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The discovery and optimization of pyrimidinone-containing MCH R1 antagonists

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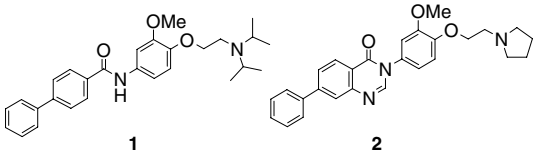
Abstract—Optimization of a series of constrained melanin-concentrating hormone receptor 1 (MCH R1) antagonists has provided compounds with potent and selective MCH R1 activity. Details of the optimization process are provided and the use of one of the compounds in an animal model of diet-induced obesity is presented.

Obesity has reached epidemic proportions in both the United States and Western Europe. Obesity has been linked to a number of comorbidities including type 2 diabetes, coronary artery disease, breast and colon cancers, and hypertension. Clearly, effective therapies to address obesity and its comorbidities are needed.

The evidence for the potential use of melanin-concentrating hormone receptor antagonists, and MCH R1 antagonists in particular, as agents for the treatment of obesity is significant. This evidence includes reports that (1) intracerebroventricular (icv) administration of MCH stimulates feeding in rodents;[1] (2) fasting upregulates MCH mRNA in both lean and obese animals;[1] (3) transgenic animals lacking MCH feed less, have reduced body weight, and increased leanness relative to their wild-type counterparts;[2] and (4) transgenic animals devoid of MCH R1 are resistant to diet-induced obesity.[3] This evidence supporting a role for MCH in the regulation of feeding and body weight has led to the active pursuit of MCH R1 antagonists for the treatment of obesity.[4]

We have previously described the biphenyl amide MCH R1 antagonist **1** and detailed its optimization first to the constrained quinazolinone **2** and later to the thienopyrimidinone **3**.[5] We report herein our efforts at further development of structure–activity relationships (SAR) within these thienopyrimidinone analogs.



Modification of the left-hand aryl substituent was accomplished through two different synthetic methods. For compounds **5a**–**c**, coupling of acid **4**[6] with 3-methoxy-4-(2-pyrrolidin-1-ylethoxy)aniline provided amide **5**. Subsequent nitro reduction and treatment with reflux-

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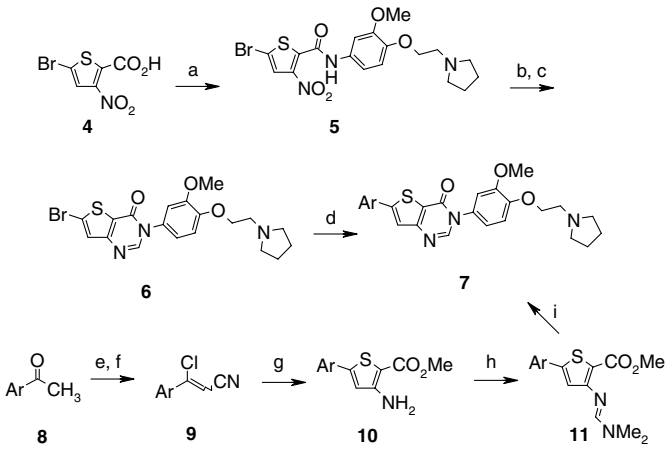


Scheme 1. Reagents and conditions: (a) 3-methoxy-4-(2-pyrrolidin-1-ylethoxy)aniline, HOBT, EtN(*i*-pr)$_2$, CH_2Cl_2, 25 °C, 72 h, 31%; (b) $SnCl_2{\cdot}H_2O$; EtOH, 78 °C, 0.5 h; (c) formic acid, 100 °C, 1 h, 42% (two steps); (d) ArB(OH)$_2$, Pd(dppf)$_2$Cl$_2$, 1 M Na_2CO_3, EtOH, THF, 75 °C, 0.5 h, 34-47%; (e) $POCl_3$, DMF, 0 °C, 1 h; (f) hydroxylamine hydrochloride, 1 h, 0 °C, 25–54% (two steps); (g) methyl mercaptoacetate, NaOMe, MeOH, 25 °C, 10 min, 50–96%; (h) DMF–dimethyl acetal, DMF, 100 °C, 15 h, 95–100%; (i) 3-methoxy-4-(2-pyrrolidin-1-ylethoxy)aniline, phenol, 140 °C, 1.5 h, 46–65%.

