1. Benchmark MCH-R1 antagonist.

putatively interacts deep in the receptor with the conserved Asp123 (helix 3), while the biaryl system is involved in pi-stacking and pi-cationic interactions closer to the receptor surface. In addition, the amide bond appears to be involved in a hydrogen bonding interaction with Gln279 and Arg197 (Fig. 2), with the carbonyl oxygen acting as the hydrogen bond acceptor, and both Arg197 and Gln279 acting as hydrogen bond donors. The methyl amide analog **5** (Fig. 3) displayed similar MCH-R1 antagonist activity compared to **4** which further confirms the fact that the amide N–H bond might not be involved in any key binding interactions. Inversion of the amide bond in compound **4** led to the synthesis of compound **6** which was equipotent (Fig. 3). This observation is in agreement with our hypothesis that a glutamine might be involved in this interaction, as simple bond rotation within its side chain allows Gln279 to act as a H-bond acceptor toward compound **6** without changing the overall MCH-R1-binding capabilities of the compound. Significant losses in biological activity were observed when the amide carbonyl was reduced to a methylene group resulting in a secondary amine linker (compound **7**).

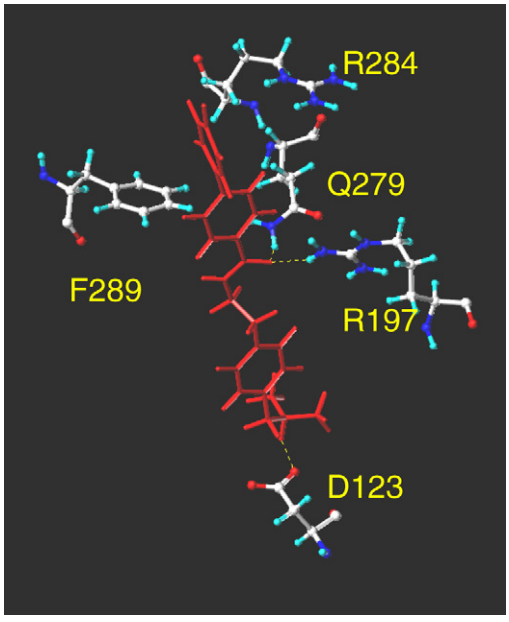


Figure 2. Compound **2** (X = H, R = H): main interactions for MCH-R1 binding.

As mentioned above, our model suggests that the biaryl moiety interacts with the extracellular region of the receptor. Indeed, we observe the formation of pi-cationic interactions between Arg284 (extra-cellular loop 3) and the external phenyl ring of our compounds, while interactions with the internal phenyl ring are dominated by steric interactions such as a weak pi-stacking with Phe 289 (helix 7). Based on this observation, we hypothesized that the terminal phenyl ring of the biaryl unit plays a more critical role in MCH-R1 binding than its internal counterpart whose role may only be as a linker to position the distal ring for optimal interactions.

The model-based observation described heretofore led us to consider the possibility to utilize the amide bond as a handle for a new linker unit or ring structure to produce potent MCH-R1 antagonists lacking the benzamide unit. Among several proposed scaffolds designed to fulfill this hypothesis, structures **8** and **9** (Fig. 4) emerged as a series of synthetically accessible compounds.

1.2. Chemistry

Compounds **14** and **15** were prepared from commercially available starting materials as depicted in Scheme 1. The synthesis of compound **14** was initiated with the N-allylation of commercially available *N*-(*tert*-butoxycarbonyl)glycine methyl ester **10** followed by the ozonolysis of the alkene unit to produce acetaldehyde **12**. The resulting material was used in a reductive alkylation reaction with 4-(1-piperidinylmethyl)-phenylethanamine. Under the present reaction conditions, the resulting secondary amine lactamized to produce ketopiperazine **13** in modest yield. Removal of the carbamate group followed by coupling of the resulting secondary amine with 4-fluorophenylacetic acid produced

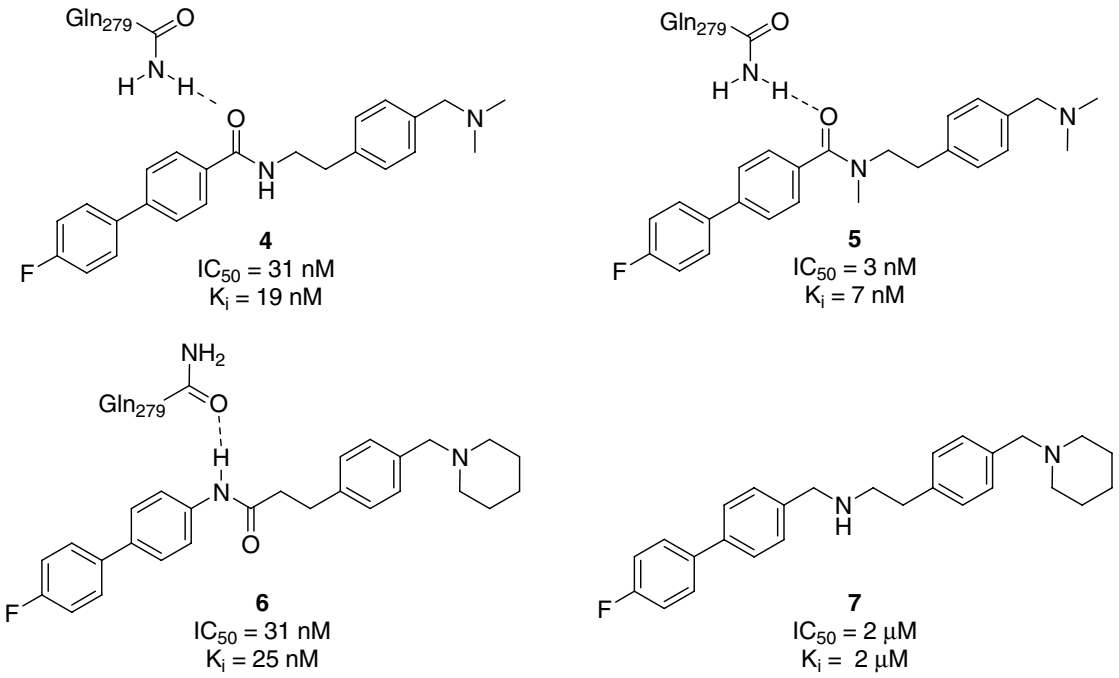


Figure 3. Biological data supporting pharmacophore model and the role of the amide functionality in MCH-R1 binding.

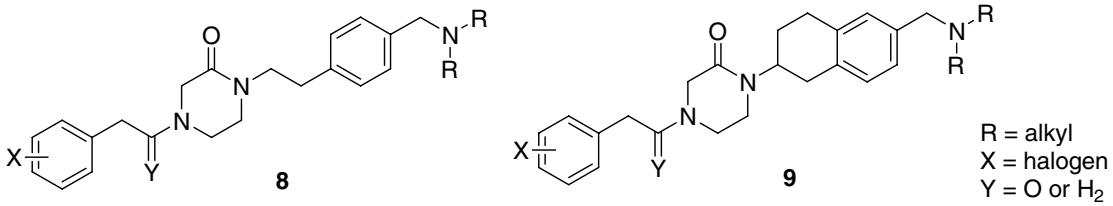
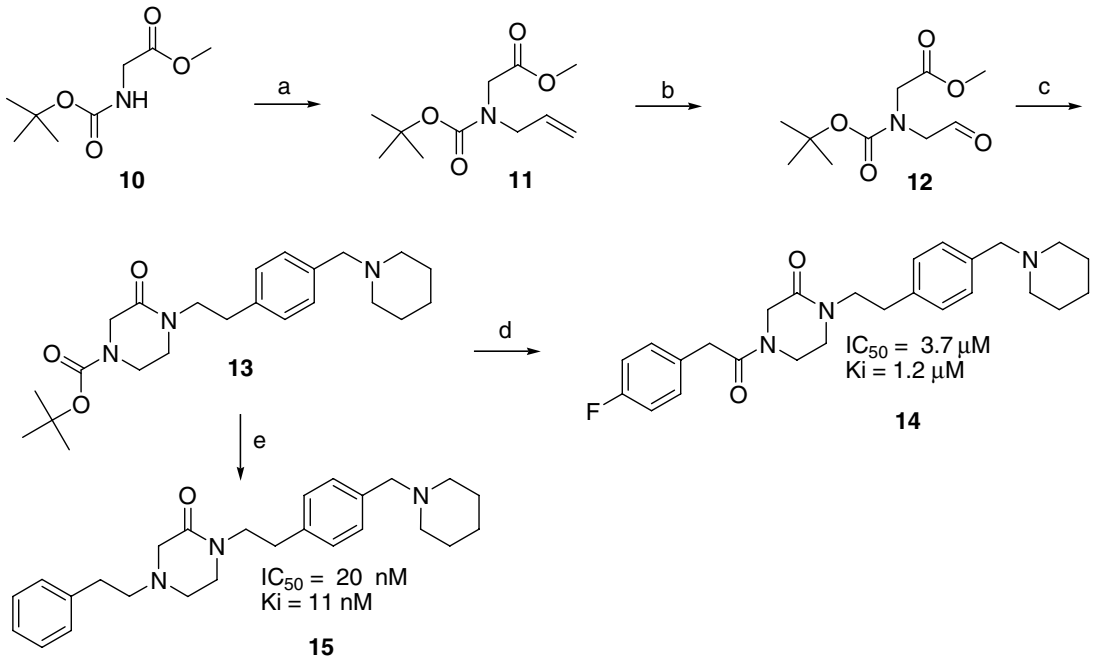


Figure 4. Proposed in silico MCH-R1 antagonist scaffolds.

