# 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

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*Received August 28, 1995*®

The antiemetic, pharmacokinetic, and metabolic profile of CP-99,994, a potent $NK_1$ receptor antagonist, has been carefully evaluated. As a result we began a medicinal chemistry program which initially identified a 3-furanyl analogue (**6**) with improved antiemetic potency and a methyl sulfone (**5**) with enhanced metabolic stability and oral bioavailability. The improved pharmacokinetic profile of methyl sulfone (**5**) was associated with its low lipophilicity, and a therefore a number of heterocyclic analogues with reduced log *D* were synthesized. Out of this program emerged **19** (GR203040), a tetrazolyl-substituted analogue. Tetrazole **19** inhibits radiation-induced emesis in the ferret with high potency when administered both subcutaneously and orally, has a long duration of action, and has high oral bioavailability in the dog. Tetrazole **19** is currently undergoing evaluation as a novel approach for the control of emesis associated with, for example, cancer chemotherapy.

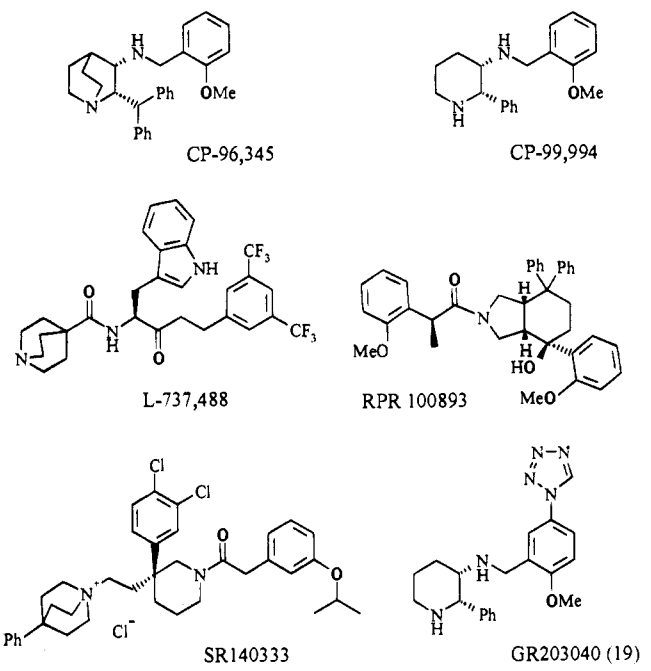
## Introduction

Substance P is a member of the mammalian tachykinin family of homologous peptides which also includes neurokinins A and B. Substance P is widely distributed in the mammalian system, being synthesized and released from both central and peripheral neurones, and is implicated in various pathological conditions including pain, neurogenic inflammation, asthma, and migraine.[1] The pharmacological and physiological effects of substance P are mediated by the neurokinin $NK_1$ receptor, one of the G-protein-coupled 7-transmembrane superfamily.[2]

A number of peptide $NK_1$ receptor antagonists have been reported,[3] but until recently potent non-peptide antagonists were not known. In 1991 Pfizer disclosed CP-96,345,[4] Chart 1, the first potent non-peptide $NK_1$ antagonist, and subsequently reported the related series of piperidines, exemplified by CP-99,994.[5] Researchers at Merck have subsequently described the related ether-linked piperidine series incorporating a 3,5-bis(trifluoromethyl)benzyl side chain.[6] This structural feature has subsequently been utilized in a number of $NK_1$ antagonists reported by Merck, most notably the tryptophan-derived analogues such as the orally active L-737,488.[7] Other structurally distinct classes of $NK_1$ antagonists include the following: RPR 100893,[8] a compound which has encouraging efficacy in animal models relevant to pain and migraine and is currently undergoing phase 2 clinical studies; the nanomolar affinity quaternary antagonist SR 140333;[9] the putative Phe-Phe dipeptide mimic CGP 49823;[10] and the rationally designed peptoid PD 154075.[11]

The development of potent and selective non-peptide $NK_1$ receptor antagonists has been crucial in providing a greater understanding of the physiological role of substance P and rationalizing the therapeutic potential of antagonists. However, although several peptide and non-peptide antagonists have been progressed for clinical studies, there has been no proven clinical utility described for this class of pharmacological agents.

**Chart 1.** Non-Peptide $NK_1$ Antagonists




The recent discovery[12] in our laboratories that $NK_1$ receptor antagonists have a potent and broad spectrum antiemetic profile offered a novel therapeutic potential for these compounds. Thus in the ferret, CP-99,994 inhibits the emetic response induced by cytotoxic drugs[12,13] (cisplatin and cyclophosphamide), radiation, morphine, ipecacuanha, and copper sulfate.[12] This important discovery indicates that $NK_1$ antagonists may be useful for the clinical control of emesis experienced

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® Abstract published in *Advance ACS Abstracts*, December 1, 1995.

0022-2623/95/1838-4985$09.00/0 

by cancer patients undergoing chemotherapy and for controlling emesis evoked by other stimuli.

In our early studies we found CP-99,994 to be significantly more potent than several other $NK_1$ antagonists in the ferret emesis model, no doubt reflecting the high $NK_1$ receptor affinity and very effective central penetration of the compound.[14] However, this compound lacked oral bioavailability (*vide infra*), and therefore we set out to discover an $NK_1$ antagonist with antiemetic potency at least as high as CP-99,994 which was also orally bioavailable. The likely clinical requirements for emesis and other potential indications would include administration by the oral route. This paper describes our medicinal chemistry program based on CP-99,994, leading to the discovery of tetrazole analogue **19**, an orally bioavailable antiemetic $NK_1$ antagonist with high potency and a long duration of action in the ferret model of emesis.

