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Information Update

Volume 1-23, Number 6

Estimated developmental phase for this month's updated products:

Preclinical

BBR-3409 (antineoplastic; Roche, Univ. Vermont)
BBR-3438 (antineoplastic; Roche, Univ. Vermont)
Emodin (antineoplastic, antibacterial, immunosuppressant; China Pharm. Univ.)

Phase I

(–)-Epigallocatechin gallate (antineoplastic, chemopreventive; Natl. Cancer Center Res. Inst.)
Halofunginone hydrobromide (treatment of scleroderma; Hoechst Marion Roussel, Collgard)
Nicanartine (hypolipidemic, antioxidant; Merz)

Phase II

N-Acetylcysteine (antioxidant, mucolytic, immunostimulant; Zambon)
Antide (treatment of female infertility, GnRH antagonist; Ares-Serono)
DX-9065a (anticoagulant, factor Xa inhibitor; Daiichi Pharm., Beijing General)
JM-216 (antineoplastic, platinum complex; Johnson Matthey, Bristol-Myers Squibb)
JTE-522 (antiinflammatory, COX-2 inhibitor; Japan Tobacco, R.W. Johnson)
Lexacalcitol (immunomodulator, vitamin D analog; Leo)

Phase III

Eniluracil (potentiator of 5-FU activity, dihydropyrimidine dihydrogenase inhibitor; Glaxo Wellcome)
HMR-3647 (ketolide antibacterial; Hoechst Marion Roussel)
Homoharringtonine (antineoplastic alkaloid; Chinese Acad. Med. Sci., Natl. Cancer Inst.)
Huperzine A (cognition enhancer, acetylcholinesterase inhibitor; Shanghai Inst. Materia Med., Chinese Acad. Med. Sci.)
Liarozole fumarate (antineoplastic; Janssen)
Lubeluzole (neuroprotectant, glutamate release inhibitor; Janssen, Kyowa Hakko) (discontinued)
NS-105 (cognition enhancer; Nippon Shinyaku)
Pirfenidone (antifibrotic; Marnac, Shionogi, Synexus)
Prasterone (immunosuppressant, treatment of SLE, antiallergic/anthiasthmatic; Genelabs, Jenapharm, Mipharm, Pharmadigm)
SB-207499 (antiallergic/antiasthmatic; PDE IV inhibitor; SmithKline Beecham)
SR-57746A (neuroprotectant, treatment of ALS, 5-HT_{1A} agonist; Sanofi-Synthélabo)

Pregistered

Azimilide hydrochloride (antiarrhythmic; Procter & Gamble, Tanabe)
Dofetilide (antiarrhythmic; Pfizer)
Etilefrine pivalate hydrochloride (treatment of vasovagal syncope; Klinge)
Nicaraven (neuroprotectant; Chugai)

Registered/Year

Nateglinide (antidiabetic; Ajinomoto, Yamanouchi, Novartis)/1999
Ziprasidone hydrochloride (antipsychotic, dopamine D_2 antagonist, 5-HT_{2A} antagonist; Pfizer)/1998

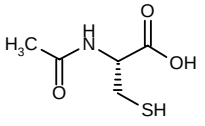
Launched/Year

Alprostatil (treatment of erectile dysfunction; Janssen, AstraZeneca, MacroChem, Harvard Scientific, NexMed, Vivus, Bio-Medic Inst.)/1979
Cerivastatin sodium (hypolipidemic, HMG-CoA reductase inhibitor; Bayer, Takeda, Fournier)/1997
Citalopram (antidepressant; Biovail, Lundbeck, Nycomed Amersham, Forest)/1989
Dexketoprofen trometamol (antiinflammatory, analgesic; Menarini, Chiroscience)/1996
Dolasetron mesilate (antiemetic, 5-HT_3 antagonist; Hoechst Marion Roussel, Abbott)/1997
Eptifibatide (platelet antiaggregatory, fibrinogen gpIIb/IIIa antagonist; COR Therapeutics, Schering-Plough)/1998
Gabapentin (anticonvulsant, treatment of neurogenic pain; Fujisawa, Warner-Lambet)/1993
Lamotrigine (anticonvulsant, glutamate release inhibitor; Glaxo Wellcome, DuPont Pharm., Faes)/1990
Loratadine (antihistaminic; Schering-Plough)/1988
Mosapride citrate (prokinetic, treatment of GERD; Dainippon, AstraZeneca, Dae Wong)/1998
Moxonidine hydrochloride hydrate (antihypertensive, imidazoline I_1 agonist; Lilly, Solvay)/1991
Oxaliplatin (antineoplastic, platinum complex; Lilly, Sanofi-Synthélabo)/1996
Paricalcitol (treatment of thyroid disease; Abbott)/1998
Simvastatin (hypolipidemic, HMG-CoA reductase inhibitor; Merck & Co., Mediolanum, Amrad)/1988
Vigabatrin (anticonvulsant, treatment of alcohol withdrawal syndrome; Hoechst Marion Roussel, Novartis)/1989

N-Acetylcysteine

Antioxidant
Mucolytic
Immunostimulant

EN: 091298



$C_5H_9NO_3S$ **Zambon**

N-Acetylcysteine (NAC) was shown to prevent tumor angiogenesis while protecting endothelial cells from apoptosis and damage *in vitro* and *in vivo*. NAC dose-dependently decreased the ability of endothelial cells to invade reconstituted basement membrane (ID_{50} = 0.24 nM) and chemotaxis was inhibited with a 10-fold higher dose; gelatinase activity of cells was also inhibited by treatment. Revascularization was potently inhibited *in vivo* by NAC in the matrigel assay using Kaposi's sarcoma cell products while protecting endothelial cells from TGF-β-induced apoptosis and genotoxin-induced cytogenetic damage (1).

Dinitroacetylcysteine (DiNAC) (0.003-30 μmol/kg p.o.) was shown to be a potent immunomodulator of contact sensitivity and delayed-type hypersensitivity in mice *in vivo*. DiNAC-treated animals showed enhanced contact sensitivity in response to oxazolone and 100-1000 times more potency was observed with DiNAC as compared to NAC; the disulfide structure was found to be required for activity. Delayed type hypersensitivity of methylated BSA-induced footpad-swelling was reduced by DiNAC. Simultaneous treatment with NAC and buthionine sulfoximine blocked and enhanced, respectively, the DiNAC-induced enhancement in contact sensitivity, indicating that redox processes are involved in DiNAC action. Increased numbers of $CD8^+$ cells were observed in oxazolone-sensitized and -challenged specimens from ears and contact sensitivity was also enhanced by DiNAC when fluorescein isothiocynate was the sensitizer, suggesting a Th1 type response (2).

The efficacy of NAC in the prevention of defective endothelium-dependent relaxation was evaluated in diabetic rats. Oral administration of NAC 250 mg/l did not affect increased blood glucose or reduced serum insulin levels, although reductions in total glycosylated hemoglobin levels were observed. Endothelium-dependent relaxation induced by acetylcholine in precontracted thoracic aortic rings was inhibited by NAC, and long-term exposure to NAC prevented defective relaxation produced by exposure to acetylcholine (3).

The protective efficacy of NAC against dopamine-induced toxicity was examined in animals receiving NAC 500 mg/kg i.p. 30 min prior to intrastriatal injections of dopamine. Significant reductions in cysteinyl-dopamine and cysteinyl-DOPAC were observed in animals treated with NAC as compared to untreated animals. Treatment with NAC also reduced the size of tyrosine hydroxylase zone loss, suggesting that NAC may be a treatment option for Parkinson's disease (4).

Administration of NAC 300 mg/kg i.p. in mice did not inhibit acetaminophen-induced arylation of liver cell proteins, but when administered concomitantly with acetaminophen, a 50% reduction in binding was observed. Acetaminophen-induced induction of hsp25 and hsp70i was also unaffected by NAC, consistent with the hypothesis that toxicant adduction of proteins triggers hsp induction (5).

The effects of NAC on acute renal failure induced by inferior vena cava occlusion were evaluated in anesthetized dogs. Treatment produced progressive recovery of glomerular filtration rate and demonstrated positive effects on tubular dysfunction during reperfusion. Renal response to acetylcholine was preserved during reperfusion in NAC-treated animals (6).

Administration of NAC prior to liver perfusion in rats under normal and hyperoxic conditions dose-dependently increased glutathione concentrations in bile, liver and perfusate. However, when administered together with buthionine sulfoximine, these effects were absent and oxidative stress was evident. Thus, NAC protects against oxidative stress most likely by supplying cysteine for glutathione synthesis (7).

Administration of NAC (0.1 or 0.5 g/kg p.o.) in mice significantly reduced the clastogenicity and multiplicity of carcinogen-induced lung tumors. The results justified the prediction of lung tumor yield based on the intensity of the early genotoxicity biomarker – micronucleated normochromatic erythrocytes in peripheral blood (8).

The effects of NAC on the vascular response of mesenteric artery were evaluated in spontaneously hypertensive rats. Administration of NAC (4 g/kg/d) augmented the relaxant effects of acetylcholine to a greater degree as compared to untreated animals. The enhanced endothelium-dependent vasodilation by NAC suggests that an enhanced NO synthase activity or a reduced rate of NO degradation may be responsible for mesenteric artery vasorelaxation (9).

Exposure of LLC-PK1 cells to 1 mM NAC almost completely suppressed cellular damage induced by cadmium and suppressed cadmium-induced increases in c-Fos protein expression, although the total c-Fos protein content was not affected. In addition, NAC lowered the uptake of cadmium into cells without affecting the efflux of the metal, indicating that protection against cadmium-induced toxicity is mainly achieved through the inhibition of cadmium uptake (10).

The vascular endothelial function in aortic rings from oophorectomized and ovary-intact rats were compared. In addition, the effect of NAC on endothelial function was assessed. As found, a lack of ovary estrogens is related to vascular endothelium dysfunction, which is reversible with the addition of NAC (11).

A clinical study demonstrated that the antioxidants, NAC and α-lipoic acid, restored peripheral blood mononuclear cell (PBMC) function in 10 advanced stage lung or ovarian cancer patients with cachectic symptoms, indicating that oxidative stress may be involved in impairment of the immune system in cancer. Cancer patients had

higher serum levels of all cytokines as compared to healthy controls and lower PBMC proliferative responses. While expression of CD25 and CD95 on unstimulated PBMCs was the same in both groups, anti-CD3 MAb-stimulated cancer patient PBMC responses were lower and fewer PBMCs progressed into the S-phase as compared to normal subjects. Addition of NAC and α-lipoic acid to anti-CD3 MAb-stimulated PBMCs increased expression of CD25 and CD95 significantly more in cancer patients (12).

NAC significantly reduced TNF-α levels in lipopolysaccharide-stimulated and -unstimulated alveolar macrophages in bronchoalveolar lavage fluid obtained from lung transplant recipients. The reduced TNF-α protein levels were associated with reduced TNF-α mRNA expression, indicating that treatment with antioxidants may retard the inflammatory process in lipopolysaccharide-induced macrophages and may represent a treatment option in lung transplantation, preventing the loss of allograft function (13).

NAC treatment did not prevent trimethoprim-sulfamethoxazole (TMP-SMX) hypersensitivity reactions in *Pneumocystis carinii* pneumonia prophylaxis. In the trial, 238 HIV-positive patients were randomized to receive NAC (3 g of a 20% liquid solution) 1 h prior to each dose of TMP-SMX. After 2 months, 45 patients, (25% from the TMP-SMX alone group and 21% receiving TMP-SMX and NAC) discontinued due to rash, fever or pruritus (14).

NAC was shown to improve *Helicobacter pylori* eradication with no effects on ulcer healing in a randomized study involving 100 *H. pylori*-positive patients with or without duodenal ulceration. Patients received omeprazole (20 mg b.i.d. for 4 weeks) + clarithromycin (500 mg b.i.d. for 2 weeks) with or without NAC (200 mg t.i.d. for 4 weeks) or NAC alone. Ulcer healing was observed in 95% of all patients with ulceration. *H. pylori* was negative in 50% of patients with ulcers with or without added NAC therapy and in 64% and 55% of the nonulcerated patients receiving combination treatment with or without NAC, respectively; only 6% of the patients treated with NAC alone were negative. After 6 months, significantly more NAC-treated patients achieved eradication of *H. pylori* (75% *vs.* 37%), suggesting that NAC may prevent duodenal ulcer relapse (15).

The efficacy of NAC (300 mg/d via aerosol for 20 d) was investigated in 10 patients with COPD and 3 with chronic bronchitis, with results showing that circulating reactive oxygen metabolites were significantly reduced in 12/13 cases as assessed by lung function tests, hemogas analysis and analysis of arterial blood. No changes in PO_2, PCO_2 pH, VC, FEV_1/VC%, RV or RV/TLC% were observed (16).

Improved early liver function and less injury were observed in a study in which 62 liver donors received either NAC (600 mg/kg *i.v.*) or placebo at least 1 h prior to extraction. The NAC group had lower transaminase levels, improved AST levels on day 1 posttransplant, significantly greater prothrombin time on days 1-4 and statistically higher bile production on days 3 and 5. Less acute rejection was also observed in the NAC group (36% *vs.* 57%) and 1-year survival was 92% *vs.* 81% in the placebo group (17).

Chronic administration of a high dose of NAC to 26 patients with stable angina pectoris was shown to prevent nitrate tolerance. Patients on β-blocker therapy were randomized to receive ISDN (40 mg t.i.d.) with 200 or 600 mg NAC (t.i.d.) and evaluated using an ergometric exercise test and Holter monitoring before and 1 h and 5 d after treatment. The low dose of NAC had no affect on nitrate tolerance (18).

The plasma cystine-thiol ratio, an indicator of the redox state, was shown to increase with old age and in cancer patients, suggesting that treatment of cancer patients with thiol-containing antioxidants such as NAC may improve the quality of life. Two studies were conducted in which venous blood samples were randomly examined from a total of 204 healthy volunteers and 70 cancer patients receiving oral NAC (0.6-4.2 g t.i.d.), IL-2 (6 x 106 IU s.c. twice/week) or a combination and 38 healthy males administered oral NAC (200 mg b.i.d. 3 d/week) or placebo in a double-blind, randomized manner for 4 weeks. Increases in body cell mass were observed in NAC-treated healthy subjects with high plasma cystine-thiol ratios, and increases in body cell mass, plasma albumin and functional capacity were noted in cancer patients treated with NAC alone or in combination with IL-2 (19).

