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Synthesis and evaluation of urea-based indazoles as melanin-concentrating hormone receptor 1 antagonists for the treatment of obesity

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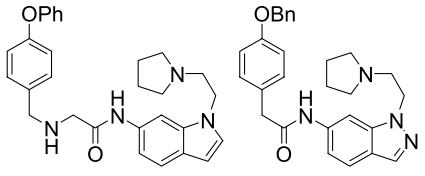
Abstract—A series of urea-based *N-1*-(2-aminoethyl)-indazoles was synthesized and evaluated for melanin-concentrating hormone receptor 1 (MCHr1) antagonism in both binding and functional assays. Several compounds that acted as MCHr1 antagonists were identified, and optimization afforded a compound with excellent binding affinity, good functional potency, and oral efficacy in a chronic model for weight loss in diet-induced obese mice.

Melanin-concentrating hormone (MCH) is a cyclic 19-amino acid neuropeptide that serves as an important mediator in the regulation of energy balance and food intake in mammals.[1,2] Transgenic mice overexpressing the MCH gene are susceptible to insulin resistance and obesity,[3] while mice lacking the gene encoding MCH are hypophagic, lean, and maintain elevated metabolic rates.[4] Similarly, genetically altered animals that lack the gene encoding the MCH receptor maintain elevated metabolic rates and remain lean despite hyperphagia on a normal diet.[5,6] This evidence suggests that antagonism of MCH signaling could be an effective therapy for obesity, and multiple reports of small molecule antagonists of MCHr1 have appeared in the recent literature.[7]

A previous report[8] from these laboratories described the optimization of compound **1**, which was identified via high-throughput screening against MCHr1 (Fig. 1). Substitution of the indole core with an indazole and removal of the basic amine-containing side chain in favor of 4-benzyloxyphenylacetic acid afforded a compound (**2**) with significantly improved in vitro and in vivo properties. During the process of exploring the indazole pharmacophore, we set out to investigate the structure–activity relationships (SARs) of analogs with urea-based side chains. In this report, we disclose the SAR of this series of MCHr1 antagonists, as well as the identification of a compound with excellent binding affinity, good functional activity, and efficient CNS penetration upon oral dosing in diet-induced obese (DIO) mice. Additionally, we describe the evaluation of this



	1	2
MCHr1 IC_{50} (nM)[a]	299	1.40
Ca^{2+} release IC_{50} (μM)[a]	1.81	0.011
Plasma AUC (μg ·hr/mL)[b]	1.16	2.12
Brain AUC (μg ·hr/g)[b]	0.674	1.33

Figure 1. Indole-based MCHr1 antagonists. [a]Values represent an average of at least two determinations where each determination is within ±35% of the mean value shown. [b]10 mg/kg, po in DIO mice, interanimal variability was less than 25% for all values.

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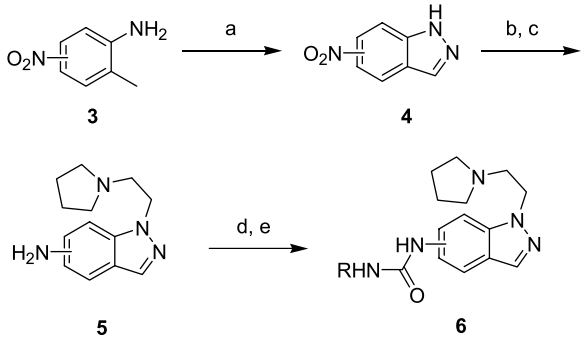
compound in a two-week efficacy model for weight loss in DIO mice.

To explore the urea-based side chain SAR around the indazole pharmacophore, we initially synthesized a set of 6-substituted analogs with side chains that were biased to contain the extended aromatic ethers necessary for activity in the indazole amide-based series as exemplified by **2**. To investigate the positional requirements of the side chain, indazoles substituted at the 4- and 5-positions were also prepared.

