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2-Aryl Indole NK_1 Receptor Antagonists: Optimisation of Indole Substitution

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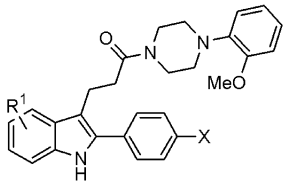
Abstract—The synthesis and biological evaluation of a series of 2-aryl indoles with high affinity for the human neurokinin-1 (hNK_1) receptor are reported, concentrating on optimisation of the indole substitution.

The mammalian tachykinin substance P (SP) has been implicated in numerous conditions[1–3] including migraine, cystitis, asthma, depression and cytotoxin-induced emesis. This wide range of therapeutic indications has led to the development of various potent antagonists[3] of the receptor to which SP preferentially binds, neurokinin-1 (NK_1). Here we report the synthesis and biological activity of a new series of such compounds, concentrating on optimisation of the indole substitution; other publications will report work on other parts of the molecule.

The lead compound for this series was obtained from a combinatorial library[4] which comprised an array of 2-aryl indoles bearing a pendant amide substituent at the 3-position. Deconvolution of active mixtures showed that the compound with highest affinity in the in vitro NK_1 binding assay[5] was **1a** (hNK_1 IC_{50} 1.0 nM). A convenient in vivo assay for CNS penetration is the foot-tapping exhibited by gerbils when under stress. This action can be induced by the central infusion of an NK_1-selective agonist (GR 73632);[6] the effect (inhibition of foot-tapping or otherwise) of systemic administration of the test compounds prior to this infusion provides an indication of brain penetration and central duration of action. The result is given as a percentage inhibition of values observed in vehicle-treated animals or an ID_{50} calculated by non-linear least-squares regression analysis of mean data. This assay showed that **1a** was weak in vivo, giving only 46% inhibition of foot-tapping with a dose of 3 mg/kg iv immediately following pre-treatment. It also exhibited poor pharmacokinetics having a bioavailability of only 3% in rat but its nanomolar binding affinity in vitro and structural novelty as a NK_1 receptor antagonist made it a very good starting point for further research.



1a R^1=5-Me, X=Br

A number of analogues of type **1** (see Table 1) were made to investigate the SAR of substitution around the 4, 5, 6 and 7 positions of the indole nucleus. All amide couplings were carried out using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) as coupling agent (hereafter referred to as 'standard coupling'. Compound **1c** (R^1 = H, X = Cl) was obtained from the coupling of indole-3-propionic acid followed by selective bromination[7] at the 2-position, and Suzuki[8] coupling with 4-chlorobenzeneboronic acid. Compound

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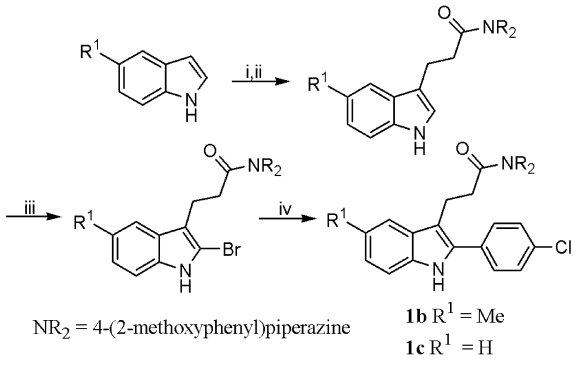
1b (R^1 = 5-Me, X = Cl) was made in the same way, the 5-methylindole-3-propionic acid being obtained from reaction of 5-methylindole with acrylic acid (Scheme 1).

Compounds **1d**, **1e** and **1g** were made via a Fischer indole synthesis followed by standard coupling (Scheme 2). Compounds **1f** and **1h–k** were made using a resin-bound Fischer indole synthesis:[9] resin **2** (0.52 mmol/g),[10] based on Kenner's safety catch linker,[11] was coupled with 4-(4-chlorobenzoyl)butyric acid to give **3**. This was treated with substituted phenylhydrazines to form the indoles which were released from the resin by treating with bromoacetonitrile followed by standard coupling (Scheme 3).

