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Substituted chromones and quinolones as potent melanin-concentrating hormone receptor 1 antagonists

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Abstract—A series of substituted chromones were designed, synthesized, and evaluated for their ability to bind melanin-concentrating hormone receptor 1. Compounds with subnanomolar binding affinity and 66% oral bioavailability in rats were discovered.

The epidemic spread of obesity throughout the developed world has given the pharmaceutical industry great incentive to develop novel antiobesity medications.[1] Many molecular targets for this disease are being pursued, including the cannabinoid receptor 1, for which the inverse agonist rimonabant is currently under review by the FDA.[2] Among the newer biological targets, melanin-concentrating hormone receptor 1 (MCH1R) has emerged at the forefront, demonstrating convincing preclinical evidence that suggests the potential for efficacy in humans. Central administration of melanin-concentrating hormone (MCH) produces hyperphagia upon acute treatment and weight gain upon chronic exposure in rodents.[3,4] Mice deficient in MCH or its receptor are lean and the latter are resistant to diet-induced obesity.[5,6] A number of MCH1R antagonists are active in rats and mice in various sub-chronic and chronic obesity models and efficacy was also demonstrated in dogs which, like humans, have a second functional MCH receptor.[7,8] Moreover, at least two companies have advanced MCH1R antagonists into clinical trials.[9] There is also a growing body of evidence suggesting a role for MCH1R antagonists in the treatment of anxiety and depression.[7a,10,11]

A number of structurally diverse MCH1R antagonists have been patented and published, and this literature was recently reviewed.[12] Figure 1 shows three such compounds (**1**–**3**), which have demonstrated efficacy in preclinical obesity models and appear to have a related pharmacophore. We discovered the pyridine derivatives **3**, which were designed in part based on the first published MCH1R antagonist **1**.[7h,b] In the case of these pyridines, although they are potent in vitro and show good oral bioavailability in rats, the lead compound was rapidly cleared, which resulted in a terminal half life of less than three hours. Our goal was to improve the pharmacokinetics of these compounds while maintaining high levels of brain penetration, an essential feature of a drug for this CNS target. The strategy used was to replace the metabolically labile benzamide moiety with heterocyclic groups. The carbonyl group of compound **3** is essential for binding affinity; therefore, the bicyclic group was designed such that it would retain this feature. We envisaged that a chromone- or quinolone-based molecule (i.e., **4** or **5**) would be active, and the fact that there are a number of related molecules in various drug programs suggested the possibility of producing an orally absorbed compound.[13] The potential success of this strategy was further supported by the activity of the putative clinical compound **2**, in which a carbonyl group is also contained within a bicyclic ring system.[8,12] An alternative series of chromone-containing MCH1R antagonists was recently reported.[14]

Keywords: MCH; Obesity; Anorectic; Anxiety; Depression; GPCR.
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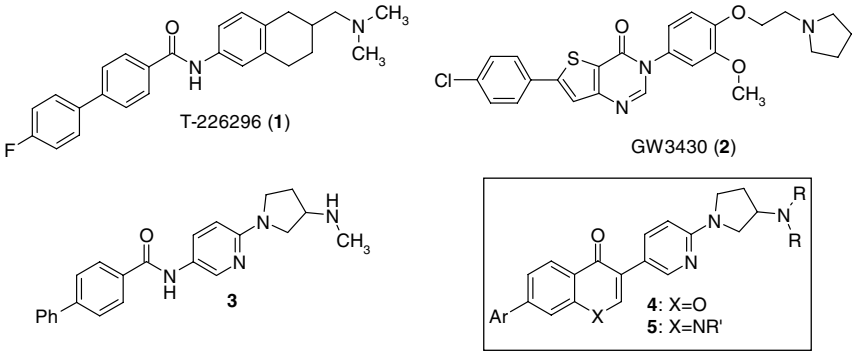
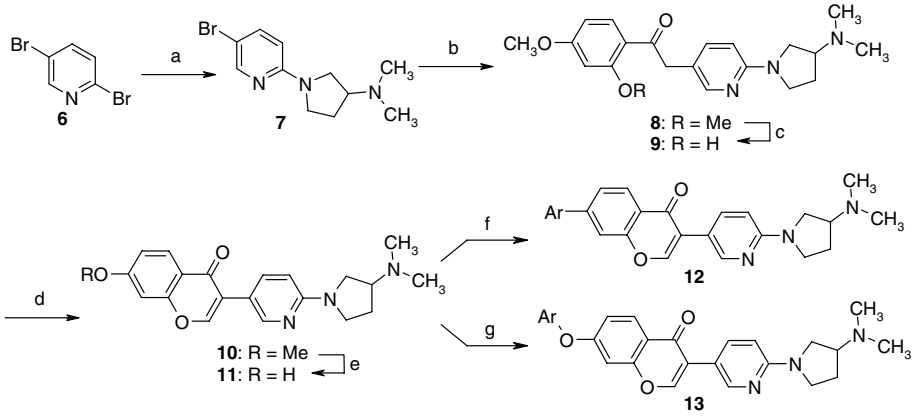


