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Spirocyclic NK_1 Antagonists I: [4.5] and [5.5]-Spiroketals

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Abstract—A series of novel spiroketal-based 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.
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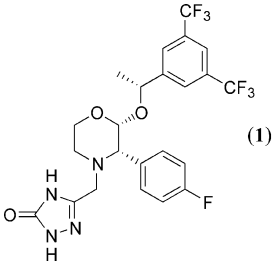
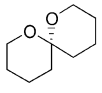
Introduction

We have previously described our ongoing studies to define the NK_1 receptor antagonist pharmacophore.[1] This work culminated in the identification of MK-869 (**1**),[2] the first in a new class of anti-emetics, allowing superior and sustained protection from acute and delayed chemotherapy-induced nausea and vomiting.[3] MK-869 has also shown efficacy in major depression; this seminal discovery represents the first novel mechanism of action to treat depression in 40 years.[4]



(1)



(2)

A common feature of our high affinity NK_1 antagonists, based on NMR and crystallographic evidence,[1] is the presence of an intramolecular edge-to-face or face-to-face π–π interaction between two aromatic rings which may be important in stabilizing the bioactive conformation. In our back-up program we were interested in conformationally restricted ligands in which the disposition of these two key aromatic rings would be fixed by virtue of the structural framework. One system we considered was based on the spirocyclic ketal 1,7-dioxaspiro[5.5]undecane (**2**). Stereoelectronic effects have long been recognized that influence the conformation of acetals and indeed it has been shown that spiro system **2** exists in conformation **2a** only (below). This conformer benefits from two reinforcing anomeric effects: both C–O bonds being antiperiplanar to an oxygen lone pair in the spiro ring. These effects are additive and it has been estimated that **2a** is 9.5 kJ/mol lower in energy than **2b**, possessing only a single anomeric effect, and 19 kJ/mol lower than **2c**. Thus **2** is regarded as a conformationally rigid system.[5]

(2a) (2b) (2c)

Molecular modelling indicated that the optimal disposition of the aryl rings for binding to the receptor would be achieved by the 5*S*,6*S*,9*S*-stereoisomer (**3**).

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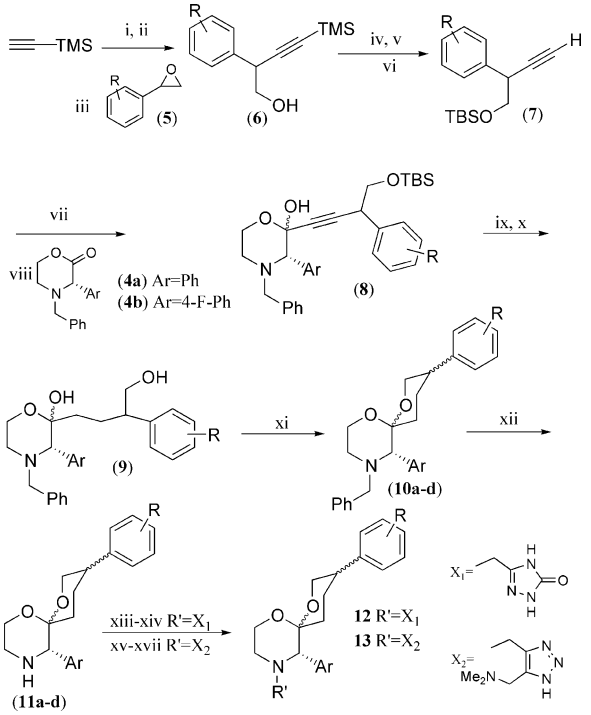
Furthermore, a key H-bond between the receptor and the antagonist would be possible from O7.[1]

We herein report the synthesis and biological profile of a series of [5.5] and related [4.5]-spiroketals—novel NK_1 receptor antagonists.

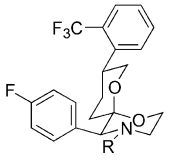
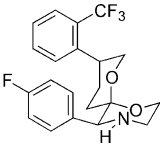
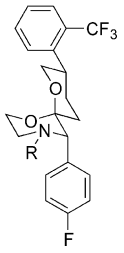
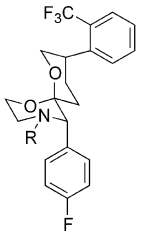
Synthetic Chemistry

