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Synthesis and structure–activity relationships of spirohydantoin-derived small-molecule antagonists of the melanin-concentrating hormone receptor-1 (MCH-R1)

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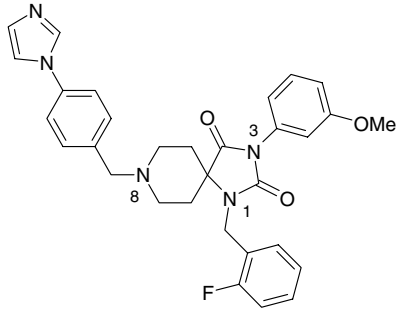
Abstract—The design, synthesis, and SAR of a series of substituted spirohydantoins are described. Optimization of an in-house screening hit gave compounds that exhibited potent binding affinity and functional activity at MCH-R1.

Melanin-concentrating hormone receptor-1 (MCH-R1) has recently become the subject of great interest within the pharmaceutical industry. MCH-R1 is activated by the peptide melanin-concentrating hormone (MCH), and it has been known for some time that in mammals, both MCH and MCH-R1 are involved in the regulation of feeding behavior and energy homeostasis. For instance, transgenic mice overexpressing MCH peptide are hyperphagic and obese,[1] whereas those deficient in MCH are hypophagic and lean.[2] In addition, mice lacking MCH-R1 are hyperphagic, lean, and resistant to diet-induced obesity.[3] Not surprisingly therefore, it was hypothesized that a selective MCH-R1 antagonist may be successful in treating obesity in humans.[4] To this end a number of laboratories have recently reported the discovery of orally active small-molecule MCH-R1 antagonists effective in controlling weight gain in rodents,[5] though it still remains to be seen whether this translates to safe clinical efficacy in humans.

As part of our efforts to discover and develop novel small-molecule MCH-R1 antagonists,[5b,6] we identified a high-affinity ligand from an in-house high-throughput screen (compound **1**, Fig. 1). Compound **1**, derived from a spirohydantoin scaffold, exhibited a K_i of 50 nM at



1

Figure 1. Structure of MCH-R1 high-throughput screening hit.