Figure 1. Published and proposed MCH1R antagonists.

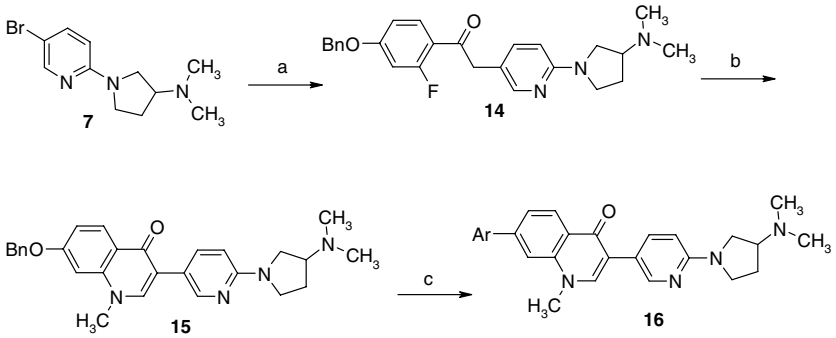
The synthesis of the chromone-based compounds is shown in Scheme 1. The more active bromide of 1,5-dibromopyridine (**6**) was displaced with 3-(dimethylamino)pyrrolidine to produce **7**. This compound was coupled with 2′,4′-dimethoxyacetophenone using the conditions reported by Buchwald to afford ketone **8**.[15] Reaction with boron tribromide allowed for the chelation-controlled demethylation of the methoxy group ortho to the carbonyl substituent, while leaving the 4-methoxy group untouched.[16] The resulting phenol **9** underwent cyclization with dimethylformamide dimethyl acetal thereby providing the chromone core **10**. Demethylation of the remaining methoxy group required more forcing conditions without the participation of an ortho acyl group, and so the material was heated in concentrated hydrobromic acid. The resulting phenol **11** was converted to the corresponding triflate, and an ensuing Suzuki coupling provided target compounds **12**. Alternatively, the phenol **11** was also subjected to Ullmann-type coupling with aryl halides to provide the aryloxy derivatives **13**.[17]

The synthesis of the quinolone derivatives is shown in Scheme 2. Bromopyridine **7** was coupled to 4′-benzyloxy-2′-fluoroacetophenone in the same manner as above to provide **14**. Aminomethylenation with dimethylformamide dimethyl acetal provided the pre-cyclization intermediate which, upon reaction with methylamine, provided the quinolone core (**15**). Removal of the benzyl protecting group gave the phenol, which was converted to the triflate and coupled with aryl boronic acids as described above to provide the target quinolones **16**.

