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Cyclopentane-based human NK1 antagonists. Part 1: Discovery and initial SAR

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Abstract—An initial investigation of the novel cyclopentane scaffold **6** afforded low nanomolar human NK1 antagonists having enhanced water solubility properties compared to morpholine **1**. A synthesis of this cyclopentane scaffold, having three contiguous chiral centers, and the unexpected determination that the 1,2-*trans*-2,3-*trans*-ring stereochemistry, as opposed to the *cis*-ether/phenyl configuration of the known structures **1**–**5**, is optimal for this class of antagonist are described.

The neurokinin-1 receptor (NK1) is a member of the seven-transmembrane G-protein coupled family of receptors and is associated with sensory neurons in the periphery and specific areas of the CNS. The natural ligand for NK1 is the tachykinin peptide substance P (SP) which has been implicated in the pathophysiology of a diverse range of conditions including asthma, inflammatory bowel disease, pain, psoriasis, migraine, movement disorders, cystitis, schizophrenia, emesis, and anxiety/depression.[1] To date, the morpholine **1** (Aprepitant, hNK1 $IC_{50} = 0.09$ nM)[2] is the only currently marketed hNK1 antagonist and was approved by the FDA for use as an anti-emetic for chemotherapy-induced nausea and vomiting (CINV).[3] During the course of this work, **1** was also being extensively investigated as an anti-depressant for major depressive disorder.[4] While **1** has been demonstrated in the clinic to have good bioavailability upon oral administration, a parenteral formulation was not possible due to its low solubility in appropriate aqueous vehicles (0.2 μg/mL in isotonic saline, pH 8.2).[5] This limitation was initially addressed with the development of the aqueous soluble *N*-phosphoryl prodrug **2**.[5] While increased solubility was also addressed with the development of the more soluble, fully basic derivative **4**,[6] the identification of additional suitably soluble parent entities for both oral and parenteral use still remained an important need.[7–9]

As part of our ongoing pursuit of structurally diverse NK1 antagonists, the use of the 1,2-*cis*-2,3-*trans*-cyclohexane scaffold **5** (hNK1 $IC_{50} = 1.5$ nM)[10] was previously investigated as a replacement for the core morpholine of structure **3** (hNK1 $IC_{50} = 0.09$ and 1.1 nM for **3a** and **3b**)[11] from which **1** was later derived.[2] Herein, we report the initial synthesis of several isomers of the ring-contracted cyclopentane core structure **6**.[7] The structure–activity relationships (SAR) for this scaffold are discussed in terms of the stereochemistry at the three contiguous chiral centers and the enhanced water solubility achieved with this scaffold via incorporation of various basic moieties at C-3. Initial efforts first targeted derivatives based on our original morpholine structures **3a** and **3b**, having a 3,5-bis-trifluoromethylbenzyl ether at C-1 and an unsubstituted phenyl at C-2.[12] Subsequent efforts are detailed in the accompanying manuscript.[13]

