N-Heteroaryl-2-phenyl-3-(benzyloxy)piperidines: A Novel Class of Potent Orally Active Human NK_1 Antagonists

T. Ladduwahetty,* R. Baker, M. A. Cascieri,† M. S. Chambers, K. Haworth, L. E. Keown, D. E. MacIntyre,† J. M. Metzger,† S. Owen, W. Rycroft, S. Sadowski,† E. M. Seward, S. L. Shepheard, C. J. Swain, F. D. Tattersall, A. P. Watt, D. W. Williamson, and R. J. Hargreaves

Neuroscience Research Centre, Merck Sharp and Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, U.K., and Merck Research Laboratories, Rahway, New Jersey 07065

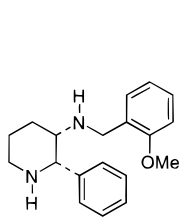
Received September 1, 1995[⊗]

The preparation of a series of *N*-heteroarylpiperidine ether-based human NK_1 antagonists is described. Two of the compounds (3-[{(2*S*,3*S*)-3-(((3,5-bis(trifluoromethyl)phenyl)methyl)oxy)-2-phenylpiperidino}methyl]-1,2,4-triazole (**11**) and 5-[{(2*S*,3*S*)-3-(((3,5-bis(trifluoromethyl)-phenyl)methyl)oxy)-2-phenylpiperidino}methyl]-3-oxo-1,2,4-triazolone (**12**)), in particular, are orally bioavailable and exhibited significant improvements in potency, both *in vitro* and *in vivo*, over the lead (carboxamidomethyl)piperidine ether **1**. Rat liver microsome studies on a selected number of compounds from this series show the triazolone heterocycle to be considerably more stable than the others. Furthermore, both **11** and **12** have been profiled in a number of assays that may be predictive of the clinical utility of substance P antagonists.

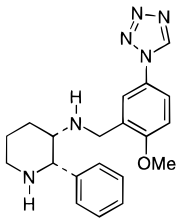
Substance P (SP) is a member of the tachykinin peptide family that acts primarily through the NK_1 receptor. There is considerable evidence to show that this undecapeptide is implicated in a number of both central and peripheral functions, clearly suggesting the possible clinical potential of a SP antagonist. For instance, it has been reported that SP is involved in nociception, particularly in the presence of peripheral inflammation,[1,2] suggesting a role for NK_1 antagonists as non-opioid analgesics or as agents for the treatment of rheumatoid arthritis.[3] Furthermore, experimental evidence shows that the stimulation of the trigeminal nerve leads to the release of neuropeptides[4a] causing inflammation of the dura mater, which can be blocked by NK_1 antagonists thus indicating their possible role in the treatment of migraine.[4b,c] More recently it has been suggested that centrally active NK_1 antagonists may have a role in controlling the emesis induced by a variety of cytotoxic agents.[5]

Several factors preclude a number of SP antagonists that have been disclosed so far from being of clinical utility. For instance CP-99,994, one of the first non-peptide NK_1 antagonists to be reported in the literature, suffers from poor oral bioavailability.[10] The lack of central nervous system (CNS) penetration[7] and, in some cases, activity at L-type calcium channels[8] are other concerns regarding currently existing antagonists. The recent disclosure by Armour *et al.* of GR203040, a potent, orally active 5-triazolyl analogue of CP-99,994, is a testament to the fact that making some discerning structural changes to existing leads can in fact overcome some of these problems.[10]

In earlier work we had identified a series of quinuclidine-[6e] and piperidine[9a]-based benzyl ethers that led to the identification of **1**, a high-affinity NK_1 antagonist that is also devoid of any activity at the L-type calcium channel (hNK_1 IC_{50} 1.3 nM, Ca^{2+} IC_{50} > 30 mM).[9b] We attribute this reduction in calicum channel affinity to the reduced pK_a of the piperidine nitrogen in **1**.[6j]

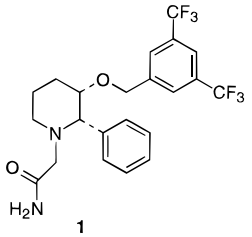


CP-99,994



GR203040

Having recognized that the primary carboxamide moiety could potentially be a liability with regards to the *in vivo* pharmacokinetics of **1**, we embarked on a program to replace it with a series of 5-membered heterocycles. We report herein the culmination of this program, with the synthesis and *in vitro* and *in vivo* profiles of a novel orally active NK_1 antagonist **12** (L-741,671) displaying high affinity and selectivity with excellent *in vivo* activity.



1

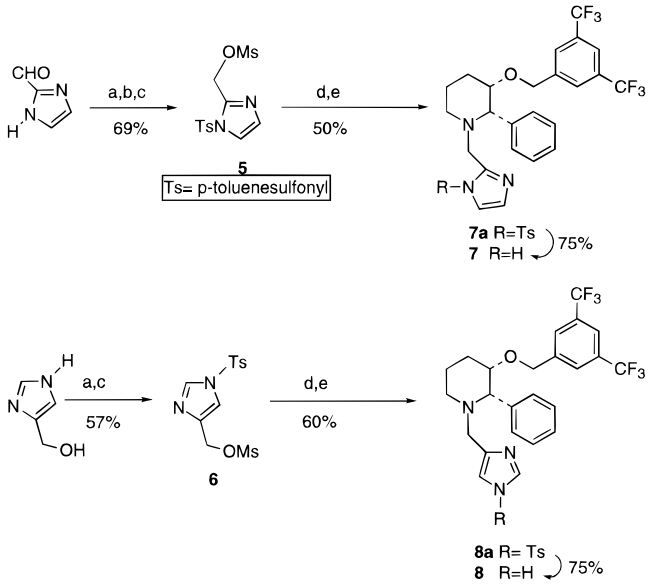
Chemistry

The syntheses of the isomeric imidazole analogues are as shown in Scheme 1. Commercially available 4-(hydroxymethyl)imidazole and 2-imidazolecarboxaldehyde were converted to their corresponding mesylates and alkylated with the parent piperidine **2**[9c] to furnish the N-protected derivatives **7a** and **8a**. Protection of the imidazole nitrogen as the electron-withdrawing sulfonamide significantly enhanced the yield of the alkylation. Removal of the sulfonamide to give the parent imidazoles **7** and **8** was accomplished under acidic conditions. The triazole **11** and triazolone **12** (Scheme 2) were

† Merck Research Laboratories, NJ.
⊗ Abstract published in *Advance ACS Abstracts,* July 1, 1996.

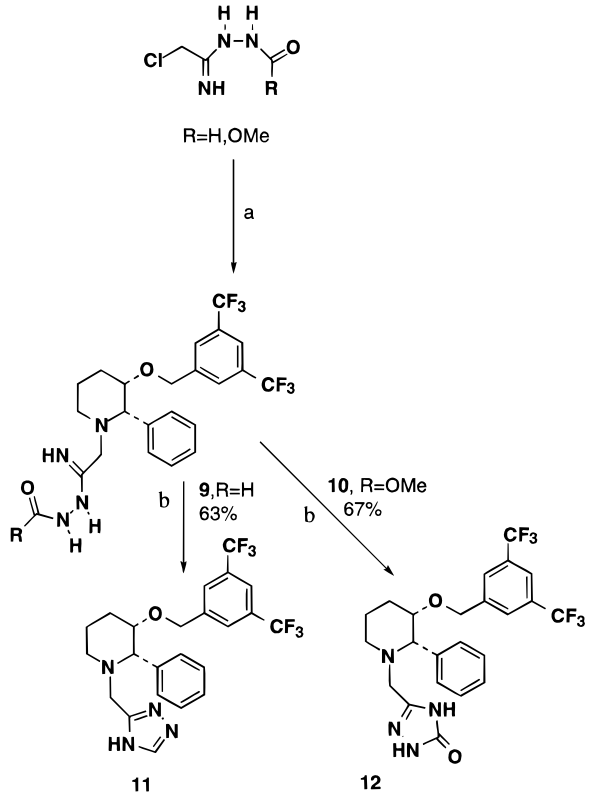
S0022-2623(95)00653-4 CCC: $12.00

Scheme 1[a]



[a] (a) *p*-Toluenesulfonyl chloride, Et_3N; (b) $NaBH_4$, methanol; (c) MsCl, pyridine; (d) **2**, K_2CO_3, DMF; (e) HCl.

