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Aminomethyl tetrahydronaphthalene ketopiperazine MCH-R1 antagonists—Increasing selectivity over hERG

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Abstract—A direct correlation between hERG binding and QTc prolongation was established for a series of aminomethyl tetrahydronaphthalene ketopiperazine MCH-R1 antagonists. Compounds within this class with greater selectivity over hERG were developed. Compound **4h** proved to have the best profile, with MCH-R1 $K_i = 16$ nm and hERG $IC_{50} = 25\ \mu M$.

The G-protein-coupled receptor melanin-concentrating hormone receptor 1 (MCH-R1) has received significant attention in recent years as a potential target for an effective anti-obesity therapy.[1] It has been suggested that CNS-located MCH-R1 is involved in biological processes related to mammalian feeding behaviors and energy expenditure.[2] Identification of a small molecule MCH-R1 antagonist is being heavily pursued by many laboratories trying to find an effective drug-molecule for the treatment of obesity.[3]

We recently disclosed aminomethyl tetrahydronaphthalene ketopiperazine **1** as a potent MCH-R1 antagonist.[4] Compound **1** dosed at 20 mg/kg po BID promoted 4.5 ± 0.9% body weight reduction in a 4 day mouse diet induced obesity (mDIO) weight loss model. In addition, compound **1** dosed at 20 mg/kg po QD promoted 7.5 ± 1.0% decrease in body weight in a 10 day mDIO study.[4] Magnetic resonance relaxometry (MRR)[5] body weight composition analysis of the mice in both studies revealed a reduction in fat mass with negligible change in lean mass. Despite the attractive in vivo results, further development of **1** as an MCH-R1 antagonist was compromised by its hERG channel activity ($IC_{50} = 8.1\ \mu M$).[6] Additionally, compound **1** induced a dose dependent QTc interval increase in anesthetized dogs[7] at serum concentrations comparable to those obtained at mDIO efficacious doses. QTc prolongation is associated with potentially lethal arrhythmias known as torsades de *pointes* (TdP), which has led to removal of several marketed drugs.[8]

These observations required SAR studies to identify aminomethyl tetrahydronaphthalene ketopiperazine compounds analogous to **1** but having lower hERG blockage activity. These compounds, in combination with additional QTc interval studies, could potentially allow us to establish the relationship between hERG in vitro activity and the observed QTc interval prolongation for this class of MCH-R1 antagonists.

Review of recent literature[9] led us to postulate that **1** may interact with hERG in the following fashion (Fig. 1). In this hypothesis, either the benzylic or the ketopiperazine tertiary amine may participate in a cation-π interaction with the Tyr-652 residue of the hERG channel. In addition, the tetrahydronaphthalene and 4-fluorophenyl moieties may interact with hydrophobic

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Keywords: Melanin-concentrating hormone; MCH-R1 antagonists; Obesity; hERG; QTc prolongation; Aminomethyl tetrahydronaphthalene ketopiperazines.

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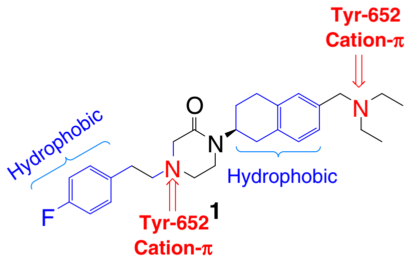
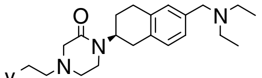


Figure 1. Postulated interactions between **1** and hERG.

residues of the hERG channel such as Phe-656. We chose to keep the aminomethyl tetrahydronaphthalene ketopiperazine core intact and focused efforts to discover compounds with greater selectivity over hERG through substitution at the 4-fluorophenyl and benzylic tertiary amine sites.

Substitutions at the 4-fluorophenyl site of **1** are summarized in Table 1.[10] The synthesis of **2a–d** was previously outlined.[4] The substitution of fluorine with chlorine (**2a**) resulted in a more potent hERG and MCH-R1 binder. 3-Trifluoromethylphenyl analog **2b** had decreased MCH-R1 activity and increased hERG potency compared to **1**. Substitution with cyclohexyl (**2c**) did not decrease hERG activity, suggesting that hydrophobic volume at this position, and not aromaticity, is required for high affinity binding with hERG. This result is in agreement with postulated interactions between the Phe-656 residue of hERG and compounds that block it.[9a] Of this series, thiophene **2d** was the least active hERG blocker with MCH-R1 activity <100 nM. Unfortunately, **2d** exhibited no weight loss in our 4 day mDIO model. We hypothesized that compound **2d** was not active in vivo likely due to insufficient brain exposure.

