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Optimization of piperidin-4-yl-urea-containing melanin-concentrating hormone receptor 1 (MCH-R1) antagonists: Reducing hERG-associated liabilities

Susanne Berglund [a], Bryan J. Egner [a], Henrik Gradén [a], Joakim Gradén [a], David G. A. Morgan [b], Tord Inghardt [a,*], Fabrizio Giordanetto [c,*]

[a] Medicinal Chemistry, AstraZeneca R&D Mölndal, Pepparedsleden 1, SE-431 83, Mölndal, Sweden
[b] CVGI Bioscience, AstraZeneca R&D Alderley Park, Macclesfield, Cheshire SK104TG, UK
[c] Lead Generation, AstraZeneca R&D Mölndal, Pepparedsleden 1, SE-431 83, Mölndal, Sweden

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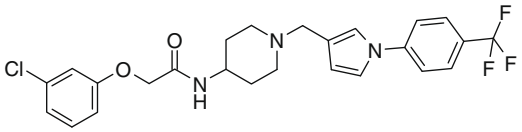
ABSTRACT

The discovery and optimization of piperidin-4-yl-urea derivatives as MCH-R1 antagonists is herein described. Previous work around the piperidin-4-yl-amides led to the discovery of potent MCH-R1 antagonists. However, high affinity towards the hERG potassium channel proved to be an issue. Different strategies to increase hERG selectivity were implemented and resulted in the identification of piperidin-4-yl-urea compounds as potent MCH-R1 antagonists with minimized hERG inhibition.

Melanin-concentrating hormone (MCH) is a 19 residue cyclic neuropeptide expressed in the lateral hypothalamus which has been shown to finely regulate the balance between energy intake and expenditure in rodents.[1,2] MCH exerts its physiological action through binding to its cognate receptors. Rodents display a single receptor (MCH-R1) while humans also possess a second receptor (MCH-R2) of yet unknown function. Mounting evidence suggests MCH-R1 as an attractive target to modulate feeding behavior and weight control. Intracerebroventricular (icv) infusion of MCH in rats stimulated food consumption, and chronic administration led to increased body weight.[3] Additionally, mice overexpressing the MCH gene demonstrated obesity traits, hyperphagia, hyperglycemia and insulin resistance,[4] whilst transgenic MCH receptor 1 (MCH-R1) knockout mice displayed hyperactivity, a lean phenotype and were resistant to diet-induced obesity.[5] Consequently, MCH-R1 antagonists are currently being pursued by several laboratories as means to reduce food intake and body weight, hopefully serving as effective pharmacological treatments for obesity.[6–10] Unfortunately, the typical chemotype affording MCH-R1 antagonism consists of a basic functionality and a number of hydrophobic regions and, as such, has been linked to the inhibition of the hERG potassium channel.[11,12] This may represent a serious threat to the development of safe MCH-R1 antagonists because of the cardiovascular liabilities associated with hERG blockade (e.g., death, proarrhythmia and QT interval prolongation).[13–15] The discovery of novel, potent MCH-R1 antagonists devoid of hERG inhibition is herein reported.

We previously described the discovery of 1,3-disubstituted-pyrroles as potent MCH-R1 antagonists.[16] Unfortunately, the most active compounds were found to inhibit the hERG potassium channel at submicromolar concentrations, as shown in Figure 1. A number of in-house guidelines, based on in-house examples, scientific literature and statistical modeling, have been developed to assist the optimization of hERG inhibition at AstraZeneca,[17] and a useful medicinal chemistry review has been recently published.[18] Specifically, the formation of zwitterionic compounds was reported to ameliorate hERG inhibition.[17,18] Although zwitterions are known to have limited cellular membrane permeability, we promptly



MCH-R1 IC_{50} = 29 nM
Patch Clamp assay: hERG IC_{50} = 560 nM

Figure 1. Piperidin-4-yl amide MCH-R1 antagonist.

* Corresponding authors. Tel.: +46 31 7761954; fax: +46 31 7763724 (T.I.), tel.: +46 31 7065723; fax: +46 31 7763710 (F.G.).
E-mail addresses: tord.inghardt@astrazeneca.com (T. Inghardt), fabrizio.giordanetto@astrazeneca.com (F. Giordanetto).