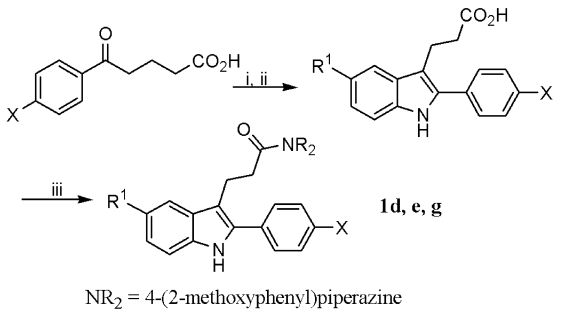
Table 1. Indole substitution and NK_1 activity for compounds **1a–k**

Compound	R^1	X	hNK_1 IC_{50} (nM)[a]
1a	5-Me	Br	1.0±0.2
1b	5-Me	Cl	0.6±0.16
1c	H	Cl	31±11
1d	5-F	H	87±43
1e	5-Cl	H	5.6±2.8
1f	4-Cl	Cl	950±40
1g	5-Cl	Cl	0.89±0.36
1h	6-Cl	Cl	4.9±1.8
1i	5,7-Cl_2	Cl	14±8
1j	5-OCF_3	Cl	8.9±6.7
1k	4,6-Cl_2	Cl	570±354

[a]Displacement of [^{125}I]-labelled substance P from the cloned hNK_1 receptor expressed in CHO cells (n = 3).



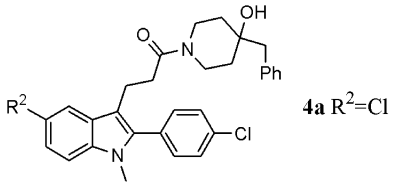
Scheme 1. Reagents: (i) acrylic acid, Ac_2O, AcOH (rt, 7 days, 50%); (ii) 4-(2-methoxyphenyl)piperazine·HCl, HOBt, Et_3N, EDC, THF (rt, 16 h); (iii) TMSBr, DMSO (rt, 30 min, 50%); (iv) 4-chlorobenzeneboronic acid, $Pd(dppd)Cl_2$, Na_2CO_3, DMF (80 °C, 18 h).



Scheme 2. Reagents: (i) R^1-$PhNHNH_2$·HCl, Et_3N, EtOH (rt, 4h); (ii) TFA (reflux, 2 h, 11–32% over two steps); (iii) 4-(2-methoxyphenyl)piperazine·HCl, 1-hydroxybenzotriazole, Et_3N, EDC, THF (rt, 16 h, 44–84%).

The in vitro NK_1 binding results for these compounds are shown in Table 1. It can be seen that substitution at the 5-position is necessary for good binding affinity and substitution at position 4, 6 or 7 is detrimental. Comparison of **1d** and **1e** shows that methyl and chloro are significantly better than fluoro, whilst comparison of **1b** and **1g** shows that methyl and chloro are similar. This could be due to the size, the fluoro being too small to have an effect on the critical part of the binding site. The chloro compound was taken on as the preferred lead over the methyl because it was thought that there would be less chance of metabolic oxidation of the comparatively electron-poor aromatic ring.

Other work had shown that generally the optimum aryl group at the 2-position is 4-chlorophenyl and *N*-methylation improves the overall profile.[12] The gerbil foot-tapping assay showed that better in vivo results were achieved for amides derived from 4-benzyl-4-hydroxypiperidine instead of 4-(2-methoxyphenyl)piperazine.[13] Combining these changes with the preferred 5-chloro substituent led to compound **4a** which had higher NK_1 binding affinity (hNK_1 IC_{50} 0.16 nM) and showed significant improvement over the lead **1a** in the gerbil assay (ID_{50} 0.3 mg/kg iv) immediately following pre-treatment. Analogues of type **4** (see Table 2) were then made to further optimise the 5-substituent of the indole.

