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1-Amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid as a Tic mimetic: Application in the synthesis of potent human melanocortin-4 receptor selective agonists

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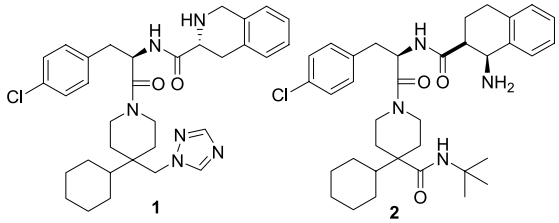
Abstract—The discovery of 1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid analogs as potent human melanocortin-4 selective agonists is described.

Over the last decade, the melanocortin-4 receptor (MC4R) subtype has attracted the considerable attention of medicinal chemists and biologists because of its potential in the treatment of obesity and sexual dysfunction.[1] Melanocortin receptors are a member of the family of seven-transmembrane G-protein-coupled receptors. Five different subtypes of melanocortin receptors (MC1R–MC5R) have been identified and cloned. Peptide melanocyte-stimulating hormone (MSH) and adrenocorticotropic hormone (ACTH), which are produced by the cleavage of a proopiomelanocortin (POMC), are natural ligands of these receptors. These receptors have different tissue distributions and mediate diverse physiological functions such as hair color, adrenal function, sebaceous gland activity, feeding, energy homeostasis, erectogenic activity, etc. The pharmacological link between MC4R and feeding behavior comes from the studies with both agonists and the antagonists.[2] MC4R antagonist SHU9119 and agouti protein (MC1R and MC4R antagonists) increase food intake and body weight in rodents.[3] Both non-selective peptide MC4R agonist MTII[3b] and a selective small molecule MC4R agonist **1**[4] lower food intake and reduce body weight in rodents. MC4R agonist **1** also stimulates erectile activity in rodents.[4]



Compound **1** served as an important tool for studying the MC4R pharmacology, but its limited oral bioavailability precluded further development as a viable development candidate. Herein, we disclose that the synthesis and biological profile of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) mimic **2** that incorporates the novel Tic surrogate[5] and addresses some of the core issues associated with **1**.

Keywords: MC-4 agonist; Tic; Obesity.
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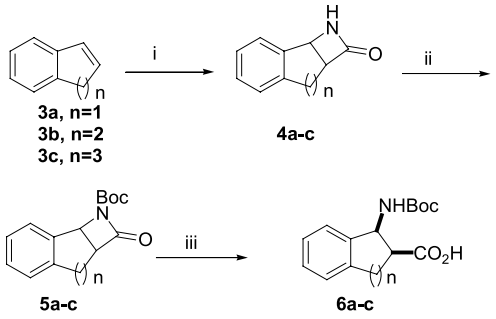


Scheme 1. Reagents: (i) chlorosulfonyl isocyanate/ether; (ii) $(Boc)_2O$/DMAP/Et_3N/CH_2Cl_2; (iii) (a) LiOH/THF/H_2O, (b) HCl.

Tic mimetic amino acids **6a**–**c** were synthesized using the chemistry described in Scheme 1. The reaction of olefins **3a**–**c** with chlorosulfonyl isocyanate furnished azet-2-ones **4a**–**c** in good yield.[6] The azet-2-ones were converted to the Boc intermediates **5a**–**c** and subsequently hydrolyzed with lithium hydroxide to give the *cis* amino acids **6a**–**c**.[7]

The amino acids **6a**–**c** were coupled with capped peptide **10** (Scheme 2) to give MC4R compounds **11**, **12**, and **13** as diastereomeric mixtures. Intermediate **10** itself was obtained by EDC coupling of *N*-Boc-D-(4-Cl)Phe **7** with privileged structure **8**, followed by the removal of the Boc protecting group.

The diastereomeric mixtures **11**, **12**, and **13** were evaluated for MC4 activity in competitive binding assay (Table 1) and functional assay (Table 2).[8] Compound **12** was 2- to 3-fold more potent in competitive binding assay (Table 1) and 6-fold more potent in functional assay (Table 2) compared to **11** and **13**. This result clearly suggests that the ring size was important and that tetralin ring in **12** was the preferred choice. Compound **12** was further separated by preparative reverse-phase HPLC to afford diastereomer **2** (*cis* 1*R*,2*R*)[9] and **14** (*cis* 1*S*,2*S*). Analog **2** was 4-fold more potent in functional assay compared to the 1*S*,2*S* diastereomer **14**, suggesting that there is a chiral recognition of the tetralin ring at the binding site. Furthermore, all these compounds had good selectivity in binding against MC3 and MC5 receptors.