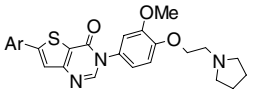
ing formic acid (Scheme 1) provided pyrimidinone **6**. Suzuki coupling with the appropriate boronic acid then provided the desired analogs **7a**–**c**.

The analogs **7d**–**r** were prepared through a sequence involving conversion of the acetophenone derivatives **8** to the corresponding nitriles **9**. Thiophene formation was then accomplished by treatment of the nitriles with the sodium anion of methyl mercaptoacetate. Conversion to the amidines **11d**–**r** was followed by a convenient cyclization with 3-methoxy-4-(2-pyrrolidin-1-ylethoxy)aniline to provide the pyrimidinones **7d**–**r** (Scheme 1).[7] Compound **7s** was made from commercially available methyl 3-amino-2-thiophenecarboxylate (**10s**, Ar = H) using the same two-step sequence described for compounds **7d**–**r**.

The compounds were evaluated in a functional assay for MCH R1 activity utilizing luciferase activity as a readout (Table 1).[8] Several of the analogs substituted at the 4-position of the aromatic ring proved to be more potent than the unsubstituted phenyl analog **7a**. These compounds included the 4-flouro (**7b**, pIC$_{50}$ 8.9), 4-chloro (**7c**, pIC$_{50}$ 9.3), and 4-methoxy (**7d**, pIC$_{50}$ 9.0) derivatives. It should be noted that not all of the 4-substituted derivatives gained potency relative to **7a**. Larger groups at the 4-position of the aromatic ring proved especially detrimental to activity (examples **7h**,**j**). Small polar groups such as amino, cyano, and nitro (examples **7f**,**g**, and **7i**, respectively) were not well tolerated. None of the mono-substituted analogs with substitution at either the 2- or 3-positions of the aromatic ring (examples **7k**,**m**,**n**) proved to be as potent as the phenyl-substituted **7a**. Several heteroaryl derivatives were synthesized (examples **7o**–**r**) and all of them had potencies less than that of phenyl-substituted **7a**. The preference for small, lipophilic substituents in the 4-position of the aryl ring suggests that the aryl ring may reside in a tight hydrophobic pocket within the receptor.

An investigation into the effects of altering the five-membered ring fused to the pyrimidinone was investigated. Thus, the furan, benzo, and thiazole analogs were prepared with the remaining portions of the molecules held constant.

Table 1. MCH R1 functional activity (pIC$_{50}$) of thienopyrimidinone analogs **4**[8]



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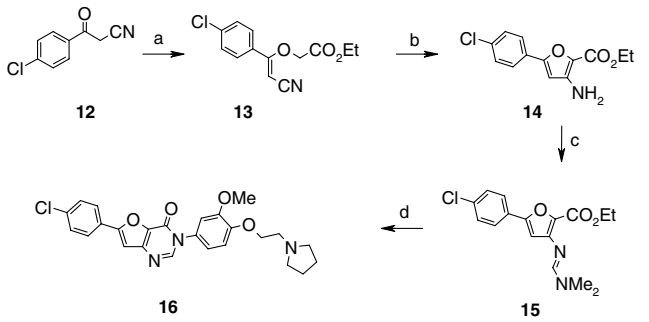
Compound	Ar	MCH R1 pIC$_{50}$
7a	Ph	8.7
7b	4-F-Ph	8.9
7c	4-Cl-Ph	9.3
7d	4-OMe-Ph	9.0
7e	4-CF_3-Ph	8.6
7f	4-NH_2-Ph	7.9
7g	4-CN-Ph	7.7
7h	4-SO_2Me-Ph	5.9
7i	4-NO_2-Ph	8.3
7j	4-$NHCOCH_3$-Ph	5.5
7k	3-Cl-Ph	8.2
7l	3,4-DiCl-Ph	8.8
7m	3-I-Ph	7.6
7n	2-Cl-Ph	8.3
7o	4-Pyridinyl	6.7
7p	3-Pyridinyl	5.8
7q	3-Thiophene-yl	7.6
7r	2-Thiophene-yl	7.0
7s	H	5.4

Furan derivative **16** was synthesized as detailed in Scheme 2. Using conditions adapted from those of Redman and co-workers, Mitsunobu reaction of 3-(4-chlorophenyl)-3-oxo-propanenitrile (**12**) with ethyl glycolate was followed by sodium hydride-affected ring closure to provide aminofuran **14**.[9] Treatment with DMF–DMA provided amidine **15** which was then converted to pyrimidinone **16** through heating with 3-methoxy-4-(2-pyrrolidin-1-ylethoxy)aniline in ethanol at reflux.

