Structural Optimization Affording 2-(*R*)-(1-(*R*)-3,5-Bis(trifluoromethyl)phenylethoxy)-3-(*S*)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine, a Potent, Orally Active, Long-Acting Morpholine Acetal Human NK-1 Receptor Antagonist

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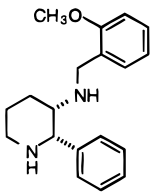
Received May 13, 1998

Structural modifications requiring novel synthetic chemistry were made to the morpholine acetal human neurokinin-1 (hNK-1) receptor antagonist **4**, and this resulted in the discovery of 2-(*R*)-(1-(*R*)-3,5-bis(trifluoromethyl)phenylethoxy)-3-(*S*)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methyl morpholine (**17**). This modified compound is a potent, long-acting hNK-1 receptor antagonist as evidenced by its ability to displace [^{125}I]Substance P from hNK-1 receptors stably expressed in CHO cells (IC_{50} = 0.09 ± 0.06 nM) and by the measurement of the rates of association ($k_1 = 2.8 \pm 1.1 \times 10^8$ M^{-1} min^{-1}) and dissociation (k_{-1} = 0.0054 ± 0.003 min^{-1}) of **17** from hNK-1 expressed in Sf9 membranes which yields K_d = 19 ± 12 pM and a $t_{1/2}$ for receptor occupancy equal to 154 ± 75 min. Inflammation in the guinea pig induced by a resiniferatoxin challenge (with NK-1 receptor activation mediating the subsequent increase in vascular permeability) is inhibited in a dose-dependent manner by the oral preadmininstration of **17** (IC_{50} (1 h) = 0.008 mg/kg; IC_{90} (24 h) = 1.8 mg/kg), indicating that this compound has good oral bioavailbility and peripheral duration of action. Central hNK-1 receptor stimulation is also inhibited by the systemic preadministration of **17** as shown by its ability to block an NK-1 agonist-induced foot tapping response in gerbils (IC_{50} (4 h) = 0.04 ± 0.006 mg/kg; IC_{50} (24 h) = 0.33 ± 0.017 mg/kg) and by its antiemetic actions in the ferret against cisplatin challenge. The activity of **17** at extended time points in these preclinical animal models sets it apart from earlier morpholine antagonists (such as **4**), and the piperidine antagonists **2** and **3** and could prove to be an advantage in the treatment of chronic disorders related to the actions of Substance P. In part on the basis of these data, **17** has been identified as a potential clinical candidate for the treatment of peripheral pain, migraine, chemotherapy-induced emesis, and various psychiatric disorders.

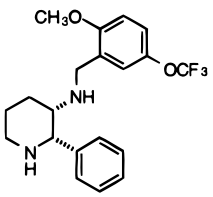
Introduction

The central and peripheral actions of the mammalian tachykinin Substance P (SP) have been associated with numerous inflammatory conditions including migraine,[1] rheumatoid arthritis,[2] asthma,[3] and inflammatory bowel disease[4] as well as mediation of the emetic reflex[5] and the modulation of central nervous system (CNS) disorders such as Parkinson's disease[6] and anxiety.[7] This profile has stimulated a search for potent, nonpeptide antagonists of the human neurokinin-1 (hNK-1) receptor to which SP preferentially binds.[8] This search has further intensified in recent years due in part to the demonstration that a selective hNK-1 antagonist (CP 99,994, **1**) exhibits antiemetic activity in mammals against a broad spectrum of emetogens.[9] This property of **1** coupled with its reported modest oral bioavailability[10] serves to further emphasize the clinical utility of a hNK-1 receptor antagonist exhibiting a favorable pharmacokinetic profile. The modification of **1**, carried

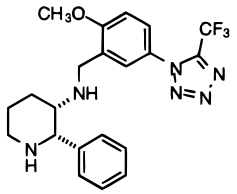


CP 99,994, **1**

out independently by groups at Pfizer and Glaxo-Wellcome, has resulted in the discovery of CP 122,721[11] (**2**) and GR 205,171[12] (**3**), both of which are reported to



CP 122,721, **2**



GR 205,171, **3**

exhibit enhanced potency and oral activity in animal

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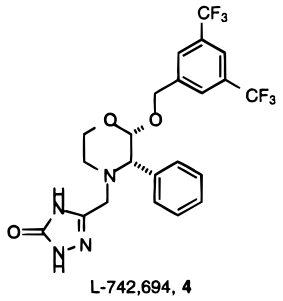
10.1021/jm980299k CCC: $15.00
Published on Web 10/02/1998

models of SP-induced inflammation and emesis.[13] The first report of the prevention of chemotherapy-induced emesis in humans by an hNK-1 receptor antagonist (**2**) has appeared.[14]

Our efforts to target a series of potent, orally active hNK-1 antagonists based on a morpholine acetal core and exemplified by **4** were recently disclosed;[15] the biochemical characterization[16] and the antiemetic activity[17] of this compound have been subsequently documented. The continuation of work in this area focused on identifying the features of **4** that could be considered



