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4-ALKYLPIPERIDINES RELATED TO SR-48968: POTENT ANTAGONISTS OF THE NEUROKININ-2 (NK_2) RECEPTOR

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Abstract: A series of 4-alkylpiperidine derivatives related to the potent neurokinin-2 (NK_2) receptor antagonist SR-48968 (**1**) is described. Simple aliphatic derivatives were found to be poorly active, but appropriate placement of an alcohol functional group afforded compounds that were of similar activity to **1**. Several representatives in this series, such as the 4-(1-hydroxy-1-ethylpropyl)piperidine (**14**), were found to exhibit oral activity in a model of labored abdominal breathing in guinea pigs. These results expand the latitude of substituents available in this region of this series of NK_2 receptor antagonists.

The tachykinins are a family of peptides characterized by a common C-terminal sequence that are found to be localized in unmyelinated sensory afferent neurons (C-fibers) in the airways, as well as numerous other areas in both the peripheral and central nervous systems.[1] In individuals suffering from asthma, it has been suggested that such neurons are exposed due to damage to the epithelial layer.[2] The three most common peptides of this family—substance P, neurokinin A, and neurokinin B—are potent constrictors of smooth muscle. Several receptors have been discovered that exhibit selectivity for each of the tachykinins: NK_1 receptors exhibit selectivity for substance P, NK_2 receptors prefer neurokinin A, and NK_3 receptors are most strongly affected by neurokinin B.[3] These observations have suggested that blockade of the NK_1, NK_2 and/or NK_3 receptors might be an approach to reducing the severity and frequency of asthmatic episodes.

In 1992, SR-48968 (**1**) was the first nonpeptide antagonist of the NK_2 receptor reported in the literature.[4] Structure activity studies at Sanofi[5] and in our own laboratories demonstrated that a wide variety

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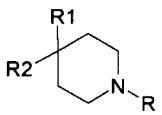
of substituent patterns were tolerated in the *N*-methylbenzamide region, but little information was known about the SAR of the piperidine region. We report here the SAR of compounds where the 4-phenyl-4-acetamido substitution pattern found in SR-48968 has been replaced with simple alkyl and acyl substituents.

Our initial efforts focused on simple aliphatic piperidine derivatives, as summarized in Table 1.[6,7] The 4-*n*-propyl (**3**) piperidine was approximately tenfold less active in binding to the NK_2 receptor[8] and almost two orders of magnitude less effective at the blockade of contraction of guinea pig trachea induced by an NK_2-receptor agonist,[9] when compared to the *racemic* SR-48968 analog (**2**). The 4-(2-hydroxyethyl)piperidine derivative (**4**), while some 40-fold less active in the binding assay, was only tenfold less active in the in vitro functional screen, and was found to exhibit weak oral activity in a neurokinin A-induced dyspnea model.[10]

Table 1. Simple Alkyl Substituents

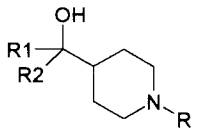


No.	R_1	R_2	K_i (nM)[a]	pK_B (n)[b]	po ED_{50} (μmol/kg)[c]
1 **(SR 48968)**	Ph	NHAc	0.6	9.1 (2)	1.97
2 **(±-SR 48968)**	Ph	NHAc	1.75	9.2 (2)	NT[d]
3	n-C_3H_7	H	9.9	7.5 (2)	NT
4	$HO(CH_2)_2$	H	47	8.3 (2)	7%[e]
5	$AcO(CH_2)_2$	H	40	7.8 (2)	NT
6	$AcNH(CH_2)_2$	H	66	7.9 (2)	NT
7	$HOCH_2$	H	142	8.0 (2)	13%[e]

[a] Displacement of 3H-NKA from a cloned human NK-2 receptor expressed in MEL cells, see ref 8. [b] Inhibition of [β-Ala_8]NKA(4-10)-induced contraction of isolated guinea pig trachea, see ref 9. [c] In a guinea pig dyspnea model, see ref 10. [d] Not tested. [e] Percent inhibition at 5 μmol/kg.