The binding affinity of the chromones and quinolones for MCH1R is shown in Table 1, combined with the data from a GTPγS functional assay, and intrinsic clearance values obtained in vitro from human liver microsomes (HLM). The parent chromone **17a** demonstrated potent binding and functional activity, thereby indicating that the newly incorporated ring system is well tolerated in vitro. With the exception of larger groups such as the trifluoromethoxy group of **17h**, substitution at the four position of the phenyl ring had minimal influence over affinity (**17b**–**17g**), and when this substituent was halogen, a modest improvement in the intrinsic clearance was afforded (**17b**–**17d**). Alkyl substitution at the four position, as exemplified by ethyl derivative **17e**, resulted in a loss of binding affinity and functional activity relative to **17a**, and led to more rapid clearance in HLM. Not surprisingly, fluorination of the alkyl group, as in **17f**, reduced clearance to levels comparable to **17a**, but the binding affinity of this compound was still suboptimal. Introduction of a 4-methoxy group provided **17g**, which demonstrated a subnanomolar K_i

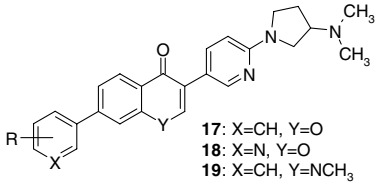


Scheme 1. Reagents and conditions: (a) 3-Dimethylaminopyrrolidine, toluenesulfonic acid monohydrate, 130 °C; (b) 2′,4′-dimethoxyacetophenone, sodium *tert*-butoxide, 2-(dicyclohexylphosphino)-2′-methylbiphenyl, palladium(II) acetate, THF, 80 °C; (c) boron tribromide, DCM, −25 °C; (d) dimethylformamide dimethyl acetal, DCM, 20 °C; (e) sodium iodide, 48% hydrobromic acid, 100 °C; (f) i—trifluoromethanesulfonic anhydride, DIEA, DCM, 0 °C; ii—$ArB(OH)_2$, $Pd(dppf)_2Cl_2$, potassium carbonate, aqueous DMF, 80 °C; (g) Ar-Br or Ar-I, copper(II) oxide, pyridine, 130 °C.



Scheme 2. Reagents and conditions: (a) 2′-Fluoro,4′-benzyloxyacetophenone, sodium *tert*-butoxide, 2-(dicyclohexylphosphino)-2′-methylbiphenyl, palladium(II) acetate, THF, 65 °C; (b) i—dimethylformamide dimethyl acetal, DCM; ii—aqueous methylamine, ethanol; (c) i—10% palladium on carbon, hydrogen, 40 psi; ii—trifluoromethanesulfonic anhydride, TEA, DCM, 0 °C; iii—$ArB(OH)_2$, $Pd(dppf)_2Cl_2$, potassium carbonate, aqueous DMF, 80 °C.

Table 1. In vitro data for **17**–**19**



Compound	R	K_i[a] (nM)	IC_{50}[a] (nM)	Clearance[b] (mL/min/kg)
3[c]	N.A.	5.2	12	
17a	H	4.1	15	22
17b	4-F	2.0	8.4	16
17c	4-Cl	2.1	10	16
17d	4-Br	3.0	20	18
17e	4-C_2H_5	8.8	44	36
17f	4-CF_3	10	59	24
17g	4-CH_3O	0.6	7.8	258
17h	4-CF_3O	24	N.D.[d]	N.D.[d]
17i	2,4-Cl_2	14	30	12
17j	4-Cl,3-CH_3	10	59	22
17k	4-Cl,2-CH_3	7.1	24	24
17l	2-CH_3,4-CH_3O	3.3	12	66
17m	2,4-$(CH_3O)_2$	16	60	38
17n	3,4-OCH_2O	4.7	33	112
17o	3,4-$O(CH_2)_2O$	5.4	120	65
18a	4-CH_3O	18	55	22
18b	4-CF_3	29	130	37
(***R***)-**17c**	4-Cl	1.6	20	N.D.[d]
(***S***)-**17c**	4-Cl	1.4	12	N.D.[d]
19a	4-Cl	24	41	53
19b	4-CF_3	120	N.D.[d]	49

[a] Values are averaged from at least two experiments. Observed values typically fell within a 2-fold range of this mean. See Refs. 7n and 18 for assay details.

[b] Intrinsic hepatic clearance measured in human liver microsomes.[19]

[c] Ref. 7h.

