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Privileged structure based ligands for melanocortin receptors—4,4-Disubstituted piperidine derivatives

Steven L. Kuklish,* Ryan T. Backer, Karin Briner, Christopher W. Doecke, Saba Husain, Jeffrey T. Mullaney, Paul L. Ornstein, John M. Zgombick, Thomas P. O'Brien and Matthew J. Fisher

Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46258, USA

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Abstract—Homologation and cyclization back to the chiral methine of compound **3** yields achiral 4,4-disubstituted piperidine privileged structures (e.g., **8a**) useful in the construction of melanocortin 4 receptor (MC4R) ligands. The piperidine nitrogen was replaced with carbon, oxygen, sulfur, and sulfone with minor erosion of binding. The methyl cyclohexane substituent was the most potent while significant affinity was still seen for smaller lipophilic groups such as ethyl.

The melanocortin 4 receptor (MC4R) is one of five type I G-protein-coupled receptors (GPCRs) which have the melanocortin peptides α-, β-, and γ-melanocyte-stimulating hormones (MSH) as their endogenous ligands.[1] The MC4R is expressed in the hypothalamus and is thought to regulate a variety of processes including feeding, metabolism, and reproductive behaviors.[2] We have been interested in developing ligands for the melanocortin receptors to facilitate their pharmacological characterization, and our efforts to date have yielded compounds primarily selective for MC4R. The compound series developed thus far have all required a dipeptide address element coupled to a C-terminal privileged structure cap (Fig. 1).[3]

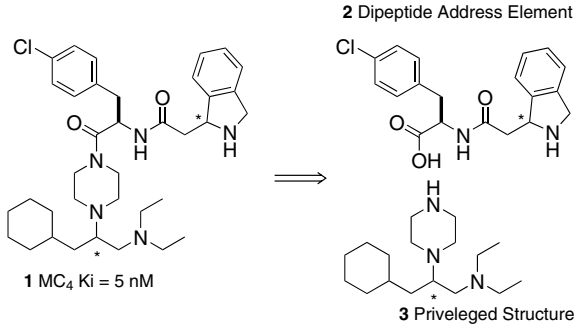

Figure 1.

Pharmacophore requirements for the piperazine-containing subunits have generally included both hydrophobic and polar moieties. We have found that a number of structurally related piperazine-containing moieties afford reasonable activity and a fair degree of interchangeability when attached to the dipeptide address element. Recently, we have reported on several new structurally related families, the latest of which is exemplified by structure **3**.[4,5] This scaffold uses a chiral tertiary carbon atom to link the key lipophilic and polar pharmacophores.

While the activity achieved with these structures has been adequate for pharmacological characterization, the chiral center afforded an unnecessary level of complexity in synthesis. We wondered if this chiral carbon and attached polar moiety could be replaced with a symmetrical subunit that still allowed the desired privileged structure pharmacophores to be presented in a similar orientation. Specifically, we thought that cyclization of the polar residue back to the methine position of the chiral carbon of **3**, affording an achiral 4,4-disubstituted piperidine (**8a**), might provide topography similar to our previously described privileged structures (Fig. 2).

Keywords: Melanocortin; MC4; Privileged structure; G-protein coupled receptors; GPCR.
* Corresponding author. Tel.: +1 317 433 6519; e-mail: Kuklish_steven@lilly.com

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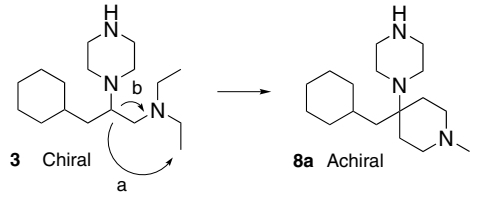
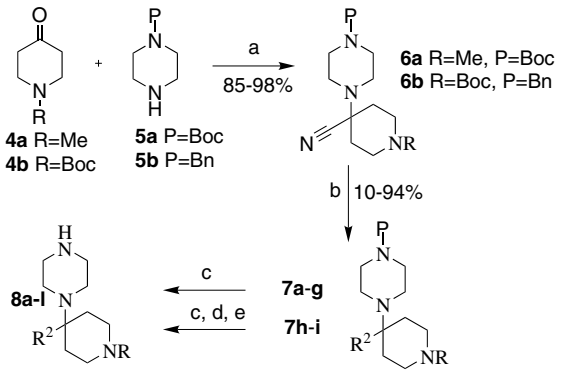


Figure 2. The design strategy to mitigate asymmetry in our previous privileged structure was achieved by the cyclization and homologation, **a** and **b**, respectively.

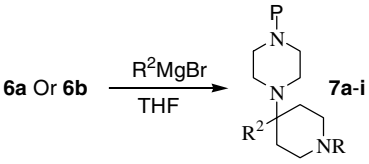
Simple modeling of the 4,4-disubstituted piperidine of **8a** revealed that many of the conformations accessible to **3** remain available to the more constrained 4,4-disubstituted piperidine **8a**. Herein, we report on the reduction of this hypothesis to practice and the continued progress on the preparation and use of novel 4,4-disubstituted piperidine structures in the construction of ligands for the melanocortin receptors.

