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2-Aryl Indole NK_1 Receptor Antagonists: Optimisation of the 2-Aryl Ring and the Indole Nitrogen Substituent

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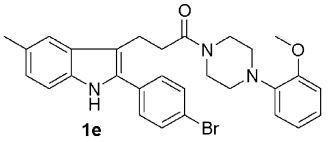
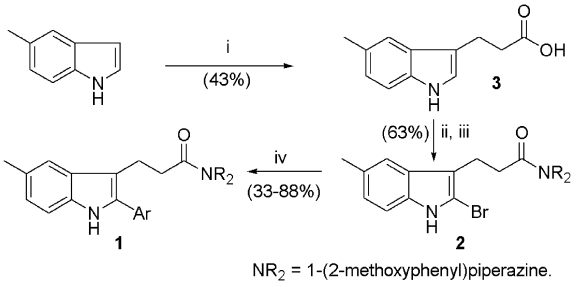
Abstract—Novel 2-aryl indole hNK_1 receptor ligands were prepared utilising palladium cross-coupling chemistry of a late intermediate as a key step. Compounds with high hNK_1 receptor binding affinity and good brain penetration (e.g., **9d**) were synthesised.

The human neurokinin-1 (hNK_1) receptor in the central nervous system is a potential therapeutic target for a number of indications, including chemotherapy-induced emesis, anxiety and depression.[1–3] This wide range of indications has led to the development of various potent NK_1 antagonists.[3]



1e

Compound **1e** was a screening hit identified from a combinatorial library[4] comprising an array of 2-aryl indoles with pendant amide substituents at the 3-position which showed high affinity for the hNK_1 receptor (IC_{50} 1.0 nM).[5] The high binding affinity and structural originality of **1e** as an NK_1 receptor antagonist made this an excellent starting point for a medicinal chemistry programme. Here we report the synthesis of a new series of compounds where the importance of the nitrogen substituent and 2-aryl ring substitution pattern for biological activity was investigated. The Fischer indole synthesis used to synthesise the library did allow flexibility in substitution of the 2-aryl ring, however this group is introduced early in the synthesis. An alternative approach which introduced the 2-aryl group at a later stage in the synthesis was required in order to conveniently optimise this group. This was achieved using palladium catalysed Suzuki coupling reactions[6] of the key 2-bromoindole **2** with commercially available boronic acids to give compounds of type **1**. The 2-bromoindole **2** was synthesised from the commercially available 5-methylindole by alkylation with acrylic acid in the presence of acetic anhydride and acetic acid followed by amide coupling using 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) with 1-(2-methoxyphenyl)piperazine. This compound was then selectively brominated in the 2-position



Scheme 1. (i) Acrylic acid, Ac_2O, AcOH, 3 days, rt; (ii) 1-(2-methoxyphenyl)piperazine hydrochloride, EDC, HOBt, Et_3N, THF; (iii) Me_3SiBr, DMSO; (iv) $ArB(OH)_2$, $Pd(dppb)Cl_2$, Na_2CO_3, DME, 80 °C.

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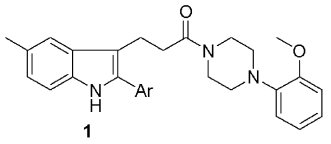
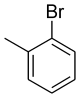
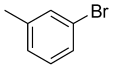
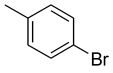
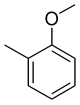
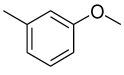
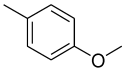
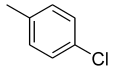
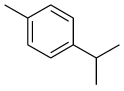
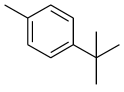
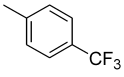
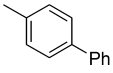
using bromotrimethylsilane in dimethylsulfoxide[7] to give **2** (Scheme 1). A number of analogues of type **1** were then made and their corresponding biological activities are shown in Table 1.

Table 1.