## Biological Evaluation of Compounds

Binding data was determined using Chinese hamster ovary cells stably expressing the human $NK_1$ receptor. Antiemetic activity was determined against radiation-induced emesis in the ferret. Antagonists were routinely administered by the subcutaneous (sc) route 90 min before (90 min pretreatment time (ptt)), or immediately after (0 min ptt), induction of emesis in the ferret by whole body X-irradiation. Results are presented as the lowest dose of antagonist which inhibited emesis by at least 90% compared with untreated irradiated control animals ($ID_{90}$). The relative metabolic stability of compounds *in vitro* was assessed in a preparation of dog hepatic microsomes by HPLC measurement of the percentage turnover of parent compound after a 25 min incubation period under standard conditions. Compounds of interest were progressed to a pharmacokinetic study in the beagle dog to determine preliminary oral bioavailability and clearance data.

## Results and Discussion

At the commencement of our studies we undertook a pharmacokinetic study of CP-99,994 to assess the degree of oral bioavailability and to identify any limiting factors, for example absorption and metabolism. In the beagle dog the compound shows high iv clearance at a rate in excess of liver blood flow, and when orally dosed at 2 mg $kg^{-1}$ CP-99,994 has only a low bioavailability (Table 3). It is likely that the compound is vulnerable to hepatic first pass metabolism in the dog.[15] Therefore our target profile for potential drug candidates included greater metabolic stability than CP-99,994 and, in particular, oral bioavailability in the dog. This would increase our confidence for ultimately achieving oral bioavailability in humans. In pursuing this objective, we hoped to retain, and indeed improve upon, the pharmacodynamic properties of CP-99,994 in the ferret model of emesis.

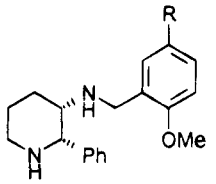
We hypothesised that the electron rich (*o*-methoxybenzyl)amino side chain was at least partially responsible for the metabolic instability of CP-99,994, and we therefore focused part of our strategy toward suitably modifying this side chain. CP-99,994 is probably susceptible to cytochrome P450 mediated O-demethylation of the methoxy group. However, the known SAR in the related quinuclidine series suggests that the *o*-methoxy group is essential for receptor affinity at sub-nanomolar concentrations.[16] We therefore directed our attention to modifying the substitution pattern of the side chain aromatic ring, rather than searching for methoxy surrogates, in an attempt to modulate metabolic stability. The 5-position of the aromatic ring, in a *para* disposition to the methoxy, is a likely site for hydroxylation, and we therefore prepared a number of derivatives (Table 1) to investigate the effect of 5-substitution on receptor potency, antiemetic activity, and metabolic stability.

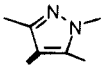
Initially we prepared derivatives containing substituents of varying size, lipophilicity, and electronic properties (Table 1, entries 1–5). All of these analogues show sub-nanomolar *in vitro* affinity for the $NK_1$ receptor. Of the analogues tested in the ferret emesis model, fluoro analogue **2** and thioether **4** show a level of potency around that of **1**. Surprisingly, however, methyl sulfone **5** is virtually inactive in the ferret model despite a receptor affinity quantitatively similar to CP-99,994. Methyl sulfone **5** has a measured log $D$[17] of 0.2, significantly the lowest of this series of analogues, and herein, we believe, lies the explanation for its low antiemetic activity. Recent evidence has suggested that the antiemetic effect of $NK_1$ antagonists is centrally mediated.[14] We suspected therefore that the low lipophilicity of methyl sulfone **5** prevents effective transport across the blood–brain barrier and access to central $NK_1$ receptors. In order to confirm our hypothesis, we carried out a series of *ex vivo* binding experiments in the gerbil to compare methyl sulfone **5** with CP-99,994 (Table 3). When dosed subcutaneously, methyl sulfone **5** was found to only weakly displace $^3H$-labeled substance P binding in the cortex with an $ED_{50} > 0.3$ mg $kg^{-1}$. In contrast CP-99,994 is at least 10-fold more potent with $ED_{50} = 0.02$ mg $kg^{-1}$. While aware of possible species differences between gerbil and ferret, we concluded that to achieve antiemetic activity analogues would need to be more lipophilic than methyl sulfone **5**.

The methyl sulfone **5** analogue is also notable for its lower *in vitro* turnover in the presence of dog hepatic microsomes. We were interested in exploring whether this would translate into greater oral bioavailability. Gratifyingly, we found that methyl sulfone **5** has significant oral bioavailability in the dog (42%) and a much reduced rate of plasma clearance than CP-99,994 when dosed intravenously (Table 3). We believe that methyl sulfone **5** is inherently more metabolically stable than CP-99,994 and attribute this stability to its low lipophilicity.[18] Thus methyl sulfone **5**, despite its low antiemetic potency, was a milestone compound in our medicinal chemistry program. Ultimately (*vide infra*) we were encouraged to aim for log $D$ values at a level between those of CP-99,994 and methyl sulfone **5** to obtain an optimal combination of pharmacodynamic and pharmacokinetic properties.

