Potent, Brain-Penetrant, Hydroisoindoline-Based Human Neurokinin-1 Receptor Antagonists

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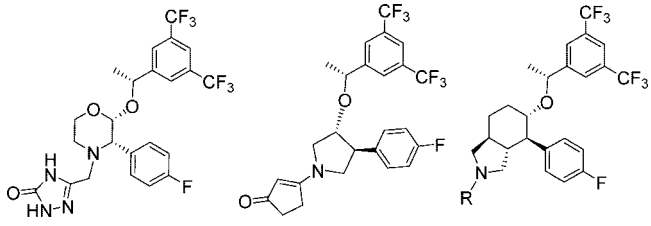
3-[(3a*R*,4*R*,5*S*,7a*S*)-5-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy}-4-(4-fluorophenyl)octahydro-2*H*-isoindol-2-yl]-cyclopent-2-en-1-one (**17**) is a high affinity, brain-penetrant, hydroisoindoline-based neurokinin-1 (NK_1) receptor antagonist with a long central duration of action in preclinical species and a minimal drug−drug interaction profile. Positron emission tomography (PET) studies in rhesus showed that this compound provides 90% NK_1 receptor blockade in rhesus brain at a plasma level of 67 nM, which is about 10-fold more potent than aprepitant, an NK_1 antagonist marketed for the prevention of chemotherapy-induced and postoperative nausea and vomiting (CINV and PONV). The synthesis of this enantiomerically pure compound containing five stereocenters includes a Diels−Alder condensation, one chiral separation of the cyclohexanol intermediate, an ether formation using a trichloroacetimidate intermediate, and bis-alkylation to form the cyclic amine.

Introduction

Substance P is the most abundant neurokinin in the mammalian central nervous system (CNS[a]). The substance-P-preferring neurokinin receptor (NK_1) is highly expressed in brain regions that are critical for mediation of a variety of biological effects.[1] This laboratory discovered the non-peptide NK_1 antagonist aprepitant (**1**) and has demonstrated that it had clinical antiemetic activity in phase III studies. The FDA has approved acute dosing of aprepitant for prevention of chemotherapy-induced nausea and vomiting (CINV) and for prevention of postoperative nausea and vomiting (PONV). Merck has also disclosed the results of a phase IIa study in which aprepitant was shown to have efficacy in the treatment of overactive bladder syndrome.[2] NK_1 receptor antagonists may act like capsaicin by inhibiting sensorial input from the bladder to the spinal cord, thus increasing the threshold to initiate micturition.[3] Aprepitant has also been tested clinically as a therapy for depression.[4]



1 **2** **3**

Aprepitant has been shown to have a moderate inhibitory effect as well as a possible inductive effect on cytochrome P450 (CYP-3A4).[5] Thus, there was an interest in identifying an NK_1 antagonist with a diminished potential to cause drug−drug interactions, especially for conditions that require chronic therapy. Identifying a preclinical candidate with minimal CYP-3A4 inhibition and induction was one strategy to achieve this goal. An alternative approach to reduce the adverse effects might be to improve potency and brain penetration, thereby increasing the central receptor occupancy at a lower systemic exposure level of the NK_1 antagonist to afford a larger window with respect to CYP inhibition or induction.

CNS penetration of an NK_1 antagonist has been suggested to be essential for treatment of overactive bladder.[2] PET studies in rhesus have shown that aprepitant requires a plasma level of as high as 900 nM (470 ng/ml) to achieve 90% receptor occupancy in rhesus.[6] Therefore, a more potent NK_1 receptor antagonist that provides a high receptor occupancy at a lower drug level in plasma in rhesus PET studies would be highly desirable. The results of the rhesus PET studies are assumed to be correlated to the human NK_1 receptor occupancy.

Modification of the compound properties may also provide a way to improve tolerability. Many basic amine-based NK_1 antagonists have previously been reported,[7] but few nonbasic ones were found in literature. Therefore, our efforts have focused on nonbasic NK_1 antagonists in the hope of improving brain penetration and reducing off-target activities associated with basic amine functionalities. Indeed, a neutral vinylogous amide-based NK_1 antagonist (**2**) recently disclosed by our group had shown excellent potency, selectivity, pharmacokinetic profile, and in vivo activity as compared to aprepitant.[8] However, compound **2** showed poor in vitro inositol 1-phosphate (IP-1)[9] functional activity by Schild analysis and minimal improvement of the drug exposure in plasma required to achieve more than 90% NK_1 receptor occupancy in rhesus PET studies compared to aprepitant.[8] The limited potency of compound **2** in the rhesus PET studies may have been related to a fast off-rate from the NK_1 receptor as evidenced by the poor in vitro IP-1 activity.

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[a] Abbreviations: NK_1, neurokinin-1; PET, position emission tomography; CINV, chemotherapy-induced nausea and vomiting; PONV, postoperative nausea and vomiting; CNS, central nervous system; IP-1, inositol 1-phosphate; CHO, Chinese hamster ovary.

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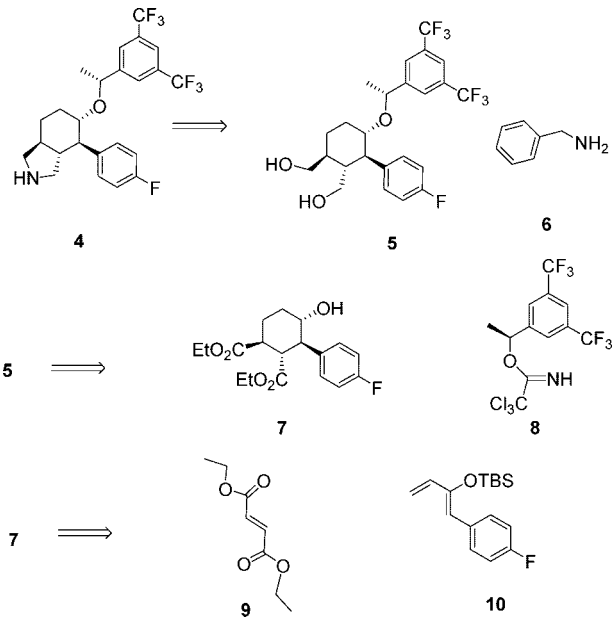
Scheme 1



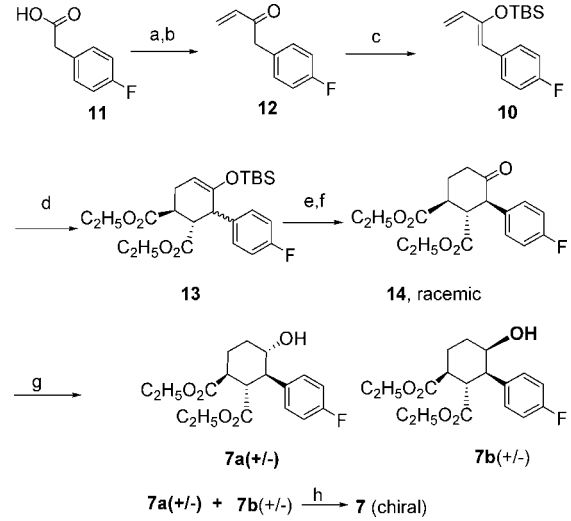
Our continued pursuit of nonbasic NK_1 antagonists focused on identifying a new core from which to attach heterocycles with the potential to increase IP-1 activity, improve potency in rhesus PET studies, and minimize drug−drug interaction potential. Among our newly designed lead structures, hydroisoindolines **3** can be viewed as a new class of compounds with a hybrid core derived from aprepitant **1** and compound **2**. We herein report the total synthesis of enantiomerically pure hydroisoindolines **3** which afforded enhanced hNK_1 antagonist potency with the potential for fewer drug−drug interactions compared to aprepitant.

