New Spiropiperidines as Potent and Selective Non-Peptide Tachykinin NK_2 Receptor Antagonists

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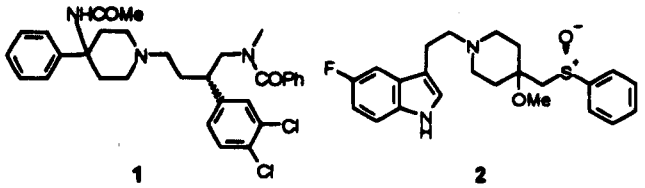
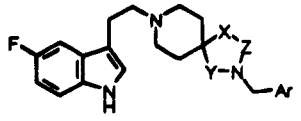
The synthesis of a series of 2-(5-fluoro-1*H*-indol-3-yl)ethyl spiropiperidines is described together with their tachykinin NK_2 receptor affinities measured in a rat colon binding assay. Equivalent NK_2 receptor binding affinity was observed for the spirooxazolidinone 3-benzyl-8-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-1-oxa-3,8-diazaspiro[4.5]decan-2-one (**3a**), the imidazolidinone 3-benzyl-8-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-1,3,8-triazaspiro[4.5]decan-2-one (**3s**), and the pyrrolidinone 2-benzyl-8-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-2,8-diazaspiro[4.5]decan-3-one (**3t**). Substitution in the phenyl ring of compound **3a** produced no significant enhancement in NK_2 binding affinity. Replacement of the phenyl ring in **3a** with other aromatic rings resulted in a significant loss in binding affinity. Compound **3a** was shown to be a potent NK_2 receptor antagonist in guinea pig trachea where it also demonstrated 1000-fold selectivity for NK_2 receptors over NK_1. In the anesthetized guinea pig, compound **3a** administered by the intravenous or oral route displayed potent and long-lasting antagonist activity against NK_2 receptor agonist induced bronchoconstriction.

Introduction

The tachykinin neuropeptides substance P (SP), neurokinin A (NKA), and neurokinin B (NKB), acting at NK_1, NK_2, and NK_3 receptors, respectively, play a key role in a wide range of biological processes. These include pain transmission, vasodilatation, smooth muscle contraction, salivary secretion, bronchoconstriction, emesis, activation of the immune system, neurogenic inflammation, and anxiety.[1-6] Hence, the identification of new potent and selective non-peptide antagonists for tachykinin receptors is a goal of potentially great importance in a number of therapeutic areas. However, while there have been numerous recent reports describing non-peptide NK_1 antagonists,[7] there remain relatively few examples of potent and selective non-peptide NK_2 antagonists in the literature. Currently, the most potent non-peptide NK_2 antagonists which have been described are SR 48986 (**1**)[8] and the 2-(5-fluoro-1*H*-indol-3-yl)ethyl-containing sulfoxide GR 159897 (**2**).[9] Sulfoxide **2** was discovered as a result of a program of activity optimization based on initial leads with weak NK_2 affinity identified by directed screening of our in-house compound archive. The original notion used in this optimization process was that both a phenyl ring and an indole were required for efficient NK_2 receptor binding. This hypothesis arose from early work on low molecular weight NK_2 antagonists derived from peptides.[10,11] During the course of our studies based on this initial hypothesis, in addition to GR 159897 (**2**), we have discovered a further series of potent NK_2 antagonists. Compounds in this new series are spiropiperidine derivatives of general formula **3**. They are structurally related to compound **2** in that they retain the 2-(5-fluoro-1*H*-indol-3-yl)ethylamine moiety and also contain a second aromatic ring. In this paper we report the synthesis and NK_2 receptor affinities of compounds **3a**–**v** which illustrate this new class of non-peptide NK_2 antagonist.





Chemistry

Synthesis of Oxazolidinones 3a–q. The spiro-fused oxazolidinone derivatives **3a–q** were prepared according to the route outlined in Scheme **1**. *N*-tBoc-piperidone (**4a**) was converted to the key intermediate **5** in three stages. Initially **4a** was reacted with the lithium enolate of ethyl acetate. Secondly, the adduct ethyl ester formed in the first stage was hydrolyzed with aqueous sodium hydroxide, and finally, the cyclization to the spirooxazolidinone was achieved by treatment of the hydroxy acid with diphenyl phosphorazidate (DPPA).[12] In the last stage, an initial Curtius rearrangement occurs, and the intermediate isocyanate is trapped by the hydroxyl group in an intramolecular reaction. The three steps described above are routinely carried out without any purification of the intermediates, and **5** can be isolated analytically pure without any chromatography. To prepare the target compounds **3a–q**,

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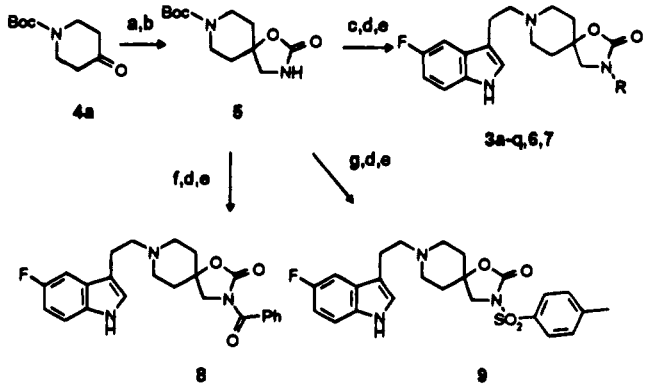
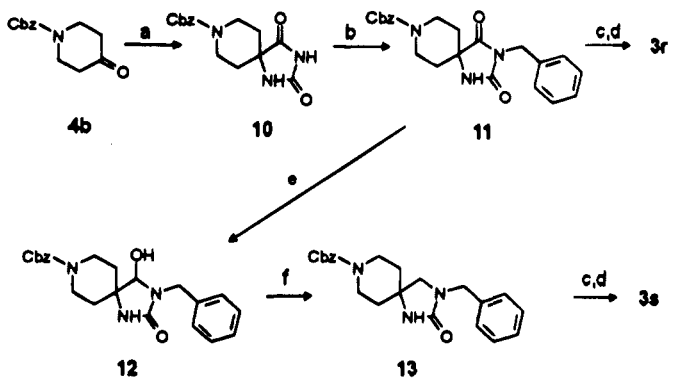
Scheme 1[a]



[a] (a) (i) CH_3CO_2Et, LiHMDS, (ii) NaOH, MeOH; (b) DPPA, TEA (60% overall); (c) NaH, DMF, RX (X = Cl, Br, or I); (d) HCl/dioxane; (e) 2-(5-fluoro-1*H*-indol-3-yl)ethyl bromide; (f) NaH, PhCOCl (49%); (g) NaH, TsCl (61%).

Scheme 2[a]



[a] (a) $(NH_4)_2CO_3$, KCN (94%); (b) $PhCH_2Br$, K_2CO_3, DMF (89%); (c) H_2, 10% Pd on C, MeOH; (d) 2-(5-fluoro-1*H*-indol-3-yl)ethyl bromide (46%, 11 → 3r; 53%, 13 → 3s); (e) $LiAlH_4$, THF; (f) $NaBH_4$, HCOOH (65% over two stages).

