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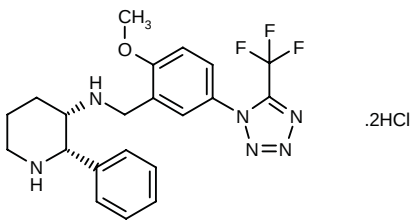
CCC: 0377-8282/99

GR-205171

Antiemetic
Tachykinin NK_1 Antagonist

(2*S*,3*S*)-*N*-[2-Methoxy-5-[5-(trifluoromethyl)-1-tetrazolyl]benzyl]-*N*-(2-phenylpiperidin-3-yl)amine dihydrochloride



$C_{21}H_{23}F_3N_6O.2Cl$ H Mol wt: 505.374

CAS: 168266-51-1
CAS: 168266-90-8 (as free base)

EN: 235944

Synthesis

The acylation of 4-benzyloxyaniline (I) with trifluoroacetyl chloride and triethylamine in dichloromethane gives the corresponding amide (II), which is treated with resin-supported triphenylphosphine and CCl_4 to yield the iminochloride (III). The cyclization of (III) with sodium azide in hot acetic acid affords the tetrazole (IV), which is debenzylated with H_2 over Pd/C in ethanol/THF, giving the phenol (V). The reaction of (V) with hexamethylenetetramine (HMT) in hot trifluoroacetic acid yields the benzaldehyde (VI), which by methylation with methyl iodide/K_2CO_3 in acetone affords 2-methoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]benzaldehyde (VII). Finally, this compound is reductocondensed with (2*S*,3*S*)-2-phenylpiperidin-3-amine (VIII) by means of sodium triacetoxyborohydride/acetic acid in dichloromethane (1, 2). Scheme 1.

The chiral (2*S*,3*S*)-2-phenylpiperidin-3-amine (VIII) has been obtained as follows: The condensation of 2-chloro-3-nitropyridine (IX) with phenylboronic acid (X) by means of palladium tetrakis(triphenylphosphine) and Na_2CO_3 in dimethoxyethane gives 3-nitro-2-phenylpyridine (XI), which is hydrogenated with H_2 over Pd/C in ethanol/HCl, yielding (±)-*cis*-2-phenylpiperidin-3-amine (XII). Finally, this compound is submitted to optical resolution by means of di-*p*-toluoyl-L-tartaric acid in ethanol/water (1). Scheme 1.

Description

[α] +50.35° (c 3 mg/ml, water) (2).

Introduction

Vomiting, or emesis, is a protective reflex response to rid the body of an ingested toxin. However, nausea and vomiting are observed in other conditions including pregnancy and motion sickness, where the benefits of such a response are unclear, and also represent disturbing side effects which accompany many medical interventions such as radiotherapy, cancer chemotherapy, postoperative recovery and medically induced abortion. Therefore, research has focused on finding a strategy to block emesis.

The 5-HT_3 receptor antagonists, ondansetron and granisetron, were shown to potently inhibit acute chemotherapy-induced emesis. However, these agents were found to have a restricted profile, being ineffective against opioid and dopaminergic agonists, copper sulphate and motion-induced emesis (3).

Evidence suggests that the mechanism responsible for controlling vomiting is located in the medulla of the brainstem, although the neurochemicals involved in regulation have not been identified (3). The ideal strategy to block emesis would be to pharmacologically depress neurons within the medullary emesis circuitry. Recent studies have demonstrated that blocking tachykinin receptors can result in potent antiemetic activity.

Tachykinins are neuropeptides which regulate various biological responses through stimulation of specific tachykinin receptors (NK_1, NK_2 and NK_3) expressed in a variety of tissues. Progress in defining the biological role of these agents has been greatly facilitated by the development of selective NK_1, NK_2 and NK_3 antagonists. Tachykinin NK_1 receptor antagonists have a variety of potential clinical uses and several of these compounds have progressed to clinical trials, as shown in Table I (4, 5). One of the most important potential therapeutic uses of tachykinin NK_1 antagonists is based on their effectiveness in preventing emesis.

