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Discovery of imidazo[1,2-*a*]pyridines as potent MCH1R antagonists

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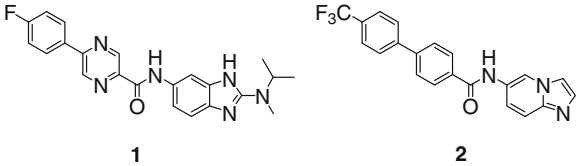
ABSTRACT

A series of imidazo[1,2-*a*]pyridine derivatives was identified and evaluated for MCH1R binding and antagonistic activity. Introduction of a methyl substituent at the 3-position of imidazo[1,2-*a*]pyridine provided compounds with a significant improvement in MCH1R affinity. Representative compounds in this series exhibited good potency and brain exposure in rats.

Melanin-concentrating hormone (MCH) is a cyclic nonadecapeptide with a disulfide bond mainly expressed in the lateral hypothalamus and zona incerta region of the brain. MCH is believed to play an important role in the regulation of food intake and energy homeostasis.[1,2] Up-regulation of prepro-MCH mRNA is reported in several obese animals.[3–5] Chronic intracerebroventricular (icv) infusion of MCH stimulates food intake, causing obesity with hyperphagia.[6,7] Targeted disruption of the prepro-MCH gene reduces food intake and increases metabolic rate, generating a lean phenotype.[8] In contrast, overexpression of the prepro-MCH gene makes mice susceptible to insulin resistance and causes moderate obesity.[9] Recently, we showed that chronic administration of MCH1R antagonists suppresses food intake and body weight gain in diet-induced obesity (DIO) rats and mice.[10,11] These data indicate that MCH1R antagonists could be novel therapeutic agents for the treatment of obesity.[12,13]

In our previous Letter,[14] we described the discovery of a series of 2-aminobenzimidazole derivatives as potent MCH1R antagonists, as exemplified by compound **1** (IC_{50} of 2.7 nM, Fig. 1). After oral administration of 10 mg/kg of compound **1** in rats, plasma and brain levels after 2 h were 1.05 μM and 0.29 nmol/g, respectively. To identify more brain permeable novel MCH antagonists, we initiated a SAR study of the newly identified imidazo[1,2-*a*]pyridine lead **2**. Systematic modification of **2** resulted in the identification of potent and brain permeable derivatives. In this Letter, we describe the detailed structure–activity relationships (SAR) of a series of imidazo[1,2-*a*]pyridine derivatives and the discovery of derivatives **8b** and **8j**, which are more brain permeable than compound **1**.

A general synthetic route for the preparation of imidazo[1,2-*a*]pyridine derivatives is outlined in Scheme 1. The key intermediate **6** was prepared from commercially available 2-amino-5-nitropyridine (**5**). Treatment of ketone **3** with bromine in methanol provided α-bromoketone derivative **4** in moderate yields. Subsequent cyclization of α-bromoketone **4** with 2-amino-5-nitropyridine (**5**) under thermal conditions afforded 2- or 2,3-disubstituted-6-nitroimidazo[1,2-*a*]pyridines **6**. In general, 2-substituted imidazo[1,2-*a*]pyridine **6** (R^1 = H) was produced in good yields, while 2,3-disubstituted imidazo[1,2-*a*]pyridine **6** was obtained only in modest yields due to sterical hindrance by the R^1 group (R^1 = Me, Et or cyclopropyl). Reduction of the nitro group of **6** by hydrogenation over 10% palladium on carbon afforded the corresponding aniline derivatives, which were coupled with the desired biaryl carboxylic acid to provide the imidazo[1,2-*a*]pyridine-6-carboxamide derivatives **7a–h**, **8a–r**, **9**, and **10**. The diverse biaryl carboxylic acid partners were



1 **2**

Figure 1.