Keywords: MCH; MCH-R1; MCH antagonists; Melanin-concentrating hormone receptor-1 antagonists; Spirohydantion; CYP3A4; Obesity.
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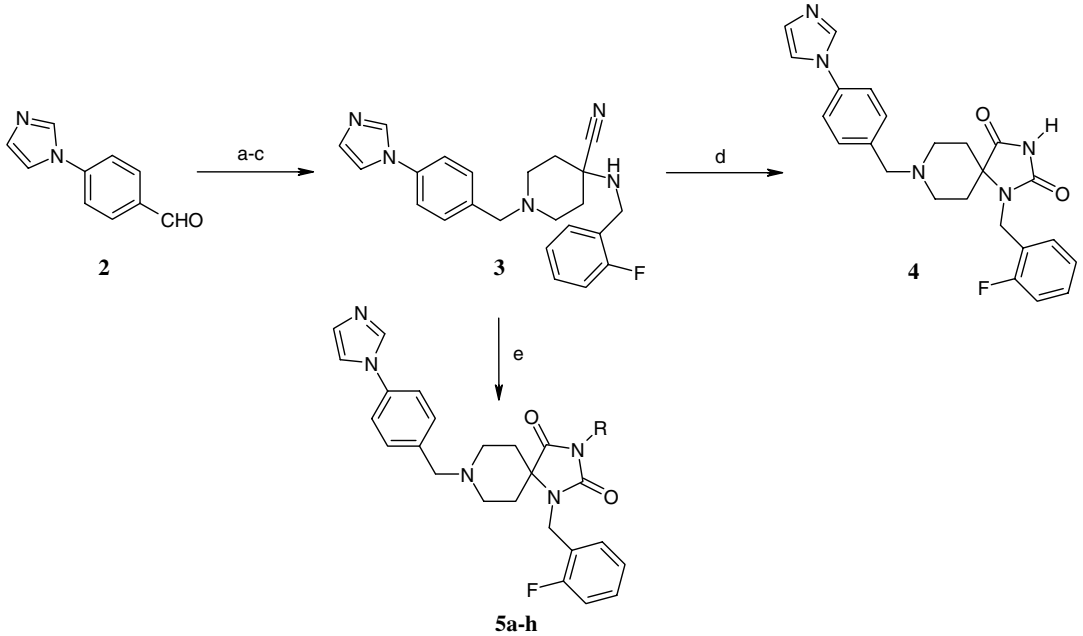
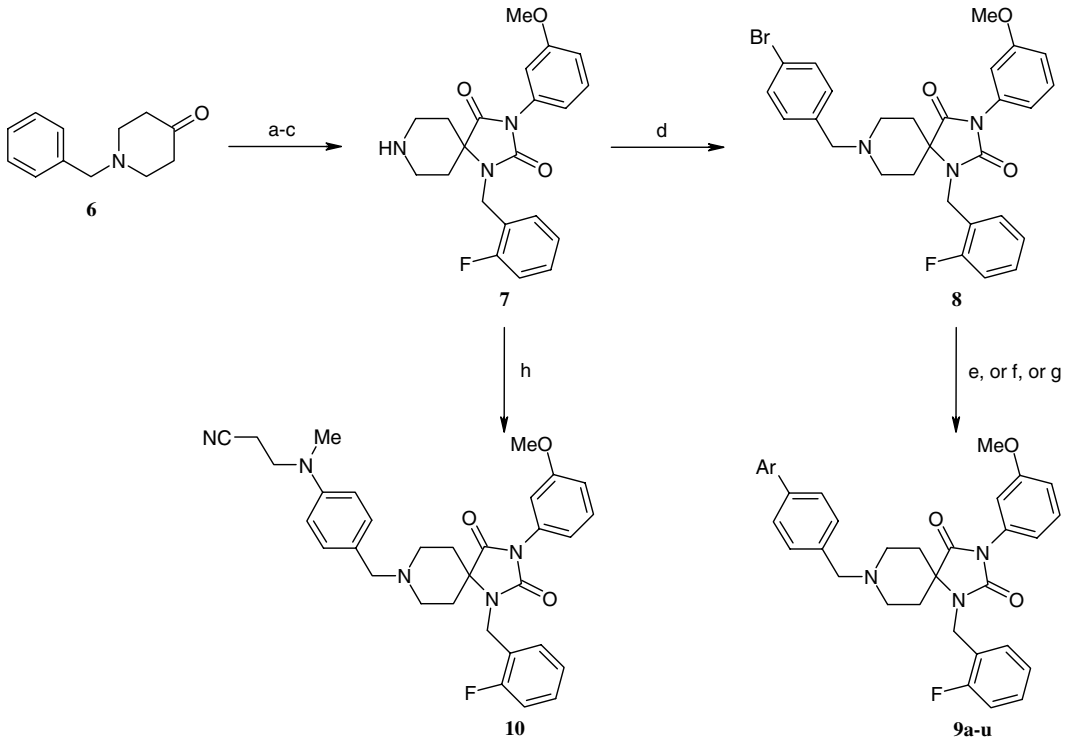
MCH-R1. Unfortunately, compound **1** also proved to be a potent inhibitor of CYP3A4 (IC_{50} = 35 nM). As approximately 50% of all known drugs are metabolized to some degree by CYP3A4, inhibition of this enzyme in vivo can lead to undesirable drug–drug interactions.[7] Therefore, any subsequent optimization campaign would have to address not only binding and functional activity at MCH-R1, but also the reduction of inhibition at CYP3A4. In this letter, we describe efforts toward the optimization of this lead, which led to the discovery of a novel series of highly potent and functional MCH-R1 antagonists, with an improved CYP3A4 profile.

