Bioorganic & Medicinal Chemistry Letters 20 (2010) 7015–7019

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

5-(Pyridinon-1-yl)indazoles and 5-(furopyridinon-5-yl)indazoles as MCH-1 antagonists

Matthew D. Surman [a,*], Emily E. Freeman [a], James F. Grabowski [a], Mark Hadden [a], Alan J. Henderson [a], Guowei Jiang [a], Xiaowu (May) Jiang [a], Michele Luche [a], Yuri Khmelnitsky [a], Steven Vickers [b], Jean Viggers [b], Sharon Cheetham [b], Peter R. Guzzo [a]

[a] AMRI, 26 Corporate Circle, PO Box 15098, Albany, NY 12212-5098, USA
[b] RenaSci Consultancy Ltd, Biocity, Nottingham, NG1 1GF, UK

ARTICLE INFO

Article history:
Received 6 August 2010
Revised 3 September 2010
Accepted 8 September 2010
Available online 16 September 2010

Keywords:
Melanin concentrating hormone
MCH-1 antagonists
Obesity
Indazoles

ABSTRACT

A new series of 5-(pyridinon-1-yl)indazoles with MCH-1 antagonist activity were synthesized. Potential cardiovascular risk for these compounds was assessed based upon their interaction with the hERG potassium channel in a mini-patch clamp assay. Selected compounds were studied in a 5-day diet-induced obese mouse model to evaluate their potential use as weight loss agents. Structural modification of the 5-(pyridinon-1-yl)indazoles to give 5-(furopyridinon-5-yl)indazoles provided compounds with enhanced pharmacokinetic properties and improved efficacy.

Obesity is a growing concern for public health in industrialized nations across the globe. The World Health Organization (WHO) estimates that nearly 1 billion people worldwide are overweight as defined as having a body mass index (BMI) of 25 kg/m^2 or greater.[1] Additionally, approximately one third of the overweight population is obese as defined as having a body mass index of 30 kg/m^2 or greater. In the United States, over 60% of the population is overweight and over 30% of these people are obese.[2] Obesity is associated with a variety of comorbidities such as diabetes,[3] dyslipidemia,[4] coronary heart disease,[5] stroke[6] and certain cancers.[7] Indeed, even modest weight loss (5–10%) can provide significant improvements in risk factors such as blood pressure, glucose tolerance and lipid profile.[8] However, weight loss through life style management (dieting and exercise) generally has proven to have limited effectiveness for long term weight maintenance. Additionally, current pharmaceutical treatments suffer from weak efficacy and significant side effects that limit their use. Thus, a major need exists for new pharmaceutical agents that can provide a safe and effective mechanism for inducing weight loss.

Antagonists of the melanin concentrating hormone receptor-1 (MCH-1) have generated considerable interest as potential new weight loss agents. Indeed, a variety of small molecule MCH-1 antagonists have been shown to effectively reduce body weight in rodent models of obesity.[9]

Many of the MCH-1 antagonists described in the literature suffer from cardiovascular risks. In fact, such risks have been proposed as a major reason for the scarcity of MCH-1 antagonists reaching the clinic.[10] Therefore, we sought to discover high affinity MCH-1 antagonists with minimized cardiovascular risk, namely by reducing interaction with the hERG potassium channel. Herein, we describe a series of 5-(pyridinon-1-yl)indazoles with such properties. We found that adjustments to a pendant amine group could be used to attenuate hERG binding. Further modification of the 5-(pyridinon-1-yl)indazole core to a 5-(furopyridinon-5-yl)indazole scaffold provided compounds with enhanced pharmacokinetic properties and improved in vivo efficacy.

Two general strategies were employed to construct the 5-(pyridinon-1-yl)indazole core. One method involved the use of an initial SNAr reaction between benzyloxypyridinone **1** and fluoronitrotoluene **2** (Scheme 1). Reduction of the nitro group with iron powder and ammonium chloride followed by treatment of the resulting aniline with sodium nitrite provided 5-(benzyloxypyridinon-1-yl)indazole **4**. Pendant amines could be attached to the indazole ring using several methods. Selectivity for N1 versus N2 alkylation varied based upon the alkylating agent.[11] Indazole **4** was reacted with bromo-alkylchloride **5** under basic conditions to give substituted indazoles **6**. Treatment of **6** with a variety of amines afforded indazole derivatives **7**. A hydroxyl group was incorporated into the linker between the indazole and the amine by alkylating the indazole with epoxide **8**. The epoxide was opened with lithium perchlorate and dimethyl amine to give indazole

* Corresponding author.
E-mail address: matthew.surman@amriglobal.com (M.D. Surman).