The early analogues in this series (Table 1, **1**–**5**) suggested that the $NK_1$ receptor tolerates significant size in the 5-substitution position, for example the bromo derivative **3**. This encouraged us to prepare some heterocyclic derivatives through Suzuki type coupling (*vide infra*). All of these analogues (**6**–**11**, Table 1) show high receptor affinity, and most promisingly, the 3-furanyl derivative **6** is very potent in the ferret emesis model ($ID_{90} = 0.3$ mg $kg^{-1}$), a 3-fold increase in potency

**Table 1.** 5-Substituted Analogues




| No[a] | R | pKi[b] | Turnover[c] | log *D* | Ferret Emesis[d] 0 ptt | Ferret Emesis[d] 90 ptt | Formula |
|---|---|---|---|---|---|---|---|
| 1 | H | 9.6 ± 0.1 | 100 | 1.4 | 1.0(3) | 1.0[e] (3) | |
| 2 | F | 9.8 ± 0.1 | NT | 1.8 | 3.0(4) | NT | $C_{19}H_{23}FN_2O$ 2HCl.0.8$H_2O$ |
| 3 | Br | 10.3 ± 0.2 | 60 | 2.5 | NT | NT | $C_{19}H_{23}N_2OBr$ .2HCl |
| 4 | SMe | 10.1 ± 0.1 | 94 | 2.0 | 1.0(2) | NT | $C_{20}H_{26}N_2OS$ .2HCl |
| 5 | $SO_2Me$ | 9.3 ± 0.2 | 25 | 0.2 | >10(1) | >10(1) | $C_{20}H_{26}N_2O_3S$ .2HCl |
| 6 |  | 10.2 ± 0.2 | 85 | 2.5 | 0.3(2) | 0.3(2) | $C_{23}H_{26}N_2O_2$ .2HCl.1.2$H_2O$ |
| 7 |  | 10.5 ± 0.2 | 92 | 3.1 | >3(2) | NT | $C_{23}H_{26}N_2OS$ .2HCl |
| 8 |  | 9.3 ± 0.2 | 100 | 3.0 | NT | >3(1) | $C_{23}H_{26}N_2O_2$ .2$C_7H_8O_3S$.1.7$H_2O$ |
| 9 |  | 9.1 ± 0.1 | 61 | 2.3 | >3(1) | NT | $C_{22}H_{25}N_3OS$ .2.5HCl.1.5$H_2O$ |
| 10 |  | 10.3 ± 0.2 | 92 | 2.3 | NT | 1.0(1) | $C_{24}H_{29}N_3O_2$ .2HCl |
| 11 |  | 9.1 ± 0.2 | 82 | 2.3 | NT | NT | $C_{25}H_{32}N_4O$ .2HCl.6$H_2O$ |

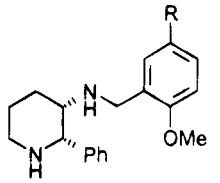
[a] Compound 1 (2*S*,3*S*) enantiomer; all other analogues racemic. [b] p$K_i$ determinations are the mean values with standard errors from at least three experiments. [c] Metabolic turnover is expressed as percentage parent lost as determined by HPLC analysis after exposure to dog hepatic microsomes under standard conditions. [d] Activity in the radiation-induced ferret emesis model is expressed as an $ID_{90}$ (mg $kg^{-1}$) as defined in biological methods; *n* = number in parentheses. [e] >80% inhibition at this dose. NT = not tested.

over CP-99,994. Rather less promisingly the compound shows poor *in vitro* metabolic stability, but at this early stage of our program we progressed it to a pharmacokinetic study. Disappointingly the compound was rapidly cleared and had a low oral bioavailability (<10%) in the dog (Table 3). However the pharmacokinetic profiles of the methyl sulfone **5** and the 3-furanyl analogue **6** increased our confidence that the dog hepatic microsome assay is a qualitative predictor of metabolic stability *in vivo*. The somewhat variable *in vivo* potency of analogues **6**–**11** in Table 1 does not correlate well with receptor affinity. In particular 3-thiophene analogue **7**, despite a 10-fold higher receptor affinity over CP-99,994, shows poor antiemetic activity at 3 mg $kg^{-1}$.

The encouraging antiemetic potency of the 3-furanyl analogue led us to synthesize a number of other heterocyclic derivatives. Ideally we hoped to retain the improved pharmacodynamic properties of the 3-furanyl analogue while increasing metabolic stability. In the light of the sulfone **5** showing improved metabolic stability and our association of this effect with its low log *D*, we chose to synthesize heterocyclic analogues with reduced lipophilicity, and these are presented in Table 2.

The compound series **1**–**19** displays a range of binding affinities of between p$K_i$ 8.6 and 10.5. We have examined whether these differences can be explained by the local environment of the 5-substituent of the phenyl ring. Preliminary molecular modeling has not indicated a strong correlation between binding affinity and structure. However within the compound subset of 5-membered ring heterocycles, the following observations are noted. The presence of a heteroatom in the 3 or 4 position of the heterocycle (relative to the point of attachment to the *o*-methoxyphenyl ring) appears to confer the highest level (p$K_i$ >10) of receptor affinity (compare for example 3-furan **6**, 3-thiophene **7**, isoxazole **10**, and N-linked tetrazole **19** with 2-furan **8**, 2-thiazole **9**, and 2-imidazole **17**). In addition, in the presence of an optimally located heteroatom, substitution of the 2 and 5 position of the heterocycle is well tolerated (for example isoxazole **10** and C-linked tetrazole **16**). How-

**Table 2.** Heterocyclic Analogues of Reduced Lipophilicity




| No[a] | R | pKi[b] | Turnover[c] | log *D* | Ferret Emesis[e] 0 ptt | Ferret Emesis[e] 90 ptt | Formula |
|---|---|---|---|---|---|---|---|
| 12 |  | 10.2 ± 0.1 | 98 | 2.2 | 0.3(3) | NT | $C_{24}H_{27}N_3O$ 3HCl.2.4$H_2O$ |
| 13 |  | 9.8 ± 0.1 | 36[d] | 1.4 | 3(2) | >3(1) | $C_{23}H_{26}N_4O$ .2HCl.0.5$H_2O$ |
| 14 |  | 9.8 ± 0.1 | 55 | 1.2 | 3(2) | >3(3) | $C_{21}H_{25}N_5O$ .2HCl. 0.5$H_2O$ |
| 15 |  | 8.6 ± 0.2 | 63 | 1.4 | NT | >3(1) | HRMS[f] |
| 16 |  | 9.7 ± 0.1 | 27 | 0.5 | NT | >3(1) | $C_{21}H_{26}N_6O$ .2HCl.0.5$H_2O$ |
| 17 |  | 8.7 ± 0.1 | 90 | 1.2 | NT | >3(1) | $C_{23}H_{28}N_4O$ .3HCl.3$H_2O$ |
| 18 |  | 9.9 ± 0.2 | 65 | 0.8 | NT | >1(1) | $C_{20}H_{24}N_6O$ .2HCl |
| 19 |  | 10.3 ± 0.1 | 51 | 0.8 | 0.1(3) | 0.1(3) | $C_{20}H_{24}N_6O$ .2HCl |