Keywords: Neurokinin-1 receptor; NK1 antagonist; Cyclopentane-based structure.
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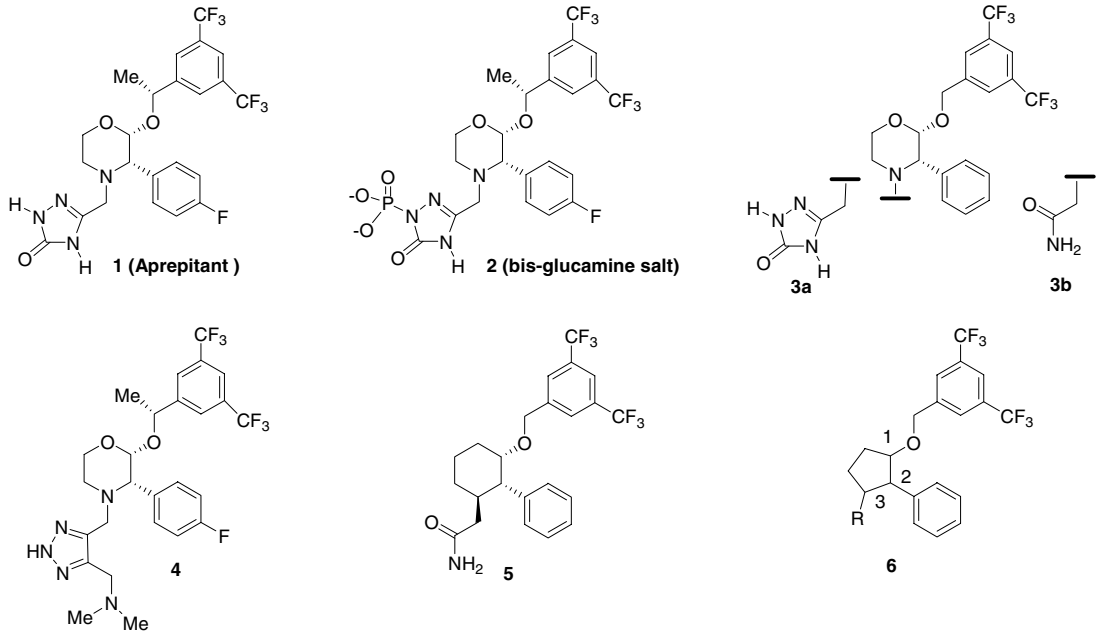
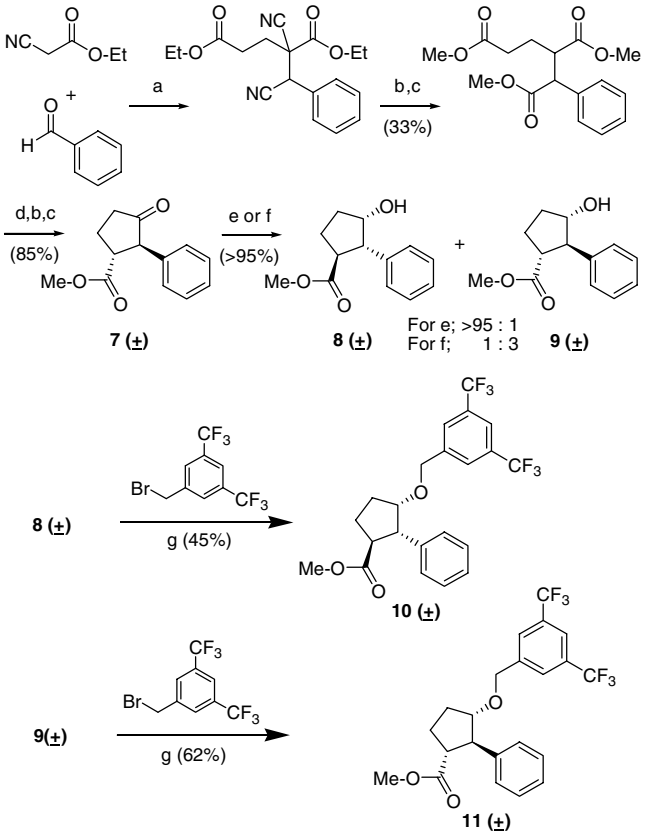
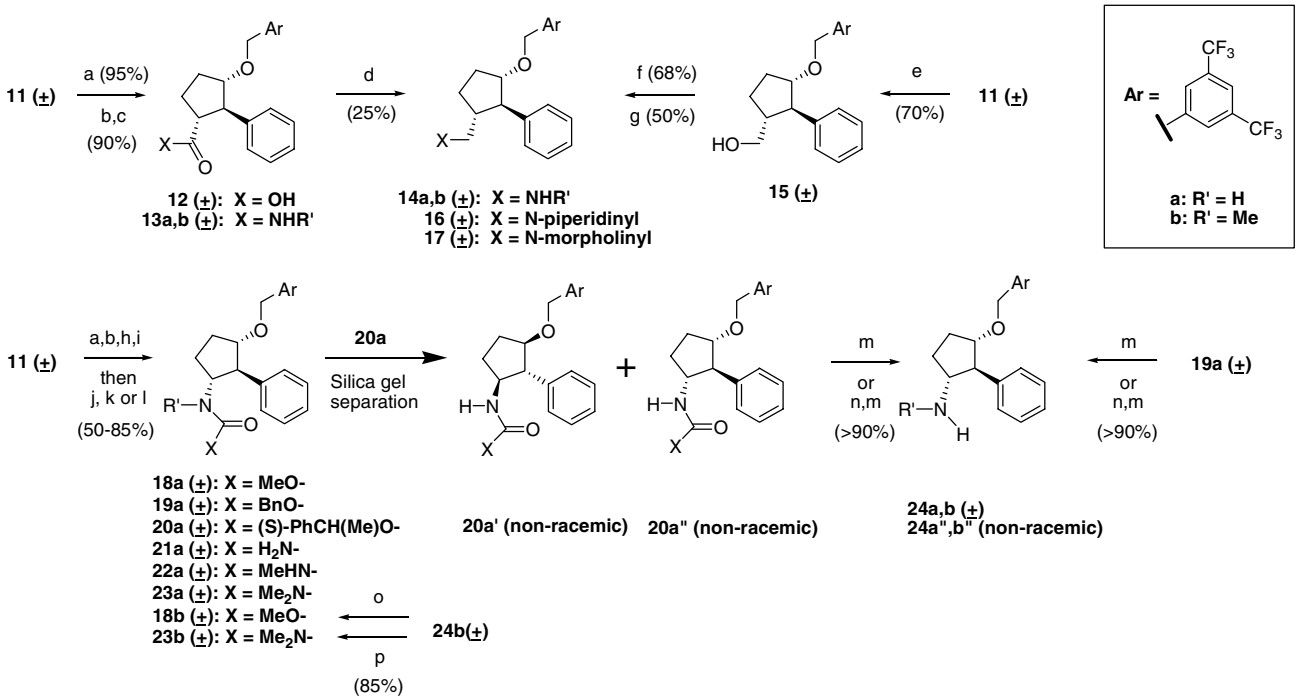


