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Design and synthesis of substituted quinolines as novel and selective melanin concentrating hormone antagonists as anti-obesity agents

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Abstract—A novel series of substituted quinoline analogs were designed and synthesized as potent and selective melanin concentrating hormone (MCH) antagonists. These analogs show potent (nM) activity (**12a**–**k**) with a moderate selectivity. Conversely, the conformationally constrained thienopyrimidinone analogs (**18a**–**g**) showed improved activity in MCH-1R and selectivity over 5HT2C.

Obesity is a growing health issue in industrialized countries and developing nations.[1] With the increased obese and overweight population are increased risk of morbidity and mortality as well as an increase in health care costs due to the primary and secondary complications of the epidemic.[2] Thus, obesity and overweight present a major burden on the economies of developed countries.[2] Currently available therapeutic agents sibutramine (Reductil or Meridia), an appetite suppressant, and orlistat (Xenical), an inhibitor of fat absorption, both suffer from limited efficacy and significant undesirable side effects.[3] Therefore, there is great need for effective obesity pharmacotherapy. A major pharmaceutical effort has focused on central nervous system (CNS) targets for treating obesity. These CNS targets include the melanocortin, cannabionoid, and melanin concentrating hormone receptors.

MCH is a cyclic 19 amino acid peptide, which is synthesized in the lateral hypothalamus and zona incerta in the brain.[4] MCH is highly conserved in vertebrate species and appears to play an important role in regulating energy feeding behavior and body weight. Fasting leads to an increase in brain MCH expression in rats and CNS administration of MCH stimulates food intake in rats.[5,6] Furthermore, mice lacking MCH are lean and resistant to diet induced obesity, a consequence of reduced feeding and increased metabolic rate.[6] In contrast, transgenic mice that overexpress MCH are obese and insulin resistant.[7]

Several small molecule MCH antagonists are reported in the literature (Fig. 1),[8–11] among them aminotetralin (**1**, T-226296) was the first reported small molecule MCH antagonist.[8] Oral dosing of T-226296 (IC_{50} 5.5 and 8.6 nM at human and rat MCH-1R, respectively) blocked the hyperphagic effects of MCH injections into the lateral ventricle of lean rats.[8]

Most of the recently disclosed MCH antagonists contain a basic amine group and two aromatic groups joined by an appropriate linker. Based on this design principle, our proposed MCH antagonists were created via linking a basic amino group and the aromatic portion to a quinoline platform (Fig. 2).[12] The quinoline scaffold was selected due to presumed desirable PK properties (e.g., solubility, metabolism, etc.)

The requisite 3,8-substituted quinoline central core was constructed via a Gould–Jacob condensation of substituted aniline **5** with ethoxymethylene malonate.[13]

The quinolone was then converted to the final compounds via a series of synthetic transformations as illustrated in Scheme 1. These compounds were then evaluated for binding to the MCH-R1 using cells that

Keywords: Melanin concentrating hormone antagonists; Anti-obesity; Quinolines.
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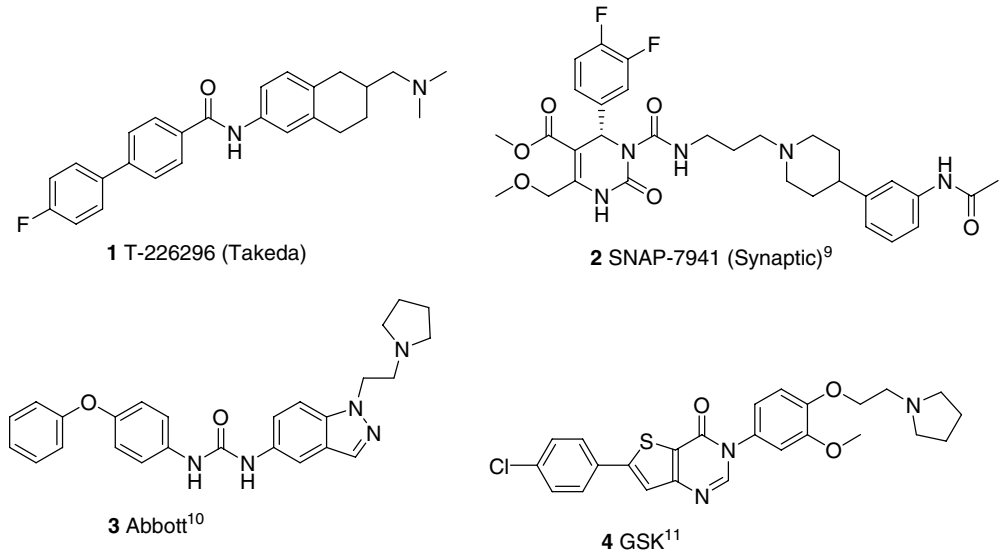


Figure 1. Small molecule MCH antagonists.