Preparations of structures **8a**–**l** containing functionalized piperidines are outlined in Scheme 1. Intermediates **6a**, **b** were conveniently prepared from the corresponding protected piperidines **4a**, **b** using a modified Strecker synthesis.[6] Treatment of amino nitrile **6a** with alkyl Grignards gave modest yields (10–50%) of the 4,4-disubstituted piperazines **7a**–**g**.[7,8] The reactions of amino nitrile **6b** with alkyl Grignards were more efficient for the preparation of intermediates **7h** (86% yield) and **7i** (94% yield) (Table 1). Deprotection of the Boc-protected piperazines **7a**–**g** with TFA yielded the *N*-methyl piperidines **8a**–**g**. Piperidine intermediates **7h** (R = Boc) and **7i** (R = Boc) were deprotected with TFA, then sulfonylated, acylated or reductively aminated to yield the corresponding benzyl-protected, functionalized 4,4-disubstituted piperidines. The functionalized piperidines were then debenzylated under palladium-mediated hydrogenolysis to yield structures **8h**–**l**. Cyclic ketones **9a**–**c** were transformed in a similar manner as outlined for the above piperidine ketones (Scheme 2). Notably, reaction of the amino nitrile with an alkyl Grignard was again more efficient (91–98% in route to **10a**–**c**) than observed for compounds **7a**–**g**. Compounds that contain a basic piperidine nitrogen such as **7a**–**g** were typically

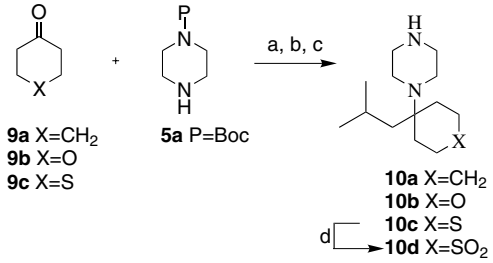


Scheme 1. Reagents: (a) TMSCN, ZnI_2; (b) R^2MgBr, THF; (c) TFA, DCM; (d) One of the following; MsCl, Alkyl-COCl, Alkyl-COH and $NaBH_4$; (e) Pd/C, H_2, EtOH.

Table 1.



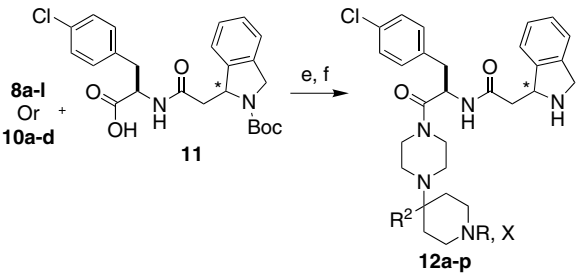
Compound	P	R	R^2	Compound
6a	Boc	Me	Ph	**7a**
6a	Boc	Me	Bn	**7b**
6a	Boc	Me	*c*-C_6H_{11}—CH_2	**7c**
6a	Boc	Me	*n*-C_6H_{13}	**7d**
6a	Boc	Me	Et	**7e**
6a	Boc	Me	2-Propene	**7f**
6a	Boc	Me	$(CH_3)_2CH$—CH_2	**7g**
6b	Bn	Boc	*c*-C_6H_{11}—CH_2	**7h**
6b	Bn	Boc	$(CH_3)_2CH$—CH_2	**7i**



Scheme 2. Reagents: (a) TMSCN, ZnI_2; (b) *i*Bu-MgBr, THF, 91–98%; (c) TFA, DCM; (d) MsOH, mCPBA, DCM.

less efficient in Grignard substitution reactions when compared to those without the basic amine. Oxidation of the thiomorpholine **10c** with mCPBA in the presence of methanesulfonic acid yielded **10d**. The piperazine structures **8a**–**l** and **10a**–**d** were coupled to the Boc-protected dipeptide[9,10] **11** in the presence of HATU as previously described.[11] The penultimate compounds were then treated with TFA to generate **12a**–**p** as the corresponding TFA salts (Scheme 3).

