Discovery of Bicycloalkyl Urea Melanin Concentrating Hormone Receptor Antagonists: Orally Efficacious Antiobesity Therapeutics

Mark D. McBriar,* Henry Guzik, Ruo Xu, Jaroslava Paruchova, Shengjian Li,† Anandan Palani, John W. Clader, William J. Greenlee, Brian E. Hawes, Timothy J. Kowalski, Kim O'Neill, Brian Spar, and Blair Weig

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033-0539

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Abstract: Melanin concentrating hormone (MCH) is involved in regulation of food intake and energy homeostasis. Antagonists of the MCH receptor are expected to affect food intake and weight gain, making MCH-R1 an attractive target for obesity treatment. Herein, we report the discovery of a novel, orally active series of MCH-R1 antagonists that exhibit in vivo efficacy in rodent obesity models.

Recognized as one of the top 10 global health problems by the World Health Organization, the rising pandemic of obesity affects over 30% of the adult population in the U.S. alone, with another 30% of U.S. adults being classified as overweight.[1] Estimates of direct and indirect costs in the U.S. due to obesity are >$117 billion annually.[2] More than an aesthetic problem, morbidities related to obesity include hyperlipidemia, type 2 diabetes mellitus, stroke, cardiovascular disease, osteoarthritis, sleep apnea, and several types of cancers.[3,4] Antiobesity agents such as orlistat (Xenical) and sibutramine (Meridia) suffer from variable efficacy or undesirable side effects that have limited their therapeutic potential.[5] Melanin concentrating hormone (MCH) is a cyclic nonadecapeptide that regulates feeding behavior and energy homeostasis via interaction with the central melanocortin system.[6] Central to this process is the G-protein-coupled receptor MCH-R1, which is expressed in several regions of the mammalian central nervous system. Seminal observations of elevated levels of MCH in genetically obese mice and the orexigenic effects of icv administration of MCH were followed by studies documenting that mice null for MCH-R1 exhibit a lean phenotype while being resistant to diet-induced obesity.[6,7] Consequently, antagonists of MCH-R1 have become attractive targets as potential treatments for obesity, though limited data on in vivo efficacy are available.[8]

Recently, MCH-R1 antagonists that demonstrate oral activity have been described (Figure 1). T-226296 **(1)** exhibited >90% suppression of MCH stimulated food intake at 30 mpk in lean rats.[9] Aventis reported a 64% reduction in milk consumption in a fasted mouse model following oral administration of **2**.[10] Aryl tetrazole derivatives such as **3** demonstrate oral activity up to 2 h in rats,[11] while quinoline derivatives such as **4** reduce food intake by >30% over 6 h.[12] Subchronic efficacy has been recently demonstrated with GW-803430 (**5**), showing ∼13% weight loss after 12 days.[13] Recently, ATC-0175 (**6**) has been shown to exhibit oral efficacy (15−20% body weight reduction) in rats over 4 days.[14] While the above compounds display varying degrees of oral efficacy, no measure of MCH-R1 occupancy has been reported for these compounds. Herein, we report the results of an effort to discover a new class of MCH-R1 antagonists that exhibit in vivo efficacy and correlate this efficacy with occupancy at the MCH-1 receptor following an oral dosing regimen.

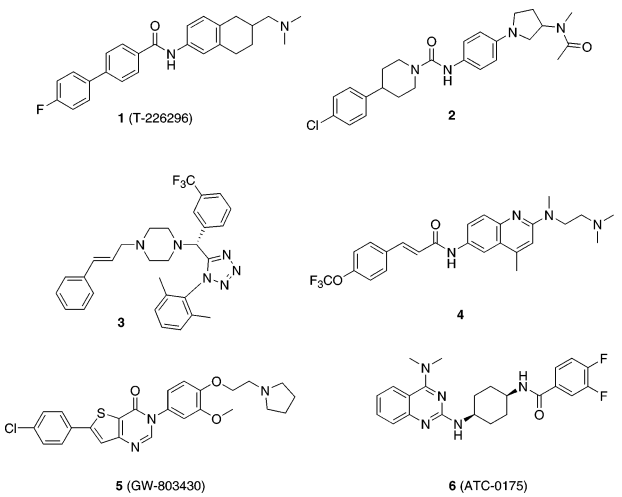

Figure 1. Orally active MCH-R1 antagonists.