The corresponding acetate **5** or acetamide **6** were of similar in vitro activity, as was the 4-hydroxymethyl piperidine 7. When screened in our in vivo model, 7 exhibited oral activity similar to that observed for **4**. Based on the functional and oral activities observed for **6** and 7, a series of related 4-hydroxymethylpiperidines was prepared (Table 2). Binding affinity was found to increase with increasing chain length of simple secondary alcohols (e.g., **8–10**), although all three compounds were approximately equipotent in the in vitro functional assay. The corresponding achiral tertiary alcohols (e.g. **11–13**) did not exhibit a similar dependence of binding affinity on chain length, and afforded superior functional activity. In particular, the diethyl derivative **12** and the dipropyl derivative **13** were found to be nearly as potent as **1** both in vitro and following oral administration in the dyspnea model . The (*S*)-enantiomer of **12** (i.e., **14**) was prepared, and was of similar activity both in vitro and in vivo.[11]

Table 2. 4-Hydroxymethyl piperidines

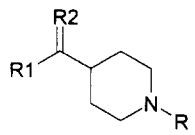


No.	R_1	R_2	K_i (nM)	pK_B (n)	po ED_{50} (μmol/kg)	iv ED_{50} (μmol/kg)
8	CH_3	H	33.5	7.8 (2)	NT	NT
9	C_2H_5	H	13.1	7.9 (2)	NT	NT
10	n-C_3H_7	H	3.7	7.5 (2)	NT	NT
11	CH_3	CH_3	7.7	7.5 (2)	NT	NT
12	C_2H_5	C_2H_5	3.5	8.8 (2)	63%[a]	NT
13	nC_3H_7	nC_3H_7	4.7	8.4 (2)	1.40	0.54
14[b]	C_2H_5	C_2H_5	0.84	8.1 (2)	3.49	0.40

[a]Percent inhibition at 5 μmol/kg. [b](*S*)-enantiomer of **12**.

Concurrent with our evaluation of the alcohols, we examined the corresponding ketone **15**, oxime **16,** and *O*-methyloxime **17** derivatives related to **9** and **12**. While **15** and **16** were approximately equipotent with **9** and **12**, **17** was significantly less active in the in vitro functional assay. When the (*S*) enantiomer of **16** was prepared, the (*E*)-**18** and (*Z*)-**19** oxime isomers were separated and evaluated individually, and found to be approximately equipotent in vitro. When evaluated in vivo, **18** was found to be significantly less active following oral administration than **14**.