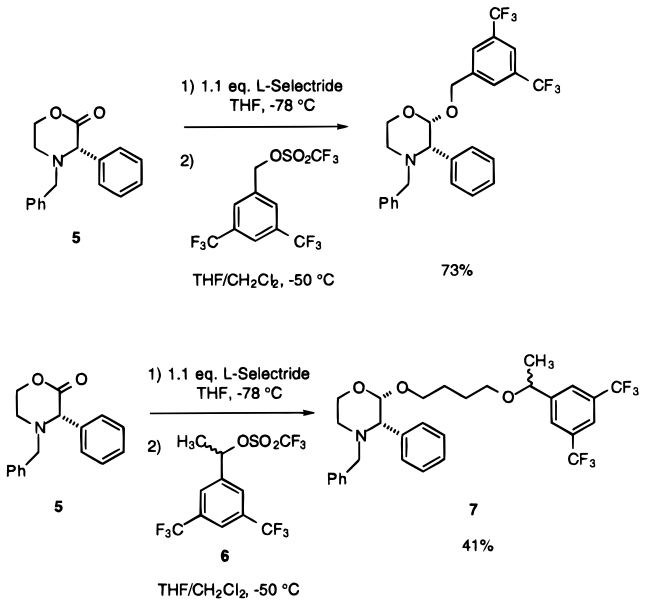
L-742,694, **4**

to be potential metabolic liabilities and making structural changes to **4** that would lessen their effect while not compromising the pharmacologic profile initially observed with this class of compounds. Specifically, it was reasoned that debenzylation of **4**, via either a hydrolytic or oxidative pathway, would be slowed by substituting one of the benzylic hydrogens with a methyl group.[18] While oxidative metabolism of the electron-poor 3,5-bis(CF_3)-substituted phenyl ring of **4** seemed to be unlikely, such a process seemed possible with the phenyl ring at C3 of the morpholine. Substituting the para position of this phenyl ring (the most likely point for metabolism) with a fluorine atom would serve to block metabolism and slow oxidation at other positions of the ring. Metabolism of the (3-oxo-1,2,4-triazol-5-yl)methyl functionality of **4** or dealkylation of the morpholine nitrogen also seemed possible, but we chose to maintain this structural feature as the structure−activity relationship of pendant heterocycles that was developed for the closely related piperidine ether hNK-1 antagonists[19] indicated that this feature exhibited appreciable stability in vitro toward rat liver microsomal incubation and optimally imparted favorable in vivo properties to these molecules. We report herein the novel synthetic chemistry employed to prepare the compounds targetted as the result of our reasoning and the resulting optimization of these morpholine acetal compounds which afforded hNK-1 antagonists exhibiting high potency and enhanced duration of action in vivo as compared to compounds **1**−**4**.

Chemistry

The key step in the preparation of morpholine acetal hNK-1 antagonists such as **4** was a reduction/alkylation sequence in which 3-(*S*)-phenyl-4-benzyl-2-morpholinone (**5**) was first treated with lithium tri-*sec*-butylborohydride (L-Selectride) in THF at −78 °C and the resulting intermediate was reacted at low temperature with 3,5-bis(trifluoromethyl)benzyl triflate (Scheme 1).[15] This reaction afforded an intermediate morpholine acetal in which the substituents at C2 and C3 of the morpholine are in the preferred cis configuration. An

Scheme 1

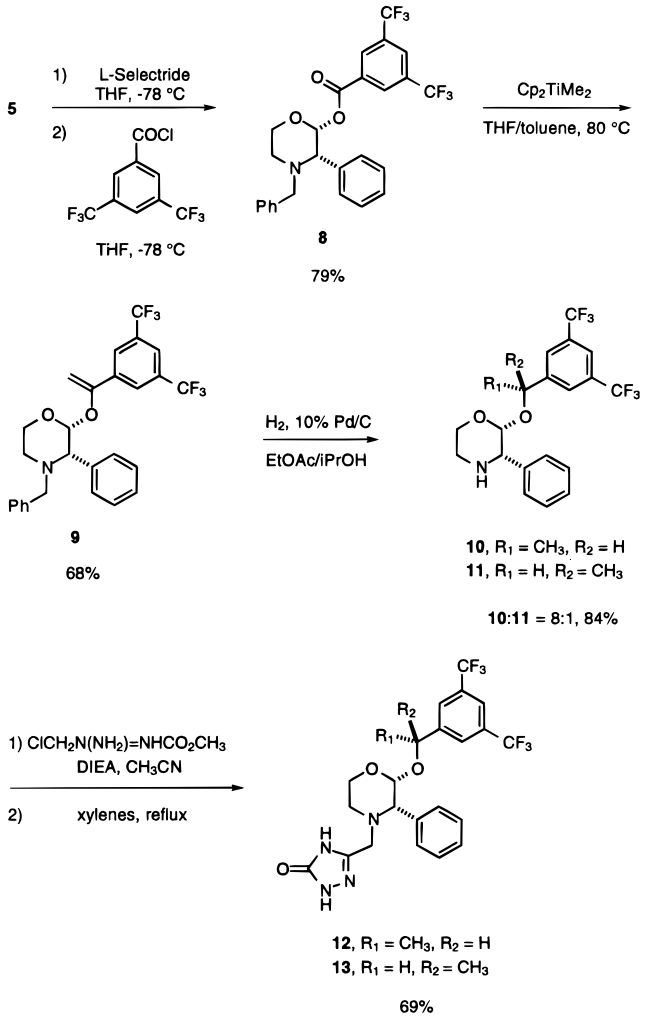


analogous strategy for the preparation of compounds with α-methyl substitution on the C2 benzyl ether was not effective. The secondary triflate (**6**) required for this reaction was readily obtained and handled, but it could not be used in the reduction/alkylation sequence. There was no direct alkylation by **6** of the intermediate obtained during L-Selectride reduction of **5** under the previously employed reaction conditions; the only product seen was **7** which results from the reaction of **6** with the THF solvent and the subsequent alkylation of the "L-Selectride alkoxide" by the resulting oxonium ion.

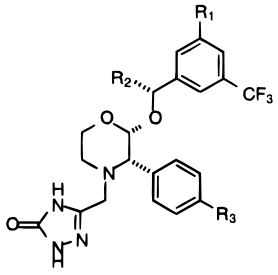
A different strategy that takes advantage of the facile acylation of the morpholinone "L-Selectride alkoxide" met with more success (Scheme 2). Morpholinone **5** was again reacted with L-Selectride in THF at −78 °C, and the reaction was quenched with 3,5-bis(trifluoromethyl)-benzoyl chloride to afford acyl acetal **8** in 79% yield. This compound was first reacted with Tebbe reagent[20] to provide the stable enol ether **9** in 15% yield which has the carbon skeleton of the desired C2 α-methyl benzyl ether compounds, albeit in the wrong oxidation state. The low yield for the acyl acetal to enol ether conversion was attributed to the Lewis acidity of the Tebbe reagent and was improved to 69% by employing dimethyl titanocene;[21] this reagent generates an analogous titanium ylide under neutral conditions. Catalytic hydrogenation of **9** to give **10** and **11** was first carried out stepwise: the enol ether double bond was reduced in the presence of rhodium on alumina or rhodium on carbon (affording a 2:1 mixture of α-methyl diastereomers), and the primary N-benzyl group was reduced in the presence of palladium on carbon. It was subsequently found that concomitant reduction of the double bond and the N-benzyl substituent was possible by carrying out the hydrogenation of **9** in the presence of palladium on carbon catalyst; this resulted in an increased diastereoselection (8:1) favoring the formation of **10** which has the α-(*R*)-methyl stereochemistry.[22] Both **10** and **11** were converted to the corresponding methylene-linked 3-oxo-1,2,4-triazol-5-yl derivatives, **12** and **13**, using conditions previously reported.[15]

