Phosphorylated Morpholine Acetal Human Neurokinin-1 Receptor Antagonists as Water-Soluble Prodrugs

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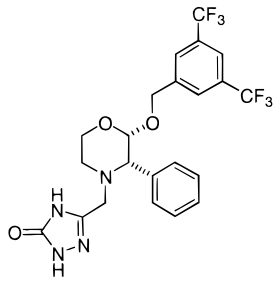
The regioselective dibenzylphosphorylation of **2** followed by catalytic reduction in the presence of *N*-methyl-D-glucamine afforded 2-(*S*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluoro)phenyl-4-(5-(2-phosphoryl-3-oxo-4*H*,-1,2,4-triazolo)methylmorpholine, bis(*N*-methyl-D-glucamine) salt, **11**. Incubation of **11** in rat, dog, and human plasma and in human hepatic subcellular fractions in vitro indicated that conversion to **2** would be expected to occur in vivo most readily in humans during hepatic circulation. Conversion of **11** to **2** occurred rapidly in vivo in the rat and dog with the levels of **11** being undetectable within 5 min after 1 and 8 mg/kg doses iv in the rat and within 15 min after 0.5, 2, and 32 mg/kg doses iv in the dog. Compound **11** has a 10-fold lower affinity for the human NK-1 receptor as compared to **2**, but it is functionally equivalent to **2** in preclinical models of NK-1-mediated inflammation in the guinea pig and cisplatin-induced emesis in the ferret, indicating that **11** acts as a prodrug of **2**. Based in part on these data, **11** was identified as a novel, water-soluble prodrug of the clinical candidate **2** suitable for intravenous administration in humans.

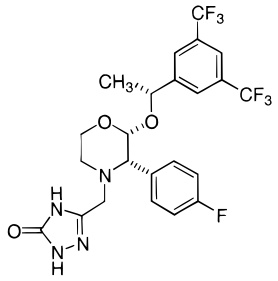
Introduction

Emesis induced by radiation and/or chemotherapeutic agents is a major side effect in the treatment of various malignancies.[1] The use of 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonists has impacted cancer treatment in a positive manner due to the efficacy these drugs have in controlling the emesis that immediately follows the administration of chemotherapeutic agents.[2] Improving the treatment of the second phase of chemotherapy-induced emesis (delayed emesis) as well as identifying agents that are efficacious against a wider variety of emetogens remains the focus of current research.[3] Recent disclosures of the effectiveness of human neurokinin-1 receptor (hNK-1) or Substance P (SP) receptor antagonists in controlling emesis in both preclinical[4] and clinical[5] settings indicate that compounds of this class represent a potentially significant advance in the treatment of chemotherapy-induced emesis and of nausea and vomiting in general.

The details of our efforts to modify **1** (L-742,694)[6] which resulted in the discovery of the potent, orally bioavailable, CNS-penetrant hNK-1 antagonist **2** (L-754,030, MK-0869) have been reported.[4] This compound has high affinity for the hNK-1 receptor ($IC_{50} = 90 \pm 50$ pM for the displacement of [^{125}I]-SP from hNK-1 expressed in CHO cells) and inhibits the actions of SP in vivo after oral and intravenous dosing in animal models of peripheral inflammation and emesis. In recent clinical trials, **2** was well tolerated with no serious adverse effects in healthy male volunteers[7] and highly efficacious in the treatment of acute chemotherapy-induced emesis when given in combination with granisetron and dexamethasone, while being superior to placebo in the prevention of delayed chemotherapy-induced emesis.[5a]



1



2

The sparing water solubility of **2** (0.2 μg/mL in isotonic saline) precludes its formulation in a vehicle acceptable for intravenous administration in humans. Since the availability of both an oral and an intravenous formulation of **2** was deemed to be necessary in order to provide maximum clinical flexibility with this compound, we sought ways to overcome the solubility issues associated with it. Pharmaceutically acceptable sulfonic acid salts[8] (methane sulfonate, ethane disulfonate) of weakly basic **2** were prepared, but these salts dissociated in aqueous media which resulted in the precipitation of the free base from the acidic solution. The viability of preparing a prodrug[9] of **2** was therefore examined. Since a prodrug of **2** would be used primarily for intravenous administration, we hoped to identify an entity that had good

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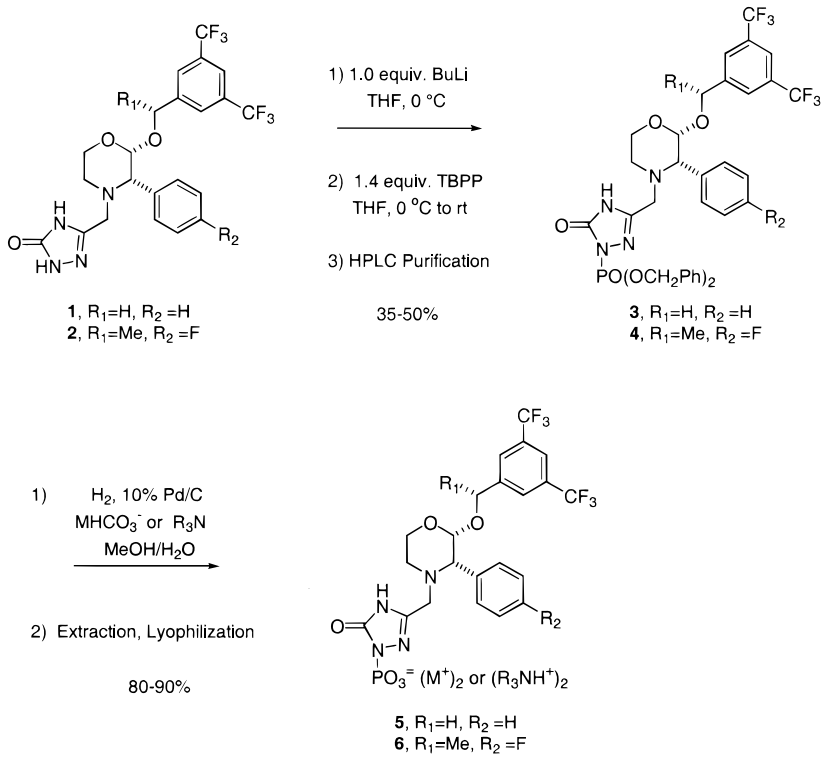
Scheme 1. Preparation of N2 Phosphoryl Derivatives of **1** and **2**