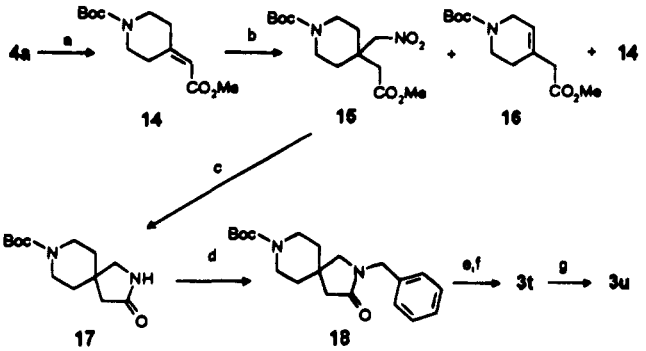
compound **5** was deprotonated with sodium hydride and alkylated using the appropriate arylmethyl bromide in DMF. Following the alkylation step, the *N*-Boc protecting group was removed by treatment with HCl in dioxane, and finally the 2-(5-fluoro-1*H*-indol-3-yl)ethyl group was introduced by alkylation of the intermediate amine with 2-(5-fluoro-1*H*-indol-3-yl)ethyl bromide. 2-(5-Fluoro-1*H*-indol-3-yl)ethyl bromide was prepared in three steps from commercially available 5-fluoroindole using the method of Neumeyer.[13]

The related analogues **6** and **7** were also prepared by this method via alkylation of **5** with methyl iodide and phenethyl bromide, respectively. Acylation of **5** with benzoyl chloride led ultimately to the formation of the imide **8**, and sulfonylation with *p*-toluenesulfonyl chloride led to the preparation of **9**.

Acyclic Analogues 3w,x. The amino alcohol **3w** was prepared directly from **3a** by hydrolysis with aqueous sodium hydroxide. Acetylation of **3w** afforded the *N*-acetyl derivative **3x**.

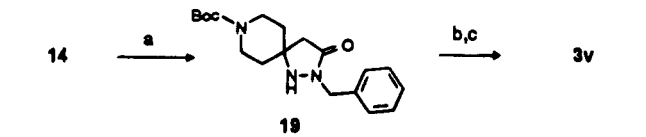
Synthesis of Hydantoin 3r and Imidazolidinone 3s. The hydantoin **3r** and the imidazolidinone **3s** were prepared as outlined in Scheme 2. *N*-Cbz-piperidone (**4b**) was converted to the spirohydantoin **10** using potassium cyanide and ammonium carbonate.[14] The hydantoin intermediate **10** was selectively alkylated on the more acidic imide N-3 nitrogen using benzyl bromide and potassium carbonate in DMF, affording **11**. Removal of the Cbz protection from **11** by hydrogenolysis and subsequent alkylation, as before, with 2-(5-fluoro-1*H*-indol-3-yl)ethyl bromide afforded the spirohydantoin **3r**. To prepare the imidazolidinone **3s**, the hydantoin intermediate **11** was reduced in a stepwise fashion. Firstly treatment of **11** with lithium aluminum hydride formed the intermediate hydroxyimidazolidinone **12**. Interestingly, no further reduction of **12** to the required imidazolidinone **13** was observed with lithium aluminum hydride. However, smooth reduction of **12** to the imidazolidinone **13** was achieved by reaction with sodium borohydride in formic acid. Finally the intermediate **13** was converted to the target imidazolidinone **3s** by an analogous two-step sequence to that used for converting **11** into **3r**.

Scheme 3[a]



[a] (a) $Ph_3P{=}CHCO_2Me$ (94%); (b) CH_3NO_2, 1,1,3,3-tetramethylguanidine (35%); (c) Raney nickel, aqueous ethanol (81%); (d) $PhCH_2Br$, NaH (99%); (e) HCl/dioxane; (f) 2-(5-fluoro-1*H*-indol-3-yl)ethyl bromide (59% over two stages); (g) BH_3–Me_2S (47%).

Scheme 4[a]

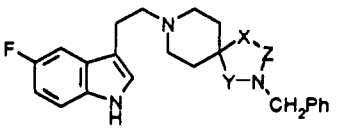


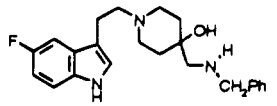
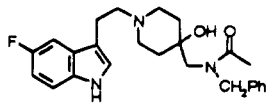
[a] (a) $PhCH_2NHNH_2$ (34%); (b) HCl/dioxane; (c) 2-(5-fluoro-1*H*-indol-3-yl)ethyl bromide (59% over two stages).

Synthesis of Pyrrolidinone 3t and Pyrrolidine 3u. The pyrrolidinone **3t** and the pyrrolidine **3u** were prepared as shown in Scheme 3. Wittig olefination of *N*-tBoc-piperidone (**4a**) with (carbomethoxymethylene)-triphenylphosphorane produced the unsaturated ester **14**. This compound was dissolved in nitromethane and refluxed in the presence of 1,1,3,3-tetramethylguanidine to produce a moderate yield (35%) of the Michael adduct **15**, together with starting olefin **14** and its regioisomer **16**. Adduct **15** was next reduced with Raney nickel. During this reaction, spontaneous cyclization of the intermediate amino ester occurred, and only the pyrrolidinone product **17** was isolated. Alkylation of **17** with benzyl bromide and sodium hydride then afforded **18**. Acidolysis of **18** and subsequent alkylation with 2-(5-fluoro-1*H*-indol-3-yl)ethyl bromide, as described above, afforded the required pyrrolidinone **3t**. Reduction of **3t** with borane–methyl sulfide complex afforded the pyrrolidine **3u**.

Synthesis of Pyrazolidinone 3v. Pyrazolidinone **3v** was prepared as shown in Scheme 4. The unsaturated ester **14** was treated with *N*-benzylhydrazine and gave exclusively the required pyrazolidinone regiosomer **19** in moderate yield. This intermediate was elaborated

Table 1. Effects of the Spiro Ring on NK_2 Binding



	X	Y	Z	Rat Colon pKi
3a	O	CH_2	CO	8.9
3r	NH	CO	CO	6.9
3s	NH	CH_2	CO	8.9
3t	CH_2	CH_2	CO	8.9
3u	CH_2	CH_2	CH_2	8.2
3v	CH_2	NH	CO	8.0
3w				7.0
3x				8.8

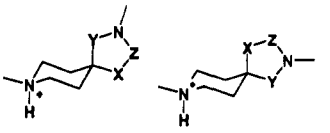
using the methods described in the previous sections to afford the required pyrazolidinone **3v**.

All the analogues prepared in Schemes 1–4 above were converted to either their hydrochloride or methanesulfonate salt prior to biological evaluation. This improved the aqueous solubility of the compounds considerably.

Biological Results and Discussion

Rat Colon NK_2 Receptor Binding Affinity *in Vitro*. The NK_2 receptor affinity of compounds **3a–x** and **6–9** was determined in an NK_2 receptor binding assay, which measured displacement of the radiolabeled tetrapeptide NK_2 antagonist [^{3}H]GR 100679[10,15] from rat colon membranes, as previously described.[16] The measured binding affinities are shown as pK_i values in Tables 1 and 3. (pK_i = -log K_i where K_i is the concentration of the test (competing) ligand which would occupy 50% of the receptors if no radioligand was present. It is calculated from the IC_{50} value using the Cheng–Prusoff equation: $K_i = IC50/(1 + [L]/K_D)$. The IC_{50} is the concentration of competing ligand which displaces 50% of the specific binding of the radioligand.)

Variations in the Spirocyclic Ring (Table 1). The NK_2 binding affinities of the compounds in Table 1 are influenced by the nature of the spirocyclic ring. Spirocycles **3a,s,t** all have similar high affinities for the rat colon NK_2 receptor (pK_i 8.9). However, reduced affinity was observed with the pyrazolidinone **3v** (pK_i 8.2), and a marked reduction in binding was observed for the spirohydantoin **3r** (pK_i 6.9). These binding affinities can be rationalized in terms of the preferred conformation adopted by the spirocycles. We reasoned that two distinct chair conformations, structures A and B shown in Figure 1, are possible for the spiro compounds. These two geometries differ in the positions of the heteroatoms associated with the five-membered rings relative to the piperidine ring and in the regions in space which are accessible to the aromatic groups. Energy optimizations were carried out to determine which of the chair



Conformer A *Conformer B*

Figure 1. Two possible low-energy conformations for the spiropiperidine-based inhibitors.

