4,4-Disubstituted Piperidine High-Affinity NK_1 Antagonists: Structure−Activity Relationships and *in Vivo* Activity

Graeme I. Stevenson,* Ian Huscroft, Angus M. MacLeod, Christopher J. Swain, Margaret A. Cascieri,§ Gary G. Chicchi,§ Michael I. Graham, Timothy Harrison, Fintan J. Kelleher, Marc Kurtz,§ Tamara Ladduwahetty, Kevin J. Merchant, Joseph M. Metzger,§ D. E. MacIntyre,§ Sharon Sadowski,§ Balbinder Sohal, and Andrew P. Owens

Department of Medicinal Chemistry, Neuroscience Research Centre, Merck, Sharp and Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, U.K., and Departments of Pharmacology, Molecular Pharmacology, and Biochemistry, Merck Research Laboratories, Rahway, New Jersey 07065

Received June 19, 1998

Previously reported studies from these laboratories described the design of a novel series of high-affinity NK_1 antagonists based on the 4,4-disubstituted piperidine ring system. Further structure−activity studies have now established that for high NK_1 affinity the benzyl ether side chain must be 3,5-disubstituted and highly lipophilic, the optimal side chain being the 3,5-bis(trifluoromethyl)benzyl ether, **12** (hNK_1 IC_{50} = 0.95 nM). Additional studies have shown that this class of NK_1 antagonist tolerates a wider range of substituents on the piperidine nitrogen, including acyl (**38**) (hNK_1 IC_{50} = 5.3 nM) and sulfonyl (**39**) (hNK_1 IC_{50} = 5.7 nM) derivatives. Following preliminary pharmacokinetic analysis, two compounds (**32** and **43**) were selected for *in vivo* study in the resiniferotoxin-induced vascular leakage model, both showing excellent profiles (ID_{50} = 0.22 and 0.28 mg/kg, respectively).

The discovery of CP-96,345[1] (**1**) (Chart 1), the first selective non-peptide NK_1 antagonist, has led to an intensive exploration of the pharmacology of the NK_1 receptor. This quinuclidine-based compound has spawned several classes of selective non-peptide substance P antagonists including the aminopiperidine-based CP-99,994[2] (**2**) and GR 203040[3] (**3**), the (benzyloxy)-piperidine-based L-733,060[4] (**4**) and L-741,671[5] (**5**), and the related morpholine acetal L-742,694[6] (**6**) as well as more diverse structures such as L-732,138[7] (**7**) and SR 140333[8] (**8**). Together with the availability of the cloned human NK_1 receptor,[9] these non-peptide ligands have been used to define a putative pharmacophore for NK_1 antagonists.[2] Substance P and the NK_1 receptor have been implicated in neurogenic inflammation,[10] transmission of pain,[11] vasodilation,[12] airway smooth muscle contraction,[13] regulation of the immune response,[14] and dural inflammation in migraine[15] and as a central component of cytotoxin-induced emesis.[16]

Many of the early non-peptide NK_1 antagonists suffered from poor central nervous system (CNS) penetration,[17] lack of oral activity, and unwanted affinity at L-type calcium channels.[4,18] With the establishment of a working NK_1 pharmacophore, the emphasis in the field has now shifted toward the fine-tuning of *in vivo* properties in order to exploit the undoubted benefits of NK_1 receptor blockade. In this paper we present our efforts in this area utilizing the 4,4-disubstituted piperidine class of NK_1 antagonist.[19]

Simplification of **1** by conversion to **2** established the *cis*-(2*S*,3*S*)-piperidine as a basic framework for high-affinity NK_1 antagonists. Furthermore, studies from our laboratories[20] have established that, with the appropriate choice of aryl substituent, the benzylamine side chain of **2** can be replaced by a benzylic ether and that further deletions can be made to afford an acyclic series of NK_1 antagonists based on phenylglycine[21] (**9**) (Figure 1). This type of system probably contains the minimum elements required for binding to the human NK_1 receptor and is in good agreement with published pharmacophore models. However, although ligands such as **9** have modest affinity for the NK_1 receptor (IC_{50} = 13.5 nM), with six freely rotatable bonds such a flexible system probably suffers a loss in binding through entropic factors. Studies from our laboratories established that conformational restriction of **9** in a *cis*-(2*S*,3*S*)-piperidine ring gave the high-affinity NK_1 antagonist **4** (hNK_1 IC_{50} = 1.0 nM[4]) (Figure 1).

An alternative conformationally restricted system based on **9** can be achieved by introducing a piperidine ring to produce a 2,2-geminally disubstituted system (**10**) (Figure 1) in which the unsubstituted phenyl group occupies an axial position.[22] Modeling studies predicted that aryl rings in both **4** and **10** could occupy similar positions in space with respect to the basic nitrogen and should therefore have similar affinities. This indeed proved to be the case for **10** (hNK_1 IC_{50} = 1.0 nM), suggesting that the piperidine ring had no specific binding role at the NK_1 receptor, other than as a conformational support.

In an extension to this approach[19] we then varied the distance between the basic nitrogen and the diaryl ether portion of the pharmacophore to give a 3,3-geminally disubstituted piperidine system (**11**) (Figure 1) which suffered a 20-fold loss in affinity compared to **4** and **10**. However the 4,4-disubstituted piperidine system **12** (Figure 1) retained affinity (hNK_1 IC_{50} = 0.95 nM) comparable to **4** and **10**. This compound does not fit current NK_1 pharmacophore models in that the basic nitrogen lies outside the given distance constraints to

§ Merck Research Laboratories, Rahway, NJ.

10.1021/jm980376b CCC: $15.00
Published on Web 10/09/1998

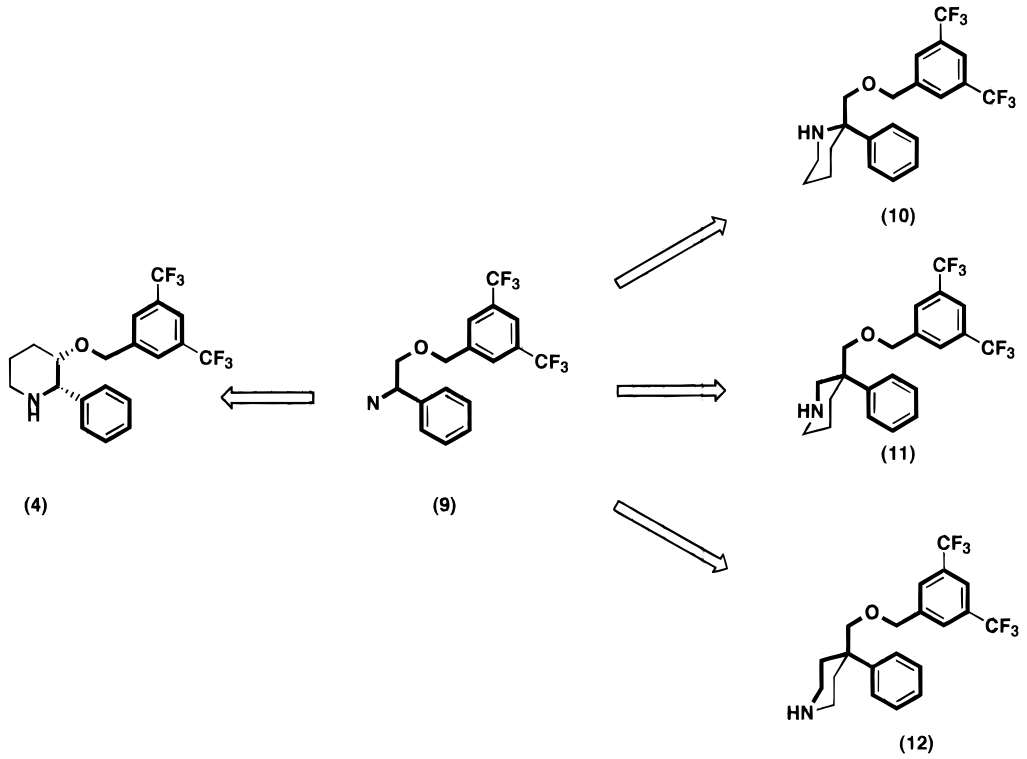
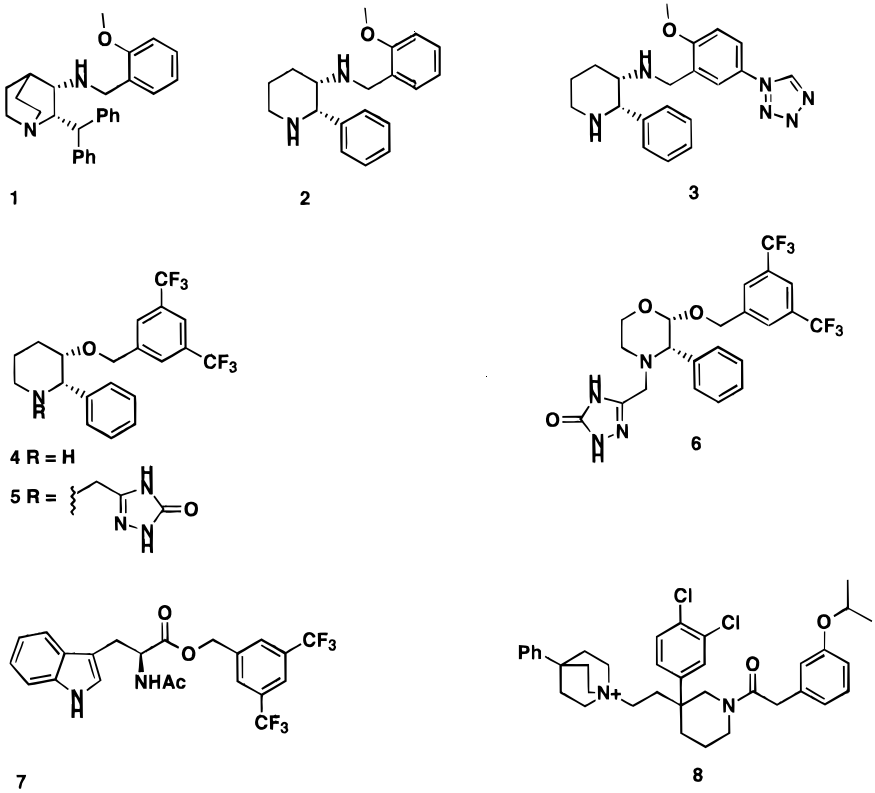


Figure 1. Derivation of the 4,4-disubstituted piperidine system.

Chart 1

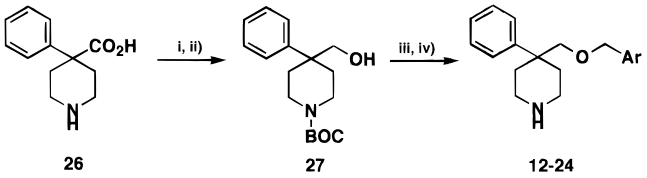


the rest of the pharmacophore[2] and it is achiral, in contrast to the stereochemical requirements observed in other series of NK_1 antagonists.[4] In a recent communication[19] we described the development and initial studies on this type of NK_1 antagonist; in this paper we now present a full examination of the structure–activity relationship (SAR) of 4,4-disubstituted piperidine-based NK_1 antagonists.

