Melanin-Concentrating Hormone-1 Receptor Antagonists for the Treatment of Obesity

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Introduction

Obesity is one component of a collection of risk factors, termed metabolic syndrome, that is characterized by high blood pressure, insulin resistance, dyslipidemia, and excessive visceral adiposity. Adipose tissue is more than a passive repository of triglycerides. It is also an endocrine gland that produces and excretes the hormone leptin, which serves as a key mediator in the feedback loop linking peripheral adiposity with the central control of feeding and energy expenditure.[1,2] As fatness increases, more leptin is produced. Under normal physiological conditions, leptin enters the hypothalamus and inhibits the formation of orexigenic neuropeptides such as neuropeptide Y (NPY), melanin-concentrating hormone (MCH), orexin, galanin, and agouti-related protein (AGRP). Hypothalamic leptin simultaneously up-regulates anorectic peptides such as α-melanocyte stimulating hormone (α-MSH), corticotropin-releasing hormone (CRH), and cocaine- and amphetamine-regulated transcript (CART).[3] Obesity is characterized by resistance to leptin, the cause of which has been the subject of much investigation, but may result from a failure of leptin receptor signaling in the brain.[4] Obese patients are found to have high levels of circulating leptin, and administering recombinant leptin as an antiobesity treatment has given mixed results.[5] Instead, pharmaceutical intervention could be directed toward the orexigenic and anorectic neuropeptide receptors that operate downstream of leptin signaling.

One of the orexigenic neuropeptide receptors that has emerged as an exciting drug target for the treatment of obesity is melanin-concentrating hormone-1 receptor (MCHR-1). In this article we intend to outline the rationale supporting a role for MCH antagonists in the treatment of obesity and to review the progress that has been made to date in the discovery of MCHR-1 antagonists. We will also discuss some of the possible limitations that MCH antagonists may have in the treatment of obesity. For other perspectives in the MCH field, we direct the reader to several excellent reviews that have appeared recently.[6−10]

MCH was first isolated in 1983 from salmon pituitaries, where it has a role in pigmentation of fish scales. MCH is a cyclic peptide of 19 amino acids with a single disulfide bridge that is identical in all mammals studied so far.[7] In 1999 two research groups reported simultaneously that MCH binds to and activates the formerly orphan receptor SLC-1 (somatostatin-like receptor, also known as GPR24).[11,12] The newly identified MCH-1 receptor (MCHR-1) is a member of the 7TM GPCR (seven transmembrane G-protein-coupled receptor) superfamily of receptors. In 2001 a second human MCH receptor was identified (MCHR-2) that shares 38% amino acid identity with MCHR-1.[13] MCHR-2 is not expressed in rodents, and the lack of animal models has hampered efforts to investigate the role of MCHR-2 in feeding and energy balance.

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MCH has no known role in the pigmentation of human skin. In mammals MCH is synthesized predominantly in the brain. For example, in rats, MCH synthesis has been localized to the lateral hypothalamus and zona incerta with lesser amounts in the olfactory tubercle and pons.[14] MCH neurons project widely into other regions of the brain including the cerebral cortex, hippocampus, amygdala, and nucleus of the solitary tract, areas that are thought to control feeding and motivational behavior.[15] The MCH-1 receptor has been localized to areas of the brain that coordinate feeding behavior including the paraventricular nucleus, the dorsomedial, ventromedial, and arcuate nucleus and areas involved in olfaction.[16] In the human brain, MCH binding sites have been found in the cerebral cortex, hypothalamus, thalamus, pons, medulla oblongata, and cerebellum.[17]

MCH and the Central Control of Energy Balance

The role of MCH in feeding went unrecognized for many years until it was discovered in 1996 that MCH is up-regulated during fasting in both normal and obese mice. Among fasted animals, MCH mRNA was increased 4-fold in wild type mice and almost 3-fold in leptin-deficient ob/ob mice. Furthermore, it was found that if MCH is directly infused into the intracerebroventricular (icv) region of the rat brain, the consumption of food doubled for the next 6 h.[18] More recently it has been reported that chronic icv infusion of MCH over 14 days to mice on a high-fat diet led to a large increase in caloric intake and body weight. The body weight gains were attributed to gains in fat mass and in liver mass. In addition, the MCH-treated animals showed increases in glucose, insulin, and leptin levels that parallel human metabolic syndrome.[19]

Further investigation of the functions of MCH focused on animals in which the MCH gene had been deleted. MCH knockout mice were found to consume fewer calories than control mice and weighed significantly less although they grew normally in every other way. Furthermore, it was found that the MCH knockout animals were resistant to developing obesity when placed on a high-fat diet and they consumed more oxygen, suggesting that they had an enhanced metabolic rate compared to controls.[20] The results from the MCH knockout experiments are in sharp contrast to results from corresponding studies that have been carried out for other orexigenic peptides such as NPY, galanin, and β-endorphin, in which the knockout phenotypes were found to exhibit normal feeding behavior, body weight, and metabolism.[21]

Further characterization of MCH utilized mice that were designed to overexpress the MCH gene. The transgenic mice were found to have a 2-fold increase in MCH mRNA. When placed on a high-fat diet, the MCH overexpressers consumed 10% more calories and gained 12% more weight than controls. It was also reported that the MCH overexpressers had high blood glucose and were insulin-resistant, consistent with a prediabetic state.[22]

