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Optimization of a privileged structure leading to potent and selective human melanocortin subtype-4 receptor ligands

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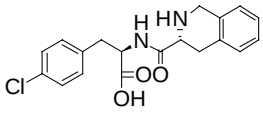
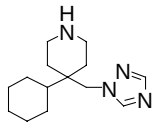
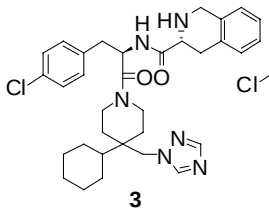
Abstract—Design and synthesis of potent MC4 selective agonists based on cyclohexylpiperidine derived cyclic urea, oxazolidinones, and sulfonamide based privileged structures are disclosed.

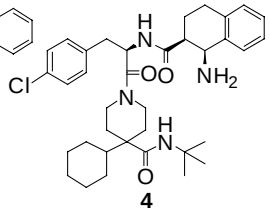
Melanocortin receptors are members of the family of seven-transmembrane G-protein-coupled receptors.[1] To date five different subtypes (MC1R–MC5R) have been identified and cloned. Specifically, the melanocortin-4 receptor (MC4R) is implicated in the regulation of feeding behavior, energy homeostasis, and sexual dysfunction.[1] Peptides melanocyte-stimulating hormone (MSH) and adrenocorticotropic hormone (ACTH) which are produced by cleavage of proopiomelanocortin are the endogenous ligands for these receptors. The relationship of melanocortin with feeding behavior is very well documented by the use of both non-selective peptides and MC4R selective small molecules.[2] Recently, we reported the design of peptidomimetic MC4R ligands based on the privileged structure concept.[3,4] These ligands mimic the His-Phe-Arg-Trp (HFRW) pharmacophore found in MSH and cyclic peptide MT-II.[3] The peptidomimetic contains a dipeptide address element **1** coupled to a privileged structure **2** that incorporates both a hydrophobic group and polar residues. Previously, we disclosed selective MC4R ligands **3** and **4** which lower food intake and body weight in rodents.[3a,4] Additionally, these compounds were shown also to augment erectile activity in rodents.[3a,4]

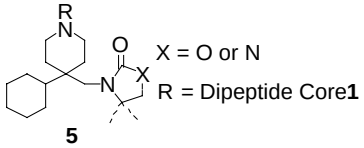
In order to gain further insights into this MC4R privileged structure, we decided to identify a functional mimetic of the highlighted substituents by combining the heterocyclic and lipophilic structural features found in MC4R ligands **3** and **4**. Herein, we disclose our efforts on the synthesis of newer analogs of generic structure **5** inspired by ligands **3** and **4**.[5]











Our initial efforts were focused on optimization of the five-membered heterocyclic ring of **5**. The cyclic ureas **11** and **12** were probed initially and their synthesis was accomplished as shown in Scheme 1. The aldehyde **7** critical to our need was obtained from the alcohol **6**

Keywords: Privileged structure; Melanocortin-4.
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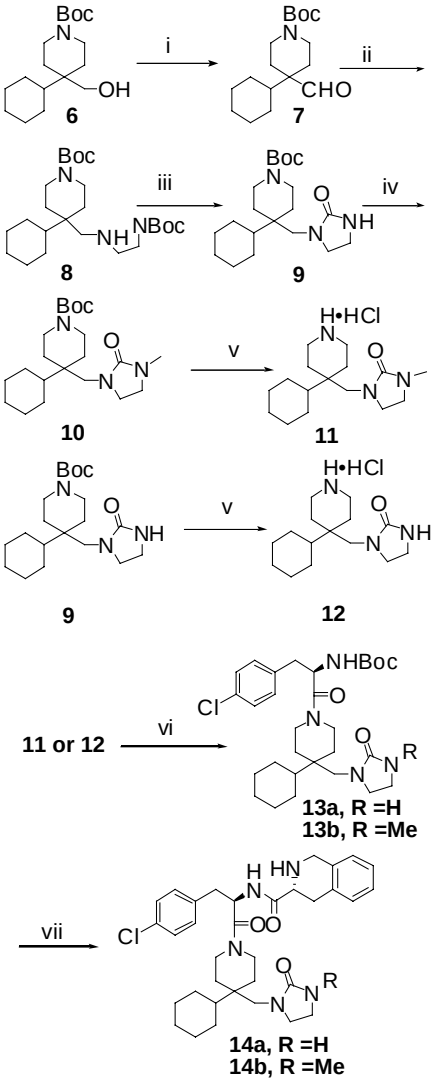
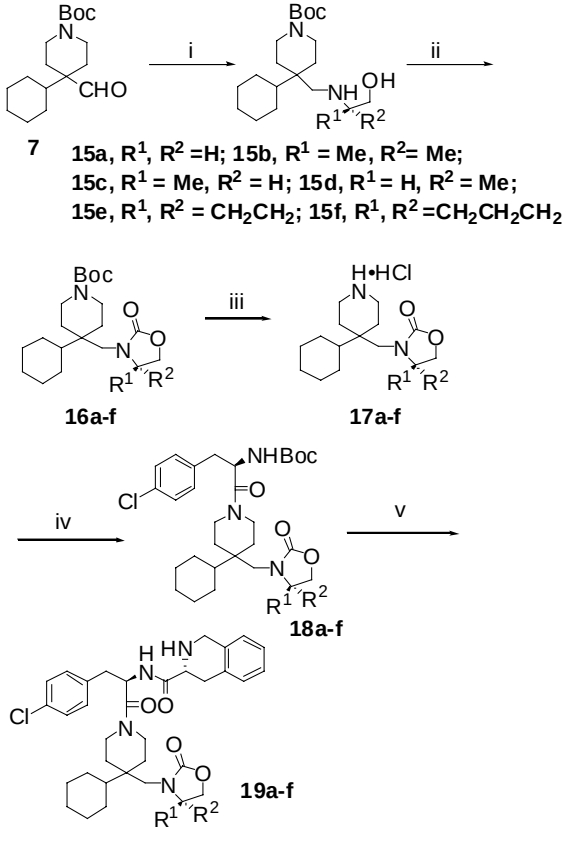


