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Identification of *ortho*-amino benzamides and nicotinamides as MCHr1 antagonists

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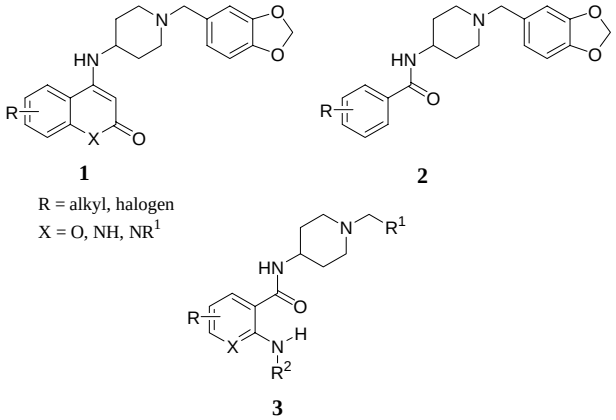
Abstract—Several potent and efficacious MCHr1 antagonists containing an *ortho*-amino benzamide or nicotinamide chemotype have been identified, exemplified by **28** and **50**.

Melanin concentrating hormone (MCH) is an orexigenic neuropeptide found in the lateral hypothalamus.[1,2] ICV injection of MCH stimulates food intake in mice and rats, and mice lacking MCH are lean, hypophagic, and have an increased metabolic rate.[3] Furthermore, the murine MCH receptor knockout displayed a normal body weight with reduced fat mass, was hyperphagic on regular chow, and was less susceptible to diet-induced obesity.[4,5] Infusion (ICV) of MCH did not induce food intake or obesity in the knockout mice. The pharmacological validation from these studies suggests that MCHr1 antagonists may provide a novel therapy for obesity.[6]

We have previously reported the identification of coumarin and quinolone-containing MCHr1 antagonists, **1**.[7] Optimization of a distinct series of compounds originating from a high throughput screening hit led to the identification of potent MCHr1 antagonists of general structure **2**.[8] During the SAR investigation leading to the identification of **2**, introduction of hydrophobic substituents at the *ortho* position of the phenyl ring led to a significant diminution of MCHr1 inhibition.[8] However, working under the assumption that **1** and **2** should interact with MCHr1 in similar orientations, we hypothesized that introduction of an *ortho*-amino group on the benzamide scaffold (**2** → **3**) should allow for conformational restriction via intramolecular hydrogen bonding between the amine N–H (donor) and the carbonyl (acceptor). Not only should such compounds adopt a similar binding motif to MCHr1 as **1**, the ensuing structural simplification would allow for an additional synthetic handle and increased ease of chemical manipulation. These efforts are described in this letter.



Keywords: MCH; Obesity; Benzamides; Nicotinamides; Melanin concentrating hormone.
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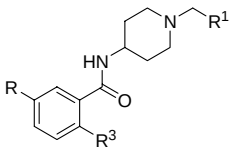
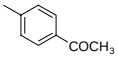
Table 1. MCHr1 binding affinity (IC_{50}) and functional activity (IC_{50}), in μM, of benzamide analogs[a]



No.	R	R^1	R^3	IMR32 binding	IMR32 FLIPR™
7[8]	Cl		H	0.11	—
8	Cl		OH	0.08	0.51
9	Cl		NH_2	0.009	0.20
10	Cl		$NHCH_3$	0.68	—
11	Cl		$NHSO_2CH_3$	0.56	—
12	OCH_3		$NHSO_2CH_3$	0.26	—
13	OCH_3		$NHSO_2CH_3$	0.16	—
14	OCH_3			0.22	—
15	OCH_3			0.01	0.09
16	OCH_3			0.05	1.06
17	OCH_3			0.02	0.04
18	OCH_3			0.009	0.07
19	OCH_3			0.07	0.22
20	OCH_3			0.02	0.05
21	OCH_3			0.09	0.10
22	OCH_3			0.39	1.94
23	OCH_3			0.07	0.10
24	H			0.41	—
25	Cl			0.01	0.24
26	OCH_3			0.02	0.07
27	Cl			0.02	0.37
28	Cl			0.002	0.016
29	Cl			0.006	0.04
30	Cl			0.02	0.03

[a] Values are means of three experiments.

