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CCC: 0377-8282/2002

Aprepitant and L-758298

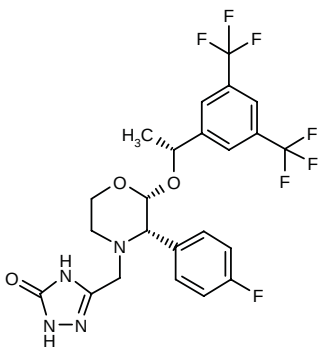
Antiemetic
Antidepressant
Tachykinin NK_1 Antagonist

Aprepitant

Prop INN; USAN

L-754939
MK-869

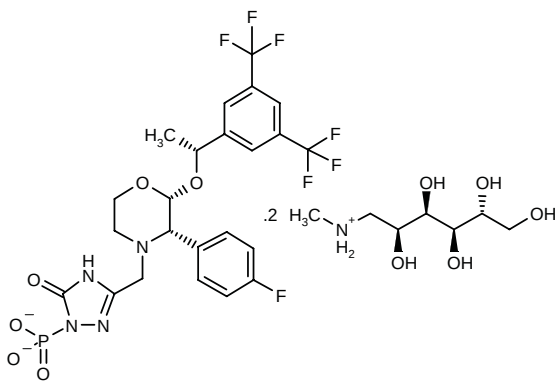
5-[2(*R*)-[1(*R*)-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3(*S*)-(4-fluorophenyl)morpholin-4-ylmethyl]-3,4-dihydro-2*H*-1,2,4-triazol-3-one



$C_{23}H_{21}F_7N_4O_3$
Mol wt: 534.438
CAS: 170729-80-3
EN: 250157

L-758298

3-[2(*R*)-[1(*R*)-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3(*S*)-(4-fluorophenyl)morpholin-4-ylmethyl]-5-oxo-4,5-dihydro-1*H*-1,2,4-triazole-1-phosphinic acid bis(*N*-methyl-D-glucamine) salt



$C_{23}H_{22}F_7N_4O_6P.2C_7H_{17}NO_5$
Mol wt: 1004.8350
CAS: 265121-04-8
EN: 250158

Abstract

Despite recent progress in the development of better tolerated and more effective treatments for controlling chemotherapy-induced nausea and vomiting, emesis continues to be problematic for many patients receiving chemotherapy. A new class of antiemetics that are nonpeptide antagonists to the tachykinin neurokinin NK1 receptor (the substance P receptor) have emerged as potential candidates for antiemetic therapy as well as other widespread therapeutic applications. One such compound, aprepitant and its prodrug (L-758298), have demonstrated an excellent preclinical and clinical ability to antagonize the emetic effects of a number of stimuli, including chemotherapy agents such as cisplatin. The agent has also shown promise in preclinical and clinical studies of depression and anxiety.

Synthesis of Aprepitant

Aprepitant can be synthesized by two different ways:

a) Reduction of morpholinone (I) with L-Selectride in THF at –78 °C produced the intermediate lactol (II), which is condensed at low temperature with 3,5-bis(trifluoromethyl)benzoyl chloride (III) to afford the acyl acetal (IV). Reaction of compound (IV) with dimethyl titanocene in THF/toluene at 80 °C provides the enol ether (V). Catalytic hydrogenation of the double bond of (V) with concomitant *N*-benzyl group hydrogenolysis, yields a 8:1 mixture of diastereomers, from which the major isomer (VI) is isolated by column chromatography (1-7). Alkylation of the morpholine derivative (VI) with *N*-(methoxycarbonyl)-2-chloroacetamidrazone (VII) – obtained by reaction of chloroacetonitrile (VIII) with MeONa and methyl carbazate in MeOH – in the presence of diisopropylethylamine (DIEA) in acetonitrile gives intermediate (IX), which is finally cyclized to the desired triazolone in refluxing xylene (1-3). Scheme 1.

Morpholinone (I) can be obtained as follows: Treatment of 4-fluorophenylacetic acid methyl ester (X) with pivaloyl chloride (XI) and Et_3N in Et_2O followed by reaction with 4(*S*)-benzyl-2-oxazolidinone (XII) in THF and *n*-BuLi in hexane affords the oxazolidinone derivative (XIII).