Chemistry

Compounds **12**–**24** were prepared from the amino acid **26** by a one-pot reduction/protection sequence to give the key intermediate alcohol **27**. Deprotonation of **27** followed by treatment with the appropriate benzyl bromide and subsequent deprotection afforded the final compounds (Scheme 1).

Scheme 1[a]



[a] Reagents: (i) $LiAlH_4$, THF; (ii) BOC_2O, THF, H_2O; (iii) NaH (60%), DMF, $ArCH_2Br$; (iv) HCl, Et_2O.

The *N*-alkyl derivatives **28**−**30** were prepared by reductive amination of the appropriate aldehyde (Scheme 2). The oxadiazole (**31**) and thiazole (**32**) derivatives were prepared by direct alkylation using the commercially available heteroarylmethyl chlorides (Scheme 2). Alkylation using methyl bromoacetate afforded **33** (Scheme 2).

The methylene-linked triazole **34** and the corresponding triazolone **35** were prepared by alkylation using the appropriate imidrazone **36** or **37**, followed by thermally induced cyclization to give the desired products **34** and **35** (Scheme 3).

The acetamide (**38**) and sulfonamide (**39**) analogues were prepared via acylation with the appropriate acid chloride (Scheme 4). Compounds **40**−**48** were prepared by coupling **12** to the appropriate acid under standard amide bond formation conditions using bis(2-oxo-3-oxazolidinyl)phosphinic chloride/Et_3N (Scheme 4).

The compounds bearing an amino-based linking group (**48** and **49**) were derived from the commercially available nitrile **50** by reduction/protection to give the amine **51**, followed by alkylation to give **48** and **49** (Scheme 5).

Treatment of methyl 3,5-bis(trifluoromethyl)benzoate (**52**) with the anion of dimethyl methylphosphonate afforded dimethyl 2-(3,5-bis(trifluoromethyl)phenyl)-2-ketoethylphosphonate (**53**), which when combined with the aldehyde **54**, obtained via reduction of **50**, gave the α,β-unsaturated ketone **55**. Complete reduction to the alcohol **56** followed by activation as the phenyl thionocarbonate and treatment with AIBN/tributyltin hydride gave the *n*-propyl-linked derivative **57**, (Scheme 6).

Biology

A stable CHO cell line expressing the human NK_1 receptor was used to determine the binding affinity of the compounds prepared in this study. [^{125}I]Tyr^8 substance P (0.1 nM) was used as the radioligand. Inhibition of substance P-induced accumulation of inositol phosphate in CHO cells expressing the hNK_1 receptor was assayed as previously described.[23]

***In Vivo* Studies.** Male Hartley guinea pigs (VAF, ∼400−600 g of body weight) were anesthetized by intramuscular injection with ketamine (30 mg/kg) plus xylazine (6 mg/kg). Test compounds were administered at 1.0 mg/kg in ethanol (5%):Cremophor (5%):saline (90%). After 10 min, Evans blue dye (25 mg/mL solution in saline, containing 50 mmol/mL heparin) was filtered through a 0.22-μm disk filter and 0.5 mL injected intravenously via a saphenous vein. Twenty minutes postinjection of Evans blue dye, animals were challenged intravenously by injection of resiniferatoxin (7.0 nmol administered over 30 s) via the penile vein. Ten minutes postchallenge the animals were euthanized using CO_2 gas, and a 1-mL heparinized blood sample was obtained via cardiac puncture. Cell-free plasma was prepared by centrifugation (8000*g*, 5 min, 20 °C) and a portion (100 mL) stored for analysis. The vena cava and aorta were transected to exsanguinate the animal prior to removal of the esophagus. The tissues were place in tared vials, dried (65 °C, 24 h), and reweighed. Dried tissue samples and an aliquot (100 mL) of plasma from each animal were extracted/incubated in formamide (1 mL, 65 °C, 24 h). The extent of plasma extravasation was assessed by comparing the absorption ($OD_{650\ nm}$) of the formamide extracts of tissue to that of cell-free plasma from the same animal.

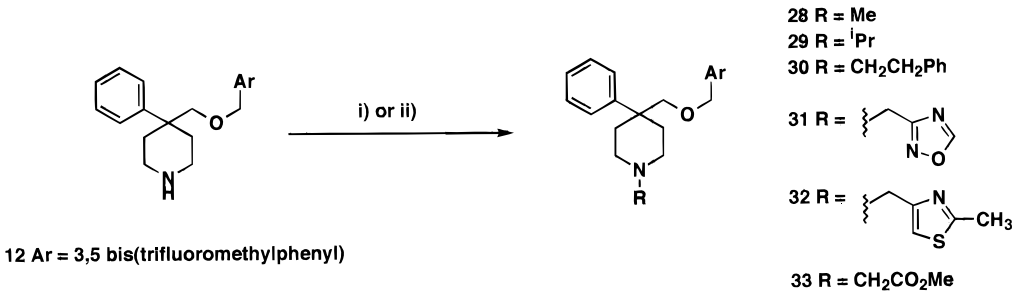
Results and Discussion

The preliminary study of this class of NK_1 antagonist established the 4,4-disubstituted piperidine system as a suitable framework for high NK_1 affinity.[19] A brief exploration of the substitution type and pattern of the benzyl ether side chain established that the nature of this moiety was a critical determinant of the level of binding achieved. In common with other benzyl ether-based NK_1 antagonists, the 3,5-bis(trifluoromethyl)-benzyl side chain provided a compound with subnanomolar receptor affinity (**12**, IC_{50} = 0.95 nM). We therefore decided that in extending this series we should begin by examining the scope for substitution on the benzyl ether side chain.

The simple unsubstituted benzyl ether **13** (Table 1) provides a baseline for this study; with an IC_{50} of 1.133 μM, it illustrates how much binding energy is gained from the 3,5-bis(trifluoromethyl) substitution. The 3,5-bis(trifluoromethyl) function **(12)** affords a highly lipophilic but electron-deficient aryl ring. Deletion of one of the trifluoromethyl groups (**14**) results in a 50-fold loss in affinity, as does changing to the 2-trifluoromethyl (**15**), while the 4-trifluoromethyl (**16**) results in complete loss in affinity. This confirms that both substituents are required for high-affinity binding. Replacement of the trifluoromethyl groups with chlorine (**17**) results in a 4-fold loss in affinity, with the equivalent dimethyl derivative (**18**) being 9-fold less active. Given that there is a larger difference in the electronic effects of methyl and chlorine with respect to trifluoromethyl than there is in their respective lipophilic parameters, these results would suggest that lipophilicity is predominant. This was confirmed by maintaining one substituent as methyl while the other was increased in bulk to ^{t}Bu or bromo (**19** and **20**), both of which had similar affinity to **12**. Monosubstituted benzyl ethers with a large lipophilic substituent in the *meta* position such as the iodo (**21**), ^{t}Bu (**22**), and trifluoromethoxy (**23**) analogues suffer a significant loss in binding affinity compared to **12**. The overall conclusion from this study is that the benzyl ether side chain requires at least one *meta* substituent, but for high NK_1 affinity it must be 3,5-disubstituted and preferably highly lipophilic.

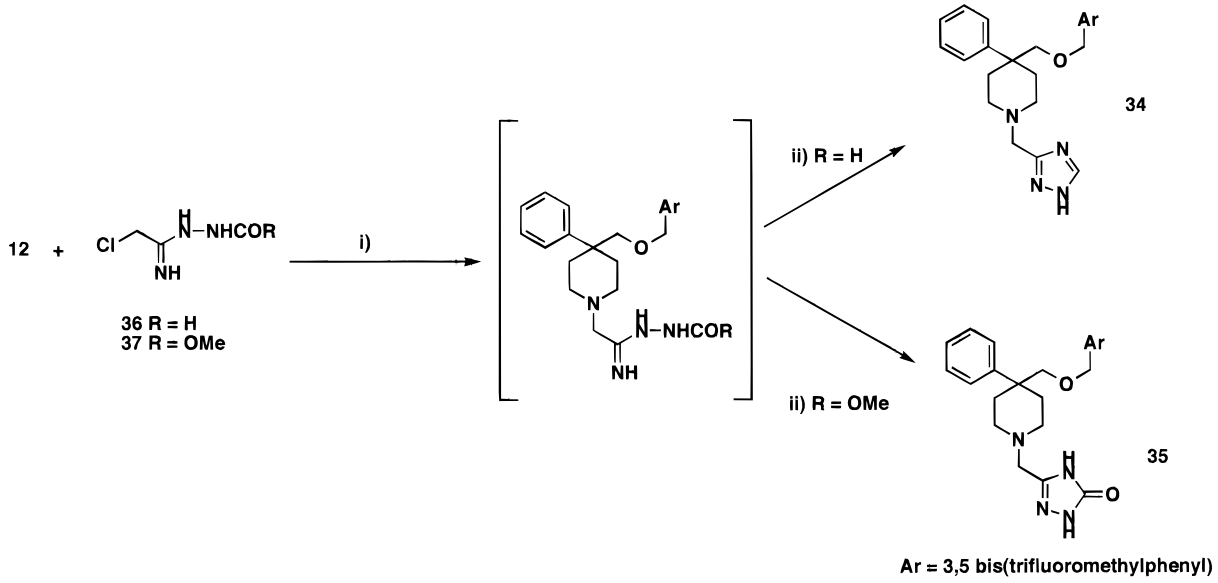
These gross observations can be interpreted as follows: Unlike other classes of NK_1 antagonists, the 4,4-disubstituted piperidines have three freely rotatable bonds in the linking chain and are relatively flexible molecules. Solution NMR studies confirm the axial

Scheme 2[a]



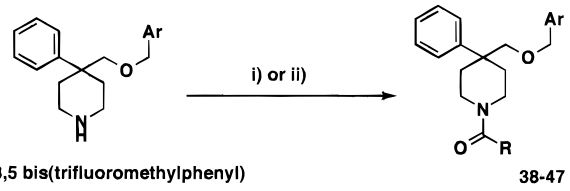
[a] Reagents: (i) RCHO, $NaCNBH_3$, MeOH, AcOH; (ii) RCH_2Br, Et_3N, DCM.

Scheme 3[a]



[a] Reagents: (i) K_2CO_3, DMF; (ii) DMF 140 °C.