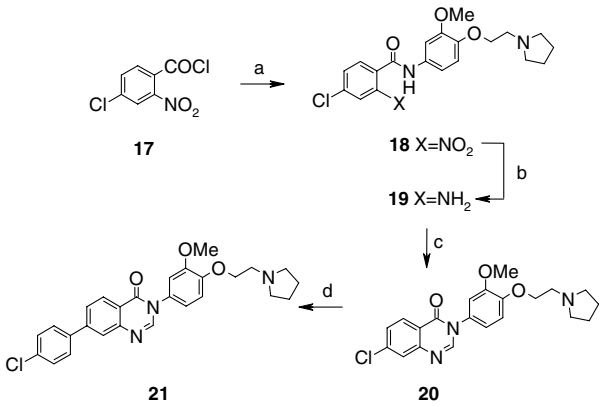


Scheme 2. Reagents and conditions: (a) PPh_3, DIAD, THF, ethyl glycolate, 25 °C, 14 h, 34%; (b) NaH, THF, 25 °C, 3 h, 85%; (c) DMF–dimethyl acetal, 104 °C, 6 h, 99%; (d) 3-methoxy-4-(2-pyrrolidin-1-ylethoxy)aniline, ethanol, 78 °C, 24 h, 44%.

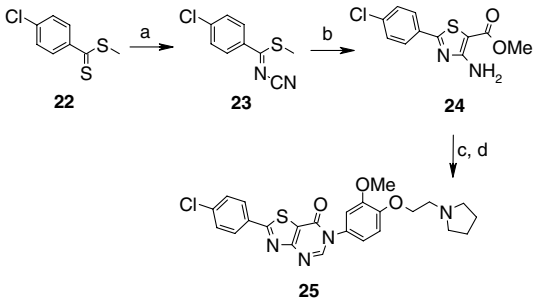
The benzo derivative **21** was synthesized as detailed in Scheme 3. Coupling acid chloride **17** with 3-methoxy-4-(2-pyrrolidin-1-ylethoxy)aniline provided compound **18** which was then reduced with stannous chloride to provide amine **19**. Pyrimidinone formation was followed by Suzuki coupling to provide analog **21**.

Finally, thiazole derivative **25** was synthesized as detailed in Scheme 4. Reaction of methyl 4-chlorobenzenecarbodithioate (**22**) with cyanamide and potassium methoxide in methanol yielded compound **23**. Treatment of compound **23** with methyl-mercaptoacetate and triethylamine afforded thiazole **24** which was then converted to pyrimidinone **25**.

The difference in the MCH R1 antagonist activities of the analogs was striking, with pIC_{50}'s ranging from a high of 9.3 for **7c** to a low of 6.9 for furan **16** (Table 2). Molecular modeling was employed to identify key differences between the analogs that might help to explain the differences in potency. Figure 1 shows the relationship of the benzo, thieno, and furan derivatives with the C and D rings overlaid (the right-hand alkoxyamine fragment has been omitted for clarity).[10]

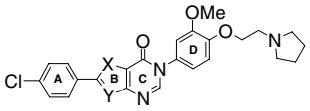


Scheme 3. Reagents and conditions: (a) 3-methoxy-4-(2-pyrrolidin-1-ylethoxy)aniline, Et_3N, CH_2Cl_2, 25 °C, 14 h, 69%; (b) $SnCl_2$ H_2O; EtOH, 78 °C, 4 h, 97%; (c) formic acid, 100 °C, 3 h, 91%; (d) (4-ClPh)B(OH)$_2$, 2-(di-*tert*-butylphosphino)biphenyl, $Pd(OAc)_2$, KF, 1 M Na_2CO_3, THF, 70 °C, 3 h, 60%.