[a] Compounds **18** and **19** (2*S*,3*S*) enantiomer; all other analogues racemic. [b] p$K_i$ determinations are the mean values with standard errors from at least three experiments. [c] Metabolic turnover is expressed as percentage parent lost as determined by HPLC analysis after exposure to dog hepatic microsomes under standard conditions. [d] Parent compound coeluted with metabolite. [e] Activity in the radiation induced ferret emesis model is expressed as an $ID_{90}$ (mg $kg^{-1}$), as defined in biological methods; n = number in parentheses. NT = not tested. [f] High-resolution mass spectrum correct.

ever substitution in the 3 or 4 position gives compounds of relatively low receptor affinity (pyrazole **11** and C-linked tetrazole **15**). Although these conclusions are tentative, the data may suggest an interaction to an uncharacterized binding domain within the $NK_1$ receptor antagonist binding site. Confirmation of this hypothesis awaits suitable receptor site-directed mutagenesis studies. What is clear is that the presence in this series of a suitable heterocycle at the 5-position of the *o*-methoxybenzyl side chain leads to the highest affinity $NK_1$ receptor antagonists reported to date.

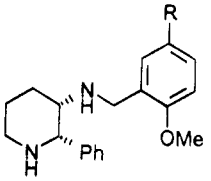
Within the series of compounds with reduced lipophilicity (Table 2), most analogues were generally of low potency *in vivo* against radiation-induced ferret emesis. However, the 4-pyridinyl analogue **12** ($ID_{90}$ = 0.3 mg $kg^{-1}$, 0 ptt) shows *in vivo* potency around the level of the 3-furanyl analogue **6** whereas the 5-tetrazolyl analogue **19** ($ID_{90}$ = 0.1 mg $kg^{-1}$) is significantly the most potent analogue *in vivo*. It is interesting to contrast this potent effect with the relatively less potent isomeric unsubstituted tetrazole analogue **18**. We assessed the series for *in vitro* metabolic stability and were encouraged that the 5-tetrazolyl analogue **19** also showed relatively low turnover in the presence of dog hepatic microsomes. In view of its promising profile, this compound was progressed to pharmacokinetic analysis in the dog (Table 3).

When administered intravenously at a dose of 2 mg $kg^{-1}$, analogue **19** had significantly lower clearance in the dog than both CP-99,994 or the 3-furanyl analogue **6**. This translated into an oral bioavailability of 76%. In view of the improved pharmacokinetic data, we extended our study of the *in vivo* properties of tetrazole **19**. In a gerbil *ex vivo* binding experiment, **19** shows a dose-dependent inhibition of [$^3$H]substance P binding in the cortex ($ED_{50}$ = 0.015 mg $kg^{-1}$, sc), thus confirming that the compound readily penetrates into the CNS to access central $NK_1$ receptors. In the ferret, **19** shows potent inhibition of emesis induced by cytotoxic drugs, morphine, ipecacuanha, and copper sulfate.[19] Notably, when administered *orally* (90 min ptt), **19** shows 100% inhibition of radiation-induced emesis at a dose of 0.3 mg $kg^{-1}$. Furthermore the compound effectively suppresses radiation-induced emesis when administered 6 h prior to radiation at a sc dose of 0.1 mg $kg^{-1}$. Finally, when administered iv at 0.1 mg $kg^{-1}$, directly after administration of cisplatin, **19** effectively prevents emesis over a period of 8 h. Full details of the potent and long-acting antiemetic profile of **19** will be reported separately.[19,20]

## Chemistry

The final compounds (**2**–**19**) were prepared by reductive aminations of *cis*-2-phenylpiperidin-3-ylamine[5] (**20**),

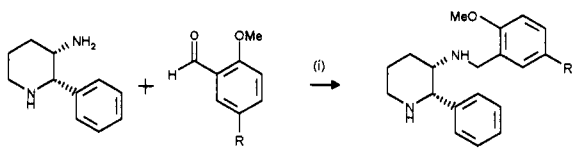
**Table 3.** Pharmacokinetic, Metabolic, and *ex Vivo* Binding Parameters for Key Compounds




| | | | dog pharmacokinetics[b] | | |
|---|---|---|---|---|---|
| compd[a] | R | *in vitro* metabolism turnover (%) | *F* (%) | CLp (mL/(min/kg)) | gerbil *ex vivo* binding[c] $ED_{50}$ (mg $kg^{-1}$) |
| **1** | H | 100 | <10 | 94 | 0.018 |
| **5** | $SO_2Me$ | 25 | 42 | 23 | >0.3 |
| **6** | 3-furanyl | 85 | <10 | 45 | NT |
| **19** | 5-tetrazolyl | 51 | 76 | 24 | 0.015 |

[a] Compounds 1 and **19** (2*S*,3*S*) enantiomer; compounds **5** and **6** racemic. [b] *F* = oral bioavailability and CLp = plasma clearance after iv dosing; iv and po doses at 2 mg $kg^{-1}$. [c] *Ex vivo* binding measured 15 min post administration.

