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2-Aryl Indole NK_1 Antagonists: Optimisation of the Amide Substituent

Duncan Shaw,[a,*] Gary G. Chicchi,[c] Jason M. Elliott,[a] Marc Kurtz,[c] Denise Morrison,[a] Mark P. Ridgill,[a] Nicola Szeto,[a] Alan P. Watt,[a] Angela R. Williams[b] and Christopher J. Swain[a]

[a]*Department of Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*

[b]*Department of Pharmacology, Merck Sharp & Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*

[c]*Department of Biochemistry, Merck Research Laboratories, 126 E. Lincoln Ave, Rahway, NJ 07065, USA*

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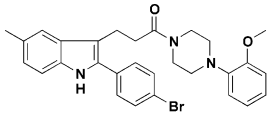
Abstract—The in vivo properties of a series of 2-arylindole NK_1 antagonists have been improved, by modification of the amide substituent. The 1-(2-methoxyphenyl)piperazine amide was identified as a major area of metabolism in the lead compound **1**. Replacement of this amine moiety by a 4-benzyl-4-hydroxypiperidine resulted in a compound **18** with reduced clearance and improved central duration of action. © 2001 Published by Elsevier Science Ltd.

Neurokinin 1 (NK_1) antagonists have long been described as potential therapeutic agents and numerous small molecule ligands have been described. The progress in this area has been recently reviewed.[1]



1

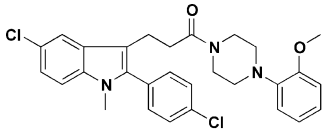
The 2-arylindole **1** was identified as an interesting lead compound from screening of a combinatorial library, prepared using the chemistry described by Hutchins et al.[2] The profile of this lead was promising in that it showed good hNK_1 binding (hNK_1 $IC_{50} = 1.0 \pm 0.20$ nM) and modest in vivo activity in the gerbil foot tapping assay[3] (46% inhibition at 3 mg/kg iv at the 0 h. time point).

The pharmacokinetic profile of **1** in rats showed great scope for improving the activity of this lead in vivo (Table 1). Although the compound distributes out of body water, it is compromised by an extremely high clearance rate.[4] This leads to a short half life and low oral bioavailability (3%).

*Corresponding author. Fax: +44-1279-440390; e-mail: duncan_shaw@merck.com

To investigate whether the high clearance rate was due to hepatic metabolism, a rat liver microsome study was conducted.[5] This showed that the primary routes of metabolism were initial *O*-demethylation of the aryl methyl ether and *N*-dephenylation of the arylpiperazine group. There is extensive literature precedent for this process in other related 2-methoxyphenylpiperazine systems (Scheme 1).[6]

We have recently reported our studies of the optimisation of the indole core[7] which lead to the identification of the *N*-methyl-5-chloro-2-(4-chlorophenyl)indole, exemplified by **2** which showed improved affinity for the hNK_1 receptor (IC_{50} 0.28 ± 0.14 nM).



2

The desired *N*-methyl-5-chloro-2-(4-chlorophenyl) indole acid was synthesised using the chemistry depicted in Scheme 2. This allowed access to a wide range of amides by using a simple peptide coupling modified to be applicable to rapid analogue synthesis.

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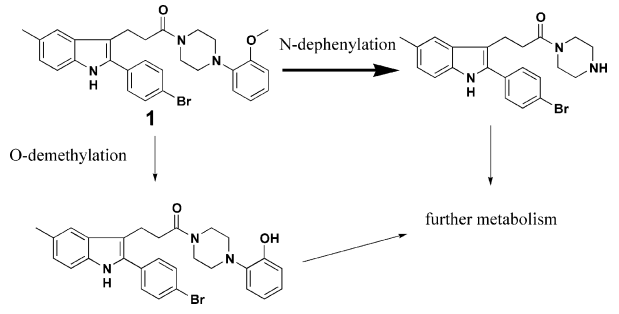
Modification of the amide substituent began with investigation of piperazine amides in order to find potential replacements for the 2-methoxyphenyl group.

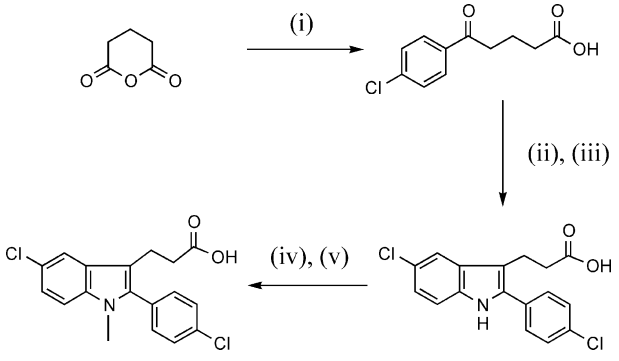
The initial results of this study were encouraging; reasonable binding affinity was achieved with a range of lipophilic substituents (Table 2). For example, the benzyl piperazine amide **3** was equipotent with the lead structure **2**. Closer examination of the data identified a requirement for a lipophilic substituent of clearly defined size. The preferred size of this substituent was well illustrated by the fact that whilst isopropyl **4** appeared to be too small to give good binding affinity, cyclopropylmethyl **5** exhibited good potency. The cyclohexylmethyl **6** substituent appeared to be slightly too large for the lipophilic pocket, in contrast to cyclohexyl **7** which gave high affinity. Another feature was that alkyl substituents containing quaternary carbon atoms gave moderate affinity (e.g., *neo*-pentyl **8**) whilst branched alkyl groups gave good binding (e.g., 3-methylbutyl **9**). The *N*-methylphenylglycinamide **10** exhibited extremely good binding affinity whereas the *N*-phenylglycinamide **11** was much weaker; again this was consistent with a lipophilic pocket which does not tolerate a polar NH group.