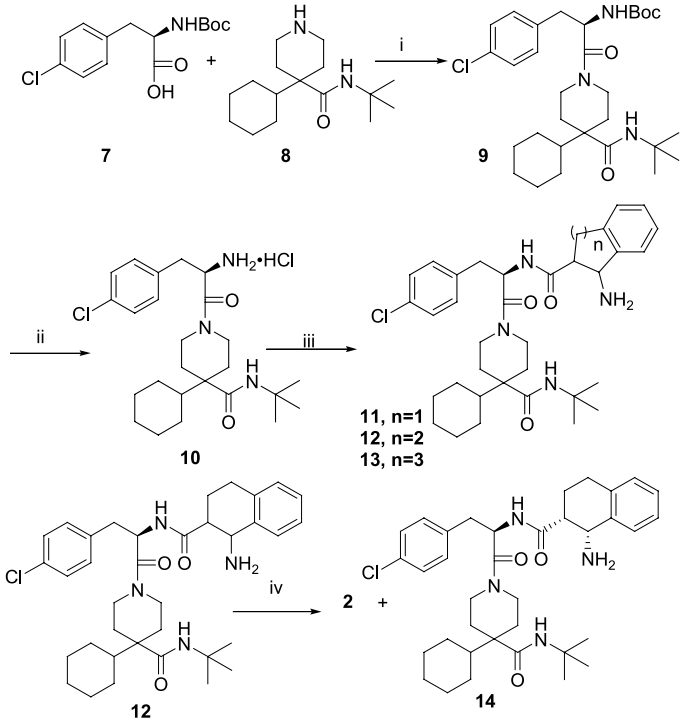
Table 1. Binding affinity and selectivity for the human MC4R[a]

Compound	IC_{50}[b] (nM)			
	MC1R	MC4R	MC3R	MC5R
1	2063 ± 73	1.2 ± 0.11	761 ± 31	326 ± 9
11	1400 ± 120	1.9 ± 0.32	83 ± 14	34 ± 1.6
12	940 ± 58	0.56 ± 0.09	48 ± 4.2	40 ± 6.2
13	220 ± 0.47	1.1 ± 0.16	97 ± 46	54 ± 23
2	530 ± 86	0.37 ± 0.02	120 ± 16	64 ± 6.3
14	980 ± 95	0.77 ± 0.07	32 ± 2.7	24 ± 2.8
15	620 ± 16	1.1 ± 0.25	170 ± 57	31 ± 12

[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.

Compound **2** was further evaluated in pharmacokinetic (PK) studies in rats and dogs (Table 3). Clearance in the rat was rapid, resulting in a short half-life and low oral bioavailability. The pharmacokinetics of **2** in the dog was improved and exhibited slower clearance and better oral bioavailability.



Scheme 2. Reagents: (i) EDC, HOBT, NMM, CH_2Cl_2; (ii) HCl/dioxane, CH_2Cl_2; (iii) (a) **6a**–**c**, EDC, HOBT, NMM, CH_2Cl_2; (b) HCl/dioxane, CH_2Cl_2; (iv) HPLC separation.

Table 2. Functional activity of compounds at human melanocortin receptors[a]

Compound	EC_{50}[b] (nM) [%max][c]			
	MC1R	MC4R	MC3R	MC5R
1	2850 ± 450[95]	2.1 ± 0.2[97]	2487 ± 43[32]	737 ± 65[61]
11	1000 ± 180[26]	21 ± 2.6[34]	110 ± 8.4[26]	180 ± 33[75]
12	430 ± 93[21]	3.3 ± 0.55[52]	150 ± 12[19]	200 ± 32[87]
13	280 ± 26[32]	17 ± 5.1[51]	[12]	800 ± 75[60]
2	780 ± 43[23]	1.9 ± 0.13[81]	[4]	250 ± 18[68]
14	280 ± 40[22]	7.1 ± 0.64[48]	99 ± 31[24]	130 ± 19[94]
15	960 ± 45[19]	1.5[108]	390 ± 41[26]	140 ± 10[100]

[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.

Table 3. Pharmacokinetic data for **2**

PK parameter	Rat[a]	Dog[b]
F (%)	11	42
Cl (mL/min/kg)	35	11
V_{dss} (L/kg)	3.9	2.9
$t_{1/2}$ (h)	2	3.4
t_{max} (h)	1.13	2

[a] Compound dosed in Sprague–Dawley rats as a EtOH/PEG/water (1:4:5) solution at 1 mg/kg iv and 4 mg/kg po.
[b] Compound dosed in beagles as a solution in EtOH/PEG/water (1:4:5) at 0.5 mg iv and 2.0 mg/kg po.