Chemistry

Hydroisoindolines **3** represent a novel structural class of NK_1 antagonists. Scheme 1 shows the retrosynthesis of the unsubstituted analogue **4** on the nitrogen. We envisioned that the construction of the cyclohexanol core **7** might be accomplished by a Diels−Alder condensation of diene **10** with trans-dienophiles **9** and that the (*R*)-α-methyl bis(trifluoromethyl)-benzyl ether could be installed by nucleophilic displacement on (*S*)-trichloroacetimidate **8** with the cyclohexanol **7**. Bis-alkylation of an amine **6** with diol **5** via a bis-mesylate intermediate would then provide the trans-fused pyrrolidine ring in **4**.

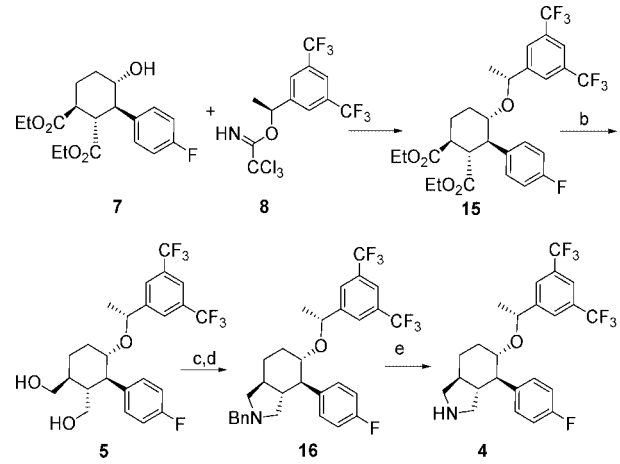
Diene **10** was prepared from commercially available 4-fluorophenylacetic acid **11** (Scheme 2). Thus, treatment of 4-fluorophenylacetic acid with *N,O*-dimethylhydroxylamine and EDC followed by reaction with vinylmagnesium bromide gave α,*β*-unsaturated ketone **12**. Because of the instability of the α,*β*-unsaturated ketone under basic conditions, it was required that the Grignard reaction be quenched by pouring the reaction mixture into a mixture of ice and 2 N hydrochloric acid to prevent the decomposition of **12**. The crude **12** was directly treated with potassium *tert*-butoxide and *tert*-butyldimethylsilyl chloride to give **10** in about 85% yield. The Diels−Alder reaction of the crude **10** with diethyl fumarate was carried out in xylenes in a 150−160 °C oil bath for 5 h to give adduct **13** as a mixture of the two phenyl isomers, as suggested by ^1H NMR of the crude **13** which showed multiplets of the olefinic signals. Without purification, the silyl group in **13** was removed with hydrogen fluoride in acetonitrile and gave a mixture of

Scheme 2[a]



[a] Reagents: (a) EDC/DMAP, CH_3NHOCH_3−HCl/CH_2Cl_2, 20 °C; (b) CH_2=CHMgBr/THF−ether, 0 °C (80% yield for two steps); (c) *t*-BuOK, TBSCl/THF, −78 to 20 °C (85%); (d) diethyl fumarate/xylene, 150−160 °C; (e) HF in CH_3CN (2 M), 20 °C; (f) aq NaOH/CH_3CN, 20 °C; (g) $NaBH_4$/MeOH, −78 to 20 °C; (h) silica gel separation, then ChiralPak AD column (17.2% yield for five steps from step d to step h).

Scheme 3[a]

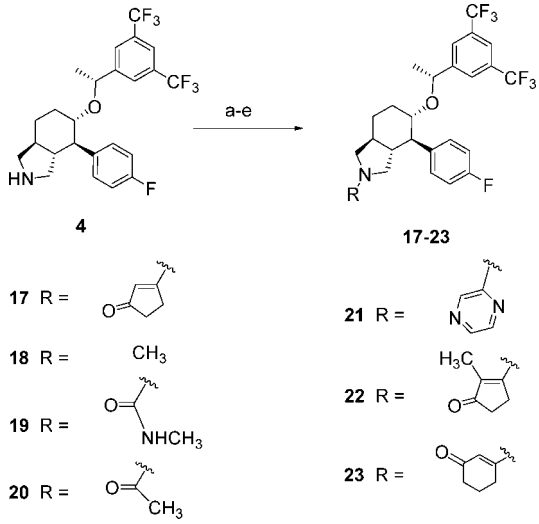


[a] Reagents: (a) cat. HBF_4−Et_2O/dichloromethane−cyclohexane (1:3), −5 to 0 °C (59%); (b) $LiBH_4$/THF, 75 °C (95%); (c) MsCl, TEA, cat. DMAP/CH_2Cl_2, −5 °C; (d) $PhCH_2NH_2$/EtOH, 150 °C (57% for two steps c and d); (e) $Pd(OH)_2$/C, H_2, 45 psi/EtOH, 20 °C (90%).

two ketone isomers which were epimerized with sodium hydroxide in acetonitrile for 10 min to give the trans−trans racemic ketone **14** as the predominant product. Racemic **14** was reduced with sodium borohydride at −78 to 20 °C to generate about 4:1 mixture of the desired all-trans alcohol **7a** and the 3,4-cis diastereomeric alcohol **7b**. The desired enantiomer **7** was separated from the mixture of **7a** and **7b** by chiral column chromatography on a ChiralPak AD column (eluted with heptane−isopropanol). The absolute configuration of the active series was shown to be compound **7** by NMR analyses of compound **17** (see Scheme 4).

