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Bicyclo[3.1.0]hexyl urea melanin concentrating hormone (MCH) receptor-1 antagonists: Impacting hERG liability via aryl modifications

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Abstract—Herein, we report the discovery of an effective strategy to modulate liabilities related to affinity of previously disclosed bicyclohexane MCHR-1 antagonists for the hERG channel. This paper describes one of several strategies incorporated to limit hERG binding via modifications of a terminal aryl group in an otherwise promising bicyclohexyl urea series.

Melanin concentrating hormone (MCH) is a 19-amino acid cyclic peptide found in the brains of all vertebrate species which has been clearly established as an important regulator of food intake and energy homeostasis.[1,2] Central administration of MCH in rats stimulates food intake,[3] and chronic infusion induces hyperphagia leading to obesity.[4] Similarly, mice overexpressing the MCH gene are hyperphagic, obese, hyperglycemic, and insulin resistant.[5] In contrast, mice null for the gene encoding MCH (prepro-MCH) are lean and hypophagic.[6] Two MCH receptor subtypes have been identified, of which MCHR-1 is only found in rodents. Several groups, including our own, have disclosed small molecule MCH receptor antagonists which have demonstrated oral efficacy in rodent feeding models.[7,8]

We recently reported the discovery of bicyclo[3.1.0]hexyl urea **1** as a potent and selective MCH-R1 antagonist which exhibited in vivo efficacy in rodents.[8] As a result of efforts aimed at removing a mutagenic biaryl aniline substructure from an earlier series,[9] the bicyclohexane **1** served as a structurally unique substitute. Unique in an alternative sense, the SAR of the distal aryl substituent of the bicyclo[3.1.0]hexane indicated that, contrary to the biaryl anilines and related bicyclo[4.1.0]heptanes,[10] the substituent could be appended at the *m*- or *p*-positions of the aryl ring. As a result, further exploration of both structure and positional attachment of substitution on this ring was undertaken.[8]

During biological profiling of the bicyclo[3.1.0]hexane series, in vitro assays aimed at estimating cardiovascular liabilities related to hERG (human ether-a-go-go-related gene) affinity were employed.[11] The potassium channel encoded by hERG is a voltage gated ion channel involved in cardiac repolarization. Mutations in hERG are responsible for one type of congenital long QT syndrome (LQT2), which is associated with an increased risk of *torsade de points*, ventricular fibrillation, and sudden death. Pharmacological blockade of this potassium channel is a side effect profile of many drug candidates, and is also associated with QT prolongation, proarrhythmia, and death.[12–14] Recent methods in drug discovery have been aimed at measuring inhibition of hERG currents of potential drug candidates. The most reliable procedure in this regard is the whole-cell voltage clamp technique, however, the labor intensive nature of this procedure limits throughput. One of the higher throughput screens for evaluation of hERG liability is the rubidium efflux assay which, while serving as a useful screen, does not exhibit ideal potency correlations with the voltage clamp method. This limitation notwithstanding, the correlation between Rb efflux data and

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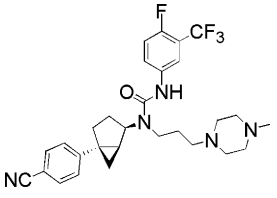
voltage clamp enables one to employ the Rb efflux assay as a useful tool for the preliminary evaluation of hERG liabilities in the discovery process.

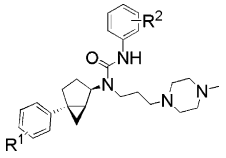
As a preliminary screen, a rubidium efflux assay (Rb efflux) was used to determine inhibition of the voltage-gated potassium channel encoded by hERG.[15] In this assay, bicyclohexyl urea **1** (Fig. 1) showed 86% inhibition at 5 μg/mL, which was of significant concern recognizing the potential for widespread patient use of an antiobesity agent and the inherent necessity of limiting the side effect profile. Follow up in a voltage clamp assay showed that **1** had an IC_{50} of 52 nM for the hERG channel, which validated our concerns.[16] Experimentally determined potency shifts of the Rb efflux data relative to conventional patch clamp methods have been detailed elsewhere.[16] Efforts to limit or eliminate the cardiovascular liabilities associated with inhibition of hERG were then undertaken in the bicyclohexane series, of which we chronicle our focus on aryl modifications in this letter.



1
MCH-R1 *Ki* = 2.7 nM
Rb efflux = 86%inh @ 5 mg/mL

Figure 1. Bicyclo[3.1.0]hexyl urea MCHR-1 antagonist (**1**).

