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

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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.
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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

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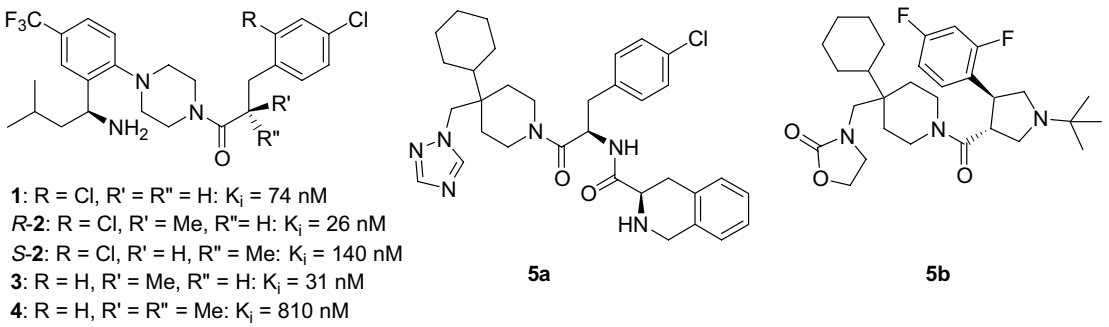


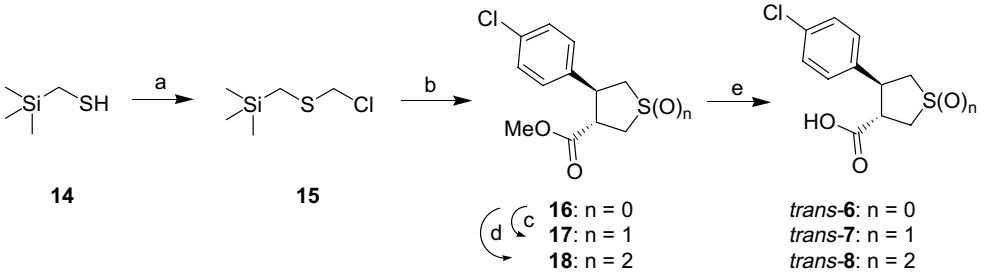
Figure 1. Chemical structures of MC4R ligands **1**–**5**.

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]

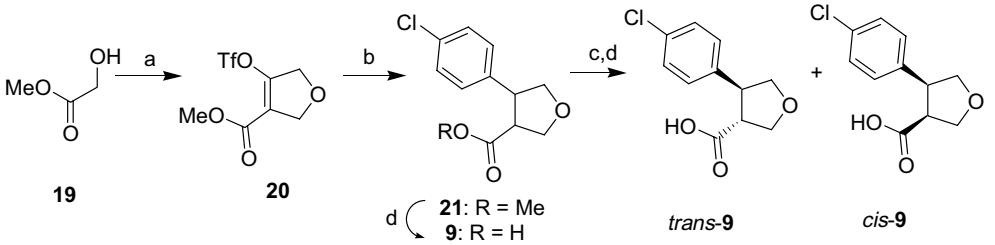
The synthesis of 4-(4-chlorophenyl)-2,3,4,5-tetrahydrofuran-3-carboxylic acid **9** is described in Scheme 2. Methyl 4-oxotetrahydrofuran-3-carboxylate, prepared from methyl acrylate and methyl glycolate **19** under basic conditions,[13] was converted to the triflate **20**, which was subjected to a 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]

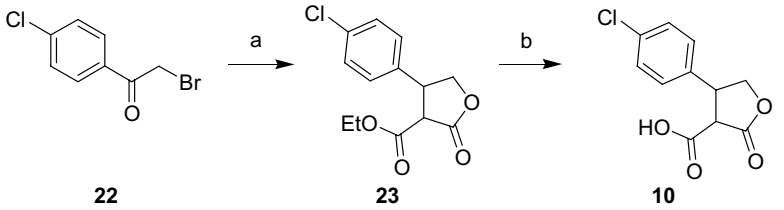
The synthesis of *trans*- and *cis*-2-(4-chlorophenyl)tetrahydrofuran-3-carboxylic acid **11** is shown in Scheme 4 and uses a procedure similar to that described by Makosza and Judka.[17] Thus, γ-butyrolactone **24** was converted to *tert*-butyl 4-chlorobutyrate **25** using thionyl