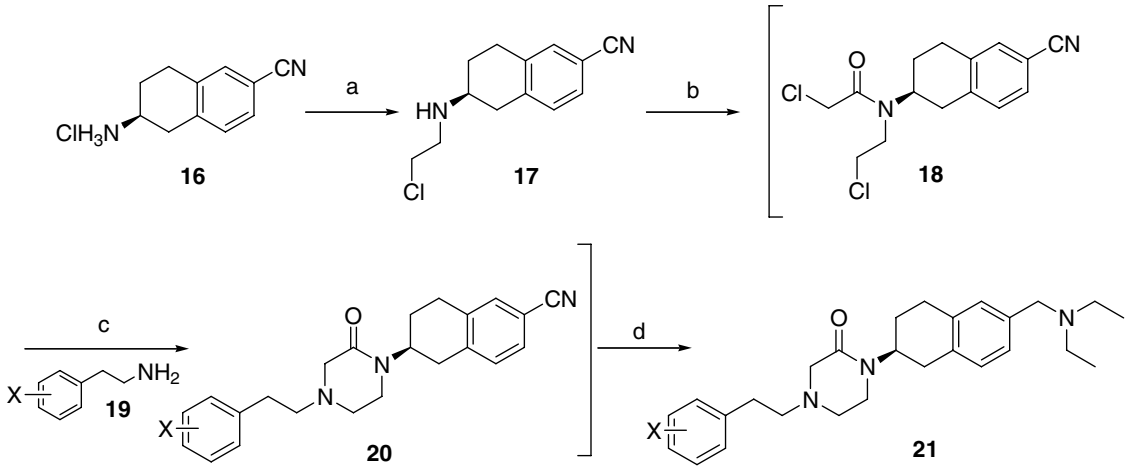
the desired compound **14.** Compound **15** was obtained from the synthetic intermediate **13** via a two-step protocol which involved the removal of the carbamate group followed by a reductive alkylation of the resulting secondary amine with phenylacetaldehyde.

The desired compounds **21a–k** were initially prepared as depicted in Scheme 2. The synthesis departed from the commercially available (*S*)-6-amino-5,6,7,8-tetrahydronaphthalene-2-carbonitrile hydrochloride **16**. Reductive alkylation of **16** with chloroacetaldehyde followed by reaction of the resulting secondary amine with chloro acetylchloride led to the key intermediate **18**. This material reacted with primary amines under basic conditions to produce the ketopiperazine compounds **20** in poor–modest yields. Finally, the desired compounds were obtained by converting the nitrile functionality into a diethyl benzyl amine via a two-step protocol that consisted of a Raney nickel reduction followed by reductive alkylation with two equivalents of acetaldehyde. This synthetic route was effective to produce small amounts (100–200 mg) of these compounds for the purpose of in vitro biological testing and SAR development. Performing this synthetic protocol on multi-gram scale proved to be challenging and inefficient. Several attempts to satisfactorily purify nitrile intermediates (**20**) were ineffective and repeatedly led to low overall yields of the desired products **21a–k**. An alternative synthetic route was designed to address the need for multi-gram preparation of these compounds for further biological evaluation.

In order to overcome some of the limitations of our initial synthetic approach, we envisioned that the ketopiperazine unit of **20** could be built in a single synthetic operation via a novel multi-step ring-forming transformation (Scheme 3). The synthetic precursors are a methyl 2-(2-chloroethyl-phenethylamino)-acetate (**23**) unit and (*S*)-6-amino-5,6,7,8-tetrahydronaphthalene-2-carbonitrile (**16**). Compounds **23** were easily prepared directly from the corresponding phenethyl amine **19** and without isolating intermediate **22**. Under microwave conditions (Biotage Personal Chemistry System) and with catalytic amounts of sodium iodide, the ketopiperazine compound **20** was consistently obtained in moderate yields. The reaction did not work without the addition of sodium iodide (recovered starting material and thermal decomposition). Attempts



Scheme 1. Synthesis of MCH-R1 antagonists **14** and **15**. Reagents and conditions: (a) NaH, allyl bromide, 0 °C, 90 min, 70%; (b) i—O_3, pyridine, MeOH, CH_2Cl_2, −78 °C, 90 min; ii—methyl sulfide, −78 to 25 °C, 16 h, 80%; (c) 4-(1-piperidinylmethyl)-phenylethanamine, $NaCNBH_3$, AcOH, MeOH, 25 °C, 16 h, 55%; (d) i—DCM, TFA, 25 °C, 2 h; ii—*p*-fluorophenylacetic acid, EDCI, HOBT, NMM, DMF, 25 °C, 16 h, 78%; (e) i—DCM, TFA, 25 °C, 2 h; ii—phenylacetaldehyde, $NaCNBH_3$, AcOH, MeOH, 25 °C, 16 h, 22%.

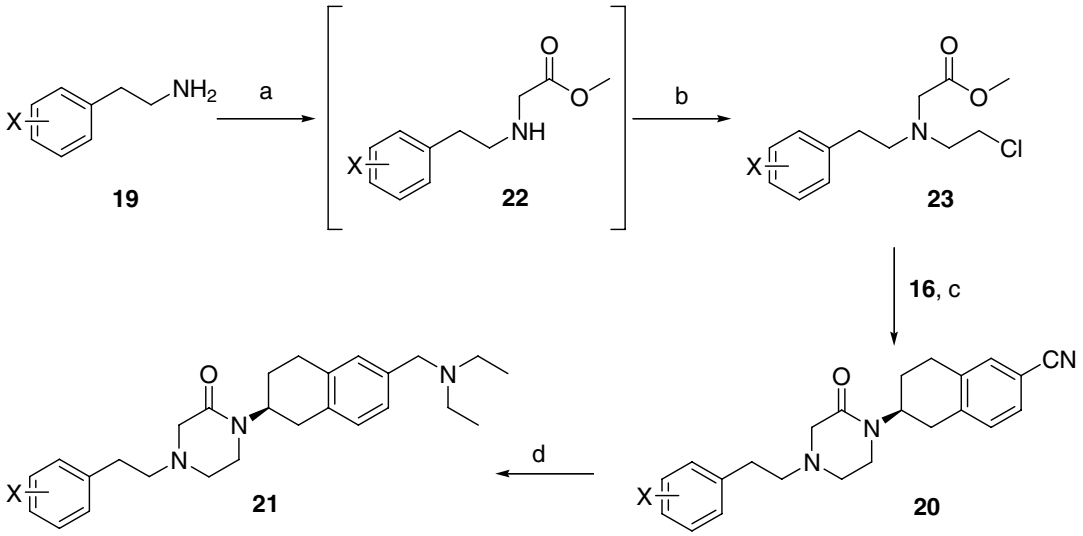


Scheme 2. Initial synthesis of MCH-R1 antagonists **21**. Reagents and conditions: (a) chloroacetaldehyde, $NaCNBH_3$, MeOH, AcOH, 4 h, 75%; (b) chloroacetic anhydride, DIPEA, CH_3CN, −20 °C to rt, 30 min; (c) NaI, MW 2-W, 70 °C , 10 min, 20% over two steps; (d) i—Raney nickel, H_2, NH_4OH, DMF, 16 h; ii—acetaldehyde, $NaCNBH_3$, MeOH, AcOH, 15 min, 40% overall yield from **20**.

to promote this process using conventional heat (60–100 °C) produced limited amounts of halogen displacement and did not promote lactamization to produce **20**. The reaction worked well whenever carried out at high concentrations, which allowed for the production of 5 g of material in a 20-mL reaction vessel in about 20 min (see Section 3). Multi-gram preparations for selected compounds **21** (those included in Table 2) were achieved in batch-mode by employing an automated-sample microwave system (see Section 3).

1.3. Biological results and discussion

Testing of compound **14** in the MCH-R1 binding assay[12] revealed a mediocre activity ($IC_{50} = 3.7 \pm 9$ μM, $K_i = 1.2 \pm 1$ μM), which is 100-fold lower than that of our benchmark (compound **2**). Although docking of this compound in the homology model satisfied interactions with Gln279, Arg197, Asp123, and Arg284 described above, the newly added distal carbonyl interacted unfavorably with the phenyl ring of Phe289. Since this was the only unfavorable



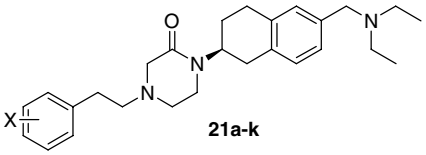
Scheme 3. Scale-up synthesis of MCH-R1 antagonists **21**. Reagents and conditions: (a) methyl chloroacetate, diisopropylethylamine, CH_3CN, 0 °C; (b) chloroacetaldehyde, $NaCNBH_3$, MeOH, AcOH, 56% over two steps; (c) (*S*)-amino-5,6,7,8-tetrahydronaphthalene-2-carbonitrile hydrochloride (**16**), diisopropylethylamine, CH_3CN, microwave, 130 °C, 30 min, 53–66%; (d) i—Raney Ni, H_2, NH_4OH, DMF, 16 h; ii—acetaldehyde, $NaCNBH_3$, MeOH, AcOH, 15 min, 87–93% from **20**.

pharmacophoric point when compared to the pharmacophore requirements of compound **2** described above, it was suggested to remove this carbonyl unit and synthesize the phenethyl analog **15**.

This phenethyl ketopiperazine **15** displayed improved MCH-R1 in vitro activity compared to compound **14**. Contrary to the biaryl-containing MCH-R1 antagonists, compounds **15** had very high-water solubility (>45 mg/mL) allowing us to easily formulate it for in vivo studies. However despite its high in vitro MCH-R1 antagonist activity, **15** did not promote significant weight loss in a mouse diet induced obesity study (mDIO). We hypothesized that its lack of efficacy in our 4-day mDIO weight loss model was due to limited blood–brain barrier penetration. This hypothesis was supported by Caco-2 cell assay[13] data identifying **15** as a potential efflux substrate (A–B/B–A = 11/21).[14] In addition, the hydrophilic nature of **15** ($c\log P = 2.1$)[15] could also have contributed to its suspected inability to effectively cross the blood–brain barrier. This led us to consider making compounds **21** with increased lipophilicity ($c\log P$ range = 2.6–3.2) and less free bond rotation in an attempt to address the blood–brain barrier penetration hypothesis postulated with compound class **15**. The subsequent synthesis of **21a–k** (see chemistry section) represents a new class of potent MCH-R1 antagonists.