Table 2. Calculated Energies (kcal/mol) of Model Compounds in Conformers A and B (See Figure 1) Obtained Using the CVFF91 Force Field

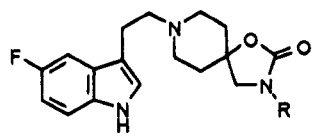
inhibitor	A	B	ΔE (A – B)
3a	7.8	3.0	4.8
3r	−11.5	-9.9	−1.6
3s	−27.6	−28.6	1.0
3t	−0.6	−1.7	1.1
3v	−3.9	−4.5	0.6

conformers A and B is most likely to be adopted by **3a,r–t,v** in solution. The alkylindole and benzyl substituents are the same in these five compounds. Preliminary calculations indicated that these groups do not influence the relative stabilities of the two proposed conformations of the spirocycles and do not favor alternative folded or collapsed boat conformations (results not included). Model compounds were therefore examined, with methyl groups in place of the aryl substituents. Table 2 lists the calculated energies for the proposed conformations of each spirocycle. Our results suggest that spirohydantoin **3r** would adopt conformer A in solution, whereas all of the more active compounds would adopt conformer B. With spirohydantoin **3r** in geometry A, there is a favorable electrostatic interaction between the positive charge in the piperidine ring and the α-carbonyl oxygen. Furthermore, conformer B would be destabilized due to unfavorable interactions between the charge and the amide proton in the five-membered ring. These calculated results were fully supported by structures found in the Cambridge Crystallographic Database; all molecules containing the spiro-*N*-R-piperidine-C(O)···NH moiety as in **3r** were in conformation type A. Thus, it is proposed that the preferred binding mode for these spiro compounds is conformation B. This would result in a conformational energy penalty upon binding of spirohydantoin **3r**, which would account for its lower activity.

In addition to the possible effects of the spirocycle on conformation, our results suggest that within this series there is potentially an important carbonyl group–receptor interaction contributing to the overall binding affinity. Thus the pyrrolidine **3u** (pK_i 8.2) has lower NK_2 affinity than the pyrrolidinone **3t** (pK_i 8.9). A similar, more pronounced difference is observed between the acyclic compounds **3w** (pK_i 7.0) and **3x** (pK_i 8.8), with the receptor affinity of the latter similar to the affinities of **3a,s,t**.

Structural Modifications in the Oxazolidinone Series (Table 3). Analogues designed to explore the structural requirements for optimum NK_2 receptor binding were prepared as spirooxazolidinones, since the oxazolidinone **3a** was the easiest of the active parent spiro compounds to prepare. Initially, analogues with substituted phenyl rings were prepared (**3a–i**). In most cases, substitution of the phenyl ring resulted in a decrease in NK_2 binding affinity. Only the 4-methyl- and 3-fluoro-substituted analogues **3d,i** had comparable

Table 3. Effects of Phenyl Replacement on NK_2 Binding



	R	yield from **5** (%)	rat colon pK_i
3a	CH_2Ph	50	8.9
3b	CH_2(4-fluorophenyl)	33	8.4
3c	CH_2(4-cyanophenyl)	46	7.0
3d	CH_2(4-methylphenyl)	43	9.0
3e	CH_2(4-chlorophenyl)	32	8.0
3f	CH_2(4-methoxyphenyl)	29	8.4
3g	CH_2(2-methylphenyl)	38	7.9
3h	CH_2(3-carbomethoxyphenyl)	34	7.1
3i	CH_2(3-fluorophenyl)	66	8.8
3j	CH_2(2-pyridyl)	31	7.8
3k	CH_2(4-pyridyl)	15	7.0
3l	CH_2(3-pyridyl)	20	6.7
3m	CH_2(2-naphthyl)	42	7.7
3n	CH_2(1-naphthyl)	39	8.1
3o	CH_2(2,4- difluorophenyl)	46	8.2
3p	CH(Me)Ph	33	7.7
3q	$CHPh_2$	28	7.7
6	Me	26	5.8
7	CH_2CH_2Ph	17	8.0
8	COPh	18	8.6
9	SO_2(4-MePh)	47	8.3

binding affinity to **3a**. However, the loss of binding was only dramatic for the 4-cyano and 2 carbomethoxy analogues **3c,h**.

Replacing the phenyl ring with a basic pyridine (**3j–l**) resulted in a significant loss in NK_2 binding affinity. Introducing a second phenyl ring, either as a naphthyl group in **3m,n** or as a diphenylmethyl group in **3q** also reduced NK_2 binding significantly.

The very poor binding affinity observed for the *N*-methyl derivative **6** confirmed the initial hypothesis that there is a requirement for both an indole and a further aryl ring in order to achieve a compound which has efficient NK_2 receptor binding. Extending the carbon chain linker between the spirocycle and the phenyl ring (compound **7**) also resulted in reduced receptor affinity. The benzoyl and sulfonyl analogues **8** and **9** showed binding affinities which were slightly reduced when compared with **3a,d** respectively.

In summary, none of the substitutions or replacements of the phenyl ring afforded a compound with significantly improved rat colon NK_2 binding affinity over the unsubstituted analogue **3a** (pK_i 8.9 ± 0.1). As a consequence of these results, compound **3a** was selected for further biological evaluation.

***In Vitro* NK_2 Antagonism by Compound 3a and Affinity for NK_2 Receptors of Other Species.** In guinea pig trachea, the NK_2 agonist GR 64349[17] caused concentration-related contractions which were displaced to the right by compound **3a** in a concentration dependent and parallel manner, yielding a pK_B value for **3a** of 8.6 ± 0.1 (n = 5), which was in good agreement with its binding affinity in rat colon. (Antagonist affiinity was determined from the parallel displacement of standard agonist concentration–response curves. pK_B = $\log_{10}$(concentration ratio − 1) − $\log_{10}$(molar concentration of antagonist), where the concentration ratio is the ratio of equiactive molar concentrations of the agonist in the presence and absence of the antagonist.)

Table 4. Receptor Affinities of Compound **3a**

NK_2 (rat colon)	pK_i	8.9 ± 0.1 (n = 3)
NK_2 (GPT)	pK_B	8.6 ± 0.1 (n = 5)
NK_2 (human CHO)	pK_i	8.1 ± 0.1 (n = 6)
NK_1 (GPT)	pK_B	< 5 (n = 2)
NK_1 (rabbit cortex)	pK_i	5.1 (n = 1)
NK_3 (GPC)	pK_i	4.1 ± 0.1 (n = 4)

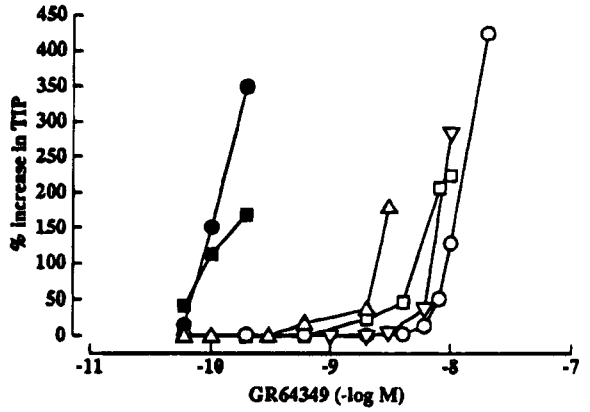


Figure 2. Antagonism of GR 6439-induced bronchoconstriction by compound **3a** in the anesthetized guinea pig. Guinea pigs (starved overnight) were dosed orally with either compound **3a** (20 mg kg^{-1}; □, ○, △, ▽) or its vehicle (distilled water; ■, ●); 2 h later, animals were anesthetized and surgically prepared. A single sequential dose–response curve to intravenous GR 64349 was then constructed, and increases in tracheal inflation pressure (TIP) were measured.

