Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 814–818
Bioorganic & Medicinal Chemistry Letters

Aminomethyl tetrahydronaphthalene biphenyl carboxamide MCH-R1 antagonists—Increasing selectivity over hERG

Kenneth M. Meyers,[†] Nicholas Kim, José L. Méndez-Andino,[*] X. Eric Hu,[‡] Rashid N. Mumin, Sean R. Klopfenstein, John A. Wos, Maria C. Mitchell, Jennifer L. Paris, David C. Ackley, Jerry K. Holbert, Scott W. Mittelstadt and Ofer Reizes[§]

Procter & Gamble Pharmaceuticals, 8700 Mason-Montgomery Road, Mason, OH 45039, USA

Received 15 September 2006; revised 16 October 2006; accepted 23 October 2006
Available online 25 October 2006

Abstract—Aminomethyl tetrahydronaphthalene biphenyl carboxamide MCH-R1 antagonists with greater selectivity over hERG were identified. SAR studies addressing two distinct alternatives for structural modifications leading to improve hERG selectivity are described.

Estimates indicate that more than 30% of the U.S. adult population is obese, and that obesity-related health care costs are in the range of $100 billion per year.[1,2] The G-protein-coupled receptor MCH-R1 has received significant attention in recent years as a potential target for effective anti-obesity therapy.[3] It has been suggested that CNS-located MCH-R1 is involved in biological processes related to mammalian feeding behaviors and energy expenditure.[4] Identification of a small molecule MCH-R1 antagonist is being heavily pursued by many laboratories trying to find drug-molecule that may be effective for the treatment of obesity.[5]

We recently disclosed aminomethyl tetrahydronaphthalene biphenyl carboxamide **1** as a potent MCH-R1 antagonist.[6] Compound **1** dosed at 20 mg/kg PO BID promoted 5.7% vehicle corrected body weight reduction in a 4 day mouse diet induced obesity (mDIO) weight loss model.[4b,c] In addition, compound **1** exhibited excellent weight loss in our long-term mouse model. In a 28 day mDIO study, **1** dosed at 20 mg/kg PO QD promoted 7.8% decrease in body weight compared to vehicle. Magnetic Resonance Relaxometry (MRR)[7] 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 a MCH-R1 antagonist for the treatment of obesity was compromised by its potent hERG ion channel activity (IC_{50} = 1.8 μM).[8] hERG blockers may induce QTc interval prolongation, which is associated with potentially lethal arrhythmias known as torsades

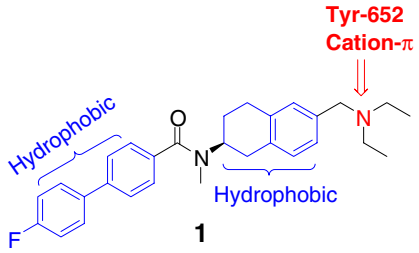


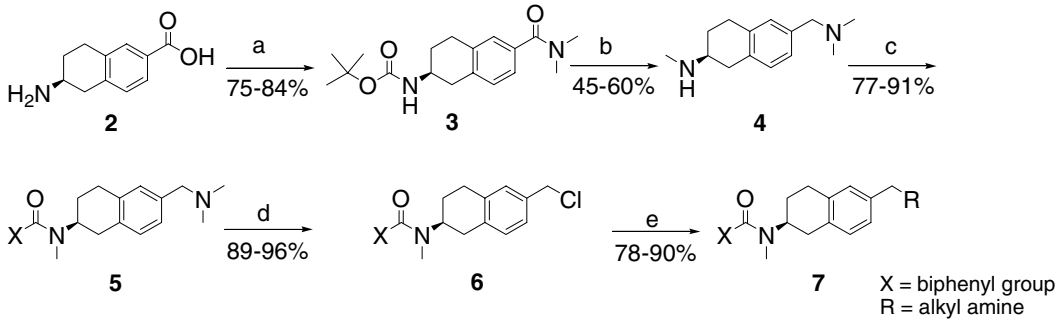
Figure 1. Postulated interactions between **1** and hERG.