Scheme 4[a]



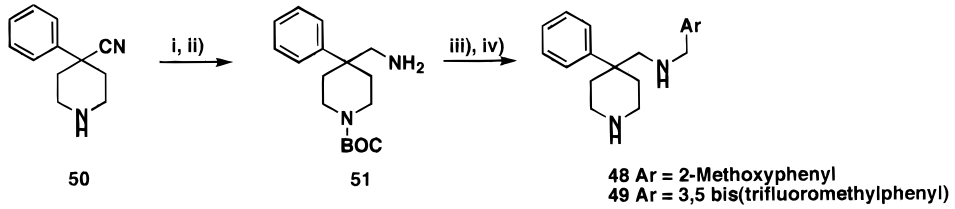
[a] Reagents: (i) CH_3COCl or CH_3SO_2Cl, Et_3N, DCM; (ii) RCO_2H, BOPCl, Et_3N, DCM.

orientation of the phenyl ring, placing the more flexible benzyl ether side chain equatorial. No definitive conformation of this side chain has been observed in these studies. Structural studies on other classes of NK_1 antagonists have indicated that some degree of interaction of their respective aryl rings is beneficial to high-affinity binding.[2] In general this is maintained by a relatively well-defined rigid conformation via specific stereochemistry and hindered rotation. Consequently various different aryl substitutions such as those used in the *cis*-(2*S*,3*S*)-piperidine benzyl ether series (as exemplified by **4**) have been utilized to achieve subnanomolar affinities. Indeed the SAR of the benzyl ether function in the 4,4-disubstituted piperidines follows this general trend; however, due to the flexibility of the side chain, any interaction of the two aryl rings must be driven by the electrostatic characteristics of the rings themselves, perhaps aided by hydrophobic collapse.[24] It would appear that this is best provided by inclusion of the 3,5-bis(trifluoromethyl)benzyl ether side chain (**12**).

Currently most NK_1 antagonists conform to a simple pharmacophore consisting of two aryl rings separated by a four-atom link containing a putative H bond donor/acceptor residing within a specific distance to a basic nitrogen and some degree of enantioselective binding.[2,4] This pharmacophore is based on the observed SAR of the *cis*-(2*S*,3*S*)-piperidine-based NK_1 antagonists at both the wild type and selective mutant human NK_1 receptors.[25] The 4,4-disubstituted piperidine type NK_1 antagonist cannot display enantioselective binding; however it is likely that the role of the two aryl rings is consistent with the established models. Having established that the SAR of the benzyl ether in this series resembled that in other benzyl ether-derived NK_1 antagonists, we now proceeded to explore the role of the basic nitrogen.

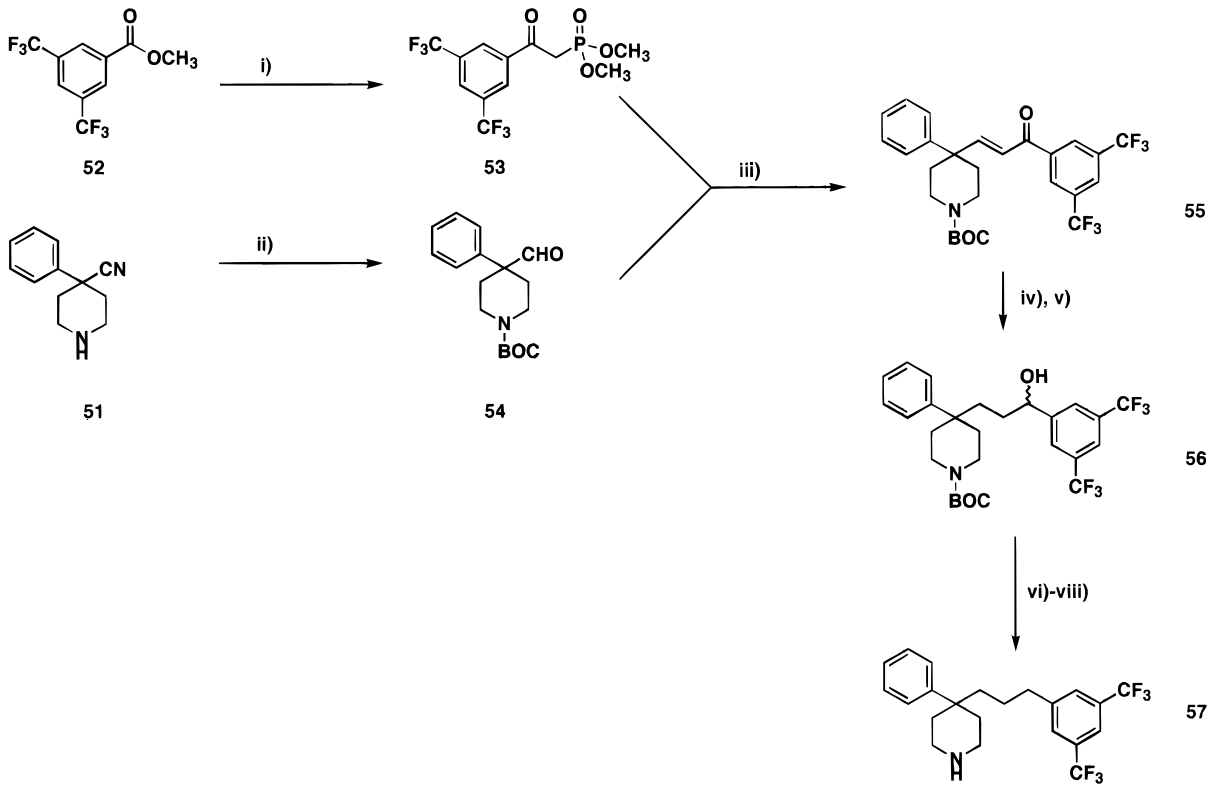
In previous piperidine-based NK_1 antagonist series (such as **2** and **4**), significant affinity for L-type calcium channels has been observed, a feature which can be avoided by decreasing the pK_a of the piperidine nitrogen via N-substitution with electron-withdrawing groups. We were encouraged to find that **12**, although having a more basic piperidine nitrogen ($pK_a = 9.8$) than **1** ($pK_a = 8.92$), showed only weak affinity for L-type calcium channels ($IC_{50} = 4.3\ \mu M$). Retention of a basic piperi-

Scheme 5[a]



[a] Reagents: (i) BOC_2O, Et_3N, DCM; (ii) $LiAlH_4$, THF; (iii) BzBr, Et_3N, DCM; (iv) HCl, Et_2O.

Scheme 6[a]



[a] Reagents: (i) dimethyl methylphosphonate, NaH, DMF; (ii) DIBAL-H, BOC_2O; (iii) K_2CO_3, DMF; (iv) H_2, Pd/C; (v) $NaBH_4$; (vi) PhOCSCl, DMAP, DCM; (vii) AlBN, Bu_3Sn, toluene; (viii) HCl, Et_2O.

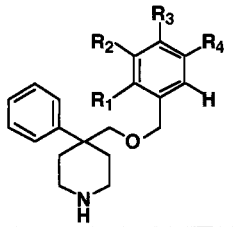
dine nitrogen in this system therefore offered greater scope for substitution.

The simple *N*-methyl derivative **28** is equipotent with **12** (Table 2). Increasing the size of the *N*-alkyl group does cause a decrease in affinity, but with some degree of steric tolerance (**29**−**30**). A variety of heterocycles such as oxadiazole (**31**), thiazole (**32**), triazole (**34**), and triazolone (**35**) can be incorporated without significant losses in NK_1 affinity. The ester derivative **33** also retains affinity.

The net effect of these electron-withdrawing groups will be to reduce the pK_a of the piperidine nitrogen. The fact that this did not adversely affect the NK_1 affinity raised the question of whether a basic nitrogen was required at all. To examine this the simple acyl (**38**) and sulfonyl (**39**) derivatives (Table 3) were prepared and, remarkably, were found to have retained good affinity compared to **12**. There are two relevant factors which need to be taken into account to explain this observation. First, in the *cis*-(2*S*,3*S*)-piperidine-based NK_1 antagonists (e.g., **2**) the C-3 benzylic amino group is directly attached to the piperidine ring. For this reason it is unlikely that at physiological pH both the ring and side chain nitrogens will be protonated (**2**, $pK_a^{N-1} = 8.92$, $pK_a^{N-2} = 4.98$). Any decrease in pK_a^{N-1} caused by the introduction of an electron-withdrawing group or by acylation of the piperidine nitrogen would, however, allow protonation of the side chain nitrogen, removing H bond acceptor capacity, resulting in reduced affinity. Second, acylation of the *cis*-(2*S*,3*S*)-piperidine-based system would by virtue of A_{1-3} strain invert the piperidine ring, placing the 2-phenyl group in an axial position, an effect which is likely to lower affinity by limiting the possibilities for interaction between the two aryl rings. Similar observations have been made in the *cis*-(2*S*,3*S*)-piperidine-based NK_1 antagonists.[18c] In compounds such as **12** there is no second nitrogen, and the lack of any C-2 substituent means that there is no A_{1-3} strain to be relieved on acylation; consequently there is no change in conformation or affinity.

If a second, basic nitrogen is introduced into the acyl side chain (**40**), then sub nanomolar affinity is regained. Displacement by an ethyl linker (**41**) maintains high affinity, while extension to a propyl linker (**42**) results in a slight loss in affinity. As can be seen from compound **43**, the basic center can itself be incorporated

Table 1. Benzyl Ether Substitutions



Compound	R_1	R_2	R_3	R_4	hNK$_1$ IC$_{50}$[a]	Formula	Analysis
12	H	CF_3	H	CF_3	0.95 ± 0.41	$C_{21}H_{21}NOF_6$	C, H, N
13	H	H	H	H	1113 ± 333	$C_{19}H_{23}NO$	C, H, N
14	H	CF_3	H	H	57 ± 25	$C_{20}H_{22}F_3NO$	C, H, N
15	CF_3	H	H	H	84 ± 32	$C_{20}H_{22}F_3NO$	C, H, N
16	H	H	CF_3	H	730 ± 269	$C_{20}H_{22}F_3NO$	C, H, N
17	H	Cl	H	Cl	4.6 ± 2.3	$C_{19}H_{21}Cl_2NO$	C, H, N
18	H	CH_3	H	CH_3	9.1 ± 6.0	$C_{21}H_{27}NO$	C, H, N
19	H	CH_3	H	^{t}Bu	2.4 ± 0.5	$C_{24}H_{33}NO$	C, H, N
20	H	CH_3	H	Br	2.9 ± 0.8	$C_{20}H_{24}NOBr$	C, H, N
21	H	I	H	H	38 ± 8	$C_{19}H_{22}NOI$	C, H, N
22	H	^{t}Bu	H	H	55 ± 5	$C_{23}H_{31}NO$	C, H, N
23	H	OCF_3	H	H	170 ± 36	$C_{20}H_{22}NO_2F_3$	C, H, N
24	H	OCH_3	H	OCH_3	90 ± 20	$C_{21}H_{27}NO_3$	C, H, N

[a] Displacement of [^{125}I]-labeled substance P from the cloned receptor expressed in CHO cells (n = 3).

into a saturated ring, with no significant loss in affinity, or it can be incorporated in a heterocyclic system (**44**−**47**).

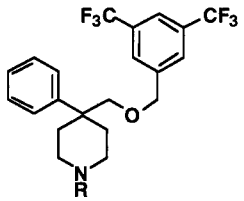
The conclusions that can be drawn from this study are that a highly basic center is not required for binding in this class of NK_1 antagonist and that the area of the molecule around the piperidine nitrogen may not interact with the receptor, given the wide tolerability to substituent size and character.

