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Synthesis and structure–activity relationships of retro bis-aminopyrrolidine urea (rAPU) derived small-molecule antagonists of the melanin-concentrating hormone receptor-1 (MCH-R1). Part 1

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Abstract—The design, synthesis, and SAR of a series of retro bis-aminopyrrolidine ureas are described. Compounds from this series exhibited potent binding affinity and functional activity at MCH-R1, and good oral bioavailability in rat.
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Mammalian melanin-concentrating hormone (MCH) is a 19 amino acid cyclic peptide, first isolated from the brain tissue of rats.[1] It has since been shown that in mammals, expression of MCH occurs throughout the brain, though particularly high concentrations are found in the lateral hypothalamus,[2] an area known to be involved in the control of feeding behavior. MCH selectively binds and activates two 7-transmembrane G protein-coupled receptors, namely MCH-R1 and R2.[2a] Although it is not yet clear what role MCH-R2 plays in vivo, recent research suggests that MCH-R1 is involved in the modulation of energy homeostasis, food intake, and body weight. In rodents, increased brain levels of MCH leads to increased food intake, obesity, and insulin resistance.[3] Conversely, mice lacking the MCH peptide (mch−/−) are lean and hypophagic, whereas those deficient in MCH-R1 (mch1−/−) are lean, hyperphagic, and resistant to diet-induced obesity.[3] It has also been shown that administration of a potent and selective small-molecule MCH-R1 antagonist to rats leads to a significant reduction in food intake and/or weight loss in these animals.[4] These and other data suggest that in man, blockade of MCH-R1 may lead to a clinical treatment for chronic obesity, and a number of groups have recently reported on their efforts toward the development of selective small-molecule MCH-R1 antagonists.[4,5]

We recently disclosed the discovery and SAR of a series of bis-aminopyrrolidine urea (APU) derived small-molecule MCH-R1 antagonists, exemplified by **1** (Fig. 1).[5i,k] APU **1** is a potent functional antagonist of MCH-R1, but exhibits low metabolic stability in an in vitro human liver microsome (HLM) assay and had only moderate oral exposure in rat.[6] Metabolite profiling of

Keywords: Melanin-concentrating hormone (MCH); Melanin-concentrating hormone receptor (MCH-R1); Melanin-concentrating hormone receptor antagonists (MCH-R1 antagonists); Obesity; Aminopyrrolidine urea; Retro aminopyrrolidine urea.
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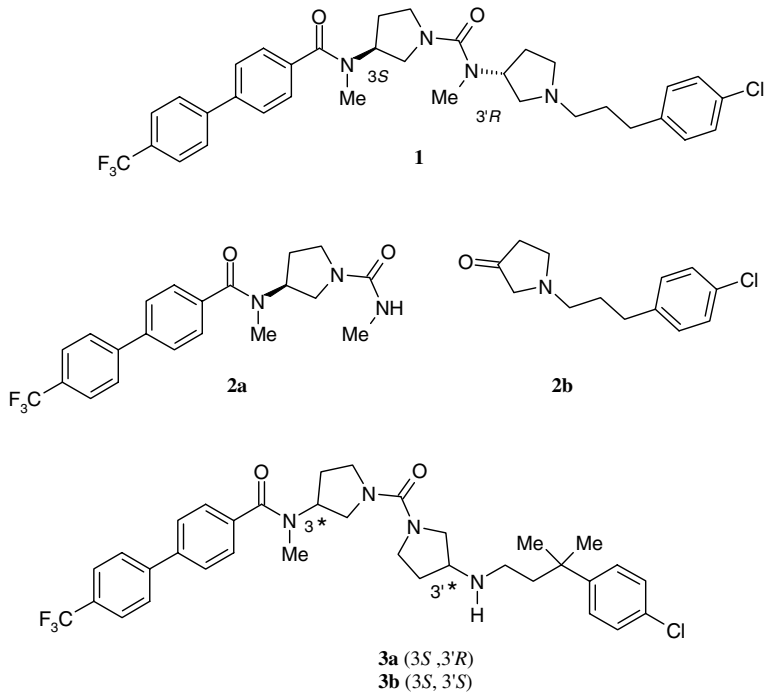
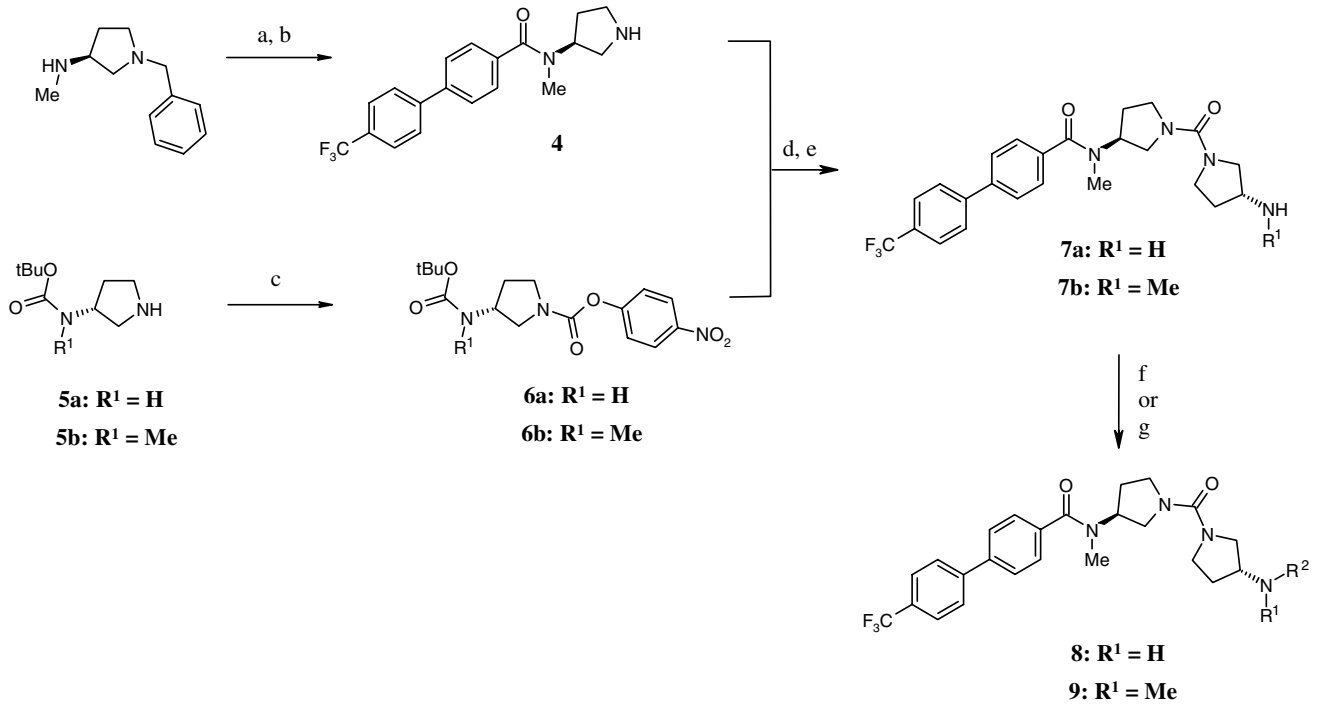