A multicenter, randomized trial was conducted in 2592 patients with early stage head and neck cancer given either retinyl palmitate (300,000 IU/d for 1 year then 150,000 IU/d for 1 year), NAC (600 mg/d for 2 years), a combination of the two or no treatment. Of the 2573 evaluable patients, 23% of the 1932 patients randomized to one of drug treatments discontinued and 13% had irregular intake. Treatments were well tolerated with more toxicity observed in patients receiving retinyl compared to the group receiving NAC alone (45% *vs.* 24%). After 49 months follow-up, 912 patients had an event including recurrence, tobacco-related and nontobacco-related secondary tumors and death in 563, 170, 43 and 134 patients, respectively (20).

The effects of NAC on cognitive, affective and functional status have been studied in patients with probable AD. Thirty-two patients received either NAC (50 mg/kg/d p.o.) or placebo for 6 months in a double-blind trial. Although more patients withdrew before the end of the study on NAC (4 *vs.* 1 on placebo), no significant difference in side effects was noted between the two treatment groups. Treatment with NAC resulted in modest improvement in several cognitive measures and, overall, the results suggest that antioxidants may be useful for preventing or delaying further degeneration in patients at high risk for developing AD (21).

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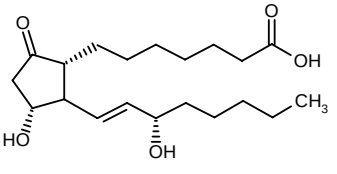
Alprostadil
Befar®
Muse®
Topiglan®

Treatment of Erectile Dysfunction

EN: 091363



$C_{20}H_{34}O_5$

Janssen; AstraZeneca; MacroChem; Harvard Scientific; NexMed; Vivus; Bio-Medic Inst.

A 4-year multicenter European study has demonstrated the long-term efficacy and safety of alprostadil alfadex for the treatment of chronic erectile dysfunction of

organogenic or psychogenic origin. One hundred and sixty-two patients were included in the open-label study and self-administered a total of 16,886 protocolled injections of alprostadil alfadex. Total efficacy over the 4-year period (erection sufficient for successful intercourse) was 93.1%. Painful erections were reported by 29% in the first year, decreasing to 12.1% in the fourth year. Prolonged erections (>6 h) occurred in just 1.2% of patients in the first year. Febrile penile alterations occurred in 11.7% of the study subjects; these healed spontaneously in 48% of the cases. Fifty-four men completed the 4-year study, 91.4% of whom were satisfied with the tolerability of intracavernous injection of alprostadil alfadex. Female partners were also polled: 51.7% were very satisfied and 39.7% were satisfied with the treatment. This study is the longest running prospective trial ever to evaluate this type of self-treatment for erectile dysfunction (1).

NexMed announced the successful completion of Chinese phase III trials evaluating its topical treatment for erectile dysfunction, Befar®. A total of 143 men with erectile dysfunction were recruited at 3 sites in China and evaluated in the double-blind, open-label trial. Fifty-four men were categorized as severely impotent and 89 as mildly to moderately impotent. The total overall efficacy rate was 75%, and no significant side effects were noted in this patient group. NexMed plans to file with the China Drug Administration for marketing approval (2).

MacroChem Corp. announced that its topical gel formulation of alprostadil (Topiglan®) showed promising efficacy and safety in a preliminary analysis of a phase IIb study in patients with erectile dysfunction. The double-blind, randomized, placebo-controlled study evaluated 1% alprostadil in a SEPA-formulated gel (Topiglan®) compared to the SEPA-formulated gel without alprostadil. Sixty patients with erectile dysfunction, many of whom had failed available therapies, received either treatment applied topically to the head of the penis along with visual and tactile stimulation in an office setting. Topiglan® was associated with significantly greater penile rigidity and tumescence compared to placebo, as assessed by the physician and the patient: 6 times more patients receiving Topiglan® reported an erection sufficient for vaginal intercourse. Transient, mild symptoms of localized warmth, mild burning or tingling were reported, with no significant difference between drug and placebo treatments (3).

Harvard Scientific has developed a topically applied product for the treatment of male erectile and sexual dysfunction that incorporates the company's lyophilized liposomal delivery of alprostadil but does not utilize a transdermal enhancer. This product, which will be administered locally to the penis as a lotion and is very similar to the company's new, recently announced treatment for female sexual dysfunction, will complement its aqueous solution, intrameatal delivery treatment for male sexual dysfunction (4).

Astra (AstraZeneca) has launched Vivus's Muse® (transurethral alprostadil) for the treatment of erectile dysfunction in Germany, bringing the total to 39 countries. Muse® is also available in Canada from Janssen-Ortho and Bio-Medic Institute will market the compound in Japan upon approval from the Japanese regulatory authorities (5-11).

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5. *Canadian launch for minimally invasive impotence treatment.* DailyDrugNews.com (Daily Essentials) Sept 17, 1998.

6. *E.U.-wide marketing approval granted for Muse*. DailyDrugNews.com (Daily Essentials) Dec 14, 1998.

7. *E.U.-wide Muse approval triggers license and milestone payments from Astra.* DailyDrugNews.com (Daily Essentials) Dec 21, 1998.

8. *Muse granted marketing approval in Germany.* DailyDrugNews.com (Daily Essentials) Feb 26, 1999.

9. *Further marketing authorizations granted in Europe for Muse.* DailyDrugNews.com (Daily Essentials) March 19, 1999.

10. *Vivus signs registration and marketing agreement in Japan for Muse.* DailyDrugNews.com (Daily Essentials) May 24, 1999.

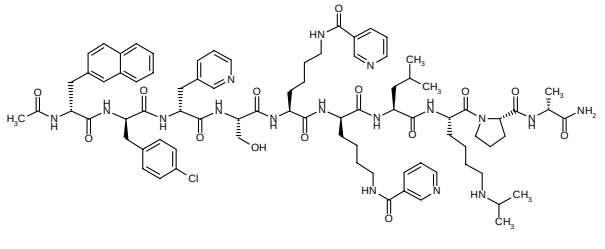
11. *Vivus announces another European launch for Muse.* DailyDrugNews.com (Daily Essentials) June 10, 1999.

Original monograph - Drugs Fut 1987, 12: 541 (published as Lipo-Alprostadil).

Antide
Iturelix

Treatment of Female Infertility
GnRH Antagonist

EN: 147696



$C_{82}H_{108}ClN_{17}O_{14}$ **Ares-Serono**

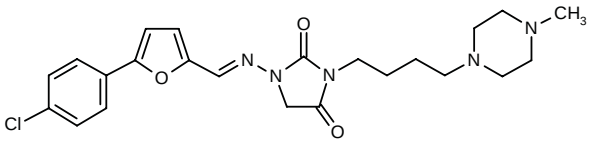
Iturelix is the proposed international nonproprietary name for antide (1).

1. *Proposed international nonproprietary names (Prop. INN): List 79.* WHO Drug Inf 1998, 12(2): 107.

Original monograph - Drugs Fut 1991, 16: 529.

Azimilide Hydrochloride *Antiarrhythmic*
Stedicor®

EN: 195716



.2HCl

$C_{23}H_{28}ClN_5O_3.2HCl$ **Procter & Gamble; Tanabe**

Azimilide (50, 100 and 125 mg/d p.o.) was compared to placebo and assessed for its efficacy in reducing symptomatic recurrences of atrial fibrillation in a multicenter, randomized trial. Time to recurrence was significantly longer with azimilide as compared to placebo. Torsades de pointes was observed in 1 patient administered 100 mg (1).

The steady-state pharmacokinetics and pharmacodynamics of azimilide were evaluated in 119 healthy male and female volunteers. Two groups, 1 comprising 18-40 year-olds and another including subjects >55 years, were administered doses of 35, 100, 150 or 200 mg/day with 1, 2 or 3 days of loading. Mean peak steady-state concentrations ranged from 186-1030 ng/ml and mean trough steady-state azimilide concentrations ranged from 108-549 ng/ml. Pharmacokinetics were dose-proportional except for renal clearance and did not differ among the two groups. Pharmacodynamics were not dose-dependent. The mean E_{max} was a 24-28% change in QT and a concentration of 432-542 ng/ml was necessary to achieve one half E_{max}. The equilibration half-life was < 1 min (2).

Findings from pivotal phase III studies of azimilide hydrochloride have recently been reported. These studies form part of the Azimilide Supraventricular Arrhythmia Program (ASAP) and demonstrate that azimilide reduces the risk of recurrence in patients with symptomatic paroxysmal supraventricular tachycardia (PSVT). In the study, azimilide (100, 75 or 35 mg) or placebo was administered daily to 133 patients (65% women) with PSVT. The patients were tracked over 180-270 days. Patients receiving placebo had a 135% greater risk of a symptomatic arrhythmia recurrence compared to patients treated with azimilide. On the average, patients receiving azimilide were 60% more likely to be free from a symptomatic occurrence on any given day than patients receiving placebo. In the ASAP trials to date, azimilide has been generally well tolerated, with headache being the most common side effect. The observed overall torsade de pointes rate was approximately 1%. Azimilide is the first antiarrhythmic agent to effectively block both the slow and fast potassium channels in the heart. Procter & Gamble has submitted an NDA to the U.S. Food and Drug Administration for azimilide, as well as applications for regulatory approvals in Canada and Europe (3, 4).

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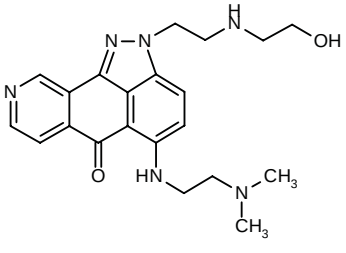
BBR-3409 *Antineoplastic*

EN: 210577



$C_{21}H_{26}N_6O_2$ **Roche; Univ. Vermont**

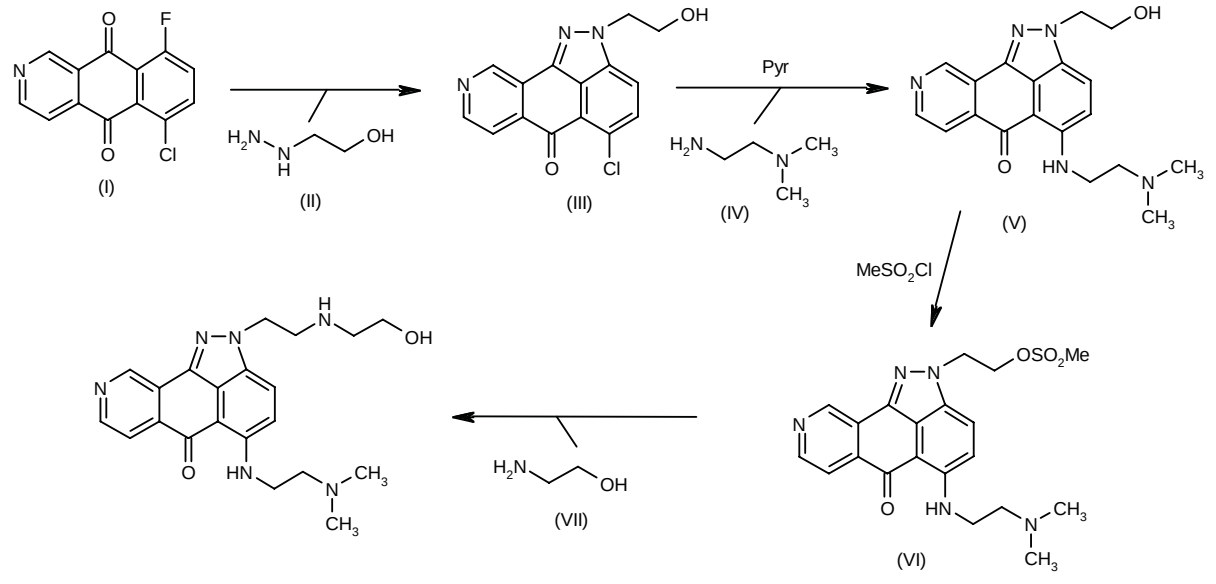
A synthesis of BBR-3409 has been described: The cyclization of 6-chloro-9-fluorobenz[*g*]isoquinoline-5,10-quinone (I) with 2-hydroxyethylhydrazine (II) in hot pyridine gives 2-(2-hydroxyethyl)-5-chloroindazolo[4,3-*gh*]-isoquinolin-6(2*H*)-one (III), which is condensed with 2-(dimethylamino)ethylamine (IV) in hot pyridine, yielding the corresponding 5-[2-(dimethylamino)ethylamino] derivative (V). The mesylation of the OH group of (V) with mesyl chloride and triethylamine in dichloromethane affords the mesylate (VI), which is finally condensed with hot ethanolamine (VII).

Description: red solid, m.p. 184-6 °C; dimaleate, m.p. 170.6 °C (decomp., DSC) (1). Scheme 1.

1. Krapcho, A.P. et al. *Synthesis and antitumor evaluation of 2,5-disubstituted-indazolo[4,3-gh]isoquinolin-6(2H)-ones (9-aza-anthrapyrazoles).* J Med Chem 1998, 41(27): 5429.

Original monograph - Drugs Fut 1997, 22: 641.

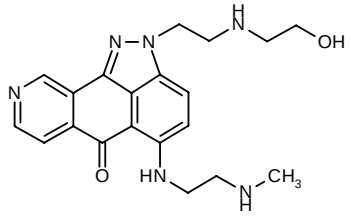
Scheme 1: Synthesis of BBR-3409



BBR-3438

Antineoplastic

EN: 210576



$C_{20}H_{24}N_6O_2$ **Roche; Univ. Vermont**

The synthesis of BBR-3438 has been described: The cyclization of 6-chloro-9-fluorobenz[*g*]isoquinoline-5,10-quinone (I) with 2-hydroxyethylhydrazine (II) in hot pyridine gives 2-(2-hydroxyethyl)-5-chloroindazolo[4,3-*gh*]-isoquinolin-6(2*H*)-one (III), which is condensed with *N*-(2-aminoethyl)-*N*-methylcarbamic acid *tert*-butyl ester (IV) in hot pyridine, yielding the corresponding 5-[2-[*N*-(*tert*-butoxycarbonyl)-*N*-methylamino]ethylamino] derivative (V). The mesylation of the OH group of (V) with mesyl chloride and triethylamine in dichloromethane affords the mesylate (VI), which is condensed with hot ethanolamine (VII) to give the protected compound (VIII). Finally, this compound is deprotected with HCl, yielding BBR-3438.

Description: trihydrochloride, m.p. 270-3 °C (1). Scheme 2.

