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Cyclopentane-based human NK1 antagonists. Part 2: Development of potent, orally active, water-soluble derivatives

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Abstract—The synthesis and optimization of a cyclopentane-based hNK1 antagonist scaffold **3**, having four chiral centers, will be discussed in the context of its enhanced water-solubility properties relative to the marketed anti-emetic hNK1 antagonist EMEND® (Aprepitant). Sub-nanomolar hNK1 binding was achieved and oral activity comparable to Aprepitant in two in vivo models will be described.

The human neurokinin-1 receptor (hNK1) is a member of the seven-transmembrane G-protein coupled family of receptors and is primarily associated with sensory neurons in the periphery and specific areas of the CNS. The natural ligand for the NK1 receptor 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 nausea.[1] The potent, orally active hNK1 receptor antagonist **1** (Aprepitant) (hNK1 $IC_{50} = 0.09$ nM)[2] was recently approved by the FDA for the treatment of both moderate and highly emetic chemotherapy-induced nausea and vomiting (CINV).[3,4] During clinical trials morpholine **1** was found to have good bioavailability upon oral administration, however, a parenteral formulation was not possible due to its low aqueous solubility (0.2 μg/mL in isotonic saline, final pH 8.2).[5] While the development of a soluble *N*-phosphoryl pro-drug has been disclosed,[5] the identification of a suitably soluble parent entity for both oral and parenteral use still remained an important need. In addition to other morpholine,[6] piperidine,[7] and cyclohexane[8] core-based compounds that had been reported, the preceding manuscript described the synthesis and some preliminary hNK1 binding results for a novel cyclopentane-based scaffold **2**.[9] Herein, we report on our subsequent investigation of the modified five-membered scaffold **3** having an α-methyl on the benzyl ether and a 4-fluoro on the phenyl as present in structure **1**, as well as additional structure–activity relationship (SAR) studies at the C-3 position. The effects of these modifications in terms of additional improvements to the hNK1 binding affinity, enhanced aqueous solubility compared to **1**, and the demonstration of efficacy in both peripheral and CNS-based in vivo models are described herein.[10]

Keywords: Neurokinin-1: substance P; NK1 antagonist: cyclopentane-based structure.
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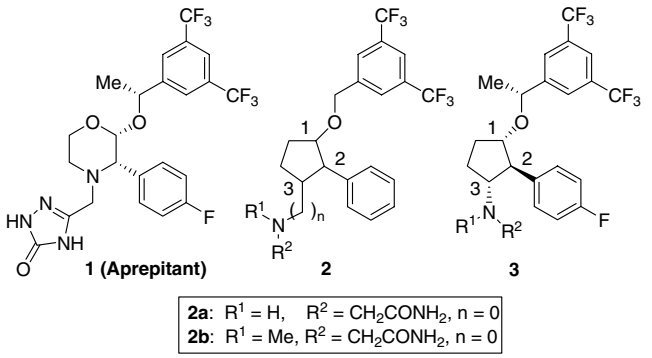
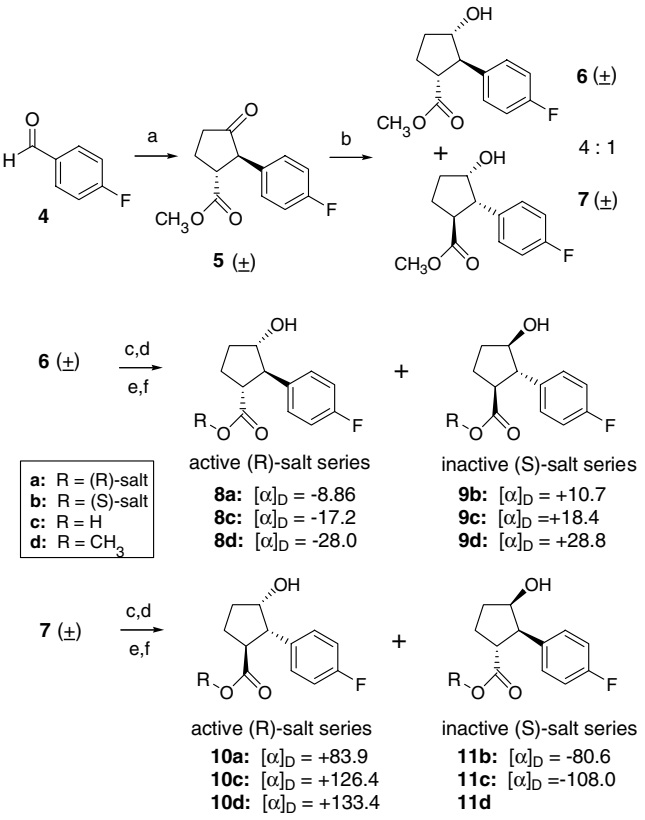


The initial evaluation of hNK1 binding affinity for several derivatives of the cyclopentane scaffold **2**, having three contiguous chiral centers on the cyclopentane ring, revealed an unexpected result. Unlike the established six-membered piperidine and morpholine core structures which favored a *cis* configuration between the ether and phenyl, in the case of the five-membered cyclopentane scaffold better hNK1 affinity was achieved with the 1,2-*trans*-2,3-*trans* configuration rather than the anticipated 1,2-*cis*-2,3-*trans* arrangement. In addition, it was shown that a more basic nitrogen moiety could be appended to the cyclopentane scaffold at C-3; thus, enhanced water solubility was achieved compared to the relatively non-basic morpholine structures ($pK_a < 3.5$ in 1:1 methanol/water).[11] This feature was deemed critical for development of an intravenous formulation and spurred our further investigation of these cyclopentane-based structures. Incorporation of an (*R*)-α-methylbenzyl ether and a 4-fluorophenyl onto the morpholine scaffold had been shown to afford equivalent hNK1 binding, but dramatically enhanced in vivo activity compared to the original morpholine structure.[2,11] Similar modifications of cyclopentane **2** as indicated in structure **3** were followed by a more in-depth investigation of the SAR at C-3.

