Drugs of the Future 1998, 23(1): 79-115

Information Update

Volume 1-22, Number 1

Estimated developmental phase for this month's updated products:

Preclinical

ER-30346 (antifungal; Eisai, Bristol-Myers Squibb)
Ro-15-5458 (antiprotozoal; Roche)

Phase I

CI- 959 (antiallergic/antiasthmatic, cell activation inhibitor; Warner-Lambert)
FTY-720 (immunosuppressant; Yoshitomi, Taito, Novartis)
PEG-hemoglobin (blood substitute; Enzon)
S-16020-2 (antineoplastic; Servier)

Phase II

AD-5423 (dopamine D_2 antagonist, 5-HT_2 receptor antagonist, antipsychotic; Dainippon)
BTA-243 (antidiabetic, antiobesity, β_3-adrenoceptor agonist; American Cyanamid, Wyeth-Ayerst)
Cystemustine (antineoplastic, alkylating agent; CNRS, INSERM)
Decitabine (antineoplastic; Pharmachemie, Natl. Cancer Inst.)
DHAC (antineoplastic; Ilex Oncology, Natl. Cancer Inst.)
Didox (antineoplastic, ribonucleotide reductase inhibitor; Molecules for Health)
FK-409 (antianginal, vasodilator; Fujisawa)
HGP-30 (AIDS vaccine; CEL-SCI)
Iganidipine hydrochloride (antihypertensive, calcium channel blocker; Kyoto Pharm.)
ME-3407 (gastric antisecretory, antiulcerative; Meiji Seika)
Mildronate (antianginal, antiischemic agent; Inst. Org. Sint. Akad. Nauk, Taiho)
Nibentan (antiarrhythmic, Center Chem. Drugs)
Suritozole (cognition enhancer, antidepressant; Hoechst Marion Roussel)
Talsaclidine fumarate (cognition enhancer, muscarinic M_1 agonist; Boehringer Ingelheim)
VP-63843 (antiviral; ViroPharma)

Phase III

δ-Aminolevulinic acid (photodynamic therapy, antineoplastic, agent for actinic keratoses; Dusa)
Colestilan (hypolipidemic, bile acid-binding resin; Mitsubishi Chem., Tokyo Tanabe)
Dexmedetomidine (sedative, analgesic; Farmos, Abbott)
Edobacomab (treatment of septic shock; Xoma, Pfizer)
Flesinoxan hydrochloride (anxiolytic, antidepressant; Duphar)
Loxiglumide (CCK-A antagonist, agent for pancreas disorders, agent for irritable bowel syndrome; Rotta Research, Kaken, Tokyo Tanabe)
Naftopidil (antihypertensive, treatment of BPH, treatment of dysuria; Boehringer Mannheim, Asahi Chem., Asta, Kanebo)
Nebracetam fumarate (cognition enhancer; Boehringer Ingelheim)
Nefiracetam (cognition enhancer, nootropic agent; Daiichi Pharm.)
Rolipram (antidepressant, cognition enhancer; Schering AG, Meiji Seika)
Roquinimex (immunomodulator, antineoplastic; Pharmacia & Upjohn)
Zaleplon (sedative/hypnotic; American Cyanamid)
Zopolrestat (symptomatic antidiabetic, aldose reductase inhibitor; Pfizer)

Registered/Year

Fenoldopam mesilate (antihypertensive, dopamine D_1 agonist; SmithKline Beecham, Neurex)/1994

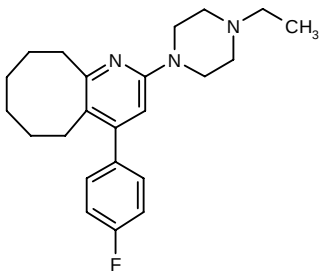
Launched/Year

Aranidipine (antihypertensive, calcium channel blocker; Maruko, Bristol-Myers Squibb, Taiho)/1996
Calcipotriol (antipsoriatic, vitamin D analog; Leo, Schering AG, Bristol-Myers Squibb)/1991
Donepezil hydrochloride (cognition enhancer, acetylcholinesterase inhibitor; Eisai, Pfizer, Bracco, Wyeth-Ayerst)/1997
Famotidine (gastric antisecretory, antipsychotic; Yamanouchi, Merck & Co., Novopharm)/1985
Fluoxetine hydrochloride (antidepressant, 5-HT reuptake inhibitor; Lilly)/1987
Ibandronic acid monosodium salt monohydrate (bisphosphonate, bone resorption inhibitor; Boehringer Mannheim, Rhône-Poulenc Rorer)/1996
Milnacipran hydrochloride (antidepressant; Pierre Fabre, Asahi Chem., ProdesFarma, Synthélabo)/1995
Ondansetron hydrochloride (antiemetic, 5-HT_3 receptor antagonist; Glaxo Wellcome)/1990
Paclitaxel (antineoplastic; Bristol-Myers Squibb)/1993
Rabeprazole sodium (gastric antisecretory, H^+/K^+-ATPase inhibitor; Eisai, Lilly, Janssen)/1997
Sumatriptan succinate (antimigraine, 5-HT_{1D} agonist; Glaxo Wellcome)/1991

AD-5423
Blonanserin

Dopamine D_2 Antagonist
5-HT_2 Receptor Antagonist
Antipsychotic

EN: 165688



$C_{23}H_{30}FN_3$ **Dainippon**

Blonanserin is the new proposed international nonproprietary name for AD-5423 (1).

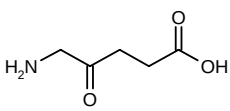
1. *Proposed international nonproprietary names (Prop. INN): List 76.* WHO Drug Inform 1996, 10(4): 198.

Original monograph - Drugs Fut 1992, 17: 9.

δ-Aminolevulinic Acid
Levulan®

Photodynamic Therapy
Antineoplastic
Agent for Actinic Keratoses

EN: 191307



$C_5H_9NO_3$ **Dusa**

In rats with hepatic tumors, photodynamic therapy using δ-aminolevulinic acid (60 mg/kg i.v.)-induced protoporphyrin IX sensitization and laser light was shown to be effective in decreasing the tumor growth rate when measured 3 and 6 days posttreatment (1).

A study in rats determined that 5-aminolevulinic acid and *meta*-tetrahydroxyphenylchlorin were effective tumor localizers with potential use in photodynamic therapy of glial tumors (2).

A study in rabbits transurethrally administered 5-aminolevulinic acid (3%) with or without taurodeoxycholic acid (100 μM) determined that 30 min may be sufficient for uptake of the drug into the bladder wall and that taurodeoxycholic acid may not enhance the uptake. Significant accumulation of protoporphyrin in the bladder wall occurred 3 h after dosing and intravesical administration of the drug did not appear to induce extravesical photosensitization (3).

Photodynamic therapy of superficial skin malignancies with δ-aminolevulinic acid resulted in a high cure response rate. Correlation of clinical response with erythema measurements was suggested to be a reliable predictor of therapeutic outcome (4).

A study in 18 patients with premalignant and malignant lesions of the mouth sensitized with 5-aminolevulinic acid (60 mg/kg p.o.) prior to photodynamic therapy demonstrated that treatment produced consistent epithelial necrosis in all cases. The 12 patients with dysplasia showed improvement and excellent healing without scarring. Only 2 of 6 patients with squamous cell carcinoma benefitted from treatment. No patient experienced cutaneous photosensitivity for longer than 2 days (5).

Following topical application of 5-aminolevulinic acid in 11 patients with neoplastic lesions of the oral cavity, drug-induced protoporphyrin IX fluorescence was shown to accumulate earlier and to a greater extent in neoplastic tissue compared to host tissue (10:1 ratio), with maximum fluorescence occurring within 1-2 h following application. These results suggest that the procedure would not only be useful for diagnosing head and neck cancer but also in fluorescence guided resection of tumors (6).

Results of a study on intravesically instilled 5-aminolevulinic acid (1, 5 and 20% solution) in conjunction with integral irradiation in patients with superficial bladder cancer refractory to BCG showed that treatment produced a complete remission in 17 of 21 patients with carcinoma *in situ* and partially reduced the spread of cancer in 3 of 7 patients. No bladder shrinkage or photodermatosis was observed and accumulation of protoporphyrin IX was limited to the urothelium. No serious side effects were reported (7).

A study on the toxic effects of oral 5-aminolevulinic acid (30-60 mg/kg) in the photodynamic treatment of cancer showed that treatment produced very high plasma levels (400-700 μmol/l) with a terminal half-life of 45-55 min. Aspartate aminotransferase levels rose to 2-5 times the normal level, but returned to normal within 72 h. Alkaline phosphatase levels were unaffected and no evidence of peripheral neuropathy was observed even in patients with the highest plasma levels. The drug was well tolerated with nausea and vomiting occurring in approximately 30% of patients (8).

Photodynamic therapy using topical 5-aminolevulinic acid (20% w/w) in patients with superficial skin malignancies or actinic keratosis resulted in a complete response rate of 79% of the basal cell carcinoma lesions and 3 of 5 actinic keratosis areas. Partial remissions were obtained in 1 area with Morbus Bowen, 2 areas with chronic inflammation and 2 areas of actinic keratosis. In 3 patients with basal cell naevus syndrome, there was 1 complete response, 1 partial response and good palliation in the third patient. Treatment was well tolerated, with healing usually occurring within 2 weeks, and cosmetic results were good to excellent (9).

5-Aminolevulinic acid (60 mg/kg p.o.) administered 6 h prior to photoradiation in 15 patients with Barrett's adenocarcinoma or severe dysplasia resulted in a complete response in 80% of the patients following an average of 2.1 treatments. The drug was well tolerated with mild nau-

sea and a transient increase in hepatic enzymes occurring in 10 patients (10).

A pilot dose-ranging study in 40 patients with actinic keratoses demonstrated that topical photodynamic therapy with 10, 20 or 30% δ-aminolevulinic acid resulted in total clearing of 91% of face and scalp lesions and 45% of trunk and extremities lesions. All concentrations were equally effective and well tolerated (11).

Dusa has reported positive results from two pivotal phase III trials with Levulan® Photodynamic Therapy for the treatment of precancerous actinic keratoses of the face and scalp (12).

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10. Gossner, L., Sroka, R., Stolte, M., Seitz, G., Hahn, E.G., Ell, C. *Barrett's esophagus with severe dysplasia and/or superficial cancer: Initial results of photodynamic therapy using 5-aminolaevulinic acid.* Gastroenterology 1996, 110(4, Suppl.): A521.

11. Jeffes, E.W., McCullough, J.L., Weinstein, G.D., Fergin,P.E., Nelson, J.S., Shull, T.F., Simpson, K.R., Bukaty, L.M., Hoffman, W.L., Fong, N.L. *Photodynamic therapy of actinic keratosis with topical 5-aminolevulinic acid: A pilot dose-ranging study.* Arch Dermatol 1997, 133(6): 727.

12. *Dusa reports positive phase III results for Levulan PDT.* Prous Science Daily Essentials October 24, 1997.

Original monograph - Drugs Fut 1997, 22: 11.

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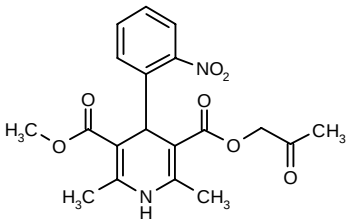
Aranidipine
Bec®
Sapresta®

Antihypertensive
Calcium Channel Blocker

EN: 122198



$C_{19}H_{20}N_2O_7$ **Maruko; Bristol-Myers Squibb; Taiho**

Binding studies of aranidipine showed that its two active metabolites (M-1(α) and M-1(β) have less potent and slower kinetic binding affinities and calcium antagonistic actions compared with other dihydropyridines. The slower kinetic properties of the drug may contribute to its long-lasting vasodilating effect *in vivo* (1).

A comparison of aranidipine with other calcium channel blockers in isolated rat portal veins showed that all the drugs concentration-dependently inhibited potassium-induced contractions. However, aranidipine was more potent against the low K^+-induced contraction than the high K^+-induced contraction, whereas the other drugs were equally potent against both K^+ concentrations (2).

1. Miyoshi, K., Miyake, H., Ichihara, K., Kamei, H., Nagasaka, M. *Contribution of aranidipine metabolites with slow binding kinetics to the vasodilating activity of aranidipine.* Naunyn-Schmied Arch Pharmacol 1997, 355(1): 119.