As shown in Scheme 1, 4-nitro indazole was synthesized from 3-nitro-*o*-tolylamine (**3**), while the 5- and 6-nitroindazoles were obtained from commercial sources. Alkylation of the individual nitroindazoles (**4**) and purification of the corresponding *N-1*-alkylated isomers were followed by iron-mediated reduction to afford the diamine intermediates **5**. Reaction with phenyl carbonate afforded the intermediate carbamates, and subsequent derivitization with various amines under microwave heating conditions afforded the final analogs **6**. Alternatively, the appropriate isocyanates could be directly reacted with the diamine intermediates **5** to afford the final products.

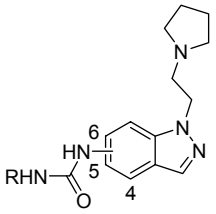


Scheme 1. Reagents and conditions: (a) $NaNO_2$, AcOH, rt, 95%; (b) chloroethylpyrrolidine hydrochloride, K_2CO_3, DMF, 60 °C, then SiO_2 chromatography, 27–67%; (c) Fe, NH_4Cl, 65 °C; (d) phenylcarbonate, THF; or $PhOC_6H_4NCO$, THF, 60 °C, 90%; (e) R_1R_2NH, NMP, 220 °C, μw.

The corresponding indazole urea analog of **2** (Table 1, compound **7**) showed a dramatic decrease in both binding affinity and functional potency. Contraction of the terminal ether portion of the side chain from a benzyloxy to a phenoxy substituent afforded compound **8**, which had similar discouraging activity. However, insertion of a methylene unit prior to the phenoxyphenyl substituent proved to be beneficial, as homologated analog **9** was significantly more potent in the functional assay than both **7** and **8**, and showed greater binding affinity. The presence of an additional methylene unit (**10**) brought an additive increase in activity, affording the most potent 6-substituted analog from this set. Replacing either of the phenyl portions of the extended aromatic ether side chain with other heterocycles or alkyl chains afforded predominantly inactive compounds, as exemplified by the 1-*N*-benzyl-4-amino-piperidinyl containing analog **11**. Side chains with other polar functionality in this region were also inactive (data not shown).

A similar set of analogs was prepared starting from 5-nitroindazole in order to probe the effects of moving the side chain around the core. The 4-benzyloxyphenyl-substituted urea **12** showed a considerable increase in binding affinity relative to the corresponding 6-substituted analog **7**, but no improvement in functional potency. Contraction of the terminal benzyloxy

Table 1. Binding affinity and functional potency of MCHr1 antagonists[a]



Compd	R	Pos	MCHr1 binding IC_{50} (nM)[b,d]	Ca^{2+} release IC_{50} (μM)[c,d]
7	$BnOC_6H_4$–	6	113	7.14
8	$PhOC_6H_4$–	6	581	>10
9	$PhOC_6H_4CH_2$–	6	78.5	0.626
10	$PhOC_6H_4(CH_2)_2$–	6	34.3	0.178
11	(1-*N*-Bn-piperidin-4-yl)–	6	4509	>10
12	$BnOC_6H_4$–	5	41.3	>10
13	$PhOC_6H_4$–	5	12.0	0.104
14	$PhOC_6H_4CH_2$–	5	508	>10
15	$PhOC_6H_4(CH_2)_2$–	5	545	>10
16	(1-*N*-Bn-piperidin-4-yl)–	5	971	>10
17	$BnOC_6H_4$–	4	1053	>10
18	$PhOC_6H_4$–	4	1851	>10

[a] All compounds were >95% pure by HPLC and characterized by ^1H NMR and HRMS.
[b] Displacement of [^{125}I]-MCH from MCHr1 expressed in IMR-32 (I3.4.2) cells (MCH binding $K_d = 0.66 \pm 0.25$ nM, $B_{max} = 0.40 \pm 0.08$ pmol/mg).
[c] Inhibition of MCH-mediated Ca^{2+} release in whole IMR-32 cells (MCH $EC_{50} = 62.0 \pm 3.6$ nM).
[d] Values represent an average of at least two determinations where each determination is within ±40% of the mean value shown.

