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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 15 (2005) 4174–4179

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

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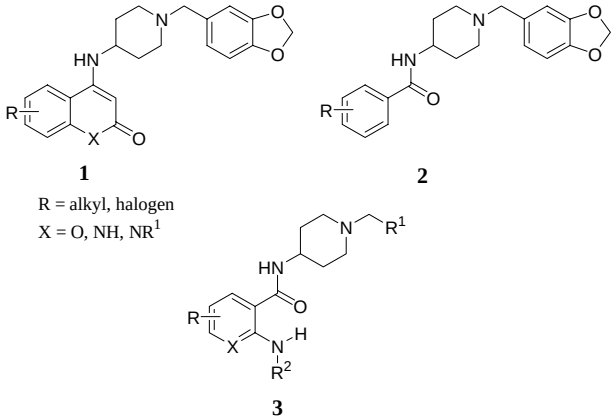
Received 6 May 2005; revised 27 June 2005; accepted 29 June 2005

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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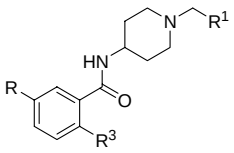
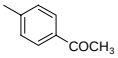
0960-894X/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.bmcl.2005.06.089

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.