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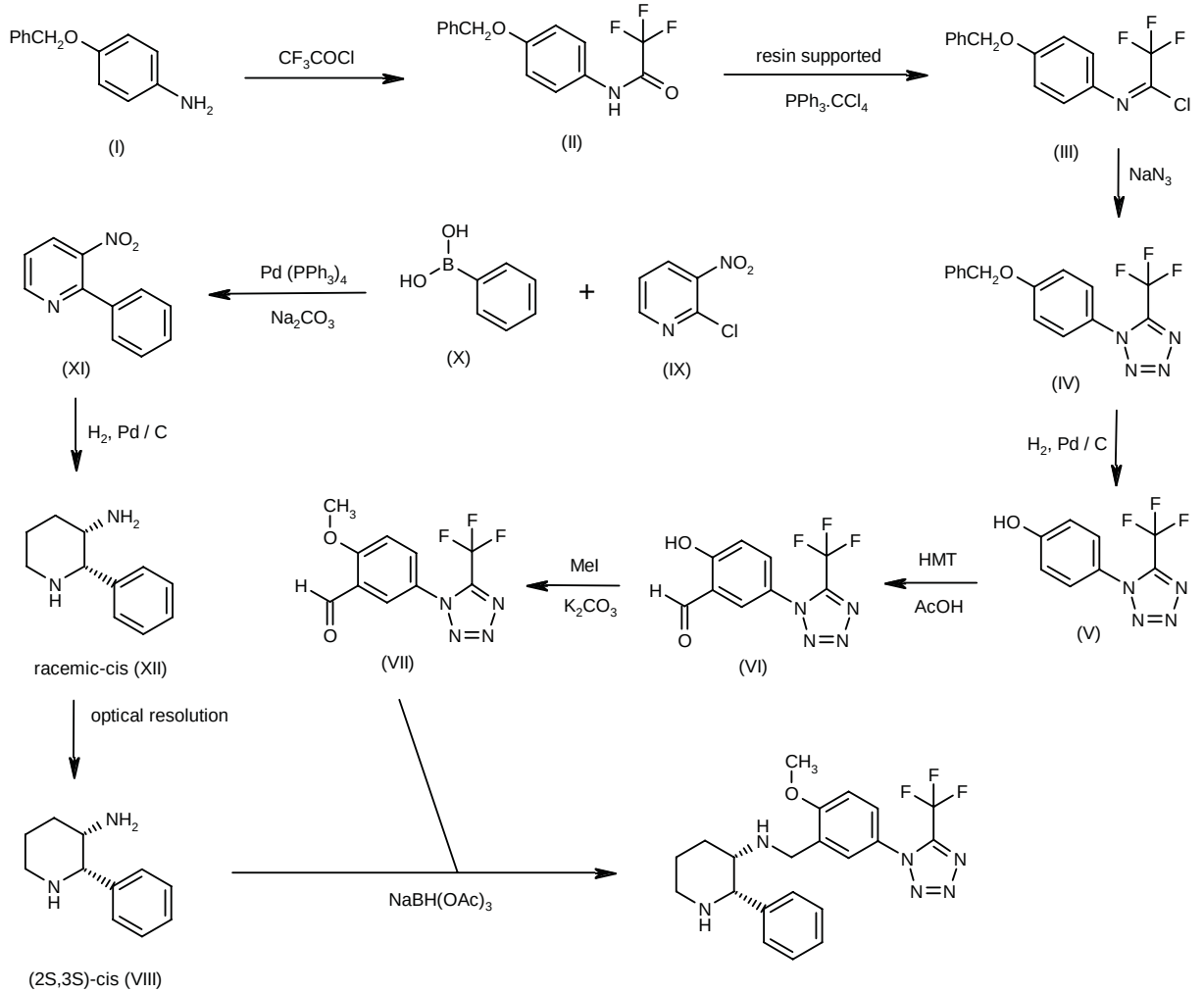
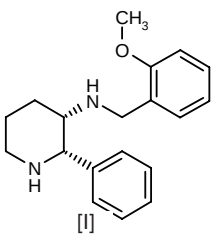
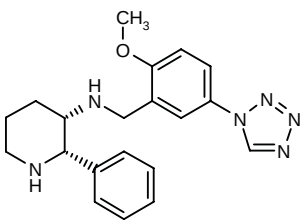
Scheme 1: Synthesis of GR-205171



