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Quinazoline and benzimidazole MCH-1R antagonists

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Abstract—We have modified the previously reported 2-aminoquinoline **1** to provide two novel series of MCH-1R antagonists. Representative compounds from the quinazoline and benzimidazole series have been shown to be potent and selective, with promising in vitro eADME profiles.
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Melanin-concentrating hormone (MCH) is a cyclic 19-amino acid peptide that is produced predominantly by neurons in the lateral hypothalamus and zona incerta, which project throughout the brain. The effects of MCH are mediated through two distinct receptors, MCH-1R and MCH-2R, both of which are members of the G protein-coupled receptor (GPCR) super-family. MCH-1R has been identified in mammals and rodents, whereas functional MCH-2R has not been found in rodents. The evidence for the role of MCH and the MCH-1R in body weight and feeding regulation is abundant,[1] and supports the hypothesis that MCH-1R antagonists should provide a novel treatment for obesity. The large number of patents that disclose novel MCH-1R antagonists provides an indication of the interest that this target has generated.[2]

We previously reported the discovery[3] and optimisation[4] of a series of quinolines as MCH-1R antagonists. Compound **1** (Fig. 1) was one of the most potent and selective analogues prepared during this optimisation. Recently, others have reported the identification and structure–activity relationships (SAR) of a related series of quinolines, exemplified by compound **2**.[5]

During the course of our work on the quinoline series, a patent application disclosing related compounds was published by Devita et al. at Merck.[6] Example 1 in this application is depicted as compound **3**, and the similarity to our compounds is evident. Related 2-aminoquinolines have been the subject of a recent publication by Jiang et al. at Merck,[7] with compound **4**[†] selected for in vivo efficacy studies. In order to obtain compounds that did not lie within the generic scope of the Merck patent, we decided to investigate the replacement of the quinoline by alternative ring systems. The first quinoline replacement investigated was the quinoxaline. Subsequently, we investigated quinazolines and benzimidazoles in parallel, and the results obtained are disclosed herein.

Quinoxalines were prepared using the route depicted in Scheme 1. Commercially available 2-hydroxyquinoxaline was nitrated using potassium nitrate in concentrated sulfuric acid to give the 6-nitro derivative **5** selectively in 95% yield. Treatment of **5** with phosphorus oxychloride and phosphorus pentachloride gave the chloro derivative **6** in 89% yield. Displacement of the chloro substituent with the appropriate amine followed by reduction of the nitro group gave the amine **7**, which was coupled with the appropriate carboxylic acids under standard conditions to provide an initial set of quinoxaline amides.

The synthetic route used to prepare a series of quinazolines is depicted in Scheme 2. Acylation of 2-aminoacetophenone with trichloroacetyl chloride followed by cyclisation mediated by ammonium acetate in dimethylsulfoxide provided dihydroquinazolinone **8** in overall

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† The structure depicted in reference 7 does not match the compound name, and we believe that compound **4** is the correct structure.