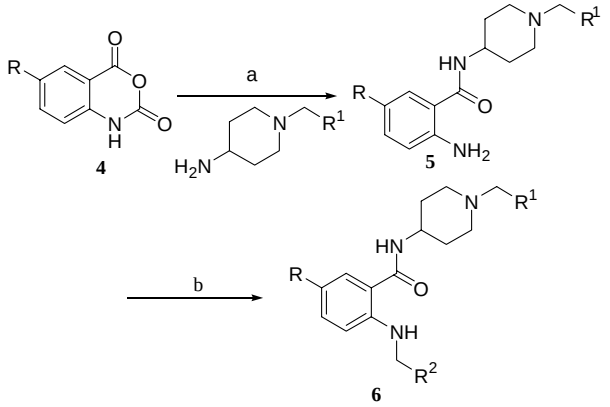
The synthesis of the compounds containing an *ortho*-amino benzamide scaffold was accomplished via ring opening of a substituted isatoic anhydride by a suitably functionalized 4-amino-piperidine followed by reductive amination with various alkyl and aryl groups using sodium triacetoxyborohydride as shown in Scheme 1.

Using these synthetic strategies, several *ortho*-amino benzamide analogs were synthesized. MCHr1 binding data for selected analogs, determined using methods described previously,[9] are shown in Table 1. Compounds demonstrating MCHr1 binding affinity less than 100 nM were evaluated in an IMR32 FLIPR-based assay[9] for functional activity. Introduction of a hydroxy or amino moiety to afford **8** (MCHr1 IC_{50} = 80 nM) and **9** (MCHr1 IC_{50} = 9 nM), respectively, at the *ortho* position to the benzamide resulted in an improvement in MCHr1 binding affinity compared to **7** (MCHr1 IC_{50} = 110 nM)[8]. However, the functional potency for both analogs was weaker than 200 nM. *N*-methylation of **9** resulted in a significant reduction in MCHr1 binding affinity. Sulfonylation and urea formation at the amino group of **9** also decreased MCHr1 binding affinity, illustrated by piperonyl and *para*-chloro phenyl substituted analogs **11**–**14**. Functionalization of the *ortho*-amino group with alkyl substituents larger than methyl afforded potent MCHr1 antagonists, with **15** and **17** demonstrating MCHr1 functional antagonism less than 100 nM. Introduction of heteroaryl moieties at this position afforded interesting results. In general, it was observed that a variety of heterocyclic substituents such as imidazoles, pyrimidines, and thiazoles afforded potent MCHr1 inhibitors, though the nature of the R^1 substituent played a major role in the inhibitory potency of these analogs. The pyrimidine substituted analog **18** was as potent as **9** in binding activity, though the functional potency was improved approximately 3-fold. Imidazole substituted analogs were in general less potent than **18**—however, significant differences in MCHr1 binding affinity and functional antagonism were observed depending on the nature of the R^1 substituent (**20**, **22**, **23**, and **25**).

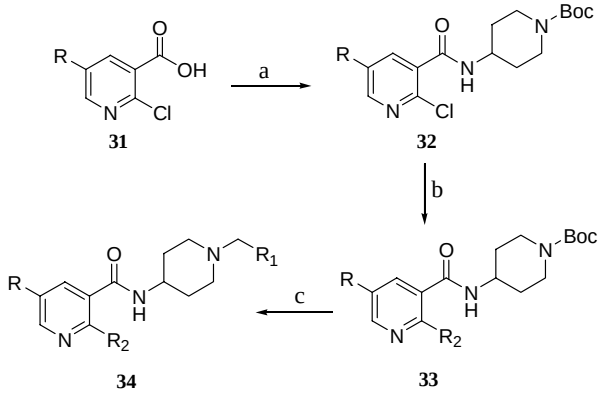
Acylation of the *ortho*-amino group afforded compounds comparable in potency to the reductively aminated compounds, though the functional potency was compromised (**27** and **26**, respectively). Introduction of a 2-thiazolyl moiety afforded **28**, with the best combination of MCHr1 inhibition and functional activity. The 2-thiazolyl moiety was well tolerated with various other R^1 substituents as well, illustrated by compounds **29** and **30**.

The effect of introduction of a nitrogen atom in the benzamide scaffold to afford nicotinamide analogs was also investigated. It was postulated that if potent MCHr1 antagonists could be realized from this series, they would afford different brain:plasma distribution compared to the benzamide analogs.[10] The synthesis of these nicotinamide analogs was accomplished as shown in Scheme 2. Acylation of 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester with a suitably substituted nicotinic acid, followed by nucleophilic displacement, deprotection, and reductive amination afforded the desired analogs.