The required spiroketals were prepared by reaction of N-protected 3-(*S*)-phenylmorpholinone (**4**)[1] with a suitably substituted acetylene anion (Scheme 1). The required acetylene for the synthesis of the [5.5] spiroketals was obtained using Seebach[6] chemistry: this involved the regiospecific attack of a TMS-protected titanium acetylide complex at the benzylic position of an aromatic epoxide **5** to afford the homopropargylic alcohol **6**. Clean TMS-deprotection was achieved by treatment of **6** with silver nitrate followed by potassium cyanide.[7] Following protection of the alcohol, acetylene **7** was reacted with morpholinone **4** to give hemiacetal **8**. Saturation and deprotection afforded the key intermediate diol **9**. We anticipated that acetalisation of **9** under acid catalysis might be problematic due to the proximity of the basic nitrogen; indeed, no cyclisation



Scheme 1. Reagents and conditions: (i) nBuLi, THF, −78 °C; (ii) $(O^iPr)_3TiCl$, −50 °C; (iii) (**5**), THF, −78 °C; (iv) $AgNO_3$, EtOH, 0 °C; (v) KCN, H_2O; (vi) 2,6-lutidine, TBS triflate, CH_2Cl_2, 0 °C; (vii) nBuLi, THF, −78 °C; (viii) (**4**), THF, −78 °C; (ix) H_2, 30 psi, PtO_2, EtOAc; (x) $MeOH/H^+$; (xi) 6 N HCl, MeOH, reflux; (xii) H_2, 40 psi, Pd/C, $MeOH/H^+$; (xiii) chloromethylamidrazone, K_2CO_3, DMF, 60 °C; (xiv) xylene, 140 °C; (xv) $ClCH_2C{\equiv}CCH_2Cl$, K_2CO_3, DMF; (xvi) NaN_3, DMSO; (xvii) $NHMe_2$, dioxane, 80 °C.

Table 1. Effect of stereochemistry on hNK_1 binding affinity[a]

(5*S*,6*S*,9*R*) 	(5*S*,6*S*,9*S*) 
10a R = Bn **11a** R = H (hNK_1 44% @ 1 μM)	**10b** R = Bn **11b** R = H (hNK_1 28 ± 10 nM)
(5*S*,6*R*,9*S*) 	(5*S*,6*R*,9*R*) 
10c R = Bn **11c** R = H (hNK_1 47% @ 1 μM)	**10d** R = Bn **11d** R = H (hNK_1 400 ± 108 nM)

[a]Displacement of [^{125}I]-labelled substance P from the cloned human receptor expressed in CHO cells.[12] Values are displacements or IC_{50}s ± S.D. and are means of three experiments.

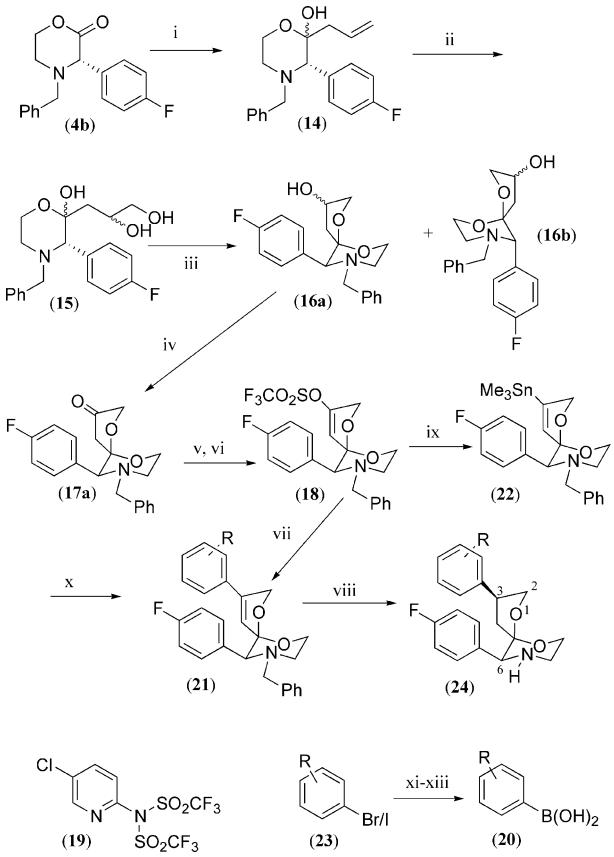
was observed upon treatment with a variety of mild acid catalysts. However, cyclisation was achieved by heating at reflux in strong mineral acid. This gave rise to a mixture of the four possible diastereoisomers (**10a**–**d**) (a:b:c:d = 6:3:3:1 Table 1) which were separated by chromatography or crystallization. It was not possible to re-equilibrate **10a** under these conditions.