Keywords: Melanin-concentrating hormone; MCH-R1 antagonists; Obesity; hERG; Aminomethyl tetrahydronaphthalene biphenyl carboxamide.
* Corresponding author. Tel.: +1 513 622 0304; fax: +1 513 622 1433; e-mail: mendezandino.jl@pg.com
† Present address: Boehringer Ingelheim Pharmaceuticals, 900 Ridgebury Road, Ridgefield, CT 06877, USA.
‡ Present address: Genome Research Institute, University of Cincinnati, 2180 E. Galbraith Road, Cincinnati, OH 45237, USA.
§ Present address: Lerner Research Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue-NC10, Cleveland, OH 44195, USA.

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.10.053

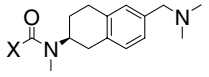
de *points* (TdP). hERG associated TdP has led to the removal of several drugs from the market.[9] We desired aminomethyl tetrahydronaphthalene biphenyl carboxamide compounds analogous to **1** but having lower hERG inhibition activity.

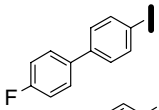
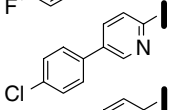
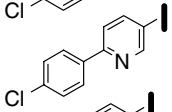
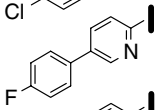
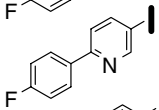
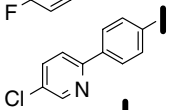
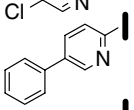
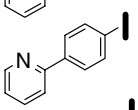
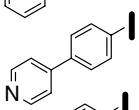
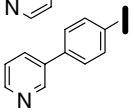
Review of recent literature led us to postulate that **1** may interact with hERG in the following fashion (Fig. 1).[10] The benzylic tertiary amine may participate in a cation-π interaction with the Tyr-652 residue of the hERG channel. In addition, the lipophilic tetrahydronaphthalene and biphenyl moieties may interact with hydrophobic residues of the hERG channel such as Phe-656. We chose to keep the aminomethyl tetrahydronaphthalene biphenyl carboxamide core intact and focused efforts to discover compounds with greater selectivity over



Scheme 1. Reagents and conditions: (a) i—Boc-anhydride, NaOH, THF, H_2O, rt; ii—dimethylamine, EDCI, HOBt, NMM, DMF, rt; (b) LAH, THF, 0 °C; (c) biphenyl carboxylic acid, EDCI, HOBt, NMM, DMF, rt; (d) ethylchloroformate, *N*,*N*-diisopropylethylamine, CH_3CN, rt; (e) secondary alkyl amine, CH_3CN, MW 100 W, 120 °C, 5 min.

Table 1. Biphenyl substitutions



Compound	X	hERG (μM)	MCH-R1 K_i (nM)	$5HT_{2C}$ IC_{50} (μM)
1		IC_{50} = 1.8	7.4	55
5a		IC_{50} = 2.6	11	56
5b		IC_{50} = 5.1	12	9.5
5c		IC_{50} = 5.2	20	17
5d		IC_{50} = 10	184	16
5e		IC_{50} = 14	18	27
5f		IC_{50} = 20	118	22
5g		IC_{50} = 30	140	>100
5h		% inh. at 10 μM < 50	2480	>100
5i		% inh. at 10 μM < 50	890	>100

hERG through substitution at the benzylic tertiary amine and biphenyl sites.

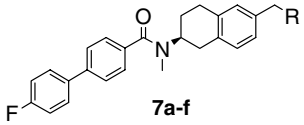
The synthesis of **1** and its tertiary amine and biphenyl analogs is outlined in Scheme 1. Commercially available amino acid **2** was protected as a Boc carbamate and coupled with dimethylamine to yield **3**. Reduction of both the carbamate and amide with LAH yielded diamine **4**. Reaction with various biphenyl carboxylic acids (either commercial or prepared via Suzuki reaction) and EDCI/HOBt yielded **5**. The dimethylamino group was reacted with ethyl chloroformate[11] to yield benzylic chloride **6**. Displacement of the chloride with secondary amines yielded compounds **7**.

