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Potent, selective MCH-1 receptor antagonists

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Abstract—This paper describes the lead optimization of a new series of potent, selective, orally bioavailable, brain-penetrant MCH-1 receptor antagonists. A major focus of the work was to achieve a selectivity profile appropriate for in vivo efficacy studies and safety.

Obesity is a major risk factor for many serious diseases including diabetes mellitus, hypertension, cardiovascular disease, and stroke.[1] At the present time, more than 1 billion adults are overweight (BMI $\geqslant$ 25) and 300 million are obese (BMI $\geqslant$ 30). Perhaps more troubling, the number of obese adolescents has tripled since 1980. A clear factor in this trend has been an increase in calorie consumption. The past 50 years has seen an increased accessibility of pre-packaged, calorie-dense foods that are high in fat and simple sugars.[2] During the same period of time, it has been established that the hypothalamus is a critical 'feeding center'[3] and that numerous receptors in the hypothalamus and other brain regions mediate satiety[4] and that these receptors are likely to become dysregulated upon chronic overfeeding and caloric imbalance.[5] Returning these receptors to a state resembling normal function via small-molecule drugs is potentially a viable therapeutic strategy for obesity.

Melanin concentrating hormone (MCH) is a peptide hormone that was first isolated from teleost fish pituitary gland in which it plays a role in skin pigmentation.[6] In rats, MCH is a 19-amino acid peptide that is expressed primarily in the lateral hypothalamus, a brain region known to play a central role in appetite and energy homeostasis. MCH is the native ligand of two G-protein-coupled receptors, MCHR1 and MCHR2. The two receptors show 37% sequence homology. Rodents express only MCHR1; humans, monkeys, dogs, and other higher mammals express both MCHR1 and MCHR2. The role of MCHR2 in humans is not clear and the published studies quite clearly show that MCHR1 mediates the effects of MCH peptide on satiety and energy balance.[6b] MCHR1 knockout mice are lean and hypophagic.[7] Central (icv) administration of MCH elicits increased food intake and body weight gain in rodents[8] and in sheep.[9] Although there are no reports of the effects of MCH antagonists in humans, increased MCH receptor levels were observed in the infundibular nucleus levels in human post-mortem brain tissue from cachectic patients.[10] Taken together, these studies suggest that a selective, small-molecule MCHR1 antagonist would be an effective drug for the treatment of human obesity.

There are a relatively large number of published research papers and patent applications describing MCHR1 antagonists.[11] Based upon our analysis of the published data as well as our experimental evaluation of reported compounds we conclude that potent *and* selective MCH receptor antagonists are quite rare and were obtained through considerable chemical lead optimization. The critical importance of compound

Keywords: MCHR1; Antagonist; Indanylmethyl; Selectivity.
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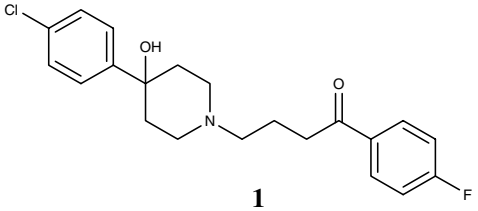
selectivity is twofold: (1) high selectivity over a broad spectrum of receptors and enzymes is essential for an acceptable human safety profile and (2) compound selectivity is critical in pre-clinical animal studies in order to establish that the effects of the compound on food intake and body weight loss can be attributed to the target receptor rather than to any of the myriad causes for reduction in food intake and body weight in rodents such as stress, sedation, nausea, and other toxicities. This paper will describe our effort to develop potent and selective MCH receptor antagonists for the treatment of obesity.

Our high-throughput screen for MCHR1 antagonists produced numerous hits, among them haloperidol (**1**) and 2-hydroxypropanolamine (**2**). Haloperidol has been reported by other groups to be an MCHR1 antagonist.[12] A series of diamines of which **2** is a prototype was the focus of our initial efforts but compounds of this type showed brain accumulation in vivo when dosed sub-chronically.