The ether formation of a secondary alcohol with (1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl-2,2,2-trichloroacetimidate (**8**) has been documented in literature.[10] S_N2 reaction of the enantiomerically pure alcohol **7** with **8** in the presence of a catalytic amount of tetrafluorohydroboric acid gave ether **15** in 59% yield with generation of about 15% of the undesired more polar (1*S*)-diastereomer (Scheme 3) which was readily removed

Scheme 4[a]



[a] Reagents: (a) cyclic 1,3-diketone, cat. PTSA/toluene, 110 °C for **17**, **22**, and **23**; (b) aq CH_2O, $NaBH_3CN$/MeOH, 0 °C for **18**; (c) CH_3NCO/CH_2Cl_2, 20 °C for **19**; (d) CH_3COCl, TEA/CH_2Cl_2, 20 °C for **20**; (e) 2-Cl-pyrazine/EtOH, 120 °C for **21**.

by silica gel column chromatography. Treatment of compound **15** with lithium borohydride in refluxing THF afforded alcohol **5**, which was then converted into dimethanesulfonate by reaction with methanesulfonyl chloride at 0 °C for 5 min. The crude dimethylsulfonate was heated in a 150 °C oil bath with benzylamine (3.0 equiv) to provide bicyclic amine **16**. Finally, the *N*-benzyl group of **16** was removed by hydrogenolysis to give compound **4**. Intermediate **4** was used to make various N-substituted analogues including tertiary amine **18**, urea **19**, acetamide **20**, vinylogous amides **17**, **22**, **23**, and *N*-aryl analogue **21** using standard conditions (Scheme 4).

The final compounds and most intermediates were characterized by ^{1}H NMR and LCMS. Compound **17** was thoroughly studied by NMR with complete ^{1}H and ^{13}C NMR signal assignments being obtained by using 1D and 2D NMR techniques (COSY, NOESY, HSQC, and HMBC). The absolute configuration was assigned on the basis of the known *R*-benzyl chiral center adjacent to the ether oxygen, which was originally obtained from commercially available (1*S*)-[3,5-bis(trifluoromethyl)phenylethanol used in the preparation of imidate **8**.[10] The compound exists as two distinct rotamers around the cyclopentenone−pyrrolidine C−N bond in solution, the result of the compound being a vinylogous amide.

Results and Discussion

In Vitro Biology. The in vitro human NK_1 binding affinities for compounds in Table 1 for biological data were determined using Chinese hamster ovary (CHO) cells stably expressing the recombinant hNK_1 receptor.[11] By use of standard competitive radioligand binding techniques, the affinities of test compounds were measured using [^{125}I]substance P. All compounds in Table 1 have shown high hNK_1 receptor binding affinities. The hNK_1 receptor binding data for compounds **4**, **18**, **19**, and **20** suggested that a carbonyl group attached to the nitrogen increased the receptor affinity, and basicity of compounds **4** and **18** has no contribution to NK_1 receptor binding. High affinity for the NK_1 receptor was also seen with vinylogous amides, especially compound **17**, which had the highest affinity shown in Table 1. Vinylogous amide **23** with a six-membered ring or **22** with an α-methyl substituted five-membered ring afforded nearly

Table 1. IC_{50} for Inhibition of Binding of ^{125}I-Substance P to the hNK_1 Receptor in Vitro without and with 50% Human Serum, Inhibition of IP-1 Generation, and ID_{50} for Inhibition of GR73632-Induced Gerbil Foot Tapping by hNK_1 Antagonists

	IC_{50}, nM			ID_{50} (iv), mg/kg	
compd	hNK_1 binding	hNK_1 binding with 50% human serum	IP-1 at 100 nM (% of substance P response remaining)	1 h pretreatment	24 h pretreatment
4	0.15	7.3	44		
17	0.06	9.5	5	0.08	0.46
18	0.255	17	54		
19	0.09	9.8	58		
20	0.11	7.8	40		
21	0.525	73	79		
22	0.10	11	9	0.13	0.20
23	0.13	22	4	0.18	0.30

equipotent hNK_1 receptor affinity. However, an analogue with an aromatic ring directly attached to the pyrrolidine nitrogen atom as in compound **21** reduced the NK_1 receptor affinity about 5-fold. The inclusion of 50% human serum to the binding media decreased the affinity of most compounds in Table 1 by over 100-fold, suggesting that these compounds have high plasma protein binding. Compound **17** also showed excellent selectivity for hNK_1 over the hNK_2 and hNK_3 receptors, with affinity values of 2.4 μM for both receptors.[12]

NK_1 antagonists inhibit substance-P-evoked IP-1 formation in CHO cells stably expressing the recombinant human NK_1 receptor and can decrease the maximal response to substance P.[9] The decrease in the maximal achievable substance P response by compound **17** was concentration-dependent (Figure 1), suggesting that it acts as a noncompetitive antagonist or that it has a slow dissociation rate from the receptor. Table 1 shows the IP-1 functional activity induced by 10 μM substance P in the presence of 100 nM of test compounds. Although most of the antagonists in Table 1 have similar hNK_1 receptor binding affinities, vinylogous amides **17**, **22**, and **23** showed the most potent IP-1 functional blockade after substance P challenge up to 10 μM, with less than 10% of the substance P response remaining (i.e., insurmountable antagonism). Similar effects were observed with aprepitant but with a somewhat attenuated maximal response to substance P (about 11% of the maximal substance P response remaining with 100 nM aprepitant versus 5% for compound **17** (Figure 2). In contrast, despite its high hNK_1 binding affinity, compound **2** demonstrated only modest effects in this screen with 93% of the maximal substance P response remaining. The poor in vitro receptor blockade of

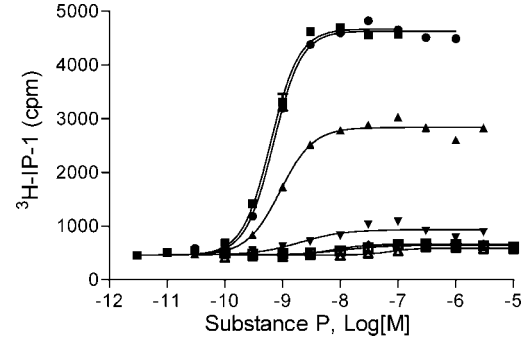


Figure 1. Functional antagonism of substance-P-induced inositol phosphate generation in CHO cells expressing human NK_1 receptors by compound **17**. Substance P, at the indicated concentrations, was incubated in the absence (squares) or presence of 0.3 nM (circles), 1 nM (triangles), 3 nM (inverted triangles), 10 nM (open squares), 30 nM (open circles), or 100 nM (open triangles) compound **17**.

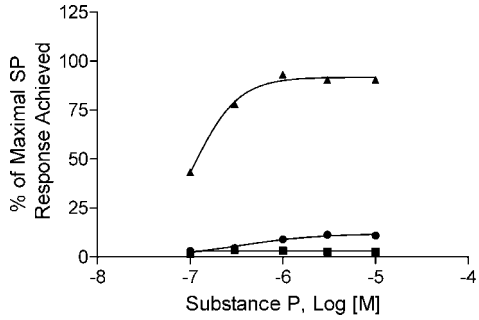


Figure 2. Comparison of the abilities of compounds **1** (aprepitant), **2**, and **17** to reduce the maximal achievable response of substance-P-induced inositol phosphate generation in CHO cells expressing human NK_1 receptors. Substance P, at the indicated concentrations, was incubated in the presence of 100 nM each of **1** (circles), **2** (triangles), or **17** (squares).

compound **2** was likely due to a rapid off-rate from the hNK_1 receptor ($t_{1/2}$ of 13 min versus 154 min for aprepitant, data not shown).

