Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 9, pp. 1015-1020, 1996

0960-894X/96 $15.00 + 0.00

S0960-894X(96)00163-1

TETRAZOLE NK_1 RECEPTOR ANTAGONISTS: THE IDENTIFICATION OF AN EXCEPTIONALLY POTENT ORALLY ACTIVE ANTIEMETIC COMPOUND.

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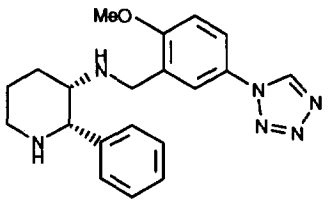
Abstract: The medicinal chemistry strategy is described which led to the identification of GR205171, an orally active non-peptide neurokinin-1 receptor antagonist that is the most potent broad-spectrum antiemetic agent reported to date.

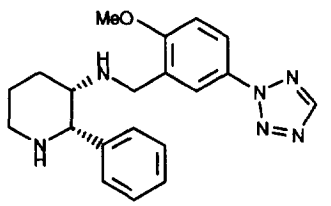
Introduction.

The discovery that CP-99,994,[1] the prototypical neurokinin-1 (NK_1) receptor antagonist is a broad-spectrum antiemetic agent[2] has stimulated the field of antiemetic research. We have recently described the strategy which resulted in the identification of GR203040 (**1**),[3] an orally bioavailable non-peptide NK_1 receptor antagonist, which has high affinity *in vitro* and is highly efficacious *in vivo* as an antiemetic agent against a wide range of emetic stimuli. Herein we describe the synthesis and preliminary pharmacological evaluation of a further range of tetrazole derivatives, culminating in the discovery of GR205171 (**13k**), an exceptionally potent, orally active antiemetic NK_1 receptor antagonist[4].

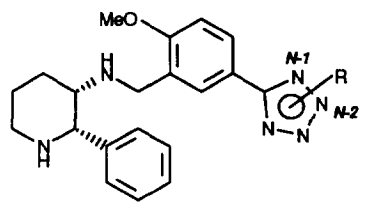
Having identified GR203040 (**1**) we were keen to further optimise the antiemetic properties of this series of compounds. Our initial work[3a] had highlighted the unique role of the tetrazole in this series - other heterocycles were less potent *in vitro* or *in vivo*, or had poor pharmacokinetic properties. The regiochemistry of the tetrazole was also highlighted as being of importance since both the N-2 linked tetrazole (**2**) and the C-linked tetrazoles (**3a**) and (**3b**) were either less potent *in vitro* or less effective *in vivo*. These observations provided the impetus to explore opportunities for substitution at the C-1 position of the tetrazole ring of (**1**).



GR203040 (**1**)



(**2**)



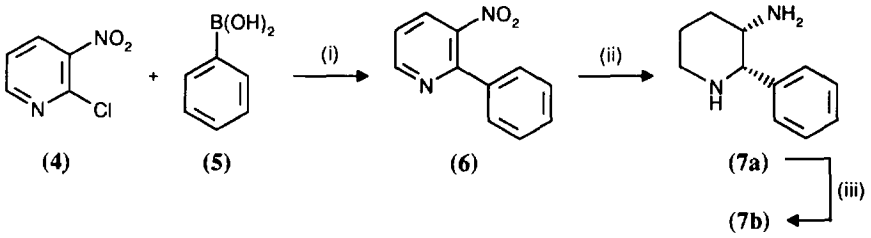
(**3a**) N-1 R = Me

(**3b**) N-2 R = Me

Chemistry

The target compounds were prepared by the reductive amination of the homochiral diamine (**7b**) with appropriately substituted benzaldehydes. We have developed an expedient three-step route for the preparation of (**7b**) which is highly efficient on a multi-kilo scale (Scheme 1). Palladium-catalysed coupling of the commercially available 2-chloro-3-nitropyridine (**4**) with phenylboric acid (**5**) gave nitro-pyridine (**6**) which was readily hydrogenated with Pearlman's catalyst under acidic conditions to give the cis-diamine (**7a**). Resolution with di-*p*-toluoyl-L-tartaric acid gave the desired homochiral diamine (**7b**) in good yield.