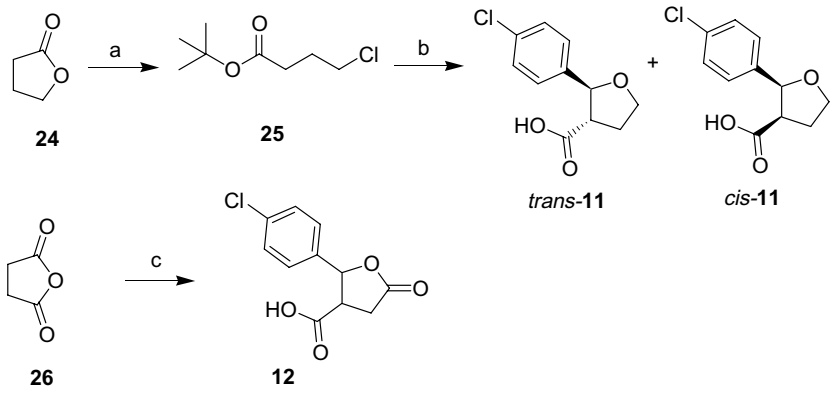
Scheme 1. Reagents and conditions: (a) HCl (gas)/trioxane/−10 to 0 °C, 16 h, 53%; (b) methyl *trans*-4-chlorocinnamate/TBAF/THF/rt, 1 h, quantitative; (c) H_2O_2/$(CF_3)_2CHOH$/rt, 1 h, 67 %; (d) mCPBA/CH_2Cl_2/rt, 2 h, 25%; (e) NaOH/THF/MeOH/H_2O, 90–96%.



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%.



Scheme 3. Reagents and conditions: (a) i—$EtOOCCH_2COOK$/DMSO/rt, 80 min, then NH_4OAc/rt, 8 h; ii—AcOH/$NaBH_4$/0 °C to rt, 3 h; (b) NaOH/MeOH/H_2O/rt, 8 h, 21% overall yield.



Scheme 4. Reagents and conditions: (a) i—$SOCl_2$/$ZnCl_2$/55 °C, 12 h, 74%; ii—*t*-BuOH/Py/rt, 4 h, 25%; (b) i—4-ClC_6H_4CHO/*t*-BuOK/THF/−30 °C, 0.5 h, 15%; ii—Chromatography; iii—TFA/CH_2Cl_2/rt, 1 h, quantitative; (c) 4-ClC_6H_4CHO/NaOAc/toluene/reflux, 10 h, 33%.

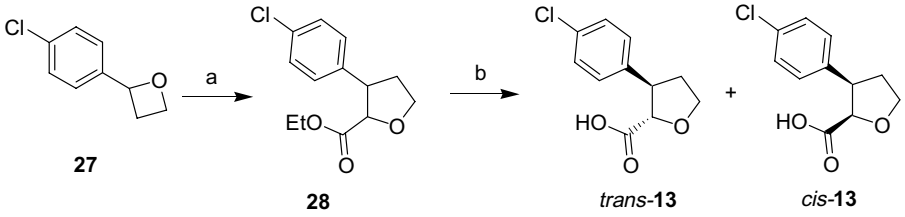
chloride and zinc chloride,[18] which was cyclized with 4-chlorobenzaldehyde promoted by potassium *tert*-butoxide to give a *tert*-butyl ester intermediate as a mixture of *trans*- and *cis*-isomers. These isomers were separated by chromatography on silica gel and then converted to the corresponding acids *trans*-**11** and *cis*-**11** by a trifluoroacetic acid treatment.

2-(4-Chlorophenyl)-5-oxotetrahydrofuran-3-carboxylic acid **12** was obtained by a condensation and cyclization process between 4-chlorobenzaldehyde and succinic anhydride in the presence of sodium acetate.[19] Its ratio of *trans*- and *cis*-isomers was not determined.

