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Bioorganic & Medicinal Chemistry Letters 18 (2008) 1124–1130
Bioorganic & Medicinal Chemistry Letters

Syntheses of tetrahydrothiophenes and tetrahydrofurans and studies of their derivatives as melanocortin-4 receptor ligands

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Received 25 October 2007; revised 28 November 2007; accepted 30 November 2007
Available online 5 December 2007

Abstract—Piperazinebenzylamine derivatives from *trans*-4-(4-chlorophenyl)tetrahydrothiophene-3-carboxylic acid **6** and its *S*-oxide **7** and sulfone **8**, and the tetrahydrofuran **9** and its two regioisomers **11** and **13** were synthesized and studied for their binding affinities at the human melanocortin-4 receptor. These five-membered ring constrained compounds possessed similar or lower potency compared to the acyclic analogs.

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 are able to reverse lean body mass loss as well as food intake reduction in animal models,[3] indicating the potential utility in the treatment of cancer cachexia.[4,5]

In our efforts to find small molecule MC4R antagonists, we have found that a series of acylpiperazinebenzylamines exemplified by *R*-**2** and **3** possess potent binding affinities. In the course of these studies, we have observed that introducing an *R*-configured methyl group at the α-position of the 2,4-dichlorophenylpropionyl moiety of **1** (K_i = 74 nM, Fig. 1) improves its potency (*R*-**2**, K_i = 26 nM) and an *S*-methyl slightly does the opposite (*S*-**2**, K_i = 140 nM).[6] While these steric effects may seem insignificant, incorporating an additional methyl to the α-position of *R*-methyl compound **3** (K_i = 31 nM) reduces its binding affinity over 25-fold (**4**, K_i = 810 nM), demonstrating a profound role of this methyl group. We speculate that in the low-energy conformations of **1**–**4,** the 'correct' positioning of the 4-chlorophenyl ring relative to the benzylamine moiety is critical for the interaction of these molecules with the receptor, and a small group such as methyl at the α-position of the propionyl moiety contributes to the orientation of this 4-chlorophenyl functionality.

To further explore and understand the structure–activity relationship (SAR) of these compounds, we cyclized the α-position of the 4-chlorophenylpropionyl group of **1** to the adjacent benzylic carbon by a five-membered ring, and this eliminated the flexibility of the carbon–carbon bond between the benzylic and α-carbon and limited the free rotation of 4-chlorophenyl functionality. Based on the X-ray crystal structure of the MC4R agonist **5a** (Fig. 1), the 4-chlorophenyl ring is almost parallel to the piperidine plane in the solid state.[7] Preliminary computational studies indicate the position of the 4-chlorophenyl ring favors this conformation in a five-membered constrained system such as tetrahydrofuran. Ujjainwalla has recently reported that a series of pyrrolidines are potent MC4R agonists.[8] For example, compound **5b** has an IC_{50} of 14 nM in a binding assay although this is a functional agonist with an EC_{50} of 2 nM. Here we report the synthesis of tetrahydrothiophenes and tetrahydrofurans and the SAR investigation of their derivatives as MC4R ligands.

Methyl *trans*-4-(4-chlorophenyl)-2,3,4,5-tetrahydrothiophene-3-carboxylate **16** was synthesized based on a

Keywords: Synthesis; Tetrahydrothiophene; Tetrahydrofuran; Melanocortin-4 receptor; Cyclization; Heterocycle; Piperazinebenzylamine; Stereoisomer; Binding affinity.
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doi:10.1016/j.bmcl.2007.11.128