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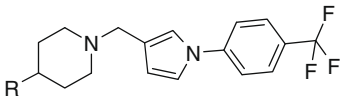
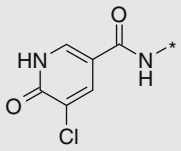
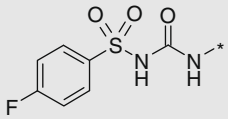
Table 1
In vitro MCH-R1 and hERG binding data for **1** and **2**



No.	R	MCH-R1 IC_{50}[a] (μM)	hERG IC_{50}[b] (μM)
1		0.196	19.6
2		0.617	>31.6[c]

[a] Values are mean of at least two experiments. Compounds competed with ^{125}I-MCH for binding at the human MCH1 receptor (h-MCH-R1) expressed in the HEK293 cell line.
[b] Values are mean of at least two experiments. Patch clamp assay using IONWORKS™ technology in hERG-expressing CHO cells.
[c] No hERG inhibition at the highest measured concentration (31.6 μM).

investigated whether such an approach could diminish hERG binding in our series. To this end, introduction of slightly acidic moieties such as 3-chloro-pyridone (**1**) and *N*-sulfonyl-urea (**2**) was pursued, as detailed in Table 1. Synthetic procedures to afford **1** and **2** have already been published.[19] The synthesized zwitterionic compounds provided a significant reduction in hERG inhibition. However, they also displayed a clear deterioration of MCH-R1 potency, which was deemed as an inappropriate starting point for subsequent explorations. These findings prompted us to consider a different strategy.

Increasing the polar character of a compound has been reported as another fruitful way of tackling hERG-related liabilities.[17,18] Data analysis of proprietary compounds that are structurally related to our series indicated that there seems to be a correlation between polarity and hERG inhibition constants (Figure ure2). Encouraged by the *N*-sulfonyl-urea group of **2**, we reasoned that the piperidin-4-yl-urea scaffold could serve as a more polar alternative to piperidin-4-yl-amides. A number of urea derivatives were then designed to verify our assumptions, as outlined in Table 2.

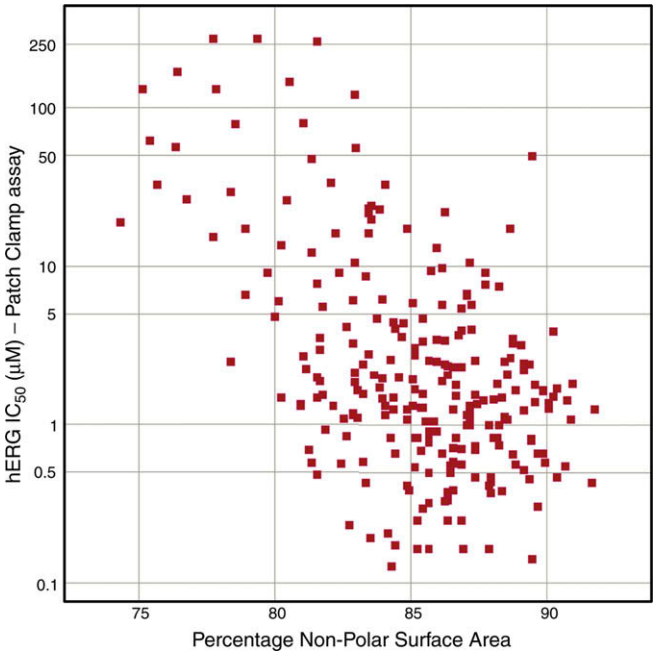
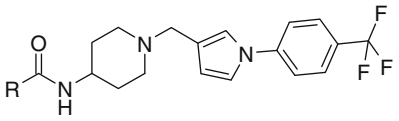
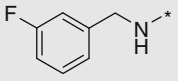
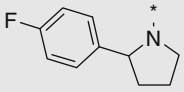
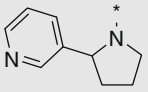
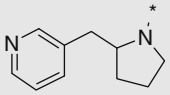
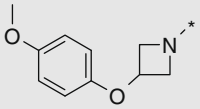
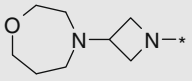
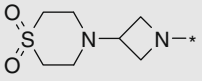
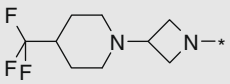
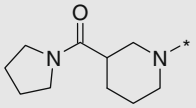
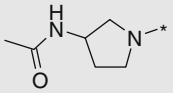
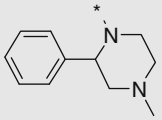
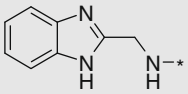


