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Thienopyrimidinone bis-aminopyrrolidine ureas as potent melanin-concentrating hormone receptor-1 (MCH-R1) antagonists

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Abstract—A series of thienopyrimidinone bis-aminopyrrolidine ureas were designed, synthesized, and evaluated for their ability to bind melanin-concentrating hormone receptor-1. These compounds exhibit potent binding affinity (K_i = 3 nM) and good in vitro metabolic stability.

Melanin-concentrating hormone (MCH) is a 19-member cyclic peptide strongly associated with feeding behavior in mammals.[1] Although MCH is expressed throughout the brain, concentrations are higher in the hypothalamus, a region linked with control of feeding.[2] Elevated levels of MCH peptide have been observed in both fasting ob/ob and wild-type mice[3] and central administration of MCH induces hyperphagia and diet-induced obesity (DIO).[4,5] Knockout mice which lack the MCH peptide (mch $^{-/-}$) are lean and hypophagic,[6] while mice which lack the MCH-R1 receptor (mchr1 $^{-/-}$) are lean and hyperphagic, indicating alterations occur in metabolism as well as in feeding.[7] Recently, structurally diverse small molecule MCH-R1 antagonists have been reported and several have shown oral efficacy in various animal models.[8] These data suggest that a potent oral antagonist of MCH-R1 would be clinically useful as an anti-obesity agent.

Our group has previously reported a novel aminopyrrolidine urea (APU) core that has produced potent MCH-R1 antagonists, exemplified by **1** (Fig. 1).[9] Compound **1** displayed potent binding (K_i = 7 nM) and functional activity (IC_{50} = 14 nM); however, the compound was rapidly metabolized in an in vitro human liver microsome (HLM) assay with an intrinsic clearance of 59 mL/min/kg.[10] In addition, **1** was a moderately potent inhibitor of CYP2D6 (IC_{50} = 4.9 μM). Scientists at GlaxoSmithKline recently disclosed a series of constrained-amide MCH-R1 antagonists (e.g., **2**)[8o,11,12] with good pharmacokinetic characteristics (bioavailability = 31%, $t_{1/2}$ = 11 h). We hypothesized that constraining the amide in our APU system in a similar manner might improve the metabolic stability and modifications near the basic nitrogen might alter inhibition of CYP2D6.[13] In this letter, we report the synthesis and SAR of APU compounds with a thienopyrimidinone ring (**3**) and the effect these changes have on metabolic stability and CYP2D6 inhibition.

The synthesis of the thienopyrimidinone APU series is shown in Scheme 1. 3-Amino-5-(4-chloro-phenyl)-thiophene-2-carboxylic acid methyl ester **7** was treated with *N*,*N*-dimethylformamide dimethyl acetal followed by reaction with Boc-protected (*S*)-3-aminopyrrolidine to form the thienopyrimidinone **8**. Subsequent deprotection followed by coupling with *p*-nitrophenyl carbamate derivative **6** gave urea **10**. Finally, removal of the Boc protecting group gave amine **11** and reductive alkylation or acylation provided an efficient method to compounds **12** with a variety of substituents.