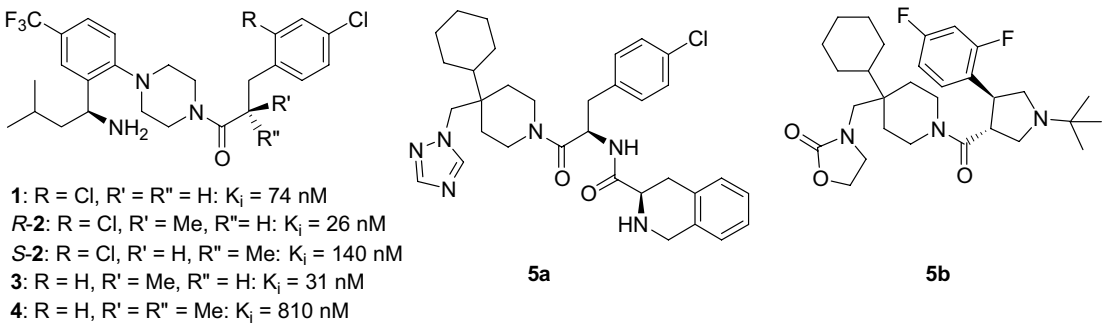


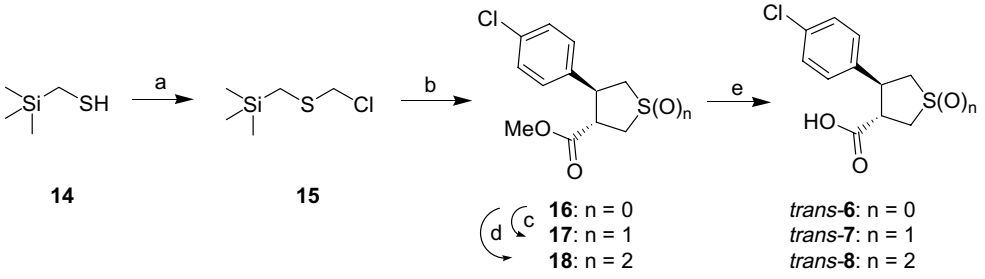
Figure 1. Chemical structures of MC4R ligands **1**–**5**.

procedure similar to that described by Hosomi et al.[9] as shown in Scheme 1. Thus, chloromethyl trimethylsilylmethyl sulfide **15**, prepared from trimethylsilylmethyl sulfide **14**, trioxane, and HCl gas, was cyclized with methyl *trans*-4-chlorocinnamate to give **16**, which was oxidized to the corresponding sulfoxide **17** using hydrogen peroxide in hexafluoroisopropanol.[10] Alternatively, sulfone **18** was obtained from **16** by an oxidation with mCPBA in dichloromethane.[11] Hydrolysis of **16**–**18** under basic conditions (aq NaOH) afforded the corresponding acids **6**–**8** in good yields.[12]

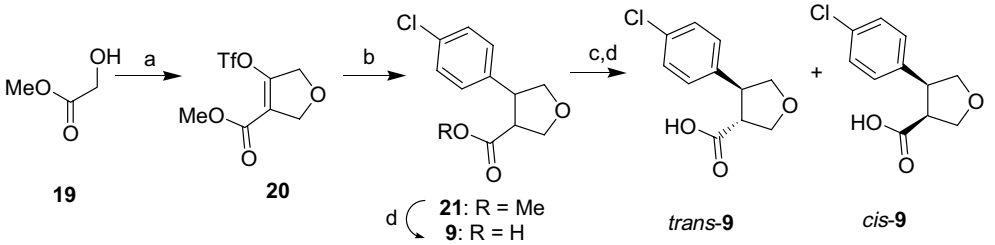
The synthesis of 4-(4-chlorophenyl)-2,3,4,5-tetrahydrofuran-3-carboxylic acid **9** is described in Scheme 2. Methyl 4-oxotetrahydrofuran-3-carboxylate, prepared from methyl acrylate and methyl glycolate **19** under basic conditions,[13] was converted to the triflate **20**, which was subjected to a palladium-catalyzed coupling reaction with 4-chlorophenylboronic acid, followed by a nickel-catalyzed reduction with sodium borohydride in methanol, to give the target ester **21** as a mixture of *trans*- and *cis*-isomers (85:15 ratio), which could be separated by chromatography. Hydrolysis of **21** afforded the corresponding acid **9**.

trans-2-Oxo-4-(4-chlorophenyl)tetrahydrofuran-3-carboxylate **23**[14] was synthesized via ethyl 2-oxo-4-(4-chlorophenyl)-2,5-dihydrofuran-3-carboxylate,[15] which was prepared by cyclization of 4-chlorophenacylbromide **22** with malonic acid monoethyl ester potassium salt in DMSO. Reduction of the resulting intermediate with sodium borohydride, followed by a basic hydrolysis, provided the corresponding acid **10** in a moderate overall yield (Scheme 3).[16]

The synthesis of *trans*- and *cis*-2-(4-chlorophenyl)tetrahydrofuran-3-carboxylic acid **11** is shown in Scheme 4 and uses a procedure similar to that described by Makosza and Judka.[17] Thus, γ-butyrolactone **24** was converted to *tert*-butyl 4-chlorobutyrate **25** using thionyl



Scheme 1. Reagents and conditions: (a) HCl (gas)/trioxane/−10 to 0 °C, 16 h, 53%; (b) methyl *trans*-4-chlorocinnamate/TBAF/THF/rt, 1 h, quantitative; (c) H_2O_2/$(CF_3)_2CHOH$/rt, 1 h, 67 %; (d) mCPBA/CH_2Cl_2/rt, 2 h, 25%; (e) NaOH/THF/MeOH/H_2O, 90–96%.



Scheme 2. Reagents and conditions: (a) i—Methyl acrylate/NaH/DMSO/0 °C to rt, 1 h, 26%; ii—NaH/Tf_2O/Et_2O/0 °C to rt, 1.5 h, 23%; (b) i—4-ClPhB$(OH)_2$/$Pd(PPh_3)_4$/Et_3N/DMF/100 °C, 12 h, 40%; ii—$NiCl_2$/$NaBH_4$/MeOH/0 °C to rt, 6 h, 76%; (c) chromatography separation on silica gel; (d) NaOH/MeOH/65 °C, 3 h, ~97%.