Drugs of the Future 2001, 26(1): 61-105

CCC: 0377-8282/2001

Information Update

Volume 1-25, Number 1

Estimated developmental phase for this month's updated products:

Phase I

ER-30346 (antifungal; Eisai, Bristol-Myers Squibb)
Orazipone (immunomodulator; Orion Corp.)

Phase II

AG-7088 (anti-rhinovirus, HRV 3C protease inhibitor; Agouron)
Avasimibe (hypolipidemic, treatment of atherosclerosis, ACAT inhibitor; Pfizer)
Cystemustine (oncolytic; CNRS, INSERM)
Decitabine (oncolytic; Pharmachemie, SuperGen)
Didox (anti-HIV, oncolytic, ribonucleoside reductase inhibitor; Molelcules for Health)
FK-409 (nitric oxide donor; Fujisawa)
Flibanserin (antidepressant; Boehringer Ingelheim)
FTY-720 (treatment of transplant rejection, immunosuppressant; Welfide, Taito, Novartis)
GW-420867X (anti-HIV, reverse transcriptase inhibitor; GlaxoSmithKline, Aventis Pharma, Bayer)
LY-333328 (glycopeptide antibiotic; Lilly)
Mildronate (antianginal, cardioprotectant; Latvian Inst. Org. Synth., Taiho)
MKT-077 (oncolytic; Novartis, Fuji Photo Film)
Nibentan (antiarrhythmic, potassium channel blocker; Russian Acad. Med. Sci., Center Chem. Drugs)
RMP-7 (absorption promoter, bradykinin B_2 agonist; Alkermes, Alza)
S-16020-2 (oncolytic; Servier)
Talsaclidine fumarate (cognition enhancer, muscarinic M_1 agonist; Boehringer Ingelheim)

Phase III

Bay-12-9566 (MMP inhibitor; Bayer)
Flesinoxan hydrochloride (anxiolytic, antidepressant; Solvay, Duphar)
Gavestinel sodium (neuronal injury inhibitor; GlaxoSmithKline)
Iloperidone (antipsychotic, dopamine D_2 antagonist, 5-HT_{2A} antagonist; Aventis Pharma, Titan, Novartis)
Pleconaril (antiviral; Sanofi-Synthélabo, ViroPharma)
Sabcomeline hydrochloride (cognition enhancer; GlaxoSmithKline)
SDZ-RAD (immunosuppressant; Novartis)
Tegaserod maleate (treatment of IBS, treatment of GERD, 5-HT_4 agonist; Novartis, Bristol-Myers Squibb)
Zenarestat (treatment of diabetic nephropathy, aldose reductase inhibitor; Fujisawa)

Preregistered

Loxiglumide (treatment of pancreatic disorders, CCK_A antagonist; Rotta, Mitsubishi-Tokyo Pharm., Kaken)
Nefiracetam (cognition enhancer; Daiichi Pharm., Beijing General)

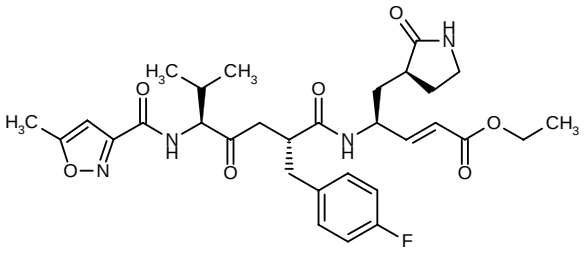
Launched/Year

Aminolevulinic acid hydrochloride (treatment of acne, treatment of actinic keratoses, treatment of restenosis; Dusa, Schering AG, Draxis Health)/2000
Anastrozole (oncolytic, aromatase inhibitor; AstraZeneca)/1995
Cefpodoxime proxetil (cephalosporin antibiotic; Sankyo)/1989
Cimetidine (gastric antisecretory, histamine H_2 antagonist; GlaxoSmithKline)/1977
Dexmedetomidine hydrochloride (sedative/hypnotic, non-opioid analgesic; Orion Corp., Abbott, Maruishi)/2000
Diflunisal (non-opioid analgesic; Merck & Co.)/1978
Donepezil hydrochloride (cognition enhancer, treatment ADHD; Eisai, Pfizer, Bracco)/1997
Fluoxetine hydrochloride (antidepressant, treatment of premenstrual syndrome; Lilly, Interneuron)/1987
Ibandronic acid monosodium salt (bisphosphonate, bone resorption inhibitor; Roche)/1996
Nabumetone (antiarthritic; GlaxoSmithKline)/1985
Ondansetron hydrochloride (antiemetic; GlaxoSmithKline, Sankyo)/1990
Paclitaxel (oncolytic, antiarthritic, antipsoriatic, treatment of multiple sclerosis; Bristol-Myers Squibb, Alcon, Angiotech, Ivax)/1993
Rabeprazole sodium (antiulcer, treatment of GERD, eradication of *H. pylori*; Eisai, Janssen-Cilag)/1997
Sumatriptan succinate (antimigraine; GlaxoSmithKline)/1991
Thalidomide (oncolytic, treatment of IBD, antiarthritic, treatment of leprosy; Celgene, Andrulis, EntreMed, Natl. Cancer Inst.)/1998
Tranilast (treatment of restenosis, antiallergic/antiasthmatic; Kissei, GlaxoSmithKline)/1982
Zaleplon (sedative/hypnotic; Wyeth-Ayerst, Lundbeck)/1999

AG-7088

Anti-Rhinovirus
HRV 3C Protease Inhibitor

EN: 268306



$C_{31}H_{39}FN_4O_7$ **Agouron**

A method using an optic light microscope with a polarizing filter and image analysis was developed to determine AG-7088 drug aggregates (crystals) in an aqueous nasal spray suspension (microcrystalline and sodium carboxymethyl cellulose). Aggregates were identified from drug substance using differences in birefringence and 0-20 aggregates (10-50 microns in size) were detected per slide. The quantity of the drug was estimated to be < 1% of the total suspended drug according to aggregate size distribution. The method was designed to be used in development studies for formulation and manufacturing controls and not for routine release and stability testing (1).

Results of an *in vitro* study showed that the broad spectrum activity of AG-7088 against 48 human rhinovirus (HRV) serotypes, coxsackieviruses (A21, B2, B3, B5), echoviruses (6, 9 and 11) and enterovirus 70 correlated with conservation of critical amino acids in the 3C protease-coding region of HRV. Results indicate the importance of the 3C protease as an antiviral target (2).

The *in vitro* activities of pleconaril and AG-7088 (0.01, 0.1 and 1 μg/ml) were examined against 5 numbered HRV serotypes and 46 clinical HRV isolates of undefined serotype obtained from patients with the common cold. Results showed that AG-7088 was more potent with broader antirhinoviral activity against the clinical isolates. The EC_{50} values obtained from cytopathic effect inhibition assays against the numbered HRV were significantly but only slightly lower for AG-7088 as compared to pleconaril; results from a spectrophotometric assay showed that activities of the 2 agents were the same. Significantly different EC_{50} values were obtained for AG-7088 (0.01 μg/ml range) and pleconaril (0.07 μg/ml range) against the clinical isolates. The median EC_{50} for AG-7088 for all clinical isolates was < 1 μg/ml while this value for pleconaril was > 10 μg/ml for 9% of the isolates (3).

The antiviral activity of AG-7088 and its effects on IL-6 and IL-8 production were evaluated in human bronchial epithelial cells (BEAS-2B). AG-7088 reduced the levels of infectious virus in HRV 14-infected cells in a significant, concentration-dependent manner. Additionally, AG-7088 significantly reduced the release of IL-6 and IL-8 into the cell supernatant. The replication of HRV 2 and HRV 16 was also inhibited by AG-7088. Furthermore, the compound produced a reduction in the levels of infectious virus, IL-6 and IL-8 even when added 14-26 h after HRV 14 infection. AG-7088 is, therefore, able to inhibit *in vitro* HRV-induced cytokine production when added throughout the virus life cycle and may offer potential efficacy both as a prophylactic agent and as a therapeutic agent for reducing symptoms (4).

1. Surakitbanharn, Y., O'Connell, S., Shiao, A., Rowlings, C. *Microscopic evaluation of AG7088 nasal spray suspension.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 4018.

2. Binford, S.L., Meador, J.W., Maldonado, F., Brothers, M.A., Weady, P.T., Isaacson, J.S., Maldonado, O., Worland, S.T., Matthews, D.A., Zalman, L.S., Patick, A.K. *Conservation of amino acids in human rhinovirus 3C protease correlates with broad spectrum antiviral activity of AG7088, a novel HRV 3C protease inhibitor.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst H-1162.

3. Kaiser, L., Crump, C.E., Hayden, F.G. *In vitro activity of pleconaril and AG7088 against selected serotypes and clinical isolates of human rhinoviruses.* Antivir Res 2000, 47(3): 215.

4. Zalman, L.S., Brothers, M.A., Dragovich, P.S., Zhou, R., Prins, T.J., Worland, S.T., Patick, A.K. *Inhibition of human rhinovirus-induced cytokine production by AG7088, a human rhinovirus 3C protease inhibitor.* Antimicrob Agents Chemother 2000, 44(5): 1236.

Original monograph - Drugs Fut 2000, 25: 9.

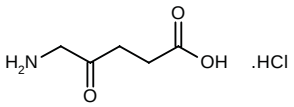
Additional Reference

Dragovich, P.S. et al. *Structure-based design of ketone-containing human rhinovirus 3C protease inhibitors.* 219th ACS Natl Meet (March 26-30, San Francisco) 2000, Abst MEDI 2.

Aminolevulinic Acid Hydrochloride
Levulan® Kerastick
Levulan®

Treatment of Acne
Treatment of Actinic Keratoses
Treatment of Restenosis

EN: 191307



$C_5H_9NO_3.HCl$ **Dusa; Schering AG; Draxis Health**

The efficacy of aminolevulinic acid (ALA; topical 5-ALA 20% + dimethylsulfoxide 99% or topical methyl-ester ALA 20% w/w in cream)-based photodynamic therapy (PDT; 50-200 J/cm^2) after radiotherapy was examined in 20 patients with residual or recurrent basal cell carcinomas (BCCs). A total of 22 lesions were treated of which 3, 12, 3, 1 and 2 lesions were exposed to 1, 2, 3, 4 and 5 sessions, respectively. At a mean of 22 months (6-40 months), 18 lesions were in remission with excellent or good cosmetic outcome. Three lesions showed partial responses and 1 recurred 21 months after therapy; of these 4 lesions, 2 were characterized as morpheaform BCC (1).

  CCC: 0377-8282/2001

A study in 6 patients with extensive alopecia areata showed that topical PDT with ALA (5, 10 and 20% 3 h before phototherapy twice/week for 20 sessions) did not induce hair regrowth. One patient showed an increase in red protoporphyrin IX fluorescence 3 h following topical application of ALA in the epidermis and sebaceous gland but not in the inflammatory infiltrate surrounding the hair; red fluorescence subsequently decreased after light exposure (2).

The efficacy of local anesthetic PDT using 3% ALA solution (50 ml intravesical) was examined in 8 patients with recurrent superficial bladder cancer (stage Ta, grades 1-2). Four hours after ALA sensitization, the solution was replaced with 2% lignocaine (40 ml for 45 min) followed by 150 ml of saline and laser light was delivered using a flexible cystoscope (50 J/cm^2, 633 nm). Treatment was well tolerated and not painful. One patient suffered from bladder irritability for 4 weeks posttreatment, after which function stabilized. No skin photosensitivity events, postphotodynamic changes in bladder function or hyperthermic effects were noted. At the 2-month follow-up, 2 patients had a complete response and 4 had a partial response (> 50% reduction in size/number of visible tumors). A lesser response was seen in 1 of the remaining 2 patients (3).

An open study in 20 patients with bladder carcinoma showed the tolerability and safety and reported the pharmacokinetics of intravesical administration of 5-ALA. Plasma C_{max} (340 ng/ml) was achieved at 0.55 and 0.62 h in patients administered the agent 2 or 4 h, respectively, prior to endoscopic resection. The elimination $t_{1/2}$ values obtained were 0.74 and 0.79 h, respectively. Plasma levels of the agent were measurable in 5 patients from 2-5 h postdosing (4.3-14 ng/ml) and then decreased to below detection after 9 h. Only 1% of the dose was absorbed by the bladder. No drug-related adverse events were seen during the 96-h observation period (4).

A study in 3 patients with 24 nodular BCCs showed the efficacy and safety of 1 treatment of topically applied 5-ALA PDT (100 mW/cm^2, 120 J/cm^2) 3 weeks after debulking of BCCs. Of the 24 BCCs, 22 showed a complete response upon histological examination of lesions 3 months after PDT (5).

Dusa has initiated a new phase I/II clinical trial with ALA (Levulan®) PDT in the treatment of acne vulgaris. The 2-site study, which will involve a minimum of 50 patients with moderate to severe acne vulgaris of the face, will test the safety and effectiveness of varying ALA PDT drug concentrations with red light for the treatment of acne. Results from a study involving 22 patients demonstrated obvious and significant improvement in acne of the back for at least 10 weeks after a single PDT treatment and for at least 20 weeks after 4 treatments with 20% ALA and red light. In addition to the significant and extended improvement in acne demonstrated over time after treatment with ALA PDT, a significant decrease in sebum (oil gland) output for the entire 20 weeks of the study was also seen in the treated areas. Sebaceous glands were also reduced in size after therapy and remained smaller for the duration of the 20 weeks of follow-up. Additionally, *Propionibacterium acnes* appeared to be significantly decreased for at least 20 weeks after PDT with ALA (6).

Draxis Health has filed a New Drug Submission with the Therapeutic Products Program of the Canadian Health Protection Branch for Levulan® (ALA hydrochloride) 20% topical solution with PDT for the treatment of actinic keratoses of the face and scalp. Draxis Health holds the exclusive Canadian rights to Levulan® PDT through Dusa (7).

Levulan® Kerastick™ has been available since September in the U.S. for the treatment of nonhyperkeratotic actinic keratoses of the face or scalp in conjunction with blue light illumination using the BLU-U Blue Light PDT Illuminator. Levulan® Kerastick™ is the first combined drug and device treatment designed for targeted treatment limited to the lesion site. The early detection and treatment of actinic keratoses is expected to reduce the incidence of skin cancer. The treatment is a 2-stage process involving the topical application of ALA directly to the individual lesions, followed 14-18 h later by PDT. Levulan® Kerastick™ for Topical Solution is supplied in a single-unit dosage form consisting of a plastic tube containing 2 sealed glass ampoules and an applicator tip. One ampoule contains 1.5 ml of solution vehicle and the other 354 mg of ALA hydrochloride (8).

1. Soler, A.M., Warloe, T., Tausjo, J., Giercksky, K.E. *Photodynamic therapy of residual or recurrent basal cell carcinoma after radiotherapy using topical 5-aminolevulinic acid or methylester aminolevulinic acid.* Acta Oncol 2000, 39(5): 605.

2. Bissonnette, R., Shapiro, J., Zeng, H., McLean, D.I., Lui, H. *Topical photodynamic therapy with 5-aminolaevulinic acid does not induce hair regrowth in patients with extensive alopecia areata.* Br J Dermatol 2000, 143(5): 1032.

3. Shackley, D., Whitehurst, C., Moore, J.V., Gilhooley, A., Betts, C.D., Clarke, N.W. *Local anaesthetic photodynamic therapy for superficial bladder cancer: Early clinical results.* Br J Cancer 2000, 83(Suppl. 1): Abst P193.

4. Popken, G., Schultze-Seemann, W., Seiler, K.U., Birkel, M., Wetterauer, U. *Intravesical administration of 5-aminolevulinic acid (5-ALA) - Safety and pharmacokinetics of 5-ALA and its metabolite protoporphyrin IX.* Eur J Clin Pharmacol 2000, 56(3): 241.

5. Thissen, M.R.T.M. et al. *Photodynamic therapy with delta-aminolaevulinic acid for nodular basal cell carcinomas using a prior debulking technique.* Br J Dermatol 2000, 142(2): 338.

6. *Dusa moves Levulan into phase I/II for the treatment of acne.* DailyDrugNews.com (Daily Essentials) Nov 29, 2000.

7. *Draxis seeks approval of Levulan PDT in Canada.* DailyDrugNews.com (Daily Essentials) March 31, 2000.

8. *Berlex now marketing Levulan Kerastick photodynamic therapy in U.S.* DailyDrugNews.com (Daily Essentials) Dec 13, 2000.

Original monograph - Drugs Fut 1997, 22: 11.

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Kontoyiannis, D.P., May, G.-S. *Delta-aminolevulinic acid (delta-ALA) modulates the resistance to fluconazole in the hem1 mutant.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-244.

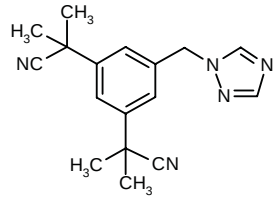
Krieg, R.C. et al. *Photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) induced protoporphyrin IX (PPIX): The intracellular localization influences cellular damages.* Gastroenterology 2000, 118(4, Suppl. 2, Part 1): A521.

Orenstein, A. et al. *Photodynamic therapy of cutaneous lymphoma using 5-aminolevulinic acid topical application.* Dermatol Surg 2000, 26(8): 765.

Anastrozole
Arimidex®

Oncolytic
Aromatase Inhibitor

EN: 147754



$C_{17}H_{19}N_5$ **AstraZeneca**

Health Canada has approved anastrozole (Arimidex®) as first-line therapy for postmenopausal women with advanced breast cancer. The results of a North American study in 353 women with advanced breast cancer showed anastrozole to be more effective than tamoxifen, and a European study in 668 patients showed anastrozole to be as effective as tamoxifen. The North American study found that patients taking anastrozole were 31% more likely to experience a delay in the spread of cancer pain than those taking tamoxifen and had their tumor growth halted for twice as long (11.1 months *vs.* 5.6 months). In addition to its ability to halt the spread of cancer, anastrozole is generally well tolerated by patients. Investigators found that women on anastrozole experienced 50% fewer thromboembolic side effects compared to the tamoxifen group, while other side effects were similar to tamoxifen (1).

The FDA has approved anastrozole (Arimidex®) as a new treatment option for postmenopausal women first diagnosed with advanced or locally advanced breast cancer whose cancers are hormone receptive. Anastrozole is the first aromatase inhibitor to be approved for first-line treatment in the U.S. Previously, the drug was only approved for use after disease progression following tamoxifen treatment (2).

Results presented at the second annual European Breast Cancer Conference confirmed that anastrozole (Arimidex®) as first-line therapy for postmenopausal women with hormone receptor-positive advanced breast cancer does not compromise tamoxifen's efficacy when the latter is used subsequently as second-line therapy. A prospective combined analysis of 1021 patients from 2 randomized, double-blind trials of identical design compared the efficacy and tolerability of anastrozole (1 mg/day) with tamoxifen (20 mg/day) as first-line therapy. Primary endpoints were time to progression (TTP), objective response and tolerability. At a median follow-up of 18.2 months, analysis of data from 611 hormone receptor-positive women demonstrated that anastrozole has a significant clinical benefit over tamoxifen in terms of TTP (median values of 10.7 *vs.* 6.4 months). Both treatments were well tolerated, although favorable numerical differences were seen with respect to thromboembolic events and cases of vaginal bleeding in patients treated with anastrozole (4.5% *vs.* 7.6% and 1.0% *vs.* 2.2%, respectively). At 18.2-month follow-up, 137 patients who received anastrozole as first-line therapy were known to have received second-line treatment with tamoxifen. Preliminary data on 98 of these patients revealed that 56 women showed clinical benefit (complete or partial response or long-term stable disease, *i.e.*, more than 24 weeks) from tamoxifen as second-line therapy after anastrozole. Anastrozole in combination with tamoxifen is currently undergoing evaluation in the ATAC (Arimidex®, Tamoxifen, Alone or in Combination) study, the largest adjuvant breast cancer study ever conducted. ATAC will compare anastrozole and tamoxifen in terms of efficacy and tolerability in early breast cancer and will also reveal if combination of the two drugs provides enhanced efficacy in the adjuvant setting (3).

1. *Arimidex receives Canadian approval for treatment of advanced breast cancer.* DailyDrugNews.com (Daily Essentials) June 7, 2000.

2. *Arimidex approved by FDA as first-line therapy of breast cancer.* DailyDrugNews.com (Daily Essentials) Sept 4, 2000.

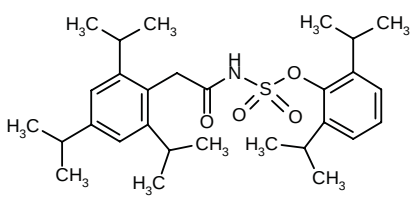
3. *Arimidex does not compromise subsequent treatment of breast cancer with tamoxifen.* DailyDrugNews.com (Daily Essentials) Oct 6, 2000.

Original monograph - Drugs Fut 1995, 20: 30.

Avasimibe

Hypolipidemic
Treatment of Atherosclerosis
ACAT Inhibitor

EN: 217771



$C_{29}H_{43}NO_4S$ **Pfizer**

A study in 16 healthy volunteers given midazolam (2 mg p.o. given before and after avasimibe) showed that

avasimibe (50 or 750 mg/day p.o. for 8 days) dose-dependently induced CYP3A4 activity. Avasimibe dose-dependently induced midazolam metabolism with mean CL/F values significantly increased about 3- and 8-fold with the 50 and 750 mg doses, respectively. In addition, midazolam AUC and 1-OH values significantly decreased by 37 and 74%, respectively, and the urine 6β-hydroxycortisol:cortisol ratio increased (1).

1. Milad, M.A., Stern, R., Strenkoski-Nix, L.C., Lathia, C.D. *Dose dependent induction of oral midazolam metabolism by avasimibe.* Clin Pharmacol Ther 2000, 67(2): Abst PII-88.

Original monograph - Drugs Fut 1999, 24: 9.

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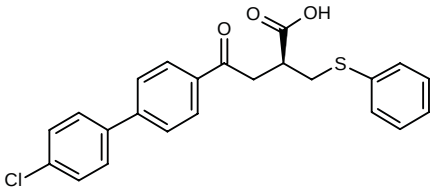
Bay-12-9566 Tanomastat

MMP Inhibitor

EN: 238610



$C_{23}H_{19}ClO_3S$ **Bayer**

The efficacy and safety of oral Bay-12-9566 (100-1600 mg once daily given as 400 mg q.i.d. or 800 mg b.i.d. for 4 weeks) were examined in a phase I dose escalation study conducted in 29 patients with advanced solid tumors. The maximum tolerated dose was not achieved since plasma levels of the agent did not increase with dose. Absorption was saturated at the higher doses. The most common toxicities included asymptomatic, reversible effects on platelets and transaminases and mild anemia. No complete or partial responses were seen, although 18 patients had stable disease; 13 patients had progressive disease. The recommended dose for further studies was 800 mg twice daily (1).

