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Aminopiperidine indazoles as orally efficacious melanin concentrating hormone receptor-1 antagonists

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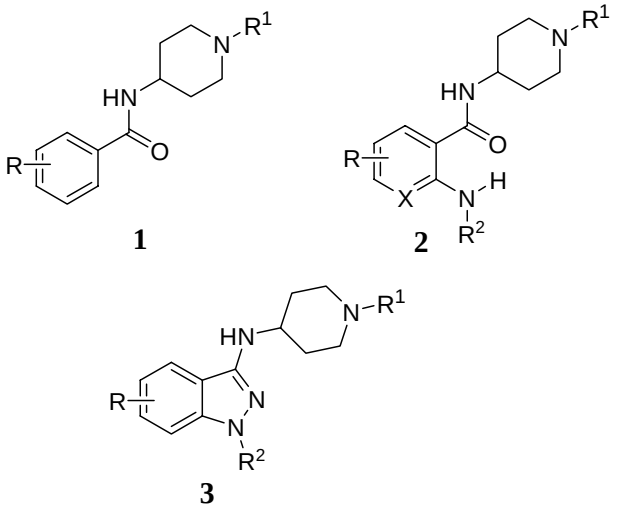
Abstract—The synthesis and biological evaluation of novel 3-amino indazole melanin concentrating hormone receptor-1 antagonists are reported, several of which demonstrated functional activity of less than 100 nM. Compounds **19** and **28**, two of the more potent compounds identified in this study, were characterized by high exposure in the brain and demonstrated robust efficacy when dosed in diet-induced obese mice.

Melanin concentrating hormone (MCH) is an orexigenic neuropeptide, that is produced predominantly by neurons in the lateral hypothalamus and zona incerta.[1] Central MCH administration stimulates food intake while fasting results in an increase in MCH expression.[2] Mice lacking the MCH encoding gene are lean, hypophagic, and maintain elevated metabolic rates,[3] whereas mice over-expressing the MCH gene are susceptible to obesity and insulin resistance.[4] The prospect of MCHr1 as an attractive target for anti-obesity therapy has been reviewed extensively.[5]

We have previously reported the identification of MCHr1 antagonists based on a benzamide scaffold, **1**.[6] Subsequent optimization led to the identification of *ortho* amino benzamides **2**.[7] In this Letter, we describe our continuing efforts aimed at exploring multiple chemotypes for potential MCHr1 inhibition, wherein the *ortho* amino benzamide scaffold is replaced by an indazole moiety to afford compounds such as **3**.



The synthesis of the target compounds was accomplished as described in Scheme 1 or 2. Refluxing a solution of the suitably substituted *ortho* fluoro benzonitrile **4** with hydrazine hydrate in butanol afforded the 3-amino indazole nucleus **5** in moderate to excellent yields, depending on the nature of the R-group. Reductive amination with 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester, followed by deprotection and reductive amination with a variety of monocyclic and bicyclic

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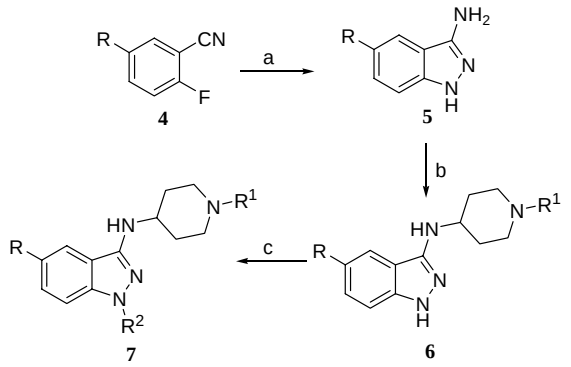
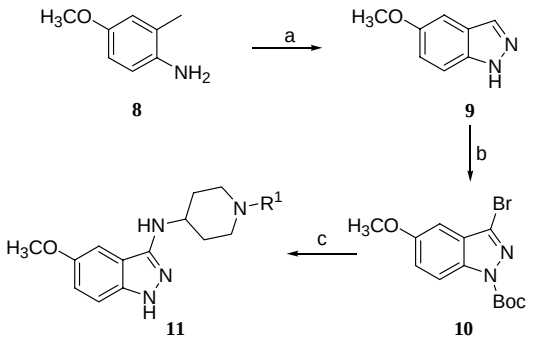


Scheme 1. Reagents and conditions: (a) $NH_2NH_2{\cdot}H_2O$, *n*-BuOH, reflux, 4 h; (b) 1. 4-Oxo-piperidine-1-carboxylic acid *tert*-butyl ester, $NaCNBH_3$, AcOH, 50 °C, 12 h; 2. 4 N HCl/dioxane; 3. ArCHO, $NaCNBH_3$, CH_3OH, AcOH (cat.); (c) R^2COOH, PS-DCC, HOBt, *N*,*N*-DMF or NaH, R^2Br, *N*,*N*-DMF.