Table 3. 4-Acylpiperidine derivatives

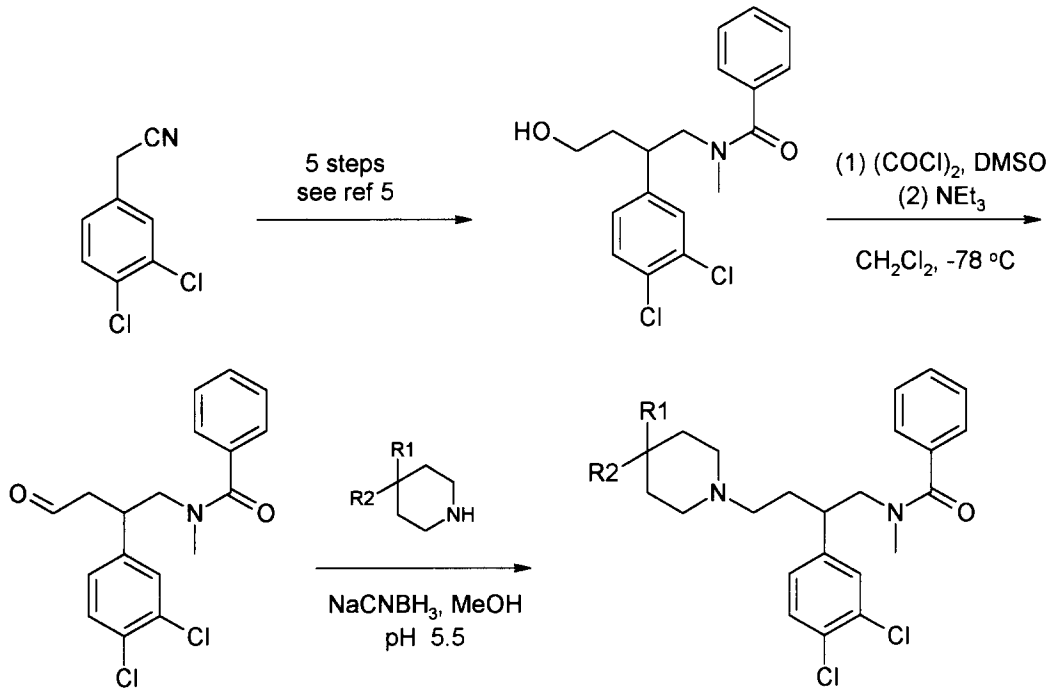


No.	R_1	R_2	K_i (nM)	pK_B (n)	% inhib @ 5 μmol/kg[a]
15	C_2H_5	O	9.2	8.6 (2)	NT
16	C_2H_5	NOH	2.7	9.1 (2)	NT
17	C_2H_5	$NOCH_3$	6.5	7.6 (2)	NT
18	C_2H_5	NOH (*E*)	1.3	8.8 (2)	20%[a]
19	C_2H_5	NOH (*Z*)	2.1	8.8 (2)	NT

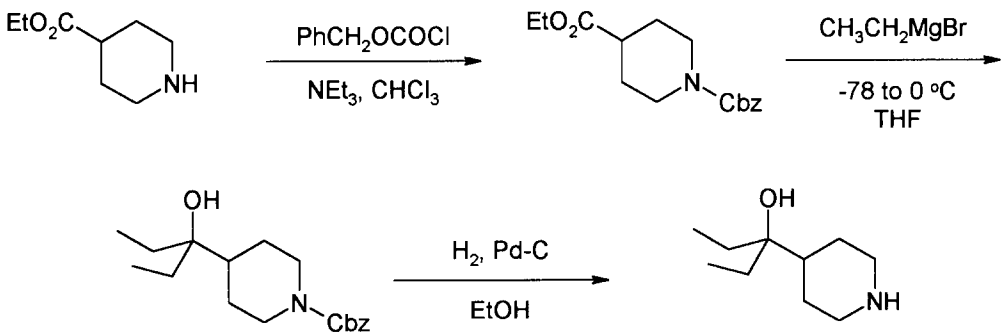
[a] In a guinea pig dyspnea model, see ref 10.

All of the compounds examined in this study were prepared by the synthetic route depicted in Scheme 1. Following the literature route of Sanofi,[5] *N*-[2-(3,4-dichlorophenyl)-4-hydroxybutyl-N-methylbenzamide (**20**) was prepared in six steps from 3,4-dichlorophenylacetonitrile. Oxidation of **20** using Swern conditions provided the somewhat unstable aldehyde **21**, which was coupled with the desired piperidine derivative under reductive amination conditions to provide the desired drug candidates.[12] The tertiary alcohol piperidine derivatives were prepared from ethyl isonipectotate as depicted in Scheme 2. Protection of the secondary amine as the benzyl carbamate, addition of a Grignard or alkyllithium reagent to the ester moiety and deprotection by hydrogenolysis afforded the desired piperidine alcohols. Compounds **8–10** and **15–19** were prepared via the *N,O*-dimethyl carbamoyl piperidine,[13] which was prepared as depicted in Scheme 3.

