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Bioorganic & Medicinal Chemistry Letters 17 (2007) 6887–6890
Bioorganic & Medicinal Chemistry Letters

Stereoselective synthesis of a novel 2-aza-7-oxabicyclo-[3.3.0]octane as neurokinin-1 receptor antagonist

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Received 2 August 2007; revised 28 September 2007; accepted 3 October 2007
Available online 5 October 2007

Abstract—A novel neurokinin-1 receptor antagonist, (±)-(1*R**,3*S**,4*S**,5*S**)-4-[(*N*-(2-methoxy-5-trifluoromethoxybenzyl)amino]-3-phenyl-2-aza-7-oxabicyclo[3.3.0]octane (**1**), was synthesized stereoselectively using Padwa's intramolecular 1,3-dipolar cycloaddition methodology as the key step. Compound (±)-**1** showed high affinity for the NK-1 receptors in human IM-9 cells with an IC_{50} value of 0.22 nM. This new structural scaffold demonstrated significant in vivo antagonistic activity in the guinea pig ureter capsaicin-induced plasma extravasation model with an ED_{50} value of 1–10 mg/kg, po.

The neurokinin-1 (NK-1) receptor is a member of the seven-transmembrane G-protein coupled family of receptors and is associated with sensory neurons in the peripheral and specific areas of the central nervous system. The neuropeptide 'Substance P' and its human neurokinin-1 (hNK-1) receptor have been associated to various biological disorders such as anxiety, depression, emesis, asthma, and inflammatory bowl disease (IBD).[1] Recently, the brain transitional NK-1 receptor antagonists, Aprepitant (Merck; Emend®)[2] for the treatment of chemotherapy (cisplatin)-induced emesis in human and Maropitant (Pfizer; Cerenia®)[3] for motor sickness in animals, have been launched (Fig. 1).

In the course of a Pfizer program geared at developing NK-1 receptor antagonists as anti-inflammatory and analgesic drugs, it was hypothesized that incorporation of a heteroatom into the prototype NK-1 antagonist,[4], the ethylenediamine-based (±)-**2**, would promote the penetration to peripheral tissues by the decrease of $\log D_{7.4}$ and lead to compounds with higher binding affinity and superior pharmacological properties as anti-inflammatory and analgesic agents. We also anticipated that the newly designed compound (±)-**1** would fit the NK-1 antagonistic pharmacophore model, similarly to the modifications (**4**, **5**, and Aprepitant) made by the Merck group[2,5] from the CP-99,994 (**3**) lead discovered at Pfizer,[6] as shown in Figure 2.

The novel (±)-4-[(*N*-(2-methoxy-5-trifluoromethoxybenzyl)amino]-3-phenyl-2-aza-7-oxabicyclo[3.3.0]octane) (**1**) was thus synthesized stereoselectively employing Padwa's intramolecular 1,3-dipolar cycloaddition methodology[7] on intermediate **6** as the key step (Fig. 3).

Aziridine (±)-**6**, a logical substrate for the intramolecular 1,3-dipolar cycloaddition reaction, was provided in quantities only after minor modifications of the original procedure of Padwa (Scheme 1).[7] Commercially available dibromide **8** was dehydrobrominated[8] to give bromoolefin **9** in quantitative yield as a 1:5 mixture of the *E*- and *Z*-isomers. Without separation, the mixture was subjected to the Harada conditions for stereocon-

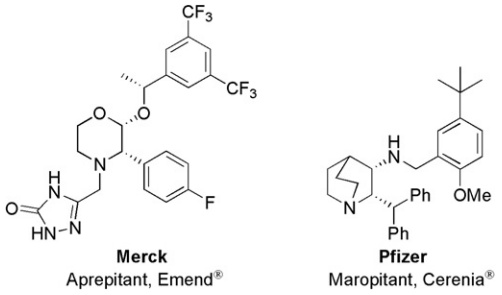

Figure 1. NK-1 receptor antagonists as anti-emetic drugs in animals and humans.