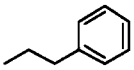
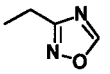
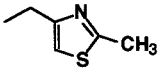
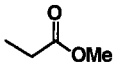
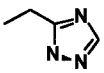
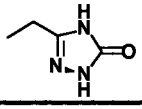
One of the distinguishing features of the 4,4-disubstituted piperidine NK_1 antagonists described here is the flexible portion of the molecule linking the benzyl ether to the phenylpiperidine ring. On the basis of current NK_1 pharmacophores,[2] the ether link in the side chain should behave as a hydrogen bond acceptor. However in the case of the 4,4-disubstituted piperidine system, it must also allow or induce any aryl−aryl interactions.

If the 3,5-bis(trifluoromethyl)benzyloxy side chain of 12 is replaced by the 2-methoxybenzylamino group found in **1** and **2** to give **48**, the resulting compound has poor affinity for the NK_1 receptor (31% @ 1 μM). This is a significant departure from the observed SAR of the cis-(2*S*,3*S*)-piperidine-based series where the O- for N-substitution provided equipotent compounds (although it should be noted that 2-methoxybenzyl ether side chain in the quinuclidine type NK_1 antagonist has poor NK_1 affinity[26]). The explanation for this may lie in the fact that in compounds such as **2** the benzylic amino group is directly attached to the piperidine/quinuclidine ring (see above). In the case of **48** the benzylic nitrogen is not directly attached to the piperidine ring and is consequently more basic (**48**, pK_a^{N-1} = 10.6, pK_a^{N-2} = 8.2). If at physiological pH both the piperidine and side chain nitrogens protonate, the benzylic nitrogen will no longer be able to act as a hydrogen bond acceptor. A secondary factor may be that *ortho* substituents are not well-tolerated in this system (Table 1). To examine the effect of the pK_a of the side chain nitrogen, the 3,5-bis(trifluoromethyl)benzylamino compound **49** was prepared. The inductive effect of the trifluoromethyl groups now decreases the electron density at the nitrogen (**49**, pK_a^{N-1} = 10.13, pK_a^{N-2} = 5.92), and it will therefore be less likely to protonate at physiological pH. This would indeed appear to be the case as **49** (IC_{50} = 12.6 nM), although less active than **12** (IC_{50} = 0.95 nM), did recover most of the lost affinity. Mutagenesis studies using **48** and **49** have also lent weight to this theory.[24] In the case where Lys^{106} has been mutated to Glu^{106}, **48** shows a large increase in NK_1 affinity from >100 to 30 nM, indicating that the protonated form of **48** develops a more favorable interaction between ligand and receptor. The NK_1 affinity of **49** is however decreased by this same mutation (from 8.0 to 47 nM).

The compound bearing an all-carbon linking side chain (**57**) shows a 200-fold loss in affinity (IC_{50} = 180 nM), and this is to be expected from the loss of a

Table 2. *N*-Alkyl Substituents



Compound	R	hNK_1 IC_{50}[a]	Formula	Analysis
28	Me	0.9 ± 0.2	$C_{22}H_{23}NOF_6$	C, H, N
29	i_{Pr}	2.9 ± 0.9	$C_{24}H_{27}NOF_6$	C, H, N
30		6.9 ± 2.5	$C_{30}H_{34}NOF_6$	C, H, N
31		7.3 ± 4.5	$C_{24}H_{23}N_3O_2F_6$	C, H, N
32		2.8 ± 0.8	$C_{25}H_{25}N_2OSF_6$	C, H, N
33		3.1 ± 2.2	$C_{24}H_{25}NO_3F_6$	C, H, N
34		1.8 ± 2.2	$C_{24}H_{24}N_4OF_6$	C, H, N
35		1.7 ± 2.1	$C_{24}H_{24}N_4O_2F_6$	C, H, N

[a] Displacement of [^{125}I]-labeled substance P from the cloned receptor expressed in CHO cells ($n = 3$).

hydrogen-bonding interaction. By mutating the receptor so that Gln^{165} is replaced by Ala, the observed affinity of **57** is now 70 nM, whereas the affinity of **12** drops to 55 nM. This represents a loss in binding energy of around 2.5 kcal, which is again consistent with a hydrogen bond. The conclusion reached from this study of the side chain is that, as expected, it must contain a hydrogen bond acceptor, preferably an ether oxygen, but alternatively a weakly basic nitrogen is tolerated.

***In Vivo* Studies**. Initial examination of **12** *in vivo* showed it to be poorly orally bioavailable. We therefore carried out pharmacokinetic studies on a range of N-substituted compounds to establish possible candidates for *in vivo* screening.

Compounds were selected for this study on the basis of high NK_1 affinity and low affinity at L-type calcium channels. Using these criteria **32** and **43** were selected, and their respective pharmacokinetic profiles in rats were determined. The results of these studies are represented in Table 5.

Compound **32** shows good oral bioavailability, with a relatively low plasma clearance rate. The magnitude of peak plasma concentration and the time in which it is reached were acceptable for *in vivo* studies of the type intended. Compound **43** was found to have a marginally superior pharmacokinetic profile to **32** with respect to half-life and higher oral bioavailability. However this has been attained at the cost of a much higher volume of distribution and a slower rise to a lower maximum plasma concentration.

Compounds (**32**) and (**43**) were tested *in vivo* using the resiniferatoxin-induced vascular leakage model of NK_1 antagonist activity.[27] The respective results are displayed in Figure 2. Both **32**, ($ID_{50} = 0.28$ mg/kg) and **43** ($ID_{50} = 0.22$ mg/kg) have a rapid onset of action. The effect of the relatively long plasma half-life of **43** manifests itself as a long and flat tail off of the inhibitory effect which is still significant 24 h after dosing. Compound **32** has a rapid onset of action and still shows significant inhibition at 16 h, after which the effect tails off.

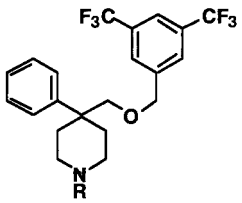
Conclusion

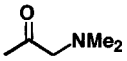
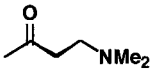
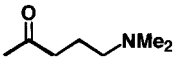
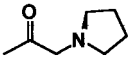
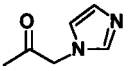
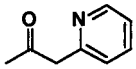
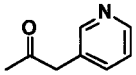
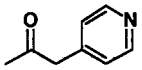
We have developed a series of high-affinity NK_1 antagonists based on a 4-phenyl,4-arylmethyloxymethyl-substituted piperidine ring. This class of NK_1 antagonist challenges currently accepted models of the NK_1 pharmacophore with respect to stereochemistry and the absolute requirement for a basic nitrogen. Compounds such as **32** and **43** have good oral bioavailability and pharmacokinetics and display excellent activity and extended duration of action in an *in vivo* model of substance P-induced extravasation. Further details of the *in vivo* properties of this class of NK_1 antagonist will be reported in due course.

Experimental Section

Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. NMR spectra were recorded at 360 MHz on a Bruker AM360 instrument. The term "dried" refers to drying of an organic phase over

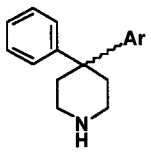
Table 3. *N*-Acyl Subtituents

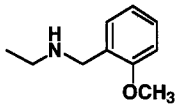
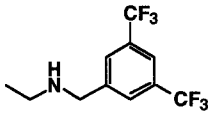
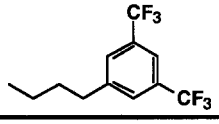


Compound	R	hNK1 IC_{50}[a]	Formula	Analysis
38	$COCH_3$	5.3 ± 2.7	$C_{23}H_{23}NO_2F_6$	C, H, N
39	SO_2CH_3	5.7 ± 2.4	$C_{22}H_{23}NOF_6S$	C, H, N
40		0.5 ± 0	$C_{25}H_{28}N_2O_2F_6$	C, H, N
41		0.6 ± 0.35	$C_{26}H_{30}N_2O_2F_6$	C, H, N
42		1.2 ± 0.2	$C_{27}H_{32}N_2O_2F_6$	C, H, N
43		0.24 ± 0.08	$C_{26}H_{30}N_2O_2F_6$	C, H, N
44		0.32 ± 0.21	$C_{25}H_{25}N_3O_2F_6$	C, H, N
45		1.8 ± 0.9	$C_{26}H_{26}N_2O_2F_6$	C, H, N
46		1.8 ± 0.8	$C_{26}H_{26}N_2O_2F_6$	C, H, N
47		0.94 ± 0.49	$C_{26}H_{26}N_2O_2F_6$	C, H, N

[a] Displacement of [^{125}I]-labeled substance P from the cloned receptor expressed in CHO cells ($n = 3$).

Table 4. Alternative Linkers



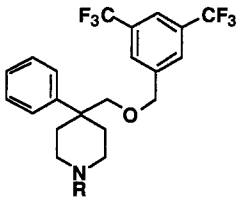
Compound	Ar	hNK1 IC_{50}[a]	Formula	Analysis
48		> 100[b]	$C_{20}H_{27}N_2O$	C, H, N
49		12.6 ± 8.8	$C_{21}H_{22}N_2F_6$	C, H, N
57		63 ± 7	$C_{22}H_{23}NF_6$	C, H, N*

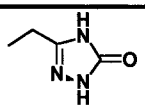
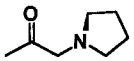
[a] Displacement of [^{125}I]-labeled substance P from the cloned receptor expressed in CHO cells ($n = 3$). [b] 31% and 25% @ 0.1 μM. *$C_{22}H_{23}NF_6$ requires 415.1734, found 415.1750.

anhydrous magnesium sulfate and then filtering, and organic solvents were evaporated on a Büchi rotary evaporator at reduced pressure. Column chromatography was carried out on silica gel (Merck Art 7734). Elemental analyses were determined by Butterworth Laboratories Ltd., Teddington, England.

General Procedure for the Preparation of Compounds 12−24. 1-(*tert*-Butoxycarbonyl)-4-phenyl-4-(hydroxymethyl)piperidine (27). A solution of lithium aluminum hydride (4.02 g, 106 mmol) in dry THF (106 mL) was added dropwise to a stirred solution of 4-phenyl-4-carboxypiperidine tosylate (**26**) (20.0 g, 52.9 mmol) in dry THF (100 mL) at 0 °C.

Table 5. Pharmacokinetic Studies



Compound	R	Dose[a] mg/Kg	CL (mL.min^{-1} Kg^{-1})	$t_{1/2}$ /h*	Time to C_{MAX}/ h*	V_{SS} l. Kg^{-1}	F %
32		3.0	22	2.3	1	2.8	36
43		2.0	26	>7.0	2	12.0	48

[a] Study carried out in male rats, equal doses administered orally and iv. * Oral dosing.

