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The discovery of potent, selective, and orally bioavailable hNK_1 antagonists derived from pyrrolidine

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Abstract—SAR studies on amides, ureas, and vinylogous amides derived from pyrrolidine led to the discovery of several potent hNK_1 antagonists. One particular vinylogous amide (**45b**) had excellent potency, selectivity, pharmacokinetic profile, and functional activity in vivo. An in vivo rhesus macaque brain receptor occupancy PET study for compound **45b** revealed an estimated $Occ_{90} \sim 300$ ng/ml.

Interest in the agonist neuropeptide substance P (SP) began in 1931[1] when the 11-amino acid peptide was first isolated from extracts of horse intestines and brains, and its pharmacological action demonstrated by stimulating atropine resistant contraction of rabbit ileum. It was several years more before other functions of SP in mammalian biochemistry became known and the existence of a G protein-coupled receptor, the neurokinin-1 (NK_1) receptor, was established.[2] SP is purportedly involved in a number of biochemical pathways which include the transmission of the sensation of pain and an overexpression of SP has been implicated in several medical conditions: emesis, CNS disorders, and urinary incontinence.[3] Consequently, this sparked interest in finding neurokinin antagonists for medicinal use. The first disclosure of a selective small molecule NK_1 antagonist occurred in 1991[4] and since then potent clinical candidates based on several different scaffolds have been discovered.[5] There is currently one drug for use in man which works through blockade of the human NK_1 (hNK_1) receptor available in the medicinal formulary: aprepitant[6] [Emend® (**1**)]. Emend® was approved for use in conjunction with cancer treatment drugs to alleviate chemotherapy-induced nausea and vomiting[7] (CINV) in 2003 and for post-operative nausea and vomiting (PONV) in 2006.

We wish to describe our initial synthetic work and new structure–activity relationships (SAR) on a scaffold based on a simple pyrrolidine ether **3**. Some work in a cyclopentane series, such as **2**, related to the pyrrolidine described below was disclosed recently.[8] We have extended that previous work to investigate the effect of incorporation of the nitrogen into the five-membered cyclic system, but still β to the phenyl, and which offers a different orientation of substituents (Fig. 1).

The pyrrolidine compounds initially used in our studies[9] were synthesized as shown in Scheme 1. An epoxidation of Boc-protected $\Delta^{3,4}$ pyrroline **4** with mCPBA gave the expected meso-epoxide **5** and then a copper(I) iodide assisted ring opening of epoxide **5** with phenylmagnesium bromide afforded a racemic mixture of the pyrrolidine alcohols **6a**. The racemic mixture was resolved into alcohols **7a** and **13a** by HPLC on a Chiralpak-AD column. Both of these alcohol enantiomers, separately, were