## Scheme 1

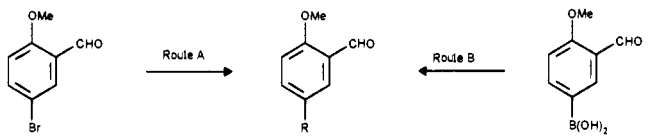



cis [+/-] **(20a)** [2S, 3S] **(20b)** **(21a-q)** **(2-19)**

(i) sodium triacetoxyborohydride, dichloromethane, acetic acid (cat), 23°C.

**(21a):** R= F **(21b):** R= Br **(21c):** R= SMe **(21d):** R= furan-3-yl **(21e):** R= thiophen-3-yl **(21f):** R= furan-2-yl **(21g):** R= 2-thiazolyl **(21h):** R= 3,5-dimethyl-isoxazol-4-yl **(21i):** R= 1,3,5-trimethyl-1H-pyrazol-4-yl **(21j):** R= 4-pyridinyl **(21k):** R= 5-pyrimidinyl **(21l):** R= 1H-1,2,4-triazol-1-yl **(21m):** R= 2-methyl-2H-tetrazol-5-yl **(21n):** R= 1-methyl-1H-tetrazol-5-yl **(21o):** R= 1-methyl-1H-imidazol-2-yl **(21p):** R= 5-tetrazol-2-yl **(21q):** R= 5-tetrazol-1-yl

## Scheme 2




Route A: **(21d-f)** $RB(OH)_2$, dimethoxyethane, 2N $Na_2CO_3$, $Pd(PPh_3)_4$, 80°C.
Route B: **(21g-k, o)** RBr, dimethoxyethane, 2N $Na_2CO_3$, $Pd(PPh_3)_4$, 80°C.

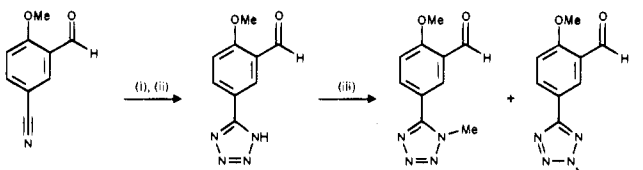
either as a racemate (**20a**) or as the more active (2*S*,3S) enantiomer (**20b**), and the appropriate benzaldehyde (**21a–q**) as outlined in Scheme 1. The sulfone analogue **5** was obtained by oxidation of the thiomethyl compound **6** using Oxone.

The majority of the aldehydes (**21a–q**) were prepared using routes A or B shown in Scheme 2 using palladium-catalyzed boronic acid couplings[21] to prepare heteroaryl compounds.

The benzaldehydes for the carbon-substituted tetrazoles, **21m** and **21n**, were synthesized *via* the known[22] nitrile **22** by treatment with with tributyltin azide,[23] Scheme 3. Methylation of the acidic tetrazole **23** gave a mixture of regioisomers **21n** and **21m** which were readily separable by flash chromatography.

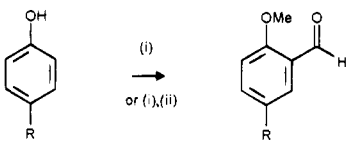
The benzaldehydes for the N-linked heterocycles **21l,p–q** were prepared using the chemistry of Scheme 4, *via* the known phenols.[24,25] *Ortho*-formylation using the Duff reaction[26] and subsequent methylation generated the desired benzaldehydes.

## Scheme 3




(i) ethylene glycol, toluene, *p*-TsOH, reflux (ii) $(n\text{-}Bu)_3SnN_3$, 160°C (iii) MeI, $K_2CO_3$, DMF, 23°C.

## Scheme 4




**(21l):** (i), **(21p-q):** (i), (ii)

(i) hexamethylenetetramine, AcOH (ii) MeI, $K_2CO_3$, DMF.

## Conclusion

Through a careful evaluation of the *in vitro* and *in vivo* properties of CP-99,994 and some simple analogues, we identified the 3-furanyl analogue **6** which had improved antiemetic potency and methyl sulfone **5**, an analogue with low lipophilicity and high metabolic stability relative to CP-99,994. We therefore investigated a series of heterocyclic-substituted analogues within a lipophilicity window between CP-99,994 and methyl sulfone **5**. From this program we discovered $NK_1$ antagonists with the highest receptor affinity reported to date. Tetrazole analogue **19** is a highly potent antiemetic agent when administered both orally and subcutaneously in the ferret and is orally bioavailable in the dog.

Further pharmacological studies have confirmed that **19** is a potential candidate for clinical evaluation as a novel treatment for emesis. Additionally **19** may prove useful for the treatment of migraine, pain, and inflammation.

## Experimental Section

All solvents were reagent-grade and used without further purification. Normal-phase silica gel used for flash chromatography was Merck 9385. Proton NMR spectra ($^1H$ NMR) were recorded on a Bruker 250 MHz spectrometer (AM 250) unless otherwise noted; $\delta$ values in ppm relative to trimeth-

ylsilane are given. High-resolution mass spectra were obtained using a VG Autospec. Results of elemental analyses were within 0.4% of the theoretical values unless otherwise noted. Melting points are uncorrected.