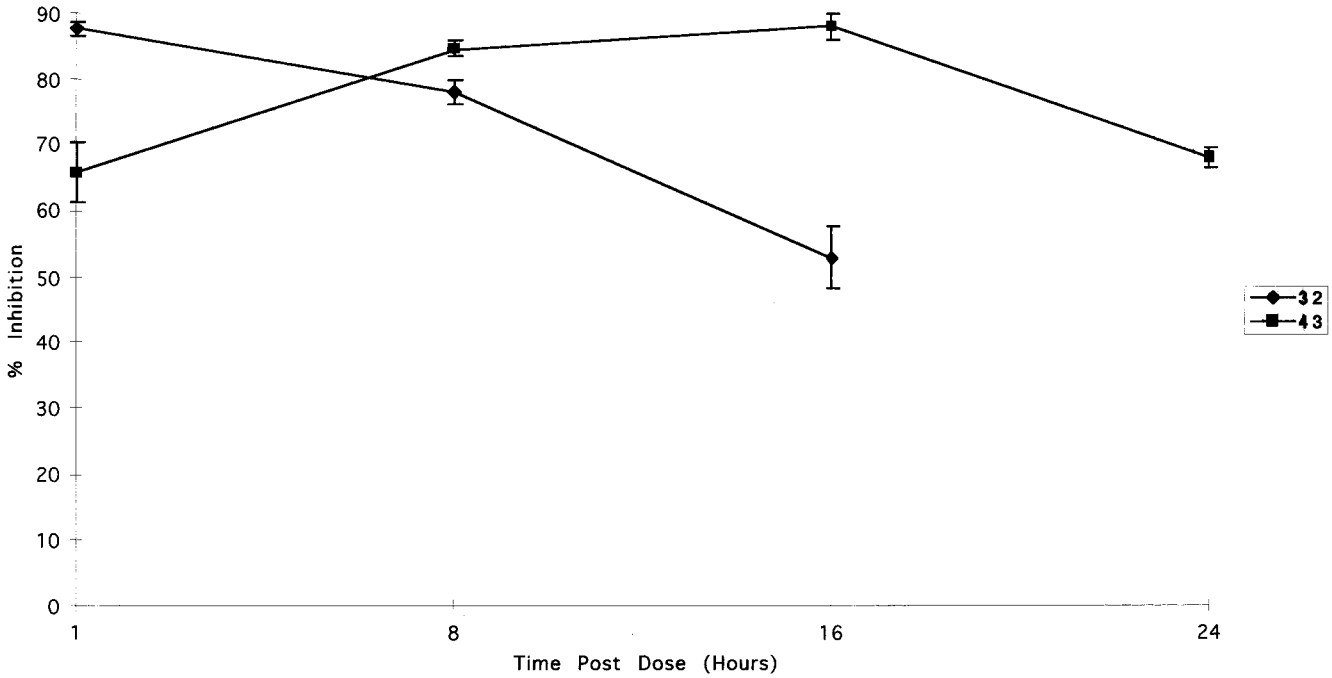


Figure 2. Time-dependent inhibition of resiniferotoxin-induced esophageal plasma extravasation by **32** and **43** at 1 mg/kg po.

After the addition was complete the reaction mixture was warmed to reflux for 90 min and then allowed to cool to room temperature. The reaction was then quenched by addition of aqueous 2 N sodium hydroxide (6.4 mL) followed by water (8.0 mL) which resulted in the formation of a white granular precipitate. A second portion of NaOH (2.1 g, 52.5 mmol) in water (25 mL) was added followed by a solution of di-*tert*-butyl dicarbonate (11.56 g, 53 mmol) in dichloromethane (65 mL). The resulting mixture was stirred at 25 °C for 18 h. After this time the reaction mixture was filtered through a pad of sodium sulfate, which was subsequently washed with dichloromethane (3 × 100 mL). The filtrate was washed with water (100 mL) and brine (100 mL), the organic layer separated, dried over $MgSO_4$, and filtered, and solvent removed under reduced pressure to afford a clear oil which crystallized on standing. Recrystallization from ether/*n*-hexane gave **27** as white needles: mp 91−94 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (9H, s), 1.64 (1H, brs), 1.75 (2H, td, J = 11.0, 10.0 Hz), 2.17 (2H, m), 3.05 (2H, td, J = 11.0, 1.0 Hz), 3.55 (2H, s), 3.73 (2H, m), 7.24−7.41 (5H, m); MS *m/e* (CI^+) 292 $(M + H)^+$; HRMS calcd $C_{17}H_{25}NO_3$ 291.1834, found 291.1851.

4-Phenyl-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]-piperidine Hydrochloride (12). Sodium hydride (120 mg, 60% dispersion in mineral oil, 3.0 mmol) was added to a stirred solution of **27** (760 mg, 2.6 mmol) and 3,5-bis(trifluoromethyl)-benzyl bromide (801 mg, 2.61 mmol) in dry dimethylformamide (5.0 mL). The resulting solution was stirred overnight at room temperature, poured into water (100 mL), and extracted into ethyl acetate (50 mL). The organic layer was separated, washed with water (3 × 50 mL) and then brine (2 × 50 mL), dried over $MgSO_4$, and filtered and the solvent removed under reduced pressure to afford a yellow oil. Purification by flash chromatography (silica gel, 15% EtOAc/*n*-Hex) afforded **12** as a clear oil (900 mg, 66%): ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 1.86 (2H, td, J = 10.0, 1.0 Hz), 2.21 (2H, m), 3.03 (2H, td, J = 10.0, 1.0 Hz), 3.45 (2H, s), 3.76 (2H, m), 4.43 (2H, s), 7.24 (2H, m), 7.33 (3H, m), 7.54 (2H, s), 7.73 (1H, s); MS *m/e* (CI^+) 518 $(M + H)^+$.

The recovered product (900 mg, 1.77 mmol) was dissolved in dry diethyl ether (50 mL) and a stream of dry hydrogen chloride gas passed through the solution for 30 min. The solution was stirred for a further 2.5 h at room temperature,

at which point the solvent was removed under reduced pressure to afford a white solid. Recrystallization from ethyl acetate afforded **12** as a white powder (760 mg, 94%): mp 139−141 °C; ^{1}H NMR (DMSO-d_6) δ 2.08 (2H, m), 2.19 (2H, m), 2.73 (2H, m), 3.21 (2H, m), 3.49 (2H, s), 4.58 (2H, s), 7.27 (5H, m), 7.77 (2H, s), 7.98 (1H, s), 9.7 (2H, brs); MS *m/e* (CI$^+$) 418 (M + H)$^+$. Anal. ($C_{21}H_{21}NOF_6$·HCl) C, H, N.

General Procedure for the Preparation of Compounds 28−30. 1-Methyl-4-phenyl-4-[3,5-bis(trifluoromethyl)-benzyloxymethyl]piperidine *p*-Toluenesulfonate (28). Sodium cyanoborohydride (147 mg, 2.82 mmol) was added to a stirred suspension of **12** (533 mg, 1.83 mmol) and formaldehyde (175 mg, 0.5 mL, 37%, 5.83 mmol) in dry methanol containing acetic acid (1.0 mL, 16.6 mmol). The resulting solution was stirred for 18 h at room temperature. After this time the solvent was removed under reduced pressure and the residual oil taken up in water and basified to pH 10. The aqueous solution was extracted into ethyl acetate, separated, and dried over $MgSO_4$. Filtration and removal of solvent gave a yellow oil. Chromatography (silica gel, 5% MeOH/DCM) afforded a clear oil (473 mg). The recovered oil was treated with a solution of *p*-toluenesulfonic acid monohydrate (207 mg) to afford the salt. Recrystallization from ethyl acetate gave the **28** as a white powder (580 mg, 52%): mp 89−91 °C; ^{1}H NMR (DMSO-d_6) δ 2.01 (2H, m), 2.21 (2H, m), 2.55 (2H, m), 2.67 (3H, s), 2.71 (2H, m), 3.37 (2H, s), 4.56 (2H, s), 7.30−7.48 (5H, m), 7.70 (2H, s), 7.99 (1H, s), 9.01 (1H, brs); MS *m/e* (CI$^+$) 432 (M + H)$^+$; HRMS calcd $C_{22}H_{23}NOF_6$ 432.1684, found 432.1664. Anal. ($C_{22}H_{23}NOF_6$·$C_7H_8SO_3$) C, H, N.

4-[3,5-Bis(trifluoromethyl)benzyloxymethyl]-1-([1,2,4]-oxadiazol-3-ylmethyl)-4-phenylpiperidine Hydrochloride (31). 3-(Chloromethyl)[1,2,4]oxadiazole (130 mg, 1.1 mmol) was added to a stirred solution of **12** (500 mg, 1.1 mmol) and diisopropylamine (426 mg, 3.3 mmol) in dry CH_3CN (20 mL). After 18 h at room temperature the solvent was removed under reduced pressure and the residue partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated, washed with aqueous $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), dried over $MgSO_4$, and filtered and the solvent removed under reduced pressure. The product was purified by flash chromatography (silica gel, 5% MeOH/DCM) to give a white solid (489 mg, 88%). The recovered product was taken up in ether (20 mL) and treated with ethereal HCl. The solvent was removed under reduced pressure and the residue recrystallized from 2-propanol to give **31** as white needles (512 mg, 86%): mp 90−91 °C; ^{1}H NMR (DMSO-d_6) δ 2.15 (4H, brm), 2.50 (2H, m), 2.51 (1H, m), 2.85 (1H, m), 3.37 (2H, m), 3.49 (2H, m), 4.58 (2H, brs), 7.39−7.45 (5H, m), 7.78 (2H, s), 7.97 (1H, s), 9.89 (1H, s), 11.00 (1H, brs); MS *m/e* (CI$^+$), 500 (M + H)$^+$. Anal. ($C_{24}H_{23}N_3O_2F_6$·HCl) C, H, N.

4-[3,5-Bis(trifluoromethyl)benzyloxymethyl]-1-(2-methylthiazol-5-ylmethyl)-4-phenylpiperidine Dihydrochloride (32). 5-(Chloromethyl)-2-methylthiazole (202 mg, 1.1 mmol) was added to a stirred solution of **12** (500 mg, 1.1 mmol) and diisopropylamine (426 mg, 3.3 mmol) in dry CH_3CN (20 mL). After 18 h at room temperature the solvent was removed under reduced pressure and the residue partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated, washed with aqueous $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), dried over $MgSO_4$, and filtered and the solvent removed under reduced pressure. The product was purified by flash chromatography (silica gel, 10% MeOH/DCM) to give a white solid (470 mg, 80%). The recovered product was taken up in ether (20 mL) and treated with ethereal HCl. The solvent was removed under reduced pressure and the residue recrystallized from ether to give **32** as white needles (490 mg, 78%): mp 110−113 °C; ^{1}H NMR (DMSO-d_6) δ 2.19 (3H, m), 2.37 (1H, m), 2.59 (3H, s) 2.74 (2H, m), 3.29 (2H, m), 3.37 (2H, s), 4.25 (2H, d, J = 1.0 Hz), 4.55 (2H, s) 7.24−7.44 (5H, m), 7.70 (1H, s), 7.73 (2H, s), 7.96 (1H, s), 11.00 (2H, brs); MS *m/e* (CI$^+$) 529 (M + H)$^+$. Anal. ($C_{26}H_{26}N_2OSF_6$·2HCl) C, H, N.