Keywords: NK_1; Neurokinin NK_1 antagonist; Tachykinin NK_1 antagonist; Substance P antagonist.
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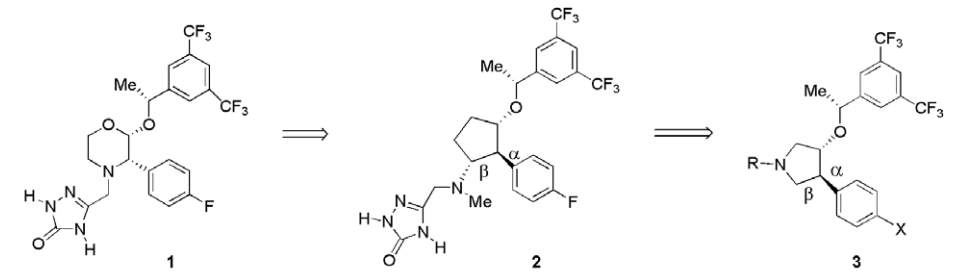
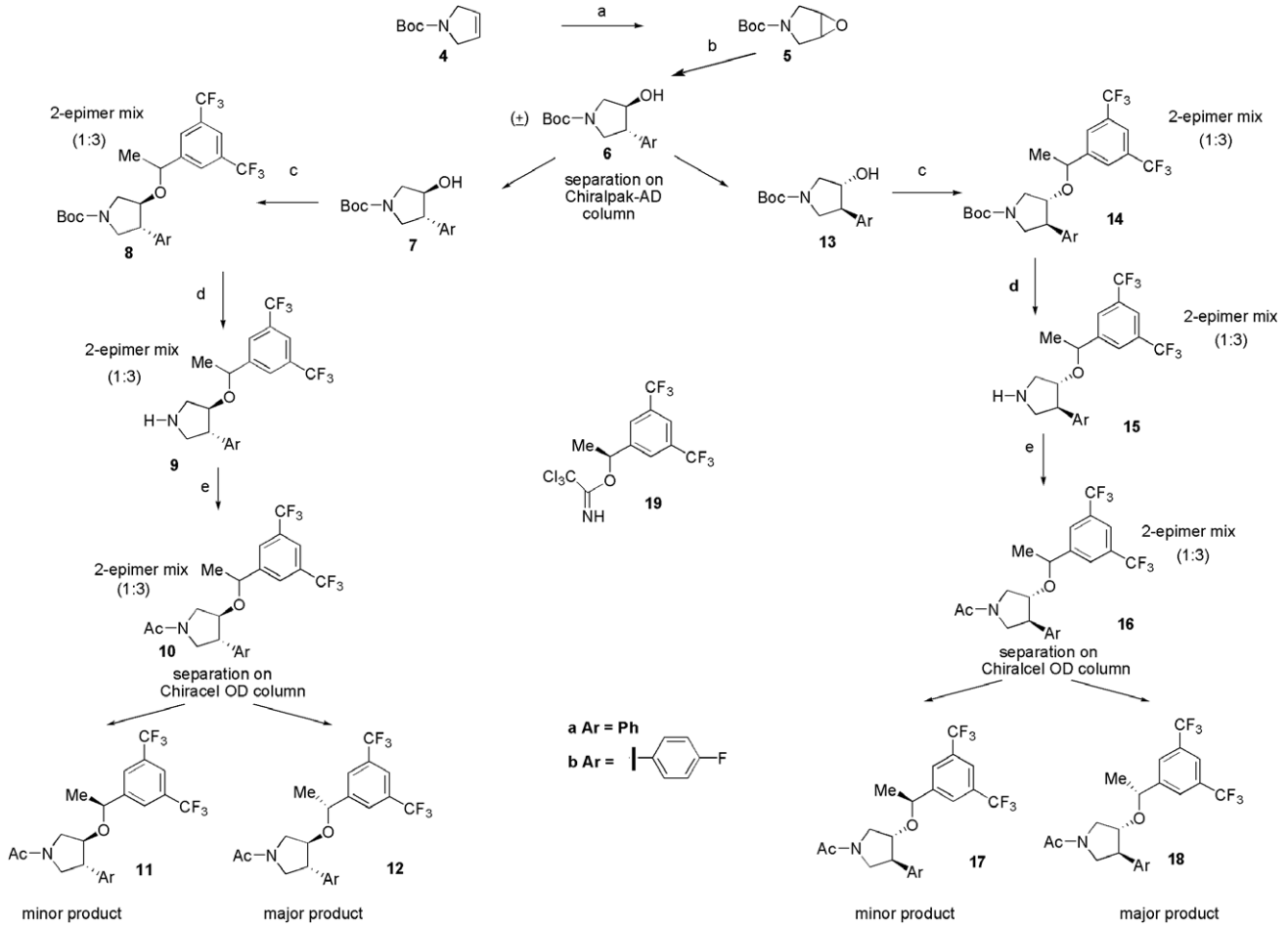


Figure 1. Evolution of SAR studies from aprepitant and the biological data for compounds **1** and **2**.



Scheme 1. Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, −78 °C to rt; (b) PhMgBr or 4-F-C_6H_4MgBr, CuI, THF, 0 °C; (c) imidate **19**, heptane-$(CH_2Cl)_2$, −30 °C to rt; (d) TFA, anisole, CH_2Cl_2, rt; (e) AcCl, NEt_3, CH_2Cl_2, rt.