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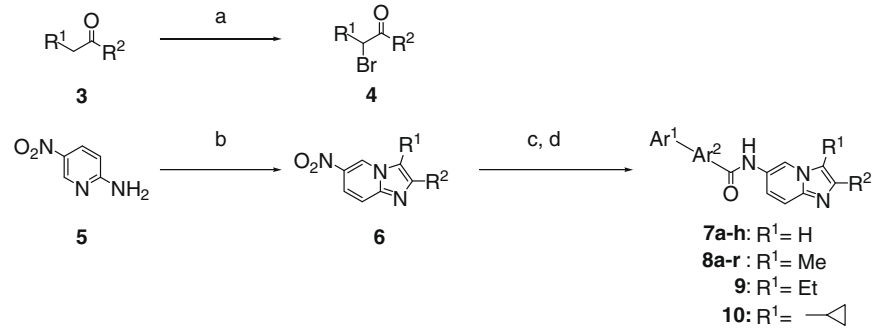
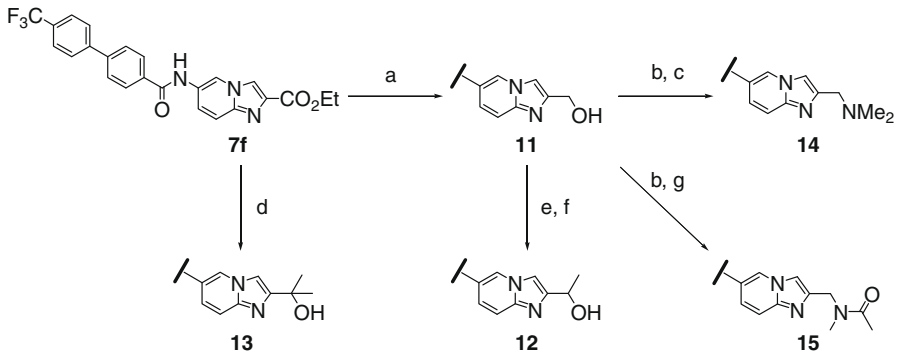


Scheme 1. Reagents and conditions: (a) bromine, MeOH, 0 °C; (b) **4**, EtOH, reflux, 12–48 h, 10–90% (two steps); (c) H_2, Pd–C, MeOH, rt, 2 h; (d) biarylcarboxylic acid, HATU, DIEA, DMF, rt, 16 h, 37–79% (two steps).



Scheme 2. Reagents and conditions: (a) LAH, THF, 0 °C, 81%; (b) MsCl, Et_3N, THF, 0 °C, 90%; (c) Me_2NH, MeOH, 23%; (d) excess MeMgBr, THF, 0 °C–rt, 50%; (e) SO_3·Py, Et_3N, DMSO, rt, 73%; (f) MeMgBr, THF, 0 °C, 44%; (g) $MeNH_2$, MeOH then AcCl, Et_3N, THF, 25%.

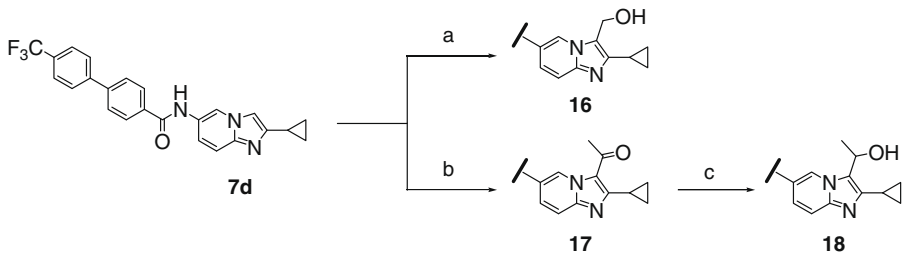
prepared by Suzuki cross coupling reactions of the corresponding aryl halides with the aryl boronic acids.

Imidazo[1,2-*a*]pyridine derivatives containing hydrophilic groups at the 2-position were prepared as outlined in Scheme 2. Ester **7f** was converted to the corresponding primary alcohol **11** by reduction with lithium aluminum hydride or, alternatively, to the *tert*-alcohol **13** by alkylation with an excess amount of MeMgBr. Oxidation of the alcohol **11** to the corresponding aldehyde followed by alkylation with MeMgBr afforded secondary alcohol **12**. Treatment of alcohol **11** with methanesulfonyl chloride followed by substitution with dimethylamine afforded dimethylamine **14**. Alternatively, the alcohol **11** was mesylated, displaced by methylamine, and acylated to afford amide **15**. Introduction of substituents at the 3-position of imidazo[1,2-*a*]pyridine derivative **7d** was achieved by treatment with formaldehyde or acetic anhydride to give **16** and **17**, respectively. Reduction of ketone **17** with $NaBH_4$ provided compound **18** (Scheme 3).