Interestingly, the binding affinity of compound **3a** for cloned human NK_2 receptors expressed in Chinese hamster ovary (CHO) cells[15] was found to be 3–6-fold lower than in the rat colon and guinea pig trachea (human pK_i 8.1 ± 0.1, n = 6, Table 4). Species differences in NK_2 receptors have previously been revealed in studies using other NK_2 antagonists and may be related to species variations in the structure of the NK_2 receptor.[16,18]

NK_2 Selectivity of Compound 3a. Compound **3a** was further evaluated as an NK_1 receptor antagonist by determining its ability to antagonize contractions induced by the selective NK_1 receptor agonist substance P methyl ester in the guinea pig trachea (GPT).[16] Compound **3a** was without effect in this preparation (pK_B <5.0), and thus, it displays at least 1000-fold selectivity for NK_2 receptors in this tissue. In addition, compound **3a** had negligible affinity for NK_1 receptors in rabbit cerebral cortex (pK_i 5.1)[19] and NK_3 receptors in guinea pig cerebral cortex (GPC) (pK_i 4.1).[16] Thus **3a** shows a high degree of selectivity for the NK_2 tachykinin receptor relative to NK_1 and NK_3 receptors.

NK_2 Antagonism of Compound 3a *in Vivo*. Compound **3a** was tested *in vivo* against GR 64349-induced bronchoconstriction in the anaesthetized guinea pig model described previously (Figure 2).[16,20] Intravenous (iv) administration of **3a** (bolus injection, 1.2 mg kg^{-1}) caused a maximum dose ratio of 176 (95% confidence limits = 98–316, n = 4), which was obtained at 9 ± 3 min after dosing, and had a duration of action which was greater than 3 h. (Dose ratio = concentration of agonist producing 50% maximum contractile response in the presence of the antagonist divided by the concentration producing the same response in the absence of the antagonist.) Compound **3a** also displayed significant oral activity in this model. Thus, 2 h after oral

administration of compound **3a** (20 mg kg^{-1}), GR 64349-induced bronchoconstriction curves were shifted to the right by 55-fold (95% confidence limits = 15−198, n = 4) (Figure 2).

Conclusions

From an initial hypothesis that an indole and a phenyl ring are critical elements for effective NK_2 receptor binding, we have discovered a novel series of potent spiropiperidine-containing NK_2 antagonists related to the previously described sulfoxide GR 159897 (**2**). Modifications of the core spirocyclic ring and the phenyl group of this new template have been described which suggest that compound **3a** represents an optimum structure for potent NK_2 receptor binding. Compound **3a** has been shown to be a highly potent and selective NK_2 antagonist at both rat and guinea pig receptors and also to display *in vivo* efficacy to antagonize NK_2 agonist-induced guinea pig bronchoconstriction.

Experimental Section

Biological Test Methods. Biological evaluations of compounds in the rat colon binding assay, guinea pig trachea, and antagonism of bronchoconstriction in guinea pig were carried out using the methods described in ref 16. For the rat colon assay, [^{3}H]GR 100679 (70−90 Ci mmol^{-1}) was prepared by Amersham. Binding data were analyzed using the curve-fitting program ALLFIT and pK_i values determined. pK_i values were determined in two to four separate experiments which were each performed in triplicate. The variability in data quoted is ≤0.3 log unit. The apparent affinity (pK_B) of compound **3a** in guinea pig trachea was estimated as previously described.[17]

Molecular Modeling. Model compounds for five inhibitors, **3a**,**r**−**t**,**v**, were constructed using the software package InsightII.[21] In these model structures methyl groups replaced the alkylindole and benzyl moieties. Two different conformations were built for each species corresponding to the geometries illustrated in Figure 1. In every case the nitrogen atom in the piperidine ring was protonated with the hydrogen atom set in the axial position. Energy minimizations were performed in Discover[21] utilizing the CVFF91 force field.[22] Steepest descents (100 steps) and conjugate gradient (500 steps) optimization modes were used. The effects of aqueous solvation were simulated by incorporating a distance dependent dielectric into the coulombic potential. Lastly, the calculated structures were compared with conformers of related species found in the Cambridge Crystallographic Database.[23]

FTIR spectra were recorded using a Nicolet 20SXB or Bio-Rad FTS-7 instrument. ^{1}H NMR spectra were recorded either at 250 MHz using a Bruker AC or AM 250 spectrometer or at 400 MHz with a Varian VXR 400 spectrometer. Mass spectra were measured on a HP Engine (thermospray positive) or VG Autospec Q (LSIMS) spectrometer. Routine microanalyses were performed on a Leco CHNS-932 or Carlo-Erba instrument. Water analyses were performed using a Mitsubishi CA-05 instrument. Flash chromatography was performed with Merck Kieselgel 9385. Drying of solutions, where indicated, was carried out using anhydrous magnesium sulfate. Reverse phase HPLC analysis was carried out on all final compounds using a Rainin C-18 83-201-C column. An acetonitrile/water gradient was employed to elute compounds from the column (0−100% acetonitrile over 20 min, flow 1 mL/min). Eluting materials were detected by measuring their UV absorbance at 230 nm.

2-Oxo-1-oxa-3,8-diazaspiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester (5). A solution of lithium hexamethyldisilazide (1 M in THF, 100 mL, 0.1 mol) at −70 °C was treated dropwise with ethyl acetate (9.8 mL, 0.1 mol). After stirring for 10 min the resultant anion was treated with a solution of *N*-Boc-piperidone (**4a**) (18.3 g, 92 mmol) in THF (40 mL), the temperature being maintained below −60 °C. Following the addition, the reaction mixture was allowed to warm to 0 °C, and then the reaction was quenched by the addition of water and the mixture extracted with ether. The combined organic extracts were washed with saturated brine, dried, and evaporated to a viscous oil. This was redissolved in methanol (100 mL) and treated with aqueous sodium hydroxide solution (2 M, 70 mL). After 1 h, the methanol was evaporated and the residual aqueous solution washed with ether and then acidified with hydrochloric acid (2 M aqueous), and the acidic solution was extracted twice with dichloromethane. The dichloromethane extracts were combined, dried, and evaporated to a viscous oil. This was directly dissolved in toluene (500 mL), treated with triethylamine (13.9 mL, 0.1 mol), and refluxed for 16 h with diphenyl phosphorazidate (DPPA) (27.0 mL, 0.125 mol). Following the reflux, the solution was cooled, diluted with ethyl acetate, and then washed with water and saturated brine. The organic layer was dried and evaporated to a brown solid which was triturated with ether to afford, after filtration and drying in vacuo, analytically pure **5** (14.2 g, 60% over the three stages) as a white solid: IR ($CHBr_3$) ν_{max} 2980, 2938 (N-H), 1754, 1697, 1681 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.52 (s, 1 H, N-H), 3.85 (br d, 2 H, H-7$_{eq}$, J = 10 Hz), 3.35 (s, 2 H, H-4), 3.25 (br t, 2 H, H-7$_{ax}$, J = 10 Hz), 1.95 (br d, 2 H, H-6$_{eq}$, J = 11.5 Hz), 1.70 (m, 2 H, H-6$_{ax}$), 1.40 (s, 9 H, tBu); MS 274 (M + NH_4^+), 203. Anal. ($C_{12}H_{20}N_2O_4$) C, H, N.