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Investigations of MCH receptor deficient mice have provided additional evidence that MCH has a role in regulation of metabolism and activity levels. MCH-1 receptor knockout mice were found to have high locomotor activity levels and high metabolic rates.[23] As a result, they displayed a lean phenotype, had reduced leptin levels, and were hyperphagic. Furthermore, when placed on a high-fat diet, the MCH-1 receptor knockout mice were found to be resistant to diet-induced obesity (DIO).[23,24] Most recently, it has been reported that the hyperactivity of the MCH-1 receptor knockout animals may be mediated by the mesolimbic dopamine system. It was found that the receptor knockouts were hyper-responsive to dopamine stimulation. The knockouts had enhanced norepinephrine transport (NET) and significantly up-regulated dopamine D1 and D2 receptors in the mesolimbic regions.[25] It is widely recognized that mesolimbic dopamine signaling underlies the reward mechanisms to pleasurable stimuli such as drugs of abuse, smoking, sex, and food intake. This suggests that MCHR-1 antagonists may have a role not only in weight management but also in treating substance abuse, aiding smoking cessation, and treating depression.

MCH and Leptin

Accumulating evidence indicates that MCH is a target of the circulating hormone leptin. MCH receptor is up-regulated in conditions of genetic obesity and during food deprivation, conditions that are characterized by having low or nonexistent levels of circulating leptin. Among ob/ob mice that lack leptin it was found that there was a 2-fold increase in MCH mRNA[18] and a 3-fold increase in MCH receptor mRNA.[16] Furthermore, leptin treatment of the ob/ob animals resulted in a significant down-regulation of MCH receptor. Diet-induced obese animals also maintain increased levels of MCH tone. A 48 h fasting of mice led to a 7-fold increase in MCH receptor mRNA that was reversed by leptin treatment.[16] Taken together, these results are consistent with a system in which leptin down-regulates MCH hormone and MCH receptor expression in the brain. What are the implications of these results for obese patients? These individuals are resistant to leptin and, on the basis of the animal results, would be expected to have increased levels of MCH tone. Considering the effects of MCH on food intake and weight gain, it seems reasonable to hypothesize that an MCH antagonist could circumvent leptin resistance and be an effective agent in the treatment of obesity.

MCH Receptor Antagonists

The cloning and identification of MCH-1 receptor and the strong association of MCH with feeding and energy balance have prompted many pharmaceutical companies to initiate MCHR-1 antagonist discovery programs. Given the long history that drug companies have had with family A GPCR targets, it is not surprising that numerous organizations have reported finding small-molecule antagonists for the MCH-1 receptor.[10,26] In the past year alone there have been several disclosures in the patent literature that describe MCHR-1 antagonists, and a few of these are shown in Table 1.

The MCH antagonists that have been described represent diverse structural types. Nevertheless, some commonality exists. The recurring structural motif is a central amide residue with an amino group at one end of the molecule and a lipophilic moiety at the other end. Argenta (Table 1, entry 1) has described a series containing a 6-amidoquinoline core. Synaptic, Yamanouchi, and Banyu (entries 2−4) have exemplified MCHR-1 antagonists that contain a 1,1-diarylacetamide core. Boeringer Ingelheim (entry 5) eliminated the amide group and incorporated an acetylenic bridge between the amine and the lipophilic group. Taisho and Arena (entry 6) described a *cis*-1,4-cyclohexanediamine series that included various aromatic heterocycles including pyrimidine, quinoline, and tetrahydroquinoline. Schering (entry 7) exemplified a series of 3,4-dihydroisoquinoline acetamides including several with very high potencies.

Scientists from Abbott Laboratories have published a series of papers[34−36] describing their MCH program in which they utilized high-throughput screening to identify a novel lead series, 2-amino-8-alkoxyquinolines. To optimize the new lead, they took advantage of parallel synthesis techniques that led to compound **1** (Figure 1) that combined high binding affinity, high functional potency, and good central nervous system (CNS) penetration. Scientists from Pharmacopeia have also utilized high-throughput chemistry to rapidly optimize a series of compounds starting with an initial hit with binding affinity in the low-micromolar range. This effort culminated in the identification of urea **2** (binding $K_i = 0.84$ nM).[37]