Methyl 2-[4-Phenyl-4-(3,5-bis(trifluoromethyl)benzyl-oxymethyl)piperidine]acetate Hydrochloride (33). Potassium carbonate (1.38 g, 10.0 mmol) was added to a stirred solution of **12** (4.47 g, 8.7 mmol) and methyl bromoacetate (1.5 g, 9.8 mmol) in dry DMF (25 mL) and the resulting mixture stirred at room temperature for 18 h. After this time the reaction was diluted with water (100 mL), extracted into ethyl acetate (50 mL), dried over $MgSO_4$, and filtered and the solvent removed under reduced pressure. The residual solid was purified by flash chromatography (silica gel, 30% EtOAc/*n*-Hex) to give a white solid. The recovered product was redissolved in dry ether and treated with ethereal HCl followed by removal of solvent under reduced pressure to give a white solid. Recrystallization form 2-propanol afforded **33** as a white powder (2.23 g, 48%): mp 63−65 °C; ^{1}H NMR (DMSO-d_6) δ 2.04−2.11 (2H, m), 2.29−2.42 (4H, m), 2.81 (2H, m), 3.19 (2H, s), 3.48 (2H, s), 3.69 (3H, s), 4.42 (2H, s), 7.21−7.36 (5H, m), 7.52 (2H, s), 7.72 (1H, s), 9.78 (1H, brs); MS *m/e* (CI$^+$) 490 (M + H)$^+$. Anal. ($C_{24}H_{25}NO_3F_6$·HCl) C, H, N.

4-[3,5-Bis(trifluoromethyl)benzyloxymethyl]-4-phenyl-1-(4*H*-[1,2,4]triazol-3-ylmethyl)piperidine Dihydrochloride (34). Potassium carbonate (608 mg, 4.4 mmol) was added to a suspension of **12** (500 mg, 1.1 mmol) and *N*-formamido-2-(chloromethyl)acetamidine (**36**) (382 mg, 2.8 mmol) in DMF (20 mL). The solution was warmed to 60 °C for 2 h and then to 140 °C for a further 1 h. The reaction was cooled to room temperature, diluted with water (100 mL), and extracted into ethyl acetate (50 mL). The organic layers were separated, washed with water (50 mL) and then brine (50 mL), and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residual oil was purified by flash chromatography (silica gel, 10% MeOH/DCM) and the recovered product treated with excess ethereal hydrogen chloride followed by removal of solvent under reduced pressure to give the hydrochloride salt. Recrystallization from 2-propanol gave **34** as a white powder (400 mg, 63%): mp 119−120 °C. H NMR (DMSO-d_6) δ 2.16 (2H, m), 2.49−2.56 (2H, m), 2.77 (2H, m), 3.37 (2H, s), 3.42−3.46 (2H, m), 4.33 (2H, s), 4.57 (2H, m), 7.26−7.44 (5H, m), 7.75 (2H, s), 7.98 (1H, s), 8.59 (1H, s), 8.62 (1H, brs), 10.01 (2H, brs); MS *m/e* (CI$^+$) 499 (M + H)$^+$. Anal. ($C_{24}H_{24}N_4OF_6$·2HCl) C, H, N.

5-[4-(3,5-Bis(trifluoromethyl)benzyloxymethyl)-4-phenylpiperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]triazol-3-one (35). *N*-(Methoxycarbonyl)(chloromethyl)imidrazone (**37**) (7.1 g, 40.3 mmol) was added to a stirred suspension of **12** (15.0 g, 33.1 mmol) and K_2CO_3 (11.12 g, 80.6 mmol) in dry DMF (100 mL) and the resulting solution stirred for 24 h at room temperature. The reaction mixture was diluted with water (400 mL) and the resulting mixture extracted into ethyl acetate (400 mL). The organic extract was washed exhaustively with water (5 × 100 mL) and brine (200 mL), dried over $MgSO_4$, and filtered and the solvent removed under reduced pressure to afford a yellow solid. The recovered solid was redissolved in dry toluene and warmed to reflux for 30 min. The solvent was removed under reduced pressure and the residue purified by chromatography (silica gel, 15% EtOAc/*n*-Hex) to give the product as a white powder (16.3 g, 95%). The recovered product was taken up in dry ether and HCl gas passed through the solution. Filtration afforded **35** as a white powder on stirring (17.1 g, 94%): mp 159−160 °C; ^{1}H NMR (DMSO-d_6) δ 2.1 (2H, m), 2.23 (2H, m), 2.61 (2H, m), 2.93 (2H, m), 3.36 (2H, s), 3.80 (1H, d, J = 15.0 Hz), 4.1 (1H, d, J = 15.0 Hz), 4.2 (2H, s), 7.1−7.25 (5H, m), 7.76 (2H, s), 7.89 (1H, brs), 8.34 (1H, s), 8.88 (1H, s), 9.02 (1H, brs); MS *m/e* (CI$^+$) 515 (M + H)$^+$. Anal. ($C_{24}H_{24}N_4O_2F_6$·HCl) C, H, N.

1-Acetyl-4-phenyl-4-(3,5-bis(trifluoromethyl)benzyl-oxymethyl)piperidine (38). Acetyl chloride (86 mg, 1.1 mmol) was added to a stirred solution of **12** (500 mg, 0.94 mmol) and triethylamine (310 mL, 4.22 mmol) in dry DCM at 0 °C. The resulting solution was allowed to warm to room temperature overnight. The reaction mixture was diluted with water (50 mL) and the organic layer separated. The aqueous layer was extracted further with dichloromethane (2 × 50 mL), the combined organic extracts were washed with 1 N aqueous

sodium hydroxide solution, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to afford a clear oil which solidified on standing. Recrystallization from hexane/ether afforded **38** as white needles (389 mg, 89%): mp 64−65 °C; ^{1}H NMR (DMSO-d_6) δ 1.70−1.80 (1H, m), 1.81−1.91 (1H, m), 1.97 (3H, s), 2.04−2.22 (2H, brm m), 2.90−2.99 (1H, m), 3.09−3.19 (1H, m), 3.51 (2H, s), 3.55−3.63 (1H, m), 3.80−3.89 (1H, m), 4.55 (2H, s), 7.20−7.45 (5H, m), 7.75 (2H, s), 7.96 (1H, s); MS *m/e* (CI$^+$) 460 (M + H)$^+$. Anal. ($C_{23}H_{23}NO_2F_6$) C, H, N.

1-(Methylsulfonyl)-4-phenyl-4-(3,5-bis(trifluoromethyl)benzyloxymethyl)piperidine (39). Methanesulfonyl chloride (125 mg, 1.1 mmol) was added to a stirred solution of **12** (500 mg, 0.94 mmol) and triethylamine (310 mL, 4.22 mmol) in dry DCM at 0 °C. The resulting solution was allowed to warm to room temperature overnight. The reaction mixture was diluted with water (50 mL) and the organic layer separated. The aqueous layer was extracted further with dichloromethane (2 × 50 mL), the combined organic extracts were washed with 1 N aqueous sodium hydroxide solution, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to afford a clear oil which solidified on standing. Recrystallization from ethyl acetate/*n*-hexane afforded **39** as white needles (410 mg, 87%): mp 102−104 °C; ^{1}H NMR (DMSO-d_6) δ 1.97−2.08 (2H, m), 2.36−2.46 (2H, m), 2.66 (3H, s), 2.80−2.90 (2H, m), 3.44 (2H, s), 3.55−3.64 (2H, m), 4.44 (2H, s), 7.24−7.44 (5H, m), 7.52 (2H, s), 7.73 (1H, s); MS *m/e* (CI$^+$) 496 (M + H)$^+$. Anal. ($C_{22}H_{23}NOF_6S$) C, H, N.

Compounds 40−47 Prepared by the Following Procedure. 1-[4-(3,5-Bis(trifluoromethyl)benzyloxymethyl)-4-phenylpiperidin-1-yl]-2-pyrrolidineacetamide *p*-Toluenesulfonate (43). Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (1.6 g, 6.29 mmol) was added to a stirred solution of **12** (2.85 g, 6.3 mmol), 2-(*N*-pyrrolidino)acetic acid hydrochloride (1.04 g, 6.3 mmol), and triethylamine (2.54 g, 25.2 mmol) in DCM (20 mL). After 18 h the reaction was washed with water (50 mL) and brine (50 mL), the organic layers were separated, dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography (grade III alumina, 0−2% MeOH/DCM). The recovered product was treated with *p*-toluenesulfonate monohydrate (720 mg) to afford the salt. Recrystallization from 2-propanol afforded **43** as white needles (1.4 g, 42%): mp 121−122 °C; ^{1}H NMR (DMSO-d_6) δ 1.8−1.97 (6H, m), 2.1−2.23 (2H, m), 2.6 (4H, m), 2.9−3.05 (1H, m), 3.08 (1H, m), 3.14 (1H, d, J = 12 Hz), 3.20 (1H, d, J = 12 Hz), 3.26 (2H, s), 3.88 (1H, dt, J = 10, 4 Hz), 4.21 (1H, dt, J = 10, 4 Hz), 4.22 (2H, s), 7.2−7.4 (5H, m), 7.56 (2H, s), 7.78 (1H, s) MS *m/e* (CI$^+$) 529 (M + H)$^+$. Anal. ($C_{27}H_{30}N_2O_2F_6 \cdot C_7H_8SO_3$) C, H, N.

4-Phenyl-4-(aminomethyl)-1-(*tert*-butoxycarbonyl)piperidine (51). Di-*tert*-butyl dicarbonate (20 g, 91.7 mmol) was added to a stirred solution of 4-phenyl-4-cyano piperidine hydrochloride (**50**) (20.0 g, 90.09 mmol) and triethylamine (9.5 g, 94.05 mmol) in dry DCM (100 mL). The resulting solution was stirred overnight at room temperature. The reaction mixture was then washed with water (2 × 100 mL) and the organic layer separated and dried over $MgSO_4$. Filtration and removal of solvent under reduced pressure afforded a white solid. Recrystallization from hexane gave *N*-(*tert*-butoxycarbonyl)-4-phenyl-4-cyanopiperidine as white needles (25.62 g, 99%): mp 64 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 1.90 (2H, m), 2.04 (2H, m), 3.20 (2H, m), 4.26 (2H, m), 7.26−7.49 (5H, m); MS *m/e* (CI$^+$) 287 (M + H)$^+$.

The recovered product was taken up in 15% acetic acid/ethanol (300 mL) and hydrogenated at 50 psi over platinum dioxide (0.5 g) for 18 h. The catalyst was filtered off and the solvent removed under reduced pressure. The residue was partitioned between ethyl acetate (100 mL) and aqueous 2 N sodium hydroxide (100 mL) solution. The organic extract was separated, dried over $MgSO_4$, and filtered and the solvent removed under reduced pressure to afford **51** as a clear oil (23.2 g, 80%): ^{1}H NMR ($CDCl_3$) δ 1.45 (9H, s), 1.67 (2H, m), 2.20 (2H, m), 2.75 (2H, s), 3.05 (2H, m), 3.50 (2H, brs), 3.71 (2H, m), 7.21−7.39 (5H, m); MS *m/e* (CI$^+$) 291 (M + H)$^+$; HRMS calcd $C_{17}H_{26}N_2O_2$ 290.1994, found 290.2012.