Keywords: MCH; Melanin-concentrating hormone; Obesity.
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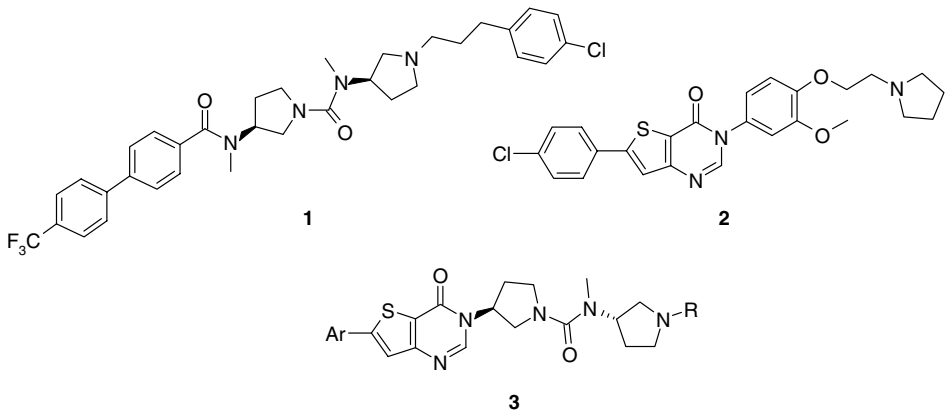
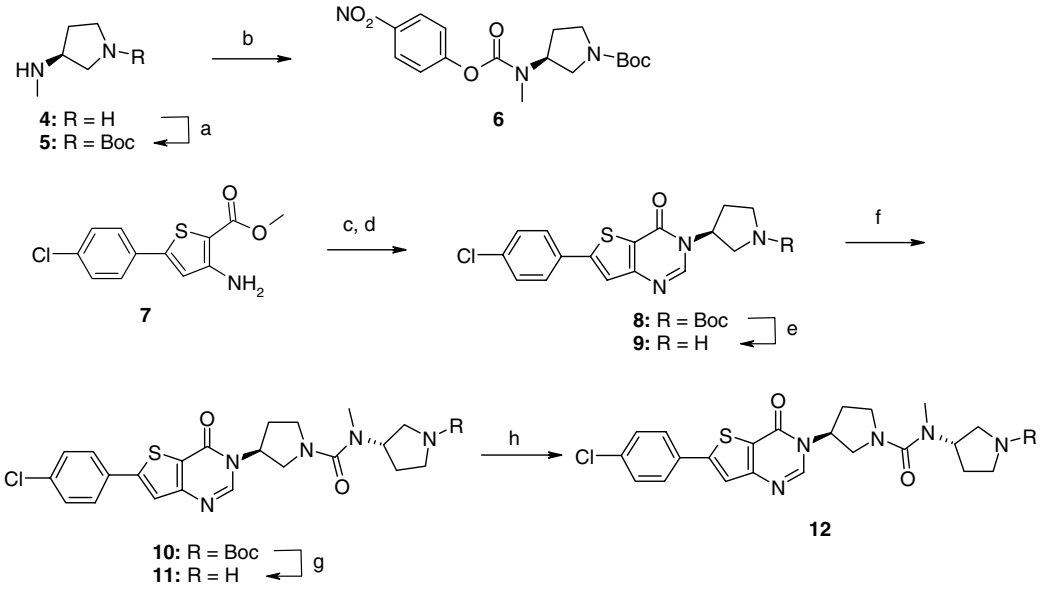


Figure 1. MCH-R1 antagonists.

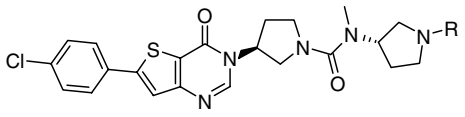


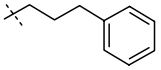
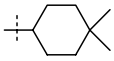
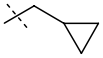
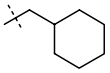
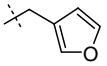
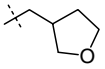
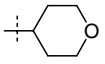
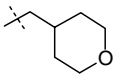
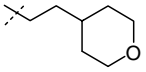
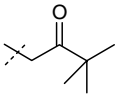
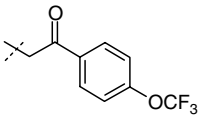
Scheme 1. Reagents and conditions: (a) $(Boc)_2O$, DCM, 0 °C, 1 h, 99%; (b) 4-nitrophenyl chloroformate, TEA, THF, 0 °C to rt, 12 h, 97%; (c) *N*,*N*-dimethylformamide dimethyl acetal, EtOH, 90 °C, 2 h; (d) (*S*)-3-amino-1-*N*-Boc-pyrrolidine, EtOH, 100 °C, 16 h, 74% over 2 steps; (e) TFA, DCM, 0 °C, 30 min, 89%; (f) **6**, TEA, DMA, 80 °C, 24 h, 95%; (g) TFA, DCM, 0 °C, 30 min, 76%; (h) for **12a**–**m**: aldehyde or ketone, $NaBH(OAc)_3$, DCM, MeOH, rt, 12 h, 20–70%; for **12n**–**o**: acyl bromide, TEA, DMF, 60 °C, 24 h, 10–30%.

Data from both MCH binding and GTPγS functional assays for the thienopyrimidinone APUs are shown in Table 1. The thienopyrimidinone **12a** is analogous to compound **1** and showed comparable binding activity (K_i = 6 nM). Intrinsic clearance (41 mL/min/kg) and CYP2D6 inhibition (8.6 μM) were moderately improved relative to **1**, providing a promising starting point for SAR studies. When the 3-phenylpropyl side chain was removed (**11**), the binding affinity decreased 3-fold relative to **12a**, although no decrease in functional activity was observed. A methyl substituent (**12b**) retained most of the binding affinity of **12a** and had very low CYP2D6 inhibition (IC_{50} = 99 μM). Small cyclic aliphatics (**12d**–**g**) gave potent MCH antagonists; however, these compounds showed moderate CYP2D6 inhibition (**12f**, IC_{50} = 3.4 μM). In contrast, ether derivatives (**12j**–**12m**) were equally potent, but showed significantly less CYP2D6 inhibition (**12k**, IC_{50} = 22.5 μM). Although aliphatic ketone **12n** was moderately potent (K_i = 17 nM), aromatic ketone **12o** had significantly reduced binding affinity (K_i = 80 nM). Based on the binding and CYP2D6 data, compounds **12b** and **12k** were chosen for further optimization.