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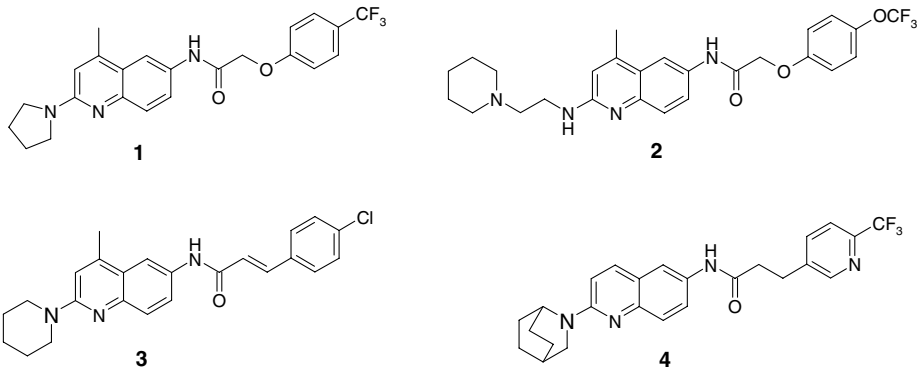
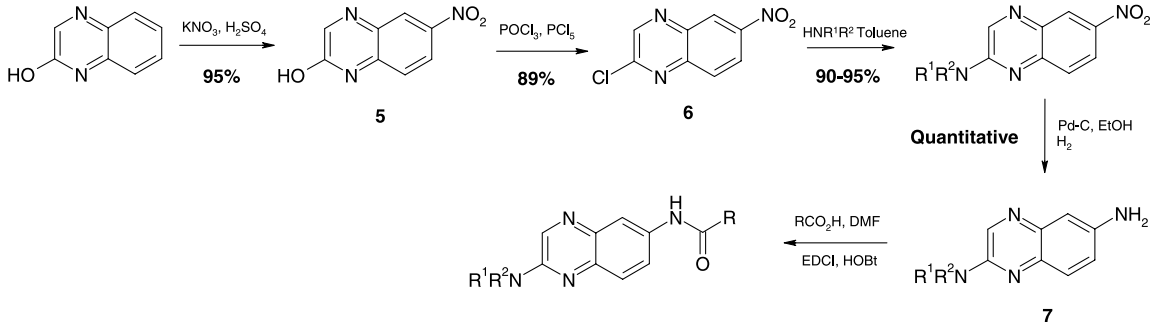
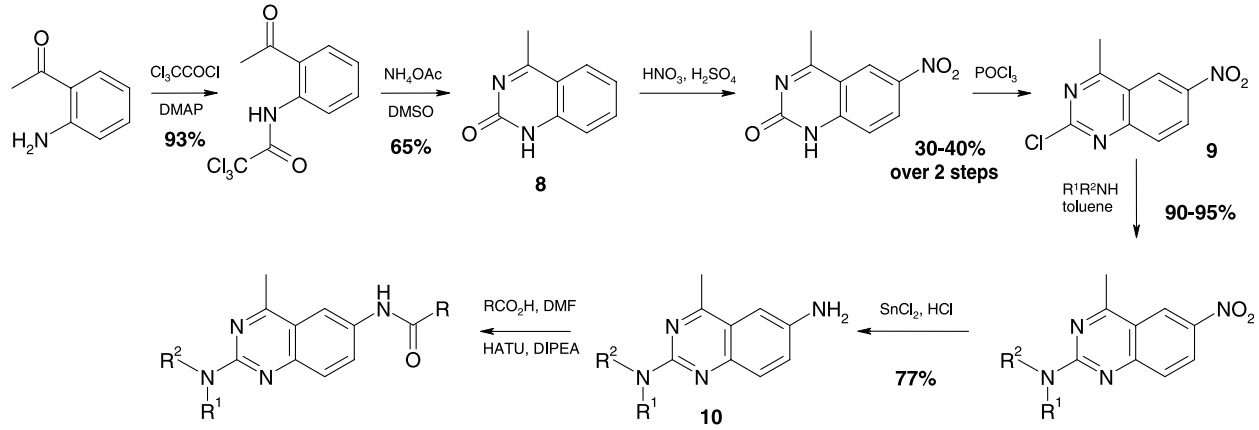


Figure 1. Compound structures.



Scheme 1. Synthesis of quinoxalines.