water solubility, rapidly reverted to the parent while releasing innocuous residues in vivo, and exhibited sufficient chemical stability to allow for its routine handing and storage. The recent example of the anticonvulsant fosphenytoin[10] highlights one successful approach for introducing solubility-enhancing phosphate functionality into a bioactive nitrogenous heterocycle,[11] but we wished to avoid functionalized Mannich adducts of **2** which would necessitate the release in vivo of formaldehyde or other low molecular weight aliphatic aldehydes. The simplest approach to introduce phosphate functionality into **2** would be the direct phosphorylation of the 1,2,4-triazol-3-one group, and we were encouraged to pursue this as a prodrug strategy on finding that the O-thiophosphorylation of some structurally simple 1,2,4-triazol-3-ones had been reported.[12] We wish to disclose herein our efforts toward the preparation of chemically stable *N*-phosphoryl derivatives of both **1** and **2**, the details of their structure determination, and the characterization of the *N*-phosphoryl derivative of **2** as a prodrug in vitro and in vivo.

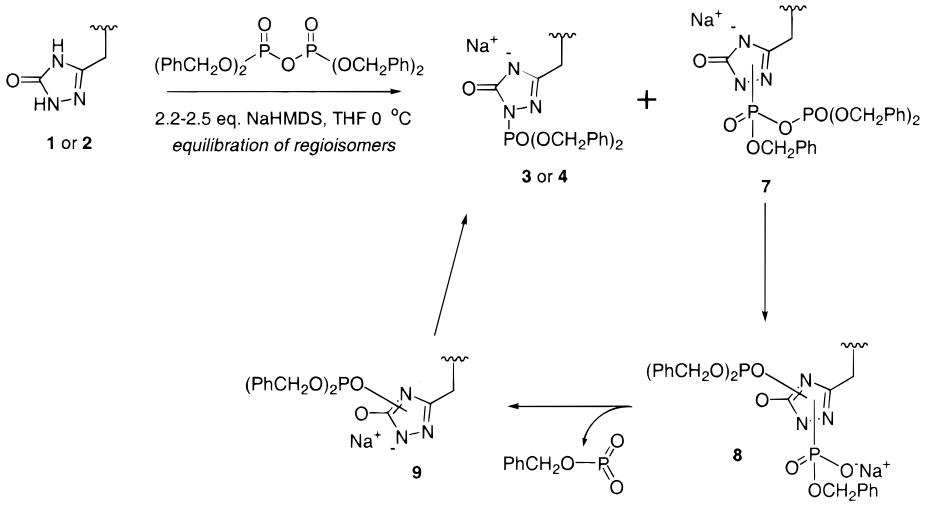
Chemistry

Treatment of a solution of the lithium salt of **1** or **2** in THF at 0 °C with tetrabenzyl pyrophosphate (TBPP)[13] afforded mixtures of the starting materials and two products (Scheme 1). Under these conditions, approximately 60% of **1** or **2** was converted to the products, and the product ratio ranged from 5:1 to 10:1. The products of these reactions were stable to aqueous workup conditions (saturated aqueous $NaHCO_3$ solution), but they were found to decompose on exposure to silica gel during column chromatography which initially hindered the separation and purification of reaction mixtures. The major reaction products did exhibit sufficient stability to neutral or mildly acidic aqueous solvents to allow for their purification using preparative reverse-phase HPLC and were determined to be the N2 phosphoryl derivative **3** or **4** via a series of NMR experiments (see below). Altering the base (sodium or potassium bis(trimethylsilyl)amide, *tert*-butylmagnesium chloride, triethylamine) or the phosphorylating agent (dibenzylphosphoryl chloride,[14] dibenzylphosphoryl flouride,[15] dibenzyl *N*,*N*-diethylphosphoramidite[16]) did not improve the yield of **3** or **4** as compared to the reaction of the lithium salt of **1** or **2** with TBPP; in many cases the reaction mixtures contained the starting material as the sole morpholine species.