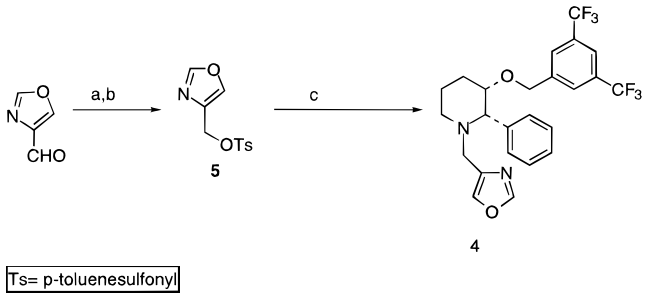
Scheme 2[a]



[a] (a) **2**, K_2CO_3, DMF; (b) DMF, 140 °C.

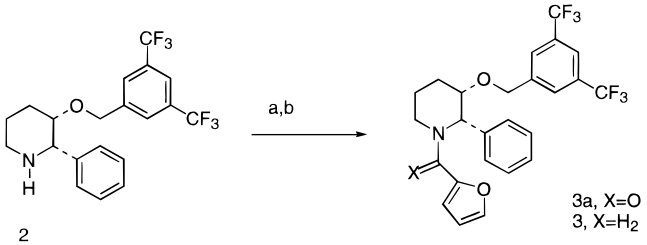
prepared by cyclization of the intermediates **9** and **10** obtained by alkylation of the parent piperidine with the corresponding (chloromethyl)amidrazone. The other heterocyclic analogues were synthesized by direct alkylation of **2** with the tosylate of the requisite heterocycle (Scheme 3), reduction of the amide formed by acylation of **2** with the heterocyclic carboxylic acid chloride (Scheme 4), or using established methodology involving easily accessible intermediates such as the hydrazide **13** for **14** and **15** (Scheme 5) and nitrile **16** for **17** (Scheme 6).

Scheme 3[a]



[a] (a) $NaBH_4$, methanol; (b) TsCl, pyridine; (c) **2**, Et_3N, DMF, 60 °C.

Scheme 4[a]



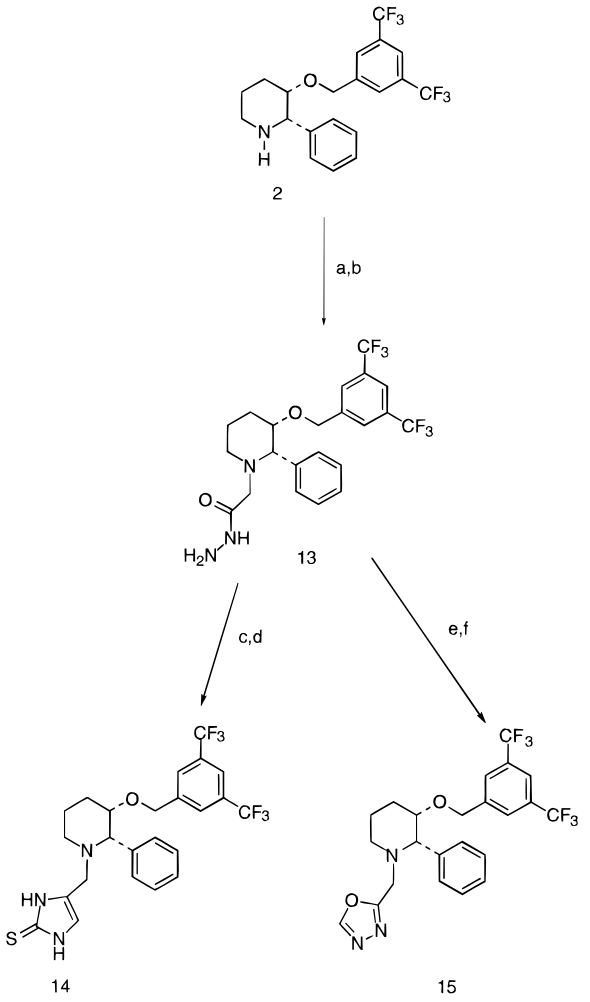
[a] (a) 2-Furoyl chloride, Et_3N, CH_2Cl_2; (b) BH_3–DMS, THF, reflux.

In Vitro Biology

The results (Table 1) indicate that while substitution of the carboxamide in **1** (hNK_1 IC_{50} 1.3 nM) by a lipophilic heterocycle such as furan (**3**, 30 nM) has a deleterious effect on the binding to the NK_1 receptor, this loss in affinity can be regained by the addition of polar atoms into the heterocyclic ring. The oxazole analogue **4** (1.0 nM) and the oxadiazole **15** (0.97 nM), the latter being a heterocycle that has previously been established as a stable replacement for a carboxamide *in vivo*,[12] have the same affinity for the NK_1 receptor as the carboxamide. The isomeric imidazoles **7** (0.9 nM) and **8** (0.53 nM) also have a similar affinity for the NK_1 receptor although their affinity for the Ca^{2+} channel is significantly greater than that of those analogues that contain neutral heterocycles. Thus the relationship between Ca^{2+} channel and basicity[9b] in this region of the molecule is once again confirmed.[6j] However moving to the triazole analogue **11** (0.22 nM) gave a significant increase in affinity over **1**, while the triazolone **12** (0.05 nM) afforded a 25-fold increase. Polar heteroatoms are most beneficial to this region of the receptor since replacement of the polar carbonyl group in the triazolone with the more lipophilic thiocarbonyl, as in **14** (0.8 nM), leads to some loss in affinity. However, inclusion of a negatively charged polar group such as the tetrazole, as in **17** (43 nM), results in a significant loss in affinity for the NK_1 receptor.

Two of the compounds, the triazolone **12** and the triazole **11**, were fully evaluated and shown to display high affinity for the NK_1 receptor while retaining excellent selectivity over other neurokinin receptors (NK_2, NK_3 > 1000 nM). In addition, the reduced basicity of the piperidine nitrogen in L-741,671 (pK_a 5.3)[13] results in the complete abolition of binding to the calcium channel (IC_{50} > 10 000 nM). Both compounds have also been screened against a variety of G-protein-linked receptors and ion channels and no significant interactions identified.

Scheme 5[a]



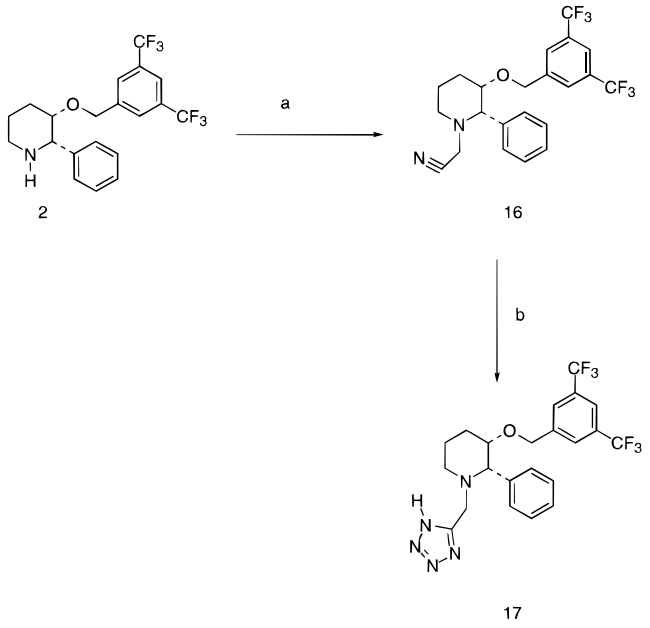
[a] (a) K_2CO_3, ethyl bromoacetate, DMF; (b) NH_2NH_2, EtOH, reflux; (c) KOCN, HCl (conctd), reflux; (d) NaOH (2 N), reflux; (e) pentafluorophenyl formate, 50 °C; (f) $SOCl_2$, Et_3N, $PhCH_3$, 90 °C.

