Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 6825–6831
Bioorganic & Medicinal Chemistry Letters

Synthesis and characterization of *trans*-4-(4-chlorophenyl) pyrrolidine-3-carboxamides of piperazinecyclohexanes as ligands for the melanocortin-4 receptor

Caroline W. Chen,[a] Joe A. Tran,[a] Beth A. Fleck,[b] Fabio C. Tucci,[a,†] Wanlong Jiang[a] 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*

Received 25 July 2007; revised 5 October 2007; accepted 8 October 2007
Available online 17 October 2007

Abstract—A series of *trans*-*N*-alkyl-4-(4-chlorophenyl)pyrrolidine-3-carboxamides of piperazinecyclohexanemethylamines was synthesized and characterized for binding and function at the melanocortin-4 receptor (MC4R), and several potent benzylamine derivatives were identified. Compound **18v** was found to bind MC4R with potent affinity (K_i = 0.5 nM) and high selectivity over the other melanocortin subtypes and behaved as a functional antagonist (IC_{50} = 48 nM).

The melanocortin-4 receptor (MC4R) is a member of the G-protein-coupled receptor superfamily and plays an important role in biological functions, including regulation of feeding behavior.[1] MC4R agonists have been extensively studied in an effort to discover small molecules for the treatment of obesity,[2] and several small molecule MC4R agonists from different chemical classes have been reported.[3] MC4R antagonists, on the other hand, have been shown to reverse lean body mass loss and increase food intake in animal models of cachexia, suggesting potential in cancer cachexia treatment.[4,5]

Pyrrolidine derivatives were first reported by Ujjainwalla as potent and selective MC4R agonists.[6] An example of this chemical class is compound **1b**, which has a binding IC_{50} of 14 nM and a functional EC_{50} of 2 nM (Fig. 1). This functional activity is similar to that reported for THIQ **1a**.[7] One advantage of compound **1b** is its pyrrolidine structure. This structure is much different than many reported small molecule MC4R agonists, such as **1a**, in which a Tic-(4-Cl)Phe dipeptide is required as an 'address element'.[2] We have recently shown that by combining the *trans*-4-arylpyrrolidine-3-carbonyl moiety of **1b** with the piperazinebenzylamine *N*,*N*-dimethylaminopropionamide of the antagonist **2**, potent MC4R agonists have been identified from the resulting compounds. For example, **3** (K_i = 4.7 nM) possesses an EC_{50} value of 16 nM with intrinsic activity (IA) of 102% relative to the endogenous ligand α-MSH.[8] We have also previously reported that the piperazinecyclohexanes with the Tic-(4-Cl)Phe dipeptide are MC4 agonists and can be converted into functional antagonists by replacing the dipeptide. Thus, **4** is a potent agonist (K_i = 16 nM, EC_{50} = 33 nM, IA = 96%),[9] while the β-Ala-(2,4-Cl)Phe analog **5a** is a functional antagonist (K_i = 8.8 nM, IC_{50} = 260 nM).[10] Like the amide **5a**, the benzylamine **5b** (K_i = 18 nM) also possesses potent binding affinity.

Because of the success in converting antagonist **2** into agonist **3**, we were interested in the pharmacological properties of compounds derived from the combination of the left-side of compound **4** with the pyrrolidine moiety of **1b**. Here we report the synthesis and characterization of *trans*-4-(4-chlorophenyl)pyrrolidine-3-carboxamides of 1-(1-piperazine)cyclohexanemethylamine derivatives **7**–**22** as MC4R ligands.

Keywords: Synthesis; Pyrrolidine; Melanocortin-4 receptor; Agonist; Antagonist; Structure–activity relationship.
* Corresponding author. Tel.: +1 858 617 7600; fax: +1 858 617 7967; 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.