ether to a phenoxy ether afforded compound **13**, which had excellent binding affinity and greatly improved functional activity relative to any of the previously tested urea-based compounds. In contrast to the trend observed in the 6-substituted series, the addition of one and two methylene unit spacers between the urea nitrogen and phenoxyphenyl substituent (compounds **14** and **15**, respectively) produced a decreasing trend with respect to binding affinity. This is readily apparent when comparing the decreasing affinities of analogs **13**–**15** to the increasing affinities of the corresponding 6-substituted analogs **8**–**10**, and suggests that the additional two methylene units found in the 6-substituted analog **10** may allow for the placement of the phenoxyphenyl substituent into similar space as that occupied in the potent 5-substituted analog **13**.

As observed with all isomers, attempt to incorporate polarity within the side chain and/or replace the phenyl substituents afforded significantly less active or inactive compounds. This is exemplified by compound **16**, which showed improved binding affinity relative to the 6-substituted derivative **11**, but a similar lack of functional activity. Finally, all of the 4-substituted analogs tested showed poor binding affinities and functional potencies.

The two most potent compounds from this initial set, **10** and **13**, were evaluated for plasma and brain exposure in DIO mice (10 mg/kg, po). As shown in Table 2, the 6-substituted analog **10** exhibited moderate plasma exposure but negligible brain penetration. In contrast, the 5-substituted analog **13** showed excellent plasma exposure and slightly improved brain penetration relative to indazole amide **2**.[9]

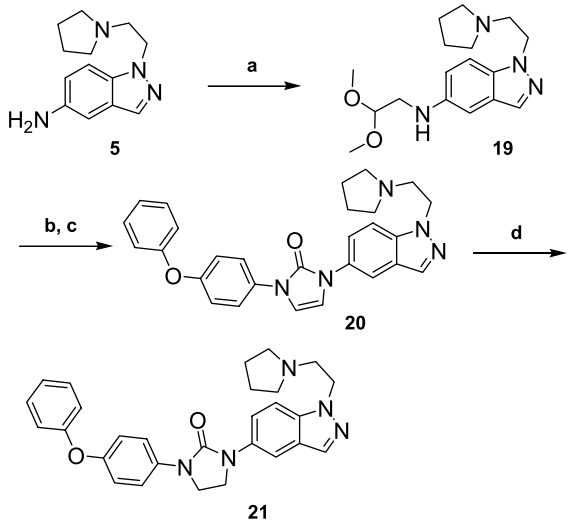
While compound **13** showed promising levels of CNS penetration, the high plasma exposure afforded a $brain_{AUC}$:$plasma_{AUC}$ ratio of 0.3. In an effort to improve the brain to plasma ratio, we sought to limit the hydrogen-bonding ability of the urea pharmacophore with the hypothesis that reduced polarity within this region of the molecule could improve the brain penetration. It was further envisioned that an imidazolone could achieve this task while introducing limited perturbation to the molecule. To this end, *N-1*-alkylated indazole **5** was reductively aminated with dimethoxyglyoxal to afford the secondary aniline **19** (Scheme 2). Reaction with phenoxyphenyl isocyanate followed by acid treatment under heated conditions afforded the 1,3-disubstituted imidazolone **20**. Subsequent reduction under a hydrogen atmosphere afforded the saturated imidazolidinone **21**.

The cyclic analogs **20** and **21** were evaluated in the MCHr1 binding and functional assays (Table 3). Interestingly, both compounds had binding affinities that were very similar to **13**, but functional potencies that decreased 6- and 10-fold for **20** and **21**, respectively. The more potent unsaturated analog **20** was further evaluated in DIO mice to determine the effects of reducing the hydrogen-bonding network of the urea on brain penetration (Table 3). Interestingly, the CNS exposure was modestly improved relative to parent compound **13**, and the distribution was biased in favor of the brain ($brain_{AUC}$:$plasma_{AUC}$ = 1.3).