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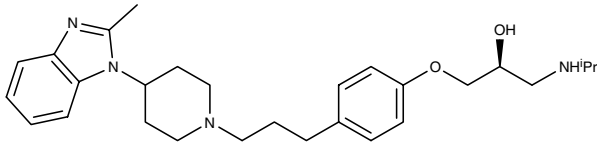


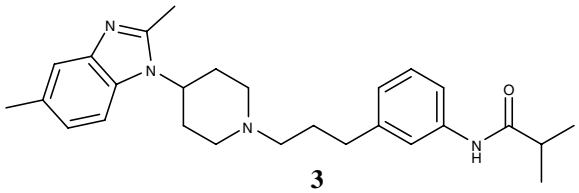
2

A focused effort to remove the hydroxypropanolamine side chain from **2** gave rise to aryl amide **3**. Selectivity data for **3** are shown in Table 1. The receptors for the selectivity panel were chosen based on the following considerations: (1) the receptor is known or likely to influence food intake and/or energy expenditure; (2) the receptor is known to have an affinity for arylpiperidines; (3) receptors critical for an acceptable safety profile. Finally, cost of attaining selectivity data was an issue in maintaining the number of receptors in the panel to 10–15.

The relatively high potency at opioid mu and the serotonin and norepinephrine transporters was unacceptable; moreover, a functional assay showed **3** to be a full agonist at the opioid mu receptor. The salient SAR of compound **3** and related analogs are the following: (1) numerous 4-arylpiperidines gave potent compounds but 3-[2-methylbenzimidazolyl]piperidine analogs were superior in terms of selectivity; (2) lengthening or shortening the 3-carbon chain gave inactive compounds; (3) the presence of a 5-methyl group on benzimidazole improves potency and selectivity; (4) para-substitution of the aryl amide gave inactive compounds; (5) small alkyl amides were preferred. The addition of a methoxy group at the 3-position to give piperidine, **4**, gave a marginally better selectivity profile. Both enantiomers of the 3,4-disubstituted piperidines gave similar potency and selectivity.

Our surmise was that rigidifying the flexible three carbon 'linker' between the piperidine and the aryl ring was critical to improving receptor selectivity. We identified numerous linkers that gave potent analogs including cyclopentyl, cyclobutyl, cyclopropylmethyl, and dihydrobenzofuran but indanylmethyl, **5**, was clearly superior in terms of receptor selectivity. The analog shown is the R-indane but we found that both enantiomers of indane gave similar potency and selectivity.

Table 1. Selectivity profile for compounds **3**, **4** and **5**[13]



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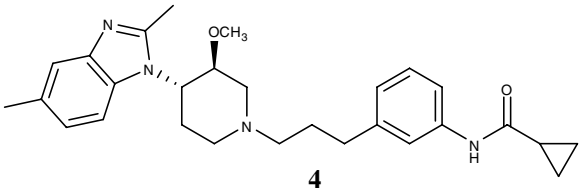

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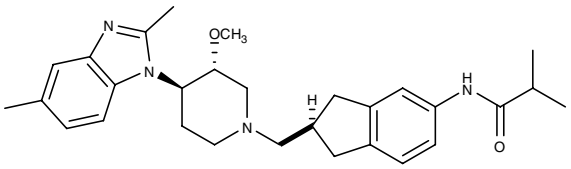


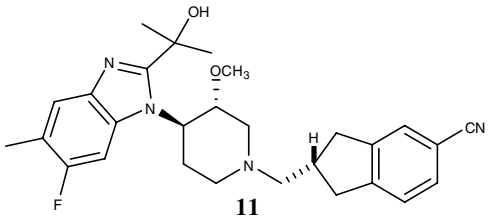
5

Receptor/compound	3	4	5
MCHR1; K_i[a] (nM)	25	5.2	31
MCHR1; EC_{50}[b] (nM)/max. eff.	175/96%	20/82%	40/74%
Human receptors[c,d]			
Adrenergic α_{2A}	37	15	7
Dopamine D_3	46	52	13
Muscarinic M2	18	11	3
Opiate κ	46	38	13
Opiate μ	97	74	45
Serotonin $5HT_{2C}$	4	−23	3
Somatostatin-5 (SST5)	13	16	−12
Dopamine transporter	23	32	10
Norepinephrine transporter	57	61	1
Serotonin transporter	83	67	32