Scheme 1. Reagents and conditions: (i) TPAP/NMO/CH_2Cl_2/4 Å molecular sieves; (ii) a—*N*-Boc-1,2-diaminoethane/toluene/AcOH/reflux using Dean–Stark; b—PtO_2/H_2/AcOH; (iii) NaH/THF/reflux; (iv) NaH/MeI/THF; (v) HCl dioxane/CH_2Cl_2; (vi) *N*-Boc-D-(4-Cl)Phe/EDC/HOBT/NMM/CH_2Cl_2; (vii) a—HCl/dioxane/CH_2Cl_2; b—*N*-Boc-D-Tic/EDC/HOBT/NMM/CH_2Cl_2; c—HCl/dioxane/CH_2Cl_2.

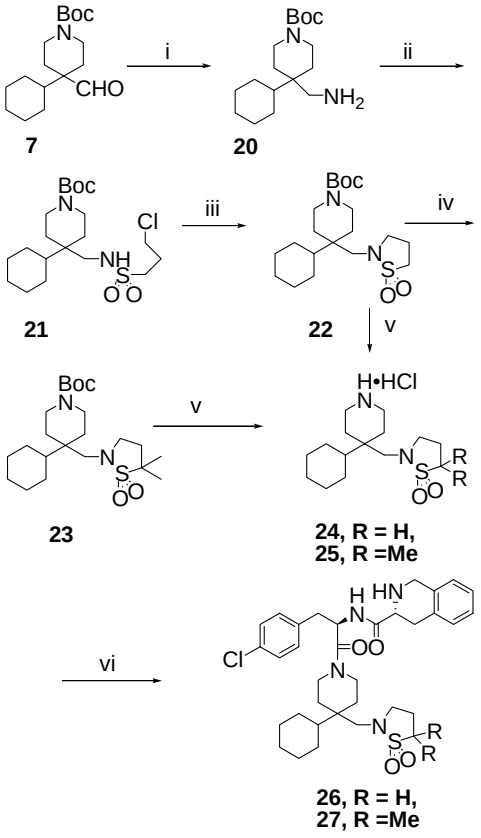
by TPAP oxidation.[6] Reductive amination of aldehyde **7** with *N*-Boc-1-2-diaminoethane to afford **8** was accomplished first by forming the imine (azeotropic removal of water by refluxing in toluene in the presence of a catalytic amount of acetic acid). This was followed by subsequent catalytic hydrogenation (PtO_2) of the intermediate imine in acetic acid. The amine **8** on reaction with NaH in THF underwent cyclization to furnish the cyclic urea **9**, which was alkylated with methyl iodide to furnish the *N*-methyl intermediate **10**. Removal of Boc protection in **9** and **10** with HCl furnished the amines **11** and **12** as their hydrochloride salts. The intermediates **11** and **12** were then coupled with *N*-Boc-D-(4-Cl)Phe under EDC coupling conditions to give the capped peptides **13a** and **13b**. Removal of Boc protection in **13a** and **13b** followed by EDC coupling with *N*-Boc-Tic and subsequent Boc removal furnished **14a** and **14b**.

Preparation of the oxazolidinones **17a–f** (Scheme 2) also began with aldehyde **7**. Reductive amination of **7** with appropriate aminoalcohols under the conditions described for **8** furnished aminoalcohols **15a–f**. The aminols **15a–f** on treatment with triphosgene in the presence of DIEA furnished oxazolidinones **16a–f**. Removal of the Boc group gave the privileged structures **17a–f**. These were then fully elaborated to compounds **19a–f** using the chemistry described in Scheme 1.