Table 1. Selected bicyclohexane aryl SAR



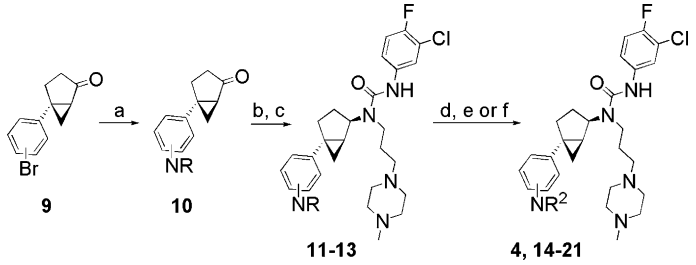
Compound	R^1	R^2	MCH-R1 K_i[a] (nM)	Rb efflux[b] (% inh.)
1	*p*-CN	3-CF_3, 4-F	2.7	86
2	H	3-Cl, 4-F	8.9	58
3	*p*-CO_2Me	3-CF_3, 4-F	5.4	63
4	*m*-NH_2	3-Cl, 4-F	9.6	25
5	*p*-F	3-Cl, 4-F	2.6	87
6	*m*-OCH_3	3-Cl, 4-F	2.7	70
7	*p*-SO_2Me	3-CF_3, 4-F	8.5	46
8	*p*-CONHMe	3-CF_3, 4-F	17	25

[a] Mean values (n = 8) ± SEM.
[b] Measured at 5 μg/mL.

Preliminary results indicated that several substituents at the aryl terminus provided little or no improvement with respect to hERG liabilities. Electron withdrawing or electron donating groups were equally offensive. Notably, sulfones such as **7**, amines (**4**), and amides (**8**) showed a significant reduction of hERG inhibition. Having established the requirements for electron withdrawing groups on the aryl urea and the presence of an ionizable nitrogen atom on the side chain, it was decided to further pursue reduction of hERG liability by exploration of aryl variations, as several different aryl functional groups were tolerated.

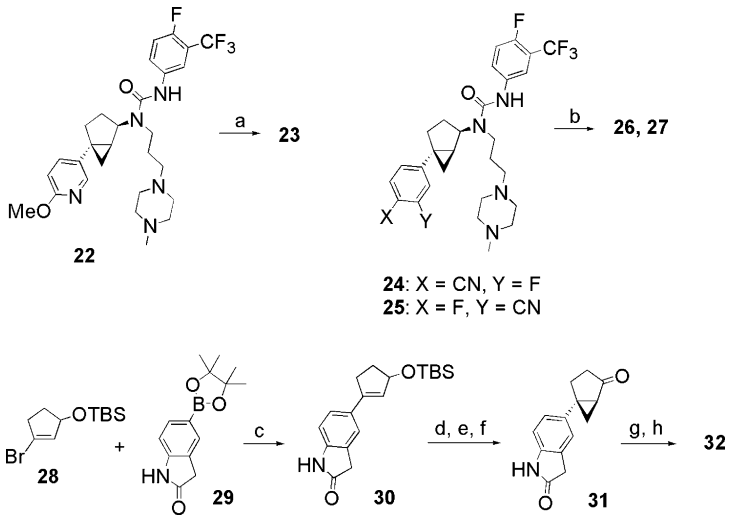
The synthesis of the bicyclohexyl ureas has been previously detailed; however, specific modifications of the aryl region are included in Schemes 1 and 2.[8] For the aminoaryl bicyclohexanes, the synthetic sequence proceeded according to Scheme 1. Amination of the aryl bromide **9** was followed by side chain installation and isocyanate treatment to provide the fully elaborated ureas **11**–**13**. Unmasking of the aniline nitrogen atom with TFA was followed by reductive amination, acylation or sulfonylation to provide the aminoaryl bicyclohexanes **4**, **14**–**21**.

Heteroaryl bicyclohexyl ureas were synthesized as shown in Scheme 2. Methoxypyridine **22**[17] was treated with TMSI to provide pyridone **23**. The aminobenzisoxazoles **26** and **27** were derived from **24** [17] and **25**[17], respectively, via treatment with acetohydroxamic acid and in situ cyclization. The pinacol derivative of oxindole was coupled to vinyl bromide **28**, followed by standard manipulations to provide the oxindolyl bicyclohexyl urea **32**.



9 **10** **11-13** **4, 14-21**

Scheme 1. Reagents and conditions: (a) carbamate or amide, *N*,*N*′-dimethylethylenediamine, CuI, K_2CO_3, toluene, 110 °C; (b) 1-(3-aminopropyl)-4-methylpiperazine, Ti(O-*i*-Pr)$_4$, 18 h, then $NaBH_4$, MeOH; (c) aryl isocyanate, *i*-Pr_2NEt, CH_2Cl_2; (d) TFA, CH_2Cl_2 (for R = BOC); (e) aldehyde, $NaB(OAc)_3H$, CH_2Cl_2; (f) acid chloride, isocyanate or sulfonyl chloride, *i*-Pr_2NEt, CH_2Cl_2.