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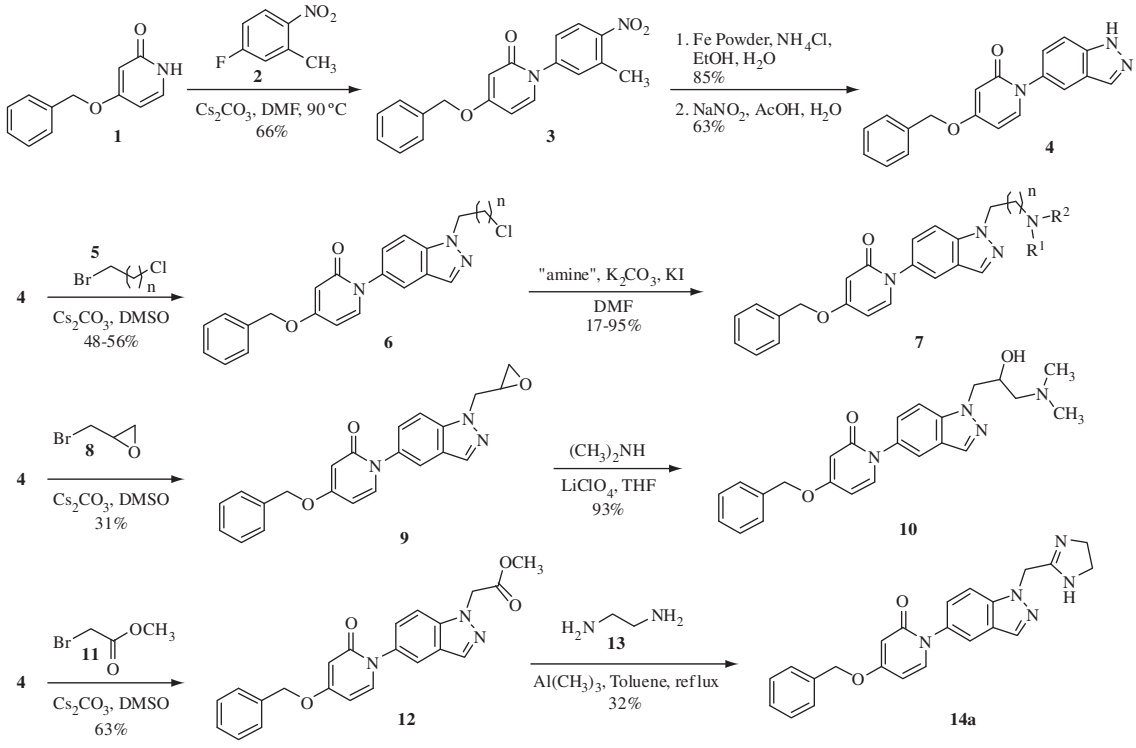
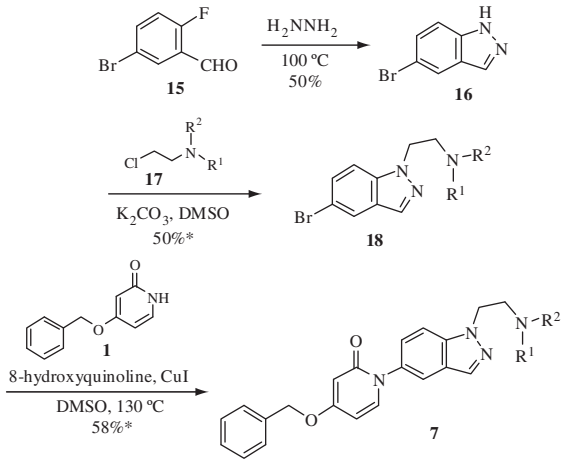
doi:10.1016/j.bmcl.2010.09.039



Scheme 1. Synthesis of 5-(pyridinon-1-yl)indazole MCH-1 antagonists.

derivative **10**.[12] Imidazoline derivatives were made by alkyling indazole **4** with methyl bromoacetate to give substituted indazole **12**. Treatment of indazole **12** with ethylenediamine and trimethylaluminum gave imidazoline derivative **14a**.

The 5-(pyridinon-1-yl)indazole core also was made through the assembly of the indazole portion of the molecule, followed by coupling to the benzyloxypyridinone segment. As shown in Scheme 2, 5-bromoindazole (**16**) was made from commercially available 5-bromo-2-fluorobenzaldehyde (**15**) by treatment with anhydrous hydrazine at 100 °C. Attachment of the desired aminoethyl group using the corresponding alkyl chloride and potassium carbonate provided indazoles **18** (generally as a 2:1 mixture of N1 and N2 regioisomers, separable by column chromatography). Coupling of indazoles **18** with benzyloxypyridinone **1** with copper(I) iodide and 8-hydroxyquinoline at 130 °C afforded 5-(benzyloxypyridon-1-yl)indazoles **7**.