Compound **2** was evaluated in an overnight food intake study at 10 mg/kg po in diet induced obese (DIO) Sprague–Dawley rats for its effect on food intake and body weight. The compound was administered orally, by gavage, 1 h before lights off and food intake, and body weight was measured 18 h post-dosing. Compound **2** was efficacious both in food intake reduction (20%) and body weight reduction (7 g).[10]

Erectogenic activity of compound **2** was evaluated in a rat ex copula model. In this model, each rat served as its own control where the effect of compound was compared to that produced by the vehicle. The mean number of erections elicited over a 15-min period was determined by a visual count of video-taped events. As shown below **2** (Fig. 1), increasing the number of erectile events in rat ex copula erectogenic assay[11] at 2 and 5 mg/kg, iv (57% and 94%), failed to elicit significant pro-erectile activity at oral doses up to 20 mg/kg (35%: $P = 0.05$).

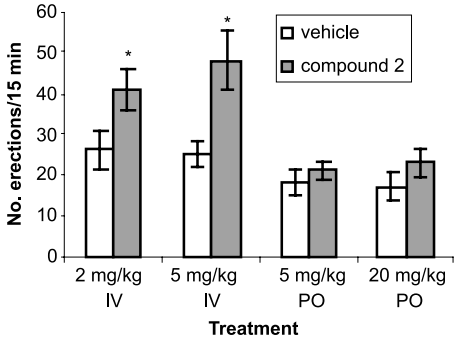
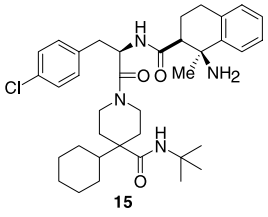


Figure 1. Ex copula erectogenic effect of compound **2** monitored 60–75 min post-dose. *$P < 0.05$ paired t test.

Studies of the in vitro metabolism of compound **2** in human liver microsomes indicated that it was both a reversible and time-dependent inhibitor of CYP3A4.[12]

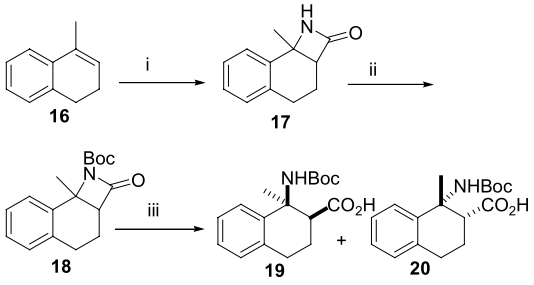
Since CYP3A4 is an enzyme that is involved in the metabolism of many drugs, time-dependent inhibition of this enzyme by compound **2** was of great concern to us because of potential drug–drug interactions. We reasoned that an understanding of the metabolism of compound **2** would help us design analogs that did not have this potential liability. Those studies indicated that oxidation of the amino group of the tetralin was involved in the time-dependent inhibition of CYP3A4.[12]



15

It was envisioned that introducing the methyl group α to the basic amine, as shown in compound **15**, might attenuate the oxidation of amine by CYP3A4. Route to **15** began with amino acid **20** whose synthesis is described in Scheme 3 and in ways was analogous to **6a**–**c**. The transformation of the desired amino acid **20** to **15** was accomplished by using chemistry described in Scheme 1.

The human MC4R receptor binding (Table 1) and functional activity (Table 2) of compound **15** were similar to those of compound **2**. Unlike compound **2**, however, compound **15** was not a potent reversible inhibitor of



Scheme 3. Reagents: (i) chlorosulfonyl isocyanate/ether; (ii) $(Boc)_2O$/DMAP/Et_3N/CH_2Cl_2; (iii) (a) Separation of enantiomers by chiral HPLC, (b) LiOH/THF/H_2O, (c) HCl.

human CYP3A4 and it was also not a time-dependent inhibitor of that enzyme. Thus, as we had hoped, introduction of the methyl group α to the basic amine prevented the time-dependent inhibition of CYP3A4.

In summary, we report the design, synthesis, and biological profile of MC4R agonists based on tetralin Tic mimetic **2**. This compound was a potent MC4 agonist and was efficacious in animal models for food intake and erectile dysfunction. Compound **15** was designed as an MC4R agonist that had a lower potential for drug–drug interactions based on the results from in vitro metabolism studies.

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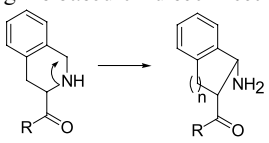
5. Tic mimic 2 design is based on disconnection shown below



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