Figure 1. General structures of APU and rAPU MCH-R1 antagonists.

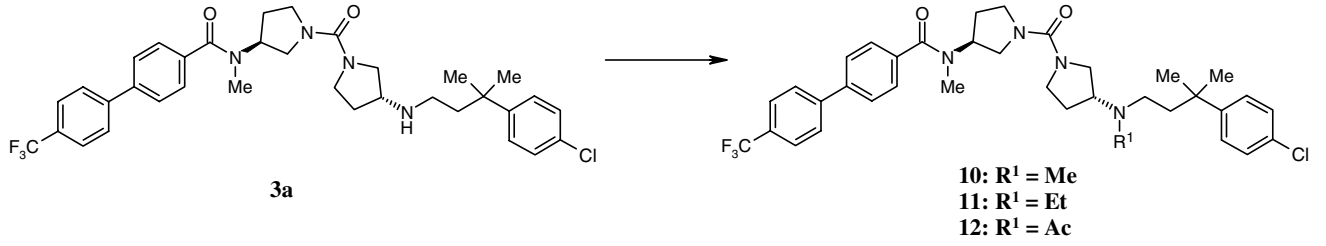
1 in HLM identified compound **2a** as the major metabolite (Fig. 1), which probably occurs via oxidative deamination of the right-hand pyrrolidine ring of **1** giving 3-pyrrolidinone in the process. We reasoned that reversal of the connectivity of the bis-aminopyrrolidine ring system to give the retro bis-aminopyrrolidine urea (rAPU) core (exemplified by **3a** and **3b**, Fig. 1) might prevent this metabolic pathway from occurring. This could yield molecules with increased metabolic stability, without adversely affecting potency at MCH-R1. In this letter we report on the synthesis and SAR of this novel series of small-molecule MCH-R1 antagonists and, in particular, we describe basic SAR around both the amine and biarylcarboxamide motifs, by reporting binding affinity data (K_i) for MCH-R1.