Compounds **14** and **15** were also prepared from **5** by

Scheme 2



simply substituting the appropriate benzoyl chloride in the reduction/acylation step. Compounds **16** and **17**, which have a fluorine atom at the 4-position of the C3 phenyl ring, were prepared from (*S*)-(4-fluoro)phenylglycine[23] using the methods previously described[15] or the methods described above. The preparation of [^{3}H]-**17** used for a portion of its in vitro functional characterization required the modification of the synthetic chemistry described above and will be detailed elsewhere.[24]



14, R_1 = F, R_2 = CH_3, R_3 = H
15, R_1 = H, R_2 = CH_3, R_3 = H
16, R_1 = CF_3, R_2 = H, R_3 = F
17, R_1 = CF_3, R_2 = CH_3, R_3 = F

In Vitro Biochemistry

The binding affinities of test compounds were determined by measuring the displacement of [^{125}I]SP from the hNK-1 receptor, [^{125}I]neurokinin A from the human NK-2 receptor, and [^{125}I]Bolton-Hunter-labeled eledoisin from the human NK-3 receptor, all stably expressed in CHO cells.[25] The ability of test compounds to inhibit [^{3}H]diltiazem binding to the L-type calcium channel in rabbit skeletal muscle[26] was also determined.

Table 1. hNK-1 Receptor Binding

compd	hNK-1 IC_{50} (nM)[a]
1	0.5 ± 0.1
(±)-**2**	0.14 ± 0.06
3	0.08 ± 0.05
4	0.09 ± 0.03 (n = 6)
12	0.88 ± 0.03
13	0.09 ± 0.03
14	0.10 ± 0.02
15	0.27 ± 0.03
16	0.07 ± 0.05
17	0.09 ± 0.06 (n = 7)

[a] Displacement of ^{125}I-labeled SP from the human NK-1 receptor expressed in CHO cells. Data are reported as the mean ± SD for n = 3 determinations unless otherwise noted.

The data obtained for hNK-1 receptor binding are shown in Table 1. The hNK-1 binding affinities for **12** and **13** indicate that the α-(*R*) stereochemistry is required for methyl-substituted C2 benzyl ethers to avoid a significant loss of affinity. Replacement of one of the trifluoromethyl groups in the C2 benzyl ether with a fluorine (**14**) afforded another compound that was equipotent to **4**, while removal of the trifluoromethyl group (**15**) led to a 3-fold decrease in receptor affinity. Substitution of the phenyl ring at C3 of **4** with a fluorine atom at its 4-position gave **16**, which has the highest affinity of this series. High affinity for the hNK-1 receptor was also seen in **17** (which incorporates the α-(*R*)-methyl group of **12** and the fluorine substitution of **16**), demonstrating that both structural changes could be made to **4** without a deleterious effect on this property. The most potent morpholine compounds (**4**, **12**, **14**, **16**, **17**) had hNK-1 receptor affinity comparable to that of the piperdine compounds **2** and **3**. All of the new compounds prepared had hNK-2 IC_{50} > 1 μM, hNK-3 IC_{50} > 100 nM, and L-type Ca^{2+} channel IC_{50} > 1 μM.

These initial observations prompted the further characterization of **17**. As was previously reported for **4**,[16] preincubation (15 min at 37 °C) of CHO cells expressing hNK-1 receptors with increasing concentrations of **17** increases the apparent EC_{50} for SP stimulation of inositol phosphate synthesis and decreases the maximal stimulation observed (Figure 1). Thus, **17** produces an insurmountable antagonism of SP in this test system. These data suggest that **17** is a noncompetetive or pseudo-irreversible hNK-1 antagonist. In addition, the level of inositol phosphate synthesis in the absence of added SP is higher in CHO cells expressing the hNK-1 receptor than the levels in null CHO cells that do not express the receptor (Figure 2). Inositol phosphate synthesis is partially inhibited by **17** in CHO cells expressing the hNK-1 receptor, but not in null CHO cells, although this effect has proven to be variable depending on the lot of serum utilized to support the growth of these cells (Figure 2). These data suggest that the high levels of heterologous expression of the hNK-1 receptor result in a population of receptors that are activated in the absence of agonist and that **17** attenu-

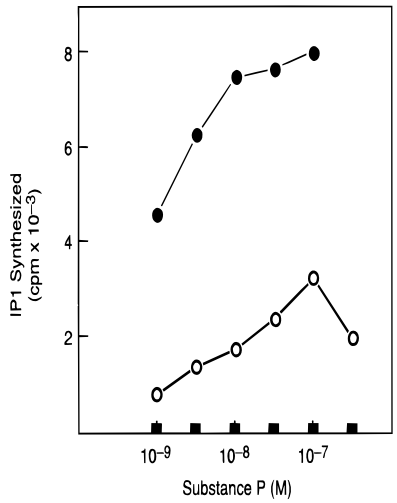


Figure 1. Inhibition of SP-induced inositol-1-phosphate (IP1) synthesis in hNK-1/CHO cells by **17**. SP was incubated in the absence (-●-) or presence of 0.3 (-○-) or 1 nM (-■-) **17** added 15 min before addition of SP.

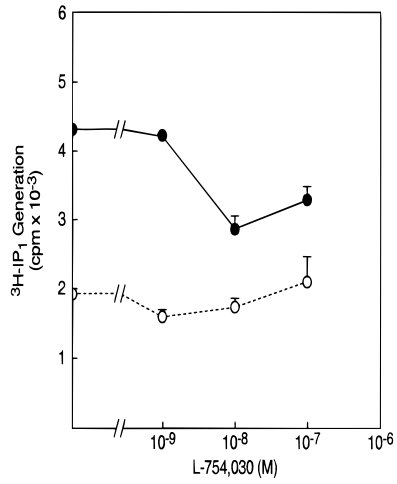


Figure 2. Effect of **17** on inositol phosphate synthesis in CHO cells in the absence (-○-) or presence (-●-) of transfected hNK-1 receptor. Mean data ± SEM are shown for two determinations for two independent experiments.

ates this activation. This suggests that **17** is an inverse agonist of the hNK-1 receptor in this system and shows similar pharmacological activity to that observed with some other antagonists of G protein-coupled receptors.[27] Similar observations have been made using **1** and **3**, suggesting that this property is not unique to **17** (data not shown). In addition, the enantiomers of these compounds are much less active as inverse agaonists, consistent with their poorer affinity for the hNK-1 receptor. It should be noted that the relevance of this inverse agonist activity as observed in test systems with highly overexpressed receptors to the activity of the compounds in vivo in tissues expressing physiological levels of receptors is unclear.