Keywords: Neurokinin-1; Antagonist; 1,3-Dipolar cycloaddition; NK-1 antagonist.
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doi:10.1016/j.bmcl.2007.10.010

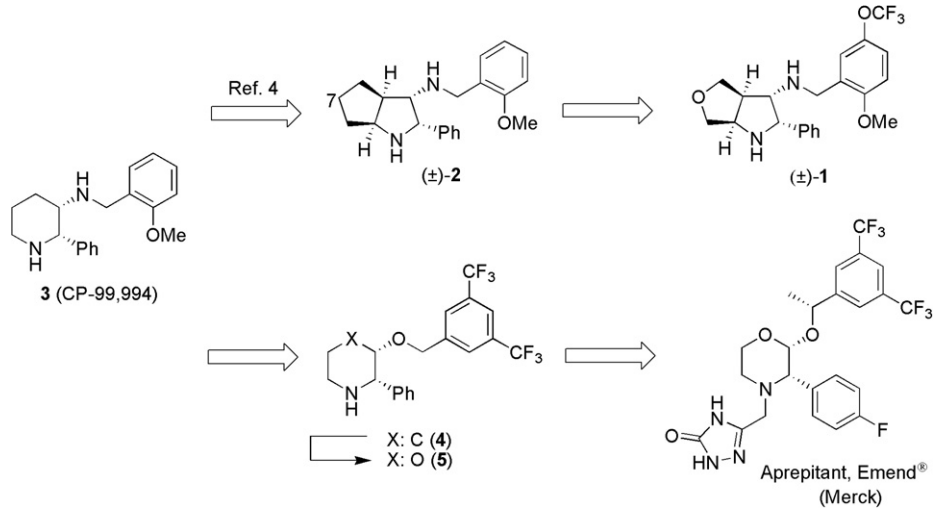


Figure 2. Design of compound (±)-**1** based on CP-99,994.

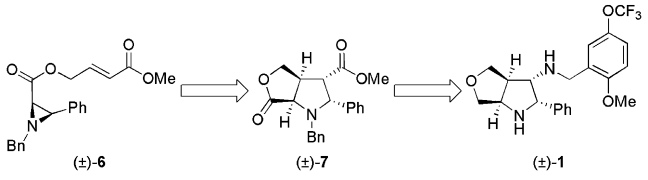
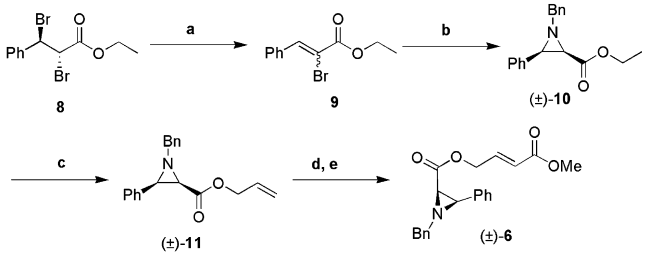


Figure 3. Synthetic strategy of compound (±)-**1**.