Table 2. Selected pharmacokinetic parameters of **10** and **13** in DIO mice (10 mg/kg po)[a]

Compd	Plasma AUC (μg h/g)[b]	Plasma C_{max} (ng/mL)[b]	Brain AUC (μg h/g)[b]	Brain C_{max} (ng/g)[b]
2	2.12	596	1.33	177
10	0.335	86.0	0.00	0.00
13	5.35	246	1.43	260

[a] All values are mean values (n = 3 unless specified otherwise). Inter-animal variability was less than 30%. Compounds are dosed in DIO mice at 10 mg/kg, po in a vehicle containing 1% Tween 80 and water.
[b] The three mice with highest plasma and brain concentrations were averaged to provide the peak plasma and brain concentrations (C_{max}), respectively. The mean plasma or brain concentration data were submitted to multi-exponential curve fitting using WinNonlin. The area under the mean concentration–time curve from 0 to t h (time of the last measurable concentration) after dosing (AUC_{0-t}) was calculated using the linear trapezoidal rule for the concentration–time profile. The residual area was extrapolated to infinity, determined as the final measured mean concentration (C_t) divided by the terminal elimination rate constant (β), and was added to AUC_{0-t} to produce the total area under the curve ($AUC_{0-\infty}$).

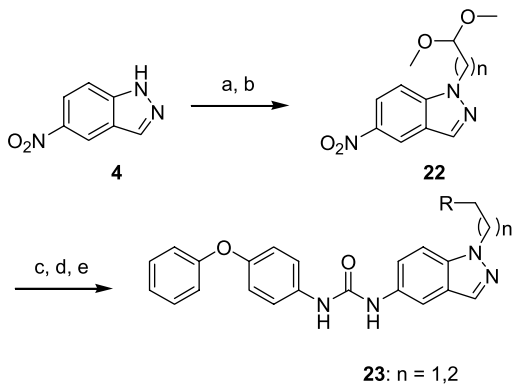


Scheme 2. Reagents and conditions: (a) 1,1-dimethylglyoxal, 1:1 DCE/MeOH (1% AcOH), $NaBH_3CN$, 55 °C; (b) $PhOC_6H_4NCO$, THF, 60 °C; (c) *p*-TsOH, THF/H_2O (4:1), 60 °C; (d) $Pd(OH)_2$, H_2, 60 psi.

Table 3. Selected in vitro and pharmacokinetic properties of cyclic ureas[a]

	20	**21**
MCHr1 binding IC_{50} (nM)[b]	5.90	19.8
Ca^{2+} release IC_{50} (μM)[b]	0.654	1.12
Plasma AUC (μg h/mL)[c]	1.35	NT
Plasma C_{max} (ng/mL)[c]	543	NT
Brain AUC (μg h/g)[c]	1.71	NT
Brain C_{max} (ng/g)[c]	183	NT

NT, not tested.
[a] All compounds were >95% pure by HPLC and characterized by ^1H NMR and HRMS.
[b] See Table 1, footnote d.
[c] See Table 2, footnote b.



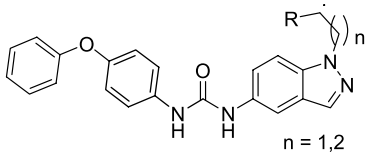
Scheme 3. Reagents and conditions: (a) 1,1′-dimethoxy-2-bromoethane, or 1,1′-dimethoxy-3-bromopropane, K_2CO_3, DMF, 60 °C, then SiO_2 chromatography (41–57%); (b) Fe, NH_4Cl, 65 °C, 90%; chloroethylpyrrolidine hydrochloride, K_2CO_3, DMF, 60 °C, then SiO_2 chromatography (32, 45%); (c) $PhOC_6H_4NCO$, THF, 85%; (d) 2/1 2 N HCl/acetone, 60 °C; (e) R_1R_2NH, MeOH (1% AcOH), MP-$CNBH_3$.

