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Spirocyclic NK_1 Antagonists II: [4.5]-Spiroethers

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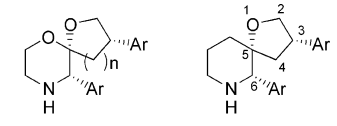
Abstract—A series of novel spiroether-based neurokinin-1 (NK_1) antagonists is described. The effect of modifications to the spiroether ring and aromatic substituents are discussed, leading to the identification of compounds with high affinity and excellent CNS penetration.

The use of neurokinin-1 (NK_1) antagonists for the treatment of depression represents a breakthrough discovery and provides the first novel therapeutic approach to this disease for many years.[1] In our previous paper[2] we described a conformational approach to the design of NK_1 antagonists in which [5.5] and [4.5]-spiroketals **1** were used as structural scaffolds to dispose key elements of the NK_1 antagonist pharmacophore. The conformational preference of the spirocycle was influenced by stereoelectronic stabilization afforded by the anomeric effect.[3]



(**1**) (**2**)

We hypothesised that [4.5]spiroether equivalents **2** may have improved acid stability than the corresponding spiroketal even in the absence of a proximal basic nitrogen atom. It was not clear, however, whether this change, that of removing one of the anomeric oxygen atoms, would result in compounds with a similar overall conformation and hence retention of high affinity for the NK_1 receptor. In this communication we describe the synthesis and NK_1 antagonist activity of these [4.5]-spiroethers.

The spiropiperidines **2** were synthesized diastereoselectively and in homochiral form from the resolved *cis* (3*S*)-hydroxy-(2*S*)-phenylpiperidine **3**.[4] This route relied on the stereoselective addition of the Grignard reagent **4** (Scheme 1) to homochiral N-protected (2*S*)-ketone **5** (Scheme 2).[5a,6,9] Preparation of the Grignard reagent **4** required very careful activation of the magnesium to allow formation at low to ambient temperatures in order to prevent self condensation via attack of the formed organometallic reagent on the allylic phenyl ether system.[7] Initially the Grignard reagent was transmetallated to the zincate **7**,[7] however similar yield and chiral purity of the product **6** was obtained with either organometallic species when the addition to the ketone **5** was performed slowly at 0 °C. Palladium mediated cyclization of the allyl system **6** under basic conditions gave excellent yields of the exocyclic allylic ether **8**. Ozonolysis

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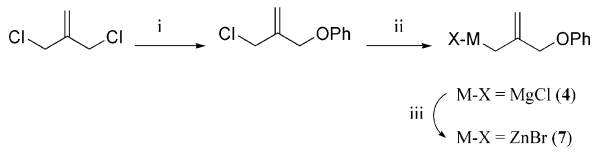
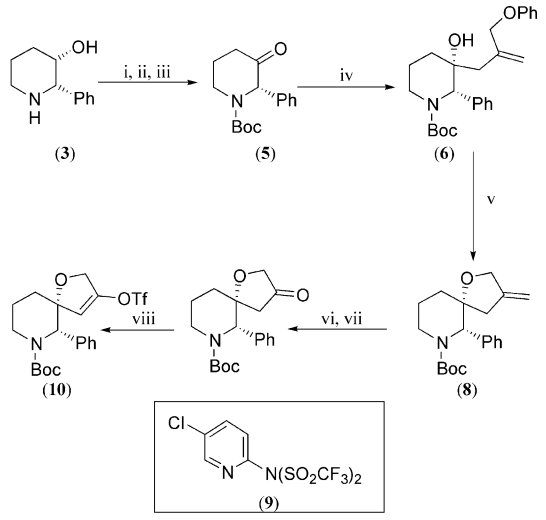
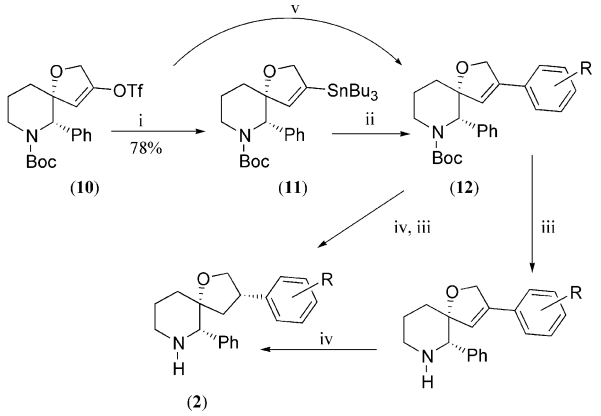


Scheme 1. Reagents and conditions: (i) PhOH, NaH; (ii) Mg, 20 °C, THF; (iii) $ZnBr_2$.