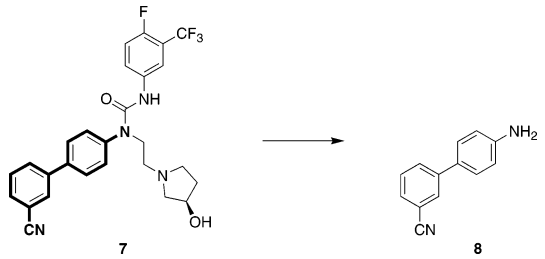

Figure 2. Potential liability of biarylurea MCH-R1 antagonists.

Small-molecule MCH-R1 antagonists have been discovered in our laboratories, exemplified by the biarylurea **7** (Figure 2).[15] While compounds such as **7** have excellent in vitro activity, the biarylaniline **8** embedded in the parent structure was found to be highly mutagenic as indicated by a strong positive result in an Ames assay.[16] Although the parent ureas themselves are nonmutagenic and there is no evidence to suggest that **8** is generated in vivo, the risk of possible exposure to the highly mutagenic biarylamine intermediate at any stage of the development of this series was considered unacceptable.

Our focus in these studies was to identify a nonmutagenic functional group that otherwise closely resembles the biarylaniline. The vast SAR generated in the biaryl series was useful in the present application.[15] Among the various strategies that were explored, modification of the central phenyl ring was most fruitful.

* To whom correspondence should be addressed. Phone: 908-740-2618. Fax: 908-740-7152. E-mail: mark.mcbriar@spcorp.com.
† Current address: Johnson and Johnson Pharmaceutical Research Institute, Raritan, New Jersey.

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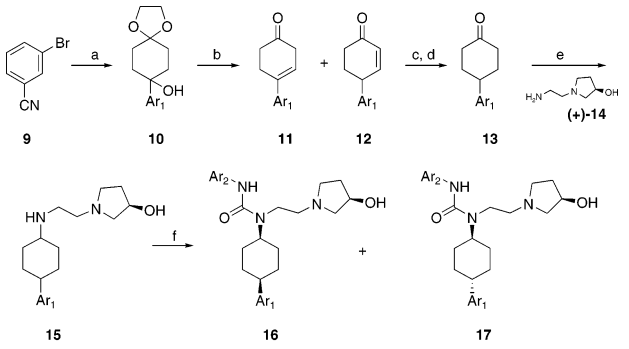
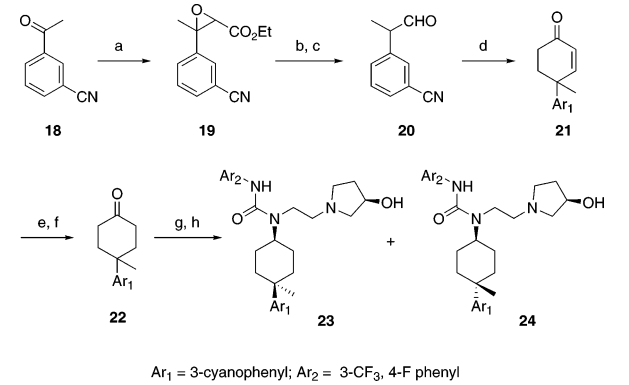
Scheme 1[a]



[a] Reagents and conditions: (a) butyllithium, THF, −100 °C, then 1,4-dioxaspiro[4,5]decan-8-one, −100 to −75 °C, 82%; (b) TFA, 50 °C, 94%; (c) Pd/C, H_2, 45 psi, MeOH, 98%; (d) Dess−Martin periodinane, pyridine, CH_2Cl_2, 63%; (e) (+)-**14**, Ti(O-*i*-Pr)$_4$, 18 h, then $NaBH_4$, MeOH, 65%; (f) 4-fluoro-3-(trifluoromethyl)phenyl isocyanate, *i*-Pr_2NEt, CH_2Cl_2, 80%.