The discovery of the broad spectrum antiemetic activity of CP-99994 [I], the prototypical NK_1 receptor antagonist, generated considerable interest in the potential application of NK_1 antagonists in antiemetic research (1). Scientists at Glaxo Wellcome recently described a strategy which resulted in the identification of GR-203040 [II] (6-8), an orally active NK_1 receptor antagonist which has high affinity *in vitro* and is highly effective *in vivo* as an antiemetic agent against a wide range of emetic stimuli, acting centrally, peripherally and at a mixed site.



[I]



[II]

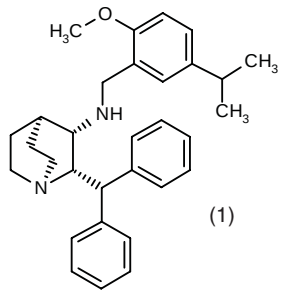
More recently, scientists at Glaxo Wellcome described the synthesis and preclinical evaluation of a further series of tetrazole derivatives, which culminated in the discovery of GR-205171 (1).

Pharmacological Actions

Preliminary studies have shown that GR-205171 has a high affinity for NK_1 receptors (rat pK_i = 9.5; human

Table I: Tackykinin NK_1 antagonists that have been reported to be in clinical trials (from Prous Science Ensemble database).

Compound	Indication	Status	Company
1. CJ-11974	Nausea and vomiting	Phase II	Pfizer
2. CP-122721	Nausea and vomiting	Phase II	Pfizer
3. FK-888	Asthma	Phase II	Fujisawa
4. GR-205171	Nausea and vomiting	Phase II	Glaxo Wellcome
5. L-732138*	Neuropathic pain	Preclinical	Merck & Co.
6. L-754030	Nausea and vomiting	Phase III	Merck & Co.
7. L-758298**	Migraine	Phase II	Merck & Co.
8. Lanepitant	Pain	Phase II	Lilly
9. Nalpitantium chloride	Psychiatric disorders	Phase I	Sanofi
10. SDZ-NKT-343	Pain	Phase I	Novartis



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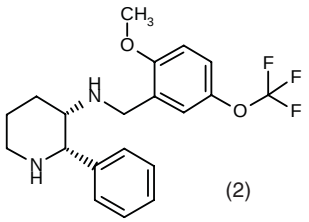

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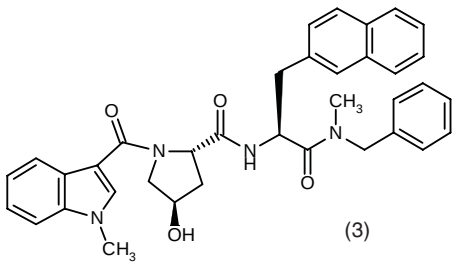

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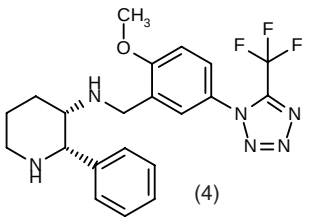
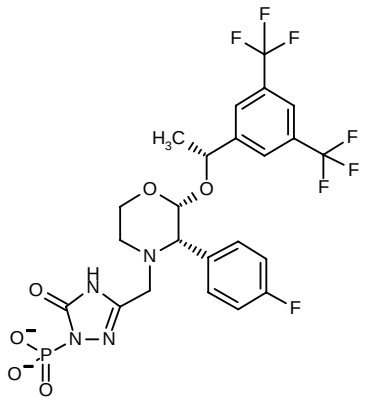
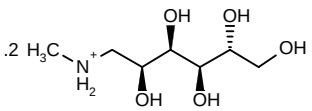


