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Synthesis and SAR of 4-aryl-1-(indazol-5-yl)pyridin-2(1*H*)ones as MCH-1 antagonists for the treatment of obesity

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ABSTRACT

A new series of 4-aryl-1-(indazol-5-yl)pyridin-2(1*H*)ones possessing MCH-1 receptor antagonism is presented. Suzuki coupling of boronic acids with key triflate **6** allowed rapid generation of a range of analogs. The SAR of the MCH-1 receptor was explored with a variety of aryl and heterocyclic moieties. Selected compounds were studied in a five-day diet induced obese mouse model to evaluate their potential use as weight loss agents.

Melanin concentrating hormone is a 19 amino acid cyclic neuropeptide that is expressed in the central nervous system of vertebrates.[1] In mammals, the MCH-1 receptor is highly expressed in the hypothalamus and exerts effects on food intake and body weight regulation.[2] Intracerebroventricular injection of MCH increases food intake in rodents and MCH mRNA levels are elevated in fasted animals that are normal weight or obese.[3]

Knock-out studies, in which the gene encoding MCH was deleted, led to mice with reduced body weight and fat mass compared to wild type.[4] Weight loss was higher than expected from the observed reduction in food intake and an increase in oxygen consumption pointed to an elevated metabolic rate as a contributing factor. Transgenic mice lacking the MCH-1 receptor are resistant to diet induced obesity compared to wild type.[5] Despite being hyperphagic when maintained on normal chow, the animals demonstrated a lean phenotype and normal fat mass with increased metabolism and hyperactivity offsetting the increased food intake. This has lead to the development of MCH-1 antagonists as one class of centrally acting targets being explored for the treatment of obesity.[6] Indeed, a variety of small molecule MCH-1 receptor antagonists have been shown to effectively reduce body weight in rodent models of obesity.[7] Two representative examples are shown in Figure 1 (compounds **1** and **2**).[8,9]

Compound **3** was identified in a previously explored 5-(pyridinon-1-yl)indazole series and in a five-day diet induced obese (DIO) mouse feeding study showed 2.8% weight loss (60 mg/kg, po, qd).[10,11] Given the high affinity of compound **3** for the MCH-1 receptor (K_i = 2.6 nM), the modest weight loss was attributed, at

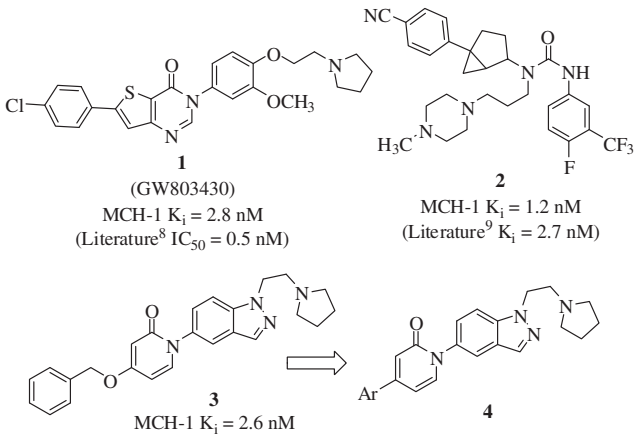

Figure 1.

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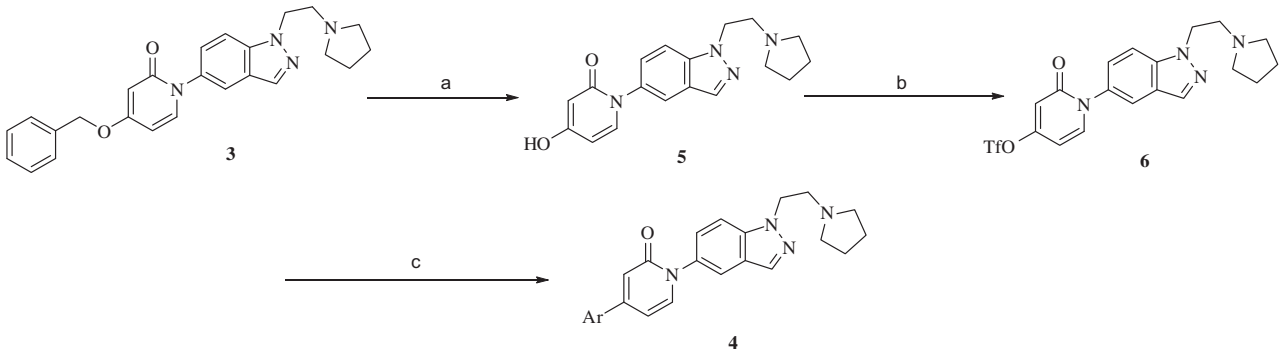
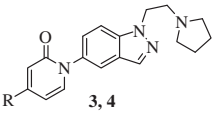