Scheme 2[a]

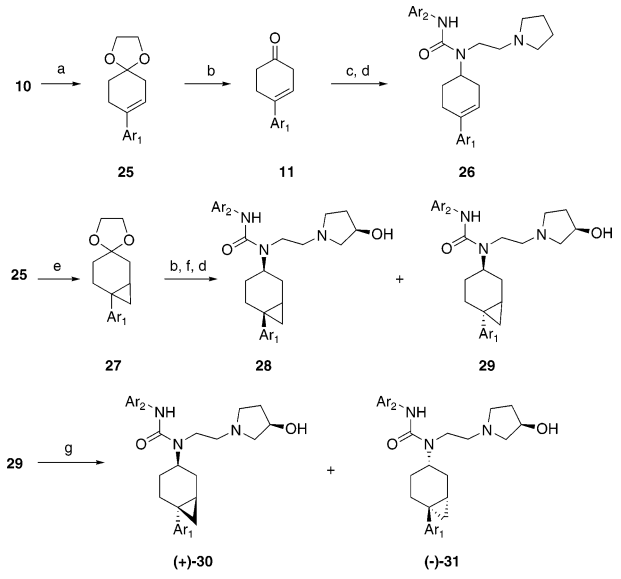


[a] Reagents and conditions: (a) ethyl chloroacetate, K(O-*t*-Bu), *t*-BuOH, 79%; (b) NaOH, EtOH; (c) 2 N HCl, 100 °C, 14% (two steps); (d) methyl vinyl ketone, KOH, EtOH, H_2O; (e) H_2 Pt/C, MeOH; (f) Dess−Martin periodinane, pyridine, CH_2Cl_2, room temp, 77% (three steps); (g) (+)-**14**, $NaBH(OAc)_3$, CH_2Cl_2, 76%; (h) 4-fluoro-3-(trifluoromethyl)phenyl isocyanate, *i*-Pr_2NEt, CH_2Cl_2, 20%.

The synthesis of saturated biaryl surrogates is shown in Scheme 1. Metal−halogen exchange of *m*-bromobenzonitrile followed by addition to 4-dioxaspiro[4,5]-decan-8-one gave rise to alcohol **10**. Acidic treatment of **10** proceeded with concomitant dehydration and olefin migration to provide **11** and **12**. Hydrogenation of this mixture also resulted in ketone reduction, and treatment of the crude product with Dess−Martin periodinane[17] afforded **13**. Introduction of the amine side chain **14**[18] to provide **15** was achieved via reductive alkylation. Importantly, the incorporation of sodium borohydride gave predominately the trans diastereomers with respect to the bicyclic core. Urea formation with an aryl isocyanate followed by chromatographic separation gave cis and trans isomers **16** and **17**.

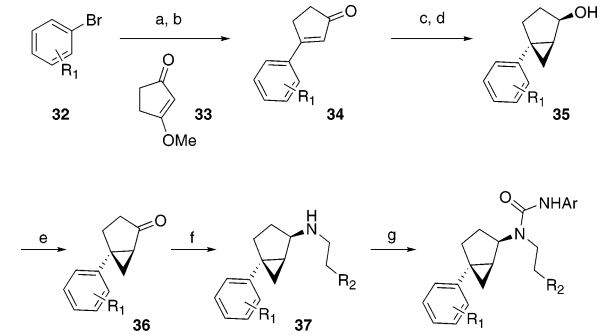
Synthesis of targets containing a benzylic methyl group was achieved as shown in Scheme 2. Darzens condensation[19] of 3-acetylbenzonitrile provided aldehyde **20**, which in turn underwent annulation[20] to generate ketone **21**. Olefin reduction again proceeded with ketone reduction, which necessitated an oxidation to provide **22.** Reductive amination and isocyanate treatment afforded the respective cis and trans isomers **23** and **24**.

Scheme 3[a]



[a] Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 91%; (b) 20% TFA/CH_2Cl_2, 85%; (c) 1-(2-aminoethyl)pyrrolidine, Ti(O-i-Pr)$_4$, 18 h, then $NaBH_4$, MeOH, 52%; (d) 3-chloro-4-fluorophenyl isocyanate, *i*-Pr_2NEt, CH_2Cl_2, 50%; (e) Et_2Zn, TFA, CH_2I_2, CH_2Cl_2, 0 °C, 57%; (f) (+)-**14**, Ti(O-*i*-Pr)$_4$, 18 h, then $NaBH_4$, MeOH, 84%; (g) chiral HPLC, AD column.

Scheme 4[a]



[a] Reagents and conditions (yields for **40**): (a) butyllithium, THF, −78 °C, then **33**, −78 to −20 °C; (b) 1 N HCl, 59% (two steps); (c) $NaBH_4$, $CeCl_3$, MeOH, 0 °C to room temp, 80%; (d) Et_2Zn, CH_2I_2, CH_2Cl_2, 0 °C to room temp, 93%; (e) Dess−Martin periodinane, pyridine, CH_2Cl_2, 0 °C to room temp, 89%; (f) 1-(3-aminopropyl)-4-methylpiperazine, Ti(O-*i*-Pr)$_4$, 18 h, then $NaBH_4$, MeOH; (g) 4-fluoro-3-(trifluoromethyl)phenyl isocyanate, *i*-Pr_2NEt, CH_2Cl_2, 48% (two steps).