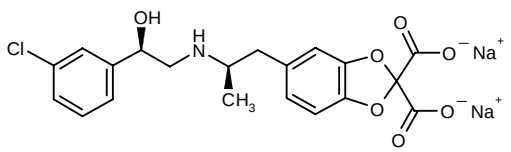
2. Okumura, K., Ichihara, K., Nagasaka, M. *Effects of aranidipine, a novel calcium channel blocker, on mechanical responses of the isolated rat portal vein: Comparison with typical calcium channel blockers and potassium channel openers.* J Cardiovasc Pharmacol 1997, 29(2): 209.

Original monograph - Drugs Fut 1991, 16: 25.

BTA-243
CL-316243 (former code)

Antidiabetic
Antiobesity
β_3-Adrenoceptor Agonist

EN: 177769



$C_{20}H_{18}ClNNa_2O_7$ **American Cyanamid; Wyeth-Ayerst**

The synthesis, oral absorption and pharmacokinetics of diester prodrugs of CL-316243 have been evaluated in rodent and primate models showing improved bioavailability as compared to parent compound (1).

In rat adipocytes, CL-316243 was shown to suppress insulin-stimulated phosphatidylinositol 3-kinase activity via a cAMP-dependent mechanism (2).

Infusion of CL-316243 (1 mg/kg/day) in obese rats reduced abdominal fat, increased metabolic resting rates and decreased food intake. Although the drug did not cause mature white adipocytes to disappear, it did remodel them with a marked change in cell composition (3).

Treatment with CL-316243 (1 mg/kg/day s.c. for 10-12 days) in nonobese, nondiabetic Sprague-Dawley rats improved basal and insulin-stimulated glucose disposal in the absence of a decrease in free fatty acids and body weight (4).

A study of CL-316243 (0.05 mg/kg/min i.v.) in anesthetized prairie dogs showed that the drug inhibits motility of the sphincter of Oddi by modulating the frequency and amplitude of the phasic wave. The results suggest an inhibitory role for β_3-adrenergic activity in biliary motility (5).

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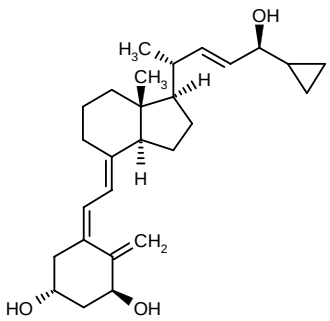
Calcipotriol
Dovonex®

Antipsoriatic
Vitamin D Analog

EN: 139088



$C_{27}H_{40}O_3$ **Leo; Schering AG; Bristol-Myers Squibb**

Leo's vitamin D analogue calcipotriol (Dovonex®) as cream and ointment has been cleared in the U.K. for use in children aged 6 and over with psoriasis (1).

1. *Dovonex cleared for use in children in the U.K.*. Prous Science Daily Essentials July 9, 1997.

Original monograph - Drugs Fut 1990, 15: 15.

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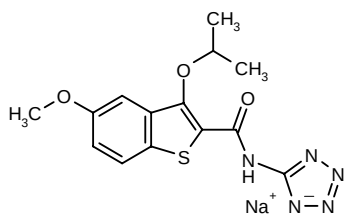
CI-959

Antiallergic/Antiasthmatic
Cell Activation Inhibitor

EN: 161770



$C_{14}H_{14}N_5NaO_3S$ **Warner-Lambert**

CI-959 was shown to suppress polarity and locomotion of Walker carcinosarcoma cells. This activity was independent of Ca^{2+} and not related to cell-substratum adhesion which was associated with a reduction in F-actin levels (1).

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Original monograph - Drugs Fut 1994, 19: 17.

Colestilan
MCI-196

Hypolipidemic
Bile Acid-Binding Resin

EN: 185277

Mitsubishi Chem.; Tokyo Tanabe

Results from a study of MCI-196 (1.5 g b.i.d. for 12 weeks) in 25 patients with type II hyperlipoproteinemia showed that the drug reduced total cholesterol, low density lipoprotein-cholesterol and apolipoprotein B levels and increased high density lipoprotein-cholesterol and apolipoprotein AI levels. The drug was safe, efficacious and easy to administer (1).

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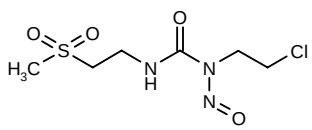
Original monograph - Drugs Fut 1993, 18: 15.

Cystemustine

Antineoplastic
Alkylating Agent

EN: 113740



$C_6H_{12}ClN_3O_4S$ **CNRS; INSERM**

Data from a phase II trial in 32 evaluable patients with recurrent gliomas showed that cystemustine (60 mg/m^2 every 2 weeks) administered as a 15-min infusion resulted in partial responses in 3 patients, stable disease in 11 and progressive disease in 12. Leukopenia, neutropenia and thrombopenia were the most frequently reported adverse events (1).

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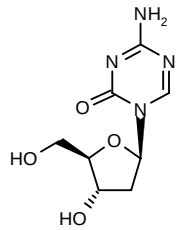
Original monograph - Drugs Fut 1994, 19: 27.

Decitabine

Antineoplastic

EN: 125366



$C_8H_{12}N_4O_4$ **Pharmachemie; Natl. Cancer Inst. (US)**

Results of a study evaluating the long-term toxicity of decitabine (0.06, 0.3, 6.0 mg/kg i.p.) administered for 86 weeks in male and female rats showed that the drug was well tolerated, although due to induction of malignant tumors, survival time was reduced in all groups except those receiving the lowest dose of 0.06 mg/kg. Histological observation revealed that the target organs of the drug's toxic action were the skeleton, nervous tissue, hematopoietic system, skin and female mammary glands (1).

Single-dose administration of decitabine (200-660 mg/m^2 i.v. infusion over 8 h) was investigated in a phase I-II study in 15 patients with metastatic lung cancer. In 9 evaluable patients receiving 1 or more treatment cycles, the median survival duration was 6.7 months, with 3 patients surviving longer than 15 months. The drug's steady-state plasma concentration was estimated to be in the same range as that producing activation of tumor suppressor genes. Hematopoietic toxicity was the major side effect, requiring 5-6 weeks of recovery before the next cycle of therapy (2).

A pilot phase I-II study of decitabine (200-660 mg/m^2 i.v.) administered as a single 8-h infusion in 9 assessable patients with stage IV non-small cell lung cancer showed that the drug increased survival time. The median survivial time was 6.7 months with 2 patients surviving longer than 15 months and 1 patient surviving more than 63 months. Hematopoietic toxicity was the primary adverse event (3).

A phase II study of decitabine (75 mg/m^2 i.v. as a 1-h infusion every 8 h for 3 doses repeated every 5-8 weeks) given to 14 men with progressive, metastatic prostate cancer recurrent after androgen blockade and flutamide withdrawal showed that the drug was well tolerated with no significant changes in urinary concentrations of the angiogenic factor bFGF in 7 unselected patients with progressive disease. Activity was limited to 2 African-American patients in whom the disease was stable for more than 10 weeks (4).

In a phase II study, 25 patients with advanced non-small cell lung cancer and no prior cytotoxic therapy and normal kidney, liver and bone marrow function were administered cisplatinum (20-33 mg/m^2) followed by decitabine (45-120 mg/m^2) as a 1-h infusion on 3-5 consecutive days every 3 weeks for 1-3 cycles. Only 2 partial responses were observed, lasting 4 and 8 weeks, respec-

tively. Adverse events included grade 3-4 granulocytopenia and thrombocytopenia, nausea and vomiting, mucositis and alopecia. Thus, decitabine at this dose and schedule did not enhance the antitumor effects of cisplatinum (5).

A study of decitabine administered as a low-dose 72-h infusion in 29 elderly patients with high-risk myelodysplastic syndrome showed that the treatment produced a partial response in 15 patients and a compete response in 8 patients. Myeolosuppression was the major adverse event leading to 5 toxic deaths (6).

Results of a study of decitabine (125 mg/m^2 as a 6-h infusion every 12 h for 6 days) in combination with either amsacrine (120 mg/m^2 as a 1-h infusion on days 6 and 7) or idarubicin (12 mg/m^2 as a 15-min infusion on days 5, 6 and 7) in 63 patients with relapsed acute myeloid or lymphocytic leukemia showed that 36.5% of patients obtained a complete remission (8/30 with amsacrine and 15/33 with idarubicin). The median disease-free survival time was approximately 8 months, with 20% of patients being in remission for more than 1 year. Compared to standard induction schedules, digestive tract and hematologic toxicity was prolonged (7).

Preliminary results of an ongoing phase II trial in 6 evaluable nonpretreated patients with myeloid leukemia administered a combination of decitabine (90 mg/m^2 as a 4-h i.v. infusion for 5 days) with daunorubicin (50 mg/m^2 on days 1-3) showed that after 2 courses, treatment produced complete remission in all 6 patients. Bone marrow suppression, mucositis, alopecia, nausea and vomiting were the main side effects (8).

Studies of decitabine alone (1000 mg/m^2) or in combination (400 mg/m^2) with busulfan (12 mg/kg) and cyclophosphamide (100 mg/kg) showed that decitabine therapy is well tolerated in allogeneic stem cell transplantation. It produced complete remission in 3/3 patients treated for relapse posttransplant and complete cytogenetic and hematologic remission in 2/4 patients conditioned for allogeneic stem cell transplantation (9).

The activity of decitabine (75 or 100 mg/m^2 over 6 h every 12 h for 10 doses) was evaluated in 37 patients with accelerated or blastic phases of chronic myelogenous leukemia. Results showed responses in 9 patients in accelerated phase and 5 patients in blastic phase, with respective overall response rates of 53% and 25%. The most significant side effect was prolonged myelosuppression, with febrile episodes occurring in 68% of patients (10).

Pharmachemie has announced that they will continue their clinical trial program for decitabine in several hematological malignancies, including myelodysplastic syndromes, acute myeloid leukemia and chronic myeloid leukemia. The drug has been investigated in clinical trials for more than 10 years and, to date, no second malignancies have been reported in the patients studied, including those aged 60 years and older (11).

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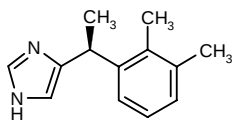
Dexmedetomidine

Sedative
Analgesic

EN: 145584



$C_{13}H_{16}N_2$ **Farmos; Abbott**

Dexmedetomidine (3.0 μg/kg s.c.) in rats was shown to reduce response tendency in attention and working memory tasks, but did not affect choice accuracy. The results indicate that activation of postsynaptic α_2-adrenoreceptors may be responsible for the drug's effects (1).

Results of a study in anesthetized dogs showed that intraventricular dexmedetomidine (100 μg/ml, total dose 300 μg) reduced cerebral blood flow during normoxia (from 76 ± 6 to 44 ± 4 ml/min.100g) and prevented adequate oxygen delivery during hypoxia (2).

Epidurally administered dexmedetomidine (2 μg/kg) in 15 anesthetized patients was shown to significantly decrease total EEG power, mean blood pressure and heart rate. These effects were observed within 10 min following injection of the drug and lasted for 4-6 h postoperatively. Treatment with dexmedetomidine reduced the amount of analgesia required by 70% for 24 h (3).

A double-blind, placebo-controlled study of dexmedetomidine (50 ng/kg/min) administered as a 30 min i.v. infusion prior to induction of anesthesia, and then 7 ng/kg/min until the end of surgery, in 80 coronary artery bypass patients showed that the drug decreased intraoperative sympathetic tone, attenuated hyperdynamic responses to anesthesia and surgery and increased hypotension (4).

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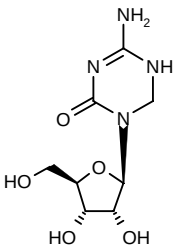
DHAC
NSC-264880

Antineoplastic

EN: 090632



$C_8H_{14}N_4O_5$ **Ilex Oncology; Natl. Cancer Inst. (US)**

A multicenter phase II trial was conducted to evaluate the efficacy of a 120-h continuous infusion of DHAC (1500 mg/m^2/day every 21 days) in 41 patients with malignant mesothelioma. The overall response rate was 17% with 1 patient having a complete response, 2 a partial response and 4 regression of disease. There was no significant hematological toxicity. Chest pain and nausea were the most common toxicities and supraventricular tachycardia and pericardial effusion occurred in 20% and 15% of patients, respectively (1).

MGI Pharma has acquired the worldwide rights to DHAC from ILEX Oncology, and plans to initiate a phase II study with the drug in the U.S. for the treatment of myelodysplastic syndrome (2).