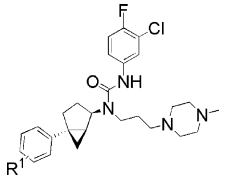


Scheme 2. Reagents: (a) TMSI, CH_2Cl_2; (b) acetohydroxamic acid, K(O-*t*-Bu), DMF; (c) Pd(dppf)Cl_2, K_3PO_4, DME/H_2O; (d) Et_2Zn, $ClCH_2I$, CH_2Cl_2; (e) TBAF, THF; (f) Dess–Martin periodinane, pyridine, CH_2Cl_2; (g) 1-(3-aminopropyl)-4-methylpiperazine, Ti(O-*i*-Pr)$_4$, 18 h, then $NaBH_4$, MeOH; (h) aryl isocyanate, *i*-Pr_2NEt, CH_2Cl_2.

Given the promising reduction of hERG affinity observed with aniline **4**, a series of derivatives were made from the parent anilines in order to probe the boundaries of acceptable changes that would reduce hERG inhibition while retaining activity for MCH-R1 (Table 2). Substitution at either the *m*- or *p*-positions with amines and relatively small alkyl amides (branched or *n*-alkyl) proceeded with good retention of MCH-R1 binding while significantly reducing hERG inhibition. Unfortunately, pharmacokinetic properties suffered as indicated by low rat AUC data. It was speculated that cyclic amides would impart increased stability in vivo, which was indeed the case with pyrrolidinone **13**, though a significant loss in MCH-R1 affinity was observed. The cyclopropylamide **19** served to improve binding and AUC, however, increased hERG inhibition as well. Small alkyl ureas such as **21** also served to balance affinity and hERG liability, while sulfonamides, *t*-butyl carbamates, and pivaloyl amides all were inferior.

Further efforts to reduce hERG channel affinity focused on heterocyclic aryl groups (Table 3). Heterocycles such as pyridines[17] and thiophenes[17] were tolerated; however, these did not significantly affect hERG affinity. In contrast, thiazole **35**[17] produced a significant drop in hERG liability along with a decrease in MCH-R1 activity. Elaboration to methoxypyridine **22** provided a promising reduction in hERG affinity, as did the pyridone derivative **23**, however, the pyridones suffered from inferior activity for MCH-R1. Oxindoles such as **32** retained

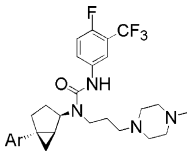
Table 2. Aminoaryl bicyclohexane SAR

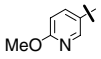
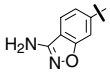


Compound	R^1	MCH-R1 K_i[a] (nM)	Rb efflux[b] (% inh.)	Rat $AUC_{0-6\ h}$[c] (ng h/mL)
4	*m*-NH_2	9.6	25	
11	*p*-NHBOC	139	87	
12	*m*-NH-azetidinyl	25	29	
13	*m*-NH-pyrrolidinyl	57	14	822
14	*p*-NH_2	4.4	16	
15	*m*-NHAc	2.5	19	251
16	*p*-NHAc	4.8	18	
17	*m*-NH-propionyl	3.1	34	533
18	*m*-NH-isopropionyl	15.1	37	339
19	*m*-NH-cyclopropionyl	6.8	46	634
20	*m*-NH-pivaloyl	115	27	
21	*m*-NHCONHEt	28	17	127

[a] Mean values ($n = 8$).
[b] Measured at 5 μg/mL.
[c] Mean values ($n = 3$). Dosed at 10 mg/kg po.

Table 3. Heteroaryl bicyclohexane SAR



Compound	Ar	MCH-R1 K_i[a] (nM)	Rb efflux[b] (% inh.)	Rat $AUC_{0-6\ h}$[c] (ng h/mL)
33	3-Pyridyl[d]	2.0	97	1001
34	3-Thienyl	13	75	
35	2-Thiazolyl	56	27	
22		8.6	36	757
23		43	9	
26		21	26	733
27		46	46	
32		15	50	

[a] Mean values ($n = 8$).
[b] Measured at 5 μg/mL.
[c] Mean values ($n = 3$). Dosed at 10 mg/kg po.
[d] 3-Cl, 4-F aryl urea.

acceptable MCH-R1 inhibition, and showed significant reductions in hERG binding, as did aminobenzisoxazole **26**. Follow up in a voltage clamp assay showed that **26** had an IC_{50} of 0.69 μM in a voltage clamp assay. Pharmacokinetic studies with **26** indicated that acceptable exposure in rodents could be obtained. Interestingly, the regioisomeric derivative **27** exhibited a 2-fold reduction in affinity relative to **26**.

In summary, the Rb efflux assay provided a reliable initial screen for evaluation of hERG liabilities in bicyclohexyl MCH-R1 antagonists.[16] Changes in the terminal aryl region provided impact on the hERG binding properties, with amide substituents providing consistent reductions in hERG affinity. Further studies revealed that aminomethyl substituents and several heteroaryl derivatives also exhibited significant reductions in hERG binding while maintaining acceptable activity for MCH-R1 and reasonable pharmacokinetic properties such as AUC.

Acknowledgments

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17. Synthesized via Method B in reference 8.