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Design and synthesis of 3-arylpyrrolidine-2-carboxamide derivatives as melanocortin-4 receptor ligands

Joe A. Tran,[a] Fabio C. Tucci,[a,†] Melissa Arellano,[a] Wanlong Jiang,[a] Caroline W. Chen,[a] Dragan Marinkovic,[a] Beth A. Fleck,[b] Jenny Wen,[c] Alan C. Foster[d] and Chen Chen[a,*]

[a]*Department of Medicinal Chemistry, Neurocrine Biosciences, Inc., 12790 El Camino Real, San Diego, CA 92130, USA*
[b]*Department of Pharmacology, Neurocrine Biosciences, Inc., 12790 El Camino Real, San Diego, CA 92130, USA*
[c]*Department of Preclinical Development, Neurocrine Biosciences, Inc., 12790 El Camino Real, San Diego, CA 92130, USA*
[d]*Department of Neuroscience, Neurocrine Biosciences, Inc., 12790 El Camino Real, San Diego, CA 92130, USA*

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Abstract—Based on 3-phenylpropionamides, a series of 3-arylpyrrolidine-2-carboxamide derivatives was designed and synthesized to study the effect of cyclizations as melanocortin-4 receptor ligands. It was found that the 2*R*,3*R*-pyrrolidine isomer possessed the most potent affinity among the four stereoisomers.

The melanocortin-4 receptor (MC4R) is a member of the G-protein-coupled receptor (GPCR) superfamily and plays an important role in regulating feeding behavior.[1] While MC4R agonists are pursued for reducing body weight,[2] MC4R antagonists have been shown to reverse both lean body mass loss and food intake reduction in animal models, suggesting their potential to be used for the treatment of cancer cachexia.[3,4] In addition, recent studies have shown that selective MC4R antagonists may also be useful in the treatment of anxiety and depression.[5]

We have previously identified a series of α-benzylpropionylpiperazines, such as **2a** (K_i = 26 nM, Fig. 1), as MC4R antagonists.[6] Compound **2a** is more potent than the 3-phenylpropionyl analog **1** (K_i = 74 nM)[7] but similar to the phenylalanine **2b**, suggesting a small role of the methyl group in **2a** or the amino moiety in **2b**. In contrast, the α,α-dimethyl analog **3** (K_i = 810 nM) displayed a much lower binding affinity than its monomethyl analog **2c** (K_i = 31 nM), indicating a strong steric effect caused by the additional α-methyl moiety on the 3-phenylpropionyl group. Therefore, we can conclude that the position and orientation of the substituted phenyl ring in a low-energy conformation is critical for high potency. When a nitrogen-containing moiety is used to replace the α-methyl group of **2a**, binding affinity is further improved.[8] For example, the acetamido **4** (K_i = 1.9 nM) is significantly more potent than **2a**. However, this improvement could result from the direct interaction of the acetyl group with the receptor. Since a small change in this region of the molecule has a large impact on its biological activity, we decided to synthesize constrained derivatives of **4** by cyclizing the acetamide moiety to lock the location of the important 4-chlorophenyl group as shown in Figure 2. Here we report the design, synthesis and structure–activity relationship study of these compounds.

2-Oxo-4-(4-chlorophenyl)methyloxazolidine-4-carboxylic acid **13** was synthesized using a procedure similar to that described by Qi et al. from 4-chlorophenylalanine **8**.[9] This was converted to the corresponding acid chloride **14**, which was coupled with the phenylpiperazine **15a**[10] to afford the desired product **6** after deprotection with HCl in methanol (Scheme 1).

Ethyl 5-oxo-3-(4-chlorophenyl)pyrrolidine-2-carboxylate **18** was synthesized using a procedure similar to that

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* Corresponding author. Tel.: +1 858 617 7600; fax: +1 858 617 7602; e-mail: cchen@neurocrine.com
† Present address: Department of Medicinal Chemistry, Tanabe Research Laboratories, U.S.A., Inc., 4540 Towne Centre Ct., San Diego, CA 92121, USA.

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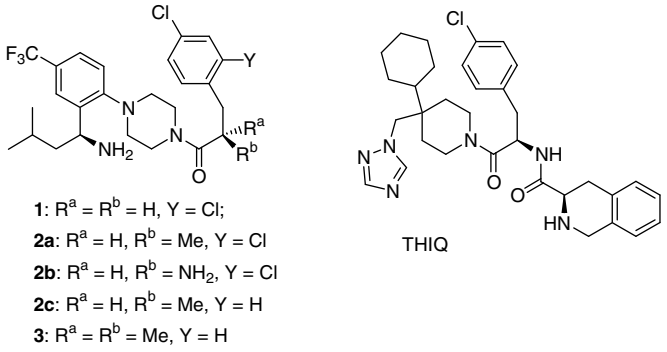


Figure 1. Chemical structures of previously reported MC4R antagonists **1**–**3** and agonist THIQ.