For the APU series, incorporation of a biarylcarboxamide moiety was favored for optimal receptor binding. In addition, of the four possible diastereoisomers the (3*S*,3′*R*) and (3*S*, 3′*S*) configurations were preferred (see **1**, Fig. 1).[5i,k] The rAPU derivative **3a** (3*S*,3′*R*) is a comparable analog to APU **1**, and exhibited a somewhat similar K_i value of 14 nM ($n = 3$), with the diastereoisomer **3b** (3*S*, 3′*S*) being equipotent ($K_i = 22$ nM, $n = 3$). The metabolic stability of **3a** in human liver microsomes did indeed show improvement, with a scaled predicted intrinsic clearance of 19 mL/min/kg versus 60 mL/min/kg for compound **1**.[7,8] In addition, compound **3a** exhibited greater oral bioavailability in rat, $\%F = 42$,[9] however brain exposure was low and needed to be addressed. Compound **1** also showed strong inhibition ($IC_{50} = 170$ nM) of the HERG potassium channel, in a whole cell patch-clamp assay.[10] Therefore, we were pleased to discover that compound **3a** showed significantly less activity ($IC_{50} = 2600$ nM) in the HERG patch-clamp assay, which may be due to the incorporation of a secondary amine.[11] Compound **3b** displayed a very similar in vitro and in vivo profile to that described for **3a**. In light of the above findings we decided to further explore the rAPU series.

In order to investigate the SAR around the basic nitrogen of the rAPU template, compounds **7**–**12** (Schemes 1, 2 and Table 1) were prepared incorporating both the 4-(4-trifluoromethylphenyl)phenylcarboxamide group and the (3*S*,3′*R*) stereoconfiguration, as employed in the lead compound **3a**. Compounds **8a**–**l** and **10**–**12** were obtained from primary amine **7a**, whereas compounds **9a**–**j** were obtained from secondary amine **7b**. The synthetic route employed for the preparation of both intermediates (**7a** and **7b**) is outlined in Scheme 1. Coupling of commercially available (*S*)-1-benzyl-3-(methylamino)pyrrolidine[12] with 4-(4-trifluoromethylphenyl)benzoyl chloride, followed by N-debenzylation, gave pyrrolidine **4** in good yield. Carbamates **6a** and **6b** were obtained directly via reaction of 4-nitrophenyl chloroformate with (*R*)-3-(*tert*-butoxycarbonyl)aminopyrrolidines **5a** and **5b**, respectively.[13] Reaction of pyrrolidine **4** with either carbamate **6a** or **6b** in the presence of *N*,*N*-4-dimethylaminopyridine in DMF gave, after N-Boc deprotection, **7a** and **7b**, respectively. Both coupled intermediates (N-Boc protected **7a** and **7b**) were obtained in only modest yield due to formation of a mixture of unidentified by-products. Subsequent *N*-alkylation of **7a** and **7b** gave compounds **3a**, **8a**–**l**, and **9a**–**j**, respectively.[14] Compounds **10**–**12** were accessed from compound **3a**, as outlined in Scheme 2. All rAPUs described herein (Tables 1 and 2) were obtained as single diastereoisomers and were subsequently assayed for their ability to displace radiolabeled [^{125}I-Tyr^{13}]-MCH in a competitive binding assay.[15] The assay was performed using human MCH-R1 that is modified for



Scheme 1. Reagents and conditions: (a) 4-(4-trifluoromethylphenyl)benzoyl chloride, TEA, DCM, rt, 12 h, quantitative; (b) H_2 (40 psi), $Pd(OH)_2/C$, MeOH, rt, 2 h, 63%; (c) 4-nitrophenyl chloroformate, TEA, THF, 0 °C to rt, 2 h, 83% (**6a**) and 90% (**6b**); (d) DMAP, TEA, DMF, 100 °C, 12 h; (e) For **7a**: TFA, DCM, rt, 1 h, 38% (from **6a**); for **7b**: HCl, Et_2O, DCM, rt, 12 h, 35% (from **6b**); (f) aldehyde or ketone, $NaCNBH_3$ or $NaBH_4$, MeOH, rt, 12 h, 20–60%; (g) alkyl bromide, NaI, K_2CO_3, DMF, 80 °C, 3 h, 20–50%.