Synthesis of cyclic sulfonamide analogs **24** and **25** were deemed important targets to complete the SAR of the privileged structure. Thus, amine **20** was obtained from aldehyde **7** by catalytic reduction of the corresponding oxime intermediate. The amine **20** was converted to the sulfonamide **21** by reaction with 3-chloropropanesulfonyl chloride. Cyclization of **21** to **22** was accomplished by treatment with NaH in DMF. Further alkylation of **22** with methyl iodide resulted in the formation of **23**. Removal of the Boc group in **22** and **23** with HCl gave **24** and **25**, which were transformed to **26** and **27** by following the chemistry described for **14a**,**b** and **19a–f** in Schemes 1 and 2.



Scheme 2. Reagents and conditions: (i) a—aminoalcohol/toluene/AcOH/reflux using Dean–Stark; b—PtO_2/H_2/AcOH; (ii) triphosgene/DIEA/CH_2Cl_2/DMAP; (iii) HCl/dioxane/CH_2Cl_2; (iv) *N*-Boc-D-(4-Cl)Phe/EDC/HOBT/NMM/CH_2Cl_2; (v) a—HCl/dioxane/CH_2Cl_2; b—*N*-Boc-D-Tic/EDC/HOBT/NMM/CH_2Cl_2; c—HCl/dioxane/CH_2Cl_2.



Scheme 3. Reagents and conditions: (i) a—NH_2OH/EtOH; b—PtO_2/H_2/AcOH; (ii) 3-chloropropanesulfonyl chloride/CH_2Cl_2/pyridine; (iii) NaH/DMF/80 °C; (iv) a—LDA/THF/−78 °C; b—MeI; (v) HCl/dioxane/CH_2Cl_2; (vi) as in Schemes 1 and 2.

The cyclic urea, oxazolidinone, and sulfonamide analogs synthesized (Schemes 1–3) were evaluated for MC4 activity in both the competitive binding assay (Table 1) and functional assay (Table 2)[7] as shown below. Surprisingly, the cyclic urea analogs **14a** and **14b** were equipotent in both the binding and functional assays. In the oxazolidinone series analog **19b** with a geminal dimethyl group was at least 5-fold more potent compared to the parent **19a** in the binding assay. This was more or less true also for the mono-substituted analog **19c** (4*R*-methyl). The complementary 4*S*-methyl analog (**19d**) was less potent in comparison to **19c**, suggestive of the fact that there is some chiral recognition at the binding site. Continuing forward the spiro-cyclopropyl and cyclopentyl analogs **19e** and **19f** were as potent as oxazolidinone **19a**. The functional potencies for **19a**–**19f** were similar to binding potencies in that both **19c** and **19b** were better than others in the series. Cyclic sulfonamides **26** and **27** displayed the best potency among the analogs we studied. Thus, they were 4-fold more potent than the unsubstituted oxazolidinone **19a** and cyclic ureas **14a** and **14b** in the MC4 binding assay (Table 1), but in the functional assay (Table 2) oxazolidinone **19a** and cyclic sulfonamides

Table 1. Binding affinity and selectivity for the human MCR[a]

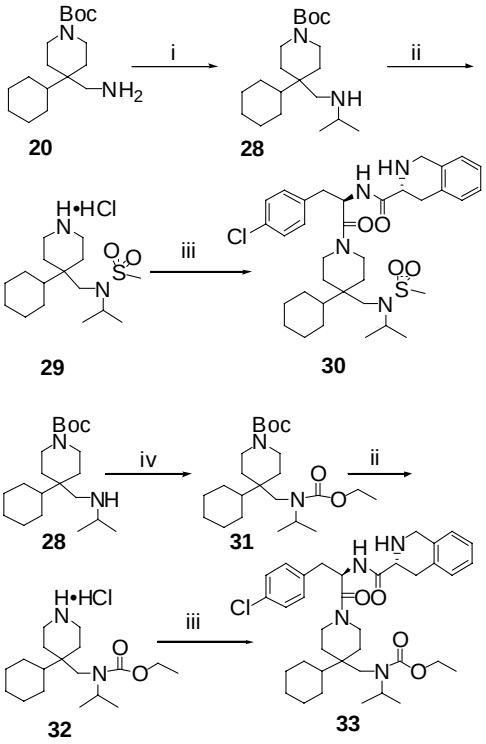
Compound	IC_{50}[b] (nM)			
	MC1BR[c]	MC4R	MC3R	MC5R
3	2063 ± 73	1.2 ± 0.11	761 ± 31	326 ± 9
14a	1100 ± 230	4.8 ± 2.6	520 ± 120	150 ± 25
14b	1800 ± 10	4.3 ± 2	660 ± 38	160 ± 28
19a	2000 ± 250	4.0 ± 2	460 ± 75	180 ± 15
19b	1100 ± 150	0.8 ± 0.31	230 ± 48	80 ± 7
19c	1700 ± 180	1.3 ± 0.12	210 ± 10	110 ± 3
19d	2400 ± 910	4.5 ± 1.5	840 ± 193	220 ± 18
19e	2400 ± 280	4.6 ± 0.24	490 ± 9	170 ± 10
19f	2100 ± 250	7.9 ± 0.06	400 ± 34	210 ± 5
26	1300 ± 260	0.91 ± 0.25	310 ± 64	170 ± 17
27	1200 ± 180	0.62 ± 0.13	760 ± 350	190 ± 30
30	1300 ± 310	2.1 ± 0.89	380 ± 52	200 ± 9
33	1100 ± 60	8.1 ± 2	630 ± 72	630 ± 41