[a] MCHR1 binding assay (see Supplemental Data).
[b] Functional cAMP assay (see Supplemental Data).
[c] Experiments were conducted at MDS-Panlabs.
[d] Values are % inhibition of receptor ligand binding at 10 μM.

Isobutyryl amide, **5**, is selective and potent but showed high in vivo clearance and poor brain exposure when dosed orally. Data from related analogs suggested that the aryl amide negatively influenced both of these parameters. Table 2 shows the SAR of additional indane analogs. 5-Methyl carbamate, **6**, is potent and metabolically more stable than amide 5 but much less selective. Surprisingly, **7**, the 5-bromo analog, was found to be a potent, functional MCHR1 antagonist. The unsubstituted indane, **8**, is also a potent antagonist. Replacing the 2-methyl of benzimidazole with carbinol improved metabolic stability. Antagonist **9** is potent and selective with acceptable oral exposure, metabolic stability, and brain penetration. Despite potent binding at the opioid mu receptor, analog **9** is only a weak partial agonist (EC_{50} = 24.9 μM; 57% max. response). 5-Cyanoindane analog, **10**, improves upon the potency and selectivity of **9** (Table 3).

We found subsequently that 6-fluoro substitution on benzimidazole, **11**, further improved potency and microsomal stability, K_i = 0.5 nM.



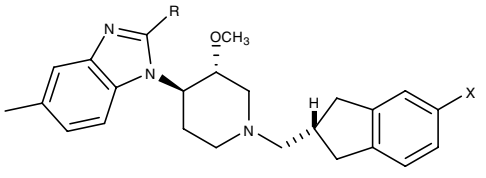
11

K_i = 0.5 nM

Salient SAR features of the des-amido indanes include: (1) no strong enantioselective binding at either the 3,4-disubstituted piperidine or the indane. (2) 2-Carbinol benzimidazole analogs show improved metabolic stability compared to 2-methyl with no significant reduction on potency, oral exposure or brain penetration. (3) –CN improves selectivity and has no significant effect on potency or brain penetration when compared to –Br.

In order to best select compounds for in vivo studies, the ADME properties in lean Sprague–Dawley rat of potent and selective analogs were evaluated. Table 4 shows a comparison between two potent and selective MCHR1 analogs, aryl amide **5** and aryl nitrile **10**. Our efforts to achieve brain penetration were rewarded at moderate expense to the plasma AUC and CL.

Table 2. Indane analogs



Compound	R	X
6	$-CH_3$	$NHCO_2CH_3$
7	$-CH_3$	–Br
8	$-CH_3$	–H
9	$-C(CH3)_2OH$	–Br
10	$-C(CH3)_2OH$	–CN

In a rat efficacy experiment,[15] MCHR1 antagonist **10** caused a 28% reduction (p = 0.001) of food intake in an acute DIO rat model (30 mg/kg). In two weeks of dosing at 30 mg/kg bid **10** caused a −0.7% loss of body weight (p = 0.00001) compared to an increase of 5.1% in the vehicle group. Clinical chemistry and histopathology of the animals following the study showed no adverse findings (Scheme 1).

trans-4-Benzimidazolyl-3-methoxy-Boc-piperidine: Piperine (1,2,3,6-tetrahydropyridine) was Boc protected and epoxidized using standard conditions.[16] Epoxide opening with azide produced the racemic *trans*-4-azido-3-hydroxy- and 3-azido-4-hydroxypiperidines in approximately 4:1 ratio. We explored a variety of reaction conditions to improve the ratio without success. Thus, the regioisomeric mixture was hydrogenated under palladium and the resulting amines were arylated under forcing conditions using 3-nitro-4-fluorotoluene. Fortuitously, washing the crude reaction product with hexane removed the undesired regioisomer as well as excess 3-nitro-4-fluorotoluene. Hydrogenation afforded the phenylenediamine as a racemate. Chiral purification by super-critical fluid chromatography (SFC)[17] afforded pure enantiomer.