(4)





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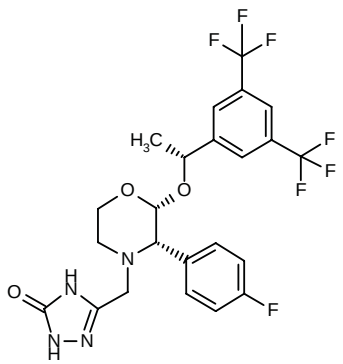

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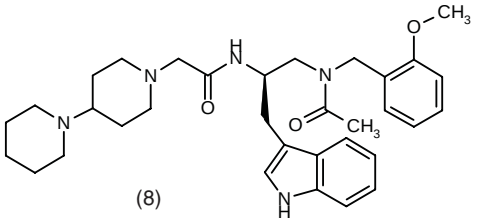

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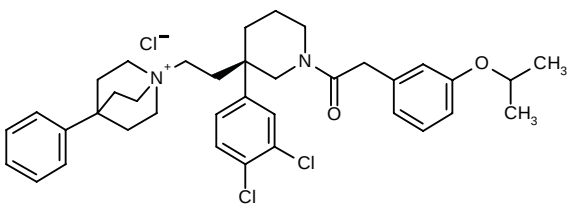

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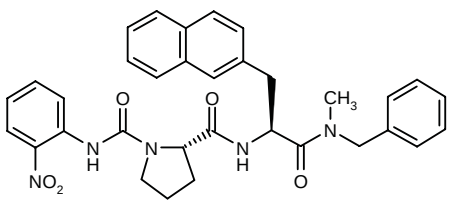

(10)

*Structure not yet detected. **Prodrug of L-754030.

Table II: Affinities of selected compounds for tachykinin NK subtype receptors (from Prous Science MFLine database).