*Yields given for the synthesis of **7b**.

Scheme 2. Alternative synthesis of 5-(pyridinon-1-yl)indazole MCH-1 antagonists.

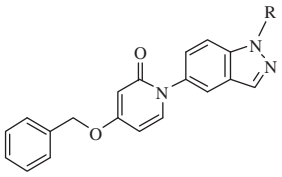
Early MCH-1 SAR around the 5-(pyridinon-1-yl)indazole scaffold highlighted the importance of including a basic amine off of the indazole ring. For example, 1-butyl indazole **19** showed little, if any MCH-1 binding (Table 1). However, the addition of a dimethylaminoethyl group on the indazole ring created a compound (**7a**) with single digit nanomolar MCH-1 affinity.

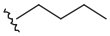
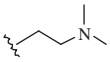
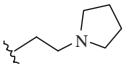
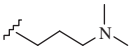
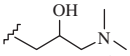
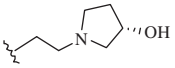
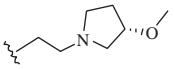
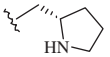
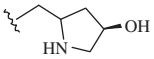
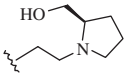
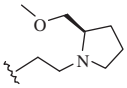
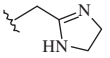
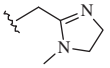
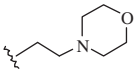
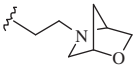
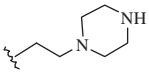
When the dimethylamine was replaced with a pyrrolidine ring, the resulting compound (**7b**) maintained high MCH-1 affinity. Compound **7b** also showed a 1000-fold separation between the MCH-1 K_i value and the hERG IC_{50} (as measured in a mini-patch clamp assay).

Interaction with the hERG channel could be reduced through the incorporation of a hydroxyl group in a position β to the basic amine. For example, addition of a hydroxyl group on the propyl linker in compound **10** decreased hERG binding nearly ninefold compared to compound **7c**. Similarly, adding a hydroxyl group on the pyrrolidine ring in compounds **7d** and **20b** provided reduced hERG interaction compared with the parent compounds **7b** and **20a**, respectively. Interestingly, conversion of the hydroxyl moiety to a methoxy group decreased or eliminated the beneficial effect on hERG (compare compounds **7d** to **7e** and **7f** to **7g**).

Incorporation of the pendant amine into a variety of heterocycles provided positive effects on hERG. Imidazoline derivative **14a** showed a nearly fivefold decrease in hERG binding compared to dimethylamine derivative **7a**. This benefit was lost by methylating the imidazoline to give compound **14b**. Morpholine derivative **7h** showed very little hERG interaction (IC_{50} >30 μM); however, the MCH-1 affinity dropped approximately ninefold compared to dimethylamine analogue **7a**. The MCH-1 affinity could be improved 2.5-fold by converting the morpholine to bicyclic structure **7i**. Compound **7i** maintained a nearly 1000-fold separation between MCH-1 and hERG binding. Similar to morpholine, piperazine derivative **7j** showed reduced hERG interaction (ninefold) compared to dimethylamine analogue **7a**.

Table 1
Indazole amine SAR



Compound	R	MCH-1 binding[a,b] K_i (nM)	hERG[c] IC_{50} (μM)
19		>5000	Not determined
7a		4.7	1.8
7b		2.6	2.5
7c		12.6	1.4
10		37.7	12.1
7d		4.7	9.0
7e		9.4	1.8
20a		12.0	2.0
20b		33.0	>30
7f		3.1	2.3
7g		11.2	0.8
14a		22.6	8.5
14b		30.4	3.3
7h		43.4	>30
7i		17.3	16.0
7j		24.3	16.4

[a] Displacement of [^3H]compound **7b** 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.
[c] Mini-patch clamp assay using HEK cells stably expressing the hERG potassium channel.

A selected set of analogues was chosen for further in vitro and in vivo analysis (Table 2). Compounds **7b**, **7d** and **14a** showed good aqueous solubility and greater than 1000-fold separation between MCH-1 affinity and cytochrome P450 inhibition (six isoforms tested). Compounds **7b**, **7d** and **14a** also were examined in a 5-day diet-induced obese (DIO) mouse model of weight loss (Figure 1). All three compounds showed statistically significant reductions in body weight when given at a screening dose of 30 mg/kg twice daily.