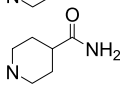
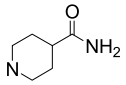
Despite the enhanced $brain_{AUC}$:$plasma_{AUC}$ ratio of compound **20**, the deleterious effect of urea cyclization on functional potency encouraged us to concentrate on **13** for additional SAR development. Since the phenoxyphenylurea represented the preferred side chain for optimal potency, we retained this substituent while altering the tertiary amine and linker length of the 1-(2-pyrrolidin-1-yl-ethyl) portion of the molecule. A panel of hydrophobic and hydrophilic amines was selected, along with two and three carbon linkers. As shown in Scheme 3, 5-nitro indazole (**4**) was alkylated with 1,1′-dimethoxy-2-bromoethane or 1,1′-dimethoxy-3-bromopropane and the desired *N-1*-functionalized isomer **22** separated via chromatography. Following iron-mediated reduction and amide bond formation, the latent aldehyde was liberated with aqueous acid. Reductive amination with various primary and secondary amines afforded the final compounds **23**.

As displayed in Table 4, substituted pyrrolidine analogs **24** and **25** showed decreased functional potency as compared to parent analog **13**, although the 2-methoxymethyl analog **25** had similar binding affinity. The secondary and tertiary amines **26** and **27**, respectively, demonstrated excellent binding affinities, both improving approximately 10-fold. Interestingly, the methylisobutylamine analog **27** showed a 7-fold decrease in functional potency, while **26** was comparable to **13**. Nearly all of the piperidine analogs evaluated (represented by analog **28**) were weak binders of MCHr1, with the exception of amide-substituted piperidine analog **29**, which showed good binding affinity and nearly equipotent functional antagonism. Incorporation of larger cyclic amines such as hexamethyleneamine afforded compounds that demonstrated no improvement relative to **13** (data not shown).

The three carbon linked analogs were generally less active than the corresponding two carbon linked compounds. Analogs **30** and **31** were approximately 2-fold less than the corresponding compounds **25** and **26** in both assays. Additionally, the 4-amido-piperidine analog **32** showed a 3-fold improvement in binding affinity relative to the two-carbon linked derivative **29**, yet demonstrated a significant loss of functional activity. A notable exception was 4-hydroxy-piperidine analog **33**, which showed greater than 65-fold improvement in binding affinity and a significant increase in functional potency relative to **28**.

Table 4. Binding affinity and functional potency of MCHr1 antagonists[a]



Compd	R	*n*	MCHr1 binding IC_{50} (nM)[c]	Ca^{2+} release IC_{50} (μM)[c]
13[b]		1	12.0	0.104
24[b]		1	305	>10
25		1	38.7 ± 18.2	0.516 ± 0.358
26		1	2.40 ± 0.03	0.147 ± 0.044
27		1	1.80 ± 0.90	0.751 ± 0.195
28[b]		1	6130	>10
29		1	134 ± 64	0.171 ± 0.089
30[b]		2	82.9	1.177
31		2	8.50 ± 1.20	0.275 ± 0.116
32		2	40.6 ± 15.6	2.88 ± 1.21
33[b]		2	91.5	0.894

[a] All values are mean values ± SEM ($n = 3$ unless specified otherwise).
[b] Values represent an average of at least two determinations where each determination is within ±45% of the mean value shown.
[c] See Table 1, footnote c.

The SAR from this focused batch of compounds revealed some interesting trends, yet no analogs offered a significant improvement in functional potency relative to parent **13**. Therefore, we selected this compound for evaluation in an in vivo efficacy model in order to assess the potential of the urea-based pharmacophore. For a two-week period, DIO mice fed a high-fat diet ad libitum were dosed orally with **13** (10, 30, and 100 mg/kg, bid), D-fenfluramine[10] (10 mg/kg, qd) as a drug-treatment control, or vehicle. Food intake and body weight were measured at days 1, 5, 7, 11, and 14 for each group.