MGI has discontinued development of dihydro-5-azacytidine (DHAC) and will return the technology to ILEX Oncology. MGI had been investigating DHAC's ability to treat myelodysplastic syndrome and hormone-refractory prostate cancer. A more advanced, competing product recently produced positive clinical results, making it less likely that DHAC would be a lucrative project (3).

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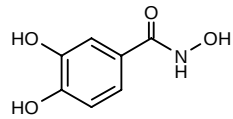
Original monograph - Drugs Fut 1984, 9: 15.

Didox

Antineoplastic
Ribonucleotide Reductase Inhibitor

EN: 126587



$C_7H_7NO_4$ **Molecules for Health**

In a murine immunodeficiency model of AIDS, mice were treated with didox or trimidox alone or in combination with didanosine. Results showed that didox or trimidox alone significantly increased survival to more than 1 year, markedly suppressed viremia and reduced hypergammaglobulinemia and lymphadenopathy (1).

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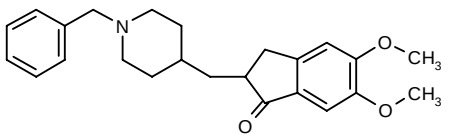
Donepezil Hydrochloride *Cognition Enhancer*
E-2020 *Acetylcholinesterase Inhibitor*
Aricept®
Memac®

EN: 150920



.HCl

$C_{24}H_{29}NO_3$.HCl **Eisai; Pfizer; Bracco; Wyeth-Ayerst**

An *in vitro* study of cholinergic transmission at mouse neuromuscular junctions showed that E-2020 (1.0 μM) was more potent than huperzine A or tacrine at increasing the amplitude, time-to-peak and half-decay time of miniature end-plate potentials (1).

A double-blind, placebo-controlled trial of donepezil (5 or 10 mg for 24 weeks) administered once-daily to 473 patients with mild to moderate Alzheimer's disease showed that the drug, as compared to placebo, delayed the onset of loss of activities of daily living by 68, 91 and 123 weeks for the placebo, 5-mg and 10-mg groups, respectively (2).

Results for the first 110 weeks of a randomized, placebo-controlled, open-label extension of a phase II trial in patients with Alzheimer's disease showed that donepezil (5 mg/day increased to 10 mg/day) improved the Alzheimer's Disease Assessment Scale-cognitive subscale and Clinical Demential Rating-Sum of the Boxes scores by approximately 20%. The results suggest that the drug's benefits are enhanced or sustained during long-term treatment (3).

The new proposed international nonproprietary name for E-2020 is donepezil hydrochloride (4).

Pfizer Canada's donepezil hydrochloride (Aricept™) has been approved by Health Canada as the first Canadian drug for the symptomatic treatment of mild to moderate Alzheimer's disease (5).

Donepezil hydrochloride (Aricept™) has been comarketed by Eisai and Pfizer in the U.S. for the treatment of Alzheimer's disease and is supplied as tablets of 5 and 10 mg (6).

Eisai and Pfizer have jointly launched donepezil hydrochloride (Aricept®) in Germany for the symptomatic treatment of Alzheimer's disease. The acetylcholinesterase inhibitor is available in tablets of 5 and 10 mg (7).

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3. Rogers, S.L., Friedhoff, L.T. *Donepezil provides long-term clinical benefits for patients with Alzheimer's disease (AD).* J Neurol Sci 1997, 150(Suppl.): Abst 5-12-21.

4. *Proposed international nonproprietary names (Prop. INN): List 75.* WHO Drug Inform 1996, 10(2): 96.

5. *Aricept now available in Canada.* Prous Science Daily Essentials September 8, 1997.

6. *New product intros.* Drug News Perspect 1997, 10(1): 26.

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Edobacomab
E5®
Promune-E5®
Xomen-E5®

Treatment of Septic Shock

EN: 136508

Xoma; Pfizer

Xoma and Pfizer have announced the decision to discontinue the U.S. clinical trial of the E5® (edobacomab) monoclonal antibody product as a treatment for Gram-negative sepsis. Results of an interim analysis recently completed on 1,000 patients in a phase III (U.S.) clinical trial conducted by Pfizer did not support continuation of the trial. Although there were no safety concerns and a benefit was shown for patients treated with E5®, the results were not sufficient to meet the predetermined efficacy criteria deemed necessary to continue the trial (1).

Based on Xoma's decision to discontinue the U.S. phase III sepsis trial of E5®, Pfizer has decided to terminate its marketing agreement for this product, thereby returning all rights to this product to Xoma (2).

1. *Data analysis does not support continuation of U.S. phase III clinical trial for E5.* Xoma Corp. Press Release 1997, April 24.

2. *Pfizer terminates E5 marketing agreement.* Prous Science Daily Essentials June 10, 1997.

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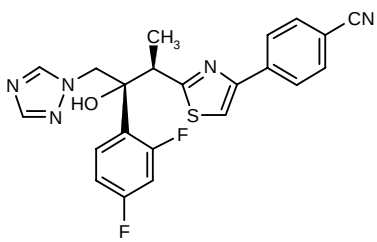
ER-30346
BMS-207147

Antifungal

EN: 226621



$C_{22}H_{17}F_2N_5OS$ **Eisai; Bristol-Myers Squibb**

In an *in vitro* study against 250 strains from 44 fungal species, BMS-207147 was shown to have antifungal and fungicidal activities comparable to those of itraconazole and better than those of fluconazole against *Cryptococcus neoformans* and most aspergillus strains. BMS-207147 also had a broader spectrum of activity against *Candida* spp. than itraconazole and fluconazole (1).

An *in vitro* study evaluating the antifungal activities of BMS-207147 and itraconazole against fluconazole-resistant or dose-dependent susceptible yeast strains showed that both compounds have comparable activity, although BMS-207147 was more potent against strains of *Candida krusei*. Both compounds were also active against most *Candida albicans* strains and some *Torulopsis glabrata* strains (2).

Bristol-Myers Squibb has acquired an exclusive license worldwide for Eisai's ER-30346, except in Japan, where it has a semiexclusive license with Eisai to develop and market the drug. Under the terms of the agreement, Bristol-Myers Squibb will provide up-front and milestone payments to Eisai, as well as royalty payments after marketing. The drug will be administered as an oral formulation and will be developed for the treatment of systemic fungal infections such as candidiasis, aspergillosis and cryptococcal meningitis, as well as non-life threatening fungal infections such as orpharyngeal candidiasis (3).

1. Fung-Tomc, J. et al. *In vitro antifungal activity of a new triazole BMS-207147 (ER-30346).* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-68.

2. Fung-Tomc, J., White, T., Minassian, B., Huczko, E., Bonner, D. *In vitro activity of BMS-207147 (ER-30346) and itraconazole (ITR) againt yeast strains that are resistant or dose-dependent susceptible (DD-S) to fluconazole (FLU).* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-69.

3. *Bristol-Myers Squibb acquires novel antifungal from Eisai. Broad-spectrum antifungal to expand Bristol-Myers Squibb's infectious disease franchise.* Bristol-Myers Squibb Press Release 1996, December 12.

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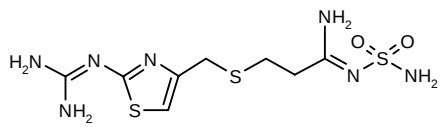
Famotidine
Gaster®
Pepcid®

Gastric Antisecretory
Antipsychotic

EN: 115235



$C_8H_{15}N_7O_2S_3$ **Yamanouchi; Merck & Co.; Novopharm**

Recent reports on the similarities between the deficit symptoms of schizophrenia in adults and the social deficit

symptoms of autism indicate that famotidine may be useful in the treatment of children with autism (1).

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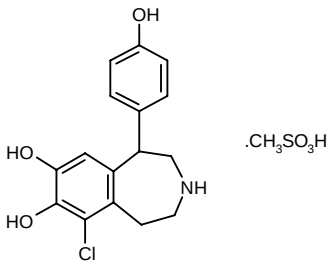
Fenoldopam Mesilate
Corlopam®

Antihypertensive
Dopamine D_1 Agonist

EN: 090634



$C_{16}H_{16}ClNO_3.CH_4O_3S$

SmithKline Beecham; Neurex

The Cardiovascular and Renal Drugs Advisory Committee recommended that the FDA approve Neurex's Corlopam® as intravenous therapy for the short-term treatment of hypertension when oral therapy is not feasible or possible, including use in patients who are undergoing surgery or who otherwise cannot take medication by mouth. The panel also recommended approval for the use of the product in the treatment of severe or malignant hypertension (1).

The U.S. FDA has granted final marketing approval for Neurex's fenoldopam mesylate. The product is indicated for the in-hospital, short-term (up to 48 h) management of severe hypertension when rapid, but quickly reversible, emergency reduction of blood pressure is clinically indicated, including malignant hypertension with deteriorating end-organ function. Transition to oral therapy with another agent can begin at any time after blood pressure is stabilized with Corlopam® (2).

Neurex has announced completion of a study in healthy human subjects, the first in the Corlopam Renal Program, designed to characterize the beneficial effects of the drug on the kidney. Future studies will focus on the drug's action in hypertensive patients and patients with compromised renal function (3).

1. *FDA advisory committee recommends Corlopam approval.* Prous Science Daily Essentials June 30, 1997.

2. *FDA grants final marketing approval for Corlopam.* Prous Science Daily Essentials September 25, 1997.

3. *Neurex initiates Corlopam renal program: Studies focused on beneficial effect on the kidney.* Neurex Corp. Press Release 1997, February 5.

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Everitt, D.E. et al. *Effect of intravenous fenoldopam on intraocular pressure in ocular hypertension.* J Clin Pharmacol 1997, 37(4): 312.

Dunbar, L. et al. *Emergency department management of hypertensive emergencies: A comparison of Corlopam® versus sodium nitroprusside.* Amer J Hypertension 1997, 10(4, Part 2): 91A.

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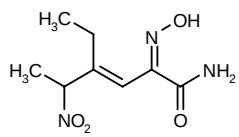
FK-409
FR-900409

Antianginal
Vasodilator

EN: 150837



$C_8H_{13}N_3O_4$

Fujisawa

In vitro studies of FK-409 in isolated ring preparations of arteries from rats showed that the drug fully reversed precontractions on main pulmonary artery and caused an 80% reversal of precontractions on interlobar pulmonary artery. In rats with chronic hypoxia-induced pulmonary hypertension, the drug was 4.5- and 12-fold less potent on main and intralobar pulmonary arteries, respectively, than on control arteries. This reduction in potency was suggested to be due to the presence of one or more reac-

tive oxygen species (1).

Incubation of cultured porcine aortic endothelial cells with FK-409 was shown to result in a concentration (25 and 50 μM)- and time (3-24 h)-dependent decrease in endothelin-1 (ET-1) release and inhibition of the expression of prepro ET-1 mRNA (2).

Results from studies of FK-409 and its derivatives in human platelet-rich plasma indicate a close correlation between NO-releasing rates and *in vitro* antiplatelet activity. However, in isolated rat aorta the vasorelaxant activities did not correlate with NO-releasing rates (3).

In studies in rats, FK-409 was shown to have cytoprotective effects on isolated heart tissue stored under cold conditions before transplant (4).

Intrarenal arterial infusion of FK-409 (0.25 μg/kg/min) in anesthetized dogs had no effect on renal nerve stimulation (RNS)-induced decreases in urine flow and urinary sodium excretion, and increases in norepinephrine secretion rate. However, in the presence of N^G-nitro-L-arginine, the drug significantly suppressed the RNS-induced enhancement of antidiuresis, renal vasoconstriction and norepinephrine secretion rate (5).

Studies using the rat formalin test showed that topical administration of FK-409 alone had no effect on flinching behavior. However, following subcutaneous administration of morphine the drug dose-dependently depressed flinching behavior (6).

The effects of FK-409 on norepinephrine overflow and renal actions induced by renal nerve stimulation have been investigated in anesthetized dogs. Infusion of FK-409 (0.25 μg/kg/min) into the renal artery had no effect on the decreases in urine flow and urinary excretion of sodium, and increases in norepinephrine secretion rate in response to both low- and high-frequency renal nerve stimulation. However, under NO-depleted conditions in the presence of an NO synthase inhibitor, FK-409 abolished the enhancement of antidiuresis, renal vasoconstriction and norepinephrine secretion rate in response to renal nerve stimulation (7).