A multicenter, randomized, placebo-controlled phase III trial evaluated the efficacy of oral Bay-12-9566 (800 mg b.i.d.) in 243 patients with stage 3 or 4 advanced ovarian cancer who had responded to platinum/paclitaxel-containing chemotherapy. The drug was generally well tolerated, with grade 1 or 2 toxicities reported. Nausea (20%), fatigue (18%), diarrhea (13%) and rash (10%) were the most frequent side effects, occurring in more than 10% of patients. Hematologic toxicity was mild; equal to or greater than grade 3 thrombocytopenia occurred in only 2% of patients (2).

Tanomastat is the proposed international nonproprietary name for Bay-12-9566 (3).

1. Hirte, H., Hoel, R., Major, P. et al. *A phase I dose escalation study of the matrix metalloproteinase inhibitor BAY 12-9566 administered orally in patients with advanced solid tumours.* Ann Oncol 2000, 11(12): 1579.

2. Hirte, H., Vergote, I., Jeffrey, J. et al. *NCIC CTG OV12: An international multicentre phase III study of BAY 12-9566 (BAY) versus placebo in patients (pts) with advanced ovarian cancer (OVCA) responsive to primary surgery/paclitaxel + platinum containing chemotherapy.* Ann Oncol 2000, 11(Suppl. 4): Abst 714IN.

3. *Proposed international nonproprietary names (Prop. INN): List 82.* WHO Drug Inf 1999, 13(4): 288.

Original monograph - Drugs Fut 1999, 24: 16.

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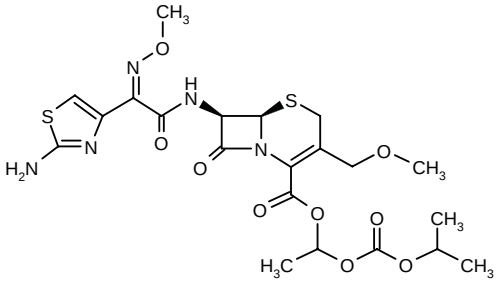
Goel, R. et al. *Phase I/pharmacokinetic (PK) study of the metalloproteinase and angiogenesis inhibitor Bayer 12-9566 (BAY) in conjunction with 5-fluorouracil/folinic acid (FU/FA).* Proc Am Soc Clin Oncol 2000, 19: Abst 911.

Moore, M.J. et al. *A comparison between gemcitabine (GEM) and the matrix metalloproteinase (MMP) inhibitor Bay 12-9566 (9566) in patients (pts) with advanced pancreatic cancer.* Proc Am Soc Clin Oncol 2000, 19: Abst 930.

Cefpodoxime Proxetil Banan®

Cephalosporin Antibiotic

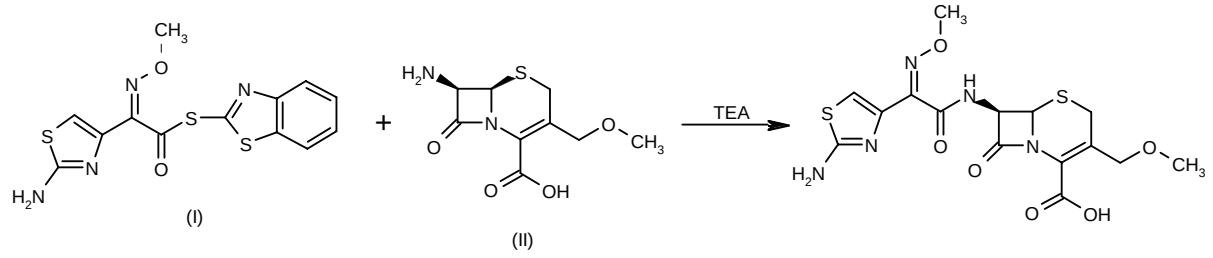
EN: 127911



$C_{21}H_{27}N_5O_9S_2$ **Sankyo**

A new process for the preparation of cefpodoxime, which can be converted into cefpodoxime proxetil by known methods, has been described: The condensation of 2-(2-aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetic acid 2-benzothiazolyl ester (I) with (6*R*,7*R*)-7-amino-3-(methoxymethyl)-3-cephem-4-carboxylic acid (II) by means of an organic base such as triethylamine, pyridine, *N*-methylpiperidine, DBU or DMAP in either THF/water, acetone/water, DMF/water, dimethylacetamide or dichloromethane directly gives cefpodoxime (1). Scheme 1.

Scheme 1: Synthesis of Cefpodoxime

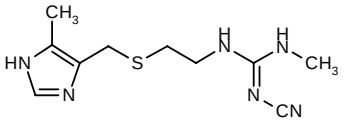


1. Kumar, Y., Arora, R.K., Singh, K., Nizar, H., De, S. Khanna, J.M. (Ranbaxy Laboratories Ltd.). *Process for the preparation of cefpodoxime acid.* WO 0068234.

Cimetidine
Tagamet®

Gastric Antisecretory
Histamine H_2 Antagonist

EN: 091556



$C_{10}H_{16}N_6S$ **GlaxoSmithKline**

Immunohistochemical evidence points to a significantly increased CD4/CD8 lymphocyte ratio in regressing warts and high doses of cimetidine have been reported to increase the number of CD4 lymphocytes, suggesting an ability to enhance the cell-mediated immune response. In a 3-month, open-label study, 47 patients with multiple, recalcitrant, nongenital viral warts were treated with oral cimetidine to evaluate its efficacy. Patients received 30-40 mg/kg/day cimetidine in 3 divided doses for 3 months. At the end of the trial, evaluable data were obtained from 41 of the patients ranging in age from 4-56 years. The results of the study showed that 87% of children and 68% of adults improved with treatment, and only 2 children and 8 adults failed to respond. Of the 16 children who improved with cimetidine treatment, 14 achieved a complete response or marked clinical improvement. Of the 25 adults who responded to treatment, 11 showed complete resolution, 3 a good response and 3 partial improvement. The data revealed that 75% of hand warts, 64% of plantar warts and the single case of facial warts improved with cimetidine treatment. No side effects were reported by the children in the study; 7/25 adults reported side effects such as diarrhea, nausea, abdominal pain, dry mouth, headache and dizziness, but only 2 adults discontinued treatment due to side effects. No antiandrogen effects were observed. Follow-up data using a postal questionnaire were obtained for 30 patients 2-20 months after the end of treatment. The data showed no recurrence in 83% of those whose warts had cleared completely during treatment; however, in patients who had stopped treatment before all warts had resolved, the viral growths tended to persist or recur. Despite the promising success rate of the present study, the efficacy of cimetidine is still inconclusive and requires larger placebo-controlled trials to fully evaluate its potential in the treatment of viral warts (1).

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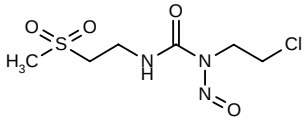
Cystemustine

Oncolytic

EN: 113740



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

A phase II study in 39 adult patients with high-grade brain tumors (14 glioblastomas, 20 grade 3-4 astrocytomas and 3 grade 3 oligodendrogliomas) showed moderate clinical activity of cystemustine (60 mg/m^2 15 min infusion every 2 weeks). Of the 37 evaluable patients, 4 had partial responses (2 grade 3 oligodendroglioma and 2 glioblastoma) for an overall response rate of 10.8%; 4 other patients had unconfirmed partial responses. Twelve patients had stable disease at 8 weeks and 15 patients had progressive disease. Grade 3-4 leukopenia (16.2%), neutropenia (29.7%) and thrombopenia (27%) were the common toxicities seen; no other toxicities greater than grade 2 were reported (1).

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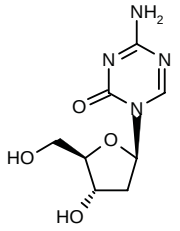
Decitabine

Oncolytic

EN: 125366



$C_8H_{12}N_4O_4$ **Pharmachemie; SuperGen**

An *in vitro* study using 5 myeloma cell lines (ARH-77, HS-Sultan, OPM-2, RPMI 8226, U266) showed that decitabine, sodium butyrate or trichostatin A reactivated expression of a silenced Stat-1 gene expression and increased interferon-α responsiveness in the HS-Sultan cell line. Results revealed that, with the exception of HS-Sultan, all cell lines displayed constitutive expression of Stat-1, Stat-2, Stat-3 and Stat-5; expression of Stat-1 was undetectable in the HS-Sultan line. Moreover, interferon-α (310, 1250 and 5000 U/ml)-induced growth inhibition was markedly enhanced in HS-Sultan cells pretreated for 72 h with decitabine (1 μM) or butyrate (1 mM). Decitabine pretreatment resulted in 66.0 ± 17.3, 73.4 ± 10.1 and 83.2 ± 6.5% growth inhibition for the respective interferon-α doses as compared to 34.6 ± 10.9, 43.3 ± 11.5 and 52.1 ± 7.0%, respectively, seen in control cells and 63, 35 and 79%, respectively, observed in butyrate-pretreated cells (1).

A preliminary clinical trial has evaluated decitabine in patients with stage IV non-small cell lung cancer who had not received prior chemotherapy. The patients were treated with decitabine at doses of 200-660 mg/m^2 by 8-h i.v. infusion every 5-7 weeks. Median survival in 6 patients receiving at least 2 treatment cycles was over 16 months, and 1 patient survived 81 months following 5 cycles of decitabine and 1 of vindesine. The onset of antitumor action of decitabine, as for differentiation-inducing agents, appeared to be delayed. The finding of DNA methylation of the retinoic acid receptor RARbeta in one-third of the lung tumor biopsies pointed to another molecular target for decitabine (2).

The effect of repeated doses of decitabine (0.3 mg/kg/day, 5 days/week for 2 weeks, followed by a 4-week observation period to allow recovery of neutropenia) on hemoglobin (Hb) and fetal hemoglobin (HbF) levels and on toxicity was determined in 7 patients with sickle cell anemia, 5 of whom were hydroxyurea nonresponders. The average Hb and HbF levels of all patients during the last 20 weeks of treatment were 8.72 ± 0.46 g/dl and 15.2 ± 3.12%, respectively, compared to pretreatment values of 7.41 ± 0.96 g/dl and 4.37 ± 4.16%, respectively. HbF levels remained elevated over several treatment cycles, even in the 5 patients requiring dose reductions, which was probably due to the increase in number of reticulocytes available to synthesize HbF. No cumulative toxicity was observed, which allowed for shorter intervals between treatment cycles (3).

The results of a study in 124 elderly, high-risk patients (median age = 70 years) with myelodysplastic syndrome and chromosomal abnormalities have demonstrated that repeated low-dose decitabine can induce cytogenetic remissions in a significant number of patients. Major cytogenetic responses were seen in 31% (19/61) of patients with clonal chromosomal abnormalities after 3 courses of treatment, with a median duration of responses of 7.5 months. A subgroup analysis by cytogenetic risk groups showed response rates of 60% (3/5), 20% (6/30) and 38% (10/26) in the low-, intermediate- and high-risk groups, respectively, with median survival of 30, 8 and 13 months for the respective groups (4).

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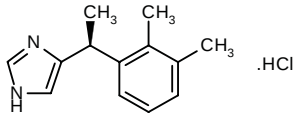
Dexmedetomidine Hydrochloride

Primadex® *Sedative/Hypnotic*
Precedex® *Non-Opioid Analgesic*

EN: 145584



$C_{13}H_{16}N_2$.HCl **Orion Corp.; Abbott; Maruishi**

Results from an *in vitro* study in astrocytes showed that the neuroprotective effects of dexmedetomidine during ischemia may be through stimulation of glutamine oxidation. The agent exerted its effect on α_2-adrenergic receptors and not on imidazoline-binding sites (1).

An *in vitro* study examined the effects of dexmedetomidine, clonidine and oxymetazoline (10, 50 and 100 nM and 1 μM) on arginine vasopressin (AVP)-induced sodium and urea transport in isolated rat inner medullary collecting duct (IMCD). The ED_{50} values for inhibition of sodium transport were 7.7, 106.1 and 194.6 nM, respectively. Dexmedetomidine had no effect on urea transport while the ED_{50} values for clonidine and oxymetazoline were 281.7 and 168.9 nM, respectively. Micromolar but not nanomolar concentrations of the imidazoline antagonist, BU-239, partially reversed dexmedetomidine-induced inhibition of sodium transport and epinephrine-induced inhibition of urea transport. Results suggest that α_2-adrenergic receptors mediate sodium and urea transport in IMCD and imidazoline receptors are not involved in inhibition of AVP-induced transport (2).

The effect of cardiac output on the pharmacokinetics of dexmedetomidine (i.v. via a computer-controlled infusion pump) was examined in healthy subjects. When plasma concentrations of the agent were 0, 0.6 and 1.2 ng/ml, estimated cardiac outputs were 5.6 ± 0.85, 5.1 ± 0.67 and 4.5 ± 0.83 l/min, respectively. The decreases seen in cardiac output at these concentrations were similar to decreases observed with clonidine. The mean clearances were 40 ± 10, 38 ± 9 and 35 ± 8.5 l/h, respectively, and the elimination half-life and V_{ss} values for the agent were 1.9 ± 0.62 h and 72 ± 19 l, respectively. The decrease in cardiac output observed with increasing drug concentrations corresponded to a decrease in elimination (≤ 12%). The decrease in clearance was not considered clinically significant (3).

A pharmacokinetic study in 15 patients with mild, moderate or severe hepatic failure and 15 healthy subjects showed that dexmedetomidine (0.6 μg/kg) dose adjustments are required in patients with severe failure. Significant differences in steady state (3.2 ± 0.32 *vs.* 2.18 ± 0.22 l/kg), clearance (0.32 ± 0.04 *vs.* 0.64 ± 0.15 l/h/kg) and half-life (7.51 ± 1.80 *vs.* 2.59 ± 0.39 h) were observed between patients with severe hepatic failure and controls. BIS levels, which were similar at baseline, were also significantly decreased in patients with severe hepatic failure (54.16 ± 16 *vs.* 89.33 ± 4 units) as compared to controls (4).

Abbott launched dexmedetomidine hydrochloride (Precedex™) for the first time in the U.S. The drug is indicated for the sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting and is administered by continuous i.v. infusion for a period not to exceed 24 h. The drug is supplied in 2-ml glass vials and ampoules containing 100 μg/ml as the base (5).

The E.U. marketing authorization application for dexmedetomidine hydrochloride has been withdrawn from the review process at the request of the Committee for Proprietary Medicinal Products for clinical studies comparing dexmedetomidine with therapies currently used in the intensive care unit (6).

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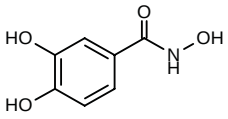
Didox

Anti-HIV
Oncolytic

EN: 126587 *Ribonucleoside Reductase Inhibitor*



$C_7H_7NO_4$ **Molecules for Health**

The *in vivo* and *in vitro* antiviral efficacy of didox and trimidox were examined and compared with hydroxyurea. All 3 agents decreased development of immunodeficiency and viremia and increased survival *in vivo* against HuPBMC SCID-HIV, murine AIDS and Rauscher leukemia models and decreased viral replication *in vitro* in HIV-infected cell lines. In contrast to hydroxyurea, no hematopoietic suppression or toxicity was observed with didox or trimidox treatment (1).

A study using HIV-infected SCID-Hu mice compared the antiviral efficacies and toxicities of didox and trimidox with hydroxyurea as monotherapies or in combination with ddI. Disease progression was inhibited after 8 weeks of treatment with any of the agents alone. At week 4, treatment with didox and trimidox combined with ddI resulted in better antiviral responses as compared to hydroxyurea combined with ddI. Disease progression was also significantly inhibited when treatment was delayed until 9 weeks postinfection. While no significant bone marrow toxicity was observed with didox and trimidox, hydroxyurea treatment resulted in marked hematopoietic toxicity (2).

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Diflunisal
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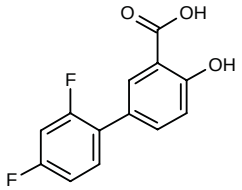
Non-Opioid Analgesic

EN: 091354



$C_{13}H_8F_2O_3$ **Merck & Co.**

An easy preparation method for diflunisal has been reported: Reaction of 2,4-difluoroiodobenzene (I) with powdered Zn activated with 1,2-dibromoethane in DMF gives the 2,4-difluorophenylzinc iodide (II), which is condensed with 2-acetoxy-5-iodobenzoic acid methyl ester (III) by means of $Pd(PPh_3)_4$ in DMF to yield 4-acetoxy-2',4'-difluorobiphenyl-3-carboxylic acid methyl ester (IV). Finally, this compound is deacetylated and hydrolyzed with $NaHCO_3$ in THF/water (1). Scheme 2.

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Donepezil Hydrochloride
Memorit®
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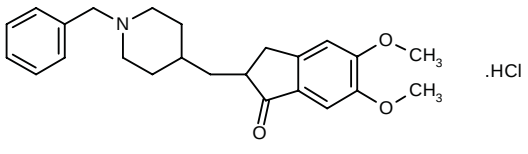
Cognition Enhancer
Treatment of ADHD

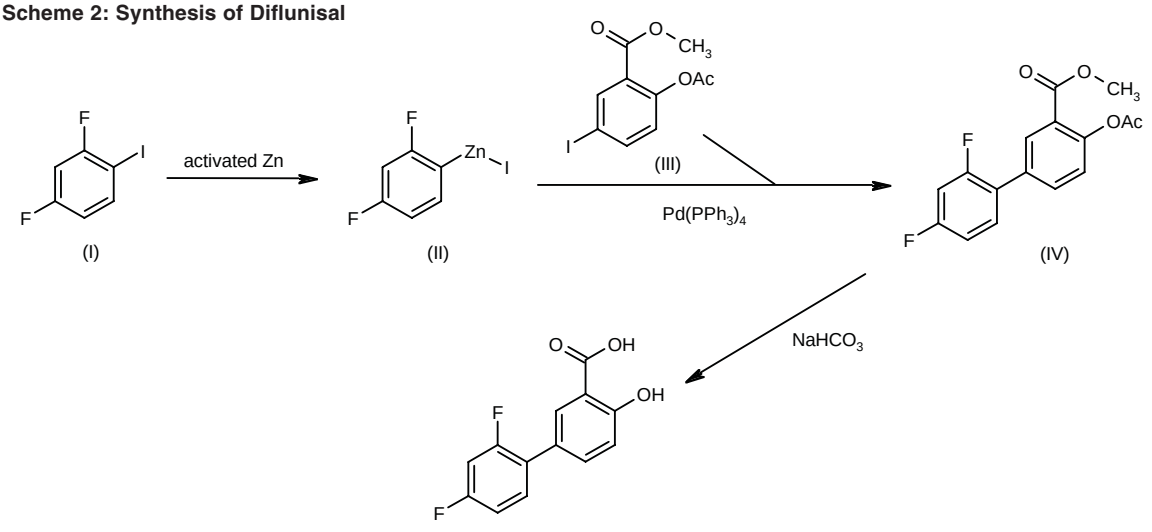
EN: 150920



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

A study in 16 patients on stable dose (average dose = 426 mg/day) opiates for at least 2 months examined the

Scheme 2: Synthesis of Diflunisal



efficacy of donepezil (5-15 mg in 1 or 2 doses) in treating opiate-induced sedation. Thirteen patients reported moderate improvement and 1 patient mild improvement in self-rating scales. The average Epworth Sleepiness Scale (ESS), linear analog sleepiness scale (LASS) and average pain scores in patients while on donepezil were 12.6, 51 and 4, respectively, as compared to 20, 80.1 and 4.1, respectively, when patients were off donepezil. In 6 of the 8 responders, the average decreases in ESS and LASS were 46 and 50%, respectively. Adverse events were mild and transient and a tendency for drug tolerance was seen in 6/9 patients given donepezil for more than 2 months (1).

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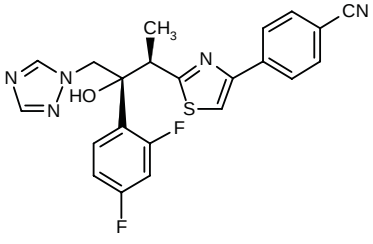
Original monograph - Drugs Fut 1991, 16: 16.

ER-30346 *Antifungal*
Ravuconazole

EN: 226621



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

Researchers have compared the *in vitro* activities of ravuconazole, fluconazole and itraconazole against 541 clinical isolates of *Cryptococcus neoformans*. Ravuconazole was found to have greater activity than the reference compounds, with MIC_{90} values of 0.25 μg/ml, 0.5 μg/ml and 8 μg/ml for ravuconazole, itraconazole and fluconazole, respectively. Ravuconazole at concentrations of ≤ 1 μg/ml was able to inhibit over 90% of isolates inhibited by a minimum of 16 μg/ml fluconazole. The potency of the new triazole and its favorable pharmacokinetic properties indicate that further clinical testing in cryptococcal infectious diseases should be performed (1).

The efficacy of ravuconazole was shown *in vitro* against *Trypanosoma cruzi* epimastigotes and clinically relevant intracellular amastigotes cultured in Vero cells and *in vivo* in acutely infected (trypomastigotes) mice treated with the agent (10 mg/kg p.o. daily or b.i.d. starting 24 h postinfection and continuing for 28 days followed by a 1-week rest period and 15 days of further treatment). Results suggest that the agent may be effective against Chagas disease. The MICs against epimastigotes and amastigotes were 0.3 μM and 1 nM, respectively. When exposed to the MIC of the agent, parasitic C4,14-desmethyl sterols were replaced by di- and trimethylated sterols. Infected mice treated with the agent b.i.d had 100% survival and 70% of the animals had parasitological cures; no significant cures were observed with nifurtimox (50 mg/kg/day) or ketoconazole (40 mg/kg/day) treatment (2).

The *in vitro* activity of ravuconazole was compared to itraconazole and amphotericin B against 80 clinical isolates of *Aspergillus*. Geometric mean MIC values for ravuconazole, itraconazole and amphotericin B were 1.71, 0.67 and 0.63 μg/ml, respectively. Ravuconazole was highly active against *A. fumigatus* but showed little activity against *A. terreus* and *A. flavus*. Although 8 itraconazole-resistant (MIC = > 8 μg/ml) *A. fumigatus* strains were found, none were resistant to ravuconazole (3).

