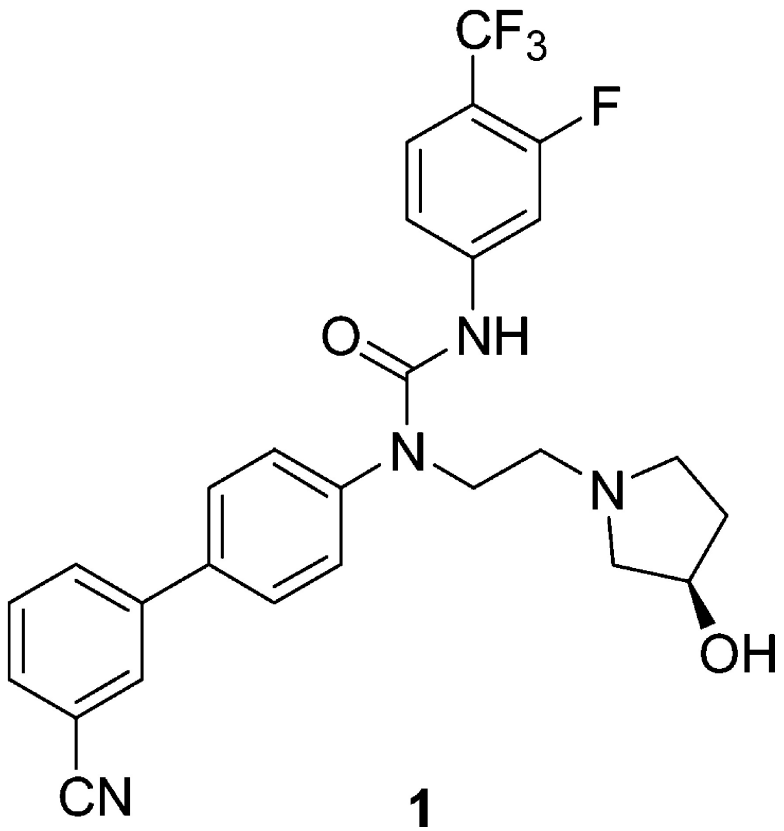
Journal of Medicinal Chemistry

Letter

Biaryl Ureas as Potent and Orally Efficacious Melanin Concentrating Hormone Receptor 1 Antagonists for the Treatment of Obesity

Anandan Palani, Sherry Shapiro, Mark D. McBriar, John W. Clader, William J. Greenlee, Brian Spar, Timothy J. Kowalski, Constance Farley, John Cook, Margaret van Heek, Blair Weig, Kim O'Neill, Michael Graziano, and Brian Hawes

J. Med. Chem., **2005**, 48 (15), 4746-4749• DOI: 10.1021/jm0503852 • Publication Date (Web): 24 June 2005



1

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information

Journal of Medicinal Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Letters

Biaryl Ureas as Potent and Orally Efficacious Melanin Concentrating Hormone Receptor 1 Antagonists for the Treatment of Obesity

Anandan Palani,* Sherry Shapiro, Mark D. McBriar, John W. Clader, William J. Greenlee, Brian Spar, Timothy J. Kowalski, Constance Farley, John Cook, Margaret van Heek, Blair Weig, Kim O'Neill, Michael Graziano, and Brian Hawes

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033

Received April 22, 2005

Abstract: Herein, we report a small molecule MCH-R1 antagonist which demonstrates oral efficacy in chronic rodent models. Substituted phenyl biaryl urea derivatives were synthesized and evaluated as MCH-R1 antagonists for the treatment of obesity. The structure−activity relationship studies in this series resulted in identification of urea **1** as a potent and selective MCH-R1 antagonist. Compound **1** exhibited oral efficacy in chronic (28 d) rodent models at 3−30 mpk showing significant reduction in food intake and weight gain relative to controls.