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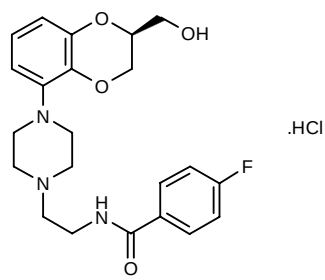
Flesinoxan Hydrochloride

Anxiolytic
Antidepressant

EN: 124142



$C_{22}H_{26}FN_3O_4.HCl$ **Duphar**

A study of the stimulatory effects of flesinoxan (0.3, 1.0 and 3.0 mg/kg) in male Wistar rats with experimentally induced impaired sexual behavior showed that the drug stimulated ejaculation frequency but did not produce premature ejaculation (1).

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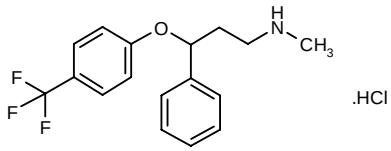
Fluoxetine Hydrochloride *Antidepressant*
Prozac® *5-HT Reuptake Inhibitor*

EN: 131699



$C_{17}H_{18}F_3NO.HCl$ **Lilly**

A study of fluoxetine (20 mg/day for 1 week then 40 mg/day for 5 weeks) in 23 men with premature ejaculation showed that the drug increased intravaginal ejaculation latency time 3 and 6 weeks following treatment, as compared to placebo. Symptom improvement was reported by the patients and adverse events were minimal (1).

A single-center, single-blind, placebo-controlled, dose-escalating study of oral fluoxetine (7.5, 15, 30 and 45 mg/day for 32 weeks) in 38 evaluable subjects with premature ejaculation showed that after 4-6 weeks of treatment, the drug significantly improved sexual dysfunction, with a low incidence of adverse events (2).

A prospective, double-blind, placebo-controlled, crossover study in 40 men with premature ejaculation (PE) and/or erectile dysfunction showed that fluoxetine increased the time to ejaculation with coitus in the PE group, with a slight increase in relationship satisfaction. There was no increase in ejaculation latency in the other groups. No change in erections, nocturnal penile tumescence, libido or side effects were observed (3).

A 12-week double-blind, placebo-controlled, parallel group study in 51 patients with comorbid major depressive disorder and alcohol dependence showed that fluoxetine, as compared to placebo, significantly reduced alcohol consumption and improved depressive symptoms (4).

The U.S. Food and Drug Administration has given Eli Lilly clearance to market Prozac® for the treatment of bulimia nervosa. According to a company spokesperson, 8 weeks of treatment with 60 mg of the drug leads to a significant reduction in binge eating and vomiting episodes. The most common side effects reported in clinical trials included insomnia, nausea, asthenia and anxiety (5).

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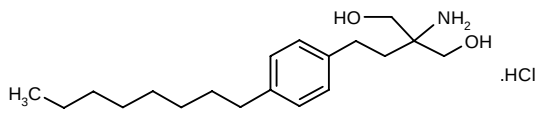
FTY-720

Immunosuppressant

EN: 210392



$C_{19}H_{33}NO_2.HCl$ **Yoshitomi; Taito; Novartis**

The immunosuppressant effects of FTY-720 on the function of Th1-, Th2- and B-cells indicate that the drug would be useful in preventing acute rejection in allogeneic and heterogeneic transplant, autoimmune diseases and allergic reactions (1).

The immunosuppressant effects of FTY-720 were suggested to be due to increased levels of intracellular calcium in the lymphatic system and induction of apoptosis (2).

Administration of FTY-720 was shown to accelerate lymphocyte homing of circulating lymphocytes from peripheral blood and spleen to lymph nodes and Peyer's patches (3).

FTY-720 was shown to decrease the number of circulating T-cells in peripheral blood of rats by accelerating lymphocyte homing. The drug also had synergistic effects when administered in combination with ciclosporin A (4).

FTY-720 (0.1-3.0 mg/kg p.o.) in combination with ciclosporin A (3 mg/kg p.o.) or FK-506 (1 mg/kg p.o.) was found to induce immunotolerance in a rat model of cardiac allograft (5).

Results from a study of renal allograft in rats demonstrated that treatment with FTY-720 significantly prolonged graft survival, most likely due to the drug's effect on decreasing the total number of circulating lymphocytes (6).

In a rat model of orthotopic liver transplantation, combined treatment with FTY-720 (0.03 mg/kg p.o.) and FK-506 (0.3 mg/kg p.o.) showed a synergistic effect, which was suggested to be due to induction of apoptosis in lymphocytes (7).

Results from studies in rats indicate that FTY-720 would be a suitable drug for preventing graft-*versus*-host reaction in pancreas transplantation (8).

In a study in rats, short-term administration of FTY-720 in combination with nonprofessional APC prior to transplant was shown to induce immunotolerance in recipients (9).

Yoshitomi has signed an agreement granting Novartis a license to the novel immunosuppressant FTY-720 (10).

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HGP-30

AIDS Vaccine

EN: 159052

H-Tyr-Ser-Val-His-Gln-Arg-Ile-Asp-Val-Lys-Asp-Thr-Lys-Glu-Ala-Leu-Glu-Lys-Ile-Glu-Glu-Glu-Gln-Asn-Lys-Ser-Lys-Lys-Lys-Ala-OH

$C_{154}H_{259}N_{45}O_{52}$ **CEL-SCI**

Data presented at the 9th Annual Meeting of the National Cooperative Vaccine Development Groups, held on May 4, 1997 at the National Institutes of Health, has shown that CEL-SCI's HGP-30 AIDS vaccine can induce antibodies in humans and mice that recognize the corresponding regions of the HIV subtypes B, C and E. This finding is important because of the substantial variability accompanied by continued mutation between these different HIV subtypes. Results of studies suggest that it may be possible to create a broadly protective HIV vaccine for human use (1).

1. *HGP-30 AIDS vaccine shows recognition of major HIV subtypes in human and animal studies.* Cel-Sci Corp. Press Release 1997, May 5.

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Ibandronic Acid Monosodium Salt Monohydrate

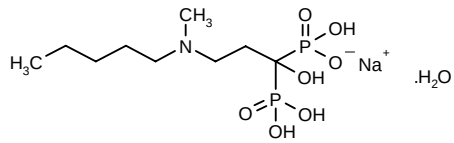
Bisphosphonate

Bondronat™

Bone Resorption Inhibitor

Bonviva®

EN: 187240



$C_9H_{22}NNaO_7P_2.H_2O$ **Boehringer Mannheim; Rhône-Poulenc Rorer**

A study of ibandronate (1 or 2 mg/kg) administered as single bolus injection in 12 healthy men and 5 postmenopausal women showed that in men the 1-mg dose suppressed bone resorption for 1-2 months and the 2-mg dose for more than 3 months, with transient changes in calcium and slight gain in bone metabolism. In women the effects of 1 mg lasted for 3 months but were less pronounced (1).

1. Thiébaud, D., Husi, B., Jacquet, A.F., Burckhardt, P. *Effects of ibandronate i.v. bolus injection in healthy men and postmenopausal women.* J Bone Miner Res 1997, 12(Suppl. 1): Abst F468.

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Coleman, R.E. *New bisphosphonates.* Eur J Cancer 1996, 32A(Suppl. 2): Abst SY-8-4.

Grauer, A. et al. *No evidence for bisphosphonate resistance after ibandronate retreatment in Paget's disease of bone.* J Bone Miner Res 1997, 12(Suppl. 1): Abst T675.

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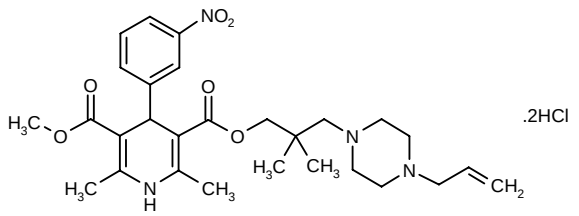
Thiebaud, D. et al. *Three monthly intravenous injections of ibandronate in the treatment of postmenopausal osteoporosis.* Amer J Med 1997, 103(4): 298.

Iganidipine Hydrochloride
NKY-722

Antihypertensive
Calcium Channel Blocker

EN: 148351



$C_{28}H_{38}N_4O_6.2HCl$ **Kyoto Pharm.**

A study of iganidipine (0.3, 1.0 and 3.0 mg/kg/day) in Dahl salt-sensitive rats fed a high-salt diet showed that the drug dose-dependently reduced glomerulosclerosis and renal arterial and tubular injuries. At 3.0 mg/kg/day, the drug completely prevented hypertensive death and improved plasma creatinine, serum urea nitrogen and glomerular filtration rate. At all doses, the drug increased urinary prostaglandin I_2 and PGE_2, but not $PGF_{2\alpha}$ or thromboxane B_2, and decreased plasma angiotensin II level and renin activity. The drug also reduced the incidence of cerebral infarction (1).

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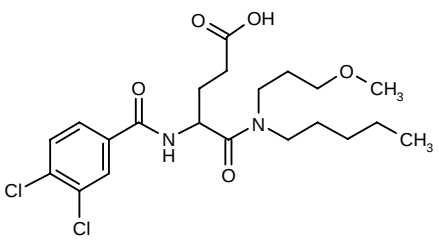
Shirahase, H. et al. *Preventive effect of iganidipine on renal and cerebral injuries in salt-sensitive Dahl rats.* Jpn J Pharmacol 1997, 73(Suppl. 1): Abst P-23.

Loxiglumide

CCK-A Antagonist
Agent for Pancreas Disorders
Agent for Irritable Bowel Syndrome

EN: 135822



$C_{21}H_{30}Cl_2N_2O_5$ **Rotta Research; Kaken; Tokyo Tanabe**

Loxiglumide (1, 5, 10 and 50 μM for 24 h) dose-dependently decreased the invasiveness and activity of matrix metalloproteinase-9 in a human pancreatic cancer cell line, indicating that the compound may be useful in the treatment of human pancreatic cancers (1).

A randomized study of loxiglumide administered as an i.v. infusion in 9 healthy volunteers prior to a fat meal revealed that the drug significantly attenuated the fall in lower esophageal sphincter (LOS) pressure and reduced the number of transient LOS relaxations and reflux episodes (2).

Results of a double-blind, placebo-controlled, randomized study in 6 obese patients showed that postprandial loxiglumide (10 mg/kg/h i.v.) significantly reduced the rate of transient lower esophageal sphincter relaxations (TLESRs) compared to placebo. The drug also inhibited the meal-induced decrease in basal lower esophageal sphincter pressure and reduced the meal-induced increase in TLESRs (3).

The results of a randomized, placebo-controlled, double-blind, parallel-group study of loxiglumide (2.4 g/day) administered to 64 patients with advanced pancreatic cancer did not demonstrate sure efficacy for the drug in this indication (4).

A randomized, double-blind study of loxiglumide (10 mg/kg/h) and cholecystokinin (30 ng/kg/h) administered by perfusion to 10 healthy subjects showed that loxiglumide significantly decreased the occurrence of transient lower esophageal sphincter relaxations (to 5.3 ± 2.5/30 min) relative to saline (8.3 ± 1.7/30 min), while cholecystokinin significantly increased their frequency (13.1 ± 5/30 min) relative to saline (9.1 ± 4/30 min). The results suggest that CCK-A receptors are involved in gastroesophageal reflux disease (5).

A double-blind, placebo-controlled study in 8 healthy male volunteers showed that loxiglumide (7 mg/kg/h i.v. infusion) decreased compliance of the proximal stomach, suggesting that cholecystokinin-A receptors do not play a major role in the postprandial relaxation of the proximal stomach (6).

In 9 patients with gastroesophageal reflux disease and excess acid exposure, loxiglumide (30 mg/kg/h for 10 min then 10 mg/kg/h i.v.) administered prior to a fat meal inhibited transient lower esophageal sphincter relaxation and attenuated the fall in basal lower esophageal sphincter pressure (7).

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3. Fakhry, N., D'Amato, M., Hirsch, D., Holloway, R.H., Vrij, V., Mathus-Vliegen, E.M.H., Tytgat, G.N.J., Boeckxstaens, G.E. *Loxiglumide inhibits meal-induced transient LES relaxations in*

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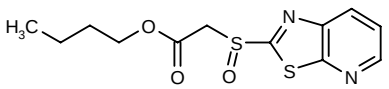
ME-3407
EF-4040

Gastric Antisecretory
Antiulcerative

EN: 169044



$C_{12}H_{14}N_2O_3S_2$ **Meiji Seika**

Studies of ME-3407 in rats and rabbits have shown that the drug inhibits acid secretion via interference with the redistribution of H^+/K^+ ATPase (1).