Benzimidazoles were synthesized from each of the enantiomerically pure 4-phenylenediaminopiperidines by well-established methods: (A) direct condensation with a carboxylic acid, (B) condensation with an orthoester or (C) condensation with aldehyde and subsequent oxidation using oxone.[18] In no instance was racemization observed by chiral HPLC analysis. Absolute configuration of the 3,4-disubstituted piperidines was established by X-ray structure of 4-[2,5-dimethylbenzimidazolyl]-Boc-piperidine shown in Figure 1.[19]

Indane synthesis: (*S*)-(+)-5-Bromo-2-indanoic acid and its enantiomer were synthesized according to a published synthesis.[20] The carboxylic acid was reduced to hydroxymethyl with borane. A copper-catalyzed aryl amination effected the –Br to –NHBoc transformation.[21] Bromoindan-2-ol was converted to 5-cyanoindan-2-ol by known methods.[22]

Indane—piperidine coupling: Hydroxymethyl indanes were oxidized to aldehyde with the Dess–Martin reagent and coupled to 4-benzimidazolylpiperidines by reductive amination. Chiral HPLC analysis of reaction products allowed us to optimize oxidation and reductive amination conditions such that less than 2% epimerization was observed.

In summary, our lead optimization of MCHR1 antagonists rapidly resulted in a series of potent analogs. Selectivity was achieved by two critical modifications: the addition of a 3-methoxy group to 4-benzimidazoloyl

Table 3. Selectivity of compounds **6**–**10**

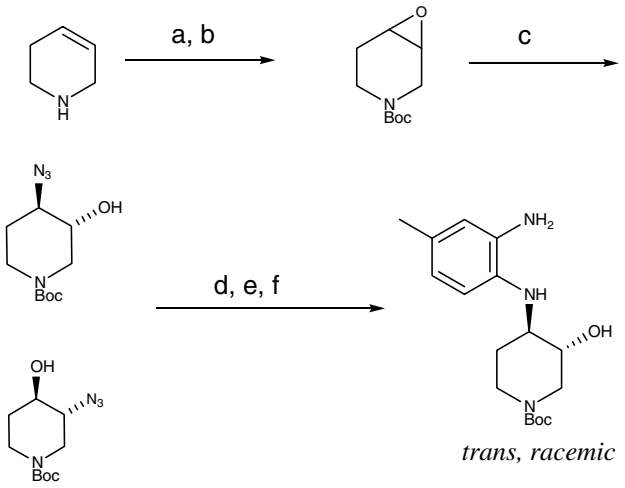
Receptor/compound	**6**	**7**	**8**	**9**	**10**
MCHR1; K_i[a] (nM)	20	5	47	10	3
MCHR1; EC_{50}[b] (nM)/max. eff.	20/81%	20/92%	69/90%	30/98%	17/85%
Human receptors[c,d]					
Adrenergic α_{2A}	14	81	33	34	12
Dopamine D_3	28	84	40	79	22
Muscarinic M2	22	48	6	−8	3
Opiate δ	n.d.	47	15	42	30
Opiate κ	55	91	76	61	32
Opiate μ	85	91	76	94	67
Serotonin $5HT_{2C}$	8	−11	−8	14	−21
Serotonin $5HT_{1A}$	29	31	63	17	14
Somatostatin-5 (SST5)	10	54	−2	n.d.	23
Dopamine transporter	65	80	8	68	−6
Norepinephrine transporter	64	69	24	77	12
Serotonin transporter	95	59	14	28	6

[a] MCHR1 binding assay (see Supplemental Data).
[b] Functional cAMP assay (see Supplemental Data).
[c] Experiments were conducted at MDS-Panlabs.
[d] Values are % inhibition of receptor ligand binding at 10 μM.