The purified major reaction products (**3** and **4**) slowly decomposed at room temperature, so they were immediately converted to phosphate salts **5** and **6**. Catalytic hydrogenation of **3** or **4** was carried out in the presence of 2 molar equiv of a metal bicarbonate or an amine to directly provide the desired crude phosphate salt. After filtration of the catalyst and concentration of the filtrate, **5** or **6** was extracted into water and lyophilized, which served to remove the minor amounts (∼10%) of the parent compound **1** or **2** that invariably formed during the hydrogenation. Phosphate salts prepared in this manner were determined to contain only the product and residual **1** or **2** (<1%) as the sole organic components. Various salt forms of **5** and **6** were prepared in this manner; salt forms were also interconverted using ion exchange chromatography.[17]

Further experimentation provided an indication as to the possible identity of the side product formed during the phosphorylation reaction and led to reaction conditions that circumvented the need for the HPLC purification of **3** and **4**. If a mixture of **1** or **2** and TBPP in THF at 0 °C was treated with 1 equiv of a nonnucleophilic base such as sodium bis(trimethylsilyl)amide (NaH-

Scheme 2. Potential Pathway for the Formation and Consumption of Byproduct **7** during the Dibenzyl Phosphorylation Reaction



MDS), the reaction profile observed was the same as that seen when the preformed lithium salt of the 3-oxo-1,2,4-triazole was treated with TBPP. The addition of excess TBPP to the reaction mixture did not affect the amounts of the other reaction components present, indicating that the base had been consumed. However, the addition of excess NaHMDS served to consume residual **1** or **2**, TBPP, *and the byproduct that was detected in the reactions using 1 equiv of base*. If 2.2−2.5 equiv of NaHMDS was gradually added to a mixture of **1** or **2** and a slight excess of TBPP in THF at 0 °C, the phosphate diester **3** or **4** was observed to be the major organic species present with residual starting material (∼5%) being the other major component. After aqueous workup, the crude diester **3** or **4** was subjected to the hydrogenation and extraction/lyophilization protocol that was previously employed with diester that was obtained after HPLC purification to afford the phosphate salts **5** and **6**.

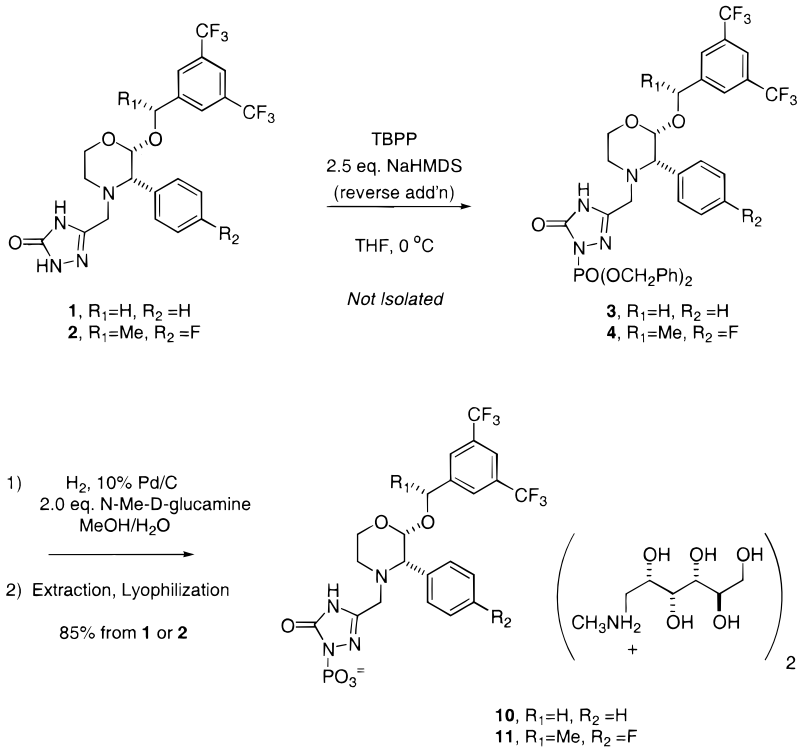
The dibenzylphosphorylation **1** and **2** is regioselective, and this selectivity presumably arises from the equilibration of any of the dibenzylphosphorylated 3-oxo-1,2,4-triazole species that are formed to the N2 isomer via intermolecular dibenzylphosphoryl transfer and/or intramolecular dibenzylphosphoryl 1,3-shifts (Scheme 2). If the product (**3** or **4**) of the phosphorylation reaction is more acidic than the starting material (**1** or **2**), 2 molar equiv of base are required for the phosphorylation reaction to proceed to completion under equilibration conditions. Consumption of the byproduct as excess base added to the reaction mixture is noteworthy. While attempts to isolate the byproduct in pure form by HPLC were unsuccessful, examination of reaction mixtures by HPLC-MS provided insights regarding its identity. Analysis of the components in an aliquot removed from the phosphorylation reaction of **1** or **2** after 1 molar equiv of NaHMDS had been added revealed that the byproduct was not a phosphate dibenzyl ester isomeric to **3** or **4** or a bis(dibenzylphosphoryl) species but rather a product (**7**) that results from the displacement of one of the benzyloxy groups from the TBPP (Scheme 2). As the reaction proceeds, both the desired product (**3** or **4**) and **7** can consume excess base (NaHMDS, sodium benzyloxide, or the sodium salt of **1** or **2**). While the sodium salt of **3** or **4** is presumably stable, **7** can potentially isomerize under basic conditions to an intermediate (**8**) which can eliminate benzyl phosphite to give **9** and provide the product (**3** or **4**) at equilibrium.[18]