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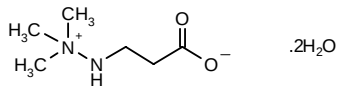
Mildronate
Quaterin

Antianginal
Antiischemic Agent

EN: 145694



$C_6H_{14}N_2O_2.2H_2O$ **Inst. Org. Sint. Akad. Nauk (RU); Taiho**

Studies in isolated perfused rat heart showed that pretreatment with MET-88 (100 mg/kg/day p.o. for 10 days) attenuated hydrogen peroxide-induced metabolic derangement but not hydrogen peroxide-induced mechanical dysfunction. When added directly to isolated perfused hearts, the drug did not attenuate metabolic derangement, whereas γ-butyrobetaine did. These results suggest that the beneficial effect of oral pretreatment with MET-88 may be mediated by γ-butyrobetaine (1).

Results of a study in anesthetized dogs with occlusion of the left anterior descending coronary artery showed that pretreatment with MET-88 (50, 100 or 200 mg/kg/day p.o. for 10 days) dose-dependently attenuated the decreased tissue levels of adenosine triphosphate, adenosine diphosphate and creatine phosphate and the increased tissue levels of adenosine monophosphate and lactate in the ischemic area but had no signigicant effect in the nonischemic area (2).

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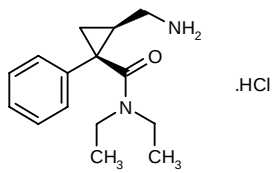
Milnacipran Hydrochloride
Dalcipran®
Toledomin®
Ixel®

Antidepressant

EN: 090753



$C_{15}H_{22}N_2O.HCl$ **Pierre Fabre; Asahi Chem.; ProdesFarma; Synthélabo**

A review of milnacipran pharmacokinetics showed that the drug has high bioavailability, low plasma protein binding and is eliminated in the urine as the parent drug or as a glucuronide, suggesting a low probability of interaction with other drugs. Furthermore, dose adjustment does not appear to be necessary in the elderly or in patients with liver impairment (1).

A review of 3 multicenter, placebo-controlled trials of milnacipran (50 or 100 mg b.i.d.) in patients with major depression demonstrated that the drug was superior to placebo, indicating its efficacy in cases of severe depression(2).

A summary of 7 randomized, double-blind, clinical trials comparing milnacipran (50 mg b.i.d.) with tricyclic antidepressants in patients with major depression showed that milnacipran had a similar response rate, was better tolerated and had an improved safety profile (3).

A meta-analysis of major clinical trials comparing milnacipran (50 mg b.i.d.) with the serotonin reuptake inhibitors fluoxetine (20 mg once daily) or fluvoxamine (100 mg b.i.d.) in patients with major depression demonstrated that milnacipran produced greater response rates and higher remission rates (39 *vs*. 28%) and produced fewer gastrointestinal side effects. However, milnacipran produced more headaches, dry mouth and dysuria (4).

A review of milnacipran (50 mg b.i.d.) administered to 2462 patients with major depressive disorders showed that the drug is better tolerated than tricyclic antidepressants and is more efficacious than selective serotonin reuptake inhibitors. Furthermore, the drug's reproducible pharmacokinetic profile presents additional advantages over both classes of drugs (5).

Pierre Fabre Research Institute has been granted a marketing authorization from the French Medicinal Products Agency for milnacipran (Ixel®) for use in the treatment of major depression. The company plans to initiate registration procedures for the drug in major European countries and Japan in the near future (6).

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2. Lecrubier, Y., Pletan, Y., Solles, A., Tournoux, A., Magne, V. *Clinical efficacy of milnacipran: Placebo-controlled trials.* Int Clin Psychopharmacol 1996, 11(Suppl. 4): 29.

3. Kasper, S., Pletan, Y., Solles, A., Tournoux, A. *Comparative studies with milnacipran and tricyclic antidepressants in the treatment of patients with major depression: A summary of clinical trial results.* Int Clin Psychopharmacol 1996, 11(Suppl. 4): 35.

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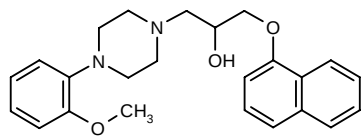
Naftopidil
Flivas®

Antihypertensive
Treatment of BPH
Treatment of Dysuria

EN: 105012



$C_{24}H_{28}N_2O_3$

Boehringer Mannheim; Asahi Chem.; Asta; Kanebo

A multicenter, double-blind, placebo-controlled study of naftopidil (25 mg/day for 1 week then 25, 50 or 75 mg/day for 4 weeks) in 333 patients with urinary obstruction caused by benign prostatic hyperplasia showed that the drug dose-dependently improved maximum flow rate, average flow rate and global improvement, with the 50- and 75-mg doses being statistically superior to placebo. The drug was well tolerated with no significant difference between the placebo and drug-treated groups in the frequency of adverse events and overall safety (1).

1. Yamaguchi, O., Fukaya, Y., Shiraiwa, Y. et al. *Dose-dependent effects and clinical usefulness of naftopidil (KT-611) on urinary obstruction caused by benign prostatic hyperplasia - Double-blind comparative study compared with placebo.* Clin Rep 1997, 31(3): 373.

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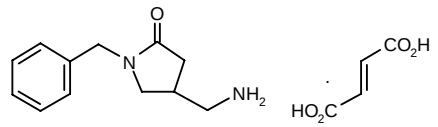
Nebracetam Fumarate Memolog®

Cognition Enhancer

EN: 144179



$C_{12}H_{16}N_2O.1/2C_4H_4O_4$ **Boehringer Ingelheim**

Results of an *in vivo* microdialysis study in rats indicate that it is unlikely that nebracetam, at a pharmacologically effective dose, changes dopamine or serotonin uptake in the brain nerve terminal (1).

A study in rats with microsphere embolism-induced cerebral ischemia showed that nebracetam (30 mg/kg p.o. b.i.d.) restored hippocampal 5-HT synthesis but did not affect striatal dopamine turnover rate (2).

1. Takeo, S., Hayashi, H., Tadokoro, M., Takagi, K., Miyake, K., Takagi, N., Oshikawa, S. *Effects of nebracetam on synaptosomal monoamine uptake of striatal and hippocampal regions in rats.* Biol Pharm Bull 1997, 20(4): 360.

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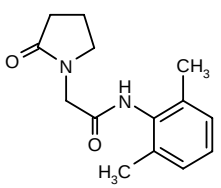
Takagi, K. et al. *Effects of delayed treatment with nebracetam on energy metabolism of brain regions following microsphere embolism-induced cerebral ischemia.* Jpn J Pharmacol 1997, 73(Suppl. 1): Abst P-362.

Nefiracetam Translon®

Cognition Enhancer
Nootropic Agent

EN: 105128



$C_{14}H_{18}N_2O_2$ **Daiichi Pharm.**

In young rabbits trained in the 750 ms delay eyeblink classical conditioning paradigm, nefiracetam (10 or 15 mg/kg for 15 days) was shown to reverse the effects of both nicotinic and muscarinic cholinergic antagonists, suggesting that the drug could have potential for ameliorating impaired cognition in Alzheimer's disease (1).

1. Woodruff-Pak, D.S., Hinchliffe, R.M. *Nefiracetam reverses muscarinic and nicotinic antagonists in eyeblink conditioning in rabbits.* Soc Neurosci Abst 1996, 22(Part 1): Abst 174.13.

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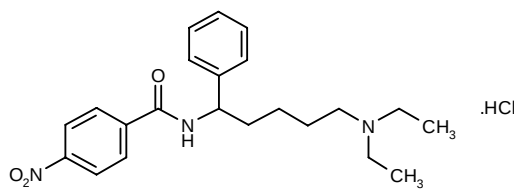
Nibentan

Antiarrhythmic

EN: 226458



$C_{22}H_{29}N_3O_3.HCl$ **Center Chem. Drugs (RU)**

Results of a study on the electrophysiologic effects of nibentan on canine cardiac tissue showed that the drug had significant ability to prolong repolarization while

decreasing heterogeneity of repolarization, and that the extent of the drug's action potential prolongation effect differed depending on the different cardiac tissues (1).

In rat ventricular myocytes, nibentan (2.5-25 μmol/l) concentration-dependently inhibited the delayed rectifier outward potassium current (IC_{50} = 15 μmol/l), but did not significantly affect the transient outward and inward rectifier potassium current (2).

A clinical study of nibentan administered as intravenous bolus doses (0.125-0.5 mg/kg) in 71 patients with ventricular arrhythmias and other cardiac rhythm disturbances showed that the drug produced pronounced antiarrhythmic effects in 57% of patients with frequent and coupled ventricular premature beats and paroxysmal unsustained ventricular tachycardia. Proarrhythmic effects were observed in 8% of patients with supraventricular tachycardia, atrial fibrillation and flutter, and in none of the patients with paroxysmal supraventricular arrhythmias (3).

Results from a study in 10 patients with paroxysmal ventricular tachycardia showed that nibentan (0.125 mg/kg i.v.) prolonged QT and QTc intervals and significantly increased right atrial, right ventricular and His-Purkinje system's refractory period. Polymorphic ventricular tachycardia was observed in 1 patient (4).

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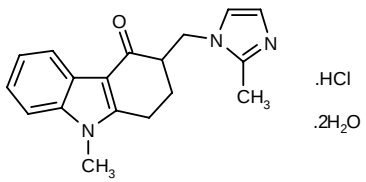
Original monograph- Drugs Fut 1997, 22: 30.

Ondansetron Hydrochloride *Antiemetic*
Zophran® *5-HT_3 Receptor Antagonist*
Zophren®

EN: 130944



$C_{18}H_{19}N_3O.HCl.2H_2O$ **Glaxo Wellcome**

Ondansetron has been reported to improve symptoms of psychosis in patients with advanced Parkinson's disease. This potential new indication was studied in 13 parkinsonian patients and 3 patients with diffuse Lewy body disease who received the drug in an open-label study for periods ranging from 5 days to 10 months. No patients had deterioration of motor function, but 7 patients discontinued ondansetron treatment because of side effects such as sedation or increased hallucinations. Eight patients improved, and 1 patient had neither benefits nor adverse effects, for a final improvement rate of 50%. This was much lower than the 94-100% improvement reported in previous studies. Nevertheless, the investigators concluded that ondansetron does control psychiatric symptoms in some patients with Parkinson's disease, and further trials should be carried out (1).

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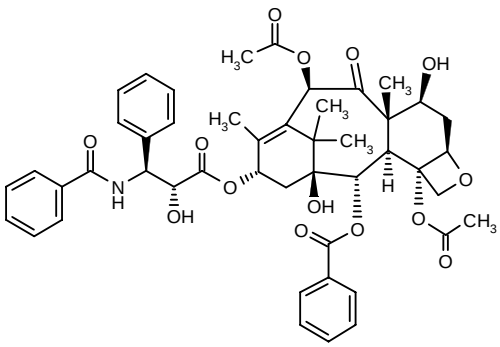
Paclitaxel
Anzatax®
Paxene®
Taxol®
Yewtaxan®

Antineoplastic

EN: 101438



$C_{47}H_{51}NO_{14}$

Bristol-Myers Squibb

Three partial syntheses of Taxol are described starting from Taxol analogues such as Taxol C (I) or Taxol B (cephalomannine) (VI) (1):

1) The reaction of Taxol C (I) with triethylsilyl chloride (TES-Cl) in pyridine gives the bis(triethylsilyl) derivative (II), which by reduction with zirconocene chloride hydride [bis(cyclopentadienyl)zirconium chloride hydride] in dry THF yields compound (III). The hydrolytic cleavage of (III) with simultaneous desilylation by means of HCl in ethanol affords [2a*R*-[2aα,4β,4aβ,6β,9α(2*R*,3*S*),11β,12α,12aα,12bα]]-6,12b-diacetoxy-9-(3-amino-2-hydroxy-3-phenylpropionyloxy)-12-benzoyloxy-4,11-dihydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one (IV) with a free amino group, which is benzoylated with benzoyl chloride (V) and pyridine to Taxol. Scheme 1.