A study examining the penetration of ravuconazole (10 mg/kg) into rat tissue (plasma, lung and uterus) following oral administration concluded that the agent may be a potential candidate for treatment of deep-seated fungal infections. Concentrations of the agent in uterus were 2- to 6-fold higher than in blood and the plasma to lung concentration ratios were higher than those reported for other azoles (4).

Findings from experiments on the pharmacodynamics of ravuconazole in the treatment of disseminated candidiasis in a neutropenic mouse model have been reported. The results indicated that once-daily dosing of ravuconazole is feasible in humans. Ravuconazole gave respective ED_{50} values when given at 6-, 12- and 24-h intervals of 17.4, 17.4 and 9.20 mg/kg by oral gavage, and respective ED_{90} values of 100, 75.6 and 86.3 mg/kg (5).

In an open-label study in 20 healthy volunteers, concomitant administration of a single dose of ravuconazole increased the simvastatin AUC by only 2-fold, and multiple doses of the drug resulted in only a 4-fold increase in the AUC for simvastatin, indicating that ravuconazole is a less potent inhibitor of cytochrome CYP3A4 than other triazole antifungals (6).

Ravuconazole was shown to be safe and well tolerated in double-blind, placebo-controlled, ascending-dose studies in healthy subjects given both single and multiple doses. Following single oral doses of 50-800 mg as gelatin capsules, headache was the most frequently reported adverse event in both ravuconazole and placebo groups. The antifungal exhibited modest intersubject variability in pharmacokinetics and had a long half-life, ranging from 83-157 h, supporting once-daily dosing (7).

In a double-blind, placebo-controlled, multiple-dose study, healthy subjects were administered ravuconazole at doses of 50-400 mg orally once daily for 14 days. Multiple doses were associated with about a 10-fold accumulation of drug on the last day of dosing, consistent with its long half-life. The highest dose gave plasma levels exceeding the MIC_{90} for *Candida albicans* from 1 h after dosing to day 42, and that for *Aspergillus* spp. from day 4 to day 31. Headache was the most frequent adverse event. The drug did not appear to induce CYP3A isozymes (8).

Ravuconazole is the proposed international nonproprietary name for ER-30346 (9).

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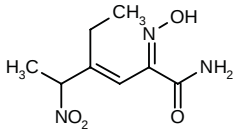
FK-409

Nitric Oxide Donor

EN: 150837



$C_8H_{13}N_3O_4$ **Fujisawa**

FK-409 was studied in an *in situ* model of small bowel ischemia/reperfusion injury in dogs. Dogs were administered either vehicle or FK-409 at a dose of 5 μg/kg/min i.v. for 30 min before the induction of ischemia, followed by administration from 15 min before to 45 min after reperfusion. Histological analysis at 1, 3, 6 and 12 h after reperfusion demonstrated a significant reduction in injury in the FK-409 group. Intramucosal pH in the ileum was higher in the treated group at 1, 3 and 12 h after reperfusion, arterial pH levels were higher at 12 h and serum NO levels were also higher in treated animals compared to controls. These results thus provide further evidence for an NO-mediated protective effect of FK-409 (1).

FK-409 has been tested for its protective effects in perfused guinea pig hearts subjected to normothermic global ischemia for 40 min followed by 40 min of reperfusion. FK-409, at a concentration with minimum inotropic effects in nonischemic hearts, was added to the cardioplegic solution prior to the induction of ischemia. Hearts treated with FK-409 showed reductions in left ventricular end-diastolic developed pressure (LVDP) during and after ischemia, as well as improved postichemic recovery of LVDP. A significant increase in the flow rate was also seen compared to drug-free hearts. FK-409 treatment was associated with significant preservation of tissue ATP levels at the end of ischemia or reperfusion, and it significantly attenuated the reduction in NO release during ischemia. It was concluded that FK-409 appears to have potential during cardiac surgery due to its ability to induce NO-mediated vasorelaxation and to protect against reperfusion injury (2).

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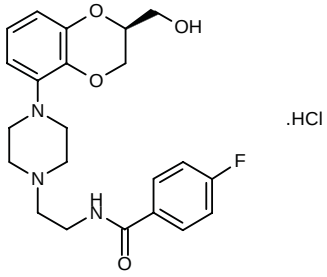
Flesinoxan Hydrochloride

Anxiolytic
Antidepressant

EN: 124142



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

An *in vivo* study in rats showed that flesinoxan (5 mg/kg i.p.) increased hippocampal extracellular noradrenaline levels and locomotor activity. WAY-100635 (1 mg/kg i.p.) or clonidine (50 μg/kg i.p.) pretreatment blocked the effects of flesinoxan. Flesinoxan (200 nmol in 2 μl) administered as a bilateral intrahippocampal injection increased locomotor activity, whereas intrahippocampal perfusion with the agent increased extracellular noradrenaline levels. Hippocampal serotonin and its major metabolite or striatal dopamine and its metabolites were not affected by i.p. flesinoxan treatment (1).

A study conducted in 39 healthy volunteers (22 males, 17 females; mean age = 35.5 ± 10.7 years) reported that neither age nor gender affected flesinoxan (1 mg/70 kg i.v.)-induced effects on neurophysins and temperature. Similar hypothermic responses (–32.4 ± 22.1 *vs.* –34.6 ± 29.3 °C min), total neurophysins (48 ± 133.9 *vs.* 75.4 ± 148.2 pg min/l), vasopressin (18.3 ± 35.8 *vs.* 19 ± 37.5 pg min/l) and oxytocin (29.8 ± 116.7 *vs.* 56.5 ± 118.8 pg min/l) responses were obtained for males and females and no significant effect of age was seen on these parameters (2).

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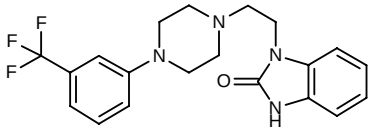
Flibanserin *Antidepressant*

EN: 197146



$C_{20}H_{21}F_3N_4O$ **Boehringer Ingelheim**

The activity of flibanserin was determined in the infant rat ultrasonic vocalization (USV) model of anxiety. The effects of flibanserin were compared to those of the anxiolytic diazepam and the antidepressant imipramine. In the study, rat pups 7-8 days old were separated from their mother and littermates, then observed for USVs, locomotor behavior, negative geotaxis and body temperature. The administration of flibanserin at doses of 5, 10, 25 and 50 mg/kg s.c. caused a reduction in USVs without influencing locomotor behavior or negative geotaxis. Diazepam (0.25, 0.5, 1 and 2 mg/kg s.c.), however, caused an increase in rolling and in the latency of the negative geotaxic response, in addition to reducing USVs. Imipramine (10, 15, 20 and 30 mg/kg s.c.) led to a reduction in USVs and an increase in total locomotor activity and rolling, with no effects on negative geotaxis. Body temperature was not altered by any of the drugs tested. Due to the compound's efficacy in reducing USVs without producing motor side effects, flibanserin is suggested to show promise as a potential therapy for anxiety (1).

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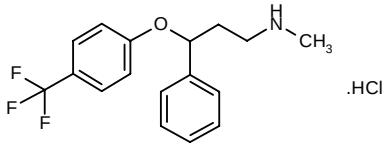
Fluoxetine Hydrochloride *Antidepressant*
Sarafem® *Treatment of Premenstrual Syndrome*
Prozac®

EN: 131699



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

Lilly has filed an NDA with the FDA for a unique once-weekly formulation of fluoxetine hydrochloride (Prozac®) for the treatment of depression. If approved by the FDA, it will be the first and only antidepressant available in a once-weekly formulation (1).

The FDA has approved fluoxetine hydrochloride (Sarafem®) for the treatment of premenstrual dysphoric disorder (PMDD), making it the first and only prescription medication indicated for the treatment of PMDD. In clinical studies, women treated with the drug experienced statistically significant improvement in mood and physical symptoms, as well as social functioning, compared with women taking placebo. These improvements were demonstrated by the first menstrual cycle on treatment. Fluoxetine's effectiveness for the treatment of PMDD was established in 2 double-blind, placebo-controlled trials. In the first study, 320 patients were given fluoxetine continuously throughout the menstrual cycle. This study showed that the drug was significantly more effective than placebo by measurements of changes in mood and physical symptoms of PMDD. In a second study, 19 patients were treated with fluoxetine and placebo continuously throughout the menstrual cycle for a period of 3 months each. In this study, fluoxetine was significantly more effective than placebo on a scale measuring changes in mood, physical and social impairment symptoms (2).

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2. *FDA approves Sarafem for treatment of premenstrual dysphoric disorder.* DailyDrugNews.com (Daily Essentials) July 7, 2000.

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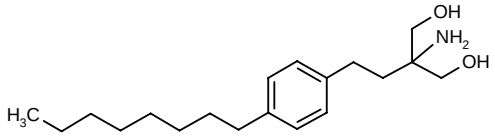
FTY-720

Treatment of Transplant Rejection
Immunosuppressant

EN: 210392



.HCl

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

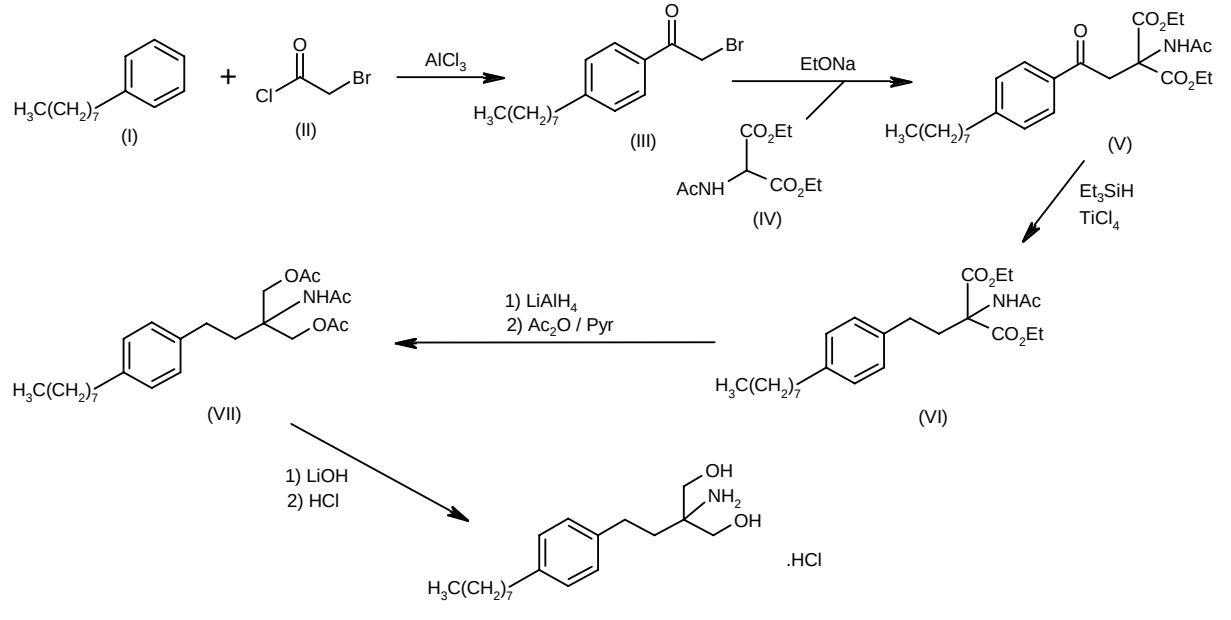
A new synthesis of FTY-720 has been described: The Friedel Crafts condensation of octylbenzene (I) with bromoacetyl chloride (II) by means of $AlCl_3$ in dichloromethane gives the phenacyl bromide (III), which is condensed with 2-acetamidomalonic acid diethyl ester (IV) by means of EtONa in ethanol/THF to yield the ketone-malonic ester adduct (V). Reduction of (V) with Et_3SiH by means of $TiCl_4$ in dichloromethane affords compound (VI), which is then reduced with $LiAlH_4$ in THF followed by acetylation with acetic anhydride and pyridine to provide the acetate (VII). Finally, compound (VII) is hydrolyzed with LiOH in refluxing methanol/water and treated with HCl in ethyl ether (1). Scheme 3.

The effects of FTY-720 (0.1 mg/kg/day) were compared with tacrolimus against development of experimental autoimmune myocarditis (immunization with porcine cardiac myosin in complete Freud's adjuvant on day 0) in rats. FTY-720 treatment in normal rats resulted in significantly reduced circulating lymphocyte counts. In myocarditic rats, FTY-720 significantly lowered the areas of myocarditis at days 14 and 28. These areas were significantly smaller than those evident in tacrolimus-treated myocarditic rats. Early administration of FTY-720 (days 0-10) resulted in significantly lower myocarditis-affected areas on day 28 as compared to controls (2).

A study in mice showed that FTY-720 enhanced chemokine-dependent lymphocyte chemotaxis in response to TCA-4/SLC, MIP-3β/ELC, MCP-1, RANTES and BCA. Treatment of plt/plt mutant mice (which have decreased TCA-4/SLC and MIP-3β/ELC expression but normal BCA expression in lymphoid organs) with the agent resulted in depletion of B cells with little effect on T cells. Treatment did not significantly upregulate chemokine or chemokine receptor expression. However, leukocyte phosphatidylinositol-3 kinase was activated by treatment, resulting in intrinsically enhanced locomotion (3).

A study using Lewis rats with Fischer renal allografts showed the efficacy of FTY-720 pretreatment (0.5 mg/kg

Scheme 3: Synthesis of FTY-720



p.o. 24 h before transplant) in preventing preservation-reperfusion injury. Posttransplant acute renal failure did not occur in FTY-720-treated animals as compared to controls (creatinine clearance = 0.62 ± 0.8 *vs.* 2.24 ± 0.18 mg/dl). FTY-720 treatment also resulted in lower acute tubular necrosis scores and less neutrophil and lymphocyte infiltration. Postischemic IL-1 levels were also lower in treated animals (211 ± 36.4 *vs.* 724.98 ± 86.3 in controls) (4).

A study using rats subjected to 60-min right renal artery occlusion and left nephrectomy showed the protective effects of FTY-720 (1 mg/kg i.v. after ischemia) against ischemic reperfusion injury in the kidney. Plasma creatinine was normalized faster in treated rats, occurring on day 5 postsurgery as compared to day 7 in controls and animals treated with 0.5 mg/kg FTY-720. Mortality in the FTY-720-treated group was reduced to 25% as compared to 40% and 50% in 0.5 mg/kg FTY-720 and control groups, respectively. Histological examination of renal tissue also revealed less damage in FTY-720-treated animals as compared to controls (5).

An *in vivo* study in rats (PVG [RT1c]) with heterotopic heart (Htx) or orthotopic intestinal (Itx) transplants (from RA [RT1p] donors) reported differential effects of FTY-720 (5 mg/kg/day p.o. on days 15, 14 and 13 pretransplantation) on DSBT (1.5 ml on day 12 pretransplantation)-induced tolerance induction. No significant difference was observed in survival of FTY-720-treated and untreated Itx animals (18.6 ± 2 and 18 ± 4 days, respectively). Treatment with DSBT alone significantly increased survival to 101.9 ± 18 days. Treatment with FTY-720 before DSBT significantly decreased survival to 55 ± 44.7 days. FTY-720-treated and untreated Htx animals survived 9.3 ± 1 and 9.0 ± 0.6 days, respectively. However, Htx animals treated with DSBT alone or in combination with FTY-720 survived indefinitely (> 150 days). All long-term surviving Htx and Itx animals accepted secondary grafts (6).

FTY-720 (0.3 or 0.1 mg/kg/day for 3 days or 0.03 mg/kg/day for 10 days p.o.) was shown to effectively deplete both T and B cells in Chacma baboons. Within 4 h of treatment with 0.3 mg/kg, significant reductions in circulating lymphocytes were observed which were further reduced by 60-80% at 24-48 h. The effect of the agent was slightly more rapid and more marked on T cells as compared to B cells and CD4+ cells were more susceptible than CD8+ cells. Maximum effects were observed with doses of 0.03-0.3 mg/kg. Blood FTY-720 levels correlated with dose but not with reductions in lymphocyte counts, indicating good tissue distribution. Baboons showed a lower initial exposure and response to the agent as compared to cynomolgus monkeys at 24 h following 1 or 2 doses (0.03-0.3 mg/kg). However, steady-state FTY-720 levels and peripheral depletion of lymphocytes were similar in both species after a 7-day treatment with 0.03 mg/kg (7).

An *in vivo* study using H-Y antigen sensitized female rats challenged with syngeneic male skin grafts showed that pretreatment with FTY-720 (10 mg/kg 4 weeks after sensitization) preserved immunological acquired memory. Sensitized animals pretreated with FTY-720 showed a restored ability to reject subsequent H-Y incompatible skin isografts (mean survival = 33.9 ± 11.9 days) as compared to untreated controls (mean survival = 300 days) (8).

A study using a rat renal transplantation model showed the efficacy of FTY-720 (0.05-3 mg/kg/day p.o.) in significantly and dose-dependently prolonging allograft survival. Rats treated with the agent at doses of 0.05, 0.1, 0.5, 1 and 3 mg/kg/day had mean allograft survival values of 12.2 ± 3.3, 11.2 ± 2.4, 13.6 ± 0.9, 14.6 ± 1.7 and 20.2 ± 0.8 days, respectively, as compared to 7.2 ± 0.4 days in untreated controls. Peripheral blood lymphocytes were significantly decreased in animals treated with 3 mg/kg/day and the percentage of IL-2 receptor positive cells in allografts was significantly less (3.10 ± 0.86 *vs.* 6.34 ± 0.81% in untreated animals). No differences in the CD4/CD8 ratio of splenic cells and graft infiltrate were observed between treated and untreated animals (9).

An *in vivo* study using rats with heterotropic cardiac transplants reported that treatment with FTY-720 (2 mg/kg/day from days 3-9 posttransplantation) significantly delayed acute rejection. Allograft survival in treated animals was 30.5 ± 6.7 days as compared to 9 ± 1.9 days in untreated controls. Increasing FTY-720 to 4 and 8 mg/kg/day (24.9 ± 7.5 and 21.5 ± 6.4 days, respectively) also resulted in significantly longer survival time as compared to controls. In addition, treated animals had less lymphocytic infiltration in allografts examined 7 days posttransplantation (10).

The efficacy of FTY-720 alone (0.03, 0.1 and 0.3 mg/kg/day p.o. starting 3 days before grafting and for 28 days thereafter) or in combination with SDZ-RAD (0.03, 0.1 and 0.3 mg/kg/day p.o.) was examined in a study using rats with heterotopic (DA to Lewis) cardiac grafts. Results showed that peripheral lymphocyte counts predicted graft survival. FTY-720 alone dose-dependently prolonged graft survival to 7, 9.5 and 15 days, respectively, as compared to 6 days with placebo; SDZ-RAD alone also prolonged survival to 8.5, 18 and 37.5 days, respectively. Low-dose FTY-720 combined with low-dose SDZ-RAD was also effective in prolonging graft survival and caused normal weight gain while treatment including high-dose SDZ-RAD (1 mg/kg/day or more) resulted in delayed weight gain. Peripheral lymphocyte counts were significantly and dose-dependently reduced by FTY-720 and counts correlated with graft survival. Combination treatment did not induce any adverse event with respect to well-being or weight gain and was better tolerated than SDZ-RAD monotherapy (11).

Combination treatment with FTY-720 (10 mg/kg p.o. day 1 to rejection) and deoxyspergualin (DSG; 2.5 mg/kg i.m. days 1-10) was shown to prolong survival (14.4 ± 0.5 days) of concordant hamster heart xenografts in splenectomized Lewis rats. Although FTY-720 alone had no effect on graft survival (4.8 ± 0.2 days), DSG alone significantly prolonged survival as compared to splenectomized controls (7.5 ± 0.4 *vs.* 4.6 ± 0.2 days). However, DSG treatment alone was accompanied by weight loss

and diarrhea and thus could not be administered for long periods (12).

A study using Lewis rats transplanted with DA rat heart allografts showed that CTLA41G-gene transfection (1×10^9) pfu of the adenoviral vector AxCAhCTLA4Ig via the tail vein) combined with FTY-720 (5 mg/kg p.o. the day before and day of transplantation) prolonged graft survival. Animals treated with the control vector (AxCALacZ) rejected grafts 6-7 days posttransplant as compared to 9, 24 and 42.5 days observed in animals treated with FTY-720 alone and AxCAhCTLA4Ig alone or in combination, respectively. Cell infiltration was minimal in the groups treated with AxCAhCTLA4Ig alone or in combination with FTY-720. While CD2- and CD25-positive cells were numerous in the control group, very few were observed in the combination treatment group. In addition, apoptotic cells were numerous in the controls and in animals treated with FTY-720 alone as compared to very few observed in the groups receiving the adenoviral vector alone or with FTY-720 (13).

A study using Lewis rats transplanted with DA rat liver allografts showed that tacrolimus (0.3 mg/kg p.o. days 0-14) combined with FTY-720 (0.03 mg/kg p.o. days 0-14) prolonged graft survival. Animals treated with tacrolimus alone (1 mg/kg p.o. days 0-14) or FTY-720 alone (0.1 or 0.5 mg/kg p.o. days 0-14) also showed significantly prolonged median survival to 31, 26 and 34 days, respectively, as compared to 11 days in untreated controls; tacrolimus given at low doses of 0.3 mg/kg prolonged survival only to 17 days. Combination therapy also decreased lymphocyte infiltration in grafts and decreased IL-2, IFN-gamma and granzyme B mRNA expression as compared to controls and animals treated with either agent alone (14).

A study using canine kidney transplant recipients demonstrated that FTY-720 (5 mg/kg/day p.o.) prolonged allograft survival. FTY-720 was administered on days –3, –2 and –1 before surgery (group 1), days 0, 1 and 2 posttransplant (group 2), days 3, 4 and 5 posttransplant (group 3) or as a single dose on the day of transplant (group 4). Median days of graft survival were 21, 19.5, 15 and 24 days for the respective treatment groups as compared to 12 days in the untreated control group. Significant differences were observed between groups 1 and 4 and the controls. The delayed treatment in group 3 had no significant effect on graft survival. Numbers of peripheral blood lymphocytes in groups 1, 2 and 4 were decreased on day 1 posttransplantation and remained low until rejection. A decrease was also observed in group 3 only on days 3 and 5 following FTY-720 administration (15).

The antiarthritic effects of FTY-720 (0.03-0.3 mg/kg p.o. for 21 days starting on the day of inoculation) were shown to be more potent than those of ciclosporin A (1-10 mg/kg p.o.) or tacrolimus (0.3-3 mg/kg p.o.) in a study using rats with adjuvant-induced arthritis. All agents suppressed the incidence of arthritis, hindpaw edema and bone destruction. However, FTY-720 markedly reduced peripheral blood lymphocyte counts, an effect not seen with tacrolimus. FTY-720 (10 mg/kg), unlike ciclosporin (10 mg/kg), was also effective against hindpaw edema and bone destruction when administered only on days 6-10 postinoculation (16).