Compounds **21a–k** proved to have high binding affinity for MCH-R1 (Table 1). Halogen variations at the phenethyl unit suggested that, for a single halogen substitution, the para-position was optimal while the ortho-position produced less active compounds (see **21d–f** and **21h–j**). We observed that this effect increased with the increased size of the halogen atom or group. The effect was most notable for the trifluoromethyl group, intermediate for chlorine and negligible for fluorine.

Table 1. SAR-phenethyl halogen substitution and MCH-R1 binding affinity



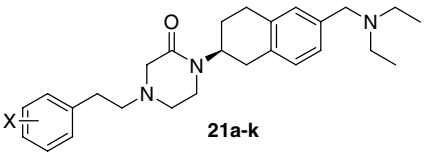
21a-k

Compound	X	MCH-R1 K_i[a] (nM)
21a	H	16
21b	**4-F**	**3**
21c	3-F	10
21d	2-F	12
21e	4-Cl	4
21f	3-Cl	19
21g	2-Cl	194
21h	4-Br	4
21i	4-CF3	42
21j	3-CF3	93
21k	2-CF3	374

[a] $n = 2$ for all compounds except for **21b** and **21i** where $n = 4$.

In contrast to compound **15**, molecule **21b** promoted weight loss and decreased food intake in mice. Other compounds within this novel class of MCH-R1 antagonists showed similar results (Table 2). It is interesting to note that, in agreement with the in vitro data, the meta-substituted **21j** (3-trifluoromethyl) appeared to be less active in vivo than its para-substituted counterpart **21i** (4-trifluoromethyl). All the para-halogenated compounds displayed similar in vivo activity with the chloro-containing compound **21d** appearing to be sligthly better. In order to corroborate these preliminary results and further our understanding or the MCH-R1 antagonist activity of this class, we choose **21b** as an early lead and submitted it to a more comprehensive biological evaluation.

Table 2. 4-day mouse DIO studies (20 mg/kg dose BID)



21a-k

Compound	X	MCH-R1 K_i[a] (nM)	MCH-R1 IC_{50}[a] (nM)	hERG[b,16] IC_{50} (μM)	% body weight loss in 4-d MDIO (vehicle)	% food intake reduction in 4-d MDIO	[drug in serum]/μM[c]	
							at 2 h	at 5 h
21b	4-F	3 ± 1	10 ± 3	8.1	7.0 ± 0.3 (2.5 ± 0.6)	30 ± 5	10 ± 2	7 ± 1
21e	4-Cl	4 ± 1[a]	—	3.3	9.3 ± 0.7 (1.5 ± 0.4)	45 ± 3	6.5 ± 0.8	5.1 ± 0.3
21i	4-CF_3	42 ± 12	38 ± 7	—	7.8 ± 0.4 (2.5 ± 0.6)	30 ± 3	5.5 ± 0.7	4.4 ± 0.3
21j	3-CF_3	93 ± 17[a]	—	1.7	4.7 ± 0.7 (1.5 ± 0.4)	18 ± 4	4.4 ± 0.7	3.0 ± 0.6

[a] $n = 4$ for **21b** and **21i**; $n = 2$ for **21e** and **21j**.
[b] Patch–clamp hERG IC_{50} determinations were carried out as described in Ref. 16.
[c] Levels of drug in serum measured at day 5 of dosing.

1.4. Lead evaluation

Both in vitro and in vivo evaluations were performed to assess the ability of compound **21b** to cross the blood–brain barrier. The Caco-2 cell assay[13] predicted **21b** to passively permeate across the blood–brain barrier (A–B/B–A = 10/16). Serum and brain concentrations of **21b** at 2 h after a single po dose in mice at 20 mg/kg were 1.1 ± 0.1 mg/mL and 3.2 ± 0.6 mg/g, respectively. These results supported the idea that compound **21b** had the ability to penetrate the blood–brain barrier in order to antagonize the CNS-located MCH-R1.

In a 10-day mouse diet induced obesity study, MCH-R1 antagonist **21b** was dosed once a day in at 2, 7, and 20 mg/kg leading to −3.3 ± 1.0%, −6.0 ± 0.8%, and −7.5 ± 1.0% reductions in body weight, respectively (Fig. 5). The vehicle treated mice displayed a −2.1 ± 1.0% change from their initial body weight (Table 3). The effect of compound **21b** on body weight was associated with a significant effect on food intake compared to vehicle treated mice (Fig. 6). Compound **21b** dosed at 20 mg/kg and 7 mg/kg had an effect on weight with significant reduction in food intake, while

Table 3. Body weight change in 10-day mDIO study for **21b**[a]

Group	Day 0 BW (g ± SEM)	Day 10 BW (g ± SEM)	% change (% ± SEM)
Vehicle	44.5 ± 0.9	43.6 ± 0.8	−2.1 ± 1.0
2 mg/kg	44.8 ± 1.1	43.3 ± 1.4	−3.3 ± 1.0
7 mg/kg	44.7 ± 0.8	42.0 ± 0.9	−6.0 ± 0.8
20 mg/kg	44.8 ± 1.1	41.5 ± 1.3	−7.5 ± 1.0

[a] Body weight (BW) of all groups of mice treated with vehicle or compound **21b** at days 0 and 10 of the study with percent change in BW relative to baseline.

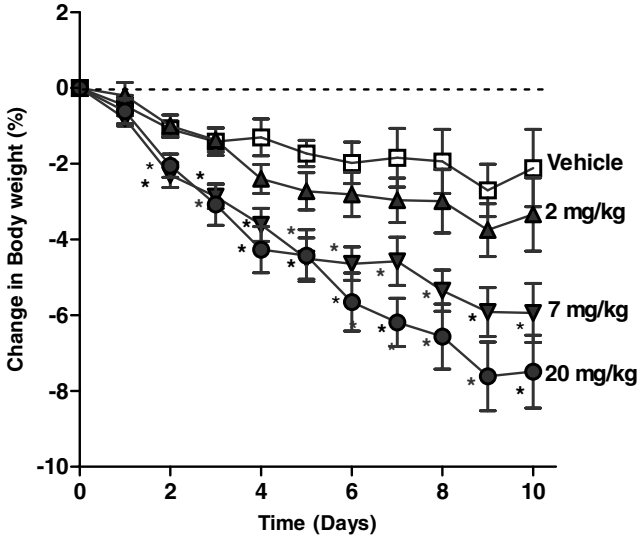


Figure 5. Percent change in body weight from baseline of compound **21b** tested at 2, 7, and 20 mg/kg, and vehicle (2% Tween 80/saline) at 5 mL/kg po QD. All values are mean values ± SEM for $n = 8$. Asterisk (*) indicates statistical significance at $p \leqslant 0.05$ compared to vehicle treated mice.

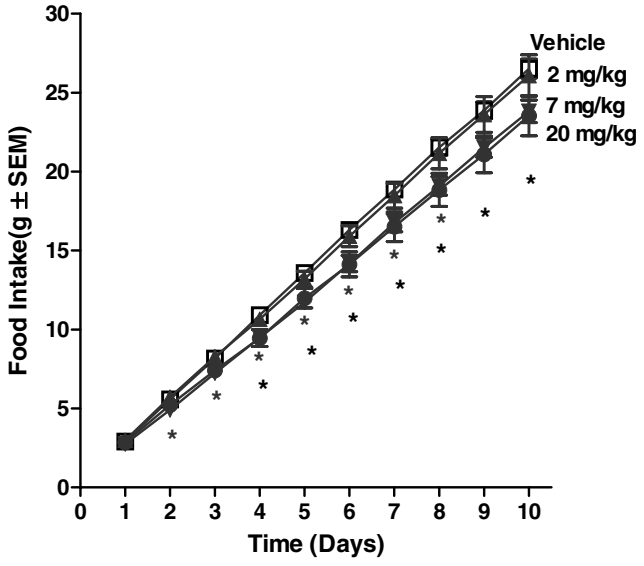


Figure 6. Cumulative food intake of DIO mice treated with compound **21b** at 2, 7, and 20 mg/kg, and vehicle (2% Tween 80/saline) at 5 mL/kg po QD. Food intake was measured daily throughout the study. All values are mean values ± SEM for $n = 8$. Asterisk (*) Indicates statistical significance at $p \leqslant 0.05$ compared to vehicle treated mice.

it did not show a significant reduction in food intake when dosed at 2 mg/kg. The cumulative food intake amounts for compound **21b** treated mice were 26.1 ± 1.3, 23.8 ± 0.7, and 23.5 ± 1.3 g for mice dosed with 2, 7, and 20 mg/kg of the compound, respectively, while cumulative food intake for vehicle treated mice was 26.5 ± 0.6 g. This resulted in a −1.7 ± 4.9%, −10.2 ± 2.7% and −11.3 ± 4.8% inhibition of food intake compared to vehicle treated mice at 2, 7, and 20 mg/kg, respectively.

Magnetic Resonance Relaxometer (MRR) analysis[17] (performed as part of the 10-day mDIO) revealed a reduction in fat mass for mice treated with compound **21b** at 7 and 20 mg/kg compared to vehicle treated mice with −1.7 ± 0.5 and −2.4 ± 0.6 fat gram changes, respectively, though the data did not reach significance (Fig. 7). Mice treated with 2 mg/kg of compound **21b** showed no reduction in fat mass compared to vehicle treated mice with a change of −0.9 ± 0.7 fat grams. Vehicle treated mice showed a reduction of −0.9 ± 0.6 fat grams. MRR data revealed no significant reduction in lean mass for mice treated with compound **21b** at 2, 7, and 20 mg/kg compared to vehicle treated mice with −0.6 ± 0.4, −1.3 ± 0.6, and −1.0 ± 0.4 lean gram changes, respectively (Fig. 8). Vehicle treated mice showed a reduction of −0.5 ± 0.4 lean grams. The reduction in fat and lean mass was determined by comparing the final to initial MRR fat and lean mass.