Results from DNA-binding studies examining BBR-3438- and BBR-3576-stimulated topoisomerase II-mediated DNA cleavage showed that both agents have a high affinity for DNA and sequence preferences for G-C steps in double helical B-DNA; results were confirmed using DNAase I footprinting. The bioisoteric substitution at position 9 in the planar ring was shown to be important for modulating the affinity of anthrapyrazoles for the nucleic acid, for the geometry of the intercalation complex and for the sequence-specific contacts on the DNA chain (2).

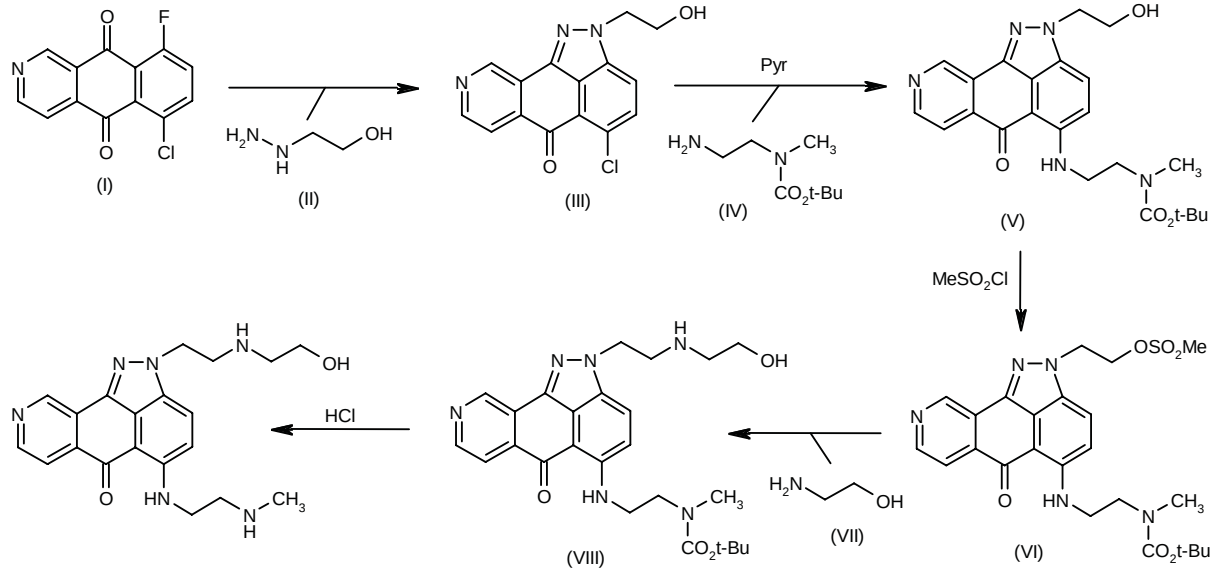
BBR-3438 showed favorable activity in head-to-head comparisons with doxorubicin and DuP-941 and was selected for further testing. It showed equipotent activity to DuP-941 against MX-1 mammary and A2780 ovarian carcinomas and was more potent than doxorubicin in the former case. The compound's activity was most remarkable in the case of prostatic carcinoma. Its activity was superior to that of doxorubicin in all three lines tested and was better than DuP-941 in two of the three. Based on these promising findings, BBR-3438 appears to have therapeutic potential in the treatment of prostatic carcinoma, a type of tumor that is often refractory to conventional cytotoxic agents, although the mechanism underlying this unusual responsivity has not yet been elucidated (3).

1. Krapcho, A.P. et al. *Synthesis and antitumor evaluation of 2,5-disubstituted-indazolo[4,3-gh]isoquinolin-6(2H)-ones (9-aza-anthrapyrazoles).* J Med Chem 1998, 41(27): 5429.

2. Sissi, C. et al. *DNA-interactive aza-anthrapyrazoles: Physicochemical and biological studies relevant to the mechanism of action.* Proc Amer Assoc Cancer Res 1999, 40: Abst 1912.

3. Beggiolin, G., Pezzoni, G., Spinelli, S., Menta, E., Supino, R., Pratesi, G., Polizzi, D., Palumbo, M., Zunino, F. *BBR 3438: A new 9-aza-anthrapyrazole endowed with high antitumor activity in human prostatic carcinoma xenografts.* 10th NCI-EORTC

Scheme 2: Synthesis of BBR-3438



Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 136.

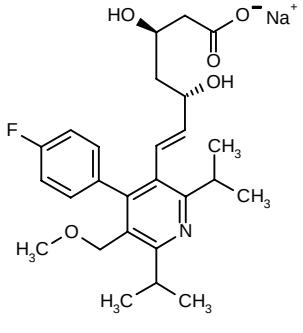
Original monograph - Drugs Fut 1997, 22: 641.

Cerivastatin Sodium

Baycol®
Certa®
Lipobay®

Hypolipidemic
HMG-CoA Reductase Inhibitor

EN: 189237



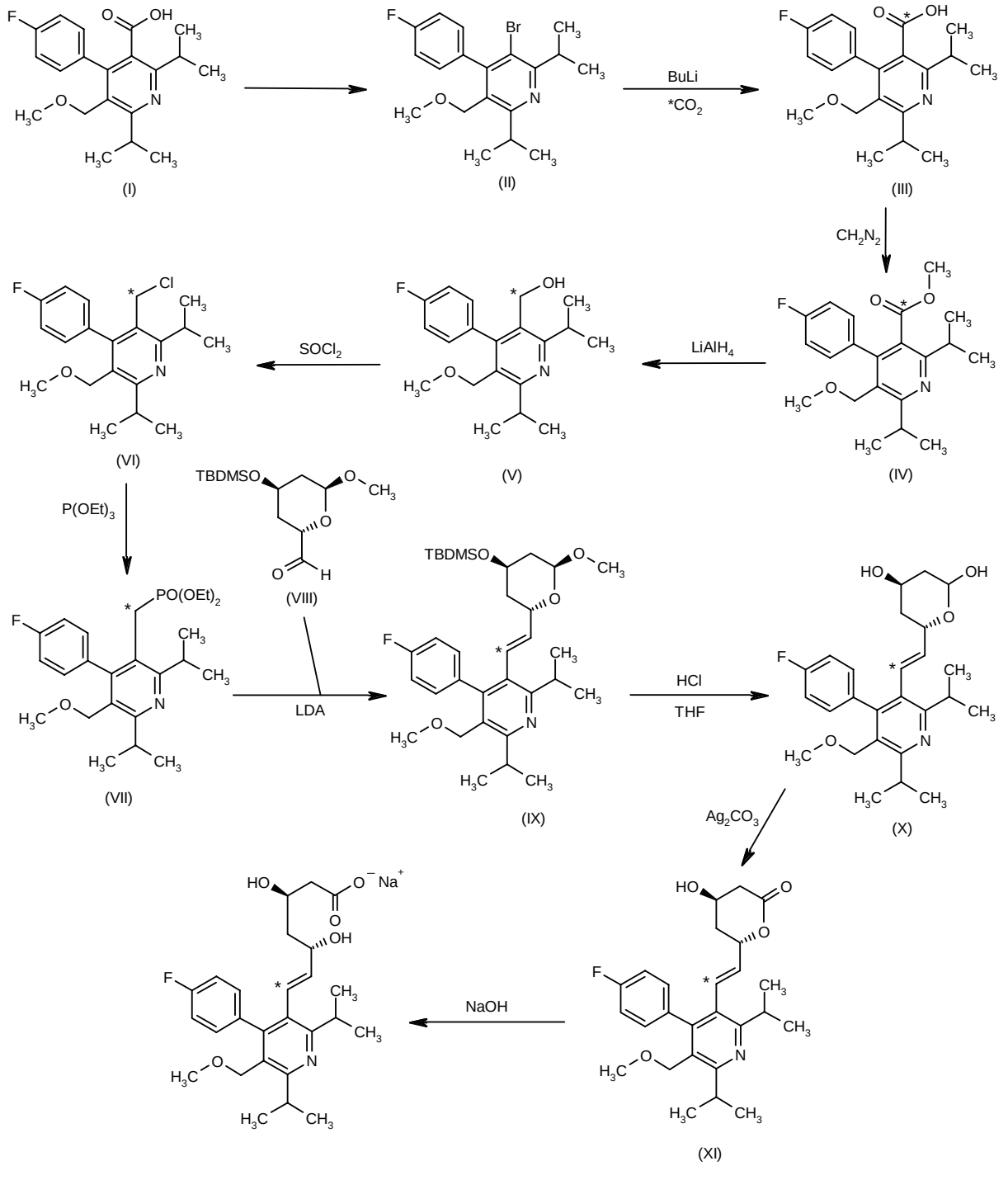
$C_{26}H_{33}FNO_5.Na$ **Bayer; Takeda; Fournier**

A synthesis of [^{14}C]-labeled cerivastatin has been developed: The decarboxylative bromination of 4-(4-fluorophenyl)-2,6-diisopropyl-5-(methoxymethyl)pyridine-3-carboxylic acid (I) gives the bromopyridine (II), which is treated with BuLi and [^{14}C]-labeled CO_2, affording the labeled carboxylic acid (III). The methylation of (III) with diazomethane gives the corresponding methyl ester (IV), which is reduced with $LiAlH_4$ in ether to the alcohol (V). The reaction of (V) with $SOCl_2$ affords the chloromethyl derivative (VI), which is condensed with triethyl phosphite at 180 °C to give the phosphonate (VII). The condensation of (VII) with the tetrahydropyran-2-carbaldehyde (VIII) by means of LDA in THF yields the olefine (IX), which is treated with HCl in aqueous THF, eliminating the protecting groups and thus providing the epimeric mixture of hemiacetals (X). The oxidation of (X) with silver carbonate in refluxing toluene affords the lactone (XI), which is finally treated with NaOH in water/acetonitrile (1). Scheme 3.

Bayer and Fournier have agreed to comarket cerivastatin sodium in Germany, France, Italy, Spain, Belgium and Luxembourg. The compound is already available in the U.K. and Germany as Lipobay® and in Canada and the U.S. as Baycol® (2).

The FDA has approved a 0.4-mg strength tablet of cerivastatin sodium (Baycol®) as the recommended dose for patients with primary hypercholesterolemia and mixed dyslipidemia. In a clinical study in 349 patients, 40% of patients taking 0.4 mg of cerivastatin achieved >40% reduction in LDL cholesterol (LDL-C). In addition, the product received expanded indications to reduce triglycerides (TG) and apolipoprotein (apoB) in patients with primary hypercholesterolemia and mixed dyslipidemia. Bayer is also continuing to evaluate higher doses of the drug, as well as its potential in special patient populations. The 0.4-mg approval is based on clinical data from 2 large multicenter, placebo-controlled, dose response studies of patients with primary hyperchlolesterolemia. Results showed that with 0.4 mg/day of cerivastatin in

Scheme 3: Synthesis of [^{14}C]-Labeled Cerivastatin Sodium



conjunction with dietary therapy for 8 weeks, patients achieved mean reductions in LDL-C and total cholesterol (TC) of 34% and 24%, respectively. Reductions in apoB levels of 26% were also observed. The recommended dose is 0.4 mg once daily, in the evening, with or without food (3).

Bayer and Takeda have launched cerivastatin for hyperlipemia in Japan. Bayer is selling the product under

the trade name Baycol® and Takeda is marketing the medication as Certa®. Cerivastatin is already being marketed in 15 countries and has been approved in 55 additional countries. The drug was jointly developed for the Japanese market by Bayer and Takeda (4).

1. Radtke, M., Angerbauer, R. *Synthesis of [^{14}C]cerivastatin.* J Label Compd Radiopharm 1999, 42(2): 101.

2. *Bayer, Fournier to copromote statin in some EU countries.* DailyDrugNews.com (Daily Essentials) Sept 7, 1998.

3. *New dose of Baycol approved in the U.S. for treatment of hypercholesterolemia.* DailyDrugNews.com (Daily Essentials) May 27, 1999.

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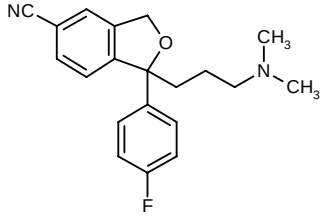
Citalopram
Celexa®
Cipramil®

Antidepressant

EN: 090241



$C_{20}H_{21}FN_2O$

Biovail; Lundbeck; Nycomed Amersham; Forest

Biovail entered a multifaceted agreement with H. Lundbeck A/S concerning citalopram, licensed to Forest for marketing in the U.S. under the trade name Celexa®. Under terms of the agreement, Biovail will develop, manufacture and supply a controlled-release version of citalopram for commercial exploitation by Lundbeck or its licensees worldwide. In addition, Biovail's Crystaal subsidiary will market the immediate-release version of citalopram in Canada in collaboration with Lundbeck. Canadian regulatory approval of the product is expected shortly (1, 2).

Celexa® was approved by Health Canada's Health Protection Branch for the symptomatic relief of depression. The drug's benefits and antidepressant effects have been demonstrated in several large, placebo-controlled clinical trials, as well as in a number of clinical studies comparing it with tricyclic antidepressants and other SSRIs. Celexa® has proved effective and well tolerated in clinical trials involving over 23,000 patients and is currently marketed in 68 countries. Biovail's Canadian marketing division Crystaal Corp. will copromote the drug in collaboration with Lundbeck Canada (3).

Lundbeck and Nycomed Denmark have entered into a comarketing agreement for the Danish market for Cipramil®. Nycomed expects to be ready to service pharmacies, hospitals, psychiatrists and general practitioners by September of this year (4).

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2. *Biovail signs multifaceted agreement with Lundbeck for citalopram.* DailyDrugNews.com (Daily Essentials) Jan 20, 1999.

3. *Celexa approved in Canada.* DailyDrugNews.com (Daily Essentials) Feb 17, 1999.

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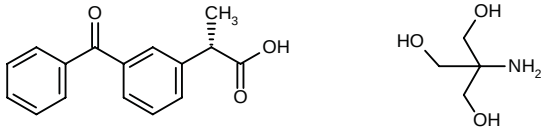
Stahl, S.M. et al. *Double-blind comparison of citalopram, sertraline and placebo.* 152nd Annu Meet Am Psychiatr Assoc (May 15-20, Washington) 1999, Abst NR695.

Thase, M.E. et al. *Citalopram treatment of fluoxetine nonresponders.* 152nd Annu Meet Am Psychiatr Assoc (May 15-20, Washington) 1999, Abst NR640.

