Letters

A Thienopyridazinone-Based Melanin-Concentrating Hormone Receptor 1 Antagonist with Potent in Vivo Anorectic Properties

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Abstract: Melanin-concentrating hormone receptor antagonists containing thieno- and a benzopyridazinone cores were designed and tested as potential anorectic agents. These ligands showed high affinity for the receptor, potent functional activity in vitro, and good oral bioavailabilty in rats. The thiophene analogue exhibited low iv clearance, long half-life, and high brain penetration. In obese rats, the thienopyridazinone demonstrated a dose-dependent reduction in feeding and body weight with doses between 1 and 10 mg kg^{-1}.

Obesity has reached epidemic proportions in the developed world, and the impact of this disease on the health care and economies of affected countries is difficult to overestimate.[1] Many potential biological targets for treating obesity have recently emerged, including the cannabinoid receptor 1, for which the inverse agonist rimonabant is currently under review by the FDA.[2] The discovery of other anorectics, preferably working through disparate mechanisms, remains a high priority. The melanin-concentrating hormone receptor 1 (MCH1R) has recently been the focus of considerable scrutiny as such a target. Acute or chronic treatment of rats with melanin-concentrating hormone (MCH) produces increased feeding or body weight, respectively.[3,4] Mice lacking the gene coding for the MCH precursor are lean and hypophagic, and those lacking the receptor are lean but slightly hyperphagic in order to compensate for higher energy expenditure.[5,6] Several groups have reported

**Chart 1.** Published and Proposed MCH1R Ligands
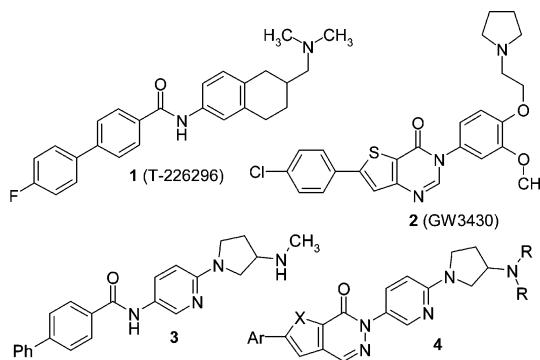
efficacy for MCH1R antagonists in preclinical models of obesity in rodents and dogs, and at least two compounds have advanced into human clinical trials.[7-9] Some evidence is also emerging that suggests a role for such antagonists in the treatment of anxiety and depression.[7a,10,11] We have discovered a novel MCH1R antagonist that demonstrates some of the most potent in vivo efficacy reported to date in a rat model of diet-induced obesity (DIO).
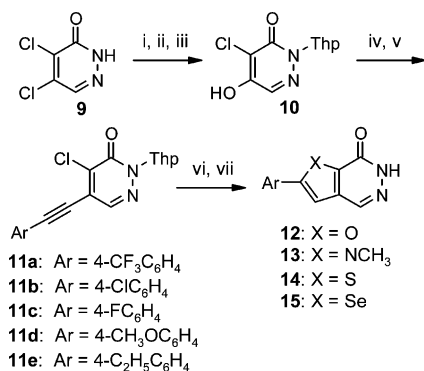
Chart 1 shows several reported MCH1R antagonists, which topologically have similar features. Among these, the recently disclosed aminopyrrolidine-substituted pyridine **3** was shown to have an excellent in vitro profile but suffered from high clearance in rats.[7h] It also showed strong interaction with the hERG channel ($K_i = 0.2$ μM, dofetilide binding). To improve the metabolic stability of this compound class, we replaced the potentially labile carboxamide group with heterocyclic ring systems. SARs from previous series convinced us of the necessity of retaining a carbonyl group in this vicinity, possibly as a result of the interaction of this group with Gln212 of transmembrane 5 in the native receptor.[12] As such, we pursued the pyridazinone derivatives **4** because they retain most of the features of **3** essential for high-affinity binding while removing the acyclic carboxamide group present in the latter.