Scheme 2. Reagents and conditions: (i) Boc_2O, DCM; (ii) DMSO, $(COCl)_2$; (iii) Et_3N, −40 to 0 °C, ref 9; (iv) **4** or **7**, THF, 0 °C; (v) ^{n}BuLi in hexanes, $ZnCl_2$, THF; $((Ph)_3P)_4Pd$; (vi) O_3, DCM, MeOH, −80 °C; (vii) Me_2S, rt, 16 h; (viii) NaHMDS, −80 °C, 1 h, **9**, −80 °C−rt, THF.



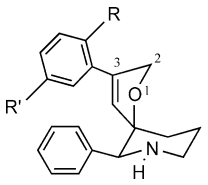
Scheme 3. Reagents and conditions: (i) $(^nBu)_6Sn_2$, $((Ph)_3P)_4Pd$, LiCl, Li_2CO_3, 60 °C, 16 h,THF; (ii) Ar-Br, $((Ph)_3P)_4Pd$, LiCl, toluene, 90 °C, 20 h; (iii) TFA; (iv) H_2, Pd/C; (v) Ar-$B(OH)_2$, $((Ph)_3P)_4Pd$.

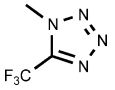
to the ketone and regioselective enol triflate formation with 2-[*N,N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine[8] (**9**) gave the enol triflate **10** as a single regioisomer in 88% yield.

Formation of the vinyl stannane **11** (Scheme 3) was achieved by reaction of **10** with hexabutylditin and catalytic palladium (0). Subsequent palladium catalysed cross coupling with the appropriate aryl bromide[10] afforded the styrene derivatives **12**. Alternatively, Suzuki coupling of the triflate **10** with phenylboronic acid provided access directly to the styrene derivative **12** (R = H). Deprotection under acidic conditions, followed by hydrogenation which occurred from the more exposed face, gave the desired epimer **2** with good facial selectivity.[5] The presence or absence of the Boc- protecting group during the hydrogenation step had little influence on the epimeric ratio of the hydrogenation (3-*S*: 3-*R* 95:5). ^{1}H NMR evidence confirmed the oxygen substituent adopts an axial conformation with respect to the piperidine ring in spiroethers **2** as desired.

This synthesis strategy gives access to the (3*S*,5*R*,6*S*)aryl- substituted [4.5]spiropiperidines with good diastereo and enantio control. We have recently reported[5] conditions which enhance and extend this synthetic approach and which provide access to epimers from both (3*S*)aryl and (3*R*)aryl- series.

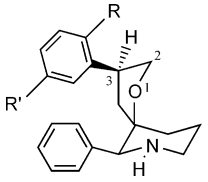
Table 1. hNK_1 Binding affinity of 3-styryl[4.5]-spiroether NK_1 antagonists

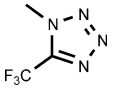


Compd	R	R′	NK_1 IC_{50} (nM)[a]	Gerbil foot tapping[b] (ID_{50} mg/k iv)
13	2-OMe	H	49	ND
14	2-OMe	5-OCF_3	0.35	0.2
15	2-OMe		0.08	0.1

[a]Displacement of [^{125}I]-labelled substance P from the cloned human receptor expressed in CHO cells (ref 11). Values are IC_{50}s and are means of three experiments.
[b]Foot-tapping induced by the central infusion of an NK_1-selective agonist (GR 73632) (ref 12). Inhibition of foot tapping 5 min after *intravenous* administration of antagonist.

Table 2. hNK_1 Binding affinity of [4.5]-spiroether NK_1 antagonists



Compd	R	R′	NK_1 IC_{50} (nM)[a]	Gerbil foot tapping[b] (ID_{50} mg/k iv)
16	H	H	133	ND
17	2-OMe	H	6.5	ND
18	2-OMe	5-OCF_3	0.30	0.3
19	2-OMe		0.11	0.1

[a]Displacement of [^{125}I]-labelled substance P from the cloned human receptor expressed in CHO cells (ref 11).·Values are IC_{50}s and are means of three experiments.
[b]Foot-tapping induced by the central infusion of an NK_1-selective agonist (GR 73632) (ref 12). Inhibition of foot tapping 5 min after *intravenous* administration of antagonist.