In order to fully explore SAR around this spirohydantoin scaffold, we developed synthetic strategies which enabled the incorporation of a variety of substituents at both the N-1 and N-3 nitrogens of the hydantoin, and variation of the terminal ring of the biaryl motif (Schemes 1–3). Variation of the substituent at N-3 was achieved via the route outlined in Scheme 1. Reductive amination of commercially available 4-(1H-imidazol-1-yl)benzaldehyde **2** with 4-hydroxypiperidine, then oxidation to the ketone followed by a Strecker reaction employing 2-fluorobenzylamine, gave aminonitrile **3** in moderate yield. Cyclization to the corresponding spirohydantoin was achieved using either chlorosulfonyl isocyanate followed by acid hydrolysis to give N–3(H) derivative **4**, or a variety of substituted isocyanates followed by acid hydrolysis to yield compounds **5a**–**h**. Variation of the terminal ring of the biaryl motif was achieved as outlined in Scheme 2. Intermediate **7** was obtained in good yield from *N*-benzylpiperidin-4-one **6** via a Strecker reaction with 2-fluorobenzylamine, subsequent cyclization with 3-methoxyphenyl isocyanate then acid hydrolysis, followed by *N*-debenzylation. Reductive alkylation with 4-bromobenzaldehyde gave intermediate **8** which can participate in a palladium-mediated Suzuki coupling, either directly or via conversion to a pinacol boronate ester, to yield compounds **9c**–**u**. In addition, copper-mediated coupling with the corresponding N(H)-heterocycle gave compounds **9a** and **b**. Compound **10** was obtained via the reductive alkylation of intermediate **7** with commercially available 3-[(4-formylphenyl)methylamino]propionitrile. Variation at N-1 was achieved via the routes outlined in Scheme 3. Unsubstituted derivative **13** was obtained in two steps from 4-amino-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid **11** via cyclization with 3-methoxyphenyl isocyanate followed by reductive alkylation with 3-(4-formylphenyl)benzonitrile. Substituted derivatives **16a**–**f** were obtained in four steps from 4-piperidone hydrochloride **14**. Alkylation of **14** with 4-bromobenzyl bromide, then Suzuki coupling with 3-cyanophenyl boronic acid, followed by a Strecker reaction with the corresponding primary amine gave intermediates **15a**–**f** in high yield. Subsequent cyclization with 3-methoxyphenyl isocyanate followed by acid hydrolysis gave the final compounds **16a**–**f**. The N–3(H) hydantoin derivative **17** was obtained via reaction of **15f** with chlorosulfonyl isocyanate, followed by acid hydrolysis. Compound **18** was obtained via a copper-mediated coupling of **17** with 3-bromotoluene. All final compounds described herein (Tables 1–3) were assayed for their ability to displace radiolabeled [^{125}I-Tyr^{13}]-MCH in a competitive binding assay.[8] The functional antagonism of select compounds was further confirmed based upon their ability to inhibit, in a dose-dependent manner, MCH stimulated G-protein-GTPγ^{35}S binding in cells expressing native human MCH-R1.[9]

We initially examined SAR around N-3 of the hydantoin core, keeping the substituents at both N-1 (2-fluorobenzyl) and N-8 [4-(imidazol-1-yl)benzyl] constant