Melanin concentrating hormone (MCH) is a 19-amino acid cyclic peptide found in the brains of all vertebrate species which serves as an important mediator in the regulation of food intake and energy balance.[1,2] An icv injection of MCH in rats stimulates food intake,[3] and chronic administration leads to increased body weight.[4] Mice overexpressing the MCH gene are hyperphagic, mildly obese, hyperglycemic, and insulin resistant.[5] In contrast, mice that lack the gene encoding MCH are lean and hypophagic.[6] These observations suggest that MCH antagonists could be useful for the treatment of obesity. Several companies have published their efforts in identification of small molecule MCH receptor antagonists.[7−9] We report herein our initial SAR studies which resulted in discovery of biaryl ureas as potent and selective MCH-R1 antagonists as exemplified by compound **1** (Figure 1).

Our initial SAR optimization of the original screening hit from our compound collection resulted in identification of urea **2**.[10] This compound is a potent but nonselective MCH-R1 antagonist (K_i = 3.9 nM) which also antagonized the muscarinic M2 receptor (M2 K_i = 532 nM). Truncation of the carbon chain between the biaryl and urea functionalities provided compound **3** which exhibited an improvement in selectivity versus the M2 receptor while retaining MCH-R1 potency. Replacement of the urea functionality in compound **3** with an amide or sulfonamide resulted in complete loss of activity. Also, N-methylation of the urea resulted in a significant drop in affinity, confirming the importance of the urea N−H and its possible hydrogen bonding interaction with the receptor. In this paper, we describe SAR derived from varying substituents at the biaryl and urea and replacement of the piperidine ring with an amino ethyl side chain.

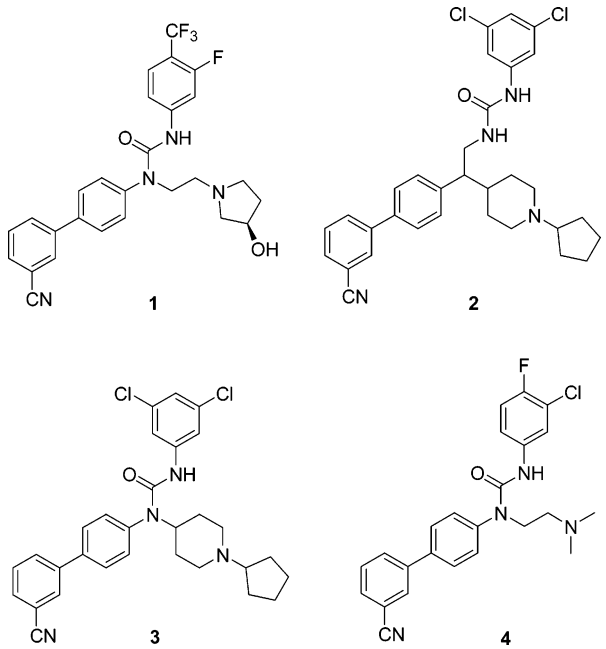
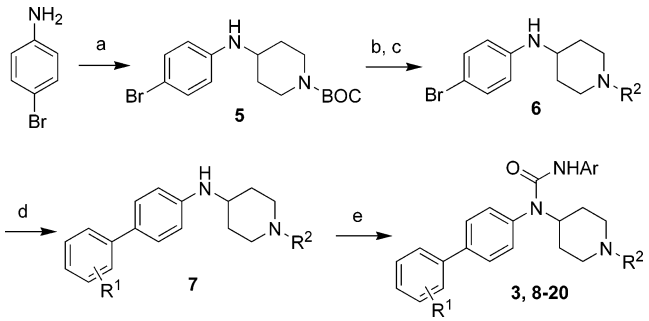


Figure 1. Biaryl urea containing MCH-R1 antagonists.