Table 1. hERG binding of phenyl ring analogs **2a–d**



2a-d

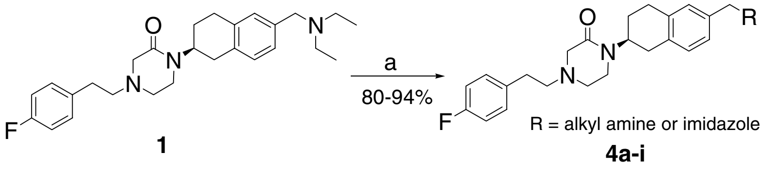
Compound	X	hERG IC$_{50}$ (μM)	MCH-R1 binding K_i (nM)[10]
1	4-Fluorophenyl	8.1	15
2a	4-Chlorophenyl	3.3	3.3
2b	3-Trifluoromethylphenyl	1.7	93
2c	Cyclohexyl	3.3	32
2d	2-Thiophene	13.2	47

The synthesis of benzylic tertiary amine analogs **4** is outlined in Scheme 1. A variant of the von Braun reaction[11] was utilized to convert **1** into a benzyl chloride, which was reacted with various primary or secondary amines to yield **4a–i**. This route allowed for efficient recycling of **1**, which had been scaled up previously for in vivo studies.

The benzylic tertiary amine analogs are summarized in Table 2. All compounds except for **4i** retained MCH-R1 antagonist activity ($K_i \leqslant 100$ nM), suggesting a tolerance for broad range of substitution at the benzylic tertiary amine position while keeping MCH-R1 activity in comparable range with that of **1**. Analogs **4a–4c** were synthesized to determine the relationship between amine basicity and hERG activity. Imidazole analog **4b** was a more potent hERG blocker despite being less basic than **1**. The increased activity of **4b** may be due to the fact that the imidazole ring may participate in π–π as well as cation-π interactions with the hERG ion channel. Fluorine substituted compounds **4a** and **4c** had increased hERG activity despite lower predicted basicity than **1**. As with the earlier phenyl substitutions, introduction of the liphophilic trifluoromethyl group proximal to the benzylic amine resulted in more potent hERG binding. We suspect our attempts to modulate hERG activity through basicity (compounds **4a–c**) were unsuccessful because decreased basicity of **4a–c** was achieved through functionalities that may have increased affinity for hERG (i.e., imidazole, trifluoromethyl).

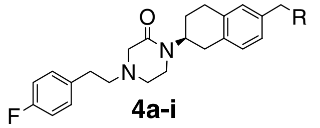
Compound **4d** is one of a series of compounds synthesized to determine if hERG binding could be affected through sterics. Unfortunately, incorporation of a sterically hindered tertiary amine such as 2,6-dimethylpiperidine did not decrease hERG activity. Recent work published by Bilodeau[12] in which selectivity over hERG was enhanced by incorporation of polar functional groups proximal to a tertiary amine led us to synthesize **4e–i**. This strategy was also successful for our series of compounds. Analogs incorporating polar functional groups such as sulfonamide (**4f**), sulfone (**4g**), and amide (**4h–i**) were the least active hERG binders of the compounds tested. *N*-Acetyl piperazine derivative **4h** was the most selective of the series, with a threefold decrease in hERG activity with comparable MCH-R1 activity to **1**.

Due to their increased selectivity over hERG and MCH-R1 activity <100 nM, **4f–h** were selected for in vivo evaluation. Despite comparable MCH-R1 binding activity to **1**, compounds **4f–h** did not promote significant weight

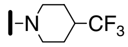
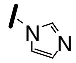
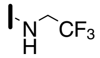
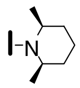
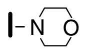
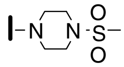
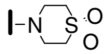
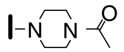
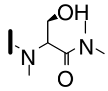


Scheme 1. Reagents and conditions: (a) ethylchloroformate, *N*,*N*-diisopropylethylamine, CH_3CN, rt, 5 min; secondary or primary amine, CH_3CN, MW 100 W, 120 °C, 5 min.

Table 2. hERG binding for benzylic tertiary amine substitutions



4a-i

Compound	R	hERG IC_{50} (μM)	MCH-R1 binding K_i (nM)[10]
1	Diethylamino	8	15
4a		2	8.7
4b		4	52
4c		% inh. at 10 μM > 50	100
4d		% inh. at 10 μM > 50	62
4e		11	15
4f		13	30
4g		24	94
4h		25	16
4i		25	270

loss in our 4 day mDIO model (Table 3). Total serum levels 2 h post-dosing (20 mg/kg) of **4f–h** were greater than levels achieved for **1**. However, these high levels of **4f–h** in serum did not correspond to similar or greater in vivo efficacy than **1**. We postulate that the disconnection between in vitro and in vivo activity of **4f–h** may be due to poor blood–brain barrier penetration, a requirement since the MCH-R1 receptor is located in the CNS. Caco-2[13] and brain/serum concentration measurements support this hypothesis. Compound **1** was predicted to transport passively across the blood–brain barrier (Caco-2) and in fact promoted statistically significant weight loss from vehicle in our 4 day mDIO model. Compounds **4g–h** were predicted efflux substrates and did not show in vivo activity. In addition, it is worth noting that in vivo inactive **4h** had a [brain]/[serum] ratio of 0.3, which is 10-fold less than active **1**. These data suggests that the incorporation of polar functionality into the tertiary amine moieties of **4f–h** that resulted in decreased hERG activity may prevent **4f–h** from crossing the blood–brain barrier.