The other three stereoisomers of **12k** were synthesized (Table 2) to determine the effect of stereochemistry on binding affinity. The two chiral centers in the molecule could be independently controlled by using different chiral aminopyrrolidines at steps d and f (Scheme 1). The stereochemistry of the pyrrolidine closer to the thienopyrimidinone had a greater effect on binding. The (*S*,*S*) diastereomer **12k** was the most potent isomer with a K_i of 3 nM. Binding affinity decreased 7-fold for the (*S*,*R*) diastereomer **13** (K_i = 21 nM) and 20-fold for the (*R*,*R*) diastereomer **14** (K_i = 69 nM). The (*R*,*S*) diastereomer **15** was the least potent with a 50-fold decrease

Table 1. Binding affinities and functional activities for **11** and **12**



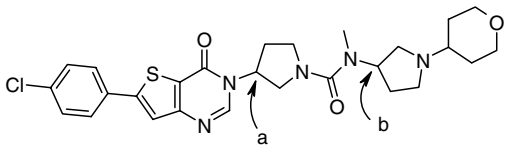
Compound	R	K_i[a] (nM)	IC_{50}[a] (nM)
11	H	17	29
12a		6	31
12b	Me	10	20
12c	*i*Pr	5	23
12d		1	9
12e		4	13
12f		2	10
12g		3	10
12h		50	53
12i		4	15
12j		4	10
12k		3	23
12l		7	11
12m		7	11
12n		17	44
12o		80	N.D.[b]

[a] Values are averaged from at least two experiments. Observed values typically fell within a 2-fold range of this mean.
[b] Not determined.

(K_i = 154 nM) compared to **12k**. This stereochemical preference is slightly different from the original APU series where the most potent isomer is the (*S*,*R*) diastereomer.[9]

To further explore the SAR of the thienopyrimidinone APU series, the aryl group was modified on **12b** and **12k**. Scheme 2 shows how the synthetic route was altered to allow different phenyl groups to be introduced late in the synthesis. 3-Amino-thiophene-2-carboxylic

Table 2. Effect of stereochemistry on MCH-R1 receptor binding affinity



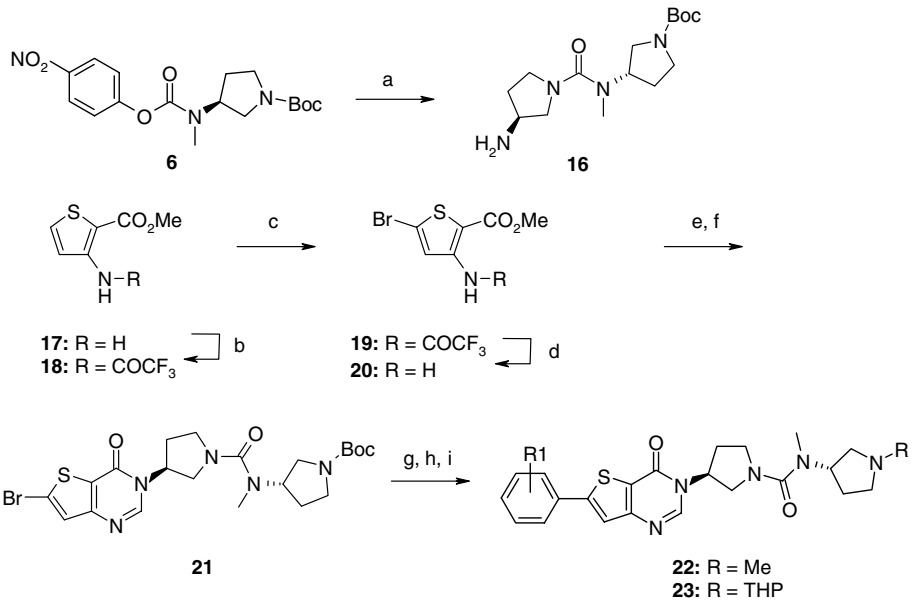
Compound	a,b	K_i[a] (nM)
12	*S*,*S*	3
13	*S*,*R*	21
14	*R*,*R*	69
15	*R*,*S*	154

[a] Values are averaged from at least two experiments. Observed values typically fell within a 2-fold range of this mean.

acid methyl ester **17** was reacted with trifluoroacetic anhydride and pyridine to give the protected amine **18**. Lithiation at the C-5 position of the thiophene was achieved using LDA, followed by bromination with dibromoethane to give **19**. Removal of the trifluoroacetyl group, condensation with *N*,*N*-dimethylformamide dimethyl acetal, and reaction with amine **16** gave the versatile intermediate **21**, which allowed modifications to be introduced at both ends in the last stages of synthesis. Removal of the Boc protecting group, then reductive alkylation, followed by Suzuki couplings with aryl boronic acid gave compounds **22** and **23**.