Compound	Receptor	Binding affinity	Radioligand	Material	Ref.
CP-122721	NK_1	0.14[a]	[^{125}I]-Substance P	CHO cells with human receptor	28
	NK_2	>1000[a]	[^{125}I]-Neurokinin A	CHO cells with human receptor	28
		<10000[a]	[^{125}I]-Neurokinin A	CHO cells with human receptor	29
	NK_3	>1000[a]	[^{125}I]-BH-Eledoisin	CHO cells with human receptor	28
		<10000[a]	[^{3}H]-Neurokinin A	CHO cells with human receptor	29
CP-99994	NK_1	0.42[b]	[^{3}H]-Substance P	CHO cells with human receptor	30
		0.50[a]	[^{125}I]-Substance P	CHO cells with human receptor	28
	NK_2	>1000[a]	[^{125}I]-Neurokinin A	CHO cells with human receptor	28
		17000[b]	[^{3}H]-Neurokinin A	CHO cells with human receptor	30
	NK_3	>1000[a]	[^{125}I]-BH-Eledoisin	CHO cells with human receptor	28
		>10000[b]	[^{3}H]-Neurokinin B	CHO cells with human receptor	30
FK-888	NK_1	0.72[a]	[^{125}I]-BH-Substance P	COS cells with human receptor	31
		2.13[b]	[^{3}H]-Substance P	COS cells with human receptor	32
	NK_2	810[a]	[^{125}I]-Neurokinin A	COS cells with human receptor	28
		1202[b]	[^{3}H]-Neurokinin A	CHO cells with human receptor	33
	NK_3	2200[a]	[^{125}I]-BH-Substance P	COS cells with human receptor	31
		5620[a]	[^{125}I]-BH-Eledoisin	Brain cortex, guinea pig	34
GR-203040	NK_1	0.05[b]	[^{3}H]-Substance P	CHO cells with human receptor	8
	NK_2	<10000[b]	[^{3}H]-GR-100679	CHO cells with human receptor	8
	NK_3	<1000[b]	[^{3}H]-Senktide	Brain cortex, guinea pig	8
GR-205171	NK_1	0.08[a]	[^{125}I]-Substance P	CHO cells with human receptor	28
	NK_2	>1000[a]	[^{125}I]-Neurokinin A	CHO cells with human receptor	28
	NK_3	>1000[a]	[^{125}I]-BH-Eledoisin	CHO cells with human receptor	28
L-732138	NK_1	2.30[a]	[^{125}I]-Substance P	CHO cells with human receptor	35
	NK_2	>2000[a]	[^{125}I]-Neurokinin A	CHO cells with human receptor	35
	NK_3	>2000[a]	[^{125}I]-BH-Eledoisin	CHO cells with human receptor	35
L-754030[c]	NK_1	0.09[a]	[^{125}I]-Substance P	CHO cells with human receptor	28
	NK_2	>1000[a]	[^{125}I]-Neurokinin A	CHO cells with human receptor	28
	NK_3	>1000[a]	[^{125}I]-BH-eledoisin	CHO cells with human receptor	28
Lanepitant	NK_1	0.15[b]	[^{125}I]-Substance P	IM9 cells with human receptor	36
	NK_2	>1000[b]	[^{125}I]-Neurokinin A	NR	36
	NK_3	>1000[b]	NR	NR	36
Nalpitantium chloride	NK_1	0.027[b]	[^{125}I]-BH-Substance P	Brain cortex, rat	37
		0.15[b]	[^{3}H]-Substance P	COS cells with human receptor	32
	NK_2	>1000[b]	[^{125}I]-Neurokinin A	Duodenum, rat	37
	NK_3	500[b]	[^{125}I]-Neurokinin B	Brain cortex, guinea pig	37
		>1000[b]	[^{125}I]-Neurokinin B	Brain cortex, rat	37
NKT-343	NK_1	0.16[b]	[^{3}H]-Substance P	COS cells with human receptor	38
		0.62[a]	[^{3}H]-Substance P	COS cells with human receptor	32
	NK_2	84.0[b]	[^{3}H]-Neurokinin A	COS cells with human receptor	32
	NK_3	1850[b]	[^{3}H]-Senktide	COS cells with human receptor	32
Substance P	NK_1	0.12[a]	[^{125}I]-BH-Substance P	COS cells with human receptor	31
		2.80[b]	[^{3}H]-Substance P	CHO cells with human receptor	30
	NK_2	150[a]	[^{125}I]-Neurokinin A	COS cells with human receptor	31
		129[b]	[^{125}I]-Neurokinin A	CHO cells with human receptor	30
	NK_3	35.0[a]	[^{125}I]-BH-Substance P	COS cells with human receptor	31
		1290[b]	[^{3}H]-Neurokinin B	CHO cells with human receptor	30

[a]IC_{50}, nM; [b]K_i, nM; [c]active metabolic of L-758298; BH: Bolton-Hunter; NR: Not reported.

pK_i = 10.5) and is highly selective for NK_1 receptors over NK_2 and NK_3 receptors (Table II). GR-205171 has also been shown to have significant and potent inhibitory activity against various emetic stimuli including cisplatin, cyclophosphamide, morphine, ipecacuanha, X-irradiation, copper sulfate, motion and inhaled anesthetics in ferret, dog and shrew models (9, 10).

The potent antiemetic effects of GR-205171 were further demonstrated in a recent study showing inhibition of both acute and delayed phases of cisplatin-induced emesis in piglets. Fifteen minutes before receiving cisplatin (5.5 mg/kg i.v.), animals were given a single dose of GR-205171 (0.01-1.0 mg/kg i.v.); 2 separate groups of animals were administered the agent (1.0 mg/kg) either 15 min before the onset of the delayed phase or every 6 h for 60 h. The total number of emetic episodes decreased in a dose-dependent manner in animals pretreated with GR-205171 15 min prior to cisplatin, and a dose of 1 mg/kg completely inhibited vomiting in 62% of the piglets throughout the experiment. Although animals receiving the agent 15 min before the onset of the delayed phase exhibited an acute response to cisplatin, vomiting was inhibited during this phase. The multiple injection regimen proved to be the most effective in inhibiting nausea-like behavior and vomiting (11). The antiemetic activity of GR-205171 and other selected NK_1 antagonists is summarized in Table III.