Monobasic and dibasic salts of **5** and **6** were prepared with the goals of identifying a crystalline derivative that would further aid in their purification and impart solid state stability to these compounds. While none of the salts that were prepared were crystalline, qualitative examination of the lyophilized solids afforded useful information regarding their solid state stability. The degradation of the monobasic salts to **1** or **2** and inorganic phosphate was found to occur more rapidly than with the dibasic salts. The degradation of salts with metal counterions (Na, K) was found to be more rapid than for salts derived from amine bases. The lyophilized salts of **5** or **6** with three pharmaceutically acceptable amine bases[8] (choline, tris(hydroxymethyl)-methylamine, *N*-methyl-D-glucamine) were found to be appreciably stable. While the bis(choline) and bis(tris-(hydroxymethyl)methylamine) salts were hygroscopic, the bis(*N*-methyl-D-glucamine salts (**10** and **11**) were tractable solids which made this the salt form of choice. Degradation of **10** and **11** occurred at a rate of less than 0.1% per day under ambient conditions, and samples of these salts showed no detectable degradation after storage for 6 months at −20 °C. As expected, **11** showed greatly enhanced aqueous solubility (12 mg/mL in isotonic saline) as compared to **2**. The optimized preparation of **10** and **11** is shown in Scheme 3.

Regioisomer Determination

The diester **4** was sufficiently stable to allow for its characterization by ^{1}H and ^{13}C NMR spectroscopy, and these experiments provided the key data for the determination of the regiochemical outcome of the dibenzylphosphorylation reaction (Figure 1). The ^{13}C spectrum of **4** in d_6-DMSO solution showed ^{13}C-^{31}P coupling to both C3 and C5. The magnitude of these couplings (13.2 and 11.9 Hz, respectively) is consistent with each of the carbon atoms of the 3-oxo-1,2,4-triazole ring being two or three atoms removed from the phosphorus atom, which indicated that one of the nitrogen atoms and not the oxygen atom of the heterocycle had been dibenzylphosphorylated. Examination of the ^{13}C NMR spectra

Scheme 3. Optimized Preparation of **10** and **11**



in d_6-DMSO solution of partially deuterated **2** and **4** was used to confirm the assignment of the chemical shifts for the two carbons of the 3-oxo-1,2,4-triazole ring of **2** and to determine which nitrogen atom of the heterocycle of **2** had been phosphorylated.[19] Since proton exchange is slow in DMSO, adding sufficient D_2O to 50% deuterate the 3-oxo-1,2,4-triazole ring nitrogens of **2** allowed for the observation of two secondary isotope shifts of 0.13 ppm each for the 156.2 ppm signal, indicating that it corresponds to a carbon between two nitrogens and therefore must correlate to C3. A secondary isotope shift of 0.12 ppm and a tertiary isotope shift of 0.04 ppm were observed for the 143.8 ppm signal, indicating that this resonance must be due to C5. A similar deuterium isotope experiment with **4** revealed isotope shifts to C3 of 0.14 ppm and to C5 of 0.13 ppm, which is only consistent with N2, and not N1 or N4, of the 3-oxo-1,2,4-triazole being the ring nitrogen atom that had been dibenzylphosphorylated. It was therefore reasoned that **4** is the correct structure for the product of the dibenzylphosphorylation reaction.

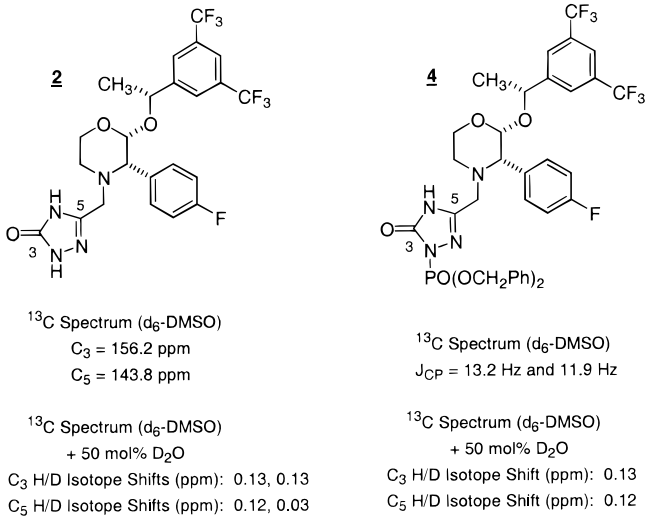


Figure 1. ^{13}C NMR data for the determination of the regiochemistry of **4**.

Conversion of 11 to 2 in Vitro and in Vivo

A series of experiments were carried out to examine the stability of **11** in plasma and hepatic subcellular fractions in vitro and to demonstrate that the metabolic conversion of **11** to **2** occurs in vivo.[20] Control incubations of **11** at concentrations ranging from 1 μg/mL to 25 μg/mL in fresh, heparinized rat and dog blood at 0 °C in the presence of vanadate were first carried out to establish that **11** was stable in plasma in the absence of alkaline phosphatase and that the conversion of **11** to **2** ex vivo was low. Similar incubations of **11** at a concentration of 10 μg/mL in the absence of vanadate in rat, dog, and human blood (Table 1) indicated that appreciable conversion to **2** occurred in rat blood ($t_{1/2} \cong$ 30 min), but was much slower in dog blood ($t_{1/2} >$ 300 min). Compound **11** was very stable in human blood with only about 10% conversion detected after 2 h. Since metabolic conversion of **11** to **2** could also occur in liver, the stability of **11** in human hepatic subcellular fractions was then examined (Table 2). The rate of conversion of **11** to **2** in human liver microsomes was rapid with only 3% of **11** remaining after 15 min. The rate of conversion in the cytosolic fraction was slower but still appreciable, with almost 70% conversion of **11** to **2** after 120 min. Similar results were obtained with dog hepatic subcellular fractions (data not shown). On the basis of these results, it was concluded that **11** could indeed function as a prodrug of **2** in vivo in all three species examined and that the metabolic conversion of **11** to **2** would be expected to occur primarily during hepatic circulation in humans.