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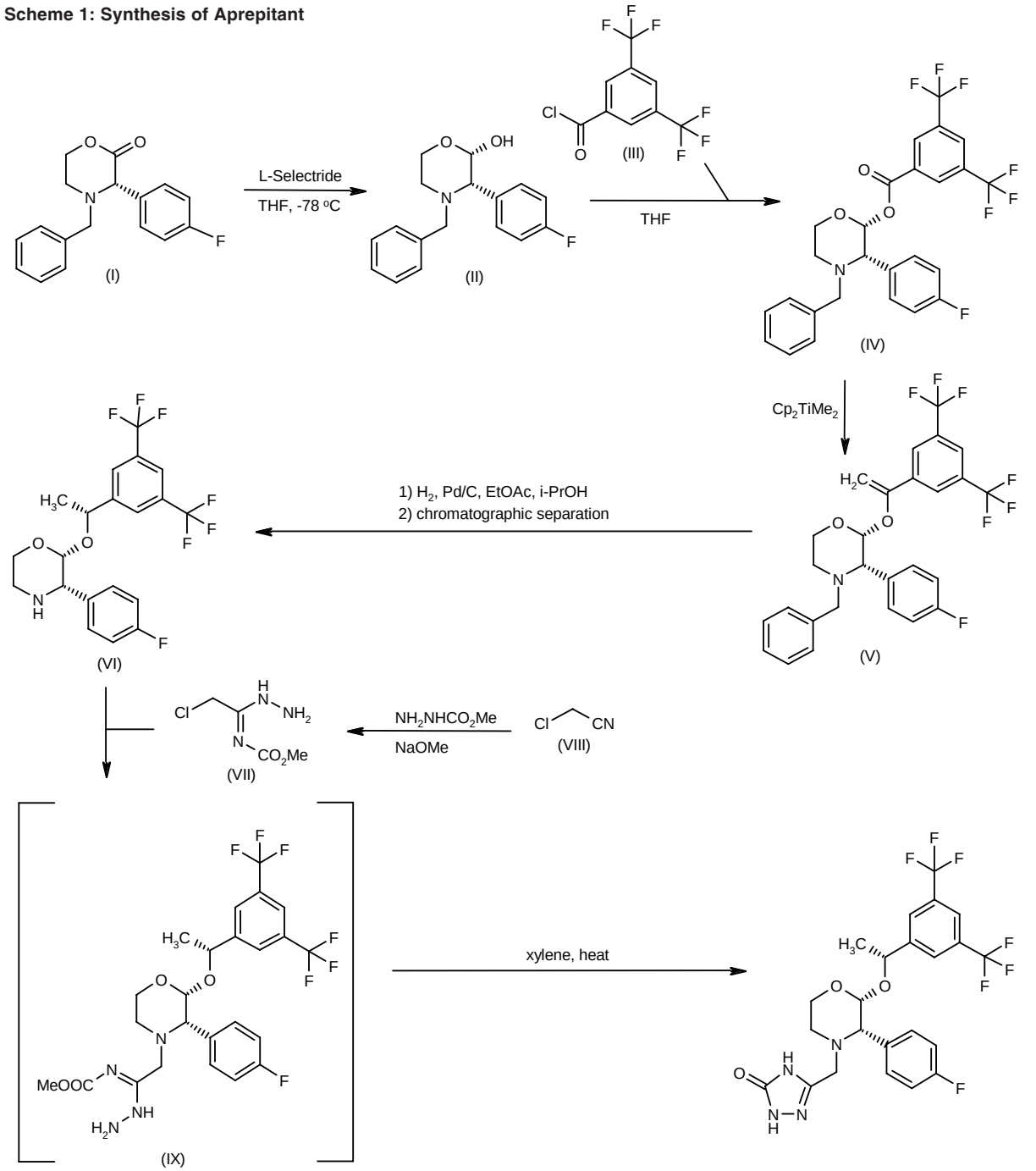
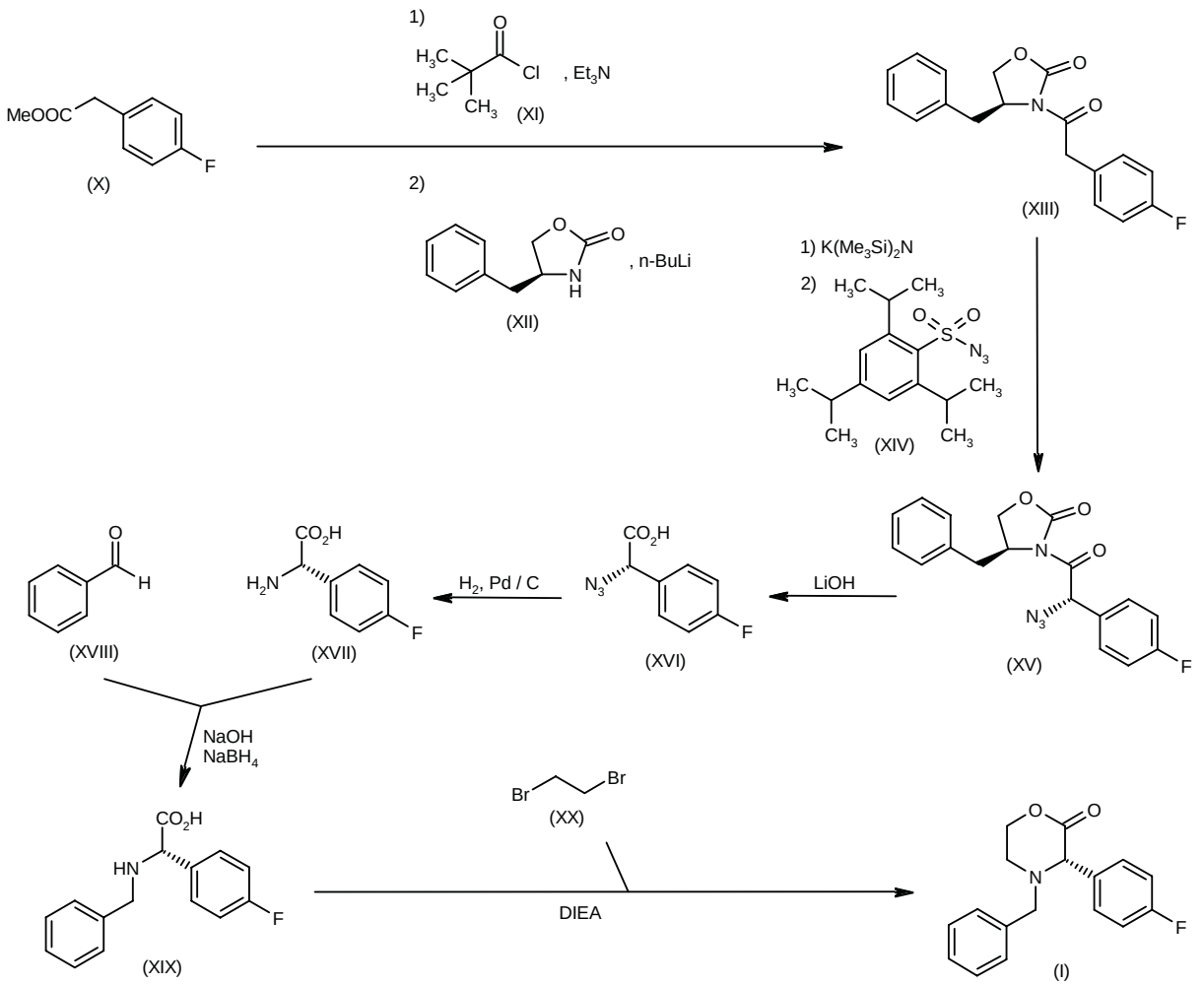
Scheme 1: Synthesis of Aprepitant



Conversion of (XIII) into azido derivative (XV) is achieved first by treatment of (XIII) in THF with a potassium bis-(trimethylsilyl)amide solution in toluene followed by treatment with 2,4,6-triisopropylphenylsulfonyl azide (XIV) in THF. Hydrolysis of azido-oxazolidinone derivative (XV) by means of LiOH in THF/H_2O yields the 2-azidoacetic acid derivative (XVI), which is then hydrogenated over Pd/C in H_2O/AcOH to afford (*S*)-(4-fluorophenyl)glycine (XVII). Treatment of compound (XVII) with benzaldehyde (XVIII), NaOH and $NaBH_4$ in MeOH yields *N*-benzyl-2(*S*)-(4-fluorophenyl)glycine (XIX), which is then cyclized with 1,2-dibromoethane (XX) in the presence of DIEA in DMF to furnish the morpholine intermediate (I) (1, 2). Scheme 2.