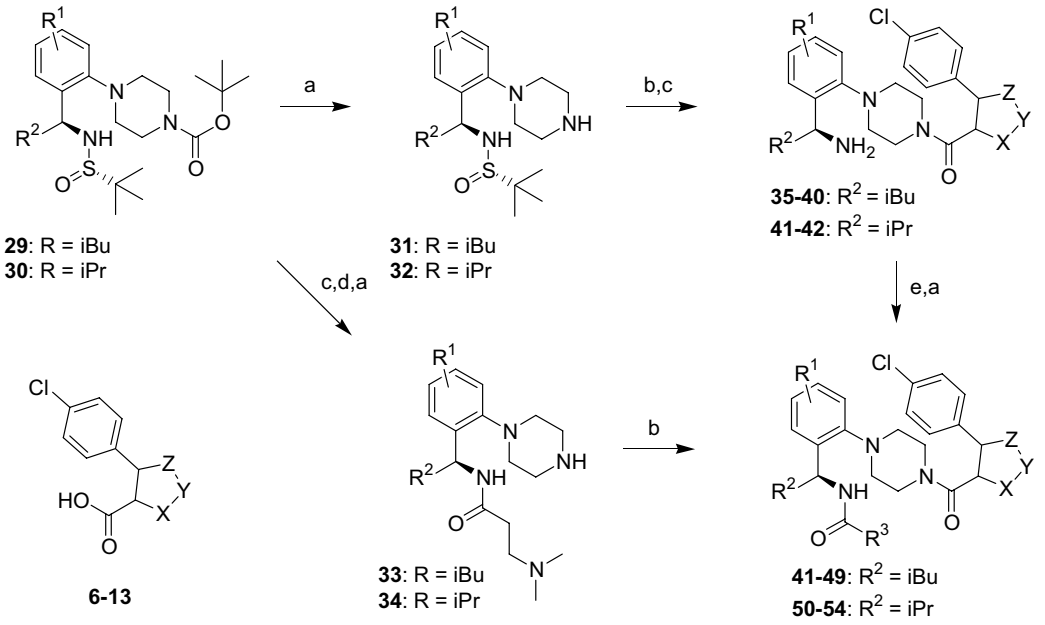
Ethyl 2,5-anhydro-3,4-dideoxy-3-(4-chlorophenyl)pentonate **28** was prepared from 2-(4-chlorophenyloxetane **27** using a procedure similar to that reported by Nozaki and coworkers.[20] Separation by chromatography on silica gel followed by hydrolysis of **28** under basic conditions gave the desired acids *trans*-**13** and *cis*-**13** in good yield (Scheme 5).

The eight heterocyclic acids **6**–**13** were then coupled with several piperazine derivatives **31**–**34** which were obtained from the double-protected precursors **29**–**30**.[21] Selective removal of the Boc group of **29**–**30** gave the piperazines **31**–**32**, which were coupled with the acids **6**–**11** to afford the final products **35**–**42** after an HCl/MeOH treatment to remove the sulfinyl group.[22] Alternatively, selective deprotection of the sulfinyl group of **29**–**30** with HCl/MeOH provided the benzylamines which were coupled with *N*,*N*-dimethyl-β-alanine to give the intermediates **33**–**34** after Boc-deprotection with trifluoroacetic acid. Coupling reactions of **33**–**34** with the acids **6**–**13** afforded the final compounds **41**–**54** after purification. Several amides **43**–**49** were also prepared from **35**–**42** by a coupling reaction with an *N*-Boc amino acid followed by a TFA treatment (Scheme 6).

The binding affinities of the final compounds **35**–**54** were determined in HEK293 cells stably expressing human melanocortin-4 receptors, using [^{125}I]-NDP-MSH as the radiolabeled ligand,[23] and the results are listed in Tables 1 and 2.