Table III: Antiemetic activity of GR-205171 and other selected NK_1 antagonists (from Prous Science MFLine database).

Compound	Parameter	Value (mg/kg)	Ref.
CP-122721	ED_{50}	0.08 p.o.	39
	ED_{90}	3.0 i.v.	40
CP-99994	ED_{50}	0.18 p.o.	41
GR-203040	ED_{50}	0.05 p.o.	41
GR-205171	ED_{90}	0.20 i.v.	42
L-754030	ED_{90}	0.30 i.v.	42

GR-205171 (0.05-0.7 mg/kg i.v.) also completely abolished vagal stimulated- and medial solitary nucleus-induced retching in decerebrate dogs within 5 min of administration. However, the results from this study demonstrated that firing of neurons from the medial solitary nucleus was not altered in response to pulse-train and sustained vagal simulation even after retching was inhibited. These results indicate that substance P, an endogenous NK_1 agonist, is not the neurotransmitter between vagal afferents and the medial solitary nucleus (12).

In addition to antiemetic activity, preclinical studies have also investigated other actions of GR-205171. The compound was found to inhibit carrageenan-induced Fos-like immunoreactivity in laminae I and II of the rat lumbar spinal cord, suggesting that NK_1 receptors may be involved in nociceptive transmission. When GR-205171 (3 mg/kg s.c.) was administered 30 min prior to 2% carrageenan (0.1 ml i.p.) to induce paw edema, total Fos-like immunoreactivity nuclei were reduced by 20%, with decreases of 38% and 49% observed in laminae I and II and lateral V and VI, respectively, although treatment did not visibly alter edema (13).

Although brain Fos-like immunoreactivity was not altered in rats treated with GR-205171 (0.3 and 3 mg/kg s.c.) alone, apomorphine-induced increases in expression in the nucleus tractus solitarius (NTS) were significantly reduced by 47% with the higher dose (14). These results, together with those of another study demonstrating that changes in local NTS cerebral glucose utilization induced by apomorphine were significantly reduced with GR-205171 treatment, suggest that an important site of action of NK_1 antagonists may be the NTS (15).

Another study using the rat spinal cord has shown that noxious stimulus-evoked dorsal horn activity is not mediated by substance P, since GR-205171 (10 mg/kg s.c.) did not affect pinch-evoked c-fos expression in neurons positively labeled for NK_1. However, GR-205171 reduced pinch-evoked NK_1 internalization by 77.4% in lamina I neurons of the L4 segment (16).

In a rat model of neuropathic pain, GR-205171 (1 and 3 mg/kg) dose-dependently reversed the reduction in ipsilateral paw withdrawal latencies observed following sciatic nerve ligation, suggesting that NK_1 receptors may be involved in central sensitization of the dorsal horn neurons (17).

Pretreatment with GR-205171 (0.1-1.0 mg/kg s.c.) has been shown to block apomorphine (0.25 mg/kg s.c.)- and amphetamine (0.5 mg/kg s.c.)-induced conditioned taste aversion in rats, as compared to the 5-HT_3 antagonist ondansetron (0.001-0.1 mg/kg s.c.). Although both agents dose-dependently blocked apomorphine-induced taste aversion, GR-205171 alone inhibited amphetamine-induced aversion, whereas ondansetron only attenuated the response (18).

GR-205171 (2 mg/kg i.p. t.i.d. for 48 h) treatment in rats significantly reduced renal damage caused by cisplatin (7.5 mg/kg i.p.). GR-205171 administration was started 5 min prior to cisplatin. After 48 h, less severe epithelial damage and only moderate edema were observed in GR-205171-treated rats, in addition to improved renal function reflected in creatinine excretion and lithium clearance (19).