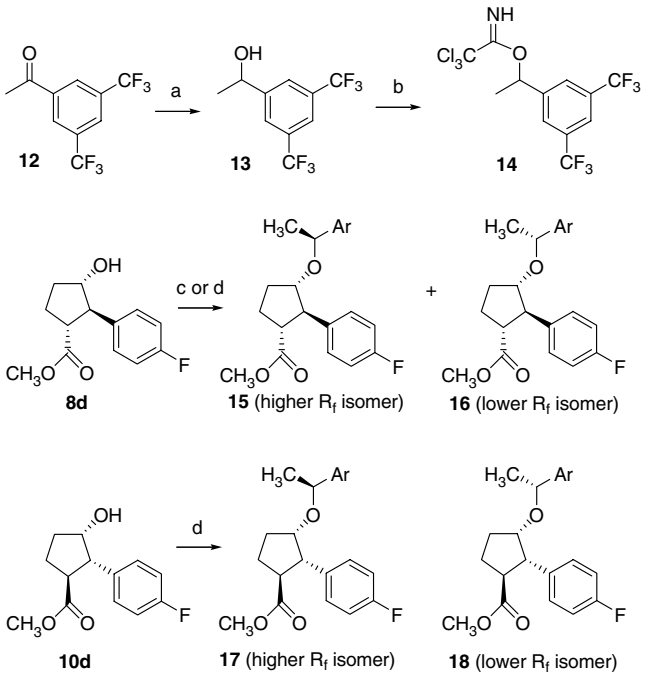
The synthesis[12,13] of methyl 3-keto-2-(4-fluorophenyl)cyclopentane carboxylate (**5**) starting from commercially available 4-fluorobenzaldehyde (**4**) was based on a literature procedure[14] and was described in the preceding manuscript in the des-fluoro series (Scheme 1).[9] Reduction of the ketone **5** with sodium borohydride afforded a separable 4:1 mixture of the racemic *trans* and *cis* alcohols **6** and **7**. Hydrolysis to the individual hydroxy acids allowed for their resolution as either the (*R*)-α-methylbenzylamine salts **8a** and **10a** or (*S*)-α-methylbenzylamine salts **9b** and **11b**. After conversion to the free acids **8c–11c**, re-esterification provided the two non-racemic 1,2-*trans* methyl esters **8d** and **9d**, and the two corresponding 1,2-*cis* esters **10d** and **11d**. While the absolute stereochemistry for the more potent *trans* enantiomer (see below) had previously been tentatively assigned as in structure **8**, the *trans* salt **9b** was found to be amenable to a single crystal X-ray structure analysis and the assignments for the three cyclopentane centers were unequivocally determined.[15] Subsequent to this work, an improved route to racemic **6**[16] and a stereospecific synthesis of **8d**[17] were developed.



Scheme 1. Reagents: (a) see Refs. 9,13,14 (50–60% from **4**); (b) $NaBH_4$, MeOH (**6** (77%) and **7** (19 %)); (c) NaOH, MeOH (98%); (d) (*S*)-(−)- or (*R*)-(+)-$PhCH(Me)NH_2$; (e) HCl (aq), ether (100%); (f) HCl (g), MeOH (>95%).

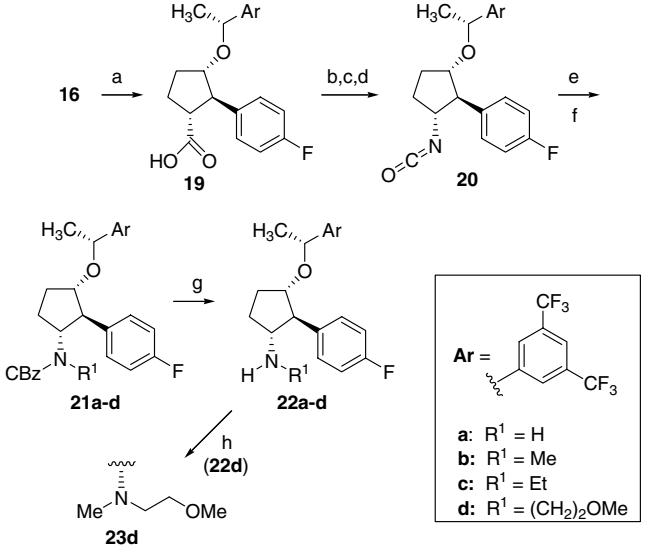
A first attempt at installing the α-methylbenzyl ether moiety on racemic alcohol **6** using α-methylbenzyl bromide (10-fold excess) with NaH in DMF gave mostly elimination to the styrene and a 20–40% yield of a 1:1 racemic mixture of the *trans* ethers **15** and **16** (Ar = 3,5-bis-(trifluoromethyl)phenyl). Fortunately, use of resolved **8d** and a 2-fold excess of racemic trichloroacetamidate **14** (derived from ketone **12** via alcohol **13**) in the presence of triflic acid (10–20 mol%) in 1:1 cyclohexane/dichloromethane afforded an improved 70–90% yield of the non-racemic **15** and **16** as an easily separable 1:1 mixture (Scheme 2).[18] In the *cis* series, alkylation of **10d** provided a 24% and 34% yield, respectively, of the non-racemic α-methyl isomers **17** and **18** with 40% recovery of the unreacted alcohol. Thus, resolution of all four stereocenters was achieved.