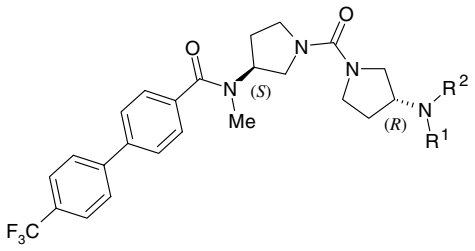


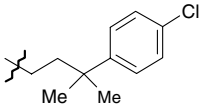
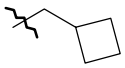
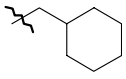
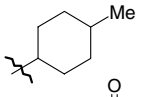
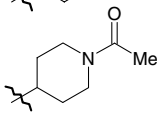
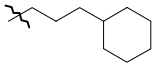
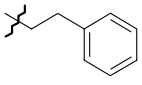
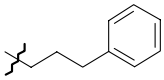
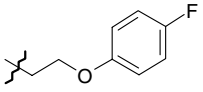
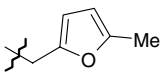
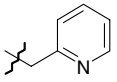
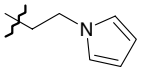
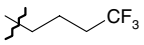
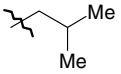
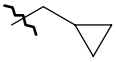
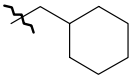
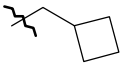
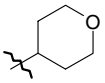
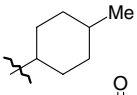
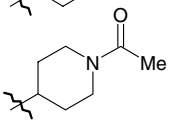
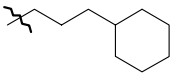
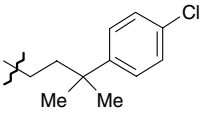
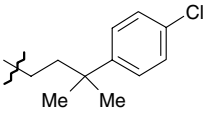
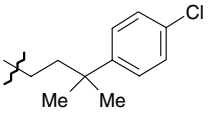
Scheme 2. Reagents and conditions: for **10**: formaldehyde, $NaCNBH_3$, MeOH, rt, 12 h, 61%; for **11**: acetaldehyde, $NaBH_4$, MeOH, rt, 12 h, 59%; for **12**: acetyl chloride, TEA, DCM, rt, 12 h, 92%.

optimal expression in HEK293 cells. The functional antagonism of all compounds with measured K_is less than 50 nM was further confirmed based on their ability to inhibit, in a dose-dependent manner, MCH-stimulated G protein-GTPγ^{35}S binding in cells expressing native human MCH-R1.[16]

The unsubstituted amine alone was reasonably potent (compound **7a**, Table 1), having a measured K_i of 51 nM. Addition of a methyl group (**7b**, $K_i = 53$ nM) did not improve potency, though the introduction of larger lipophilic substituents increased potency up to 5-fold. For instance, the cyclobutylmethyl (compound **8a**, $K_i = 11$ nM), cyclohexylmethyl (**8b**, $K_i = 12$ nM), and 4-methylcyclohexyl (**8c**, $K_i = 13$ nM) derivatives were equipotent. Unfortunately, although molecules such as **8b** and **8c** were very potent MCH-R1 antagonists, they also exhibited potent inhibition of the metabolizing enzyme *CYP*2D6. For example, compound **8c** inhibited *CYP*2D6 with an IC_{50} of 55 nM.[17] The addition of a phenyl containing substituent in this region of the molecule gave potent MCH compounds and interestingly seemed to significantly reduce *CYP*2D6 activity. The phenethyl (**8f**), phenpropyl (**8g**), and 3-(4-chlorophenyl)-3-methylbutyl (**3a**) derivatives had K_is of 17, 10, and 14 nM, respectively, and compounds **8g** and **3a** had IC_{50}s at *CYP*2D6 of 2000 and 3300 nM, respectively. Saturation of the aryl ring did not adversely affect potency at the receptor as the cyclohexyl propyl derivative **8e** had a K_i of 22 nM, though incorporation of relatively polar heteroaryl groups close to the basic nitrogen, such as (5-methyl-2-furanyl)methyl (**8i**) or (2-pyridyl)methyl (**8j**), was detrimental for receptor potency.[18] Combined, these results suggest that the region of the receptor surrounding this part of the molecule is relatively open, lipophilic in nature, and prefers relatively non-polar groups. In addition to secondary amines, a number of tertiary amines were also prepared. The *N*,*N*-dimethyl derivative (**9a**, $K_i = 34$ nM) was approximately equipotent to the corresponding second-

Table 1. Binding affinities of rAPUs **3a** and **7–12** toward MCH-R1

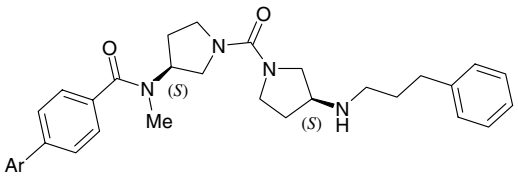


Compound	R^1	R^2	K_i (pK_i)[a] (nM)
3a[b,d]	H		14 (7.85 ± 0.05)
7a	H	H	51 (7.29 ± 0.1)
7b	H	Me	53 (7.27 ± 0.05)
8a[c]	H		11 (7.98 ± 0.2)
8b[b]	H		12 (7.91 ± 0.2)
8c[b]	H		13 (7.88 ± 0.2)
8d[b]	H		21 (7.68 ± 0.2)
8e[b]	H		22 (7.66 ± 0.2)
8f[c]	H		17 (7.78 ± 0.2)
8g[b]	H		10 (8.01 ± 0.05)
8h[c]	H		19 (7.73 ± 0.2)
8i[b]	H		110 (6.96 ± 0.2)
8j[b]	H		180 (6.74 ± 0.1)
8k[c]	H		40 (7.40 ± 0.2)
8l[c]	H		16 (7.79 ± 0.2)
9a[b]	Me	Me	34 (7.47 ± 0.1)
9b[b]	Me	Et	54 (7.27 ± 0.1)
9c[b]	Me		38 (7.42 ± 0.1)
9d[b]	Me		28 (7.55 ± 0.1)
9e[b]	Me		24 (7.62 ± 0.1)
9f[c]	Me		42 (7.38 ± 0.1)
9g[b]	Me		51 (7.29 ± 0.1)
9h[b]	Me		29 (7.54 ± 0.2)
9i[b]	Me		33 (7.48 ± 0.3)
9j[b]	Me		26 (7.59 ± 0.1)
10	Me		14 (7.84 ± 0.05)
11	Et		27 (7.57 ± 0.1)
12	Ac		48 (7.32 ± 0.1)

