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Synthesis and characterization of pyrrolidine derivatives as potent agonists of the human melanocortin-4 receptor

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Abstract—A series of *trans*-4-phenylpyrrolidine-3-carboxamides were synthesized and characterized as potent ligands of the human melanocortin-4 receptor. Interestingly, a pair of diastereoisomers **20f-1** and **20f-2** displayed potent functional agonist and antagonist activity, respectively. Thus, the 3*S*,4*R*-compound **20f-1** possessed a K_i of 11 nM and an EC_{50} of 24 nM, while its 3*R*,4*S*-isomer **20f-2** exhibited a K_i of 8.6 and an IC_{50} of 65 nM. Both compounds were highly selective over other melanocortin receptor subtypes. The MC4R agonist **20f-1** also demonstrated efficacy in diet-induced obese rats.

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 and other biological functions.[1] Therefore, MC4R agonists have been extensively studied in efforts to discover small molecules for the treatment of obesity.[2] Several MC4R agonists from different chemical classes have been reported.[3] Recently, a series of pyrrolidines exemplified by **1** (Fig. 1) has been characterized as potent and selective MC4R agonists.[4] In our efforts to find orally active small molecule MC4R antagonists, we have discovered a series of piperazinebenzylamines attaching a 3-phenylpropionyl group (**2**) as potent and selective MC4R antagonists.[5] Introducing a small group next to the carbonyl moiety increases the binding affinity of **2a** (K_i = 74 nM). Thus the *R*-methyl derivative **2b** displayed a K_i of 26 nM, while the pyrrolidinone **2c** (K_i = 4.5 nM) had over 15-fold improvement over **2a**, demonstrating a role of a small group at this site. To further reduce flexibility of the molecule, we synthesized a *trans*-pyrrolidine **3** (K_i = 610 nM), which exhibited only moderate binding affinity. We then embarked upon an SAR study around this core structure, and here we report the characterization of this series of compounds as potent agonists and antagonists of the human MC4 receptor.

A set of close analogs of **3** were synthesized as shown in Scheme 1. Coupling reactions of the *trans*-*N*-benzylpyrrolidinecarboxylic acids **5** with the benzylamine **4**[6] afforded the amides **6**. Selective deprotection of **6b** using HCl in methanol gave the Boc-derivative **8**. Treatment of **6** with trifluoroacetic acid selectively removed the Boc-group to afford the key intermediates **7**. Acylation of **7b** provided, after a HCl/MeOH treatment, the amides **9a**–**c**, while treatment of **7b** with methanesulfonyl chloride in the presence of triethylamine gave the sulfonamide **10**. Reductive alkylations of **7** with carbonyl compounds afforded the tertiary amines **3**, **11a**–**c**, and **12**, after removing the sulfinyl protecting group. The aniline **11d** was obtained by the reaction of **7b** with bromobenzene under palladium-catalyzed conditions,[7] followed by HCl in methanol at room temperature for 1 h. For the compounds with a Boc-protected amine