The initial in vitro results for racemic **15–18** (hNK1 binding assay IC_{50} = 100, 3, >100, and 8 nM, respectively, see below) revealed that there was a significant difference in binding affinity related to the α-methyl isomers and that the lower R_f diastereomers in both cases possessed the greater activity. Examination of models and by analogy to the established morpholine series, as well as analysis of the ^1H NMR and TLC data (both more potent ethers **16** and **18** had similar ^1H NMR α-methyl shifts and were both the lower R_f diastereomer) resulted in the assignment of the (*R*)-methyl stereochemistry for

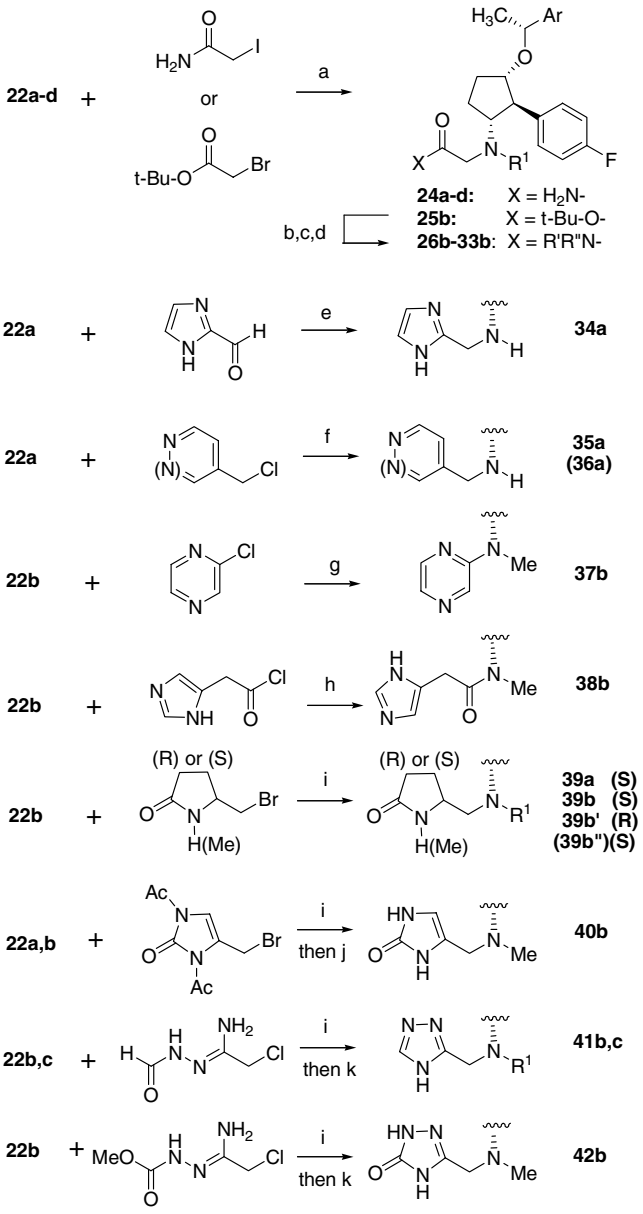


Scheme 2. Reagents: (a) $NaBH_4$, THF (97%); (b) NaH, Cl_3CCN, Et_2O (98%); (c) (±)-α-methylbenzyl bromide (10 equiv), NaH (10 equiv), DMF (20–40%); (d) **14**, triflic acid (10–20% cat.), 1:1 DCM/cyclohexane (from **8d**, **15** (36%) and **16** (40%); from **10d**, **17** (24%), **18** (34%), and recovered **10d** (40%)).

both the *cis* and *trans* series.[18] As expected, the 1,2-*trans* diastereomer **16** (and compounds derived from **16**) possessed significantly better binding affinity for hNK1 than 1,2-*cis* **18**; thus, the former series was more extensively investigated as illustrated in Schemes 3 and 4 (although similar chemistry was also carried out in the 1,2-*cis* series).



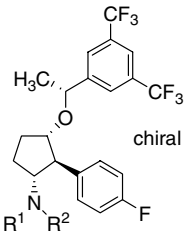
Scheme 3. Reagents and conditions: (a) NaOH, MeOH, 60 °C (98%); (b) Oxalyl chloride, DMF (cat.), DCM; (c) NaN_3, acetone/water, −10 °C; (d) toluene, 80 °C; (e) BnOH, DIPEA, DMAP (cat.), toluene, 100 °C (75–85% from **19**); (f) MeI, EtI or $ClCH_2CH_2OMe$, NaH, DMF (**22b**, 93%; **22c**, 90%; **22d**, 80%); (g) H_2, Pd/C, EtOH (>95%); (h) COH_2, H_2, 10% Pd/C, MeOH (>90%).

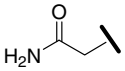
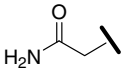
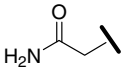
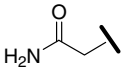
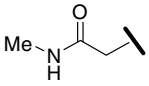
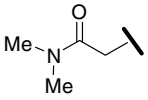
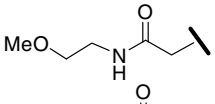
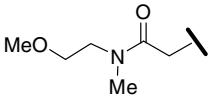
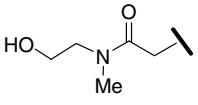
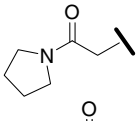
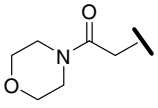


Scheme 4. Reagents and conditions: (a) DIPEA, MeCN, (**24a**, 62%; **24b**, 87%; **24c**, 65%; **24d**, 57%; **25b**, 93% (at 50 °C)); (b) TFA; (c) oxalyl chloride, DMF (cat.), DCM; (d) R′R″NH, DCM (40–80% from **25b**); (e) $NaCNBH_3$, HOAc, DCE (59%); (f) DIPEA, DCM (**35a**, 37%; **36a**, 44%); (g) K_2CO_3, DMF (22%); (h) DIPEA, DCM (75%); (i) DIPEA, MeCN, rt (for **39**, 90 °C) (50–75%); (j) $HNMe_2$ (82%); (k) xylenes, 140 °C (**41b**, 45%; **41c**, 34%; **42b**, 36%).