***cis*-[5-(Methylthio)-2-methoxybenzyl](2-phenylpiperidin-3-yl)amine Dihydrochloride (4).** 2-Methoxy-5-(methylthio)benzaldehyde[27] **(21c)** (730 mg) and acetic acid (230 μL) were added to a solution of 2-phenylpiperidin-3-ylamine[5] **(20a)** (775 mg) in dichloromethane (40 mL). Sodium triacetoxyborohydride (1.28 g) was added and the mixture stirred for 18 h. The solvent was removed *in vacuo* and the mixture partitioned between 2 M sodium carbonate solution (80 mL) and ethyl acetate (80 mL). The aqueous layer was further extracted with ethyl acetate (2 × 80 mL), and the combined organics were dried (sodium sulfate) and evaporated *in vacuo*. The crude product was purified by flash chromatography using 7% ethanol–dichloromethane as eluant to give a gum which was dissolved in ethanol (30 mL) and treated with 1 M ethereal HCl (20 mL). The solvent was removed *in vacuo* and the solid recrystallized from 2-propanol to give product as white needles (1.04 g, 63%): $^1$H NMR ($CDCl_3$ + NaOD) δ 1.50 (1H, m), 1.58 (1H, m), 1.90 (1H, m), 2.12 (1H, m), 2.38 (1H, m), 2.80 (2H, m), 3.26 (1H, m), 3.38 (1H, d, $J$ = 14 Hz), 3.44 (3H, s), 3.63 (1H, d, $J$ = 14 Hz), 3.88 (1H, m), 6.62 (1H, d, $J$ = 6 Hz), 6.99 (1H, d, $J$ = 1 Hz), 7.12 (1H, dd, $J$ = 6, 1 Hz), 7.2–7.4 (5H, m). Anal. ($C_{20}H_{26}N_2OS$·2HCl) C, H, N, S.

***cis*-[5-(Furan-3-yl)-2-methoxybenzyl](2-phenylpiperidin-3-yl)amine Dihydrochloride (6).** Prepared according to the method given for **4** using benzaldehyde **21d** to give product as a white crystalline solid (35 mg, 9%): $^1$H NMR ($CDCl_3$ + NaOD) δ 1.41 (1H, m), 1.60 (1H, m), 1.93 (1H, m), 2.15 (1H, m), 2.78 (1H, m), 2.85 (1H, s), 3.26 (1H, m), 3.43 (1H, d, $J$ = 15 Hz), 3.48 (3H, s), 3.67 (1H, d, $J$ = 15 Hz), 3.89 (1H, s), 6.60 (1H, s), 6.69 (1H, d, $J$ = 9 Hz), 7.11 (1H, d, $J$ = 2 Hz), 7.20–7.35 (6H, m); high-resolution mass spectrum found $MH^+$ 363.2087, $C_{23}H_{27}N_2O_2$ requires 363.2072. Anal. $C_{23}H_{26}N_2O_2$·2HCl·1.2$H_2O$ (C, H, N).

**(2-Methoxy-5-tetrazol-2-ylbenzyl)(2(*S*)-phenylpiperidin-3(*S*)-yl)amine Dihydrochloride (18).** To a solution of 2(*S*)-phenylpiperidin-3(*S*)-ylamine **(20b)** (173 mg) and 2-methoxy-5-tetrazol-2-ylbenzaldehyde **(21p)** (200 mg) in dichloromethane (20 mL) were added sodium triacetoxyborohydride (312 mg) and 2 drops of glacial acetic acid. The mixture was stirred at room temperature under nitrogen atmosphere for 18 h. The solvent was evaporated *in vacuo* and the residue quenched with 2 N solution of sodium carbonate (20 mL) and extracted with ethyl acetate (20 mL). The organic layer was treated with 2 N hydrochloric acid (20 mL) and the acidic portion basified with 2 N sodium carbonate solution, extracted with ethyl acetate (3 × 30 mL), dried (sodium sulfate), and concentrated to give a residue which was purified by flash chromatography (dichloromethane/methanol/ammonia (945:50:5)) to give a yellow oil which was dissolved in ethanol (20 mL) and treated with 1 M hydrochloric acid solution in ether (3.6 mL). The solvent was evaporated *in vacuo* to afford the product as a white solid (285 mg, 67%): mp 222 °C; $^1$H NMR ($D_2O$) δ 2.2–2.60 (4H, m) 3.22–3.40 (1H, m), 3.60–3.76 (4H, m), 4.00–4.08 (1H, m), 4.16 (1H, d, $J$ = 14 Hz), 4.39 (1H, d, $J$ = 14 Hz), 4.95 (1H, d, $J$ = 4 Hz), 7.13 (1H, d, $J$ = 9 Hz), 7.24–7.33 (2H, m), 7.44–7.52 (3H, m), 7.88 (1H, d, $J$ = 3 Hz), 8.11 (1H, dd, $J$ = 3, 9 Hz), 8.93 (1H, s). Anal. ($C_{20}H_{24}N_6O$·2HCl) C, H, N.

**(2-Methoxy-5-tetrazol-1-ylbenzyl)(2(*S*)-phenylpiperidin-3(*S*)-yl)amine Dihydrochloride (19).** Prepared according to the method given for **18** using benzaldehyde **21q** to give product as a white solid (280 mg, 67%): mp 242–243 °C; $^1$H NMR ($D_2O$) δ 2.05–2.62 (4H, m), 3.35 (1H, m), 3.70 (3H, s), 3.72 (1H, m), 4.10 (1H, m), 4.19 (1H, d, $J$ = 14 Hz), 4.43 (1H, d, $J$ = 14 Hz), 5.02 (1H, d, $J$ = 2 Hz), 7.14 (1H, d, $J$ = 6 Hz), 7.34 (2H, m), 7.50 (3H, m), 7.62 (1H, d, $J$ = 2 Hz), 7.83 (1H, dd, $J$ = 2, 6 Hz), 9.59 (1H, s). Anal. ($C_{20}H_{24}N_6O$·2HCl) C, H, N, Cl.