Saturation binding analysis with increasing concentrations of [^{3}H]-**17** demonstrates that the ligand specifically binds to the hNK-1 receptor expressed in Sf9 membranes[16] with $K_d = 0.2$ nM (data not shown). [^{3}H]-**17** dissociates from the hNK-1 receptor with simple monophasic kinetics with a rate of dissociation (k_{-1}) of 0.0054 ± 0.003 min^{-1} ($n = 3$) and $t_{1/2}$ for receptor occupancy of 154 ± 75 min (Figure 3, $n = 2$). The rate

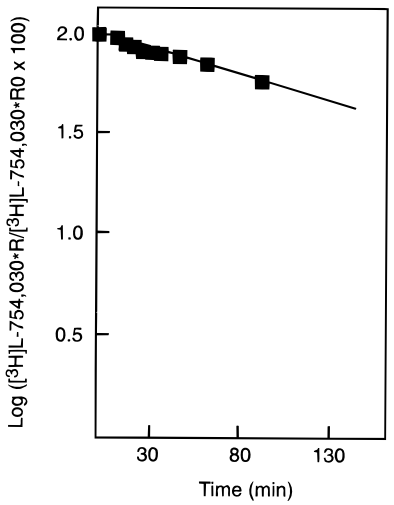


Figure 3. Dissociation of [^{3}H]-**17** from the hNK-1 receptor at 22 °C. The ligand (1.2 nM) was incubated with hNK-1 expressed in baculovirus-infected Sf9 cells until equilibrium, and dissociation was initiated with addition of 100-fold excess of unlabeled ligand. Data shown are the average of two experiments.

Table 2. Inhibition of Resiniferatoxin-Induced Systemic Vascular Leakage in Guinea Pig (SYVAL)

compd	ID_{50} (po, 1 h, mg/kg)[a]	ID_{90} (po, 24 h, mg/kg)[a]
(±)-**2**	0.010	>10[b]
3	0.007	>10[c]
4	0.006	5.4
13	0.010	2.3
16	0.008	2.3
17	0.008	1.8

[a] Antagonist was administered po followed by resiniferatoxin challenge at the time indicated. Dose−response data was determined for $n = 4$−12 animals/data point. [b] 12 ± 25% inhibition at 10 mg/kg. [c] 33 ± 14% inhibition at 10 mg/kg.

constants for the association of [^{3}H]-**17** with the hNK-1 receptor at 22 °C at 4.7, 7.8, and 22.3 nM are 1.7, 2.6, and 3.4 min^{-1}, respectively, and the calculated rate of association (k_1) from these data is 2.8 ± 1.1 × 10^8 M^{-1} min^{-1}. Calculation of the K_d from the ratio of k_{-1}/k_1 gives a value of 19 ± 12 pM, which likely represents the true affinity of **17** for the hNK-1 receptor.

In Vivo Pharmacology

Intravenous administration of resiniferatoxin induces a dose-dependent vascular leakage in the esophagus, trachea, and bladder of guinea pigs. This response results from the neuropeptide liberation from capsaicin-sensitive nerve fibers that is induced by resiniferatoxin (with SP mediating the increase in vascular permeability) and is inhibited by the systemic administration of hNK-1 receptor antagonists. This provides a ready method for examining the ability of a test compound to prevent NK-1-mediated inflammation in the periphery and, when the compound is administered po, an indication of its oral bioavailability. The results of the assay (SYVAL[28]) based on these phenomena for the series of compounds described herein are shown in Table 2. Piperidines (±)-**2** and **3** and the morpholines **4**, **13**, **16**, and **17** were all potent inhibitors of this response (ID_{50} ≤ 0.1 mpk, po) when given 1 h prior to resiniferatoxin challenge. Differences in potency were seen in the morpholine compounds when these were administered

Table 3. Inhibition of GR 73632-Induced Foot Tapping in Gerbils

	ID_{50} (iv, mg/kg)[a]		
compd	$t = 0$ h	$t = 4$ h	$t = 24$ h
(±)-**2**	0.03	0.24	5.37
(±)-**3**	0.04	0.02	>10[b]
4	0.85	nd[c]	2.88
13	0.16	0.04	1.11
16	0.30	0.07	1.24
17	0.36	0.04	0.33

[a] Test compounds were administered iv followed by GR 73632 challenge icv at the time indicated. ID_{50} data was calculated by nonlinear least-squares regression analysis of mean data. Between 3 and 9 animals received one dose of each test compound or vehicle. [b] 47 ± 12% inhibtion at 10 mg/kg. [c] Not determined.

24 h prior to challenge, with **17** being 3 times more potent than **4**. The duration of action of the series of morpholine compounds in this assay greatly differs from that of either piperidine compound; both (±)-**2** and **3** are essentially inactive at the 24 h time point. These results indicate that all of the compounds tested have appreciable oral bioavailability and that the piperidine compounds are metabolized and/or excreted at a rate higher than that of the morpholine compounds. The trend in increasing potency seen in the morpholine series could be attributed to the enhanced metabolic stability afforded by the structural changes that were made in modifying **4** to **17**.

Foot tapping in gerbils can be induced by the central infusion of an NK-1-selective agonist (GR 73632).[17] This readily quantifiable response can be inhibited by the systemic adminstration of brain penetrant NK-1 antagonists and therefore provides a convenient assay for CNS penetration. The activity in such an assay of several of the compounds described herein is shown in Table 3. The piperidines (±)-**2** and (±)-**3** are potent inhibitors of the foot tapping response when dosed immediately prior to NK-1 agonist challenge; (±)-**3** maintains this activity when administered 4 h before GR 73632 challenge. The morpholines **4**, **13**, **16**, and **17** are less potent on immediate pretreatment but have comparable potency to (±)-**3** at 4 h, indicating that they penetrate the CNS more slowly than do either (±)-**2** or (±)-**3**. Two observations are notable regarding the data that were obtained when the test compounds were administered 24 h prior to GR 73632 challenge. First, the trend in the duration of action of the morpholine compounds **4**, **13**, **16**, and **17** that was observed for perpheral NK-1 blockade (SYVAL, see preceding paragraph) is even more distinct in this assay of central NK-1 blockade. The most active morpholine (**17**) is 9 times more potent than the least active morpholine (**4**), indicating that the structural modifications made to **4** are pharmacodynamically beneficial. Second, **17** exhibits a central duration of action superior to either of the piperidine compounds as it was greater than 16 times more potent than (±)-**2** and 33 times more potent than (±)-**3** at this time point. This result indicates that while the piperidine compounds (±)-**2** or (±)-**3** quickly penetrate the CNS, they also clear from the CNS and/or dissociate from central NK-1 receptors more rapidly than does **17**.