Efficacy in Animal Models of Obesity

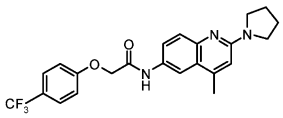
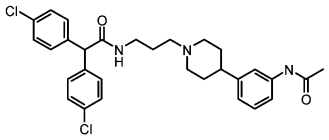
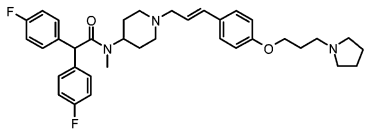
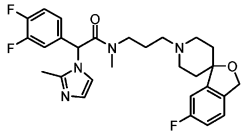
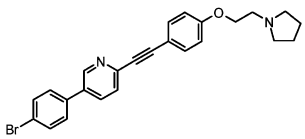
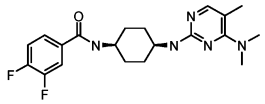
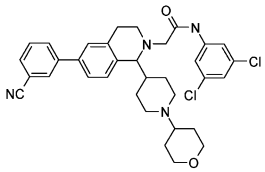
Synaptic has reported anorectic and antidepressant effects of an MCH receptor antagonist **3** (SNAP-7941, $K_i = 15$ nM, Figure 1).[38] They reported that **3** attenuated MCH-induced food intake when dosed ip at 10 mg/kg to male Wistar rats. At the same dose, **3** caused a 26% weight loss in healthy growing young rats compared to controls. Compound **3** was found to decrease the consumption of highly palatable food (sweetened condensed milk) by 41% at a dose of 10 mg/kg and 59% (30 mg/kg) without affecting conditioned taste aversion. When dosed ip twice daily at 10 mg/kg to diet-induced obese Long-Evans rats, **3** led to significant and sustained weight loss over the 28-day treatment period, resulting in a 26% weight loss compared to controls. In the same experiment, D-fenfluramine at 3 mg/kg led to weight loss for the first 14 days but was then followed by rebound weight gain over the next 14 days, culminating in a 14% weight loss over the 28-day treatment period.

Through the screening of a GPCR-directed small-molecule library and subsequent lead optimization, scientists from Takeda discovered an orally active MCHR-1 antagonist **4** (T-226296, $IC_{50} = 5.5$ nM).[39] When **4** was dosed orally at 30 mg/kg to male Sprague-Dawley rats followed by injection of MCH (5 μg) into the lateral ventricle, it was found that **4** obliterated the MCH-induced feeding response. Subsequently, scientists from Schering reported that **4** decreased food intake in diet-induced obese male Sprague-Dawley rats. Through carefully monitoring of animals over a 24-h period, they concluded that **4** at 10 mg/kg reduced food intake by decreasing the size of the meal consumed rather than by decreasing the number of meals consumed. Compound **4** at 10 mg/kg had no effect on locomotor activity in the animals studied, suggesting that the feeding effect is not due to a general malaise.[40]

GlaxoSmithKline has reported that **5** (GW 803430X, $IC_{50} = 0.5$ nM), when administered orally to diet-induced obese AKR mice, gave a robust and continuous weight loss over a 12-day period. At 3 mg/kg orally, **5** gave a 13% weight loss over the course of the study, whereas sibutramine at the same dose gave a 3% weight loss.[41]

In 2005, scientists from Neurocrine Biosciences described compound **6** ($K_i = 2.3$ nM) and investigated its effect in a 7-day weight loss study. Animals treated with **6** ate less food than control-treated animals and lost a significant amount of weight. The study included pair-fed animals that were not treated with

Table 1. Chemical Structures of MCHR-1 Antagonists Described in Patent Applications

Entry	Organization	Structure	Potency
1	Argenta[27]		IC_{50}=10nM[a,c]
2	Synaptic[28]		Ki=0.3nM[b,d]
3	Yamanouchi[29]		IC_{50}=0.18nM[a,e]
4	Banyu[30]		IC_{50}=0.2nM[b,c]
5	Boeringer Ingelheim[31]		IC_{50}=8nM[b,c]
6	Taisho/Arena[32]		IC_{50}=2.1nM[a,c]
7	Schering[33]		Ki=6.4nM[b]

[a] Functional assay. [b] Binding assay. [c] Human MCHR1. [d] Rat MCHR1. [e] Mouse MCHR1.

compound but were restricted to eating the same amount of food as the treated animals. Although both the treated and pair-fed animals lost weight, it was found that the treated animals lost significantly more weight, suggesting that compound **6** had effects on metabolic rate in addition to its anorectic effects.[42] Recently, scientists from Schering-Plough have reported that compound **7** (K_i = 8.9 nM) caused a dose-dependent reduction in food intake and weight gain in DIO rats over a 28-day period. At a dose of 10 mg/kg, compound **7** caused a selective decrease in fat mass while lean mass increased as the animals grew over the course of the study.[43]

Scientists at Abbott Laboratories have optimized a series of aminopiperidine benzamides resulting in the identification of compound **8** (binding IC_{50} = 3 nM). Compound **8** was investigated for its effect on food intake and body weight in DIO mice over a 14-day period. At an oral dose of 30 mg/kg, **8** caused a 6% loss in body weight but had no effects on food intake relative to controls. The authors of this study concluded that **8** caused weight loss by increasing energy expenditure.[44] In another 2005 report, scientists at Abbott identified compound **9** (binding IC_{50} = 1.4 nM) that combined high functional antagonism, favorable pharmacokinetics, and good CNS penetration. When dosed to DIO mice at 30 mg/kg over a 14-day period, **9** caused a 15% reduction in body weight that reflected a loss of fat mass rather than lean mass. It is noteworthy that **9** did not cause a change in food intake at this dose. As with **8**, the conclusion was that **9** caused weight loss by increasing energy expenditure, although changes in locomotor activity were not observed.[45]

Opportunities and Challenges

The compelling results with MCH antagonists in animal feeding and weight loss studies support the hypothesis that MCH antagonists will be effective treatments for obesity. Nevertheless, there are several hurdles that must be overcome before we deem them safe and effective therapies. How might MCH receptor antagonists not live up to the high expectations that have been set?