Scheme 5. Reagents and conditions: (a) N_2CH_2COOEt/$CuSO_4$/80 °C, 4 h, 80%; (b) i—Chromatography separation on silica gel; ii—NaOH/MeOH/H_2O/rt, 6 h, ~ 90%.



Scheme 6. Reagents and conditions: (a) TFA/CH_2Cl_2/rt, 0.5 h, quantitative; (b) **6**–**13**/EDC/HOBt/Et_3N/DMF/rt, 1–16 h, various yields, conditions were not optimized; (c) HCl/MeOH/rt, 1 h; (d) $Me_2NCH_2CH_2COOH$/EDC/HOBt/Et_3N/CH_2 Cl_2/rt, 8 h, 60–90%; (e) R^3COOH/EDC/HOBt/Et_3N/CH_2Cl_2, rt, 8 h, 20–60%.

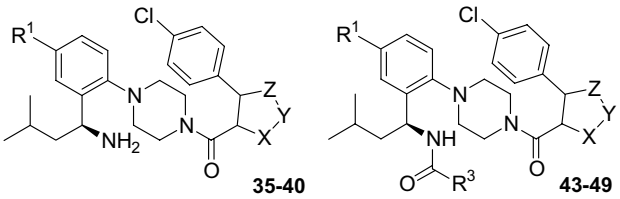
The tetrahydrothiophene *trans*-**35** (K_i = 280 nM) as a pair of diastereoisomers was significantly less potent than the *R*-configured α-methylpropionyl analog **3** (K_i = 31 nM). The corresponding *S*-oxide *trans*-**36** (K_i = 120 nM) as a mixture of *S*- and *R*-isomers was slightly more potent than *trans*-**35**, while the sulfone *trans*-**37** (K_i = 38 nM) was 7-fold better compared to *trans*-**35**, and similar to **3** in binding affinity (Table 1). The tetrahydrofuran (THF) **38** as a *trans*/*cis* mixture (85:15) exhibited similar binding affinity to *trans*-**35**, which also matched with the lactone **39**. The fact that the *trans*-2-(4-chlorophenyl)tetrahydrofuran-3-carboxamide *trans*-**40a** possessed a similar K_i value to its isomeric THF **38** (mainly *trans*-isomer) suggests that the *trans*-THF ring may distort a preferred conformation in which the 4-chlorophenyl ring is parallel to the piperazine plane and opposite to the basic benzylamine based on the X-ray crystal structure of a close analog of **3**.[24] Similar binding affinity was also obtained from the THF *trans*-**40b** with a 4-chlorophenylpiperazine group.

We have previously found that incorporating an amino acid side chain to the benzylamine such as **2** increases potency by 5- to 10-fold.[25] For the current study, adding a flexible amino side chain might refine the relationship between the 4-chlorophenyl group and the basic amine. However, incorporating various amino amides (*trans*-**43a**–**d**) to the benzylamine of tetrahydrothiophene *trans*-**35** had a minimal effect. A similar result (*trans*-**44**, K_i = 230 nM) was also observed for the *S*-oxide *trans*-**35**. For the sulfone *trans*-**37**, this change decreased its binding affinity (*trans*-**45a**–**d**). For the THF analog **38**, however, a 4-fold increase in binding affinity was observed after incorporating an *N*,*N*-dimethyl-β-alanine (**46**, K_i = 71 M). In comparison, the lactone derivatives **47a**–**b** displayed similar binding affinity to their parent **39**.

For the second THF analog *trans*-**40a** with a CF_3-group at the left-side molecule, incorporating a β-alanine had a minimal effect (*trans*-**48a**). However, a 4-fold increase from *trans*-**40b** was observed for *trans*-**48**. The *cis*-**48** possessed a K_i value of 87 nM which was similar to that of *trans*-**48** and the lactone **49**.