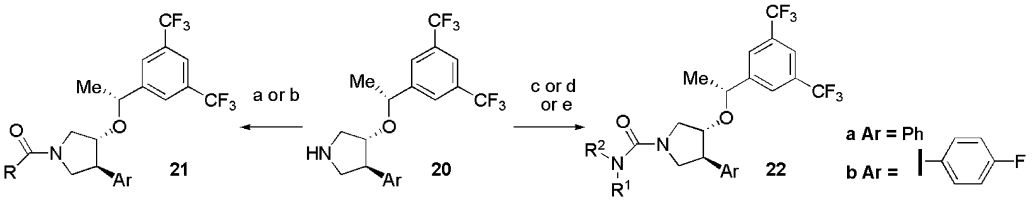
taken through the following reaction sequence described here for alcohol **7a**. Reaction of the homochiral alcohol **7a** with (*S*)-imidate[10] **19** gave a 1:3 mixture of epimeric ethers (**8a**) and subsequent treatment with TFA removed the Boc-protecting group to reveal the amines **9a**. The 1:3 mixture of pyrrolidines **9a** was reacted with acetyl chloride and the two epimeric amides **10a** thus obtained were resolved into the homochiral amides **11a** and **12a** by HPLC on a Chiralcel-OD column: amide **12a** having the (*R*)-ether being the major isomer as expected.[10] Similarly, the amides **17a** and **18a** in homochiral form were obtained from the pyrrolidine

alcohol **13a**. The corresponding 4-fluorophenyl analogs **17b** and **18b** were synthesized using 4-fluorophenylmagnesium bromide in a similar reaction and separation sequence as shown in Scheme 1.

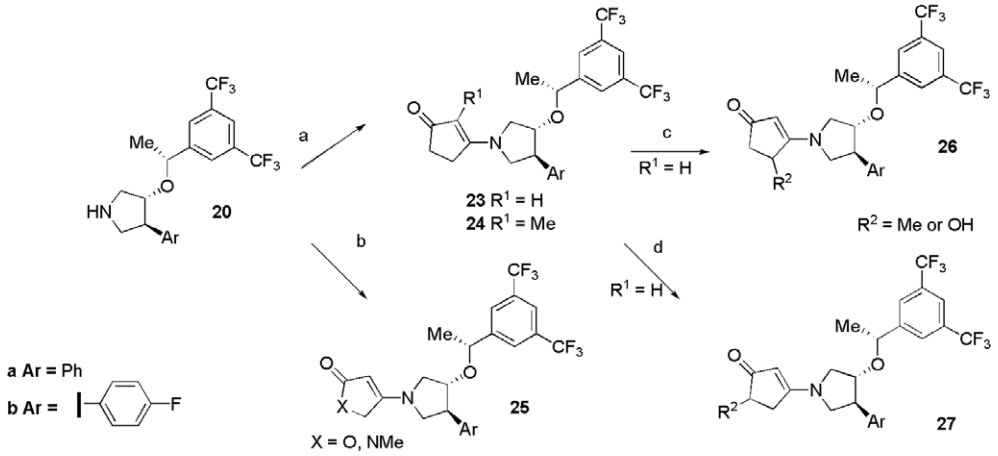
Since the major isomer, **18a**, derived from **14a** was the most active (see below), in later work (Scheme 2) the major isomers in the epimeric mixture of ethers (**14a** and **14b**) were separated by HPLC using a Chiralpak-AD column and the Boc-protecting group was then removed using TFA. These two resulting pyrrolidines **20a** and **20b** served as starting materials for the preparation of various simple derivatives on the pyrrolidine nitrogen.