Scheme 1[a]



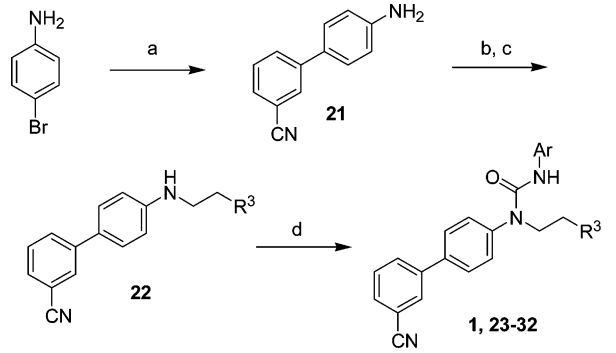
[a] Reagents and conditions: (a) 1-*tert*-butoxycarbonyl-4-piperidone, Ti(O-*i*-Pr)$_4$, 18 h, then $NaCNBH_3$, MeOH, 50%; (b) TFA, rt, CH_2Cl_2, 90%; (c) $(R^2)_2CO$ or R^2CHO, $NaBH(OAc)_3$, AcOH, CH_2Cl_2 50-90%; (d) R^1-aryl boronic acid, Na_2CO_3, $Pd(PPh_3)_4$, toluene: EtOH:H_2O or $PdCl_2(PPh_3)_2$, Na_2CO_3, DME:H_2O, 30-80%; (e) ArNCO, Et_3N, CH_2Cl_2, 75-100%.

The synthesis of biaryl anilino-piperidine ureas is outlined in Scheme 1. Reductive amination of 1-*tert*-butoxycarbonyl-4-piperidone with *p*-bromoaniline afforded compound **5**. Carbamate removal with trifluoroacetic acid and reductive amination of the resultant amine with the various aldehydes or ketones under standard conditions gave the desired product **6**. Palladium-catalyzed Suzuki coupling followed by treating **7** with aryl isocyanates afforded the desired biaryl urea products **3** and **8**−**20**. Alternatively, palladium-cata-

* To whom correspondence should be addressed. Tel: 908-740-7158. Fax: 908-740-7152. E-mail: anandan.palani@spcorp.com.

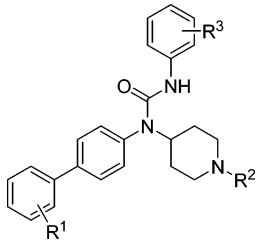
10.1021/jm0503852 CCC: $30.25
Published on Web 06/24/2005

Scheme 2[a]



[a] Reagents and conditions: (a) 3-cyanophenyl boronic acid, Na_2CO_3, $Pd(dppf)Cl_2$, DME:H_2O, 66% (b) $ClCH_2CHO$, $NaCNBH_3$, HCl, MeOH, 67%; (c) amine, K_2CO_3, NaI, CH_3CN, 99%; (d) ArNCO, Et_3N, CH_2Cl_2, 75-100%.

Table 1. MCH Receptor Binding for Biaryl Piperidine Urea Modifications



compd	R^1	R^2	R^3	h-MCH-R1 K_i (nM)[a]	h-MCH-R1 K_b (nM)[b]
3	*m*-CN	cyclopentyl	3,5-diCl	2.6 ± 0.4	5.5 ± 1.4
8	*m*-OCF_3	cyclopentyl	3,5-diCl	20 ± 1	
9	*m*-CF_3	cyclopentyl	3,5-diCl	197 ± 5	
10	*m*-Cl	cyclopentyl	3,5-diCl	12.5 ± 0.9	
11	*m*-CN	cyclopentyl	H	233 ± 10	
12	*m*-CN	cyclopentyl	3-Cl	5.8 ± 0.4	
13	*m*-CN	cyclopentyl	3-OCH_3	98 ± 2	
14	*m*-CN	cyclopentyl	4-OCH_3	139 ± 7	
15	*m*-CN	cyclopentyl	3-Cl,4-F	1.6 ± 0.1	1.3 ± 0.5
16	*m*-CN	cyclopentyl	4-F,3-CF_3	1.9 ± 0.5	
17	*m*-CN	Et	4-F,3-CF_3	7.1 ± 2.0	
18	*m*-CN	cyclopropyl-methyl	4-F,3-CF_3	4.0 ± 0.8	
19	*m*-CN	$EtSO_2^-$	4-F,3-CF_3	166 ± 14	
20	*m*-CN	*i*-propyl-(CO)-	4-F,3-CF_3	374 ± 7	