The synthesis[14] of the core cyclopentane scaffold having an oxygen functionality at C-1, the required phenyl at C-2, and a functionalizable ester moiety at C-3 was based on the reported synthesis of **7** in 28% yield (Scheme 1).[15] Subsequent to this work, an improved racemic route[16] to **7** and an asymmetric synthesis[17] of **9** were developed. The stereochemistry at the C-2 phenyl/C-3 ester was always the thermodynamically more stable *trans*-configuration.[17,18] Reduction of **7** with L-Selectride® produced exclusively the 1,2-*cis*-diastereomer **8**, while use of sodium borohydride in methanol resulted in a chromatographically separable 1:3 mixture of predominantly the lower R_f *trans*-isomer **9**. This stereochemical selectivity allowed for a thorough evaluation of both alcohol isomers. The *trans*-assignment for **9** was confirmed by an ^{1}H NMR NOE experiment.[19] Separate hydroxyl alkylation of **8** and **9** with 3,5-bis-trifluoromethylbenzyl bromide and sodium hydride afforded the intermediate racemic ethers **10** and **11**. Interestingly, the hNK1 affinity of derivatives prepared from the 1,2-*trans*-ester **11** was generally 3- to 5-fold greater than that of those derived from the 1,2-*cis*-ester **10** (see below); thus, the *trans*-series was preferentially investigated.

Hydrolysis of ester **11** gave acid **12** (Scheme 2) which was converted into amides **13**. (Note that the *cis*-derivatives can be similarly prepared from ester **10**.) Borane reduction then afforded the methylene-spaced amines **14** which could be alkylated to give a variety of derivatives (see Scheme 3). Alternatively, lithium borohydride reduction of **11** afforded the alcohol **15**. Conversion to the bromide and alkylation of piperidine or morpholine afforded **16** and **17** as an alternate synthesis of aminomethylene derivatives. The ester **11** could also be converted to several *N*-cyclopentylamino derivatives via Curtius rearrangement of acid **12** and reaction of the intermediate isocyanate with either alcohols, to afford carbamates **18a**–**20a**, or with amines, to afford ureas **21a**–**23a**. Methylation and/or hydrogenation of the CBz group of **19a** afforded the racemic *N*-cyclopentyl amines **24a** and **24b** which on alkylation (see Scheme 3) afforded analogs of structures **3** and **5**. Acylation of **24b** also afforded the N–Me derivatives **18b** and **23b**.



Scheme 1. Reagents and conditions: (a) (i) piperidine, EtOH, 35–65 °C; (ii) NaCN, 35–80 °C, 1 h; (iii) $ClCH_2CH_2CO_2Et$, 35–80 °C, 5 h; (b) 6 M HCl, reflux, 48 h; (c) MeOH, HCl (g), $HC(OMe)_3$, 65 °C, 16 h; (d) NaOMe, MeOH or LiHMDS, THF; (e) L-Selectride®, THF (selective for **8**); (f) $NaBH_4$, MeOH (1:3 ratio of **8**:**9**); (g) NaH, DMF.