Reaction of the pyrrolidines **20a** and **20b** with acid chlorides or acids and EDC led to the formation of pyrrolidine amides **21a** and **21b**, and with isocyanates or carbamoyl chlorides, or phosgene and amine, to afford ureas **22a** and **22b**. Some cyclic vinylogous amides (**23** and **24**) were synthesized (Scheme 3) by reacting the pyrrolidines **20a** and **20b** with cyclic 1,3-diketones and a catalytic amount of acid. The vinylogous amides with heteroatoms incorporated within the ring as in **25** were made similarly from tetronic acid or from *N*-methyltetramic acid. Methylation or hydroxylation of vinylogous amide **23** was achieved by treatment with base and then reaction with methyl iodide or with Vedejs's reagent[11] MoOPH (Scheme 3). The products derived from kinetic deprotonation were obtained using LDA as the base, while products from thermodynamic deprotonation were obtained with LiHMDS.[12]

The hNK_1 binding affinities for the pyrrolidine analogs were determined by measuring the ability of the compounds to displace [^{125}I]-SP from the hNK_1 receptor stably expressed in CHO cells.[13,14] Using the hNK_1 binding assay results, the ranking in terms of potency of the isomers **11a**, **12a**, **17a**, and **18a** was established, the most potent being **18a** (IC_{50} = 0.09 nM) then, in order of activity **12a** (IC_{50} = 32 nM), **17a** (IC_{50} = 80 nM), and **11a** (18% I at 100 nM). From these binding data and work done in the cyclopentane series[15] isomer **18a** was tentatively assigned as being derived from the (3*R*,4*S*)-pyrrolidine, the carbon bearing the benzylic methyl was (*R*) based on the mechanism[10] of the etherification reaction while the less potent epimer, **17a**, was the (3*R*,4*S*)-pyrrolidine with the (*S*)-chirality adjacent to the benzylic ether oxygen. Consequently, **11a** and **12a** were (3*S*,4*R*)-pyrrolidine derivatives. The major product from the etherification, **12a**, had the (*R*)-configuration next to the oxygen, while the minor ether **11a** had an (*S*)-center. Later the tentative stereochemistry assignment of **18a** was confirmed through determining the relative stereochemistry of the three chiral centers in urea **28b** (IC_{50} = 0.11 nM) (Fig. 2) in a single crystal X-ray analysis.[16] Since the benzylic carbon of the ether may be reasonably assigned as (*R*) from the aforementioned



Scheme 2. Reagents and conditions: (a) RCOCl, NEt_3, CH_2Cl_2, 0 °C to rt; (b) RCO_2H, EDC, HOBt, NEt_3, CH_2Cl_2, rt; (c) RNCO, NEt_3, CH_2Cl_2, 0 °C to rt; (d) R^1R^2NCOCl, NEt_3, CH_2Cl_2, rt; (e) $COCl_2$ in toluene 0 °C, then R^1R^2NH, NEt_3, CH_2Cl_2 rt.



Scheme 3. Reagents and conditions: (a) cyclopentane-1,3-dione or 2-methylcyclopentane-1,3-dione, TsOH, toluene, 80 °C; (b) tetronic or *N*-methyltetramic acid, TsOH, toluene, 80 °C; (c) LiHMDS (0.95 equiv), THF, HMPA, −78 °C then MeI (R^2 = Me) or MoOPH (R^2 = OH); (d) LDA (1.1 equiv), THF −78 °C then MeI (R^2 = Me) or MoOPH (R^2 = OH).