Additional biological data were collected on compound **21b** to assess its potential as an effective orally dosed MCH-R1 antagonist. Compound **21b** was estimated to have moderate bioavailability (40%) following oral dosing in male Sprague–Dawley rats. Peak plasma levels were observed at 0.5 h with an estimated half-life of approximately 4 h. In addition, compound **21b** was tested for chromosomal aberrations and was concluded to be negative for the induction of structural and numerical

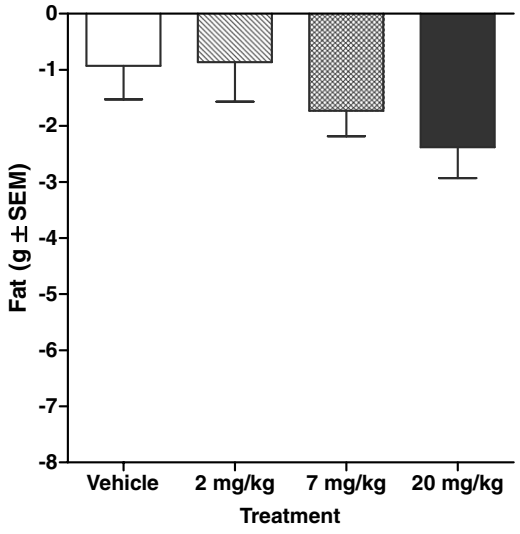


Figure 7. Fat mass loss determination: MRR for mice treated with compound **21b** at 2, 7, and 20 mg/kg, and vehicle (2% Tween 80/saline) at 5 mL/kg po QD.

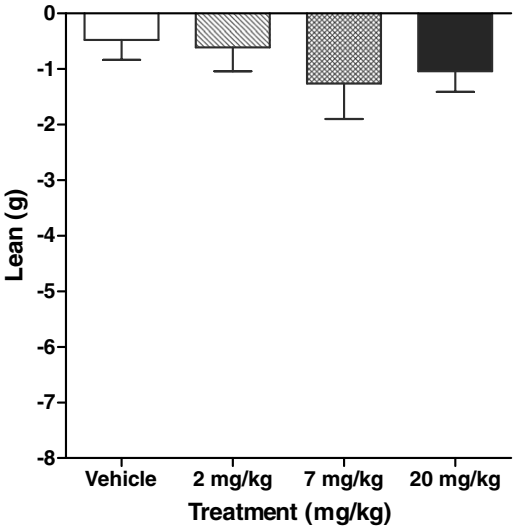


Figure 8. Lean mass loss determination: MRR for mice treated with compound **21b** at 2, 7, and 20 mg/kg, and vehicle (2% Tween 80/saline) at 5 mL/kg po QD.

chromosome aberrations in CHO cells. Amazingly, cytotoxic levels were determined to be the order of 1.25 mg/mL, which represent a 25-fold improvement when compared to the cytotoxic level range (0.040–0.050 mg/mL) observed for the benchmark MCH-R1 antagonists (**1**, **2**, **3**).

Despite the attractive in vitro profile and in vivo results, further development of **21b** and its analogs as MCH-R1 antagonists was compromised by significant hERG channel binding in vitro. This class of ketopiperazine-aminotetralin compounds proved to be effective hERG blockers at concentrations comparable to those of drug in serum at administered doses (Table 2). hERG blockers can induce QT interval prolongation which is frequently associated with potentially lethal arrhythmias known as torsades de pointes (TdP), which has led to the removal of several drugs from the market.[18] At this point, it was necessary to assess if the observed hERG activity was indicative of the potential for compound **21b** to induce QT interval prolongation.

Unfortunately, we found that **21b** promotes a dose-dependent increase in QT interval in anesthetized dogs (Fig. 9).[19] A statistically significant dose-dependent decrease in heart rate and an increase in QT interval at 10 mg/kg were observed. The heart rate decreased from 111 ± 10 beats/min at the end of the vehicle infusion to 93 ± 6 beats/min at the end of the 10 mg/kg infusion. QT interval increased from 330 ± 22 ms at the end of the vehicle infusion to 368 ± 36 ms at the end of the 10 mg/kg infusion. The plasma concentrations of **21b** after 1 mg/kg and 10 mg/kg were 1190 ± 218 ng/ml and 9280 ± 973 ng/mL, respectively. This study demonstrated that **21b** prolonged QT interval in the anesthetized dogs at plasma concentrations of 9280 ng/mL. This concentration was of the same order of magnitude as that which caused a 50% inhibition of hERG (IC50 = 8.1 μM ≈ 3500 ng/mL).

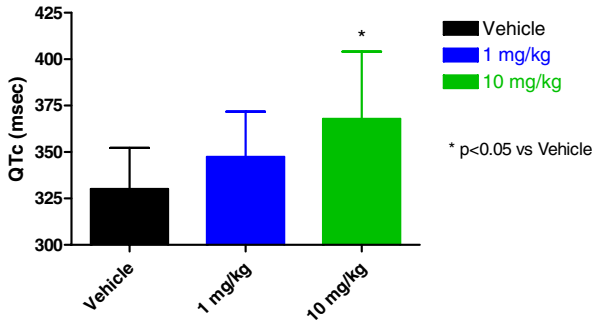


Figure 9. Effect of **21b** on QT interval (ms) in the anesthetized dog. Plots of mean and SD ($n = 4$) measurements for incremental concentrations. Measurements were made during the last minute of a 15-min perfusion of each concentration. *Significantly different ($p < 0.05$) from vehicle.

Currently, our efforts are focused on the design of aminotetrahydronaphthalene ketopiperazine compounds analogous to **21b** with lower hERG blockage activity for which we have recently founds compounds with improved hERG profiles which will be discussed in a later report.

2. Conclusions

In this work, medicinal chemistry efforts in tandem with molecular modeling studies have led to the synthesis of aminotetrahydronaphthalene ketopiperazine **21b** which acts as a novel class of potent MCH-R1 antagonists. Compound **21b** promoted significant body weight reduction in a pair of mouse diet induced obesity studies. In addition, Magnetic Resonance Relaxometer body weight composition analysis of the mice in both studies revealed a significant reduction in fat mass with negligible changes in lean mass. Despite the attractive in vitro profile and in vivo results, further development of compond **21b** as an MCH-R1 antagonist was compromised by its hERG blockage activity leading to an observed dose-dependent increase in QT interval in anesthetized dogs at serum concentrations comparable to those obtained at efficacious doses.

3. Experimental

3.1. General methods

All solvents and reagents unless otherwise noted were purchased from commercial sources and used without further purification. Reactions were carried-out under argon or nitrogen in oven-dried glassware. Mass spectra were recorded using an electro-spray ionization mass detector from Micromass. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Varian or Bruker NMR spectrometer operating at the frequencies indicated, and the chemical shifts (given in ppm) were referenced against the residual protons of the deuterated solvents. Products were purified by flash column chromatography using Aldrich silica gel 60, Biotage Flash 40 or by RP-HPLC on a Varian ProStar Prep HPLC (column: Polaris C18-A 10 μm, 250 × 500 mm. Mobile phase: 95% H_2O (1% TFA), 5% ACN for 30 s then linear gradient to 100% ACN over 40 min followed by a 16 min hold at 100% ACN. Flow rate 60 mL/min) Analytical RP-HPLC analysis was performed on an Agilent 1100 series instrument or a Spectra Physics AS3000 (Column: Polaris 3 μm C18-A 250 × 4.6 mm. Mobile phase: 80% H_2O (0.1% H_3PO_4), 20% ACN linear gradient over 20 min to 100% ACN followed by a hold for 5 min at 100% ACN. Flow rate 1 mL/min).

3.2. Modeling

A model of the MCH-R1 receptor was constructed by mapping the sequence of the MCH-R1 receptor onto the 2.8 Å resolution crystal structure of rhodopsin.[20] Several intermediate models were produced using the in-house protein engineering software PROTENG whose core revolves around a simplified energy function and libraries derived from scans of conformations of both side chains and backbones for mutated residues. The energy function is simplified for rapid calculation of packing, hydrogen bonding, and salt bridges. The model with the best packing quality was selected for subsequent validation which was performed using mutagenesis data obtained for both the receptor[21] and the melanin-concentrating hormone generated in-house. The model was subsequently refined iteratively as SAR data generated across various compound classes in our laboratory became available. Coordinates of the resulting model are published.[11]

3.3. Chemistry

3.3.1. *N*-Allyl-*N*-(*tert*-butoxycarbonyl)glycine methyl ester (11). To a 0 °C solution of *N*-(*tert*-butoxycarbonyl)glycine methyl ester (1.8 mL, 12 mmol) in 30 mL DMF was added allyl bromide (1.6 mL, 18 mmol, 1.5 equiv) followed by sodium hydride (0.64 g, 18 mmol, 1.5 equiv). The reaction was maintained at 0 °C for 90 min. Saturated ammonium chloride solution and EtOAC were added. The layers were separated and the aqueous layer was extracted with fresh EtOAC. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel flash chromatography to yield 2.0 g of a colorless oil (70%). ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of rotational isomers) δ 5.85–5.72 (m, 1H), 5.19–5.10 (m, 2H), 3.98–3.94 (m, 2H), 3.89 (d, $J = 5.6$ Hz, 1H), 3.86–8.82 (m, 1H), 3.73 (s, 3H), 1.47–1.43 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of rotational isomers) δ 170.8, 155.8, 155.3, 133.9, 133.8, 117.8, 17.0, 80.6, 52.1, 51.0, 50.5, 48.1, 47.7, 28.5. LRMS (M+H): 230.2, 174.1.

3.3.2. *N*-Acetaldehyde,*N*-(*tert*-butoxycarbonyl)glycine methyl ester (12). A solution of *N*-allyl,*N*-(*tert*-butoxycarbonyl)glycine methyl ester (**11**) (2.7 g, 11.8 mmol) in 50 mL dichloromethane, 6 mL methanol, and 1 mL pyridine was cooled to −78 °C. Ozone was bubbled through this solution for 45 min. Oxygen was then bubbled through the blue solution until it became colorless.