Twice daily dosing was found to be necessary for robust weight loss. In the case of compound **7b**, providing the same overall daily dose in a single dose (60 mg/kg po, qd) reduced the efficacy in the 5-day DIO mouse model (2.8% weight loss versus 6.0% at 30 mg/kg b.i.d.).

Table 2
Additional in vitro and in vivo data for selected 5-(pyridinon-1-yl)indazoles

Compound	CYP 3A4[a] IC_{50} (μM)	Half-life (min)		Aqueous solubility[d] (μM)	Weight loss[e] (%)
		MLM[b]	HLM[c]		
7b	10	695	303	492	6.0
7d	7.7	433	289	>500	3.3
14a	38	580	260	410	3.5

[a] 1A2, 2B6, 2C9, 2C19, 2D6 and 3A4 isoforms tested. Isoforms not reported have IC_{50}s greater than 10 μM.
[b] Mouse liver microsomes.
[c] Human liver microsomes.
[d] PBS at pH 7.4.
[e] 5-day DIO mouse study at 30 mg/kg po, b.i.d.; see Figure 1.

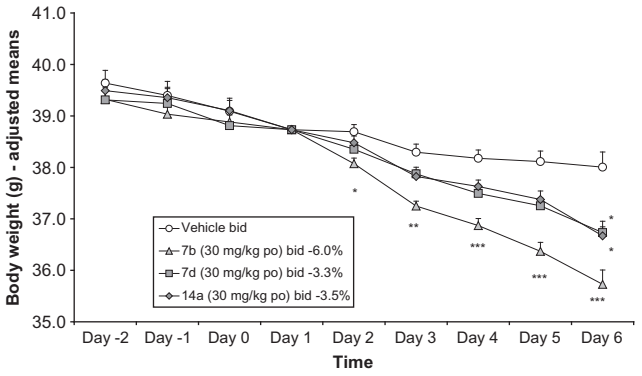
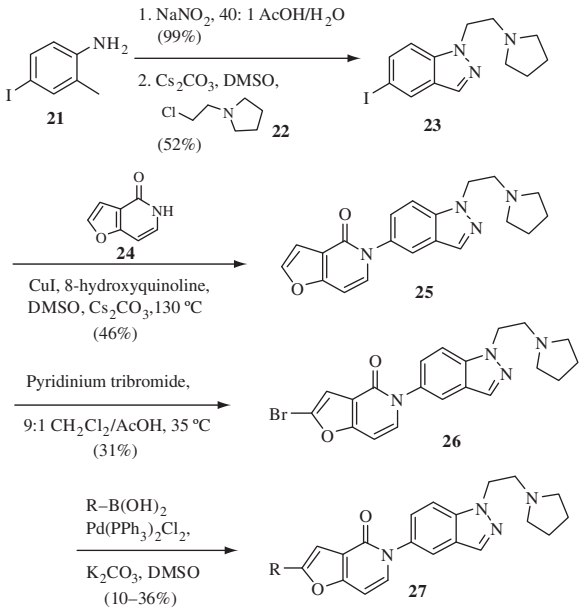


Figure 1. Effect of compounds **7b**, **7d** and **14a** (dosed at 30 mg/kg, po, b.i.d. in 1% methylcellulose in water) on the body weight of male C57BL/6 J DIO mice. Data are adjusted means (n = 10). SEMs are calculated from the residuals of the statistical model. Data analysed by ANCOVA with body weight 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 5 days dosing).

The requirement for twice daily dosing was attributed, at least in part, to suboptimal PK and CNS penetration. Therefore, a strategy was employed to remove potential metabolically labile positions to improve PK and to reduce the number of rotatable bonds to improve CNS exposure. The furopyridinone scaffold was explored as a structural derivative of the benzyloxypyridinone system that would achieve these structural changes. The furopyridinone removes a benzylic site of potential metabolism and eliminates two rotatable bonds. The increased rigidity of the furopyridinone was anticipated to improve brain penetration[13] and hence improve in vivo efficacy.

The strategy utilized to synthesize the furopyridinone derivatives is shown in Scheme 3. Reaction of aniline **21** with $NaNO_2$ in 40:1 AcOH/H_2O and subsequent alkylation of the indazole intermediate with alkyl chloride **22** and Cs_2CO_3 afforded indazole **23** in 52% yield over the two steps. A small amount of the undesired alkylation regiosiomer (2-position of the indazole) was also obtained. The regioisomers were separable by column chromatography. Treatment of **23** with furopyridinone **24**,[14] CuI, 8-hydroxyquinoline and Cs_2CO_3 in DMSO at 130 °C gave furopyridinone **25** in 46% yield. Selective bromination of **25** at the 2-position of the furopyridinone was accomplished with pyridinium tribromide in 9:1 CH_2Cl_2/AcOH at 35 °C to afford compound **26** in 31% yield. Suzuki or Stille coupling of **26** with the appropriate aryl boronic acid or heteroaryl stannane afforded a small library of compounds **27a–j** in 10–36% yield.