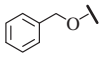
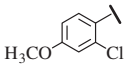
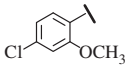
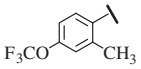
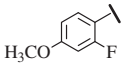
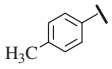
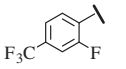
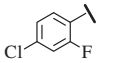
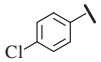
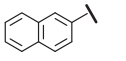
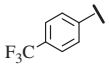
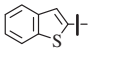
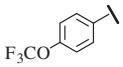
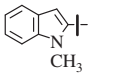
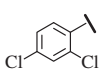
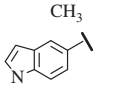
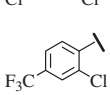
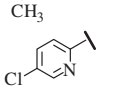
Scheme 1. Reagents and conditions: (a) NH_4OCHO, Pd/C, MeOH, 70 °C, 30 min, 86%; (b) $PhNTf_2$, LiHMDS, THF, 50–75%; (c) arylboronic acid, $PdCl_2$(dppf), K_2CO_3, DMSO, 90 °C, 16 h, 15–44%.

least in part, to suboptimal PK and CNS penetration (brain to plasma ratio of 0.7 at 6 h in DIO mice). Therefore, a strategy was employed to remove potential metabolic positions to improve PK and to reduce the number of rotatable bonds to improve CNS exposure. Removal of the methyleneoxy linker between the phenyl and pyridinone rings was seen as a way to remove a benzylic site of potential metabolism and to remove two rotatable bonds. The increased rigidity of the biaryl pyridinone ring system of compound **4** was expected to reduce metabolic clearance, improve brain penetration and hence improve in vivo efficacy. The biaryl system was also expected to be amenable to rapid analog development.

The benzyl group of **3** (synthesis described previously)[11] was removed by hydrogenolysis with ammonium formate and palladium on carbon to give 4-hydroxypyridinone **5** (Scheme 1). Conversion of the hydroxyl group to triflate **6**, followed by palladium-catalyzed coupling with various boronic acids provided a library of 4-aryl-1-(indazol-5-yl)pyridin-2(1*H*)ones **4** in 15–44% yield.

Table 1
SAR of 4-arylpyridin-2(1*H*)one



Compound	R	MCH-1 binding[a,b] K_i (nM)	Compound	R	MCH-1 binding[a,b] K_i (nM)
3		2.6	**4k**		2.8
4a		>1000	**4l**		19
4b		539	**4m**		3.9
4c		>1000	**4n**		99
4d		24	**4o**		16
4e		275	**4p**		62
4f		15	**4q**		11
4g		5.0	**4r**		25
4h		23	**4s**		13
4i		3.4	**4t**		26
4j		5.8	**4u**		272

[a] Displacement of [^{3}H]compound **1** from MCH-1 expressed in CHO-K1 cells (K_d = 1.42 ± 0.08 nM and B_{max} = 13.3 ± 0.7 pmol/mg protein; mean ± SEM n = 4).
[b] Values are means of at least two determinations where each determination is within ±40% of the mean value shown.

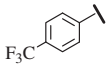
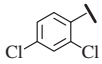
Reducing the number of rotatable bonds through the removal of the methyleneoxy linker in compound **3** to give compound **4a** resulted in a dramatic loss in MCH-1 binding (Table 1). *ortho* Methylation of the phenyl ring restored some activity (compound **4b**). However, the benefit of the methyl group was lost when moved to the *meta*-position (compound **4c**). The *para* methyl analog **4d** improved the MCH-1 affinity to within approximately 7.5-fold of the benzyloxy derivative **3**. Binding affinity was reduced by more than 10-fold when the smaller *p*-fluoro substituent was used (compound **4e**). However, larger electron withdrawing groups in the *para* position (compounds **4f** and **4g**) improved MCH-1 affinity with *p*-trifluoromethyl analog **4g** showing comparable binding affinity to benzyloxy derivative **3**. In many cases, *o*,*p*-disubstituted analogs provided additional enhancement in MCH-1 binding. For example, 2,4-dichlorophenyl derivative **4i** showed nearly 4.5-fold improvement in affinity compared to 4-chloro analog **4f**. Additionally, 2-methyl-4-trifluoromethoxyphenyl derivative **4m** demonstrated a greater than 5.5-fold enhancement in affinity, compared to 4-trifluoromethoxyphenyl derivative **4h**. The addition of a fluorine in the 2-position generally caused a drop-off in binding (**4n**–**p**).

In addition to substituted phenyl compounds, bicyclic aromatic derivatives were also well tolerated. For example, naphthyl, benzothiophenyl, and indolyl analogs **4q**–**t** showed only modest losses in MCH-1 affinity compared to the most potent phenyl derivatives. Pyridine **4u** showed almost a 20-fold decrease in binding compared with the corresponding chloro analog **4f**.