An MCH receptor antagonist alone may not provide sufficient efficacy to reach the desired clinical endpoints. As animal studies have demonstrated, fasting results in an up-regulation in MCH receptor and an increase in MCH tone. This effect may lead to a reduction in the long-term efficacy of an MCH antagonist as weight loss progresses during a calorie-restricted diet. In addition, the orexigenic neuropeptides are redundant. To get a sustained weight loss, it may be necessary to inhibit more than

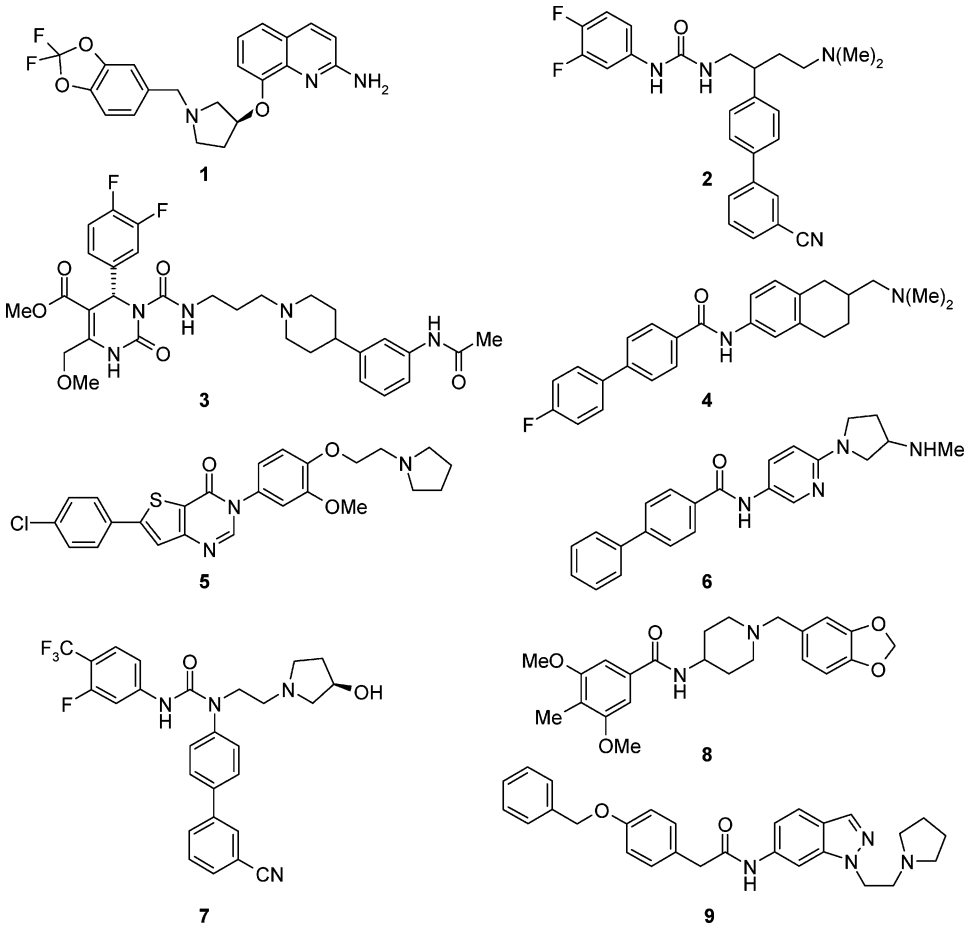


Figure 1. Chemical structures of selected MCH-1 receptor antagonists.

a single orexigenic neuropeptide for a sustained effect. For example, one may need to target NPY, orexin, and AGRP simultaneously to provide adequate weight loss and weight management over a period of time.

The role of MCHR-2 in obesity is unknown. Although MCHR-1 antagonists are effective anorectic agents in rats that possess only a single MCH receptor, it is not clear what the effect will be in humans that possess both MCHR-1 and MCHR-2. It is conceivable that MCHR-2 could functionally compensate when MCHR-1 is inhibited. One may need to inhibit both MCHR-1 and MCHR-2 to get a full effect.

The MCH receptor is widely distributed in the brain, and an antagonist may have unintended effects. MCH-producing neurons project into areas of the brain that control functions other than feeding and appetite. In addition to the hypothalamus, the MCH-1 receptor has been identified in several areas of the rat brain including the cerebral cortex, hippocampus, amygdala, and the olfactory bulb.[15] MCH plays a role in several activities in the CNS including stress, aggression, anxiety, reproduction, and memory retention.[9] Indeed, MCH antagonists have attracted attention as potential antidepressants and anxiolytic agents.[38] The MCH receptor is also expressed in many peripheral tissues including kidney, testis, white adipose tissue, skeletal muscle, and tongue although in lower amounts than in the brain.[16] It is not clear what the effect of an MCH receptor antagonist would be on the function of peripheral organs and tissues.

MCH may participate in other key functions in the hypothalamus, and inhibiting MCH receptor-1 may cause unexpected side effects. For example, a recent study has demonstrated that MCH is involved in the maintenance of bone density in rodents. MCHR-1 knockout mice have high bone turnover and a reduction in cortical bone mass.[46] It is not known whether long-term treatment with MCHR-1 antagonists at doses that would be needed to effect weight loss would also lead to complications with osteoporosis.