[d] Not determined.

for MCH1R and the most potent functional activity of the group. However, the inherent metabolic lability of a methoxy substituent was apparent from the very rapid HLM clearance of this compound. Compounds with additional substitution on this phenyl ring exhibited substantial loss of binding affinity and functional potency when compared to analogs which were exclusively substituted at the four position (**17i**–**17o**). In the case of the most potent analog **17g**, even though the addition of the 2-methyl group to give **17l** resulted in a 3-fold drop in binding affinity, the molecule was still one of the more potent analogs. Although some other variations on alkoxy-substituted phenyl derivatives, including the dimethoxy compound **17m** and the fused dioxacycles **17n** and **17o**, provided sufficient in vitro potency, none of these compounds had HLM clearance values

consistent with reasonable plasma levels upon oral administration. Replacement of the terminal phenyl ring with various heterocycles was detrimental as is exemplified by the two 2-pyridyl derivatives **18a** and **18b**, which were substantially less potent than their phenyl counterparts **17g** and **17f**, respectively.

Notably, in terms of in vitro potency, this compound class did not demonstrate a significant stereochemical preference as enantiomers (***R***)-**17c** and (***S***)-**17c** had nearly identical binding affinities and similar activity in the GTPγS assay.

The quinolones synthesized in Scheme 2 showed some affinity for MCH1R, but were not as potent as their oxygen-containing analogs. The 4-chloro quinolone **19a** had a K_i of 24 nM and a GTPγS IC_{50} of 41 nM. In addition, **19a** showed higher clearance in HLM relative to the analogous chromone **17c**.

In an attempt to incorporate some flexibility into an otherwise rigid molecule, the ether-derived compounds **20** were also tested and the in vitro data are collected in Table 2. The phenoxy compound **20a** showed slightly less binding affinity and functional activity than the phenyl compound **17a** and demonstrated an intrinsic clearance of 31 mL/min/kg. Unlike the analogs with the phenyl ring directly attached to the fused bicyclic core, the in vitro affinity of the phenoxy compounds appeared to be sensitive to the sterics of the phenyl substituent. Hence, the unsubstituted compound **20a** (K_i = 7.2 nM) was the most potent, followed by the 4-fluoro analog **20b** (K_i = 13 nM), the 4-methyl analog **20d** (K_i = 19 nM), and the 4-chloro analog **20c** (K_i = 28 nM). Larger substituents such as trifluoromethyl (**20e**), methoxy (**20f**), and a fused furyl ring (**20g**) resulted in substantial loss in binding affinity. The 4-fluoro analog was by far the most stable compound tested in HLM with an intrinsic clearance of only 3 mL/min/kg.

Due to the excellent in vitro profile of several of the chromones, one analog was evaluated in a pharmacokinetic study in rats. The chloro-substituted derivative **17c** was chosen because it is one of the most potent examples, while still demonstrating low intrinsic clearance in HLM. There was little difference in the in vitro data for the two enantiomers of **17c**; the (*R*)-isomer was arbitrarily chosen for testing. The hydrochloride salt of this compound was administered orally and intravenously to

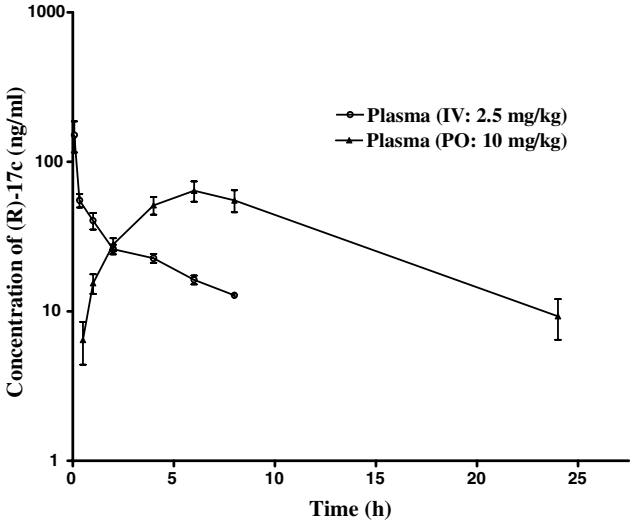


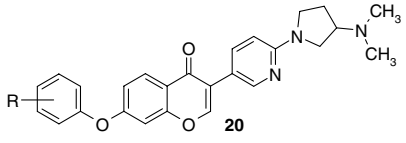
Figure 2. Concentration of (***R***)-**17c** in rats after a po (10 mg/kg) or iv (2.5 mg/kg) dose.[20]