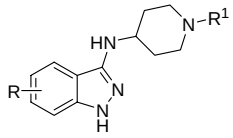


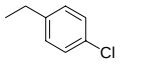
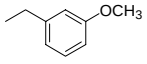
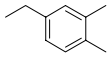
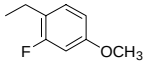
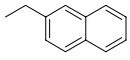
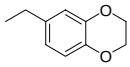
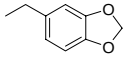
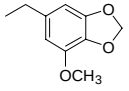
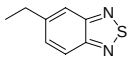
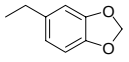
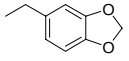
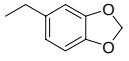
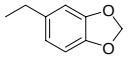
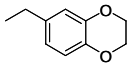
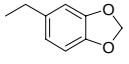
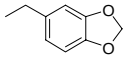
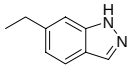
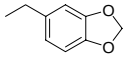
Scheme 2. Reagents and conditions: (a) 1. $NaNO_2$, AcOH; 2. Et_3N. (b) 1. KOH, NBS; 2. $(Boc)_2O$, THF. (c) 1. Functionalized 4-amino piperidine, Pd_2dba_3, Xantphos, Cs_2CO_3, dioxane; 2. HCl/*i*PrOH.

aldehydes and ketones, afforded the target compounds. An alternate synthesis shown in Scheme 2 was devised to access target compounds, where R was an electron-donating group, such as a methoxy moiety. Diazotization and cyclization of 4-methoxy-2-methyl aniline afforded 5-methoxy indazole **9**, which was brominated using *N*-bromosuccinimide. Palladium coupling of the boc-protected intermediate **10** with a suitably functionalized aminopiperidine using Xantphos[8] as the ligand afforded the desired target compounds.

All the compounds synthesized in this study were evaluated for their MCHr1 inhibition in a competitive radiometric-binding assay using receptor obtained from human neuronal IMR-32 cells.[9] Further characterization was performed in an assay designed to measure functional antagonism of MCH-mediated Ca^{2+} release using a fluorometric imaging plate reader ($FLIPR^{TM}$).[9] A cursory analysis of the binding data shown in Table 1 indicates that in general, compounds with bicyclic substituents (as R^1) afforded more potent MCHr1 inhibition compared to those with monocyclic substituents. Comparison of the activities of compound **12** with **13**–**16** indicates that the addition of hydrophobic subtituents to **12** improved MCHr1 inhibition as well as functional potency. Replacement of the phenyl substituent in **12** with a 2-naphthyl moiety (**17**) resulted in a 20-fold

Table 1. MCHr1-binding affinity (IC_{50}) and functional activity (IC_{50}) of indazole analogs



Compound	R	R^1	IMR32 binding IC_{50} (μM)	IMR32 $FLIPR^{TM}$ IC_{50} (μM)
12	5-Cl		0.85	>10
13	5-Cl		0.20	6.2
14	5-Cl		0.15	4.5
15	5-Cl		0.10	1.38
16	5-Cl		0.24	5.2
17	5-Cl		0.04	1.82
18	5-Cl		0.07	1.89
19	5-Cl		0.02	0.26
20	5-Cl		0.28	>10
21	5-Cl		0.05	4.91
22	5-H		0.44	>10
23	5-CF_3		>2	>10
24	5-CH_3		0.11	1.06
25	5-NO_2		0.006	0.07
26	5-NO_2		0.03	0.52
27	5-CN		0.22	3.4
28	5-OCH_3		0.008	0.06
29	5-OCH_3		0.05	0.38
30	4-OCH_3		0.33	>10

improvement in MCHr1 inhibition. Introduction of bicyclic heterocycles such as the 1,4-benzodioxan-6-yl (**18**), piperonyl (**19**), and benzothiadiazolyl (**21**) resulted