The biological activities of some of the nicotinamide analogs synthesized in this study are shown in Table 2, and indicate that several potent MCHr1 antagonists, some of which were also active in the FLIPR assay, were attainable with these *ortho*-amino substituted nicotinamide analogs. Two trends were apparent in the analysis of MCHr1 binding affinity of these nicotinamide analogs—the importance of the *ortho* amine functionality, as well as the influence of the R^1 substituent. The latter effect is especially apparent in the comparison of **38** with **39** and **40** with **41**. Alkyl, aryl, and heteroaryl amine moieties were generally well tolerated at R^2, depending on the R^1 substituent. Similar to the benzamide scaffold, functionalization of the *ortho*-amino group with thiazole and imidazole moieties afforded potent MCHr1 inhibition and functional antagonism. Additionally, alkyl ether substituted analogs such as **50** afforded excellent MCHr1 inhibition and FLIPR activity. Replacement of the chloro functionality at R with aryl moieties resulted in a diminution of MCHr1 affinity. Further, moving



Scheme 1. Reagents and conditions: (a) Et_3N, *N*,*N*-dimethylformamide, 100 °C, 62–90% (b) R^2CHO, $NaB(OAc)_3H$, *N*,*N*-dimethylformamide, 50 °C, 12 h, 52–75%.

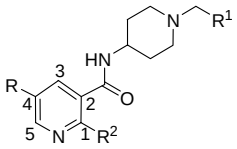


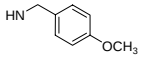
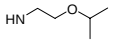
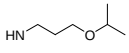
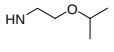
Scheme 2. Reagents and conditions: (a) 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, PS-DCC,[11] HOBt, *N*,*N*-dimethylformamide, 25 °C (72–90%); (b) R_2, *N*-methylpyrrolidone, μwave, 200 °C, 20 min, (42–65%); (c) i—4 N HCl/dioxane, 25 °C, 4 h, (quantitative); ii—R_1CHO, MP-BH_3CN[12], 1:1 1,2-dichloroethane:CH_3OH, 50 °C (51–69%).

the R^2 substituent to the 5-position of the nicotinamide nucleus resulted in abrogation of MCHr1 binding affinity (data not shown), consistent with the proposed binding mode alluded to above.

Having successfully demonstrated potent MCHr1 binding affinity and functional antagonism with these novel *ortho*-amino benzamide and nicotinamide analogs, we next sought to characterize the series further in vivo, utilizing murine pharmacokinetic (PK) analysis and weight-loss efficacy studies. Accordingly, several analogs were evaluated in a diet-induced obesity (DIO) mouse model using methods described before,[9] and selected data are shown in Table 3.

Table 2. MCHr1 binding affinity (IC_{50}) and functional activity (IC_{50}), in μM, of nicotinamide analogs[a]



No.	R	R^1	R^2	IMR32 binding	IMR32 FLIPR^{TM}
35	Cl		Cl	2.01	—
36	Cl			0.02	0.03
37	Cl			0.07	0.07
38	Cl			0.07	0.03
39	Cl			1.98	—
40	Cl			0.02	0.05
41	Cl			0.16	—
42	Cl			0.02	0.02
43	Cl			0.41	—
44	Cl			0.06	1.22
45	Cl			0.01	0.03
46	Cl			0.02	0.07
47	Cl			0.009	0.02
48	Cl			0.004	0.008
49	Cl			0.006	0.009
50	Cl			0.01	0.02
51	Cl			0.007	0.06
52	Cl			0.05	0.02
53				0.19	—
54				0.14	—

[a] Values are means of three experiments.