The chemistry used to make the benzopyridazinones is based on a procedure reported by Cherkez and co-workers and is shown in Scheme 1.[13] Bromophthalimide **5** was reduced with zinc under acidic conditions to afford hydroxylactam **6**, which cyclized to the benzopyradizinone **7** upon treatment with

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Scheme 1. Synthesis of Benzopyridazinones **8**[a]
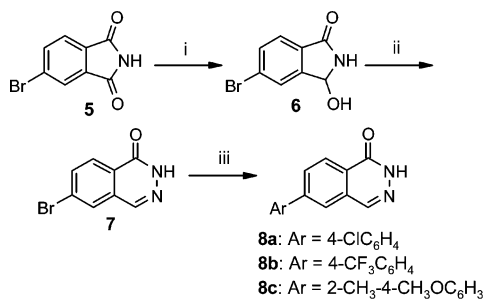
a Reagents and conditions: (i) Zn, CuSO$_4$, aqueous NaOH (95%); (ii) N$_2$H$_4$, water, 95 °C (34%); (iii) arylboronic acid, Pd(dppf)$_2$, K$_2$CO$_3$, DMF, H$_2$O, 80 °C (22−78%).
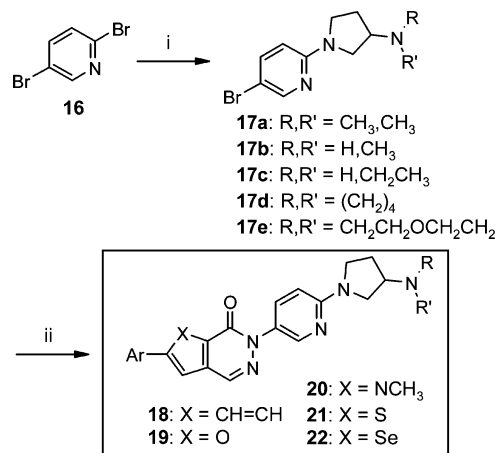
Scheme 2. Synthesis of Fused Pyridazinones **12−15**[a]

11a: Ar = 4-CF$_3$C$_6$H$_4$
11b: Ar = 4-ClC$_6$H$_4$
11c: Ar = 4-FC$_6$H$_4$
11d: Ar = 4-CH$_3$OC$_6$H$_4$
11e: Ar = 4-C$_2$H$_5$C$_6$H$_4$

12: X = O
13: X = NCH$_3$
14: X = S
15: X = Se

a Reagents and conditions: (i) DHP, TsOH, THF, reflux (87%); (ii) KOH, methanol (83%); (iii) KOH, water, reflux (75%); (iv) Tf$_2$O, TEA, DCM; (v) arylacetylene, TBAI, CuI, Pd, DCM (82%); (vi) KOH, dioxane, reflux (**12**) or CH$_3$NH$_2$, ACN, reflux; then NaHMDS, DMA, ethylene glycol, 130 °C (**13**) or Na$_2$S, DMF, 70 °C (**14**) or Se, NaBH$_4$, ethanol (**15**); (vii) HCl, water, 50 °C (17−100%).

hydrazine. Suzuki reaction allowed the introduction of various aryl substituents providing the left-hand component of the benzopyridazinones **4** (X = CH=CH).

The other fused analogues were prepared from the dichloro-pyridazinone **9** (Scheme 2). Protection as the THP derivative, selective methanolysis of the more active carbon−chlorine bond, and alkaline hydrolysis afforded **10**.[14,15] This compound was converted to the triflate to enable a Sonogashira coupling with arylacetylenes, thus providing **11**.[16] This versatile intermediate provided a series of heterocyclopyridazinones by varying the conditions used in the cyclization. Alkynyl-substituted chloro-pyridazinones have previously been described in the synthesis of furan, pyrrole, and thiophene-fused derivatives, and by using in situ generated sodium selenide, we have extended this chemistry to the selenophene.[16,17] Acid hydrolysis of the THP protecting group provided **12−15**, the left-hand side components of the heterocyclo-fused analogues of **4**.