Table 1. Pharmacokinetic profile of **1** in rat

iv dose	1.5 mg/kg
po dose	1.5 mg/kg
Half life	1.4 h
Mean residence time	0.9±0.1 h
Plasma clearance rate	179±75 mL/min/kg
Volume of distribution (steady state)	9.5±4.3 L/kg
Oral bioavailability	3±2%
C_{max}	2±1 ng/mL
T_{max}	1.1±0.9 h

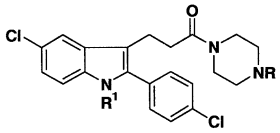


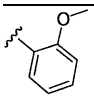
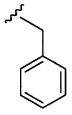
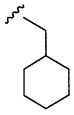
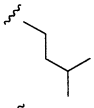
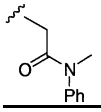
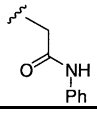
Scheme 1.



Scheme 2. (i) Chlorobenzene, $AlCl_3$; (ii) 4-chlorophenylhydrazine, EtOH; (iii) TFA; (iv) NaH, MeI, THF; (v) KOH, MeOH.

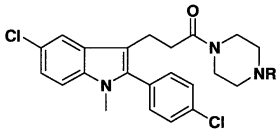
Table 2. Variation of biological properties with the introduction of aryl piperazine substituents

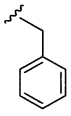
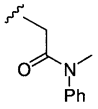


R		R^1	hNK_1 IC_{50} (nM)[a]	R		R^1	hNK_1 IC_{50} (nM)[a]
	**2**	Me	0.28 (±0.14)		**3**	Me	0.30 (±0.14)
	**4**	Me	13 (±6)		**5**	Me	0.78 (±0.29)
	**6**	Me	2.9 (±1.8)		**7**	Me	0.35 (±0.18)
	**8**	Me	2.0 (±1.4)		**9**	Me	0.34 (±0.06)
	**10**	Me	0.13 (±0.08)		**11**	H	30 (±3.2)

[a]Displacement of [^{125}I]-labelled substance P from the cloned hNK_1 receptor expressed in CHO cells ($n=3$).[8]

Table 3. Variation of in vivo activity in the gerbil foot tapping assay with the introduction of piperazine substituents



R		hNK_1 IC_{50} (nM)[a]	Gerbil foot tapping %inhibition[b]	
			$t=0$ h (mg/kg iv)	$t=2$ h (mg/kg iv)
	**3**	0.30 (± 0.14)	100@3	17@3
	**7**	0.13 (±0.08)	100@3	7@3
	**10**	0.35 (±0.18)	87@1	6@1

[a]Displacement of [^{125}I]-labelled substance P from the cloned hNK_1 receptor expressed in CHO cells ($n=3$).[8]
[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.[3]

As illustrated in Table 3, some of these modifications of the piperazine substituent gave an improved in vivo profile at $t=0$ h in the gerbil assay. This indicated that good brain penetration had been achieved. The effects, however, were of short duration because activity returned to baseline at $t=2$ h suggesting that rapid clearance of these compounds remained a problem.

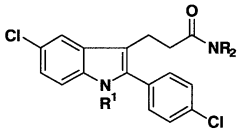
We reasoned that this deficiency was probably due to metabolic *N*-dealkylation of the piperazine and we therefore began to consider further the replacement of the piperazine ring itself.

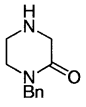
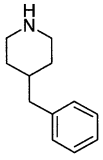
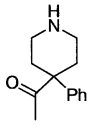
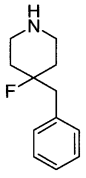
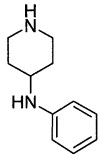
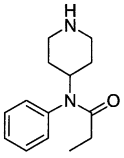
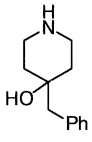
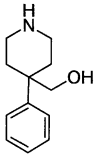
At this point, it was noted that good affinity was retained when the *N*-benzylpiperazine was replaced with a 4-*N*-benzylpiperazin-3-one group **12** (Table 4). This illustrated that it was not necessary to have a basic nitrogen atom to achieve good binding. However, exchanging the nitrogen of the piperazine with a carbon atom to give the corresponding 4-benzylpiperidine **13** resulted in a significant reduction in binding affinity suggesting the possible loss of a hydrogen bond. Furthermore, both the 4-acetyl-4-phenylpiperidine **14** and 4-fluoro-4-benzylpiperidine **15** with groups capable of acting as hydrogen bond acceptors were good piperazine replacements in terms of binding affinity.