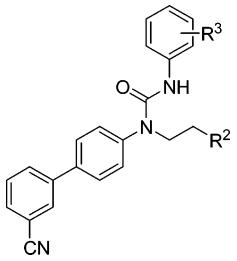
[a] Mean values ($n = 3$) ± SEM. h-MCH-R1 denotes human MCH-R1. [b] Inhibition of MCH-mediated Ca^{2+} influx into cells expressing hMCH-R1 via FLIPR assay. Affinity at h-MCH-R2 >3 μM for all compounds.

lyzed Suzuki coupling reactions could be carried out prior to carbamate removal and reductive amination.

The synthesis of biaryl anilino-aminoethyl ureas proceeded via Scheme 2. Suzuki coupling between *p*-bromoaniline and 3-cyanophenyl boronic acid afforded compound **21**. Reductive alkylation of the resulting aniline **21** with chloroacetaldehyde, followed by chloride displacement with various amines, provided compound **22**. The previously described isocyanate formation afforded the final products.

Table 1 shows the MCH-R1 activities of several representative compounds containing modifications at urea phenyl, biaryl, and alkyl groups attached to the piperidine ring. For our initial SAR we fixed the phenyl urea as 3,5-dichlorophenyl, and R^2 as cyclopentyl, and introduced varied substituents at the distal biaryl ring. We noted that for these series of compounds, meta substitution at the distal ring of the biaryl was preferred

Table 2. MCH Receptor Binding for Biaryl Aminoethyl Urea Analogues



no.	R^2	R^3	h-MCH-R1 K_i (nM)[a]	h-MCH-R1 K_b (nM)[b]	rat PK (10 mg/kg, po)[c] AUC_{0-6h} (h ng/mL)
23	NMe_2	3, 5-diCl	19 ± 8		
24	NMe_2	3-Cl,4-F	3.3 ± 0.2	3.1 ± 0.7	1950
25	NHMe	3-Cl,4-F	6.0 ± 3.5	6.2 ± 1.7	
26	NMe_2	3-F,4-CF_3	6.0 ± 0.4		4800
27	pyrrolidinyl	3-F,4-CF_3	5.6 ± 1.0		967
28	4-methyl-piperazinyl	3-F,4-CF_3	8.2 ± 0.6		542
29	(*S*)-3-OH-pyrrolidinyl	3-F,4-CF_3	7.3 ± 0.5		1449
1	(*R*)-3-OH-pyrrolidinyl	3-F,4-CF_3	8.9 ± 1.1	2.0 ± 0.2	5470
30	"	3,5-diCl	11 ± 3		1850
31	"	3-Cl,4-F	7.1 ± 1.5		1080
32	"	3-CF_3,4-F	1.8 ± 0.6	8.0 ± 0.1	2790

[a] Mean values ($n = 3$) ± SEM. h-MCH−R1 denotes human MCH-R1. [b] Inhibition of MCH-mediated Ca^{2+} influx into cells expressing hMCH-R1 via FLIPR assay. Affinity at h-MCH-R2 >3 μM for all compounds. [c] See ref 11 for procedure

over the ortho and para derivatives. Furthermore, the cyano group was found to be the best meta substituent, while potency was also observed for 3-chloro and 3-trifluromethoxy groups. With *m*-cyano determined as an optimal group at the distal aryl ring, we next studied the influence of phenyl urea substitution (R^3) and alkyl groups (R^2).

The unsubstituted phenyl urea **11** was several fold less potent than 3,5-dichloro phenyl compound **3**. In general, dihalogenated aryl ureas were slightly better than monohalogenated aryls in terms of MCH-R1 binding affinity. As illustrated by compounds **13** and **14**, the nonhalogenated electron-donating substituents, such as 3-methoxy and 4-methoxy, exhibited a significant loss of potency. The 3-chloro-4-fluorophenyl and 3-trifluoromethyl-4-fluoro substitution (**15** and **16**) were some of the best among the several disubstituted ureas prepared. One possible explanation for this increased affinity could be due to enhancement of urea N−H hydrogen bonding interaction with the receptor by electron-withdrawing groups.