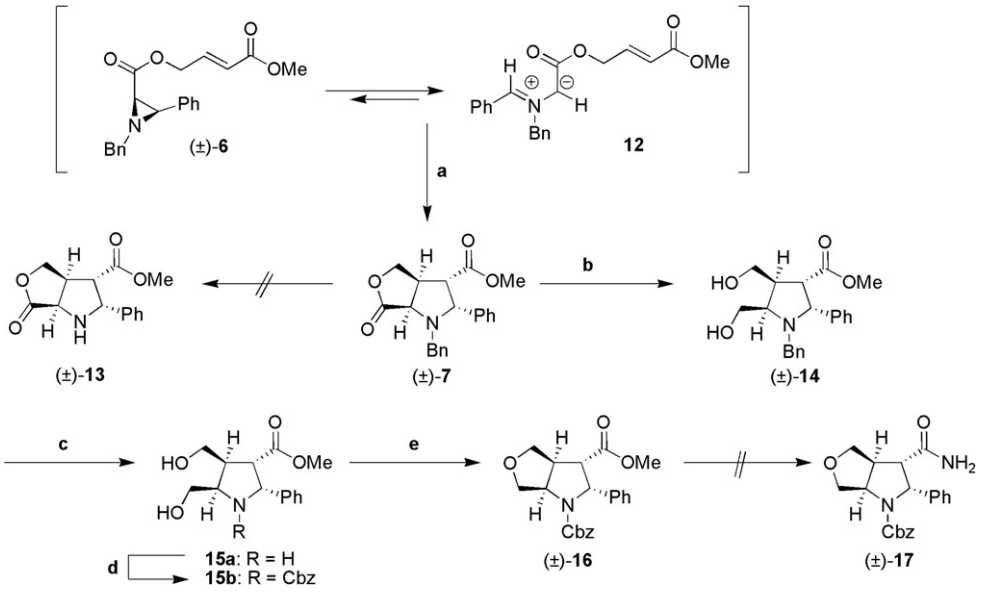


Scheme 1. Reagents and conditions: (a) *N*-methylpiperidine, PhH, reflux, 99%; (b) $BnNH_2$, MeOH, rt, 79%; (c) allyl alcohol, 5% KCN, rt, 4 days, 95%; (d) O_3, MeOH then Me_2S; (e) $Ph_3P{=}CHCO_2Me$, PhH, 88% in two steps.

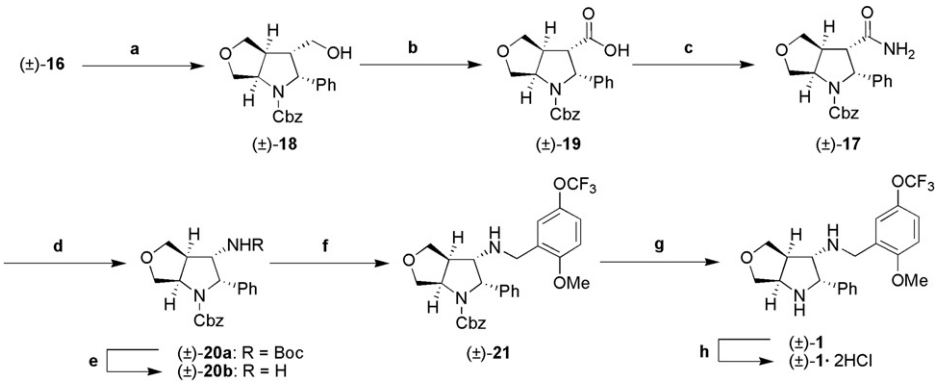
trolled aziridine formation[9] to afford *cis*-aziridine **10** in 79% yield. However, the transesterification of **10**–**11** was difficult to perform in a reproducible manner when the reaction was run according to Padwa's protocol [catalytic sodium allyloxide, allyl alcohol, rt].[7] As an alternative method, the Mori protocol for mild transesterification[10] was applied: ethyl ester **10** was converted into allyl ester **11** by the catalytic action of potassium cyanide in allyl alcohol in a high and reproducible yield. Ozonolysis of **11** followed by reductive workup and Wittig olefination of the crude aldehyde resulted in the formation of the required α,β-unsaturated ester (±)-**6** in 88% yield from **11**.

The intramolecular 1,3-dipolar cycloaddition was carried out by thermolysis of **6** in refluxing toluene to give bicyclic γ-lactone (±)-**7** in 42% yield via formation of an azomethine ylide **12** (Scheme 2). Since hydrogenolysis of the *N*-benzyl group of **7** proved difficult even under acidic conditions and medium pressure of hydrogen, reductive cleavage of the lactone ring in **7** was undertaken prior to the deprotection: being activated by the α-nitrogen of the pyrrolidine moiety, the lactone carbonyl could be reduced selectively by $LiBH_4$ in tetrahydrofuran to give diol derivative **14** in 89% yield without affecting the methyl ester function. *N*-Debenzylation of the monocyclic pyrrolidine **14** proceeded smoothly using Pearlman's catalyst to furnish **15a**, probably because the newly generated hydroxyl group(s) of **14** facilitated its adsorption to the catalyst surface. Following re-protection[11] of the nitrogen moiety on **15a** with benzyl chloroformate (Cbz-Cl), the diol was cyclized using triphenylphosphine and diethyl azodicarboxylate (DEAD)[12] to form tetrahydrofuran derivative **16** in 64% yield.