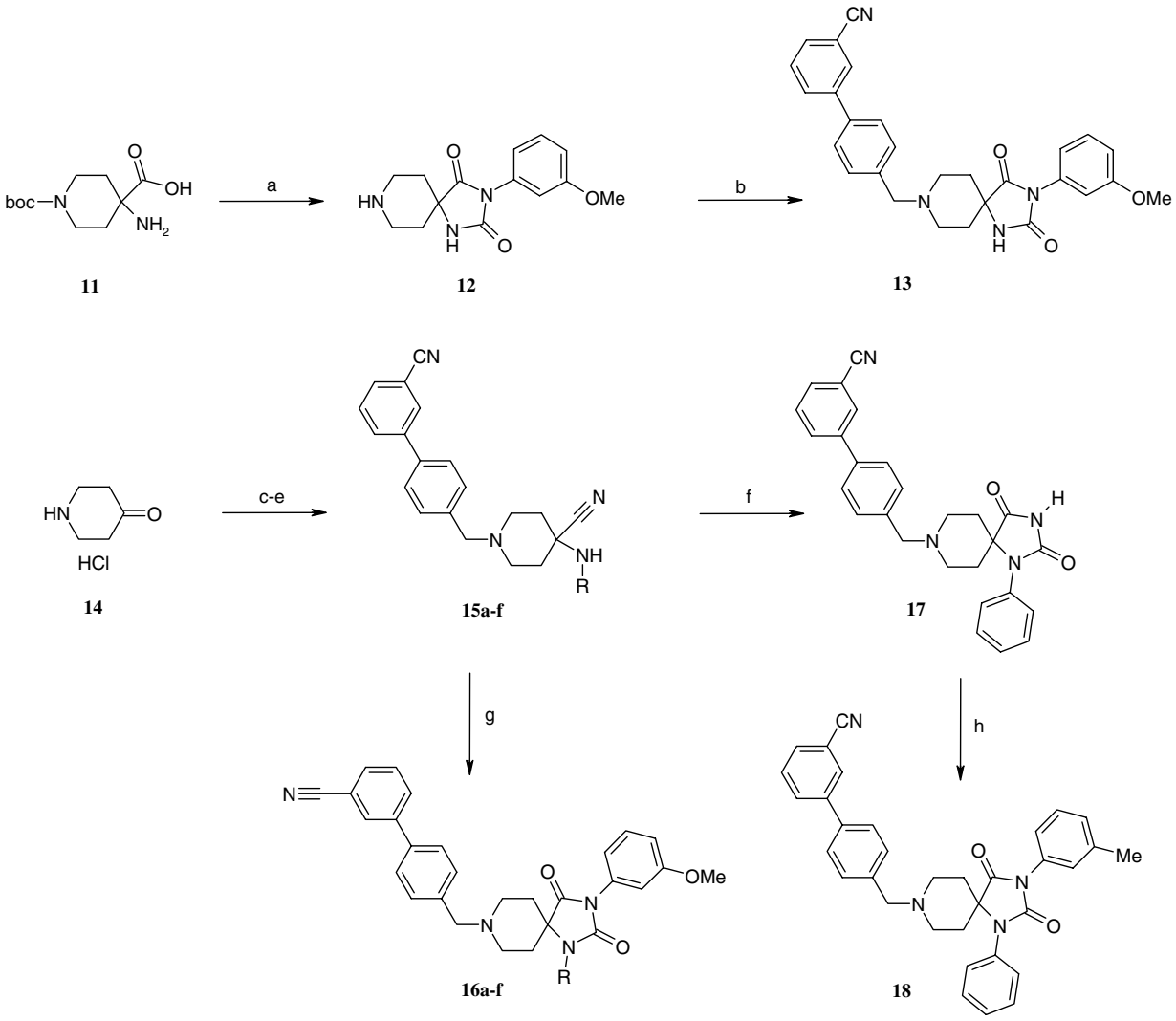
Scheme 1. Reagents and conditions: (a) 4-hydroxypiperidine, $NaBH(AcO)_3$, 1,2-dichloroethane, rt, 12 h, 20%; (b) oxalyl chloride, DMSO, DCM, −78 °C, rt, 2 h, quantitative; (c) 2-fluorobenzylamine, potassium cyanide, MeOH/H_2O, 0 °C, rt, 12 h, 40%; (d) chlorosulfonyl isocyanate, DCM, rt, 1 h, then 2 N aq HCl, EtOH, 70 °C, 12 h, 20%; (e) RNCO, EtOH, rt, 5 h, then 2 N aq HCl, EtOH, 70 °C, 12 h, 10–43%.



Scheme 2. Reagents and conditions: (a) 2-fluorobenzylamine, potassium cyanide, MeOH/H_2O, 0 °C, rt, 21 h, 96%; (b) 3-methoxyphenyl isocyanate, THF, rt, 8 h, then AcOH, H_2O, 55 °C, 16 h, 31%; (c) H_2 gas (45 psi), 20% $Pd(OH)_2$/C, 4 N aq HCl, EtOH, rt, 72 h, quantitative; (d) 4-bromobenzaldehyde, $NaBH(OAc)_3$, DCM, rt, 12 h, 30%; for compounds **9c**–**e**, **g**, **i**, **k**, **m**–**u**; (e) $ArB(OR)_2$, $Pd(PPh_3)_4$ or $Pd(dppf)_2Cl_2$·DCM, Na_2CO_3, 1,4-dioxane/H_2O, 100 °C, 12 h, 10–50%; for compounds **9f**, **h**, **j**, **l**; (f) bis(pinacolato)diboron, $Pd(dppf)_2Cl_2$·DCM, KOAc, 1,4-dioxane, 100 °C, 12 h, then ArBr, $Pd(PPh_3)_4$ or $Pd(dppf)_2Cl_2$·DCM, Na_2CO_3, 1,4-dioxane/H_2O, 100 °C, 12 h, 10–50%; for compounds **9a**, **b**; (g) NH-heterocycle, CuI, *trans*-1,2-diaminocyclohexane, Cs_2CO_3, 1,4-dioxane, 100 °C, 24 h, 10%; (h) 3-[(4-formylphenyl)methylamino]propionitrile, $NaBH(OAc)_3$, 4 Å ms, DCM, rt, 16 h, 36%.