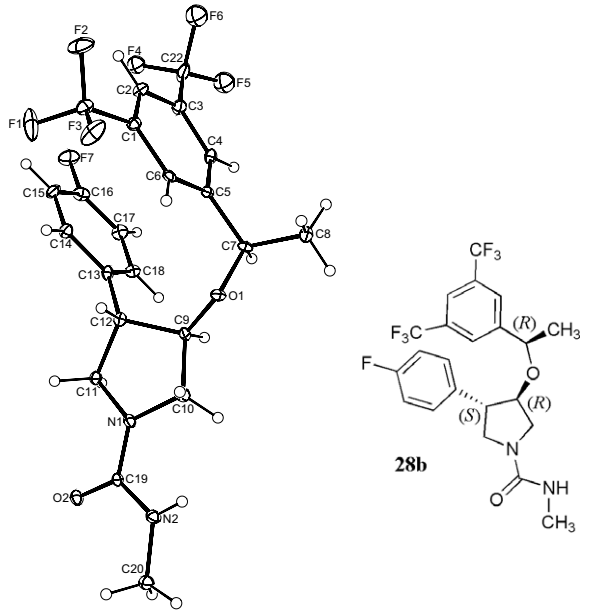


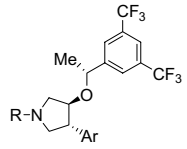
Figure 2. Perspective view (ORTEP) of **28b** showing the crystallographic numbering scheme; non-hydrogen atoms are drawn as 20% probability envelopes.

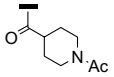
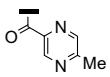
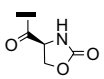
reason,[10] the absolute stereochemistry of the two centers on the pyrrolidine ring can then be assigned as (3*R*,4*S*).

The corresponding 4-fluoro analogs **17b** (IC_{50} = 40 nM) and **18b** (IC_{50} = 0.07 nM) had similar IC_{50} values to **17a** and **18a** (see above) of the phenyl series in the hNK_1 binding assay. In the gerbil foot tapping (GFT) assay that has been previously described as an in vivo pharmacodynamic model for CNS penetrant NK_1 compounds[17,18] both amides **18a** and **18b** were efficacious. The 4-fluoro analog **18b** inhibited GFT 50% after 4 h with a 2 mpk iv dose demonstrating that the amide was brain penetrant after a short time interval: the phenyl analog **18a** had 98% inhibition at 24 h with a 6 mpk iv dose. The phenyl analog **18a** was titrated in the gerbil and it had an ID_{50} = 0.6 mpk (iv) at t = 0 h and ID_{50} = 3.2 mpk (iv) at 24 h. Encouraged by the GFT data, the rat pharmacokinetic parameters of amide **18b** were determined and indicated good bioavailability (F = 65%) and half-life ($t_{1/2}$ = 5 h).

Having established potency in hNK_1 receptor binding, GFT efficacy, and bioavailability with amide **18b**, other simple amides and groups that had previously shown in vivo activity in the cyclopentane series were prepared and tested. All the amides (Table 1) had sub-nanomolar hNK_1 binding and two of the amides **31b** and **32a** inhibited GFT ~ 50% at 24 h with a 6 mpk iv dose. Three of the heterocyclic derived amides **33b**, **34b**, and **35b** had similar or better potencies at a lower dose with lactam **34b** being the most effective with 100% inhibition at a

Table 1. Synthesis and hNK_1 binding and gerbil foot tapping assay data for pyrrolidine amide compounds



Compound[a]	R	Preparation method[b]	hNK_1[c] IC_{50} (nM)	GFT[d]	
				% I at 24 h	iv dose mpk
29b[e]	CHO		0.24		
18a[f]	COMe	b	0.09	98	6
18b	COMe	b	0.07	26	6
30b	COEt	b	0.09	0	6
31b	CO^{i}Pr	b	0.15	43	6
32a	CO^{t}Bu	b	0.18	45	6
33b		c	0.07	50	3
34b[g]		c	0.12	100	3
35b		c	0.12	45	3
36b		c	0.34	13	3

[a] **a** refers to Ar = phenyl and **b** refers to Ar = 4-F-phenyl series.
[b] See Scheme 2 for preparation methods.
[c] See Ref. 13 and note 14.
[d] See Refs. 6, 17, and 18 for details.
[e] Compound **29b** was prepared by heating pyrrolidine **20b** in ethyl formate.
[f] ID_{50} = 0.6 mpk at 0 h; ID_{50} = 3.2 mpk at 24 h.
[g] ID_{50} = 0.6 mpk at 0 h; ID_{50} = 1.2 mpk at 24 h.