The right-hand side components of target compounds **4** were prepared from 2,5-dibromopyridine (**16**). Displacement of the more active 2-bromine atom with 3-aminopyrrolidines afforded the bromopyridines **17**. These compounds efficiently coupled with pyridazinones **8** and **12−15** in the presence of copper and *trans*-1,2-diaminocyclohexane to provide final compounds **18−22**.[18] Some key in vitro properties for representative pyridazi-nones **18−22** are presented in Table 1. The benzopyridazinones **18** are potent binders of MCH1R in vitro. Typically small groups are well tolerated on the exocyclic nitrogen atom of the pyrrolidine ring, with various combinations of hydrogen, methyl, ethyl, and cyclic analogues all giving comparable binding constants (**18a−d**). Oxygen-containing groups (**18e**) provided

Scheme 3. Synthesis of MCH1R Ligands **18−22**[a]

17a: R,R' = CH$_3$,CH$_3$
17b: R,R' = H,CH$_3$
17c: R,R' = H,CH$_2$CH$_3$
17d: R,R' = (CH$_2$)$_4$
17e: R,R' = CH$_2$CH$_2$OCH$_2$CH$_2$

18: X = CH=CH   **20**: X = NCH$_3$
19: X = O   **21**: X = S
                     22: X = Se

a Reagents and conditions: (i) 3-(alkylamino)pyrrolidine, TsOH, 110 °C (28−88%); (ii) **8** or **12−15**, CuI, *trans*-1,2-diaminocyclohexane, Cs$_2$CO$_3$, dioxane, 110 °C (11−85%).

Table 1. In Vitro MCH1R Affinities (nM) and HLM Clearances (mL min^{-1} kg^{-1}) for **18−22**[a]

compd	X	R^1	NR^{2}N^3	$K_i \pm SD$[a]	CL[b]
(*R*)-**18a**	C$_2$H$_2$	4-Cl	N(CH$_3$)$_2$	1.1 ± 0.6	21
(*S*)-**18a**	C$_2$H$_2$	4-Cl	N(CH$_3$)$_2$	1.1 ± 0.2	12
(*S*)-**18b**	C$_2$H$_2$	4-Cl	NHCH$_3$	1.2 ± 0.6	8.9
(*R*)-**18b**	C$_2$H$_2$	4-Cl	NHCH$_3$	1.5 ± 0.1	12
(*S*)-**18c**	C$_2$H$_2$	4-Cl	NHCH$_2$CH$_3$	1.9 ± 0.1	9.2
(*S*)-**18d**	C$_2$H$_2$	4-Cl	pyrrolidinyl	1.6 ± 0.2	16
(*R*)-**18e**	C$_2$H$_2$	4-Cl	morpholinyl	56%[c]	40
(*R*)-**18f**	C$_2$H$_2$	4-CF$_3$	NHCH$_3$	10 ± 2	6.0
(*S*)-**18f**	C$_2$H$_2$	4-CF$_3$	NHCH$_3$	8.4 ± 0.1	26
(*S*)-**18g**	C$_2$H$_2$	4-CH$_3$O-2-CH$_3$	NHCH$_3$	11 ± 2	8.8
(*S*)-**19a**	O	4-CF$_3$	N(CH$_3$)$_2$	21 ± 9	28
(*S*)-**20a**	NCH$_3$	4-CF$_3$	N(CH$_3$)$_2$	14 ± 3	48
(*S*)-**21a**	S	4-CF$_3$	N(CH$_3$)$_2$	4.4 ± 0.3	18
(*R*)-**21b**	S	4-Cl	NHCH$_3$	1.9 ± 0.3	8.4
(*S*)-**21c**	S	4-F	NHCH$_3$	2.0 ± 0.5	12
(*R*)-**21c**	S	4-F	NHCH$_3$	2.5 ± 0.5	8.2
(*S*)-**21d**	S	4-CF$_3$	NHCH$_3$	3.1 ± 1.8	ND[d]
(*R*)-**21d**	S	4-CF$_3$	NHCH$_3$	3.3 ± 1.8	8.5
(*R*)-**21e**	S	4-CH$_3$O	NHCH$_3$	1.3 ± 0.5	720
(*R*)-**21f**	S	4-CH$_3$CH$_2$	NHCH$_3$	2.6 ± 0.8	155
(*S*)-**22a**	Se	4-CF$_3$	N(CH$_3$)$_2$	28%[c]	27

a Averaged from a minimum of two replicates. *b* Intrinsic human clearance determined in HLM.[19] Estimated standard error of less than 10% based on a reference compound used as a standard. *c* Percentage inhibition at 10 μM. *d* Not determined.

less potent analogues, and there appeared to be little stereo-chemical preference exhibited by the receptor (**18a,b,f**). Although the nature of the substituent in this part of the molecule does not have a dramatic influence over binding potency, minimization of the size of this group does have a positive influence over the metabolic clearance of the molecule as predicted in human liver microsomes (HLM), and the methyl-amino substituent of **18b** appears to be optimal for this purpose. Other substitutions on the terminal phenyl ring produced analogues with reduced binding affinity and/or increased clearance in HLM (**18f,g**).