In Vivo Biology. In vivo activity of the targeted NK_1 receptor antagonists was assessed in gerbils, a species with NK_1 receptor pharmacology similar to that of human.[13] In this study, icv administration of the NK_1 agonist GR73632[13] (**24**) in gerbils elicits a vigorous, repetitive hind foot tapping response, which can be blocked by brain penetrant NK_1 antagonists but not by nonbrain penetrant antagonists.[14] Therefore, this in vivo assay provides a convenient measure of CNS penetration and antagonist efficacy. Selected compounds with both good hNK_1 receptor binding affinity and potent IP-1 activity were further evaluated in the gerbil assay. All three vinylogous amides **17**, **22**, and **23** in Table 1 showed good in vivo activity inhibiting foot tapping induced by the NK_1 agonist **24** after iv administration. The ID_{50} values ranged from 0.08 to 0.18 mg/kg after 1 h and from 0.20 to 0.46 mg/kg after 24 h of pretreatment.

The data encouraged the further characterization of compound **17**. Plasma IC_{50} values of **17** in the gerbil foot tapping assay were 6.5 nM at 1 h and 6 nM at 24 h, which means that about 6 nM compound **17** in plasma can block 50% of NK_1 agonist **24** induced gerbil foot tapping after single iv 1 and 24 h pretreatments. Thus, low plasma levels of compound **17** were able to drive and maintain complete inhibition of NK_1 agonist **24**-induced foot tapping. The results also indicate that this compound has rapid and high brain penetration in the gerbil with long central duration of action.

In rhesus monkey PET studies to determine brain NK_1-receptor occupancy,[15] compound **17** showed good receptor occupancy at low plasma concentration. Occupancy was determined by comparing NK_1 PET ligand, [^{18}F]SPARQ,[15] binding in the striatum before and after dosing with the test compound to a plasma steady state level. The protocol used was designed to minimize changes in occupancy during image acquisition by minimizing changes in plasma level of the test compound during the PET study. Thus, a steady state plasma concentration of the compound was established using an iv bolus plus a matched constant iv infusion of the compound prior to the bolus administration of [^{18}F]SPARQ with the test compound infusion being continued for the entire PET imaging. Results from this protocol are expected to be more predictive of occupancy results in clinical studies after chronic oral dosing with NK_1 antagonists to plasma steady state levels. As shown in Figure 3, compound **17** achieved 90% receptor occupancy at a plasma steady state concentration of 37 ng/mL (67 nM) and 50% occupancy at 5 ng/mL (9 nM). The plasma level necessary to achieve ≥90% occupancy with aprepitant was 470 ng/mL (900 nM), while a level of 51 ng/mL (96 nM) corresponded to 50% occupancy. For compound **2**, ≥ 90% occupancy was achieved at 390 ng/mL (780 nM), while a level of 31 ng/mL (62 nM) corresponded to 50% occupancy (historical data).[15]

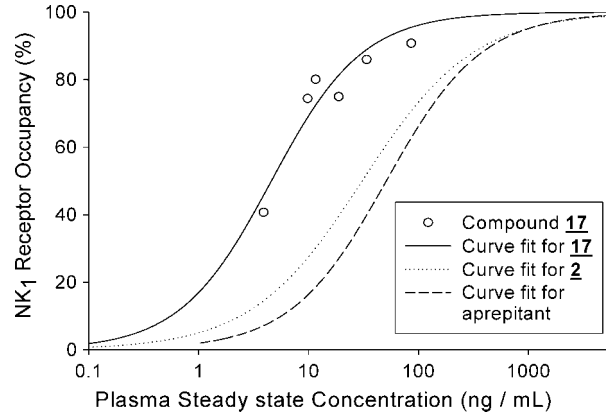


Figure 3. NK_1 receptor occupancy in rhesus brain determined by PET for compounds **2** and **17** and aprepitant. All curves were fit to a three-parameter Hill equation with the Hill coefficients equal to ~0.9 for compound **2** and ~1 for both compound **17** and aprepitant, respectively.

Table 2. Pharmacokinetics of Compound **17** after Intravenous and Oral Administration[a]

pharmacokinetic parameter	species		
	rat	dog	monkey
CL_p ((mL/min)/kg)	0.7	0.7	1
Vd_{ss} (L/kg)	1.5	2.0	2.0
$T_{1/2}$ (h)	24	31	24
F (%)	40	71	69
oral $AUC_{norm(0-\infty)}$ (μM·h per mg/kg)	13	27	18

[a] Pharmacokinetics were determined at doses of 1 mg/kg iv and 2 mg/kg po in rats and at 0.5 mg/kg iv and 1 mg/kg po in dogs and monkeys. Oral pharmacokinetics were determined using a solution formulation in ethanol/PEG400/water (20:40:40, v/v/v).

Pharmacokinetics. The pharmacokinetics of compound **17** in preclinical species was characterized by a low systemic plasma clearance, extended plasma half-life, and good oral bioavailability (see Table 2) in three species which indicate the possibility for once daily dosing in man.

Ancillary Activity Profile. Compound **17** was a weak reversible inhibitor of human CYP-3A4, 2C8, 2C9, 2C19, 2D6, and 1A2 enzymes, the IC_{50} values of which were 39, 58, 30, 29, 35, and >100 μM, respectively. Compound **17** did not significantly induce CYP-3A4 mRNA in three individual preparations of human hepatocytes. These data suggested that compound **17** should have minimal potential for drug−drug interactions in humans. Although broad-based counterscreening of compound **17** in more than 145 assays identified a number of weak activities between 1 and 10 μM, no assays for which $IC_{50} < 1$ μM were observed. Therefore, off-target activities were more than 20000-fold less potent than hNK_1 activity.

Conclusion

Hydroisoindoline-based compound **17** is a potent, nonbasic, brain-penetrant hNK_1 antagonist with a long duration of action. It showed 10-fold greater potency in rhesus PET receptor occupancy study relative to aprepitant. Compound **17** also displayed a significantly improved CYP-3A4 inhibition and

induction profile compared to aprepitant. The rigid structure of **17** afforded appreciable stability toward human liver microsomal incubation in vitro and imparted favorable in vitro and in vivo properties relative to aprepitant. Compound **17** was chosen for further development studies, the results of which will be described in the future.

Experimental Section

General. Unless specified otherwise, all materials were purchased from commercial sources and used as received. ^{1}H and ^{13}C NMR spectra were recorded on Varian 500 or Varian 600. Purity of compounds **17**−**19** and intermediate **4** for NK_1 receptor binding and gerbil foot tapping assays was determined by open access LCMS analysis (Agllent 110 system, linear gradient program using water−0.05%TFA as solvent A and acetonitrile−0.05% TFA as solvent B; t = 0 min, 10% B; t = 7 min, 100% B; flow rate, 1 mL/min; UV detection, 220 nm) as ≥95% pure and was confirmed by ^{1}H NMR before the samples were sent for testing. The ≥99.5% purity of PET sample of **17** was determined by an analytic group in house. The 100% enantiopurity of compound **17** was confirmed by chiral HPLC on four different chiral columns (Shimadzu system, 4.6 nm × 250 nm, hexane/isopropanol): ChiralCel OD, ChiralCel OJ, CiralPak AS, and ChiralPak AD.