Compounds were evaluated for their binding affinity to the membranes of CHO cells expressing human MCH1R in a competition binding assay with [^{125}I]-MCH as the radioligand. Antagonistic activity was estimated by the inhibitory effect of compounds on intracellular calcium induced by MCH using FLIPR in CHO cells expressing human MCH1R.[15]

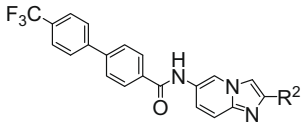
Initial modification around the substituents at the 2-position of the imidazo[1,2-*a*]pyridine ring was performed using lead compound **2** as a template (Table 1). A variety of small alkyl groups, such as methyl, ethyl (data not shown), *n*-propyl, *i*-propyl, cyclopropyl, and *tert*-butyl were effective to increase potency (**7a**–**e**). Incorporation of an electron-withdrawing ethoxylcarbonyl group as in **7f** led to a significant decrease in potency. Incorporation of polar substituents containing hydroxyl (**11**–**13**), dimethylamino (**14**), and acetoamide (**15**) groups resulted in increased binding affinities compared to lead compound **2**, however decreased potency compared to **7a**–**e**, suggesting that the receptor binding pocket around the 2-position of the imidazo[1,2-*a*]pyridine ring prefers lipophilic substituents.

Based on these binding data, further optimization of the substituent at the 3-position was conducted using **7d** as a template (Table 2). Incorporation of a methyl group to the 3-position of the imidazo[1,2-*a*]pyridine ring resulted in a comparable potency to



Scheme 3. Reagents and conditions: (a) 30% HCHO solution, AcONa, AcOH, 60 °C, 34%; (b) Ac_2O, toluene, reflux, 27%; (c) $NaBH_4$, MeOH, 0 °C, 50%.

Table 1
SAR of substituents at the 2-position of imidazo[1,2-*a*]pyridine derivatives



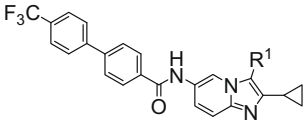
Compound	R^2	MCH1R binding IC_{50}[a] (nM)
2	H	300
7a	^{i}Pr	5.4
7b	Me	4.6
7c	^{n}Pr	11
7d		5.6
7e		7.1
7f	CO_2Et	>1000
11		130
12		30
13		17
14		83
15		35

[a] Values are means of 2 experiments. Compounds competed with [^{125}I]-MCH for binding at the human MCH1 receptor.

the unsubstituted derivative **7d**. Increasing the size of alkyl substituents as in the 3-ethyl and 3-cyclopropyl derivatives (**9** and **10**) led to a decrease in potency. Substitution with polar groups as in **16**, **17**, and **18** also led to a decrease in potency.

We next turned our attention to the left-hand side biaryl moiety of the molecule as shown in Table 3. Incorporation of a 5-trifluoromethyl-2-pyridyl group provided compound **7g** with a comparable binding affinity to the phenyl analogue **7d** (IC_{50} values of 8.2 and 5.6 nM for **7g** and **7d**, respectively). Removing the trifluoromethyl group as in **7h** resulted in a 17-fold decrease in potency. In con-

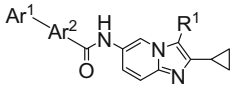
Table 2
SAR of substituents at the 3-position of imidazo[1,2-*a*]pyridine derivatives

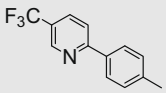
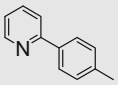
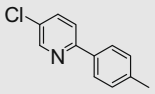
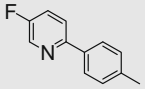
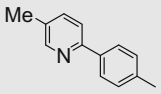
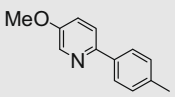
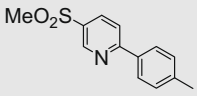
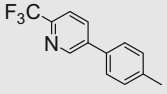
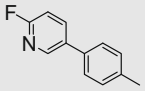
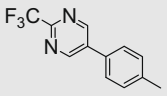
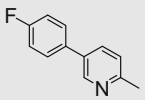
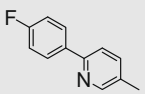


Compound	R^1	MCH1R binding IC_{50}[a] (nM)
8a	Me	4.8
9	Et	26
10		260
16		11
17		320
18		330

[a] Values are means of 2 experiments. Compounds competed with [^{125}I]-MCH for binding at the human MCH1 receptor.