1

No.	Ar	hNK_1 IC_{50}[a] (nM)	Gerbil %[b] inhibition (mg/kg iv)
1a	H	18% at 100±7%†	
1b		6.1±1.3	
1c		89±9†	
1d		37% at 100±9%†	
1e		1.0±0.2	46% at 3
1f		82±18	
1g		8.0±2.0	
1h		1.5±0.6	
1i		0.60±0.16	22% at 3
1j		0.2±0.10	100% at 3
1k		6.3±4.3	
1l		0.44±0.13	
1m		58% at 100±8%†	
1n		7.6±4.0	

[a]Displacement of [^{125}I]-labelled substance P from the cloned hNK_1 receptor expressed in CHO cells ($n=3$) unless indicated ($n=4$)†.[5]
[b]Inhibition of foot-tapping by iv administration of test compound immediately prior to icv infusion of GR73632. The duration of foot-tapping was recorded for 5 min and is expressed as a percentage inhibition of values observed in vehicle-treated animals.[8]

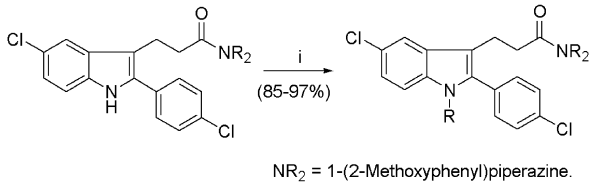
The results show that deletion of the 2-aryl ring was detrimental to hNK_1 receptor binding affinity (**1a**) and that a substituent in the 4-position appears optimal (**1b**–**h**), therefore, a range of analogues with 4-substituents (**1i**–**n**) were synthesised using similar chemistry. Compound **1n** was prepared from compound **1e** and phenyl boronic acid using the Suzuki reaction conditions described in Scheme 1.

A range of 4-substituents, including both electron withdrawing (4-chloro) and electron donating (4-isopropyl) groups improve binding affinity over the lead compound **1e**. The size of this substituent appears to be significant as larger groups (*tert*-butyl, phenyl) are less favoured. Replacement of the 2-phenyl ring with 4-pyridyl (**1m**) also resulted in loss of binding affinity.

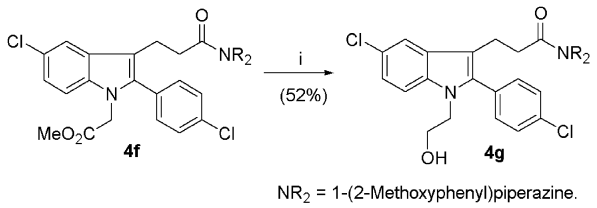
Selected compounds with high binding affinity for the hNK_1 receptor were tested for CNS activity in the gerbil foot-tapping assay.[8] In this protocol, the test compound is administered iv immediately prior to icv injection of a NK_1 receptor agonist and a percentage inhibition of foot-tapping is measured relative to control. Compound **1j** showed good activity in this assay, demonstrating it is a brain penetrant.

In order to further improve brain penetration, a series of compounds was synthesised to remove the indole N/H hydrogen bond donor and reduce the polarity of the compounds.[9] *N*-Alkylation of the indoles was achieved using sodium hydride and a suitable electrophile as depicted in Scheme 2. This series was synthesised bearing a 5-chloro substituent which has been shown to give high hNK_1 receptor binding affinity.[10] Reduction of the ester **4f** with lithium borohydride led to the alcohol **4g** (Scheme 3). The biological results are shown in Table 2.

These results suggest that there is only a limited space available in the binding site in this region of the molecule. *N*-Methylation (**4b**) improves affinity whereas larger groups, especially those with α- or β- branching, lose binding affinity.



Scheme 2. (i) NaH, DMF, RX.

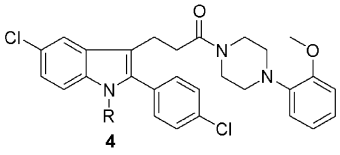


Scheme 3. (i) $LiBH_4$, $PhCH_3$, THF.

Two compounds with the 2-aryl substituent bridged to the indole nitrogen were made using intramolecular Heck reactions (Scheme 4).

