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3-Benzyloxy-2-Phenylpiperidine NK_1 antagonists: The influence of alpha methyl substitution.

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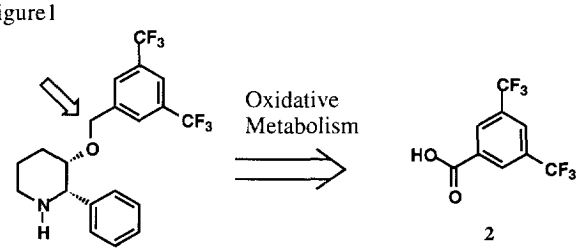
Abstract: *In vitro* metabolism studies on a series of 3,5-bis(trifluoromethyl)benzyl ethers have identified 3,5-bis(trifluoromethyl)benzoic acid as a significant metabolite possibly arising *via* oxidation of the benzylic position. A methyl group was introduced in an effort to suppress this route of metabolism. One diastereoisomer displayed an increase in affinity and a marked improvement in duration of action © 1997 Elsevier Science Ltd.

We have previously described several novel classes of NK_1 antagonists[1,2,3], that possess high receptor affinity, excellent oral activity and good CNS penetration[4]. A key feature of these compounds is the presence of a 3,5-bis(trifluoromethyl)benzyl ether that appears to play a significant role in enhancing the *in vivo* activity. *In vitro* metabolism studies using rat liver microsomes identified the presence of 3,5-bis(trifluoromethyl)benzoic acid (**2**) as a significant metabolite presumably arising via oxidation at the benzylic position highlighted in Figure 1.

Figure1



1 **2**

In an effort to improve the duration of action of this class of NK_1 antagonists we sought to block this site of metabolism by the introduction of a methyl substituent.

Alkylation of the Boc protected aminoalcohol[1] (**3**) with the appropriate secondary bromide (scheme 1) (**4**) afforded the desired substituted ethers (**5,6**) as a mixture of diastereoisomers. Separation of the diastereoisomers by chromatography and subsequent deprotection gave the corresponding piperidines (**7** or **8**). The heterocycles were then introduced using the procedure described previously yielding (**9** or **10**)[2]. The relative stereochemistry of the newly created alpha methyl was determined by nmr studies[5]. In particular, in (**7a**) H10 and H14 (Figure 2) are significantly shifted upfield (-0.56ppm) consistant with an edge to face interaction of the benzyl ether ring with the unsubstituted phenyl ring. In (**8a**) it is H7 and the *alpha* methyl protons that are shifted upfield. This

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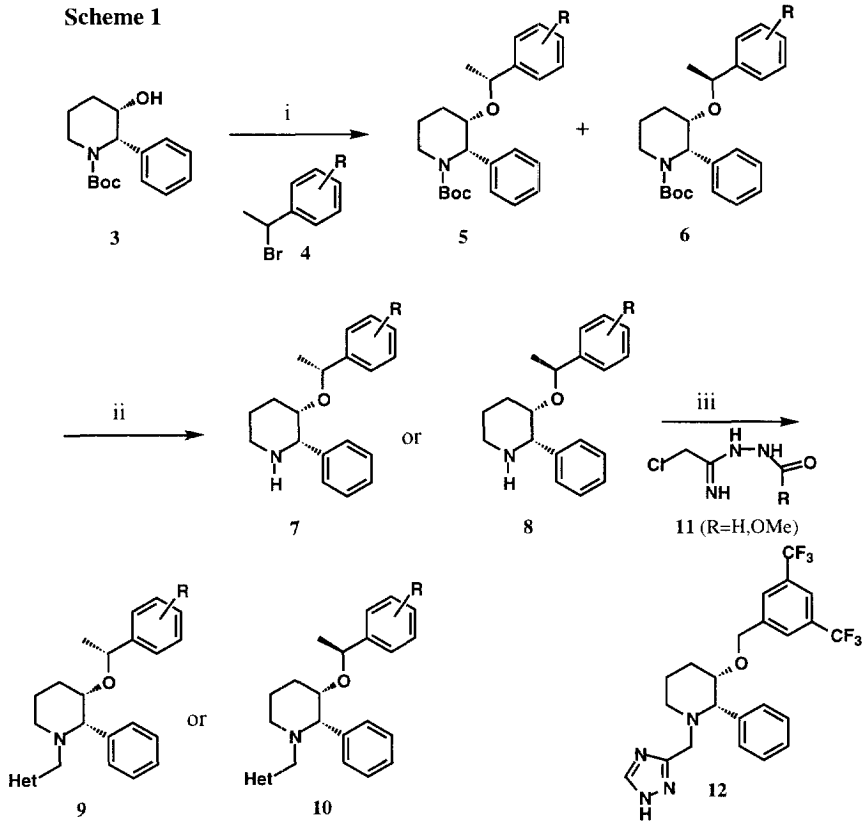
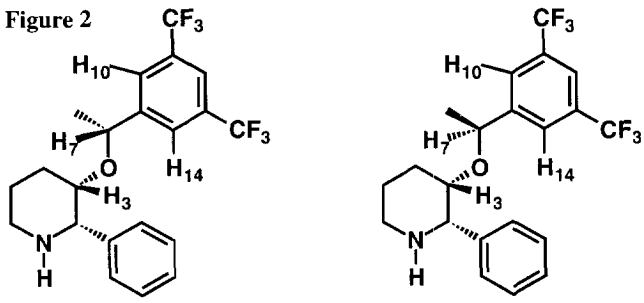
assignment is consistent with the nOe data; thus for (**7a**) a strong nOe is observed between H7 and H3, whilst for (**8a**) it is between the alpha methyl and H3. Since the absolute stereochemistry of the piperidine ring had been previously determined[6] the absolute stereochemistry of the newly created center can be established (R for **7a** and S for **8a**)