Hydrolysis of the methyl ester **16** provided the acid **19** which underwent the Curtius rearrangement to the isocyanate **20** (Scheme 3). Reaction with benzyl alcohol afforded the CBz protected C-3 amine **21a**. Alkylation with methyl or ethyl iodide or 2-methoxyethyl bromide afforded the CBz protected alkyl amines **21b–d**. Removal of the CBz by hydrogenation provided the alkyl amines **22a–d** which were then utilized in Scheme 4. Reductive amination of **22d** with formaldehyde also afforded the tertiary amine **23d**. Similar treatment of **18** afforded the corresponding 1,2-*cis* amines (structures not shown).

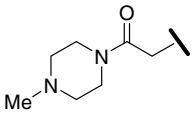
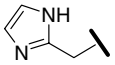
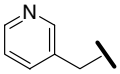
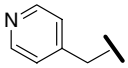
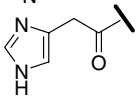
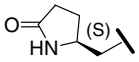
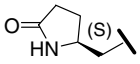
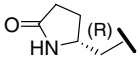
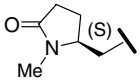
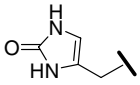
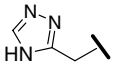
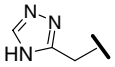
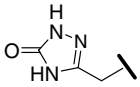
Table 1. Structures, solubility, and pK_a values for selected 1,2-*trans* cyclopentane derivatives with in vitro hNK1 binding affinities and in vivo SYVAL and gerbil foot-tapping inhibition activities



Compound	R^1	R^2	NK1[a] IC_{50} (nM) (SEM, *n*)[b]	Solubility[c] (mg/mL) [pK_a][d]	SYVAL[e] ED_{50} @ 1 h ED_{90} @ 24 h (or % I)[f]	Gerbil[g] ED_{50} @ 5 min ED_{50} @ 24 h (or % I)[h]
1	—	—	0.09	<0.0005	0.008 mg/kg 1.8 mg/kg	0.36 mg/kg 0.33 mg/kg
22a	H–	–H	1.3 (0.9, 3)			
22b	H–	–Me	0.25 (0.13, 3)			
22c	H–	–Et	0.25 (0.05, 3)			
22d	H–	$-(CH_2)_2OCH_3$	0.25 (0.08, 3)			
23d	Me–	$-(CH_2)_2OCH_3$	0.52 (0.29, 4)			
24a		–H	0.40 (0.12, 3)	0.09	58% @ 0.1 mg/kg 25% @ 1 mg/kg	65% @ 0.3 mg/kg 28% @ 3 mg/kg
24b		–Me	0.19 (0.02, 4)	0.015		0.1 mg/kg 1.1 mg/kg
24c		–Et	0.24 (0.02, 4)			57% @ 0.3 mg/kg 29% @ 3 mg/kg
24d		$-(CH_2)_2OCH_3$	0.17 (0.04, 2)	<.005		
26b		–Me	0.19 (0.02, 5)	0.041 [pK_a = 5.3]	66% @ 0.1 mg/kg 30% @ 1 mg/kg	
27b		–Me	0.39 (0.06, 3)	>6.7	66% @ 0.1 mg/kg 36% @ 1 mg/kg	
28b		–Me	0.30 (0.003, 3)	0.037		
29b		–Me	0.68 (0.07, 3)	>6.2	34% @ 0.1 mg/kg 18% @ 1 mg/kg	1.3 mg/kg nd[i]
30b		–Me	0.28 (0.01, 3)	>10	66% @ 0.1 mg/kg 12% @ 1 mg/kg	
31b		–Me	0.43 (0.05, 3)	0.8	60% @ 0.1 mg/kg 40% @ 1 mg/kg	0.88 mg/kg nd
32b		–Me	0.38 (0.03, 3)	0.46	34% @ 0.1 mg/kg 46% @ 1 mg/kg	1.0 mg/kg nd

(*continued on next page*)

Table 1 (*continued*)

Compound	R^1	R^2	NK1[a] IC_{50} (nM) (SEM, *n*)[b]	Solubility[c] (mg/mL) [pK_a][d]	SYVAL[e] ED_{50} @ 1 h ED_{90} @ 24 h (or % I)[f]	Gerbil[g] ED_{50} @ 5 min ED_{50} @ 24 h (or % I)[h]
33b		–Me	0.95 (0.48, 3)	>9		
34a		–H	0.55 (0.17, 3)	4.3	51% @ 0.1 mg/kg 44% @ 1 mg/kg	1.2 mg/kg nd
35a		–H	0.60 (0.20, 3)			
36a		–H	0.70 (0.20, 3)	0.20		
37b		–Me	1.4 (0.10, 3)	<0.005		
38b		–Me	0.27 (0.05, 3)	>7.7	53% @ 0.1 mg/kg 26% @ 1 mg/kg	
39a		H	0.34 (0.23, 3)			
39b		–Me	0.20 (0.05, 3)	0.35	nd 44% @ 1 mg/kg	0.61 mg/kg nd
39b′		–Me	0.25 (0.03, 3)	>7	25% @ 0.1 mg/kg 33% @ 1 mg/kg	
39b″		–Me	0.14 (0.04, 2)	0.038	74% @ 0.1 mg/kg 48% @ 1 mg/kg	0.2 mg/kg nd
40b		–Me	0.41 (0.05, 3)	0.54 [pK_a = 6.2]	49% @ 0.1 mg/kg 44% @ 1 mg/kg	nd >3 mg/kg
41b		–Me	0.16 (0.03, 3)	0.072	0.08 mg/kg 0.29 mg/kg	0.06 mg/kg 0.67 mg/kg
41c		–Et	0.16 (0.03, 3)	0.06	24% @ 0.1 mg/kg 18% @ 1 mg/kg	0.22 mg/kg 68% @ 3 mg/kg
42b		–Me	0.23 (0.04, 3)	<0.007 [pK_a = 4.7]	0.028 mg/kg 0.63 mg/kg	0.46 mg/kg 0.47 mg/kg