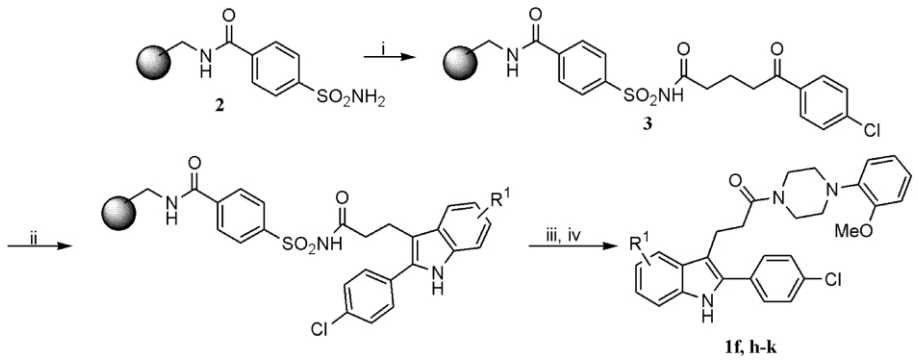


A Fischer indole synthesis followed by methylation (Scheme 4) gave the *N*-methylated indole propionic ester intermediate **5**. Hydrolysis of the ester followed by standard coupling with 4-benzyl-4-hydroxypiperidine gave **4b**. Compounds **4e–k** were obtained from palladium-catalysed couplings of the bromo-compound **4b** using Stille,[14] Suzuki[15] or Buchwald[16] conditions (Scheme 4). A Stille coupling of **5** with vinyltributyltin followed by standard hydrolysis and coupling gave **4c** and Wacker oxidation[17] of the vinyl group furnished **4d** (Scheme 5).

Table 2. 5-Substitution and NK_1 activity for compounds **4a–k**

Compound	R^1	hNK_1 IC_{50} (nM)[a]
4a	Cl	0.16±0.09[b]
4b	Br	0.22±0.10[b]
4c	Vinyl	0.27±0.19[b]
4d	Acetyl	0.19±0.09[c]
4e	2-Furyl	0.79±0.46[c]
4f	2-Pyridyl	1.7±0.9[c]
4g	3-Pyridyl	5.5±2.4[c]
4h	4-Pyridyl	5.5±2.1[c]
4i	1-Pyrrolidinyl	2.3±1.2[c]
4j	1-Piperidinyl	3.3±1.4[c]
4k	4-Morpholinyl	6.3±1.3[c]

[a]Displacement of [^{125}I]-labelled substance P from the cloned hNK_1 receptor expressed in CHO cells.
[b]n = 4.
[c]n = 3.

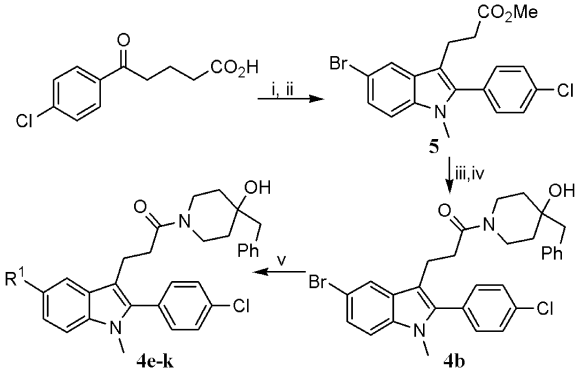


Scheme 3. Reagents: (i) 4-(4-Chlorobenzoyl)butyric acid (10 equiv), DIC (5 equiv), DMAP (1 equiv), DCM (rt, 96 h); (ii) R^1-PhNHNH$_2$·HCl (10 equiv), $ZnCl_2$ (10 equiv), AcOH (70 °C, 16 h); (ii) $BrCH_2CN$ (24 equiv), Hünig's base (5 equiv), NMP (rt, 16 h); (iii) 4-(2-methoxyphenyl)piper-

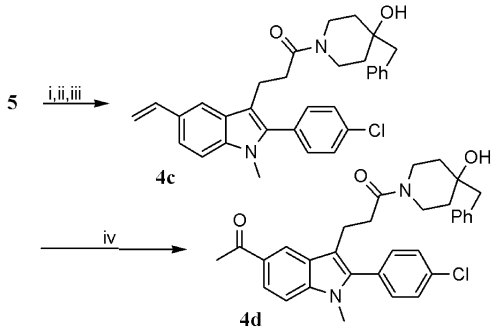
The in vitro NK_1 binding results for these compounds are shown in Table 2. Good NK_1 binding is consistently achieved. Both apolar and polar substituents are tolerated but there appears to be a size limit: the general trend is that smaller groups give better binding. The acetyl compound **4d** was tested in the gerbil assay and it was shown to be inferior to **4a**, giving only 14% inhibition of foot-tapping at 1 mg/kg iv after a pre-treatment time of 2 h. Thus, compound **4a** was still considered the best compound but it suffered from having an oral bioavailability of only 2.3% in rat. The plasma clearance rate in rats (31 mL/min/kg) was shown to be significantly lower than the hepatic blood flow, suggesting that poor oral absorption, possibly due to low water solubility, was to blame.