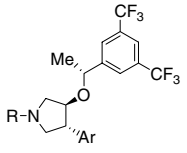
3 mpk iv dose and an ID_{50} = 1.2 mpk at 24 h and an ID_{50} = 0.6 mpk at 0 h (iv). The amide compounds in general still had weaker efficacy in the GFT assay at 24 h compared to previous structures **1** and **2** (see Fig. 1).

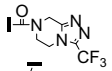
A series of ureas (**28b**, **37b**–**41b**) and a set of heterocyclic derived ureas **42b**–**44b** listed in Table 2 were assayed and, like the amides, were all potent, sub-nanomolar compounds in the hNK_1 binding assay. Some of the ureas had similar efficacy in the GFT assay to the amides **18a** and **34b** at 24 h (see Table 1 footnotes). Three of the most potent ureas **28b**, **39b**, and **40b** were titrated in the gerbil, giving ID_{50} values in the range 0.8–3 mpk at 24 h. The two ureas **39b** and **40b** inhibited GFT ~ 60% at a dose of 1 mpk (iv) and **28b** had an ID_{50} = 1.0 mpk at t = 0 h. From these data it was inferred that the three ureas **28b**, **39b**, and **40b** were rapidly brain penetrant and the compounds had reasonably long half-lives in gerbil. Urea **28b** also showed good bioavailability (F = 70%) with a half-life ($t_{1/2}$ = 1.25 h) in a rat PK study.

In attempting to broaden the SAR of polar substituents on the pyrrolidine nitrogen, two vinylogous amides **45a** and **45b**[19] were prepared. Both the phenyl and 4-fluorophenyl analogs were sub-nanomolar in hNK_1 binding. 4-Fluorophenyl analog **45b** (Table 3) distinguished itself as being superior to the phenyl example **45a** (and indeed more active than all the other analogs described above) in the GFT assay at both the t = 0 and 24 h time points. The SAR around vinylogous amide **45b** was explored by strategically introducing methyl and hydroxyl groups onto the cyclopentenyl ring. Methylation on the double bond (**46b**) or at other positions around the five-membered ring (**47b**–**49b**) afforded compounds with potent hNK_1 binding, but all of these were less potent in the GFT assay than **45b**. The two epimeric hydroxylated analogs **50b** and **51b** were both potent and more active in the GFT assay than the methylated analogs, but were still less potent than vinylogous amide **45b**. Vinylogous amides **52b** and **53b** derived from tetronic and *N*-methyltetramic acid and the cyclohexenyl examples **54a** and **55a** were also sub-nanomolar in the hNK_1 binding assay but lacked significant efficacy in the GFT assay even at a 3 mpk iv dose at 24 h. The most efficacious vinylogous amide in GFT remained the parent compound **45b**.

Further evaluation of the properties of vinylogous amide **45b** (Fig. 3) showed that this antagonist was selective for the hNK_1 receptor over the other known hNK_2 and hNK_3 sub-types.[20] Promising PK parameters were obtained in rat, dog, and rhesus measurements: **45b** was highly bioavailable and had reasonable half-lives in all three animal species consistent with once-daily dosing in man. Also, vinylogous amide **45b** performed well in two animal models of NK_1 antagonism after oral dosing. When compound **45b** was dosed orally in the GFT assay, it was efficacious at 1 h (ID_{50} = 0.9 mpk) and 4 h (ID_{50} = 0.25 mpk). In a guinea pig separation induced vocalization experiment[21] an ID_{50} = 0.17 mg/kg at 4 h (po) was obtained (Fig. 4). Vinylogous amide **45b** was also evaluated in vivo in a rhesus positron emission tomography (PET) study[22] to determine brain NK_1 receptor occupancy after a 4-h iv infusion. This study afforded an estimated 50% occupancy of NK_1 receptors (Occ_{50}) at a plasma steady state concentration of 33 ng/

Table 2. Synthesis and hNK_1 binding and gerbil foot tapping assay data for pyrrolidine urea compounds