Scheme 4. Reagents and conditions: (a) (i) cyanamide, KOMe, MeOH, 25 °C, 3 h; (ii) MeI, DMF, 25 °C, 2 h, 86% (two steps); (b) methyl mercaptoacetate, Et_3N, MeOH, 25 °C, 24%; (c) DMF–dimethyl acetal, 100 °C, 3 h; (d) 3-methoxy-4-(2-pyrrolidin-1-ylethoxy)aniline, ethanol, 78 °C, 18 h, 12%.

Table 2. MCH R1 functional activity of B-ring analogs[8]



Compound	X	Y	MCH R1 pIC_{50}
7c	S	CH	9.3
16	O	CH	6.9
21	CH=CH	CH	8.2
25	S	N	8.5

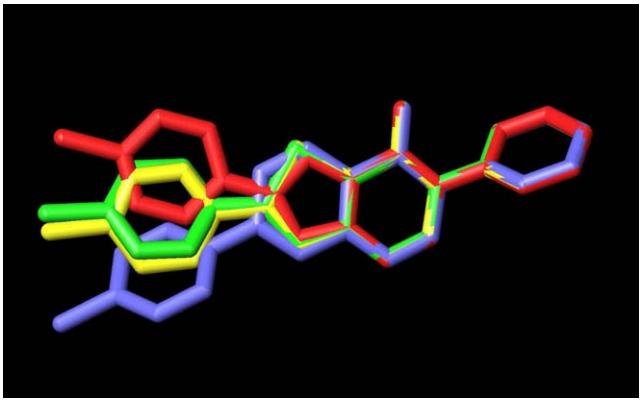
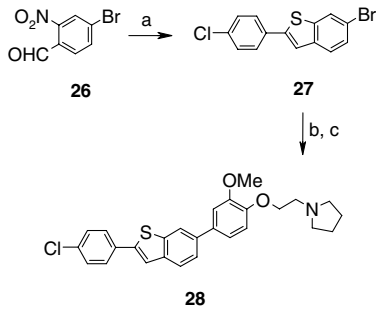


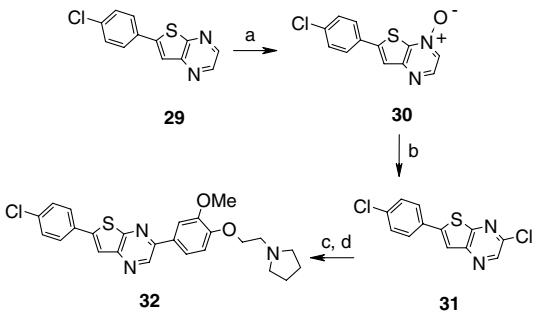
Figure 1. B-Ring comparison by molecular modeling. Red = furano (**16**); green = thieno (**7c**); yellow = thiazolo (**25**); blue = benzo (**21**).

The ground state conformations reveal a marked difference in the orientation of the A-rings as dictated by the corresponding B-rings (Fig. 1). Of particular note is the central region in space occupied by the thiophene derivative **7c** relative to the benzo and furo derivatives **21** and **16**, respectively. This analysis implies that this orientation of **7c** is optimal, and that the more 'northerly' orientation of the A-ring as dictated by the furan derivative is especially deleterious to MCH R1 activity.

We next turned our attention to determining if the amide-like carbonyl of the pyrimidinone-containing



Scheme 5. Reagents and conditions: (a) (4-chlorophenyl)methanethiol, K_2CO_3, DMF, 60 °C, 14 h then reflux, 24 h, 62%; (b) 1-(2-{[2-(methyloxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]oxy}-acetyl)pyrrolidine,[16] $Pd(PPh_3)_3$, satd $NaHCO_3$, DME, 80 °C, 45 min, 40%; (c) AlH_3, THF, 25 °C, 1 h, 50%.