Dexketoprofen Trometamol
Enantyum®
Keral®

Antiinflammatory
Analgesic

EN: 235983



$C_{16}H_{14}O_3.C_4H_{11}NO_3$ **Menarini; Chiroscience**

A total of 125 outpatients with moderate to severe pain following removal of 1 impacted third molar were randomized to dexketoprofen trometamol (12.5 or 25 mg) or dipyrone (575 mg). The overall efficacy, rated as good or excellent, was 90, 83.3 and 70% of patients on dexketoprofen 25 mg, dexketoprofen 12.5 mg and dipyrone, respectively. Fewer patients administered dexketoprofen required remedication during a 6-h postoperative period. The incidence and severity of adverse events were similar for all treatment groups (1).

Fifty-two female patients with a history of primary dysmenorrhea were randomized to dexketoprofen (12.5 and 25 mg), ketoprofen (50 mg) or placebo in a multicenter, double-blind, crossover trial to assess the drugs' efficacy and tolerability. Adverse events were reported in 20.8, 15.2, 11.6 and 10.2% of patients on dexketoprofen 25 mg, dexketoprofen 12.5 mg, ketoprofen 50 mg and placebo, respectively, and were gastrointestinal, neurologic and psychiatric in origen. Ketoprofen and dexketoprofen 25 mg showed similar mean scores on pain intensity measures and both agents had a mean time of 120 min to maximum pain relief (2).

Following receipt of approval to market dexketoprofen trometamol (Enantyum®) throughout the European Union earlier this year, Menarini has launched the product in the U.K. under the trade name Keral®. It is indicated for the treatment of musculoskeletal pain, dysmenorrhea and dental pain and is supplied as tablets, 25 mg (3).

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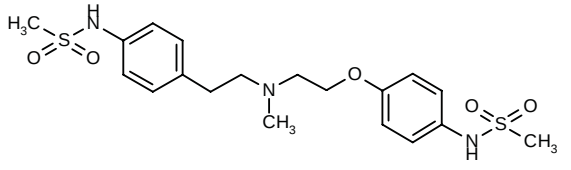
Dofetilide
Tikosyn®
Xelide®

Antiarrhythmic

EN: 138388



$C_{19}H_{27}N_3O_5S_2$

Pfizer

The effects of dofetilide (1, 10, 100 μg/kg i.v.) were examined in an *in vivo* halothane-anesthetized, closed-chest canine model with results showing that the agent selectively blocks I_{kr}. Although 1 μg/kg had no effect, 10 μg/kg dofetilide decreased heart rate and prolonged the ventricular repolarization phase and refractory period; 100 μg/kg reduced cardiac output and left ventricular contraction and heart rate and the repolarization phase and the refractory period were dose-dependently affected. No changes on afterload and preload to the left ventricular or AV nodal and intraventricular conduction were observed. Results indicate a favorable profile for antiarrhythmic therapy (1).

In 37 Danish coronary care units, 1510 patients with myocardial infarction were randomized to dofetilide or placebo in a double-blind study whose primary endpoint was all-cause mortality. Treatment with dofetilide was neutral as compared to placebo with respect to mortality. These results are consistent with those found in the DIAMOND congestive heart failure study. Although dofetilide did not affect mortality, it did beneficially affect conversion of atrial fibrillation to sinus rhythm (2).

A total of 3028 patients with severe congestive heart failure or recent myocardial infarction and a left ventricular ejection fraction of 35% and at high risk of sudden unexpected cardiac death were randomized to dofetilide or placebo in the DIAMOND study. Of these subjects, 17% had concomitant atrial fibrillation or flutter. Dofetilide effectively converted atrial fibrillation to sinus rhythm and maintained sinus rhythm in 75% of those with severely impaired left ventricular function at 1 year (3).

The efficacy, safety and dose relationship of oral dofetilide (125, 250 and 500 μg b.i.d.), sotalol (80 mg b.i.d.) and placebo were assessed in a double-blind trial including 671 patients with atrial fibrillation. One metabolically unstable diabetic woman died while taking dofetilide 500 μg b.i.d. It was concluded that dofetilide is effective and well-tolerated but requires proper monitoring upon initiation (4).

A total of 1518 patients with congestive heart failure and a left ventricular ejection fraction of 35% were randomized to dofetilide (500 μg b.i.d.) or placebo in a double-blind study. Out of 1090 patients in sinus rhythm at baseline, 35 on placebo and 11 on the drug developed atrial fibrillation. The rate of death was similar in both groups. Data from this study showed that dofetilide decreased the incidence of atrial fibrillation or atrial flutter by 70% in this patient population (5).

The efficacy and dose relationship of oral dofetilide (125, 250, 500 μg b.i.d.) and placebo were assessed in 534 patients with atrial fibrillation in a double-blind, parallel-group study. In 431 patients, sinus rhythm was reestablished by day 3 by DC conversion or pharmacologically. The drug cardioconverted significantly more patients in a dose-dependent fashion and maintained significantly more patients in sinus rhythm up to 12 months as compared to placebo. A correlation was found between dofetilide's ability to maintain sinus rhythm after 12 months and the postcardioconversion QT interval; patients with a longer interval (>425 msec) showed a 31% greater probability of staying in sinus rhythm (6).

The efficacy and safety of dofetilide (500 μg b.i.d.), placebo and propafenone (150 μg t.i.d.) were assessed in 122 adults with paroxysmal supraventricular tachycardia. In this double-blind, parallel-group study, no serious adverse events were associated with long-term treatment. No proarrhythmic events were observed with dofetilide; there were 3 cases associated with propafenone. Dofetilide was deemed more effective than placebo and as effective as propafenone in preventing paroxysmal supraventricular tachycardia (7).

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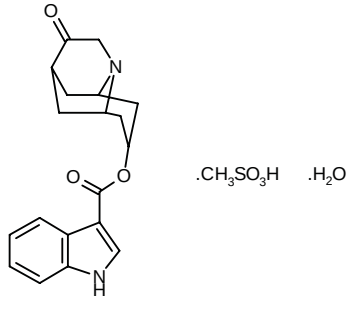
Dolasetron Mesilate
Anemet®
Anzemet®

Antiemetic
5-HT$_3$ Antagonist

EN: 151754



.CH_3SO_3H .H_2O

$C_{19}H_{20}N_2O_3.CH_4O_3S.H_2O$ **Hoechst Marion Roussel; Abbott**

Hoechst Marion Roussel's Anzemet® has been launched in the U.S. for the prevention of nausea and vomiting associated with chemotherapy and surgery. The drug is available in both intravenous and oral formulations. The intravenous form is indicated for both the prevention and treatment of postoperative nausea and vomiting (PONV), while the oral formulation is indicated only for the prevention of PONV (1).

1. *Dolasetron now available in U.S.* DailyDrugNews.com (Daily Essentials) Feb 25, 1998.

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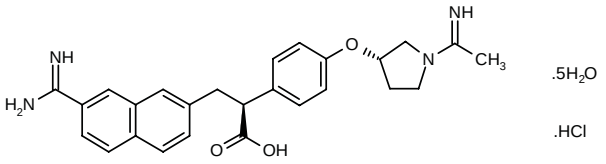
DX-9065a

Anticoagulant
Factor Xa Inhibitor

EN: 199880



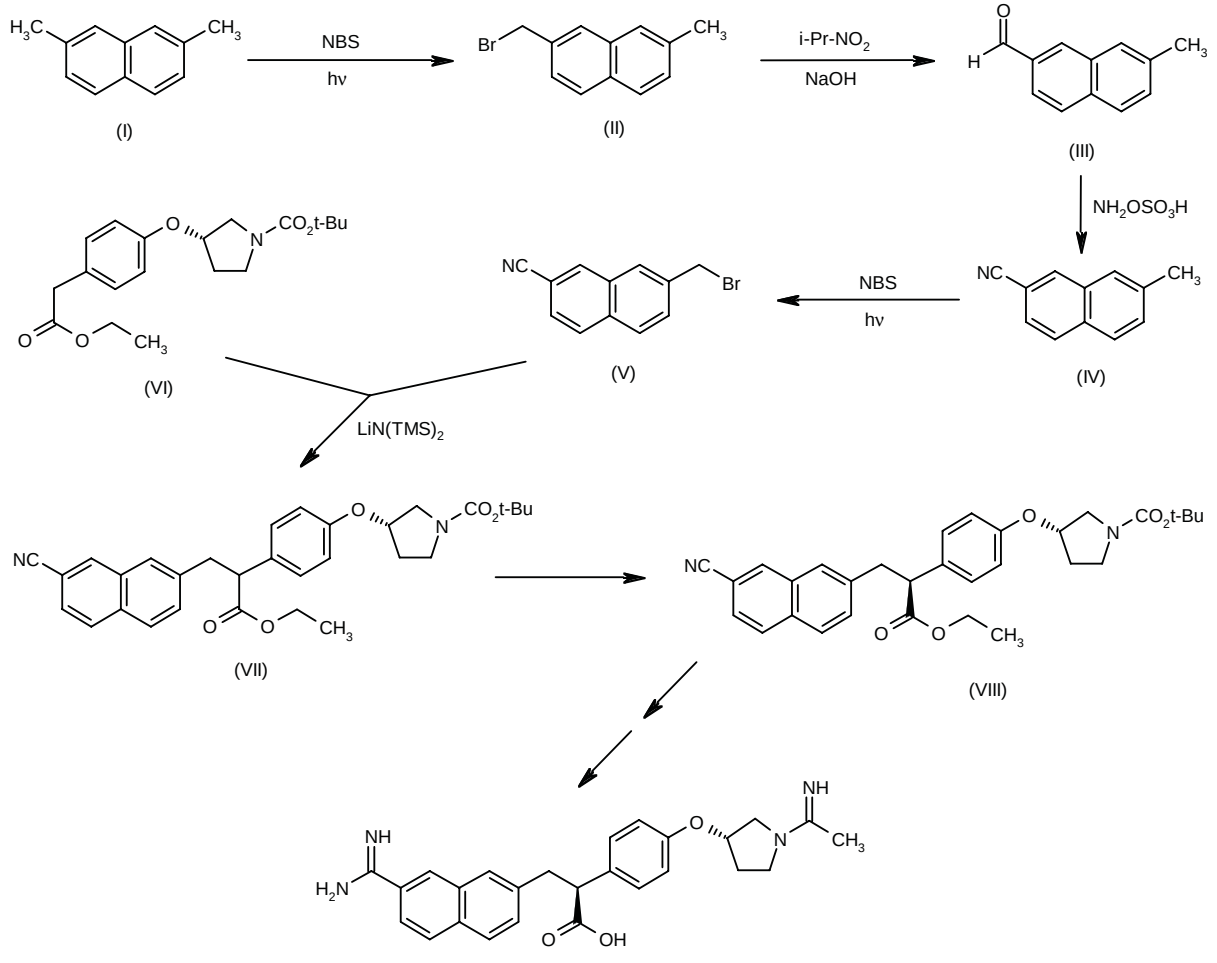
.$5H_2O$

.HCl

$C_{26}H_{28}N_4O_3.HCl.5H_2O$ **Daiichi Pharm.; Beijing General**

A new, easier and laboratory scale synthesis of 2-[4-[1-(*tert*-butoxycarbonyl)pyrrolidin-3(*S*)-yloxy]phenyl]-3-(7-cyano-2-naphthyl)propionic acid ethyl ester, a key intermediate in the synthesis of DX-9065a, has been described: The bromination of 2,7-dimethylnaphthalene (I) with *N*-bromosuccinimide (NBS) and UV light in CCl_4 gives the monobromo derivative (II), which is treated with 2-nitropropane/NaOMe to yield 7-methylnaphthalene-2-carbaldehyde (III). The reaction of (III) with hydroxylamine-*O*-sulfonic acid affords the nitrile (IV), which is brominated with NBS as before to give 7-(bromomethyl)-naphthalene-2-carbonitrile (V). The condensation of (V) with 2-[4-[1-(*tert*-butoxycarbonyl)pyrrolidin-3(*S*)-yloxy]-phenyl]acetic acid ethyl ester (VI) by means of lithium bis(trimethylsilyl)amide yields 2-[4-[1-(*tert*-butoxycarbonyl)pyrrolidin-3(*S*)-yloxy]phenyl]-3-(7-cyano-2-naphthyl)propionic acid ethyl ester (VII) as a diastereomeric mixture. This mixture is worked up as already described to obtain the target compound DX-9065a (1). Scheme 4.

Scheme 4: Synthesis of DX-9065a



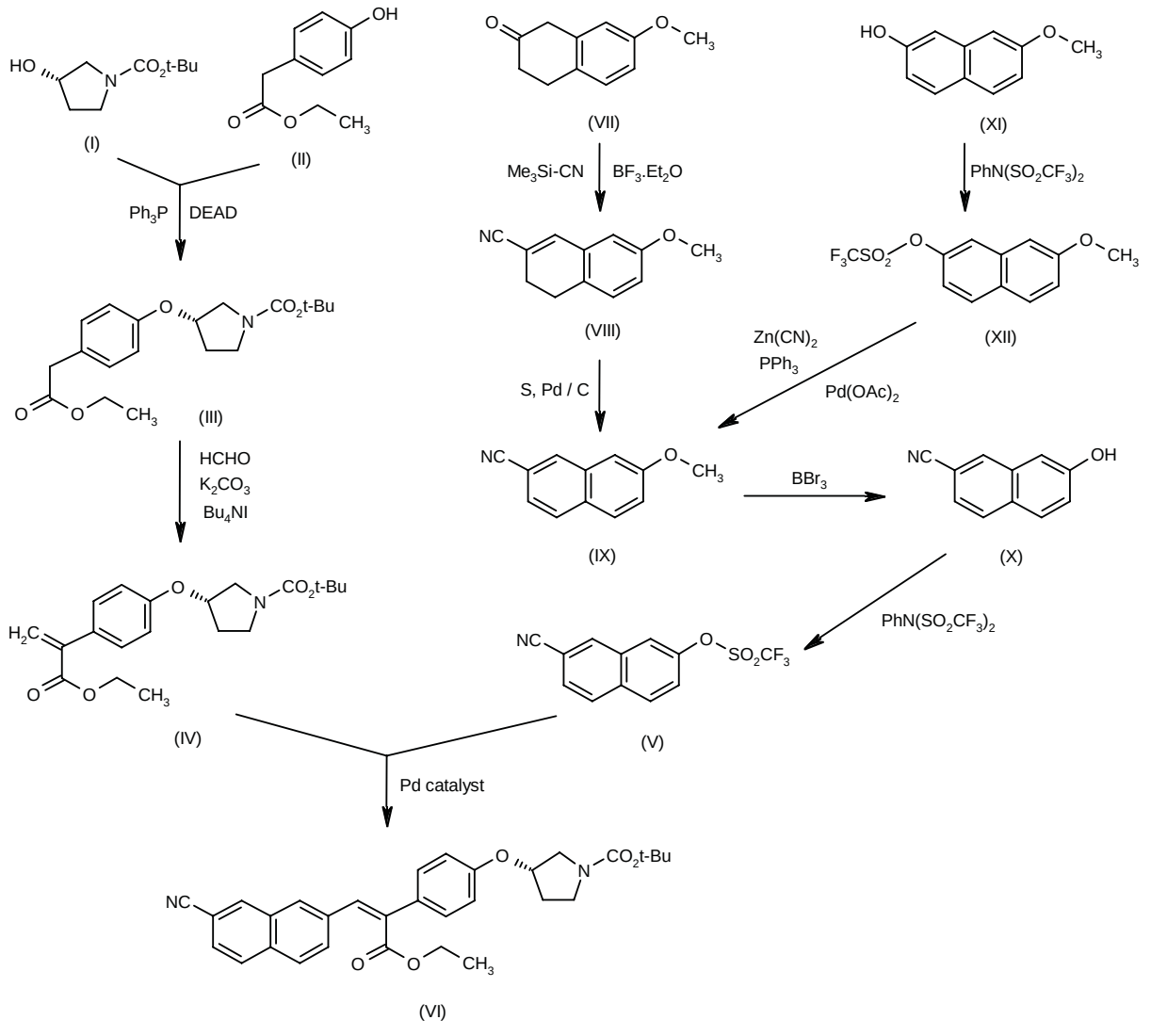
A new synthesis of 2-[4-[1-(*tert*-butoxycarbonyl)pyrrolidin-3(*S*)-yloxy)phenyl]-3-(7-cyano-2-naphthyl)-2-propenoic acid ethyl ester (VI), a key intermediate in the synthesis of DX-9065a, has been described (Scheme 5):