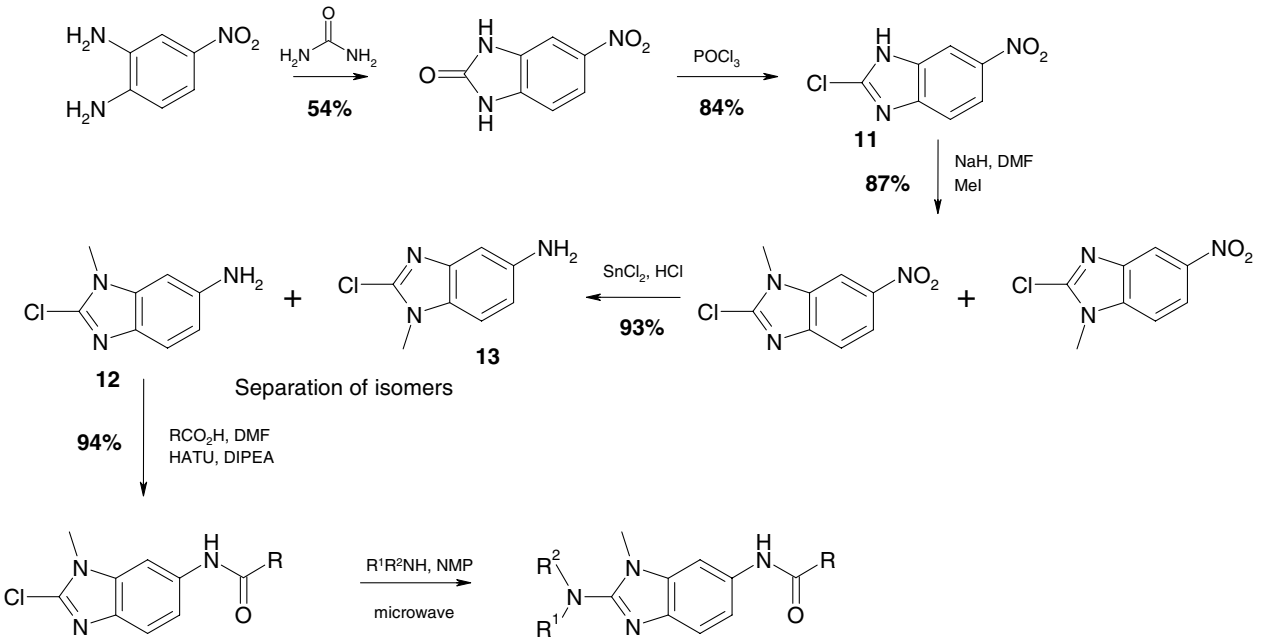


Scheme 2. Synthesis of quinazolines.

60% yield. Nitration of **8** gave the poorly soluble mononitro derivative which was directly converted to the key chloro intermediate **9** by treatment with phosphorus oxychloride in low yield. Nucleophilic displacement of the 2-chloro substituent by an amine followed by reduction of the nitro group using tin (II) chloride gave the corresponding aniline **10**. Amide formation under standard conditions provided a range of quinazolines.

The benzimidazoles were synthesized using the route shown in Scheme 3. The key intermediate, 2-chloro-5-nitrobenzimidazole **11**, was prepared in two steps from commercially available 4-nitro-1,2-phenylenediamine in overall 45% yield. *N*-methylation of **11** provided an 87% yield of a 1:1 mixture of regioisomers, which was subjected to reduction with tin (II) chloride in hydrochloric acid to give the mixture of regioisomers in 93% yield. The regioisomers were separated at this stage to provide **12** and **13**. Aminobenzimidazole **12** was converted into an amide using standard coupling conditions, and the 2-chloro substituent was displaced with an amine to provide the desired 2-aminobenzimidazoles.

Compounds were screened in a scintillation proximity assay in competition with ^{125}I-[Phe^{13},Tyr^{19}]-MCH binding to MCH-1R membranes. IC_{50} values were determined in duplicate wells using a 6-point dose–response curve. All compounds were tested on two separate occasions and



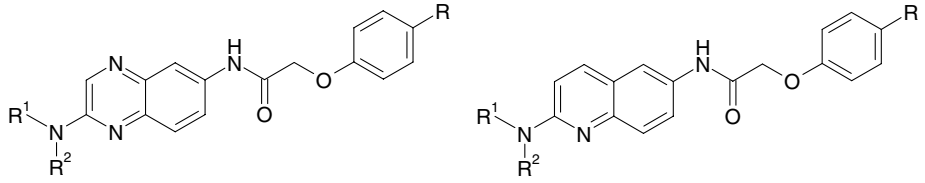
Scheme 3. Synthesis of benzimidazoles.

compared with a standard MCH-1R inhibitor. IC_{50} values from the two determinations were within 2-fold of each other. Functional activity was determined by measuring the ability of selected compounds to inhibit MCH-mediated calcium influx into cells expressing human MCH-1R using a Flexstation. Assays were run in triplicate wells using a 7-point dose–response curve. Compounds were only tested on a single occasion, since the purpose of the functional assay was to ensure that compounds acted as functional antagonists, not to delineate specific SAR. Given the differences between the binding and functional assays (including MCH concentration, amount of serum present, timing of addition of reagents) the correlation between the two assays was considered satisfactory. In general, the rank order of potency was the same in both assays.

We prepared four quinoxalines, incorporating two of the best amines (*N*-methylpiperazine and morpholine) and two of the best aryl substituents (4-chloro and 4-trifluoromethyl) previously identified in the quinoline series. We were disappointed to find that none of these analogues possessed any activity in the MCH-1R binding assay, as shown in Table 1. Since we considered that the loss of activity could be due to the lack of the 4-methyl substituent on the biaryl ring, we prepared the four analogous quinolines lacking this methyl substituent. Although there was some loss of activity compared with the corresponding 4-methylquinolines, the quinolines were consistently significantly more potent than the quinoxalines, as shown in Table 1.

Next we investigated replacement of the quinoline by a quinazoline, and in this series we were able to maintain the presence of the 4-methyl substituent. The first quinazoline synthesized was ADS102891 (see Table 2), the direct analogue of compound **1**, and we were gratified to find that this compound possessed useful activity. This compound was approximately 10-fold less active than the corresponding quinoline in both the binding assay and the functional assay (compound **1** IC_{50} 15 and 10 nM; ADS102891 165 and 100 nM, respectively).