Direct conversion of the methyl ester **16** to carboxamide **17** using the reagent derived from the reaction of trimethylaluminum with ammonium chloride (the Weinreb protocol)[13] resulted in the recovery of **16** (Scheme 2). Thus, carboxamide **17** was obtained via a three step sequence as shown in Scheme 3: (1) $LiAlH_4$ reduction of **16** to alcohol **18**; (2) ruthenium(III) chloride-catalyzed oxidation of **18** to carboxylic acid **19**[14] under the Sharpless conditions;[15] (3) treatment of **19** with ethyl chloroformate followed by concd NH_3 solution to give **17** in 62% yield from **16**. Hoffman rearrangement of **17** proceeded smoothly in *tert*-butyl alcohol in the presence of a catalytic amount of tin(IV) chloride[16] to afford *tert*-butylcarbamate **20a**, while in the absence of the tin catalyst, this reaction produced a complex mixture with a low yield of **20a**. Acid hydrolysis of the *N*-Boc group in **20a** liberated primary amine **20b**, which was subjected to $NaBH_3CN$-mediated reductive N-alkylation[17] with 2-methoxy-5-trifluoromethoxybenzaldehyde to give **21** in 54% yield from **20a**. In the final step, catalytic transfer hydrogenolysis[18] of the *N*-Cbz group followed by treatment with 10% methanolic hydrogen chloride furnished the desired compound (±)-**1**·2HCl as a crystalline solid. The structure of (±)-**1**, particularly the relative stereochemistry, was



Scheme 2. Reagents and conditions: (a) toluene, reflux, 42%; (b) $LiBH_4$, THF, rt, 89%; (c) H_2, 20% $Pd(OH)_2$–C, MeOH, 97%; (d) Cbz-Cl, aq NaOH, EtOH, 55%; (e) Ph_3P, DEAD, CH_2Cl_2, 94%.



Scheme 3. Reagents and conditions: (a) $LiAlH_4$, THF, 82%; (b) $RuCl_3$–nH_2O (cat.), $NaIO_4$, CCl_4–MeCN–H_2O (2:2:3), quant; (c) EtO_2COCl, Et_3N, concd NH_3 aq, 76%; (d) $Pb(OAc)_4$, $SnCl_4$ (cat.), *t*-BuOH, reflux, 96%; (e) concd HCl aq, EtOAc, rt, 90%; (f) 2-methoxy-5-trifluoromethoxybenzaldehyde, $NaBH_3CN$, AcOH, MeOH, 60%; (g) HCO_2NH_4, 20% $Pd(OH)_2$–C, MeOH, 82%; (h) HCl–MeOH, 87%.

Table 1. IM-9 binding and Ca^{2+} channel affinity of compound (±)-**1**

Compound	IM-9 binding[a] (IC_{50}, nM)	Calcium channel affinity[b] (IC_{50}, nM)
(±)-**1**	0.22	>1000
(±)-**2**	3.4	>1000
CP-99,994	0.63–3.0	—
Substance P	0.57	

[a] IC_{50} value versus 0.56 nM ^{3}H-substance P.
[b] Affinity to the verapamil binding site at the L-type Ca^{++} channel labeled by [^{3}H]desmethoxyverapamil.

verified using ^{1}H and ^{13}C NMR (δ, ppm, J_{CF}, Hz) and some key NOEs in $CDCl_3$.[19]

The (±)-7-oxa-2-azabicyclo[3.3.0]octane derivative (**1**) showed remarkably high affinity for the NK-1 receptor in human IM-9 cells with an IC_{50} value of 0.22 nM (Table 1). This new structural scaffold demonstrated significant po in vivo antagonistic activity in the guinea pig ureter capsaicin-induced plasma extravasation model with an ED_{50} between 1 and 10 mg/kg (10% and 94% inhibitions at 1 and 10 mg/kg, po, respectively) while showing poor affinity for the verapamil receptor (IC_{50} > 1 μM, a L-type calcium channel receptor in rat heart) with the potential to cause deleterious effects on the cardiovascular system.

Acknowledgments

The authors thank Mr. Shinichi Sakemi for NMR analysis, Dr. Bernard Hulin of ChemWrite for the editing of the manuscript, and Dr. Kunio Satake for providing helpful advice.