Having defined the SAR of aryl substituents, we next explored the influence of terminal alkyl groups (R^2) on the piperidine. The sulfonamide **19** and amide **20** were much less active, indicating the importance of maintaining basicity at the nitrogen atom. Compound **17**, where R^2 = Et, showed potency similar to the cyclopentyl-substituted compounds.

To further investigate the binding mode and the importance of the piperidine ring, we explored the possibility of replacement of the ring with aminoethyl, aminopropyl, and aminobutyl linkers. The aminoethyl linker was optimal for MCH-R1 binding. Table 2 summarizes the SAR of the MCH-R1 binding activities along

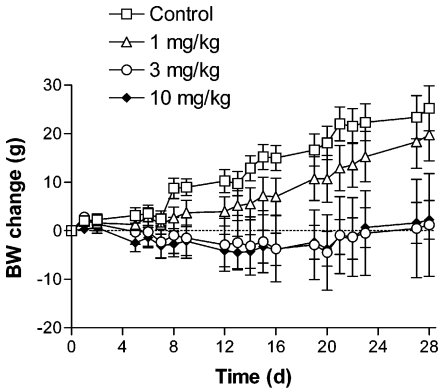


Figure 2. Effect of compound **1** (1, 3, and 10 mg/kg po for 28 days) on the body weight of DIO rats. All values are means ± SEM; $n = 11-12$/group.

with plasma levels from rat PK studies of the aminoethyl biaryl urea analogues. The SAR on the urea and biaryl portion of the molecules tracked similarly to that of the piperidine series. Compound **24** exhibited excellent potency and also showed reasonable oral plasma levels in rats. Metabolite identification studies indicated that compound **24** underwent demethylation in vivo to provide compound **25**. The metabolite, and to some extent the parent compound, exhibited potent 5-HT reuptake transporter inhibition (5-HT $K_i = 27 \pm 2$ nM for compound **25** and 1076 ± 187 nM for **24**). At this point, this was a significant issue because serotonergic modulation can also play a significant role in the regulation of food consumption and weight loss.[12] Therefore, our goal became to eliminate serotonin transporter affinity in order to understand the effects of a pure MCH-R1 antagonist as an antiobesity agent. Substitution at the aryl urea, and alkyl group alterations at the amine terminus, did not reduce 5-HT activity. However, the pyrrolidine and piperazine analogues **1** (5-HT $K_i >$ 1 uM) and **28** (5-HT $K_i >$1 uM) showed promising selectivity in addition to maintaining good MCH-R1 activity. Further SAR studies of pyrrolidine analogues resulted in the identification of **1**, which showed an excellent profile in terms of MCH-R1 affinity and selectivity over other receptors such as NPY, 5-HT, M2, MCH-R2, and 5-HT transporter inhibition (>1 μM) along with oral rat plasma levels, including good brain levels (579 ng/g) at 6 h.

Oral administration of **1** to 24 h fasted diet-induced obese (DIO) mice (30 mg/kg) significantly reduced food intake relative to vehicle control by 16 ± 6%, 17 ± 6% and 14 ± 5% at 4, 6, and 24 h postdose, respectively ($p < 0.05$, t-test). Using an ex vivo binding assay[13] as a surrogate measure of receptor occupancy, compound **1** exhibited 85 ± 3% and 56 ± 3% inhibition of MCH binding to MCH-R1 in mouse brain slices at 6 and 24 h postdose, respectively. Moreover, compounds with low ex vivo binding lacked efficacy, indicating that changes in food intake are likely due to MCH-R1 antagonism. When orally administered to DIO rats for 28 d, compound **1** (1, 3, or 10 mg/kg) produced a dose-dependent decrease in food intake [$F_{3,45} = 8.83$; $p = 0.0001$] and body weight gain [$F_{3,45} = 3.74$; $p = 0.0175$] throughout the duration of the treatment (Figure 2).[14] Specifically, **1** significantly reduced cumulative food intake by 16.9 ± 2.1% and 13.2 ± 1.6% (3 and 10 mg/kg **1**, respectively; $p < 0.05$) relative to control rats while suppressing body