Alternatively, glycine (XVII) can be obtained as follows: Reaction of 4-fluorophenylacetic (XXI) with thionyl chloride in toluene in the presence of DMF

Scheme 2: Synthesis of Intermediate (I)



provides 4-fluorophenylacetyl chloride (XXII), which is treated with bromine and light irradiation followed by reaction with methanol to furnish the methyl bromoacetate derivative (XXIII). Treatment of (XXIII) with benzyl triethylammonium chloride (XXIV) and NaN_3 in MeOH, followed by hydrogenation over Pd/C in MeOH, gives the glycine derivative (XXV) as a racemic mixture, from which (XVII) is obtained by crystallization of the corresponding dibenzoyl tartaric (DBT) salts, followed by salt hydrolysis by means of refluxing HCl (1, 2). Scheme 3.

b) By direct condensation of either the *para*-toluenesulfonic acid salt or the (*R*)-camphorsulfonic acid salt of compound (VI) with chloromethyltriazolinone (XXVI) in DMF/H_2O in the presence of K_2CO_3 or DIEA (4-6). Scheme 4.

Intermediate (XXVI) can be prepared by two different ways: i) reaction of semicarbazide (XXVII) with orthoester (XXVIII) in MeOH (5, 6); and ii) condensation of semicarbazide (XXVII) with benzyloxyacetyl chloride (XXIX) by means of NaOH in THF/H_2O to provide adduct (XXX), which is then cyclized by means of refluxing NaOH to afford triazolinone (XXXI). Finally, compound (XXVI) is obtained by debenzylation of (XXXI) by hydrogenation over Pd/C in MeOH/H_2O to yield alcohol (XXXII), followed by treatment with thionyl chloride (4, 5). Scheme 4.

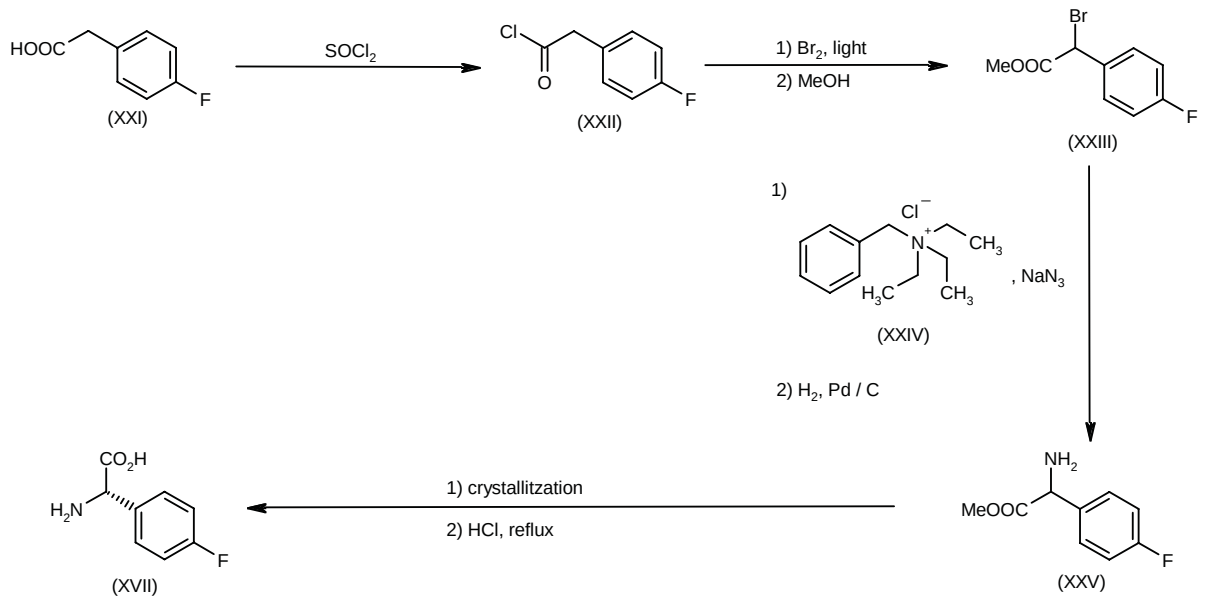
Synthesis of L-758298

Treatment of aprepitant (XXXIII) with tetrabenzyl pyrophosphate (TBPP) and NaHMDS in THF provides the dibenzyl phosphorylated derivative (XXXIV), which is finally debenzylated by hydrogenation over Pd/C in the presence of *N*-methyl-D-glucamine in MeOH/H_2O (2, 7). Scheme 5.