In rodents MCH is involved in gonadotropin secretion. When MCH (50, 100, and 200 ng) was injected into the medial preoptic area of anesthetized rats, it was found that luteinizing hormone (LH) release was stimulated over a 2-h period in a dose-dependent manner.[47] The authors of this study concluded that this effect was most likely mediated by the MCH-1 receptor although it is possible that another neuropeptide receptor could have been involved. In another study it was found that MCH increased luteinizing hormone releasing hormone (LHRH) from the median eminence and follicle stimulating hormone (FSH) from the anterior pituitary where MCH receptor mRNA has been detected.[48] Although there are other systems that are known to control the release of LHRH and FSH, it is conceivable that an MCH antagonist could inhibit the release of gonadotropins. Consequently, it is an open question whether MCH antagonists will affect reproductive health in humans.

If the weight loss that resulted from treatment with an MCH receptor antagonist was derived primarily from an increase in thermal energy output, then one would expect to see a significant effect in rodents but perhaps only a minor effect in man. Rodents and small mammals with active brown adipose tissue (BAT) have robust thermogenesis and respond well to drugs that increase energy expenditure (such as β-3 agonists). The effect of MCH antagonists on obese rodents may be BAT-mediated; hypothalamic MCH neurons project to thermogenic brown adipose tissue in the rat,[49] and there is evidence that MCH neural pathways regulate thermogenesis in BAT.[50] If an MCH antago-

nist in obese rodents works through an increase in BAT-mediated energy expenditure, then it is unclear whether one would see a comparable effect in adult humans that lack functional BAT.

For mice that lack both leptin and MCH (double-null mice), leanness was the observed phenotype even though these animals continued to display the hyperphagia consistent with leptin deficiency. The reduction in fat mass was caused by an increase in energy expenditure.[51] If the double-null mouse represents a crude model for a leptin-resistant human undergoing therapy with an MCH antagonist, then it follows that weight reduction would stem predominantly through an increase in energy expenditure rather than through a reduction in food consumption. For many patients and physicians alike, a drug that raises metabolic rate would represent a great advance in obesity therapy. It needs to be demonstrated in the clinic whether an increase in metabolism can be achieved without a concomitant increase in resting heart rate, blood pressure, or internal temperature, which may be considered adverse effects.

Conclusion

Obesity has become the scourge of the developed world, and the need for effective novel therapies has never been greater. With our current knowledge in the area of hypothalamic control of energy balance, it seems a reasonable hypothesis that an MCHR-1 antagonist would represent an efficacious pharmacotherapy for the clinical management of the overweight patient. With so many organizations involved in the discovery of MCHR-1 antagonists, it is likely that one or more of them will select clinical candidate compounds and will test the hypothesis in the clinic. We await the results with great anticipation.

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Biographies

Anthony L. Handlon received his B.A. degree in chemistry from Case Western Reserve University and Ph.D. degree in pharmaceutical chemistry from the University of California, San Francisco. Following postdoctoral research at Duke University under the direction of Bert Fraser-Reid, he joined the Burroughs Wellcome Company in 1993. Currently he is a senior investigator at GlaxoSmithKline, focusing on the discovery of medicines for the treatment of metabolic diseases.

Huiqiang Zhou received his B.S. degree in chemistry and M.S. degree in organic chemistry from Fudan University, Shanghai, China. After several years as a research associate with Professor Hungwen Liu in the Department of Chemistry, University of Minnesota, and with Professor Barry Gold in the Eppley Institute, University of Nebraska Medical Center, he joined GlaxoWellcome Inc. in 1998. Currently, he is a senior scientist working in the metabolic area at GlaxoSmithKline.