Methyl sulfide (5 mL) was added and the reaction mixture was allowed to warm to room temperature over 16 h. The reaction mixture was concentrated in vacuo, and the crude product was purified by silica gel flash chromatography to yield 2.1 g of a colorless oil (80%). ^{1}H NMR (300 MHz, $CDCl_3$): (mixture of rotational isomers) δ 9.67–9.65 (m, 1H), 4.12 (s, 1H), 4.05 (s, 1H), 4.01 (s, 1H), 3.90 (s, 1H), 3.75 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): (mixture of rotational isomers) δ 199.5, 199.1, 170.5, 170.3, 155.5, 155.2, 82.1, 81.8, 58.3, 58.2, 52.4, 50.3, 49.8, 28.3. LRMS (M+H): 232.1, 176.1.

3.3.3. *tert*-Butyl 4-(4-(piperidin-1-ylmethyl)phenethyl)-3-oxopiperazine-1-carboxylate (13). Sodium cyanoborohydride (378 mg, 6.0 mmol) was added to a solution of *N*-acetaldehyde,*N*-(*tert*-butoxycarbonyl)glycine methyl ester (**12**) (924 mg, 4.0 mmol) and 2-(4-(piperidin-1-ylmethyl)phenyl)ethanamine (1.3 g, 6.0 mmol) in methanol (20 mL). After 2 h, additional sodium cyanoborohydride (378 mg, 6.0 mmol) was added, and the mixture was stirred overnight at 25 °C. Solvent was removed in vacuo and the crude residue was diluted with 1 N NaOH and EtOAc. The layers were separated and the aqueous layer was extracted with fresh EtOAC. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by preparative reverse-phase HPLC to yield 883 mg (55%) as a thick light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 4.11 (s, 2H), 4.02 (s, 2H), 3.59 (t, J = 7.5 Hz, 2H), 3.55–3.48 (m, 4H), 3.21 (t, J = 5.5 Hz, 2H), 2.87 (t, J = 7.5 Hz, 2H), 2.85–2.81 (m, 2H), 2.57–2.50 (m, 2H), 1.90–1.83 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD): δ 168.1, 155.6, 142.7, 132.7, 131.0, 128.7, 82.3, 61.6, 54.0, 47.9, 33.9, 28.7, 24.2, 22.9; LRMS ($M+H^+$): 402.33.

3.3.4. 1-(4-(Piperidin-1-ylmethyl)phenethyl)-4-(2-(4-trifluoromethylphenyl)acetyl) piperazin-2-one (14). To a solution of *tert*-butyl 4-(4-(piperidin-1-ylmethyl)-phenethyl)-3-oxopiperazine-1-carboxylate (**13**) (200 mg, 0.5 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (1 mL). The reaction mixture was stirred at 25 °C for 90 min. The solvent was removed in vacuo. The crude residue was dissolved in 1 mL DMF. *p*-Fluorophenylacetic acid (77 mg, 0.5 mmol), EDCI (106 mg, 0.55 mmol), HOBT (74 mg, 0.55 mmol), and 4-methylmorpholine (0.2 mL, excess) were added, and the mixture was stirred at 25 °C for 16 h. The reaction mixture was poured into water and the resulting precipitate filtered off. The crude precipitate was purified by preparative HPLC. Pure fractions were combined, treated with 1 N HCl, and concentrated in vacuo to give 203 mg (78%) of product as a white powder. ^{1}H NMR: (300 MHz, CD_3OD) (mixture of rotational isomers) δ 7.65–7.59 (m, 2 H), 7.45–7.34 (series of m, 6H), 4.25 (s, 2H), 4.09 (s, 0.4 × 2H), 3.92 (s, 0.6 × 2H), 3.88–3.58 (series of m, 4H), 3.42–3.34 (m, 6H), 2.97–2.89 (m, 4H), 1.94–1.69 (series of m, 5H), 1.51–1.47 (m, 1H); ^{13}C NMR: (300 MHz, CD_3OD) (mixture of rotational isomers) δ 171.4, 167.8, 142.5, 140.9, 133.3, 132.8, 132.7, 131.2, 131.0, 128.7, 126.6, 61.6, 54.1, 47.8, 47.5, 44.1, 40.8, 40.4, 33.9, 24.2, 22.9; HRMS: calcd for $C_{27}H_{33}F_3N_3O_2$ ($M+H^+$) 488.2525, found 488.2548.

3.3.5. 1-(4-(Piperidin-1-ylmethyl)phenethyl)-4-phenethylpiperazin-2-one (15). To a solution of *tert*-butyl 4-(4-(piperidin-1-ylmethyl)phenethyl)-3-oxopiperazine-1-carboxylate (**13**) (402 mg, 1.0 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (2 mL). The reaction mixture was stirred at 25 °C for 90 min. The solvent was removed in vacuo. The crude product was dissolved in 1 mL methanol and several drops of acetic acid. Sodium cyanoborohydride (192 mg, 3.0 mmol) was added followed by excess phenylacetaldehyde. The reaction mixture was stirred for 16 h when it was poured into ethyl acetate and water. The layers were separated and the aqueous layer was extracted with fresh EtOAC. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by preparative HPLC. Pure fractions were combined, treated with 1 N HCl, and concentrated in vacuo to give 98 mg (22%) of product as a white powder. ^{1}H NMR: (300 MHz, dmso d_6) δ 7.53 (d, J = 8.0 Hz, 2H), 7.38–7.33 (m, 4H), 7.28 (d, J = 7.1 Hz, 3H), 4.21–4.19 (m, 2H), 3.85–3.74 (m, 4H), 3.58–3.22 (series of m, 8H), 3.11–3.06 (m, 2H), 2.86–2.81 (m, 4H), 1.77–1.75 (m, 5H), 1.38–1.33 (m, 1H); LRMS ($M+H^+$): 406.3.

3.3.6. (*S*)-6-(2-Chloroethylamino)-5,6,7,8-tetrahydronaphthalene-2-carbonitrile (17). To a solution of (*S*)-6-amino-5,6,7,8-tetrahydronaphthalene-2-carbonitrile hydrochloride (**16**) (1.0 g, 4.8 mmol) in 50 mL MeOH and 0.3 mL AcOH was added chloroacetaldehyde ~ 50 wt.% solution in water (1.13 mL, 1.5 equiv) followed by sodium cyanoborohydride (0.9 g, 3.0 equiv). The reaction mixture was stirred for 4 h when it was concentrated in vacuo. The crude product was purified by prep HPLC to yield a white solid (0.84 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 3.96 (t, J = 5.7 Hz, 2H), 3.72–3.63 (m, 1H), 3.61 (d, J = 5.7 Hz, 2H), 3.43–3.36 (m, 2H), 3.10–2.92 (m, 3H), 2.42–2.38 (m, 1H), 1.95–1.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 138.1, 133.7, 131.6, 130.9, 119.8, 111.8, 55.7, 47.9, 40.4, 33.1, 28.2, 26.5; LRMS ($M+H^+$): 235.15.

3.4. Representative experimental protocol for the preparation of compounds 21a–k according to Scheme 2 (the example below focuses on compound 21j, X = 3-CF_3)

To a −20 °C suspension of (*S*)-6-(2-chloroethylamino)-5,6,7,8-tetrahydronaphthalene-2-carbonitrile (**17**) (235 mg, 1.0 mmol) and *N*,*N*-diisopropylethylamine (0.35 mL, 2 mmol) in 1 mL acetonitrile was added a solution of chloroacetic anhydride (258 mg, 1.5 mmol) in 1 mL acetonitrile. The reaction mixture was allowed to warm to room temperature over 30 min. 3-(Trifluoromethyl)phenethylamine (378 mg, 2 mmol) and sodium iodide (75 mg, 0.5 mmol) were added. The suspension was microwaved at 70 °C and 2 W for 10 min. The crude reaction mixture is filtered through a short pad of silica-gel eluting with a

solvent mixture (chloroform/ethyl acetate/methanol/diisopropyl ethyl amine = 75:24:0.5:0.5). The filtrates were concentrated under reduced pressure and crude product (90 mg, ~0.2 mmol, ~20% yield) was pushed into the next step without further purification.

To a suspension of 100 mg Raney nickel slurry in 4 mL DMF under a hydrogen atmosphere was added 0.5 mL ammonium hydroxide and a solution of the crude (*S*)-6-(4-(3-(trifluoromethyl)phenethyl)-2-oxopiperazin-1-yl)-5,6,7,8-tetrahydronaphthalene-2-carbonitrile (**20j**, 90 mg, ~0.2 mmol) in 0.5 mL DMF. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 16 h. The suspension was filtered through a pad of Celite and the filtrate was concentrated in vacuo. At this point, a 10-mg cut of the primary amine intermediate was purified by preparatory HPLC for the purpose of characterization while the remainder of the crude was utilized in the next step without further purification.

3.4.1. [4-(3-(Trifluoromethyl)phenethyl)-1-(6-(aminomethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)piperazin-2-one. ^{1}H NMR (300 MHz, TFA-d_4) δ 7.70–7.60 (m, 2H), 7.33–7.20 (series of m, 5H), 5.15–5.00 (m, 1H), 4.79 (d, J = 16.2 Hz, 1H), 4.44 (s, 2H), 4.30–4.26 (m, 3H), 3.95–3.65 (series of m, 4H), 3.47–3.41 (m, 2H), 3.15–2.94 (series of m, 4H), 2.24–2.04 (m, 2H). ^{13}C NMR (75 MHz, MeOH-d_4) δ 162.8, 138.8, 137.3, 136.9, 134.0, 132.2, 131.1, 130.8, 130.5, 127.6, 126.8, 126.7, 125.1, 58.2, 53.9, 52.0, 44.2, 44.1, 39.4, 32.2, 30.9, 30.0, 27.1. ^{19}F NMR (282 MHz, MeOD-d_4) δ 99.35. HRMS calcd 432.2263; found 432.2281 for $C_{24}H_{29}F_3N_3O$. LRMS: 415.29 $[M-NH_2]^+$. $[\alpha]_D^{20}$ −40.4° (*c* 1.0, methanol)].

The crude product was dissolved in 1 mL methanol and several drops of acetic acid. Sodium cyanoborohydride (3 equiv) was added followed by excess acetaldehyde. The reaction mixture was stirred for 30 min when it was poured into ethyl acetate and water. The layers were separated and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by prep HPLC. Pure fractions were combined, treated with 1 N HCl, and concentrated in vacuo to give **21j**, as a white powder (40 mg, 40% from crude **20j**).