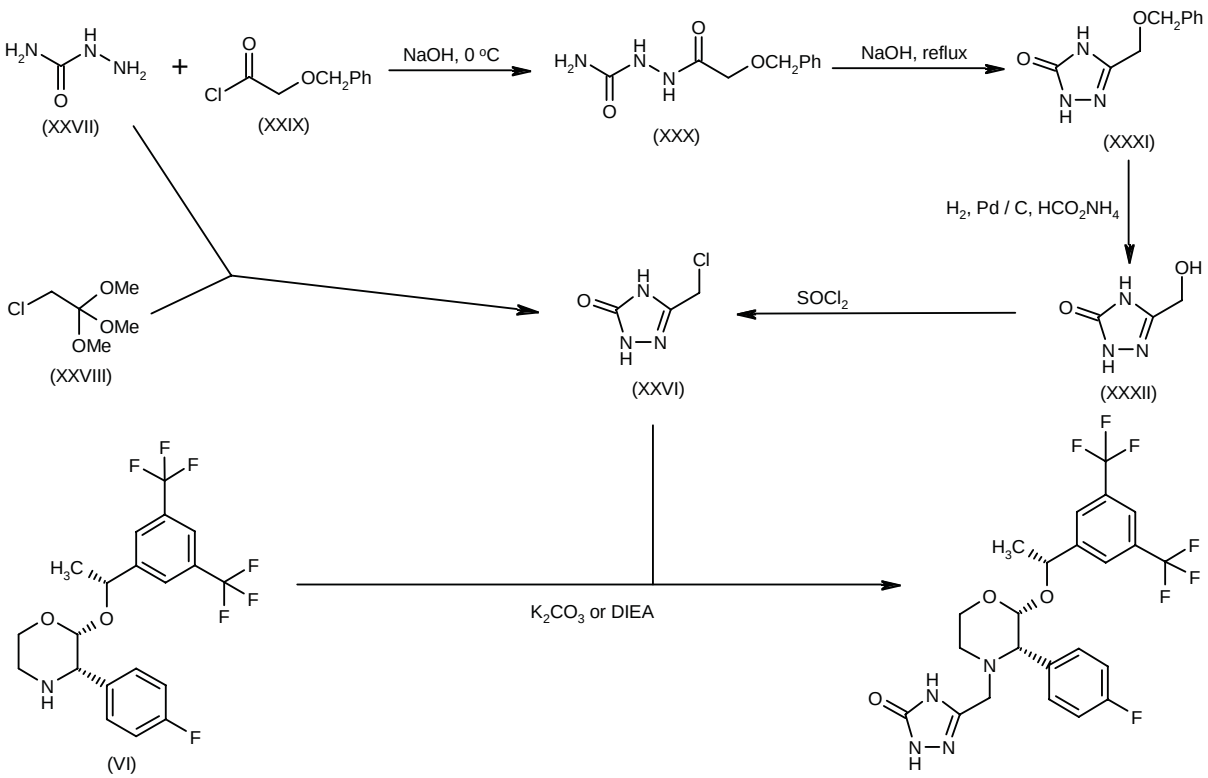
Introduction

Substance P is an endecapeptide that was discovered 80 years ago and is known to play a role in the contraction of smooth muscle such as that of the bladder,

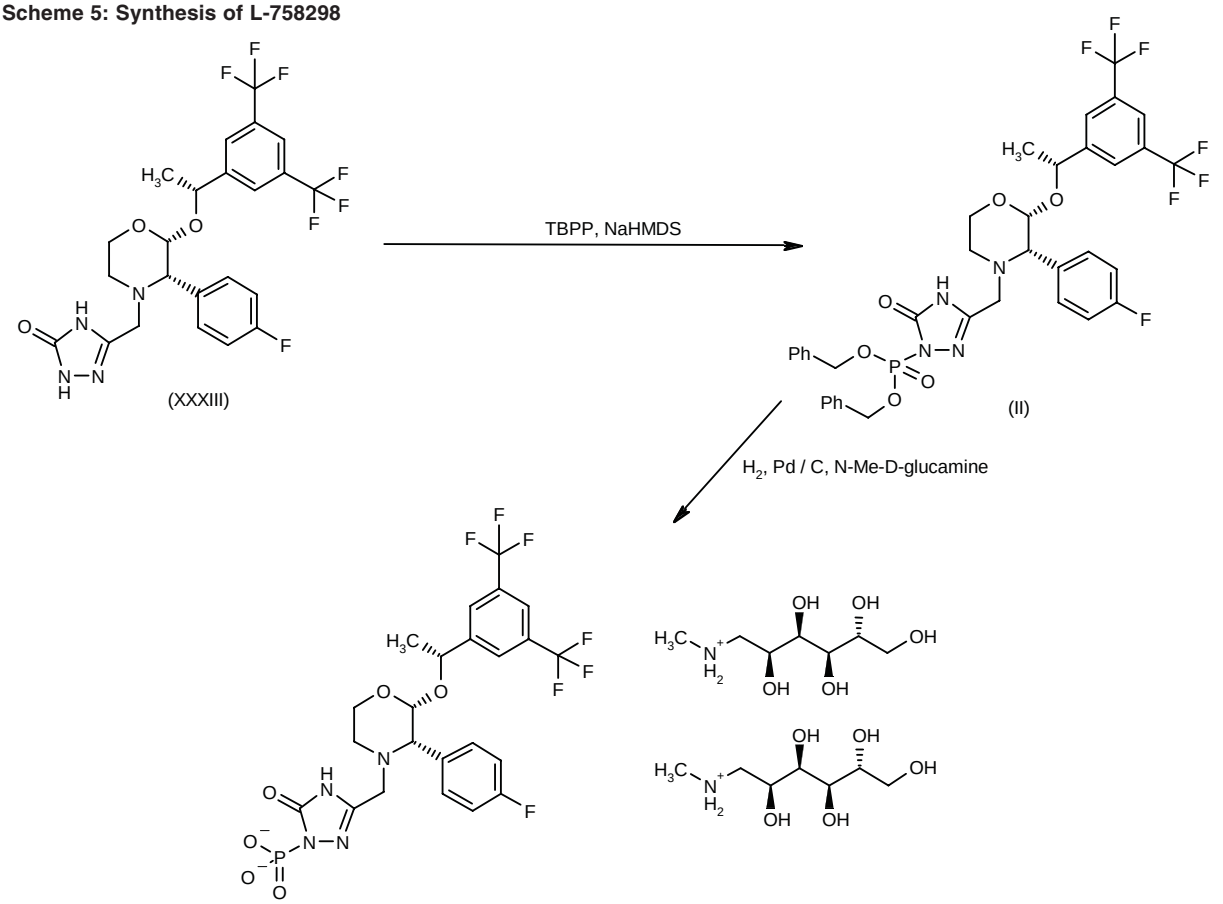
Scheme 3: Synthesis of Intermediate (XVII)



Scheme 4: Synthesis of Aprepitant



Scheme 5: Synthesis of L-758298



digestive system and other internal organs. It is a neurokinin (also known as tachykinins) which comprise a family of small peptides that share the common C-terminal amino acid sequence Phe-X-Gly-Leu-Met-NH_2. Tachykinins are widely distributed throughout the central and peripheral nervous systems where they are released from neuronal sensory afferents. In the brain, substance P is the most abundant member of the neurokinins where it functions as a neuromodulator via stimulation of neurokinin receptors. Substance P has a particularly high affinity for the G-protein-coupled type 1 NK receptor which has been localized in the locus coeruleus and amygdala, brain regions involved in the coordination of stress responses to aversive or noxious stimuli. Antagonism of the NK_1 receptor has potential widespread therapeutic applications such as the treatment of pain, inflammation, migraine, depression and anxiety. In addition, NK_1 antagonism may be particularly effective in controlling emesis (8-13).

Emesis is a reflexive response to rid the body of an ingested toxin. The medulla of the brainstem appears to be the center responsible for controlling vomiting, although the neurotransmitters involved in this response have not yet been identified. Nausea and vomiting are also observed in other conditions such as pregnancy where its function is unknown and they can accompany many medical interventions such as radiotherapy, chemotherapy and postoperative recovery. Although more effective treatments have been developed in managing chemotherapy-induced nausea and vomiting in the past years, the incomplete control of emesis continues to be problematic for a large number of patients undergoing chemotherapy. Research efforts, therefore, are ongoing in an attempt to discover more effective and better tolerated therapies for the control of emesis.