Table 1. Comparison of quinoxalines and quinolines



NR^1R^2	R	Quinoxaline	Quinoline IC_{50} (nM)
Morpholine	CF_3	IA at 1 μM	172
Morpholine	Cl	IA at 1 μM	961
N-methyl piperazine	CF_3	IA at 1 μM	122
N-methyl piperazine	Cl	IA at 1 μM	38% at 1 μM

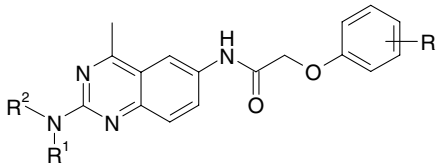
IA = <10% inhibition.

Investigation of the substitution on the phenyl ring provided SAR consistent with those observed previously.[4] Substitution at the 4-position is clearly favoured over substitution at the 2- or 3-position; the results are shown in Table 2. Replacement of the pyrrolidine by a substituted ethylenediamine (ADS103254) provided a compound with comparable MCH-1R binding affinity (IC_{50} 260 nM compared with 165 nM). The 4-chloro compound ADS103253 was selected for further profiling, and the results obtained against a range of other human GPCRs are provided in Table 3. In addition, ADS103253 was investigated for inhibition of five human cytochrome P450 enzymes (2D6, 3A4, 1A2, 2C9 and 2C19). No inhibition was observed when the compound was tested at a concentration of 1 μM. ADS103253 was not cytotoxic in in vitro assays measuring LDH release and intracellular ATP when tested at concentrations up to 300 μM. In a hERG patch-clamp assay, an IC_{50} of 10 μM was obtained.

The first benzimidazole synthesized was ADS103214, and we were gratified to find that this compound was almost as potent as the corresponding quinoline (IC_{50} 40 nM vs 15 nM). Investigation of the amino substituent was carried out, using amines that had been identified in the quinoline series, see Table 4. Pyrrolidine and isopropylamine provided the two most potent quinolines,[4] and were also found to be advantageous in the benzimidazole series. In contrast, although *N*-methylpiperazine provided a potent compound in the original quinoline series, this substituent was clearly not beneficial in the benzimidazole series. The *N*-methyl substituent on the benzimidazole ring was not required for potency (compare ADS103168 with ADS103214) but the regioisomeric *N*-methylbenzimidazole was significantly less active, with an IC_{50} of 1.5 μM (data not shown). ADS103274 was selected for further profiling, and the results obtained against other human GPCRs are shown in Table 3. ADS103274 did not inhibit human or rat cytochrome P450 enzymes at a concentration of 1 μM, was stable in human and rat microsomes, achieved moderate permeability in a Caco-2 assay and had excellent solubility (>1 mg/ml at pH 7.4).

In summary, we have modified our previously identified series of 2-aminoquinolines to provide two new series of MCH-1R antagonists. Representative compounds from

Table 2. Investigation of the quinazoline series



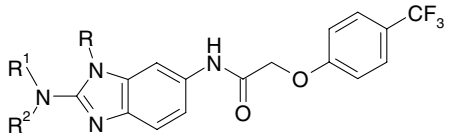
Compound	R	NR^1R^2	IC_{50} (binding assay) nM	IC_{50} (functional assay) nM
ADS102891	4-CF_3	Pyrrolidine	165	100
ADS103253	4-Cl	Pyrrolidine	250	58
ADS103293	2-Cl	Pyrrolidine	1,930	Not tested
ADS103317	3-Cl	Pyrrolidine	7% at 1 μM	Not tested
ADS103316	4-OCH_3	Pyrrolidine	390	41
ADS103254	4-CF_3	$(CH_3)_2N(CH_2)_2N(CH_3)$	260	164

Table 3. Profile of ADS103253 and ADS103274

Compound	MCH-1R	MCH-2R	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}	D2L	α1
ADS103253	250	2%	0%	1900	39%	>100 μM	28%
ADS103274	25	>30,000	22%	1500	7%	19%	27,000

IC_{50} in nM, or % inhibition at 10 μM.

Table 4. Investigation of the amino substituent in the benzimidazole series



Compound	R^1R^2N	R	IC_{50} (binding assay) nM	IC_{50} (functional assay) nM
ADS103168	Pyrrolidine	H	35	9
ADS103214	Pyrrolidine	CH_3	40	9
ADS103274	$(CH_3)_2N(CH_2)_2N(CH_3)$	CH_3	25	28
ADS103294	^{i}PrNH	CH_3	70	101
ADS103255	*N*-methylpiperazine	CH_3	37% at 1 μM	Not tested

the quinazoline and benzimidazole series have been shown to be potent and selective, with a good in vitro ADME profile.

Acknowledgments

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