[a] Displacement of [^{125}I] labeled SP from the cloned hNK1 receptor expressed in CHO cells.[22]
[b] Data are an average of 2–5 independent replicate titrations.[23]
[c] Aqueous solubilities were measured in 0.1 M sodium acetate/acetic acid buffer at pH 5 (average of $n = 2$).[19]
[d] Titrations were preformed in 1:1 methanol/water.[20]
[e] See Ref 2 for protocol. Results are an average of three animals per data point.
[f] In an initial screening, compounds were dosed po at 0.1 mg/kg at 1 h prior to challenge and at 1 mg/kg at 24 h. For compounds that were not subsequently titrated, % I are given at either 1 h and/or 24 h.
[g] See Ref. 25 for protocol.
[h] In an initial screening, compounds were dosed iv at 0.3 mg/kg 5 min prior to challenge and at 3 mg/kg at 24 h. For compounds that were not subsequently titrated, % I are given at either 1 h and/or 24 h.
[i] No data.

The key intermediate amines **22a**–**d** (or analogous 1,2-*cis* amines) were then used to prepare a variety of derivatives (Scheme 4).[9,13] Alkylation with iodoacetamide provided the glycinamide derivatives **24a**–**d**. Additional glycinamide derivatives in the N-Me series were investigated via the *t*-Bu ester **25b** with the prep-

aration of several *N*-alkyl or *N*,*N*-dialkyl amide derivatives (**26b**–**33b**, see Table 1). The imidazole analog **34a** was prepared by reductive amination of **22a** utilizing 2-imidazolecarboxaldehyde and sodium cyanoborohydride. Alkylation of **22a** with the 3- or 4-picolyl chloride afforded the 3- and 4-pyridylmethyl analogs **35a** and **36a**. The pyrazine **37b** was prepared by reaction of amine **22b** with chloropyrazine. The 4-imidazolylacetamide **38b** was prepared by acylation of amine **22b** with 4-imidazolylacetyl chloride. Several C-3 aminomethylene linked heterocycles (**39**–**42**) which are more closely related to **1** were prepared by previously described methods.[9]

Aqueous solubilities of selected compounds were determined at pH 5 (0.1 M sodium acetate/acetic acid buffer)[19] and pK_a determinations were done by potentiometric titrations in 1:1 methanol/water.[20] As demonstrated in the preceding manuscript,[9] a significant enhancement in water solubility with the cyclopentyl scaffold **2** was realized due to the increased basicity of various C-3 nitrogen derivatives (i.e., **2a**, pK_a = 6.6 and solubility = 0.8 mg/mL at pH 5) compared to morpholine **1** (pK_a < 3.5 and solubility < 0.0005 mg/mL at pH 5)[19,20] in which the nitrogen is both benzylic and part of the morpholine ring. Enhanced water solubility was also seen in many of these modified cyclopentyl structures, depending again in large part on the basicity of the C-3 nitrogen moiety as well as the size and extent of *N*-alkylation. For the glycinamide **24a**, having a free NH and a primary amide, the solubility (0.090 mg/mL) was significantly lower than that of the initial structure **2a**, although for the analogous N-Me derivatives the solubilities were comparable (0.015 mg/mL for **24b** (pK_a = 5.3) vs 0.016 mg/mL for **2b** (pK_a = 5.8)). The effect of the larger 2-methoxyethyl ether moiety of **24d** gave a further 3-fold loss. Interestingly, sequential alkylation of the terminal amide improved solubility (see Table 1) with **27b**, **29b**, and **30b** giving excellent solubilities (>6 mg/mL). This effect may be attributed to decreased crystallinity and/or increased solvation of the protonated amine salt due to the lack of an internal hydrogen bond with the N-H of the primary or secondary amides (compare **24b**, **26b**, and **27b**). This effect was not seen with the (*S*)-lactam **39b** in that the N-Me **39b**″ was 10-fold less soluble as would have been expected.

For the aromatic derivatives, the aqueous solubilities correlated with the literature pK_as of the parent heterocycles, with the order of solubilities being **34a** and **38b** > **36a** > **41b**, **c** > **37b** (literature[21a] pK_as = 7 (imidazole), 5.2 (pyridine), 2.3 (triazole), and 0.65 (pyrazine), respectively). Among the non-aromatic heterocycles more closely related to **1**, imidazolinone **40b** had good solubility (0.54 mg/mL; measured pK_a = 6.2). The solubility of the triazolinone analog **42b** was disappointingly poor (<0.007 mg/mL), consistent with the reduced basicity of the C-3 nitrogen (measured pK_a = 4.7), although the solubility of its HCl salt in unbuffered water was 3.5 mg/mL with a final pH of 2.5.