In the analogues with a five-membered heterocycle fused to the pyridazinone, the most potent example was the thiophene (*S*)-**21a** (K_i = 4.4 nM), followed by the pyrrole (*S*)-**20a** (K_i =

Table 2. In Vitro and in Vivo Properties of Selected Pyridazinone-Based MCH1R Antagonists

compd	(S)-18b	(R)-21d
MCH1R K_i (nM)[a]	1.2 ± 0.6	3.3 ± 1.8
GTPγS IC$_{50}$ (nM)[a,b]	8.5 ± 4	7.7 ± 3
V_d (L kg^{-1})[c]	14 ± 3	4.1 ± 1
CL (mL min^{-1} kg^{-1})[c]	17 ± 4	4.3 ± 0.6
AUC-po (μg h mL^{-1})[c,d]	2.2 ± 0.3	8.4 ± 7
$t_{1/2}$ (h)[c]	9.4 ± 0.3	11 ± 1
F (%)[c]	22 ± 3	24 ± 20
C_{max} (μg mL^{-1})[c,e]	0.14 ± 0.02	0.50 ± 0.40
C_{brain}, 1 h (μg g^{-1})[c,f]	0.094 ± 0.021	0.19 ± 0.05
C_{brain}, 4 h (μg g^{-1})[c,f]	1.7 ± 0.8	1.2 ± 0.2
B/P (1 h)[c]	7.8 ± 3	1.4 ± 0.3
B/P (4 h)[c]	23 ± 7	3.1 ± 0.6

[a] Averaged from a minimum of two replicates. [b] Functional assay measuring GTPγS accumulation. [c] Determined in rats by administration of 10 mg kg^{-1}, po, and 2.5 mg kg^{-1}, iv. [d] Area under the curve for oral administration. [e] Maximum plasma concentration after oral dosing. [f] Brain concentration after oral dosing.

14 nM), the furan (S)-**19a** (K_i = 21 nM), and the selenophene (S)-**22a** (28% inhibition). In the thiophenyl derivatives, a variety of 4-substituents on the phenyl ring produced comparably potent compounds, but the chloro (**21b**), the fluoro (**21c**), and the trifluoromethyl groups (**21d**) provided the most metabolically stable compounds in vitro.

Because of their excellent in vitro properties, the pharmacokinetics of the benzopyridazinone (S)-**18b** and the thienopyridazinone (R)-**21d** were evaluated in rats. Compound (S)-**18b** showed good bioavailability (F) and half-life ($t_{1/2}$) when administered orally. However, the compound demonstrated a high volume of distribution (V_d), indicating extensive partitioning into tissues. The compound also showed extremely high brain penetration reaching more than 20-fold plasma levels after 4 h. On the other hand, the thienopyridazinone (R)-**21d** demonstrated comparable oral bioavailability to its benzo counterpart but had much more reasonable V_d, clearance (CL), and brain-to-plasma ratio (B/P) values. The excellent in vitro and pharmacokinetic profiles of the thienopyridazinone (R)-**21d** (NBI-845) prompted its evaluation in a preclinical model of obesity. Male Sprague-Dawley rats were made obese by allowing ad libitum access to a medium-high-fat diet (Research Diets, product D12266B) for 12 weeks after weaning. When rats were approximately 550 g, they were divided into four groups, balanced for body weight, then habituated to handling and oral dosing. Baseline food intake and body weight were measured over 8 days. Treatment, once daily oral dosing (during the hour prior to dark onset), was initiated and continued for 14 days. Results indicated that (R)-**21d** dose-dependently reduced both feeding ($p < 0.001$) and body weight change ($p < 0.001$). Food intake was significantly reduced by the 3 and 10 mg kg^{-1} doses (all $p < 0.001$). All doses of (R)-**21d** reduced body weight relative to vehicle (0.25% methylcellulose) treated controls. Differences in weight loss were statistically significant from controls on all days for the 3 and 10 mg kg^{-1} groups and days 2-14 for the 1 mg kg^{-1} group (all $p < 0.001$).

