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GR159897 and Related Analogues as Highly Potent, Orally Active Non-Peptide Neurokinin NK_2 Receptor Antagonists.

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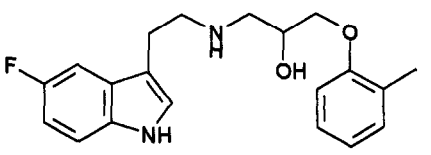
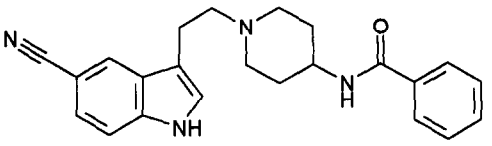
Abstract. Optimisation of NK_2 receptor affinity in a series of sulfur derivatives resulted in the identification of highly potent 5-fluoroindol-3-ylethyl[4-(phenylsulfinyl methyl)]piperidines. Further structure activity analysis led to GR 159897 an NK_2 receptor antagonist which potently blocks agonist-induced bronchoconstriction in the guinea-pig when administered by peripheral and oral routes.

There is considerable interest in the development of selective tachykinin antagonists in order to evaluate their potential therapeutic effects.[1-4] The only potent non-peptide NK_2 receptor antagonist reported in the literature to date has been described by Sanofi (SR 48986).[5] Previous work from our laboratories described how we were able, using a functional assay, to identify small peptides with high affinity and selectivity for the rat colon NK_2 receptor via a deletion-optimisation strategy.[6-8] Following the development of a binding assay, we searched our compound file for non-peptide leads using the knowledge of structure-activity requirements gained from the peptide work. All our potent peptide NK_2 antagonists contained an indole ring, and at least one other aromatic group.[6-8] Hence we selected compounds which contained these two structural features, and in this way identified the structurally related low affinity leads **1** and **2** (Rat Colon pK_i 6.0, 5.8).



1



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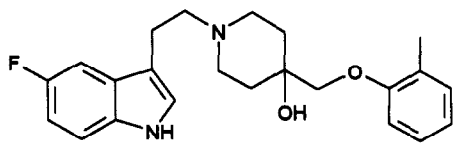

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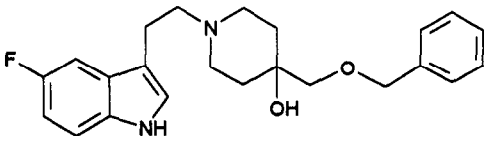
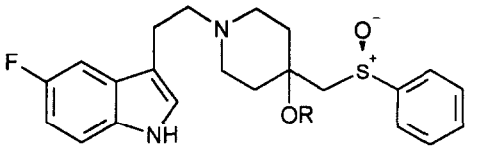


4

In our early studies to optimise binding, we prepared derivatives of **1** and **2** and established that changing substituents on the indole 5-position gave a similar pattern of NK_2 receptor affinities in both series, with fluoro

being the optimum (data not shown). By combining the ether linker of **1** with the central piperidine ring of **2** we then prepared the piperidinol derivative **3** which had significantly improved NK_2 receptor affinity (RC pK_i 7.5). The isomeric benzyl ether **4** was found to have similar affinity to **3**

Our strategy to further enhance the potency of this series was to optimise the linker group between the piperidine and aryl rings. The ether linkage in **3** was therefore replaced with the larger thioether, the sulfur being prepared in its various oxidation states. This led to the discovery of the highly potent and selective sulfoxides represented by the generic structure **5**.

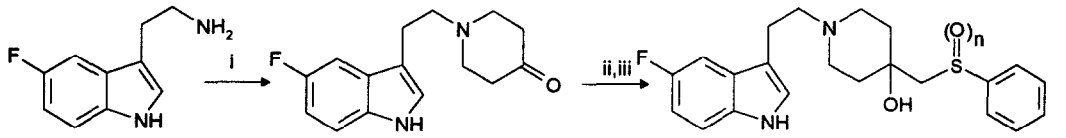


5

Chemistry

The novel compounds[9] evaluated in this investigation were synthesised as follows. The initial hydroxypiperidine derivatives **5-9** were prepared by condensation of 5-fluorotryptamine with N-