References

(1) Sahu, A. Leptin Signalling in the Hypothalamus: Emphasis on Energy Homeostasis and Leptin Resistance. *Front. Neuroendocrinol.* **2004**, *24*, 225−253.
(2) Kershaw, E. E.; Flier, J. S. Adipose Tissue as an Endocrine Gland. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 2548−2556.
(3) Jequier, E. Leptin Signaling, Adiposity, and Energy Balance. *Ann. N. Y. Acad. Sci.* **2002**, *967*, 379−388.
(4) Schwartz, M. W.; Niswender, K. D. Adiposity Signaling and Biological Defense against Weight Gain: Absence of Protection or Central Hormone Resistance? *J. Clin. Endocrinol. Metab.* **2004**, *89*, 5889−5897.
(5) Walder, K.; De Silva, A. Leptin and the Treatment of Obesity. *Drug Dev. Res.* **2000**, *51*, 66−79.
(6) Carpenter, A. J.; Hertzog, D. L. Melanin-Concentrating Hormone Receptor Antagonists as Potential Antiobesity Agents. *Expert Opin. Ther. Pat.* **2002**, *12*, 1639−1646.
(7) Pissios, P.; Maratos-Flier, E. Melanin-Concentrating Hormon: From Fish Skin to Skinny Mammals. *Trends Endocrinol. Metab.* **2003**, *14*, 243−248.
(8) Collins, C. A.; Kym, P. R. Prospects for Obesity Treatment: MCH Receptor Antagonists. *Curr. Opin. Invest. Drugs* **2003**, *4*, 386−394.
(9) Hervieu, G. Melanin-Concentrating Hormone Functions in the Nervous System: Food Intake and Stress. *Expert Opin. Ther. Targets* **2003**, *7*, 495−511.
(10) Kowalski, T. J.; McBriar, M. D. Therapeutic Potential of Melanin-Concentrating Hormone-1 Receptor Antagonists for the Treatment of Obesity. *Expert Opin. Invest. Drugs* **2004**, *13*, 1113−1122.
(11) Saito, Y.; Nothacker, H.-P.; Wang, Z.; Lin, S. H. S.; Leslie, F.; Civelli, O. Molecular Characterization of the Melanin-Concentrating Hormone Receptor. *Nature* **1999**, *400*, 265−269.
(12) Chambers, J.; Ames, R. S.; Bergsma, D.; Muri, A.; Fitzgerald, L. R.; Hervieu, G.; Dytko, G. M.; Foley, J. L.; Mertin, J.; Liu, W.-S.; Park, J.; Ellis, C.; Ganguly, S.; Konchar, S.; Cluderay, J.; Leslie, R.; Wilson, S.; Sarau, H. M. Melanin-Concentrating Hormone Is the Cognate Ligand for the Orphan G-Protein-Coupled Receptor SLC-1. *Nature* **1999**, *400*, 261−265.
(13) Sailer, A. W.; Sano, H.; Zeng, Z.; McDonald, T.; Pan, J.; Pong, S.-S.; Feighner, S. D.; Tan, C. P.; Fukami, T.; Iwaasa, H.; Hreniuk, D. L.; Morin, N. R.; Sadowski, S. J.; Ito, M.; Bansal, A.; Ky, B.; Figueroa, D. J.; Jiang, Q.; Austin, C. P.; MacNeil, D. J.; Ishihara, A.; Ihara, M.; Kanatani, A.; Van der Ploeg, L. H. T.; Howard, A. D.; Liu, Q. Identification and Characterization of a Second Melanin-Concentrating Hormone Receptor, MCH-2R. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 7564−7569.
(14) Bittencourt, J. C.; Presse, F.; Arias, C.; Peto, C.; Vaughan, J.; Nahon, J.-L.; Vale, W.; Sawchenko, P. E. The Melanin-Concentrating Hormone System of the Rat Brain: An Immuno- and Hybridization Histochemical Characterization. *J. Comp. Neurol.* **1992**, *319*, 218−245.
(15) Katsuura, G.; Inui, A. Melanin-Concentrating Hormone as a Metabolic and Cognitive Regulatory Factor. *Curr. Med. Chem.: Cent. Nerv. Syst. Agents* **2003**, *3*, 217−227.
(16) Kokkotou, E.; Tritos, N. A.; Mastaitis, J. W.; Slieker, L.; Maratos-Flier, E. Melanin-Concentrating Hormone Receptor Is a Target of Leptin Action in the Mouse Brain. *Endocrinology* **2001**, *142*, 680−686.
(17) Sone, M.; Takahashi, K.; Murakami, O.; Totsune, K.; Arihara, Z.; Satoh, F.; Sasano, H.; Ito, H.; Mouri, T. Binding Sites for Melanin-Concentrating Hormone in the Human Brain. *Peptides* **2000**, *21*, 245−250.
(18) Qu, D.; Ludwig, D. S.; Gammeltoft, S.; Piper, M.; Pelleymounter, M. A.; Cullen, M. J.; Foulds Mathes, W.; Przypek, J.; Kanarek, R.; Maratos-Flier, E. A Role for Melanin-Concentrating Hormone in the Central Regulation of Feeding Behaviour. *Nature* **1996**, *380*, 243−247.
(19) Gomori, A.; Ishihara, A.; Ito, M.; Mashiko, S.; Matsushita, H.; Yumoto, M.; Ito, M.; Tanaka, T.; Tokita, S.; Moriya, M.; Iwaasa, H.; Akio, K. Chronic Infusion of MCH Causes Obesity in Mice. *Am. J. Physiol. Endocrinol. Metab.* **2002**, *284*, E583−E588.
(20) 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.
(21) Willie, J. T.; Chemelli, R. M.; Sinton, C. M.; Yanagisawa, M. To Eat or To Sleep? Orexin in the Regulation of Feeding and Wakefulness. *Annu. Rev. Neurosci.* **2001**, *24*, 429−458.
(22) 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.
(23) Marsh, D. J.; Weingarth, D. T.; Novi, D. E.; Chen, H. Y.; Trumbauer, M. E.; Chen, A. S.; Guan, X.-M.; Jiang, M. M.; Feng, Y.; Camacho, R. E.; Shen, Z.; Frazier, E. G.; Yu, H.; Metzger, J. M.; Kuca, S. J.; Shearman, L. P.; Gopal-Truter, S.; MacNeil, D. J.; Strack, A. M.; Macintyre, D. E.; Van der Ploeg, L. H. T.; Qian, S. Melanin-Concentrating Hormone 1 Receptor-Deficient Mice Are Lean, Hyperactive, and Hyperphagic and Have Altered Metabolism. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 3240−3245.
(24) Chen, Y.; Changzhi, H.; Chiun-Kang, H.; Zhang, Q.; Bi, C.; Asnicar, M.; Hsiung, H. M.; Fox, N.; Slieker, L. J.; Yang, D. D.; Heiman, M. L.; Shi, Y. Targeted Disruption of the Melanin-Concentrating Hormone Receptor-1 Results in Hyperphagia and Resistance to Diet-Induced Obesity. *Endocrinology* **2002**, *143*, 2469−2477.