Compounds 48 and 49 Prepared by the Following Procedure. 4-Phenyl-4-[3,5-bis(trifluoromethyl)benzylaminomethyl]piperidine Dihydrochloride (49). A solution of 3,5-bis(trifluoromethyl)benzyl bromide (2.59 g, 8.48 mmol) in dry DCM was added dropwise to a chilled solution of **51** (2.46 g, 8.48 mmol) in dry DCM. The reaction was allowed to warm to room temperature, stirred for 2 h, and diluted with water (50 mL) and the organic layer separated and dried over $MgSO_4$. Filtration and removal of solvent under reduced pressure afforded a yellow oil, which was further purified by MPLC (SiO_2/EtOAc/*n*-Hex, 1:1). The recovered product was treated with HCl/Et_2O for 18 h. The solvent was removed under reduced pressure and the product recrystallized from EtOAc to give **49** (2.1 g, 54%): mp 210−215 °C; ^{1}H NMR (DMSO-d_6) δ 2.08 (2H, m), 2.40 (2H, m), 2.49 (2H, s), 2.76 (2H, m), 3.22 (2H, m), 4.20 (2H, m), 7.34−7.45 (5H, m), 7.84 (2H, brs), 8.13 (1H, s), 8.23 (2H, s), 9.01 (2H, brs); MS *m/e* (CI$^+$) 417 (M + H)$^+$. Anal. ($C_{21}H_{22}N_2F_6 \cdot 2HCl$) C, H, N.

4-Phenyl-4-(2-methoxybenzylaminomethyl)piperidine dihydrochloride (48): prepared analogously to **49**; mp 178−180 °C; ^{1}H NMR (DMSO-d_6) δ 2.14 (2H, m), 2.37 (2H, m), 2.69 (2H, s), 2.78 (2H, m), 3.19 (2H, s), 3.33 (2H, s), 3.57 (3H, s), 6.91 (1H, d, J = 6.0 Hz), 6.96 (1H, t, J = 6.0, 1.0 Hz), 7.25 (1H, d, J = 6.0 Hz), 7.37 (1H, t, J = 6.0, 1.0 Hz), 7.41−7.73 (5H, m), 9.30 (2H, brs); MS *m/e* (CI$^+$) 311 (M + H)$^+$. Anal. ($C_{20}H_{27}N_2O \cdot 2HCl$) C, H, N.

Dimethyl 2-(3,5-Bis(trifluoromethyl)phenyl)-2-ketoethylphosphonate (53). *n*-Butyllithium (165 mL of a 2.5 M solution in hexane, 410 mmol) was added dropwise to a solution of dimethyl methylphosphonate (50.1 g, 403 mmol) in dry THF (500 mL) stirring under a dry nitrogen atmosphere at −78 °C. After 1 h, methyl 3,5-bis(trifluoromethyl)benzoate (**52**) (18.7 g, 68.75 mmol) in dry THF (50 mL) was added slowly over a period of 30 min and stirred for a further 30 min. The reaction was then quenched with aqueous 5 N hydrochloric acid (500 mL) and the THF removed under reduced pressure. The residual liquid was extracted with ethyl acetate (2 × 100 mL), the organic layer separated, dried over $MgSO_4$, and filtered, and the solvent removed under reduced pressure. The residue was distilled under high vacuum to give **53** (bp 160−162 °C @ 1 mmHg): ^{1}H NMR (DMSO-d_6) δ 3.66 (3H, s), 3.69 (3H, s), 3.89 (2H, d, J = 21.0 Hz), 8.45 (1H, s), 8.50 (2H, s); MS *m/e* (CI$^+$) 365 (M + H)$^+$.

***N*-(*tert*-Butoxycarbonyl)-4-phenylpiperidine-4-carboxaldehyde (54).** A solution of **50** (5.0 g, 17.4 mmol) in dry toluene (100 mL) at −78 °C was treated with a solution of DIBAL-H (27.7 mL, 1.0 mol) in toluene. The reaction was maintained at −78 °C for 2 h, at which time it was quenched by slow addition of a saturated aqueous solution of NH_4Cl (20 mL) and allowed to warm to room temperature. The reaction mixture was poured into water (100 mL) and extracted into ethyl acetate. The organic layers were separated, dried over $MgSO_4$, and filtered, and solvent was removed to give a yellow oil. Chromatography on silica gel (20% EtOAc in hexane) afforded **54** as a clear oil (2.1 g, 41%): ^{1}H NMR ($CDCL_3$) δ 1.45 (9H, s), 1.95 (2H, m), 2.07 (2H, m), 3.12 (2H, m), 3.85 (2H, m), 7.26−7.40 (5H, m), 9.40 (1H, s); MS *m/e* (CI$^+$) 290 (M + H)$^+$; HRMS calcd $C_{17}H_{23}NO_3$ 289.1678 (290.1756 M + H$^+$), found 290.1764.

4-(3-(3′,5′-Bis(trifluoromethyl)phenyl)-3-ketopropyl)-4-phenyl-*N*-(*tert*-butoxycarbonyl)piperidine (55). Sodium hydride (800 mg, 60% dispersion in mineral oil, 20.0 mmol) was added to a solution of **53** (4.6 g, 15.9 mmol) and **54** (5.8 g, 15.9 mmol) in dry DMF (100 mL). After 1 h 2-propanol (50 mL) was added, and after a further 1 h the solvents were removed under reduced pressure. The residue was purified by flash chromatography (EtOAc/*n*-Hex, 1:9) to afford the intermediate α,β-unsaturated ketone as a clear oil (6.2 g, 73%): ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 1.86−2.10 (2H, m), 2.30−2.46 (2H, m), 3.04−3.20 (2H, m), 3.84−3.98 (2H, m), 6.61

(1H, d, J = 8.7 Hz), 7.15 (1H, d, J = 8.7 Hz), 7.21−7.48 (5H, m), 7.99 (1H, s), 8.10 (2H, s).

The recovered ketone (6.2 g, 11.7 mmol) was dissolved in ethanol (50 mL) and hydrogenated at 50 psi over 10% Pd/C (1.0 g) for 16 h. The catalyst was filtered off and the solvent removed under reduced pressure to afford **55** as a clear oil (6.1 g, 98%). A portion of the recovered product (100 mg, 0.19 mmol) was treated with ethereal hydrogen chloride for 16 h and then concentrated under reduced pressure to give a white solid. Recrystallization from ethyl acetate gave the hydrochloride salt as white needles (79 mg, 88%): mp 54−55 °C; ^{1}H NMR (DMSO-d_6) δ 1.96−2.03 (4H, brm), 2.35 (2H, m), 2.79−2.84 (4H, brm), 3.18 (2H, m), 7.21 (1H, m), 7.34−7.42 (4H, m), 8.29 (2H, s), 8.36 (1H, s), 9.03 (2H, brs); MS *m/e* (CI^+) 430 $(M + H)^+$. Anal. ($C_{22}H_{21}NOF_6$·HCl) C, H, N.

(±)-4-(3-(3′,5′-Bis(trifluoromethyl)phenyl)-3-hydroxypropyl)-*N*-(*tert*-butoxycarbonyl)-4-phenylpiperidine (56). Sodium borohydride (0.3 g. 7.89 mmol) was added to **55** (1.5 g, 3.49 mmol) in methanol (20 mL). After 1 h the reaction mixture was poured into water and extracted into ethyl acetate. The organic layers were separated, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography (silica gel, 25% EtOAc/*n*-Hex) to give **56** (1.2 g, 64%): ^{1}H NMR ($CDCl_3$) δ 1.43 (9H, s), 1.47−1.73 (2H, m), 2.04−2.17 (4H, m), 2.43 (1H, brs), 3.02−3.24 (4H, m), 3.58−3.66 (2H, m), 4.56−4.58 (1H, m), 7.19−7.34 (5H, m), 7.61 (2H, s), 7.74 (1H, s); MS *m/e* (CI^+) 532 $(M + H)^+$; HRMS calcd $C_{27}H_{31}NO_3F_6$ 531.2208, found 531.2230.

4-(3-(3′,5′-Bis(trifluoromethyl)phenyl)propyl)-4-phenylpiperidine Hydrochloride (57). Phenyl chlorothioformate (0.43 g, 2.5 mmol)) was added to a stirred solution of **56** (0.7 g, 1.62 mmol) and 4-(dimethylamino)pyridine (0.32 g, 2.62 mmol) in dichloromethane (50 mL) at 0 °C. The solution was allowed to warm to 20 °C and stirred for 16 h. The mixture was diluted with ethyl acetate and washed successively with a 10% aqueous solution of citric acid (20 mL), water (20 mL), aqueous sodium bicarbonate solution (50 mL), and brine (50 mL). The solution was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was dissolved in toluene (25 mL) which was purged with nitrogen gas, α,α-azoisobutyronitrile (0.49 g, 2.98 mmol) and tributyltin hydride (0.58 g, 1.99 mmol) were added, and the solution was heated under reflux for 5 h, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 10% EtOAc/*n*-Hex) and then treated with ethereal hydrogen chloride for 16 h. The solvent was removed under reduced pressure and the residue crystallized from ethyl acetate to give **57** (290 mg, 39%): ^{1}H NMR (DMSO-d_6) δ 1.22−1.32 (2H, m), 1.54−1.64 (2H, m), 1.83−1.94 (2H, m), 2.26−2.34 (2H, m), 2.62 (2H, t, J = 7.5 Hz), 2.72 (2H, t, J = 10.0 Hz), 3.08−3.18 (2H, m), 7.21−7.37 (5H, m), 7.76 (2H, s), 7.86 (1H, s), 8.74 (2H, brs); MS *m/e* (CI^+) 416 $(M + H)^+$; HRMS calcd $C_{22}H_{23}NF_6$ 415.1734, found 415.1750. Anal. ($C_{22}H_{23}NF_6$·HCl) C, H; N: calcd, 3.10; found, 2.38.

Supporting Information Available: ^{1}H NMR data of compounds **13**−**24**, **29**, **30**, **40**−**42**, and **44**−**47** (5 pages). Ordering information is given on any current masthead page.

References

(1) Snider, R. M.; Constantine, J. W.; Lowe, J. A.; Longo, K. P.; Lebel, W. S.; Woody, H. A.; Drozda, S. E.; Desai, M. C.; Vinick, F. J.; Spencer, R. W.; Hess, H. J. A Potent Non-Peptide Antagonist of the Substance P (NK1) Receptor. *Science* **1991**, *251*, 435−437.

(2) (a) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. Discovery of a Potent Substance P Antagonist: Recognition of the Key Molecular Determinant. *J. Med. Chem.* **1992**, *35*, 4911−4913. (b) McLean, S.; Snider, R. M.; Desai, M. C.; Rosen, T.; Bryce, D. K.; Longo, K. P.; Schmidt, A. W.; Heym, J. CP-99,994, A Nonpeptide Antagonist of the Tachykinin NK1 Receptor. *Regulat. Pept.* **1993**, *46*, 329−331. (c) McLean, S.; Ganong, A.; Seymour, P. A.; Snider, R. M.; Desai, M. C.; Rosen, T.; Bryce, D. K.; Longo, K. P.; Reynolds, L. S.; Robinson, G.; Schmidt, A. W.; Siok, C.; Heym, J. Pharmacology of CP-99,994; A Nonpeptide Antagonist of the Tachykinin Neurokinin-1 Receptor. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 472−479. (d) Lowe, J. A., III. Nonpeptide tachykinin antagonists: Medicinal Chemistry and molecular biology. *Med. Res. Rev.* **1996**, *16* (6), 527−545. (e) Boks, G. J.; Tollenaere, J. P.; Kroon, J. Possible ligand receptor interactions for NK_1 antagonists as observed in their crystal structures. *Bioorg. Med. Chem.* **1997**, *5* (3), 535−547.