Preclinical studies have demonstrated that the retching and vomiting induced by emetogens such as cisplatin, apomorphine, and morphine can be attenuated by the preadministration of an NK-1 receptor antagonist.[9−12] The fact that 5-HT_3 receptor antagonists, which are currently used in the treatment of chemotherapy-induced emesis, are ineffective against centrally acting emetogens (apomorphine, morphine) and the gastric irritant copper sulfate[29] suggests that NK-1 receptor antagonists may provide protection against a broader spectrum of emetogens than do the existing therapies. The antiemetic action of **17** against cisplatin, apomorphine, and morphine is shown in Table 3. Suppression of emesis by **17** was seen on cisplatin, apomorphine, and morphine challenge at doses that compare favorably to the effective doses reported for **2**[11a] and **3**.[12] In addition, **17** was found to be 10 times more potent than **4** (ID_{90} = 3.0 mg/kg, iv) in inhibiting cisplatin-induced emesis, indicating again that the structural changes made to **4** resulting in **17** are pharmacologically favorable.

Conclusion

Structural modifications requiring novel synthetic chemistry were made to the morpholine hNK-1 receptor antagonist L-742,694 (**4**), and this has resulted in the discovery of L-754,030 (**17**). This compound is a potent inverse agonist of the hNK-1 receptor in the in vitro systems described herein and antagonizes the effects of SP in a pseudo-irreversible or noncompetitive manner. Kinetic analysis of the rates of association and dissociation of **17** from the hNK-1 receptor are consistent with the hypothesis that **17** is a competitive antagonist that can behave as a pseudo-irreversible antagonist under some conditions due to its slow rate of dissociation from the receptor. The actions of SP are potently antagonized by **17** in a dose-dependent manner in vivo in both the periphery and the CNS, and this compound exhibits antiemetic activity comparable to the piperidine hNK-1 receptor antagonists **2** and **3**. The observed enhanced duration of action of **17** as compared to piperidines **2** and **3** and the morpholine hNK-1 antagonist **4** sets it apart from these compounds; this property could be advantageous if an hNK-1 antagonist proves to be useful in the treatment of disorders related to the sustained actions of SP. The data presented herein support the further evaluation of **17** as a potential clinical candidate for the treatment of pain,[30]

Table 4. Antiemetic Actions of **17** in the Ferret[a]

emetogen	dose of **17**	retches	vomits	control retches	control vomits
cisplatin, 10 mg/kg, iv	3.0 mg/kg, po	2.8 ± 1.7	0.5 ± 0.3	154.8 ± 14.5	22.3 ± 2.1
cisplatin, 10 mg/kg, iv	0.3 mg/kg, iv	5.3 ± 3.3	1.0 ± 0.7	100.0 ± 24.4	12.7 ± 3.8
apomorphine, 0.25 mg/kg, sc	3.0 mg/kg, po	4.1 ± 1.8	0.7 ± 0.4	28.3 ± 6.5	3.3 ± 0.8
morphine, 0.5 mg/kg, sc	3.0 mg/kg, po	6.0 ± 3.0	0.5 ± 0.3	44.7 ± 7.3	5.5 ± 1.1

[a] **17** was adminstered iv or po followed by emetogen challenge after 3 min (iv experiment) or 60 min (po experiments). Drug vehicle (control) was PEG 300 (iv experiment) or 0.5% Methocel (po experiment). Between 4 and 7 animals received one dose of **17** or drug vehicle.

migraine, chemotherapy-induced emesis,[31] and psychiatric disorders.

Experimental Section

General. See Supporting Information for general experimental details.

(±)-1-(3,5-Bis(trifluoromethyl)phenyl)ethyltrifluoromethylsulfonate (6). A solution of 5.00 g (19.5 mmol) of 3,5-bis(trifluoromethyl)acetophenone in 100 mL of MeOH at 0 °C was treated with 400 mg (10.6 mmol) of $NaBH_4$. The resulting mixture was stirred cold for 15 min, the reaction was quenched with 25 mL of 2.0 N HCl, and the MeOH was removed in vacuo. The resulting aqueous mixture was partitioned between 250 mL of ether and 25 mL of 2.0 N HCl, and the layers were separated. The organic layer was washed with 100 mL of saturated $NaHCO_3$ and 100 mL of saturated NaCl, dried, and concentrated. The resulting solid was recrystallized from 50 mL of hexanes at −78 °C to afford 4.70 g (93%) of (±)-1-(3,5-bis(trifluoromethyl)phenyl)ethanol: ^{1}H NMR (200 MHz) 1.55 (d, J = 6.5, 3H), 2.11 (br s, 1H), 5.05 (q, J = 6.5, 1H), 7.79 (s, 1H), 7.84 (s, 2H).

A solution of 2.58 g (10.0 mmol) of (±)-1-(3,5-bis(trifluoromethyl)phenyl)ethanol and 2.57 g (12.5 mmol) of 4-methyl-2,6-di-*tert*-butylpyridine in 30 mL of CCl_4 was treated with 1.85 mL (11.0 mmol) of trifluoromethanesulfonic anhydride, and the resulting mixture was stirred at room temperature for 45 min. The mixture was filtered using a Schlenk apparatus, and the filtrate was concentrated. The residue was redissolved in 10 mL of CH_2Cl_2 and used immediately. ^{1}H NMR (200 MHz) of the crude triflate revealed that it was an 8:1 mixture of **6** (6.03, J = 6.5, −C*H*(CH_3)−OSO_2CF_3) and diastereomeric symmetrical benzyl ethers (4.36, J = 6.8 and 4.60, J = 6.6, Ar*CH*(CH_3)O*CH*(CH_3)Ar).