[a] K_i (pK_i ± SEM, $n = 3$ or greater).[15]
[b] Prepared via a reductive alkylation as the last step.
[c] Prepared via a Finkelstein alkylation as the last step.
[d] Prepared from compound **7a** and 3-(4-chlorophenyl)-3-methylbutyraldehyde.[21]

ary amine **7b**, and the addition of larger lipophilic groups such as ethyl (**9b**, $K_i = 54$ nM) or isobutyl (**9c**, $K_i = 38$ nM) did not improve potency. In most cases we discovered that going from a secondary to tertiary amine resulted in a reduction in binding affinity. For instance, the *N*-methyl-(cyclobutylmethyl) derivative **9f** ($K_i = 42$ nM) was approximately 4-fold less potent than the corresponding secondary amine **8a** (with a $K_i = 11$ nM). An exception proved to be compound **10** ($K_i = 14$ nM), which was equipotent with the corresponding secondary amine **3a**. Unfortunately compound **10** proved to be very metabolically unstable, the scaled predicted intrinsic clearance (in HLM) being 500 mL/min/kg, 25-fold greater than for **3a**. Presumably

Table 2. Binding affinities of rAPUs **16** toward MCH-R1



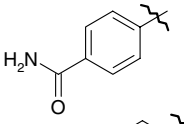
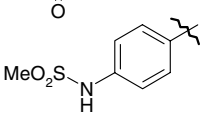
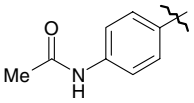
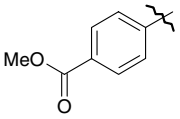
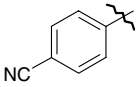
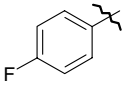
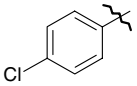
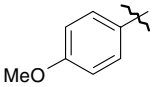
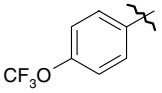
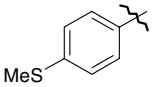
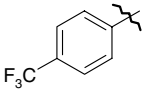
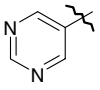
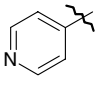
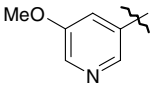
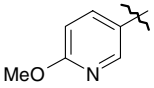
Compound	Ar	K_i (pK_i)[a] (nM)
16a		630 (6.20 ± 0.05)
16b		>10,000
16c		4000 (5.40 ± 0.1)
16d		73 (7.13 ± 0.2)
16e		49 (7.31 ± 0.1)
16f		19 (7.73 ± 0.2)
16g		6 (8.19 ± 0.2)
16h		8 (8.09 ± 0.2)
16i		7 (8.13 ± 0.2)
16j		4 (8.42 ± 0.2)
16k		11 (7.96 ± 0.05)
16l		4800 (5.32 ± 0.1)
16m		400 (6.40 ± 0.05)
16n		640 (6.20 ± 0.02)

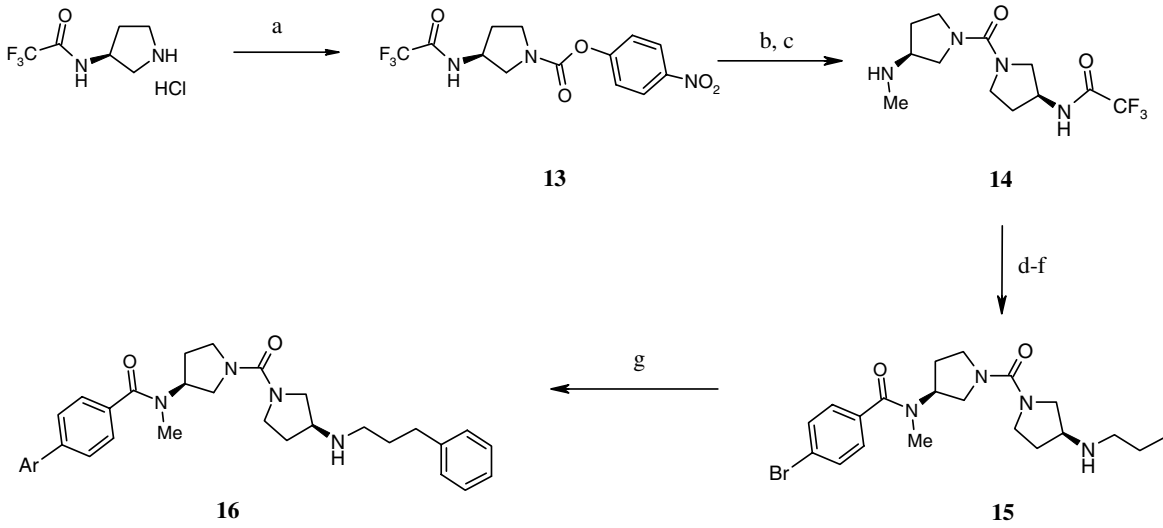
Table 2 (*continued*)