1) The condensation of 3(*R*)-hydroxypyrrolidine-1-carboxylic acid *tert*-butyl ester (I) with 4-hydroxyphenylacetic acid ethyl ester (II) by means of triphenylphosphine and diethyl azodicarboxylate (DEAD) in THF gives 4-[1-(*tert*-butoxycarbonyl)pyrrolidin-3(*R*)-yloxy]phenylacetic acid ethyl ester (III), which is treated with formaldehyde, K_2CO_3 and tetrabutylammonium iodide in hot toluene, yielding 2-[4-[1-(*tert*-butoxycarbonyl)pyrrolidin-3(*R*)-yloxy]phenyl]-2-propenoic acid ethyl ester (IV). Finally, this compound is condensed with 7-(trifluoromethylsulfonyloxy)naphthalene-2-carbonitrile (V) by means of a Pd catalyst in hot DMF to afford the target compound (VI).

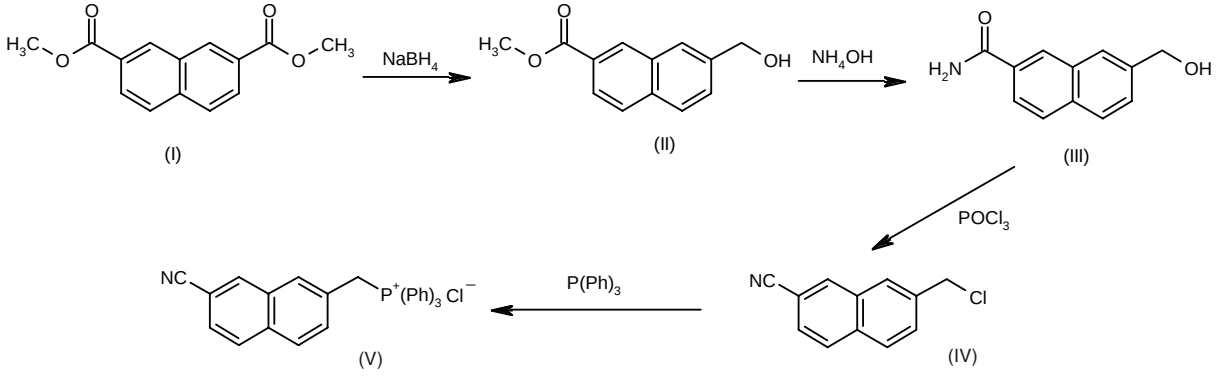
2) Compound (V) has been obtained as follows: The reaction of 7-methoxy-1,2,3,4-tetrahydronaphthalen-2-one (VII) with trimethylsilyl cyanide using BF_3 ethearate as catalyst gives 7-methoxy-3,4-dihydronaphthalene-2-carbonitrile (VIII), which is aromatized with sulfur and Pd/C to naphthalene (IX). The demethylation of (IX) with BBr_3 in dichloromethane affords 7-hydroxynaphthalene-2-carbonitrile (X), which is finally converted into the triflate (V) with $PhN(SO_2CF_3)_2$ as triflating agent. Alternatively, the triflation of 7-methoxy-2-naphthol (XI) as before gives the triflate (XII), which is converted into the already obtained carbonitrile (IX) by reaction with $Zn(CN)_2$ catalyzed by triphenylphosphine and palladium acetate in hot 1-methyl-2-pyrrolidone (2).

A new easier synthesis of the phosphonium salt 7-cyano-2-naphthyl(triphenyl)phosphonium chloride (V), a key intermediate in the synthesis of DX-9065a, has been described: The partial reduction of naphthalene-2,7-dicarboxylic acid dimethyl ester (I) with $NaBH_4$ in methanol gives 7-(hydroxymethyl)naphthalene-2-carboxylic acid methyl ester (II), which by reaction with ammonia yields the amide (III). The reaction of (III) with $POCl_3$/diisopropylamine affords 7-(chloromethyl)naphthalene-2-carbonitrile (IV), which is finally treated with triphenylphosphine to afford (V) (3). Scheme 6.

Scheme 5: Synthesis of Intermediate (VI) of DX-9065a



Scheme 6: Synthesis of Intermediate (V) of DX-9065a



The effects of DX-9065a against platelet activation induced by various agonists have been evaluated in whole blood. At a concentration of 10 mg/ml, DX-9065a completely inhibited tissue factor- or factor Xa-induced platelet activation, whereas it exhibited no effect against platelet activation induced by γ-thrombin, TRAP or arachidonic acid. It was concluded that interference with the coagulation system at the level of factor Xa is able to effectively prevent platelet activation induced by tissue factor or factor Xa via inhibition of thrombin generation and prevention of thrombin-mediated platelet reactions (4).

The effects of DX-9065a (10 or 30 mg/kg p.o.) and warfarin (0.75 mg/kg p.o.) were compared on bleeding time and blood loss in the rat tail transection model and on blood loss in the rat HCl-induced gastrointestinal hemorrhage model with results demonstrating that DX-9065a did not facilitate hemorrhage. Animals were treated with the agent 1 h and 15-21 h prior to transection- and HCl-induced hemorrhage, respectively. Although bleeding time was prolonged by both agents in the rat tail model, only warfarin facilitated blood loss. Only warfarin was found to increase blood loss in the gastrointestinal model about twice as much as controls (5).

The prolongation of coagulation time and factor Xa inhibition by DX-9065a were evaluated after single 1-h i.v. infusions of 5, 10, 20 or 30 mg or multiple 1-h i.v. infusions of 15 mg o.d. or b.i.d. for 1 week. Seventy-two healthy volunteers were randomized to nine regimens of active drug or placebo (6 subjects/group). DX-9065a exerted good anticoagulation which was dose-responsive and directly related to plasma concentration. Good tolerance and no tendency to bleeding were also reported (6).

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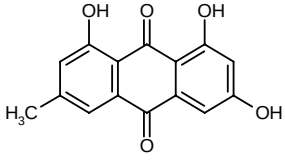
Emodin

Antineoplastic
Antibacterial
Immunosuppressant

EN: 237157



$C_{15}H_{10}O_5$

China Pharm. Univ.

Emodin (0.005-0.02 mg/ml) in combination with glycyrrhizin (0.5-7 mg/ml) was assessed for its effects on *in vitro* cancer cell proliferation and its mode of action. The combination was found to effectively inhibit tyrosine kinase activity and increase apoptosis. Additionally, the combination increased the cellular concentration of hydrogen peroxide (1).

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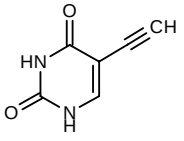
Eniluracil *Potentiator of 5-FU Activity*
776C85 *Dihydropyrimidine Dhydrogenase Inhibitor*

EN: 184938



$C_6H_4N_2O_2$ **Glaxo Wellcome**

The *in vivo* tissue and tumor pharmacokinetics of 5-FU (1 mg/m^2 p.o. b.i.d. x 28 d) following dihydropyrimidine dehydrogenase (DPD) inactivation with eniluracil (20 mg/m^2 b.i.d. p.o. x 28 d) were examined by positron emission tomography in 6 patients with advanced gastrointestinal cancers. By 60 min before DPD inactivation, < 1% of 5-FU was unmetabolized in plasma, whereas 4 h after DPD inactivation, 97% was metabolized in 10/11 plasma samples. Liver and kidney AUC values were higher before DPD inactivation and time-activity curves after DPD inactivation of liver, kidney and spleen were similar to plasma, peaking early with a rapid washout. Peak 5-FU vertebrae concentrations were low (< 5 mcM) and tumor AUCs were similar before and after DPD inactivation, with values lower than in normal tissue due to reduced tumor blood flow (1).

Plasma uracil concentrations were measured over a range of 0.025-250 μM using a validated gas chromatography/mass spectroscopy assay in a study involving 9 patients given oral eniluracil (20 mg q12h). After 2 doses, plasma levels increased by more than 100-fold from 0.16 ± 0.05 to 20.4 ± 5.6 μM, indicating inhibition of DPD. Levels were increased another 2.6-fold over 24 h following 5-fluorouracil administration, suggesting increased intracellular uracil release due to inhibition of thymidylate synthase (2).

Thirteen patients with advanced squamous cell carcinomas of the head and neck received eniluracil (20 mg q12h) and escalating doses of 5-FU (2.5-7.5 mg/m^2) and concomitant radiotherapy. Systemic toxicity (myelosuppression) was dose-limiting in this regimen (3).

Eniluracil was shown to inactivate DPD activity in colorectal tumors in a study in 10 patients given the agent (10 mg/m^2 p.o. b.i.d. x 3 d before surgery) and 10 untreated patients. No intratumoral or mononuclear cell (WBC) DPD activity was detected in treated patients as compared to activities of 30-92 and 265-494 pmol/min/mg protein, respectively, observed in untreated patients; DPD protein or mRNA were unchanged in both groups. Plasma uracil also increased from < 0.2 to 27.76 μM presurgery, also indicative of systemic inactivation of DPD (4).

Preliminary results from a multicenter, open-label, ongoing phase II study demonstrated the tolerability of oral eniluracil and 5-FU (10 and 1 mg/m^2 b.i.d. for 28 d) treatment in 35 chemotherapy naive patients with inoperable hepatocellular carcinoma or patients who failed one anthracycline regimen. Patients received 109 cycles with no grade 3 or 4 hematologic toxicities observed. The most common adverse effects were 5 patients experiencing grade 3 or 4 toxicities, including diarrhea (9%) and dehydration (6%). One case each of fatigue, nausea, weakness, dysplasia, mucositis and hypotension were also reported. Response data from 21 evaluable patients included 5 (24%) patients with stable disease of a duration of 8-52+ weeks and 16 (76%) patients with progression (5).

The pharmacokinetics and pharmacodynamics of fluorouracil (FUra) with eniluracil and leucovorin were examined in patients with solid tumors. Patients were given 1 dose of FUra (2300 mg/m^2/24 h infusion) on day 2 with leucovorin (15 mg b.i.d. p.o. days 1-3) and 2 weeks later, eniluracil and leucovorin (20 and 15 mg b.i.d. p.o. on days 1-3) and FUra (15 mg/m^2 b.i.d. p.o.). None of the first 3 patients completed the planned every week x 6 of 8 courses due to dose-limiting toxicity, including granulocytes < 500/μl, grade 3 diarrhea or pulmonary embolus. In 5/7 patients, decreasing the dose of oral FUra to 10 mg/m^2 b.i.d. with the same doses of the other agents given every week x 3 of 4 courses was well tolerated. Pharmacokinetic results suggest that local gut rather than plasma exposure to FUra contributes to diarrhea (6).

In an open-label, crossover study, 7 patients with advanced solid tumors refractory to standard therapy were given 50 mg/day of eniluracil for 3 days and 35 mg (p.o. or i.v.) of [^{14}C]-5-FU on day 2, followed by a 14-day washout period, after which eniluracil/5-FU treatment was repeated with the alternative route of administration for 5-FU. Systemic exposure to 5-FU and elimination were similar after i.v. and oral dosing; > 50% of unchanged 5-FU was recovered in urine and < 2% in feces, indicating renal elimination (7).

An ongoing multicenter, pilot phase II study demonstrated the efficacy and tolerability of eniluracil and 5-FU (10 and 1 mg/m^2 b.i.d. x 28 d q35d) in 33 women with advanced breast cancer. Out of the 29 evaluable patients, 15 had objective partial response. Treatment was well tolerated with low incidence of grade 3-4 toxicities observed in all 33 patients, which included thrombocytopenia (3%), leukopenia (3%), neutropenic sepsis (3%) and chest infection (3%). No grade 3/4 diarrhea or mucositis was observed. The most common grade 1-2 adverse effects were diarrhea (36%), fatigue/lethargy (27%), nausea (24%), vomiting (12%), mucositis (12%) and headache (9%) (8).

An ongoing phase II study demonstrated the efficacy and tolerability of eniluracil and 5-FU (10 and 1 mg/m^2 b.i.d. x 28 d q35d) in 35 women with anthracycline and taxane refractory breast cancer. Minimal hematologic toxicity was observed with 2 patients showing grade 4 granulocytopenia and grade 3-4 thrombocytopenia. Diarrhea was reported in 41% of the patients, although grade 3-4 was observed in only 3 patients. Nonhematologic toxicities were observed in < 15% of the patients and included nausea, malaise and fatigue, mucositis and anorexia. Out of the 25 patients evaluable for response, 3 had partial responses, 14 had stable disease and 8 had progression (9).