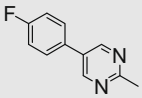
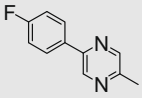
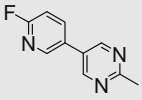
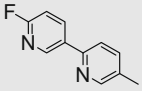
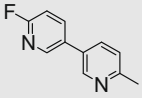
Table 3
SAR of a variety of biaryl analogs



Compound	Ar^1–Ar^2	R^1	MCH1R binding IC_{50}[a] (nM)	MCH1R FLIPR IC_{50}[a] (nM)	*clog P*[b]
7g		H	8.2	nd	5.0
8b		Me	3.5	1000	5.4
7h		H	140	nd	3.6
8c		Me	3.3	26	4.1
8d		Me	2.2	100	4.9
8e		Me	5.4	90	4.0
8f		Me	4.8	85	4.5
8g		Me	6.0	122	4.3
8h		Me	48	94	2.6
8i		Me	4.0	109	5.5
8j		Me	4.4	20	4.1
8k		Me	160	nd	3.9
8l		Me	2.0	59	4.4
8m		Me	4.0	94	4.6

(*continued on next page*)

Table 3 (*continued*)

Compound	Ar^1–Ar^2	R^1	MCH1R binding IC_{50}[a] (nM)	MCH1R FLIPR IC_{50}[a] (nM)	clog P[b]
8n		Me	6.8	29	3.7
8o		Me	2.5	70	4.2
8p		Me	102	164	2.5
8q		Me	61	217	3.3
8r		Me	44	121	3.2

[a] Values are means of 2 experiments. Compounds competed with [^{125}I]-MCH for binding at the human MCH1 receptor.

[b] clog *P* values were calculated by ACD software. nd = not determined.

trast, introduction of a methyl group to the 3-positon of the imidazo[1,2-*a*]pyridine ring as in **8c** exhibited good binding activity (IC_{50} value of 3.3 nM), a 40-fold improvement over the 3-unsubstituted imidazo[1,2-*a*]pyridine derivative **7h**. Furthermore, **8c** has significantly improved functional activity (IC_{50} value of 26 nM) compared with **8b**. Using the 2-cyclopropyl-3-methylimidazo[1,2-*a*]pyridine core as a template, we further explored the biaryl region. A variety of substituents at the *para*-position of the terminal aromatic ring and installation of heteroaromatic rings were investigated. The trifluoromethyl (**8b**) and chloro (**8d**) derivatives exhibited good binding affinities. However, their functional activities were considerably lower (IC_{50} values of 1000 and 100 nM for **8b** and **8d**, respectively), perhaps due to their high lipophilicity. While small substituents such as fluoro (**8e**), methyl (**8f**), and methoxy (**8g**) were well-tolerated, introduction of a relatively large methylsulfonyl group as in **8h** resulted in a drop in potency. Replacement of the 2-pyridyl group of **8b** and **8e** by a 3-pyridyl group as in **8i** and **8j** resulted in comparable binding affinities (IC_{50} values of 4.0 and 4.4 nM, respectively). Furthermore, compound **8j**, which has relatively lower lipophilicity than **8i**, exhibited a significant improvement in functional activity with an IC_{50} value of 20 nM. Installation of a pyrimidine ring at the left-hand side of the biaryl moiety was detrimental to potency (**8k**), whereas **8n** containing a pyrimidine ring at the right-hand side was better tolerated. Similarly, the pyridine derivatives **8l** and **8m** and the pyrazine derivative **8o** displayed good binding and functional activities. Finally, incorporation of either a bipyridyl or pyridyl–pyrimidyl moiety, as in **8p**–**r**, led to comparably reduced activities.

The representative imidazo[1,2-*a*]pyridine derivatives **8b** and **8j** were evaluated for brain penetration in rats (Table 4). After oral administration of 10 mg/kg of compound **8b** in rats, good brain exposure was observed. Brain and plasma concentrations at 2 h following oral dosing were 1.6 nmol/g and 1.4 μM, respectively. In the case of **8j**, which had a good combination of binding and functional activities, high brain and plasma concentrations were observed 2 h after oral dosing (2.5 nmol/g and 5.0 μM for brain and plasma levels, respectively). The brain level of **8j** was eightfold higher than that of **1**.

Table 4
Brain penetrability of imidazo[1,2-*a*]pyridine compounds **8b** and **8j**[a]

Compound	Plasma (μM)	Brain (nmol/g)
8b	1.4	1.6
8j	5.0	2.5

[a] Values are means of 3 experiments. The plasma and brain concentrations were measured 2 h following oral administration of 10 mg/kg of compounds in SD rat.

In conclusion, we have discovered imidazo[1,2-*a*]pyridine analogs as potent MCH1R antagonists. Detailed SAR studies around the imidazo[1,2-*a*]pyridine series revealed that incorporation of a methyl substituent at the 3-position of the imidazo[1,2-*a*]pyridine ring significantly improves binding and functional activity. Furthermore, appreciable brain exposure was achieved in rats after oral administration of imidazo[1,2-*a*]pyridine derivative **8j**.

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