***cis*-[5-(Methylsulfonyl)-2-methoxybenzyl](2-phenylpiperidin-3-yl)amine Dihydrochloride (5).** Oxone (444 mg) in water (3 mL) was added to a solution of *cis*-[5-(methylthio)-2-methoxybenzyl](2-phenylpiperidin-3-yl)amine (**4**) in methanol (3 mL). The mixture was stirred at 23 °C for 24 h, and then 2 N sodium carbonate (10 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried (sodium sulfate) and evaporated *in vacuo*. Flash chromatography with 10% methanol–dichloromethane as eluent gave a gum which was dissolved in dichloromethane and treated with 2 M ethereal hydrogen chloride. The solid was collected and recrystallized from aqueous methanol to give the product as a white solid (43 mg, 21%): $^1$H NMR ($CDCl_3$ + NaOD) δ 1.45 (1H, m), 1.60 (1H, m), 1.90 (1H, m), 2.10 (1H, m), 2.80 (2H, m), 3.27 (1H, m), 3.40 (1H, d, $J$ = 10 Hz), 3.56 (3H, s), 3.68 (1H, d, $J$ = 10 Hz), 3.9 (1H, m), 6.78 (1H, d, $J$ = 6 Hz), 7.2–7.4 (5H, m), 7.63 (1H, d, $J$ = 1 Hz), 7.75 (1H, dd, $J$ = 6, 1 Hz). Anal. ($C_{20}H_{26}N_2O_3S$·2HCl) C, H, N, S.

**5-(Furan-3-yl)-2-methoxybenzaldehyde (21d).** A mixture of 5-bromo-*o*-anisaldehyde (473 mg), 3-furanylboronic acid (224 mg), and tetrakis(triphenylphosphine)palladium(0) (45 mg) in dimethoxyethane (5 mL) and 2 N sodium carbonate (5 mL) was heated at 80 °C for 4 h under nitrogen and left overnight at 20 °C. A further portion of boronic acid (20 mg) was added and the mixture heated at 80 °C for 2 h. After cooling the mixture was extracted with diethyl ether (3 × 20 mL). The combined organics were dried (sodium sulfate) and reduced to an oil. Purification by flash chromatography with 10% diethyl ether/petroleum ether gave product as a white solid (204 mg, 46%): $^1$H NMR ($CDCl_3$) δ 3.97 (3H, s), 6.69 (1H, d, $J$ = 1 Hz), 7.02 (1H, d, $J$ = 9 Hz), 7.48 (1H, t, $J$ = 1 Hz), 7.67 (1H, dd, $J$ = 2.5, 9 Hz), 7.73 (1H, s), 7.94 (1H, d, $J$ = 2.5 Hz), 10.50 (1H, s).

**2-Methoxy-5-tetrazol-1-ylbenzaldehyde (21q).** A solution of 4-tetrazol-1-ylphenol (1.62 g) in trifluoroacetic acid (20 mL) and hexamethylenetetramine (5.6 g) was heated at 70 °C for 18 h, cooled to room temperature, quenched with 2 N sulfuric acid (50 mL), extracted with ethyl acetate (3 × 100 mL), dried (magnesium sulfate), filtered, and concentrated to give a residue which was purified by flash chromatography using 9:1 dichloromethane–methanol as eluent to afford 2-hydroxy-5-tetrazol-1-ylbenzaldehyde (0.57 g, 30%): $^1$H NMR ($CDCl_3$) δ 5.86 (2H, d, $J$ = 9 Hz), 6.50 (2H, d, $J$ = 9 Hz), 8.57 (1H, br s), 8.74 (1H, br s).

To a solution of 2-hydroxy-5-tetrazol-1-ylbenzaldehyde (0.50 g) in dimethylformamide (5 mL) were added potassium carbonate (0.546 g) and iodomethane (560 mg), and the mixture was stirred under nitrogen atmosphere for 2 h and then poured into water (100 mL). The white solid precipitate was filtered to afford the product (360 mg, 67%): $^1$H NMR ($CDCl_3$) δ 4.07 (3H, s), 7.32 (1H, d, $J$ = 9 Hz), 8.11 (1H, dd, $J$ = 2, 9 Hz), 8.21 (1H, d, $J$ = 2 Hz), 9.72 (1H, s), 10.49 (1H, s).

**2-Methoxy-5-tetrazol-2-ylbenzaldehyde (21p).** Hexamethylenetetraamine (5.6 g) was added to 4-tetrazol-2-ylphenol (1.6 g) in trifluoroacetic acid (40 mL) and the mixture heated at 60 °C for 24 h. On cooling, the solution was poured into sulfuric acid (2 N, 100 mL), extracted with ether (3 × 100 mL), dried (sodium sulfate), and evaporated. The residue was purified by flash chromatography to give 2-hydroxy-5-tetrazol-2-ylbenzaldehyde as a yellow solid (930 mg, 49%): $^1$H NMR ($CDCl_3$) δ 7.24 (1H, d, $J$ = 9 Hz), 8.33 (1H, dd, $J$ = 2, 9 Hz), 8.40 (1H, d, $J$ = 2Hz), 8.52 (1H, s), 8.93 (1H, br s).

Potassium carbonate (1.06 g) and methyl iodide (0.5 mL) were added to a solution of 2-hydroxy-5-tetrazol-2-ylbenzaldehyde (930 mg) in dimethylformamide (6 mL) at room temperature. The mixture was stirred for 2 h and then evaporated to give an orange solid. This was dissolved in water (40 mL), extracted with dichloromethane (3 × 30 mL), dried (sodium sulfate), and evaporated. The residue was purified by flash chromatography using dichloromethane as eluent to give product as a yellow solid (423 mg, 42%): $^1$H NMR ($CDCl_3$) δ 4.05 (3H, s) 7.20 (1H, d, $J$ = 9 Hz), 8.34 (1H, dd, $J$ = 2, 9 Hz), 8.58 (1H, d, $J$ = 2 Hz), 8.66 (1H, s), 10.52 (1H, s).