(25) Smith, D. G.; Tzavara, E. T.; Shaw, J.; Luecke, S.; Wade, M.; Davis, R.; Salhoff, C.; Nomikos, G. G.; Gehlert, D. R. Mesolimbic Dopamine Super-sensitivity in Melanin-Concentrating Hormone-1 Receptor-Deficient Mice. *J. Neurosci.* **2005**, *25*, 914−922.
(26) Browning, A. Recent Developments in the Discovery of Melanin-Concentrating Hormone Antagonists: Novel Antiobesity Agents. *Expert Opin. Ther. Pat.* **2004**, *14*, 313−325.
(27) Arienzo, R.; Clark, D. E.; Cramp, S.; Daly, S.; Dyke, H. J.; Lockey, P. M.; Norman, D.; Roach, A. G.; Stuttle, K.; Tomlinson, M.; Wong, M.; Wren, S. P. Structure−Activity Relationships of a Novel Series of Melanin-Concentrating Hormone (MCH) Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **2004**, 4099−4102.
(28) Marzabadi, M. R.; Wetzel, J. M.; Chen, C.; Jiang, Y.; Lu, K. Substituted Alkyl Amido Piperidines. WO2004/064764, 2004.
(29) Kaku, H.; Kondoh, Y.; Hayashibe, S.; Kamikubo, T.; Iwasaki, F.; Matsumoto, S. Antagonists to Melanin-Concentrating Hormone Receptor. WO2004/046110, 2004.
(30) Moriya, M.; Sakamoto, T.; Ishikawa, M.; Kanatani, A.; Fukami, T. Melanin-Concentrating Hormone Receptor Antagonists Containing Piperidine Derivatives as the Active Ingredient. WO2004/069798, 2004.
(31) Muller, S. G.; Stenkamp, D.; Arndt, K.; Roth, G. J.; Lotz, R. R. H.; Lehmann-Lintz, T.; Lenter, M.; Lustenberger, P.; Rudolf, K. Novel Alkyne Compounds Having an MCH Antagonistic Effect and Medicaments Containing These Compounds. WO2004/039780, 2004.
(32) Sekigushi, Y.; Kanuma, K.; Busujima, T.; Tran, T.; Han, S.; Casper, M.; Kramer, B. A.; Semple, G.; Zou, N. Quinoline, Tetrahydroquinoline and Pyrimidine Derivatives as MCH Antagonist. EP1464335, 2004.
(33) Sasikumar, T. K.; Wu, W.; Burnett, D. A.; Qiang, L. Biaryltetrahydroisoquinoline Piperidines as Selective MCH Receptor Antagonists for the Treatment of Obesity and Related Disorders. WO2004/078745, 2004.
(34) Souers, A. J.; Wodka, D.; Gao, J.; Lewis, J. C.; Vasudevan, A.; Gentles, R.; Brodjian, S.; Dayton, B.; Ogiela, C. A.; Fry, D.; Hernandez, L. E.; Marsh, K. C.; Collins, C. A.; Kym, P. R. Synthesis and Evaluation of 2-Amino-8-alkoxy Quinoline as MCHR1 Antagonists. Part 1. *Bioorg. Med. Chem. Lett.* **2004**, 4873−4877.
(35) Vasudevan, A.; Wodka, D.; Verzal, M. K.; Souers, A. J.; Gao, J.; Brodjian, S.; Fry, D.; Dayton, B.; Marsh, K. C.; Hernandez, L. E.; Ogiela, C. A.; Collins, C. A.; Kym, P. R. Synthesis and Evaluation of 2-Amino-8-alkoxy Quinoline as MCHR1 Antagonists. Part 2. *Bioorg. Med. Chem. Lett.* **2004**, 4879−4882.
(36) Souers, A. J.; Wodka, D.; Gao, J.; Lewis, J. C.; Vasudevan, A.; Brodjian, S.; Dayton, B.; Ogiela, C. A.; Fry, D.; Hernandez, L. E.; Marsh, K. C.; Collins, C. A.; Kym, P. R. Synthesis and Evaluation of 2-Amino-8-alkoxy Quinolines as MCHr1 Antagonists. Part 3. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4883−4886.
(37) Guo, T.; Hunter, R. C.; Gu, H.; Rokosz, L. L.; Stauffer, T. M.; Hobbs, D. W. Discovery and SAR of 4-Amino-2-biarylbutylurea MCH 1 Receptor Antagonists through Solid-Phase Parallel Synthesis. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3691−3695.
(38) Borowsky, B.; Durkin, M. M.; Ogozalek, K.; Marzabadi, M. R.; DeLeon, J.; Heurich, R.; Lichtblau, H.; Shaposhnik, Z.; Daniewska, I.; Blackburn, T. P.; Branchek, T. A.; Gerald, C.; Vaysse, P. J.; Forray, C. Antidepressant, Anxiolytic and Anorectic Effects of a Melanin-Concentrating Hormone-1 Receptor Antagonist. *Nat. Med.* **2002**, *8*, 825−830.
(39) Takekawa, S.; Asami, A.; Isihara, Y.; Terauchi, J.; Kato, K.; Shimomura, Y.; Mori, M.; Murakoshi, H.; 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.