Thirteen patients with recurrent, metastatic or high-risk head and neck cancer were treated with concomitant chemoradiotherapy every other week. Eniluracil was given at 20 mg b.i.d. for 7 consecutive days and radiotherapy was administered to 1 patient once-daily at 2.0 Gy fractions while the others received hyperfractionated therapy at 1.5-Gy fractions b.i.d. 5-FU was initiated at 2.5 mg/m^2 b.i.d. and was then escalated by 2.5 mg/m^2 increments. All patients showed completely or almost completely inactivated dihydropyrimidine dehydrogenase activity. Cumulative myelosuppression was seen in the fourth and fifth cycles and was dose-limiting. Four patients experienced grade 3 mucositis; no grade 4 mucositis or grade 3-4 dermatitis was seen. Significant radiosensitization was not observed (10).

A phase II study has demonstrated the efficacy and tolerability of eniluracil and 5-FU (10 and 1 mg/m^2 p.o. b.i.d. for 28 d) treatment in chemotherapy naive patients with advanced squamous cell head and neck cancer. Of 28 patients, 27 and 23 were evaluated for toxicity and response, respectively, with 2 complete and 4 partial responses observed and an overall response rate of 26.1%. Toxicities were primarily grade 1 and 2 and included lethargy, nausea or diarrhea in 20-30% of the patients and anorexia, vomiting, stomatitis, infection, rash, skin changes or edema in 10-19%. Mild hematologic toxicities were observed with grade 4 leukopenia and grade 3-4 thrombocytopenia in 3 patients. One patient was hospitalized for rehydration and another died from thrombocytopenic bleeding 11 days after starting treatment (11).

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Original monograph - Drugs Fut 1994, 19: 565.

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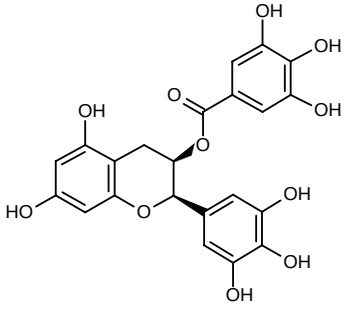
(–)-Epigallocatechin Gallate

Antineoplastic
Chemopreventive

EN: 183411



$C_{22}H_{18}O_{11}$ **Natl. Cancer Center Res. Inst. (JP)**

A study has shown that [^{3}H]-epigallocatechin gallate (EGCG) administered directly into the stomachs of CD-1 mice was widely distributed in tissues. Total radioactivity was excreted in female and male mice within 24 h in urine in 6.6 and 6.4%, respectively, and in feces in 37.7 and 33.1%, respectively. In urine, 0.03-0.59% of the parent compound and at least 5 metabolites were excreted. Levels of the agent were enhanced 4-6 times in blood, brain, liver, pancreas, bladder and bone in females when a second dose was given after a 6-h interval (1).

A study has reported that EGCG and other tea polyphenols inhibited growth of a human cancer cell line (PC-9) in the G_2/M phase. The agent was found to be distributed in skin, stomach, duodenum, colon, liver, lung and pancreas after direct administration of [^{3}H]-EGCG into mouse stomachs. In humans, cancer onset was 8.7 and 3 years later in female and male patients, respectively, who consumed over 10 cups/day of green tea as compared to patients consuming under 3 cups/day. The mechanism of action of EGCG was suggested be through inhibition of TNF-α (2).

An *in vitro* study has shown that [^{3}H]-EGCG incorporation in a human lung cancer cell line (PC-9) was enhanced by (–)-epicatechin, an inert tea polyphenol present in whole green tea without the galloyl moiety. (–)-Epicatechin also dose-dependently enhanced EGCG and other tea polyphenol-induced apoptosis and growth inhibition in PC-9 cells and inhibition of TNF-α from BALB/c-3T3 cells. Sulindac and tamoxifen were shown to act synergistically with EGCG on apoptosis. Thus, whole green tea was concluded to be a more effective mixture for cancer prevention in humans than EGCG alone (3).

Several novel mechanisms of action have been reported for EGCG. The agent interacted with phospholipid membrane, confirming its sealing effect, and inhibited TNF-α gene expression and release in PC-9 cells. In addition, high consumption of green tea was associated with decreased numbers of axillary lymph node metastases in premenopausal Stage I and II breast cancer patients and increased expression of estrogen and progesterone receptors was observed in postmenopausal breast cancer patients (4).

EGCG and (–)-epicatechin-3-gallate (ECG) were shown to be specific inhibitors of IκB kinase activity in intestinal epithelial cells. IkappaB activation was dose-dependently blocked by both agents (up to 0.4 mg/ml) resulting in reduced NFκB activation and IL-8 production. Both agents also directly inhibited TNFα-induced IκB activity (IC_{50}= 18 μM for EGCG and 90 μM for ECG) in a cell-free system, with the gallate group required for inhibition and the catechin structure enhancing the inhibitory effect (5).

A study demonstrated that oral administration of EGCG in drinking water *ad libitum* to mice for 2 weeks during tumor initiation phase reduced nitric oxide-induced papillomas as compared to untreated animals (6).

A study has shown that EGCG inhibits cisplatin-induced weight loss and lung tumorigenesis in mice. Mice were treated with EGCG (1 mg/ml in tap water) or cisplatin (1.62 mg/kg i.p. once/wk x 10) alone or in combination and sacrificed at week 30. Tumor incidence was 30, 100, 93 and 25% in ECG-, cisplatin- and EGCG + *cis*-platin-treated and control mice, respectively, and tumor multiplicity was 0.2 ± 0.97, 5.11 ± 2.10, 2.83 ± 2.33 and 0.4 ± 0.73 tumors/mouse, respectively. EGCG treatment significantly decreased cisplatin-induced tumor multiplicity and weight loss at 16-24 weeks (7).

A study has shown that EGCG may have tissue specific effects on NFκB other than cell-cycle regulatory effects in human tumor cells. Tumorigenic (SCC-9), non-tumorigenic (HaCaT) human keratinocyte cell lines and a human melanoma cell line (A375) transfected with a plasmid containing a minimal NFκB promoter upstream of a luciferase reported gene, were treated with EGCG (50 μM) for 40 h. Results showed significantly reduced luciferase activity in the keratinocyte cell lines but not in the melanoma cell line. Exposure of asynchronous HaCaT cells in log-phase growth to EGCG (10-100 μM) for 48 h had no effect on cell-cycle distribution (8).

A study using human epidermoid carcinoma cells (A431) and normal human epidermal keratinocytes cells showed that EGCG differentially regulates NFκB in normal and cancer cells. EGCG (10-80 μM) dose-dependently inhibited TNF-α- and LPS-induced nuclear activation of NFκB in an electromobility shift assay. Inhibition of NFκB also occurred in normal cells but only with high EGCG concentrations (40 and 80 μM). Activation of NFκB/p65 nuclear protein was also suppressed by EGCG via phosphorylative degradation of its inhibitory protein, IκB-α (9).

EGCG has been shown to provide protection against UVB-induced inflammatory responses in C3H/HeN mice. Topical application of EGCG (3 mg/mouse) prior to UVB exposure (72 mJ/cm^2) reversed inhibition of contact sensitivity response and tolerance induction to the contact sensitizer (DNFB). UVB-induced production of IL-10 in skin and draining lymph nodes was decreased and increased IL-12 production and expression of B7-2 in draining lymph nodes were observed. Restoration of B7-2 and IL-12 levels from immunosuppressed and tolerance state-inhibited levels may initiate Th-1 type immune responses. Protection by EGCG may be via inhibition of UVB-induced photocarcinogenesis (10).

The antiproliferative effects of EGCG were investigated using androgen-dependent (LNCaP) and -independent (DU145) prostate cancer cells. EGCG (20-80 μM) in both cell types dose-dependently inhibited cell growth, arrested cells in the G_0/G_1 phase, induced apoptosis and increased WAF1/p21. EGCG caused a dose-dependent increase in p53 in LNCaP cells carrying wild-type p53 but not DU145 which had mutant p53. Thus, EGCG may inhibit growth in human prostate cancer via WAF1/p21, independent of p53 and androgen association (11).

EGCG decreased nitric oxide production (NO) *in vitro* in LPS- and IFNγ-activated mouse peritoneal cells via reduced expression of inducible nitric oxide synthase (iNOS) and inhibition of enzyme activity. EGCG (1-10 μM) induced dose-dependent reductions in iNOS mRNA of 82-14%. Inhibition of iNOS and neuronal NOS enzyme activity with 50-750 μM EGCG was also dose-dependent, resulting in reductions of 85-14% and 93-56%, respectively. Binding of arginine and tetrahydrobiopterin and the gallate structure were also competitively inhibited by the agent (12).

Prevention of carcinogenesis by EGCG may occur through macrophage activation. A study has demonstrated that EGCG (10 μg/ml) administered to mice activated peritoneal macrophages. A markedly enhanced macrophage activation was also shown when mouse peritoneal cells (including B and T cells and macrophages) were incubated for 30 min with EGCG (1 μg/ml) in the presence of vitamin D-binding protein (Gc protein; 1 ng/ml).

Activation did not occur when macrophages alone were treated with EGCG in the absence or presence of Gc protein or lymphocytes, indicating that the inducible β-galactosidase of EGCG-primed B cell and Gc protein are required (13).

EGCG and quercetin were shown to scavenge oxygen and nitrogen free radicals thus inhibiting oxidative DNA damage in Jurkat T-lymphocytes *in vitro*. EGCG and quercetin were first shown to decrease DPPH by 97 and 47%, respectively. Jurkat cells treated with H_2O_2 or peroxynitrite had comet scores of 186 and 120, respectively, indicating DNA damage. Comet scores were decreased by 43 and 24% when EGCG (10 μM) was added to cells prior to H_2O_2 or peroxynitrite, respectively, and quercetin pretreatment decreased scores by 60 and 29%, respectively (14).

The effects of EGCG and sarcophytol on tobacco-specific nitrosamine- and stimulated human phagocyte-induced DNA strand breakage were examined in a study using NNK (5 mM)-treated fetal human lung fibroblasts incubated with TPA (100 nM)-stimulated human phagocytes. Cells treated with EGCG and sarcophytol 1 h prior to NNK and TPA stimulation displayed significantly less DNA damage (95% of controls); no effects of the agents were observed on superoxide anion production. Sarcophytol treatment blocked the production of hydrogen peroxide, indicating that the effect of this agent was mediated by impaired production of the reactive oxygen species (15).

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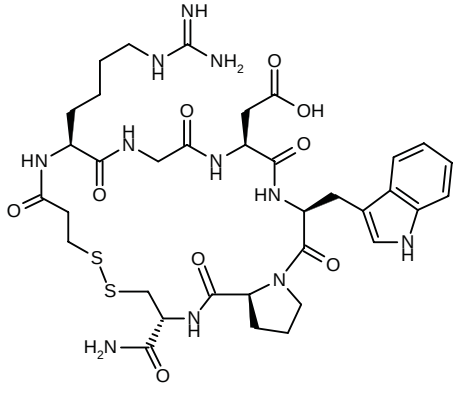
Eptifibatide

C68-22
SB-1
Sch-60936
Integrilin™
Integrelin®

Platelet Antiaggregatory
Fibrinogen gpIIb/IIIa Antagonist

EN: 190747



$C_{35}H_{49}N_{11}O_9S_2$ **COR Therapeutics; Schering-Plough**

With the intent to investigate the possible acceleration of endogenous fibrinolysis without an exogenous plasminogen activator and passivation of the damaged arterial surface by a short-acting, reversible peptide inhibiting the platelet GP IIb/IIIa receptor, eptifibatide i.v. was evaluated in a canine model of coronary thrombosis with endothelial disruption and superimposed high-grade distal stenosis. Eptifibatide with heparin and aspirin accelerated fibrinolysis and restored coronary blood flow with equal frequency to recombinant tissue plasminogen activator (rt-PA). Eptifibatide outperformed rt-PA in sustaining reflow by completely abolishing PA. With low-dose rt-PA, eptifibatide potentiated thrombolysis and prevented reocclusion by passivating the damaged arterial surface. Due to its potency, rapid action and reversibility, eptifibatide is suitable for early reperfusion therapy of acute myocardial infarction (1).

The results of a multicenter, double-blind trial have demonstrated the efficacy of eptifibatide in the prevention of death or nonfatal myocardial infarction in patients with acute myocardial infarction or unstable angina. A total of 10,948 patients with ischemic chest pain (within the last 24 h) and electrocardiogram indication of ischemia without persistent ST segment elevation, or high plasma levels of creatine kinase MB isoenzyme levels, received eptifibatide or placebo as a bolus (180 μg/kg) followed by infusion (2.0 μg/kg/min) until discharge or 72 h later; infusion was continued for an additional 24 h if coronary intervention was performed close to the 72-h period. A significant (1.5%) absolute decrease in the incidence of death or nonfatal myocardial infarction was observed at 96 h and maintained for 30 days in eptifibatide-treated patients (14.2% *vs.* 15.7% in the placebo-treated group). The reduction was observed in most major subgroups with the exception of women, where no significant effects were observed; no physiological explanation for the ineffectiveness of eptifibatide in this group was evident. Although risk and occurrence of hemorrhagic stroke were not increased by eptifibatide treatment, a greater incidence of bleeding at the femoral artery access site was observed in eptifibatide-treated patients undergoing cardiac revascularization procedures (2).

With the objective of identifying potential predictors of vascular access site (VAS) complications, 4010 patients undergoing percutaneous transluminal coronary revascularization received one of three bolus/20- to 24-h infusion arms: placebo bolus/placebo infusion, 135 μg/kg eptifibatide bolus/0.5 μg/kg/min eptifibatide infusion or 135 μg/kg eptifibatide bolus/0.75 μg/kg/min eptifibatide infusion. Early sheath removal, avoiding placement of venous sheaths and limiting heparin dosing may reduce VAS complications. As revealed in this study, early sheath removal during inhibition of platelet aggregation by eptifibatide is possible (3).

A total of 9461 patients hospitalized within 24 h of ischemic chest pain without persistent ST-elevation were randomized to eptifibatide (180 μg/kg bolus + 2.0 μg/kg/min i.v. infusion) or placebo for 72 h. Percutaneous transluminal coronary angioplasty was performed in a subgroup of 1249 patients during drug treatment. Eptifibatide significantly decreased the rate of death or nonfatal myocardial infarction (2.2% *vs.* 3.8% for placebo). The drug further lowered the rate of death or nonmyocardial infarction in the angioplasty subgroup (2.8% *vs.* 6.8% for placebo) (4).