In an attempt to determine the correlation between decreased hERG binding and QTc interval for this series of compounds, we conducted a QTc prolongation study (Fig. 2) with **4h**, the compound with the greatest selectivity over hERG. As with **1**, compound **4h** was dosed at 1, 10, and 30 mg/kg to anesthetized dogs and at the end of 15 min infusion, the change in the QTc interval was measured. Compound **4h** with a hERG $IC_{50} = 25$ μM did not promote a statistically significant change in the QTc interval at 10 mg/kg, whereas **1** with a hERG $IC_{50} = 8$ μM did. The threefold decrease in hERG binding between **4h** and **1** translated into having no effect on the QTc interval at the 10 mg/kg dose for compound **4h**. These limited data suggests that there is a correlation between hERG binding and QTc interval prolongation for this series of MCH-R1 antagonists. Unfortunately, at the 30 mg/kg dose (total serum level concentrations of **4h** comparable to those obtained with mDIO efficacious doses of **1** at 20 mg/kg po QD) **4h** promoted statistically significant changes in the QTc interval. For this series of compounds at serum levels efficacious for weight loss to have no effect on the QTc interval, we predict that hERG IC_{50}'s much greater than 25 μM (**4h**) must be achieved. Alternatively, it would be suggestive to find compounds within this class having in vivo efficacy at much lower serum levels to ensure sufficient separation between hERG IC_{50} and serum concentrations.

In summary, MCH antagonists with improved selectivity over hERG were achieved by incorporating polar functionality proximal to the benzylic tertiary amine moiety of an aminomethyl tetrahydronaphthalene ketopiperazine scaffold. However, these structural changes resulted in compounds devoid of in vivo activity despite high MCH-R1 binding affinity, due possibly to poor CNS penetration. A direct correlation between hERG binding and QTc prolongation was established for this series of compounds. A threefold decrease in hERG

Table 3. In vivo results for select compounds

Compound	4 day mDIO weight loss[a]	Caco-2 A-B/B-A	Caco-2 prediction	[Serum][b] (μM)	[Brain]/[serum][c]
1	4%	9.6/15.7	Passive	2	3
4f	3%	7.4/9.4	Passive	9	—
4g	<2%	4.6/14.9	Efflux	16	—
4h	<2%	2.9/9.6	Efflux	4	0.3

[a] Dosed 20 mg/kg po BID. Percent difference from vehicle.

[b] Total serum in mouse 2 h post 20 mg/kg dose.

[c] Determined 2 h post 20 mg/kg dose.

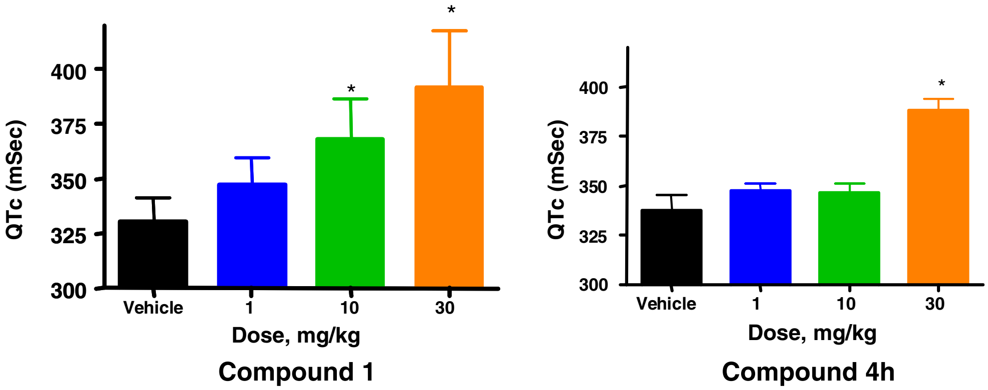


Figure 2. QTc prolongation study in anesthetized dogs, end of 15 min infusion for compounds **1** and **4h**. *Indicates statistical significance ($p < 0.05$) versus vehicle.

binding resulted in no statistical prolongation of the QTc interval at a 10 mg/kg dose. However, this threefold difference did not prevent prolongation at the efficacious dose (30 mg/kg) in mice. A further decrease in hERG potency or in vivo efficacy at lower serum concentrations would be required for this class of compounds to avoid QTc prolongation.

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