2) The silylation of Taxol B (VI) with triethylsilyl chloride as before gives the bis(triethylsilyl) compound (VII), which by reduction with zirconocene chloride hydride as described yields compound (VIII). Finally, the hydrolytic cleavage of (VIII) with simultaneous desilylation with HCl in ethanol affords the already reported compound (IV) with its free amino group easily benzoylated to Taxol. Scheme 2.

3) The ozonolysis of the silylated Taxol B (VII) with O_3 in methanol gives compound (IX) which is reduced with zirconocene as before yielding the 2-oxopropylideneimine (X). Finally, the hydrolytic cleavage of (X) with simultaneous desilylation with HCl in ethanol affords the already reported compound (IX) with its free amino group easily benzoylated to Taxol. Scheme 2.

The preparation of poly(lactic-co-glycolic acid) (PLGA) microspheres containing Taxol, with potential utility for chemoembolization therapy of cancer, has been published: A solution of PLGA and Taxol in dichloromethane, cooled at 4 °C, was loaded into a glass syringe with a 26-gauge and then added in a dropwise manner to a 4% (w/v) aqueous solution of gelatin maintained at 35 °C, and stirred at 600 rpm. In order to evaporate the dichloromethane, the stirring was maintained for 1 hour, then the gelatin solution was diluted with water and the microspheres separated by centrifugation at 3000 rpm for 10 min. After elimination of the gelatin solution the microspheres were collected by filtration through a cellulose nitrate membrane (pore diameter 1 μm), washed with water and dried at room temperature under vacuum. The trapping efficiency of Taxol in the microspheres (diameter 20-45 μm) was greater than 90% and reproducible (2).

A total synthesis of paclitaxel and intermediates previously described (see Masters, J.J. et al. Angew Chem Int Ed Engl 1995, 34(16): 1723) have been claimed in patent literature (3).

A partial synthesis of Taxol starting from [2a*R*-[2aα,4β,4aβ,6β,9α(2*R*,3*S*),11β,12α,12aα,12bα]]-12b-acetoxy-12-benzoyloxy-4,6,9,11-tetrahydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one (deacetyl Baccatin III) (XI) has been developed (4). Scheme 3:

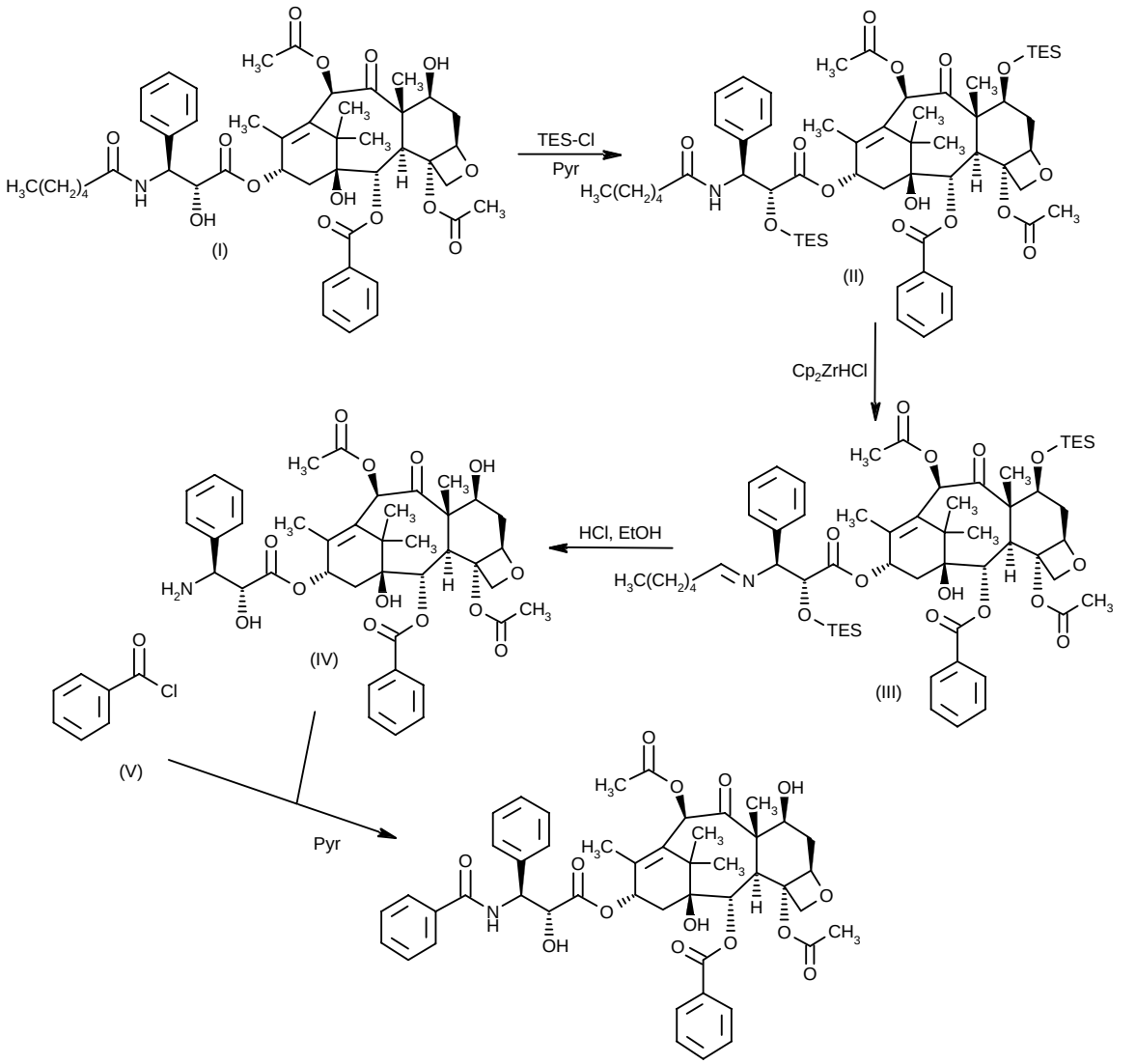
1) The esterification of 3(*S*)-(benzyloxycarbonyl)-2(*R*)-(benzyloxymethoxy)-3-phenylpropionic acid (I) with [2a*R*-[2aα,4β,4aβ,6β,9α(2*R*,3*S*),11β,12α,12aα,12bα]-6,12b-diacetoxy-12-benzoyloxy-9,11-dihydroxy-4a,8,13,13-tetramethyl-4-(triethylsilyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one (silylated Baccatin III) (II) by means of diisopropylcarbodiimide (DICD) and dimethylaminopyridine in toluene gives the corresponding ester (III), which is submitted to a partial deprotection by hydrogenation with H_2 over Pd/C at 1 atm pressure yielding ester (IV) with the free amino group. The benzoylation of (IV) with benzoyl chloride (V) and triethylamine in ethyl acetate affords the fully protected Taxol derivative (VI), which is desilylated with HF in acetonitrile giving the partially protected Taxol derivative (VII). Finally, this compound is fully deprotected by hydrogenation with H_2 over Pd/C in isopropanol at 40 atm to give Taxol.

2) The starting compounds, the acid (I) and the silylated Baccatin III (II) have been obtained as follows:

a) The reaction of 3(*S*)-amino-2(*R*)-hydroxy-3-phenylpropionic acid ethyl ester (VIII) with benzyloxycarbonyl chloride and Na_2CO_3 in ethyl or *tert*-butyl ether/water gives 3(*S*)-(benzyloxycarbonylamino)-2(*R*)-hydroxy-3-phenylpropionic acid ethyl ester (IX), which is condensed with benzyloxymethyl chloride by means of BuLi in THF yielding the fully protected ester (X). The hydrolysis of (X) with LiOH in ethanol/water affords the desired acid (I).

b) The silylation of [2a*R*-[2aα,4β,4aβ,6β,9α(2*R*,3*S*),11β,12α, 12aα,12bα]]-12b-acetoxy-12-benzoyloxy-4,6,9,11-tetrahydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one (deacetyl

Scheme 1: Synthesis of Paclitaxel



Baccatin III) (XI) with triethylsilyl chloride in pyridine gives the monosilylated deacetyl Baccatin III (XII), which is then acetylated with acetyl chloride in pyridine or BuLi in THF to afford the desired silylated Baccatin III (II).

Paclitaxel was approved for marketing in Japan for the treatment of ovarian cancer. The company has filed supplemental applications in Japan for approval in the treatment of breast and non-small cell lung cancer (5).

Draxis Health has acquired exclusive Canadian marketing rights to the Mylan formulation of paclitaxel. Under the agreement, Mylan will provide Draxis with all submissions to the FDA and other clinical data relating to the drug. Draxis will be responsible for obtaining Health Protection Branch approval and for the marketing, distribution and sales of the product in Canada. The two companies will share the marketing and sales profits from Canada according to a mutual agreement (6).

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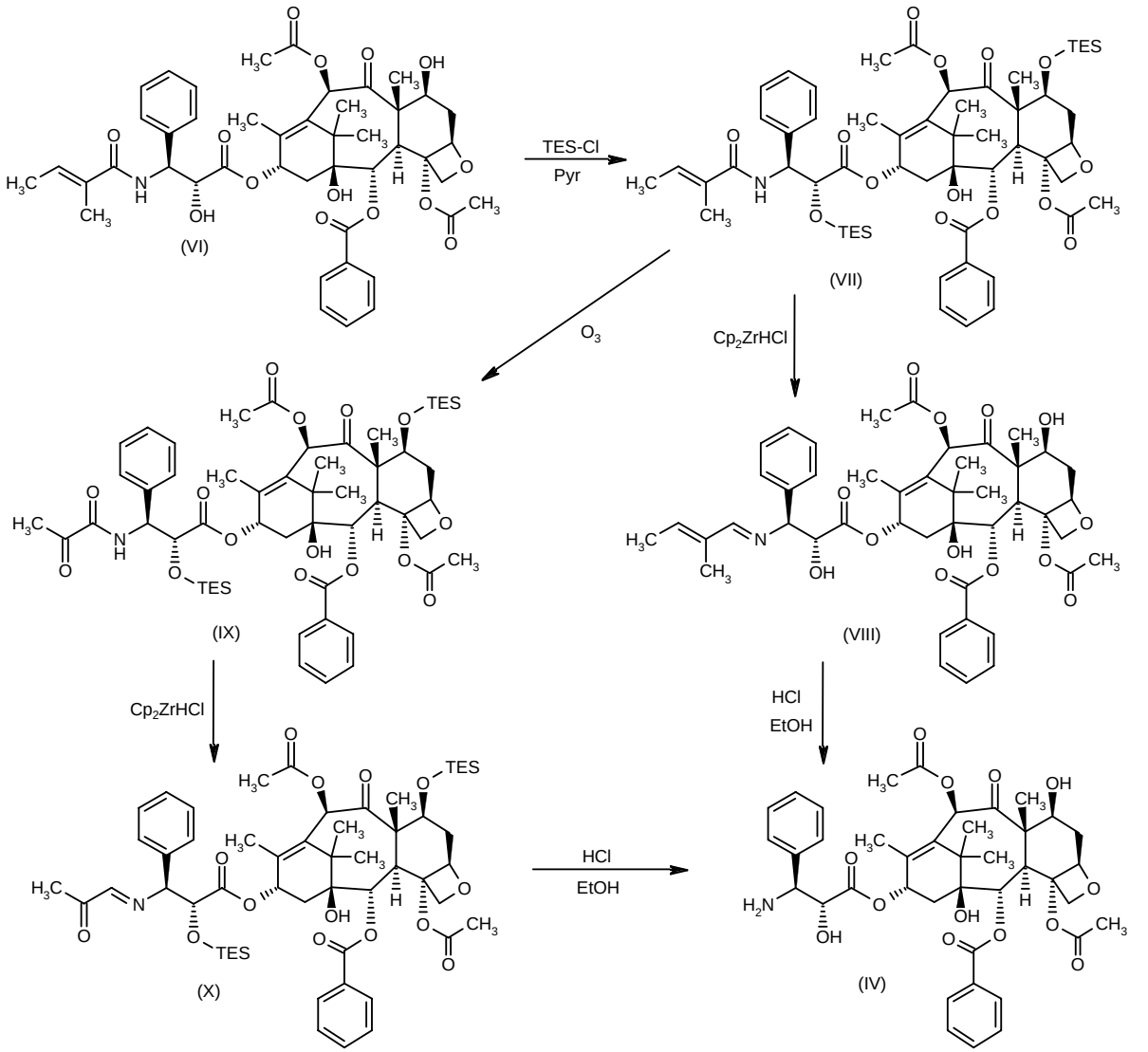
5. *Japanese approval for Taxol.* Prous Science Daily Essentials July 18, 1997.