1-(4-Fluorophenyl)but-3-en-2-one (12). To a solution of 4-fluorophenylacetic acid **11** (16.7 g, 108.4 mmol) in dry methylene chloride (200 mL) under nitrogen was added hydrogen chloride salt of *N,O*-dimethylhydroxylamine (13.8 g, 141.5 mmol), triethylamine (20 mL, 143.7 mmol), 4-dimethylaminopyridine (14.2 g, 119.3 mmol), and EDC (27 g, 140.6 mmol). The reaction mixture was stirred at room temperature for 4 h. The mixture was washed consecutively with hydrochloric acid (2 N), brine, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried ($MgSO_4$) and concentrated under vacuum to give a crude 2-(4-fluorophenyl)-*N*-methoxy-*N*-methylacetamide (21 g),which was used without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (2 H, m), 7.02 (2 H, m), 3.77 (2 H, s), 3.65 (3 H, s), 3.21 (3 H, s). To a solution of vinylmagnesium bromide (220 mL, 1.0 M) in THF (100 mL) was added dropwise under nitrogen at 0 °C a solution of 2-(4-fluorophenyl)-*N*-methoxy-*N*-methylacetamide (21 g, 106.6 mmol) in ether (150 mL). The mixture was stirred at 0 °C for 0.5 h, then poured slowly into a mixture of ice (150 g) and hydrochloric acid (2 N, 300 mL). The resulting mixture was diluted with ether (200 mL). The organic layer was separated, and the aqueous was extracted with ether. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated under vacuum to give the crude title compound (14.2 g, 80% for two steps), which was used without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.19 (2 H, m), 7.02 (2 H, t, J = 9.5 Hz), 6.42 (1 H, dd, J_1 = 14.2 Hz, J_2 = 11 Hz), 6.34 (1 H, d, J = 14.2 Hz), 5.86 (1 H, d, J = 11 Hz), 3.87 (2 H, s).

1*E* and 1*Z*-*tert*-Butyl{[1-(4-fluorobenzylidene)prop-2-en-1-yl]oxy}-dimethylsilane (10). To a solution of potassium *tert*-butoxide (1.0 M in THF, 104 mL) in THF (100 mL) under nitrogen at −78 °C was added a solution of 1-(4-fluorophenyl)but-3-en-2-one (**12**, 14.2 g, 86.6 mmol) and *tert*-butylchlorodimethylsilane (13.0 g, 86.6 mmol) in THF (100 mL). The reaction mixture was stirred at −78 °C for 6 h, then at room temperature for 6 h. The mixture was quenched with water (50 mL) and diluted with hexanes (150 mL), and the organic layer was separated. The organic layer was washed with brine and dried ($MgSO_4$), and the solvent was evaporated under vacuum to give the crude title compounds (20.5 g, 85.1% as the crude product), which were used without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (2 H, m), 6.98 (2 H, m), 6.33 (1 H, dd, J_1 = 13.2 Hz, J_2 = 8.5 Hz), 5.97 (1 H, s), 5.52 (1 H, d, J = 13.2 Hz), 5.17 (1 H, d, J = 8.5 Hz).

Diethyl 4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-(4-fluorophenyl)cyclohex-4-ene-1,2-dicarboxylate (13). A solution of compound **10** (37 g, ∼80% pure, 133.1 mmol) and diethyl (2*E*)-but-2-enedioate (18 g, 104.6 mmol) in xylenes (200 mL) under nitrogen was heated in a 150−160 °C oil bath for 5 h. The solvent was evaporated under vacuum to give an oil which was used without further purification.

Racemic Diethyl (1*S*,2*S*,3*R*)-3-(4-Fluorophenyl)-4-oxocyclohexane-1,2-dicarboxylate and Diethyl (1*R*,2*R*,3*S*)-3-(4-Fluorophenyl)-4-oxocyclohexane-1,2-dicarboxylate (14). To a solution of intermediate **13** in acetonitrile (30 mL) in a plastic reaction flask was added a solution of HF in acetonitrile (2.5 M, 200 mL) at room temperature. The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was added to a mixture of sodium hydroxide (5.0 N, 125 mL) and ice (100 g), then stirred for 10 min. The resulting mixture was diluted with ether (300 mL), and the organic layer was separated. The aqueous layer was saturated with sodium chloride and extracted with an additional portion of ether. The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvent was evaporated under vacuum to give the crude title compounds (40.8 g). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.10 (2 H, m), 7.05 (2 H, m), 4.23−4.15 (2 H, m), 3.90−3.80 (3 H, m), 3.32 (1 H, td, J_1 = 13.0 Hz, J_2 = 4.0 Hz), 3.21 (1 H, t, J = 12.9 Hz), 2.68 (2 H, m), 2.55 (1 H, m), 2.07 (1 H, m), 1.30 (3 H, t, J = 7.2 Hz), 0.85 (3 H, t, J = 7.2 Hz).

Mixture of All-*trans*-Racemic Diethyl 3-(4-Fluorophenyl)-4-hydroxycyclohexane-1,2-dicarboxylate (7a) and 3,4-*cis*-Diethyl (3-(4-Fluorophenyl)-4-hydroxycyclohexane-1,2-dicarboxylate (7b). To a solution of the crude intermediate (**14**, 40.2 g, 119.3 mmol) in methanol (150 mL) was added $NaBH_4$ powder (4.1 g, 108.5 mmol) under nitrogen at −78 °C. The resulting mixture was stirred at −78 °C for 2 h. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature, then stirred for 2 h. The reaction was carefully quenched by the addition of 30 mL of water and acidified with hydrochloric acid (2 N). The resulting mixture was diluted with ether, and the organic layer was separated. The aqueous layer was saturated with sodium chloride and extracted with an additional portion of ether. The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvent was evaporated under vacuum. The residue was dissolved in ether, washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under vacuum to give the crude title compounds which were preliminarily purified by column chromatography (4:1 hexane/ethyl acetate) to afford a 21 g mixture for the chiral separation.