Although numerous neurotransmitters are implicated in the emetic response, substance P is thought to play a crucial role due to its localization on gastrointestinal afferent neurons and in the medulla of the brainstem. Thus, researchers have developed nonpeptide NK_1 receptor antagonists as potential antiemetics. In addition to potential antiemetic effects, tachykinin NK_1 receptor antagonists show promise as a treatment for depression and other psychological disorders (11, 12). One such compound, aprepitant (MK-869; L-754030), has emerged as a long-lasting, highly selective, NK_1 receptor antagonist

with good brain penetration. A significant drawback has been that aprepitant is poorly soluble in aqueous solutions. However, *N*-phosphorylation of the agent has resulted in the readily aqueous soluble prodrug L-758298 which undergoes rapid conversion to aprepitant. Both aprepitant and L-758298 have been selected for further development as antiemetics and as treatments for depression, migraine and pain (3, 7).

Pharmacological Actions

Aprepitant displayed high affinity for the gerbil, guinea pig and marmoset NK_1 receptor (IC_{50} = 0.3-0.5 nM) and for the human NK_1 receptor expressed in CHO cells (IC_{50} = 0.09 ± 0.06 nM). In contrast, IC_{50} values for the agent for the human NK_2 and NK_3 receptors expressed in CHO cells and the L-type calcium channel in rabbit skeletal muscle were > 1 μM, > 100 nM and > 1 μM, respectively. Aprepitant was over 3000 times (IC_{50} = 3 μM or greater) more selective for the human substance P receptor than for 90 other G-protein-coupled receptors and ion channels tested, including monoamine oxidase A or B, norepinephrine, dopamine or serotonin reuptake sites; 5-HT_{1A} or 5-HT_{2A} receptors; monoamine transporters; or μ, δ or κ opiate receptors (3, 14, 15).

Saturation binding studies using increasing [^{3}H]-aprepitant concentrations and the human NK_1 receptor expressed in Sf9 membranes resulted in a K_d value of 0.2 nM. The agent dissociated from the receptor with simple monophasic kinetics with a rate of dissociation (k^{-1}) of 0.0054 ± 0.003 min^{-1} and a $t_{1/2}$ value for receptor occupancy of 154 ± 75 min (3). The binding profiles of aprepitant and other NK_1 receptor antagonists are shown in Table I.

The prodrug L-758298 exhibited a 10-fold lower binding affinity for the human NK_1 receptor expressed in CHO cells (IC^{50} = 1.2 ± 1.2 nM). Experiments performed *in vitro* in which the prodrug was incubated with plasma from humans, rats and dogs in human hepatic subcellular fractions suggested that the conversion to aprepitant would occur in humans during hepatic circulation. When the prodrug was administrated to rats (1 and 8 mg/kg i.v.) and dogs (0.5, 2 and 32 mg/kg i.v.) *in vivo*, it was rapidly converted to aprepitant, becoming undetectable within 5 min in rats and 15 min in dogs (7).

Aprepitant has also demonstrated *in vivo* efficacy in a number of animal models. The compound potently inhibited resiniferatoxin-induced systemic vascular leakage in guinea pigs (ID_{50} = 0.008 mg/kg p.o.) which indicates potent inhibition of NK_1-mediated inflammation to the periphery. Aprepitant inhibited NK_1-agonist (GR-73632)-induced foot tapping in gerbils with an ID_{50} value of 0.4 mg/kg i.v. for immediate pretreatment and 0.3 mg/kg i.v. after 24 h pretreatment (3). Similarly, aprepitant (0.3- 3 mg/kg i.p.) was effective in significantly and dose-dependently blocking electrical shock (2 mA)-induced foot tapping in gerbils (16).

An *in vitro* study performed using guinea pig pups demonstrated the ability of aprepitant (ID_{50} = 0.7 mg/kg p.o.) to potently inhibit separation-induced vocalization when administered 4 h prior to maternal separation. Results indicate the excellent ability of the agent to penetrate the CNS since compounds such as CGP-49823, L-743310 and LY-303870 that have poor brain penetration, showed very little activity (ID_{50} > 30 mg/kg i.p.) in other studies using this assay (14, 17-21).

The antianxiolytic effects of aprepitant were shown in some *in vivo* anxiolytic animal models. Although aprepitant was ineffective in the murine light-dark box test and the human threat test in marmosets, the agent at a dose of 10 mg/kg was active in the forced swimming test in mice and in the gerbil elevated plus-maze test where it was more potent than diazepam, chlordiazepoxide, L-733060, buspirone, L-742694, paroxetine, CP-122721, CP-99994 and fluoxetine (15, 22).

Results from several *in vivo* studies in ferrets have demonstrated the antiemetic effects of aprepitant. When administered i.v. (0.1, 0.3 or 1 mg/kg) or p.o. (3 mg/kg) prior to emetogen challenge (10 mg/kg i.v. cisplatin, 0.25 mg/kg s.c. apomorphine or 0.5 mg/kg s.c. morphine), aprepitant effectively reduced retching and vomiting; the antiemetic effects of aprepitant were enhanced when it was coadministered with dexamethasone (20 mg/kg i.v.) or ondansetron (0.1 mg/kg i.v.). Further characterization of the antiemetic effects of aprepitant in ferrets revealed that the agent was effective against both the acute and delayed phase cisplatin-induced emesis. Pretreatment with aprepitant (2 and 4 mg/kg once daily p.o.) dose-dependently inhibited cisplatin-induced emesis; vomiting and retching were suppressed in 3 of 4 ferrets treated with the agent (4 mg/kg p.o.) at 24 or 48 h after cisplatin when the acute phase of emesis was already established (3, 7, 23) (Table II).

An *in vitro* and *in vivo* study examined the stability of the prodrug, L-758298, in blood and subcellular fractions from rats, dogs and humans and the conversion of the prodrug to aprepitant following i.v. administration in rats and dogs. L-758298 was rapidly converted to aprepitant in rat blood but was stable in dog and human blood; however, the prodrug was rapidly converted in dogs and human liver microsomes. Intravenous dosing of rat and dogs with the prodrug also resulted in rapid conversion to aprepitant. The extent of exposure of aprepitant after administration of the prodrug at doses of 1 and 8 mg/kg i.v. in rats and 0.5 mg/kg in dogs was estimated to be approximately 90, 100 and 59%, respectively. The AUC versus time curve of aprepitant was found to nonproportionally increase following i.v. administration of the prodrug to dogs at doses of 0.5-32 mg/kg, indicating that elimination of aprepitant may be saturated at high doses (24).

Clinical Studies

The pharmacodynamics of the prodrug L-758298 were examined in a double-blind, randomized, placebo-controlled trial conducted in 16 healthy male volunteers.

Table I: Binding profile of NK_1 receptor antagonists (from Prous Science Integrity®).