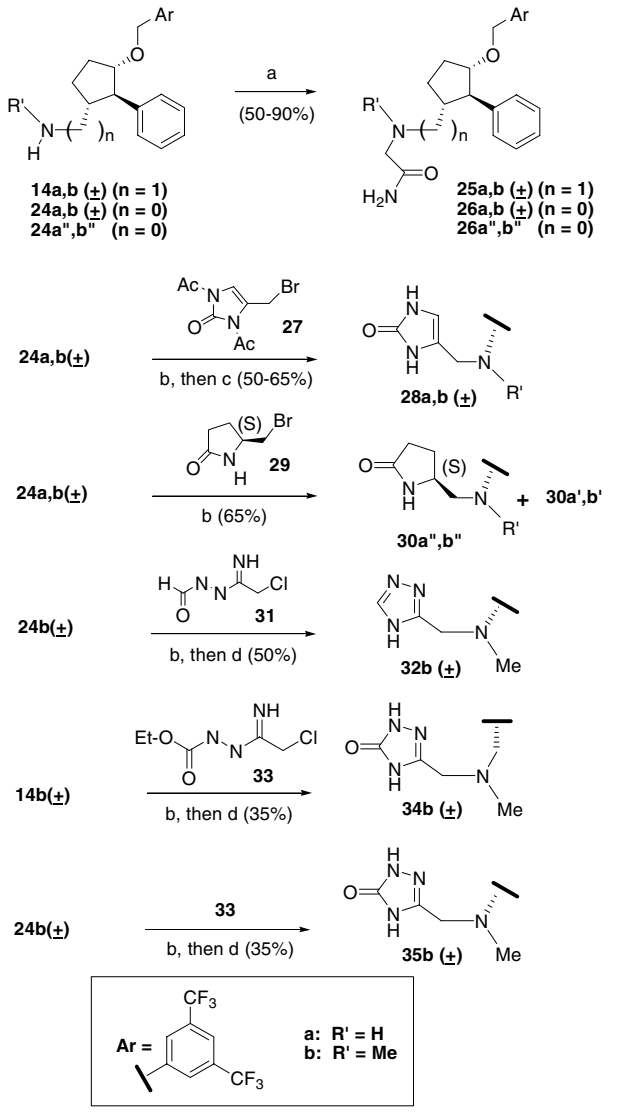


Scheme 2. Reagents and conditions: (a) NaOH, MeOH; (b) oxalyl chloride, DMF (cat), DCM; (c) NH_3 or $MeNH_2$ (aq, excess), THF; (d) BH_3–Me_2S, THF; (e) $LiBH_4$, THF; (f) Ph_3P–Br_2, MeCN; (g) piperidine or morpholine (excess), MeCN; (h) NaN_3, acetone/water, −10 °C; (i) PhMe, 85 °C; (j) MeOH, DIPEA, DMAP (cat); (k) BnOH or (*S*)-PhCH(Me)OH, DIPEA, DMAP (cat), PhMe, 85 °C; (l) NH_3, $MeNH_2$ or Me_2NH (aq, excess), dioxane; (m) H_2 (50 psi), 10% Pd/C, EtOH; (n) MeI, NaH, DMF; (o) $ClCO_2Me$, DIPEA, DCM; (p) $ClCONMe_2$, DIPEA, DCM. The 1,2-*cis* derivatives were similarly prepared from **10** and are designated as **c** (R′ = H) and **d** (R′ = Me) in the text and Table 1.

Alternatively, reaction of the above isocyanate with (S)-α-methylbenzyl alcohol afforded **20a** as a silica gel separable mixture of the diastereomeric CBz intermediates **20a′** and **20a″**. The 1,2-*cis*-series also gave the two corresponding separable diastereomers; thus, all four enantiomerically enriched forms of **24** were available. The binding data (see below) were initially used to differentiate the more active and less active diastereomers. Based on modeling and by analogy to the known morpholine *cis*-stereochemistry, the stereochemistry for the active *trans*-enantiomer was tentatively assigned as [1*S*,2*S*,3*R*] as shown for structure **24** in Scheme 2 and structure **C** in Table 1 (for R = NH_2). The absolute assignment for the *trans*-series was later confirmed by single-crystal X-ray analysis of a resolved 4-fluorophenyl acid salt derivative of **9**.[12,13] The absolute stereochemistry of the active enantiomer in the *cis*-series was assumed to be the same as that of structure **3**, i.e., [1*S*,2*R*,3*S*] as in structure **D**, Table 1 (for R = NH_2).