2-(*R*)-(4-(1-(*RS*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxyl)butyloxy)-3-(*S*)-phenyl-4-benzylmorpholine (7). A solution of 1.00 g (3.7 mmol) of **5**[15] in 15 mL of THF at −78 °C was treated with 4.20 mL of 1.0 M L-Selectride in THF. The resulting mixture was stirred cold for 1 h and then was treated with a solution of **6** in 10 mL of CH_2Cl_2. The reaction was stirred at −78 °C for 2 h and at −50 °C for 20 h, quenched with 50 mL of saturated $NaHCO_3$, and extracted with 100 mL of ether. The organics were separated, washed with 50 mL of 0.5 N $KHSO_4$ and 50 mL of saturated NaCl, dried, and concentrated. Flash chromatography on 50 g of silica gel using 20:1 v/v and then 10:1 v/v hexanes/CH_2Cl_2 afforded 890 mg (41%) of **7** as a 3:2 mixture of inseparable diastereomers: ^{1}H NMR (400 MHz) 1.39 (d, J = 6.5) and 1.45 (d, J = 6.5), diastereomeric −OCH(CH_3)Ar; 4.54 (d, J = 2.7) and 4.57 (J = 2.7), diastereomeric −O−*CH*−O−; FAB-MS 582 (M + H).

2-(*R*)-(3,5-Bis(trifluoromethyl)benzoyloxy)-3-(*S*)-phenyl-4-benzylmorpholine (8). A solution of 2.67 g (10.0 mmol) of **5**[15] in 40 mL of THF at −78 °C was treated with 12.5 mL of 1.0 M L-Selectride solution in THF, maintaining the internal temperature below −70 °C. The resulting solution was stirred cold for 45 min and then was charged with 3.60 mL (20.0 mmol) of 3,5-bis(trifluoromethyl)benzoyl chloride. The resulting yellow mixture was stirred cold for 30 min and then quenched with 50 mL of saturated $NaHCO_3$. The quenched mixture was partitioned between 300 mL of ether and 50 mL of water, the layers were separated, and the organic layer was dried. The aqueous layer was extracted with 300 mL of ether; the extract was dried and combined with the original organic layer. The combined organics were concentrated. Flash chromatography on 250 g of silica gel using 20:1 v/v and then 10:1 v/v hexanes/ether as the eluant gave 4.74 g of impure **8** as an oil. Crystallization from 100 mL of cold ^{i}PrOH (0 °C) afforded 4.04 g (79%) of **8** as a solid, mp = 104−105 °C: [α] = +130.3 (c = 1.0); ^{1}H NMR (200 MHz) 2.50 (dt, J = 3.4, 12.0, 1H), 2.94−3.00 (m, 1H), 2.99 and 4.00 (ABq, J = 13.6, 2H), 3.72−3.79 (m, 1H), 3.82 (d, J = 2.6, 1H), 4.20 (dt, J = 2.4, 12.0, 1H), 6.22 (d, J = 2.6, 1H), 7.22−7.37 (m, 8H), 7.58 (app d, J = 6.8, 2H), 8.07 (s, 1H), 8.47 (s, 2H); FAB-MS 510 (M + H). Anal. ($C_{26}H_{21}F_6NO_3$) C, H, N, F.

2-(*R*)-(1-(3,5-Bis(trifluoromethyl)phenyl)ethenyloxy)-3-(*S*)-phenyl-4-benzylmorpholine (9). A solution of 2.50 g (4.9 mmol) of **8** in 75 mL of THF was treated with 75.0 mL of 1.0 M dimethyl titanocene[21] solution in toluene, and the resulting mixture was stirred in an oil bath set at 85 °C for 18 h. The reaction mixture was cooled and concentrated. Flash chromatography on 150 g of silica gel using 3:1 v/v hexanes/CH_2Cl_2 as the eluant afforded 1.71 g (69%) of **9** as a solid. An analytical sample was obtained by recrystallization from ^{i}PrOH, mp 112−114 °C: [α] = +105.4 (c = 1.0); ^{1}H NMR (400 MHz) 2.42 (dt, J = 3.6, 12.0, 1H), 2.87−2.91 (m, 1H), 2.92 and 4.00 (ABq, J = 13.6, 1H), 3.62−3.66 (m, 1H), 3.73 (d, J = 2.8, 1H), 4.09 (dt, J = 2.4, 12.0, 1H); 4.75 (d, J = 3.2, 1H), 4.79 (d, J = 3.2, 1H), 5.36 (d, J = 2.8, 1H), 7.24−7.42 (m, 8H), 7.63 (app d, J = 7.2, 2H), 7.79 (s, 1H), 7.91 (s, 2H); FAB-MS 508(M + H). Anal. ($C_{27}H_{23}F_6NO_2$) C, H, N, F.

2-(*R*)-(1-(*R*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-phenylmorpholine (10) and 2-(*R*)-(1-(*S*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-phenylmorpholine (11). A mixture of 1.50 g (2.9 mmol) of **9** and 750 mg of 10% palladium on carbon in 25 mL of 3:1 v/v EtOAc/^{i}PrOH was stirred under an atmosphere of H_2 for 48 h. The catalyst was filtered onto a pad of Celite; the reaction flask and filter cake were rinsed well with EtOAc (∼500 mL). The filtrate was concentrated. Flash chromatography on 60 g of silica gel using 2:1 v/v hexanes/ether as the eluant afforded 106 mg (9%) of **11** as an oil; further elution with 3:2 v/v ether/hexanes afforded 899 mg (75%) of **10** as an oil. For **10**: ^{1}H NMR (400 MHz) 1.46 (d, J = 6.4, 3H), 1.92 (br s, 1H), 3.13 (dd, J = 12.0, 3.2, 1H), 3.24 (dt, J = 3.2, 12.0, 1H), 3.61−3.64 (m, 1H), 4.04 (d, J = 2.4, 1H), 4.14 (dt, J = 2.8, 12.0), 4.48 (d, J = 2.4, 1H), 4.90 (q, J = 6.4, 1H), 7.21−7.33 (m, 7H), 7.64 (s, 1H); NH_3/CI-MS 420 (M + H). Anal. ($C_{20}H_{19}F_6NO_2$) C, H, N, F. For **11**: ^{1}H NMR (400 MHz) 1.14 (d, J = 6.4, 3H), 1.82 (br s, 1H), 3.04 (dd, J = 12.0, 2.8, 1H), 3.19 (dt, J = 3.6, 12.4, 1H), 3.44−3.48 (m, 1H), 3.83 (dt, J = 2.4, 12.0, 1H), 4.12 (d, J = 2.4, 1H), 4.69 (q, J = 6.4, 1H), 4.91 (d, J = 2.4, 1H), 7.29−7.42 (m, 5H), 7.72 (s, 2H), 7.76 (s, 1H).