Scheme 1. ***Preparation of (2S)-phenylpiperidin-(3S)-ylamine (7b).***



Reagents and Conditions:
(i) 2N aq Na_2CO_3, dimethoxyethane, Pd $(PPh_3)_4$, reflux, 99% (ii) H_2, PdOH/C, EtOH, cHCl, 75%
(iii) Di-*p*-toluoyl-L-tartaric acid, EtOH, H_2O, 76% (97% e.e.).

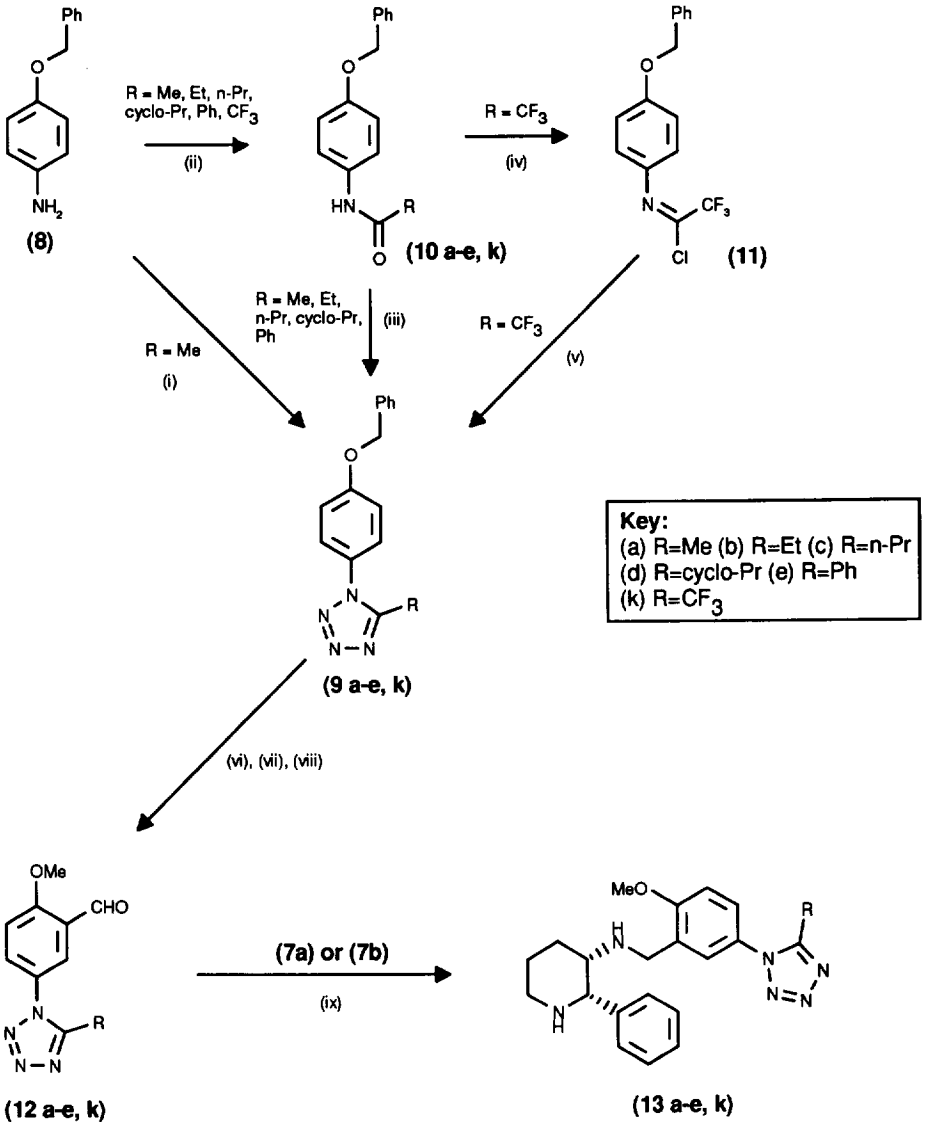
The majority of the target compounds (**13a-e, k**) were prepared by the chemistry described in Scheme 2. Three methods were used to install the tetrazole moiety. The methyl tetrazole (**9a**) could be prepared by simple condensation of trimethylorthoacetate with commercially available 4-benzyloxyaniline (**8**) in acetic acid with sodium azide,[5] although the yields from this reaction were highly variable. More generally the methyl tetrazole and other substituents (for which the orthoesters were not available) could be prepared *via* a two-step acetylation/ tetrazole formation procedure.[6] Surprisingly, this cyclisation reaction would not work for the trifluoromethyl substituent - the trifluoroacetamide (**10k**) was recovered unchanged under the reaction conditions. Accordingly the trifluoroacetamide (**10k**) was converted to the imino-chloride (**11**) using resin-supported triphenylphospine and carbon tetrachloride in a modification of the method of Tamura *et al*,[7] then cyclised with sodium azide and acetic acid The resultant tetrazoles (**9a-e, k**) could then be elaborated to the desired compounds using standard methods.[3a]