Alkylation of the N–Me and N–H amines **14** and **24** (Scheme 3) afforded a variety of amine derivatives of varying basicity. Iodoacetamide afforded the glycinamide derivatives **25-26** as analogs of **3b**, *N*,*N*-diacetyl bromomethylimidazolinone (**27**) gave **28** after removal of the *N*-acetyl groups, and use of (*S*)-bromomethylpyrrolidinone (**29**) allowed for the direct separation of diastereomeric lactams **30** (lower R_f diastereomers **30a″** and **30b″** being derived from the more potent enantiomer). Alternatively, the N–Me derivatives could also be alkylated with *N*-formyl- (**31**) or *N*-(methoxycarbonyl)-2-chloroacetamidrazone (**33**) followed by cyclization at 150 °C in xylenes to afford the triazole **32b** and triazolinones **34b** and **35b**, which were analogous to the triazolinone morpholine structure **3a**.[2,11]

While non-basic morpholine **1** has been found to have good bioavailability upon oral administration to several species (e.g., rat, $F = 53\%$; dog, $F = 40\%$), formulation for parenteral use was not possible due to its low solubility in appropriate aqueous vehicles (0.2 μg/mL in isotonic saline, final pH 8.2).[5] The possibility of enhanced water solubility was expected for this more basic cyclopentane scaffold, since an exocyclic nitrogen would no longer be benzylic nor part of a morpholine ring. Both of these features greatly diminish the basicity of the morpholine nitrogen (pK_a of **3a** <3.5 in 1:1 methanol/water).[11,20] Indeed, as listed in Table 1, the water solubility at pH 5 (0.1 M sodium acetate/acetic acid buffer) for many of these derivatives was found to be significantly enhanced over that of **1** (<0.0005 mg/mL at pH 5).[21] For the N–H glycinamides **25a** and **26a** (0.59 and 1.1 mg/mL) the solubility enhancement was over 1000-fold, while the solubility for the corresponding N–Me analogs **25b** and **26b** (0.30 and 0.016 mg/mL) was less impressive. Good solubilities were also seen for 1,2-*trans*-heterocyclic derivatives **28b**, **30a″**, and **30b″** (0.45, 4.0, and 0.51 mg/mL, respectively) with the N–Me triazolinone **35b** (0.20 mg/mL) giving at least a 400-fold increase. In this case, the corresponding less active 1,2-*cis*-triazolinone **35d** (see Table 1) was also slightly less soluble (0.08 mg/mL). These enhanced solubilities are most likely due to the increased basicity of these derivatives. For example, the *trans*-derivatives **26a** and **26b**



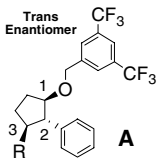
Scheme 3. Reagents and conditions: (a) ICH_2CONH_2, DIPEA, CH_3CN; (b) DIPEA, CH_3CN (for **29**, 90 °C in sealed vial); (c) $MeNH_2$, THF; (d) xylenes 150 °C. The 1,2-*cis* derivatives in Table 1 were similarly prepared from *cis*-**24** and are designated **c** (R′ = H) and **d** (R′ = Me).

had measured pK_as of 6.6 and 5.8 in 1:1 methanol/water.[20]