3-Benzyl-2-oxo-1-oxa-3,8-diazaspiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester. Oxazolidinone **5** (6.0 g, 23.4 mmol) was added to a suspension of sodium hydride (60% dispersion in oil, 1.0 g, 25 mmol) in DMF (50 mL) under nitrogen at room temperature. After 30 min, benzyl bromide (2.8 mL, 23.5 mmol) was added and the mixture stirred at room temperature for a further 18 h. Water and ethyl acetate were then added, and the organic layer was separated, dried, and evaporated to afford the title compound as a colorless oil which crystallized from petroleum ether (7.15 g, 90%): IR ($CHBr_3$) ν_{max} 1754, 1747, 1694, 1682 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.4−7.2 (m, 5 H, Ph), 4.43 (s, 2 H, $PhCH_2$), 3.75 (m, 2 H, H-7$_{eq}$), 3.28 (br t, 2 H, H-7$_{ax}$, J = 10 Hz), 3.1 (s, 2 H, H-4), 1.85 (m, 2 H, H-6$_{eq}$), 1.6 (m, 2 H, H-6$_{ax}$), 1.4 (s, 9 H, tBu); MS 364 (M + NH_4)$^+$, 308. Anal. ($C_{19}H_{26}N_2O_4$) C, H, N.

3-Benzyl-8-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-1-oxa-3,8-diazaspiro[4.5]decan-2-one (3a). 3-Benzyl-2-oxo-1-oxa-3,8-diazaspiro[4.5]decane-8-carboxylic acid *tert*-butyl ester (2.95 g, 8.5 mmol) was dissolved in a solution of hydrogen chloride in dioxane (Aldrich; 4 M, 70 mL) and stirred at 20 °C for 1 h. The resulting white slurry was dissolved in methanol and evaporated to a white solid which was triturated from ether and collected by filtration affording 3-benzyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one hydrochloride (2.30 g, 95%): IR (KBr) ν_{max} 3217, 2932, 2875 (N-H), 1731 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.9 (br s, 2 H, NH_2^+), 7.42−7.2 (m, 5 H, Ph), 4.38 (s, 2 H, $PhCH_2$), 3.29 (s, 2 H, H-4), 3.2 (dt, 2 H, H-7$_{eq}$, J = 4, 10 Hz), 3.08 (dt, 2 H, H-7$_{ax}$, J = 6, 10 Hz), 2.1−1.9 (m, 4 H, H-6); MS 493 (2M + H)$^+$, 247 (M + H)$^+$. Anal. ($C_{14}H_{18}N_2O_2$·HCl) C, H, N.

The hydrochloride salt prepared above (0.30 g, 1.06 mmol) was dissolved in DMF (4 mL) and treated with triethylamine (0.37 mL, 2.65 mmol) and 2-(5-fluoro-1*H*-indol-3-yl)ethyl bromide (0.28 g, 1.15 mmol). The reaction mixture was stirred at room temperature for 16 h and then partitioned between water and ethyl acetate. The organic layer was further washed with saturated aqueous sodium bicarbonate solution and then with brine, dried, and concentrated to an oil which was purified by flash column chromatography (eluant chloroform:methanol, 19:1) to afford the free base of the title compound **3a** as a colorless solid (0.25 g, 58%).

The hydrochloride salt of **3a** was readily prepared in quantitative yield by treating an ether solution of the free base with an excess of HCl in ether (1 M solution). The salt precipitated from the solution and was collected by filtration. The resulting hygroscopic solid was washed with further ether and dried in vacuo. All the HCl salts of compounds below were similarly prepared. The methanesulfonate salt of compound **3a** was prepared by addition of a stoichiometric quantity of

methanesulfonic acid to a solution of the free base in THF and then evaporation of solvent and drying in vacuo. **3a** methanesulfonate: IR (KBr) ν_{max} 1747 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.08 (s, 1 H, indole N-H), 9.4 (br s, 1 H, NH^+), 7.46–7.24 (m, 8 H, Ar-H), 6.95 (dt, 1 H, indole H-6, J = 2, 9 Hz), 4.4 (s, 2 H, $PhCH_2$), 3.62 (m, 2 H, H-7), 3.43–3.1 (m, 6 H, H-7, H-1′, H-2′), 3.32 (s, 2 H, H-4), 2.37 (s, 3 H, $CH_3SO_3^-$), 2.2–1.9 (m, 4 H, H-6); MS 408 $(M + H)^+$; HPLC t_R 14.19 min (98.2%); HRMS found MH^+ 408.2084, calcd for $C_{24}H_{27}FN_3O_2$ 408.2087.

Prepared by a similar three-step sequence via the reaction of **5** with sodium hydride and the appropriate alkyl bromide were **3b–q**, **6**, and **7**.

1-[2-(5-Fluoro-1*H*-indol-3-yl)ethyl]-4-[(benzylamino)-methyl]piperidin-4-ol (3w). A solution of compound **3a** (0.42 g, 1.02 mmol) in methanol (4 mL) was treated with water (1 mL) and potassium hydroxide (0.42 g, 7.4 mmol). The mixture was refluxed for 96 h and then filtered, neutralized, and purified directly by reverse phase preparatory HPLC (aqueous acetonitrile with trifluoroacetic acid), affording, after freeze-drying, the title compound as its trifluoroacetate salt (0.45 g, 67%): ^1H NMR (DMSO-d_6) δ 11.08 (s, 1 H, indole N-H), 9.6 (br s, 1 H, NH^+), 8.95 (br s, 2 H, NH_2^+), 7.6–7.25 (m, 8 H, Ar-H), 6.95 (dt, 1 H, indole H-6, J = 2, 9 Hz), 5.55 (br s, 1 H, OH), 4.2 (s, 2 H, $PhCH_2$), 3.5–2.9 (m, 10 H, H-2, H-5, H-1′, H-2′), 1.9–1.6 (m, 4 H, H-2); MS 382 $(M + H)^+$. Anal. ($C_{23}H_{28}FN_3O \cdot 2.5CF_3CO_2H$) C, H, N, F.

***N*-Benzyl-*N*-[[1-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-4-hydroxypiperidin-4-yl]methyl]acetamide (3x).** To a solution of **3w** (0.20 g, 0.524 mmol) in dry THF (10 mL) were added triethylamine (0.11 mL, 0.789 mmol) and acetyl chloride (0.056 mL, 0.788 mmol) at 20 °C. The resulting suspension was stirred for 30 min and then diluted with ethyl acetate and washed with water. The organic layer was dried and evaporated to a colorless foam which was purified by flash chromatography (eluant 8% methanol in chloroform), affording the title compound **3x** as the free amine which was converted to the HCl salt as described above (0.125 g, 52%): IR (KBr) ν_{max} 3313, 1640 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.1 (s, 1 H, indole N-H), 10.35, 9.9 (2 br s, 1 H, NH^+), 7.45–7.1 (m, 8 H, Ar-H), 6.92 (dt, 1 H, indole H-6, J = 2, 9 Hz), 4.8 (ABq, 2 H, $PhCH_2$), 4.8 (s, 2 H, H-5), 3.5–3.0 (m, 9 H, H-3, H-1′, H-2′, OH), 2.0 (s, 3 H, CH_3CO), 2.0–1.6 (m, 4 H, H-2). Anal. ($C_{25}H_{30}FN_3O_2 \cdot HCl \cdot 0.45\ H_2O$) C, H, N, Cl, H_2O.