Compound	Ar	K_i (pK_i)[a] (nM)
16o		1000 (6.00 ± 0.1)
16p		44 (7.36 ± 0.1)

[a] K_i (pK_i ± SEM, n = 3 or greater).[15]

N-demethylation occurs rapidly, giving the corresponding secondary amine **3a**. Replacement of the *N*-methyl group of **10** with either ethyl (**11**, K_i = 27 nM) or acetyl (**12**, K_i = 48 nM) gave compounds with slightly reduced binding affinity and did very little to improve metabolic stability. Surprisingly the *N*-acetyl derivative **12**, though exhibiting moderately potent binding affinity, did not show appreciable functional activity. This suggests that for this series at least, the presence of a basic center in this region of the molecule is important for functional activity.

We were also interested in the SAR around the terminal aryl of the biarylcarboxamide motif. Compounds **16a**–**p** were prepared as the (3*S*,3′*S*) diastereomers (which display comparable potency at MCH-R1; compare **3a**, K_i = 14 nM, with **3b**, K_i = 22 nM) and were directly obtained from intermediate **15** as outlined in Scheme 3. Reaction of commercially available (*S*)-3-(trifluoroacetamido)pyrrolidine hydrochloride with 4-nitrophenyl chloroformate in the presence of a base gave carbamate **13** in good yield. Subsequent reaction of **13** with (*S*)-3-[(*tert*-butoxycarbonyl)methylamino]pyrrolidine[19] followed by N-Boc deprotection gave the intermediate methyl amine **14**. Coupling of **14** with 4-bromobenzoyl chloride, followed by N-deprotection then reductive alkylation with hydrocinnamaldehyde, gave intermediate **15**. Subsequent reaction of **15** with a variety of aryl boronic acids via a Suzuki coupling gave final compounds **16a**–**p**. We examined the effect of varying the *para* substituent on the terminal phenyl ring (compounds **16a**–**k**) and, not too surprisingly, discovered that the SAR was very similar to that of the original APU series.[5k] The electron-donating/withdrawing capability of the *para* substituent (its σ value) did not seem important. Rather, potency was determined by the substituent's relative lipophilicity (or π value).[20] For example those compounds containing a phenyl ring substituted by very polar groups such as carboxamide (**16a**, K_i = 630 nM; $\pi = -1.5$), sulfonamide (**16b**, K_i > 10,000 nM; $\pi = -1.9$) and acetamide (**16c**, K_i = 4000 nM; $\pi = -0.8$) proved to be poor MCH-R1 binders. The incorporation of more lipophilic functionality in this position resulted in a dramatic increase in potency. The 4-methylcarboxylate (**16d**; $\pi = 0$) and 4-cyano (**16e**; $\pi = -0.3$) derivatives had measured K_is of 73 and 49 nM, respectively, whereas the 4-chloro (**16g**; $\pi = 0.8$), 4-trifluoromethoxy (**16i**; $\pi = 1.2$) and 4-thiomethyl (**16j**; $\pi = 0.6$) had K_is of 6, 7, and 4 nM,



Scheme 3. Reagents and conditions: (a) 4-nitrophenyl chloroformate, TEA, THF, 0 °C to rt, 2 h, 85%; (b) (*S*)-3-*tert*-butoxycarbonyl (methylamino)pyrrolidine, TEA, DMF, 70 °C, 10 h, 25%; (c) TFA, DCM, rt, 1 h, quantitative; (d) 4-bromobenzoyl chloride, TEA, DCM, rt, 12 h; (e) K_2CO_3, MeOH, H_2O, 75 °C, 12 h; (f) hydrocinnamaldehyde, TEA, $NaBH_4$, MeOH, rt, 12 h, 44% (from **14**); (g) aryl boronic acid, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, H_2O, 90 °C, 12 h, 25–65%.