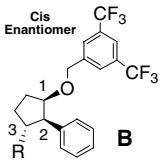
The hNK1 binding affinities for both the neutral and basic target compounds, as well as several of the intermediates, were determined by measuring their ability to displace [^{125}I]SP from human NK1 receptor stably expressed in CHO cells.[22] The hNK1 binding results are summarized in Table 1 with significant binding affinity being observed in several classes of compounds. The initial *cis*-derivatives **18c** and **21c** indicated some hNK1 affinity (hNK1 IC_{50} = 5.3 and 9.8 nM), however, unexpectedly the corresponding *trans*-isomers **18a** and **21a** actually showed enhanced affinity (IC_{50} = 0.89 and 3.5 nM). Also, other neutral *trans*-nitrogen derivatives (i.e., **13a**, **18b**, **22a**, and **23a**; IC_{50} = 7.2, 6.2, 2.7, and 5.0 nM, respectively) and even the alcohol intermediate **15** (IC_{50} = 0.77 nM) achieved moderate potency, although the acid **12** had poor hNK1 affinity. While previous studies in the six-membered core piperidine[9b] and morpholine[11] scaffolds had reported that the *cis*-configuration afforded significantly better potency than the *trans*-configuration (~200-fold for the [2*S*,3*S*] morpholine **3a** and its *trans* [2*S*,3*R*] isomer), in this cyclopentane scaffold the opposite relationship was found. With the possible exceptions of **24a** and **24c** and **26b** and **26d** the *trans*-derivatives generally afforded a 2- to 5-fold enhancement over the *cis*-configuration. More importantly, although the racemic 1,2-*cis*-N–H glycinamide **26c** indicated poorer binding affinity compared to **5**[10] and the equivalent acetamide derivative **3b**[11] (IC_{50} = 8.3 nM vs 1.5 and 1.1 nM, respectively), the non-racemic [1*S*,2*S*,3*R*] *trans* N–H derivative **26a**″ was very comparable (IC_{50} = 0.95 nM). At the time, potential use of the 1,2-*trans*-cyclohexane had not been considered based on the earlier morpholine results. Although the effect of an additional *N*-methyl to afford the tertiary amines was beneficial in the *cis*-series (IC_{50} = 8.3 vs 2.1 nM for **26c** and **26d**), the results in the more potent *trans*-series were mixed (IC_{50} = 1.3 vs 2.7 nM for **26a** and **26b**; 5.2 vs 2.4 nM for **28a** and **28b**; 1.5 vs 0.81 nM for **30a**″ and **30b**″). Insertion of an additional methylene as in analogs **25a** and **25b** also made little difference in binding. Reversing the amide as in the (*S*)-lactams **30a**″ and **30b**″ gave comparable results to the glycinamides, although the corresponding (*R*)-lactams generally showed about 2-fold poorer affinity (data not shown). Unfortunately, the targeted imidazolinone, triazole, and triazolinone derivatives (**28b**, **32b**, and **35b**; IC_{50} = 2.4, 1.1, and 2.0 nM, respectively) did not show the anticipated 10-fold improvement obtained with the morpholines (IC_{50} = 0.09 vs 1.1 nM for **3a** and **3b**).[11] As would be expected, there was an enantiomeric preference as seen with the chiral amines **24a**′ and **24a**″ (IC_{50} = 100 and 2.3 nM), glycinamides **26a**′ and **26a**″ (IC_{50} = 45 and 0.95 nM), and (*S*)-lactams **30a**′ and **30a**″ (IC_{50} = 260 and 1.5 nM).

This general enhanced affinity of the 1,2-*trans*-series over the 1,2-*cis*-series is likely due to the increased flexibility of the five- versus six-membered ring in which the 1,2-*trans* orientation of the two phenyl moieties can afford a more optimal hNK1 pharmacophore fit. Interestingly, the extent of this enhancement is also quite dependent on the C-3 substituent, ranging from a *cis*:*trans* IC_{50} ratio of 0.8 for **26b** and **26d** to 6 for **26a** and **26c**. The nature of the C versus N linkage at C-3 might also be important, although the N-substituent would be expected to be similarly '*trans*' to the phenyl. Thus, it is noteworthy that it is the relative 2,3-substituent configurations which are reversed while the ether absolute configuration is conserved. In addition, these results again demonstrate that potent hNK1 binding is not dependent on the presence of a fully basic nitrogen at the 3-position relative to the ether, in fact, the *trans*-amine **14a** showed less hNK1 affinity than the alcohol **15**. This toleration of a wide variety of functionality at the C-3 position suggests that the receptor binding domain in the region of the C-3 moiety is relatively unstructured, although there is a general preference for a polar, small to moderately sized moiety (see **16**, **17**, **19a**, **23a** and **23b** having larger R′ groups). However, the choice of substituent at the C-3 position was

Table 1. Structures, solubilities, pK_as, and hNK1 binding affinities of selected compounds



A



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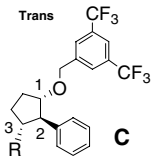