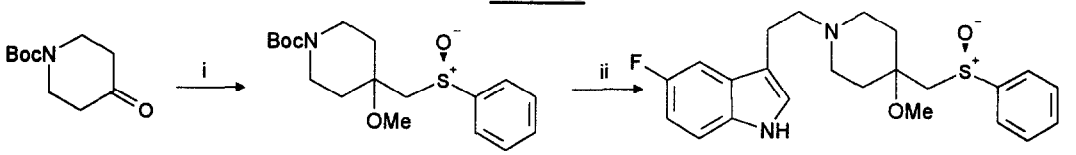
Scheme 1



5-9

i) N-methylpiperidone methiodide, K_2CO_3, EtOH (62%) ii) $PhS(O)_nCH_3$, LiHMDS, THF -70° (n = 1 or 2) (67-80%) iii) a) BH_3.THF, THF b) MeOH, reflux (n = 1→ n = 0) (70%)

Scheme 2



10

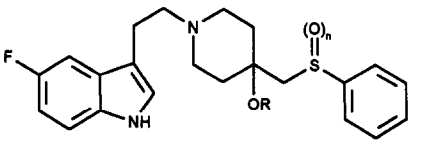
i) a) (R)-$PhS(O)CH_3$, LiHMDS, THF -70° (37%) b) MeI, KOH, DMSO (78%) ii) a) pTSA, MeCN (99%) b) 5-fluoroindol-3-yl ethyl bromide, DMF (73%).

methylpiperidone methiodide[10] followed by the addition of the appropriate sulfur stabilised anion (two equivalents) into the resulting piperidone (Scheme 1). The corresponding sulfide was obtained by borane reduction of the sulfoxide. The asymmetric sulfoxides were synthesised using the appropriate enantiomer of methyl phenyl sulfoxide, prepared by the chiral sulfinate procedure of Kagan.[11] The stereochemical integrity of the enantiomerically pure sulfoxide compounds was confirmed by circular dichroism spectroscopy and chiral HPLC.[12] Attempted alklation of **8** gave only the N-methyl indole derivative. The methyl ether **10** was therefore synthesised from the N-Boc protected piperidone (Scheme 2). Following the addition of chiral methyl phenyl sulfoxide anion the key step was the potassium hydroxide mediated alkylation of the tertiary alcohol with methyl iodide.[13]

Biology

NK_2 Receptor Affinity *in vitro*

Replacement of the ether oxygen in **3** with sulfur afforded a series of compounds (**5-7**) in the three possible oxidation states. While the phenyl sulfone **7** was only equiactive with the parent ether, the corresponding sulfide **5** and sulfoxide **6** showed a significant increase in NK_2 binding affinity. The effect of sulfoxide chirality on affinity was investigated by enantiospecific synthesis of **8** and **9**. The (R)-sulfoxide **8** was shown to be about 30 fold more potent than the corresponding (S)-enantiomer **9**. The NK_2 antagonist activity was further enhanced by the methylation of the tertiary hydroxy to give the methyl ether **10**.



Compound	Chirality	n	R	RC pK_i [14]
5	-	0	H	8.4
6	-	1	H	9.3
7	-	2	H	7.5
8	R	1	H	9.5
9	S	1	H	8.1
10	R	1	Me	10.0

The selectivity of compounds **8** and **10** with respect to other neurokinin receptors was investigated. In isolated guinea-pig trachea, **8** and **10** were potent competitve antagonists of the NK_2 receptor selective agonist GR64349 (NK_2 pK_B = 8.7 +/- 0 1 and 9.7 +/- 0.1 respectively), but showed little or no effect against the selective NK_1 agonist, substance P methyl ester (NK_1 pK_B <5) Both compounds were also highly selective with respect to NK_3 receptor binding in guinea-pig cortex,[15] (NK_3 pK_i 4 4, 4 7 respectively). Compound **10** also shows high affinity at the human NK_2 receptor expressed in chinese hamster ovary cells[16] (pK_i = 9 5).

NK_2 Receptor Antagonism *in vivo*

Compounds **5, 8** and **10** were tested *in vivo* by their ability to inhibit bronchoconstriction (induced by the NK_2 receptor agonist GR64349) in the guinea-pig [17] After intravenous administration the two sulfoxide antagonists **8** and **10** showed high *in vivo* potency and a significant duration of action (as measured by their biological half-life) In contrast the sulfide **5** was significantly less potent (Fig 1) The sulfoxides also showed potent antagonist activity after intraduodenal administration (Fig 2) Oral administration of the methoxy sulfoxide **10** (10μmol/kg, po) markedly antagonised GR64349 induced increases in tracheal inflation pressure (dose ratio = 51, 40 and 15 at pretreatment times of 1, 2 and 4 hours respectively) The bioavailability of compound **10** was confirmed by area under the curve (AUC) studies in beagle dog. Following administration of **10** to two animals in an intravenous then oral dose route cross-over study, the oral bioavailability (plasma AUC_{po}/AUC_{iv} corrected for dose) was 87%