In Vitro Metabolism/Pharmacokinetics

Examining a selected number of the heterocyclic analogues in rat liver microsomes (Table 3) suggests that the stability of the compounds vary considerably depending on the heterocyclic substituent. Hence, while the oxazole **4** is unstable to rat liver microsomes, most of the compound being degraded in 15 min, the imidazole **8** is more stable, 18% of the compound remaining 24 h after incubation. The triazole **11** appears to be even more stable, while the triazolone **12** is more stable still, with 84% of the compound remaining after 24 h.

Prompted by the promising results of the rat microsomal study of **11** and **12**, their full pharmacokinetic profiles were evaluated (Table 4). Thus **12** displays excellent oral bioavailability in rat (46%), the result of a relatively high clearance being compensated for by a high volume of distribution. The triazole **11** also shows a respectable oral bioavailability of 18% in rat, even though the more favorable clearance rate relative to **12** is counterbalanced by a lower volume of distribution. Furthermore the triazolone **12** has also been shown to be orally bioavailable in rhesus monkey (24%), displaying an excellent profile that includes a low clearance (2.3 mL/kg/min) and a half-life of 2.7 h.

Scheme 6[a]



[a] (a) K_2CO_3, DMF, bromoacetonitrile; (b) NaN_3, $Et_3N{\cdot}HCl$, *N*-methyl-2-pyrrolidone.

In Vivo Biology

The *in vivo* properties of **11** and **12** were explored in three different assays intended to evaluate their therapeutic potential in the treatment of inflammation, migraine, and emesis (Table 2). The SP-induced dermal extravasation (SPIDER) assay measures the extent of vascular leakage of Evans blue dye in the guinea pig after the oral administration of a test compound.[14] Both compounds are extremely potent in this assay with **12** showing >40-fold increase in potency over CP-99,994. This increase is greater than that predicted by comparing the *in vitro* affinities of the two compounds and therefore can only be attributed to the more favorable pharmacokinetic profile of **12**. The presence of the heterocycle also improves oral activity in the piperidine ether series since comparison with **1** shows **12** to have a >20-fold increase in potency.

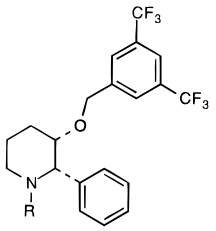
The stimulation of the trigeminal nerve leads to the release of neuropeptides causing inflammation of the dura mater.[4] The extent of leakage can be assessed by use of the plasma marker [^{125}I]bovine serum albumin. This extravasation in rats can be blocked by **12** in a dose dependent manner, with an ID_{50} of 28 μg/kg iv, while the triazole **11** showes an even greater potency at 8 μg/kg iv. Thus both compounds display greater potency than CP-99,994 in this migraine model.[15]

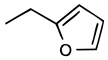
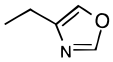
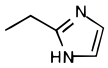
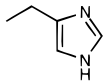
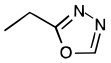
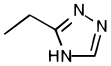
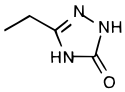
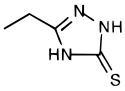
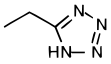
The effects of the NK_1 antagonist **12** were assessed against the emesis induced by the cytotoxic chemotherapeutic agent cisplatin (10 mg/kg iv) in the ferret.[5] A dose dependent inhibition of emesis was observed (ID_{90} 1.0 mg/kg iv), with a dose of 3 mg/kg iv giving complete blockade for the 4 h observation period.

Conclusion

Examining a series of 5-membered heterocycles as a stable replacements for the carboxamide in **1** has culminated in the synthesis of the triazole and triazolone analogues **11** and **12**, where the latter shows a 25-fold increase in *in vitro* affinity over the initial lead. Furthermore evaluation of a number of heterocyclic

Table 1. *In Vitro* Binding Affinities



	R	Stereo	NK_1(nM)[a]	Ca^{++}(μM)[b]
CP- 99,994		2S,3S	0.5 ± 0.1	4.0
1	CH_2CONH_2	2S,3S	1.3 ± 0.5	16% @ 30μM
3		±	36 ± 30	NT
4		2S,3S	1.0 ± 0.2	23
7		2S,3S	0.53 ± 0.12	2.06
8		2S,3S	0.90 ± 0.14	2.3
15		2S,3S	0.97 ± 0.12	10
11		2S,3S	0.22 ± 0.13	>100
12		2S,3S	0.05 ± 0.02	12.6
14		2S,3S	0.8 ± 0.5	10
17		2S,3S	43 ±12	>5

[a] Displacement of [^{125}I]Tyr^8 SP from the cloned human NK_1 receptor expressed in CHO cells. Data reported as the mean ± SD for n = 3 unless otherwise noted. [b] Displacement of [^{3}H]dilitiazam from the rabbit skeletal muscle calcium channel.

Table 2. *In Vivo* Properties

compd	SPIDER[a] ID_{50} (mg/kg po)	rat trigeminal model[b] ID_{50} (mg/kg iv)	ferret emesis[c] ID_{90} (mg/kg iv)
1	0.8	NT	NT
11	0.4	0.008	NT
12	0.037	0.028	1.0
CP-99,994	1.6	0.052[4c]	3.0[5a]

[a] Inhibition of SP-induced dermal extravasation in the guinea pig. Antagonist was administered po followed by SP challenge id after 1 h. Dose−response data were determined for n = 5−12 animals/data point. [b] Inhibition of plasma extravasation produced in the dura mater of the rat after iv administration of test compound, n = 8−10. [c] Effects of the test compound on the wretching and vomiting response in ferrets induced by cisplatin (10 mg/kg iv, n = 6−8).

Table 3. Microsomal Incubation Analysis[a]

	time			
compd	15 min	1 h	4 h	24 h
4	0.05			
8		0.72	0.55	0.18
11		0.87	0.61	0.33
12		1.04	0.90	0.84

[a] Degradation of compound in incubations at 25 μM with normal rat liver microsomes (n = 1 determinations). Substrate concentrations are shown relative to an initial concentration of 1.0. P-450 concentration was 1.45 nM/mg of microsomal protein.

analogues in rat liver microsomes shows **12** to be the most stable. This is borne out by the fact that **12** displays good bioavailability in two species, rat and rhesus monkey. The triazolone **12** therefore represents a novel class of potent, orally active NK_1 antagonists. In addition **12** has also been shown to be active in a number of animal models that display the therapeutic potential of antagonists at the NK_1 receptor. The

Table 4. Pharmacokinetics[a]

compd	F (%)	C_1 (mL/kg/min)	V_D (L/kg)
	Rat Pharmacokinetics		
11	18	44	2.6
12	46	73	6.5
	Rhesus Pharmacokinetics		
12	23.7	2.4	0.55

[a] F = bioavailability, C_1 = plasma clearance after iv dosing; iv and po dosing at 3 mg/kg.

distinct advantage of the triazolone heterocycle for both the *in vitro* and *in vivo* potencies of the piperidine ether series is currently being taken advantage of in other classes of SP-antagonists.