The efficacy of FTY-720 (0.03, 0.06, 0.1 mg/kg/day) was shown in an experimental autoimmune uveoretinitis model in rats. FTY-720 treatment dose-dependently reduced the incidence and severity of uveoretinitis in S-antigen immunized rats. Treatment also significantly decreased serum antibodies against S-antigen, antigen-specific lymphocyte proliferation and the number of peripheral lymphocytes; the number of neutrophils was not affected. The agent may be effective for treatment of patients with autoimmune uveitis (17).

Monotherapy with CTLA4Ig or FTY-720, or their combination, for inhibiting chronic rejection was assessed in a mouse model of heterotopic trachea transplantation. Although the monotherapeutic regimens tested were not sufficient to inhibit chronic rejection, combination of the two drugs, with different immunosuppressive mechanisms, completely inhibited chronic rejection (18).

An *in vitro* study using a human myelogenous leukemia cell line (HL-60), a human lymphoid T cell line (Jurkat) transfected with human bcl-2 and cell-free systems examined the mechanism of FTY-720-induced apoptosis. Results showed that the agent first induces permeability transition to cause further apoptotic activity. Caspase-3 was required for FTY-720-induced apoptosis but caspase-1 was not involved. The agent directly affected mitochondrial activity before caspase activation, including a reduction in transmembrane mitochondrial potential and induction of cytochrome c release. Bcl-2 overexpression resulted in suppression of all apoptotic activity in both intact cells and cell-free systems. No direct effects of the agent were observed on isolated nuclei or cytosol (19).

An *in vivo* study using BALB/c mice reported that long-term FTY-720 treatment (1 mg/kg/day i.p. for 20 days) prevented migration of mature thymocytes from the thymus to the periphery, resulting in accumulation of CD3+ and CD26Lhi cells in the medulla. Treatment increased the number of mature thymocytes (CD4SP and CD8SP) by 3-fold (20).

An *in vivo* study in mice showed that FTY-720 did not impair the induction of humoral and cellular immunity in response to lymphocytic choriomeningitis virus, vesicular stomatitis virus and *Listeria monocytogenes* or affect the clearance of the infectious agents. *In vitro* studies supported results showing that the agent had no effect on T- or B-cell proliferation, Th1 or Th2 cytokine production or antibody production (21).

The metabolism of FTY-720 was examined in 4 healthy volunteers who were given 1 mg of the [^{14}C]-labeled compound. Excretion of radioactivity was slow with only 30% excreted during the first 3 days postdosing. About 65% of the dose was recovered in urine and feces over the 11-day period. Excretion in feces occurred during the first 96 h postdosing, while linear accumulation over 10 days was observed for urinary excretion. Most of

the radioactivity was excreted in urine as compared to feces (81 *vs.* 19%). The parent compound was not detected in urine or feces, although the major inactive metabolites, M2 (about 20%) and M3 (about 50-60%), were found in urine (22).

An ongoing, multicenter, double-blind, placebo-controlled, time-lagged, ascending dose study with a 28-day follow-up reported the pharmacokinetics and safety of multiple-dose FTY-720 (0.125, 0.25, 0.5, 1 and 2.5 mg once daily for 28 days) administered to stable renal transplant recipients on ciclosporin and steroids. Preliminary results from 39 patients and the first 3 dose levels indicated that the agent was well tolerated. Of the 5 serious adverse events reported, 2 (orthopnea with stiffening of the left ventricular on day 2 and nonproductive cough on day 23) were probably FTY-720-related. Eleven patients developed mild infections unrelated to treatment of which urinary tract infections were the most common. Reductions in peripheral blood lymphocytes were observed at 2 h after the first dose and nadir (45-75% of baseline) was reached at week 3 and was maintained during the 28-day treatment. Recovery of counts was detected 2 days following the last dose and counts were within 10% of baseline by week 3 after the last dose. The agent did not interfere with the pharmacokinetics of ciclosporin (23).

Results from a placebo-controlled phase I study in 16 renal allograft recipients showed that single-dose FTY-472 (0.25-3.5 mg p.o.) upregulated CCR5 receptor expression on T lymphocytes. A significant decrease in peripheral lymphocytes of 40-65% was observed 4-6 h postdosing. Lymphocyte counts returned to normal within 12-24 h with all doses except 3.5 mg, which reduced counts for 96 h; no change in lymphocyte counts was observed in placebo. CCR5 receptor expression on T lymphocytes was significantly increased 10-50% at 4-12 h postdosing and returned to baseline by 12-24 h or 96 h for the 3.5 mg dose. Neither treated nor placebo groups showed significant increases in peripheral blood mononuclear cells (PBMCs) apoptosis rates (2-3%). In contrast, FTY-720 (10 μM) induced 25% apoptosis in PBMCs collected from healthy volunteers (24).

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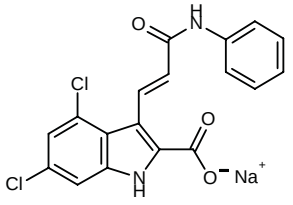
Gavestinel Sodium

Neuronal Injury Inhibitor

EN: 202359



$C_{18}H_{11}Cl_2N_2NaO_3$ **GlaxoSmithKline**

An *in vitro* study has characterized GV-150526A receptor binding in rat cerebral cortical membranes using the tritiated compound. A high affinity binding site (pK_d = 9.08; K_d = 0.8 nM) was identified with a B_{max} of 3.4 pmol/mg protein. Association kinetics of binding were monophasic (k_{on} = 0.047 nM^{-1}/min^{-1}) and addition of excess glycine (k_{off} = 0.027 min^{-1}), GV-150526A (k_{off} = 0.068 min^{-1}) or 5,7-dicholorkynurenic acid (k_{off} = 0.069 min^{-1}) caused dissociation of the labeled compound. Results suggest that glycine agonists and antagonists allosterically bind to discrete sites (1).

Findings of the first phase III clinical trial of gavestinel sodium have been confirmed in a second phase III trial. According to the final analysis of data, there was no difference in outcome compared to placebo in the acute treatment of stroke. As a consequence, GlaxoSmithKline has decided not to continue the development of the drug for this indication. No safety issues were seen in the phase III trials (2).

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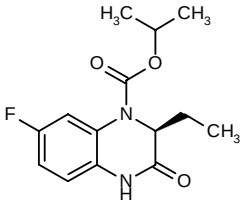
Warach, S. et al. *The effect of GV150526 on ischemic lesion volume: The GAIN Americas and GAIN International MRI substudy.* Neurology 2000, 54(7, Suppl. 3): Abst S18.003.

GW-420867X
GW-867
HBY-1293

Anti-HIV
Reverse Transcriptase Inhibitor

EN: 272215



$C_{14}H_{17}FN_2O_3$ **GlaxoSmithKline; Aventis Pharma; Bayer**

The urinary metabolites of GW-420867X were identified in rabbits, mice and humans following oral administration. The parent compound was biotransformed in all species resulting in hydroxylated metabolites and glucuronide conjugates on the aromatic ring and ethyl and isopropyl side chains. A minor cysteine adduct was also detected in rabbit urine only (1).

No viral resistance was reported to develop during short-term clinical use of GW-420867X. Sixty subjects were enrolled in a phase II placebo-controlled, dose-ranging study designed to evaluate the antiviral activity of GW-420867X monotherapy (50, 100 and 200 mg o.d. x 7) followed by combination therapy with zidovudine (300 mg) and lamivudine (150 mg), administered twice daily for 21 days. Analysis of plasma samples, taken on days 1-15, 21 and 28 using the Amplicor assay, confirmed that this treatment regimen was not associated with the development of NNRTI resistance (2).

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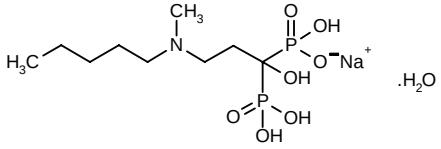
Original monograph - Drugs Fut 2000, 25: 24.

Ibandronic Acid Monosodium Salt Monohydrate
Bondronat®
Bonviva®

Bisphosphonate
Bone Resorption Inhibitor

EN: 187240



$C_9H_{22}NNaO_7P_2.H_2O$ **Roche**

Ibandronate sodium has been claimed to be useful for the improvement of osseointegration of cement-free anchored prostheses, particularly hip-joint endoprostheses, by short-term application within 2-4 weeks after the operation. The secondary stability of the implant, usually attained a few months after the osseointegration, is obtained in 5 weeks or less after the operation, ensuring long-term stability of the prosthesis (1).

1. Bauss, F., Kurth, A.A. *(Roche Diagnostics GmbH). Use of ibandronate for promoting osseointegration of endoprostheses.* WO 0033849.

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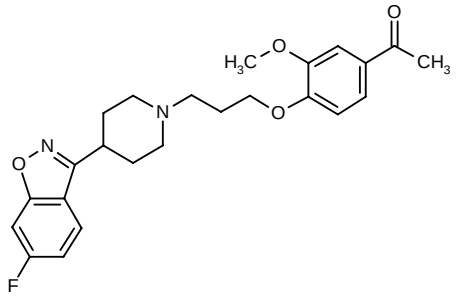
Iloperidone
ILO-522
HP-873
Zomaril®

Antipsychotic
Dopamine D_2 Antagonist
5-HT_{2A} Antagonist

EN: 165804



$C_{24}H_{27}FN_2O_4$ **Aventis Pharma; Titan; Novartis**

An *in vitro* study compared the potency of iloperidone in blocking recombinant human α_{2C}-adrenoceptors or dopamine D_{2A} receptors expressed in cells, with the activities of clozapine, risperidone, olanzapine, haloperidol, melprone, setoperone, quetiapine, yohimbine and 2 metabolites of iloperidone (P88-8991 and P95-12113). Yohimbine (pK_B = 8.50 ± 0.02) and iloperidone (pK_B = 7.83 ± 0.06) were the most potent agents in blocking α_{2C}-adrenoceptors, while haloperidol (pK_B = 8.73 ± 0.06) and olanzapine (pK_B = 8.36 ± 0.06) were the most potent in blocking the dopamine receptors. The highest α_{2C}/D_{2A} activity was observed with clozapine, iloperidone and P95-12113, with respective α_{2C}:D_{2A} values of 11, 2 and 17 (1).

A radioligand binding study reported the affinity of iloperidone and its metabolites (P88-8991 and P95-12113) for several adrenoceptor, dopamine and serotonin receptor types. The parent compound showed higher affinity for most receptor types as compared to its metabolites. P88-8991 showed high affinity at D_2, α_1, α_{2C} and 5-HT_{2A} receptors which may be responsible for the efficacy and good tolerability profile obtained for iloperidone. The affinity for α_{2A}, α_{2B} and α_{2C} receptors did not decrease with metabolism, indicating that the metabolites may be more effective than iloperidone at these receptor types (2).

Positive safety and efficacy data have been reported from a phase III trial of iloperidone for the treatment of schizophrenia. The worldwide trial involved more than 600 patients in the U.S., Europe, Canada, Australia and South Africa. Results demonstrated that both dose levels of iloperidone used in the study achieved a highly statistically significant reduction in the symptoms of schizophrenia as assessed by the Brief Psychiatric Rating Scale. These finding were also supported by highly statistically significant improvements in the total score for the Positive and Negative Syndrome Scale with both dose levels. In addition, the study confirmed that iloperidone possesses an excellent tolerability profile, with no extrapyramidal symptoms, little weight gain and no effect on serum prolactin (3).

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2. Subramanian, N., Kalkman, H.O. *Receptor affinity of two human metabolites of iloperidone, a new antipsychotic agent.* Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.01.163.

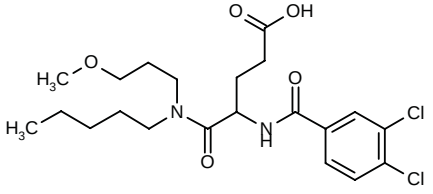
3. *Promising antischizophrenia agent shows safety and efficacy in phase III.* DailyDrugNews.com (Daily Essentials) Sept 26, 2000.

Original monograph - Drugs Fut 2000, 25: 29.

Loxiglumide
Loxizin®

Treatment of Pancreatic Disorders
CCK_A Antagonist

EN: 135822



$C_{21}H_{30}Cl_2N_2O_5$ **Rotta; Mitsubishi-Tokyo Pharm.; Kaken**

Mitsubishi-Tokyo Pharmaceuticals has filed loxiglumide (Loxizin®) for approval for the treatment of acute pancreatitis; the compound is also in phase III clinical trials for the treatment of chronic pancreatitis. Loxiglumide was licensed from Rotta by Mitsubishi-Tokyo Pharmaceuticals and is being codeveloped with Kaken (1).

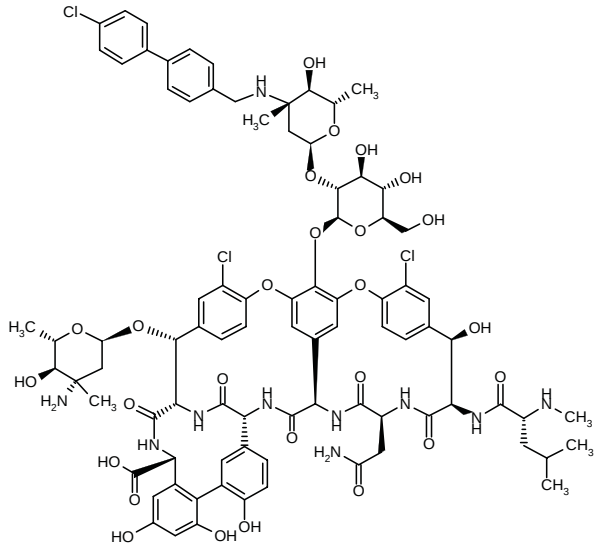
1. Mitsubishi-Tokyo Pharmaceuticals Product Pipeline, March 31, 2000.

Original monograph - Drugs Fut 1990, 15: 32.

LY-333328
Oritavancin

Glycopeptide Antibiotic

EN: 226450



$C_{86}H_{97}Cl_3N_{10}O_{26}$ **Lilly**

The *in vitro* activity of LY-333328 was examined and compared to other antimicrobials against 1479 nosocomial Gram-positive isolates. The MIC_{90} values for LY-333328 against *Enterococcus faecalis* (351 strains), *Enterococcus faecium* (100), *Staphylococcus aureus* (593), coagulase-negative *Staphylococcus* spp. (325) and *Streptococcus pneumoniae* (110) were 1, 1, 2, 2 and 0.015 μg/ml, respectively. LY-333328 also showed activity against vancomycin-resistant enterococci, oxacillin-resistant staphylococci and penicillin-resistant pneumococci (1).

A sensitive bioassay technique for determining LY-333328 concentrations has been described. The assay used *Micrococcus luteus* (ATCC #9341) and *Bacillus subtilus* (ATCC #6633) as test organisms plated in agar wells in antibiotic media #11 (pH 9-10) and incubated with the agent (1-150 μg/ml) for 24 h at 37 °C. The percent coefficient of variance for high, medium and low concentrations of the agent was < 5% and assay performance was linear for both types of organisms (r^2 = > 0.95). The presence of protein did not alter assay performance (2).

The activity of LY-333328 alone and in combination with gentamicin was examined *in vitro* and *in vivo* in a rabbit experimental model of vancomycin-susceptible (JH2-2) and -resistant (BM4316, BM4275) *E. faecalis*-induced endocarditis. The MICs for LY-333328 and gentamicin were 2 and 16 μg/ml, respectively, for all strains tested *in vitro*. LY-333328 was bactericidal at 24 h at concentrations of 2 and 30 μg/ml against the susceptible and resistant strains, respectively. Combination treatment was synergistic with bactericidal activity at 24 h observed with concentrations of 2 and 8 μg/ml, for susceptible and resistant strains, respectively. Peak and trough serum levels of the agent following i.v. administration of LY-333328 alone *in vivo* were 83.3 ± 1.3 and 3.8 ± 0.2 μg/ml, respectively; LY-333328 alone was inactive against infections due to BM4316, BM4275 and other mutants resistant to LY-333328. However, combination treatment was active against all strains and prevented emergence of resistant mutants (3).

The activity of single dose LY-333328 (1, 2.5, 10 or 40 mg/kg over 30 min given 12 h after infection) was examined *in vivo* in rabbits infected intracisternally with penicillin-sensitive *S. pneumoniae* meningitis; control animals were given ceftriaxone (20 mg/kg bolus followed by continuous infusion of 10 mg/kg/h). LY-333328 doses of 2.5 and 10 mg/kg reduced cerebral spinal fluid (CSF) bacterial titers as rapidly as ceftriaxone (by –0.26 ± 0.22 and –0.29 ± 0.21, respectively, *vs.* –0.33 ± 0.15 ΔlogCFU/ml/h). LY-333328 at a dose of 40 mg/kg reduced CSF bacterial titers by –0.52 ± 0.02 ΔlogCFU/ml/h; the 1 mg/kg dose was only bacteriostatic. *In vitro*, LY-333328 at a dose of 10 mg/l killed *S. pneumoniae* cultures within 1 h as compared to 12 h with 10 mg/l ceftriaxone. The half-maximal dose and maximum bactericidal rate for LY-333328 were 4.6 mg/kg and –0.68 ΔlogCFU/ml/h, respectively. Neuronal damage was not reduced with LY-333328 treatment (4).

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Original monograph - Drugs Fut 1998, 23: 17.

Additional Reference

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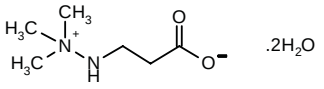
Mildronate
MET-88

Antianginal
Cardioprotectant

EN: 145694



$C_6H_{14}N_2O_2.2H_2O$ **Latvian Inst. Org. Synth.; Taiho**

An *in vitro* study using isolated rat hearts with ischemia/reperfusion (30 min/20 min)-induced dysfunction showed the cardioprotective effects of MET-88 (50 and 100 mg/kg once daily p.o. for 10 days). MET-88 had no effect on cardiac function before ischemia as compared to nifedipine (30 mg/kg p.o. 30 min before experiments), which significantly increased coronary flow. Both agents promoted recovery during reperfusion of ischemia-decreased cardiac function (*i.e.*, heart rate, left ventricular systolic pressure, coronary flow) and decreased ventricular fibrillation. In addition, MET-88 decreased ischemia-induced accumulation of long-chain acylcarnitine, possibly indicating a mechanism of action for the cardioprotective effects of the agent (1).

A study in rats examined the disposition, metabolism and excretion of MET-88 (2, 20 and 60 mg/kg p.o.). Nonlinear pharmacokinetics were obtained. Increasing MET-88 doses were found to cause a shift in the major excretion route from exhaled CO_2 to urinary excretion. The major metabolites detected in plasma were glucose, succinic acid and 3-hydroxypropionic acid. Examination *in vitro* showed that the agent was converted to 3-hydroxypropionic acid by γ-butyrobetaine hydroxylase and then biosynthesized to glucose and metabolized to CO_2 through the glycolytic and tricarboxylic pathways. In addition, CO_2 gas excretion of the agent as assayed using an isolated liver perfusion model was decreased following addition of iodoacetic acid, DL-flurocitric acid or γ-butyrobetaine (2).

The efficacy of MET-88 (100 mg/kg/day p.o. for 20 days starting on day 2 after ligation) was shown in a study using rats with congestive heart failure induced by left coronary artery ligation. The median 50% survival of treated rats was 103 days as compared to 79 days in controls. MET-88 prevented expansion of the left ventricular cavity in a manner similar to captopril (20 mg/kg). The agent also reduced the increases seen in atrial pressure, enhanced cardiac function against increased load and improved the myocardial energy state as compared to untreated animals (3).

An *in vivo* study in rats showed that long-term treatment with MET-88 (50, 100, 200 or 400 mg/kg/day p.o. for 10, 30 or 60 days) dose-dependently reduced liver and heart carnitine content without affecting lipid content of the heart. Only the high 400 mg/kg dose of MET-88 increased liver lipid content. Reductions in carnitine seen with each dose reached peaks after 30 days of treatment. Histological examination showed no pathological findings, and no changes in liver glutamic-oxaloacetic and glutamic-pyruvic transaminases were seen (4).

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2. Yoshisue, K., Yamamoto, Y., Yoshida, K., Saeki, M., Minami, Y., Esumi, Y., Kawaguchi, Y. *Pharmacokinetics and biological fate of 3-(2,2,2-trimethylhydrazinium)propionate dihydrate (MET-88), a novel cardioprotective agent, in rats.* Drug Metab Dispos 2000, 28(6): 687.

3. Hayashi, Y., Kirimoto, T., Asaka, N., Nakano, M., Tajima, K., Miyake, H., Matsuura, N. *Beneficial effects of MET-88, a γ-butyrobetaine hydroxylase inhibitor in rats with heart failure following myocardial infarction.* Eur J Pharmacol 2000, 395(3): 217.

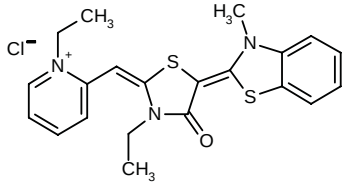
4. Hayashi, Y., Muranaka, Y., Kurimoto, T., Asaka, N., Miyake, H., Matsuura, N. *Effects of MET-88, a γ-butyrobetaine hydroxylase inhibitor, on tissue carnitine and lipid levels in rat.* Biol Pharm Bull 2000, 23(6): 770.

Original monograph - Drugs Fut 1989, 14: 29.

MKT-077

Oncolytic

EN: 237755



$C_{21}H_{22}ClN_3OS_2$ **Novartis; Fuji Photo Film**

An *in vitro* study using COS 7, NIH 3T3/Ras, normal human lung fibroblasts (MRC-5), cervical carcinoma (HeLa), breast carcinoma (MCF-7), bladder carcinoma (EJ) and fibrosarcoma cells (HT1080) examined the selective cytotoxic action of MK-077. Results showed that the agent binds to mortalin (mot-2) and interacts with the tumor suppressor protein p53. Treatment of cancer cells with MKT-077 resulted in release of wild-type p53 that was sequestered as p53-mot-2 complexes in the cytoplasma and restoration of transcriptional activity; this effect was not observed in normal cells. Results indicate that the agent may be particularly effective against cancers with wild-type p53 (1).