3.4.2. 4-(3-(Trifluoromethyl)phenethyl)-1-(6-((diethylamino)methyl)-1,2,3,4-tetrahydronaphthalen-2-yl)piperazin-2-one (21j). Yield: 40%, ^{1}H NMR (300 MHz, CD_3OD) δ 7.68 (s, 1H), 7.63–7.52 (m, 3H), 7.28–7.19 (m, 3H), 4.74–4.68 (m, 1H), 4.26 (s, 2H), 4.10 (s, 2H), 3.78–3.76 (m, 4H), 3.55–3.51 (m, 2H), 3.49–3.10 (series of m, 6H), 3.05–2.88 (m, 4H), 2.03–1.95 (m, 2H), 1.32 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 163.1, 139.1, 138.6, 134.3, 132.8, 131.8, 131.3, 129.9, 129.2, 127.1, 125.6, 58.7, 57.4, 54.3, 52.5, 50.3, 48.3, 39.8, 32.6, 31.3, 30.4, 27.4, 9.4; HRMS calcd for $C_{28}H_{37}F_3N_3O$ (M+H$^+$): 488.2889, found 488.2892; $[\alpha]_{365}^{20}$ −90.8° (*c* 1.0, methanol).

3.4.3. (*S*)-1-(6-((Diethylamino)methyl)-1,2,3,4-tetrahydronaphthalen-2-yl)-4-phenethylpiperazin-2-one (21a). Yield: 29%, ^{1}H NMR (300 MHz, CD_3OD): δ 7.39–7.22 (m, 8H), 4.80–4.70 (m, 1H), 4.28 (s, 2H), 4.08 (s, 2H), 3.79–3.75 (m, 4H), 3.55–3.50 (m, 2H), 3.24–2.90 (series of m, 10H), 2.04–2.03 (m, 2H), 1.35 (t, J = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD): δ 162.8, 138.3, 138.0, 137.4, 132.5, 131.5, 130.2, 130.0, 129.6, 128.9, 128.6, 59.0, 57.1, 54.1, 52.2, 50.3, 48.0, 39.5, 32.3, 31.4, 30.1, 27.1, 9.2; HRMS calcd for $C_{27}H_{38}N_3O$ (M+H$^+$): 420.3015, found 420.3008; $[\alpha]_{365}^{20}$ −101.2° (*c* 1.0, methanol).

3.4.4. (*S*)-4-(4-Fluorophenethyl)-1-(6-((diethylamino)-methyl)-1,2,3,4-tetrahydronaphthalen-2-yl)piperazin-2-one (21b). Yield: 21%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–7.12 (m, 4H), 7.05 (d, J = 7.7 Hz, 1H), 6.97 (t, 8.4 Hz, 2 H), 4.79–4.68 (m, 1H), 4.19–4.00 (m, 4H), 3.94–3.65 (m, 2H), 3.47–2.90 (series of m, 14H), 1.87–1.70 (m, 2H), 1.37 (t, J = 6.4 Hz, 6 H); ^{13}C NMR (75 MHz, CD_3OD) δ 164.0 (d, J = 244 Hz), 162.9, 138.6, 138.3, 133.5, 132.8, 132.1 (d, J = 8 Hz, 2C), 131.8, 129.9, 129.2, 117.1 (d, J = 22 Hz, 2C), 68.5 (2C), 59.1, 57.4, 54.3, 52.5, 39.8, 32.6, 30.8, 30.4, 27.4, 9.4 (2C). ^{19}F NMR (282 MHz, CD_3OD) δ 45.2; LRMS found: 438.36, HRMS found: 438.2925; Calcd: 438.2921 for $C_{27}H_{36}FN_2O$+H$^+$.

3.4.5. (*S*)-4-(3-Fluorophenethyl)-1-(6-((diethylamino)-methyl)-1,2,3,4-tetrahydronaphthalen-2-yl)piperazin-2-one (21c). Yield: 32%, ^{1}H NMR (300 MHz, CD_3OD): δ 7.43–7.36 (m, 1H), 7.31–7.24 (m, 3H), 7.20–7.14 (m, 2H), 7.08–7.02 (m, 1H), 4.77–4.70 (m, 1H), 4.29 (s, 2H), 4.12–4.08 (m, 2H), 3.80–3.76 (m, 4H), 3.58–3.52 (m, 2H), 3.36–3.30 (m, 2H), 3.23–2.92 (series of m, 8H), 2.06–2.05 (m, 2H), 1.36 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD): δ 164.6 (d, J = 245 Hz), 162.8, 140.2, 138.3, 138.0, 132.5, 132.0 (d, J = 8.5 Hz), 131.5, 129.6, 128.9, 126.0, 116.9 (d, J = 22 Hz), 115.3 (d, J = 21 Hz), 58.6, 57.2, 54.1, 52.2, 50.1, 48.0, 39.5, 32.2, 31.0, 30.1, 27.1, 9.2; HRMS calcd for $C_{27}H_{37}FN_3O$ (M+H$^+$): 438.2921, found 438.2934; $[\alpha]_{365}^{20}$ −106.0° (*c* 1.0, methanol).

3.4.6. (*S*)-4-(2-Fluorophenethyl)-1-(6-((diethylamino)-methyl)-1,2,3,4-tetrahydronaphthalen-2-yl)piperazin-2-one (21d). Yield: 27%, ^{1}H NMR (300 MHz, CD_3OD) δ 7.42 (t, J = 7.4 Hz, 1H), 7.38–7.29 (m, 3H), 7.24–7.11 (m, 3H), 4.75–4.70 (m, 1H), 4.28 (s, 2H), 4.13 (s, 2H), 3.81–3.77 (m, 4H), 3.56–3.51 (m, 2H), 3.26–3.13 (m, 6H), 3.07–2.90 (m, 4H), 2.05–2.03 (m, 2H), 1.35 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 162.9 (d, J = 243 Hz), 163.0, 138.5, 138.2, 132.8 (2C), 131.8, 131.2 (d, J = 8 Hz), 129.9, 129.2, 126.4, 124.4 (d, J = 15 Hz), 117.0 (d, J = 22 Hz), 57.6, 57.4, 54.3, 52.5, 50.2, 48.3 (2C), 39.8, 32.6, 30.4, 27.4, 25.3, 9.5 (2C); HRMS calcd for $C_{27}H_{37}FN_3O$ (M+H$^+$): 438.2921, found 438.2906; $[\alpha]_{365}^{20}$ −110.2° (*c* 1.1, methanol).

3.4.7. (*S*)-4-(4-Chlorophenethyl)-1-(6-((diethylamino)-methyl)-1,2,3,4-tetrahydronaphthalen-2-yl)piperazin-2-one (21e). Yield: 42%, ^{1}H NMR (300 MHz, CD_3OD): δ 7.37 (s, 4H), 7.31–7.23 (m, 3H), 4.76–4.70 (m, 1H), 4.29

(s, 2H), 4.10 (s, 2H), 3.80–3.76 (m, 4H), 3.56–3.52 (m, 2H), 3.27–2.93 (series of m, 10H), 2.06–2.04 (m, 2H), 1.36 (t, $J = 7.0$ Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 163.0, 138.6, 138.3, 136.5, 134.7, 132.8, 132.0, 131.8, 130.5, 129.9, 129.2, 58.9, 57.4, 54.3, 52.5, 50.3, 48.3, 39.9, 32.6, 30.9, 30.4, 27.4, 9.5; HRMS calcd for $C_{27}H_{37}ClN_3O$ (M+H$^+$): 454.2625, found 454.2646; $[\alpha]_{365}^{20}$ −107.3° (*c* 1.0, methanol).

3.4.8. (*S*)-4-(3-Chlorophenethyl)-1-(6-((diethylamino)-methyl)-1,2,3,4-tetrahydronaphthalen-2-yl)piperazin-2-one (21f). Yield: 37%, ^{1}H NMR (300 MHz, CD_3OD): δ 7.41 (s, 1H), 7.37–7.21 (m, 6H), 4.79–4.68 (m, 1H), 4.27 (s, 2H), 4.07 (s, 2H), 3.75–3.73 (m, 4H), 3.54–3.48 (m, 2H), 3.23–2.89 (series of m, 10H), 2.04–2.02 (m, 2H), 1.34 (t, $J = 7.3$ Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD): δ 162.9, 139.8, 138.3, 138.0, 135.9, 132.5, 131.7, 131.5, 130.2, 129.6, 128.9, 128.7, 128.6, 58.5, 57.1, 54.1, 52.2, 50.0, 48.0, 39.6, 32.3, 31.0, 30.1, 27.1, 9.2; HRMS calcd for $C_{27}H_{37}ClN_3O$ (M+H$^+$): 454.2625, found 454.2621; $[\alpha]_{365}^{20}$ −106.8° (*c* 1.0, methanol).

3.4.9. (*S*)-4-(2-Chlorophenethyl)-1-(6-((diethylamino)-methyl)-1,2,3,4-tetrahydronaphthalen-2-yl)piperazin-2-one (21g). 26%, ^{1}H NMR (300 MHz, CD_3OD): δ 7.46–7.40 (m, 2H), 7.34–7.20 (m, 5H), 4.79–4.68 (m, 1H), 4.27 (s, 2H), 4.12 (s, 2H), 3.79–3.75 (m, 4H), 3.52–3.46 (m, 2H), 3.30–2.89 (series of m, 10H), 2.04–2.01 (m, 2H), 1.33 (t, $J = 7.2$Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD): δ 162.8, 138.3, 138.0, 135.2, 135.0, 132.5, 131.5, 131.1, 130.6, 129.6, 129.0, 128.9, 57.1, 57.0, 54.0, 52.2, 50.0, 48.0, 39.5, 32.3, 30.1, 29.3, 27.1, 9.2; HRMS calcd for $C_{27}H_{37}ClN_3O$ (M+H$^+$): 454.2625, found 454.2614; $[\alpha]_{365}^{20}$ −85.4° (*c* 1.4, methanol).

