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Microwave assisted synthesis of isothiazolo-, thiazolo-, imidazo-, and pyrimido-pyrimidinones as novel MCH1R antagonists

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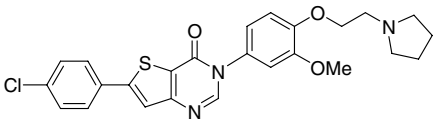
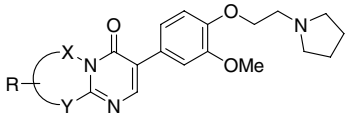
Abstract—An efficient microwave assisted condensation of α-heteroarylamines with 3-dimethylamino-2-aryl-propenoates has been developed to synthesize various fused bi-heterocyclic compounds, including isothiazolo-, thiazolo-, imidazo-, and pyrimido-pyrimidinones as novel MCH1R antagonists.

Melanin concentrating hormone (MCH), a cyclic 19-amino acid neuropeptide, plays an important role in the central regulation of food intake and energy homeostasis in mammals.[1] Central administration of MCH in mice stimulates food intake while fasting results in an increase in MCH expression. Transgenic mice over-expressing MCH are susceptible to obesity and insulin resistance, whereas MCH deficient mice are hypophagic and leaner than wild-type mice but otherwise healthy. MCH-1 receptor (MCH1R) is a G-protein-coupled receptor (GPCR) found in all mammals. MCH1R knockout mice are lean and resistant to a diet induced obesity. As such, MCH1R antagonists are believed to have potential as possible treatments for obesity. A wide variety of small molecule MCH1R antagonists have been reported recently,[1] among which, GW-803430, an orally efficacious MCH1R antagonist discovered by GSK scientists,[2] has advanced into human clinical investigation for the treatment of obesity.



GW-803430
MCH1R K_i = 0.5 nM

In our search for novel MCH1R antagonists, we designed a series of bi-heterocyclic compounds (**1**) that include isothiazolo-, thiazolo-, imidazo-, and pyrimido-pyrimidinone cores to replace the thienopyrimidinone core in GW-803430.



1

The synthesis of fused bi-heterocyclic compounds has been reported via condensation of heteroarylamines with 3-dimethylamino-2-aryl-propenoates using conventional heating methods which requires long reaction time and gives only poor to moderate yields,[3,4a] for example, heating of 2-aminothiazole with 3-dimethylamino-2-(indol-3-yl)-propenoate in AcOH at reflux for 5 h produced a fused bicyclic thiazolo-pyrimidinone product in 30% yield.[4a] In contrast, microwave assisted synthesis has been described for the preparation of several fused bi-heterocyclic compounds, which requires much reduced reaction time but gives significantly increased yields,[4b,c] for example, microwave heating of 2-aminopyridine with 3-dimethylamino-2-(benzamido)-propenoate in AcOH at 180 °C for 10 min generated a fused bicyclic pyrido-pyrimidinone product in 77% yield.[4b] We wish to report here an efficient microwave assisted synthesis of bi-heterocyclic compounds (**1**) as novel MCH1R antagonists.