Final products **12a**–**p** were evaluated for binding at the MC4 receptor by determining competitive inhibition of [^{125}I]NDP-α-MSH binding in HEK293 cells stably transfected with human MC4 receptors as previously described.[12,13] Compound **12a**, an achiral analog of **1**, yielded high affinity with a K_i of 7 nM. This observation suggests that this new achiral structure can mimic



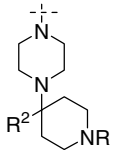
Scheme 3. Reagents: (e) HATU, DIEA, DCM; (f) TFA, DCM.

the key topography afforded by chiral analog **1**. Using **12a** as a lead structure, we next explored the nature of the aliphatic group R^2, while holding the *N*-methyl piperidine constant (**12a–g**, Table 2). The aromatic counterpart to **12a**, where R^2 = Bn (**12b**), displayed a 6-fold decrease in binding affinity (K_i = 44 nM). Removal of the methylene spacer of **12b** (R^2 = Bn) yields compound **12c**, (R^2 = Ph) whose K_i of 215 nM is 31-fold less than analog **12a**. The alkyl substituted compound **12d** (R^2 = *n*-hexyl) was 10-fold less active than compound **12a**. Contracting the aliphatic unit of **12d** (R^2 = *n*-hexyl) to yield compound **12e** (R^2 = ethyl) decreased binding affinity by 5-fold (K_i = 370 nM). The isopropyl analog **12f** resulted in binding affinity 9-fold better (K_i = 42 nM) than its non-branched counterpart **12e** (R^2 = ethyl). Homologation of **12f** afforded the isobutyl analog **12g** (R^2 = isobutyl) which had a 3-fold improvement in binding relative to **12f**.

Next we turned our attention to functionalization of the piperidine nitrogen, while holding R^2 constant as isobutyl. We observed minimal effects on binding affinities for the family of alkyl substitutions on nitrogen. Both **12h** (R = ethyl) and **12i** (R = isopropyl) failed to differentiate from the parent compound **12g** (R = methyl) with binding affinities of 16, 13, and 13 nM, respectively. Acylation of the nitrogen yielded **12j** (R = acetyl) which resulted in a 3-fold loss in binding affinity (K_i = 38 nM) relative to **12g**. The branched alkyl amide of **12k** (R = $COCH(CH_3)_2$) demonstrated lower binding affinity (K_i = 101 nM) than its simple alkyl amine counterpart **12g**.

The focus then turned to replacement of the piperidine ring with carbocycles and non-basic heterocycles (Table 3). Here we found that both all aliphatic carbocycle (**12m** X = CH_2) and heterocycles **12n–p** (X = O, X = S, and X= SO_2, respectively) produced binding affinities typically 2- to 6-fold less than their tertiary amine- and tertiary sulfonamide-containing counterparts **12g** (R = methyl) and **12l** (R = SO_2CH_3).

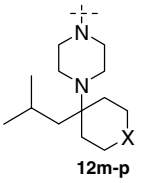
Table 2.



Compound	R	R^2	MC4 K_i (nM)
12a	Me	*c*-C_6H_{11}—CH_2	6.8
12b	Me	Bn	43.9
12c	Me	Ph	214.6
12d	Me	*n*-C_6H_{13}	69.6
12e	Me	Et	369.9
12f	Me	$(CH_3)_2CH$	41.8
12g	Me	$(CH_3)_2CH$—CH_2	12.7
12h	Et	$(CH_3)_2CH$—CH_2	15.6
12i	$(CH_3)_2CH$	$(CH_3)_2CH$—CH_2	12.9
12j	$COCH_3$	$(CH_3)_2CH$—CH_2	37.5
12k	$COCH(CH_3)_2$	$(CH_3)_2CH$—CH_2	100.7
12l	SO_2CH_3	$(CH_3)_2CH$—CH_2	27.3

The K_i data are the average of at least two determinations with the average error of 15%.

Table 3.



12m-p

Compound	X	MC4 K_i (nM)
12m	CH_2	46.9
12n	O	31.4
12o	S	68.4
12p	SO_2	75.8

The K_i data are the average of at least two determinations with an average error of 15%.

The above data demonstrate that replacement of the chiral structure **3** with a 4,4-disubstituted piperidine yields structures which can be employed in the construction of a new and physicochemically diverse set of MC4R ligands. Consistent with our hypothesis, the presumed decrease in conformational mobility afforded by the ring structure of **8a** did not preclude this new scaffold from attaining the required conformation for binding to the MC4R. In addition to the elimination of a stereocenter, the synthetic route was straightforward with many of the piperazine fragments being prepared in three steps. For the MC4R, the amine moiety of the disubstituted piperidine can posses an alkyl group (**12g**, polar, charged) or be converted to a sulfonamide (**12l**, polar, non-charged) with minimal loss of affinity. Similarly, this piperidine nitrogen can be replaced by carbon, oxygen, sulfide, and sulfone while still displaying good MC4R affinity.

In summary, we have described a convenient synthesis of useful 4,4-disubstituted piperidines and heterocycles as achiral privileged structures with widely varying physical properties for the preparation of MC4R ligands. Further, the subunits described here may afford an attractive path to probe numerous GPCRs given the highly conserved nature of the binding domains across GPCRs. Understanding of privileged structure topographical requirements and developing a collection of these subunits can present a significant opportunity to rapidly prepare ligands for the pharmacological exploration of a variety of GPCRs.

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13. Data given are the average of at least two determinations with an average error of 15%. Biological testing was conducted on either the resulting TFA salt or the hydrochloride salt.