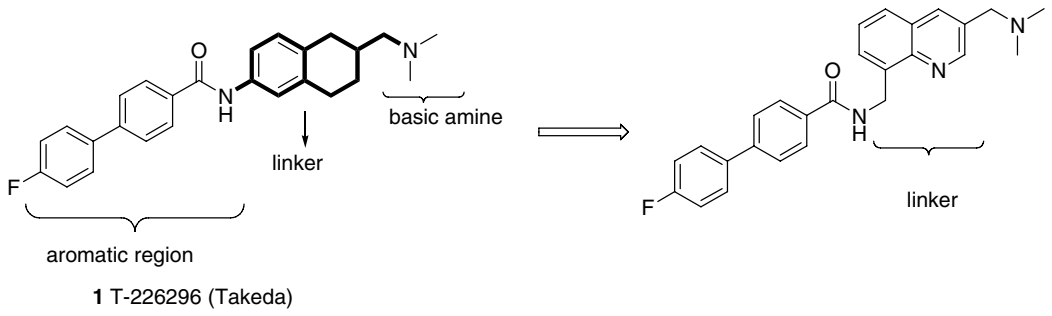
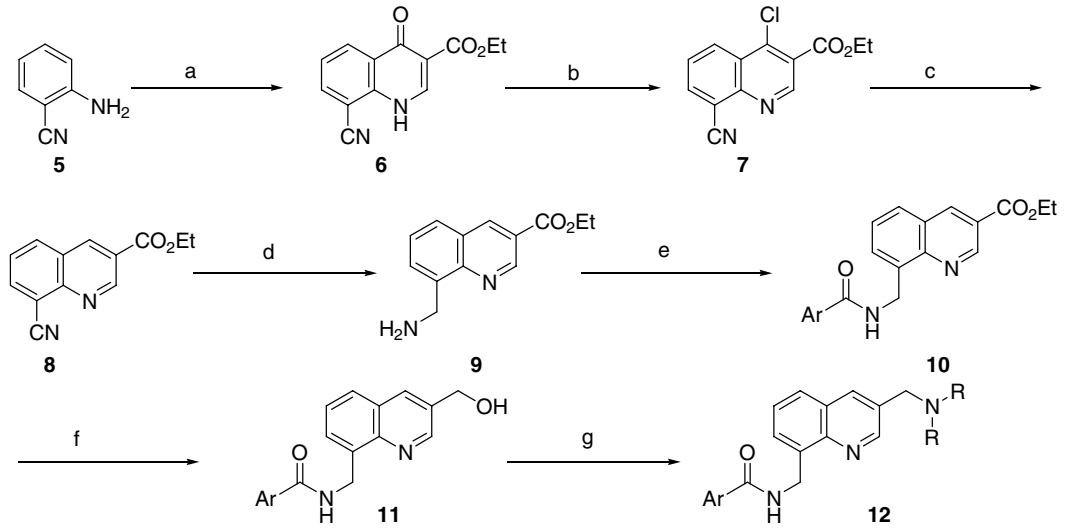


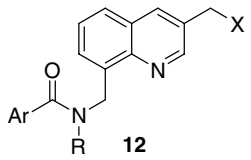
Figure 2. Design concept of new MCH antagonists.



Scheme 1. Reagents and conditions: (a) Ph_2O/250 °C/ethoxymethylenemalonate (60%); (b) $SOCl_2$ (80%); (c) H_2/Pd/EtOH/Et_3N (65%); (d) RaNi/H_2/N_2H_4 (60%); (e) $ArCO_2H$/HBTU/iPr_2EtNH/DMF (80%); (f) $LiB(C_2H_5)_3H$/THF/(70%); (g) (1) MsCl/Et_3N/CH_2Cl_2; (2) NHR^1R^2/DMF (80%).

overexpressed the short form of the receptor (SLC-1).[14] Selectivity against the serotonin receptor (5HT2C)[15] was also evaluated because we and others had determined this receptor showed similarity in the pharmacophore binding pocket to the MCH-1R (Table 1).