The benzylamines **41** (K_i = 790 nM) with an α-isopropyl group had significantly lower affinity than the THF **38** (K_i = 280 nM) as a mixture of 85:15 *trans*-/*cis*-isomers,[26] but incorporating a β-alanine side chain increased its potency by almost 20-fold (**51**, K_i = 40 nM, Table 2). More detailed studies showed that the binding affinity of the *cis*-isomer was not significantly different from that of the *trans*-analog. Thus, *trans*-**51** or *cis*-**51** exhibited a very similar K_i value (30 and 28 nM, respectively). For the THF analogs **42b**, the *trans*-compound was slightly more potent than the *cis*-isomer, and incorporating a β-alanine side chain improved the binding affinity of the *cis*-isomer (*cis*-**42b**, K_i = 2100 nM) by 4-fold (*cis*-**53**, K_i = 480 nM). Similar results were also obtained for the 4-methyl analogs *cis*-**42a** and *cis*-**52** (Table 2). However, for the THF compounds **54**, the *cis*-isomer (*cis*-**54**, K_i = 10 nM) was about 4-fold better than the *trans*-analog (*trans*-**54**, K_i = 43 nM). The overall conformations of these THF stereoisomers were not significantly different except the THF rings (Fig. 2). The individual isomers of the *trans*-sulfone **50** were separated by HPLC and studied for their stereo-effects. Thus, one isomer (*trans*-**50**–**2**, K_i = 37 nM) was 10-fold more potent than the other (*trans*-**50**–**1**, K_i = 380 nM).

Table 1. SAR of compounds **35–40** and **43–49** at *h*MC4R[a]



Compound	R^1	X	Y	Z	R^3	K_i (nM)
trans-**35**	4-CF_3	CH_2	S	CH_2		280
trans-**43a**	4-CF_3	CH_2	S	CH_2	$CH_2CH_2NMe_2$	130
trans-**43b**	4-CF_3	CH_2	S	CH_2	CH_2CH_2NHMe	170
trans-**43c**	4-CF_3	CH_2	S	CH_2	*R*-CH(Me)NH_2	130
trans-**43d**	4-CF_3	CH_2	S	CH_2	CH_2NHMe	250
trans-**36**[b]	4-CF_3	CH_2	SO	CH_2		120
trans-**44**[b]	4-CF_3	CH_2	SO	CH_2	$CH_2CH_2NMe_2$	230
trans-**37**	4-CF_3	CH_2	SO_2	CH_2		38[f]
trans-**45a**	4-CF_3	CH_2	SO_2	CH_2	$CH_2CH_2NMe_2$	170
trans-**45b**	4-CF_3	CH_2	SO_2	CH_2	CH_2CH_2NHMe	190
trans-**45c**	4-CF_3	CH_2	SO_2	CH_2	*R*-CH(Me)NH_2	100
trans-**45d**	4-CF_3	CH_2	SO_2	CH_2	CH_2NHMe	180
38[c]	4-CF_3	CH_2	O	CH_2		280
46[c]	4-CF_3	CH_2	O	CH_2	$CH_2CH_2NMe_2$	71
39[d]	4-CF_3	CO	O	CH_2		260
47a[d]	4-CF_3	CO	O	CH_2	$CH_2CH_2NMe_2$	290
47b[d]	4-CF_3	CO	O	CH_2	$CH_2CH_2NH_2$	180
trans-**40a**	4-CF_3	CH_2	CH_2	O		330
trans-**48a**	4-CF_3	CH_2	CH_2	O	$CH_2CH_2NMe_2$	200
trans-**40b**	4-Cl	CH_2	CH_2	O		280
trans-**48b**	4-Cl	CH_2	CH_2	O	$CH_2CH_2NMe_2$	74
cis-**48b**	4-Cl	CH_2	CH_2	O	$CH_2CH_2NMe_2$	87
49[e]	4-CF_3	CH_2	CO	O	$CH_2CH_2NH_2$	110

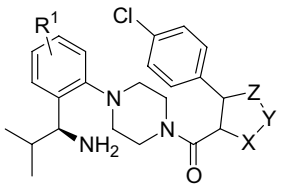
[a] Data are average of two or more independent measurements; the affinity measurements for each compound differed by less than 3-fold, resulting in an average coefficient of variance of 25% for the binding assay K_i values.
[b] The sulfoxide consisted of about 1:1 *S*-and *R*-isomers.
[c] The ratio of *trans*/*cis* was 85:15 based on NMR analysis.
[d] The *trans–cis* isomers are interchangeable.
[e] Stereochemistry was not determined.
[f] Dose-dependently inhibited α-MSH-stimulated cAMP release with an IC_{50} of 690 nM.