Diethyl (1*S*,2*S*,3*R*,4*S*)-3-(4-Fluorophenyl)-4-hydroxycyclohexane-1,2-dicarboxylate (7). An amount of 21 g of the racemic mixture of diethyl (1*S*,2*S*,3*R*,4*S*)-3-(4-fluorophenyl)-4-hydroxycyclohexane-1,2-dicarboxylate and diethyl (1*R*,2*R*,3*S*,4*R*)-3-(4-fluorophenyl)-4-hydroxycyclohexane-1,2-dicarboxylate was separated by preparative chiral HPLC using ChiralPak AD column, eluting with heptanes/*i*-PrOH (9/1) to afford 9.09 g (20.2% yield for four steps and 17.2% for five steps from diene **10**) of the desired first eluting isomer diethyl (1*S*,2*S*,3*R*,4*S*)-3-(4-fluorophenyl)-4-hydroxycyclohexane-1,2-dicarboxylate. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25 (2 H, m), 7.05 (2 H, t, J = 8.2 Hz), 4.20−4.05 (2 H, m), 3.85−3.72 (3 H, m), 2.85 (2 H, m), 2.70 (1 H, t, J = 7.8 Hz), 2.25 (2 H, m), 1.70 (1 H, m), 1.60 (1 H, m), 1.25 (3 H, t, J = 7.2 Hz), 0.85 (3 H, t, J = 7.2 Hz).

(1*S*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl-2,2,2-trichloroethanimidoate (8). To a solution of (1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethanol (25.8 g, 100 mmol) in ether (200 mL) under nitrogen atmosphere was added DBU (3 mL, 20 mmol) at 0 °C. After the mixture was stirred at 0 °C for 10 min, trichloroacetonitrile (15 mL, 150 mmol) was added dropwise over 15 min. The resulting mixture was stirred at 0 °C for 2 h, during which time it became deep-yellow in color. The volatiles were removed under vacuum in a water bath (<35 °C) to give a pale-brown mobile liquid which was purified by column chromatography on silica gel (3 in. × 10 in. pad) in two batches, eluting with hexanes/EtOAc (9/1) and then hexanes/EtOAc (4/1). The product fractions were combined and the solvent removed under vacuum to give 37.5 g (93.6% yield) of the title compound as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.74 (3 H, d, J = 6.5 Hz), 6.07 (1 H, q, J = 6.5 Hz), 7.82 (1 H, s), 7.86 (2 H, s), 8.40 (1 H, br s) ppm.

Diethyl (1*S*,2*S*,3*R*,4*S*)-4-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)cyclohexane-1,2-dicarboxylate (15). To a solution of the enantiomer **7** (9.09 g, 26.9 mmol)) and imidate **8** (21.5 g, 53.5 mmol) in cyclohexane/1,2-chloroethane (3/1, 250 mL) under nitrogen atmosphere at −5 °C was added HBF_4 (54% in ether, 0.51 mL, 3.58 mmol). The reaction mixture was stirred at −5 to 0 °C for 24 h, then diluted with ether. The mixture was washed with saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), and the solvent was evaporated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/hexanes (1/4) to give 9.2 g (59.2% yield) of the title compound. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (1 H, s), 7.20 (2 H, s), 7.00 (2 H, m), 6.85 (2 H, t, J = 8.5 Hz), 4.43 (1 H, q, J = 6.0 Hz), 4.20−4.10 (2 H, m), 3.80−3.73 (2 H, m), 3.36 (1 H, m), 2.90−2.76 (2 H, m), 2.40 (1 H, m), 2.28 (1 H, m), 1.63−1.55 (2 H, m), 1.33 (3 H, d, J = 6.0 Hz), 1.25 (3 H, t, J = 7.2 Hz), 0.82 (3 H, t, J = 7.2 Hz). Unreacted starting alcohol could be recovered by flushing the column with EtOAc and reused in the above reaction.

[(1*S*,2*R*,3*R*,4*S*)-4-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)cyclohexane-1,2-diyl]dimethano (5). To a solution of diethyl (1*S*,2*S*,3*R*,4*S*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)cyclohexane-1,2-dicarboxylate (9.2 g, 15.9 mmol) in THF (100 mL) under nitrogen atmosphere at room temperature was added $LiBH_4$ powder (2 g, 112.4 mmol, excess). The resulting mixture was heated at 75 °C for 2 h. The reaction mixture was quenched by dropwise addition of water (30 mL). The mixture was stirred for 0.5 h, and then hydrochloric acid (2 N, 100 mL) was carefully added. The mixture was diluted with ethyl acetate (150 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated under vacuum to give 7.5 g (95% yield) of the crude diol as an oil which was used without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (1 H, s), 7.20 (2 H, s), 7.00 (2 H, m), 6.87 (2 H, t, J = 8.2 Hz), 4.20 (1 H, q, J = 6.0 Hz), 3.78 (1 H, m), 3.67 (1 H, m), 3.52 (1 H, m), 3.30−3.20 (2 H, m), 2.58 (1 H, t, J = 11.9 Hz), 2.32 (1 H, m), 1.87 (1 H, m), 1.65 (1 H, m), 1.58−1.35 (3 H, m), 1.30 (3 H, t, J = 6.0 Hz).

(3a*R*,4*R*,5*S*,7a*S*)-2-Benzyl-5-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-4-(4-fluorophenyl)octahydro-1*H*-isoindole (16). To a solution of [(1*S*,2*R*,3*R*,4*S*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)cyclohexane-1,2-diyl]dimethanol (**5**, 2.82 g, 85% pure, 4.9 mmol) in methylene chloride (50 mL) cooled to −5 °C in an ice/salt bath was added methanesulfonyl chloride (1.0 mL), triethylamine (2.1 mL), and DMAP (44 mg). The reaction mixture was stirred at −5 °C for 10 min, then quenched with hydrochloric acid (2 N, 50 mL) at the same temperature. The organic layer was separated, and the aqueous layer was extracted with additional methylene chloride (50 mL). The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvent was evaporated under vacuum to give [(1*S*,2*R*,3*R*,4*S*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)cyclohexane-1,2-diyl]di(methylene) dimethanesulfonate as an oil which was used without further purification. In a pressure tube was placed a solution of crude [(1*S*,2*R*,3*R*,4*S*)-4-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)cyclohexane-1,2-diyl]di(methylene) dimethanesulfonate (from 2.82 g of crude diol) in ethanol (20 mL) and benzylamine (1.2 mL, excess). The pressure tube was sealed and heated at 150 °C in an oil bath for 3 h. The mixture was cooled to room temperature and was stirred with NaOH (2 N, 20 mL) for 5 min. The volatiles were removed under vacuum. The residue was diluted with 100 mL of ethyl acetate, washed with brine, dried over $MgSO_4$, and the solvent was evaporated under vacuum. The residue was purified by column chromatography on silica gel, eluting with EtOAc to give 1.6 g (57.0% for two steps) of the title compound. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (1 H, s), 7.35−7.20 (5 H, m), 7.20 (2 H, s), 6.97 (2 H, m), 6.85 (2 H, t, J = 8.2 Hz), 4.42 (1 H, t, J = 6.0 Hz), 3.75 (2 H, d, J = 13.4 Hz), 3.50 (2 H, d, J = 13.4 Hz), 3.30 (1 H, m), 2.96 (1 H, m), 2.52 (3 H, m), 2.19 (2 H, m), 1.98 (1 H, m), 1.97 (1 H, m), 1.86 (2 H, m), 1.57 (1 H, m), 1.33 (3 H, t, J = 6..5 Hz), 1.30 (1 H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.6 (d, J = 245.6 Hz), 146.2, 137.1, 131.3 (q, J = 32.7 Hz), 129.0, 128.7, 128.4, 127.1, 126.3, 123.2 (q, J = 272.5 Hz), 121.3, 115.2, 115.0, 81.0, 74.9, 61.3, 61.2, 58.1, 58.9, 53.2, 49.0, 44.2, 32.1, 26.6, 24.4. MS: $(MH)^+$ 566.2238 (566.2294).