respectively. Replacing the phenyl with a more polar aromatic ring, such as pyrimidyl (**16l**, $K_i = 4800$ nM), 3-pyridyl (**16m**, $K_i = 400$ nM) or 4-pyridyl (**16n**, $K_i = 640$ nM), resulted in a large decrease in potency. Interestingly, by introducing a methoxy substituent *para* to the biaryl bond, potency was regained. The 2-methoxypyrid-5-yl derivative **16p** ($K_i = 44$ nM) was approximately 10-fold more potent than the corresponding unsubstituted pyridyl **16m**. As observed previously with the APU series, compounds containing a *meta*-substituted aryl ring were much less tolerated by the receptor. For instance, the 3-methoxypyrid-5-yl derivative **16o** ($K_i = 1000$ nM) was approximately 20-fold less potent than **16p**, suggesting that the same steric factors may play a role in this series. Overall these data suggest that the receptor binding pocket surrounding the biaryl motif is sterically tight and lipophilic in nature, as only relatively non-polar groups are tolerated and *para* substitution is preferred. A proposed model, based on site-directed mutagenesis, of the interaction of biphenylcarboxamide containing antagonists with MCH-R1 supports these general conclusions.[22]

In conclusion, we have discovered a novel series of potent and functional MCH-R1 antagonists based around a rAPU scaffold. SAR around both the basic nitrogen and biarylcarboxamide groups was explored and potent MCH-R1 binding was achieved via incorporation of both a lipophilic substituted secondary amine and a lipophilic *para* substituted biphenylcarboxamide group. Examples from this series exhibited good oral exposure and metabolic stability, with improved profiles against the HERG channel. Unfortunately, issues with both inhibition of *CYP*2D6 and poor brain penetration were identified, and our efforts toward addressing these problems will be reported in our next letter.

Acknowledgments

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Napier, J. J.; Brune, M. E.; Bush, E. N.; Brodjian, S. J.; Dayton, B. D.; Shapiro, R.; Hernandez, L. E.; Marsh, K. C.; Sham, H. L.; Collins, C. A.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2752; (f) Huang, C. Q.; Baker, T.; Schwarz, D.; Fan, J.; Heise, C. E.; Zhang, M.; Goodfellow, V. S.; Markison, S.; Gogas, K. R.; Chen, T.; Wang, X.-C.; Saunders, J.; Zhu, Y.-F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3701; (g) Vasudevan, A.; LaMarche, M. J.; Blackburn, C.; Che, J. L.; Luchaco-Cullis, C. A.; Lai, S.; Marsilje, T. H.; Patane, M. A.; Souers, A. J.; Wodka, D.; Geddes, B.; Chen, S.; Brodjian, S.; Falls, D. H.; Dayton, B. D.; Bush, E.; Brune, M.; Shapiro, R. D.; Marsh, K. C.; Hernandez, L. E.; Sham, H. L.; Collins, C. A.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4174; (h) Palani, A.; Shapiro, S.; McBriar, M. D.; Clader, J. W.; Greenlee, W. J.; Spar, B.; Kowalski, T. J.; Farley, C.; Cook, J.; Van Heek, M.; Weig, B.; O'Neill, K.; Graziano, M.; Hawes, B. *J. Med. Chem.* **2005**, *48*, 4746; (i) Kym, P. R.; Iyengar, R.; Souers, A. J.; Lynch, J. K.; Judd, A. S.; Gao, J.; Freeman, J.; Mulhern, M.; Zhao, G.; Vasudevan, A.; Wodka, D.; Blackburn, C.; Brown, J.; Che, J. L.; Cullis, C.; Lai, S. J.; LaMarche, M. J.; Marsilje, T.; Roses, J.; Sells, T.; Geddes, B.; Govek, E.; Patane, M.; Fry, D.; Dayton, B. D.; Brodjian, S.; Falls, D.; Brune, M.; Bush, E.; Shapiro, R.; Knourek-Segel, V.; Fey, T.; McDowell, C.; Reinhart, G. A.; Preusser, L. C.; Marsh, K.; Hernandez, L.; Sham, H. L.; Collins, C. A. *J. Med. Chem.* **2005**, *48*, 5888.