Compound[a]	R	Preparation method[b]	hNK_1[c] IC_{50} (nM)	GFT[d] % I at iv dose (ID_{50})	
				0 h	24 h
28b	CONHMe	c	0.11	100% at 2 mpk (1.0 mpk)	77% at 6 mpk (3.0 mpk)
37b	$CONMe_2$	d	0.38	nd	nd
38a		d	0.16	40% at 1 mpk	
39b	CONHEt	c	0.10	61% at 1 mpk	93% 6 mpk (1.0 mpk)
40b	$CONH^iPr$	c	0.06	64% at 1 mpk	86% at 6 mpk (0.8 mpk)
41b	$CONH^tBu$	c	0.14	28% at 1 mpk	6% at 6 mpk
42b		e	0.30		57% at 3 mpk
43b		e	0.47		66% at 3 mpk
44b		e	0.58		24% at 3 mpk

nd, not determined at t = 0 and 24 h.

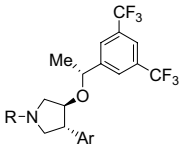
[a] **a** refers to Ar = phenyl and **b** refers to Ar = 4-F-phenyl series.

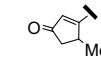
[b] See Scheme 2 for preparation methods.

[c] See Ref. 13 and note 14.

[d] See Refs. 6, 17, and 18 for details.

Table 3. Synthesis and hNK_1 binding and gerbil foot tapping assay data for pyrrolidine vinylogous amide compounds



Compound[a]	R	Preparation method[b,c]	hNK_1[d] IC_{50} (nM)	GFT[e] % I at iv dose (ID_{50})	
				0 h	24 h
45a		a	0.07	100% at 3 mpk (0.9 mpk)	100% at 3 mpk (1.1 mpk)
45b		a	0.11	100% at 1 mpk (0.1 mpk)	100% at 3 mpk (0.045 mpk)
46b		a	0.13		67% at 3 mpk
47b	 diastereomer A	c	0.16		85% at 3 mpk
48b	 diastereomer B	c	0.09		2% at 3 mpk
49b	 two diastereomer mix	d	0.11		79% at 3 mpk
50b	 diastereomer A	c	0.22	100% at 3 mpk (0.5 mpk)	100% at 3 mpk (0.7 mpk)
51b	 diastereomer B	c	0.30	100% at 3 mpk (1.1 mpk)	95% at 3 mpk (0.5 mpk)
52b		b	0.16		67% at 3 mpk
53b		b	0.12		8% at 3 mpk
54a		a	0.18		12% at 3 mpk
55a		a	0.13		5% at 3 mpk

[a] **a** refers to Ar = phenyl and **b** refers to Ar = 4-F-phenyl series.
[b] See Scheme 3 for preparation methods.
[c] Compounds **54a** and **55a** were obtained from the appropriate cyclohexa-1,3-diones and pyrrolidine **20a**.
[d] See Ref. 13 and note 14.
[e] See Refs. 6, 17, and 18 for details.

ml and a 90% occupancy (Occ_{90}) at a concentration of 300 ng/ml (Fig. 5). Overall the vinylogous amide **45b** had excellent potency, selectivity, pharmacokinetic profile, and functional activity in vivo.

Amide, urea, and a vinylogous amide derived from a new pyrrolidine scaffold design were prepared as hNK_1 receptor antagonists. The hNK_1 binding results from amides **11a**, **12a**, **17a**, and **18a**, and the X-ray structure of urea **28a** allowed the stereochemistry of the active series to be identified. The active series of pyrrolidine amides showed potent in vitro hNK_1 binding, but most were modestly or weakly active in vivo in the GFT functional assay at 24 h—the exceptions were amides **18a** and **34b**. A series of ureas was then prepared and evaluated and these compounds were also sub-nanomolar in hNK_1 binding. The best three ureas **28b**, **39b**, and **40b** were comparable or were more potent in the GFT assay at 24 h (iv) and slightly less potent at $t = 0$ h than the amides **18a** and **34b**. These then led to preparation of the vinylogous amide derivatives. These vinylogous amides in both the phenyl and 4-fluorophenyl series