Table 1. Concentrations (μM) of **11** and **2** in Plasma after Incubation in Rat, Dog, and Human Blood[a]

time (min)	rat		dog		human	
	11	**2**	**11**	**2**	**11**	**2**
0	23 ± 0.5	0.6 ± 0.05	26 ± 0.7	1.2 ± 0.1	26 ± 0.9	0.8 ± 0.05
15	18 ± 0.5	5.8 ± 0.3	26 ± 1.1	1.8 ± 0.05	27 ± 0.8	1.0 ± 0.1
30	13 ± 1.0	8.0 ± 0.4	25 ± 0.3	2.4 ± 0.05	26 ± 0.4	1.1 ± 0.1
60	6.4 ± 0.5	11 ± 0.5	24 ± 0.6	3.9 ± 0.2	26 ± 0.9	1.4 ± 0.1
120	1.9 ± 0.1	15 ± 0.9	20 ± 1.1	6.0 ± 0.5	26 ± 0.7	2.3 ± 0.4

[a] Incubation of **11** (16.3 μM, 3 samples/data point) in fresh, heparinized blood at 37 °C for the specified time was followed by treatment with vanadate (5 mM) at 4 °C to minimize ex vivo conversion of **11** to **2**. Plasma samples were obtained by centrifugation at 4 °C, subjected to solid-phase extraction, and analyzed for **11** and **2** by LC/MS/MS.

Table 2. Conversion of **11** to **2** in Human Hepatic Subcellular Fractions[a]

time (min)	microsomal		cytosolic	
	11 (μM)	**2** (μM)	**11** (μM)	**2** (μM)
0	8 ± 0.3	0.6 ± 0.1	7.5 ± 0.1	0.1 ± 0.05
15	0.2 ± 0.05	5.3 ± 0.1	6.8 ± 0.2	0.9 ± 0.05
30	*blq*[b]	5.2 ± 0.3	6.1 ± 0.1	1.7 ± 0.1
60	*blq*[b]	5.1 ± 0.2	4.5 ± 0.2	2.8 ± 0.1
120	*blq*[a]	5.1 ± 0.1	2.4 ± 0.2	4.4 ± 0.1

[a] Incubation of **11** (8.1 μM, 3 samples/data point) in human hepatic microsomal or cytosolic fractions at 37 °C for the specified time was followed by solid-phase extraction and analysis for **11** and **2** by LC/MS/MS. [b] Below limit of quantitation.

Table 3. Average AUC Measurements of **2** after Intravenous Administration of **11** and **2** in the Rat

dose of **11** (mg/kg)	1	8	25
AUC of **2** (ng·h/mL)	570 ± 120	6300 ± 1400	22000 ± 1200
dose of **2** (mg/kg)	2	5	
AUC of **2** (mg·h/mL)	2700 ± 340	6400 ± 1200	

Table 4. Average AUC Measurements of **2** after Intravenous Administration of **11** and **2** in the Dog

dose of **11** (mg/kg)	0.5	2	32
AUC of **2** (ng·h/mL)	1100 ± 300	8900 ± 1500	370000 ± 55000
dose of **2** (mg/kg)	0.5	2	
AUC of **2** (mg·h/mL)	3800 ± 1100	38000 ± 8000	

The conversion of **11** to **2** in vivo after intravenous administration in rats and dogs was demonstrated. Three doses of **11** (1, 8, and 25 mg/kg of body mass) were administered in the rat (Table 3). A near proportional increase in the AUC of **2** was seen after the 8 mg/kg dose as compared to the 1 mg/kg dose, and an additional 4-fold increase in the AUC of **2** was seen after the 25 mg/kg dose. Concentrations of **11** in these experiments fell below the limits of quantitation by HPLC-MS/MS within 5 min at the two lower doses and by 1 h at the higher dose. In separate experiments, the kinetics of **2** in the rat after intravenous administration were found to be linear with near proportional increases in the AUC at doses of 0.2, 2, and 5 mg/kg of body mass (0.2 mg/kg data not shown). After 1 and 8 mg/kg doses of **11**, the resulting exposure of **2** was found to be quantitatively proportional to the dose of **11** within experimental error.

Conversion of **11** to **2** in dogs after intravenous administration (0.5, 2.0, and 32.0 mg/kg of body mass) was also found to be rapid with the plasma concentration of **11** being below the limits of detection within 15 min at all three doses tested. The exposure of **2** after the administration of the 0.5 mg/kg dose of **11** was found to be quantitatively proportional within experimental error (Table 4). Calculations at higher doses were complicated by the nonlinear kinetics exhibited by **2** which suggests that elimination of **2** might be saturated at doses greater or equal to 2 mg/kg of body mass in the dog.