(3a*R*,4*R*,5*S*,7a*S*)-5-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy}-4-(4-fluorophenyl)octahydro-1*H*-isoindole (4). To a solution of (3a*R*,4*R*,5*S*,7a*S*)-2-benzyl-5-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-4-(4-fluorophenyl)octahydro-1*H*-isoindole (**16**) (0.5 g, 0.88 mmol) in EtOH (50 mL) was added $Pd(OH)_2C$ (0.2 g, 20% by weight). The reaction mixture was hydrogenated at 50 psi for 16 h at room temperature. The catalyst was filtered and the solvent of the filtrate was evaporated under vacuum to give the title compound (0.38 g, 90% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (1 H, s), 7.20 (2 H, s), 6.95 (2 H, m), 6.87 (2 H, t, J = 8.5 Hz), 4.42 (1 H, q, J = 6.5 Hz), 3.31 (2 H, m), 2.80 (1 H, m), 2.65 (1 H, m), 2.50 (2 H, m), 2.40 (1 H, m), 2.05 (1 H, m), 1.77 (2 H, m), 1.53 (1 H, m), 1.31 (2 H, d, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.7(d, J = 245.6 Hz), 145.8, 136.0, 131.36 (q, J = 33.6 Hz), 128.6, 126.2, 123.1 (q, J = 272.5 Hz), 121.4, 115.4, 115.2, 80.2, 74.9, 52.4, 49.4, 48.9, 48.2, 43.8, 31.5, 25.5, 24.3. MS: $(MH)^+$ 476.1810 (476.1824).

3-[(3a*R*,4*R*,5*S*,7a*S*)-5-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy}-4-(4-fluorophenyl)octahydro-1*H*-isoindol-2-yl]cyclopent-2-en-1-one (17). To a solution of amine **4** (0.73 g, 1.5 mmol) in toluene (25 mL) was added cyclopentane-1,3-dione (0.18 g, 1.8 mmol) and *p*-toluenesulfonic acid (0.03 g, 0.15 mmol). The mixture was heated at reflux for 2 h, and the reaction was monitored by LCMS. The solvent was removed under vacuum, and the residue was purified by preparative TLC, eluting with $CHCl_3$/2 N NH_3 in MeOH (9/1) to afford 0.49 g (0.88 mmol, 57%) of the title compound. The compound could be crystallized (mp = 216.5−217.5 °C) from hexanes/EtOAc or hexanes/EtOH. ^{1}H NMR (CD_3CN, 600 MHz) δ 7.71 (1 H, s), 7.23 (2 H, s), 7.00 (2 H, m), 6.93 (2 H, t, J = 8.2 Hz), 4.89, 4.48 (1 H, s), 4.47 (1 H, m), 3.71, 3.48 (1 H, m), 3.35 (1 H, m), 3.28−3.17 (1 H, m), 2.95 (1 H, m), 2.95, 2.81 (1 H, m), 2.68 (2 H, m), 2.45 (2 H, m), 2.37 (2 H, m), 2.15 (1 H, m), 1.93 (2 H, m), 1.60 (1 H, m), 1.38 (1 H, m), 1.36 (3 H, t, J = 6.0 Hz). ^{13}C NMR(CD_3CN, 150 Mz) 201.8, 175.3, 161.6 (d, J_{CF} = 243 Hz), 147.1, 137.60, 130.7 (q, J_{CF} = 33 Hz), 129.4, 126.9, 123.7 (q, J_{CF} = 272 Hz), 121.3, 114.9, 98.5, 80.5, 74.7, 54.2, 52.9, 52.5, 52.5, 51.2, 48.3, 43.5, 34.0, 31.7, 27.4, 25.6, 23.7, 11.9. MS: $(MH)^+$ 556.2081 (556.2087).

(4*R*,5*S*)-5-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy}-4-(4-fluorophenyl)-2-methyloctahydro-1*H*-isoindole (18). To a solution of amine **4** (0.025 g, 0.055 mmol) and aqueous formaldehyde (0.008 mL, 37% aqueous, 0.107 mmol) in methanol was added potassium acetate (15.5 mg, 0.158 mmol) and sodium cyanoborohydride (6.7 mg, 0.105 mmol) at 0 °C. The mixture was stirred at room temperature for 0.5 h, diluted with ether, and washed with brine. The organic layer was separated, dried over $MgSO_4$, and concentrated. The mixture was purified by preparative TLC (ethyl acetate, 23 mg, 89%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (1 H, s), 7.22 (2 H, s), 7.00 (2 H, m), 6.88 (2 H, t, J = 8.5 Hz), 4.43 (1 H, q, J = 6.5 Hz), 3.33 (2 H, m), 2.78 (2 H, m), 2.66 (1 H, m), 2.64 (3 H, s), 2.55 (1 H, t, J = 10.5 Hz), 2.42 (1 H, m), 2.08 (1 H, m), 2.00 (2 H, m), 1.58 (1 H, m), 1.37 (1 H, m), 1.33 (3 H, d, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.8 (d, J = 245.7 Hz), 145.8, 135.7, 131.3 (q, J = 33.6 Hz), 128.6, 126.1, 123.1 (q, J = 273.1 Hz), 121.4, 115.5, 115.4, 80.0, 75.0, 60.0, 58.8, 52.4, 48.7, 43.8, 43.1, 31.5, 25.7, 24.3. MS: $(MH)^+$ 490.2000 (490.1981).

(3a*R*,4*R*,5*S*,7a*S*)-5-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy}-4-(4-fluorophenyl)-*N*-methyloctahydro-2*H*-isoindole-2-carboxamide (19). To a solution of amine **4** (20 mg, 0.042 mmol) in methylene chloride (2 mL) at room temperature was added several drops of methyl isocyanate. The resulting mixture was stirred at room temperature for 2 h. Several drops of NaOH (2 N) were added to the reaction mixture. The organic layer was separated and dried over $MgSO_4$, and the solvent was removed under vacuum. The residue was purified by preparative TLC, eluting with EtOAc (18 mg, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (1 H, s), 7.23 (2 H,

s), 6.98 (2 H, m), 6.85 (2 H, m), 4.45 (1 H, m), 4.00 (1 H, m), 3.68 (1 H, m), 3.36 (1 H, m), 3.08 (1 H, m), 2.93 (1 H, m), 2.77 (3 H, s), 2.76 (1 H, m), 2.55 (1 H, m), 2.45 (1 H, m), 2.10 (1 H, d, J = 12.5 Hz), 1.82 (2 H, m), 1.60 (1 H, m), 1.30 (1 H, m). 1.30 (3 H, d, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.7 (d, J = 245.6 Hz),157.4, 146.0, 136.4, 131.1 (q, J = 33.6 Hz), 128.7, 126.2, 124.3, 123.1 (q, J = 272.5 Hz), 121.4, 115.4, 115.2, 80.4, 74.8, 52.8, 50.7, 49.4, 49.0, 43.7, 31.7, 27.3, 27.2, 26.1, 26.0, 24.4. MS: $(MH)^+$ 533.2047 (533.2039).