In vitro results for substitutions at the biphenyl position (**5a**–**b**) are summarized in Table 1. We desired selectivity over $5HT_{2C}$ due to its suggested role in the modulation of feeding behavior that could interfere with effects related to inhibition of MCH-R1.[12] We sought to decrease the lipophilicity of **1** and potentially its hERG binding affinity by substituting either of the aromatic rings of the biphenyl moiety with a pyridine ring. Introduction of nitrogen into the inner aromatic ring decreased hERG binding compared to **1**. The position of the nitrogen in the inner aromatic ring affected hERG activity; **5b** and **5d** were less active than their corresponding isomers **5a** and **5c**.

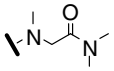
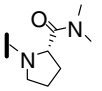
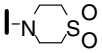
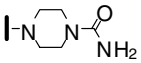
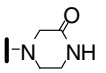
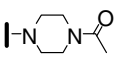
The greatest effects on decreasing hERG binding were achieved through terminal aromatic ring substitutions. Halogen substitution of the outer aromatic ring effected hERG activity (4-chloro (**5a**) > 4-flouro (**5c**) > unsubstituted (**5f**)). Introduction of nitrogen in the terminal aromatic ring decreased hERG activity considerably (**5g**–**i**). These results suggest that interactions between the terminal aromatic ring and hydrophobic residues of the hERG ion channel are critical for high affinity binding. A general trend for **5g**–**i** was structural changes that resulted in decreased hERG binding had a negative effect on MCH-R1 activity[13] but resulted in selectivity over $5HT_{2c}$.[14]

We also incorporated polar functionality proximal to the tertiary amine, a technique utilized previously in the literature to reduce hERG binding.[15] Results are summarized in Table 2. Unfortunately, substitution at the tertiary amine did not have as dramatic an effect as biphenyl substitutions. Introduction of an amide moiety beta to the benzylic tertiary amine had no effect on hERG for glycine derivative **7a**; however, this substitution resulted in decreased hERG binding for both proline **7b** and ketopiperazine **7e** derivatives. The restricted rotation of **7b** and **7e** may present the amide moiety in such a fashion that prevents high affinity binding with hERG. Urea and acetyl piperazines **7d** and **7f** also had decreased hERG activity compared to **1**. Except for sulfone **7c**, moderate MCH-R1 activity was retained within this series of compounds, suggesting a tolerance by the MCH-R1 receptor for polar functionality proximal to the benzylic tertiary amine, a key interaction site. Compounds **7a**–**f** did not bind to $5HT_{2C}$, suggesting that incorporation of polar functionality proximal to the benzylic tertiary amine helps to decrease $5HT_{2C}$ activity. *N*-Acetyl piperazine was identified as the best tertiary amine group having decreased hERG activity with retained MCH-R1 activity.

Table 2. Benzylic tertiary amine substitutions

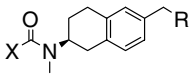


7a-f

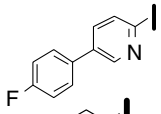
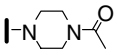
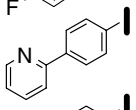
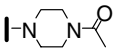
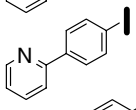
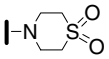
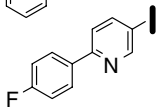
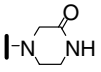
Compound	R	hERG (μM)	MCH-R1 K_i (nM)	$5HT_{2C}$ IC_{50} (μM)
7a		IC_{50} = 1.8	24	>100
7b		IC_{50} = 5.0	146	>100
7c		IC_{25}[a] = 2.5	755	>100
7d		IC_{50} = 6.7	129	>100
7e		IC_{25}[a] = 7.6	145	>100
7f		% inh. at 10 μM < 50	103	>100

[a] Activity measured as IC_{25}. Compound insolubility prevented IC_{50} determination.