Compound	Receptor	Parameter	Value (nM)	Radioligand	Material	Ref.
Aprepitant	NK-1	IC_{50}	0.09-0.10	Sunstance P	CHO cells with human receptor	3, 23
	NK-2	IC_{50}	>1,000-4,500	Neurokinin A	CHO cells with human receptor	3, 23
	NK-3	IC_{50}	>100	Eledoisin	CHO cells with human receptor	3
	NK-3	IC_{50}	300	Neurokinin B	CHO cells with human receptor	23
CP-122721	NK-1	IC_{50}	0.14	Substance P	CHO cells with human receptor	3
	NK-1	IC_{50}	0.16	Substance P	IM9 human lymphoblasts	38
	NK-2	IC_{50}	>10,000	Neurokinin A	CHO cells with human receptor	38
	NK-3	IC_{50}	>10,000	Eledoisin	Brain cortex, guinea pig	38
CP-99994	NK-1	IC_{50}	0.50	Substance P	CHO cells with human receptor	3
	NK-1	IC_{50}	0.50	Substance P	IM9 human lymphoblasts	38
	NK-1	K_i	0.27-0.42	Substance P	CHO cells with human receptor	39, 40
	NK-2	IC_{50}	>10,000	Neurokinin A	CHO cells with human receptor	38
	NK-2	K_i	>10,000-17,000	Neurokinin A	CHO cells with human receptor	39, 40
	NK-3	IC_{50}	>10,000	Eledoisin	Brain cortex, guinea pig	38
	NK-3	K_i	>10,000	Neurokinin B	CHO cells with human receptor	39, 40
DNK-333	NK-1	IC_{50}	4.80	Substance P	Retina, bovine	41
	NK-1	K_i	12.60	NR	Human receptor	42
	NK-2	IC_{50}	5.50	Neurokinin A	CHO cells with human receptor	41
	NK-2	K_i	6.31	NR	Human receptor	42
	nk-3	K_i	135.0	NR	Human receptor	42
GR-203040	NK-1	K_i	0.05	Substance P	CHO cells with human receptor	43
	NK-2	K_i	>10,000	GR-100679	CHO cells with human receptor	43
	NK-3	K_i	>1,000	Senktide	Brain cortex, guinea pig	43
L-742694	NK-1	IC_{50}	0.09	Substance P	CHO cells with human receptor	3
	NK-2	IC_{50}	>1,000	Neurokinin A	CHO cells with human receptor	3
	NK-3	IC_{50}	>100	Eledoisin	CHO cells with human receptor	3
L-758298*	NK-1	IC_{50}	2.80	Substance P	CHO cells with human receptor	23
	NK-2	IC_{50}	>10,000	Neurokinin A	CHO cells with human receptor	23
	NK-3	IC_{50}	>10,000	Neurokinin B	CHO cells with human receptor	23
Nalpitantium Chloride	NK-1	IC_{50}	0.79	Substance P	IM9 human lymphoblasts	38
	NK-1	K_i	0.019	Substance P	IM9 human lymphoblasts	44
	NK-1	K_i	0.082	Substance P	Ileum, guinea pig	44
	NK-2	IC_{50}	316.0	Neurokinin A	CHO cells with human receptor	38
	NK-2	K_i	>1,000	Neurokinin A	Duodenum, rat	44
	NK-3	IC_{50}	2512	Eledoisin	Brain cortex, guinea pig	38
	NK-3	K_i	500.0	Neurokinin B	Brain cortex, guinea pig	44
NKP-608	NK-1	K_i	1.10	Substance P	CHO cells with human receptor	45
	NK-2	K_i	794	Neurokinin A	CHO cells with human receptor	45
	NK-3	K_i	562	Neurokinin B	CHO cells with human receptor	45
RP-67580	NK-1	IC_{50}	63.1	Substance P	IM9 human lymphoblasts	38
	NK-2	IC_{50}	2512	Neurokinin A	CHO cells with human receptor	38
	NK-3	IC_{50}	>10,000	Eledoisin	Brain cortex, guinea pig	38

*Aprepitant prodrug. NR: not reported.

Table II: Inhibition of cisplatin-induced emesis in ferrets by NK_1 receptor antagonists (from Prous Science Integrity®).

Compound	ED_{50} (mg/kg)	Route	Ref.
Aprepitant	0.3	iv	7, 23
	0.3[a]	po	
CP-122721	0.08	po	46
CP-99994	0.18	po	47
GR-203040	0.05	po	47
L-742694	0.18	po	47
L-758298*	0.8	iv	7

*Aprepitant prodrug. [a]Lowest effective oral dose tested

Subjects were administered substance P infusions (0.125-128 pmol/min) before, during (0.25, 1, 1.43 or 5 mg i.v.) and 24 h after (1.43 mg i.v.) infusion with the prodrug or placebo and forearm blood flow was measured using venous occlusion plethysmography. Substance P-induced vasodilation was significantly and dose-dependently inhibited by treatment with the prodrug. Moreover, when substance P was infused 24 h after the prodrug and plasma concentrations of aprepitant were 2-3 ng/ml, a significant shift in response to substance P vasodilation of approximately 34-fold was observed. L-758298 was well tolerated with no serious adverse events reported (25).

Box 1: Antidepressant efficacy and safety of aprepitant (26) [from Prous Science Integrity®].

Design	Randomized, placebo-controlled, multicenter, double-blind, comparative clinical study
Population	Patients with major depressive disorder (n = 213)
Treatments	Aprepitant, 300 mg od x 6 wks Paroxetine, 20 mg od x 6 wks Placebo
Withdrawals	A: adverse events 9% Pa: adverse events 19% Pl: adverse events 9%
Adverse Events	A: sexual dysfunction 3% Pa: sexual dysfunction 26%, nausea Pl: sexual dysfunction 4%
Results	Hamilton Rating Scale for Depression score, change @ 6 wks: A* (–13.6) ≥ Pa** (–12.8) > Pl (–9.3) [*p = 0.003 *vs.* Pl; **p = 0.010 *vs.* P1] ≥ 50% reduction, rate: A* (39) ≥ Pa (12) ≥ Pl 12) [*p = 0.033 *vs.* Pl] Effect observed by 1 week and increased over the study period Hamilton Rating Scale for Anxiety score, change *vs.* Pl @ 4 wks: A (–2.6) [p = 0.047]
Conclusions	Aprepitant was well tolerated and effective as an antidepressant and anxiolytic