A phase I study in 13 patients with advanced solid tumors examined the safety and pharmacokinetics of MKT-077 (42-126 mg/m^2/week 30 i.v. infusion for 4 weeks every 6 weeks). Grade 3 renal magnesium wasting was the dose-limiting toxicity in 2 patients given 84 and 126 mg/m^2 doses, respectively. Grade 2 hypomagnesemia which improved with magnesium infusion was seen in 3 patients given the recommended dose of 126 mg/m^2/week. A large volume of distribution (685 ± 430 l/m^2) and a prolonged half-life (37 ± 17 h) was observed for the

agent. Peak plasma concentrations were 1.2 ± 0.31-6.3 ± 5.3 μg/ml which were higher than *in vitro* IC_{50} values obtained for human colon, breast, pancreas, bladder and melanoma tumor cell lines (2).

1. Wadhwa, R., Sugihara, T., Yoshida, A., Nomura, H., Reddel, R.R., Simpson, R., Maruta, H., Kaul, S.C. *Selective toxicity of MKT-077 to cancer cells is mediated by its binding to the hsp70 family protein mot-2 and reactivation of p53 function.* Cancer Res 2000, 60(24): 6818.

2. Britten, C.D., Rowinsky, E.K., Baker, S.D. et al. *A phase I and pharmacokinetic study of the mitochondrial-specific rhodacyanine dye analog MKT 077.* Clin Cancer Res 2000, 6(1): 42.

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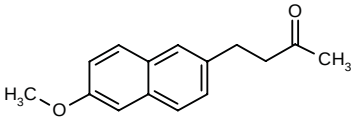

$C_{15}H_{16}O_2$ **GlaxoSmithKline**

A short, simple and economical process for large-scale preparation of nabumetone has been reported: Condensation of commercially available 2-acetyl-6-methoxynaphthalene (2-acetylnaroline) (I) with ethyl acetate (II) by means of potassium *sec*-butoxide (*sec*-BuOK) in DMSO gives the ketoenol (III), which is reduced with H_2 over Pd/C in ethyl acetate with a catalytic amount of sulfuric acid (1). Scheme 4.

1. Prabhakar, C., Reddy, G.B., Reddy, C.M., Nageshwar, D., Babu, J.M., Devi, A.S., Vyas, K., Sarma, M.R., Reddy, G.O. *Process research and structural studies on nabumetone.* Org Process Res Dev 1999, 3(2): 121.

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Nefiracetam *Cognition Enhancer*
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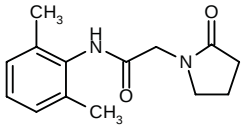

$C_{14}H_{18}N_2O_2$ **Daiichi Pharm.; Beijing General**

A study in epileptic mutant EL mice showed that nefiracetam (10 mg/kg o.d. p.o. for 5 days) provided protection against DNA fragmentation in the hippocampus but not in the parietal cortex; untreated animals and animals treated for 1 day only showed DNA fragmentation in both brain regions. It was suggested that hippocampal DNA protection and GABA enhancement may be responsible for the antiepileptic effects of the agent (1).

1. Murashima, Y.L., Watabe, S., Shiotani, T., Yoshii, M. *Evidence for DNA protection by the nootropic nefiracetam observed in the hippocampus of epileptic mutant EL mice.* Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.06.12.

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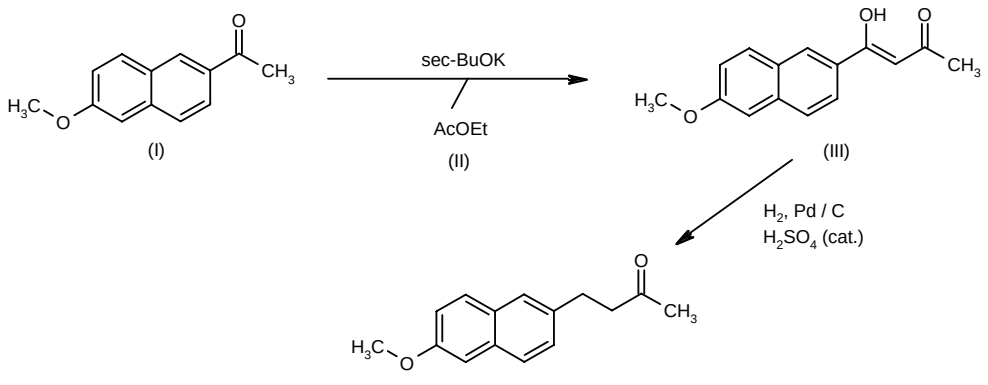
Scheme 4: Synthesis of Nabumetone



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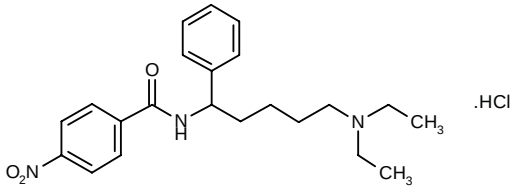
Shiotani, T. et al. *Anticonvulsant actions of nefiracetam on epileptic EL mice and their relation to peripheral-type benzodiazepine receptors.* Brain Res 2000, 859(2): 255.

Watanabe, S. et al. *Nefiracetam induces an LTP-like facilitation of hippocampal neurotransmission as a result of modulation of nicotinic ACh receptors.* Jpn J Pharmacol 2000, 82(Suppl. 1): Abst S18-5.

Nibentan

Antiarrhythmic
Potassium Channel Blocker

EN: 226458



$C_{22}H_{29}N_3O_3.HCl$ **Russian Acad. Med. Sci.; Center Chem. Drugs (RU)**

Results from *in vitro* and *in vivo* studies demonstrated that nibentan suppresses spontaneous activity of sinus node cells via an increase in action potential duration. *In vitro* results from isolated rabbit sino-atrial node showed that nibentan (0.023, 0.23 and 2.3 μM) significantly and dose-dependently increased action potential duration by 12 ± 1, 32 ± 3 and 59 ± 9%, respectively, which resulted in significant increases in the duration of sinus length (6 ± 2, 23 ± 4 and 47 ± 4%, respectively). Nibentan at doses of 0.23 and 2.3 μM also decreased the slope of phase 4 diastolic depolarization by 29 ± 4 and 45 ± 6%, respectively. Nibentan-induced prolongation of the action potential was less marked in the presence of carbachol (0.03 μM) (1).

The antiarrhythmic effects of nibentan (0.063, 0.125 and 0.250 mg/kg i.v.) were examined in anesthetized open-chest dogs during vagally induced atrial fibrillation. The 3 doses prevented atrial fibrillation in 78, 88 and 100% of the animals, respectively, and protected 11, 63 and 90%, respectively, of the animals against fibrillation reinduction. The atrial effective refractory period was significantly and rate-independently increased with all doses (55 ± 9, 82 ± 12 and 90 ± 6%, respectively). The antiarrhythmic efficacy of the agent was due to a decrease in simultaneous reentrant wavelets and an increase in wavelength for reentry (47 ± 7, 68 ± 12 and 72 ± 4%, respectively). Suppression of the delayed rectifier (I_K) and muscarinic I_K.ACh currents may be responsible for these effects (2).

1. Fedorov, V.V., Sharifov, O.F., Rosenshtraukh, L.V. *Chronotropic effects of a new class III drug nibentan in mammalian atria.* Eur Heart J 2000, 21(Suppl.): Abst P1774.

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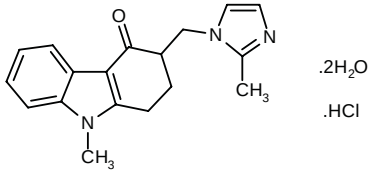

$C_{18}H_{19}N_3O.HCl.2H_2O$ **GlaxoSmithKline; Sankyo**

A clinical trial which found ondansetron to be an effective treatment for early-onset alcoholism lends support to the hypothesis that serotonergic neurotransmission plays a role in the pathophysiology of alcohol dependence and to rational efforts to discover medications to treat the condition. In the double-blind trial, 271 patients diagnosed with alcoholism underwent a 1-week placebo lead-in phase and were then randomized to ondansetron 1, 4 or 16 mg/kg twice daily or placebo. After 11 weeks, early-onset alcoholism patients in the ondansetron group reported fewer drinks per day and fewer drinks per drinking day than those on placebo. Those administered the 4 mg/kg ondansetron dose had a significant increase in the percentage of abstinent days and a decrease in the intensity of alcohol intake as compared with placebo. Self-reported alcohol consumption results were validated by measurements of carbohydrate-deficient transferrin. Drinking behavior in patients with late-onset alcoholism was similar in the ondansetron and placebo groups (1).

1. Johnson, B.A. et al. *Ondansetron for reduction of drinking among biologically predisposed alcoholic patients.* JAMA - J Am Med Assoc 2000, 284(8): 963.

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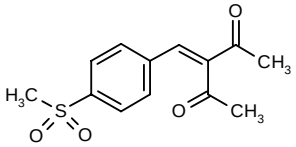
Orazipone

Immunomodulator

EN: 251434



$C_{13}H_{14}O_4S$ **Orion Corp.**

Orion's orazipone is a new locally acting antiinflammatory agent that modulates thiol groups and inhibits inflammatory cell activation and decreases proinflammatory cytokine production. In anesthetized guinea pigs, orazipone (0.1-1 mg) given by intratracheal infusion 1 h before PAF provided dose-dependent inhibition of eosinophilia at 24 h in lung lavage fluid. In a model of allergen-induced lung inflammation in actively sensitized Brown Norway rats, pretreatment with a single dose of 3 mg/kg or multiple doses of 0.3 mg/kg/day, also given intratracheally, significantly inhibited antigen-induced eosinophil accumulation at 72 h in lung lavage fluid. These findings indicate the potential of this novel agent as a treatment for asthma (1).

1. Ruotsalainen, M., Koponen, A., Nissinen, E., Hyttilä, M. *Efficacy of a new anti-inflammatory compound, orazipone, in the models of airway eosinophilia in rat and guinea pig.* Eur Respir J 2000, 16(Suppl. 31): Abst P3958.

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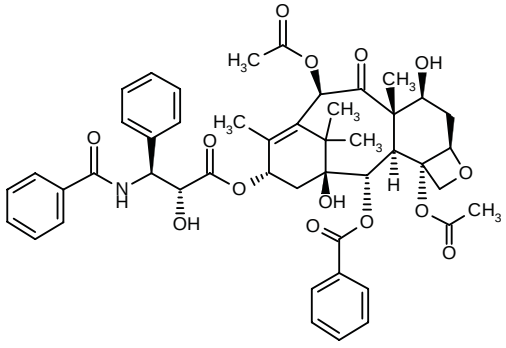


$C_{47}H_{51}NO_{14}$ **Bristol-Myers Squibb; Alcon; Angiotech; Ivax**

A new enantioselective total synthesis of paclitaxel by two related ways has been reported:

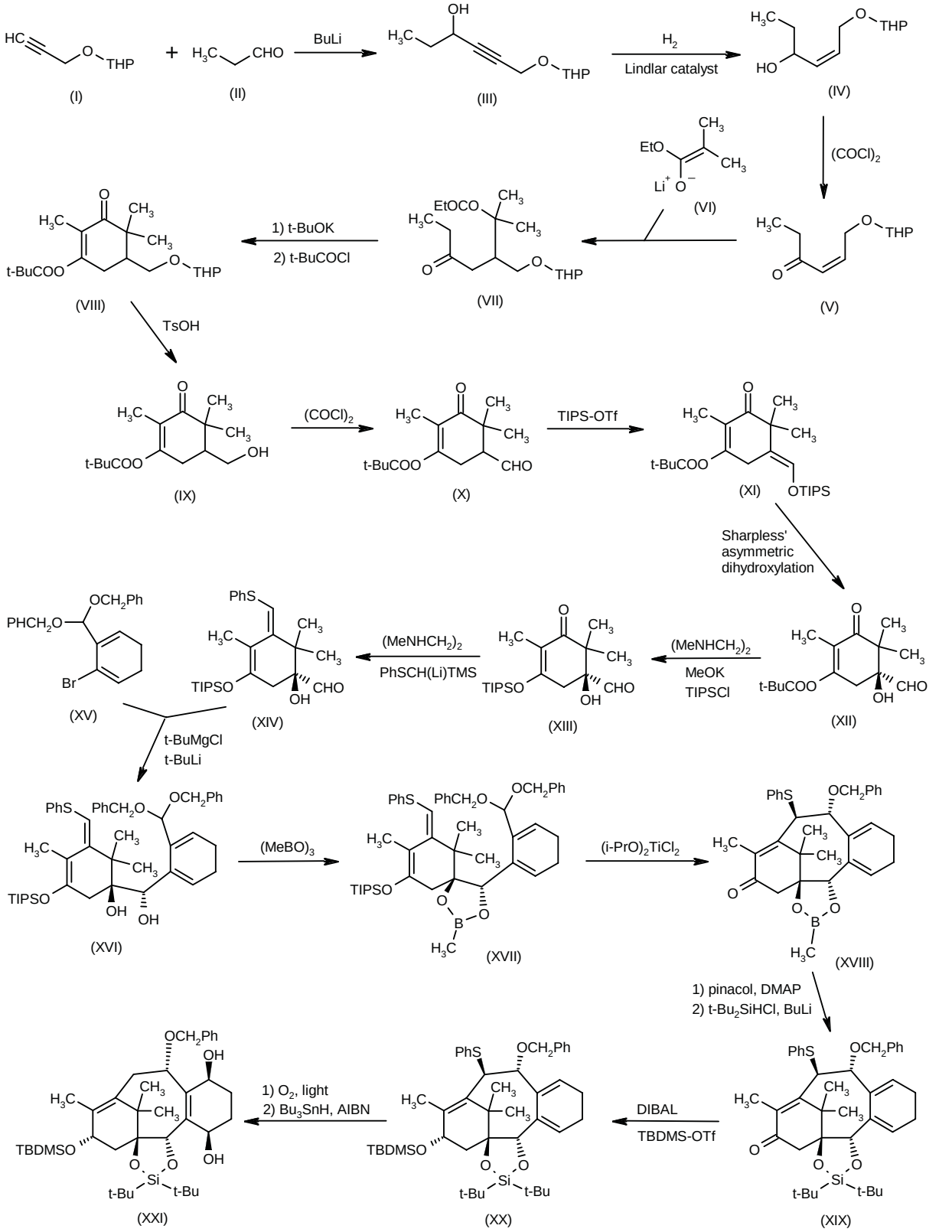
1) The condensation of the acetylenic tetrahydropyranyl ether (I) with propionaldehyde (II) by means of BuLi in THF gives 6-(tetrahydropyranyloxy)-4-hexyn-3-ol (III), which by reduction with H_2 over Lindlar catalyst in hexane yields compound (IV). The Swern oxidation of (IV) with oxalyl chloride in dichloromethane affords enone (V), which is condensed with the lithium enolate (VI) in THF to afford the addition keto ester (VII). Cyclization of (VII) by means of potassium *tert*-butoxide, followed by acylation with pivaloyl chloride gives the cyclohexenone (VIII). Elimination of the tetrahydropyranyl protecting group of (VIII) with TsOH in methanol yields the carbinol (IX), which is oxidized with oxalyl chloride and TEA in dichloromethane to afford the carbaldehyde (X). The enolization of the aldehyde group of (X) with TIPSOTf, DBU and DMAP in dichloromethane provides exclusively the (*E*)-enol ether (XI), which is submitted to a Sharpless' asymetric dihydroxylation using DHQ-PHN as a chiral ligand to give the chiral α-hydroxy aldehyde (XII). Elimination of the pivaloyl group of (XII) with *N*,*N*'-dimethylethylenediamine and potassium methoxide in refluxing benzene, followed by reprotection with TIPSCl in THF provides aldehyde (XIII). The reaction of the ketonic group of (XIII) with PhSCH(Li)TMS in THF affords the dienol silyl ether (XIV), which by condensation with 2-bromo-4,5-dihydrobenzaldehyde dibenzyl acetal (XV) by means of *t*-BuLi in the presence of *t*-BuMgCl furnishes the expected addition compound (XVI) as a single isomer. Protection of the vicinal diol of (XVI) with trimethyl borate and pyridine in benzene gives the boronic ester (XVII), which is cyclized by means of $(i\text{-PrO})_2TiCl_2$ in dichloromethane to yield the polycyclic compound (XVIII). The hydrolysis of the boronic ester of (XVIII) with pinacol and DMAP in benzene, followed by silylation with

t-Bu_2SiHCl and BuLi in THF affords the cyclic silyl ether (XIX). Reduction of the ketonic group of (XIX) with DIBAL in dichloromethane, followed by silylation with TBDMS-OTf affords the silyl ether (XX), which is dihydroxylated by oxidation with O_2 and light using TPP as catalyst and desulfurized by treatment with Bu_3SnH and AIBN in refluxing benzene to provide diol (XXI). Hydrogenation of (XXI) with H_2 over Pd/C in ethanol gives the triol (XXII), which is treated with benzaldehyde dimethyl acetal and camphorsulfonic acid (CSA) in dichloromethane to yield the cyclic ketal (XXIII). The cyclopropanation of (XXIII) with chloro(iodo)methane and Et_2Zn in toluene affords compound (XXIV), which is oxidized with Dess-Martin periodinane (DMPI) in dichloromethane to provide the ketonic compound (XXV). The deproctection of (XXV) with H_2 over $Pd(OH)_2$ in ethanol in order to remove the benzylidene ketal group, followed by reaction with triphosgene in order to form a cyclic carbonate, and finally selective desilylation of the cyclic silyl ether with TBAF furnishes diol (XXVI). The protection of the diol moiety of (XXVI) with benzaldehyde dimethylacetal, followed by cleavage of the cyclic carbonate with K_2CO_3 in methanol provides the diol (XXVII), which is submitted to cyclopropane ring-opening with SmI_2 and TBAF in THF to give the enol (XXVIII). Enol-keto isomerization of (XXVIII) by treatment with NaOMe in methanol yields ketone (XXIX), which is treated with phenylboronic acid and pyridine to afford the cyclic phenylboronic ester (XXX). Silylation of the remaining hydroxy group of (XXX) with TBDMS-OTf gives the silyl ether (XXXI), which is then treated with H_2O_2 and $NaHCO_3$ in water/ethyl acetate to remove the boron-protecting group and yield diol (XXXII). The selective oxidation of diol (XXXII) with Dess-Martin periodinane in dichloromethane, followed by protection of the remaining OH group as a 2-methoxy-2-propyl (MOP) ether by reaction with 2-methoxypropene (XXXIII) and PPTS in THF gives diketone (XXXIV), which is enolized with $PhNTf_2$ and KHMDS in THF yielding the enol triflate (XXXV). The introduction of a methylene group in (XXXV) by reaction with the Grignard reagent $TMSCH_2MgCl$ and $Pd(PPh_3)_3$ as catalyst in ethyl ether, affords the trimethylsilylmethyl compound (XXXVI), which is chlorinated with *N*-chlorosuccinimide (NCS) in methanol and treated with 2-methoxypropene (XXXIII) and PPTS to provide the chloro derivative (XXXVII). Regioselective hydroxylation of (XXXVII) is performed by enolization with LDA, followed by oxidation with MoO_5/pyridine in HMPA and final acylation with Ac_2O to give the α-acetoxy compound (XXXVIII). This acetate (XXXVIII) is isomerized to the corresponding β-isomer (XXXIX) by heating with a base such as DBN. The dihydroxylation of the *exo*-methylene moiety of (XXXIX) with OsO_4 and pyridine in ethyl ether yields the corresponding dihydroxy compound (XL), which is cyclized with DBU in refluxing toluene in order to form the oxetane ring of (XLI). The removal of the MOP group of (XLI) with PPTS, followed by reprotection with TES-Cl in DMF gives the triethylsilyl ether (XLII). Cleavage of the cyclic benzylidene ketal of (XLII) with H_2 over $Pd(OH)_2$, followed by reaction with triphosgene and pyridine yields the cyclic carbonate (XLIII), which is acetylated at the tertiary OH group with acetic anhydride and DMAP to yield the acetoxy compound (XLIV). Reaction of (XLIV) with phenyl lithium in THF gives the benzoate (XLV), which is selectively desilylated with HF/pyridine and reprotected with 2,2,2-trichloroethyl chloroformate (Troc-Cl) to yield the intermediate (XLVI). Compound (XLVI) is again desilylated with tris(diethylamino)sulfoxonium difluorotrimethylsiliconate (TASF) to afford the secondary alcohol (XLVII). Condensation of (XLVII) with the chiral azetidinone (XLVIII) by means of LiHMDS in THF provides the protected paclitaxel precursor (XLIX), which is finally deprotected with Zn in AcOH/water (1). Scheme 5.

2) Alternatively, condensation of the dienol silyl ether intermediate (XIV) with 2-bromobenzaldehyde dibenzyl acetal (L) by means of *t*-BuLi in the presence of *t*-BuMgCl in THF furnishes the expected addition compound (LI). Protection of the vicinal diol moiety of (LI) with trimethyl borate and pyridine in benzene gives the boronic ester (LII), which is cyclized by means of $SnCl_4$ in dichloromethane to yield the tricarbocyclic compound (LIII). Hydrolysis of the boronic ester of (LIII) with pinacol and DMAP in benzene affords the vicinal diol (LIV), which is reduced at the keto group with DIBAL in dichloromethane and silylated at the resulting alcohol with TBDMS-OTf in the same solvent to give the fully protected intermediate (LV). Elimination of the phenylthio group of (LV) by means of Bu_3SnH and AIBN in refluxing benzene yields the tricyclic compound (LVI), which is debenzylated with H_2 over Pd/C and treated with Swern oxidant to provide the ketone (LVII). Selective hydrogenation of (LVII) with potassium in liquid ammonia in the presence of 2,2,4-trimethyl-3-isopropyl-3-pentanol furnishes the dihydro intermediate (LVIII), which is selectively desilylated with TBAF in THF to yield the vicinal diol (LIX). Silylation of diol (LIX) with *t*-Bu_2SiHCl and BuLi in THF affords the cyclic silyl ether (LX), which is reduced at the carbonyl group with $NaBH_4$ and $CeCl_3$ in methanol to give the secondary alcohol (LXI). Finally, this compound is dihydroxylated by oxidation with O_2, light and rose bengal as photoinductor to furnish the triol (XXII), already reported (1). Scheme 6.