Data from a subgroup of patients enrolled in the PURSUIT study who received eptifibatide and underwent percutaneous coronary intervention within 2 h showed a 7.4% reduction in death and myocardial infarction at 30 days when compared to placebo. Data from all patients who underwent percutaneous coronary intervention within 4 and 6 h of enrollment showed 6.4% and 5.7% reductions in death and myocardial infarction, respectively. Eptifibatide was associated with a beneficial effect in this patient population (5).

Of the 9461 patients with non-ST-elevation acute coronary syndromes who were randomized to eptifibatide or placebo for up to 72 h in the PURSUIT trial, those who received active drug experienced fewer myocardial infarctions, fewer large myocardial infarctions and more small myocardial infarctions. Thus, eptifibatide may reduce the incidence and size of myocardial infarctions (6).

The Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products recommended approval of Schering-Plough's eptifibatide (Integrilin™) for the prevention of myocardial infarction in patients presenting with unstable angina or non-Q wave myocardial infarction, serious heart conditions known collectively as acute coronary syndrome. The CPMP opinion serves as the basis for a European Commission approval, which is typically issued in approximately 4 months (7).

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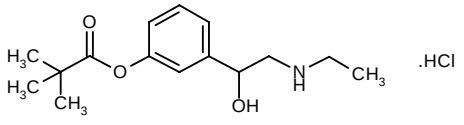
Etilefrine Pivalate Hydrochloride

Treatment of Vasovagal Syncope

EN: 090242



$C_{15}H_{23}NO_3.HCl$ **Klinge**

Etilefrine (25 mg p.o. t.i.d.) or placebo were administered to 126 patients with recurrent vasovagal syncope in a randomized, multicenter study. Etilefrine and placebo did not differ with respect to the incidence of the first syncopal recurrence, the time to first syncopal recurrence, the number of patients who experienced at least 1 presyncope during the follow-up period or the number of presyncopal episodes. Oral etilefrine was not superior to placebo for the prevention of vasovagal syncope (1).

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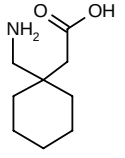
Gabapentin
Neurontin®

Anticonvulsant
Treatment of Neurogenic Pain

EN: 090276



$C_9H_{17}NO_2$ **Fujisawa; Warner-Lambert**

The efficacy and safety of gabapentin monotherapy were examined in an open-label trial in patients with painful AIDS-related neuropathy refractory to or intolerant of other analgesics. The starting dose was 300 mg/day, which was increased to 900 mg/day over 1 week and could be increased up to a maximum of 3600 mg/day. Therapy was continued for 4 months, although if good pain relief was achieved the patient could discontinue therapy after 3 months, followed by a 1-month observation period. Fifteen patients were treated at a mean dose of 1480 mg/day, although 1 patient had almost complete disappearance of pain at the starting dose. As assessed on a visual analog scale, all but 2 patients experienced improvement, and 1 of these had improved sleep despite no decrease in pain scores. Four patients had complete or almost complete disappearance of pain and discontinued therapy after 3 months; benefit was maintained over the 1-month follow-up period. No changes in electromyographic exams for sensory and motor nerve conductance were detected. Overall, a 77% reduction in pain and an 81% reduction in sleep disruption were obtained on gabapentin (1).

The acute and steady-state cognitive effects of gabapentin, lamotrigine and topiramate were evaluated in healthy volunteers randomized to one of the drugs for 4 weeks. Tests were administered to measure attention, psychomotor speed, language, memory and mood at baseline, after a single dose and at 2 and 4 weeks. Of the 3 drugs, only topiramate was shown to have a statistically significant negative effect on attention and word fluency after both acute and steady-state administration. Neither gabapentin nor lamotrigine was associated with significant changes in the parameters studied (2).

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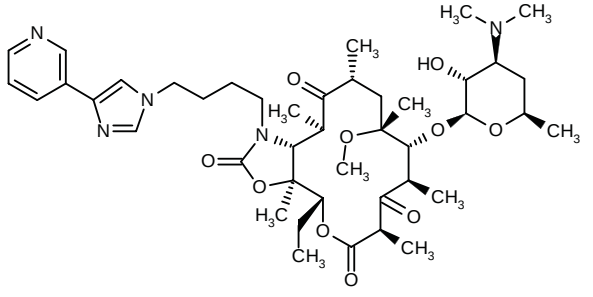
HMR-3647
RU-66647
Telithromycin

Ketolide Antibacterial

EN: 230662



$C_{43}H_{65}N_5O_{10}$ **Hoechst Marion Roussel**

The activity of HMR-3647 was compared to other agents against 235 strains of *Enterococcus faecalis* with results showing that HMR-3647 was the most active (MIC_{50} and MIC_{90} = 0.06 and 4.0 μg/ml) as compared to erythromycin A (4 and > 32 μg/ml), azithromycin (16 and > 32 μg/ml), clarithromycin (2 and > 32 μg/ml), roxithromycin (32 and > 32 μg/ml), clindamycin (32 and > 32 μg/ml) and quinupristin-dalfopristin (8 and 16 μg/ml). Only bacteriostatic effects were observed with the agents (1).

HMR-3647 was shown to be a potential treatment for anaerobic infections. Its antimicrobial activity was higher than azithromycin, roxithromycin, clarithromycin, erythromycin, cefoxitin, clindamycin and metronidazole against 218 strains; HMR-3647 was most active against *Clostridium* and had activity similar to clarithromycin against *Bacteriodes* sp. MIC_{50}/MIC_{90} (mg/l) values were 0.5/4 for *B. fragilis*, 0.25/8 for other *Bacteroides* sp., 0.06/0.125 for *C. perfringens*, 0.125/4 for *C. difficile* and 0.125/16 for other *Clostridium* sp. Complete killing of inoculum occurred at 8 h and lowering the pH from 7.6 to 7.0 and increasing inoculum size from 10^5 to 10^7 CFU/spot slightly altered HMR-3647 activity (MIC_{50} = 0.06-0.125 mg/l) (2).

HMR-3647 was shown to be a potential treatment for anaerobic infections. HMR-3647 was more active than clindamycin, tetracycline, chloramphenicol and penicillin against 292 strains with MIC_{50}/MIC_{90} (mg/l) values of 4/4 for *B. fragilis*, *B. ovatus*, *B. thetaiotaomicron*, *Fusobacterium* sp. and *Bilophila wadsworthia*, 2/2 for *B. caccae*, 1/4 for *B. vulgatus*, 0.25/4 for *Prevotella sp.* and < 0.03/≤0.5 for *Clostridium*. Inhibitory concentrations of metronidazole and imipenem were 3 and 2 dilutions lower, respectively (3).

Results from a study comparing the activity of HMR-3647 with HMR-3004, erythromycin, clarithromycin and levofloxacin against 97 *Legionella* isolates *in vitro*, in infected macrophages and in a guinea pig model of Legionnaire's disease showed that HMR-3647 should be evaluated for treatment of Legionnaire's disease in

humans. *In vitro*, the MIC_{50} value for HMR-3647 was 0.06. HMR-3647 also reduced log_{10} counts of *L. pneumophila* strain grown in guinea pig alveolar macrophages. When guinea pigs with *L. pneumophila* pneumonia were treated with HMR-3647 (10 mg/kg/d i.p.) peak plasma levels at 0.5 and 1 h postdosing were 1.4 and 1 mcg/ml, respectively, with a plasma elimination $t_{1/2}$ of 1.4 h. After 5 days of treatment, 16/16 treated guinea pigs survived for 9 days as compared to 14/16 and 0/12 erythromycin- and saline-treated animals, respectively (4).

The *in vitro* activity of HMR-3647 was tested against 492 clinical isolates of Gram-positive bacteria including multiply-resistant strains. The compound inhibited all tested streptococci at $\leq$ 0.5 mg/l. HMR-3647 showed greater potency than erythromycin against staphylococci. An MIC_{90} of 8 mg/l was observed against enterococci. The ketolide also inhibited *Erysipelothrix*, *Pediococcus*, *Leuconostoc* and *Lactobacillus* species, as well as JK diphtheroids and *Listeria moncytogenes* (5).

HMR-3647 was evaluated for its *in vivo* activity in treating intraabdominal abscess caused by *B. fragilis* in mice. The compound was as effective as clindamycin (6).

Assessment of the penetration of HMR-3647 into human neutrophils and peritoneal macrophages showed that intracellular concentrations were 130 and 65 times higher than extracellular ones in the two cell types, respectively. The intracellular to extracellular concentration ratios in tissue-cultured cells were higher than in phagocytic cells, and the uptake of the drug was rapid and nonsaturable in all cells evaluated, while efflux from phagocytic cells was slow (7).

HMR-3647 and HMR-3004 were evaluated for their extra- and intracellular killing rate of *Helicobacter pylori*, as well as their postantibiotic sub-MIC effects. Both compounds demonstrated a concentration-dependent killing of the bacterium, and HMR-3647 produced a 5 log reduction in CFUs after 24 h. Both compounds demonstrated a postantibiotic effect; subinhibitory concentrations in the postantibiotic phase yielded a long sub-MIC effect (8).

The MICs for HMR-3647 against penicillin- and erythromycin-susceptible strains of *S. pneumoniae* were 0.0078 μg/ml, while against resistant strains its MIC was 0.125 μg/ml. At a concentration of 1/4 x MIC, HMR-3647 demonstrated bacteriostatic activity against the susceptible strains, while at 4 x MIC, the drug reduced bacterial viability by 3.2 logs. Evaluated in resistant strains, a drug concentration of 4 x MIC reduced viability by 2.5 logs. Intracellular activities against all strains were similar in cell-free media (9).

Evaluation of the activity of HMR-3647 against *H. influenzae* produced a broth MIC of 1-4 μg/ml. At a concentration of 4 x MIC, HMR-3647 killed 7/10 strains, while at 8 x MIC, 99% of all strains were killed. The drug's killing rate was comparable to those of erythromycin and clarithromycin, although HMR-3647 displayed the lowest MIC (10).

The MICs of HMR-3647 against *B. ragalis*, *B. betaiotaomicron*, *P. bivia*, *P. intermedia*, *F. nucleatum*, *P. magnus* and *C. perfringens* ranged from 0.03-8 μg/ml, while those for erythromycin and azithromycin were 0.25-16 and 0.25-8 μg/ml, respectively. The kinetics of all drugs in relation to their MICs were similar (11).

The antibacterial activity of HMR-3647 against *E. faecalis* was compared to erythromycin, azithromycin, clarithromycin, roxithromycin, clindamycin and quinupristin/dalfopristin. All drugs tested demonstrated bacteriostatic activity with no killing rates of 99% or higher observed. HMR-3647 demonstrated lowest MICs of all drugs (0.03-1 μg/ml) (12).

HMR-3647 produced the lowest MICs against beta-lactamase positive and negative cultures of *Haemophilus influenzae* (2-8 μg/ml), comparable to the MICs for azithromycin and superior to those of pristinamycin, erythromycin, clarithromycin and roxithromycin. All compounds demonstrated high activity against *Moraxella catarrhalis* (13).

The lowest EC concentration of HMR-3647 and erythromycin which inhibited the IC multiplication of *L. pneumophilia* serogroup 1 (Lp1) was determined to be 0.05 mg/l for both compounds, while the survival rates for guinea pigs infected with Lp1 were 89 and 60% for animals treated with HMR-3647 and erythromycin, respectively (14).

The mean MIC_{90} of HMR-3647 against 30 β-lactamase-producing *H. influenzae* type b (Hib) clinical isolates was 2 μg/ml, while those of azithromycin, clarithromycin, erythromycin and pristinamycin were 2, 16, 16 and 4 μg/ml. In a mouse model of pneumonia, HMR-3647 was as effective as azithromycin and more effective than erythromycin, clarithromycin and pristinamycin, as evaluated by each drug's respective clearance of pulmonary Hib (15).

In vivo evaluation of MICs and PD_{50}s of HMR-3647 against 4 strains of enterococci administered as single and double doses of 64 mg/kg in a mouse peritonitis model showed that the drug possesses better antimicrobial activity than erythromycin. MICs for the drug ranged from 0.015-8 μg/ml (16).

HMR-3647 inhibited 94 erythromycin-susceptible and 107 erythromycin-resistant strains of *Enterococcus* sp. with MICs of 0.007-0.06 and 0.03-8 μg/ml, respectively. The drug also inhibited 18 vanA-positive and 29 highly penicillin-resistant isolates of *Enterococcus* sp., all erythromycin resistant, with an MIC range of 0.015-4 μg/ml (17).

HMR-3647 yielded MIC_{50} and MIC_{90} values of 2 and 4 μg/ml against 249 isolates of *H. influenzae* and 50 isolates of *M. catarrhalis*. The drug was bacteriostatic against 10 isolates of *H. influenzae* and 5 isolates of *M. catarrhalis* (18).

In vitro evaluation of the antibacterial activity of HMR-3647 showed that the compound was most active against methicillin-resistant and nonresistant staphylococci of sensitive or resistance-inducible phenotypes with MIC_{90}s of 0.25 and 2 mg/l, respectively. Constitutively resistant strains were unaffected. High activity was observed against erythromycin-sensitive enterococci with an MIC_{90} of 0.06 mg/l, irrespective of vancomycin resis-

tance. MIC_{90}s against erythromycin-sensitive and -resistant pneumococci were 0.03 and 0.25 mg/l, respectively (19).

The effects of HMR-3647 on the production of virulence factors by *Stenotrophomonas maltophilia* were evaluated *in vitro*. The MIC range for HMR-3647 was estimated to be 8-32 mg/l, with significant inhibitory activities against protease, lipase and elastase at sub-MIC concentrations (8 mg/l). DNase was poorly inhibited. The results indicate that HMR-3647 indeed inhibits the production of virulence factors (20).

In vitro analysis of the activity of HMR-3647 against *S. pneumoniae* and *H. influenzae* demonstrated that the MIC_{90}s for HMR-3647, azithromycin and clarithromycin increased against *S. pneumoniae*, and the MIC_{90}s for HMR-3647 and β-lactam against *H. influenzae* increased parallel with the MIC for cefuroxime (21).

The comparison of agar dilution MICs of HMR-3647 and other macrolide-type agents indicated that HMR-3647 was more active against non-*B. fragilis* group anaerobic Gram-negative bacteria than against the *B. fragilis* group. The compound was also very active against Gram-positive anaerobic strains, except for *C. difficile*. The MICs for HMR-3647 were the lowest of all agents tested (22).