Table 1. Activity and SAR relationship of substituted quinoline analogs against MCH and 5HT2C



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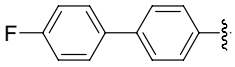
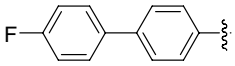
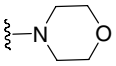
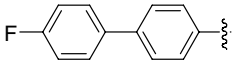
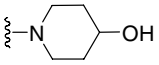
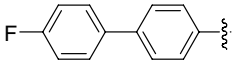
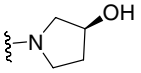
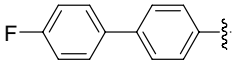
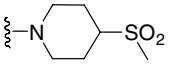
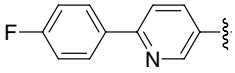
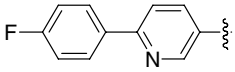
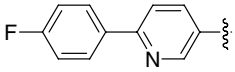
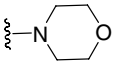
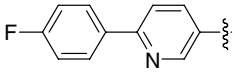
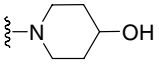
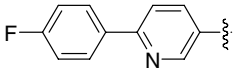
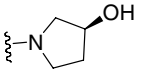
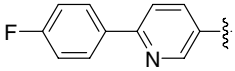
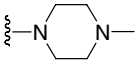
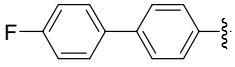
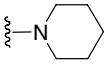
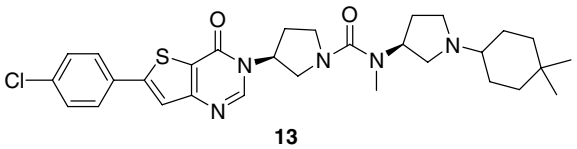
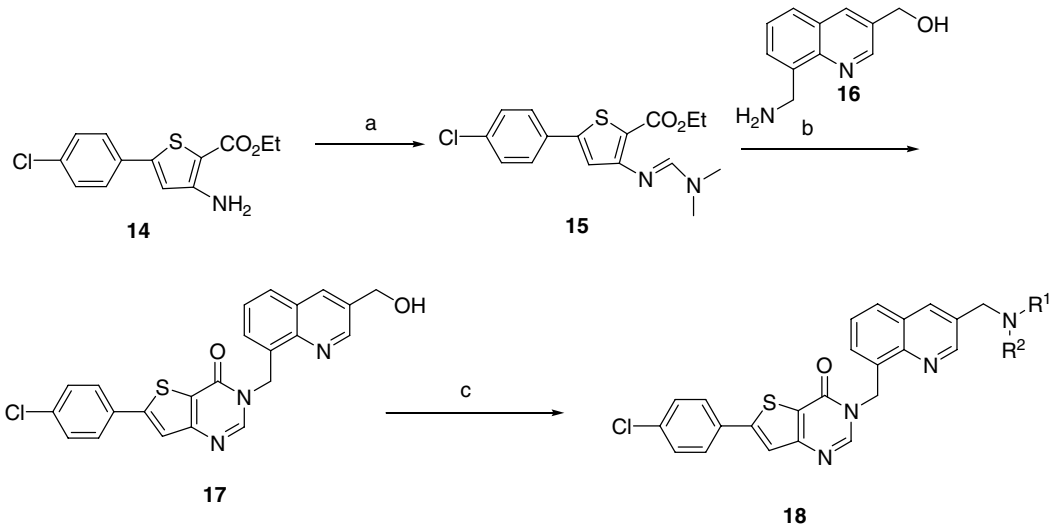
Entry	Ar	R	X	MCH (nM)	5HT2C IC50 (nM)
12a		H		102	4.163
12b		H		1,408	7.467
12c		H		195	2.807
12d		H		142	3.595
12e		H		310	>100,000
12f		H		414	10,321
12g		H		310	14,123
12h		H		20,119	>100,000
12i		H		803	14,641
12j		H		1153	16,515
12k		H		3544	20,230
12l		Me		31	4188