Another example of this is the 4-(*N*-phenyl)piperidine **16** which had moderate affinity whereas the corresponding propionamide **17** (a potential hydrogen bond acceptor) was highly potent, and brain penetrant although it exhibited poor duration of action. The exact position of the heteroatom also had a profound effect on NK_1 binding. The 4-benzyl-4-hydroxy piperidine **18** was an excellent replacement for the *N*-benzylpiperazine but the 4-hydroxymethyl-4-phenyl piperidine **19** showed decreased binding affinity.

The best replacement identified for the benzylpiperazine in terms of in vivo activity was the 4-benzyl-4-hydroxypiperidinol **18**, which was potent in vivo at $t=0$ h and showed good activity at the 2-h time point. **18** was the first compound in this series to achieve good central duration of action in this assay (Table 5).

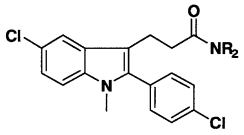
Table 4. Variation of binding affinities with the introduction of various non piperazine amide substituents

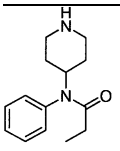
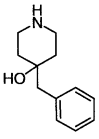


HNR_2	R^1	hNK_1 IC_{50} (nM)[a]	HNR_2	R^1	hNK_1 IC_{50} (nM)[a]
	**12** Me	0.39 (±0.08)		**13** Me	2.2 (± 0.1)
	**14** Me	0.53 (± 0.14)		**15** Me	0.55 (± 0.36)
	**16** Me	1.3 (± 0.26)		**17** Me	0.16 (± 0.11)
	**18** Me	0.21 (±0.01)		**19** H	55 (± 11)

[a]Displacement of [^{125}I]-labelled substance P from the cloned hNK_1 receptor expressed in CHO cells ($n=3$).[8]

Table 5. Variation of in vivo properties in the gerbil foot tapping assay with the introduction of non-piperazine amide substituents



HNR_2	hNK_1 IC_{50} (nM)[a]	Gerbil foot tapping %inhibition[b]	
		$t=0$ h (mg/kg iv)	$t=2$ h (mg/kg iv)
 **17**	0.16 (± 0.11)	100@3	50@3
 **18**	0.21 (±0.01)	$ID_{50}=0.3$ mg/kg	$ID_{50}=0.9$ mg/kg

[a]Displacement of [^{125}I]-labelled substance P from the cloned hNK_1 receptor expressed in CHO cells ($n=3$).[8]
[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.[3]

Table 6. Pharmacokinetic profile of **18** in rat

iv dose	1 mg/kg
po dose	1 mg/kg
Half life	3.1 h
Mean residence time	1.8±0.3 h
Plasma clearance rate	31±2 ml/min/kg
Volume of distribution (steady state)	3.5±0.7 L/kg
Oral bioavailability	3±1%
C_{max}	4±1 ng/mL
T_{max}	1.2±0.8 h

The pharmacokinetic properties of **18** in rat (Table 6), showed some interesting differences from that of the original lead **1**. Since the clearance of **18** had been reduced to 50% of liver blood flow, although the volume of distribution has decreased this still leads to a modest increase in half life. Disappointingly, however, the oral bioavailability of **18** (3%) was not improved relative to **1**. It is not known whether this is due to metabolism, poor absorption or both. Absorption is possibly compromised for this compound due to poor aqueous solubility (<0.1 mg/mL) (as the molecule has no basic centre). The replacement of the indole core with an azaindole offered a potential solution to this problem.[7a]

In this study we were able to identify and decrease the metabolic liabilities of **1**, and identify compound **18** which showed improved iv pharmacokinetics.

By alteration of the amide substituent we were able to demonstrate that considerable variation in this area of the molecule was tolerated. The requirement for a lipophilic group of defined size and a hydrogen bond donor in a specific region of space was identified. By looking at the in vivo properties of the more potent compounds we were able to select for improved activity in the gerbil foot-tapping assay.[3] This allowed us to identify **18**, which showed high binding affinity good brain penetration and significantly improved central duration of action.

References and Notes

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4. This clearance figure is greater than the liver blood flow rate in rat, suggesting that hepatic metabolism may be augmented by significant systemic metabolism (i.e., lung and kidney).
5. **1** was incubated at 10 μM concentration with rat liver microsomes and a S9 preparation in conditions suitable for oxidative metabolism. Samples were analyzed by LC–UV and LC–MS to identify metabolic pathways.
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