Table 3. Combined benzylic tertiary amine and biphenyl substitutions



7g-j

Compound	X	R	hERG IC_{25}[a] (μM)	MCH-R1 K_i (nM)	$5HT_{2C}$ IC_{50} (μM)
7g			14	302	>100
7h			20	727	>100
7i			30	NA	>100
7j			34	3465	>100

[a] Activity measured as IC_{25}. Compound insolubility prevented IC_{50} determination.

Our next series of compounds combined SAR learnings from the biphenyl and benzylic tertiary amine substitutions (Table 3). We desired compounds with much lower hERG activity while retaining MCH-R1 activity. Compounds **7g–j** exhibited decreased hERG activity compared to **1**. Unfortunately, the combined changes of introducing a nitrogen into the biphenyl and polar functionality proximal to the benzylic tertiary amine resulted in greatly reduced MCH-R1 activity. As predicted from the above SAR studies, **7g–j** did not exhibit $5HT_{2C}$ activity.

In summary, aminomethyl tetrahydronaphthalene biphenyl carboxamide MCH-R1 antagonists with greater selectivity over hERG were identified. A nitrogen-containing biphenyl moiety was necessary for decreasing hERG activity for this series of compounds. Also, *N*-acetyl piperazine was identified as an optimal tertiary amine group for hERG selectivity with retained MCH-R1 activity. By incorporating changes at both the biphenyl and tertiary amine moieties, decreases in hERG binding came at the expense of reduced MCH-R1 binding activity.

References and notes

1. *The Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity*: Office of the Surgeon General, US Department of Health and Human Services: Rockville, MD, 2001; www.surgeongeneral.gov/topics/obesity.
2. (a) Powell, D. R. *Obes. Rev.* **2006**, *7*, 89; (b) Heal, David J.; Rowley, Helen L.; Jackson, Helen C. *Prog. Obes. Res.* **2003**, *9*, 260.
3. (a) Dyke, H. J.; Ray, N. C. *Expert Opin. Ther. Patents* **2005**, *15*, 1303; (b) Carpenter, A. J.; Hertzog, D. L. *Expert Opin. Ther. Patents* **2002**, *12*, 1639.
4. (a) Kowalski, T. J.; McBriar, M. D. *Expert Opin. Investig. Drugs* **2004**, *13*, 1113; (b) Receveur, J. M.; Bjurling, E.; Ulven, T.; Little, P. B.; Norregaard, P. K.; Hogberg, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5075; (c) Shearman, L. P.; Camacho, R. E.; Sloan, S. D.; Zhou, D.; Bednarek, M. A.; Hreniuk, D. L.; Feighner, S. D.; Tan, C. P.; Howard, A. D.; Van der Ploeg, L. H.; MacIntyre, D. E.; Hickey, G. J.; Strack, A. M. *Eur. J. Pharmacol.* **2003**, *475*, 37.
5. (a) Kanuma, K.; Omodera, K.; Nishiguchi, M.; Funakoshi, T.; Chki, S.; Semple, G.; Tran, T.-A.; Kramer, B.; Hsu, D.; Casper, M.; Thomsen, B.; Sekiguchi, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3853; (b) Souers, A. J.; Gao, J.; Brune, M.; Bush, E.; Wodka, D.; Vasudevan, A.; Judd, A. S.; Mulhern, M.; Brodjian, S.; Dayton, B.; Shapiro, R.; Hernandez, L. E.; Marsh, K. C.; Sham, H. L.; Collins, C. A.; Kym, P. R. *J. Med. Chem.* **2005**, *48*, 1318; (c) Ulven, T.; Little, P. B.; Receveur, J.-M.; Frimurer, T. M.; Rist, Ø.; Nørregaard, P. K.; Högberg, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1070; (d) Palani, A.; Shapiro, S.; McBriar, M. D.; Clader, J. W.; Greenlee, W. J.; Spar, B.; Kowalski, T. J.; Farley, C.; Cook, J.; van Heek, M.; Weig, B.; O'Neill, K.; Graziano, M.; Hawes, B. E. *J. Med. Chem.* **2005**, *48*, 4746.
6. Hu, X. E. Patent WO 2005/033063.
7. (a) Nicholson, Janet R.; Kohler, Gotz; Schaerer, Florian; Senn, Claudia; Weyermann, Philipp; Hofbauer, Karl G. *J. Pharmacol. Exp. Ther.* **2006**, *317*, 771; (b) Tinsley, F. C.; Taicher, G. Z.; Heiman, M. L. *Obes. Res.* **2004**, *12*, 150.
8. Patch-clamp hERG IC_{50} determinations were carried out as described in Zhou, Z.; Gong, Q.; Ye, B.; Fan, Z.; Makielski, J. C.; Robertson, G. A.; January, C. T. *Biophys. J.* **1998**, *74*, 230.
9. Redfern, W. S.; Carlsson, L.; Davis, A. S.; Lynch, W. G.; MacKenzie, I.; Palethorpe, S.; Siegl, P. K. S.; Strang, I.; Sullivan, A. T.; Wallis, R.; Camm, A. J.; Hammond, T. G. *Cardiovasc. Res.* **2003**, *58*, 32.
10. (a) Fernandez, D.; Ghanta, A.; Kauffman, G. W.; Sanguinetti, M. C. *J. Biol. Chem.* **2004**, *279*, 10120; (b) Cavalli, A.; Poluzzi, E.; De Ponti, F.; Recanatini, M. *J. Med. Chem.* **2002**, *45*, 3844; (c) Sanguinetti, M. C.; Mitcheson, J. S. *Trends Pharmacol. Sci.* **2005**, *26*, 119.
11. Dai-Ho, G.; Mariano, P. S. *J. Org. Chem.* **1988**, *5*, 5113.
12. Szewczyk, J. R.; Sternbach, D. D. *Curr. Med. Chem.: Immunol. Endocr. Metab. Agents* **2005**, *5*, 73, and references therein.
13. MCH binding using a Flashplate radioligand binding assay was performed by Perkin-Elmer Biosignal (Toronto,