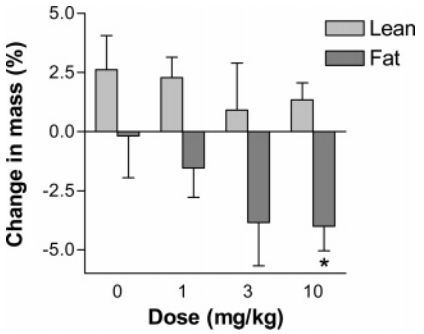


Figure 3. Effect of compound **1** (1, 3, and 10 mg/kg, po for 28 days) on the body composition of DIO rats. *($p < 0.05$ vs baseline, paired t-test).

weight gain (1.2 ± 10.6 g, and 2.2 ± 4.0 g weight gain at 3 and 10 mg/kg **1**, respectively, relative to 25.2 ± 4.6 g weight gain with control; $p < 0.05$. DEXA scanning revealed that the decrease in body weight gain at the 10 mg/kg dose was associated with a selective decrease in fat mass (Figure 3). Animals treated at a 1 mg/kg dosage did not show any significant change in body weight or food intake relative to control. Importantly, compound **1** did not cause taste aversion or place preference at a dose of 3 and 10 mg/kg.

Compound **1** showed excellent in vitro and moderate in vivo activity; however, further studies with this compound were discontinued due to the presence of a highly mutagenic, Ames positive biarylaniline subunit.[15] Although the compound **1** is nonmutagenic, and there is no evidence to suggest that biarylaniline **21** is generated in vivo, the risk of possible exposure to this highly mutagenic biarylaniline intermediate at any stage in the development of the series was considered unacceptable. Our research focus was then shifted to identify a nonmutagenic functional group exhibiting the otherwise promising profile of the biaryl urea.[13] The other strategies followed to address the mutagenicity issue will be reported in due course.

Acknowledgment. We thank Dr. Catherine Strader and Dr. John Piwinski for helpful discussions, support, and encouragement, Dr. Jesse Wong and Dr. Mark Liang for scale-up of intermediates, and Dr. Kathleen Cox for pharmacokinetic studies.

Note Added after ASAP Publication. In the version of the manuscript posted June 24, 2005, compounds **3**, **8**−**20** in Scheme 1 were drawn incorrectly. The corrected structures are presented in the version posted June 29, 2005.

Supporting Information Available: Experimental procedures and characterization data for compounds **1**, **3**, **8**−**20**, and **23**−**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Saito, Y.; Nothacker, H.-P.; Civelli, O. Melanin-concentrating hormone receptor: an orphan receptor fits the key. *Trends Endocrinol. Metab*. **2000**, *11*, 299−303.
(2) Schwartz, M. W.; Woods, S. C.; Porte, D., Jr.; Selley, R. J.; Baskin, D. G. Central nervous system control of food intake. *Nature* **2000**, *404*, 661−671.
(3) Della-Zuana, O.; Presse, F.; Ortola, C.; Duhault, J.; Nahon, J. L.; Levens, N. Acute and chronic administration of melanin-concentrating hormone enhances food intake and body weight in Wistar and Sprague−Dawley rats. *Int. J. Obesity* **2002**, *26*, 1289−1295.