The relative stereochemistries and solution conformations (Table 1) were determined by ^{1}H NMR.[8] In all isomers the pyran and morpholine oxygens were *axial* underlining the stabilizing influence of the anomeric effect in this system. Upfield shifts for the trifluoromethyl-substituted aromatic ring in isomer **10b** (5*S*,6*S*,9*S*-stereoisomer) were consistent with a conformation in which the two aromatic rings have an edge-to-face π–π interaction.

The *N*-benzyl group was removed by hydrogenolysis to afford the parent morpholines (**11a**–**d** Table 1) which were further derivatised to the corresponding triazolones **12** or triazoles **13** by alkylation and cyclisation (Scheme 1).

The same general strategy (not shown) was used to prepare the [4.5] spiroketals. The requisite acetylenes in this case were commercially available as the propargylic alcohols. A more flexible approach to the [4.5] system was also developed which allowed a rapid exploration of aromatic substitution (Scheme 2).

Addition of allylmagnesium chloride to the morpholinone **4** proceeded smoothly to afford the alkylated lactol **14**. Dihydroxylation of the double bond gave the triol **15** as a mixture of isomers. Cyclization in strong mineral acid at reflux generated two diastereomeric



Scheme 2. Reagents and conditions: (i) allylmagnesium chloride, THF, −78 °C; (ii) OsO_4, NMO, THF, ^tBuOH, H_2O; (iii) 6 N HCl, MeOH, 65 °C; (iv) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; (v) NaHMDS, THF, −78 °C; (vi) (**19**); (vii) (**20**), $Pd(PPh_3)_4$, LiCl, Na_2CO_3, DME, H_2O, 80 °C; (viii) Pd/C, HCO_2NH_4, MeOH, reflux; (ix) $Me_3SnSnMe_3$, $Pd(PPh_3)_4$, LiCl, Li_2CO_3, THF, H_2O, 80 °C; (x) (**23**), $Pd(PPh_3)_4$, LiCl, DMF, 80 °C; (xi) nBuLi, THF, −78 °C; (xii) $B(OMe)_3$; (xiii) HCl, 0 °C.

pairs of alcohols **16** which were oxidized to afford the ketones **17**. These were separated by chromatography and ketone **17a** was enolised regioselectively using NaHMDS; quenching of the resulting enolate with triflimide **19**[9] gave reproducible yields of the enol triflate **18**. The triflate was then cleanly displaced under Suzuki conditions using appropriately substituted aromatic boronic acids **20** to give the dihydrofuran intermediates **21**. The triflate could also be converted to the trimethylstannane derivative **22** which was cross-coupled with a variety of aryl bromides **23** under Stille conditions. The requisite aryl bromides **23** and boronic acids **20** were either commercially available or prepared by standard literature procedures.[10]

The dihydrofuran intermediates **21** were reduced to the product tetrahydrofurans by hydrogenation to give the desired 3*S* stereoisomers **24**; the 10-aryl substituent apparently blocked one face of the double bond from the hydrogenation catalyst. This stereochemistry was confirmed by ^1H NMR nOe studies. *N*-Debenzylation occurred concomitantly under the hydrogenation conditions and the resulting amines were *N*-substituted, if required, using the same conditions described in Scheme 1.

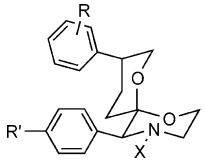
Discussion

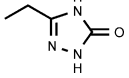
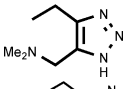
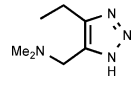
A comparison of the four possible epimers of the [5.5] spiroketals at the 5- and 9-positions confirmed that the 5*S*,6*S*,9*S*-stereochemistry was preferred (Table 1), consistent with our pharmacophore model. The parent unsubstituted [5.5]-spiroketal had modest NK_1 binding affinity (**25** IC_{50} 170 nM, Table 2), but it is well documented that appropriate aromatic and *N*-substitution can have a dramatic effect on NK_1 affinity.[1,11] Accordingly, a 10-fold increase in affinity was observed upon *N*-substitution with a polar heterocycle (**26** IC_{50} 19 nM); alternatively, substitution at the *ortho* position of the 9-phenyl ring was also beneficial (**11b** IC_{50} 28 nM). In contrast, substitution in the *meta* or *para* positions (**27**, **28**) resulted in a considerable reduction in affinity. Combining *ortho* substitution in the 9-phenyl ring with *N*-substitution, and indeed, with fluorine substitution at the 4-position of the 5-phenyl ring afforded compounds with very high NK_1 binding affinity (**29**, **30**).