3-Benzoyl-2-oxo-1-oxa-3,8-diazaspiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester. Oxazolidinone **5** (0.50 g, 1.95 mmol) was dissolved in DMF (5 mL) and treated with sodium hydride (60% dispersion in oil, 95 mg, 2.39 mmol). After 30 min benzoyl chloride (0.22 mL, 1.86 mmol) was added and the solution stirred at room temperature for a further 16 h. The reaction mixture was then diluted with ethyl acetate, washed with 10% aqueous citric acid and then saturated with sodium bicarbonate, dried, evaporated in vacuo, and purified by column chromatography (eluant ethyl acetate:cyclohexane, 1:4) to afford the title compound (0.38 g, 54%): IR ($CHBr_3$) ν_{max} 1782, 1697, 1668 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.7–7.4 (m, 5 H, Ph), 3.85 (m, 2 H, H-7_{eq}), 3.8 (s, 2 H, H-4), 3.36 (dt, 2 H, H-7_{ax}, J = 8.5, 1 Hz), 2.02 (br d, 2 H, H-6_{eq}, J = 11.5 Hz), 1.83 (m, 2 H, H-6_{ax}), 1.45 (s, 9 H, tBu); MS 378 $(M + NH_4)^+$, 322. Anal. ($C_{19}H_{24}N_2O_5$) C, H, N.

3-Benzoyl-8-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-1-oxa-3,8-diazaspiro[4.5]decan-2-one (8). The intermediate prepared above was treated with HCl in dioxane and then with 2-(5-fluoro-1*H*-indol-3-yl)ethyl bromide, as described above in the preparation of **3a**, to afford compound **8** (37% yield). **8** hydrochloride: IR (KBr) ν_{max} 1782, 1681 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.1 (s, 1 H, indole N-H), 10.6 (br s, 1 H, NH^+), 7.7–7.3 (m, 8 H, Ar-H), 6.95 (dt, 1 H, indole H-6, J = 2, 9 Hz), 4.1, 3.98 (2 s, 2 H, H-4), 3.62 (m, 2 H, H-7), 3.4–3.1 (m, 6 H,H-7, H-1′, H-2′), 2.3 (m, 4 H, H-6); MS 422 $(M + H)^+$, 318 $(M + H - PhCO)^+$; HPLC t_R 14.14 min (98.3%); HRMS found MH^+ 422.1874, calcd for $C_{24}H_{25}FN_3O_3$ 422.1880. Anal. ($C_{24}H_{25}FN_3O_3 \cdot HCl \cdot 0.33H_2O$) C, H, N, Cl, H_2O.

3-(4-Tolylsulfonyl)-2-oxo-1-oxa-3,8-diazaspiro[4.5]-decane-8-carboxylic Acid *tert*-Butyl Ester. *N*-Boc-piperidone (**4a**) (0.50 g, 2.17 mmol) was dissolved in DMF (5 mL) and treated with sodium hydride (60% dispersion in oil, 95 mg, 2.39 mmol). After 30 min the anion formed was treated with *p*-toluenesulfonyl chloride (0.46 g, 2.39 mmol) and stirred for 24 h at room temperature. The reaction mixture was then diluted with ethyl acetate, washed sequentially with aqueous citric acid, aqueous sodium bicarbonate, and brine, and dried and the solvent evaporated in vacuo to afford an oil which solidified upon addition of ether, affording the title compound (0.55 g, 61%) as a solid: IR (Nujol) ν_{max} 1771, 1686 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.9 (d, 2 H, Ar-H, J = 7 Hz), 7.5 (d, 2 H, Ar-H, J = 7 Hz), 3.92 (s, 2 H, H-4), 3.6 (dt, 2 H, H-7_{eq}, J = 11.5, 2.5 Hz), 3.2 (br m, 2 H, H-7_{ax}), 2.42 (s, 3 H, Ar-CH_3) 1.75 (br t, 4 H, H-6, J = 3 Hz), 1.38 (s, 9 H, tBu); MS 428 $(M + NH_4)^+$, 372, 274; HRMS found MNH_4^+ 428.1851 (1 ppm error).

3-(4-Tolylsulfonyl)-8-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-1-oxa-3,8-diazaspiro[4.5]decan-2-one (9). The intermediate above was *N*-Boc deprotected and then alkylated with 2-(5-fluoro-1*H*-indol-3-yl)ethyl bromide using the same procedure described for preparing **3a**, affording the title compound **9** (77% yield over the two stages). **9** hydrochloride: IR (KBr) ν_{max} 1790 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.08 (s, 1 H, indole N-H), 10.5 (br s, 1 H, NH^+), 7.9 (d, 2 H, Ar-H, J = 7 Hz), 7.55 (d, 2 H, Ar-H, J = 7 Hz), 7.45–7.25 (m, 3 H, indole H-2,4,7), 6.95 (dt, 1 H, indole H-6, J = 2, 9 Hz), 4.04 (s, 2 H, H-4), 3.58 (br d, 2 H, H-7_{eq}, J = 9 Hz), 3.4–3.05 (m, 6 H, H-7_{ax}, H-1′, H-2′), 2.41 (s, 3 H, Ar-CH_3) 2.4–2.2 (m, 4 H, H-6); MS 472 $(M + H)^+$; HPLC t_R 15.03 min (95.7%); HRMS found MH^+ 472.1705, calcd for $C_{24}H_{27}FN_3O_4S$ 472.1706.

2,4-Dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxylic Acid Benzyl Ester (10). *N*-Cbz-piperidone (**4b**) (13.9 g, 59.7 mmol) was refluxed in aqueous ethanol (1:1, 120 mL) for 24 h with powdered ammonium carbonate (17.2 g, 178 mmol) and potassium cyanide (5.8 g, 89 mmol). Compound **10** was slowly precipitated from the solution. A further 200 mL of water was added; then the solution was cooled and the product collected by filtration and dried to afford **10** as a white solid (17.0 g, 94%): IR ($CHBr_3$) ν_{max} 1770, 1708 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.72 (br s, 1 H, 3-NH), 8.56 (s, 1 H, 1-NH), 7.45–7.2 (m, 5 H, Ph), 5.09 (s, 2 H, $PhCH_2$), 3.89 (br dt, 2 H, H-7_{eq}, J = 11.5, 1 Hz), 3.2 (br m, 2 H, H-7_{ax}), 1.72 (m, 2 H, H-6_{ax}), 1.53 (br d, 2 H, H-6_{eq}, J = 10 Hz); MS 321 $(M + NH_4)^+$. Anal. ($C_{15}H_{17}N_3O_4$) C, H, N.

3-Benzyl-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxylic Acid Benzyl Ester (11). Spirohydantoin **10** (2.0 g, 6.6 mmol) in DMF (30 mL) was treated with potassium carbonate (0.91 g, 6.6 mmol) and benzyl bromide (0.86 mL, 7.2 mmol). The mixture was stirred at room temperature for 24 h. The solution was filtered and the residue partitioned between ethyl acetate and water. The organic extract was dried and evaporated to a colorless oil which crystallized from diethyl ether affording **11** as a colorless solid (2.3 g, 89%): IR ($CHBr_3$) ν_{max} 1775, 1716, 1698 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.99 (s, 1 H, N-H), 7.4–7.2 (m, 10 H, 2 × Ph), 5.2 (s, 2 H, CO_2CH_2), 4.55 (s, 2 H, $PhCH_2N$), 3.92 (br dt, 2 H, H-7_{ax}, J = 11, 1 Hz), 3.23 (m, 2 H, H-7_{eq}), 1.78 (m, 2 H, H-6_{ax}), 1.59 (br d, 2 H, H-6_{eq}, J = 10 Hz); MS 411 $(M + NH_4)^+$, 394 $(M + H)^+$, 260. Anal. ($C_{22}H_{23}N_3O_4$) C, H, N.