Experimental Section

Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. NMR spectra were recorded at 250 or 360 MHz on Bruker AM360 and AC250 instruments, respectively. The term "dried" refers to drying of an organic phase over 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.

(±)-*cis*-{3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-2-phenylpiperidino}methyl]furan (3). (±)-*cis*-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-2-phenylpiperidine hydrochloride salt[9c] (400 mg) and triethylamine (300 mg) were dissolved in dichloromethane, and the mixture was stirred for 10 min at 0 °C. 2-Furoyl chloride (155 mg) was added to the solution, and the reaction mixture was stirred for 15 min. The reaction was partitioned between ethyl acetate (50 mL) and water (20 mL). The organic layer was then washed with brine, separated, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on silica gel using 20% ethyl acetate in petroleum ether, affording a clear oil: 420 mg (85%); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.6−1.8 (2H, m, CH_2), 1.9−2.1 (2H, m, CH_2), 2.99 (1H, mc, C*H*HN), 4.02 (1H, q, J = 5.0 Hz, CHO), 4.0−4.2 (1H, m, CH*H*N), 4.78 (1H, d, J = 13.0 Hz, OC*H*H), 4.86 (1H, d, J = 13.0 Hz, OCH*H*), 5.95 (1H, s, C*H*Ph), 6.62 (1H, s, furan-H), 6.99 (1H, s, furan-H), 7.25−7.36 (3H, m, ArH), 7.51−7.54 (2H, m, ArH), 7.83 (1H, s, furan-H), 7.90 (2H, s, ArH), 7.99 (1H, s, ArH); MS (CI$^+$) m/z 498 (M^+ + 1, 20).

The (±)-*cis*-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-1-(2-furoyl)-2-phenylpiperidine (340 mg) prepared as above was dissolved in tetrahydrofuran. To this solution was added borane−dimethyl sulfide complex (0.18 mL of 10 M solution), and the resulting solution was heated at reflux for 8 h. The mixture was cooled, methanol was added to quench excess borane, and the solvents were removed *in vacuo*. The residue was dissolved in methanol (10 mL), and potassium carbonate was added (238 mg). This mixture was heated at reflux for 1 h; the methanol was removed *in vacuo*, and the residue was dispersed between ethyl acetate and brine. The ethyl acetate layer was dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel using 10% ethyl acetate in petroleum ether. The product was recrystallized from ether/hexane to yield a white solid (60 mg, 20%): mp 103−104 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.4−1.5 (2H, m, CH_2CH_2), 1.8−1.9 (1H, m, $CHHCH_2N$), 2.1−2.2 (2H, m, $CHHCH_2N$, CHHN), 2.95−3.0 (1H, m, CHHN), 3.11−3.15 (1H, d, J = 15.0 Hz, NCHH-furan), 3.38 (1H, s, NCHCHO), 3.54−3.58 (1H, d, J = 15.0 Hz, NCHH-furan), 3.56 (1H, s, NCH-CHO), 4.02−4.06 (1H, d, J = 13.0 Hz, OCHH-), 4.59−4.62 (1H, d, J = 13.0 Hz, OCHH-), 6.08−6.09 (1H, m, furan-H), 6.35−6.36 (1H, m, furan-H), 7.24−7.32 (3H, m, ArH), 7.46−7.48 (2H, m, ArH), 7.55 (1H, s, furan-H), 7.68 (2H, s, ArH), 7.93 (1H, s, ArH); MS (CI$^+$) m/z 485 (M^+ + 1, 100). Anal. ($C_{25}H_{23}NF_6O$) C, H, N.

(2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-1-(carbomethoxymethyl)-2phenylpiperidine. (2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-2-phenylpiperidine hydrochloride (1 g) was liberated from the hydrochloride salt by partitioning between ethyl acetate and 2 M sodium hydroxide. The organic phase was washed successively with water and saturated brine, dried ($MgSO_4$), and evaporated *in vacuo*. To a solution of the residual oil in tetrahydrofuran (20 mL) were added triethylamine (0.4 mL) and methyl bromoacetate (400 mg), and the solution was heated at reflux under an atmosphere of nitrogen for 16 h. To the cooled solution were added ethyl acetate and water, and the organic phase was washed further with water and dried ($MgSO_4$). After the solvent had been removed *in vacuo*, the residue was chromatographed on silica gel eluting with ethyl acetate/petroleum ether (3:10). The product was recrystallized from diethyl ether/petroleum ether to give the title compound (76%): mp 81−83 °C; MS (CI$^+$) m/z 476 ($M + H)^+$. Anal. ($C_{23}H_{23}F_6NO_3 \cdot 0.1H_2O$) C, H, N.

(2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-1-((carboxyhydrazido)methyl)-2-phenylpiperidinium Hydrochloride (13). Hydrazine hydrate (3.0 mL) was added to a solution of (2*S*,3*S*)-3-(((3,5-bis-(trifluoromethyl)-phenyl)methyl)oxy)-1-(carbomethoxymethyl)-2-phenylpiperidine (2.95 g) in ethanol (80 mL). The solution was heated at reflux for 18 h, after which the ethanol was removed *in vacuo*. The residue was extracted into ethyl acetate, and the organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give the title compound (2.79 g). This was dissolved in methanol (5 mL), and a methanolic solution of hydrogen chloride was added. Methanol was removed *in vacuo*, and the salt was recrystallized from diethyl ether to give the hydrochloride salt (91%): ^{1}H NMR (360 MHz, DMSO) δ 1.77−1.93 (2H, m, CH_2), 2.08−2.21 (1H, m, CH_2), 2.22−2.35 (1H, m, CH_2), 3.56 (1H, d, NC*H*HCH$_2$), 3.64 (1H, d, J = 16.5 Hz, NC*H*HCO), 3.77 (1H, d, NCH*H*CH$_2$), 3.92 (1H, d, J = 16.5 Hz, NCH*H*CO), 3.96 (1H, brs, C*H*O), 4.37 (1H, d, J = 13.0 Hz, OC*H*H), 4.83 (1H, d, J = 13.0 Hz, OCH*H*), 4.95 (1H, s, CHPh), 7.36−7.46 (3H, m, ArH), 7.53−7.62 (2H, brs, ArH), 7.95 (2H, s, ArH), 7.97 (1H, s, ArH); MS (CI)$^+$ m/z 475.

4-[{(2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-2-phenylpiperidino}methyl]oxazole (4). (a) 4-(Hydroxymethyl)-1,3-oxazole. 1,3-Oxazole-4-carboxaldehyde[16] (0.38 g) was dissolved in anhydrous methanol and stirred under nitrogen; sodium borohydride (0.074 g) was added carefully. After 1 h no starting material was present by TLC using 50% ethyl acetate in hexane as eluent. The methanol was removed by rotary evaporator (water bath temperature 40 °C). The residue was purified by chromatography on silica gel eluting with 100% diethyl ether. This afforded the alcohol (0.27 g) as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.93 (OH), 4.63 (2H, s, CH_2OH), 7.64 (1H, s, oxazole-H), 7.90 (1H, s, oxazole-H).