The thiomethyl (**13f**) and methyl sulphone (**13g**) compounds were prepared using the chemistry of Scheme 3. The preparation of the amino-substituted tetrazoles (**13h-j**) will be reported elsewhere.[8]

Pharmacology

Binding data were determined in membranes from chinese hamster ovary cells stably expressing the human NK_1 receptor, using ^{3}H-substance P as the radioligand.[3c] Antiemetic activity was determined against radiation-induced emesis in the ferret.[3b] Antagonists were routinely administered by the subcutaneous route 90 minutes before whole body X-irradiation (2 Gy). Results are quoted as the minimum dose required for a 90% inhibition (ED_{90}) of retching and vomiting. The results of these experiments are presented in Table 1.

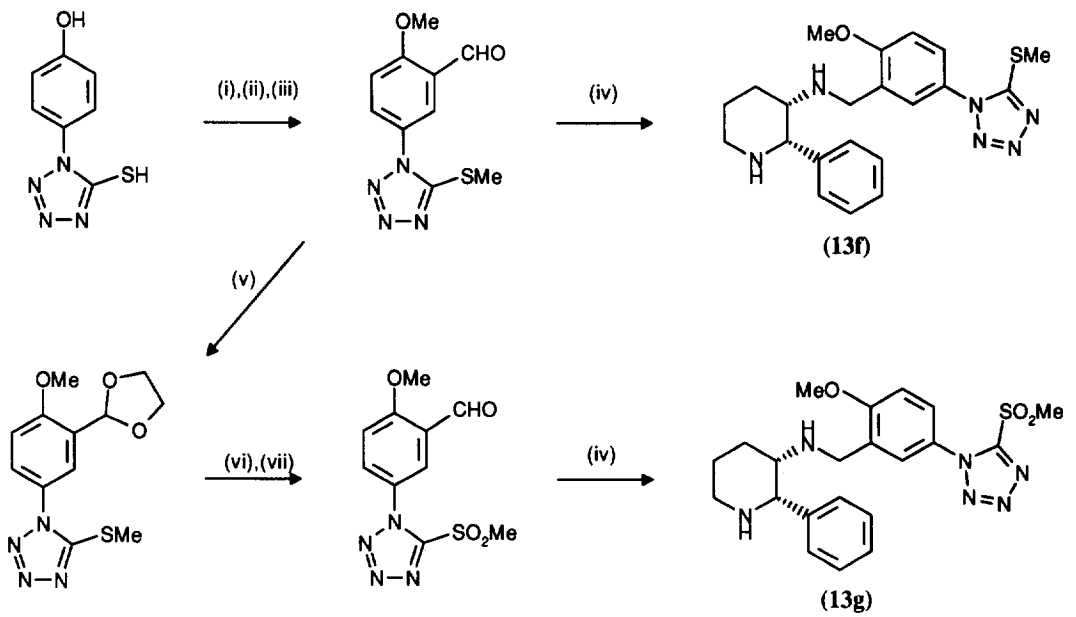
Scheme 2. ***Preparation of Alkyl- and Aryl- Substituted Tetrazoles.***



Reagents and Conditions:

(i) NaN_3, $(EtO)_3CMe$, AcOH, 75°C, 5-30 % (ii) RCOCl, 80-99% (iii) NaN_3, $(CF_3SO_2)_2O$, CH_2Cl_2, 15-47% (iv) Resin-supported PPh_3, CCl_4, 93% (v) NaN_3, AcOH, 70°C, 4h, 69% (vi) H_2, 10% Pd/C, EtOH, 86-100% (vii) Hexamethylenetetramine, AcOH, 47-75% (viii) MeI, K_2CO_3, DMF 60-96% (ix) $NaBH(OAc)_3$, 57-85%

Scheme 3. ***Preparation of Sulphur Substituted Tetrazoles.***



Reagents and Conditions:

(i) NaOH, H_2O, THF, MeI, 87% (ii) Hexamethylenetetramine, TFA, 60°C, 24h, 41% (iii) K_2CO_3, DMF, MeI, 73% (iv) **(7b)**, $NaBH(OAc)_3$, CH_2Cl_2, 46-64% (v) Ethylene glycol, *p*TsOH, toluene, reflux, -H_2O, 92% (vi) *m*CPBA, $CHCl_3$, 90% (vii) 2N HCl, THF, 45%

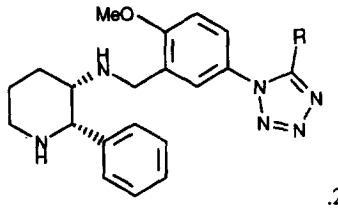
Discussion.

Our initial analogues (**1, 13a-e**) demonstrated that increasing the size of the substituent on the tetrazole has little effect on the *in vitro* affinity of these compounds, with the exception of the substantially more bulky phenyl group which is ten fold less active. Similarly both sulphur containing analogues (**13f-g**) were potent *in vitro*. Remarkably however, there was a wide variation of *in vivo* activity within this set of compounds. Most analogues were substantially less active in the ferret model of emesis. This may reflect differing levels of CNS penetration (the antiemetic action of NK_1 antagonists has been demonstrated to be centrally mediated[9]), different rates of metabolic turnover prior to the induction of emesis or possibly species differences between the ferret and human NK_1 receptors.[10] Nitrogen substituted analogues, possibly because of their electron-donating nature, were generally less potent *in vitro* and so were not progressed further.

The trifluoromethyl compound GR205171 (**13k**) had the highest *in vitro* affinity and is the most potent antiemetic agent described to date with an ED_{90} of only 0.03mgkg^{-1} *s.c.* (90 min. pretreatment) versus whole body X-irradiation in the ferret. Furthermore, following oral dosing (0.1 mgkg^{-1}, 90 min. pretreatment time), GR205171 (**13k**) completely inhibits X-irradiation-induced emesis. At similar doses, GR205171 (**13k**) provides a high degree of protection against a wide range of emetic stimuli, including cisplatin, cyclophosphamide,

morphine, copper sulphate and ipecacuanha. Even when administered at the low dose of 0.1mgkg^{-1} *s.c.* six hours before X-irradiation, GR205171 (**13k**) still provides complete antiemetic protection.[4]

Table 1. ***In Vitro and In Vivo Activity of Tetrazole Analogues.***



.2HCl

Compound No.	R	pK_i	SEM	n	X-irradiation Induced Emesis ED_{90} (mgkg^{-1}) •
GR203040 (1)	H	10.4	0.1	11	0.1
(13a)	Me	10.3	0.1	5	0.15
(13b)*	Et	10.3	0.3	4	1-3
(13c)*	n-Propyl	10.4	0.1	4	>3
(13d)*	cyclo-Propyl	10.1	0.2	4	>1
(13e)	Ph	9.4	0.3	4	>1
(13f)	SMe	10.4	0.1	4	0.3-1
(13g)	SO_2Me	10.2	-	2	>1
(13h)	NH_2	9.0	-	2	NT
(13i)	$N(Et)_2$	8.7	0.2	4	NT
(13j)	NHAc	9.6	0.3	5	NT
GR205171 (13k)	CF_3	10.6	0.2	9	0.03

* Compound prepared as racemate, all other compounds tested as (2S,3S) single enantiomer.

NT - not tested •All determinations are at least n=3

Conclusions.

We have described the essentially empirical strategy which led to the identification of GR205171 (**13k**), a NK_1 receptor antagonist with exceptional potency in the ferret model of emesis against a broad spectrum of emetogens. GR205171 is currently undergoing further preclinical evaluation, and has the potential to provide a major advance in the clinical management of emesis. Additionally, GR205171 may prove useful for the treatment of a range of other pathological conditions in which substance P has been implicated, including migraine, pain and inflammation.[11]

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Acknowledgements.

We would like to acknowledge the contributions of N. Heron to the chemistry and A. B. Hawcock, A. Jones, C. J. Gardner and D. J. Twissell to the biological evaluation of these compounds.

(*Received in Belgium* 12 *January* 1996; *accepted* 30 *March* 1996)