To try to solve this problem, several more polar compounds were made, introducing a basic nitrogen, with the aim of increasing solubility and aiding absorption. This gave rise to an imidazopyridine and a series of azaindoles, compounds **6a**–**e** (see Table 3).

Reaction of 2-amino-5-chloropyridine with 2-bromo-4′-chloroacetophenone gave the 2-aryl imidazopyridine **7**



Scheme 4. Reagents: (i) 4-Bromophenylhydrazine·HCl, TFA (65 °C, 24 h); (ii) NaH, MeI, DMF; (iii) LiOH·H_2O, MeOH, H_2O; (iv) 4-benzyl-4-hydroxypiperidine, 1-hydroxybenzotriazole, Et_3N, EDC, THF (rt, 16 h); (v) (a) R^1SnBu_3, LiCl, $Pd(PPh_3)_4$, toluene (reflux, 16 h, 20–40%) or (b) $R^1B(OH)_2$, Na_2CO_3, Pd_2dba_3, tris-(2-furyl)phosphine, DME (75 °C, 16 h, 5–30%) or (c) R_2NH, NaO^{t}Bu, BINAP, Pd_2dba_3, toluene (80 °C, 24 h, 6–19%).

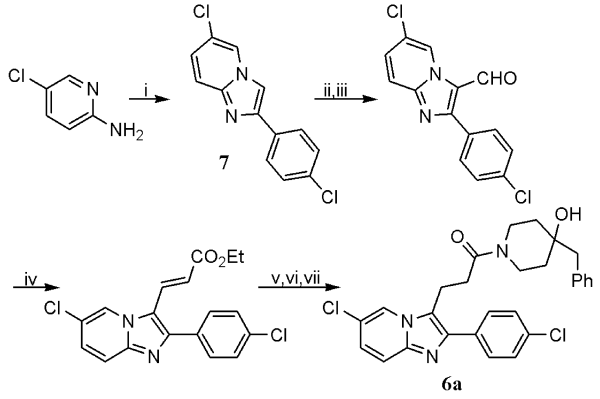


Scheme 5. Reagents: (i) Vinyltributyltin, LiCl, $Pd(PPh_3)_4$, toluene (reflux, 16 h, 41%); (ii) LiOH·H_2O, MeOH, H_2O; (iii) 4-benzyl-4-hydroxypiperidine, 1-hydroxybenzotriazole, Et_3N, EDC, THF (rt, 16 h, 73%); (iv) O_2, $PdCl_2$, CuCl, DMF, H_2O (rt, 24 h, 65%).

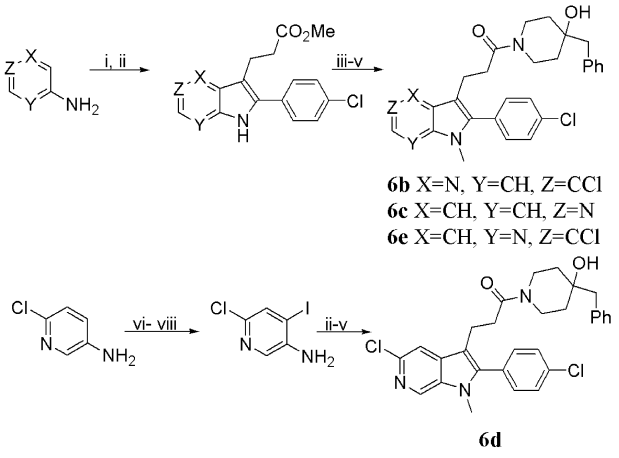
Table 3. Structure and NK_1 activity for compounds **6a**–**e**

Compound	Position of N	X	Y	hNK_1 IC_{50} (nM)[a]
6a	3a	Cl	—	0.78±0.20
6b	4	Cl	Me	2.6±0.8
6c	5	—	Me	41±16
6d	6	Cl	Me	0.22±0.07
6e	7	Cl	Me	0.15±0.02

[a]Displacement of [^{125}I]-labelled substance P from the cloned hNK_1 receptor expressed in CHO cells ($n=3$).