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6. In rat following a single iv dose of 5 mg/kg, plasma AUC_{0-24h}, CL, C_{max}, $t_{1/2}$, and V_d were determined to be 4017 ng h/mL, 19.5 mL/min/kg, 27 ng/mL, 4.4 h, and 7.6 L/kg, respectively. Following a single oral dose of 10 mg/kg, plasma AUC_{0-24h} and absolute bioavailability were determined to be 398 ng h/mL and 5%, respectively. All data were determined in male Wistar rats ($n = 3$).
7. 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.
8. Oxidative metabolism of the carbon center adjacent to the 4-chlorophenyl ring, of compound **1**, was not observed upon incubation with human liver microsomes (As confirmed by HPLC–MS-MS). This strongly suggests that the observed increase in metabolic stability (in HLM) of compound **3a** is not due to the presence of the geminal dimethyl group.
9. In rat following a single iv dose of 5 mg/kg, plasma AUC_{0-24h}, CL, C_{max}, $t_{1/2}$, and V_d were determined to be 4037 ng h/mL, 21 mL/min/kg, 326 ng/mL, 4.8 h, and 8.8 L/kg, respectively. Following a single oral dose of 10 mg/kg, plasma AUC_{0-24h} was determined to be 3396 ng hr/mL. All data were determined in male Wistar rats ($n = 3$).
10. The HERG potassium current was recorded from a HERG/HEK cell line using established patch-clamp methods. The effects of test compounds on the HERG current were determined at the end of a 5 min application. Test compound(s) were tested at six concentrations (0.1 nM, 1 nM, 10 nM, 100 nM, 1 μM, and 10 μM). Cisapride (30 nM) was used as a positive control.
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12. (*S*)-1-Benzyl-3-(methylamino)pyrrolidine is commercially available from Tokyo Chemical Industry (TCI) America, Portland, Oregon. The ee was determined to be >97%.
13. (*R*)-3-(*tert*-Butoxycarbonyl)aminopyrrolidine **5a** is commercially available from Tokyo Chemical Industry (TCI) America, Portland, Oregon. (*R*)-3-[(*tert*-Butoxycarbonyl)methylamino]pyrrolidine **5b** is obtained from commercially available (*R*)-1-benzyl-3-(methylamino)pyrrolidine (TCI America, ee > 97%) via N-3 Boc protection followed by N-1 debenzylation.
14. Typical experimental procedure for preparation of rAPU's, via reductive alkylation: Synthesis of **3a**. To a stirred solution of the HCl salt of **7a** (601 mg, 1.21 mmol) and TEA (239 mg, 2.37 mmol) in 35 mL MeOH at ambient temperature, was added a solution of 3-(4-chlorophenyl)-3-methylbutyraldehyde[21] (285 mg, 1.45 mmol) in 5 mL MeOH. Stirring was continued for a further 16 h before the addition of sodium borohydride (500 mg, 13.16 mmol). After stirring for 30 min, 10 mL of 1 N aqueous NaOH solution was added. The MeOH was removed in vacuo and the remaining aqueous phase extracted with EtOAc (2×100 mL). The combined organic layers were washed with brine then dried ($MgSO_4$). Concentration in vacuo gave an oil, which was purified by silica gel chromatography (gradient elution with 100% EtOAc to 5% MeOH in EtOAc to 9% MeOH/1% TEA in EtOAc) to afford a colorless foam, which was redissolved in a solution of methanesulfonic acid (77 mg, 0.80 mmol, in 20 mL of DCM). After stirring for 1.5 h at ambient temperature, concen-

tration in vacuo afforded the mesylate salt of **3a** (565 mg, 58%) as a colorless solid: ^{1}H NMR (DMSO-d_6) δ 7.94 (d, 2H, J = 6.6 Hz), 7.84 (d, 2H, J = 7.7 Hz), 7.82 (d, 2H, J = 6.6 Hz), 7.54 (d, 2H, J = 6.2 Hz), 7.37–7.40 (m, 4H), 3.66 (m, 1 H), 3.56 (dd, 1H, J = 9.2, 5.0 Hz), 3.25–3.50 (m, 8H), 2.91 (s, 3H), 2.63–2.66 (m, 2H), 2.34 (s, 3H), 2.05–2.10 (m, 3H), 1.91–1.95 (m, 3H), 1.29 (s, 6H); MS (m/z) 641.2 $(M+H)^+$. Anal. Calcd for $C_{35}H_{40}N_4O_2ClF_3{\cdot}CH_3SO_3H{\cdot}11/2H_2O$: C, 56.57; H, 6.20; N, 7.33. Found C, 56.79; H, 6.59; N, 7.45.

15. On each assay plate, a standard antagonist of comparable affinity to those being tested was included as a control for plate-to-plate variability. Overall pK_i values were highly reproducible, the standard error of the mean (SEM) being reported. All compounds described were assayed in at least three independent experiments.
16. For example, compound **16j** had a measured IC_{50} of 2.2 ± 1.2 nM (n = 3). 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. Key compounds (with K_i <50 nM) were assayed in at least three independent experiments.
17. The *CYP*2D6 inhibition assay was carried out in the presence of the fluorescent substrate, AMMC. Quinidine was used as positive control.
18. Calculated log*P*s for 2,5-dimethylfuran and 2-methylpyridine are 2.3 and 1.2, respectively, significantly lower than for methylcyclohexane with a log*P* = 3.9. Calculated using ACD/Labs log*P* database, Advanced Chemistry Development Inc., Toronto, Ontario, Canada (http://www.acdlabs.com).
19. Obtained in two steps from commercially available (*S*)-1-benzyl-3-(methylamino)pyrrolidine via N-3 Boc protection followed by N-1 debenzylation.
20. Craig, P. N. *J. Med. Chem.* **1971**, *14*, 680.
21. 3-(4-Chlorophenyl)-3-methylbutyraldehyde was prepared from 3-methyl-2-butenal, as described in Goodfellow, V.; Rowbottom, M.; Dyck, B. P.; Tamiya, J.; Zhang, M.; Grey, J.; Vickers, T.; Kiankarimi, M.; Wade, W.; Hudson, S. C. Patent Application WO 2004/080411, **2004**.
22. Unpublished results.