Compounds **29** and **30** were selected for further evaluation in vivo. The CNS penetration of selected compounds was assessed by their ability in gerbils to block the foot-tapping induced by central infusion of the NK_1-selective agonist GR73632.[13] Both compounds showed good CNS penetration (**29** ID_{50} 1.1 mg/kg iv; **30** ID_{50} 0.6 mg/kg *iv*) when given immediately prior to agonist challenge.

We also explored the corresponding [4.5] series (Table 3). The NK_1 affinity of the parent unsubstituted [4.5]-spiroketal (**31** IC_{50} 99 nM) compares favorably with the analogous [5.5]-spirocycle (**25** IC_{50} 170 nM). Substitution at both the *ortho* and *meta* positions of the 9-aryl ring appears to be well tolerated (**32**–**35**), although *para*

Table 2. hNK_1 Binding affinity of [5.5]-spiroketal NK_1 antagonists

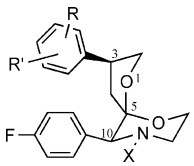


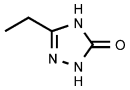
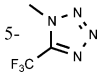
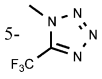
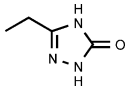
Compd	R	X	R^1	hNK_1 IC_{50}, nM[a]
25	H	H	H	170±17
26	H		H	19±3
11b	2-CF_3	H	F	28±10
27	3-CF_3	H	F	513±45
28	4-CF_3	H	F	55% @1 μM
29	2-CF_3		F	1.1±0.8
30	2-OCF_3		F	1.4±0.7

[a]Displacement of [^{125}I]-labelled substance P from the cloned human receptor expressed in CHO cells.[12] Values are displacements or IC_{50}s±S.D. and are means of three experiments.

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

(3*S*, 5*S*, 10*S*)



Compd	R	R'	X	NK_1 IC_{50} (nM)[a]
31	H	H	H	99±18
32	2-CF_3	H	H	24±19
33	3-CF_3	H	H	30±10
34	2-OMe	H	H	13±6
35	3-OMe	H	H	183±42
36	4-OMe	H	H	27%@1 μM
37	2-OMe	H		0.56±0.21
38	2-OMe	5-OMe	H	16±2
39	2-OMe	5-F	H	10±1
40	2-OMe	5-iPr	H	2.8±1
41	2-OMe	5-CF_3	H	1.3±0.4
42	2-OMe		H	0.1±0.06
43	2-OMe			0.1±0.05

[a]Displacement of [^{125}I]-labelled substance P from the cloned human receptor expressed in CHO cells.[12] Values are displacements or IC_{50}s±S.D. and are means of three experiments.

substitution (**36**) is detrimental to binding. As in the [5.5] series, introduction of a polar heterocycle onto the morpholine nitrogen provided a twenty-fold increase in affinity (**37**), thus affording the first compound in this series with sub-nanomolar NK_1 binding affinity. Alternatively, introduction of a second substituent onto the 3*S* aryl ring, most favorably at the 5-position, afforded a series of very high affinity antagonists (**38**–**42**) and obviated the need for an *N*-substituent. Re-introduction of the polar heterocycle was well tolerated (**43**) but offered no increase in affinity.

The 2-methoxy-5-(5-trifluoromethyl)tetrazolyl[14] derivative (**42**, IC_{50} 0.1 nM), was evaluated in our in vivo CNS assays. The compound showed excellent CNS penetration as measured by blockade of agonist-induced foot tapping in the gerbil (ID_{50} 0.1 mg/kg iv) when given immediately prior to agonist challenge.

In conclusion, we describe a novel series of NK_1 receptor antagonists based upon a rigid spiroketal framework which have high affinity and excellent CNS penetration. Further in vivo evaluations and additional SAR studies will be reported in subsequent publications.

Acknowledgements

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References and Notes

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8. The stereochemistry at C5 was fixed as (5*S*) and the relative stereochemistry at C9 was deduced from the values of ^3J for H9. The relative stereochemistry at the spiro centre was deduced using NOESY data; the orientation of the 5-phenyl group was equatorial for the (6*S*) isomers and axial for the (6*R*) isomers. Coupling constants were consistent with normal chair conformations for both rings in each of the isomers (**10a**–**d**).
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