2-(*R*)-(1-(*R*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine (12). A solution of 945 mg (2.3 mmol) of **10**, 447 mg (2.7 mmol) of *N*-methoxycarbonyl-2-chloroacetamidrazone,[32] and 0.78 mL of DIEA in 17 mL of MeCN was stirred at room temperature for 20 h. The mixture was concentrated, the residue was partitioned between 50 mL of CH_2Cl_2 and 25 mL of H_2O, and the layers were separated. The organic layer was dried and concentrated. Flash chromatography on 50 g of silica gel using 50:1:0.1 v/v/v CH_2Cl_2/MeOH/H_2O as the eluant afforded 1.12 g (91%) of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(*S*)-phenyl-4-(2-*N*-(methoxycarbonyl)acetamidrazono)morpholine (**10a**) as a solid, mp = 91−94 °C: [α] = +62.0 (c = 0.9); ^{1}H NMR (400 MHz) 1.46 (d, J = 6.5, 3H), 2.50 (dt, J = 3.5, 12.0, 1H), 2.55 and 3.35 (ABq, J = 14.0, 2H), 2.95 (app d, J = 12.0, 1H), 3.46 (d, J = 2.5, 1H), 3.65−3.68 (m, 1H), 3.78 (s, 3H), 4.25 (dt, J = 2.5, 12.0, 1H), 4.37 (d, J = 2.5, 1H), 4.86 (q, J = 6.5, 1H), 5.35 (br s, 2H), 7.15 (s, 2H), 7.29−7.35 (m, 5H), 7.61 (s, 1H), NH_3/CI-MS 549 (M + H).

A suspension of 1.01 g (1.8 mmol) of **10a** in 15 mL of xylenes was heated at reflux for 2 h. The mixture was cooled and concentrated. Flash chromatography on 50 g of silica gel using 40:1:0.1 v/v/v CH_2Cl_2/MeOH/H_2O as the eluants afforded 781 mg of impure **12**. Recrystallization from 50 mL of 10:1 v/v hexanes/EtOAc afforded 710 mg (76%) of pure **12**, mp = 220−221 °C: [α] = +44.5 (c = 1.0); ^{1}H NMR (400 MHz) 1.47 (d, J = 6.8, 3H), 2.01−2.05 (m, 2H), 2.55 (dt, J = 3.6, 12.0, 1H), 2.91 and 3.69 (ABq, J = 10.8, 2H), 2.95−2.98 (m, 1H), 3.49 (d, J = 2.4, 1H), 3.63−3.67 (m, 1H), 4.29 (dt, J = 2.4, 10.0), 4.38 (d, J = 2.4, 1H), 4.88 (q, J = 6.8, 1H), 7.14 (s, 2H), 7.33−7.40 (m, 5H), 7.62 (s, 1H), 9.91 (br s, 1H), 10.16 (br s, 1H); FAB-MS 517 (M + H). Anal. ($C_{23}H_{22}F_6N_4O_3$) C, H, N, F.

2-(*R*)-(1-(*S*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine (13). The title compound was prepared in 32% yield from **11** using a procedure analogous to that described to prepare

12: ^{1}H NMR (400 MHz) 1.09 (d, J = 6.4, 3H), 2.47−2.53 (m, 1H), 2.83 (app d, J = 11.6, 1H), 2.95 (d, J = 14.0, 1H), 3.51−3.65 (m, 3H), 4.01 (app t, J = 11.6, 1H), 4.60, (q, J = 6.4, 1H), 4.84 (d, J = 2.4, 1H), 7.33−7.51 (m, 5H), 7.74 (s, 2H), 7.76 (s, 1H), 9.51 (br s, 1H), 10.00 (br s, 1H); FAB-MS 517 (M + H).

The following compounds were prepared using procedures described in the Supporting Information or procedures analogous to those above or in ref 15.

(*R*)-(1-(*R*)-(3-Fluoro-3-(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine (14): ^{1}H NMR (400 MHz) 1.40 (d, J = 6.3, 3H), 2.54 (app t, J = 11.0, 1H), 2.87 (app d, J = 12.2, 1H), 2.94 (app d, J = 14.0, 1H), 3.46−3.48 (m, 1H), 3.63 (app t, J = 14.0, 2H), 4.24 (app t, J = 10.8, 1H), 4.25 (app t, J = 11.0, 1H), 4.35 (d, J = 1.5, 1H), 4.75 (q, J = 6.3, 1H), 6.62 (d, J = 6.7, 1H), 6.78 (s, 1H), 7.01 (d, J = 8.4, 1H), 7.24 (d, J = 3.9, 1H), 7.35 (app s, 4H), 9.61 (br s, 1H), 9.89 (br s). Anal. ($C_{22}H_{21}F_4N_4O_3$) C, H, N, F.

(*R*)-(1-(*R*)-(3-(Trifluoromethyl)phenyl)ethoxy)-3-(*S*)-phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine (15): ^{1}H NMR (400 MHz) 1.40 (d, J = 6.8, 3H), 2.53 (app t, J = 11.2, 1H), 2.86 (app d, J = 12.2, 1H), 2.94 (app d, J = 14.3, 1H), 3.43−3.45 (m, 1H), 3.63 (d, J = 14.0, 2H), 4.24 (app t, J = 10.8, 1H), 4.27 (app t, J = 11.5, 1H), 4.34 (d, J = 2.1, 1H), 4.76 (q, J = 6.8, 1H), 6.63 (d, J = 7.7, 1H), 7.06 (t, J = 7.6, 1H), 7.25−7.45 (m, 6H), 9.63 (br s, 1H), 9.74 (br s). Anal. ($C_{22}H_{22}F_3N_4O_3$) C, H, N, F.

2-(*S*)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(*S*)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine (16): ^{1}H NMR (400 MHz) 2.55 (dt, J = 3.6, 12.0, 1H), 2.91 (d, J = 11.6, 1H), 2.93 and 3.59 (ABq, J = 14.4, 2H), 3.57 (d, J = 2.8, 1H), 3.67−3.70 (m, 1H), 4.18 (dt, J = 2.4, 11.6, 1H), 4.48 and 4.84 (ABq, J = 13.6, 2H), 4.65 (d, J = 2.8, 1H), 7.07 (t, J = 8.4, 2H), 7.41 (s, 2H), 7.45−7.48 (m, 2H), 7.68 (s, 1H), 10.04 (br s, 1H), 10.69 (br s, 1H); FAB-MS 521 (M + H). Anal. ($C_{22}H_{19}F_7N_4O_3$) C, H, N, F.