(b) 4-(Hydroxymethyl)-1,3-oxazole (0.13 g) was dissolved in anhydrous dichloromethane (4 mL) under an atmosphere of nitrogen. Triethylamine (0.19 mL) and *p*-toluenesulfonyl chloride (0.13 g) were added to the reaction mixture which was stirred for 1 h at room temperature. A further portion of *p*-toluenesulfonyl chloride (0.13 g) and a catalytic amount of (dimethylamino)pyridine were added to the mixture. (2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-2-phenylpiperidine (1.2 g, free base) was dissolved in dimethylformamide (5 mL) and added to the reaction mixture followed by triethylamine (0.19 mL). The reaction mixture was heated at 60 °C for 2 h, and the resulting mixture was diluted with water (50 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. This was purified by chromatography on silica gel using a gradient elution of 30−60% ether in hexane to afford the title compound as a white solid (5% yield). This was recrystallized from ether/hexane: mp 102−104 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.46−1.64 (1H, m, NCH$_2$-CH$_2$C*H*H), 1.7−1.87 (1H, m, NCH$_2$CH$_2$CH*H*), 1.96−2.20 (2H, m, NCH$_2$C*H*$_2$), 2.32−2.48 (1H, m, NC*H*H), 3.20−3.46 (3H, m, NCH*H*, NC*H*H-oxazole, C*H*OCH$_2$Ar), 3.55 (1H, brs, C*H*Ph), 3.68 (1H, d, J = 14.5 Hz, NCH*H*-oxazole), 4.01 (1H, d, J = 11.5 Hz, OC*H*HAr), 4.46 (1H, d, J = 11.5 Hz, OCH*H*Ar), 7.24−

7.58 (8H, m, ArH), 7.70 (1H, s, ArH), 7.80 (1H, s, ArH); MS (CI^+) 458 ($M^+ + 1$, 100).

2-[{(2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)-oxy)-2-phenylpiperidino}methyl]-1-(*p*-tolylsulfonyl)imidazole Dihydrochloride (7). (a) *N*-(*p*-Tolylsulfonyl)-imidazole-2-carboxaldehyde. Imidazole-2-carboxaldehyde (1.92 g) was suspended in dichloromethane (20 mL). *p*-Toluenesulfonyl chloride (3.8 g) and triethylamine (2.8 mL) were added to the mixture which was stirred at room temperature for 12 h. The resulting slurry was diluted with water, and the organic layer was washed with brine, dried ($MgSO_4$), and filtered. The dichloromethane layer was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel using 50% ethyl acetate in hexane as eluent. This afforded the product as a yellow oil which crystallized on standing: ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.44 (3H, s, $ArCH_3$), 7.31 (1H, d, J = 1.5 Hz, imidazole-H), 7.37 (2H, d, J = 8.0 Hz, ArH), 7.83 (1H, d, J = 1.5 Hz, imidazole-H), 8.00 (2H, d, J = 8.0 Hz, ArH), 9.78 (1H, s, CHO); MS (CI^+) m/z 251 ($M^+ + 1$).

(b) 2-(Hydroxymethyl)-1-(*p*-tolylsulfonyl)imidazole. The aldehyde from above (3 g) was dissolved in methanol (15 mL), and sodium borohydride (114 mg) was added portionwise. This solution was stirred for 10 min. Methanol was removed *in vacuo*, and the residue was dispersed between ethyl acetate and water. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was removed *in vacuo* to afford a crystalline solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.42 (3H, s, $ArCH_3$), 4.84 (2H, s, CH_2O), 7.00 (1H, d, J = 1.5 Hz, imidazole-H), 7.36 (2H, d, J = 8.0 Hz, ArH), 7.40 (1H, d, J = 1.5 Hz, imidazole-H), 7.84 (2H, d, J = 8.0 Hz, ArH).

(c) (*N*-(*p*-Tolylsulfonyl)imidazol-2-yl)methyl Methanesulfonate. The alcohol described in part b above (12.6 mg) was dissolved in dichloromethane (2.5 mL) and triethylamine (0.07 mL). This solution was cooled to 0 °C. Methanesulfonyl chloride (0.04 mL) was added to the solution dropwise. After stirring for 10 min the solution was diluted with water, and the organic layer was separated, dried ($MgSO_4$), and filtered and the solvent removed *in vacuo* to yield a white solid which was used in the following reaction without further purification (69% from 2-imidazolecarboxaldehyde): ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.44 (3H, s, ArH), 2.94 (3H, s, SO_2CH_3), 5.51 (2H, s, CH_2SO_2), 7.08 (1H, d, J = 1.5 Hz, imidazole-H), 7.40 (2H, d, J = 8.0 Hz, ArH), 7.49 (1H, d, J = 1.5 Hz, imidazole-H), 7.92 (2H, d, J = 8.0 Hz, ArH).

(d) (*N*-(*p*-Tolylsulfonyl)imidazol-2-yl)methyl methanesulfonate (1.6 g) was added to a suspension of (2*S*,3*S*)-3-(((3,5-bis-(trifluoromethyl)phenyl)methyl)oxy)-2-phenylpiperidine hydrochloride salt (2.47 g) and potassium carbonate (800 mg) in dimethylformamide (10 mL), and the resulting mixture was heated at 100 °C for 2 h. The mixture was cooled, diluted with water (100 mL), and extracted with ethyl acetate (3 × 20 mL). The organic extracts were combined, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. This afforded a colorless oil which was purified by column chromatography on silica gel using 25−30% ethyl acetate in hexane. This afforded the product as a white crystalline solid which was recrystallized from dichloromethane/petroleum ether: 50% yield; mp 125−126 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.4−1.5 (1H, m, NCH_2CH_2CHH), 1.5−1.67 (1H, m, NCH_2CH_2CHH), 1.8−2.0 (1H, m, NCH_2CHH), 2.06−2.1 (1H, m, NCH_2CHH), 2.35 (3H, s, CH_3), 2.4 (1H, mc, NC*H*H), 2.7−2.86 (1H, m, NCH*H*), 3.50 (1H, d, J = 14.0 Hz, C*H*H-imidazole), 3.56 (1H, brs, CHO), 3.76 (1H, d, J = 1.5 Hz, CHPh), 4.08 (1H, d, J = 14.0 Hz, CH*H*-imidazole), 4.09 (1H, d, J = 12.0 Hz, OC*H*H), 4.48 (1H, d, J = 12.0 Hz, OCH*H*), 6.96 (1H, d, J = 1.0 Hz, imidazole-H), 7.12 (2H, d, J = 8.5 Hz, ArH), 7.2−7.3 (3H, m, ArH), 7.34 (1H, d, J = 1.0 Hz, imidazole-H), 7.46−7.58 (2H, m, ArH), 7.60 (2H, s, ArH), 7.71 (1H, ArH), 7.79 (2H, d, J = 8.5 Hz, ArH); MS (CI^+) m/z 638 ($M^+ + 1$). Anal. ($C_{31}H_{29}F_6N_3O_3S$) C, H, N.

The white solid was dissolved in dichloromethane, and ethereal hydrogen chloride was added. The resulting solution was stirred for 30 min, whereupon the title compound crystallized from solution. This was removed by filtration and recrystallized from ethyl acetate/methanol to afford the title compound (75% yield) as a white crystalline solid: ^{1}H NMR (360 MHz, D_2O) δ 1.61−1.74 (1H, m, C*H*H), 1.76−1.88 (1H, m, C*H*H), 2.04−2.21 (2H, m, CH_2), 3.07−3.23 (1H, m, NC*H*H), 3.41−3.51 (1H, m, NC*H*H), 3.66 (1H, s, CHO), 4.09 (1H, d, J = 13.0 Hz, OC*H*H), 4.25 (1H, d, J = 15.5 Hz, C*H*-imidazole), 4.30 (1H, s, C*H*Ph), 4.39 (1H, d, J = 15.5 Hz, CH*H*-imidazole), 4.55 (1H, d, J = 13.0 Hz, OCH*H*), 7.1−7.2 (3H, m, ArH), 7.2−7.3 (2H, m, ArH), 7.38 (2H, s, imidazole-H), 7.48 (2H, s, ArH), 7.51 (1H, s, ArH); MS (CI^+) m/z ($M^+ + 1$, 25). Anal. ($C_{24}H_{23}F_6N_3O\cdot 2HCl\cdot H_2O$) C, H, N.