**CHO/NK$_1$ Binding.** Chinese hamster ovary cells, stably transfected with the human $NK_1$ receptor, were grown to confluence in DMEM/F12 media supplemented with 10% fetal calf serum and 4 mM glutamine and harvested using PBS containing 0.05% trypsin and 0.02% EDTA. To prepare membranes, cells were homogenized in HEPES buffer (50 mM

HEPES, 0.1 mM leupeptin, 25 μg of bacitracin, 1 mM EDTA, 1 mM PMSF, and 2 μg of pepstatin A, pH 7.4), spun at 500*g* for 20 min to remove unbroken cells and nucleii and the supernatent spun at 48000*g* for 30 min. The resulting pellet was resuspended HEPES buffer without pepstatin A or PMSF, and aliquots were stored at −80 °C. A protein estimation was carried out using the method of Bradford[28] with bovine serum albumin as standard.

An assay volume of 200 μL was used, consisting of 50 μL of wash buffer (50 mM HEPES, 3 mM $MnCl_2$, pH 7.4) or test compound, 100 μL of membrane suspension (3 μg of protein) in assay buffer (wash buffer containing 0.04% bovine serum albumin, 80 μg/mL bacitracin, 8 μg/mL leupeptin, and 2 μM phosporamidon), and 50 μL of [$^3$H]substance P in wash buffer (final ligand concentration of 0.7−1.0 nM). The incubation was carried out at 22 °C for 40 min. The reaction was terminated by rapid filtration through Wallac A filtermats presoaked in poly(ethylenimine) (0.2%). The filters were washed with ice-cold wash buffer, and radioactivity on the filters was determined in a scintillation counter. Nonspecific binding was determined by the addition of CP-99,994 (1 μM). Inhibition curves were analyzed using standard statistical procedures, and inhibition constants ($K_i$ values) were determined.

**Tests for Antiemetic Activity.** The antiemetic activity of the final compounds was investigated using the protocol reported by Bountra *et al.*[12] Adult male ferrets, body weight range 1.0−1.7 kg, were used for all experiments. Emesis was induced in each animal by whole body exposure to irradiation from a Seifert Isovolt 420V X-ray source, preset to deliver 2 Gy over approximately 5 min. Doses of test compounds or vehicle controls were administered either 6, 3, or 1.5 h before, or immediately after, irradiation. Where cisplatin was used to induce emesis, the emetogen was administered ip at 200 mg $m^{-2}$ body area. The numbers of retches and vomits were recorded subsequent to the induction of emesis, and an $ID_{90}$ figure was calculated.

**Gerbil *ex Vivo* Binding.** Compounds were administered subcutaneously to Mongolian gerbils of either sex (40−60 g). Fifteen minutes following administration of the compound, the animals were anaesthetized with a lethal dose of pentobarbitone and perfused transcardially with 50 mL of ice-cold saline to remove any blood from the brain. The forebrain from each animal was removed, placed in Tris buffer (Tris base (50 mM), $MnCl_2$ (3 mM), bacitracin (40 mg $mL^{-1}$), leupeptin (4 mg $mL^{-1}$), PMSF (0.01 mM), and phosphoramidon (1.0 mM), pH 7.4) at a concentration of 60 mg $mL^{-1}$, and homogenized. The homogenate was filtered through a nylon monofilament. Next, 250 mL aliquots of membranes were incubated in the Tris buffer with [$^3$H]substance P (0.6 nM) in a total assay volume of 500 mL. Nonspecific binding was determined using CP-99,994 (1) (1 mM). Assay tubes were incubated for 45 min at room temperature and then rapidly filtered. Bound radioactivity was measured in a scintillation counter. Data was then expressed as a percentage of specific binding of vehicle-treated control rats.

***In Vitro* Turnover Assay.** Compounds at concentrations of 25 mg/mL in distilled water were incubated with dog liver microsomes and a NADPH regenerating system[29] (1 mL total volume) for a period of 2 h in a shaking bath at 37 °C. Incubates were centrifuged (10000*g* for 5 min), and the recovery of compound was determined using reverse-phase HPLC (Shandon Hypersil C18 5 mm BDS HPLC column, 50 mM ammonium acetate/acetonitrile mobile phase; detection at 215 nm). The recovery of compound was compared to a control incubation which did not contain a NADPH regenerating system and the percentage turnover calculated from the difference in peak areas.

## Pharmacokinetic Studies

Beagle dogs were housed in metabolism cages and dosed using an intravenous then oral cross-over dosing regimen. A suitable wash-out period between doses was used. Animals were sampled for blood (~6 mL) prior to dosing and then at the following nominal times postdose administration: 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, and 8 h. Blood samples were placed in lithium−heparin tubes and centrifuged at ~1550*g* for 15 min at ~5 °C to prepare plasma. Plasma samples were stored frozen prior to analysis. Concentrations of parent compound in plasma were determined using a solid phase extraction procedure followed by reversed phase HPLC−UV quantitation. Pharmacokinetic parameters were calculated using standard statistical methods.

**Acknowledgment.** We acknowledge the work of G. Kilpatrick, D. Beattie, C. Gardner, D. Twissell, T. Dale, A. Hawcock, H. Garratt, A. Jones, F. Marshall, L. Fellows, and M. Turpin for biological methods and screening; H. Birch, K. Read, and S. Cozens for drug metabolism studies; S. Guntrip for synthetic chemistry; A. Tonge for molecular modeling; and P. Brush for physical measurements.

**Supporting Information Available:** Synthesis and characterization of compounds **2**, **3**, **7**, **8**, **9**, **10**, 11, **12**, **13**, **14**, **15**, **16**, **17**, **21e−o**, and **23** (8 pages). Ordering information is given on any current masthead page.

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JM9506377