[a] Values represent means ± standard error. All data represent at least three determinations.
[b] Displacement of {^{125}I}-NDP-α-MSH from human receptors expressed in CHO cells.
[c] See Ref. 8.

Table 2. Functional potency and selectivity of compounds at the human melanocortin receptors[a]

Compound	EC_{50}[b] (nM) [% max][c]			
	MC1BR[d]	MC4R	MC3R	MC5R
3	2850 ± 450[95]	2.1 ± 0.2[97]	2487 ± 43[32]	737 ± 65[61]
14a	980 ± 210[39]	16 ± 4.9[82]	880 ± 73[23]	480 ± 150[48]
14b	950 ± 180[43]	16 ± 3.5[88]	1200 ± 190[24]	460 ± 15[63]
19a	1300 ± 190[56]	5.8 ± 1.1[76]	[11]	280 ± 17[48]
19b	550 ± 97[35]	2.4 ± 0.5[82]	[6]	340 ± 12[38]
19c	1300 ± 240[40]	1.3 ± 0.05[68]	370 ± 57[15]	400 ± 35[51]
19d	2100 ± 690[72]	8.6 ± 1.6[90]	640 ± 98[19]	400 ± 23[53]
19e	2600 ± 110[48]	6.1 ± 0.98[68]	990 ± 82[15]	620 ± 46[36]
19f	1700 ± 200[25]	15 ± 1.1[65]	[6]	1200 ± 110[32]
26	680 ± 220[41]	5.3 ± 1.3[67]	540 ± 77[19]	660 ± 85[41]
27	460 ± 260[27]	5.8 ± 1.4[74]	450 ± 21[18]	850 ± 130[39]
30	1500 ± 340[39]	5.6 ± 1.5[86]	590 ± 120[23]	800 ± 100[48]
33	970 ± 200[26]	14 ± 1.8[95]	550 ± 68[37]	3600 ± 930[51]

[a] Values represent means ± standard error. All data represent at least three determinations.
[b] Concentration of compound at 50% maximum cAMP accumulation.
[c] Percentage of cAMP accumulation at 10 μM compound relative to α-MSH.
[d] See Ref. 8.



Scheme 4. Reagents and conditions: (i) acetone/CH_2Cl_2/AcOH/$NaBH(OAc)_3$; (ii) a—CH_2Cl_2/CH_3SO_2Cl/DMAP/DIEA; b—CH_2Cl_2/dioxane/HCl; (iii) as in Schemes 1 and 2; (iv) CH_2Cl_2/EtOCOCl/DIEA/DMAP.

26 and **27** had similar MC4 functional potency. This suggests that 5-membered heterocycles are well tolerated in the binding assay, but there may be some other elements which may also influence functional potency. Furthermore, all analogs (across the series) disclosed herein displayed significant selectivity for MC4 receptors in both binding/functional assays compared to other subtype receptors.

Further probing of the relationship between the substitution on the heterocycle and the binding pocket in sulfonamide **26** and carbamate **19a** led to the synthesis of acyclic analogs **30** and **33**. The synthesis of **30** and **33** was analogous to the chemistry described previously and is shown in Scheme 4. Unfortunately, results from the biology revealed that these compounds were less potent than their corresponding cyclic analogs (Tables 1 and 2) and as a consequence were not pursued further.

In conclusion, design and the synthesis of potent and selective MC4 agonists based on cyclic ureas, oxazolidinones, and cyclic and acyclic sulfonamides privileged structures are disclosed. A methodical study of SAR of the oxazolidinone series led to the identification of 4,4-dimethyl analog (**19b**) and 4*R*-methyl group (**19c**) as potency enhancing motifs. Equally interesting were the sulfonamides **26** and **27**. Further efforts are underway to expand on the scope of these discoveries.

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6. Alcohol **6** was synthesized by following the chemistry described in Ref. 3.
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