Compounds **4g** and **4i** were chosen for further analysis, including in vivo efficacy studies (Table 2). The compounds showed good aqueous solubility and at least 400-fold separation between MCH-1 affinity and cytochrome P450 inhibition (six isoforms tested).

Compounds **4g** and **4i** also were examined in a five-day diet induced obese (DIO) mouse model of weight loss (Fig. 2). The animals were given the test compounds for five days after a three-day baseline period and body weights were recorded daily. Importantly, both **4g** and **4i** showed improved efficacy (5.7% and 3.9% weight loss, respectively at 30 mg/kg qd) compared with compound **3** (2.8% weight loss at 60 mg/kg qd) at half the dose. Both compounds also compared favorably with known MCH-1 antagonists **1** and **2** in terms of CYP inhibition, aqueous solubility, metabolic stability and in vivo efficacy.

Table 2
Additional in vitro data and in vivo efficacy

Compound	R	MCH-1 binding K_i (nM)	CYP 2C19[a] IC_{50} (μM)	CYP 3A4[a] IC_{50} (μM)	Half life (min)			Aqueous solubility[e] (μM)	Five-day DIO mouse feeding study
					HLM[b]	RLM[c]	MLM[d]		
4g		5.0	27	2.0	120	102	187	93	5.7% weight loss (30 mpk, po, qd) p <0.001
4i		3.4	40	1.7	121	66	136	100	3.9% weight loss (30 mpk, po, qd) p <0.01
1	N/A	2.8	9.3	1.6	603	196	574	10	3.6%, 6.4%[f] weight loss (10 mpk, po, qd) p <0.05, p <0.001
2	N/A	1.2	6.1	<0.05	77	109	574	54	5.1% weight loss (30 mpk, po, qd) p <0.001

[a] Six isoforms tested. Other isoforms not reported have IC_{50}'s greater than 10 mM.
[b] Human liver microsomes.
[c] Rat liver microsomes.
[d] Mouse liver microsomes.
[e] Aqueous solubility in PBS at pH 7.4.
[f] Two separate studies at the same dose.

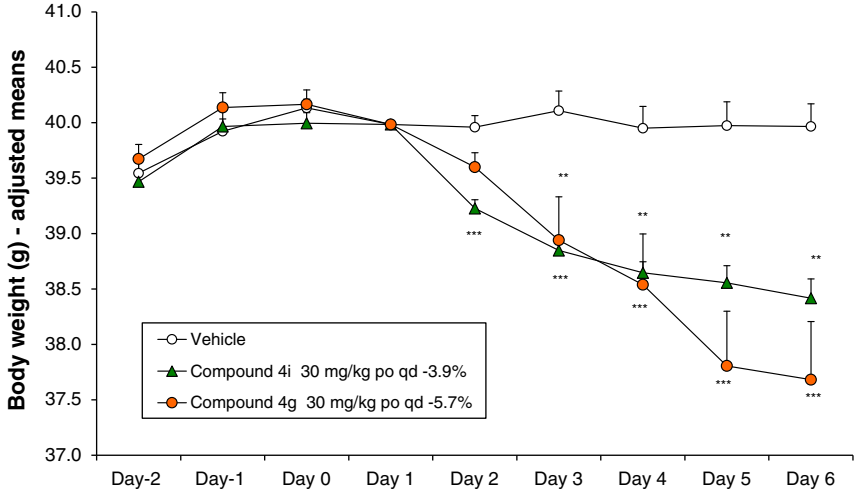


Figure 2. Effect of MCH-1 receptor antagonists **4g** and **4i** on the body weight of male DIO C57BL/6 J mice. Data are adjusted means (n = 8–10) SEMs are calculated from the residuals of the statistical model. Data analyzed by ANCOVA with body weight on day 1 as covariate followed by Dunnett's test for adjusted data; * p <0.05, ** p <0.01, *** p <0.001. Figures in legend refer to % difference from control on day 6 (i.e., after five-days dosing).

In conclusion, a variety of 4-aryl-1-(indazol-5-yl)pyridin-2(1*H*)ones were synthesized and tested for MCH-1 activity. Substitutions on the aryl ring were found to be required for good MCH-1 binding. In particular, certain *para*-substituents and *ortho*, *para*-substituent combinations were able to impart high MCH-1 affinity. Bicyclic aryl ring systems also were found to provide good binding. Selected compounds were studied in DIO mice and were found to produce statistically significant weight loss after five days supporting the potential use of these compounds as weight loss agents. Further progress toward the development of MCH antagonists with improved drug like properties will be reported in the subsequent manuscript.[12]

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