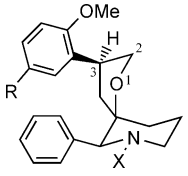
The NK_1 tachykinin activity[11] of these compounds was next determined. Comparable activity was seen for both the unsaturated derivatives (Table 1) and the saturated 3-aryl bicycles (Table 2). The unsubstituted 3-phenyl [4.5]bicycle **16** showed weak affinity for the NK_1 receptor (Table 2), however introduction of a 2-methoxy substituent (**17**) improved affinity 20 fold (IC_{50} 6.5 nM).

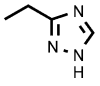
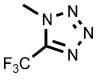
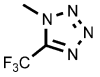
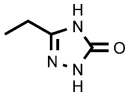
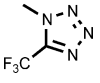
The 2,5-aryl substitution pattern, which was found previously to be optimal in the spiroketal series,[2] again provided high affinity NK_1 antagonists in the spiroether series. Incorporation of 5-trifluoromethoxy group or 5-trifluoromethyltetrazol-1-yl afforded high affinity compounds **18** (IC_{50} 0.30 nM) and **19** (IC_{50} 0.11 nM) respectively.

The ability of key compounds to block central NK_1 receptors was assessed by their ability to inhibit the foot-tapping in gerbils immediately following central administration of GR73632.[12] Excellent inhibitory activity was seen 5 min after *intravenous* administration of both **19** (ID_{50} 0.1 mg/kg) and **18** (ID_{50} 0.3 mg/kg) indicating rapid penetration of these compounds into the CNS.

Table 3 shows the effect on activity of incorporating additional *N*-substituents to compounds **18** and **19**. Although the affinity of the triazole **20** was reduced marginally compared with the unsubstituted **18**, the triazolinone **21** and imidazole **22** substituents retained high in vitro affinity comparable to **19**. However, compounds **20** and **21** showed a significantly attenuated response in vivo as shown by inhibition of the foot-tapping response in gerbils.

Table 3. hNK_1 Binding affinity of [4.5]-spiroether NK_1 antagonists



Compd	R	X	NK_1 IC_{50} (nM)[a]	Gerbil foot tapping[b] (% inhib or ID_{50} mg/kg iv)
18	**–OCF_3**	**H**	0.30	0.3
20	**–OCF_3**		0.89	(45% inhib@1 mg/kg)
19		**H**	0.11	0.1
21			0.10	(6% inhib@1 mg/kg)
22			0.11	0.5

[a]Displacement of [^{125}I]-labelled substance P from the cloned human receptor expressed in CHO cells (ref 11). Values are IC_{50}s and are means of three experiments.
[b]Foot-tapping induced by the central infusion of an NK_1-selective agonist (GR 73632) (ref 12). Inhibition of foot tapping 5 min after *intravenous* administration of antagonist.

Table 4. Anti-emetic response (ferret) of **18** and **19** after *intravenous* and oral routes of administration

Compd	Inhibition of emetic response[a] ID_{90} mg/kg	
	iv	po
18	1	3
19	0.2	1

[a]Compounds were administered iv or po following emetogen challenge after 3 min (iv experiments) or 60 min (po experiments) (see ref 13). Drug vehicle (control) was PEG 300 (iv experiment) or 0.5% Methocell (po experiment).

Preclinical studies in ferrets have demonstrated that the retching and vomiting induced by emetogens such as cisplatin can be attenuated by pre-administration of an NK_1 receptor antagonist.[13] Inhibition of the emetic response (Table 4) was seen after oral administration of **18** (po ID_{90} 3mg/kg) and **19** (po ID_{90} 1 mg/kg)) suggesting that these compounds were well absorbed and had excellent CNS penetration. Compound **19** had a favorable pharmacokinetic profile in two additional species (bioavailability $F=16\%$, $t_{1/2}$ 1.7 h rat and $F=79\%$, $t_{1/2}$ 2.7 h dog).