Although the absolute stereochemistry was not determined for these compounds, it could be speculated that *trans*-**50–2** had a *R*,*R*-configuration to match with the *R*-configured **2** which is more active than the *S*-isomer **3**.

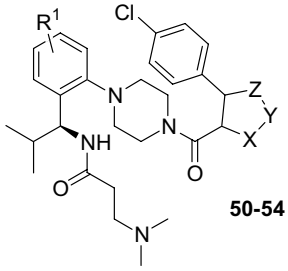
Compounds *trans*-**37** and *cis*-**54** were found to dose-dependently inhibit α-MSH-stimulated cAMP release in the in vitro functional assay with IC_{50} values of 690 and 530 nM, respectively, demonstrating functional antagonism. Based on the above results, it seems that for the α-isobutylbenzylamines with a lipophilic trifluoromethyl group (compounds **35–40a**), incorporating an amino acid side chain has a minimal and even negative effect on their binding affinity. In comparison, the α-isopropylbenzylamines **41–42** are more sensitive to such change. Thus, the K_i values in Table 2 range from 10 to 2100 nM. Further studies on the modification of related compounds will be reported in due course.

In conclusion, we synthesized a series of cyclized analogs of 4-chlorophenylpropionylpiperazine benzylamines and their derivatives, which were subsequently investigated for their interaction with the human melanocortin-4 receptor. These constrained compounds did not show improved binding affinity over the open-chain propionyl analogs. In addition, none of these tetrahydrothiophene and tetrahydrofuran derivatives showed significant cAMP stimulation in cells expressing melanocortin-4 receptor (data not shown). In contrast, 4-(4-chlorophenyl)pyrrolidine-3-carboxamide analogs have been found to be potent MC4R agonists.[27] These SAR results provide further information for the active pharmacophore of small molecule MC4R antagonists and agonists.

Table 2. SAR of compounds **41–42** and **50–54** at *h*MC4R[a]



41-42



50-54

Compound	R^1	X	Y	Z	K_i (nM)
trans-**50–1**	6-F	CH_2	SO_2	CH_2	380
trans-**50–2**	6-F	CH_2	SO_2	CH_2	37
41[b]	6-F	CH_2	O	CH_2	790
51[b]	6-F	CH_2	O	CH_2	40
trans-**51**					30
cis-**51**					28
trans-**42a**	4-Me	CH_2	CH_2	O	410
cis-**42a**					590
cis-**52**	4-Me	CH_2	CH_2	O	120
trans-**42b**	6-F	CH_2	CH_2	O	1100
cis-**42b**					2100
cis-**53**	6-F	CH_2	CH_2	O	480
trans-**54**	4-Me	O	CH_2	CH_2	43
cis-**54**	4-Me	O	CH_2	CH_2	10[c]

[a] Data are average of two or more independent measurements; the affinity measurements for each compound differed by less than 3-fold, resulting in an average coefficient of variance of 25% for the binding assay K_i values.

[b] The ratio of *trans*/*cis* was 85:15 based on NMR analysis.

[c] Dose-dependently inhibited α-MSH-stimulated cAMP release with an IC_{50} of 530 nM.

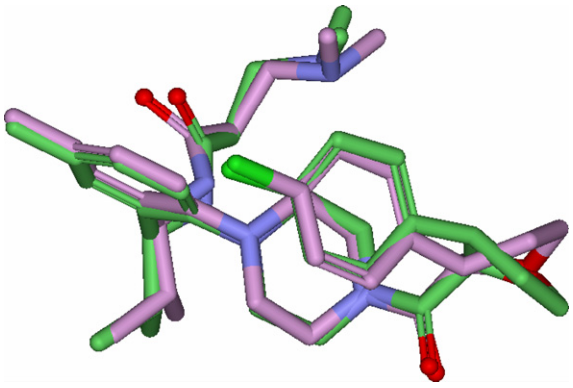


Figure 2. The overlay of the low-energy conformers of *cis*-**54** (green) and *trans*-**54** (violet) indicates no significant difference in conformations between these two stereoisomers. The 4-chlorophenyl group in both isomers is almost parallel to the piperazine ring.