(4) Gomori, A.; Ishihara, A.; Ito, M.; Mashiko, S.; Matsushita, H.; Yumoto, M.; Ito, M.; Tanaka, T.; Tokita, S.; Moriya, M.; Iwaasa, H.; Kanatani, A. Chronic intracerebroventricular infusion of MCH causes obesity in mice. *Am. J. Physiol. Endocrinol. Metab*. **2003**, *284*, E583−E588.
(5) Ludwig, D. S.; Tritos, N. A.; Mastaitis, J. W.; Kulkarni, R.; kokkotou, E.; Elmquist, J.; Lowell, B.; Flier, J. S.; Maratos-Flier, E. Melanin-concentrating hormone overexpression in transgenic mice leads to obesity and insulin resistance *J. Clin. Invest*. **2001**, *107*, 379−386.
(6) Shimada, M.; Tritos, N. A.; Lowell, B. B.; Flier, J. S.; Maratos-Flier, E. Mice lacking melanin-concentrating hormone are hypophagic and lean. *Nature* **1998**, *396*, 670−674.
(7) Kowalski, T. J.; McBriar, M. D. Therapeutic potential of melanin concentrating hormone receptor antagonists for the treatment of obesity. *Expert Opin. Invest. Drugs* **2004**, *13*, 1113−1122.
(8) Takekawa, S.; Asami, A.; Ishihara, Y.; Terauchi, J.; Kato, K.; Shimomura, Y.; Mori, M.; Murakoshi, M.; Kato, K.; Suzuki, N.; Nishimura, O.; Fujino, M. T-226296: A novel, orally active and selective melanin concentrating hormone receptor antagonist. *Eur. J. Pharmacol*. **2002**, *438*, 129−135.
(9) 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. Identification of 2-(4-benzyloxyphenyl)-*N*-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indazol-6-yl]acetamide, an orally efficacious melanin-concentrating hormone receptor-1 antagonist for the treatment of obesity. *J. Med. Chem*. **2005**, *48*, 1318−1321.
(10) Clader, J. W.; Josien, H, B. Palani. A.; Chan, T.-Y. Preparation of N-[biaryl(piperidinyl)ethyl]-N′-arylureas and analogs as melanin concentrating hormone receptor antagonists. WO 2002/076947.
(11) Cox, K. A.; Dunn-Meynell, K.; Korfmacher, W. A.; Broske, L.; Nomeir, A. A.; Lin, C. C.; Cayen, M. N.; Barr, W. H. *Drug Discovery Today* **1999**, *4(5)*, 232−237.
(12) (a) Blundell J. E.; Hill A. J.; Int. J. Dexfenfluramine and appetite in humans *Relat. Metab. Disord*. **1992**, *16*: Suppl.3: S51−S59. (b) Blundell J. E. Serotonin and appetite *Neuropharmacology* **1984**, *12B*, 1537−1551.
(13) McBriar, M. D.; Guzik, H.; Xu, R.; Paruchova, J.; Li, S.; Palani, A.; Clader, J. W.; Greenlee, W. J.; Hawes, B. E.; Kowalski, T.; O'Neil, K.; Spar, B.; Weig, B. Discovery of bicycloalkyl urea melanin concentrating hormone receptor antagonists: orally efficacious antiobesity therapeutics *J. Med. Chem.* **2005**, *48*, 2274−2277.
(14) Repeated measures ANOVA was used to compare cumulative food intake and body weight gain measures across time in rat 28d study. Where significant differences by ANOVA ($p < 0.05$) were found, posthoc analyses were carried out using Fishers PLSD.
(15) (a) Dang, L. N.; McQueen, C. A. Mutagenicity of 4-aminobiphenyl and 4-acetylaminobiphenyl in *salmonella* typhimurium strains expressing different levels of *N*-acetyltransferase *Toxicol. Appl. Pharmacol.* **1999**, *159*, 77−82. (b) Nohara, M.; Hirayama, T.; Fujioka, Y.; Ozasa, S.; Ibuki, E.; Fukui, S. Relationship between mutagenic potency in *salmonella typhimurium* and chemical structure of amino- and nitro substituted biphenyls. *Mutation Res.* **1985**, *149*, 9−15.

JM0503852