A new synthesis of (3*R*,4*S*)-1-benzyl-4-phenyl-3-(triethylsilyloxy)azetidin-2-one, a precursor of the side chain of paclitaxel, has been described: The reaction of ethyl L-tartrate (I) with benzaldehyde and TsOH, followed by reduction with $LiAlH_4$ and $AlCl_3$ gives the monobenzylated tretraol (II), which is submitted to an oxidative cleavage of the α-diol bond with $NaIO_4$ to yield the aldehyde (III). Reaction of (III) with benzylamine affords the imine (IV), which is submitted to a Grignard addition of phenylmagnesium bromide in ether providing a 1:9 mixture of aminoalcohols (VI) and (VII) separated by chromatography. Oxidation of the desired major isomer (VII) with CrO_3/H_2SO_4 gives the corresponding acid (VIII), which is then esterified with TMS-Cl in refluxing methanol to the methyl ester (IX). Deprotection of compound (IX) by hydrogenolysis with reluxing HCO_2H over Pd/C yields

Scheme 5: Synthesis of Paclitaxel



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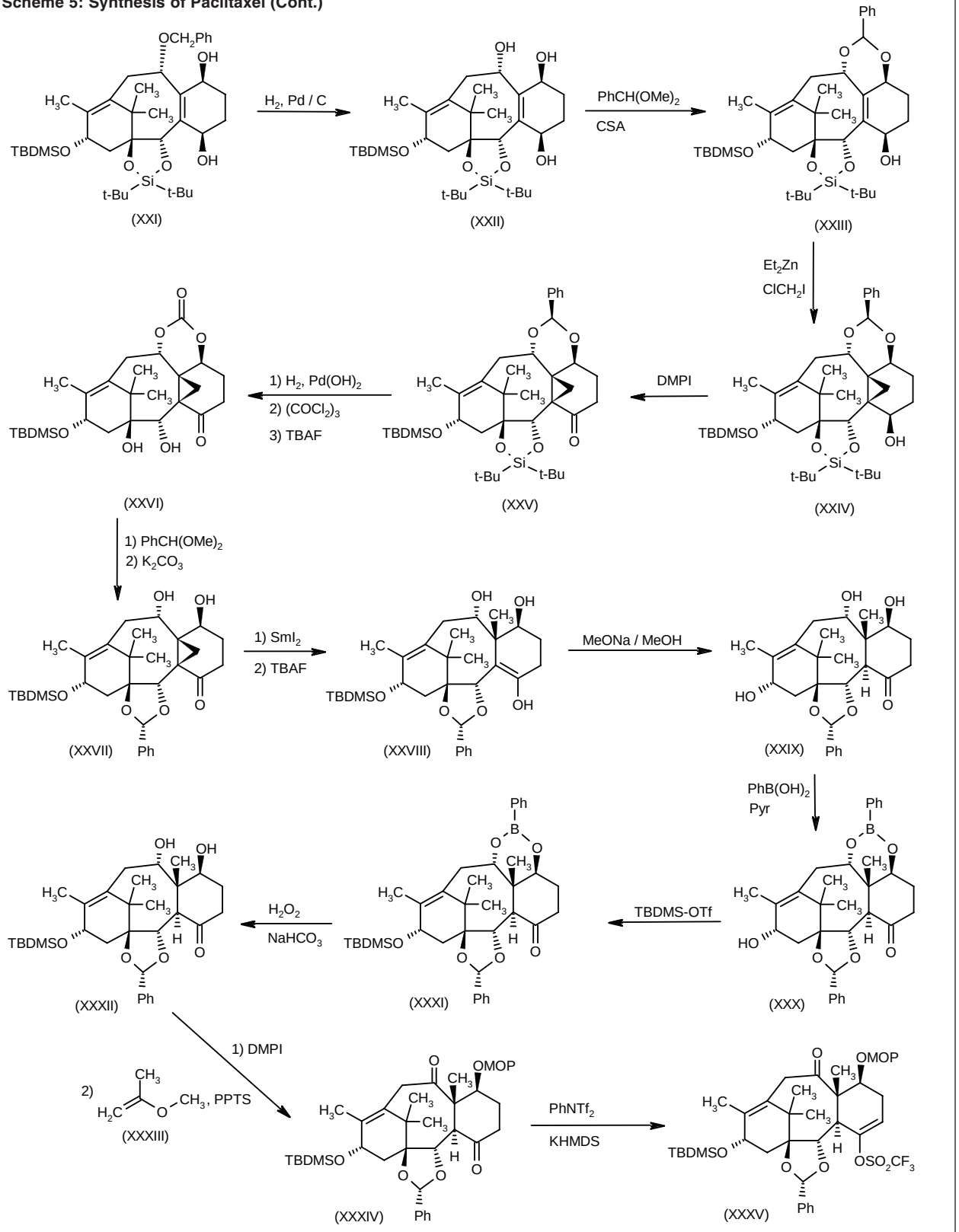
Scheme 5: Synthesis of Paclitaxel (Cont.)



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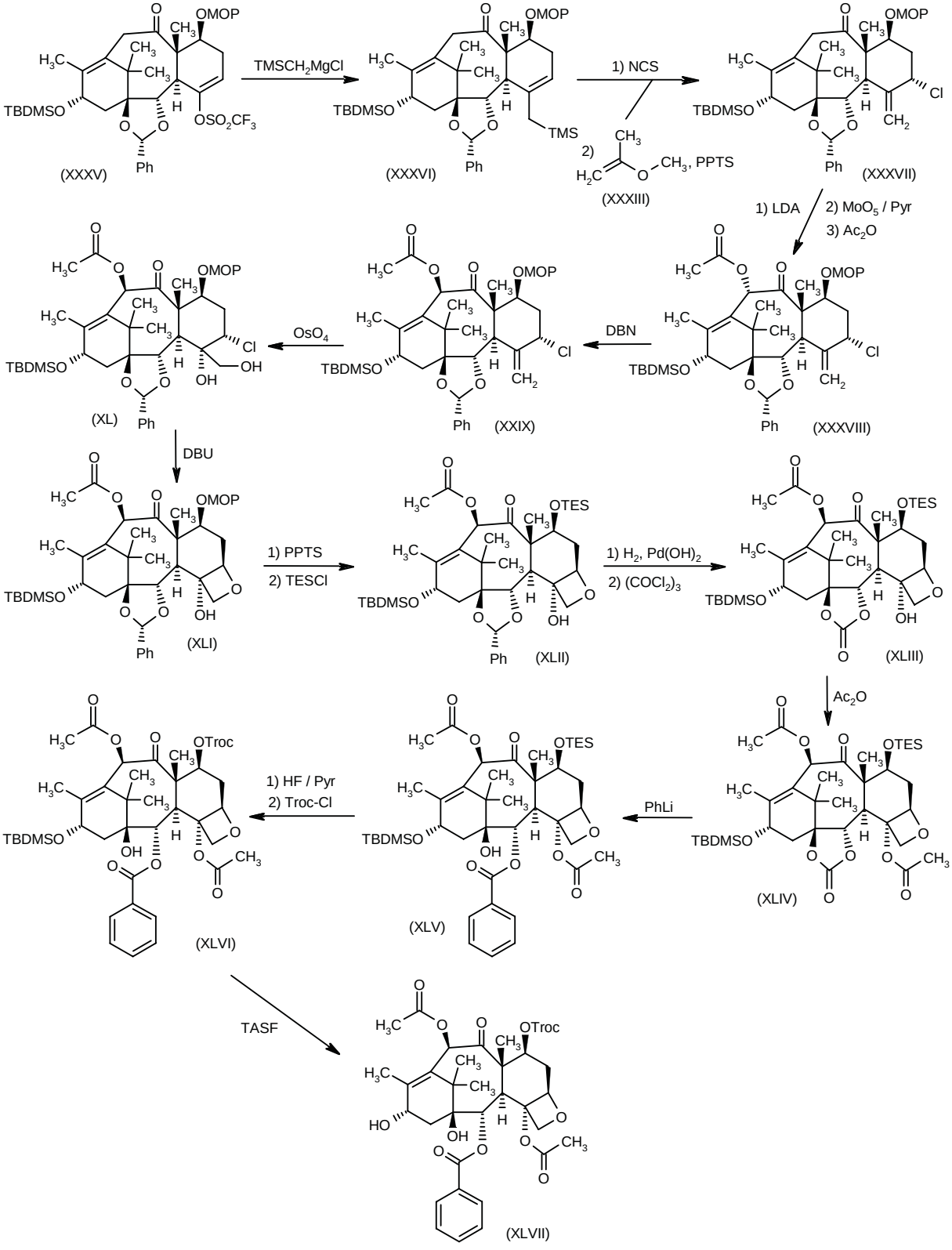
Scheme 5: Synthesis of Paclitaxel (Cont.)



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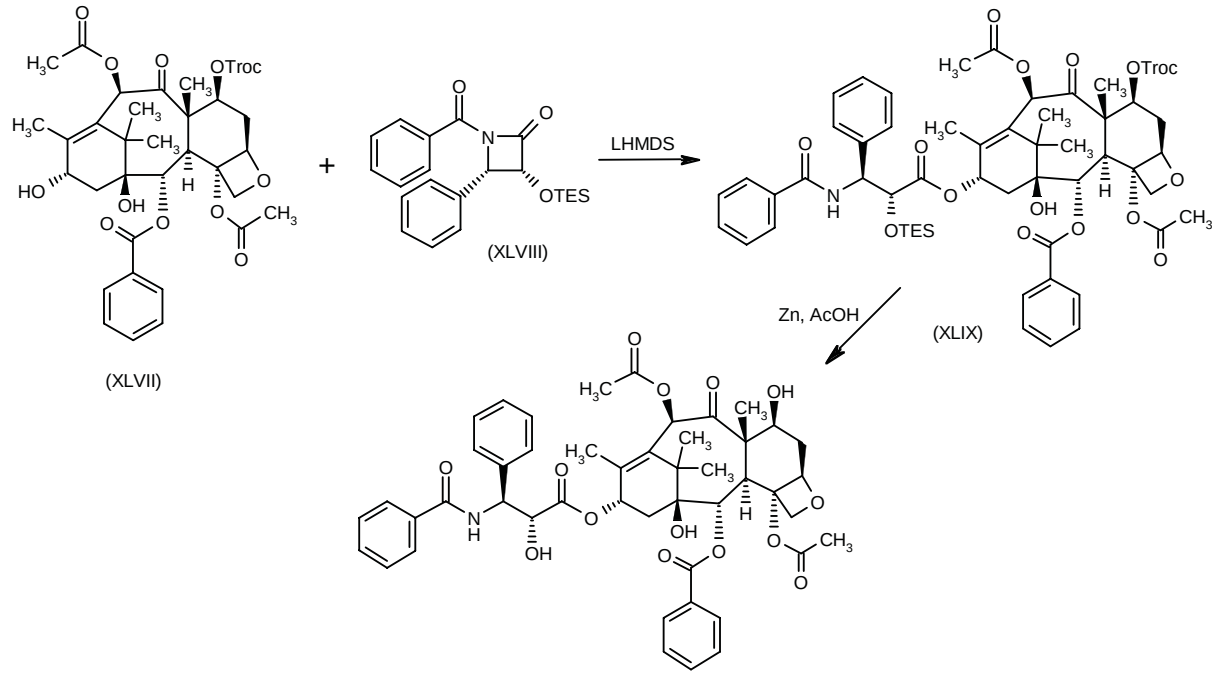
Scheme 5: Synthesis of Paclitaxel (Cont.)



3(*S*)-amino-2(*R*)-hydroxy-3-phenylpropionic acid methyl ester (X), which is silylated at the OH group with TES-Cl and TEA in ether/THF to afford the silyl ether (XI). Cyclization of (XI) by means of LHMDS in THF provides the β-lactam (XII), which is finally benzoylated with benzoyl chloride and TEA in the usual way (2). Scheme 7.

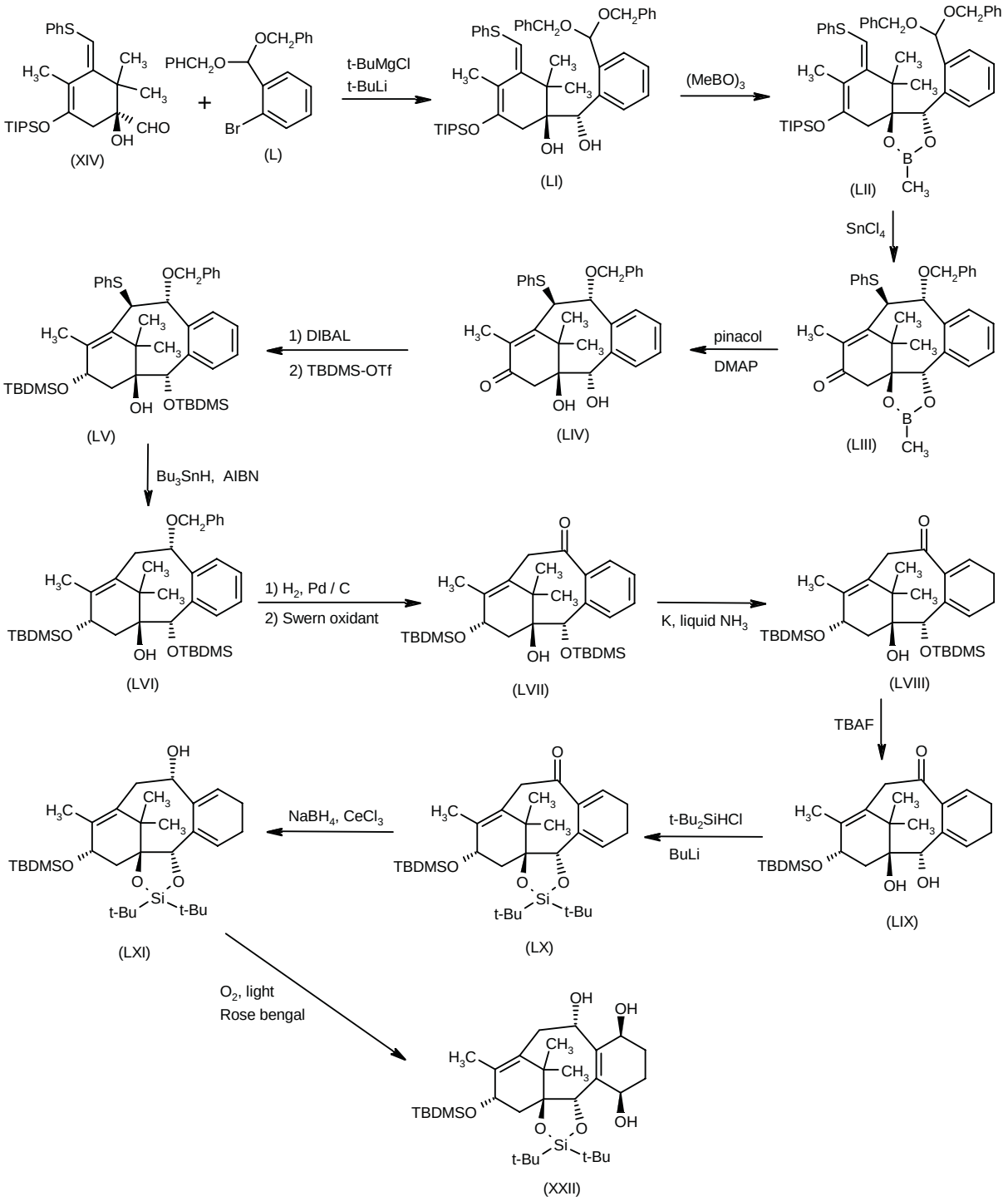
A novel semisynthetic method for the production of paclitaxel from 10-deacetylbaccantin-III using dialkyldichlorosilanes has been reported: The protection of the 7-OH of 10-deacetylbaccatin-III (I) by reaction first with dichlorodiethylsilane (II) and imidazole and then with methanol gives 7-*O*-[diethyl(methoxy)silyl]baccatin-III (III), which is regioselectively acetylated at the 10-OH with acetylimidazole and LiHMDS to yield the acetate (IV). The esterification of (IV) with the chiral oxazolinecarboxylic acid (V) by means of LiHMDS affords the corresponding ester (VI), which is treated with TFA in AcOH/water in order to perform desilylation and open the oxazoline ring to furnish paclitaxel. Other silylating agents, such as dimethyldichlorosilane, dipropyldichlorosilane, diisopropyldichlorosilane, dibutyldichlorosilane and diphenyldichlorosilane, and other alcohols, such as EtOH, PrOH, *i*-PrOH, *t*-BuOH, 3,3,3-trifluoroethanol and others, can also be used in the silylation step (3). Scheme 8.

A procedure for the production of paclitaxel by microorganisms of the *Actinomycetes* group, as well as the isolation of these microorganisms from plants of the genus *Taxus*, has been described. Well-grown agar slants of the particularly preferred microorganism *Kitasatospora* sp. CECT 4991 were inoculated in various steps into a 500-l fermenter containing 300 l of nutritive medium. After a 120-h incubation, the mycelium was removed by centrifugation and the clear liquid was submitted to a cumbersome purification process. In the final step, RP-HPLC chromatography was performed. In some of the eluted fractions, paclitaxel was detected by UV spectroscopy and mass spectrometry. The concentration of paclitaxel, determined by HPLC in comparison with Taxol calibration curves, corresponds to 1 μg/l, referring to the total volume of the broth culture (300 l) (4).

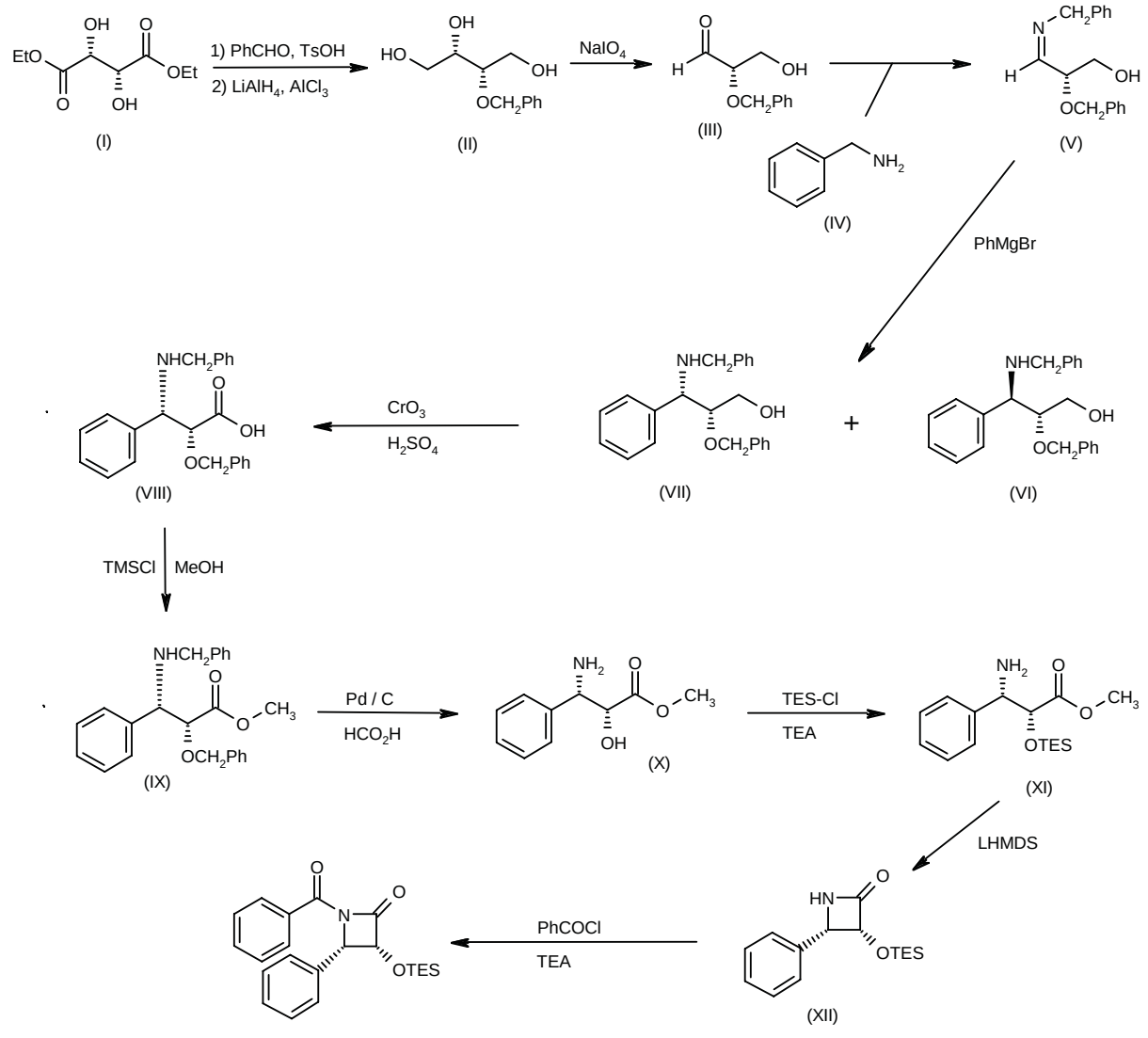
A method for large-scale separation of high purity Taxol from semipurified bark extracts of *Taxus yunnanensis* has been developed. The process consists of a preliminary purification of the bark extract with Biotage FLASH 150i system based on a prepacked normal phase silica cartidge followed by a preparative column packed with C_{18} Nova-Pak®. A Waters PrepLC™ 4000 preparative HPLC system was used (5).