Scheme 6. Reagents and conditions: (a) 30% H_2O_2, AcOH, 60 °C, 2 h; (b) $POCl_3$, reflux, 1 h, 31% (two steps); (c) 1-({[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]oxy}acetyl)pyrrolidine,[16] (1,4-bis(diphenylphosphino)butane)palladium dichloride, CsF, DME, reflux, 12 h, 41%; (d) AlH_3, THF, 25 °C, 1 h, 24%.

analogs was necessary for MCH R1 antagonist activity. Thus, we prepared analogs **28** and **32** as detailed in Schemes 5 and 6. Benzothiophene **28** was prepared from 4-bromo-2-nitrobenzaldehyde **26** using the procedure of Patel and co-workers.[11] Suzuki coupling was followed by amide reduction to provide analog **28**. Thienopyrazine **32** was prepared through selective N-oxidation of compound **29** followed by chlorination.[12] Subsequent Suzuki coupling and amide reduction provided the desired analog **32** (Scheme 6).

Interestingly, analogs **28** and **32** demonstrated no significant MCH R1 activity. Thus, the carbonyl group of the pyrimidinone appears to be critical for activity in this series. We speculate that the carbonyl oxygen is acting as a critical H-bond acceptor within this series of MCH R1 antagonists. This result is consistent with computational studies performed on related analogs.[13]

We sought to establish the utility of these MCH R1 antagonists in an animal model of obesity. The maleate salt of compound **7c** (GW803430) was deemed to be a suitable compound for such a study given its good pharmacokinetic properties (bioavailability = 31%, $t_{1/2}$ = 11 h) and brain penetration (6:1 brain:plasma concentration) in mice.[14,15] Importantly, **7c** was found to be selective (>100×) over a battery of G-protein coupled

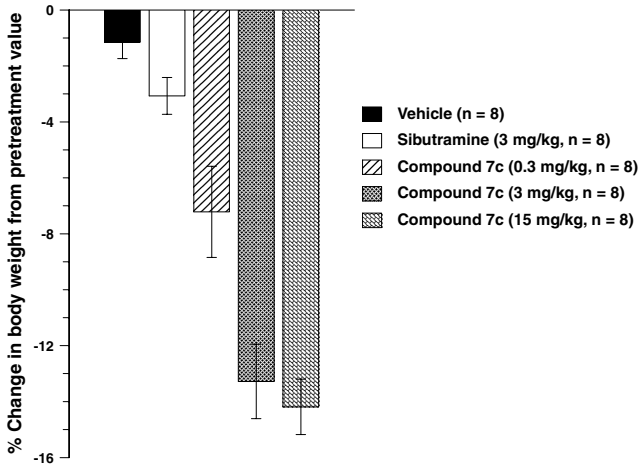


Figure 2. Effect of compound **7c** (GW803430) at 0.3, 3, and 15 mg/kg (orally, qd, $n = 8$ for each dosing group) on body weight loss in high fat diet-induced obese AKR/J mice. Weight loss is expressed as percentage weight change from pretreatment value for each treatment group (average pretreatment body weight value was 45.9 ± 0.7 g). Values are means ± SEM, n = number of mice per group.

receptors, ion channels, and enzymes. The efficacy of compound **7c** in inducing weight loss was evaluated in diet-induced obese AKR/J mice on a high fat diet (58% kcal of fat, Research Diets #D12331).

As shown in Figure 2, during a 12-day treatment, oral administration of compound **7c** at 0.3, 3, and 15 mg/kg once daily caused a sustained dose-dependent weight loss of −6.2%, −12.1%, and −13.1%, respectively, relative to vehicle controls.[17] In addition to compound **7c**, the marketed weight loss agent sibutramine (Meridia®) was dosed at 3 mg/kg, resulting in a weight loss of −1.9% relative to control animals.

In summary, a study of the structure–activity relationships of a series of pyrimidinone-containing MCH R1 antagonists was conducted and critical structural elements for MCH R1 activity were identified. One of the compounds was shown to be active in an animal model of obesity.

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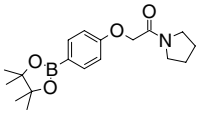
16. 1-({[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-oxy}acetyl)pyrrolidine has the following structure:



17. The weight loss achieved with GW803430 (compound **7c**) was due entirely to fat mass loss as determined by dual-energy X-ray absorptiometry (DEXA) scanning. See Al-Barazanji, K.; Grizzle, M.; Britt, C.; Lancaster, M.; Daniels, A.; Ignar, D.; Cooper, J; Hertzog, D. *Obesity Res.* **2004**, *12*, 56-OR.