Ontario). Full competition curves were generated with compound concentration varied from 100 μM to 11 fM. Potency (K_i) and maximal efficacy were determined and used to define structure–activity relationship.

14. $5HT_{2C}$ assay was performed using a membrane preparation from cells that over-express the receptor. Membranes were purchased from Euroscreen (ES-318-M) and used according to established protocols. Briefly, membranes were incubated in a reaction mixture containing varying concentrations of the compound and [^{3}H] mesulergine (final concentration 0.33 nM; Amersham), a compound known to bind to the $5HT_{2C}$ receptor. The binding buffer contained 50 mM Tris–HCl, 0.1% ascorbic acid, 5 mM $CaCl_2$, and 10 μg/ml saponin. Nonspecific binding was assessed by incubating the membranes with [^{3}H] mesulergine and excess 10 μM mianserin (ICN). After incubating the mixture at room temperature for 60 min, bound mesulergine was separated from unbound mesulergine by filtration through glass fiber B filter (GF/B) plates (Millipore). Bound radioactive mesulergine was detected using a scintillation counter.
15. Bilodeau, M. T.; Balitza, A. E.; Koester, T. J.; Manley, P. J.; Rodman, L. D.; Buser-Doepner, C.; Coll, K. E.; Fernandes, C.; Gibbs, J. B.; Heimbrook, D. C.; Huckle, W. R.; Kohl, N.; Lynch, J. J.; Mao, X.; McFall, R. C.; McLoughlin, D.; Miller-Stein, C. M.; Rickert, K. W.; Sepp-Lorenzino, L.; Shipman, J. M.; Subramanian, R.; Thomas, K. A.; Wong, B. K.; Yu, S.; Hartman, G. D. *J. Med. Chem.* **2004**, *47*, 6363.