(see Table 1). The unsubstituted derivative **4** (K_i = 2, 100 nM) proved to be approximately 40-fold less active than **1**, though introduction of a simple alkyl group did improve potency significantly, the *n*-butyl (**5b**) and cyclohexyl (**5c**) derivatives having K_i's of 200 and 340 nM, respectively. Incorporation of an unsubstituted phenyl ring resulted in a slight improvement (**5d**, K_i = 115 nM), though moving the ring further out, either one (**5e**, K_i = 150 nM) or two carbons (**5f**, K_i = 400 nM), proved detrimental. Attempts to improve potency via the introduction of substituted phenyl groups proved unsuccessful (results not shown). More than 60 analogs were prepared incorporating a variety of functional groups on the phenyl ring, though SAR around this ring proved to be very flat, showing little improvement over the 3-methoxyphenyl group incorporated in our original lead (**1**). An exception proved to be the 1-naphthyl moiety (**5g**, K_i = 25 nM) which led to a 2-fold improvement in potency with respect to **1**. Again it seemed that the aryl ring directly attached to the core was important, as saturation of this ring (compound **5h**, K_i = 340 nM) led to more than a 10-fold decrease in activity. Unfortunately, all compounds described in Table 1 still proved to be significant inhibitors of CYP3A4, with IC_{50} values similar to that observed with **1**. We hypothesized that the observed inhibition of CYP3A4 may be due to the presence of the imidazole ring, as it is well known that certain drugs containing an imidazole (such as ketoconazole) strongly bind and inhibit CYP3A4 by chelation of the imidazole nitrogen with the active heme iron atom of the CYP enzyme.[10] We reasoned that replacement of the imidazole ring in this series should result in compounds with an improved CYP3A4 profile.

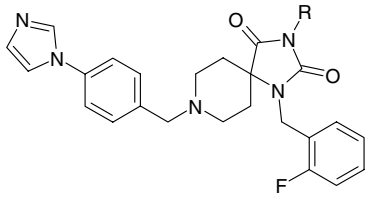
A number of biaryl derivatives were subsequently prepared, as outlined in Table 2. The *N*-pyrrolo derivative **9b**, though much less potent at MCH-R1 (K_i = 1500 nM), was also significantly less active at CYP3A4 (IC_{50} > 10,000 nM),[11] suggesting the imidazole ring is indeed important for potent inhibition of CYP3A4. We discovered that the imidazole could be replaced with either a 3-pyridyl (**9c**, K_i = 89 nM) or 4-pyridyl (**9d**, K_i = 44 nM) moiety without loss of MCH-R1 activity. The 4-pyridyl derivative **9d** was approximately 4-fold more potent at CYP3A4 than the 3-pyridyl analog **9c**, the IC_{50} values being 300 and 1100 nM, respectively. Substitution around the 3-pyridyl gave interesting results, with respect to affinity at MCH-R1. The 4-methyl-3-pyridyl (**9f**, K_i = 640 nM) and 4-methoxy-3-pyridyl (**9g**, K_i = 315 nM) derivatives were less potent than the unsubstituted analog **9c**. The introduction of a 4-amino-3-pyridyl moiety increased potency 4-fold (with respect to **9c**), compound **9h** having a K_i of 20 nM. In addition, it was interesting to observe that simply moving the 4-methoxy substituent (of **9g**) to either the 5- or 6-position resulted in a greater than 20-fold increase in potency,

