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SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF CP-122,721, A SECOND-GENERATION NK-1 RECEPTOR ANTAGONIST

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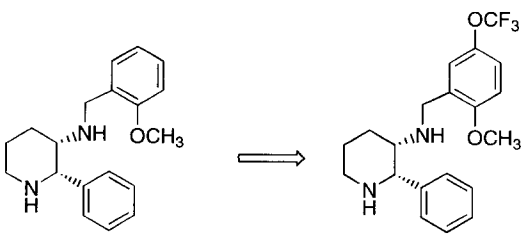
Abstract: The synthesis and SAR of benzylamine side chain analogs of the NK-1 receptor antagonist CP-99,994 are described. The 5-trifluoromethoxy analog, CP-122,721, shows superior *in vivo* blockade of NK-1 receptor mediated responses.

The structure-activity relationships (SAR) of the potent NK-1 receptor antagonist CP-99,994 (**1**)[1] and its pharmacological characterization[2] suggested that structural modification might improve its *in vivo* activity. For example, despite CP-99,994's subnanomolar affinity for the NK-1 receptor, blockade of capsaicin-induced protein plasma extravasation in the guinea pig requires an oral dose of 5 mg/kg. One possible pharmacokinetic shortcoming of CP-99,994 is metabolic lability due to demethylation of/*para*-hydroxylation to the methoxy group on the phenyl ring of the benzylamine side chain. Herein, we report that modification of the benzylamine phenyl ring with a 5-trifluoromethoxy group provides CP-122,721 (**3f**), a compound with superior *in vivo* efficacy in animal models of NK-1 receptor antagonism, warranting its designation as a "second generation" NK-1 receptor antagonist.



1, CP-99,994 **3f**, CP-122,721

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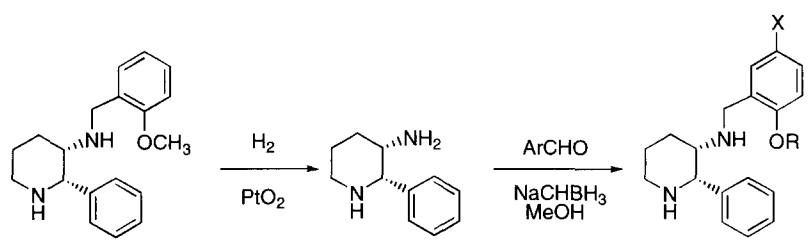
The synthesis of the benzylamine analogs of **1** and their SAR are summarized in Scheme 1. Debenzylation of CP-99,994 using catalytic platinum, followed by reductive amination with the appropriate aldehyde, afforded the desired analogs. As indicated in the SAR table, the most significant increase in NK-1 receptor affinity in this series is afforded by the analogs containing a substituent opposite (or *para*) to the 2-methoxy group. Since it has one of the highest NK-1 receptor affinities in this series, compound **3f** with the 5-trifluoromethoxy group was selected for further evaluation.[3] Analogs of **3f** at the 2-position (compounds **3i** to **3k**), did not afford improved NK-1 receptor affinity.

Scheme 1



1, CP-99,994 **2** **3**

CPD	X	R	NK-1 IC_{50}, nM*
CP-99,994	H	CH_3	0.49 ± 0.39
3a	H	$CH(CH_3)_2$	0.46 ± 0.49
3b	H	CHF_2	0.41 ± 0.33
3c	H	CF_3	0.80 ± 0.38
3d	Cl	CH_3	0.14 ± 0.10
3e	OCH_3	CH_3	0.09 ± 0.08
3f	OCF_3	CH_3	0.19 ± 0.07
3g	$N(CH_3)_2$	CH_3	0.56 ± 0.23
3h	$N(CH_3)SO_2CH_3$	CH_3	0.11 ± 0.02
3i	OCF_3	H	10.87 ± 4.47
3j	OCF_3	CH_2CH_3	0.14 ± 0.15
3k	OCF_3	$CH(CH_3)_2$	0.18 ± 0.07
Substance P			0.61 ± 0.11

*IC_{50} value for displacement of [^{3}H]Substance P in human IM-9 cells, ± S.D.[4]

Although **3f** shows only a small improvement in NK-1 receptor affinity relative to **1**, its *in vivo* efficacy is considerably improved in several assays. For example, the ID_{50} value of **3f** for blockade of locomotor activity in the guinea pig elicited by icv administered $Sar^9Met(O_2)$-SP is 0.01 mg/kg sc, while for **1** the corresponding value is 0.6 mg/kg sc.[5] Against SP-induced plasma extravasation in the guinea pig, **3f** shows an ID_{50} value of 0.05 mg/kg po, compared with a value of 31 mg/kg po for **1**. Capsaicin is a naturally-occurring substance that releases endogenous SP, eliciting SP-induced responses *in vivo*. Compound **3f** blocks capsaicin-induced plasma extravasation in the guinea pig ureter with an ID_{50} value of 0.02 mg/kg po as compared with 2.9 mg/kg po for **1**.[5] In addition, aerosolized capsaicin-induced plasma protein extravasation in guinea pig lung is blocked by **3f** (ID_{50} = 0.01 mg/kg po) more potently than by **1** (ID_{50} = 5 mg/kg po).[5] Finally, **3f** suppresses retching and vomiting induced by a broad range of emetogens in the ferret, being approximately three-fold more potent than **1** in these models.[6] For example, **3f** blocks cisplatin-induced emesis with an ID_{50} of 0.08 mg/kg when given orally.[6] The significant increase in efficacy of **3f** for blockade of SP-induced effects *in vivo* relative to **1** together with its potent anti-emetic activity qualify **3f** as a second generation NK-1 receptor antagonist. The clinical potential of **3f** is currently under evaluation. Recently, a similar approach to improving the *in vivo* activity of CP-99,994, using a 5-tetrazolyl substituent, was reported.[7]

References and Notes

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3. Analytical data for **3f** as its hydrochloride salt: mp 277-278° C, HRMS calcd for $C_{20}H_{23}F_3N_2O_2$: 380.1711. Found: 380.1704. Anal. calcd for $C_{20}H_{23}F_3N_2O_2 \cdot 2HCl$: C 52.99, H 5.55, N 6.18. Found: C 52.85, H 5.60, N 6.12, $\alpha_D = +71.2°$ (*c* 1.09, MeOH).

4. The procedure for [^{3}H]SP binding to human IM-9 cells that was used for SAR evaluation was based on the literature protocol of Payan, D. G.; Brewster, D. R.; Goetzl, E. J. *J. Immunol.* **1984**, *133*, 3260. IM-9 human lymphoblast cells (ATCC) were harvested by centrifugation, washed in ice-cold 20 mM Hepes-Hanks (pH 7.4) buffer and resuspended in assay buffer (50 mM Tris buffer, pH 7.4, 1 mM $MgSO_4$, 0.02% bovine serum albumin (BSA), 10 μM leupeptin, and 10 μM phosphoramidon). Incubations were initiated by adding cell suspension (3 x 10^6 cells/tube) to buffer containing [^{3}H]SP (tritiated substance P) (0.56 nM final concentration) and various concentrations of inhibitors. After 120 min at 4° C, the incubations were terminated by filtration onto Whatman GF/B filters (presoaked in 0.2% polyethylenimine (PEI) for 2 h) followed by three washes with ice-cold buffer. Filter-bound radioactivity was determined by a Beckman LS-5801 liquid scintillation counter. Nonspecific binding was defined as the radioactivity remaining in the presence of 1 μM SP.

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