The binding affinities were determined by the displacement of [^{125}I]-SP from human NK1 receptor stably expressed in CHO cells.[22,23] Comparison of the previous structure **2** compounds with these (*R*)-α-methylbenzyl ether analogs indicated that a 3- to 7-fold enhancement in binding affinity was realized, whereas the hNK1 affinities in the morpholine series were essentially unchanged with this modification (hNK1 IC_{50} = 0.09 nM for both).[2] Examination of simple models indicated that the (*R*)-methyl in the cyclopentane series better reinforces the phenyl/phenyl interaction for optimal pharmacophore fit, while the (*S*)-methyl forces the two phenyls apart. The introduction of the 4-fluoro moiety had minimal or no effect in binding potency for either the morpholine[2] or cyclopentane scaffolds (data not shown). While the amine intermediates **22a**–**d** and the tertiary amine **23d** were moderately potent (hNK1 IC_{50} = 1.3, 0.25, 0.25, 0.25, and 0.52 nM, respectively), off-target issues were a concern with these fully basic compounds, as had been seen with the original piperidine and morpholine compounds.[7,11] The initial glycinamide compounds **24a** and **24b** were as potent as the above amines and, more importantly, showed enhanced binding affinity compared to the des-methyl analogs (hNK1 IC_{50} = 0.95 nM vs 0.40 nM for **24a** and 2.7 (racemic) vs 0.19 nM for **24b**).[9] In general, the tertiary N-Me analogs were more potent than the secondary N-H compounds but the larger *N*-alkyl analogs did not provide further potency improvement (**24c** and **24d**, hNK1 IC_{50} = 0.24 and 0.17 nM). However, there was a trend toward lower potency with increasing overall size of the alkylated glycinamides (**24b**–**32b**) and with the dibasic piperazine **33b**. The lactams **39b** and **39b**′ were equipotent with the glycinamides with little difference seen between the (*R*)- and (*S*)-lactam stereochemistry (hNK1 IC_{50} = 0.25 and 0.20 nM) or between the NH and N-Me lactams (hNK1 IC_{50} = 0.20 and 0.14 nM). While the imidazolinone **40b** appeared slightly less potent, the basic, aromatic derivatives **34**–**37** were not suitable replacements for the amide moiety. Interestingly, the best activity was found in the derivatives analogous to triazolinone **1**, in particular the triazole **41b** and the triazolinone **42b** (hNK1 IC_{50} = 0.16 and 0.23 nM, respectively). The activity seen in the latter cases also translated into excellent in vivo activity (see below). Although there was a general preference for moderately sized, polar moieties at the C-3 position, the wide variety of functionality tolerated here suggests that either the receptor is somewhat disordered in the sub-domain which interacts with this site of the molecule or that there is a fairly large, open space around the C-3 position. The hNK1 selectivity over hNK2 (IC_{50} > 1 μM) and hNK3 (IC_{50} > 100 nM) was also maintained in this cyclopentane scaffold for all derivatives (see Ref. 2 for hNK2 and hNK3 binding protocols).

The 3- to 10-fold enhancement in hNK1 affinity seen in the previous manuscript for the 1,2-*trans* series compared to the 1,2-*cis* arrangement also carried over to these more elaborate derivatives described above and essentially followed the same SAR.[9] For example, the 1,2-*cis*-2,3-*trans* version of the triazole **41b** was 6-fold

less potent (hNK1 IC_{50} = 1.0 nM vs 0.16 nM). In addition, the *cis* derivatives were generally also less soluble; thus, the 1,2-*trans* series was preferentially investigated and primarily discussed herein.

The C-3 substituted amino compounds in Table 1 displaying low nanomolar binding affinity on the hNK1 receptor (IC_{50} < 0.5 nM) were further evaluated in vivo. As a measure of peripheral inhibition of NK1 receptor activation after oral administration, the SYVAL[24] assay was used.[2] This assay quantified the ability of a test compound to block plasma extravasation into the esophagus of guinea pigs driven by the sensorotoxin-elicited release of endogenous SP. Initial screens were run at a dose of 0.1 mg/kg orally at 1 h prior to iv challenge with resiniferatoxin and at 1.0 mg/kg orally at 24 h prior to challenge to determine their duration of action. For active compounds (% I > 75%), titrations were carried out to obtain an ED_{50} value at 1 h and an ED_{90} value at 24 h. As a reference, the reported SYVAL ED_{50} and ED_{90} results for **1** dosed po were 0.008 mg/kg at 1 h and 1.8 mg/kg at the 24 h time point, respectively.[2]

In the primary glycinamide series, **24a** gave moderate 1 h oral activity; although in the 24 h assay the activity had decreased significantly (58% at 0.1 mg/kg, 25% at 1 mg/kg, respectively). N-substitution on the terminal amide generally resulted in the same moderate SYVAL activity at the 1 and 24 h time points, with only **32b** approaching an ED_{90} of 1 mg/kg at 24 h. The lactam derivatives **39b** and **39b′** showed moderate results in the 24 h assay but **39b′** was only marginally active in the 1 h screen indicating slower absorption than the less basic glycinamides. The imidazoles **34a** and **38b** had activity in SYVAL equivalent to the glycinamides, while the less potent pyridines and pyrazine were not studied further. In contrast, the very potent triazole **41b** was highly active in the SYVAL assay at the early time point (ED_{90} = 0.08 mg/pk) and at 24 h (ED_{50} = 0.29 mg/kg) was significantly better than both the glycinamide **32b** and morpholine **1**, while also achieving some aqueous solubility (0.072 mg/mL). Although possessing about equipotent hNK1 affinity, the in vivo activity of the *N*-ethyl derivative **41c** was significantly decreased. The imidazolinone **40b** showed very encouraging solubility, but the hNK1 affinity and SYVAL activity were diminished. The triazolinone **42b** achieved an ED_{50} in SYVAL of 0.028 mg/kg at the early time point, but more importantly, an ED_{90} of 0.63 mg/kg at 24 h. Unfortunately, **42b** had attenuated aqueous solubility (<0.007 mg/mL).