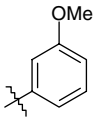
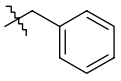
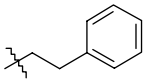
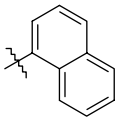
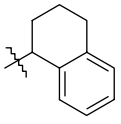


Scheme 3. Reagents and conditions: (a) 3-methoxyphenyl isocyanate, DIEA, THF, rt, then 1 N aq HCl, EtOH, 80 °C, 12 h, 50%; (b) 3-(4-formylphenyl)benzonitrile, $NaBH(OAc)_3$, MeOH/DCM, rt, 12 h, 90%; (c) 4-bromobenzyl bromide, K_2CO_3, acetonitrile, 50 °C, 6 h, 84%; (d) 3-cyanophenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, toluene/H_2O/EtOH, reflux, 5 h, quantitative; (e) RNH_2, sodium cyanide, AcOH, H_2O, rt, 12 h, 50–90%; (f) chlorosulfonyl isocyanate, DCM, rt, 1 h, then 2 N aq HCl, EtOH, reflux, 12 h, 35%; (g) 3-methoxyphenyl isocyanate, EtOH, rt, 1 h, then 2 N aq HCl, reflux, 2 h, 5–30%; (h) 3-bromotoluene, CuI, *trans*-1,2-diaminocyclohexane, Cs_2CO_3, 1,4-dioxane, 100 °C, 16 h, 27%.

compounds **9i** and **9k** exhibiting K_i's of 13 and 8 nM, respectively. The reasons for these observed differences in MCH-R1 binding affinity are not clear, but overall the data may suggest that either the pyridyl nitrogen, or the methoxy substituent, may be involved in a key hydrogen bonding interaction with the receptor. Certainly replacement of the 5-methoxy (of **9i**) with a cyano group (**9j**, K_i = 10 nM) had no effect on potency, presumably due to the potential of the cyano functionality to also act as a hydrogen bond acceptor. Unfortunately, as one might expect, the incorporation of substituted 3-pyridyl moieties in this region of the molecule did not remove the CYP3A4 inhibition liability. For instance, compounds **9i**, **9j**, and **9k** had IC_{50} values (at CYP3A4) of 2000, 6200, and 1700 nM, respectively. Incorporation of a substituted phenyl ring in place of the pyridine also gave potent MCH-R1 antagonists, though the position and nature of the substituent seemed important. The 3-cyanophenyl derivative **9o** (K_i = 20 nM) was approximately 10-fold more active than the corresponding 4-isomer **9p** (K_i = 210 nM), whereas surprisingly the 2-cyanophenyl derivative was essentially inactive. The 3-methoxyphenyl derivative (**9q**, K_i = 620 nM) was less potent, and the presence of polar groups such as hydroxyl (**9t**, K_i = 2900 nM) in this position was not well tolerated. We also discovered that a biaryl is not necessary for potency at MCH-R1. The propionitrile derivative **10** (K_i = 19 nM) proved equipotent to compound **9o**, again supporting the idea that it is the presence and position of a hydrogen bond accepting motif in this region of the molecule that is important for potency. In addition, we were pleased to discover that compound **9o** displayed minimal CYP3A4 inhibition, the IC_{50} > 10,000 nM. Taking compound **9o** as our lead, we investigated SAR around N-1 of the hydantoin core, the results of which are summarized in Table 3.

Table 1. Binding affinities of spirohydantoins **1**, **4**, and **5a–h** toward MCH-R1

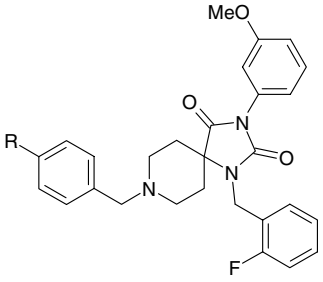


Compound	R	K_i (nM)[a]
1		50
4	H	2100
5a	Et	1100
5b	*n*-Bu	200
5c		340
5d		115
5e		150
5f		400
5g		25
5h		340