Cytoclonal has isolated a new class of genes that code for acyltransferases which are involved in the later part of the pathway for the synthesis of paclitaxel. Cytoclonal isolated these late genes to generate an optimized production system for paclitaxel using fermentation and genetic engineering. A patent has been issued

Scheme 6: Synthesis of Intermediate (XXII)



Scheme 7: Synthesis of a Paclitaxel Side Chain Precursor



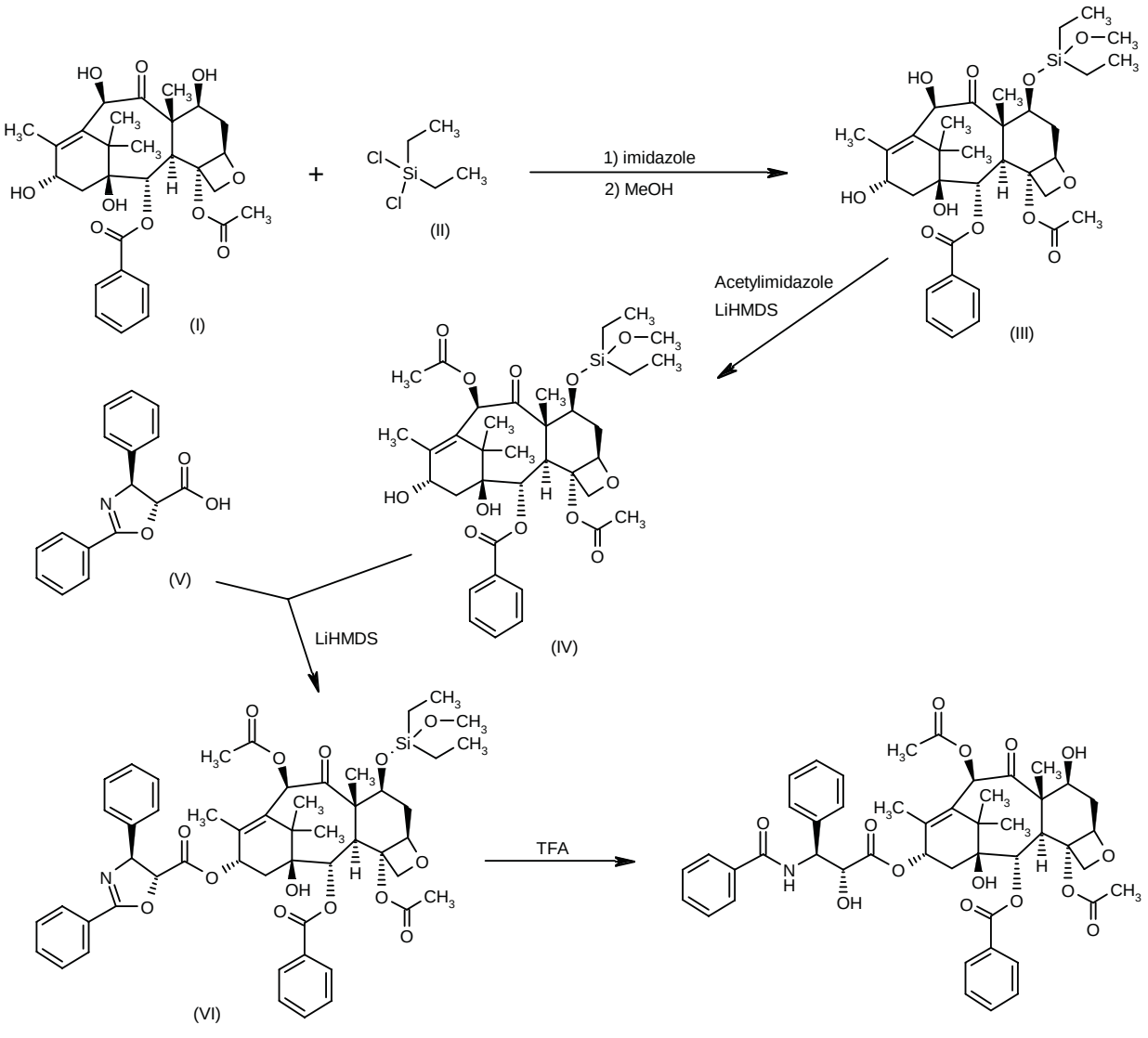
for one of the most important first steps in paclitaxel synthesis (one involving taxadiene synthase) and patents for the later genes are pending (6).

Mitotic inhibitors such as paclitaxel have enhanced antitumor activity when combined with a selective MEK inhibitor, for example PD-184352. Synergistic effect was demonstrated in cell culture assays using colon 26, HT-29 colon and non-small cell lung A549 carcinoma cells, providing the combination of paclitaxel and PD-184352 higher antitumor efficacy than either agent alone (7).

Angiotech has received approval from Health Canada to further extend its phase I/II clinical study of micellar paclitaxel for the treatment of secondary progressive multiple sclerosis (SPMS). Patients will be eligible to receive the company's micellar paclitaxel for ethical and compassionate purposes for an additional year. The company was also granted an option to offer treatment for a second year thereafter. Angiotech is continuing to enroll patients in a separate 189-patient multicenter phase II clinical study of paclitaxel for the treatment of SPMS (8).

Angiotech has initiated a phase II trial to assess the pharmacological activity of systemic micellar paclitaxel in patients with severe psoriasis who have failed at least 2 previous systemic psoriasis therapies. Patients enrolled in the study will receive monthly infusions of 75 mg/m^2 of systemic micellar paclitaxel for 6 months. The trial will initially enroll 6 patients and if at least one-third of the

Scheme 8: Synthesis of Taxol



patients have a clinical response (50% decrease in psoriasis area severity index [PASI] score), accrual will continue until a total of 13 evaluable patients have been enrolled. Earlier this year, Angiotech reported results from 2 phase I clinical trials of topical paclitaxel gel formulation for the treatment of psoriasis. The trials were designed to determine safety and tolerability of the drug applied topically in a small number of patients (20 patients per study). In both studies, the topical paclitaxel gel was safe and well tolerated (9).

Health Canada has approved Taxol® for the adjuvant treatment of node-positive breast cancer administered sequentially to a standard combination therapy of doxorubicin and cyclophosphamide (10).

Ivax has received approval to market paclitaxel (Paxene®) in Canada for the treatment of AIDS-related Kaposi's sarcoma in patients who have failed prior liposomal anthracycline therapy. Ivax also has an ANDA pending in the U.S. for a generic form of Taxol® for which the company expects 6 months of generic marketing exclusivity upon approval (11).

Angiotech has entered into an exclusive worldwide license and development agreement with Alcon providing for the use of Angiotech's paclitaxel in a polymeric carrier as a therapeutic agent for proliferative ophthalmic conditions (12).

The FDA has approved a shorter administration regimen for paclitaxel (175 mg/m^2) in combination with cis-

platin (75 mg/m^2) as a 3-h infusion every 3 weeks for the treatment of advanced ovarian cancer. The newly approved regimen was recognized to be more effective than the standard therapy consisting of cyclophosphamide (750 mg/m^2) followed by cisplatin (75 mg/m^2). Paclitaxel is also approved for use in advanced ovarian cancer at 135 mg/m^2 over a 24-h infusion period given in combination with cisplatin (75 mg/m^2) every 3 weeks. In the pivotal registrational trial for this indication, 680 women with stage IIb-IV ovarian cancer were randomized to receive either paclitaxel/cisplatin or cyclophosphamide/cisplatin for a median of 6 courses. Overall survival was significantly higher in the paclitaxel arm (35.6 months) as compared to the cyclophosphamide arm (25.9 months). Progression-free survival was also significantly higher in the paclitaxel arm (15.3 months) as compared to the cyclophosphamide arm (11.5 months). The 3-h paclitaxel/cisplatin infusion had a lower incidence of severe neutropenia, but a higher incidence of myalgia/arthralgia and severe neurotoxicity as compared to cyclophosphamide/cisplatin. Other side effects observed with paclitaxel therapy include anemia, nausea and vomiting, joint and muscle pain, infection and, occasionally, severe hypersensitivity reaction (13).

1. Kusama, H., Hara, R., Kawahara, S., Nishimori, T., Kashima, H., Nakamura, N., Morihira, K., Kuwajima, I. *Enantioselective total synthesis of (-)-Taxol.* J Am Chem Soc 2000, 122(16): 3811.

2. Kim, S.-C., Kim, H.-K. *Synthesis of new Taxol side chain precursor from L-tartaric ester.* Bull Korean Chem Soc 2000, 21(10): 1047.

3. Vemishetti, P. et al. (Bristol-Myers Squibb Co.) *Semi-synthesis of paclitaxel using dialkyldichlorosilanes.* WO 0073293.

4. Breme, U., Caruso, M., Crespi Perellino, N., Fedeli, L., Pavesi, A., Piacenza, L., Ventrella, G. (Pharmacia & Upjohn SpA). *Paclitaxel production by Actinomycetes.* WO 9942561.

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6. *Cytoclonal isolates new class of genes involved in paclitaxel synthesis.* DailyDrugNews.com (Daily Essentials) March 1, 2000.

7. Gowan, R.C., Sebolt-Leopold, J. (Pfizer Inc.). *Combination chemotherapy.* WO 0037141.

8. *Health Canada allows extension of paclitaxel trial for MS.* DailyDrugNews.com (Daily Essentials) Oct 5, 2000.

9. *Angiotech begins phase II trial with micellar paclitaxel for psoriasis.* DailyDrugNews.com (Daily Essentials) Nov 27, 2000.

10. *Taxol approved in Canada for adjuvant treatment of breast cancer.* DailyDrugNews.com (Daily Essentials) April 19, 2000.

11. *Paxene receives marketing approval in Canada for Kaposi's sarcoma.* DailyDrugNews.com (Daily Essentials) May 2, 2000.

12. *Angiotech signs license agreement with Alcon for delivery of paclitaxel.* DailyDrugNews.com (Daily Essentials) May 30, 2000.

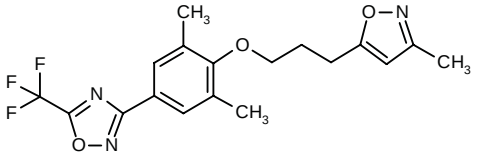
13. *Shortened Taxol regimen approved by FDA for advanced ovarian cancer.* DailyDrugNews.com (Daily Essentials) July 11, 2000.

Original monograph - Drugs Fut 1986, 11: 45.

Pleconaril

Antiviral

EN: 202115



$C_{18}H_{18}F_3N_3O_3$ **Sanofi-Synthélabo; ViroPharma**

The pharmacokinetics of a single oral dose of pleconaril solution (5 mg/kg b.w.) were characterized in 18 pediatric subjects aged 2-12 years. The plasma pleconaril concentration-time profile was best described as a one-compartment open-model with a first-order absorption in 13 of the 18 subjects over 24 h postdosing. Mean values for these 13 subjects for C_{max}, t_{max}, $AUC_{0\text{-}24h}$, Cl_{tot}, Vd_{ss} and $t_{1/2}$ were 1272.5 ± 622.1 ng/ml, 4.1 ± 1.5 h, 8131.15 ± 3411.82 ng·h/ml, 0.81 ± 0.86 l/h/kg, 4.68 ± 2.01 l/kg and 5.7 h, respectively (1).

The safety and efficacy of pleconaril (200 mg b.i.d. after initial dose of 400 mg) were evaluated in a 1-week randomized, double-blind, placebo-controlled study in 33 adults with experimentally induced coxsackievirus A21 respiratory infections. Viral shedding in nasal secretions, nasal mucus production and total respiratory illness symptom scores were statistically significantly reduced in pleconaril-treated patients as compared to placebo-treated patients. Nausea and abdominal pain were the most frequently reported adverse events (2).

A randomized, double-blind, placebo-controlled study in 875 adults with upper respiratory infections (systemic symptoms for < 36 h) of whom 378 were picornavirus positive (PV+) showed the efficacy of pleconaril (400 mg t.i.d.) in shortening the duration of illness. The treated PV+ population showed a 1.7 reduction (p = 0.07) in illness duration as compared to placebo. A significant reduction in illness duration (2.25 days) was observed in treated PV+ patients not taking concomitant cold medications. A significant reduction in total facial tissue use was also observed in the pleconaril-treated group (76 *vs.* 98 tissues) which was evident by day 2, in addition to a significant decrease in episodes of disturbed sleep (13.7 *vs.* 18.1%). The incidence of adverse events was similar in both treated and placebo groups except with respect to mild nausea which was observed in 7% of the pleconaril-treated patients as compared to 3% in the placebo group (3).

Results have been reported from 3 phase III studies of pleconaril in 2 disease indications: viral respiratory infection (VRI) in adults and viral meningitis in adults and children. As expected, clinical benefits were generally greater in patients with confirmed picornavirus infection. Adult patients in both indications showed improved time to resolution of disease based on various objective and subjective assessments of illness when compared to placebo-treated patients. In the VRI study, time to resolution of symptoms, as measured by absence of runny nose and reduction of other symptoms, decreased from 9.4 days in the placebo group to 7.7 days in the pleconaril-treated group. A greater treatment benefit was seen in picornavirus-infected patients receiving the study drug who did not take concomitant cold medication (6.75 days *vs.* 9.0 days). Objective assessments of VRI illness in all picornavirus-infected patients, such as mucus production and sleep disturbance, were reduced significantly. Reductions in cold medication use, middle ear pressure and virus shedding were also seen in these patients. Pleconaril was also evaluated for the treatment of viral meningitis in 1 study in adults and 1 study in pediatric patients. The time to complete resolution of headache was the primary endpoint in these studies. While the drug was not seen to have significant activity in this endpoint for all randomized patients with confirmed picornavirus infection, significant effects were seen in adult patients with most severe disease, *e.g.*, those presenting with severe headache and vomiting. In this patient group, the time to resolution of headache was reduced from 10 days to 7 days. Time to return to work or school was also reduced by 3 days in this patient group. In children with viral meningitis, the duration of illness observed in this study was considerably shorter than in previous studies of this patient group. Many children showed resolution of headache symptoms following lumbar puncture on study day 1. As a result, pleconaril was not seen to have significant effects. Nonetheless, illness was shortened from 4 days to 3 days in children given the study drug within 24 h of symptom onset (4).

1. Kearns, G.L., Abdel-Rahman, S., James, L.P. *Single-dose pharmacokinetics of pleconaril (VP63843) oral solution in children and adolescents.* Antimicrob Agents Chemother 1999, 43(3): 634.

2. Schiff, G.M., Sherwood, J.R. *Clinical activity of pleconaril in an experimentally induced coxsackievirus A21 respiratory infection.* J Infect Dis 2000, 181(1): 20.

3. Hayden, F.G., Kim, K., Coats, T., Blatter, M., Drehobl, M. *Pleconaril treatment shortens duration of picornaviral upper respiratory illness in adults.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst H-1161.

4. *Phase III results in for pleconaril: ViroPharma reaffirms commitment to novel antiviral drug.* DailyDrugNews.com (Daily Essentials) April 13, 2000.

Original monograph - Drugs Fut 1997, 22: 40.

Rabeprazole Sodium
Pariet®
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Antiulcer
Treatment of GERD
Eradication of H. pylori

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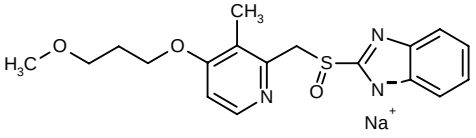

$C_{18}H_{20}N_3NaO_3S$ **Eisai; Janssen-Cilag**

A controlled prospective trial has compared the efficacy of teprenone and rabeprazole sodium for their ability to protect against piroxicam-induced gastric mucosal damage. Thirty patients received a standard dose (20 mg/day) of piroxicam for 2 weeks and 20 patients were randomized to receive either rabeprazole 10 mg once daily or teprenone 50 mg 3 times daily for 2 weeks along with piroxicam. Compared to subjects receiving only piroxicam, those given teprenone showed a tendency for less gastric damage but a similar incidence of duodenal ulcers, whereas significantly less gastroduodenal damage was detected in those given rabeprazole. These results suggest potential utility for proton pump inhibitors for suppressing gastroduodenal lesions induced by NSAIDs (1).

Rabeprazole sodium has recently been approved in the E.U. for the eradication of *Helicobacter pylori* in combination with appropriate antibacterial therapeutic regimens in patients with peptic ulcer disease. The following regimen is recommended for 7 days: rabeprazole 20 mg twice daily, clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily (2).

1. Yanagawa, A. et al. *Prophylactic efficacy of the mucosal cytoprotective agent teprenone and the proton pump inhibitor rabeprazole against gastroduodenal lesions caused by piroxicam: Controlled trial study.* Jpn J Inflamm 2000, 20(6): 675.

2. *Pariet receives E.U. approval for H. pylori eradication in peptic ulcer disease.* DailyDrugNews.com (Daily Essentials) Nov 14, 2000.

Original monograph - Drugs Fut 1991, 16: 19.

RMP-7
Lobradimil
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Absorption Promoter
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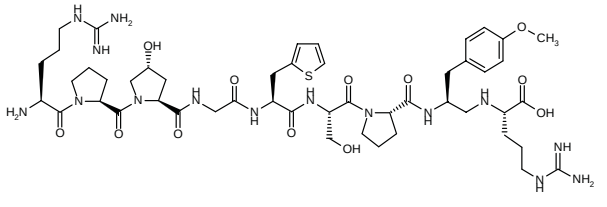


$C_{49}H_{75}N_{15}O_{12}$ **Alkermes; Alza**

Recent experiments examined the effects of RMP-7 given by i.v. infusion in rats bearing rat gliomas. RMP-7 administration was associated with a significant increase in the uptake of carboplatin into tumor and brain surrounding tumor, but it had no effect on paclitaxel uptake. The increased carboplatin uptake reflected increased platinum levels within the tumor, which were 2-fold higher than vehicle controls at the end of the RMP-7 infusion, an effect which persisted for 2 h. RMP-7 was particularly effective in eliminating parts of the blood-brain tumor barrier which are normally impermeable to carboplatin. High doses (9 μg/kg) of the drug significantly enhanced survival of tumor-bearing rats when given in combination with carboplatin, with about a 2-fold increase in survival (median of 36 days, maximum of 60 days) compared to carboplatin alone; the lower dose of 3 μg/kg was not effective. The plasma levels achieved on the high dose (25-50 nM), but not the low dose (8-16 nM), were similar to the K_i value for binding to the B_2 receptor and induction of bradykinin second messenger responses *in vitro*. Thus, i.v. RMP-7 appears to have the ideal profile for a delivery agent: a significant increase in the amount of chemotherapeutic agent delivered to the tumor, improved distribution of chemotherapeutic agent within the tumor and brain surrounding tumor and longer exposure time to increased levels of chemotherapeutic agent (1).

Lobradimil is the United States adopted name for RMP-7 (2).

1. Bartus, R.T., Snodgrass, P., Marsh, J., Agostino, M., Perkins, A., Emerich, D.F. *Intravenous Cereport (RMP-7) modifies topographic uptake profile of carboplatin within rat glioma and brain surrounding tumor, elevates platinum levels, and enhances survival.* J Pharmacol Exp Ther 2000, 293(3): 903.

2. *USAN Council. List No. 419.* Clin Pharmacol Ther 1999, 66(3): 329.

Original monograph - Drugs Fut 1998, 23: 32.

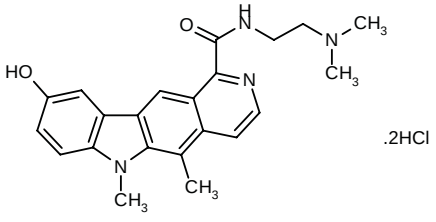
Additional Reference

Barth, R.F. et al. *Neutron capture therapy of intracerebral melanoma using Cereport (RMP-7) mediated blood-brain barrier modulation to enhance delivery of boronopheylanine.* Proc Amer Assoc Cancer Res 2000, 41: Abst 3913.

S-16020-2

Oncolytic

EN: 210038



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

An *in vitro* study examined the cellular resistance to S-16020-2 using a Chinese lung fibroblast cell line (DC-3F) and a S-12020-2-resistant subline (DC-3F/S16) that was only also weakly cross-resistant to ellipticine derivatives. The uptake and efflux rates of S-16020-2 were similar in both resistant and sensitive cells. Although expression of the topoisomerase IIalpha-isoform was the same in both cell types, expression of the topoisomerase beta-isoform was 50% lower in resistant cells. Sequencing of both enzymes revealed a point mutation that converts Arg486 to Gly in a highly conserved sequence of the α cDNA that was not evident in the β cDNA. This mutation appeared to be responsible for the resistance to S-16020-2. It was concluded after comparing S-16020-2-resistant and ellipticine-resistant (DC-3F/9-OH-E) cells that S-16020-2 may interact with the above mentioned conserved amino acid sequence of topoisomerase II via its *N*-[2(dimethylamino)ethyl]carbamoyl side chain (1).

1. Le Mée, S., Chaminade, F., Delaporte, C., Markovits, J., Saucier, J.-M., Jacquemin-Sablon, A. *Cellular resistance to the antitumor DNA topoisomerase II inhibitor S16020-2: Importance of the N-[2(dimethylamino)ethyl]carbamoyl side chain.* Mol Pharmacol 2000, 58(4): 709.

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Additional Reference

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Sabcomeline Hydrochloride
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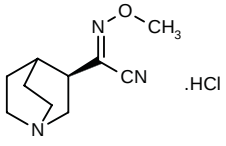

$C_{10}H_{15}N_3O.HCl$ **GlaxoSmithKline**

Vanguard has reached an agreement with GlaxoSmithKline by which the latter will take back rights that had been licensed to Cerebrus for the cognition-enhancing agent sabcomeline (1).

1. *Vanguard Medica updates status of pipeline projects following integration of Cerebrus.* DailyDrugNews.com (Daily Essentials) Feb 22, 2000.

Original monograph - Drugs Fut 1998, 23: 41.

SDZ-RAD
RAD-001
Everolimus
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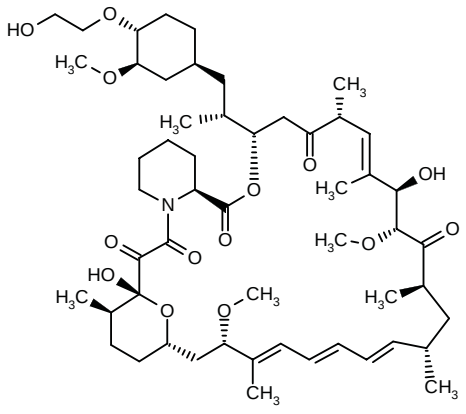
Immunosuppressant

EN: 210424



$C_{53}H_{83}NO_{14}$ **Novartis**

In vitro and *in vivo* results from a study indicated a potential efficacy of SDZ-RAD against posttransplant lymphoproliferative disorders (PTLDs). SDZ-RAD (1 nM) inhibited *in vitro* growth (60-95%) of 6 different human Epstein-Barr virus (EBV)-transfomed lymphoblastoid B cell lines derived from patients with B cell lymphoma (15A, 20A and BC-1) or T cell lymphoproliferative disorder (LCL) and from healthy individuals (A1 and A2D6). SDZ-RAD arrested cell-cycle progression in the early G_0/G_1 phase and increased apoptosis of PTLD-like B cells. The agent was also effective *in vivo* in SCID mice transplanted with EBV+ B cell lines (15A, 20A or A1 s.c.). Treatment with the agent (5 mg/kg p.o. given after tumors reached 5 mm in diameter) significantly induced regression of established tumors; the agent was most effective against A1 tumors resulting in eradication in 4/8 animals. When SDZ-RAD was given 3 days prior to inoculation, significant growth inhibition of all 3 tumor types was observed (1).

SDZ-RAD was shown to have significant growth inhibitory effects (80-100%) on 6 PTLD-like, EBV+ lymphoblastoid B cell lines. SDZ-RAD blocked the cell cycle at the G_0/G_1 phase in both normal T cells and in lymphoblastoid B cells and increased apoptosis as determined by staining with annexin V. The agent was also effective *in vivo* in SCID mice bearing (s.c.) 3 types of EBV+ B cell line xenografts. Growth of tumors was significantly delayed in animals treated with SDZ-RAD (36 *vs.* 8 days in controls). Total inhibition of tumor formation (for up to 55 days) or significantly enhanced delays in tumor growth (46 *vs.* 13 days) were observed when SDZ-RAD was given before inoculation. The agent may therefore be a potential treatment in preventing PTLDs (2).