(3) Ward, P.; Armour, D. R.; Bays, D. E.; Evans, B.; Giblin, G. M. P.; Heron, N.; Hubbard, T.; Liang, K.; Middlemiss, D.; Mordaunt, J.; Naylor, A.; Pegg, N. A.; Vinader, V.; Watson, S. P.; Bountra, C.; Evans, D. C. Discovery of an Orally Bioavailable NK-1 Receptor Antagonist, (2S, 3S)−(2-Methoxy-5-tetrazol-1-ylbenzyl)-(2-phenylpiperidin-3-yl)amine (GR203040), with Potent Antiemetic Activity. *J. Med. Chem.* **1995**, *38*, 4985−4992.

(4) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. Piperidine ether based hNK_1 Antagonists: Determination of the Relative and Absolute Stereochemical Requirements. *Bioorg. Med. Chem. Lett.* **1994,** *4* (21), 2545−2550.

(5) Ladduwahetty, T.; Baker, R.; Cascieri, M. A.; Chambers, M. S.; Haworth, K.; Keown, L.; MacIntyre, D. E.; Metzger, J. M.; Owen, S.; Rycroft, W.; Sadowski, S.; Seward, E. M.; Shepheard, S.; Swain, C. J.; Tattersall, F. D.; Williamson, D.; Hargreaves, R. J. N-Heteroaryl-2-phenyl-3-(benzyloxy)piperidines: A Novel Class of Potent Orally Active NK_1 Antagonists. *J. Med. Chem.* **1996**, *39*, 2907−2914.

(6) 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. (2-(S)-(3,5-bis(trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(5-(3-oxo-1,2,4-triazolo)methylmorpholine, A Potent, Orally Active, Morpholine-Based Human NK-1 Receptor Antagonist. *J. Med. Chem.* **1996**, *39*, 1760−1762.

(7) MacLeod, A. M.; Merchant, K. J.; Brookfield, F.; Lewis, R.; Kelleher, F.; Stevenson, G.; Owens, A.; Swain, C. J.; Baker, R.; Cascieri, M. A.; Sadowski, S.; Ber, E.; MacIntyre, D. E.; Metzger, J.; Ball, R. N-Acyl Tryptophan Benzyl Esters: Potent Substance P Antagonists. *J. Med. Chem.* **1993**, *36*, 2044−2045.

(8) Oury-Donat, F.; Lefevre, I. A.; Gautier, T.; Edmonds-Alt, X.; Le Fur, G.; Soubrie, Ph. SR 140333, A Novel and Potent Nonpeptide Antagonist of the NK_1 Receptor. *Neuropeptides* **1993**, *24*, 233.

(9) (a) Fong, T. M.; Anderson, S. A.; Yu, H.; Huang, R. R. C.; Strader, C. D. Differential activation of intracelluar effectors by two isoforms of human neurokinin-1 receptor. *Mol. Pharmacol.* **1992,** *41*, 24−30. (b) Takeda, Y.; Chou, K. B.; Takeda, J.; Sachais, B. S.; Krause, J. E. Molecular cloning, structural characterisation and functional expression of the human Substance P receptor. *Biochem. Biophys. Res. Commun.* **1991,** *179*, 1232−1240.

(10) Barnes, P. J. Neurogenic Inflamation in Airways and its Modulation. *Arch. Int. Pharmacodyn.* **1990**, *303*, 67−82. See also: Lotz, M.; Vaughan, J. H.; Carson, D. A. Effect of Neuropeptides on Production of Inflammatory Cytokines by Human Monocytes. *Science* **1988**, *241*, 1218−1221.

(11) Otsuka, M.; Yanigasawa, M. Effect of a Tachykinin Antagonist on a Nociceptive Reflex in the Isolated Spinal Cord-Tail preparation of the Newborn Rat. *J. Physiol. (London)* **1988**, *395*, 255−270.

(12) Pernow, B.; Rosell, S. Effect of Substance P on Blood Flow in Canine Adipose Tissue and Skeletal Muscle. *Acta Physiol. Scand.* **1975**, *93*, 139−141.

(13) Barnes, P. J. Asthma as an Axon Reflex. *Lancet* **1986**, 242−244.

(14) Perianin, A.; Snyderman, R.; Malfroy, B. Substance P Primes Human Neutrophil Activation: A Mechanism for Neurological Regulation of Inflammation. *Biochem. Biophys. Res. Commun.* **1989,** *161*, 520−524.

(15) (a) Shepheard, S. L.; Williamson, D. W.; Hill, R. G.; Hargreaves, R. J. The Non-peptide $Neurokinin_1$ Receptor Antagonist RP 76580 Blocks Neurogenic Plasma Extravasation in the Dura Mater of Rats. *Br. J. Pharmacol.* **1993**, *108*, 11−12. (b) Shepheard, S. L.; Williamson, D. W.; Williams, J.; Hill, R. G.; Hargreaves, R. J. Comparison of the Effects of Sumatriptan and the NK_1 Antagonist CP-99,994 on Plasma Extravasation in Dura Mater and c-fos mRNA Expression in Trigeminal Caudalis of Rats. *Neuropharmacology* **1995**, *34* (3), 255−261.

(16) (a) Tattersall, F. D.; Rycroft, W.; Hargreaves, R. J.; Hill, R. The Tachykinin NK_1 Antagonist CP-99,994 Attenuates Cisplatin Indued Emesis in the Ferret. *Eur. J. Pharmacol.* **1993**, *250*, R5−R6. (b) Watson, J. W.; Gonsalves, S. F.; Fossa, A. A.; McLean, S.; Seeger, T.; Obach, S.; Andrews, P. L. R. The Anti-Emetic Effects of CP-99,994 in the Ferret and the Dog: Role of the NK_1 Receptor. *Br. J. Pharmacol.* **1995**, *115*, 84−94. (c) Hargreaves, R. J.; Tattersall, F. D.; Rycroft, W.; Woodford, K.; Ladduwahetty, T.; Keown, L.; Merchant, K.; Swain, C.; MacLeod, A.; Baker, R.; Francis, B.; Burns, D.; Ber, E.; Cascieri, M. A.; Metzger, J.; MacIntyre, D.; Williamson, D.; Iversen, L.; Hill, R. G. Evidence that the Anti-Emetic Effects of NK_1 Receptor Antagonists are Centrally Mediated. *Can. J. Physiol. Pharmacol.* **1994**, *72* (Suppl. 2), 45.

(17) Rupniak, N. M. J.; Tattersall, F. D.; Williams, A. R.; Rycroft, W.; Carlson, E.; Cascieri, M. A.; Sadowski, S.; Ber, E.; Hale, J.; Mills, S. G.; MacCoss, M.; Seward, E. M.; Huscroft, I.; Owen, S.; Swain, C. J.; Hill, R.; Hargreaves, R. J. In vitro and in vivo predictors of the anti-emetic activity of tachykinin NK_1 receptor antagonists. *Eur. J. Pharmacol.* **1996,** *326* (2/3), 201−209.

(18) (a) Schmidt, A. W.; McLean, S.; Heym, J. The Substance P Receptor Antagonist CP-96, 345 Interacts With Ca^{2+} channels. *Eur. J. Pharmacol*. **1992**, *215*, 351−352. (b) Constantine, J. W.; Lebel, W. S.; Woody, H. A.; Benoit, P. A.; Woolfgang, E. A.; Knight, D. R. Cardiovascular Effects of CP-96,345, A Non-Peptide Blocker of Tachykinin Receptors. *Eur. J. Pharmacol*. **1994**, *252*, 275−282. (c) Harrison, T.; Owens, A. P.; Williams, B. J.; Swain, C. J.; Baker, R.; Hutson, P. H.; Sadowski, S.; Cascieri, M. A. Piperidine-ether based hNK_1 antagonists 2: Investigation of the Effect of N-substitution. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 209−212. (d) Baker, R.; Harrison, T.; Swain, C. J.; Williams, B. J. PCT WO93/04040, 1993.

(19) Stevenson, G. I.; MacLeod, A. M.; Huscroft, I.; Cascieri, M. A.; Sadowski, S.; Baker, R. 4,4-Disubstituted Piperidines: A New Class of NK_1 Antagonist. *J. Med. Chem*. **1995**, *38*, 1264−1266.

(20) Seward, E. M.; Swain, C. J.; Merchant, K. J.; Owen, S. N.; Sabin, V.; Cascieri, M. A.; Sadowski, S.; Strader, C. D.; Baker, R. Quinuclidine-Based NK_1 Antagonists I: 3-Benzyloxy-1-azabicyclo-[2.2.2]octanes. *Bioorg. Med. Chem. Lett*. **1993,** *3* (6), 1361−1366.

(21) Swain, C. J.; Cascieri, M. A.; Owens, A. P.; Saari, W.; Sadowski, S.; Strader, C. D.; Teall, M.; Van Niel, M. B.; Williams, B. J. Acyclic NK_1 Antagonists: Replacements for the Benzhydryl Group. *Bioorg. Med. Chem. Lett.* **1994,** *4* (18), 2161−2164.

(22) Harrison, T.; Williams, B. J.; Swain, C. J. *Gem*-Disubstituted Amino-Ether Based Substance P Antagonists. *Bioorg. Med. Chem. Lett.* **1994,** *4*, 2733−2734.

(23) 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. Characterisation of the Binding of a Potent, Selective Radio-iodinated Antagonist to the Human Neurokinin-1 Receptor. *Mol. Pharmacol.* **1992,** *42*, 458−463.

(24) Hart, P. A.; Rich, D. Stereochemical aspects of drug action I: Conformational restriction, steric hindrance and hydrophobic collapse. *Pract. Med. Chem*. **1996**, 393−412.

(25) Fong, T. M.; Huang, R. R.; Yu, H.; Swain, C. J.; Underwood, D.; Cascieri, M. A.; Strader, C. D. Mutational analysis of neurokinin receptor function. *Can. J. Physiol. Pharmacol.* **1995**, *73* (7), 860−5.

(26) Howson, W.; Hodgson, J.; Richardson, R.; Walten, W.; Guard, S.; Watling, K. An SAR Study for the Non-Peptide Substance P Receptor (NK_1) Antagonist, CP-96,345. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 559−564.

(27) Tattersall, F. D.; Rycroft, W.; Francis, B.; Pearce, D.; Merchant, K.; MacLeod, A. M. M.; Ladduwahetty, T.; Keown, L.; Swain, C. J.; Baker, R.; Cascieri, M. A.; Ber, E.; Metzger, J.; MacIntyre, D. E.; Hill, R. G.; Hargreaves, R. J. Tachykinin NK_1 Receptor Antagonists Act Centrally to Inhibit Emesis Induced by the Chemotherapeutic Agent Cisplatin in Ferrets. *Neuropharmacology* **1996,** *35* (8), 1121−1129.

JM980376B