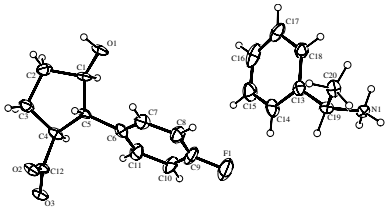
Selected compounds were also evaluated in a model measuring inhibition of central NK1 receptors in the gerbil, whose receptors have human-like pharmacology. In this assay, icv injection of an exogenous NK1 agonist into the brain of gerbils elicits a stress response (foot tapping) for which the duration can be measured and its inhibition quantified.[25] The normal screen was performed at a dose of 0.3 mg/kg iv immediately prior (5 min) to agonist injection into the brain or at 3 mg/kg iv 24 h prior to NK1 receptor stimulation in order to obtain a measure of in vivo duration. As a reference, the reported ED_{50}s in this CNS assay for **1** were 0.36, 0.04, and 0.33 mg/kg at the 5 min, 4 and 24 h time points, respectively.[2] From the glycinamide series, **24b** indicated good CNS activity with ED_{50}s of 0.1 and 1.1 mg/kg at the early and 24 h time points. Similar 24 h results were also seen with the more soluble *N*,*N*-dialkyl derivatives **31b** and **32b**. The best heterocycles in the SYVAL assay were **41b** and **42b**, and in the gerbil assay afforded inhibition at 5 min (ED_{50} = 0.06 and 0.46 mg/kg) and at 24 h (0.67 and 0.47 mg/kg, respectively) comparable to that of the clinical compound **1**.

Incorporation of an (*R*)-α-methyl at the benzyl ether and the 4-fluoro on the phenyl in the cyclopentyl scaffold **3** was accomplished and provided a 3- to 7-fold enhancement in activity over analogous structure **2** derivatives. N-H and *N*-alkyl-amino substitution at C-3 was explored with the preparation of unsubstituted and substituted acetamides as well as methylene spaced aromatic and non-aromatic heterocycles. Potent hNK1 binding was demonstrated with most of the modifications at C-3, although a moderately basic moiety was required for improved aqueous solubility. In addition, excellent in vivo activity and 24 h duration were demonstrated in two different assays of NK1 inhibition. The two best binding compounds **41b** and **42b** were found to be potent in these in vivo assays of peripheral and CNS inhibition of the hNK1 receptor comparable to the current clinical compound **1**. Triazole **41b** also achieved a greater than 100-fold enhancement in aqueous solubility at pH 5. These results led to additional investigations of the *trans* ether/phenyl motif in this and other scaffolds.[26,27]

References and notes

1. (a) Quatara, L.; Maggi, C. A. *Neuropeptides* **1998**, *32*, 1; (b) Rupniak, N. M. J.; Kramer, M. S. *Trends Pharmacol. Sci.* **1999**, *20*, 485; (c) Dando, T. M.; Perry, C. M. *Drugs* **2004**, *64*, 777.
2. Hale, J. J.; Mills, S. G.; MacCoss, M.; Finke, P. E.; Cascieri, M. A.; Sadowski, S.; Ber, E.; Chicchi, G. G.; Kurtz, M.; Metzger, J.; Eiermann, G.; Tsou, N. N.; Tattersall, F. D.; Rupniak, N. M. J.; Williams, A. R.; Rycroft, W.; Hargreaves, R.; MacIntyre, D. E. *J. Med. Chem.* **1998**, *41*, 4607, and references therein.
3. Navari, R. M.; Reinhart, R. R.; Gralla, R. J.; Kris, M. G.; Hesketh, P. J.; Khojasteh, A.; Kindler, H.; Grote, T. H.; Pendergras, K.; Grunberg, S. M.; Carides, A. D.; Gertz, B. J. *N. Engl. J. Med.* **1999**, *340*, 190.
4. Pendergrass, K.; Hargreaves, R.; Petty, K. J.; Carides, A. D.; Evans, J. K.; Horgan, K. J. *Drugs Today* **2004**, *40*, 853.
5. Hale, J. J.; Mills, S. G.; MacCoss, M.; Dorn, C. P.; Finke, P. E.; Budhu, R. J.; Reamer, R. A.; Huskey, S. W.; Luffer-Atlas, D.; Dean, B. J.; McGowan, E. M.; Feeney, W. P.; Chiu, S. L.; Cascieri, M. A.; Chicchi, G. G.; Kurtz, M. M.; Sadowski, S.; Ber, E.; Tattersall, F. D.; Rupniak, N. M. J.; Williams, A. R.; Rycroft, W.; Hargreaves, R.; Metzger, J. M.; MacIntyre, D. E. *J. Med. Chem.* **2000**, *43*, 1234.
6. Harrison, T.; Owens, A. P.; Williams, B. J.; Swain, C. J.; Williams, A.; Carlson, E. J.; Rycroft, W.; Tattersall, F. D.; Cascieri, M. A.; Chicchi, G. G.; Sadowski, S.; Rupniak, N. M. J.; Hargreaves, R. J. *J. Med. Chem.* **2001**, *44*, 4296.
7. (a) Swain, C. J. *Prog. Med. Chem.* **1998**, *35*, 57; (b) Mills, S. G.; MacCoss, M.; Cascieri, M. A.; Sadowski, S.; Patel,