The tissue distribution of SDZ-RAD (1.5 or 0.3 mg/kg/day p.o.) when administered in combination with ciclosporin (100 or 50 mg/kg/day) was examined in a study using cynomolgus monkeys with lung transplants. Ciclosporin coadministration increased the distribution of SDZ-RAD in most tissues and increased tissue-to-blood distribution coefficients; SDZ-RAD only slightly affected ciclosporin tissue and blood concentrations. Significantly fewer monkeys treated with combination therapy had rejections as compared to those on monotherapy. Histological rejection scores were found to correlate with SDZ-RAD concentrations in blood, lymph nodes, thymus and lung transplant tissue (3).

Promising new results with SDZ-RAD have been reported. Studies in rats with intimal proliferation suggested that combination of SDZ-RAD and HMG-CoA reductase inhibitors may be useful in managing immune-mediated allograft vasculopathy. *In vitro*, SDZ-RAD potently inhibited human coronary artery smooth muscle cell proliferation with an IC_{50} of 0.07 nM, while fluvastatin and pravastatin had little or no effect (IC_{50} = 10 and 2000 μM, respectively) and did not alter the IC_{50} of SDZ-RAD. However, in rats with intimal proliferation induced by balloon injury of the femoral arteries, combination of SDZ-RAD and fluvastatin exerted an additive inhibition of arterial intimal proliferation and the SDZ-RAD/pravastatin combination was significantly more effective than SDZ-RAD alone (4).

Combinations of SDZ-RAD and ciclosporin have been evaluated against host-*versus*-graft (HGV) and graft-*versus*-host (GVH) immune responses in a rat model of orthotopic small bowel transplantation. Following oral administration for up to 90 days, a synergistic to very strong synergistic effect in the HGV model was seen with SDZ-RAD + ciclosporin: doses of 2.5 mg/kg/day SDZ-RAD and 5.0 mg/kg/day ciclosporin gave a mean survival time (MST) of 70.5 ± 12.8 days *vs.* 9.5 ± 1.0 days in untreated controls, 19.2 ± 4.8 days in animals treated with SDZ-RAD 2.5 mg/kg/day and 28.8 ± 5.7 days in animals treated with 5.0 mg/kg/day ciclosporin. Similar results were obtained in the GVH model, with an MST of 63.0 ± 13.6 days for the above doses of SDZ-RAD and ciclosporin combined *vs.* 21.7 ± 3.0 days on SDZ-RAD and 27.8 ± 4.4 days on ciclosporin (untreated controls = 8.3 ± 1.2 days). Furthermore, a strong synergistic interaction was obtained in the combined HVG/GVH model (MST = 69.0 ± 5.3 days for the above combination) (5).

SDZ-RAD (0.5 mg/kg/day) was tested in an ongoing chronic renal allograft rejection model in rats. The immunosuppressant delayed the progression of chronic rejection, as evaluated by both functional and histological changes, when treatment was started at week 12, and even when it was begun at week 20 (6).

The efficacy and safety of SDZ-RAD were shown in 2 studies conducted in cynomolgus monkeys with kidney allotransplants. In the first study, animals were administered (via gavage) until allograft rejection increasing doses of a microemulsion of SDZ-RAD, a microemulsion of ciclosporin (150 mg/kg/day followed by 100 mg/kg/day 2 week posttransplant) or a combination of the two agents using a suboptimal dose (10 mg/kg/day) of ciclosporin.

A dose of 0.63 mg/kg/day SDZ-RAD resulted in rejection in 4/6 animals while combination treatment resulted in rejection at a 4-fold lower dose. Allograft survival was more than 100 days in 4/5 animals receiving ciclosporin alone while the suboptimal dose of ciclosporin resulted in allograft rejection 10-27 days posttransplant. Untreated animals had rejection between 4 and 8 days posttransplant. In the second study, animals were administered SDZ-RAD (0.75 or 1.50 mg/kg/day p.o.) or rapamycin (0.75 or 1.50 mg/kg/day p.o.). No significant differences were observed in the efficacy of the two agents. SDZ-RAD treatment resulted in median graft survival of 32 and 59 days for the 0.75 and 1.50 mg/kg/day doses, respectively, as compared to 43 and 56 days, respectively, for rapamycin (7).

RAD-001 has been examined for pharmacokinetics and pharmacokinetic interactions in a double-bind, randomized, crossover trial in 20 stable lung and heart/lung transplant recipients, 8 of whom had cystic fibrosis. Single doses of 0.03 mg/kg and 0.10 mg/kg were added to existing immunosuppressive therapy (ciclosporin, azathioprine and corticosteroids) on day 1, and patients were crossed over to the other dose following a 15-day interval. Although cystic fibrosis patients showed a slight decrease in dose-normalized C_{max}, overall systemic exposure to RAD-001 was similar in lung transplant recipients with and without cystic fibrosis. Furthermore, the addition of a single dose of RAD-001 had no significant influence on the pharmacokinetics of ciclosporin microemulsion, suggesting that these doses of the new immunosuppressant should be evaluated in efficacy trials in similar patient groups (8).

The pharmacokinetics and metabolism of SDZ-RAD (0.25-15 mg/day p.o.) were examined in 7 kidney graft patients on standard ciclosporin-based immunosuppression with results showing that the agent does not significantly affect the pharmacokinetics of ciclosporin. $AUC_{0\text{-}12h}$ values for ciclosporin before and after SDZ-RAD administration were 4244 ± 1311 and 4683 ± 1174 μg/l·h, respectively, and concomitant SDZ-RAD did not significantly affect the C_{max} and t_{max} values for ciclosporin or its metabolite pattern. The $AUC_{0\text{-}24h}$, C_{max} and t_{max} values for SDZ-RAD normalized to 1 mg were 35.4 ± 13.1 μg/l·h, 7.9 ± 2.7 μg/l·h and 1.5 ± 0.9 h, respectively. Hydroxy-SDZ-RAD was the major metabolite detected in blood, with dihydroxy-SDZ-RAD, demethyl-SDZ-RAD and an open ring form of SDZ-RAD also observed (9).

Everolimus is the proposed international nonproprietary name for SDZ-RAD (10).

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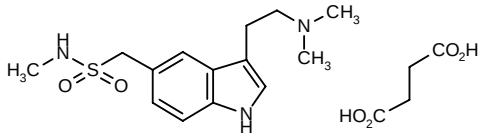

$C_{14}H_{21}N_3O_2S.C_4H_6O_4$ **GlaxoSmithKline**

Glaxo Wellcome has applied for FDA approval of sumatriptan succinate nasal spray (Imitrex®) for the acute treatment of migraine pain and associated symptoms in patients aged 12 years and older (1).

1. *FDA approval sought for Imitrex in the treatment of adolescent migraine.* DailyDrugNews.com (Daily Essentials) March 14, 2000.

Original monograph - Drugs Fut 1989, 14: 35.

Talsaclidine Fumarate

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Muscarinic M_1 Agonist

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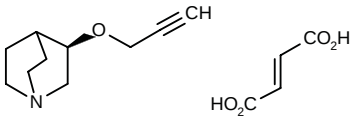

$C_{10}H_{15}NO.C_4H_4O_4$ **Boehringer Ingelheim**

The pharmacokinetics of talsaclidine were reported in mouse, rat, rabbit and monkey following single i.v. injection of the [^{14}C]-labeled compound. Distribution of the agent was extensive and similar apparent volumes of distribution were obtained for all species (2-5 l/kg). Plasma protein binding was also similar in all species and was comparable to that observed in humans (7% or less). The total plasma clearance was less in monkey (10.6 ml/min/kg) than in mouse (128 ml/min/kg) and rat (73.9 ml/min/kg). The drug was predominantly eliminated in urine (86% or more). The results obtained correlated with the pharmacokinetics reported for humans in previous studies (1).

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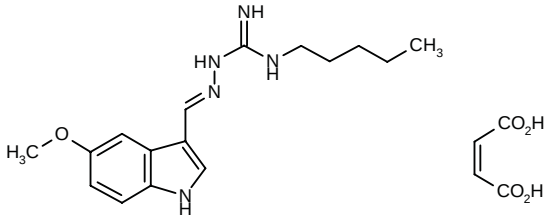

$C_{16}H_{23}N_5O.C_4H_4O_4$ **Novartis; Bristol-Myers Squibb**

A placebo-controlled, double-dummy, 3-way crossover study in 12 healthy male subjects showed that tegaserod (6 mg p.o. or 0.6 mg 2-h i.v. infusion for 3.5 days) enhanced upper and lower gastrointestinal motility. Both oral and i.v. treatment significantly decreased gastric lag time (–27 and -38%, respectively) and small bowel transit time (–30 and -37%, respectively) and increased gastric postlag emptying rates (+38 and +47%, respectively) and colonic transit (+6 and +6%) as compared to placebo. Oral treatment resulted in significantly lower stool consistency on day 1 as compared to i.v. treatment and placebo (1).

The efficacy and safety of tegaserod were assessed in a double-blind, placebo-controlled trial in 881 patients with IBS randomized to receive doses of 4 or 12 mg/day or placebo for 12 weeks following a 4-week run-in period. The principal efficacy variable was the Subjects Global Assessment (SGA) of relief including abdominal pain, bowel function and overall well-being, and response was also assessed using the SGA of abdominal discomfort/pain. The lower dose of tegaserod significantly improved both efficacy measures compared to placebo at 2 and 3 months, and the higher dose was also effective at 1 month. The drug showed a rapid onset of action (as early as 1 week) and a sustained effect. Treatment was well tolerated (2).

Tegaserod maleate was tested in a crossover trial in 19 patients with mild to moderate gastroesophageal reflux disease (GERD). The trial was designed to compare b.i.d. doses of tegaserod of 1, 4, 12 and 24 mg and placebo over 14 days each for effects on lower esophageal sphincter pressure and distal esophageal pH. The two lower doses of tegaserod produced over 50%

decreases in postprandial acid exposure in patients with abnormal acid exposure, but only the lowest dose (1 mg) had a statistically significant effect in the treatment group as a whole. The number of postprandial reflux episodes was reduced by both the 1 and 4 mg/day doses compared to placebo. Although no significant effect was seen on mean lower esophageal sphincter pressure, transient lower esophageal sphincter relaxations were reduced in the immediate postprandial period by all doses of tegaserod as compared to placebo. Tegaserod was generally well tolerated, the most frequent adverse events being gastrointestinal disturbances, especially diarrhea, and the incidence was highest on the highest dose. No clinically relevant changes in laboratory parameters were seen. It was concluded that tegaserod at a dose of 1 mg/day is able to reduce esophageal acid exposure, possibly due to enhanced esophageal acid clearance, improve gastric emptying and/or reduced transient lower esophageal sphincter relaxations. Larger studies are recommended to assess the role of tegaserod in GERD (3).

Novartis and Bristol-Myers Squibb have established an alliance for the codevelopment and copromotion of tegaserod (Zelmac®) for the treatment of women with certain symptoms associated with IBS. Preliminary analysis of data from a recently completed clinical study in 1500 women treated with tegaserod confirm the safety and efficacy of the drug for the treatment of abdominal pain/discomfort and constipation in women with IBS (4).

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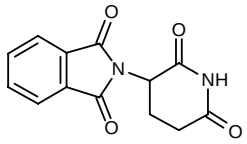

$C_{13}H_{10}N_2O_4$

Celgene; Andrulis; EntreMed; Natl. Cancer Inst. (US)

The interim analysis of 9 patients enrolled in a pilot trial of combination therapy with thalidomide and irinotecan for colorectal cancer revealed that thalidomide nearly eliminated the dose-limiting gastrointestinal toxic effects of irinotecan, though just how is unknown. In the study, metastatic colorectal cancer patients received thalidomide 400 mg daily and 2-8 cycles of irinotecan 325-350 mg/m^2 every 21 days. Nausea, diarrhea and other gastrointestinal effects usually associated with irinotecan were absent. Complete remission was achieved in 1 of 7 evaluable patients, while partial remission was attained in 2. One patient required a 50% reduction of irinotecan dose due to asthenia; another needed a 75% thalidomide dose reduction because of somnolence. Studies are planned to further evaluate thalidomide in the treatment of colorectal cancer (1).

The efficacy and maximum tolerated doses (MTDs) of thalidomide (200 mg b.i.d. increased by 200 mg every 14 days to 600 mg b.i.d.) were investigated in an ongoing escalating dose study in 14 patients with progressive renal cell cancer. Of the 8 evaluable patients, 1 patient achieved partial remission (10+ months), 2 patients had stable disease and 5 had progressive disease. The MTDs

of the agent were 600-1200 mg/day. Although somnolence and constipation were observed, no cytopenias, neuropathy or respiratory depression were seen. A few cases of arterial and venous thrombi and impaired wound healing were observed although they may not have been drug-related (2).

Improvement in clinical symptoms of refractory Crohn's disease has been reported in patients treated with thalidomide, but the mechanism of action remains unclear, although it appears to involve TNF-α suppression. In an open-label trial in 10 patients with therapy-refractory inflammatory bowel disease treated for 12 weeks with thalidomide 300 mg/day, significant improvement in disease activity was seen in all but 3 patients who withdrew due to sedative side effects; 4 of the responding patients achieved disease remission. Examination of cultures of stimulated colonic lamina propria mononuclear cells and peripheral blood monocytes from these patients demonstrated reductions in TNF-α and IL-12 during treatment with thalidomide, but no effect on IL-1beta or IL-6 production (3).

A phase II randomized trial conducted in 28 heavily treated patients with progressive metastatic breast cancer showed little efficacy of thalidomide (200 or 800 mg/day escalated to 1200 mg/day; treatment cycle = 8 weeks). No partial or complete responses were seen. Thirteen patients given 800 mg had progressive disease at or before 8 weeks and 1 discontinued. Of these patients, the dose was reduced to 600 and 400 mg in 5 and 2 patients, respectively, for somnolence and 1 and 4 patients were increased to 1000 and 1200 mg, respectively. Twelve patients given 200 mg had progressive disease and 2 had stable disease at 8 weeks; 1 patient each was discontinued for grade 3 neuropathy at week 11 and progressive disease at week 16. Adverse events not requiring dose modifications included constipation, fatigue, dry mouth, dizziness, nausea, anorexia, arrhythmia, headache, skin rash, hypotension and neutropenia (4).

Results from a single-blind, placebo-controlled crossover study in 6 obese patients with type 2 diabetes given thalidomide (150 mg p.o. for 3 weeks) indicated that the glucose tolerance of patients given the drug should be monitored. Patients were subjected to 4-h isoglycemic (about 8 mM) hyperinsulinemic clamps (500-600 pM) before and after thalidomide treatment. The agent did not affect basal glucose turnover but significantly decreased insulin-stimulated glucose uptake by 21%, which was responsible for the significant inhibition of insulin-stimulated glycogen synthesis also observed. The agent had no effect on basal or insulin-inhibited free fatty acid turnover (5).

The efficacy of thalidomide (low-dose = 200 mg/day or high-dose = 200 mg escalated to 1200 mg/day) was examined in an open-label, phase II, randomized study in 63 patients with androgen-dependent prostate cancer. PSA levels of patients receiving high- and low-dose thalidomide decreased by 68 and 58%, respectively. PSA decreases of > 50% were seen in 18% of the patients receiving the low dose; reduced levels were maintained for > 150 days. Two low-dose patients had partial responses as assessed by bone scans and 4 developed symptoms of peripheral neuropathy after receiving the agent for > 9 months. PET scans at 2 or 6 months of these 6 patients showed changes in bone or soft tissue lesions as compared to baseline scans that corresponded with changes in PSA (6).

A study conducted in 6 patients with relapsed multiple myeloma (Durie-Salmon stage IIIA and IIIB in 9 and 7 patients, respectively) showed the efficacy of oral thalidomide (200 mg/day for 2 weeks increased by 200 mg/day every 2 weeks to 800 mg/day). Partial responses lasting for 2, 4+, 8 and 10+ months were observed in 4 patients, respectively, who showed a greater than 50% reduction in serum or urine M protein levels. Major adverse events were constipation, sedation, rash and peripheral neuropathy (7).

Preclinical results with thalidomide and immunomodulatory drugs have demonstrated their ability to inhibit COX-2 production. The COX-2 enzyme is known to play a role in inflammation and angiogenesis, which may help to explain the mechanisms by which these compounds operate in certain biological pathways. Investigators treated macrophage cell lines *in vitro* with thalidomide and immunomodulatory drugs and observed a decrease in the cells' ability to produce the COX-2 enzyme. This effect differs from currently marketed COX-2 inhibitors that operate by directly inhibiting enzyme activity. Clinical trials are being conducted to evaluate the possible synergy between thalidomide and other COX-2 inhibitors (8).

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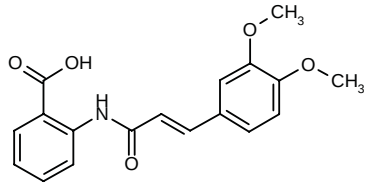

$C_{18}H_{17}NO_5$ **Kissei; GlaxoSmithKline**

Tranilast has been evaluated for immunomodulatory action *in vitro* using human monocytes. The results confirmed the ability of tranilast to inhibit A23187- and/or endotoxin (lipopolysaccharide)-induced LTC_4 and PGE_2 production (IC_{50} = 10-40 μM and 1-20 μM, respectively), and also demonstrated decreases in lipopolysaccharide-induced TxB_2 (IC_{50} = 10-50 μM), TGF-β_1 (IC_{50} = 100-200 μM) and IL-8 production (IC_{50} = 100 μM). Tranilast (100 μM) furthermore significantly suppressed the production of interferon-γ in monocyte-enriched human peripheral blood mononuclear cells (PBMCs) cocultured with IL-12 and IL-18. The compound had no significant direct effects on cyclooxygenase type 1 or 2 (COX-1 or COX-2), nor on human phospholipase A_2 (PLA_2) enzyme activities or endotoxin-induced COX-2 protein expression, suggesting an as yet unidentified mechanism of action on eicosanoid production/release. In conclusion, these findings provide further support for the potential of tranilast as a therapeutic for restenosis due to its combined direct inhibitory effect on fibroblast proliferation and immunomodulatory/antiinflammatory activity (1).

SmithKline Beecham has completed patient enrollment in its PRESTO (Prevention of Restenosis with Tranilast and its Outcomes) trial to determine if tranilast reduces the major cardiovascular adverse effects associated with restenosis, specifically death, myocardial infarction and the need for revascularization of the affected coronary artery. Of the 11,500 patients in the trial, 9200 received tranilast for either 1 or 3 months and 2300 received placebo. Following the procedure, all patients will be followed up for 9 months. Two thousand patients will be evaluated by angiography at 9 months to assess the extent of clinical manifestations of restenosis; 1000 patients will be evaluated for restenosis by intravascular ultrasound, a new technique which allows viewing of the inside of a coronary vessel and subsequent quantification of restenosis. Results from the PRESTO trial will be used to confirm the angiographic effects observed in small trials of tranilast in Japan and to extend the findings by following patients for major cardiovascular adverse effects. All clinical trial patients have finished the treatment phase of the trial. Follow-up evaluation will continue for another 6 months and the results of the trial will be available in 2001. It is expected that in the event of successful completion of PRESTO, regulatory applications for tranilast will be filed worldwide (2).

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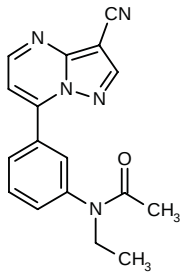
Zaleplon
Sonata®

Sedative/Hypnotic

EN: 132769



$C_{17}H_{15}N_5O$ **Wyeth-Ayerst; Lundbeck**

A multicenter, randomized, double-blind, placebo-controlled, 2-week study followed by a 7-day, single-blind, placebo run-out period was conducted in a total of 437 elderly (65 years or older) outpatients with insomnia (for at least 3 months) and showed the efficacy and safety of zaleplon (5 and 10 mg). According to results from post-sleep questionnaires, treatment with both doses significantly reduced subjective sleep latency during the 2-week treatment period and the 10 mg dose significantly improved sleep quality over placebo. No significant difference was observed between treated and placebo groups in treatment-emergent adverse events. However, a very slight tendency for the development of rebound insomnia was observed following discontinuation of the 10 mg dose (1).

Zaleplon (Sonata®) was recently launched in the U.K. by Lundbeck for the treatment of patients with severe, disabling or severely distressing insomnia. Zaleplon is structurally unrelated to the benzodiazepines and shows high selectivity and low affinity for the benzodiazepine type 1 receptor on the GABA-A receptor complex; its rapid onset and short duration of action result in rapid sleep induction without hangover effects. The product is available in capsules of 5 and 10 mg. Developed by the Wyeth-Ayerst division of American Home Products, zaleplon was first introduced in 1999 in Denmark and Sweden and has since been launched in a number of European countries and was recently approved in the U.S. (2).

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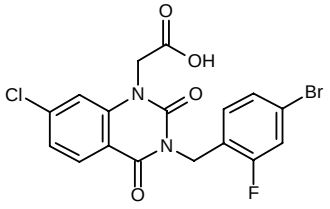
Zenarestat

Treatment of Diabetic Neuropathy
Aldose Reductase Inhibitor

EN: 132922



$C_{17}H_{11}BrClFN_2O_4$ **Fujisawa**

An *in vivo* study using Zucker diabetic fatty (ZDF) rats showed the efficacy of zenarestat (p.o. once daily for 8 weeks) against peripheral neuropathy. Although a dose of 3.2 mg/kg had no effect on sciatic nerve sorbitol accumulation, delays in F-wave minimal latency or slowing of motor nerve conduction velocity seen in control ZDF rats, 32 mg/kg improved all of these nerve function parameters and decreased nerve sorbitol to levels similar to those observed in lean rats (1).

Fujisawa has announced that phase III clinical trials for zenarestat in Japan are continuing after its development partner Pfizer announced that it had halted zenarestat development in October. Pfizer's decision was based on an interim safety analysis of 2 phase III trials with 3 treatment arms of placebo and zenarestat 600 mg/day and 1200 mg/day. In a small number of patients in those trials, zenarestat was noted to have potential renal toxicity, which appeared to be dose-dependent, with the

  CCC: 0377-8282/2001

majority of cases at the highest dose of 1200 mg/day. Based on the careful analysis of data obtained so far in Pfizer's phase III trials, as well as data from Japanese clinical trials, Fujisawa has found no serious issues which may have major impact on the continuation of the phase III trials in Japan. Therefore, the company is continuing the Japanese phase III trials, which are expected to be completed by the end of the year (2).

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