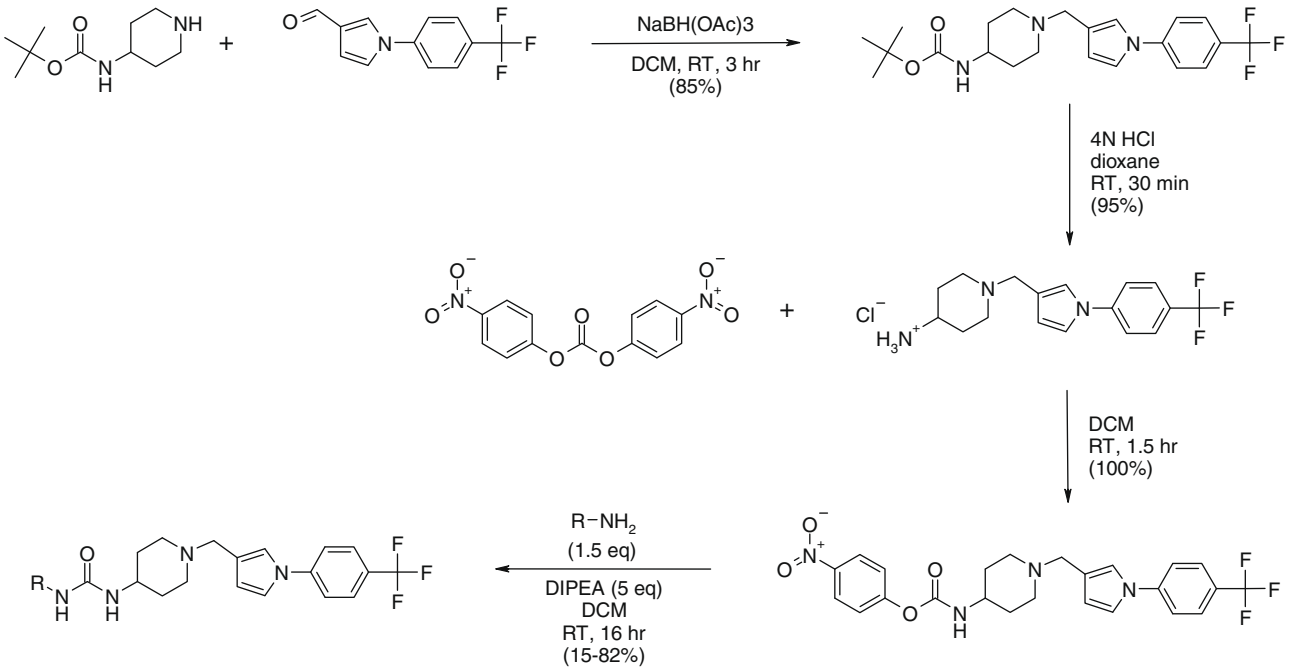
Figure 2. hERG inhibition (Patch clamp assay IC_{50}) versus molecular polarity (percentage of non-polar surface area) plot for AstraZeneca compounds ($N = 267$) structurally-related to the present chemical series (Tanimoto distance < 0.4). $r = 0.77$, $p < 0.0005$.

Table 2
In vitro MCH-R1 and hERG binding data for **3**–**14**



No.	R	MCH-R1 IC_{50}[a] (μM)	hERG IC_{50}[b] (μM)
3		0.039	1.2
4		0.013	1.81
5		0.021	3.08
6		0.026	1.73
7		0.049	2.03
8		0.236	3
9		0.099	>31.6[c]
10		0.0818	3.87
11		0.040	11.7
12		0.12	>31.6[c]
13		0.028	4.7
14		0.090	14.7

[a] Values are mean of at least two experiments. Compounds competed with ^{125}I-MCH for binding at the human MCH1 receptor (h-MCH-R1) expressed in the HEK293 cell line.
[b] Values are mean of at least two experiments. Patch clamp assay using IONWORKS™ technology in hERG-expressing CHO cells.
[c] No hERG inhibition at the highest measured concentration (31.6 μM).



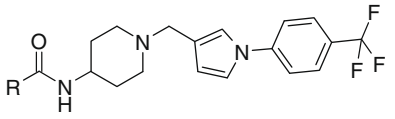
Scheme 1.