(4*R*,5*S*)-2-Acetyl-5-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-4-(4-fluorophenyl)octahydro-1*H*-isoindole (20). To a solution of amine **4** (50 mg, 0.105 mmol) in dichloromethane were added acetyl chloride (0.015 mL, 0.21mmol), trimethylamine (0.032 mL, 0.23 mmol), and a catalytic amount of DMAP. The solution was stirred at room temperature for 0.5 h and washed with 2 N hydrochloric acid and brine. The organic layer was dried over $MgSO_4$, and the solvent was removed under vacuum. The residue was purified by preparative TLC (1:1 ethyl acetate/hexane, 45 mg, 83%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (1 H, s), 7.23 (2 H, s), 6.98 (2 H, m), 6.89 (2 H, m), 4.46 (1 H, m), 3.88, 3.66 (1 H, m), 3.37, 2.78 (1 H, m), 3.36 (1 H, m), 3.10 (1 H, m), 2.55 (1 H, m), 2.42 (1 H, m), 2.10 (1 H, m), 2.01, 1.88 (3 H, two singlets), 11.88 (1 H, m), 1.62 (1 H, m), 1.34 (3 H, d, J = 6.9 Hz), 1.34 (1 H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7 169.5, 163.7 (d, J = 245.6 Hz), 145.9, 136.2, 136.1, 131.4 (q, J = 33.5 Hz), 128.7, 126.1, 123.1 (q, J = 272.5 Hz), 121.4, 115.6, 115.3, 80.2, 80.1, 74.8, 52.7, 52.5, 51.3, 50.5, 49.5, 49.1, 48.0, 44.2, 42.8, 31.6, 26.0, 24.3, 21.9. MS: $(MH)^+$ 518.1933 (518.1930).

(4*R*,5*S*)-5-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy}-4-(4-fluorophenyl)-2-pyrazin-2-yloctahydro-1*H*-isoindole (21). A solution of amine **4** (50 mg, 0.105 mmol) and pyrazine chloride (120 mg, 1.05 mmol) in ethanol was heated in a sealed tube in a 120 °C oil bath for 5 h. The solvent was removed, and the residue was purified by preparative TLC (ethyl acetate, 46 mg, 79%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (1 H, s), 7.77 (2 H, s), 7.76 (1 H, s), 7.30 (1 H, s), 7.05 (2 H, m), 6.90 (2 H, m), 4.47 (1 H, q, J = 6.5 Hz), 3.80 (1 H, m), 3.41 (1 H, m), 3.30 (1 H, m), 3.09 (1 H, m), 2.93 (1 H, m), 2.65 (1 H, m), 2.48 (1 H, m), 2.20 (1 H, m), 2.00 (2 H, m), 1.68 (2 H, m), 1.45 (2 H, m), 1.35 (3 H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.8 (d, J = 245.6 Hz), 152.9, 146.0, 142.1, 136.5, 131.5, 131.4 (q, J = 33.6 Hz), 130.4, 128.8, 126.2, 122.8 (q, J = 272.6 Hz), 121.4, 115.5, 115.3, 80.5, 74.9, 52.9, 51.4, 50.3, 48.8, 43.9, 31.8, 26.3, 24.4. MS: $(MH)^+$ 554.2048 (554.2042).

3-[(4*R*,5*S*)-5-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy}-4-(4-fluorophenyl)octahydro-2*H*-isoindol-2-yl]-2-methylcyclopent-2-en-1-one (22). 22 was prepared in 53% yield following the procedure for compound **17**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (1 H, s), 7.23 (1 H, s), 7.00 (2 H, m), 6.90 (2 H, m), 4.47 (1 H, q, J = 6.5 Hz), 3.37 (2 H, m), 2.55 (1 H, m), 2.50−2.13 (5 H, m), 2.15 (1 H, m), 1.95−1.70 (5 H, m), 1.60 (1 H, m), 1.20 (1 H, m), 1.18 (3 H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 203.2, 170.8, 161.7 (d, J = 245.7 Hz), 145.9, 136.1, 131.3 (q, J = 33.7 Hz), 130.9, 128.6, 128.4, 126.1, 123.1 (q, J = 272.5 Hz), 121.4, 115.4, 115.3, 107.3, 80.2, 74.8, 54.3, 53.1, 52.5, 32.6, 31.5, 27.6, 26.0, 25.9, 24.3, 8.8. MS: $(MH)^+$ 570.2235 (570.2243).

3-[(4*R*,5*S*)-5-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy}-4-(4-fluorophenyl)octahydro-2*H*-isoindol-2-yl]cyclohex-2-en-1-one (23). 23 was prepared in 45% yield following the procedure for compound **17**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (1 H, s), 7.29, 7.24 (2 H, two singlets), 6.98 (2 H, m), 6.93 (1 H, m), 5.0, 4.81 (1 H, m), 4.45 (1 H, m), 3.70, 3.47 (1 H, two multiples), 3.36 (1 H, m), 3.15, 3.08 (1 H, two multiples), 2.92 (1 H, m), 2.87, 2.70 (1 H, two multiples), 2.55 (1 H, m), 2.30−2.50 (3 H, m), 2.15 (3 H, m), 2.12 (1 H, m), 2.00−1.90 (4 H, m), 1.60 (1 H, m), 1.35 (1 H, m), 1.34 (3 H, d, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 1916.2, 196.0, 163.6, 163.3, 161.7 (d, J = 245.6 Hz), 145.9, 136.1, 135.9, 131.4 (q, J = 33.6 Hz), 128.5, 126.4, 126.2, 123.1 (q, J = 272.5 Hz), 121.4, 115.5, 115.3, 98.4, 98.3, 98.2, 80.2, 79.9, 74.9, 74.8, 52.8, 52.7, 52.6, 52.0, 51.7, 48.5, 48.2, 43.6, 43.0, 35.8, 35.7, 31.6, 31.6, 27.6, 27.4, 26.0, 25.0, 24.3, 22.0, 21.9. MS: $(MH)^+$ 570.2237 (570.2243).

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Supporting Information Available: Complete ^{1}H and ^{13}C NMR signal assignments of compound **17** by using 1D and 2D NMR techniques (COSY, NOESY, HSQC, and HMBC); ^{1}H and ^{13}C NMR spectra of compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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