3.4.10. (*S*)-4-(4-Bromophenethyl)-1-(6-((diethylamino)-methyl)-1,2,3,4-tetrahydronaphthalen-2-yl)piperazin-2-one (21h). Yield: 33%, ^{1}H NMR (300 MHz, CD_3OD): δ 7.53 (d, $J = 8.3$ Hz, 2H), 7.30–7.23 (m, 5H), 4.78–4.70 (m, 1H), 4.28 (s, 2H), 4.07 (s, 2H), 3.77–3.73 (m, 4H), 3.54–3.48 (m, 2H), 3.24–2.90 (series of m, 10H), 2.05–2.03 (m, 2H), 1.35 (t, $J = 7.3$ Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD): δ 162.8, 138.3, 138.0, 136.6, 133.3, 132.5, 132.0, 131.5, 129.6, 128.9, 122.4, 58.6, 57.1, 54.2, 52.2, 50.1, 48.0, 39.5, 32.3, 30.8, 30.1, 27.2, 9.2; HRMS calcd for $C_{27}H_{37}BrN_3O$ (M+H$^+$): 498.2120, found 498.2140.

3.4.11. (*S*)-4-(4-(Trifluoromethyl)phenethyl)-1-(6-((diethylamino)methyl)-1,2,3,4-tetrahydronaphthalen-2-yl)piperazin-2-one (21i). Yield: 58%, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, $J = 8.2$ Hz, 2H), 7.58 (d, $J = 8.2$ Hz, 2H), 7.32–7.23 (m, 3H), 4.29 (s, 2H), 4.13 (m, 2H), 3.82–3.78 (m, 2H), 3.68–3.57 (m, 2H), 3.26–3.14 (series of m, 7H), 3.10–2.97 (m, 4H), 2.16–2.05 (m, 4H), 1.36 (t, $J = 7.3$ Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 142.3, 138.6, 138.3, 132.8, 131.8, 131.1, 129.9, 129.2, 127.3, 127.2, 79.9, 58.6, 57.4, 55.3, 54.3, 52.5, 39.8, 32.5, 31.3, 30.4, 27.4, 9.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ 98.7. LRMS found: 488.37; calcd: 488.2889 for $C_{28}H_{36}F_3N_3O$+H$^+$.

3.4.12. (*S*)-4-(2-(Trifluoromethyl)phenethyl)-1-(6- ((diethylamino)methyl)-1,2,3,4-tetrahydronaphthalen-2-yl)piperazin-2-one (21k). Yield: 41%, ^{1}H NMR (300 MHz, CD_3OD): δ 7.73 (d, $J = 7.7$ Hz, 1H), 7.65–7.59 (m, 2H), 7.49 (t, $J = 7.0$ Hz, 1H), 7.29–7.22 (m, 3H), 4.75–4.68 (m, 1H), 4.27 (s, 2H), 4.11 (s, 2H), 3.79–3.75 (m, 4H), 3.52–3.31 (series of m, 4H), 3.25–2.95 (series of m, 8H), 2.05–2.03 (m, 2H), 1.34 (t, $J = 7.0$ Hz, 6H); HRMS calcd for $C_{28}H_{37}F_3N_3O$ (M+H$^+$): 488.2889, found 488.2882.

3.5. Representative experimental protocol for the preparation of compounds 23b, 23e, 23i, and 23j as outlined in Scheme 3 (the specific example below relates to 23e, X = 4-Cl)

Methyl chloroacetate (2.49 mL, 28.3 mmol) is added to a solution of 4-chlorophenethyl amine (4.55 g 29.2 mmol) in diisopropylethylamine (15 mL) and acetonitrile (5 mL) at 0 °C (internal temperature). After stirring at 0 °C for 1 h and the formation of a white precipitate, the resulting suspension is allowed to stir at room temperature for 15 min. Ether (100 mL) and water (50 mL) are added and stirring continued for 5 min. The reaction mixture is poured into a separatory funnel, the layers separated, and the aqueous layer extracted with ether (40 mL). The combined organics are washed with brine and concentrated under reduced pressure. A 100-mg cut of the resulting material is purified by preparatory HPLC of the purpose of characterization.

3.5.1. Methyl 2-(4-chlorophenethylamino)acetate (22e). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23–7.10 (m, 2H), 6.98 (t, $J = 8.6$ Hz, 2H), 3.85 (s, 2H), 3.75 (s, 3H), 3.32–3.20 (m, 2H), 3.10–3.04 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 162.0 (d, $J = 245$ Hz), 131.7 (d, $J = 2$ Hz), 130.2 (d, $J = 8$ Hz, 2 C), 115.8 (d, $J = 22$ Hz, 2 C), 53.0, 49.1, 47.3, 31.8. ^{19}F NMR (292 MHz, $CDCl_3$) 47.5. HRMS calcd for $C_{11}H_{15}NO_2F$, 212.1087; found 212.1081. LRMS: 212.12 (M+H).

The crude product is redissolved in methanol (200 mL) and acetic acid (15 mL). Sodium triacetoxyborohydride (10 g, 47 mmol) is added and the reaction flask placed in a water bath at room temperature (water jacket). Aqueous (50%) chloroacetaldehyde (10 mL, excess) is added over 5 min while keeping the reaction temperature below 40 °C. The reaction mixture is allowed to stir for 30 min and saturated aqueous $NaHCO_3$ (120 mL) is carefully added. After stirring for 15 min, the reaction mixture is extracted with ether (3× 100 mL). The combined organics are washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue is chromatographed in silica gel using 20% ether/hexanes as eluent to yield 4.25 g (56% overall) of the desired product as a clear oil.

3.5.2. Methyl 2-[(4-chlorophenethyl)(2-chloroethyl)amino]acetate (23e). Overall yield: 56%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, $J = 8.4$ Hz, 2H), 7.14 (d, $J = 8.4$ Hz, 2H), 3.72 (s, 3H), 3.53–3.49 (series of m, 4H), 3.06 (t, $J = 7.0$ Hz, 2H), 2.97–2.92 (m, 2H), 2.75–2.72 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9,

138.5, 130.6 (2C) 128.7 (2C), 56.5, 56.4, 55.3, 51.7, 42.4, 34.4. HRMS calcd for $C_{13}H_{18}NO_2Cl_2$, 290.0710; found 290.0715. LRMS: 290.14 (M+H), 292.15 294.16.

3.5.3. 2-[(4-Fluorophenethyl)(2-chloroethyl)amino]acetate (23b). Yield: 41% overall yield, faint yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (dd, J = 8.6, 5.5 Hz, 2H), 6.95 (t, J = 8.6 Hz, 2H), 3.69 (s, 3H), 3.55–3.39 (series of m, 4H), 3.04 (t, J = 7.0 Hz, 2H), 2.95 (m, 2H), 2.74–2.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 161.6 (d, J = 244 Hz), 135.7, 130.4 (d, J = 8 Hz, 2C), 115.4 (d, J = 22 Hz, 2 C), 56.6, 56.4, 55.3, 51.8, 45.2, 42.3. ^{19}F NMR (292 MHz, $CDCl_3$) 45.6. HRMS calcd for $C_{13}H_{18}ClFNO_2$, 274.1010; found 290.1010. LRMS: 274.18 (M+H), 276.17 (MH+2).

3.5.4. 2-[(4-Trifluoromethylphenethyl)-(2-chloroethyl)-amino]acetate (23i). Overall yield: 30%, light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 3.67 (s, 3H), 3.59–3.37 (series of m, 4 H), 3.04 (t, J = 6.9 Hz, 2H), 2.99–2.91 (m, 2H), 2.87–2.78 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 143.9, 129.0 (3 C), 125.1, 125.0, 56.0, 55.7, 54.7, 51.3, 41.9, 34.4. ^{19}F NMR (292 MHz, $CDCl_3$) 100.4. HRMS calcd for $C_{14}H_{18}NOClF_3$, 324.0978; found 324.0989. LRMS: 324.23 (M+H), 326.24 (MH+2).

3.5.5. 2-[(3-Trifluoromethylphenethyl)(2-chloroethyl)amino]acetate (23j). Overall yield: 62%, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55–7.30 (m, 4H), 3.70 (s, 3H), 3.57–3.46 (series of m, 4H), 3.06 (t, J = 7.0 Hz, 2H), 3.00–2.91 (m, 2H), 2.89–2.80 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 140.7, 132.2, 128.7, 125.4 (d, J = 3 Hz) 123.0, 122.9, 56.1, 55.9, 54.9, 51.4, 42.1, 34.6. HRMS calcd for $C_{14}H_{18}NOClF_3$, 324.0972; found 324.0978. LRMS: 324.18 (M+H), 326.18 (MH+2).

3.6. Representative experimental protocol for the preparation of compounds 20b, 20e, 20i, and 20j as outlined in Scheme 3 (the specific example below relates to 20e, X = 4-Cl)

3.6.1. (*S*)-6-(4-(4-Chlorophenethyl)-2-oxopiperazin-1-yl)-5,6,7,8-tetrahydronaphthalene-2-carbonitrile (20e). A slurry-mixture containing methyl 2-[(4-chlorophenethyl)(2-chloroethyl)amino]acetate (**23e**) (5.78 g, 20.0 mmol), (*S*)-amino-5,6,7,8-tetrahydronaphthalene-2-carbonitrile hydrochloride (4.16 g, 20.0 mmol), sodium iodide (6 g, 40 mmol), diisopropylethylamine (8 mL), acetonitrile (4 mL), and dimethyl formamide (4 mL) were heated using microwave (Microwave Apparatus = Biotage-Personal Chemistry System; absorption = high, temperature = 130 °C, time = 30 min). The crude reaction mixture was transferred into a separatory funnel with the aid of ethyl acetate (100 mL). The reaction solution was washed with water (25 mL) and brine (2 × 25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed in silica gel using a mixture of diisopropylethylamine/methanol/ethyl acetate/chloroform (0.2:0.3:20:50) as eluent to yield 4.17 g (53%) of the desired product **20e** as a white solid.