4-[{2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)-oxy)-2-phenylpiperidino}methyl]imidazole Dihydrochloride (8). This was prepared following the procedure described for **7** using (2*S*,3*S*)-3-(((3,5-bis(trifluoromethyl)phenyl)methyl)-oxy)-2-phenylpiperidine hydrochloride salt and 4-(hydroxymethyl)imidazole (Aldrich) as starting materials. This afforded the title compound as a white crystalline compound (26% overall yield): mp 206−210 °C; ^{1}H NMR (360 MHz, D_2O) δ 1.73 (1H, m, NCH_2CH_2CHH), 1.94−2.06 (1H, m, NCH_2CH_2-CH*H*), 2.22−2.40 (2H, m, NCH_2CH_2), 3.33 (1H, mc, NC*H*H), 3.70−3.81 (1H, m, NCH*H*), 3.97 (1H, brs, CHO), 4.30 (1H, d, J = 12.5 Hz, OCH*H*), 4.42 (2H, s, NCH_2-imidazole), 4.50 (1H, s, NC*H*Ph), 4.75 (1H, d, J = 12.5 Hz, OCH*H*), 7.48 (6H, brs, ArH, imidazole-H), 7.74 (2H, s, ArH), 7.95 (1H, s, ArH), 8.80 (1H, s, imidazole-H); MS (CI^+) m/z 484 ($M^+ + 1$). Anal. ($C_{24}H_{23}F_6N_3O\cdot 2HCl\cdot H_2$) C, H, N.

3-[{(2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)-oxy)-2-phenylpiperidino}methyl]-1,2,4-triazole Dihydrochloride (11). (2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)-methyl)oxy)-2-phenylpiperidine hydrochloride salt (1.0 g), anhydrous potassium carbonate (0.94 g), and *N*-formyl-2-chloroacetamidohydrazone (0.46 g)[11] were heated to 60 °C in anhydrous dimethylformamide for 3 h followed by heating at 130 °C for 12 h. The reaction mixture was cooled, diluted with ethyl acetate (100 mL), and washed with water (3 × 20 mL). The ethyl acetate layer was dried ($MgSO_4$), filtered, and evaporated to give a brown oil. This was purified on silica gel using ethyl acetate in petroleum ether (70:30) as eluent. This afforded the product as a white solid: 81% yield; mp (free base) 209−210 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.6 (2H, m, CH_2), 1.95−2.24 (2H, m, CH_2), 2.34 (1H, m, NC*H*H), 3.06 (1H, m, NCH*H*), 3.44 (1H, d, NCH*H*-triazole), 3.5 (1H, brs, N-C*H*H-triazole), 3.6 (1H, brs, NC*H*Ph), 3.8 (1H, d, C*H*O), 4.04 (1H, d, OC*H*H-Ar), 4.50 (1H, d, OCH*H*Ar), 7.3 (3H, m, ArH), 7.44 (2H, m, ArH), 7.5 (2H, s, ArH), 7.7 (1H, s, ArH), 7.9 (1H, s, triazole-H); MS (CI^+) m/z 485 ($M^+ + 1$, 35). The free base was treated with ethereal chloride to afford the product as a white crystalline solid. Anal. ($C_{23}H_{22}F_6N_4O\cdot 2HCl$) C, H, N.

5-[{2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)-oxy)-2-phenylpiperidino}methyl]-2,3-dihydro-(4*H*)-3-oxo-1,2,4-triazole Hydrochloride (12). (a) *N*-Carbomethoxy-2-chloroacetamidrazone. Sodium methoxide (0.032 g) was added to a solution of chloroacetonitrile (1.26 mL) in anhydrous methanol (15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h and then neutralized with acetic acid (0.034 mL). Methyl hydrazinocarboxylate (1.76 g) was added and the reaction mixture stirred at room temperature for 0.5 h. The solution was concentrated *in vacuo* to give the title compound as an orange solid: MS $(CI)^+$ m/z 166.

(b) (2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)oxy)-2-phenylpiperidine hydrochloride salt (0.50 g) was stirred with *N*-carbomethoxy-2-chloroacetamidrazone (0.19 g) and potassium carbonate (0.47 g) in dimethylformamide (10 mL) at 70 °C for 18 h. The reaction mixture was then stirred at 140 °C for 1 h. After cooling, the material was partitioned between ethyl acetate and water. The organic layer was washed with water, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on silica gel using 5% methanol in ethyl acetate as eluent. The product was recrystallized from ethyl acetate/petroleum ether to give the title compound as a white crystalline solid (75%). This was converted to the hydrochloride salt by treating with ethereal HCl to afford a white crystalline solid: mp 168−172 °C; ^{1}H NMR (360 MHz, DMSO) δ 1.85 (2H, m, CH_2) 2.0 (1H, m, CH), 3.29 (1H, t, NCH), 3.65 (1H, d, NCH), 3.90 (2H, m, CH_2-triazole, NC*H*Ph), 4.30 (1H, d, OCH*H*Ar), 4.73 (1H, s, C*H*O), 4.79 (1H, d, OCH*H*Ar); MS $(CI)^+$ m/z $((M + 1)^+$, 18). Anal. ($C_{23}H_{24}N_4O_{2.5}F_6Cl$) C, H, N.

5-[{(2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-2-phenylpiperidino}methyl]-2,3-dihydro-(4*H*)-3-thioxo-1,2,4-triazole Hydrochloride (14). (2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-1-[(carboxyhydrazido)methyl]-2-phenylpiperidinium hydrochloride (0.230 g), potassium thiocyanate (0.45 g), and concentrated hydrochloric acid (2.3 mL) in water (12 mL) were heated under reflux for 2 h. After cooling, solid sodium hydroxide was added until pH = 8, and the aqueous layer was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered, and evaporated to give the crude semicarbazide which was heated at reflux in 2 N sodium hydroxide solution (10 mL) for 2 h. After cooling the solution was acidified to pH = 5−6 and the product extracted into ethyl acetate. The organic layer was dried ($MgSO_4$), filtered, and evaporated. The crude triazole was chromatographed on silica gel eluting with 40% ethyl acetate/60−80 petroleum ether to give the title compound (65%) as a white solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.6 (2H, m, CH_2), 1.9−2.3 (3H, m, CH_2, NCHH), 2.95 (1H, brd, NCHH), 3.16 (1H, d, N-CHH-Het), 3.20 (1H, brs, CHO), 3.6 (1H, brs, NCHPh), 3.78 (1H, d, N-CHH-Het), 4.1 (1H, d, CHH-Ar), 4.58 (1H, d, CHH-Ar), 7.32 (5H, m, ArH), 7.5 (2H, s, Ar-H), 7.78 (1H, s, ArH); MS (FAB) *m*/*z* (M^+ + 1, 80). This was treated with ethereal hydrogen chloride to yield the crystalline hydrochloride: mp 154−157 °C. Found: C, 46.59; H, 4.52; N, 9.26; Cl, 5.84. Anal. ($C_{23}H_{22}F_6N_4OS\cdot HCl\cdot 2H_2O$) C, H, N.