As indicated in Figure 2, the vehicle group continued to gain weight throughout the study. D-Fenfluramine

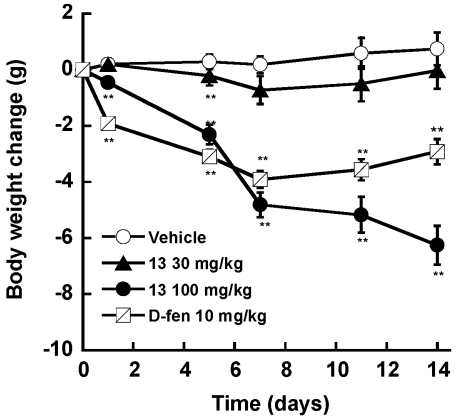


Figure 2. Effect of compound **13** (dosed at 30 and 100 mg/kg, po, bid in 1% Tween 80 in water) and D-fenfluramine (D-fen, 10 mg/kg, po, qd) on the body weight of DIO mice. Change is registered as the number of grams of body weight difference for each measurement time point relative to day zero. All values are mean values ± SEM for $n = 12$. (**) $p < 0.05$ for comparisons against vehicle group.

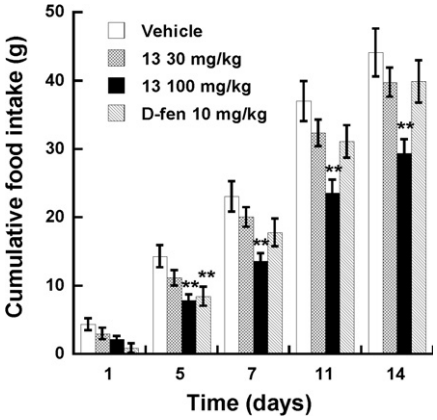


Figure 3. Effect of compound **13** (dosed at 30 and 100 mg/kg, po, bid in 1% Tween 80 in water) and D-fenfluramine (D-fen, 10 mg/kg, po, qd) on daily and cumulative food intake of DIO mice. All values are mean values ± SEM for $n = 12$. (*) $p < 0.05$ for comparisons against vehicle group.

caused a rapid decrease in body weight followed by a rebound that started on day 8 and continued until day 14. Compound **13** showed no statistically significant effect on body weight at 30 mg/kg, while treatment with 100 mg/kg caused a decrease in body weight that was observed at day 1 and continued throughout the duration of the study. At day 14, mice dosed with indazole **13** (100 mg/kg, po, bid) and D-fenfluramine (10 mg/kg, po, qd) weighed 17.1% and 9.12% less ($p < 0.01$), respectively, than the vehicle control group (Table 5).

The cumulative food intake was decreased in both dosing groups of mice treated with **13** (Fig. 3), although the reduction observed in the lower dose group was not statistically significant. Treatment with 100 mg/kg **13** resulted in a significant reduction in food intake by day 5 (Table 6) and a significant cumulative reduction by day 14. Treatment with D-fenfluramine also caused a decrease in food intake that was significant by day 5 and continued through the duration of the study.

In order to determine the contributions of changes in fat and lean mass relative to the observed decrease in body weight following the two-week study, analysis of body composition was performed with dual-energy X-ray absorptiometry[11] (DEXA). No significant decrease in fat mass or lean mass was apparent upon chronic oral treatment of **13** at 30 mg/kg, bid, while fat mass was significantly reduced in mice treated with the higher dose of 100 mg/kg, bid (16.6 ± 1.7 g vs 22.1 ± 0.1 g for vehicle-treated controls, $p < 0.05$). No significant loss of lean mass was apparent for either dose group. Administration of D-fenfluramine also resulted in a significant decrease in fat mass (12.3 ± 1.0 g, $p < 0.05$) with no change in lean mass. Finally, no significant changes in locomotor activity were observed upon administration with **13** at either dose, indicating that treatment did not cause any overt behavioral effects (data not shown).