Comparison of these conformationally restricted ring-fused compounds **5** (hNK_1 55% at 100 nM) and **6** (hNK_1 42% at 100 nM) with their closely related non-fused analogues (e.g., **1b** and **4b**) suggests that the 2-aryl group is not coplanar with the indole in the active conformation. It also provides a possible explanation for the increased affinity of **4b** over **4a**; increasing the steric bulk around the indole nitrogen by methylation forces the 2-aryl group out of coplanarity and into a more favourable conformation for binding.

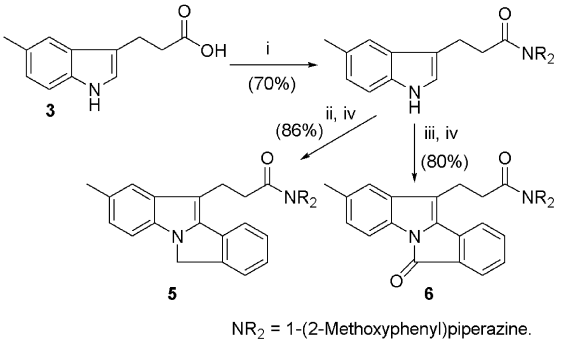
Table 2.



4

No.	R	hNK_1 IC_{50}[a] (nM)
4a		0.89±0.36
4b		0.28±0.14
4c		5.2±3.3†
4d		103±57
4e		96±56
4f		15±7
4g		0.97±0.47

[a]Displacement of [^{125}I]-labelled substance P from the cloned hNK_1 receptor expressed in CHO cells ($n=3$) unless indicated ($n=4$)†.[5]

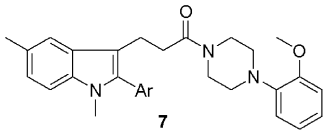


Scheme 4. (i) $R_2NH{\cdot}HCl$, HOBt, EDC, Et_3N, THF; (ii) 2-bromobenzyl bromide, NaH, DMF; (iii) 2-bromobenzoyl chloride, NaH, DMF; (iv) $Pd(PPh_3)_4$, KOAc, DMA, 160 °C.

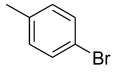
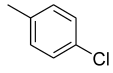
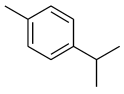
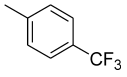
A range of compounds were then *N*-methylated under standard conditions (NaH, MeI, DMF) to give the final compounds **7** (Table 3).

It can be seen from the results that methylation of the indole nitrogen consistently gave compounds with high

Table 3.

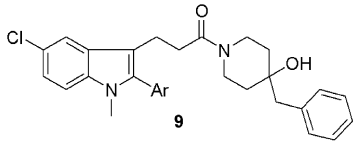


7

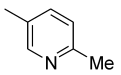
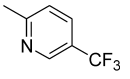
No.	Ar	hNK_1 IC_{50}[a] (nM)	Gerbil[b] (mg/kg iv)	
			% Inhib.	ID_{50}
7e		0.14±0.08	100% at 3	0.5
7i		0.11±0.05†	100% at 3	
7j		0.33±0.17	100% at 3	
7l		0.14±0.08†	93% at 3	

[a]Displacement of [^{125}I]-labelled substance P from the cloned hNK_1 receptor expressed in CHO cells ($n=3$) unless indicated ($n=4$)†.[5]
[b]Inhibition of foot-tapping by iv administration of test compound immediately prior to icv infusion of GR73632. The duration of foot-tapping was recorded for 5 min and is expressed as a percentage inhibition of values observed in vehicle-treated animals. The ID_{50} was calculated by non-linear least-squares regression analysis of mean data.[8]

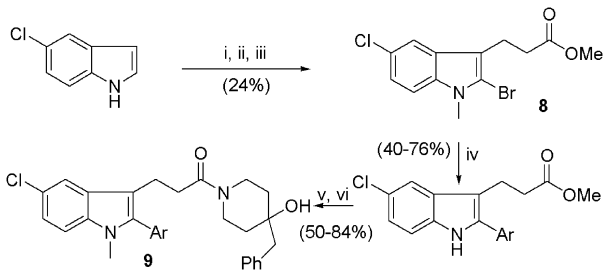
Table 4.