Table 3. Plasma and brain exposure of **28** and **50** in DIO mice after 10 mg/kg oral dose

	28	**50**
Plasma AUC (ng h/ml)	4104	677
Brain AUC (ng h/ml)	2860	570
Plasma $T_{1/2}$ (h)	3.8	2.3
Brain $T_{1/2}$ (h)	7.8	1.4
Plasma C_{max} (ng/ml)	2032	283
Brain C_{max} (ng/ml)	814	276
Brain/plasma AUC	0.7	0.84

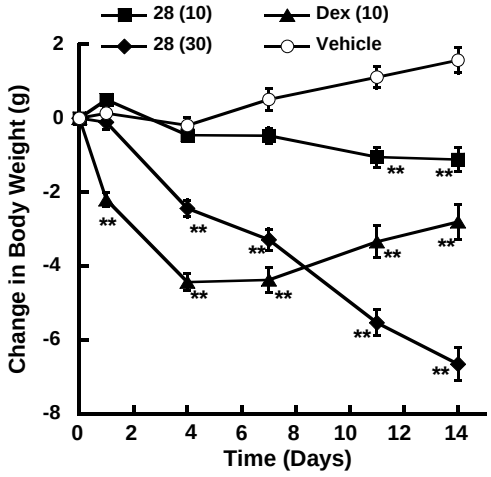


Figure 1. Effect of compound **28** (dosed at 10 and 30 mg/kg, b.i.d., p.o., in 1% Tween 80 in water) on the body weight of DIO mice.

Compound **28** provided high plasma concentrations, with a C_{max} of 2032 ng/ml and a half-life of ~4 h. Peak brain concentrations averaged 814 ng/ml, with a brain to plasma AUC ratio of 0.7. In the case of **50**, peak plasma and brain concentrations were very similar (~280 ng/ml), with plasma elimination half life averaged ~2 h, and a brain to plasma AUC ratio of 0.8.

Compounds **28** and **50** were then evaluated in an efficacy study measuring food intake and body weight in DIO mice.[9] Compounds were dosed at 10 and 30 mg/kg b.i.d. (p.o.) with body weights and food intake measured at day 0, 1, 4, 7, 11, and 14. Compound **28** dosed at 10 mg/kg produced a significant weight loss on days 11 and 14, whereas at 30 mg/kg significant weight loss was seen on days 4, 7, 11, and 14 (Fig. 1). The absolute weight loss for the 30 mg/kg dose group was approximately 7 g (15%), and subsequent dual-energy X-ray absorptiometry (DEXA)[12] analysis revealed that the change in body weight was due to loss of fat mass. Notably, food consumption and locomotor behavior were unaffected, indicating that this compound was not causing weight loss due to general overt toxicity. Compound **50**, when dosed at 30 mg/kg, b.i.d, also produced significant weight loss (Fig. 2). There was no significant weight loss seen with **50** at 10 mg/kg. In the Irwin behavioral study (data not shown), there was no evidence of hypothermia or gross abnormalities when dosed at 100 mg/kg.

In conclusion, several potent MCHr1 antagonists based on *ortho*-amino benzamide and nicotinamide scaffolds

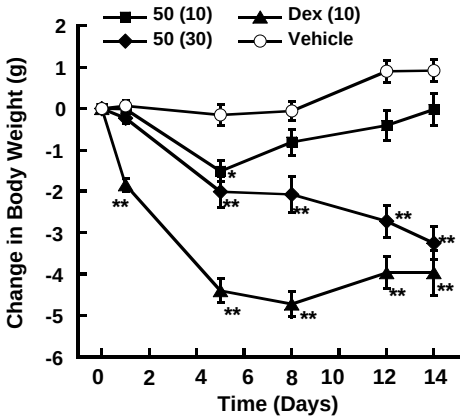


Figure 2. Effect of compound **50** (dosed at 10 and 30 mg/kg, b.i.d., p.o., in 1% Tween 80 in water) on the body weight of DIO mice.

have been designed, synthesized, and evaluated for the treatment of obesity. The intramolecular hydrogen-bonding network effectively mimics amino-piperidine coumarin and amino-piperidine quinolone MCHr1 antagonists, providing a simplified scaffold amenable to extensive SAR development. Compounds from both these series exhibit dose-dependent sustained efficacy in an obese murine weight-loss model.