Keywords: Microwave assisted synthesis; MCH1R antagonist; Isothiazolo-, thiazolo-, imidazo-, pyrimido-pyrimidinones.
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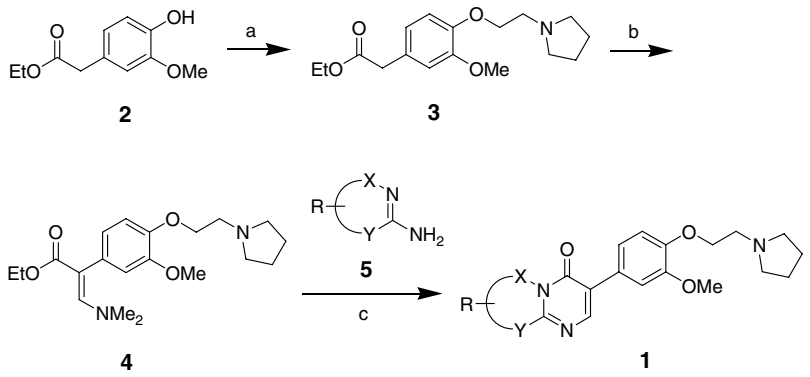
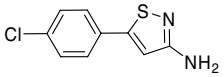
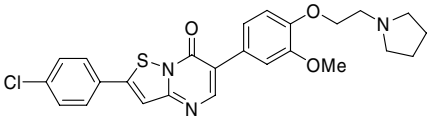
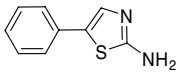
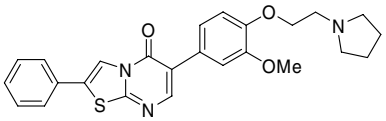
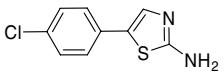
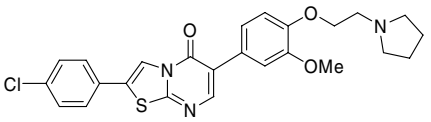
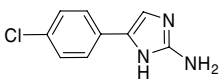
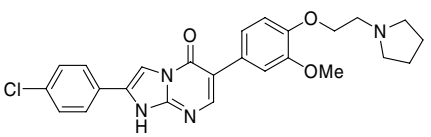
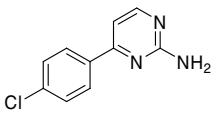
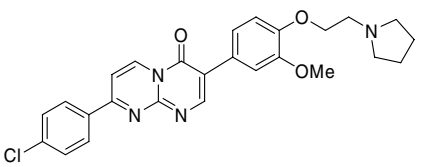


Scheme 1. Reagents and conditions: (a) NaH, 1-(2-chloroethyl)pyrrolidine, DMF, 80 °C, 16 h, 53%; (b) *tert*-butoxy-bis(dimethylamino)methane (Bredereck's reagent), 65 °C, 16 h, 80%; (c) AcOH, microwave, 200–220 °C, 200–600 s, 44–89%.

Scheme 1 illustrates the synthetic procedure for target compounds **1**. First, heating ethyl homovanilate (**2**) with NaH and 1-(2-chloroethyl)pyrrolidine in DMF provided arylacetate **3**. Then, treatment of **3** with Bredereck's reagent (*tert*-butoxy-bis-(dimethylamino)-methane) generated 3-dimethylamino-2-aryl-propenoate **4**. Finally, heating of **4** with various α-heteroarylamines **5** using microwave gave bi-heterocyclic compounds **1**.

Table 1 lists the detailed microwave conditions and yields for the preparation of isothiazolo-, thiazolo-, imidazo-, and pyrimido-pyrimidinone compounds **1a**–**e**. It

Table 1. Microwave conditions, yields, and MCH1R binding affinities for **1a**–**e**

Entry	Substrate[a]	Microwave condition	Product (yield)	MCH1R K_i[b] (μM)
1	 **5a**[5]	200 °C, 600 s, AcOH	 **1a** (44%)	1.4
2	 **5b**[6]	200 °C, 300 s, AcOH	 **1b** (89%)	3.0
3	 **5c**[6]	200 °C, 300 s, AcOH	 **1c** (65%)	3.0
4	 **5d**[7]	220 °C, 200 s, AcOH	 **1d** (63%)	0.077
5	 **5e**[8]	200 °C, 300 s, AcOH	 **1e** (49%)	1.8

[a] Substrates **5a**–**e** were prepared according to literature procedures (Refs. 5–8).
[b] MCH1R K_i was determined in a receptor binding assay (Ref. 10).

should be noted that conventional heating proved ineffective for the preparation of **1a**–**e**, for example, treatment of **4** with **5c** in AcOH at reflux (120 °C) for 15 h did not yield any detectable amount of target compound **1c**. In contrast, good to excellent yields (44–89%) of target compounds **1a**–**e** were obtained via condensation of **4** with α-heteroarylamines **5a**–**e** (prepared according to literature procedures[5–8]) under microwave conditions (AcOH, 200–220 °C, 200–600 s).[9] Also shown in Table 1 are the MCH1R binding affinities (K_i's) for **1a**–**e**.[10] Compounds **1a**–**e** displayed low to sub-micromolar K_i's, with imidazo-pyrimidinone **1d** being the most potent ($K_i = 0.077$ μM).