S.; Chapman, K. L.; Hutson, P. H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 599.
8. Mills, S. G.; MacCoss, M.; Underwood, D.; Shah, S. K.; Finke, P. E.; Miller, D. J.; Budhu, R. J.; Cascieri, M. A.; Sadowski, S.; Strader, C. D. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1345.
9. Finke, P. E.; Meurer, L. C.; Levorse, D. A.; Mills, S. G.; MacCoss, M.; Sadowski, S.; Cascieri, M. A.; Tsao, K. -L.; Chicchi, G. G.; Metzger, J. M.; MacIntyre, D. E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, (preceding manuscript page).
10. For a preliminary report on this work, see Meurer, L. C.; Finke, P. E.; MacCoss, M.; Mills, S. G.; Tsou, N.; Ball, R. G.; Sadowski, S.; Cascieri, M. A.; Metzger, J. M.; Eiermann, G.; MacIntyre, D. E.; Rupniak, N. M. J.; Williams, A.; Hargreaves, R. J. American Chemical Society 219th National Meeting, San Francisco, California, March 26–31, 2000.
11. Hale, J. J.; Mills, S. G.; MacCoss, M.; Shah, S. K.; Qi, H.; Mathre, D. J.; Cascieri, M. A.; Sadowski, S.; Strader, C. D.; MacIntyre, D. E.; Metzger, J. M. *J. Med. Chem.* **1996**, *39*, 1760.
12. Representative experimental details and spectral data have been described in reference 13. All mass spectral and ^{1}H NMR data were consistent with the assigned structures.
13. Finke, P. E.; MacCoss, M.; Meurer, L. C.; Mills, S. G.; Caldwell, C. G.; Chen, P.; Durette, P. L.; Hale, J. J.; Holson, E.; Kopka, I.; Robichaud, A. U.S. Patent 5,750,549, 1998; *Chem. Abstr*. **1997**, *127*, 17433.
14. Baker, W.; Leeds, W. G. *J. Chem. Soc.* **1948**, 974.
15. The structure of salt **9b** is shown below (ORTEP3, 20% ellipsoids) with the crystallographic atom-numbering scheme. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC [603506]. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223-336033 or e-mail:deposit@ccdc.cam.ac.uk].



16. Desai, R. C.; Cicala, P.; Meurer, L. M.; Finke, P. E. *Tetrahedron Lett.* **2002**, *43*, 4569.
17. Kuethe, J. T.; Wong, A.; Wu, J.; Davies, I. W.; Dormer, P. G.; Welch, C. J.; Hillier, M. C.; Hughes, D. L.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5993.
18. Subsequent to this work, the use of (*S*)-**14** and HBF_4 in place of triflic acid was shown to give predominantly net inversion of the (*S*) imidate to afford the (*R*) ether **16**, thus, the designated (*R*) stereochemistry was confirmed. Jeff T. Kuethe, unpublished results.
19. Solubilities of selected compounds as the free amines were determined by HPLC after sonication in buffer at 1 mg/mL and filtration. The solubility for **1** (<0.0005 mg/mL) was determined in 0.1 M potassium hydrogen phosphate buffer at pH 5, while the solubilities for selected cyclopentane compounds were determined in 0.1 M sodium acetate/acetic acid buffer adjusted to pH 5. The reported solubilities are an average of $n = 2$.
20. The reported pK_a values were obtained 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 (average value around 0.5) as compared to its value in water.[21b]
21. (a) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*; Springer: New York, NY, 1984, 154–155; (b) see page 35.
22. Cascieri, M. A.; Ber, E.; Fong, T. M.; Sadowski, S.; Bansal, A.; Swain, C. J.; Seward, E. M.; Frances, B.; Burns, D.; Strader, C. D. *Mol. Pharmacol.* **1992**, *42*, 458.
23. The assay-to-assay replicate variability for the hNK1 binding assay was usually less than 2-fold from the average of 2–6 independent determinations.
24. Acronym for resiniferatoxin-induced SY stemic VAscular Leakage.
25. Rupniak, N. M. J.; Williams, A. R. *Eur. J. Pharmacol.* **1994**, *265*, 179.
26. (a) Finke, P. E. National Medicinal Chemistry Symposium, Madison, WI. June 27–July 1, **2004**; (b) Finke, P. E.; Meurer, L. C.; Mills, S. G.; MacCoss, M.; Qi, H. U.S. Patent 6,479,518, 2002; *Chem. Abstr*. **2002**, *136*, 279139x.
27. The use of the *trans* ether/phenyl configuration was subsequently applied to other six-[28] and seven-membered ring scaffolds.[29]
28. (a) Owens, S. N.; Seward, E. M.; Swain, C. J.; Williams, B. J. U.S. Patent 6,458,830 B1, 2001; *Chem. Abstr*. **2000**, *133*, 252310x and **2000**, *133*, 266729c; (b) Nelson, T. D.; Rosen, J. D.; Smitroviych, J. H.; Payack, J.; Craig, B.; Matty, L.; Huffman, M. A.; McMamara, J. *Org. Lett.* **2005**, *7*, 55; (c) Dirat, O.; Elliott, J. M.; Jelly, R. A.; Jones, A. B.; Reader, M. *Tetrahedron Lett.* **2006**, *47*, 1295.
29. Elliott, J. M.; Carlson, E. J.; Chicchi, G. G.; Dirat, O.; Dominguez, M.; Gerhard, U.; Jelly, R.; Jones, A. B.; Kurtz, M. M.; Tsao, K. L.; Wheeldon, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2929.