Table 5. Comparison of the hNK-1 Affinities and Pharmacology of **2** and **11**

	2	**11**
Receptor Binding[a]		
hNK-1 IC_{50} (nM)	0.09 ± 0.05	1.2 ± 1.2[b]
Inhibition of SP-Mediated Vascular Leakage in the Guinea Pig (SYVAL)[c]		
ID_{50} (po, mg/kg, 1 h before RTX)	0.012	0.016
ID_{50} (iv, mg/kg, 1 h before RTX)	0.002	0.006
ID_{50} (po, mg/kg, 24 h before RTX)	0.5	0.9
Inhibition of Cisplatin-Induced Retching and Vomiting in the Ferret[d]		
mean retches, 0.1 mg/kg, iv	90 ± 26	115 ± 29
mean retches, 0.3 mg/kg, iv	5 ± 3	26 ± 5
mean retches, 1.0 mg/kg, iv	0 ± 0	2 ± 2
control	100 ± 24	164 ± 41
mean vomits, 0.1 mg/kg, iv	13 ± 4	16 ± 3
mean vomits, 0.3 mg/kg, iv	1 ± 1	4 ± 1
mean vomits, 1.0 mg/kg, iv	0 ± 0	1 ± 1
control	13 ± 4	20 ± 5
ID_{90} (iv, mg/kg)	0.3	0.8

[a] Displacement of [^{125}I]-SP from the human NK-1 receptor expressed in CHO cells. Data are reported as the mean ± SD for **2** (n = 13) and **11** (n = 8). [b] See ref 24. [c] Comound **2** or **11** was administered either po or iv followed by resiniferatoxin (RTX) challenge at the time indicated. Dose−response data were determined for n = 2−11 animals/data point. [d] The antiemetic activity of **2** and **11** in ferrets (n = 4) during a 4 h observation period after administration of cisplatin (10 mg/kg, iv). Control animals (n = 4−6) were pretreated with vehicle (PEG 300 for **2**, water for **11**).

Functional Characterization of 11

A series of experiments in preclinical assays that involve peripheral and central NK-1 blockade was carried out to establish that **11** was functionally equivalent in vivo to the parent hNK-1 antagonist **2** (Table 5). The observed increase in vascular permeability in the guinea pig after the systemic administration of resiniferatoxin (RTX) is mediated by SP, and the resulting peripheral inflammation can be inhibited by NK-1 receptor antagonists.[4] Comparison of the activities of **2** and **11** in an assay based on this phenomenon (SYVAL[21]) indicates that the two compounds are potent inhibitors of this SP-mediated response when administered both 1 h and 24 h after RTX challenge. Correcting for the fact that the molecular weight of **11** is roughly twice that of **2**, these compounds are equipotent on a molar basis at the time points tested in this assay. Retching and vomiting in the ferret can be elicited by a variety of emetogens (cisplatin, morphine, apomorphne, copper sulfate) and attenuated by the preadministration of CNS-penetrant hNK-1 receptor antagonists.[22] The

emetic response due to the chemotherapeutic agent cisplatin is suppressed in the ferret by both **2** and **11**; again these compounds are equipotent on a molar basis after correcting for the difference in molecular weight.[23]

The binding affinity of **2** and **11** to hNK-1 was determined by measuring the displacement of [^{125}I]SP from the hNK-1 receptor stably expressed in CHO cells (Table 5).[24] Compound **11** was found to have good affinity for the hNK-1 receptor (IC_{50} = 1.2 nM), but it is still 10 times less potent than **2** in the same assay.[25] The oral activity of **11** in SYVAL probably arises from the conversion of this compound to **2** in the guinea pig stomach. However, based on the observations regarding the conversion of **11** to **2** in rats and dogs in vitro and in vivo (see preceding section), the efficacy of **11** after intravenous administration almost certainly arises from its metabolic conversion to **2** in vivo. The supposition that **11** is functionally equivalent to **2** is further supported by the ability of this compound to suppress cisplatin-induced emesis in the ferret. Compound **11** would be expected to be negatively charged and poorly brain penetrant at physiologic pH; conversion of **11** to the CNS-penetrant **2** must be occurring since the requirement that SP receptor antagonists traverse the blood-brain barrier in order to elicit this response is well established.[22]

Conclusion

The sparing water solubility of the orally active, human NK-1 receptor antagonist **2** necessitated the identification of a method to deliver this compound intravenously in a manner suitable for clinical use. An unprecedented prodrug strategy was undertaken, and the *N*-phosphoryl derivative of **2** was targeted as an entity with the potential to be metabolically converted in vivo to **2**. An efficient sequence to effect a regioselective dibenzylphosphorylation of **2** with tetrabenzyl pyrophosphate giving **4** followed by catalytic hydrogenation in the presence *N*-methyl-D-glucamine to directly afford the phosphate salt **11** was established. A series of experiments were carried out to demonstrate that **11** is metabolically converted to **2** both in vitro and in vivo in rats and dogs and that **11** is functionally equivalent in vivo in assays of SP-mediated events to **2**. The data presented herein supported the further evaluation of **11** as a prodrug of **2** in a clinical setting. The reports that have appeared describing the favorable tolerability profile of **11** in humans[26] and the efficacy of **11** in the treatment chemotherapy-induced emesis[27] serve to further demonstrate the viability of this prodrug strategy for the intravenous delivery of **2**.

Experimental Section

General. General experimental details have been previously described.[6] Compounds **1**,[6] **2**,[4] and tetrabenzyl pyrophosphate[13b] (TBPP) were prepared according to the published procedures. The protocols for the examination of the metabolic conversion in vitro and in vivo of **11** to **2** in rats and dogs,[20] the inhibition of resiniferatoxin-induced systemic vascular leakage in the guinea pig,[4] and the attenuation of cisplatin-induced emesis in the ferret[22] are described elsewhere.