[a] K_i values are averaged from at least two experiments.[8]

The unsubstituted derivative **13** (K_i = 280 nM) was approximately 14-fold less potent than **9o**. It became clear that lipophilic groups were preferred at N-1, as incorporation of progressively larger groups led to a significant improvement in binding affinity. For instance, the cyclopropyl methyl (**16c**), cyclohexyl (**16d**), and cyclohexyl methyl (**16e**) derivatives had measured K_i's of 84, 12, and 16 nM, respectively. Exchanging cyclohexyl for phenyl led to a further increase in potency, compounds **16f** and **18** both exhibiting a K_i of 6 nM. Although we had obtained very potent compounds within this series, we were somewhat concerned as to the size and lipophilicity of some of these analogs. For instance, the calculated log *P*'s for compounds **9o**, **16f**, and **18** are 6.52, 6.35, and 6.40, respectively.[12] Highly lipophilic compounds can suffer from a poor pharmacokinetic profile in vivo, with poor absorption and/or high first pass metabolism often being major contributing

Table 2. Binding affinities of spirohydantoins **9a–u** and **10** toward MCH-R1



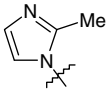
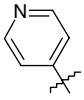
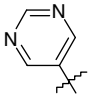
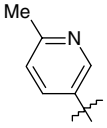
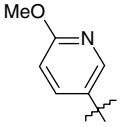
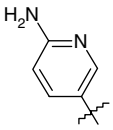
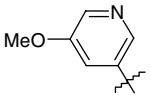
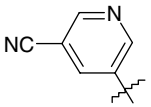
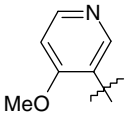
Compound	R	K_i (nM)[a]
9a		300
9b		1500
9c		89
9d		44
9e		330
9f		640
9g		315
9h		20
9i		13
9j		10
9k		8

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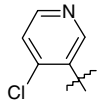
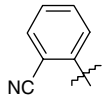
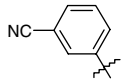
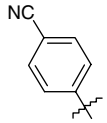
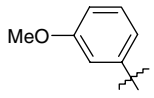
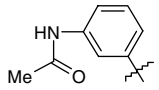
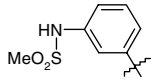
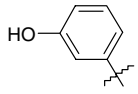
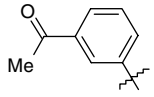
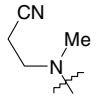
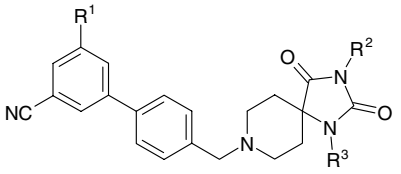
Table 2 (*continued*)

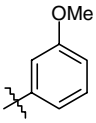
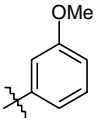
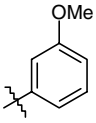
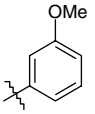
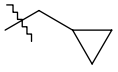
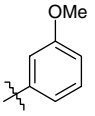
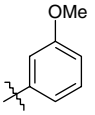
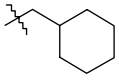
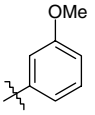
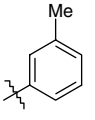
Compound	R	K_i (nM)[a]
9l		230
9m		2300
9n		>10,000
9o		20
9p		210
9q		620
9r		150
9s		8000
9t		2900
9u		32
10		19

[a] K_i values are averaged from at least two experiments.[8]

factors. Indeed, compound **18** displayed very poor oral bioavailability in rat (% $F < 5$),[13] an issue that needed to be addressed. SAR data discussed earlier may suggest that the N-3 substituent does not play a critical role in the binding of these molecules to MCH-R1 (see data in Table 1). If correct, removal of this substituent should significantly reduce log *P* without unacceptably affecting potency. Indeed, the N–3(H) derivative **17** (K_i = 45 nM) was only 8-fold less potent than compound **16f**. Importantly, we had reduced *c*log *P* by approximately 2 log units (to 4.77) and this decrease in *c*log *P* was reflected in a corresponding increase in metabolic stability and oral bioavailability. For instance, in an in vitro human liver microsome assay, compounds **9o** and **16f** had scaled intrinsic clearance values of 94 and