Scheme 1



Reagents: i) NaH, DMF; ii) MeOH, HCl, iii) K_2CO_3, DMF, 60°C for 30 mins then 140°C for 2 hours.

Figure 2



Introduction of the alpha methyl affords two diastereoisomers; in the case of the 3,5-bis(trifluoromethyl) substitution, the R-diastereomer (**7a**) shows a 5-fold increase in affinity whilst the other S-isomer has a 100-fold reduction in affinity. A similar separation in affinity was also found for the corresponding 3,5-dichloro substituted (**7b**) and unsubstituted benzyl ether (**7c**). In the absence of the alpha methyl introduction of the N-substituent gave a further 3-5 fold increase in affinity (**1a** v's **12**), however in the presence of the alpha methyl no increase in affinity was observed (eg. **7a** v's **9a**) except in the case of the unsubstituted benzyl ether were a 20-fold increase in affinity was observed (**1c** v's **9d**). In general it was observed that the beneficial influence was much greater for sub-optimal aromatic substitution[7]

Table 1 Summary of *in vitro* binding data.

No.	alpha sub	stereo	aryl sub	Het	IC_{50} (nM)	Std Dev
1a	H		3,5-Bis CF_3	H	0.8	±0.5
1c	H		H	H	160	
7a	Me	R	3,5-Bis CF_3	H	0.15	±0.05
8a	Me	S	3,5-Bis CF_3	H	87	±63
7b	Me	R	3,5-DiCl	H	0.91	±0.08
8b	Me	S	3,5-DiCl	H	85	±10
7c	Me	R	H	H	86	±23
7d	Me	S	H	H	>10,000	
12	H		3,5-Bis CF_3	Triazole	0.18	±0.14
9a	Me	R	3,5-Bis CF_3	Triazole	0.16	±0.1
9b	Me	R	3,5-Bis CF_3	Triazolinone	0.16	±0.1
9c	Me	R	3,5-DiCl	Triazolinone	0.09	±0.06
10c	Me	S	3,5-DiCl	Triazolinone	25	±6
9d	Me	R	H	Triazolinone	5.9	±2.5

All results are n=3 or 5, except 1c where n=1

The compounds were evaluated *in vivo* by their ability to antagonise the extravasation induced by the vannilloid sensorotoxin resiniferatoxin, one hour after administration of the test drug or at longer treatment times[8]. The extent of plasma protein extravasation was determined spectrophotometrically by using Evans Blue dye as a plasma marker. The bis(trifluoromethyl)benzyl ether (**12**) was a potent dose dependent antagonist after oral administration (ID_{50} 0.34 mg/kg p.o.) but displayed modest duration (55% inhibition 8 h after 1 mg/kg p.o.) and no evidence of activity at 24h. Introduction of the alpha methyl (**9a**) maintained the oral potency at the 1h and gave a significant improvement at the 8 hour time point. Replacement of the triazole with the triazolinone (**9b**) gave a modest

improvement in the oral activity (0.026 mg/kg) and a greatly improved duration (66% inhibition 24h after 1 mg/kg p.o.). In comparison the corresponding 3,5-dichloro analogue (**9c**) had only relatively modest oral activity despite having the highest affinity.

Table 2 Summary of *in vivo* studies (ID_{50} or % inhibiton at 1 mg/kg p.o.)

No.	ID_{50} @ 1h	Inhibition @ 8h	Inhibition @ 24h
12	0.034	55% @ 1	0%
9a	0.06	78% @ 1	12%
9b	0.026	97% @ 1	66% 1
9c	> 0.1	not tested	not tested

In conclusion, introduction of the alpha methyl serves to afford an increase in affinity particularly in the presence of sub-optimal benzyl ring substitution. It also gaves an increase in duration of action after oral administration. This discovery has also been utilised in the related morpholine and gem piperidine series[8].

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5.This was subsequently confirmed by a single crystal X-ray structural determination on 9c.

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7. Full details will be reported in a full paper.

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