Synthesis of the bicycloheptyl analogues proceeded via Scheme 3. Dehydration of **10** followed by ketal removal at room temperature suppressed olefin migration to cleanly provide ketone **11**. Reductive amination and urea formation as demonstrated previously afforded racemic cyclohexene **26**. Cyclopropanation of olefin **25** using the method of Shi[21] gave bicycloheptane **27**. Deprotection and reductive amination followed by urea formation gave the cis and trans bicycloheptyl isomers **28** and **29**. Further separation of **29** via chiral HPLC provided diastereomerically pure (+)-**30** and (−)-**31**.

The general synthesis of the bicyclohexyl series is outlined in Scheme 4. Addition of lithiated benzonitrile **32** to 3-methoxy-2-cyclopenten-1-one followed by acidic

Table 1. MCH Receptor Binding for Aryl Replacements[a]

compd	K_i (nM) h-MCH-R1	K_i (nM) m-MCH-R1	K_b (nM)[b] h-MCH-R1
7	8.9 ± 1.1	9.6 ± 0.3	2.0 ± 0.2
16	2020 ± 337		
17	215 ± 14		
23	>3000		
24	391 ± 41		
26	3.0 ± 1.0		9.0 ± 0.3
28[c]	1174 ± 24		
29[c]	7.9 ± 1.4	10.7 ± 0.7	1.7 ± 0.8
(+)-**30**	9.2 ± 0.1	5.9 ± 1.1	3.4 ± 0.4
(−)-**31**	8.8 ± 0.6	7.8 ± 0.6	3.0 ± 0.3
38[c]	7.1 ± 1.1		
39	18 ± 3.0		
40	2.7 ± 0.2	3.0 ± 0.5	1.9 ± 1.1

[a] Mean values (n = 3) ± SEM. h-MCH-R1 and m-MCH-R1 denote human and murine MCH-R1, respectively. [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] Denotes a mixture of diastereomers.

workup provided enone **34**.[22] Luche reduction[23] and cyclopropanation of the resultant allylic alcohol proceeded smoothly to provide **35**. Oxidation gave the requisite bicyclic ketone **36**. Though circuitous, this method was more efficient and reliable than direct conversion of **34** to **36**.[24] Reductive amination was achieved with the appropriate amine side chains. In this series, sodium borohydride provided exclusively the trans diastereomers with respect to the bicyclic core. Installation of the urea functionality was achieved via treatment of **37** with an isocyanate to provide the desired target compounds (**38**−**40**).

Table 1 shows the MCH-R1 inhibition of several representative compounds containing aryl modifications. High correlation between human and murine MCH-R1 activity was observed, and functional antagonism was confirmed in a FLIPR assay. Good selectivity with respect to MCH-R2 was seen (K_i > 3 μM for all compounds), though the phenotype exhibited by antagonists of MCH-R2 is not yet profiled.[8] Initial SAR studies were carried out on racemic cycloalkyl cores. As a result, in cases where chiral side chains were used, compounds were initally tested as a mixture of diastereoisomers. Simple saturation of the central phenyl ring provided cis and trans cyclohexane isomers **16** and **17**. Though MCH-R1 inhibitory activity is reduced with respect to the biaryls (**7**), the trans isomer was much more active than the cis isomer. Introduction of a methyl group at the benzylic position such as in **23** or **24** considerably reduced affinity. Partial reduction of the aryl to cyclohexenyl (**26**) provided increased binding affinity; however, the styryl moiety has inherent metabolic liabilities. In particular, rearomatization to the biarylaniline upon oxidation was a concern. Among strategies that were used to prevent rearomatization, cyclopropanation gave rise to bicycloheptane isomers **28** and **29**. The trans isomers of this series exhibited MCH-R1 antagonism comparable to that of the biarylaniline analogues. Further testing of the pure diastereomers (+)-**30** and (−)-**31** indicated a similar in vitro profile for each. Structure−activity relationships of the bicycloheptane series tracked similarly to those of the biarylanilines.