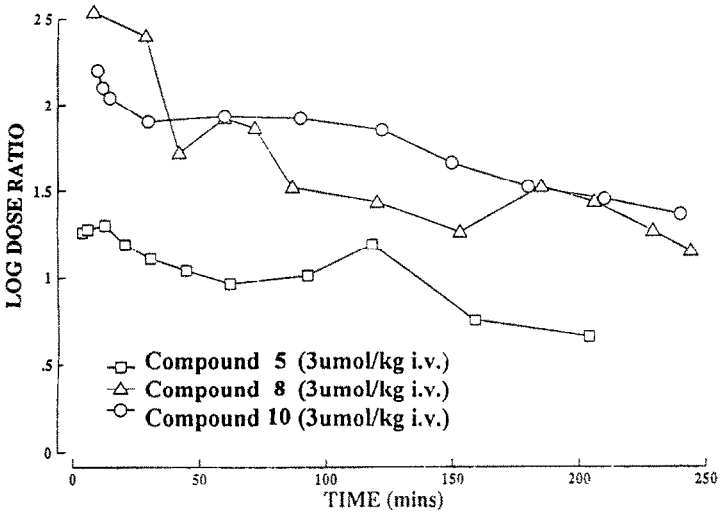


Fig 1. Antagonism of GR64349-induced bronchoconstriction in guinea-pigs

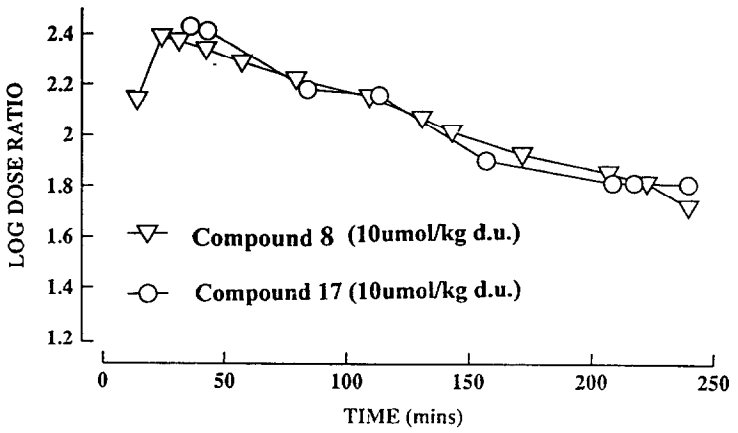


Fig 2. Antagonism of GR64349-induced bronchoconstriction after intraduodenal administration of compounds **8** and **10** in guinea-pigs.

Conclusions

From the modestly potent ethers **3**, **4** we have developed the highly potent and selective NK_2 receptor antagonists **8** (GR149861) and **10** (GR159897). The relative *in vitro* potencies of the sulfide **5** and the (R)-sulfoxide **8** indicate a positive interaction of the sulfoxide oxygen atom at the receptor. The lower potency of the sulfone **7** (and the (S)- sulfoxide **9**) may be explained by an adverse steric or electronic interaction of the 'second' oxygen atom on the sulfur. The key structural requirement in all our non-peptide NK_2 receptor antagonists has been the central tertiary amine of the piperidine nitrogen and the presence of lipophilic aromatic rings. These groups are also a feature of the only other published non-peptide NK_2 antagonist SR-48968.[5] The potency and oral activity of GR159897 (**10**), make this compound a valuable tool for studying NK_2 receptor pharmacology *in vivo*, and a drug candidate for the evaluation of the therapeutic potential of NK_2 receptor antagonists. The detailed pharmacology of GR159897 will be published elsewhere.

Acknowledgements
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12. **8** CD λmax (H_2O) 202nm (Δε -17.45), 214nm (Δε -22.26), 238nm (Δε 18.52).
9 CD λmax (H_2O) 202nm (Δε 17.45), 214nm (Δε 22.26), 238nm (Δε -18 52).
10 CD λmax (H_2O) 199nm (Δε -18.80), 214nm (Δε -21.90), 238nm (Δε 19 90).
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