2-(*S*)-(1-(*R*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluoro)phenyl-4-(1-dibenzylphosphoryl-3-oxo-4*H*,-1,2,4-triazol-5-yl)methylmorpholine (4). A solution of 3.00 g (5.6 mmol) of **2** in 120 mL of THF at 0 °C was treated with 3.90 mL of 1.6 M *n*-butyllithium solution in hexanes. The resulting mixture was stirred cold for 5 min. TBPP (4.20 g, 7.9 mmol) was added to the reaction mixture as a solid in one portion. The cooling bath was removed, and the resulting mixture was stirred at room temperature for 45 min. The reaction was quenched with 200 mL of saturated $NaHCO_3$ and extracted with 2 × 300 mL of ether. The ether extracts were combined, dried, and concentrated in vacuo. HPLC (Zorbax R_x-C8, 4.6 × 250 mm column, 65:35 v/v CH_3CN/H_2O, 1.5 mL/min, 210 nm) indicated that the reaction workup was a mixture of **2** (17%, t = 3.6 min), TBPP (33%, t = 6.8 min), **4** (44%, t = 10.8 min), and **7** (5%, t = 12.9 min).

The mixture obtained from the reaction workup was divided into three equal parts, and each portion was purified on a Waters PrepLC System 500A equipped with two 47 × 300 mm Waters Preppak Cartridges containing 300 Å 15−20 μm, Bondapak C8 reverse-phase packing material using 2:1 v/v CH_3CN/H_2O as the eluant (prepacked columns: Waters Part No. WATO38572). Fractions from the individual runs were assayed using the analytical HPLC system described above; fractions containing pure **2** were pooled and concentrated in vacuo to remove the CH_3CN. The resulting cloudy aqueous mixture was diluted with an equal volume of saturated NaCl and extracted with 3 × 250 mL of ether. The ether extracts were combined, dried, and concentrated in vacuo. A total of 1.70 g (39%) of **4** was obtained as an oil from the three chromatographic runs: ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 1.43 (d, J = 6.0, 3H), 2.50 (dt, J = 3.5, 11.5, 1H), 2.81 (d, J = 11.5, 1H), 2.91 (d, J = 14.5, 1H), 3.46 (d, J = 2.0, 1H), 3.49 (d, J = 14.5, 1H), 3.62−3.65 (m, 1H), 4.22 (dt, J = 2.0, 11.5, 1H), 4.31 (d, J = 2.0, 1H), 4.87 (q, J = 6.0, 1H), 5.19−5.30 (m, 4H), 7.08−7.38 (16H), 7.64 (s, 1H), 9.96 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz, ppm) δ 24.4, 50.5, 52.5, 59.1, 68.6, 70.4 (app d, J = 5.5), 72.3, 95.1, 115.7 (d, J = 21.1), 121.5, 125.1 (q, J = 270.9), 126.2, 128.2, 128.5, 128.7, 130.7 (d, J = 8.2), 131.6 (q, J = 33.0), 131.8, 145.2, 147.9 (d, J = 11.0), 155.7 (d, J = 11.9), 162.8 (d, J = 247.1); ESI-MS 795 (M + H, 100%).

2-(*S*)-(1-(*R*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluoro)phenyl-4-(1-phosphoryl-3-oxo-4*H*,-1,2,4-triazol-5-yl)methylmorpholine, Dipotassium Salt (6, M = K). A solution of 2.61 g (3.3 mmol) of **4** in 75 mL of MeOH was treated with a solution of 660 mg (6.6 mmol) of $KHCO_3$ in 10 mL of H_2O. Then 10% Pd/C (250 mg) was added, and the resulting mixture was hydrogenated at 40 psi for 3 h. The mixture was filtered through Celite; the reaction flask and filter cake were rinsed well with MeOH (∼750 mL). The filtrate was concentrated in vacuo. The residue was dissolved in 250 mL of H_2O; attempted extraction of the aqueous solution with 400 mL of ether resulted in the formation of an emulsion. The emulsion was transferred into 50 mL centrifuge tubes; centrifugation at 3000 rpm for 15 min effected separation of the layers. The organic layers were drawn off, the aqueous layers were combined and filtered, and the filtrate was lyophilized to afford 1.95 g (86%) of **6** (M = K) as an amorphous solid: ^{1}H NMR (D_2O, 500 MHz, ppm) δ 1.48 (d, J = 6.5, 3H), 2.61 (app t, J = 10.5, 1H), 2.95−2.97 (m, 2H), 3.57 (app s, 1H), 3.63 (d, J = 14.5, 1H), 3.76 (d, J = 10.5, 1H), 4.24 (app t, J = 11.0, 1H), 4.47 (app s, 1H), 4.87 (q, J = 6.5, 1H, peak partially obscured by HOD), 7.04 (br t, J = 8.0, 2H), 7.31−7.35 (m, 2H), 7.38 (s, 2H), 7.84 (s, 1H); ^{13}C NMR (CD_3OD, 125 MHz, ppm) δ 24.7, 52.3, 53.4, 60.5, 70.6. 73.7, 97.2, 116.1 (d, J = 21.9), 122.3, 124.6 (q, J = 271.0), 127.8, 132.2, 132.7 (q, J = 33.0), 134.3, 145.2 (d, J = 11.0), 147.6, 159.0 (d, J = 10.2), 164.0 (d, J = 244.4).