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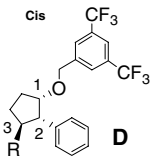
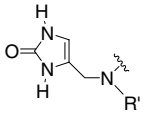
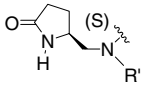
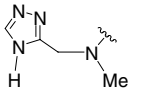
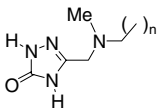


D

Compound	Stereochemistry	–R	NK1 IC_{50}[a] (nM)	(SEM, *n*)[b]	Solubility at pH 5 (mg/mL)[c]	pK_a[d]
1	(2*R*,3*S*)	—	0.09[e]	—	<0.0005	<3.5
3a	(2*S*,3*S*)	—	0.09[f]	—	0.003	<3.5
3b	(2*S*,3*S*)	—	1.1[f]	—		
5	(1*S*,2*S*,3*R*)	—	1.5[g]	—		
12	*trans*, A/C	$-CO_2H$	67	(*n* = 1)		
13a	*trans*, A/C	$-CONH_2$	7.2	(1.2, 2)		
14a	*trans*, A/C	$-CH_2NH_2$	2.7	(0.3, 3)		
14b	*trans*, A/C	$-CH_2NHMe$	1.9	(0.5,3)		
15	*trans*, A/C	$-CH_2OH$	0.77	(0.16, 3)		
16	*trans*, A/C	$-CH_2$-1-piperidinyl	5.0	(*n* = 1)		
17	*trans*, A/C	$-CH_2$-4-morpholinyl	8.2	(0.9, 3)		
18a	*trans*, A/C	$-NHCO_2Me$	0.89	(0.10, 4)		
18b	*trans*, A/C	$-NMeCO_2Me$	6.2	(1.0, 4)		
18c	*cis*, B/D	$-NHCO_2Me$	5.3	(1.7, 3)		
19a	*trans*, A/C	$-NHCO_2Bn$	40	(*n* = 1)		
19c	*cis*, B/D	$-NHCO_2Bn$	300	(*n* = 1)		
21a	*trans*, A/C	$-NHCONH_2$	3.5	(0.3, 3)		
21c	*cis*, B/D	$-NHCONH_2$	9.8	(2.2, 3)		
22a	*trans*, A/C	–NHCONHMe	2.7	(0.3, 3)		
23a	*trans*, A/C	$-NHCONMe_2$	5.0	(0.7, 3)		
23b	*trans*, A/C	$-N(Me)CONMe_2$	16	(*n* = 1)		
24a	*trans*, A/C	$-NH_2$	5.7	(*n* = 1)		
24b	*trans*, A/C	–NHMe	0.83	(0.38, 3)		
24c	*cis*, B/D	$-NH_2$	7.9	(2.4, 3)		
24d	*cis*, B/D	–NHMe	7.2	(*n* = 1)		
24a′	*trans*, A	$-NH_2$	100	(*n* = 1)		
24a″	*trans*, C	$-NH_2$	2.3	(0.2, 3)		
25a	*trans*, A/C	$-CH_2NHCH_2CONH_2$	1.9	(0.7, 3)	0.59	
25b	*trans*, A/C	$-CH_2NMeCH_2CONH_2$	1.9	(0.3, 8)	0.30	
26a	*trans*, A/C	$-NHCH_2CONH_2$	1.3	(0.1, 7)	1.1	6.6
26b	*trans*, A/C	$-NMeCH_2CONH_2$	2.7	(0.4, 6)	0.016	5.8
26c	*cis*, B/D	$-NHCH_2CONH_2$	8.3	(2.0, 3)	0.80	
26d	*cis*, B/D	$-NMeCH_2CONH_2$	2.1	(0.3, 6)		
26a′	*trans*, A	$-NHCH_2CONH_2$	45	(*n* = 1)		
26a″	*trans*, C	$-NHCH_2CONH_2$	0.95	(0.06, 6)		
28a (R′ = H)	*trans*, A/C		5.2	(0.4, 6)		
28b (R′ = Me)	*trans*, A/C		2.4	(0.7, 3)	0.45	
30a′ (R′ = H)	*trans*, A		260	(35, 3)		
30a″ (R′ = H)	*trans*, C		1.5	(0.3, 3)	4.0	
30b″ (R′ = Me)	*trans*, C		0.81	(0.35, 3)	0.51	
32b	*trans*, A/C		1.1	(0.5, 3)		
34b (*n* = 1)	*trans*, A/C		4.9	(1.3, 3)	0.01	
35b (*n* = 0)	*trans*, A/C		2.0	(0.5, 3)	0.20	
35d (*n* = 0)	*cis*, B/D		4.7	(*n* = 1)	0.08	