Contradictory results have been obtained from studies examining the efficacy of GR-205171 as a potential therapeutic agent in the treatment of migraine headaches. One study has demonstrated that the administration of the agent (0.4 μg/kg i.v.) to rabbits via the lingual artery attenuated the substance P-induced reductions in carotid arterial vascular resistance. In addition, GR-205171 administered to rats (0.1 and 1 mg/kg i.v.) and guinea pigs (1, 10 and 100 μg/kg i.v.) inhibited plasma protein extravasation in dura matter and reduced c-fos in the trigeminal nucleus caudalis in response to electrical stimuli of the trigeminal ganglion (20). However, using a model of trigeminovascular nociception in which the superior sagittal sinus was isolated and electrically stimulated in anesthetized cats, GR-205171 (100 μg/kg i.v.) had no significant effect on latency or probability of firing of cells. In addition, GR-205171 was found to have no effect on Fos expression in central trigeminal cells, suggesting that it would not be an effective antimigraine therapy (21).

Pharmacokinetics

The pharmacokinetics of GR-205171 were examined in a randomized, double-blind, placebo-controlled, ascending dose trial involving 10 healthy volunteers and in 26 patients from phase II studies evaluating the compound in chemotherapy-induced emesis and postoperative nausea and vomiting. The healthy subjects received doses of 1, 3, 10, 20 or 50 mg GR-205171 (i.v. infusion over 15 min) or placebo, with a minimum of 7 days between doses as a washout period. The 26 patients in the phase II studies received 5 or 25 mg GR-205171 i.v. for 15 min; some individuals were also administered ondansetron (8 mg for 10 min prior to GR-205171 infusion). A slight disproportionality was found for AUC, C_{max}, $t_{1/2}$ and clearance, although the authors attributed this to the fact that the methods used were not sensitive enough at the low doses tested. However, the results demonstrated that the agent was a high-clearance compound with a long elimination half-life. The parameters obtained

from patients, who were mostly female and older than the healthy subjects, were more consistent. However, only a slight age-related decrease in clearance of the drug was observed in the older patients. Furthermore, ondansetron had no effects on the pharmacokinetic parameters of GR-205171 (22, 23).

Clinical Studies

The safety and efficacy of i.v. administration of GR-205171 to prevent acute cisplatin-induced emesis and nausea alone or in combination with ondansetron (8 mg i.v.) were examined in a three-center, randomized, double-blind, parallel group study involving 16 patients. GR-205171 alone or in combination with ondansetron was administered 15 min prior to cisplatin ($\geq$ 80 mg/m^2) and observations were taken for the following 24 h. Nausea and vomiting were completely inhibited for up to 16 h in all patients receiving the high dose of GR-205171 and ondansetron; 2/7 patients on the lower dose experienced emesis and nausea between 18 and 24 h. GR-205171 in combination with ondansetron was concluded to be effective and well tolerated (24).

GR-205171 was administered to patients undergoing abdominal or vaginal hysterectomy or ovariectomy performed under general anesthesia in order to determine the efficacy of the compound in preventing postoperative nausea and vomiting. Of the 57 patients included, 37 experienced nausea and vomiting within 6 h of recovery and were administered either GR-205171 (25 mg i.v.) or placebo. Complete control of emesis and nausea was higher in the group receiving GR-205171 and significantly fewer episodes occurred as compared to the placebo group. No significant differences were observed in adverse effects or in control of pain between groups (25).

Results from a randomized, double-blind, placebo-controlled trial have shown that GR-205171 is ineffective as a treatment for migraine. Sixty-three individuals diagnosed as IHS-migrainers were administered either GR-205171 (25 mg i.v.) or placebo for a single migraine attack. No significant difference in headache relief at any time point after the start of infusion was observed between groups (26).

Glaxo Wellcome is continuing its evaluation of GR-205171 in phase II trials (27).

Manufacturer

Glaxo Wellcome plc (GB).

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