3-[{(2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-2-phenylpiperidino}methyl]-1,2,4-oxadiazole (15). A solution of pentafluorophenyl formate[17] (178 mg, 0.84 mmol) in chloroform (1 mL) was added to a stirred solution of the hydrazide (0.160 mg), in chloroform (6 mL) at 25 °C under N_2. The reaction mixture was heated to 50 °C for a period of 5 h. The solvent was evaporated and the residue partitioned between EtOAc (20 mL) and water (20 mL). The organic layer was washed further with 5% $NaHCO_3$ and water (15 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel eluting with EtOAc and then 5% MeOH/CH_2Cl_2 to give the *N*-formylhydrazide (124 mg, 59%) which was redissolved in anhydrous toluene (12 mL) and cooled to 0 °C. Triethylamine (91 mL, 0.66 mmol) was added followed by thionyl chloride (24 mL). The resulting white solid was filtered and the filtrate heated at 90 °C for 1 h. Another aliquot of triethylamine (45 mL) was added followed by thionyl chloride (12 mL); another aliquot of triethylamine (4 mL) was added followed by thionyl chloride (2 mL) and the reaction mixture heated for a further 45 min. The solvent was evaporated *in vacuo* and the residue partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel eluting with 2:1 petroleum ether/ethyl acetate followed by 1:1 petroleum ether/ethyl acetate to afford the desired product as a white solid (110 mg, 77%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.65 (s, 1H), 7.42−7.45 (m, 4H), 7.19−7.30 (m, 3H), 4.42 (d, 1H), 3.96 (d, 1H), 3.88 (d, 1H), 3.64 (d, 1H), 3.52 (s, 2H), 3.07 (brd, 1H), 2.37 (dd, 1H), 2.09 (d, 1H), 1.97 (dd, 1H), 1.49 (m, 2H). Anal. ($C_{23}H_{21}F_6N_3O_2$) C, H, N.

(2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-1-(cyanomethyl)-2-phenylpiperidinium Hydrochloride (16). (2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-2-phenylpiperidine hydrochloride salt (5 g), potassium carbonate (1.7 g), and bromoacetonitrile (0.87 mL) were suspended in dimethylformamide (15 mL), and the mixture was stirred under nitrogen at 60 °C for 3 h. The mixture was cooled, diluted with water (200 mL), and extracted with ethyl acetate (2 × 50 mL). The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated, affording a brown oil. This was purified on silica gel using ethyl acetate in petroleum ether (10%) as eluent. This afforded the product as a colorless oil (2.5, 83%). A 100 mg sample of material was converted to the hydrochloride salt by dissolution in ethereal hydrogen chloride and recrystallization from ether/hexane (60 mg, 60%): mp 133−134 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.75 (2H, mc, C*H*H), 1.90 (2H, mc, CH*H*), 2.31 (1H, mc, C*H*H), 2.71 (1H, mc, CH*H*), 3.19 (1H, mc, CH*H*N), 3.72 (1H, mc, C*H*HN), 3.81 (1H, d, *J* = 17.5 Hz, NC*H*HCN), 3.86 (1H, s, C*H*O), 4.02 (1H, d, *J* = 17.5 Hz, NCH*H*CN), 4.09 (1H, s, C*H*Ph), 4.35 (1H, d, *J* = 13.0 Hz, OC*H*H), 4.73 (1H, d, *J* = 13.0 Hz, OCH*H*), 7.4 (3H, mc, ArH), 7.69−7.73 (5H, m, ArH); MS (CI^+) *m*/*z* 443 (M^+ + 1, 30). Anal. ($C_{22}H_{18}F_6N_2O\cdot HCl$) C, H, N.

5-[{(2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-2-phenylpiperidino}methyl]tetrazole (17). The nitrile **16** (1.0 g), triethylamine hydrochloride (467 mg), and sodium azide (441 mg) were dissolved in 1-methyl-2-pyrrolidinone (5 mL), and the reaction mixture was heated at reflux under nitrogen for 2 h. The mixture was then cooled, diluted with ice/water (80 mL), and acidified to pH = 2 with methanolic hydrogen chloride. This precipitated the product as a white solid, which was purified on silica gel using a gradient elution of methanol in dichloromethane (0−5%). The product was recrystallized from ethyl/hexane (675 mg, 56%): mp 114−115 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.59−1.65 (2H, m, $NCH_2CH_2CH_2$), 2.02−2.22 (2H, m, NCH_2CH_2), 2.39−2.46 (1H, m, C*H*HN), 2.98−3.02 (1H, m, CH*H*N), 3.62 (1H, s, NCHC*H*O), 3.66 (1H, s, NC*H*CHO), 3.70−3.74 (1H, d, *J* = 15.5 Hz, NCH*H*-tetrazole), 4.05−4.10 (1H, d, *J* = 15.5 Hz, NC*H*H-tetrazole), 4.08−4.12 (1H, d, *J* = 12.0 Hz, OC*H*H), 4.51−4.54 (1H, d, *J* = 12.0 Hz, OCH*H*), 5.30 (1H, s, NH), 7.30−7.35 (3H, m, ArH), 7.45−7.47 (2H, m, ArH), 7.51 (2H, s, ArH), 7.74 (1H, s, ArH); MS (CI^+) *m*/*z* 486 (M^+ + 1, 85). Anal. ($C_{22}H_{21}F_6N_5O\cdot 0.5H_2O$) C, H, N.

Pharmacokinetic Evaluation of 3-[{(2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)-2-phenylpiperidino}methyl]-1,2,4-triazole Dihydrochloride (11) in Rat. The compound was administered at 3 mg/kg iv and po in rat. The vehicle used for both the iv and po formulations was 1 mM HCl. The animals were sampled for plasma up to 8 h postdose (3 rats/time point). The pharmacokinetic pharameters were calculated using standard equations using the following set of data presented here as a mean ± SEM.

	concentrations of **11** in plasma (mg/mL)	
time (h)	iv	po
0.0833	1763.5 ± 107.2	40.1 ± 11.3
0.25	825.5 ± 102.7	116.1 ± 35.3
0.5	581.0 ± 16.0	35.1 ± 13.1
1	303.6 ± 8.7	33.7 ± 9.3
2	71.3 ± 5.9	36.9 ± 3.1
4	13.2 ± 1.4	11.2 ± 1.7
6	<10	<10
8		<10

Pharmacokinetic Evaluation of 5-[{(2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)phenylpiperidino}methyl]-2,3-dihydro-(4*H*)-3-oxo-1,2,4-triazole Hydrochloride (12) in Rat. Sixty-six male SD rats were given a 3 mg/kg dose of **12** by either iv or oral route (33 rats/route). The compound was administered intravenously as a solution (3 mg/mL) in propylene glycol/water (48/52, v/v) and orally as a solution (3 mg/mL) in PEG 400. Three rats from each dose group were used per data point. The pharmacokinetic parameters were calculated using standard equations using the following data presented as the mean ± SEM.

	concentrations of **12** in plasma (mg/mL)	
time (h)	iv	po
0.083	599 ± 162	11 ± 5
0.25	244 ± 21	29 ± 23
0.5	291 ± 41	70 ± 30
1.0	203 ± 15	45 ± 9
2.0	135 ± 45	94 ± 15
3.0	52 ± 6	65 ± 17
4.0	30 ± 9	41 ± 11
5.0	21 ± 9	25 ± 4
6.0	9 ± 1	12 ± 3
7.0	<5	<5
8.0	<5	<5

Pharmacokinetics Evaluation of 5-[{(2*S*,3*S*)-3-(((3,5-Bis(trifluoromethyl)phenyl)methyl)oxy)phenylpiperidino}methyl]-2,3-dihydro-(4*H*)-3-oxo-1,2,4-triazole Hydrochloride (12) in Rhesus Monkey. Four Rhesus

monkeys were dosed (at 3 mg/kg in propylene glycol) intravenously and orally ($n = 2$ for each data point). The pharmacokinetic parameters were calculated using standard equations using the data shown below presented as the mean ± SEM.

	concentrations of **12** in plasma (μg/mL)	
time (h)	iv	po
0.167	5.24 ± 0.11	0.02 ± 0.02
0.5	5.02 ± 0.59	0.05 ± 0.01
1.0	3.66 ± 0.20	0.08 ± 0.004
2.0	3.08 ± 0.63	0.15 ± 0.04
4.0	1.98 ± 0.58	0.52 ± 0.03
6.0	1.22 ± 0.41	0.58 ± 0.02
8.0	0.72 ± 0.18	0.50 ± 0.02

Acknowledgment. The authors would like to thank D. O'Connor for the results of the rat liver microsome study and S. Patel for Ca^{2+} binding results.