Compound (R)-**21d** was evaluated in a selectivity screen of more than 75 receptors and channels including MCH2R but showed only modest cross-reactivity with select muscarinic receptors (M1R K_i = 260 nM; M3R K_i = 160 nM). Although M3R knockout mice are hypophagic and lean, the M3R antagonist darifenacin has not been reported to produce antiobesity effects in clinical trials.[20,21] Although we cannot entirely discount a role for this receptor in the anorectic effects of (R)-**21d** in rats, the clinical data mentioned above and the 50-fold selectivity this compound exhibits for MCH1R over M3R
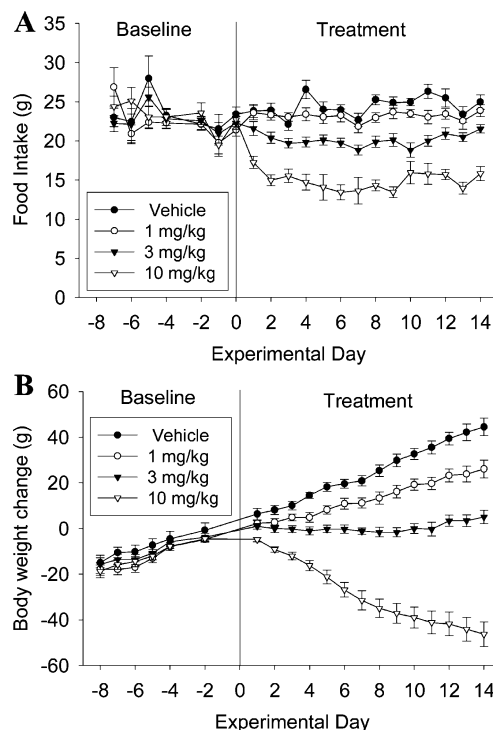
Figure 1. Effects on food intake (A) and body weight change (B) with once daily oral dosing of (R)-**21d** over 14 days in rats with DIO. All values are the mean $\pm$ SEM; $n = 7-10$ per group.

suggest that the likelihood of this is minimal. The compound was also tested and was not shown to significantly inhibit the cytochrome P450 enzymes 2D6 and 3A4 (<10% at 5 μM). A key safety concern of antiobesity and other chronic medications is cardiotoxicity, and untoward cardiovascular effects have been recently observed for some MCH1R antagonists.[7i] Compound (R)-**21d** was tested in a patch clamp assay for hERG affinity, and the compound was found to have an IC$_{50}$ of 1.8 μM. However, during 14 days of dosing at 1 mg kg^{-1}, the maximum daily plasma concentration observed in rats ranged from 0.28 μM (± 0.08 μM) on day 1 to 0.79 μM (± 0.31 μM) on day 14, indicating that efficacy was achieved at doses below those that would be expected to block the hERG channel. Preliminary toxicological studies in rats also showed no effects that would explain the observed weight loss, and when combined with the selectivity screen discussed above, these data provide strong support that the effect is MCH1R-mediated.

Modification of the benzamide group of **3** to a bicyclic derivative was an effective strategy for minimizing the clearance of these compounds and optimizing the terminal half-life. However, in the case of the fused benzene ring analogues **18**, the improved pharmacokinetics were also associated with some untoward partitioning of the compound into tissues and very high brain penetration. Replacement of the internal phenyl ring with a thiophene moiety produced a ligand with much more suitable pharmacokinetics. In addition, the molecule demonstrated dose-dependent weight loss in a rat DIO model. Compound (R)-**21d** provides an interesting research tool in the ongoing study of MCH1R antagonists in feeding and other behavioral models. Detailed in vivo studies of this compound will be reported elsewhere.

Supporting Information Available: Experimental protocols and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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