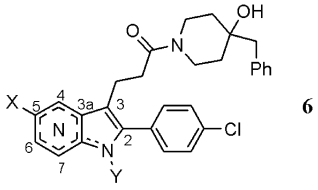


Scheme 6. Reagents: (i) 2-Bromo-4′-chloroacetophenone, DMF (150 °C, 19 h, 28%); (ii) Chloromethylene dimethylammonium chloride, DMF (75 °C, 16 h); (iii) NaOH (79%); (iv) triethyl phosphonoacetate, NaH, DMF (rt, 18 h, 47%); (v) LiOH·H_2O, MeOH, H_2O; (vi) 4-benzyl-4-hydroxypiperidine, 1-hydroxybenzotriazole, Et_3N, EDC, THF (rt, 16 h, 10%); (vii) $NaBH_4$, pyridine, MeOH.



Scheme 7. Reagents: (i) I_2, $AgSO_4$, EtOH (rt, 24 h); (ii) methyl 5-(4′-chlorophenyl)pent-4-ynoate, $Pd(OAc)_2$, LiCl, Na_2CO_3, DMF (70 °C, 24 h, 20–25%); (iii) NaH, MeI, DMF; (iv) LiOH·H_2O, MeOH, H_2O; (v) 4-benzyl-4-hydroxypiperidine, 1-hydroxybenzotriazole, Et_3N, EDC, THF (rt, 16 h); (vi) $(BOC)_2O$, 1,4-dioxane (reflux, 18 h, 94%); (vii) BuLi, I_2, TMEDA, Et_2O (−78 to −10 °C, 18 h, 55%); (viii) TFA, DCM.

A Vilsmeier formylation followed by a Wadsworth–Emmons reaction and subsequent standard hydrolysis, coupling and finally reduction gave **6a** (Scheme 6). Compounds **6b–e** were made from iodination of the corresponding amino-pyridines followed by palladium-catalysed coupling[18] with methyl 5-(4′-chlorophenyl)-pent-4-ynoate; standard methylation, hydrolysis and coupling gave the target compounds (Scheme 7).



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The in vitro NK_1 binding results for the azaindoles are shown in Table 3. NK_1 affinity is generally excellent, the exception being the 5-azaindole **6c** which is consistent with earlier results where it was shown that 5-substitution is necessary. The 6- and 7-azaindoles, **6d** and **6e**, were of most interest and compound **6e** was subjected to further in vivo investigation. In the gerbil foot-tapping assay, it gave 100% inhibition of foot-tapping at 1 mg/kg iv immediately following drug pre-treatment, showing that it was brain-penetrant, but this dropped to 10% inhibition after a pre-treatment time of 2 h, implying that the compound is rapidly cleared.

Pharmacokinetic studies conducted in portal vein cannulated rats on **4a** and **6e** gave hepatic portal AUCs of 24.7 ng/mL·h for **4a** compared with 96.8 ng/mL·h for **6e** and the systemic AUCs were <4 ng/mL·h for **4a** compared with 8 ng/mL·h for **6e**. The almost 4-fold increase in hepatic portal vein levels suggests that the azaindole was more efficiently absorbed, as had been hoped, but the fact that it did not have significantly improved systemic levels compared to **4a** shows that both compounds were subject to first pass metabolism. For **6e**, this strengthened the hypothesis drawn from the gerbil results.

In conclusion, we have explored the effect of substitution on the core of a new series of high affinity NK_1 antagonists based on 2-aryl indoles. We have shown that 5-substitution is critical for good NK_1 receptor binding but that there is considerable tolerance for different 5-substituents, provided that they are small. These compounds have high binding affinity and brain penetration but are compromised by poor oral absorption. Introduction of a second nitrogen into the 6- and 7-positions of the indole nucleus is well tolerated. These compounds have high binding affinity and good central activity, with improved absorption, but high first pass metabolism limits oral bioavailability.

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References and Notes

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