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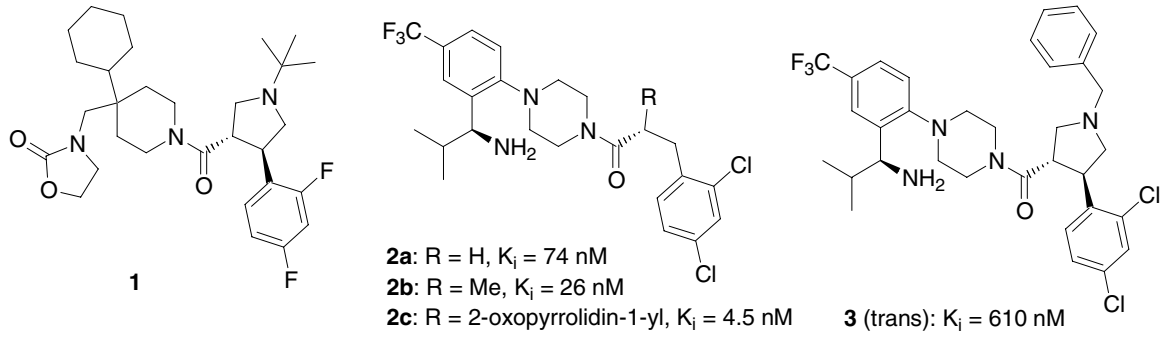
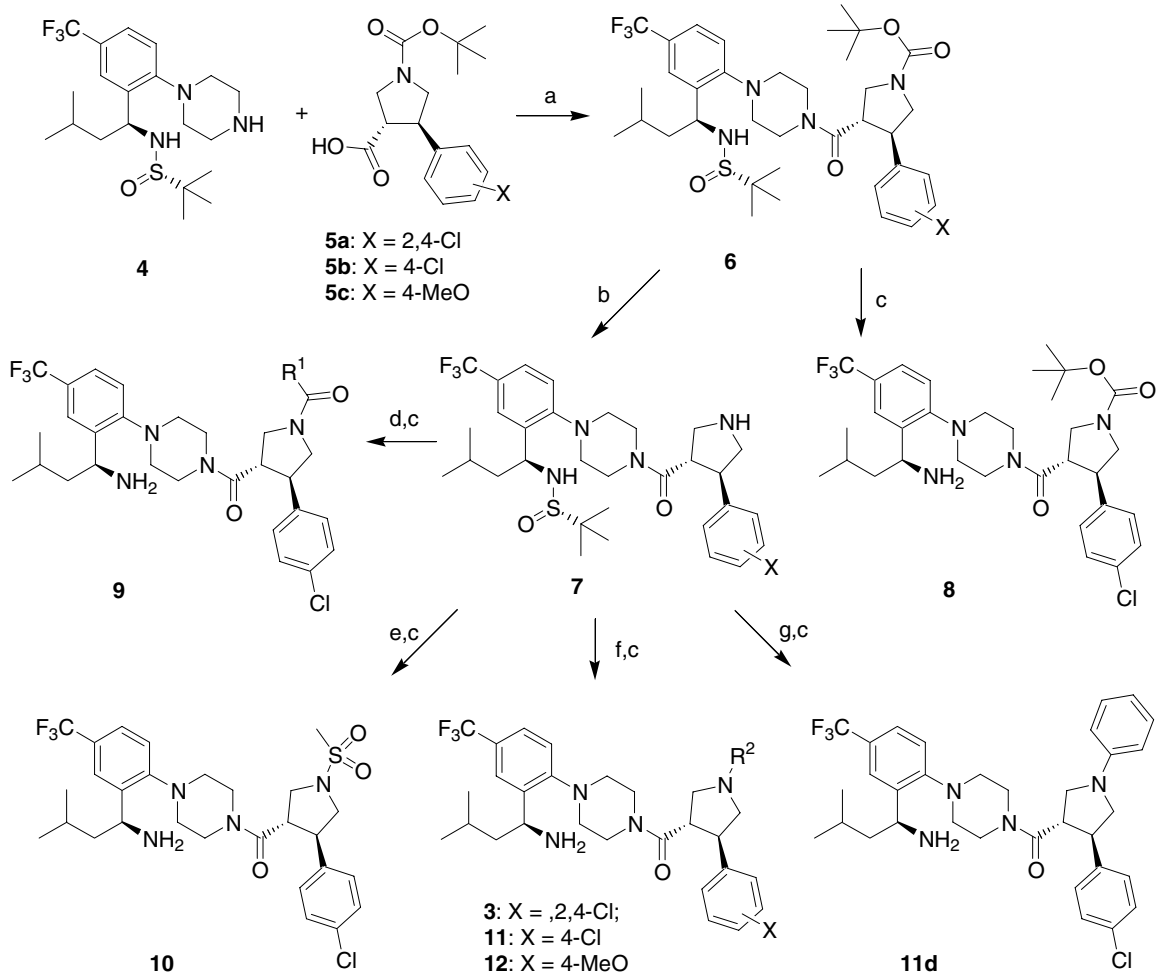


Figure 1. Chemical structures of pyrrolidine agonists and piperazinebenzylamine antagonists of the MC4 receptor.



Scheme 1. (a) EDC/HOBt/$NaHCO_3$/DMF/CH_2Cl_2/rt, 16 h, 87% for **6b**; (b) TFA/CH_2Cl_2/rt, 1 h, quantitative; (c) HCl/MeOH/rt, 1 h; (d) R^1COCl/Et_3N/THF/rt, 8 h, >30%, or $BocNHCH_2COOH$/EDC/HOBt/$NaHCO_3$/CH_2Cl_2/rt, 10 h, then TFA/CH_2Cl_2/rt, 1 h, 54% for **9c**; (e) $MeSO_2Cl$/Et_3N/THF/rt, 1 h; (f) carbonyl compound/$NaBH(OAc)_3$/HOAc/CH_2Cl_2/rt, 8 h, 17% for **11a**; (g) C_6H_5Br/$Pd(OAc)_2$/(±)BINAP/Cs_2CO_3/dioxane/100 °C, 24 h, 7.4%.

such as **9c** and **11c**, a TFA treatment was required before purification using an HPLC instrument.[8]

To obtain the two single stereoisomers of pyrrolidine **5b**, we first coupled (4*R*)-benzyl-2-oxazolidinone (*R*-**13**) with 4-chlorocinnamic acid to give the oxazoline **14**, which was cyclized with *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine to provide the pyrrolidinecarboxamides **15**, which were separated by chromatography into the two diastereoisomers **15-1** and **15-2** (Scheme 2).[9] The absolute stereochemistry of **15–2** was resolved by X-ray crystal structure determination (Fig. 2a). The crystal structure of *S*-benzyloxazolinone **16-1** was also obtained using a similar process from (4*S*)-benzyl-2-oxazolidinone to confirm the stereochemistry of **15-1** (Fig. 2b).[10] Debenzylation of **15-1** or