In summary, an efficient microwave assisted condensation of α-heteroarylamines with 3-dimethylamino-2-aryl-propenoates has been developed to synthesize various fused bi-heterocyclic compounds including isothiazolo-, thiazolo-, imidazo-, and pyrimido-pyrimidinones as novel MCH1R antagonists.

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9. *Representative microwave procedure*: A mixture of ethyl 3-(dimethylamino)-2-(3-methoxy-4-(2-(pyrrolidin-1-yl)ethoxy)-phenyl)acrylate (**4**) (154 mg, 0.42 mmol) and 5-(4-chlorophenyl)-1*H*-imidazol-2-amine (**5d**) (82 mg, 0.42 mmol, prepared according to Ref. 7) in AcOH (0.33 ml) was heated at 220 °C for 200 s in an Emrys optimizer. The reaction mixture was then neutralized with 1% KOH in MeOH to pH ~7. The solvent was evaporated and the residue was purified using reverse phase prep-HPLC (10–90% CH_3CN/H_2O with 0.05% TFA) to give 2-(4-chlorophenyl)-6-(3-methoxy-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-imidazo[1,2-*a*]pyrimidin-5(1*H*)-one (**1d**) as a TFA salt (154 mg, yield 63%). ^{1}H NMR (DMSO-d_6) δ 10.00 (br s, 1H), 8.52 (s, 1H), 8.44 (s, 1H), 8.21 (d, 2H, $J = 9.0$ Hz), 7.75 (d, 2H, $J = 8.4$ Hz), 7.61 (d, 1H, $J = 2.4$ Hz), 7.53 (m, 1H), 7.32 (d, 1H, $J = 5.4$ Hz), 4.52 (t, 2H, $J = 5.0$ Hz), 4.07 (s, 3H), 3.82–3.90 (m, 4H), 3.39 (m, 2H), 2.27 (m, 2H), 2.12 (m, 2H). MS(ESI) m/z 465.2 [$(M+H)^+$].
10. *MCH1R K_i determination*: Membranes prepared from CHO cells that express human MCH1R (0.1 mg/ml final) were incubated with wheatgerm–agglutinin (WGA) coated SPA beads (1 mg/ml final, Amersham Biosciences, Piscataway, NJ) in an assay buffer (25 mM HEPES, 10 mM NaCl, 10 mM $MgCl_2$, 5 mM $MnCl_2$, 0.1% BSA pH 7.4) for 5 min on ice and subsequently washed two times in an assay buffer. Test compound (5 μl) prepared in DMSO, DMSO (vehicle) or MCH (2.5 μM final—used to quantify the non-specific signal) were mixed with 45 μl assay buffer in 96-well assay plates (Corning #3604). Bead/membrane mixture (100 μl) was added to the compounds followed by 50 μl of [^{125}I]-MCH (0.5 nM final, Perkin Elmer, Boston, MA). The assay plates were shaken for 5 min on a plate shaker and then incubated for 2 h. Binding of [^{125}I]-MCH to the bead/membrane mixture was detected using a Microbeta Trilux^{TM} scintillation counter (Perkin Elmer). The data were fit to a one-site competition binding model for IC_{50} determination using the program GraphPad Prism (GraphPad Software, Inc., San Diego, CA) and K_i values were calculated using the Cheng–Prusoff equation. All K_i's represent the average of two or more determinations. The standard deviations were no greater than 30% from the mean.