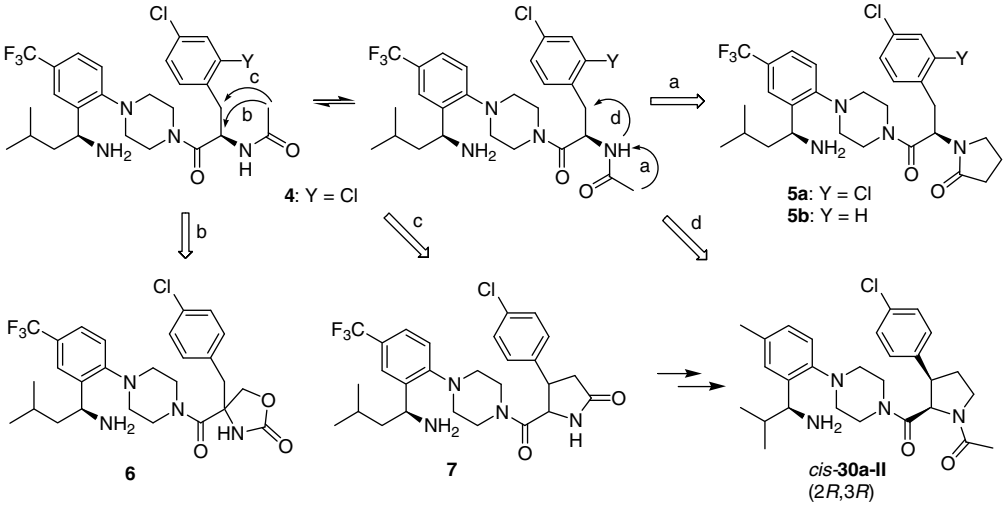
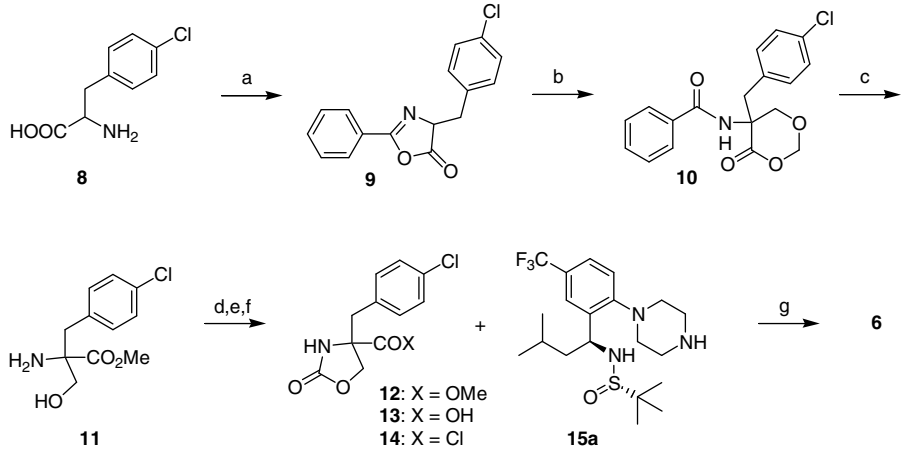


Figure 2. Strategy for constrained analogs of MC4R antagonists **4**.



Scheme 1. Reagents and conditions: (a) i—PhCOCl/NaOH/acetone/H_2O/rt, 2 h; ii—Ac_2O/80 °C, 20 min, 63%; (b) CH_2O/Py/H_2O/rt, 16 h, 63%; (c) i—5 N HCl/reflux, 3 h; ii—H_2SO_4/MeOH/rt, 8 h; (d) $COCl_2$/DMAP/DCM/0 °C to rt, 1.5 h, 60%, three steps; (e) LiOH/dioxane/65 °C, 8 h, 46%; (f) $(COCl)_2$/DMF(cat.)/DMC/rt, 1 h; (g) i—Et_3N/DCM/rt, 8 h; ii—HCl/MeOH/rt, 1 h, 4% for 3 steps.

described by Soloshonok.[11] This was then converted to compound **7** as shown in Scheme 2.

2*E*-3-Arylpropenals **20** were prepared from 4-iodobenzenes as described by Haemers et al.[12] Cyclization of **20** with acetamidomelonate gave the intermediate **21**, which was hydrolyzed, followed by decarboxylation and Boc-protection to afford 1-*tert*-butoxycarbony-3-(4-chlorophenyl)pyrrolidine-2-carboxylic acid **22** and **23a**.[13] Coupling reactions of **22** and **23a** with phenyl-