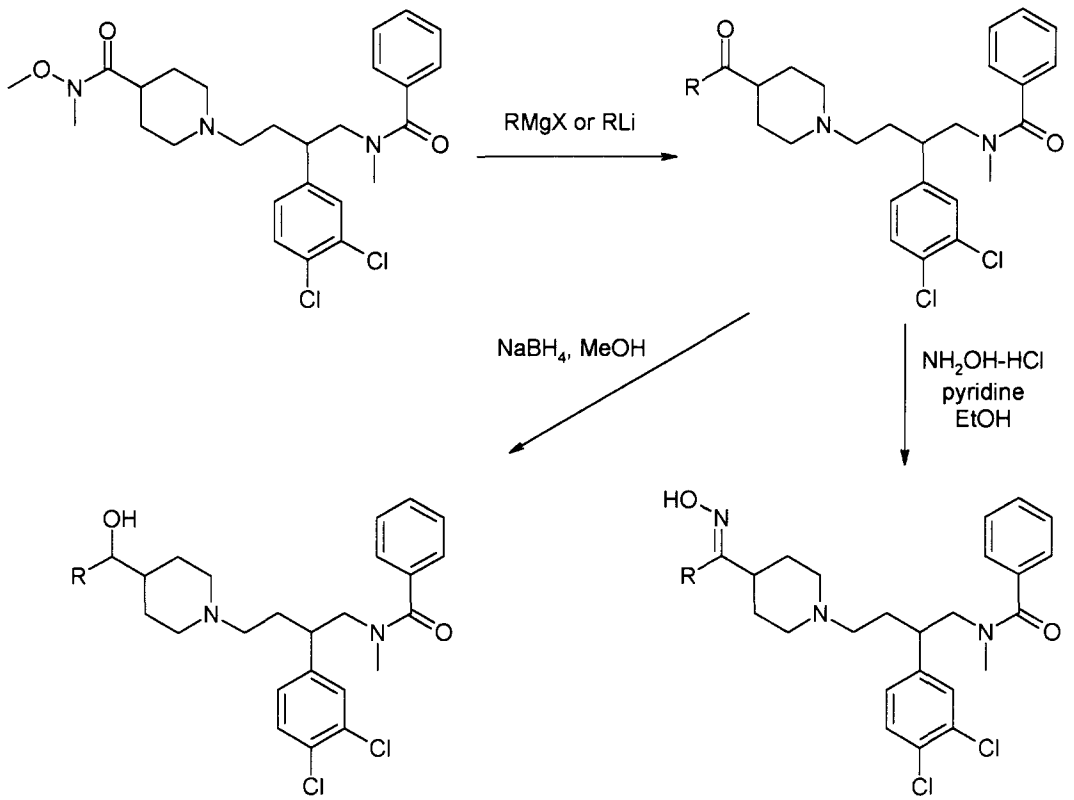
Scheme 1. General Synthetic Route.[7]



Scheme 2. Synthesis of piperidine tertiary carbinols.[7]



Scheme 3. Synthesis of piperidine secondary alcohols, ketone and oximes.[7]



In summary, a number of simple alkyl substituted piperidine derivatives of SR-48968 have been prepared and evaluated for activity, both in vitro and in vivo, as NK_2 receptor antagonists. These studies suggest that this region of the 2-(3,4-dichlorophenyl)-1,4-butanediamine scaffold can be widely varied from the 4-aryl derivatives originally reported without dramatic loss of activity. In particular, the achiral diethyl- (**12**) and dipropyl- (**13**) tertiary carbinols were found to be virtually equipotent with SR-48968 following oral dosing in a model of dyspnea in guinea pigs. These observations add to the diversity of functionality available to modify physicochemical parameters in this and related chemical series.

References and Notes

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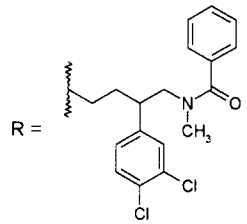
6. Throughout the manuscript, the *N*-substituent of the piperidine ring is the 3-(3,4-dichlorophenyl)-*N*-methylbenzamide identical to that found in SR-48968. Unless otherwise noted, all compounds were prepared as mixtures of stereoisomers.



7. Full details for the syntheses of the piperidine derivatives examined in this study can be found in: Jacobs, R. T., Shenvi, A. B., US Patent 5,521,199, May 23, 1996.

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11. The lower pK_B observed for **14** (8.1) as compared to **12** (8.8) is most likely due to the variability of this screen and the low number of tissues used (n = 2).

12. The pH of the reductive amination solution was adjusted to pH 5.5 by addition of glacial acetic acid.

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