Table 4. PK properties of compounds **5** and **10**

	5	**10**
Plasma AUC (h ng/mL)	8525	4730
C_{max} (ng/mL)	1280	1300
CL (mL/min kg)	36.5	49.5
$T_{1/2}$ (h)	2.5	1.9
V_{dss} (L/kg)	14.0	3.60
%*F*	61	47
Brain/plasma[14] (5 min)	0.06	0.9

5 mg/kg IV bolus; 30 mg/kg po. Formulation: IV: DMA, PEG400, HPBCD, phos buffer; po: 1% Klucel LF in H_2O with 0.1% Tween 80.



Scheme 1. Reagents: (a) Boc_2O, CH_2Cl_2; (b)NBS, H_2O, CH_3CN, KOH, CH_3OH; (c) NaN_3, EtOH, H_2O; (d) Pd/C, H_2, EtOH; (d) 3-nitro-4-fluorotoluene, Na_2CO_3, *n*-BuOH; (f) H_2, Pd/C, EtOH.

piperidine and rigidification of a carbon linker between aryl piperidine and aryl amide with indanylmethyl. Metabolic stability and brain penetration were improved by replacing aryl amide with aryl nitrile. The resulting compounds are potent, selective, and CNS drug-like

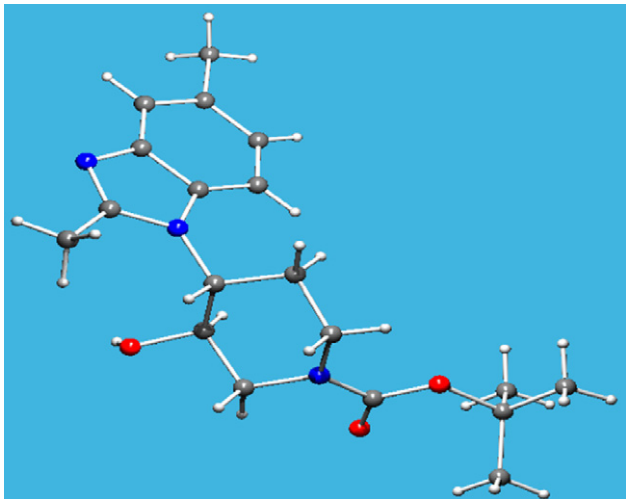


Figure 1. X-ray crystal structure of 3-hydroxy-4-[2,5-dimethylbenzimidazolyl]-Boc piperidine.

MCHR1 antagonists that cause reduction of food intake and body weight in DIO rats. Moreover, we can confidently attribute the in vivo efficacy, albeit modest, exclusively to antagonism of the MCH-1 receptor. Unfortunately, the compounds described have exhibited IC_{50} values for the hERG channel[23] ranging from 100 nM to 4.0 μM thus rendering them unsuitable for clinical development.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.01.010.

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15. Sixty male Sprague–Dawley rats were placed on a high fat diet (60% calories from fat) from research diets at the age of 7 weeks. Animals were maintained on the diet for 7 weeks. One week before the start of the study rats were acclimated by dosing with 1 mL/kg of vehicle. Rats were sorted by body weight (BW) and single caged. Treatment started on day 0 and continued for 2 weeks. Animals were weighed and dosed daily according to BW. Compound **10** was formulated as a solution or suspension in 2% Klucel LF in water w/0.1% Tween 80 and administered at the target dose level (3, 10, 30 mg/kg po bid). For animals in the efficacy arm of the study ($n = 9$ per treatment group), food intake was recorded every day for the first four days and then twice per week.
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