Table 3. Pharmacokinetic values of (***R***)-**17c** in rats[20]

Parameter	Value ± SD
V_d[a] (L/kg)	58 ± 13
CL[a] (mL/min-kg)	133 ± 9.7
$t_{1/2}$[a] (h)	5.0 ± 0.9
AUC-po[a,b] (ng h/mL)	859 ± 210
F[a] (%)	66 ± 16
Brain/plasma[a] (1 h, 4 h)	9.5 ± 2.5, 25 ± 2.8

[a] Determined by administering 2.5 mg/kg iv and 10 mg/kg po to Sprague–Dawley rats.
[b] Plasma area under the curve upon oral dosing.

Table 2. In vitro data for **20**



20

Compound	R	K_i[a] (nM)	IC_{50}[a] (nM)	Clearance[b] (mL/min/kg)
20a	H	7.2	24	31
20b	4-F	13	35	3
20c	4-Cl	28	90	17
20d	4-Me	19	58	28
20e	4-CF_3	(60%)	N.D.[c]	N.D.[c]
20f	4-MeO	138	N.D.[c]	N.D.[c]
20g	2,3-Dihydrobenzo-furan-5-yl	78	350	N.D.[c]

[a] Values are averaged from at least two experiments. Observed values typically fell within a 2-fold range of this mean. See Refs. 7n and 18 for assay details.
[b] Intrinsic hepatic clearance measured in human liver microsomes.[19]
[c] Not determined.

rats and the results from this study are presented in Figure 2 and Table 3. In rats, (***R***)-**17c** demonstrated clearance of 133 mL/kg/min and 66% oral bioavailability. The plasma half life of (***R***)-**17c** was 5.0 h and the compound showed very high brain penetration, which increased from nearly 10-fold at one hour to 25-fold at 4 h.

In summary, we have described the design and synthesis of a novel class of potent MCH1R antagonists which demonstrate very good oral bioavailability and other pharmacokinetic parameters in rats. The remarkably high brain penetration of these compounds makes them useful tools in the study of centrally acting anorectic agents operating through the MCH1R mechanism.

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20. The pharmacokinetics and blood–brain barrier (BBB) penetrations were determined in male Sprague–Dawley rats following an intravenous (iv, $N = 3$/time point) and oral (po, $N = 3$/time point) dose. The dosing solution was prepared in purified water and filtered through a 0.2 μm nylon filter before administration (2 mL/kg) via tail vein (iv) or a gavage (po). Blood and brain tissue samples were taken at pre-determined time for composite sampling. All plasma and tissue samples were flash-frozen in liquid nitrogen within 10 min of sampling and stored in −70 °C or below until analysis. The bioanalytical method applied for the measurement of test articles in plasma along with added internal standard consisted of precipitation with 200 μL of acetonitrile from 50 μL of plasma, centrifugation and recovery of the supernatant, drying down in vacuum then reconstitution in acetonitrile–water solutions before introducing into an LC-MS/MS system for analysis. The lower limit of quantification (LLOQ) for the analytical methods was 5 ng/mL of test article in plasma. The bioanalytical method applied for the measurement of test articles in brain tissue along with added internal standard consisted of homogenizing half of the brain tissue (longitude cut) in 2 mL of acetonitrile/water (50:50), centrifugation and recovery of the supernatant before introducing into an LC-MS/MS system for analysis. LLOQ for the analytical methods was 5 ng/g of test article in brain tissue. All pharmacokinetic parameters were calculated from a non-compartmental model in WinNonlin program. Brain to plasma ratio was obtained by comparing brain AUC to plasma AUC.