Scheme 1 details the generic synthetic route to provide the urea-containing MCH-R1 antagonists described in the present study, as previously reported.[19]

Urea compounds bearing hydrophobic appendages (**3**–**7**) yielded extremely potent MCH-R1 antagonists but no sought-after improvement in terms of hERG inhibition. As an example, the 2-(4-fluoro-phenyl)-pyrrolidine analog **4** afforded IC_{50} values of 13 nM and 1.81 μM against MCH-R1 and hERG, respectively. A slight reduction in hERG binding can be seen when markedly polar groups are introduced, as in the case of the piperazine (**13**, hERG IC_{50} = 4.7 μM) and benzimidazole (**14**, hERG IC_{50} = 14.7 μM) derivatives. Removal of the aromatic side chain provided compounds with diminished hERG affinity, as shown in Table 2. Here, introduction of sulfone (**9**) and amide (**11** and **12**) functionalities offered a much better separation between MCH-R1 and hERG affinities, with both **9** and **12** showing no hERG inhibition at the measured concentrations (Table 2). However, the absence of the aromatic group alone was not enough to prevent hERG inhibition as **8** and **10** indicated. Interestingly, the presence of highly polarized oxygen atoms (**9**, **11** and **12**) was detrimental to hERG inhibition, as it may perturb the interaction between the compounds and the hydrophobic binding pocket in the hERG channel. Regrettably, inclusion of those fragments did not seem to offer any advantage to MCH-R1 binding. Here, **11** offered the most potent example with an MCH-R1 IC_{50} value of 40 nM. Based on these findings, we argued that hydroxyl groups could function as amide and sulfoxide bioisosters, mimicking their positive effects on hERG while ideally providing higher affinity to MCH-R1. A new library of hydroxy-containing urea derivatives was therefore designed to verify whether MCH-R1 potency and hERG selectivity could be enhanced. The results of such exploration are presented in Table 3. Synthesis of **15**–**26** followed the general procedure outlined in Scheme 1, as previously published.[19]

Combination of an aromatic ring and a hydroxyl group (**15**–**17**) afforded potent MCH-R1 antagonists as well as single-digit micromolar hERG inhibitors (Table 3). A number of aliphatic analogs (**18**–**26**) again resulted in either good MCH-R1 affinity (IC_{50} < 30 nM) or hERG selectivity (IC_{50} > 25 μM) but not both, as

Table 3
In vitro MCH-R1 and hERG binding data for **15**–**26**



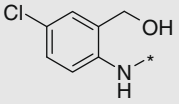
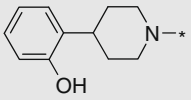
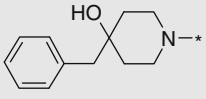
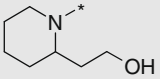
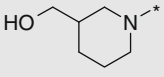
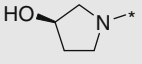
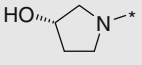
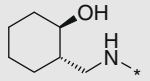
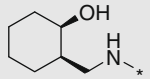
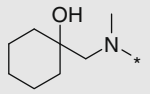
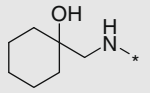
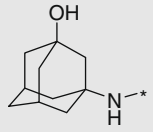
No.	R	MCH-R1 IC_{50}[a] (μM)	hERG IC_{50}[b] (μM)
15		0.111	3.33
16		0.036	4.12
17		0.063	7.93
18		0.039	3.08
19		0.023	4.89
20		0.138	>31.6[c]
21		0.125	>31.6[c]

Table 3 (*continued*)

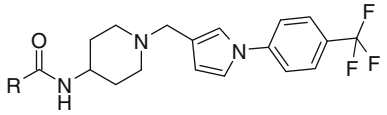
No.	R	MCH-R1 IC_{50}[a] (μM)	hERG IC_{50}[b] (μM)
22		0.046	7.33
23		0.063	3.96
24		0.057	2.16
25		0.044	>31.6[c]
26		0.082	>31.6[c]

[a] Values are mean of at least two experiments. Compounds competed with ^{125}I-MCH for binding at the human MCH1 receptor (h-MCH-R1) expressed in the HEK293 cell line.

[b] Values are mean of at least two experiments. Patch clamp assay using IONWORKS™ technology in hERG-expressing CHO cells.

[c] No hERG inhibition at the highest measured concentration (31.6 μM).