References

(1) Salter, M. W.; Henry, J. L. Responses of Functionally Identified Neurons in the Dorsal Horn of the Cat Spinal Cord to Substance P, Neurokinin A and Physalaemin. *Neuroscience* **1991**, *43*, 601−610.

(2) Laird, J. M. A.; Hargreaves, R. J.; Hill, R. G. Effect of RP 67580, A Non Peptide Neurokinin Receptor Antagonist on Facilitation of a Nociceptive Spinal Flexion Reflex in the Rat. *Br. J. Pharmacol*. **1993**, *109*, 713−718.

(3) Walsh, D. A.; Mapp, P. I.; Wharton, J.; Rutherford, R. A. D.; Kidd, B. L.; Revell, P. A.; Blake, D. R.; Polak, J. M. *Ann. Rheum. Dis*. **1992**, *51*, 313−317.

(4) (a) Mosokowitz, M. A. Neurogenic versus Vascular Mechanisms of Sumatriptan and Ergot Alkaloids in Migraine. *Trends Pharmacol. Sci*. **1992**, 307−311. (b) 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. (c) 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), 225−261.

(5) (a) Tattersall, F. D.; Rycroft, W.; Hargreaves, R. J.; Hill, R. The Tachykinin NK_1 Antagonist CP-99,994 Attenuates Cisplatin Induced 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.; Metzger, J.; MacIntyre, D.; Williamson, D.; Iverson, 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.

(6) (a) Hagiwara, D.; Miyaka, H.; Morimoto, H.; Murai, M.; Fujii, T.; Matsuo, M. Studies on Neurokinin Antagonists. 1. The Design of Novel Tripeptides Possessing the Glutaminyl-D-Tryptophylphenylalanine Sequence as Substance P Antagonist. *J. Med. Chem*. **1992**, *35*, 2015−2025. (b) Hagiwara, D.; Miyaka, H.; Igari, N.; Murano, K.; Morimoto, H.; Murai, M.; Fuji, T.; Matsuo, M. Design of a Novel Dipeptide Substance P antagonist FK888. *Regul. Pept*. **1993**, *46*, 332−334. (c) Snider, R. M.; Constantine, J. W.; Lowe, J. A., III; 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 Nonpeptide Antagonist of the Substance P (NK-1) Receptor. *Science* **1991**, *251*, 435−437. (d) Rosen, T.; Seegar, T. F.; McLean, S.; Desai, M. C.; Guarino, M. C.; Bryce, D.; Pratt, K.; Heym, J. Synthesis, *in vitro* binding profile, and autoradiographic analysis of [^{3}H]-*cis*-3-[(2-methoxybenzylamino]-2-phenylpiperidine, a Highly potent and selective Substance P receptor Antagonist Radioligand. *J. Med. Chem*. **1993**, *36*, 3197−3201. (e) Seward, E. M.; Owen, S.; Sabin, S.; Swain, C. J.; Cascieri, M. A.; Sadowski, S.; Strader, C.; Quinuclidine-Based NK-1 Antagonists 1:3-Benzyloxy-1-azabicyclo-[2.2.2]octanes. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 1361−1366. (f) Garret, C.; Carrutte, A.; Fardin, V.; Moussaoui, S.; Peyronel, J. F.; Blanchard, J.-C.; Laduron, P. M. Pharmacological properties of a Potent and Selective Nonpeptide Substance P Antagonist. *Proc. Natl. Acad. Sci. U.S.A*. **1991**, *88*, 10208−10212. (g) Ouray-Donat, F.; Lefevre, I. A.; Guathier, T.; Emonds-Alt, X.; Le Fur, G.; Soubrie, P. SR 140,333 A Novel and Potent Nonpeptide Antagonist of the NK_1 receptor. *Neuropeptides* **1993**, *24*, 233. (h) 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. (i) Mills, S.; Wu, M. T.; MacCoss, M.; Budhu, R.; Dorn, C. P.; Cascieri, M. A.; Sadowski, S.; Strader, C.; Greenlee, W. J. 1,4-Diacylpiperazine-2-(S)-[(N-aminoalkyl)-carboxamides] as Novel Potent Substance P Receptor Antagonists. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 2707. (j) Williams, B. J.; Teall, M.; McKenna, J.; Harrison, T.; Swain, C. J.; Cascieri, M. A.; Sadowski, S.; Strader, C.; Baker, R. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 1903−1908.

(7) Rupniak, N. M. J.; Tattersall, F. D.; Rycroft, W.; Carlson, E.; Webb, J. K.; Williams, A. R.; Hargreaves, R. J. Prediction of the Anti-Emetic Activity of NK_1 Antagonists in Ferrets by Their Ability to Inhibit GR73632 Induced Foot Tapping in Gerbils. For submission to *Eur. J. Pharmacol*.

(8) (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.

(9) (a) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. Piperidine-ether Based hNK_1 Antagonists: Determination of the Absolute Stereochemical Requirements. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 2545−2550. (b) 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. (c) Baker, R.; Harrison, T.; Swain, C. J.; Williams, B. J. PCT WO93/04040, 1993.

(10) 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, M. 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.

(11) Yanagisawa, I.; Hirata, Y.; Ishii, Y. Histamine H_2 Receptor Antagonists. 1. Synthesis of N-Cyano and N-Carbamoyl Amidine Derivatives and their Biological Activities. *J. Med. Chem*. **1984**, *27*, 849−857.

(12) (a) Swain, C. J.; Baker, R.; Kneen, C.; Mosely, J.; Saunders, J.; Seward, E. M.; Stevenson, G. S.; Beer, M.; Stanton, J.; Watling, K. Novel 5-HT_3 Antagonists. Indole Oxadiazoles. *J. Med. Chem*. **1991**, *34*, 140−151. (b) Saunders, J.; Cassidy, M.; Freedman, S.; Harley, E. A.; Iversen, L. L.; Kneen, C.; MacLeod, A.; Merchant, K.; Snow, R. J.; Baker, R. *Novel Quinuclidine*-Based Ligands for the Muscarinic Cholinergic Receptor. *J. Med. Chem*. **1990**, *33*, 1128−1138.

(13) pK_a determination was made using the log P−pH method; see Shaper, K. J. *J. Chem. Res*. (*Suppl*.) **1979**, 357.

(14) MacLeod, A. M.; Merchant, K. J.; Brookfield, F.; Kelleher, F.; Stevenson, G.; Owen, A. P.; Swain, C. J.; Cascieri, M. A.; Sadowski, S.; Ber, E.; Strader, C.; MacIntyre, D. E.; Metzger, J. M.; Ball, R. G.; Baker, R. Identification of L-Tryptophan Derivatives with Potent and Selective Antagonist Activity at the NK_1 Receptor. *J. Med. Chem*. **1994**, *37*, 1269−1274.

(15) The affinities of CP-99,9904, L-741,671, and L-740,141 for the rat NK_1 receptor 200, 115, and 100 nM, respectively. Hence the greater potency of **12** in comparison with CP-99,994 in this model can be accounted for by the fact that the former has a 2-fold greater affinity for rat NK_1 receptor. The even greater potency of the triazole **11** (a 7-fold increase over CP-99,994) in this assay, however, is intriguing.

(16) Hodges, J. C.; Patt, W. C.; Connolly, C. J. Reactions of Lithiooxazole. *J. Org. Chem*. **1991**, *56*, 449−452.

(17) Kisfauldy, L.; Ötvös, L., Jr. Rapid and Selective Formylation with Pentafluorophenylformate. *Synthesis* **1987**, 510.

JM9506534