(*R*)-(1-(*R*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine (17): mp = 244−245 °C; [α] = +68.1 (c = 0.6, MeOH); ^{1}H NMR ($CDCl_3$ + CD_3OD, 500 MHz) 1.48 (d, J = 6.8, 3H), 2.52 (app t, J = 10.4, 1H), 2.85−2.88 (m, 2H), 3.47 (d, J = 2.8, 1H), 3.63 (d, J = 14.4, 1H), 3.70 (dd, J = 2.0, 11.6, 1H), 4.24 (app t, J = 10.8, 1H), 4.35 (d, J = 2.8, 1H), 4.91 (q, J = 6.8, 1H), 7.07 (app t, J = 8.4, 2H), 7.15 (s, 2H), 7.37−7.40 (m, 2H), 7.65 (s, 1H); FAB-MS 535 (M + H). Anal. ($C_{23}H_{21}F_7N_4O_3$) C, H, N, F.

Sensorotoxin-Induced Systemic Vascular Leak in the Guinea Pig (SYVAL). Male Dunkin Hartley guinea pigs (400−600 g) were anaesthetized by intramuscular injection with Ketamine (30 mg/kg) plus xylazine (6 mg/kg). Evans Blue dye (25 mg/mL solution in saline, containing 100 units/mL of heparin) was filtered through a 0.22 μm disk filter and injected intravenously via a saphenous vein. The animals were challenged intravenously by injection of capsaicin or resiniferatoxin (400 μL/kg administered over 30 s) via the penile vein 10 min postinjection of the Evans Blue dye. At 10 min post resiniferatoxin challenge, the animals were euthanized using CO_2 gas, a midline incision was performed, and 1 mL of heparinized blood sample was obtained by venepunture from the vena cava. Cell-free plasma was prepared by centrifugation (8000 rpm, 5 min, 20 °C), and a portion (100 mL) was removed and stored for analyses. The bladder was then removed, and the vena cava and aorta were transected to exsanguinate the animal prior to the removal of the trachea and the esophagus. The tissues were placed in tared vials, dried in an oven (24 h, 65 °C), and reweighed. Dried tissue samples and an aliquot (100 mL) of plasma from the animal were extracted/incubated in formamide (1 mL, 65 °C, 24 h). The extent of plasma extravasation (expressed as mg plasma/g dry weight tisuue) was assessed by comparing in a plate-reading spectrophotometer the absorption ($OD_{620-650}$) of the formamide extracts of tissue to that of cell-free plasma from the same animal. Test compounds were administered ip, iv, or orally at 1 or 24 h prior to resiniferatoxin challenge. ID_{50} values were calculated by nonlinear least-squares regression analysis of the mean data.

Inhibition of GR 73,632-Induced Foot Tapping in Gerbils. Male or female Mongolian gerbils (35−70 g) were anaesthetized by inhalation of an isoflurane/oxygen mixture to permit exposure of the jugular vein through a skin incision in the neck using a blunt dissection to clear surrounding salivary gland and connective tissues. Test compound or vehicle was administered intravenously using an injection volume of 5 mL/kg. The wound was closed, and a second skin incision was made in the midline of the scalp to expose the skull. GR 73,632 was infused directly in the cerebral ventricules (3 pmol in 5 mL icv) by vertical insertion of a cuffed 27-gauge needle to a depth of 4.5 mm below bregma. The scalp incision was closed and the animal allowed to recover from the anaesthesia in a clear Perspex observation box (25 cm × 20 cm × 20 cm). The duration of hind foot tapping was then recorded continuously for 5 min using a stopclock. The time lapse from induction to recovery of anaesthesia, with intervening iv and icv injections, was 3−4 min per animal. ID_{50} values were calculated by nonlinear least-squares regression analysis of the mean data.

Inhibition of Emesis by 17 in the Ferret. Male ferrets (1.0−2.0 kg) were used in all studies. For intravenous studies, ferrets under halothane anaesthesia were dosed with **17** (0.3 mg/kg) or drug vehicle followed 3 min later by cisplatin (10 mg/kg iv). For oral studies, ferrets were dosed with **17** (3.0 mg/kg) or drug vehicle followed 60 min later by cisplatin (10 mg/kg iv, under halothane anaesthesia), apomorphine (0.5 mg/kg sc), or morphine (0.5 mg/kg sc). The animals dosed with cisplatin were observed for the next 240 min for retching and vomiting behavior, following which they were humanely killed. Animals that were used in the apomorphine and morphine experiments were observed for retching and vomiting for 30 min after injection of these emetogens and inspected daily for any clinical abnormality. No adverse effects of the drug treatments were observed following these experiments.

Acknowledgment. We thank Ms. Amy Bernick for providing mass spectral data.

Supporting Information Available: Full descriptions of the preparation and characterization of the intermediates used to prepare **16** and **17** and crystallographic data for **17** (13 pages). Ordering information is given on any current masthead page.

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(22) Single-crystal X-ray analysis of **17** determined the relative configuration to be 2-(*S*), 3-(*R*), α-(*R*). Since **17** is derived from **10**, the stereochemical outcome of the hydrogenation of **9** is as described in the text. Crystal structure details: $C_{23}H_{21}F_7N_4O_3$; $M_r = 534.438$; orthorhombic space group $P2_12_12_1$; $a = 7.770(3)$, $b = 43.031(2)$, $c = 7.403(3)$ Å; $V = 2475(2)$ Å^3; $Z = 4$; $F(000) = 1096$; $T = 294$ K. Data were collected on an AFC5 diffactometer to a θ limit of 72.68° using Cu Kα radiation. There are 2755 unique reflections with 1339 observed at the $I \geq 2\sigma(I)$ level. The structure was solved by direct methods (SHELXS), and refined (SHELXL) using full-matrix least-squares on F^2 using 323 parameters and all 2755 reflections. Final agreement statistics are $R = 0.105$, $wR = 0.284$, $S = 1.25$, $(\Delta/\sigma)_{max} = 0.03$. The atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre and further crystallographic details are available in the Supporting Information.

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JM980299K