Table 4
In vitro MCH-R1, hERG and Cyp450 (3A4) data for **27**–**40**



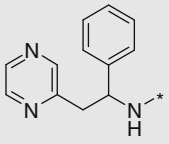
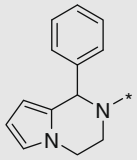
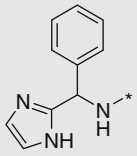
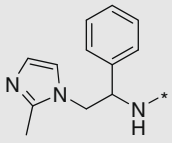
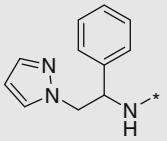
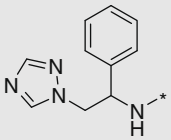
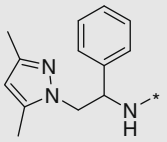
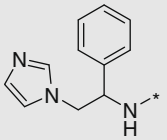
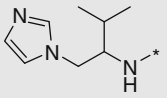
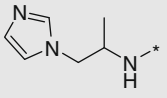
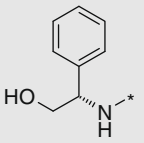
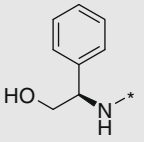
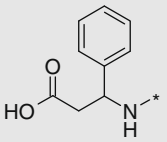
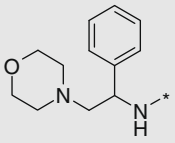
No.	R	MCH-R1 IC_{50}[a] (μM)	hERG IC_{50}[b] (μM)	CYP3A4 IC_{50}[c] (μM)
27		0.017	5.34	3.22
28		0.010	1.3	2.49
29		0.027	12.7	13.4
30		0.074	>31.6[d]	2.02

Table 4 (*continued*)

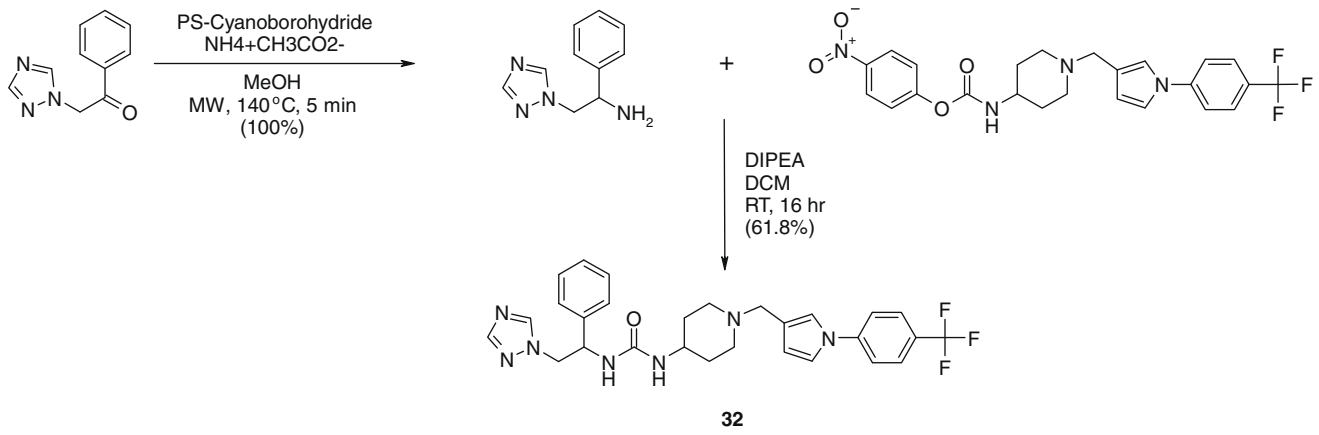
No.	R	MCH-R1 IC_{50}[a] (μM)	hERG IC_{50}[b] (μM)	CYP3A4 IC_{50}[c] (μM)
31		0.019	4.04	4.4
32		0.038	>31.6[d]	0.57
33		0.011	2.84	0.79
34		0.025	>31.6[d]	0.04
35		0.112	20.9	NA
36		0.308	>31.6[d]	0.32
37		0.035	23.9	20.6
38		0.152	25.8	NA
39		0.412	>31.6[d]	NA
40		0.066	6.9	16.5

[a] Values are mean of at least two experiments. Compounds competed with ^{125}I-MCH for binding at the human MCH1 receptor (h-MCH-R1) expressed in the HEK293 cell line.

[b] Values are mean of at least two experiments. Patch clamp assay using IONWORKS™ technology in hERG-expressing CHO cells.

[c] Inhibition of 7-benzyloxy-4-trifluoromethyl-coumarin metabolism, as mediated by human recombinant Cyp450 (3A4).

[d] No hERG inhibition at the measured concentration (31.6 μM).