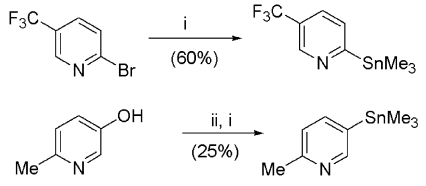
9

No.	Ar	hNK_1 IC_{50}[a] (nM)	Gerbil ID_{50}[b] (mg/kg iv)
9a		0.92±0.11	
9b		2.9±1.7†	
9c		0.12±0.10	0.68
9d		0.12±0.06	0.1

[a]Displacement of [^{125}I]-labelled substance P from the cloned hNK_1 receptor expressed in CHO cells ($n=3$) unless indicated ($n=4$)†.[5]
[b]Inhibition of foot-tapping by iv administration of test compound immediately prior to icv infusion of GR73632. The duration of foot-tapping was recorded for 5 min and percentage inhibition of values observed in vehicle-treated animals measured. The ID_{50} was calculated by non-linear least-squares regression analysis of mean data.[8]



Scheme 5. (i) Acrylic acid, Ac_2O, AcOH, 3 days, rt; (ii) NaH, DMF, MeI; (iii) Me_3SiBr, DMSO; (iv) $ArSnMe_3$, $Pd(PPh_3)_4$, LiCl, PhMe, 110 °C; (v) $LiOH{\cdot}H_2O$, MeOH, H_2O; (vi) 4-hydroxy-4-benzylpiperidine, HOBt, EDC, Et_3N, THF.



Scheme 6. (i) Me_6Sn_2, LiCl, Li_2CO_3, $Pd(PPh_3)_4$, THF, reflux; (ii) $(CF_3SO_2)O$, Et_3N, CH_2Cl_2.

hNK_1 receptor binding affinity. It was also pleasing to see that all the compounds tested in the gerbil foot-tapping assay were active and therefore brain penetrant. A significant improvement in activity was seen for **7e** and **7i** over their non-methylated analogues (**1e** and **1i**).

Other work had shown that replacement of the 2-(methoxyphenyl)piperazine group with 4-hydroxy-4-benzylpiperidine was beneficial.[11] The side chain, however, no longer contains a basic nitrogen, a feature which generally conveys good physical properties and generally aids water solubility. Several compounds were therefore made with a basic nitrogen instead incorporated into the 2-aryl ring and the effects on hNK_1 binding affinity and activity in the gerbil assay investigated. They were synthesised from compound **8** using Stille coupling reactions with pyridyl stannanes. Compound **8** was synthesised from commercially available 5-chloroindole by alkylation with acrylic acid followed by *N*-methylation and methyl ester formation in one pot using sodium hydride and iodomethane. Selective bromination then led to **8** (Scheme 5). The two pyridyl stannanes that were not commercially available were synthesised according to Scheme 6.[12] The biological results for these pyridyl compounds are shown in Table 4.

In contrast to the 4-pyridyl substituted derivative **1m**, which had poor binding affinity, these results showed that it was possible to introduce a basic centre into the 2-aryl group and achieve excellent hNK_1 receptor binding affinity. In addition, compound **9d** (hNK_1 IC_{50} 0.12 nM) showed excellent activity in the gerbil foot-tapping assay (ID_{50} 0.1 mg/kg) which represents a significant in vivo improvement over the lead compound **1e** (46% at 3 mg/kg, iv).

In summary, a new series of 2-aryl indole hNK_1 antagonists has been evaluated. It has been shown that by judicious choice of *N*-substituents and 2-aryl substitution, compounds with high binding affinity and excellent in vivo activity may be prepared. These results were achieved utilising a common synthetic intermediate to allow the production of final compounds as the last step.

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