Further studies have revealed that bicyclohexane **38** also works well as an aryl surrogate, and this series underwent further SAR development. Several representative bicyclohexyl compounds were assayed for activity at MCH-R1 (Table 1). As shown, activity was maintained with various amine side chains and arylurea substitution patterns. Contrary to what was observed in the bicycloheptyl series, aryl substitution at either the meta (**38**) or para (**39** and **40**) positions imparted acceptable binding affinity.

Table 2. MCH Receptor Ex Vivo Binding[a]

compd	6 h	24 h
(+)-**30**	50 ± 15	13 ± 6
(−)-**31**	62 ± 6	8 ± 4
38[b]	81 ± 6	
39	76 ± 6	
40	99 ± 4	58 ± 7

[a] Expressed as a percent of inhibition of MCH-ADO binding relative to vehicle control ± SEM (n = 3; dosed at 30 mpk, po). [b] Denotes a mixture of diastereomers.

Table 3. In Vivo Efficacy in DIO Mice[a]

compd	food intake at time indicated (% of vehicle) 2 h	6 h	24 h
(+)-**30**	85.0 ± 6.4	93.6 ± 5.6	94.9 ± 5.2
(−)-**31**	80.0 ± 4.3	99.0 ± 5.5	98.6 ± 3.5
38[b]	65.7 ± 11.8*	68.2 ± 7.4*	80.8 ± 5.3*
39	78.4 ± 6.7*	86.6 ± 6.0	94.7 ± 5.4
40	77.3 ± 6.9	76.0 ± 5.4*	78.1 ± 5.1*

[a] Values expressed as a percent of vehicle ± SEM (dosed at 30 mpk, po). Asterisk (*) indicates value is significantly different from that of vehicle. [b] Denotes a mixture of diastereomers.

As a measure of receptor occupancy, compounds were then subjected to an ex vivo binding assay.[25] Compounds were administered to mice po, and animals were sacrificed at 6 and 24 h postdose, at which time the brain was harvested for sectioning. Binding of MCH-ADO[26] to the sections was determined as a surrogate measure of occupancy at the MCH-1 receptor (Table 2). Values are expressed relative to control to account for nonspecific binding of the radioligand. These studies facilitated a rough quantitation of receptor occupancy for several small-molecule antagonists while negating the requirement for radiolabeling each of the individual molecules, permitting the identification of compounds providing optimal receptor coverage at several time points postdose. Compound **40** provided maximal receptor binding at 6 h, with significant binding also observed at 24 h.

In vivo efficacy was determined by incorporation of a fasted, diet-induced obese (DIO) mouse model. Mice were fasted for 24 h, dosed orally and monitored at 2, 6, and 24 h postdose for cumulative food intake relative to vehicle controls. Results of a representative set of compounds are shown in Table 3. As shown, several of these compounds have proven effective, showing a statistically significant reduction of food intake. In general, compounds demonstrating in vivo efficacy also exhibited ex vivo binding of >70% at 6 h. Importantly, compounds with low ex vivo binding lacked efficacy and served as a control, indicating that changes in food intake are unlikely a function of inherent compound toxicity. Interestingly, statistical significance in some cases is only reached at early time points. Both **38** and **40** showed efficacy at the 24 h time point, and **40** was chosen for further study on the basis of the superior receptor coverage achieved relative to **38**.

As a precursor to further rodent studies, pharmacokinetic properties of **40** were determined in rats (Table 4). Oral bioavailability of **40** was shown to be 27%, with acceptable plasma levels achieved via oral dosing.

In summary, we have identified and developed a series of novel, highly active MCH-R1 antagonists as

Table 4. Pharmacokinetic Profile of **40**[a]

oral AUC $_{(0-24h)}$ (ng h mL^{-1})	2140
iv half-life (h)	4.0
iv clearance (mL min^{-1} kg^{-1})	21.8
V_d(ss) (L kg^{-1})	5.6
bioavailability, *F* (%)	27

[a] $n = 3$; dosed at 10 mpk, iv/po.

potential antiobesity therapeutics via incorporation of a bicyclohexane moiety as a successful aryl ring surrogate. These compounds are selective for MCH-R1 over MCH-R2 and exhibit efficacy in rodent feeding models. A surrogate quantification of receptor occupancy was developed using ex vivo binding studies, which showed good correlation with in vivo efficacy. Additional studies with **40**, which has shown acceptable in vivo and pharmacokinetic properties, will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for compounds **16**, **17**, **23**, **24**, **26**, **28**−**31**, and **38**−**40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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