In conclusion, compounds from the [4.5]-spiropiperidine series and the structurally related [4.5]-spiroketal series[2] show similar solution conformations (NMR) despite the absence of an anomeric effect in the former class. [4.5]Spiroethers are high affinity antagonists at the NK_1 receptor. They have been shown to have rapid CNS penetration (gerbil foot tapping) after intravenous administration and are active orally in the ferret against emesis induced by cisplatin treatment.

Acknowledgements

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References and Notes

1. Kramer, M. S.; Cutler, N.; Feighner, J.; Shrivastava, R.; Carman, J.; Sramek, J. J.; Reines, S. A.; Liu, G.; Snavely, D.; Wyatt-Knowles, E.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Swain, C. J.; Harrison, T.; Hill, R. G.; Hefti, F.; Scolnick, E. M.; Cascieri, M. A.; Chicchi, G. G.; Sadowski, S.; Williams, A. R.; Hewson, L.; Smith, D.; Carlson, E. J.; Hargreaves, R. J.; Rupniak, N. M. *J. Science* **1998**, *281*, 1640.
2. Seward, E. M.; Carlson, E.; Harrison, T.; Haworth, K. E.; Herbert, R.; Kelleher, F. J.; Kurtz, M. M.; Moseley, J.; Owen, S. N.; Owens, A. P.; Sadowski, S. J.; Swain, C. J.; Williams, B. J. *Bioorg. Med. Chem. Lett.*, submitted for publication.

3. Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauve, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105.
4. Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545.
5. (a) Kulagowski, J. J.; Curtis, N. R.; Swain, C. J.; Williams, B. J. *Org. Lett.* **2001**, *3*, 667. (b) Wallace, D. J.; Goodman, J. M.; Kennedy, D. J.; Davies, A. J.; Cowden, C. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, Ulf-H.; Reider, P. J. *Organic Letters* **2001**, *3*, 671.
6. ^{1}H NMR shows the 2-phenyl substituent adopts a pseudo axial conformation when the piperidine nitrogen is protected with the ^{t}Boc group. In this conformation the lower face is effectively shielded resulting in selective axial attack of the incoming Grignard reagent resulting in the alkyl group being anti- to the phenyl group.
7. (a) Van der Louw, J.; van der Baan, J. L.; Stichter, H.; Out, G. J. J.; de Kanter, F. J. J.; Bicklelhauft, F.; Krumpp, G. W. *Tetrahedron* **1992**, *48*, 9877. (b) van der Baan, J. L.; van der Heide, T. A. J.; van der Louw, J.; Krumpp, G. W. *Synlett* **1995**, *1*.
8. Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.
9. Careful work up of the Swern oxidation was required to minimise racemisation of the ketone. After addition of triethylamine at $-40\,^{\circ}C$ the solution was warmed to $0\,^{\circ}C$ whereupon 10% citric acid solution was added and the product extracted with CH_2Cl_2 and dried ($MgSO_4$). After evaporation the crude ketone was used directly without chromatography (enantiomeric excess $>90\%$, Chiralpak AD column with 99:1 isohexane/ethanol as mobile phase). The enantiomeric excess of final compound (**19**) was determined to be 93% by chiral hplc suggesting that addition of Grignard reagent (**4**) caused no significant loss of chiral purity.
10. Preparation of aryl bromides were by literature procedures. For compound **19** see Description 7 Patent WO 97/19084. and for compound **18** see Description 12 Patent WO 97/49710.
11. Cascieri, M. A.; Ber, E.; Fong, T. M.; Sadowski, S.; Bansal, A.; Swain, C. J.; Seward, E. M.; Frances, B.; Burns, D.; Strader, C. D. *Mol. Pharmocol.* **1992**, *42*, 458.
12. Rupniak, N. M. J.; Tattersall, F. D.; Williams, A. R.; Rycroft, W.; Carlson, E.; Cascieri, M. A.; Sadowski, S.; Ber, E.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Seward, E.; Huscroft, I.; Owen, S.; Swain, C. J.; Hill, R. G.; Hargreaves, R. J. *Eur. J. Pharmacol.* **1997**, *326*, 201.
13. Tatttersall, F. D.; Rycroft, W.; Hargreaves, R. J.; Hill, R. G. *Eur. J. Pharmacol.* **1993**, *250*, R5.