Table 5. Body weight (BW) of all animal groups at day_0, day_{14}, and % change of the drug-treatment groups vs vehicle[a]

Group[b]	BW_{day0} (g)	BW_{day14} (g)	% Change from vehicle
Lean	31.7 ± 0.8	31.8 ± 0.8	—
Vehicle	45.0 ± 0.7	46.9 ± 0.8	—
D-Fen 10 mg/kg	42.7 ± 0.7	39.8 ± 0.8	−9.12 ± 0.0
13 30 mg/kg	42.3 ± 0.9	42.3 ± 1.1	−3.41 ± 0.00
13 100 mg/kg	42.5 ± 1.0	36.3 ± 1.3	−17.1 ± 0.0

[a] All values are mean values ± SEM ($n = 12$).

[b] All doses were given in 4-mL/kg body weight volume of vehicle (1% Tween 80 in water). Compound **13** was administered po by gavage, at doses of 30 and 100 mg/kg, bid, and D-fenfluramine at a dose of 10 mg/kg, po, qd. Food and body weights were determined on the first day and periodically thereafter for 14 days.

The significant reduction in food intake observed in the mice treated with **13** (100 mg/kg, po, bid) indicates that the measured weight loss is primarily mediated by a negative energy balance. Interestingly, while this is consistent with the MCHr1 antagonist-mediated weight loss reported for other small molecule MCHr1 antagonists,[12] it is in contrast to our findings with the related amide-based indazole antagonist **2** (Fig. 1).[8] Upon chronic administration of **2**, no decrease in food consumption was observed in the face of significant loss of body fat, indicating that increased energy expenditure was the primary component of the observed weight loss. Since both compounds selectively reduced body fat and had no effect on lean mass, and that no overt toxicity was observed upon chronic treatment with these compounds, it is likely that the pharmacological effect is at least partially mediated by antagonism of the targeted receptor. In light of the different effects upon food intake by these two efficacious compounds, it is possible that the increased energy expenditure component yields to significant effects on food intake with increasing receptor blockade. Further studies are needed to fully investigate the disparate effects of these MCHr1 antagonists.

In summary, exploration of urea-based side chains upon the previously identified *N-1*-pyrrolidinyl-ethyl-indazole core led to the identification of **13**. This compound binds with high affinity to the MCHr1 receptor, potently

Table 6. Cumulative food intake of mice treated with compound **13**, D-fenfluramine, or vehicle[a]

Group	Day 1	Day 5	Day 7	Day 11	Day 14
Lean[b]	3.10 ± 0.11	11.8 ± 0.3	20.3 ± 0.4	31.9 ± 0.6	40.6 ± 0.6
Vehicle[c]	4.36 ± 0.87	14.3 ± 1.6	23.1 ± 2.2	37.0 ± 2.9	44.1 ± 3.5
D-Fen 10 mg/kg[c]	0.89 ± 0.7	8.44 ± 1.40	17.8 ± 2.0	31.1 ± 2.4	39.9 ± 3.1
13 30 mg/kg[c]	3.00 ± 0.83	11.2 ± 1.1	20.1 ± 1.4	32.4 ± 2.0	39.8 ± 2.1
13 100 mg/kg[c]	2.17 ± 0.50	7.86 ± 0.85	13.6 ± 1.1	23.6 ± 1.9	29.4 ± 2.1

[a] All values are mean values ± SEM ($n = 12$).

[b] Lean mice were administered a purified low fat diet (D12450Bi, 10 kcal % fat, 3.8 kcal/g).

[c] Vehicle and drug-treated animal groups were fed a high fat content diet (D12492i, 60 kcal % fat, 5.2 kcal/g), both obtained from Research Diets Inc. (New Brunswick, NJ) for approximately 16 weeks. The fat content of these diets was a mixture of lard and soybean oil.

inhibits Ca^{2+} mobilization in IMR-32 cells, and shows good brain exposure upon oral dosing in DIO mice. Furthermore, chronic oral treatment with **13** at 100 mg/kg, bid, exerts a significant anorectic effect on DIO mice that appears to be the result of decreased food intake. Studies are ongoing to fully explore the pharmacological effects of treatment with this compound, and further optimization of the urea-based indazole class of MCHr1 antagonists for binding affinity and functional potency, brain penetration, and oral efficacy will be reported in due course.

Acknowledgments

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