(40) Kowalski, T. J.; Farley, C.; Cohen-Williams, M. E.; Varty, G.; Spar, B. D. Melanin-Concentrating Hormone-1 Receptor Antagonism Decreases Feeding by Reducing Meal Size. *Eur. J. Pharmacol.* **2004**, *497*, 41−47.
(41) Handlon, A. L.; Al-Barazanji, K. A.; Barvian, K. K.; Bigham, E. C.; Carlton, D. L.; Carpenter, A. J.; Cooper, J. P.; Daniels, A. J.; Garrison, D. T.; Goetz, A. S.; Green, G. M.; Grizzle, M. K.; Guo, Y.; Hertzog, D. L.; Hyman, C. E.; Ignar, D. M.; Peckham, G. E.; Speake, J. S.; Britt, C.; Swain, W. R. Discovery of Potent and Selective MCH Receptor-1 Antagonists for the Treatment of Obesity. Presented at the American Chemical Society National Meeting Symposium on Anti-Obesity Therapy, Philadelphia, PA, 2004.
(42) Huang, C. Q.; Baker, T.; Schwarz, D.; Fan, J.; Heise, C. E.; Zhang, M.; Goodfellow, V. S.; Markison, S.; Gogas, K. R.; Chen, T.; Wang, X.-C.; Zhu, Y.-F. 1-(4-Amino-phenyl)-pyrrolidin-3-yl-amine and 6-(3-amino-pyrrolidin-1-yl)-pyridin-3-yl-amine Derivatives as Melanin-Concentrating Hormone Receptor-1 Antagonists. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3701−3706.
(43) 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. Biaryl Ureas as Potent and Orally Efficacious Melanin-Concentrating Hormone Receptor 1 Antagonists for the Treatment of Obesity. *J. Med. Chem.* **2005**, *48*, 4746−4749.
(44) Vasudevan, A.; Verzal, M. K.; Wodka, D.; Souers, A. J.; Blackburn, C.; Che, J. L.; Lai, S.; Brodjian, S.; Falls, D. H.; Dayton, B. D.; Govek, E.; Daniels, T.; Geddes, B.; Marsh, K. C.; Hernandez, L. E.; Collins, C. A.; Kym, P. R. Identification of Aminopiperidine Benzamides as MCHr1 Antagonists. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3412−3416.
(45) 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.
(46) Bohlooly-Y. M.; Mahlapuu, M.; Andersen, H.; Astrand, A.; Hjorth, S.; Svensson, L.; Tornell, J.; Snaith, M. R.; Morgan, D. G.; Ohlsson, C. Osteoporosis in MCHR-1-Deficient Mice. *Biochem. Biophys. Res. Commun.* **2004**, *318*, 964−969.
(47) Murray, J. F.; Adan, R. A. H.; Walker, R.; Baker, B. I.; Thody, A. J.; Nijenhuis, W. A. J.; Yukitake, J.; Wison, C. A. Melanin-Concentrating Hormone, Melanocortin Receptors and Regulation of Luteinizing Hormone Release. *J. Neuroendocrinol.* **2000**, *12*, 217−223.
(48) Chiocchio, S. R.; Gallardo, M. G. P.; Louzan, P.; Gutnisky, V.; Tramezzani, J. H. Melanin-Concentrating Hormone Stimulates the Release of Luteinizing Hormone-Releasing Hormone and Gonadotropins in the Female Rat Acting at Both Median Eminence and Pituitary Levels. *Biol. Reprod.* **2001**, *64*, 1466−1472.
(49) Oldfield, B. J.; Giles, M. E.; Watson, A.; Anderson, C.; Colvill, L. M.; McKinley, M. J. The Neurochemical Characterisation of Hypothalamic Pathways Projecting Polysynaptically to Brown Adipose Tissue in the Rat. *Neuroscience* **2002**, *110*, 515−526.
(50) Ito, M.; Gomori, A.; Ishihara, A.; Oda, Z.; Mashiko, S.; Matsushita, H.; Yumoto, M.; M., I.; Sano, H.; Tokita, S.; Moriya, M.; Iwaasa, H.; Kanatani, A. Characterization of MCH-Mediated Obesity in Mice. *Am. J. Physiol. Endocrinol. Metab.* **2003**, *284*, E940−E945.
(51) Segal-Lieberman, G.; Bradley, R. L.; Kokkotou, E.; Carlson, M.; Trombly, D. J.; Wang, X.; Bates, S.; Myers, M. G.; Flier, J. S.; Maratos-Flier, E. Melanin-Concentrating Hormone Is a Critical Mediator of the Leptin-Deficient Phenotype. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 10085−10090.

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