3-Benzyl-8-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-1,3,8-triazaspiro[4.5]decane-2,4-dione (3r). Intermediate **11** (1.60 g, 4.07 mmol) was hydrogenated in methanol (50 mL) with 10% palladium on carbon. After 3 h the catalyst was removed by filtration and the solvent evaporated to afford 3-benzyl-1,3,8-triazaspiro[4.5]decane-2,4-dione as a white solid (0.95 g, 90%): IR (KBr) ν_{max} 3271, 2953 (N-H), 1759, 1704 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) (3:1 mixture of conformers) δ 8.8 (s, 1 H, N-H), 7.4–7.15 (m, 5 H, Ph), 4.52 (s, 2 H, $PhCH_2N$), 2.82 (m, 2 H, H-7), 2.71 (m, 2 H, H-7), 2.38–1.32 (m, 5 H, H-6, N-H); MS 260 $(M + H)^+$. Anal. ($C_{14}H_{17}N_3O_2$) C, H, N.

This material (0.52 g, 2 mmol) was alkylated with 2-(5-fluoro-1*H*-indol-3-yl)ethyl bromide as described above for the preparation of **3a**, affording the title compound **3r** (0.45 g, 51%). **3r** hydrochloride: IR (KBr) ν_{max} 1774, 1714 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) (two conformers present, 4:1 ratio) δ 11.1 (s, 1 H, indole N-H), 10.7, 10.6 (2 br s, 1 H, NH^+), 9.2, 8.75 (2 s, 1 H, N-H), 7.5–7.2 (m, 8 H, Ar-H), 6.99 (dt, 1 H, indole H-6, J = 2, 9 Hz), 4.56 (s, 2 H, $PhCH_2$), 3.7 (m, 2 H, H-7), 3.5–3.1

(m, 6 H, H-7, H-1′, H-2′), 2.4–1.9 (m, 4 H, H-6); MS 421 (M + H)$^+$; HPLC t_R 14.18 min (97.5%); HRMS found MH$^+$ 421.2040, calcd for $C_{24}H_{26}FN_4O_2$ 421.2058.

3-Benzyl-4-hydroxy-2-oxo-1,3,8-triazaspiro[4.5]decane-8-carboxylic Acid Benzyl Ester (12). To a solution of the spirohydantoin **11** (4.7 g, 11.87 mmol) in THF (100 mL) was added lithium aluminum hydride in ether (1.0 M solution, 12.0 mL, 12 mmol) under nitrogen with cooling in an ice bath. The solution was then warmed to room temperature and stirred for 18 h. At this stage the reaction was quenched by the cautious addition of wet THF and then the mixture concentrated to a small volume and partitioned between dilute hydrochloric acid (0.5 M, aqueous) and ethyl acetate. The ethyl acetate layer was washed with water and then dried and concentrated to a colorless oil (4.3 g, 95% crude). A small quantity was purified by column chromatography (eluant ethyl acetate) to afford the title compound **12** as a colorless foam: IR ($CHBr_3$) ν_{max} 1687 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.3–7.1 (m, 11 H, 2 x Ph, N-H), 5.93 (d, 1-H, OH, J = 6 Hz), 4.96 (s, 2 H, CO_2CH_2), 4.4 (d, 1 H, H-4, J = 6 Hz), 4.2 (ABq, 2 H, $PhCH_2N$), 3.56–3.1 (m, 4 H, H-7), 1.7–1.3 (m, 4 H, H-6); MS 396 (M + H)$^+$, 378. Anal. ($C_{22}H_{25}N_3O_4$) C, H, N.

3-Benzyl-2-oxo-1,3,8-triazaspiro[4.5]decane-8-carboxylic Acid Benzyl Ester (13). Crude **12** from the above experiment was dissolved in formic acid (50 mL) and cooled to 0 °C. To this solution was added sodium borohydride (1.8 g, 44 mmol) (*caution: reaction is extremely vigorous*) in small portions over 10 min. The solution was allowed to warm slowly to room temperature and then diluted with water and the product extracted with dichloromethane. The organic extracts were dried and evaporated to a colorless oil which was triturated with ether, affording **13** as a white powder (3.0 g, 65% from **11**): IR ($CHBr_3$) ν_{max} 2918, 1694, 1682 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.4–7.2 (m, 10 H, 2 × Ph), 5.3 (s, 1 H, N-H), 5.2 (s, 2 H, CO_2CH_2), 4.4 (s, 2 H, $PhCH_2N$), 3.6–3.4 (m, 4 H, H-7), 3.08 (s, 2 H, H-4), 1.85–1.6 (m, 4 H, H-6); MS 380 (M + H)$^+$. Anal. ($C_{22}H_{25}N_3O_3$) C, H, N.

3-Benzyl-8-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-1,3,8-triazaspiro[4.5]decan-2-one (3s). Hydrogenolysis and alkylation of compound **13** (2.91 g, 7.66 mmol) was carried out in an identical fashion with that described above for the conversion of **11** into **3r**, affording the title compound **3s** (1.65 g, 53%). **3s** hydrochloride: IR (KBr) ν_{max} 1682 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.1 (s, 1 H, indole N-H), 10.6, 10.4 (2 br s, 2 H, N-H, NH$^+$), 7.5–7.2 (m, 8 H, Ar-H), 6.95 (dt, 1 H, indole H-6, J = 2, 9 Hz), 4.25 (s, 2 H, $PhCH_2$), 3.5 (m, 2 H, H-7), 3.35–3.08 (m, 8 H, H-4, H-7, H-1′, H-2′), 2.1–1.8 (m, 4 H, H-6); MS 407 (M + H)$^+$; HPLC t_R 13.72 min (99.2%). Anal. ($C_{24}H_{27}FN_4O$·HCl) C, H, N, Cl.

4-[(Methoxycarbonyl)methylene]piperidine-1-carboxylic Acid *tert*-Butyl Ester (14). *N*-Boc-piperidone (**4a**) (5.0 g, 25.1 mmol) was dissolved in toluene (50 mL) and refluxed for 12 h with (carbomethoxymethylene)triphenylphosphorane (Aldrich; 10.5 g, 31.4 mmol). The solvent was evaporated in vacuo and the residue filtered through a plug of silica gel (eluant ether:petroleum ether, 1:1) affording the title compound **14** as a colorless solid (6.0 g, 94%). Recrystallization from methanol/water afforded analytically pure material: IR ($CHBr_3$) ν_{max} 1714, 1697, 1651 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.71 (s, 1 H, H-5), 3.7 (s, 3 H, CO_2Me), 3.48 (q, 4 H, H-2, J = 4 Hz), 2.92 (t, 2 H, H-3, J = 4 Hz), 2.29 (t, 2 H, H-3′, J = 4 Hz), 1.45 (s, 9 H, tBu); MS 273 (M + NH$_4$)$^+$, 256 (M + H)$^+$. Anal. ($C_{13}H_{21}NO_4$) C, H, N.

4-[(Methoxycarbonyl)methyl]-4-(nitromethyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (15). Ester **14** (2.75 g, 10.8 mmol) was dissolved in nitromethane (100 mL) and refluxed for 10 h under nitrogen with 1,1,3,3-tetramethylguanidine (0.5 mL). The mixture was then cooled, washed with 2 M aqueous hydrochloric acid, dried, evaporated, and purified by column chromatography (eluant ether:petroleum ether, 1:1) affording the title compound **15** as a pale yellow solid (1.18 g, 35%), together with a fraction containing a mixture of olefins **14** and **16** (1.50 g, 50%). **15**: IR ($CHBr_3$) ν_{max} 1733, 1693, 1688 (C=O), 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.75 (s, 2 H, CH_2NO_2), 3.7 (s, 3 H, CO_2Me), 3.55 (m, 2 H, H-2), 3.42 (m, 2 H, H-2), 2.58 (s, 2 H, CH_2CO), 1.62 (t, 4 H, H-3), 1.45 (s, 9 H, tBu); MS 334 (M + NH$_4$)$^+$, 278, 217. Anal. ($C_{14}H_{24}N_2O_6$) C, H, N.