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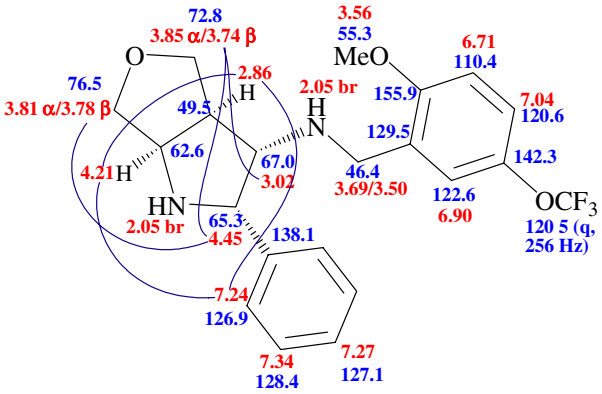
19. *(1R*,3S*,4S*,5S*)-4-[(N-(2-methoxy-5-trifluoromethoxybenzyl)amino]-3-phenyl-2-aza-7-oxabicyclo[3.3.0]octane) (compound (±)-**I**).* ^{1}H NMR (600 MHz) δ ($CDCl_3$): 2.05 (br s, 2H), 2.86 (td, J = 7.8, 3.6 Hz, 1H), 3.02 (d, J = 4.5 Hz, 1H), 3.50 (d, J = 14.2 Hz, 1H), 3.56 (s, 3H), 3.69 (d, J = 14.2 Hz, 1H), 3.74 (dd, J = 9.5, 3.6 Hz), 3.78 (dd, J = 9.7, 2.7 Hz, 1H), 3.81 (dd, J = 9.7, 5.7 Hz, 1H), 3.85 (dd, J = 9.5, 7.8 Hz, 1H), 4.18–4.24 (m, 1H), 6.71 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 2.5 Hz, 1H), 7.04 (dd, J = 8.8, 2.5 Hz, 1H), 7.23–7.29 (m, 3H), 7.31–7.36 (m, 2H) ppm. ^{13}C NMR (125 MHz) δ ($CDCl_3$): 46.4, 49.5, 55.3, 62.6, 65.3, 67.0, 72.8, 76.5, 110.4, 120.5 (q, J = 125 Hz), 120.6, 122.6, 126.9 (two carbons), 127.1, 128.2 (two carbons), 129.5, 138.1, 142.3, 155.9 ppm. IR ν_{max} (film): 3340, 1496, 1457, 1248, 1163, 1032, 917, 700 cm^{-1}. MS (ESI) *m/z* 409 $(M+H)^+$.



The structure of (±)-**1** including the relative stereochemistry was verified using ^{1}H and ^{13}C NMR (δ, ppm, J_{CF}-Hz) and some key NOEs in $CDCl_3$.

(1R,3S*,4S*,5S*)-4-[(N-(2-methoxy-5-trifluoromethoxybenzyl)amino]-3-phenyl-2-aza-7-oxabicyclo[3.3.0]octane)·dihydrochloride (**1**·2HCl).* White solid; mp 203–205 °C. ^{1}H NMR (270 MHz) δ (DMSO-d_6): 3.30–4.46 (10H, m), 3.74 (3H, s), 4.67 (1H, br s), 4.96 (1H, br s), 7.08 (1H, d, J = 9.2 Hz), 7.32–7.82 (7H, m) ppm. IR ν_{max} (film): 3450, 1582, 1563, 1504, 1457, 1278, 1261, 1244, 1217, 1174, 1032, 695 cm^{-1}. Anal. Calcd for $C_{21}H_{23}N_2O_3F_3$·2HCl: C, 52.40; H, 5.24; N, 5.82. Found: C, 52.43; H, 5.35; N, 5.75. HPLC purity: 99.8% area at 215 mm. *Conditions:* Apparatus, Alliance 2695 with 996 PDA detector, Waters; Column, XTerra MS C18, 3.5 μm, 2.1 × 100 mm, Waters; Mobile phase: A: CH_3CN/B: CH_3CN/10 mM $CH_3CO_2NH_4$ (5/95, v/v) (ca. pH7) = 5/95–95/5; Flow rate, 0.25 mL/min; Column temperature, 40 °C.

The gradient program was as follows: initially A:B (5/95, v/v), then 8 min linear gradient to A:B (95/5, v/v) and 5 min isocratic with A:B (95/5, v/v); then an additional period of 7 min linear gradient to the initial conditions.