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12. Synthesis of *trans*-4-(4-chlorophenyl)-3-tetrahydrothiophenecarboxylic acid (*trans*-**6**). HCl (g) was bubbled into a mixture of trimethylsilylmethyl sulfide (**14**, 4.98 g, 41.4 mmol) and trioxane (1.28 g, 14.2 mmol) at −10 °C for 80 min. The reaction mixture was kept at 0 °C for 16 h and the organic layer was separated and treated with $CaCl_2$ for 2 h. The crude product was distilled under reduced pressure (∼ 10 mmHg, bp 60 °C) to afford chloromethyl trimethylsilylmethyl sulfide **15** as a colorless oil (3.70 g, 53% yield).
    To a solution of **15** (1.00 g, 5.9 mmol) and *trans*-methyl 4-chlorocinnamate (900 mg, 4.6 mmol) in THF (23 mL) was added TBAF (1.0 M in THF, 6.9 mmol). The reaction was stirred at rt for 16 h, quenched with H_2O, and extracted with EtOAc. The organic phase was washed with 10% aq HCl twice and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give methyl *trans*-4-(4-chlorophenyl)-3-tetrahydro-thiophenecarboxylate *trans*-**16** as a clear oil (1.192 g, ∼80% yield).
    To a mixture of **16** (700 mg, 2.75 mmol) in H_2O/THF/MeOH (14 mL, 14 mL, 10 mL) was added aq NaOH (50%, 0.2 mL). This solution was stirred at rt for 2 h and then concentrated in vacuo. The residue was dissolved in H_2O and extracted with Et_2O. The aqueous phase was acidified with 10% aq HCl and the product was extracted with EtOAc twice. The extract was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford *trans*-4-(4-chlorophenyl)-3-tetrahydrothiophenecarboxylic acid (*trans*-**6**) (625 mg, 96% yield).
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22. Synthesis of 1-[2-[(1*S*)-1-amino-3-methylbutyl]-4-(trifluoromethyl)phenyl]-4-{[*trans*-4-(4-chlorophenyl)tetrahydro-3-thiophenyl]carbonyl}piperazine trifluoroacetate (*trans*-**35**). To a mixture of *trans*-**6** (305 mg, 1.26 mmol) and 1-[2-[(1*S*)-1-(*S*-*tert*-butylsulfinyl amino)-3-methylbutyl]-4-(trifluoromethyl)phenyl]-4-{[*trans*-4-(4-chlorophenyl)tetrahydro-3-thiophenyl]carbonyl}piperazine (**31a**, 480 mg, 1.14mmol) were added HOBt (0.5 M in DMF, 3.1 mL), HBTU (590 mg, 1.90 mmol), and DIEA (0.36 mL, 2.28 mmol). The reaction mixture was stirred at rt for 16 h and then quenched with saturated aq $NaHCO_3$. The product was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4, filtered, and concentrated in vacuo. The product 1-[2-[(1*S*)-1-(*S*-*tert*-butylsulfinylamino)-3-methylbutyl]-4-(trifluoromethyl) phenyl]-4-{[*trans*-4-(4-chlorophenyl)-tetrahydro-3-thiophenyl] carbonyl}piperazine was obtained by flash column chromatography (hexane/EtOAc 9:1–1:1) as a white foam (319 mg, 43 % yield). The above compound in MeOH (5 mL) was treated with HCl (4.0 M in 1,4-dioxane, 0.2 mL) for 0.5 h and the solution was concentrated in vacuo. One-fifth of the product was purified by HPLC to afford the titled compound *trans*-**35** (27.8 mg, 43% yield).
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