2-(*S*)-(1-(*R*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluoro)phenyl-4-(1-phosphoryl-3-oxo-4*H*,-1,2,4-triazol-5-yl)methylmorpholine, Bis(*N*-methyl-D-glucamine) Salt (11). A solution of 2.00 g (3.7 mmol) of **2** and 2.80 g (5.2 mmol) of TBPP in 50 mL of THF was cooled to 0 °C. A 1.0 M solution of NaHMDS in THF (9.4 mL, 9.4 mmol) was added to the cooled reaction mixture using a syringe pump at a rate of 1 equiv/h maintaining the internal temperature at 0 °C. After the addition of the NaHMDS solution, the reaction was stirred at 0 °C for 15 min and quenched with 100 mL of saturated $NaHCO_3$. The quenched mixture was extracted with

300 mL of ether; the ether extract was washed with 100 mL of 0.5 N $KHSO_4$, 100 mL of saturated $NaHCO_3$, and 100 mL of saturated NaCl, dried, and concentrated in vacuo. HPLC (Zorbax R_x-C8, 4.6 × 250 mm column, 50/50 v/v to 100/0 v/v gradient CH_3CN/H_2O over 25 min, 1.5 mL/min, 210 nm) indicated that the reaction workup was a mixture of **2** (3%, t = 6.3 min), TBPP (1%, t = 10.7 min), and **4** (90%, t = 13.0 min).

A solution of the crude **4** in 50 mL of MeOH, a solution of 1.45 g (7.4 mmol) of *N*-methyl-D-glucamine in 10 mL of H_2O, and 200 mg of 10% Pd/C were combined, and the resulting mixture was hydrogenated at 40 psi for 2 h. The reaction mixture was filtered through a pad of Celite; the reaction flask and filter cake were rinsed well with MeOH (400 mL). The filtrate was concentrated in vacuo. The crude product was dissolved in 25 mL of MeOH; 125 mL of ^{i}PrOH was added to the solution, and the resulting mixture was aged at room temperature for 30 min. The solid that had precipitated was filtered, washed with 75 mL of ^{i}PrOH and 75 mL of ether, and dried. The solid was partitioned between 150 mL of ether and 150 mL of water; an emulsion formed on mixing of the layers. The emulsion was transferred into 50 mL centrifuge tubes; centrifugation at 3000 rpm for 15 min caused separation of the layers. The organic layers were drawn off, the aqueous layers were combined and filtered, and the filtrate was lyophilized to afford 3.40 g (86%) of **11** as an amorphous solid: ^{1}H NMR (CD_3OD, 500 MHz, ppm) δ 1.43 (d, J = 6.6, 3H), 2.72 (s, 6H), 2.84 (d, J = 13.9, 1H), 2.94 (d, J = 10.3, 1H), 3.12−3.30 (m, 4H), 3.42−3.83 (m, 14H), 4.19−4.25 (m, 3H), 4.35 (d, J = 2.2, 1H), 7.04 (t, J = 8.5, 2H), 7.30 (s, 2H), 7.52 (br s, 2H), 7.70 (s, 1H); ^{13}C NMR (CD_3OD, 125 MHz, ppm) δ 24.7, 34.4, 52.3, 53.1, 53.5, 60.5, 64.7, 69.9, 70.4, 72.0, 72.4, 72.6, 73.6, 97.1, 116.2 (d, J = 21.9), 122.3, 124.5 (q J = 271.0), 127.7, 132.3, 132.7 (q, J = 33.8), 134.8, 145.9, 147.5, 158.9, 163.9 (d, J = 245.3); ESI-MS 615 (M + H, 100%); HPLC (Zorbax R_x-C8, 4.6 × 250 mm column, 25/75 v/v to 90/10 v/v gradient CH_3CN/H_2O over 15 min, then hold 9 min, 1.5 mL/min, 210 nm) t = 9.0 min. Anal. ($C_{37}H_{56}F_7N_6O_{16}P/4H_2O$) C, H, N, F, P.

2-(*S*)-((3,5-Bis(trifluoromethyl)benzyloxy)-3-(*S*)-phenyl-4-(1-phosphoryl-3-oxo-4*H*,-1,2,4-triazol-5-yl)methylmorpholine, Bis(*N*-methyl-D-glucamine) Salt (10). The title compound was prepared in 63% yield from **1** using procedures analogous to those described for **11**: ^{1}H NMR (CD_3OD, 500 MHz, ppm) δ 2.51 (app t, J = 9.5, 1H), 2.69 (s, 6H), 2.88−2.91 (2H), 3.08−3.17 (4H), 3.54 (d, J = 10.0, 1H), 3.60−3.81 (14H), 4.13−4.17 (3H), 4.48 (d, J = 8.5, 1H), 4.75 (d, J = 2.0, 1H), 4.82 (d, J = 8.5), 7.28−7.37 (3H), 7.55−7.59 (2H), 7.57 (s, 2H), 7.77 (s, 1H); ESI-MS 583 (M + H, 100%); HPLC (Zorbax R_x-C8, 4.6 × 250 mm column, 25/75 v/v to 90/10 v/v gradient CH_3CN/H_2O over 15 min, then hold 9 min, 1.5 mL/min, 210 nm) t = 8.8 min. Anal. ($C_{36}H_{55}F_6N_6O_{16}P$ /$6H_2O$) C, H, N; F: calcd, 10.55; found, 9.32; P: calcd, 2.87, found, 3.51.

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