Table 3. Binding affinities of spirohydantoins **13**, **16a–f**, and **17–19** toward MCH-R1



Compound	R^1	R^2	R^3	K_i (nM)[a]
13	H		H	280
16a	H		Me	180
16b	H			100
16c	H			84
16d	H			12
16e	H			16
16f	H			6
17	H	H		45
18	H			6
19	Cl	H		8

[a] K_i values are averaged from at least two experiments.[8]

47 mL/min/kg, respectively.[14] On the other hand, compound **17** had a scaled intrinsic clearance value of 25 mL/min/kg. In addition, **17** had significantly improved oral bioavailability (% $F = 65$),[15] compared to compound **18**. Compound **17** also proved to be a weak inhibitor of CYP3A4, the IC_{50} being >10,000 nM. Finally, we discovered that even without a substituent at N-3 we could access highly potent analogs. The simple addition of a chlorine atom on the left-hand phenyl ring improved potency as compound **19** exhibited a K_i of 8 nM.[16]

In summary, we have disclosed SAR for a novel series of MCH-R1 antagonists based around a spirohydantoin core. Optimization of a high-throughput screening hit led to analogs that exhibited high affinity for MCH-R1, and low inhibition at CYP3A4. Examples also demonstrated good metabolic stability in human liver microsomes and oral bioavailability in rat.

Acknowledgments

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8. The binding assay was performed using human MCH-R1 that is modified for optimal expression in HEK293 cells. On each assay plate, a standard antagonist of comparable affinity to those being tested was included as a control of plate-to-plate variability. Overall K_i values were highly reproducible with an average standard error of the mean of less than 45% for replicate determinations.
9. For example, compound **16e** had a measured IC_{50} of 5.0 ± 1.0 nM. Assays were performed using membrane preparations of CHO cells stably expressing human MCH-R1. Each experiment was run in the presence of MCH peptide (10 nM), GTPγ^{35}S (0.5 nM), and GDP (10 μM). On each assay plate, a standard antagonist of comparable IC_{50} to those being tested was included as a control for plate-to-plate variability and overall IC_{50} values were highly reproducible with an average standard error of the mean of less than 45% for replicate determinations.
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11. Inhibition assays were carried out using microsomes isolated from transfected cells expressing only CYP3A4, and in the presence of the fluorescent substrate BFC. Ketoconazole was used as a positive control.
12. Values were calculated using ACD/Labs log*P* database, Advanced Chemistry Development Inc, Toronto, Ontario, Canada (http://www.acdlabs.com).
13. In rat following a single iv dose of 2.5 mg/kg, plasma AUC_{0-24h}, CL, $t_{1/2}$, and V_d were determined to be 789 ng h/mL, 56 mL/min/kg, 6.2 h, and 30 L/kg, respec-

tively. Following a single oral dose of 10 mg/kg, plasma AUC_{0-24h} was determined to be 26 ng h/mL. All data were determined in male Sprague–Dawley rats ($n = 3$).

14. General experimental details for this assay may be found in the following reference: Guo, Z.; Zhu, Y.-F.; Gross, T. D.; Tucci, F. C.; Gao, Y.; Moorjani, M.; Connors, P. J.; Rowbottom, M. W.; Chen, Y.; Struthers, R. S.; Xie, Q.; Saunders, J.; Reinhart, G.; Chen, T. K.; Bonneville, A. L. K.; Chen, C. *J. Med. Chem.* **2004**, *47*, 1259.
15. In rat following a single iv dose of 2.5 mg/kg, plasma $AUC_{0-24\ h}$, CL, $t_{1/2}$, and V_d were determined to be 1079 ng h/mL, 32 mL/min/kg, 1.2 h, and 3.3 L/kg, respectively. Following a single oral dose of 10 mg/kg, plasma AUC_{0-24h} was determined to be 2796 ng h/mL. All data were determined in male Sprague–Dawley rats ($n = 3$).
16. Compound **19** was prepared in four steps from 4-piperidone hydrochloride (**14**) using a similar procedure outlined for **17** (Table 3).