Acknowledgments

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References and notes

1. Bittencourt, J. C.; Presse, F.; Arias, C.; Peto, C.; Vaughan, J.; Nahon, J. L.; Vale, W.; Sawchenko, P. E. *J. Comp. Neurol.* **1992**, *319*, 218.
2. Skofitsch, G.; Jacobowitz, D. M.; Zamir, N. *Brain Res. Bull.* **1985**, *15*, 635.
3. Qu, D.; Ludwig, D. S.; Gammeltoft, S.; Piper, M.; Pelleymounter, M. A.; Cullen, M. J.; Mathes, W. F.; Przypek, R.; Kanarek, R.; Maratos-Flier, E. *Nature* **1996**, *380*, 243.
4. Marsh, D. J.; Weingarth, D. T.; Novi, D. E.; Chen, H. Y.; Trumbauer, M. E.; Chen, A. S.; Guan, X.; 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.; Vander, P. L. H. T.; Qian, S. *Proc. Natl. Acad. Sci. USA* **2002**, *99*(5), 3240.
5. Chen, Y.; Hu, C.; Hsu, C.; Zhang, Q.; Bi, C.; Asnicar, M.; Hsiung, H. M.; Fox, N.; Slieker, L. J.; Yang, D. D.; Heiman, M. L.; Shi, Y. *Endocrinology* **2002**, *143*(7), 2469.
6. (a) Takekawa, S.; Asami, A.; Ishihara, Y.; Terauchi, J.; Kato, K.; Shimomura, Y.; Mori, M.; Murakoshi, H.; Kato, K.; Suzuki, N.; Nishimura, O.; Fujino, M. *Eur. J. Pharmacol.* **2002**, *438*, 129; (b) Borowsky, B.; Durkin, M. M.; Ogozalek, K.; Marzabadi, M. R.; DeLeon, J.; Lagu, B.; Heurich, R.; Lichtblau, H.; Shaposhnik, Z.; Daniewska, I.; Blackburn, T. P.; Branchek, T. A.; Gerald, C.; Vaysse, P. J.; Forray, C. *Nat. Med.* **2002**, *8*, 779; (c) Collins, C. A.; Kym, P. R. *Curr. Opin. Invest. Drugs* **2003**,

4(4), 386; (d) Browning, A. *Expert Opin. Ther. Patents* **2004**, *14*(3), 313; (e) Carpenter, A. J.; Hertzog, D. L. *Expert Opin. Ther. Patents* **2002**, *12*(11), 1639.

7. (a) Bush, E.; Fey, T.; Dickinson, R.; Shapiro, R.; Knourek-Segel, V.; Droz, B.; McDowell, C.; Jacobson, P.; Nuss, M.; Souers, A.; Iyengar, R.; Kym, P.; Collins, C.; Brune, M. *Obesity Res.* **2004**, *12*(S), A14; (b) Blackburn, C.; Lai, S.; Lee, J. G.; Maguire, M.; Patane, M. A.; LaMarche, M. J.; Cullis, C. A.; Brown, J.; Vasudevan, A.; Freeman, J. C.; Mulhern, M. M.; Lynch, J. K.; Gao, J.; Wodka, D.; Souers, A. J.; Iyengar, R. WO2003106452.; (c) Kym, P. R.; Iyengar, R.; Souers, A. J.; Lynch, J. K.; Judd, A. S.; Gao, J.; Freeman, J.; Mulhern, M.; Zhao, G.; Vasudevan, A.; Wodka, D.; Blackburn, C.; Brown, J.; Che, J. L.; Cullis, C.; Lai, S.; LaMarche, M. J.; Marsilje, T.; Roses, J.; Sells, T.; Geddes, B.; Govek, E.; Patane, M.; Fry, D.; Dayton, B. D.; Brodjian, S.; Falls, D.; Brune, M.; Bush, E.; Shapiro, R.; Knourek-Segel, V.; Fey, T.; McDowell, C.; Reinhart, G. A.; Preusser, L. C.; Marsh, K.; Hernandez, L.; Sham, H. L.; Collins, C. A. *J. Med. Chem*. [in review].
8. Vasudevan, A.; Verzal, M. K.; Wodka, D.; Souers, A.; Blackburn, C.; Che, L. C.; Lai, S.; Brodjian, S.; Falls, D.; Dayton, B.; Govek, E.; Daniels, T.; Geddes, B.; Marsh, K. C.; Hernandez, L. E.; Collins, C. A.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3412.
9. (a) 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. *Bioorg. Med. Chem. Lett.* **2004**, *14*(19), 4873; (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.
10. Clark, D. E. *J. Pharm. Sci.* **1999**, *88*(8), 815.
11. PS-DCC and MP-BH_3CN were purchased from Argonaut Technologies (www.argotech.com).
12. Sjogren, K.; Hellberg, N.; Bohlooly, Y. M.; Savendahl, L.; Johansson, M. S.; Berglindh, T.; Bosaeus, I.; Ohlsson, C. *J. Nutr.* **2001**, *131*(11), 2963.