The antidepressant efficacy and safety of aprepitant (300 mg p.o. once daily in the evening) as compared to paroxetine (20 mg p.o. once daily in the evening) were examined in a multicenter, randomized, double-blind, placebo-controlled 6-week study involving 213 patients with major depressive disorder (DSM-IV diagnosis, with a score of 22 or greater on the 17-item Hamilton Depression Scale [HAM-D] and 15 or greater on the total Hamilton Anxiety Scale [HAM-A]). Treatment with aprepitant and paroxetine for 6 weeks both resulted in significantly better mean changes in HAM-D scores from baseline as compared to placebo (–13.6 and –12.8 points, respectively, *vs.* –9.3 points); no significant difference was observed between aprepitant and paroxetine although aprepitant appeared to be better than paroxetine on the insomnia, genital symptoms and work-related items of HAM-D, the total HAM-A score and patient reported Profile of Mood states. Aprepitant was well tolerated. The frequency of adverse events was similar for both treatment groups and placebo. However, paroxetine caused significantly more cases of sexual dysfunction (26%) as compared to aprepitant (3%) and placebo (4%) (14, 26) (Box 1).

The efficacy of oral aprepitant and L-758298 against cisplatin-induced emesis has been demonstrated in several trials. A multicenter, randomized, double-blind, placebo-controlled trial involving 159 cisplatin-naive cancer patients examined the efficacy and safety of aprepitant on acute and delayed cisplatin-induced (70 mg/m^2 or greater single-dose infusion on day 1) emesis. Patients received 400 mg aprepitant or placebo before cisplatin on day 1 (acute phase) followed by 300 mg aprepitant or placebo on days 2-5 (delayed phase); all patients received granisetron (10 μg/kg i.v.) and dexamethasone (20 mg p.o.). Significantly more patients pretreated with aprepitant (before cisplatin) had no vomiting as compared to placebo (93 *vs.* 67%), indicating the efficacy of the agent in controlling the acute phase of cisplatin-induced emesis. In addition, significantly more patients treated with aprepitant before and after cisplatin had no vomiting (82%) as compared to those receiving aprepitant before cisplatin followed by the placebo (78%) and those patients receiving only the placebo before and after cisplatin (33%). Aprepitant was well tolerated with no serious adverse events reported (27). The results of this study and some of the following studies are summarized in Table III.

The appropriate oral dose of aprepitant to prevent cisplatin-induced (70 mg/m^2 i.v. on day 1) nausea and vomiting was established in a study involving 563 cancer patients. All patients received ondansetron (32 mg i.v.) and dexamethasone (20 mg p.o.) before cisplatin on day 1 and dexamethasone on days 2-5. Patients were separated in a blind manner into the following 4 treatment groups: group I: aprepitant (375 mg p.o.) 1 h before cisplatin on day 1 followed by aprepitant (250 mg p.o.) on days 2-5; group II: aprepitant (125 mg p.o.) before cisplatin followed by aprepitant (80 mg p.o.) on days 2-5; group III: aprepitant (40 mg p.o.) before cisplatin followed by aprepitant (25 mg p.o.) on days 2-5; group IV: placebo on day 1 before cisplatin and on days 2-5. All treatments were well tolerated. The proportion of patients with no vomiting or need for rescue therapy (*i.e.*, complete response) in the acute phase (day 1) was 91, 83, 76 and 71% for groups I, II, III and IV, respectively, and the proportion of patients with a complete response in the delayed phase (days 2-5) for the 4 groups was 70, 70, 64 and 46%, respectively. It was concluded that aprepitant at a dose of 125 mg on day 1 followed by 80 mg on subsequent days was appropriate for further evaluation (28).

The efficacy and safety of aprepitant in combination with granisetron plus dexamethasone or dexamethasone

Table III: Randomized, double-blind, controlled clinical trials of aprepitant and L-758298 in cisplatin-induced emesis (from Prous Science Integrity®).

Study drug	n	No vomiting (rate)		Nausea (score or rate)		Other	Conclusions	Ref.
						Mean Global Satisfaction Rating:		
Aprepitant 400 mg po + Granisetron 10 μg/kg iv + DXM (precisplatin) → Aprepitant 300 mg po x 4 d	159	77%	57%**	65%**	51%**	100 mm**	Aprepitant combined with granisetron and dexamethasone was well tolerated and effective in the prevention of acute and delayed emesis after cisplatin either as a single or multiple doses	27
Aprepitant 400 mg po + Granisetron 10 μg/kg iv + DXM (precisplatin)		85%*	44%**	61%	48%	98 mm*		
Granisetron 10 mg/kg iv x DXM (precisplatin)		59%	17%	41%	24%	82 mm		
Aprepitant 375 mg po + Ondansetron 32 mg iv + DXM → Aprepitant 250 mg x 4 d	563	91%+	70%+				Aprepitant was well tolerated at all doses, but 125 mg on day 1 and 80 mg subsequently was the best regimen providing effective control of cisplatin-induced nausea and vomiting	28
Aprepitant 125 mg po + Ondansetron 32 mg iv + DXM → Aprepitant 80 mg + DXM x 4 d		83%++	70%++					
Aprepitant 40 mg po + Ondansetron 32 mg iv + DXM → Aprepitant 25 mg + DXM x 4 d		76%	64%++					
Ondansetron 32 mg iv + DXM (`precisplatin) → DXM x 4 d		71%	46%					
Aprepitant 400 mg po + Granisetron 10 μg/kg iv + DXM (precisplatin) → Aprepitant 300 mg po x 4 d	351	80%*	63%**	1*	2*		Aprepitant plus granisetron and dexamethasone was the best regimen for the prevention of cisplatin-induced emesis. Aprepitant and granisetron were effective in decreasing cisplatin-induced emesis and nausea with a delayed effect	29
Aprepitant 400 mg po (evening precisplatin) → Aprepitant 400 mg + DMX (precisplatin) → Aprepitant 300 mg po x 4 d		46%	51%**	8.5	3*			
Aprepitant 400 mg po + DXM (precisplatin) → Aprepitant 300 mg x 4 d		43%	57%**	9.5	3			
Granisetron 10 μg/kg iv + DXM (precisplatin)		57%	29%	7.5	7			
	228					Enjoy meal / Daily function	Aprepitant was effective in improving daily life by reducing nausea and vomiting	30
Aprepitant 125 mg + Ondansetron 32 mg + DXM (precisplatin) → Aprepitant 80 mg + DXM x 4 d		93%++		76%+		Nausea: 77% / Nausea: 83% Vomit: 94% / Vomit: 96%		
Ondansetron 32 mg + DXM (precisplatin) → DXM x 4 d		68%		60%		Nausea: 55% / Nausea: 65% Vomit: 71% / Vomit: 73%		
L-758298 100 mg iv + DXM (precisplatin) → Aprepitant 300 mg po od x 4 d	176	50%++	68%+				Treatment with L-758298 followed by aprepitant was well tolerated and was the best regimen to control delayed emesis, but ondansetron was more effective in controlling acute cisplatin-induced emesis	31
L-758298 100 mg iv + DXM (precisplatin)		47%++	63%+					
Ondansetron 32 mg iv + DXM (precisplatin)		84%	41%					
		@8h:	@2-7d	@ 1 d:	@2-7 d:	Mean Global Satisfaction Rating:	L-758298 was effective in preventing emesis later but not in the acute period, as did ondansetron in cisplatin-induced emesis	32
L-758298 60-100 mg iv	53	37%++	72%+	0.3	0.4	68		
Ondansetron 32 mg iv		52%	30%	0.0	0.8	91		