[a] Displacement of ^{125}I-labeled SP from the cloned hNK1 receptor expressed in CHO cells.
[b] Except as noted (*n* = 1), data are an average of 2–8 independent replicate titrations.[22]
[c] Aqueous solubilities were measured in 0.1 M sodium acetate/acetic acid buffer at pH 5 (*n* = 2).[21]
[d] Titrations were preformed in 1:1 methanol/water.[20]
[e] See Ref. 2.
[f] See Ref. 11.
[g] See Ref. 10.

found to be critical for in vivo potency and for obtaining the desired physical properties (also see Ref. 13).

In order to determine whether these new hNK1 antagonists could inhibit the action of SP in vivo, a previously described assay (SYVAL[23]) was utilized.[2,11] Intravenous administration of capsaicin or resiniferatoxin causes a dose-dependent vascular leakage in the esophagus, trachea, and bladder of guinea pigs and can be quantified with Evans Blue dye. This response is mediated by the endogenous release of SP from capsaicin-sensitive nerve fibers and can be inhibited by the systemic administration of NK1 receptor antagonists. Test compounds were administered orally at differing doses and time intervals before capsaicin or resiniferatoxin challenge, thus serving both as a functional NK1 inhibition readout as well as a pharmacokinetic measurement. The utility of these derivatives in this assay and the in vivo importance of the C-3 moiety were initially demonstrated with two of the above compounds. When the *trans*-compound **26a** (IC_{50} = 1.3 nM) was administered orally at 1 mg/kg and 1 h prior to challenge, a 60% inhibition was achieved. However, when the neutral carbamate **18a** (IC_{50} = 0.89 nM) was administered, <25% inhibition was observed.

The initial synthesis of a variety of 3-amino and 3-aminomethylene derivatives was investigated in this 1-benzyloxy-2-phenylcyclopentane scaffold based on the previous morpholine structure **3**. The synthesis involved the stereoselective synthesis of either the 1,2-*cis* or 1,2-*trans*-hydroxy intermediates **8** and **9**. The 3-amino derivatives were also available in chiral form through separation of the diastereomeric (*S*)-α-methylbenzyl carbamates **20a** and **20c**. Several basic cyclopentane derivatives demonstrated the desired enhanced water solubility at pH 5 necessary for an intravenous formulation. The hNK1 binding affinity for this series of compounds was found to be relatively insensitive to the functionality at C-3, although moderately sized hydrophilic moieties were preferred. Preliminary results for the glycinamide derivative **26a** indicated that this class of hNK1 antagonist was also capable of in vivo inhibition of SP-elicited systemic plasma extravasation after oral administration. The finding that the 1,2-*trans*-2,3-*trans*-configuration in this scaffold was significantly better than the preferred *cis*-arrangement in our previous morpholine core structures was unexpected. These results led to additional investigations of this scaffold as discussed further in the accompanying manuscript[13] and elsewhere.[24,25]

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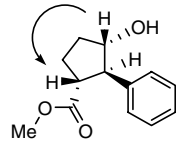
19. A ^{1}H NMR NOE experiment of the more polar isomer showed an unambiguous interaction between the C-1 and C-3 protons, thus, confirming the 1,2-*trans*-2,3-*trans* assignment for **9**.



9

20. The reported pK_a values were obtained by titration in 1:1 methanol/water. The presence of 50% MeOH in a titration has the effect of lowering the pK_a of an amine between 0.3 and 0.9 U (with 0.5 U as a typical value) as compared to its value in water (i.e., the actual pK_a of **26b** in water is likely closer to 6.3).[26]
21. Solubilities were determined by HPLC after sonication in buffer at 1 mg/mL and filtration. The solubility for **1** and **3a** was determined in 0.1 M potassium hydrogen phosphate buffer at pH 5, while the solubilities for selected cyclopentane compounds were done in 0.1 M sodium acetate/acetic acid buffer adjusted to pH 5. The reported results are an average of $n = 2$.
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