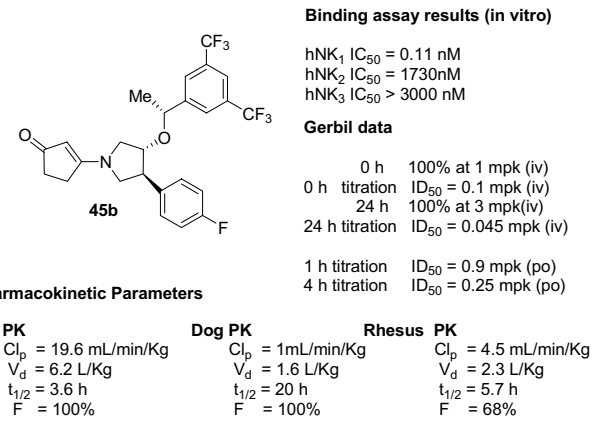


Figure 3. Data summary for vinylogous amide **45b**.

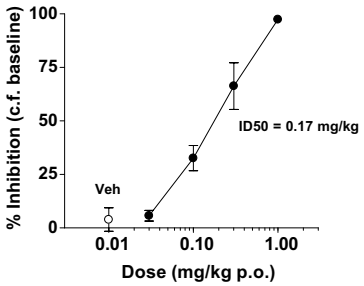


Figure 4. Inhibition of separation induced vocalizations in guinea pig pups for **45b** at $t = 4$ h.

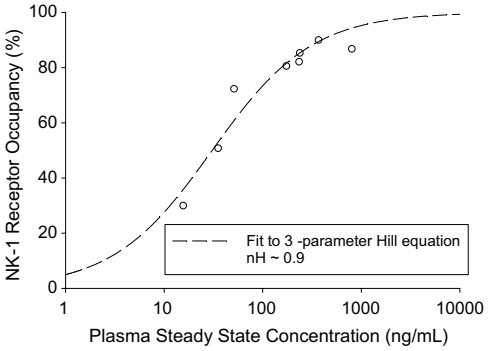


Figure 5. NK_1 receptor occupancy in rhesus brain determined by PET for compound **45b**.

were sub-nanomolar in binding but the parent **45b** was the most potent of all the analogs prepared in the gerbil assay at $t = 0$ and 24 h (iv). This particular vinylogous amide **45b** was evaluated in rat, dog, and rhesus PK, and was highly bioavailable with good half-lives in three preclinical species. The efficacy of **45b** in oral drug form was evaluated in two efficacy models: the gerbil foot tapping and guinea pig separation induced vocalization assays. The NK_1 receptor occupancy in the rhesus macaque brain was also determined in a PET study indicating plasma steady state concentrations of **45b** of $Occ_{50} \sim 33$ mg/ml and $Occ_{90} \sim 300$ mg/ml. From this work a series of pyrrolidine ether hNK_1 antagonists with a unique vinylogous amide pharmacophore was identified that afforded excellent in vitro and in vivo activity.

Acknowledgments

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14. The assay-to-assay replicate variability in the human NK_1 binding assay was typically less than 2-fold from the average of 2–6 independent determinations.
15. The potent series of cyclopentane analogs described in Ref. [8a] has the stereochemistry as shown in Figure 1, compound **2**; the pyrrolidine series that corresponds with this cyclopentane series is the (3*R*,4*S*)-pyrrolidine with the (*R*)-stereochemistry next to the benzylic ether oxygen.
16. The structure is shown with the crystallographic atom-numbering scheme. Crystallographic data (excluding structure factors) for the urea structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC [645923]. A copy of the data may be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
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19. Vinylogous amide **45b** appears to exist as two rotamers in solution, in CD_3CN, resulting from restricted rotation around the C–N bond. A variable temperature NMR experiment was conducted on a Varian Unity Inova 500 MHz spectrometer to estimate the energy barrier to rotation. The two vinylic proton signals of the rotamers coalesced at 60 °C and the exchange rate constant (k) was 56 s^{-1} at the coalescence temperature. The energy barrier ($\Delta G^{\ddagger}$) is estimated to be 16.9 kcal/mol.
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