6. *Draxis Health Inc. acquires Canadian rights to cancer drug from Mylan Laboratories. Draxis to market paclitaxel for treatx-*

Scheme 2: Synthesis of intermediate IV)



ment of refractory breast and ovarian cancer. Draxis Health, Inc. Press Release 1997, January 6.

Original monograph - Drugs Fut 1986, 11: 45.

PEG-Hemoglobin

Blood Substitute

EN: 214805

Enzon

An *in vitro* study of the interactions between PEG-conjugated bovine hemoglobin (PEG-Hb) and human blood component showed that PEG-Hb did not induce or inhibit the blood coagulation cascade. The compound (6-25 mg/ml) did not activate isolated monocytes, total lymphocytes, neutrophils, basophils or platelets nor did it affect red blood cell membrane fragility (1).

Rats exchange transfused up to a 85% hematocrit reduction with PEG-hemoglobin had survival rates of 100% during the transfusion and 79% after 48 h. In comparison, rats infused with PEG-methemoglobin, PEG-carbon monoxide hemoglobin or PEG-human serum albumin had survival rates of 30, 0 and 0% at 24 h, respectively (2).

PEG-conjugated bovine hemoglobin administered to rats with mammary carcinoma or EMT-6 tumors was shown to increase oxygenation in the tumors, without altering tissue toxicity (3).

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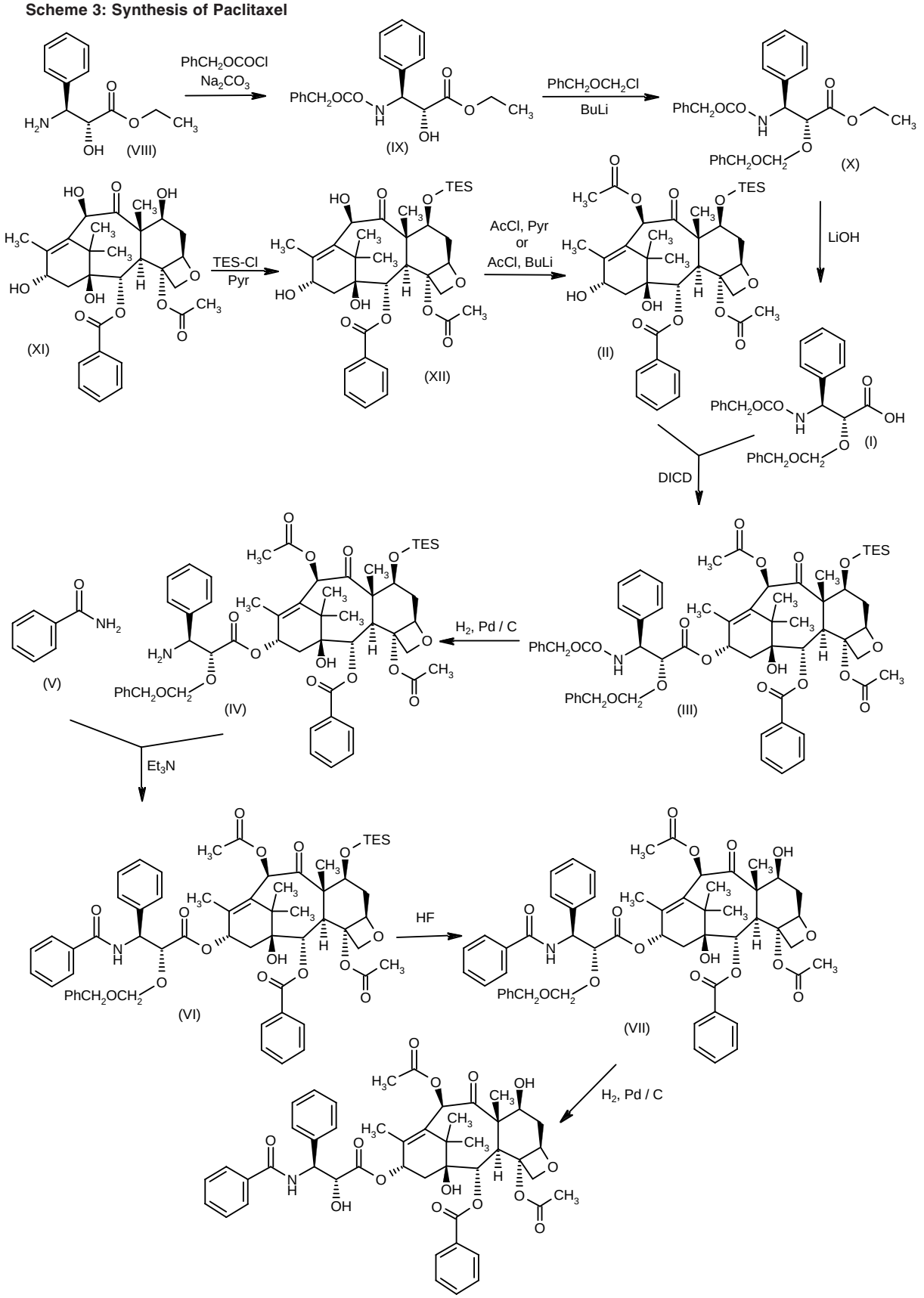
Scheme 3: Synthesis of Paclitaxel



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H^+/K^+-ATPase Inhibitor

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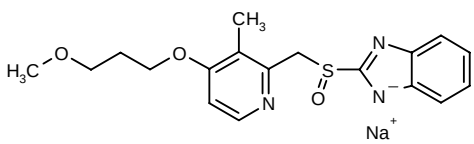

$C_{18}H_{20}N_3NaO_3S$ **Eisai; Lilly; Janssen**

A study of the pharmacokinetic parameters of the (*R*)-(+)- and (*S*)-(–)-enantiomers of rabeprazole sodium after intravenous administration to dogs (1.5 mg/kg) and rats (20 mg/kg) demonstrated the drug to be enantioselective in both species (1).

Two randomized, placebo-controlled studies in 44 healthy male subjects indicated no apparent drug interaction between rabeprazole sodium (20 mg) and warfarin (0.75 mg/kg) or oral theophylline (250 mg) (2).

Daily morning doses of rabeprazole sodium (5-40 mg) in 19 asymptomatic healthy volunteers with *Helicobacter pylori* infection dose-dependently inhibited basal and peptone-stimulated acid secretion. After 7 days, all doses produced significant and long-lasting inhibition of acid secretion. The half-time for recovery of acid secretion was 48 h at the 5 mg dose. The results suggest that the drug is as potent and long-lasting as omeprazole and lansoprazole (3).

Rabeprazole sodium (10, 20 and 40 mg/day for 7 days) in 24 healthy male subjects was shown to significantly decrease intragastric acidity and dose-dependently increase 24-h plasma gastrin as compared to placebo. There was no significant difference between doses and all doses were well tolerated (4).

A multicenter, double-blind, parallel study comparing once-daily doses of rabeprazole sodium (20 mg) and omeprazole (20 mg) in 202 patients with symptomatic, erosive or ulcerative gastroesophageal reflux disease showed that both drugs were equally well tolerated and produced similar healing rates at weeks 4 and 8 (5).

A randomized double-blind, two-period sequential trial of rabeprazole sodium (20 mg/day for 7 days) coadministered with ketoconazole (400 mg) in 18 healthy male volunteers showed that rabeprazole had a significant effect on the pharmacokinetics of ketoconazole, whereas ketoconazole did not appear to have an effect on the metabolism of rabeprazole sodium (6).

A multicenter, double-blind, randomized, placebo-controlled trial of rabeprazole sodium (20 and 40 mg for 6 weeks) in 94 patients with endoscopically documented active gastric ulcers showed that the drug produced significantly higher healing rates, independent of *Helicobacter pylori* status, and improved frequency and severity of ulcer pain. The treatment was well tolerated with the incidence of adverse events being similar in both placebo and treated groups (7).

A multicenter, double-blind, 8-week, parallel study of rabeprazole sodium (20 mg once daily) compared with ranitidine (150 mg q.i.d.) in 338 patients with erosive or ulcerative gastroesophageal reflux showed that rabeprazole-treated patients had significantly greater healing and resolution of heartburn at 4 and 8 weeks compared to ranitidine-treated patients. Both drugs significantly increased fasting serum gastrin levels and had similar adverse events profiles (8).

The effects of rabeprazole sodium (20 and 40 mg/day) in 20 patients with gastroesophageal reflux disease were evaluated in a double-blind, randomized, single-center, crossover study. Results showed that both doses significantly reduced esophageal acid exposure and the number of reflux episodes. Although the 40-mg dose appeared more efficacious, statistical analysis indicated no significant difference between the two doses (9).

The effects of rabeprazole sodium on esophageal and gastric pH in patients with gastroesophageal reflux disease have been investigated in a double-blind, randomized, crossover trial. Twenty patients were randomized to receive rabeprazole 20 mg once daily for 7 days followed by 40 mg once daily for 7 days, or *vice versa*. Both doses normalized acid reflux time and significantly decreased esophageal acid exposure (79-92%), the primary efficacy variable, by day 7. Similar decreases in the mean total number of reflux episodes and the number of episodes of over 5 min were also observed on both doses. Mean gastric pH was significantly increased on both doses already on day 1. No significant side effects were reported (10).

Eisai Co. and Janssen Pharmaceutica have announced a strategic alliance for rabeprazole sodium (E-3810). Under the terms of the agreement, the two companies will copromote the drug in the U.K., the U.S., Germany and France. Janssen will have an exclusive license to market rabeprazole in other territories except Japan and other countries in Asia, Italy, Spain, Belgium and The Netherlands. In Italy and Spain, Janssen will have a semi-exclusive license, with Eisai retaining the rights to copromote or comarket the drug in Spain. Eisai has submitted rabeprazole (Pariet®) for marketing approval in Japan and the U.K., and the drug is in phase III clinical trials in the U.S. (11)

Eisai introduced rabeprazole sodium (Pariet®) in Japan for the treatment of peptic ulcers including gastric and duodenal ulcers. The compound is supplied as tablets, 10 and 20 mg (12).

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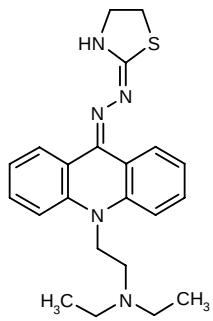
Ro-15-5458

Antiprotozoal

EN: 147771



$C_{22}H_{27}N_5S$ **Roche**

A study of Ro-15-5485 (10, 15 and 20 mg/kg) in mice infected with an Egyptian strain of *S. mansoni* showed that the drug provided a parasitological cure when administered 7-12 weeks postinfection. The drug dose-dependently decreased the number of adult worms and ova in stool, liver and intestine samples and reduced the mean number of schistosomes, as compared to the control group, by 83.6, 89.4 and 94.9% (1).

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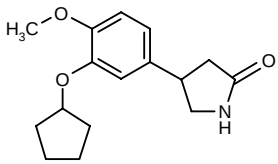
Rolipram

Antidepressant
Cognition Enhancer

EN: 107859



$C_{16}H_{21}NO_3$ **Schering AG; Meiji Seika**

Results of a study performed with freshly isolated human eosinophils showed that rolipram inhibited eotaxin-induced CD11b upregulation and transendothelial chemotaxis (1).

A study in mice with experimentally induced autoimmune uveoretinitis (EAU) showed that rolipram (3 mg/kg b.i.d.) suppressed EAU development by inhibiting the efferent, but not the afferent phase of the EAU. The results indicate that the drug inhibits only the function of uveitogenic effector T-cells, but not their priming, suggesting that continuous presence of rolipram is essential for suppresion of uveitogenic T-cell function (2).

A 6-month toxicity study of oral rolipram (0.01, 0.05, 0.2 and 2.0 mg/kg) administered to male and female rats determined the nontoxic dose to be 0.2 mg/kg (3).

Based on the results of a repeated-dose toxicity study of rolipram (5, 16 and 50 mg/kg/day p.o. for 4 weeks) in male and female cynomolgus monkeys, the nontoxic dose level was determined to be 5 mg/kg (4).

A repeated-dose toxicity study of oral rolipram (2.5, 5 and 10 mg/kg/day for 26 weeks) administered to male and female cynomolgus monkeys revealed that 2.5 mg/kg was the nontoxic dose (5).