3.6.2. (*S*)-6-(4-(4-Chlorophenethyl)-2-oxopiperazin-1-yl)-5,6,7,8-tetrahydronaphthalene-2-carbonitrile (20e). Yield: 53%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.38 (m, 2H), 7.29–7.26 (m, 2H), 7.17–7.26 (series of m, 3H), 4.91–4.83 (m, 1H), 3.97–3.30 (m, 2H), 2.29–2.27 (m, 2H), 2.99–2.92 (series of m, 4H), 2.81–2.71 (series of m, 4H), 2.68–2.63 (m, 2H), 2.02–1.87 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 140.8, 137.9, 136.7, 132.4, 132.0, 130.1, 129.9 (2 C), 129.2, 128.6 (2 C), 119.0, 109.9, 59.0, 57.6, 50.0, 48.6, 41.1, 32.7, 31.8, 28.9, 25.9. HRMS calcd for $C_{23}H_{25}N_3OCl$, 394.1686; found 394.1699. LRMS: 394.27 (M+H), 396.26 (M+H+2). $[\alpha]_D^{20}$ −52.0° (*c* 1.1, chloroform).

3.6.3. (*S*)-6-(4-(4-Fluorophenethyl)-2-oxopiperazin-1-yl)-5,6,7,8-tetrahydronaphthalene-2-carbonitrile (20b). Yield: 66%, pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.30 (m, 2H), 7.15 (dd, J = 8.3, 5.2 Hz, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.93 (t, J = 8.4 Hz, 2H), 4.77 (m, 1H), 3.95 (s, 2H), 3.66–3.60 (m, 2H), 3.55–3.50 (m, 2H), 3.36–3.31 (m, 2H), 3.08–3.03 (m, 2H), 2.89–2.80 (series of m, 4H), 1.98–1.80 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0 (d, J = 245 Hz), 160.7, 139.9, 132.3, 130.7 (d, J = 2 Hz), 130.1 (J = 8 Hz), 130.0, 129.3, 118.8, 115.9 (d, J = 22 Hz), 109.9, 57.9, 52.9, 49.9, 48.7, 37.8, 31.3, 29.4, 28.5, 25.5. LRMS: 378.3 (M + H).

3.6.4. (*S*)-6-(4-(4-Trifluoromethylphenethyl)-2-oxopiperazin-1-yl)-5,6,7,8-tetrahydronaphthalene-2-carbonitrile (20i). Yield: 54%, off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, J = 8.2 Hz, 2H), 7.39–7.33 (m, 4H), 7.15 (d, J = 8.2 Hz, 1H), 4.89–4.78 (m, 1H), 3.68 (s, 2H), 3.56 (t, J = 5.3 Hz, 2H), 3.27–3.22 (m, 2H), 3.15–3.05 (m, 4H), 2.99–2.85 (series of m, 4H), 2.03–1.86 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 140.7, 140.1, 136.4, 132.4, 130.1, 129.9, 129.4, 129.0, 125.9(d, J = 2 Hz), 118.9, 110.1, 58.0, 54.4, 49.5, 49.2, 38.9, 31.7, 31.2, 28.7, 25.8. ^{19}F NMR (292 MHz, $CDCl_3$) 100.3. HRMS calcd for $C_{24}H_{25}N_3OClF_3$, 428.1950; found 428.1952. LRMS: 428.33 (M+H).

3.6.5. (*S*)-6-(4-(3-(Trifluoromethyl)phenethyl)-2-oxopiperazin-1- yl)-5,6,7,8-tetrahydronaphthalene-2-carbonitrile (20j). Yield: 65%, off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51–7.44 (m, 2H), 7.42–7.33 (series of m, 4H), 7.14 (d, 8.5 Hz, 1H) 4.92–4.80 (m, 1H), 3.36–3.27 (series of m, 4H) 2.98–2.84 (series of m, 6H), 2.81–2.65 (series of m, 4H). 2.01–1.82 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 140.4 (d, J = 31 Hz), 136.8, 132.4, 132.0, 130.1, 129.3, 126.0, 123.2, 119.0, 109.9, 58.7, 57.7, 50.0, 48.6, 41.1, 33.2, 31.8, 28.9, 25.9. HRMS calcd for $C_{24}H_{25}N_3OF_3$, 428.1950; found 428.1946. LRMS: 428.2 (M+H). $[\alpha]_D^{20}$ −33.5° (*c* 1.1, chloroform).

3.7. Representative experimental protocol for the preparation of compounds 21b, 21e, 21i, 21j as alternatively outlined in Scheme 3 (the specific example below relates to 20b, X = 4-F)

A heterogeneous mixture of **20b** (5.55 g, 14.7 mmol), Raney nickel (5 g) in a solvent mixture of ammonium hydroxide (10 mL), DMF (10 mL), and ethanol (180 mL) was stirred overnight at room temperature

and under H_2-atmosphere. The crude reaction mixture was filtered through a pad of Celite with the aid of ethanol. The filtrates were concentrated under reduced pressure and the residue dissolved in 5%AcOH/methanol (100 mL). The resulting solution was treated with sodium cyanoborohydride (3 g, excess) and acetaldehyde (3 mL, excess). After stirring for 15 min, the solvents were removed under reduced pressure and the resulting material partitioned between ethyl acetate (150 mL) and 1 N aqueous sodium hydroxide (50 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organics were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) using diisopropylethylamine/methanol/ethyl acetate (0.5:10:89.5) as eluent to yield 6.9 g (93%) of product as a light yellow gel.

Spectral data for **21b** are presented previously within this experimental section (see above).

Employing the same protocol produced compounds **21e**, **21i**, and **21j** in 89, 92, and 87 percent yield, respectively. Spectral data for **21e**, **21i**, and **21j** are presented previously within this experimental section (see above).

3.8. Biology

3.8.1. 4-day mDIO study-methods. Male C57Bl/6J (Jackson Laboratory, Bar Harbor Maine) mice were obtained at 6 weeks of age and provided a high fat diet (High fat, 45% kcal, Research Diets, Inc.) for a 16 week period. The animals were singly housed in cages on a reversed light cycle (11:00 a.m. lights off; 11:00 p.m. lights on). This research was conducted in accordance with P&G's policy on research involving animals with strict oversight for care and welfare, and approved by the Animal Care and Use Committee.

Mice were randomized into groups ($n = 8$) based on body weight as well as fat composition, determined using magnetic resonance relaxometry (MRR) (Echo-MRI, Houston, TX). The obese mice were dosed with compound X or vehicle (2% Tween 80/saline) via oral gavage once daily for a period of 4 days. On day 5, mice ($n = 8$) from each dosing group were given a single dose and blood samples were then collected approximately 2 h after dosing from four of the mice to determine serum concentrations. Blood samples from the remaining four mice were collected approximately 5 h after dosing. The blood was put into serum separator microtainer tubes (Becton–Dickinson, Franklin Lakes, NJ) and the tubes were centrifuged after sitting at least 60 min. The serum was poured off into a tube and frozen until prepared for analysis. Food intake and body weights were measured daily and body composition was measured at the end of the study. Statistical analysis of measured parameters was performed to determine significance of the compound's effect using Student's *t*-test.

3.8.2. 10-day mDIO study-methods. Male C57Bl/6J (Jackson Laboratory, Bar Harbor Maine) mice were obtained at 6 weeks of age and provided a high fat diet (High fat, 45% Kcal, Research Diets, Inc.) for a 16-week period. The animals were singly housed in cages on a reversed light cycle (11:00 a.m. lights off; 11:00 p.m. lights on). This research was conducted in accordance with Procter & Gamble's policy on research involving animals with strict oversight for care and welfare, and approved by the Animal Care and Use Committee.

Mice were randomized into groups ($n = 8$) based on body weight as well as fat composition, determined using magnetic resonance relaxometry (MRR) (Echo-MRI, Houston, TX). The obese mice were dosed with compound × or vehicle (2% Tween 80/saline) via oral gavage once daily for a period of 10 days. On day 11, four mice from each dosing group were given a single dose and blood samples were then collected approximately 2 h after dosing to determine serum concentrations. Blood samples from the remaining four mice were collected approximately 24 h after dosing from the previous day. The blood was put into serum separator microtainer tubes (Becton–Dickinson, Franklin Lakes, NJ) and the tubes were centrifuged after sitting at least 60 min. The serum was poured off into a tube and frozen until prepared for analysis. Food intake and body weights were measured daily and body composition was measured at the end of the study. Statistical analysis of measured parameters was performed to determine significance of the compound's effect using Student's *t*-test.

3.9. QTc prolongation experiment-methods

3.9.1. Approvals. The animal components of this study were approved by the Institutional Animal Care and Use Committee and conformed to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institute of Health (NIH Publication No. 85–23, revised 1996).

3.9.2. Experimental protocol. Experiments using male ($n = 4$) mongrel dogs (11 – 13 kg) were conducted to assess the effects of **21b** on ECG parameters in anesthetized dogs. The animals were anesthetized initially with intravenous administration of sodium pentothal (25 mg/kg). After intubation with a cuffed endotracheal tube, anesthesia was maintained with 1–3% isoflurane vaporized with oxygen. A catheter for measurement of arterial blood pressure was inserted through the femoral artery and positioned in the abdominal aorta. Surface lead II ECG was obtained from limb leads. Each dog was dosed 0, 1, and 10 mg/kg, intravenously in a rising dose design. Each dose was infused over 15 min with a 30-min period between doses. ECGs were monitored continuously throughout the study and data were analyzed during the last minute of each infusion. Blood samples were also taken at the end of the infusion to assess plasma concentrations of **21b**. Acquisition and analysis of ECG data was conducted using a Notocord data acquisition system (Croissy, France). QTc was calculated using the cube root method of Fridericia (QTcF) (Spence et al., 1998).[19b]

3.9.3. Statistical analysis. Mean values were calculated for each dose and statistical comparisons were made between treatment groups using parametric statistics (repeated measures analysis of variance). Statistical significance was considered at $p < 0.05$. Data are reported as means ± SD.

Acknowledgment

We acknowledge Dr. Paul Correa for making PROTENG available to us during the course of this work.

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