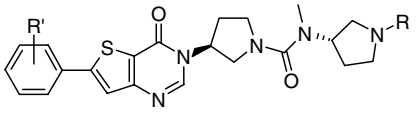
The binding affinities for the methyl and tetrahydropyranyl derivatives are shown in Table 3. The tetrahydropyranyl derivatives (**12k** and **23**) generally had 2- to 3-fold higher binding affinity for MCH-R1 than the methyl derivatives (**12b** and **22**). The two series showed similar SAR around the substitution on the phenyl group. Small substitutents in the *para* position were the most favorable with chloro (**12b** and **12k**) and ethyl (**22b** and **23b**) giving the most potent compounds. The electronic nature of the substituent did not appear to have an effect on binding affinity since the 4-methyl derivatives (**22a** and **23a**) had the same binding affinity as the 4-trifluoromethyl derivatives (**22d** and **23d**). The larger ethylenedioxy ring (**22i** and **23h**) substantially reduced affinity. Incorporation of a methyl group in the *ortho* position also led to decreased potency (**22a** vs **22c**; **22f** vs **22g**), in contrast to our previous APU series in which 2,4-disubstituted aryls were preferred.[14] These data and the different stereochemical preferences suggest that constraining the amide forces these molecules to adopt a subtly different conformation in the binding pocket.

The CYP2D6 inhibition and intrinsic clearance of the 4-chloro and 4-ethyl phenyl derivatives are shown in Table 4. The methyl derivatives (**12b** and **22b**) had virtually no inhibition of CYP2D6 and the tetrahydropyranyl derivatives (**12k** and **23b**) had weak inhibition. The intrinsic clearance of the 4-ethyl phenyl derivatives (**22b** and **23b**) was very high, indicating the ethyl moiety as a probable site of metabolism. In contrast, the 4-chloro phenyl derivatives (**12b** and **12k**) had much lower



Scheme 2. Reagents and conditions: (a) (*S*)-3-aminopyrrolidine, TEA, DMA, 70 °C, 15 h, 58%; (b) trifluoroacetic anhydride, pyridine, MeCN, 0 °C, 2 h, 99%; (c) i—LDA, THF, −78 °C, 1 h; ii—dibromoethane, −78 °C to rt, 1 h, 44%; (d) K_2CO_3, MeOH, H_2O, rt, 30 min, 98%; (e) *N*,*N*-dimethylformamide dimethyl acetal, EtOH, 90 °C, 1 h, 99%; (f) **16**, EtOH, 90 °C, 15 h, 57%; (g) TFA, DCM, 0 °C, 30 min, 98%; (h) formaldehyde or tetrahydro-4*H*-pyran-4-one, $NaBH(OAc)_3$, DCM, MeOH, rt, 1 h, 97% for **22**, 80% for **23**; (i) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, 1,4-dioxane, H_2O, 100 °C, 4 h, 10–70%.

Table 3. Binding affinities for **12b**, **12k**, **22**, and **23**



22: R = Me
23: R = THP

Compound	R′	K_i[a] (nM)
12b	4-Cl	10
22a	4-Me	15
22b	4-C_2H_5	5
22c	2,4-Me	49
22d	4-CF_3	17
22e	4-CF_3O	39
22f	4-CH_3O	21
22g	2-CH_3,4-CH_3O	46
22h	2-Cl,4-C_2H_5O	26
22i	3,4-O$(CH_2)_2O$	143
12k	4-Cl	3
23a	4-Me	14
23b	4-C_2H_5	8
23c	2,4-Me	70
23d	4-CF_3	19
23e	4-CF_3O	18
23f	2-CH_3,4-CH_3O	28
23g	2-Cl,4-C_2H_5O	14
23h	3,4-O$(CH_2)_2O$	45

[a] Values are averaged from at least two experiments. Observed values typically fell within a 2-fold range of this mean.

intrinsic clearance. Compounds **12b** and **12k** showed the best balance of potent binding, low CYP2D6 inhibition, and low intrinsic clearance in the thienopyrimidinone bis-aminopyrrolidine urea series.

Table 4. CYP2D6 inhibition and intrinsic clearance data

Compound	CYP2D6 (μM)	Clearance (mL/min/kg)
12b	99	16
22b	42%[a]	200
12k	23	24
23b	57	85

[a] % inhibition at 120 μM.

In summary, we discovered a new class of potent and functional MCH-R1 antagonists containing a thienopyrimidinone bis-aminopyrrolidine urea. The substitution on the basic nitrogen altered the interaction with CYP2D6 and very small (methyl) or hydrophilic (THP) groups significantly reduced the inhibition of CYP2D6. The series also showed improved intrinsic clearance resulting in compounds that may have a satisfactory in vivo profile.

Acknowledgments

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