The effects of rolipram (0.08, 0.4 and 2 mg/kg/day p.o.) on fertility and embryo/fetal development were investigated in male and female rats. The no-observed-adverse effect doses for general toxicity were determined to be 0.4 mg/kg and 0.08 mg/kg for male and female rats, respectively. For reproductive toxicity in parent animals and embryo/fetal development, the dose was 2.0 mg/kg (6).

Results of a teratogenicity study of rolipram (0.08, 0.4 and 2 mg/kg/day p.o.) in rats indicated that the no-observed-adverse effect doses were 0.08 mg/kg for dams and 2 mg/kg for reproductive toxicity in dams and embryo/fetal development in offspring (7).

The safety and tolerability of single-dose rolipram (0.5, 1, 2 and 3 mg p.o.) were investigated in a phase I study in 14 healthy male volunteers. Results showed that doses of 2 and 3 mg induced nausea, abdominal discomfort and diaphoresis, and slightly increased serum cortisol levels. Most of the adverse effects appeared within 30 min of treatment and disappeared within 2 h. Pharmacokinetic analysis indicated that the drug's kinetics is linear in the dose range of 0.5-3 mg (8).

Results of a placebo-controlled, phase I study of multiple-dose rolipram (1 mg t.i.d for 7 days) in healthy male volunteers showed that the drug caused transient nausea and abdominal discomfort. No drug-related abnormal changes were observed in physiological tests, clinical laboratory findings or endocrinological tests. The incidence of diarrhea was similar in both the rolipram- and placebo-treated groups (9).

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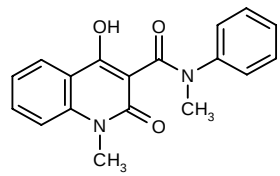
Roquinimex
Linomide®

Immunomodulator
Antineoplastic

EN: 100501



$C_{18}H_{16}N_2O_3$ **Pharmacia & Upjohn**

Results from studies on the biotransformation of roquinimex in human *in vitro* systems revealed that its oxidative metabolism is due mainly to the CYP3A4 enzyme (1).

Results of an experimental model of allergic neuritis in mice indicated that Linomide (80 mg/kg/day p.o.) appears to have pleotropic effects on various lymphocyte subsets, including downregulation of antigen presentation, reduction of the number of macrophages and T-lymphocytes expressing TCK, and induction of apoptotic cell death (2).

Results of a study of Linomide (80 mg/kg/day p.o.) in Lewis rats with experimentally induced allergic neuritis showed that none of the 12 treated rats developed clinical signs of the disease compared to 10 of 12 animals in the untreated group. The immunomodulatory effect of linomide appeared to be related to inhibition of the upregulation of ICAM-1 expression and the migration of inflammatory cells (3).

In a rat model of experimental autoimmune myasthenia gravis, Linomide (160 and 16, but not 1.6 mg/kg/day) suppressed clinical muscle weakness, accompanied by decreased acetylcholine receptor-induced T- and B-cell responses. It also suppressed the mRNA expression of the Th1 cytokines IFN-γ, IL-12 and TNF-α, and the Th2 cytokines IL-4 and IL-10. There was no difference in IL-6, IL-1β, lymphotoxin or TGF-β expression between drug-treated and control animals (4).

A study of Linomide in mice showed that the drug decreased inducible nitric oxide synthase mRNA levels and prevented the development of glomerulonephritis (5).

In a clinical pilot study, 13 patients with various malignant disorders were administered increasing doses of roquinimex (0.05-0.6 mg/kg). Pharmacokinetic analysis after a 0.2-mg/kg dose determined the C_{max}, t_{max} and elimination half-life values of the drug to be 4.0 μmol/l, 1.2 h and 42 h, respectively. Side effects included musculoskeletal discomfort, nausea and pain. No significant biochemical or hematological toxicity was observed. Also, treatment increased the numbers of phenotypic natural

killer cells, activated T-cells and monocytes. These results indicate that the drug is an active immunomodulator with acceptable toxicity (6).

A phase I/II study of Linomide (5 mg/day p.o. from week 5 for 2 weeks then 10 mg/day from week 7 to 16) in combination with interleukin-2 (10 IU/m^2/week s.c. for 8 weeks then resting for 8 weeks) in 15 evaluable patients with advanced renal cell carcinoma showed that the treatment provided no advantages in toxicity or efficacy over other therapies using interleukin-2. No objective remissions were observed, 10 patients were progredient, and fever, reduced general condition, nausea/vomiting, dyspnea, anorexia, chills and hypotension were the most frequent adverse events (7).

Results of two randomized, double-blind, placebo-controlled pilot studies of roquinimex (2.5 mg/day p.o. for 48 weeks) in 64 patients with relapsing remitting or secondary progressive multiple sclerosis showed that the drug reduced the number of new enhancing lesions and reduced the change in EDSS, although the differences were not statistically significant (8).

Pharmacia & Upjohn has reported that clinical studies with Linomide tablets for the treatment of multiple sclerosis will be discontinued due to an unexpected incidence of cardiovascular events (9).

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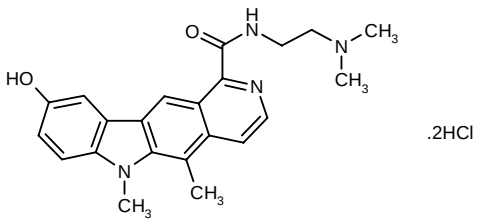
S-16020-2
NSC-D-659687
NSC-659687

Antineoplastic

EN: 210038



.2HCl

$C_{22}H_{24}N_4O_2.2HCl$ **Servier**

A study of the *in vitro* cytotoxicity of S-16020-2 in combination with various drugs in human non-small cell lung cancer cells determined that pretreatment with paclitaxel or vinca alkaloids followed by S16020-2 or cisplatin demonstrated a dramatic synergism, whereas the reverse schedule showed antagonism (1).

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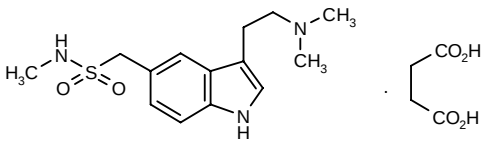
Sumatriptan Succinate
Imitrex®

Antimigraine
5-HT_{1D} Agonist

EN: 145146



$C_{14}H_{21}N_3O_2S.C_4H_6O_4$ **Glaxo Wellcome**

Glaxo Wellcome has launched Imitrex® (sumatriptan) Nasal Spray in Canada as a treatment for migraine. Imitrex®, a highly selective 5-HT_1 receptor agonist, was first launched in 1992 and is already available in tablet and subcutaneous injection formulations. The new nasal spray formulation was designed to provide particular benefit to patients who experience nausea during their migraine attacks, and also provides a viable alternative to migraine sufferers who are uncomfortable with or get skin reactions from injections (1).

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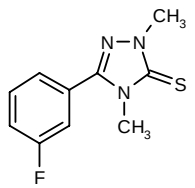
Suritozole

Cognition Enhancer
Antidepressant

EN: 135543



$C_{10}H_{10}FN_3S$ **Hoechst Marion Roussel**

The single-dose (2-465 mg) and multiple-dose (30, 60 and 120 mg b.i.d. for 28 days) pharmacokinetics of MDL-26479 were evaluated in healthy male volunteers. The plasma concentration-time profiles increased rapidly over the single-dose range, with t_{max} increasing from 0.5 to 3.8 h. The C_{max} and AUC increased disproportionately with dose, while apparent oral clearance decreased from 52.9 to 13.8 l/h. The pharmacokinetic parameters for multiple doses (30-120 mg) were consistent with those of the single dose, indicating that the drug's multiple-dose pharmacokientics can be predicted from single-dose pharmacokinetics (1).

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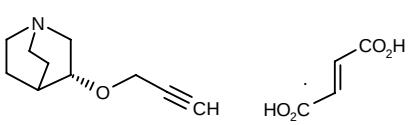
Talsaclidine Fumarate
WAL-2014-FU

Cognition Enhancer
Muscarinic M_1 Agonist

EN: 195168



$C_{10}H_{15}NO.C_4H_4O_4$ **Boehringer Ingelheim**

Talsaclidine fumarate has been shown to be a functionally selective muscarinic M_1 agonist in *in vitro* and *in vivo* studies and in humans. Pharmacokinetic studies in rats and humans demonstrated high oral bioavailability (> 95% in rats), little intersubject variability in plasma levels and excellent blood-brain barrier penetration. This profile, in addition to its previously reported stimulatory effect on the secretion of amyloid precursor protein, suggests that this compound may have beneficial effects on symptoms and disease-modifying effects in the treatment of Alzheimer's disease (1).

An *in vivo* study in anesthetized dogs showed that talsaclidine (1 mg/kg/min i.v. infusion) increased plasma catecholamine levels, epinephrine in particular, and renal vascular resistance, indicating that the drug's action is due to M_1 receptor agonism and its ability to cross the blood-brain barrier (2).

Results from a study of talsaclidine (1-64 mg/kg i.v.) in anesthetized guinea pigs indicated that the drug has bronchospastic potential which is not evident *in vivo* due to functional antagonism by β-adrenoceptors resulting from concomitant activation of the adrenals and sympathetic nervous system (3).

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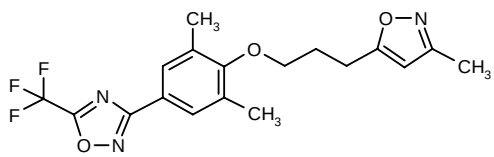
VP-63843
Pleconaril
Win-63843

Antiviral

EN: 202115



$C_{18}H_{18}F_3N_3O_3$ **ViroPharma**

The pharmacokinetics of a single oral dose of pleconaril (200 mg) in 12 healthy young adults were best characterized by a one-compartment open model with first-order absorption. Plasma concentrations at 12 h postdosing were 2.5-fold greater than those required to

inhibit 95% of enteroviruses in cell culture. The drug was well tolerated by all subjects, with no adverse effects being reported (1).

Results of a placebo-controlled, randomized, parallel-group study of pleconaril (200 or 400 mg t.i.d. for 7 days) in 32 evaluable patients with suspected enterovirus meningitis showed that the drug shortened the time to recovery by 58%, time to complete absence of headache by 64% and duration of analgesic use by 54%. There was also a 48% reduction in total analgesic use. The frequency of adverse events was similar in both drug- and placebo-treated groups (2).

ViroPharma has initiated a multicenter phase II trial to evaluate the ability of pleconaril to prevent the worsening of airways function caused by rhinovirus infections in asthmatics with common colds (3).

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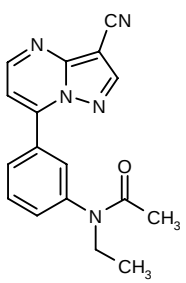
Zaleplon Sonata®

Sedative/Hypnotic

EN: 132769



$C_{17}H_{15}N_5O$ **American Cyanamid**

A study of zaleplon (0.01-10 mg/kg p.o.) in habituated rats showed that the drug, unlike triazolam (0.01-0.3 mg/kg p.o.) and nitrazepam (0.3-3.0 mg/kg p.o.), had no influence on open-field activity. However, in nonhabituated rats zaleplon and triazolam, but not nitrazepam, produced a dose-dependent decrease in ambulation and rearing (1).

Results of an electroencephalographic study in rabbits administered zaleplon (1-2 mg/kg i.v.) suggest that the hypnogenic action of the drug is partly due to the suppression of ascending reticular activating systems (2).

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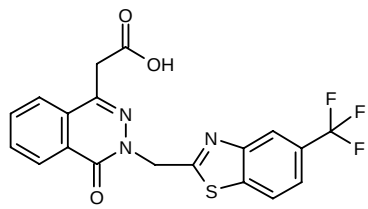
Zopolrestat Alond®

Symptomatic Antidiabetic
Aldose Reductase Inhibitor

EN: 135555



$C_{19}H_{12}F_3N_3O_3S$ **Pfizer**

Results of a phase II, multicenter, double-blind, placebo-controlled, 12-week study of zopolrestat (1000 mg) in 291 patients with peripheral diabetic polyneuropathy showed that the drug improved all sensory and motor amplitudes and significantly improved peripheral neuroelectrophysiology. The drug was well tolerated with 17 of the zopolrestat-treated patients withdrawing due to increased plasma transaminases. Headache, flatulence, nausea and abdominal pain were the most frequently reported adverse events (1).

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