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.10.032

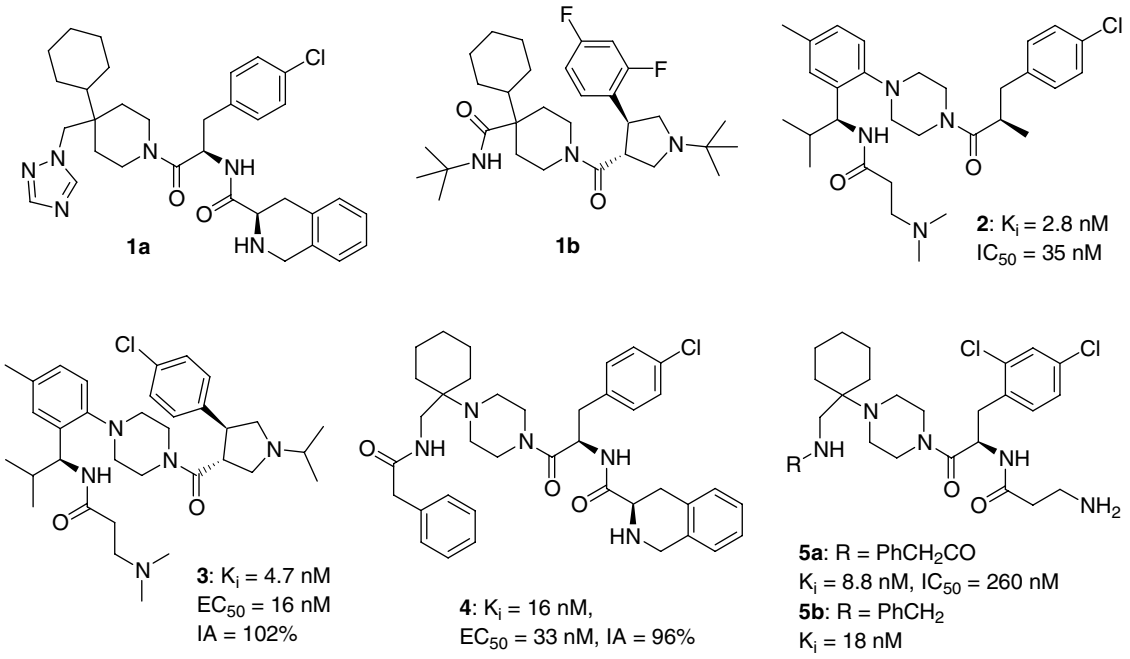


Figure 1. Chemical structures of some MC4R agonists and antagonists related to this study.

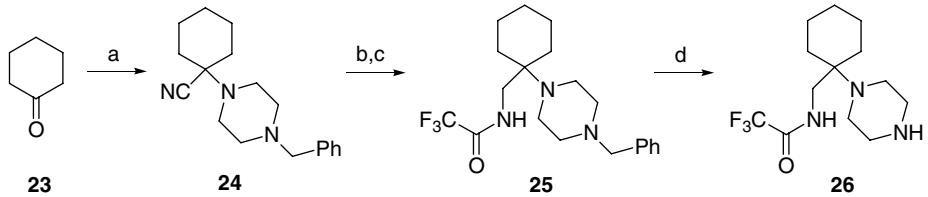
The core structure of 1-trifluoroacetamidomethyl-1-(1-piperazine)cyclohexane **26** was synthesized as shown in Scheme 1. A Strecker reaction of cyclohexanone **23** with 1-benzylpiperazine afforded the intermediate **24**, which was reduced with lithium aluminumhydride, followed by a treatment with trifluoroacetic anhydride to provide the protected diamine **25**. Debenzylation of **25** catalyzed by palladium gave the desired amine **26** in a good overall yield.

The *trans*-*N*-isopropyl-4-(4-chlorophenyl)pyrrolidine-3-carboxylic acid **28a** was synthesized from the cyclization of *N*-(methoxylmethyl)-*N*-(trimethylsilylmethyl)isopropylamine **27a** with methyl *trans*-4-chlorocinnamate mediated by trifluoroacetic acid, followed by hydrolysis with lithium hydroxide. Compound **28a** was coupled with the amine **26** to provide the amide **29a**, which was deprotected under basic conditions to give the primary amine **6a** (Scheme 2).

Coupling reactions of **6a** with various carboxylic acids afforded the amides **7**. Similarly, reactions of **6a** with several sulfonyl chlorides gave the sulfonamides **8**. Alternatively, reductive alkylations of **6a** with a variety of aldehydes provided the secondary amines **9**. A reaction of **6a** with 2-vinylpyridine in the presence of acetic acid in ethanol gave the 2-pyridinylethylamine **9r**.

The key intermediate **6b** was synthesized from *N*-(methoxylmethyl)-*N*-(trimethylsilylmethyl)benzylamine **27b** using a procedure similar to that for **6a**. Reductive alkylations of **6b** with benzaldehyde and 4-pyridylcarboxaldehyde afforded the corresponding secondary amines **10a** and **10b**, respectively. Debenzylation of **10a** or **10b** was accomplished using 1-chloroethyl chloroformate to provide the secondary amine **11a** or **11b**. Reductive alkylations of **11a** with several ketones gave the tertiary amines **12** after purification. Reactions of **11a**–**b** with acyl chlorides in the presence of triethylamine resulted in the amides **13** and **15**, respectively. Alternatively, coupling reactions of **11a** with *N*-Boc-amino acids, followed by TFA-treatment, gave the amides **14**. The urea **16** was obtained by a reaction of **11b** with ethylisocyanate, and the sulfonamide **17** was synthesized from methylsulfonyl chloride and **11b** (Scheme 3).

Reductive alkylations of **6a** with various substituted benzaldehydes gave the corresponding benzylamines **18**. The secondary amines **9p** and **18j** were further con-



Scheme 1. Reagents and conditions: (a) 1-Benzylpiperazine/KCN/$Na_2S_2O_5$/H_2O/rt, 18 h, 81%; (b) $LiAlH_4$/Et_2O/rt, 16 h, 93%; (c) $(CF_3CO)_2O$/TEA/DCM/rt, 2 h, 100%; (d) Pd–C/HCO_2NH_4/MeOH, ~100%.