32

Scheme 2.

shown in Table 3. Nevertheless, **25**, a (1-hydroxy-cyclohexylmethyl)-urea derivative yielded the first MCH-R1 antagonist with acceptable potency (IC_{50} < 50 nM) and no detectable hERG inhibition in this series. Intriguingly, simple N-methylation of **25** to provide **24**, converted a hERG inactive compound into a 2.16 μM hERG inhibitor. Whilst this finding supports modulating polarity as a mean to achieve hERG selectivity, it also clearly underlines that subtle structural modifications can have a dramatic effect on hERG potency. According to the data accumulated, it became evident that increasing polarity was effective at reducing hERG inhibition and MCH-R1 antagonism, whereas hydrophobic, preferably aromatic, groups contributed to high hERG and MCH-R1 affinity. We thus resolved to investigate whether a side chain providing both hydrophobic and polar elements could offer potent MCH-R1 antagonists with improved hERG separation, as presented in Table 4. Compounds **27**–**40** were prepared according to Scheme 1, as detailed elsewhere.[19] The full synthetic pathway to **32** is outlined in Scheme 2.

Introduction of a branched chain, providing a phenyl ring as hydrophobe and a N-containing heterocycle as polar moiety, resulted in highly potent MCH-R1 antagonists with varying degrees of hERG inhibition (**27**–**34**, Table 4). Imidazole derivatives (**29**, **30** and **33**) offered better hERG selectivity than the pyrazine (**27**), pyrrole (**28**) and pyrazole (**31**, **33**) counterparts. Interestingly, permutation of triazole (**32**) to pyrazole (**31**) transformed a compound devoid of hERG affinity into a 4 μM hERG inhibitor, highlighting once again the beneficial effect of increased polarity, in the form of minor modifications. Furthermore, **34** afforded a 25 nM MCH-R1 antagonist with a 1180-fold separation over hERG affinity. Replacement of the phenyl ring of **34** with isopropyl (**35**) maintained similar hERG affinity, whereas the marked reduction in lipophilicity associated with substitution to methyl (**36**) completely abolished hERG inhibition (Table 4). Combination of polar hydroxyl group and hydrophobic phenyl ring was also found to affect hERG inhibition: the *S*-enantiomer **37** maintained good MCH-R1 potency (IC_{50} = 35 nM) and a promising 682-fold hERG separation. Intriguingly, the *R*-enantiomer, **38**, displayed weaker MCH-R1 antagonism (IC_{50} = 152 nM) but virtually no change in hERG inhibition (Table 4). Introduction of ionic groups had also confounding effects on MCH-R1 and hERG affinity: here formation of a zwitterion via a carboxylic acid function (**39**) produced a weak MCH-R1 antagonist with undetectable hERG inhibition, while addition of a second positive charge in the molecule (**40**) yielded a compound with opposite binding characteristics. While the introduction of an imidazole ring reduced hERG inhibition in the present series, it also had a marked effect on CYP450 inhibition, as shown in Table 4 for the human 3A4 isoform. Not surprisingly, the compound with the most solvent-accessible imidazole ring in the series, **34**, was found to be a very potent 3A4 inhibitor (IC_{50} = 40 nM) while **29**, a less flexible analog, only moderately inhibited 3A4 (IC_{50} = 13.4 μM). Imidazole analogs (**27**–**29** and **31**–**33**) as well as 2-substitution (**30**) had a positive impact on 3A4 inhibition (14- to 110-fold reduction), while replacement of imidazole with an alcoholic function yielded the best compromise between MCH-R1 antagonism (IC_{50} = 35 nM), hERG (IC_{50} = 23.9 μM) and 3A4 (IC_{50} = 20.6 μM) inhibition (**37**, Table 4). Unfortunately, when dosed in rats to verify its pharmacokinetic profile, **37** was rapidly metabolized (CL = 154 ml/min/kg; N = 2) and it was therefore impractical to evaluate its effect on weight loss in rodents models.

The present study clearly demonstrated that, while simultaneous optimization of MCH-R1 and hERG binding was achieved in the present series, the structural and physicochemical requirements for MCH-R1 potency and hERG inactivity usually correspond with one another, rendering optimization at MCH-R1 while minimizing hERG inhibition a significant challenge. It was therefore the fine-tuning of polarity coupled with subtle structural modifications that allowed the successful optimization of 4-piperidin-yl-urea analogs as potent MCH-R1 antagonists with minimized hERG inhibition ability.

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