In the aromatic region, the biaryl compounds (**12a**–**e**) exhibited potent binding to the MCH receptor. Placing a heteroatom in the inner benzene of the biaryl ring system (**12f**–**k**) was detrimental to the activity. We were able to obtain potent MCH activity as well as selectivity by placing polar, hydrogen bond accepting groups on the tertiary amine region (**12d**). The most active (31 nM) as well as the most selective (~130-fold) compound was **12l**. In this instance, the hydrogen of the amide nitrogen was replaced with a methyl group. Conformational restriction around the amide bond may be directing these compounds to interact with the receptor in a favorable fashion. We and others have hypothesized that constraining this amide bond into a cyclic, rigid ring system might enhance the activity further. Such a ring system was described in two recent patents by scientists at GlaxoSmithKline (Fig. 1, **4**)[11] and Neurocrine Biosciences (Fig. 3, **13**).[16,17]



13

Figure 3. An example from Neurocrine Biosciences.



Scheme 2. Reagents and conditions: (a) DMF–DMA/EtOH/100 °C/MW (90%); (b) **16**/DMF/100 °C/MW (85%); (c) (1) MsCl/Et_3N/CH_2Cl_2; (2) NHR^1R^2/DMF (60%).

The thienopyrimidinone core can be assembled rapidly via a condensation between commercially available thiophene carboxylate **14** and DMF–dimethylacetal under microwave conditions. The resultant formamidine **15** was then condensed with amino alcohol **16** under yet another reaction using microwave conditions. The alcohol was then transformed into a mesylate and subsequently displaced with appropriate secondary amines to generate the desired compounds (Scheme 2).

We were pleased to find that these compounds were not only potent MCH ligands but also completely selective with polar groups and hydrogen bond acceptors at the amine terminus (**18d**–**g**) continuing to be selective ligands for MCH receptor over 5HT2C. In this series, the tertiary amine derived from piperidine-4-ol (**18d**) has the best activity (K_i 51 nM), while being completely selective (Table 2).

In summary, we were able to design, synthesize, and evaluate a novel series of substituted quinolines as MCH antagonists. SAR investigation revealed that conformationally constrained analogs proved to be not only more active in the MCH binding assay, but also more selective against 5HT2C, warranting them for further evaluations. The quinoline derived MCH antagonists were potent binders to the hERG channel and this problem was solved by further structural modifications. Furthermore, selected compounds in this class show efficacy in animal models. Those results will be reported in due course.

Acknowledgments

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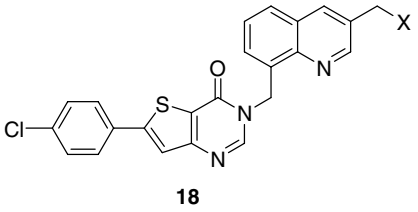
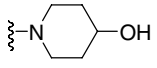
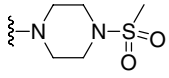
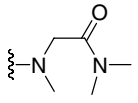
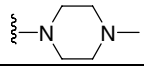
Table 2. Activity and SAR relationship of substituted quinoline derivatives against MCH and 5HT2C



18

Entry	X	MCH K_i (nM)	5HT2C IC50 (nM)
18a		197	1313
18b		126	25,210
18c		91	>100,000
18d		51	>100,000
18e		773	>100,000
18f		136	>100,000
18g		110	>100,000

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14. MCH binding using a Flashplate radioligand binding assay was performed by Perkin–Elmer Biosignal (Toronto, Canada). Full competition curves were generated with compound concentration varying from 100 μM to 11 fM. Potency (K_i) and maximal efficacy were determined and used to define structure–activity relationship.
15. 5HT2C assay was performed using a membrane preparation from cells that overexpress the receptor. Membranes were purchased from Euroscreen (ES-318-M) and used according to established protocols. Briefly, membranes were incubated in a reaction mixture containing varying concentrations of the compound and [^{3}H] mesulergine (final concentration 0.33 nM; Amersham), a compound known to bind to the 5HT2C receptor. The binding buffer contained 50 mM Tris HCl, 0.1% ascorbic acid, 5 mM $CaCl_2$, and 10 μg/ml Saponin. Nonspecific binding was assessed by incubating the membranes with [^{3}H] mesulergine and excess 10 μM mianserin (ICN). After incubating the mixture at room temperature for 60 min, bound mesulergine was separated from unbound mesulergine by filtration through glass fiber B filter (GF/B) plates (Millipore). Bound radioactive mesulergine was detected using a scintillation counter.
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