3-Oxo-2,8-diazaspiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester (17). Nitroalkane **15** (1.10 g, 3.48 mmol) was dissolved in ethanol (10 mL), and Raney nickel (Aldrich; 50% slurry in water, 3 mL) was added under nitrogen. The resulting suspension was stirred at room temperature for 24 h. The suspension was filtered through a bed of Celite and evaporated to an oil. Purification by column chromatography (eluant 5% methanol in chloroform) afforded the spiropyrrolidinone **17** (0.71 g, 81%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 6.0 (br s, 1 H, N-H), 3.5 (dt, 2 H, H-7, J = 11.5, 3 Hz), 3.38 (dt, 2 H, H-7, J = 11.5, 4 Hz), 3.2 (s, 2 H, H-1), 2.22 (s, 2 H, H-4), 1.6 (m, 2 H, H-6), 1.4 (s, 9 H, tBu).

2-Benzyl-3-oxo-2,8-diazaspiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester (18). Pyrrolidinone **17** (0.51 g, 2 mmol) was dissolved in THF (10 mL) and treated, under nitrogen at 0 °C, with sodium hydride (60% dispersion in oil, 88 mg, 2.2 mmol). Benzyl bromide (0.26 mL, 2.2 mmol) was then added and the mixture refluxed for 12 h. The solution was then cooled, filtered through Celite, concentrated to an oil, and partitioned between water and ethyl acetate. The organic extract was dried, evaporated, and purified by column chromatography (eluant ethyl acetate), affording **18** as a colorless oil (0.68 g, 99%): ^{1}H NMR ($CDCl_3$) δ 7.35–7.18 (m, 5 H, Ph), 4.45 (s, 2 H, $PhCH_2$), 3.44 (dt, 2 H, H-7$_{eq}$, J = 10, 4 Hz), 3.25 (ddd, 2 H, H-7$_{ax}$, J = 10, 6, 3 Hz), 3.02 (s, 2 H, H-1), 2.38 (s, 2 H, H-4), 1.5 (m, 4 H, H-6), 1.4 (s, 9 H, tBu); MS 345 (M + H)$^+$, 289 (M + H − tBu)$^+$, 245 (M + H − Boc)$^+$.

2-Benzyl-8-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-2,8-diazaspiro[4.5]decan-3-one (3t). Compound **18** was converted into **3t** by treatment with HCl in dioxane and then alkylation with 2-(5-fluoro-1*H*-indol-3-yl)ethyl bromide in an identical fashion as described above for the preparation of compound **3a**. The overall yield over the two stages was 59%. **3t** hydrochloride: IR (KBr) ν_{max} 1667 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) (two conformers present, 3:2 ratio) δ 11.09 (s, 1 H, indole N-H), 10.25 (br s, 1 H, NH$^+$), 7.4–7.2 (m, 8 H, Ar-H), 6.93 (dt, 1 H, indole H-6, J = 2, 9 Hz), 4.38 (s, 2 H, $PhCH_2$), 3.49 (m, 2 H, H-7), 3.38–2.9 (m, 6 H, H-7, H-1′, H-2′), 3.22, 3.07 (2 s, 2 H, H-1), 2.44, 2.32 (2 s, 2 H, H-4), 1.9–1.76 (m, 4 H, H-6); MS 406 (M + H)$^+$; HPLC t_R 13.91 min (97.6%). Anal. ($C_{25}H_{28}FN_3O$·HCl·H_2O) C, H, N, H_2O.

2-Benzyl-8-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-2,8-diazaspiro[4.5]decane (3u). Compound **3t** hydrochloride (0.105 g, 0.238 mmol) was neutralized and the free base dissolved in THF (5 mL) and refluxed with borane–THF complex (Aldrich; 1 M solution in THF, 1 mL). After 1 h, the reaction was quenched by the cautious addition of methanol and the solvent evaporated. The residue was purified by column chromatography (eluant 20% methanol in chloroform). The resulting free base **3u** was precipitated from HCl in ether, affording the dihydrochloride salt (0.054 g, 47%). **3u** hydrochloride: ^{1}H NMR (D_2O) δ 7.5–7.35 (m, 8 H, Ar-H), 7.04 (dt, 1 H, indole H-6, J = 2, 9 Hz), 4.4 (s, 2 H, $PhCH_2$), 3.6–3.3 (8 H, m, H-1, H-3, H-7), 3.45 (t, 2 H, H-1′, J = 5 Hz), 3.2 (t, 2 H, H-2′, J = 5 Hz), 2.2–1.9 (m, 6-H, H-4, H-6); MS 392 (M + H)$^+$; HPLC t_R 12.13 min (92.9%). Anal. ($C_{25}H_{30}FN_3$·2HCl·1.75H_2O) C, H, N, H_2O.

2-Benzyl-3-oxo-1,2,8-triazaspiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester (19). Benzylhydrazine dihydrochloride (1.07 g, 5.5 mmol) was dissolved in ethanol (20 mL) and neutralized with triethylamine (1.53 mL, 11 mmol). To this solution was added the ester **14** (1.28 g, 5 mmol), and the resulting mixture was refluxed for 24 h. The reaction mixture was then evaporated to dryness and partitioned between ethyl acetate and water. The organic extracts were dried, concentrated, and purified by column chromatography (eluant ethyl acetate) affording the title compound **19** as a white solid (0.65 g, 34%) together with a small amount of unreacted **14**. **19**: IR ($CHBr_3$) ν_{max} 2980, 2932 (N-H), 1693, 1682, 1672 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.4–7.3 (m, 5 H, Ph), 4.56 (s, 2 H, $PhCH_2$), 4.02 (br s, 1 H, N-H), 3.42 (dt, 2 H, H-7$_{eq}$, J = 12, 4 Hz), 3.3 (dt, 2 H, H-7$_{ax}$, J = 12, 7 Hz), 2.41 (s, 2 H, H-4), 1.6–1.5 (m, 4 H, H-6), 1.46 (s, 9 H, tBu); MS 691 (2M + H)$^+$; 346 (M + H)$^+$, 290. Anal. ($C_{19}H_{27}N_3O_3$) C, H, N.

2-Benzyl-8-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-1,2,8-triazaspiro[4.5]decan-3-one (3v). Compound **19** was converted to **3v** in 59% overall yield by treatment with HCl in dioxane and then alkylation with 2-(5-fluoro-1*H*-indol-3-yl)-ethyl bromide as described above for the preparation of **3a**. **3v** hydrochloride: ^{1}H NMR (DMSO-d_6) δ 11.05 (s, 1 H, indole N-H), 10.55 (br s, 1 H, NH^+), 7.45–7.2 (m, 8 H, Ar), 6.92 (dt, 1 H, indole H-6), 4.45 (s, 2 H, $PhCH_2$), 3.61 (s, 2 H, H-4), 3.55–2.9 (m, 8 H, H-7, H-1′, H-2′), 2.0–1.7 (m, 4 H, H-6); HRMS found MH^+ 407.2227, calcd for $C_{24}H_{28}FN_4O$ 407.2247.

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Supporting Information Available: Spectroscopic and analytical data for compounds **3b–q**, **6**, and **7** (5 pages). Ordering information is given on any current masthead page.

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