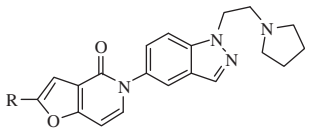


Scheme 3. Synthesis of 5-(furo[3,2-*c*]pyridin-4(5*H*)on-5-yl)indazole MCH-1 antagonists.

Exploration of the MCH-1 SAR surrounding the phenyl ring in compound **27a** revealed that substituents in the *para*-position were well tolerated (see compounds **27a**–**27c** in Table 3). Substitution in the *ortho*- or *meta*-position resulted in losses in MCH-1 affinity. For example, *ortho*- or *meta*-chloro derivatives **27d** and **27e** showed 5–7-fold increases in K_i values compared with *p*-chloro derivative **27c**. *Ortho* and *para* disubstitution was tolerated when the *ortho* group was small, as in 4-chloro-2-fluoro derivative **27g**. However, when larger *ortho* groups were introduced (such as methoxy in analogue **27h**), losses in binding affinity were observed. Replacement of the phenyl ring with aromatic heterocycles such as pyridine and pyrimidine (**27i** and **27j**, respectively) led to 6–160-fold decreases in MCH-1 affinity.

Compound **27c** was selected for additional in vitro and in vivo evaluation. Compound **27c** gave comparable results to **7b** in the MCH-1 radioligand binding assay and a functional Ca^{2+} mobiliza-

Table 3
5-(Furo[3,2-*c*]pyridin-4(5*H*)on-5-yl)indazole aryl ring SAR



Compound	R	MCH-1 binding K_i[a,b] (nM)
27a	Phenyl	9.7
27b	4-Fluorophenyl	6.1
27c	4-Chlorophenyl	5.2
27d	2-Chlorophenyl	28
27e	3-Chlorophenyl	38
27f	2,4-Dichlorophenyl	14
27g	4-Chloro-2-fluorophenyl	4.2
27h	4-Chloro-2-methoxyphenyl	48
27i	Pyridin-2-yl	59
27j	Pyrimidin-2-yl	1679

[a] Displacement of [^3H]compound **7b** 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.

Table 4
Comparison of selected in vitro and in vivo properties of compounds **7b** and **27c**

In vitro	**7b**	**27c**
MCH-1 binding K_i[a,b] (nM)	2.6	5.2
Ca^{2+} release IC_{50}[c] (nM)	14	23
Mouse PK		
Dose (mg/kg)	30	10
$[Plasma]_{6h}$[d] (ng/mL)	2224	141
$[Brain]_{6h}$[e] (ng/g)	1485	2253
B/P ratio[f]	0.7	16
5-Day DIO mouse efficacy		
Dose (mg/kg)	30 (b.i.d.), 60 (qd)	30 (qd)
Body weight loss	6.0%***, 2.8%*	4.5%***

[a] Displacement of [^{3}H]Compound **7b** 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 four determinations.
[c] Inhibition of MCH-mediated Ca^{2+} release in AequoScreen™ MCH-1 cells.
[d] Plasma concentration 6 h post dose.
[e] Brain concentration 6 h post dose.
[f] Ratio of brain concentration to plasma concentration at 6 h.
* p <0.05.
*** p <0.001.

tion assay (Table 4). However, **27c** showed a 20-fold increase in mouse brain to plasma concentration ratio (B/P = 16) compared to **7b** (B/P = 0.7), leading to increased brain exposure at one third the dose.[15] Compound **27c** also provided improved efficacy in the 5-day DIO mouse model with once daily dosing (4.5% weight loss, 30 mg/kg po, qd) compared to **7b** (2.8% weight loss, 60 mg/kg po, qd) at half the dose.

In conclusion, a potent series of 5-(pyridinon-1-yl)indazole MCH-1 antagonists was synthesized. Interaction with the hERG channel could be attenuated by adjustments to a pendant amine group. Further modification of the 5-(pyridinon-1-yl)indazole core to a 5-(furopyridinon-5-yl)indazole scaffold provided compounds with enhanced pharmacokinetic properties and improved in vivo efficacy. Additional strategies for improving the efficacy of the lead series will be described in subsequent reports.[16]

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