DXM: Dexamethasone; sd: single dose; od: once a day. $^{+}p < 0.05$ *vs.* ondansetron; $^{++}p < 0.01$ *vs.* ondansetron; $^{*}p < 0.05$ *vs.* granisetron; $^{**}p < 0.01$ *vs.* granisetron

alone in preventing acute (0-24 h postcisplatin) and delayed (days 2-7 postcisplatin) emesis was examined in a multicenter, randomized, double-blind, parallel-group trial conducted in 351 cisplatin-naive cancer patients. All patients received dexamethasone (20 mg p.o.) before a single dose of cisplatin (70 mg/m^2 or greater i.v.) on day 1 and were randomized into one of the following treatment groups: group I: granisetron (10 μg/kg i.v.) on day 1 before cisplatin followed by placebo on days 2-5; group II: aprepitant (400 mg p.o.) + granisetron on day 1 before cisplatin followed by aprepitant (300 mg p.o.) on days 2-5; group III: aprepitant (400 mg p.o. in the evening) on day 1 before cisplatin followed by aprepitant (300 mg p.o.) on days 2-5; group IV: aprepitant (400 mg p.o.) on day 1 before cisplatin followed by aprepitant (300 mg p.o.) on days 2-5. The proportion of patients without emesis in the acute phase were 57, 80, 46 and 43% for groups I, II, III and IV, respectively, with a significant difference observed between groups II and I. The proportion of patients in groups I, II, III and IV without emesis in the delayed phase was 29, 63, 51 and 57%, respectively, with groups II, III and IV significantly different from group I. The distribution of nausea scores was lower in the delayed phase for group II as compared to group I. Aprepitant was associated with serious cases of dizziness. Results indicate that the triple combination of aprepitant, the 5-HT$_3$ antagonist granisetron and dexamethasone is superior for the control of the acute phase of emesis (29).

A randomized, double-blind, phase IIb trial involving 228 cisplatin-naive cancer patients showed that the impact of chemotherapy-induced nausea and vomiting on daily life (according to patient reported Functional Living Index-Emesis scores) was reduced in more patients (85%) administered triple antiemetic therapy including aprepitant (125 mg aprepitant p.o. + 20 mg dexamethasone p.o. + 32 mg ondansetron i.v. on day 1 before cisplatin [70 mg/m^2 or greater i.v.] followed by 80 mg aprepitant + 8 mg dexamethasone on days 2-5) than in patients given standard therapy (67%; 32 mg ondansetron + 20 mg dexamethasone on day 1 followed by 8 mg dexamethasone on days 2-5) (30).

The efficacy and safety of both aprepitant and L-758298, in the prevention of acute (24 h) and delayed (days 2-5 postcisplatin) cisplatin-induced (70 mg/m^2 or more on day 1) emesis were shown in a double-blind, parallel study involving 176 cisplatin-naive cancer patients. Patients were randomized into the following 3 treatment groups: group I: single dose L-758298 (100 mg i.v.) plus dexamethasone (20 mg i.v.) on day 1 before cisplatin followed by aprepitant (300 mg once daily p.o.) on days 2-5 postcisplatin; group II: single dose L-758298 plus dexamethasone on day 1 before cisplatin followed by placebo on days 2-5; group III: ondansetron (32 mg i.v.) plus dexamethasone on day 1 before cisplatin followed by placebo on days 2-5. Although significantly more patients in group III (84%) were without emesis in the acute phase as compared to groups I and II (50 and 47%, respectively), significantly more group I and II patients (68 and 63%, respectively) were without emesis in the delayed phase as compared to group III (41%). Thus, treatment with the prodrug followed by aprepitant or placebo was superior to ondansetron in controlling delayed phase cisplatin-induced emesis. All treatments were generally well tolerated. No serious adverse events were associated with prodrug or aprepitant treatment, although diarrhea was more frequent in groups I and II (31).

Similar results were obtained for aprepitant's prodrug in another multicenter, randomized, double-blind, active agent-controlled (ondansetron) trial involving 53 cisplatin-naive cancer patients. On day 1, patients received either L-758298 (60 or 100 mg i.v.) or ondansetron (32 mg i.v.) before cisplatin (50-100 mg/m^2 on day 1) and were evaluated at 0-24 h (acute emesis phase) and 2-7 days (delayed emesis phase) postcisplatin dosing. No significant differences were observed between the two treatment groups in the acute phase (37 and 52%, respectively). However, significantly more L-758298-treated patients were without emesis in the delayed phase as compared to ondansetron-treated patients (72 *vs.* 30%). No serious adverse events were associated with the prodrug, although an increased incidence of diarrhea was observed in this group as compared to the ondansetron group (32).

In contrast to the efficacy of aprepitant and its prodrug against cisplatin-induced emesis, although well tolerated, L-758298 (60 mg i.v. over 15 min) was ineffective in preventing motion-induced nausea in a double-blind, placebo-controlled, double-dummy, balanced, 3-period crossover study conducted in 18 male subjects (33). Moreover, L-758298 (20, 40 or 60 mg i.v.) was ineffective as an abortive migraine treatment in a double-blind study involving 72 patients suffering from moderate or severe migraine and aprepitant had no activity against postherpetic neuralgia (30 mg p.o. for 2 weeks) or in preventing postoperative dental pain (300 mg in 2 h prior to surgery) in 2 placebo-controlled studies (34-36).

Aprepitant continues to undergo phase III trials for acute and delayed chemotherapy-induced nausea and vomiting. An NDA is scheduled to be filed this year. A phase III trial examining the efficacy of aprepitant as a treatment for depression is also under way (37).

Source

Merck & Co., Inc. (US).

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