The MIC_{50}s/MIC_{90} values for HMR-3647 against penicillin-susceptible and -resistant strains of *S. pneumoniae* were 0.008/0.125 and 0.063/0.125 μg/ml, respectively. The MICs for HMR-3647 were lower than those obtained for clarithromycin, azithromycin, cefdinir and levofloxacin. ED_{50} for HMR-3647 in mice infected with penicillin-resistant *S. pneumoniae* was 14.8 mg/kg, which was comparable to azithromycin and 5-7 times more effective than the other antibiotics tested (23).

Evaluation of the antibacterial activity of HMR-3647 against Gram-positive cocci demonstrated that the drug may effectively treat infections, particularly CAM-resistant pathogens, as demonstrated by MIC_{90}s of 0.12, 0.25, 0.25, 4 and < 0.12 μg/ml against *S. aureus*, *E. faecalis*, *E. faecium* and *S. pneumoniae*, respectively (24).

HMR-3647 was bactericidal against *S. aureus* at concentrations above the MIC_{90} (>128 μg/ml), and its activity reflected its MIC values in a dose-dependent manner. The compound demonstrated superior activity as compared to other compounds tested, including azithromycin, clarithromycin and levofloxacin (25).

In vitro evaluation of the antibacterial activity of HMR-3647 showed that the drug was superior to clarithromycin and azithromycin against erythromycin-resistant Gram-positive bacteria with MIC_{90}s ranging from 0.125-8 μg/ml, except for *S. aureus* (>128 μg/ml). MIC_{90}s for HMR-3647 against several other strains of Gram-positive bacteria were also lower than for clarithromycin, azithromycin, levofloxacin and cefditoren (26).

Determination of MICs for HMR-3647 and other macrolides using an agar dilution method showed that HMR-3647 had antibacterial activity 1-64 times more potent and a broader antibacterial spectrum than any other compound tested. The drug displayed superior activity against Gram-positive clinical isolates, with an MIC_{90} of 0.05 μg/ml against *S. pneumoniae*. Time-killing curves for HMR-3647 suggest that the drug has potent bactericidal activity with quick onset (27).

MIC_{50} and MIC_{90} values for HMR-3647 against erythromycin-susceptible pneumococci were 0.016 and 0.03 mg/l as determined by the agar dilution method, while against erythromycin-resistant strains, the respective MICs were 0.25 and 1 mg/l. All erythromycin-susceptible strains of *S. aureus* and coagulase-negative staphylococci were inhibited by HMR-3647 at concentrations of 0.12 and 0.25 mg/l, respectively. Against *E. faecalis* and *E. faecium*, the MIC_{50}/MIC_{90} values were 0.06/4 and 0.5/4 mg/l, respectively. These values were at least 16 times lower than those obtained with other compounds (28).

HMR-3647 demonstrated inoculum-, concentration- and time-dependent bactericidal activity against macrolide-susceptible *S. pneumoniae* that included penicillin-susceptible, -intermediate and -resistant isolates. The drug produced a killing rate of at least 99% in 12-24 h, usually superior to that of azithromycin at concentrations of 4-8 x MIC (29).

HMR-3647 demonstrated an MIC_{90} of < 0.12 against penicillin-susceptible and -resistant strains of *S. pneumoniae*, and MIC_{90} values of < 0.25 and 4 against *M. catarrhalis* and *H. influenzae*. The activity of HMR-3647 was ≥ those of erythromycin, roxithromycin, clarithromycin and azithromycin (30).

Against 59 isolates of *E. faecalis*, HMR-3647 displayed MIC_{50} and MIC_{90} values of 2 and 4 mg/l, respectively, using the NCCLS agar dilution method, with all but 4 isolates having the VanA glycopeptide-resistant phenotype. Similar antibacterial activity was observed against 474 glycopeptide-resistant isolates of *E. faecium*. A higher activity was observed against erythromycin A-susceptible isolates (31).

HMR-3647 (1-100 mg/l) inhibited the production of superoxide anion production by human neutrophils primed with the cytokines TNF-α and GM-CSF (IC_{50} = 75-80 mg/l). The degree of inhibition was comparable to unprimed cells, indicating that the drug affects the cytokine activation pathway downstream (32).

HMR-3647 and comparator agents, especially macrolides, were tested against 262 aerobic and 120 anaerobic strains isolated from skin and soft tissue infections due to human and animal bite wounds. HMR-3647 showed activity against nearly all aerobic and fastidious facultative isolates (MIC_{90} = ≤ 1 μg/ml) and against all anaerobes (MIC_{90} = ≤ 0.5 μg/ml) except *Fusobacterium nucleatum* (MIC_{90} = 8 μg/ml) and other *Fusobacterium* species (MIC_{90} = 2 μg/ml). Overall, HMR-3647 was more active than the other macrolides tested (33).

HMR-3647's *in vitro* activity was compared to those of erythromycin, roxithromycin, clarithromycin, amoxicillin-clavulanic acid and ciprofloxacin against 719 recent clinical Gram-positive, -negative and anaerobic isolates. HMR-3647 showed greater activity than the other agents except for *Staphylococcus epidermidis*, *H. influenzae*, *E. faecalis*, *E. faecium* and the anaerobes *B. fragilis* and

C. difficile. The antichlamydial activity of HMR-3647 was generally greater than commonly used agents (34).

In vitro studies have demonstrated the interactions between HMR-3647 and human polymorphonuclear neutrophils (PMNs). Following a 3-h incubation, uptake without saturation occurred in a temperature-dependent but pH-independent manner, with 60% of the agent located in the granular compartment and < 6% associated with membranes; Ca^{2+} was required for maximum HMR-3647 uptake and verapamil was shown to increase uptake of the agent at 5 min followed by a gradual inhibition. When cells were placed in drug-free media, HMR-3647 was egressed from cells. HMR-3647 time- and dose-dependently inhibited PMN superoxide anion production and only weakly stimulated granule exocytosis (35).

In vitro studies using 2563 clinical isolates of Gram-positive pathogens have demonstrated that HMR-3647 was active against macrolide-resistant streptococci including pneumococci. The agent had no effect against macrolide- and lincosamide-resistant staphylococci. HMR-3647 exhibited a potency similar to azithromycin against *H. influenzae* (36).

The activity of HMR-3647 against 77 viridans isolates from neutropenic cancer patients was tested and compared to those of penicillin, cefotaxime, erythromycin, clindamycin, vancomycin, chloramphenicol, cotrimoxazole and ciprofloxacin. The most common isolate was *S. mitis* which had high rates of penicillin (77.9%) and erythromycin resistance (38.5%). A decreased susceptibility to penicillin was observed in 40.3% of the isolates and 50 and 27 strains were erythromycin-susceptible and -resistant, respectively. HMR-3647 was the most active agent (37).

Administration of a single oral dose of HMR-3647 in 8 healthy young volunteers produced a plasma C_{max} of 0.83 mg/l after 3 h, while C_{max} in inflammatory fluid was 0.436 mg/l after 9 h. Concentrations in plasma and inflammatory fluid 12 h after dosing were 0.012 and 0.08 mg/l, respectively, and the ratio of $AUC_{0\text{-}24h}$ for blister fluid and plasma was 1.38, indicating excellent penetration of the drug into inflammatory fluid (38).

HMR-3647 was shown to be suitable for clinical use in an open, single- and multiple-dose pharmacokinetic study in which 12 healthy young volunteers were administered a single 800-mg dose, followed by a 1-week washout period and then 800 mg/day for 10 days. Treatment was well tolerated; steady state was achieved after 2 days. $AUC_{0\text{-}24h}$ and $t_{1/2}$ for the single dose and the final dose on day 10 were 7.3 ± 2.3 mg.h/l and 10.6 ± 2.5 h and 8.4 ± 2.6 mg.h/l and 13.4 ± 3.5 h, respectively (39).

Telithromycin is the new proposed international nonproprietary name for HMR-3647 (40).

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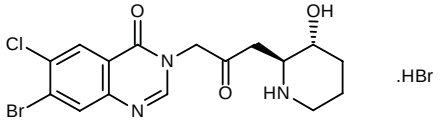

$C_{16}H_{17}BrClN_3O_3.BrH$ **Hoechst Marion Roussel; Collgard**

The effects of halofuginone on neointimal formation of rat aorta were evaluated *in vitro*. Neointimal formation of cultured rat aortas was significantly and dose-dependently inhibited by the drug. In addition, the proliferation of cell nuclear antigen index was significantly lower in halofuginone-treated cultures (1).

Collgard Biopharmaceuticals and its U.S. subsidiary are focusing on the development of human applications of halofuginone, which has shown promise in numerous animal models for the treatment of cancer, restenosis, fibrosis and certain autoimmune diseases, such as scleroderma and graft-*versus*-host disease. By discovering that halofuginone specifically inhibits the production of collagen type I, Collgard has demonstrated that collagen is essential in the response to major tissue trauma events. The company has completed a phase I clinical trial for the topical application of halofuginone for the treatment of scleroderma and phase II clinical trials are scheduled. Collgard plans to apply initially for orphan drug status for halofuginone for scleroderma and then focus on the major market indications (2).

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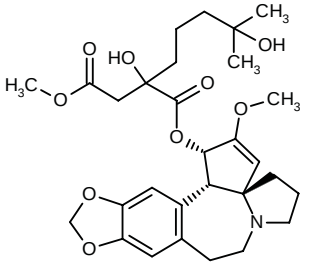
Homoharringtonine *Antineoplastic Alkaloid*

EN: 090682



$C_{29}H_{39}NO_9$ **Chinese Acad. Med. Sci.; Natl. Cancer Inst. (US)**

Use of homoharringtonine was effective and safe in delaying progression of the accelerated phase in poor prognosis patients with IFN-resistant advanced myeloid leukemia. Fourteen patients, 9 of whom were in the accelerated phase, were administered up to 14-day induction courses of continuous infusion of HHT (2.5 mg/m^2/day) followed by maintenance cycles with the same dose infused over 3-7 days. Of the patients in the accelerated phase, 78% reached a hematologic response with 4/7 achieving minor cytogenetic response; hematologic and cytogenic responses were induced in 75% of patients in the late chronic stage. All 9 patients in the accelerated phase were alive at the 14-month follow-up, although 2 progressed to blast crisis while on HHT. HHT was well tolerated and dose-limiting toxicity included thrombocytopenia in 43% of patients, resulting in delayed maintenance cycles. Two patients had central-line related thromboses and infections (1).

Homoharringtonine (1-2 mg) was administered to 6 chronic neutrophilic leukemia patients as a continuous i.v. infusion for 14 days followed by an interval of 14-21 days without treatment. Five patients received 2-3 courses and 1 received 1 course. When white blood cell count reached 3.0 Gcells/l, an additional course was administered as maintenance therapy after complete remission. Homoharringtonine was effective with no toxic or side effects (2).

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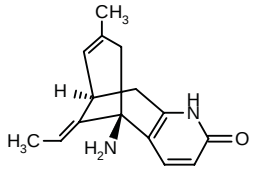
Huperzine A

Cognition Enhancer
Acetylcholinesterase Inhibitor

EN: 122853



$C_{15}H_{18}N_2O$

Shanghai Inst. Materia Med.; Chinese Acad. Med. Sci.

Huperzine A was shown to ameliorate spatial working memory impairment due to kainic acid-induced lesions in the unilateral nucleus basalis magnocellularis in rats; behavioral impairment induced by kainic acid was associated with a 40% reduction in choline acetyltransferase activity in the ipsilateral cerebral cortex. The number of correct choices to complete a working memory task increased in treated rats (1).

Huperzine A treatment improved spatial working memory in aged and scopolamine (0.03 mg/kg i.m.)-treated young monkeys with cognitive impairment. Delayed response tasks in scopolamine-treated young monkeys were significantly reversed after drug treatment (0.01-0.1 mg/kg i.m.). An optimal dose of 0.1 mg/kg improved responses to 25/30 correct from 20.2/30 prior to treatment. Choice accuracy was also significantly increased from 20.5/30 to 25.2/30 in aged monkeys at optimal doses of 0.001 and 0.01 mg/kg in 2 animals each. Improvement with huperzine A treatment was maintained for 24 h after administration. The agent may be a potential therapy for patients with Alzheimer's disease (2).

The effects of (–)-huperzine A, donepeazil hydrochloride and tacrine on scopolamine-induced memory deficits in rats were compared in a radial maze. Data showed that (-)-huperzine A was the most potent and orally active compound and most closely follows the criteria for an ideal acetylcholinesterase inhibitor to be used in clinical studies (3).

Patients (n = 120) with age-associated memory impairment (AAMI) were treated in a first trial with huperzine A (0.03-0.05 mg i.m. b.i.d.) for 14-15 days. A subset of 16 patients from the first trial were later treated at the same dosage for 4 weeks. In a second trial, 88 patients with AAMI received the drug at a dose of 0.1 mg p.o. q.i.d. In the final study, 25 patients with vascular dementia and 55 with Alzheimer's disease received huperzine A treatment (0.1 mg p.o. q.i.d.) or served as controls. MQ improved in huperzine-treated patients in all 3 studies, with efficacy as high as 68%. Side effects were mild and included dizziness, gastric discomfort, nausea and insomnia. These results, obtained from a total of 314 patients, indicate that huperzine A is a safe and effective treatment for cognitive dysfunction in the elderly (4).

Huperzine A was shown to have a higher total efficacy rate than pyritinol (66% *vs.* 38%) in a study involving 97 patients with multiple infarction dementia (5).

1. Xiong, Z.-Q., Cheng, D.-H., Tang, X.-C. *Effects of huperzine A on nucleus basalis magnocellularis lesion-induced spatial working memory deficit.* Acta Pharmacol Sin 1998, 19(2): 128.

2. Ye, J.W. et al. *Improving effects of huperzine A on spatial working memory in aged monkeys and young adult monkeys with experimental cognitive impairment.* J Pharmacol Exp Ther 1999, 288(2): 814.

3. Wang, T., Tang, X.C. *Reversal of scopolamine-induced deficits in radial maze performance by (-)-huperzine A: Comparison with E2020 and tacrine.* Eur J Pharmacol 1998, 349(2-3): 137.

4. Ma, Y.-X., Zhu, Y., Gu, Y.-D., Yu, Z.-Y., Yu, S.-M., Ye, Y.-Z. *Double-blind trial of huperzine-A (HUP) on cognitive impairment and dementia in 314 cases.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 35.194.

5. Chang, J.-J. *Huperzine A vs pyritinol in treating dementia from multiple infarctions.* New Drugs Clin Rem 1997, 16(6): 333.

Original monograph - Drugs Fut 1987, 12: 531. See also this issue, pages 647-663 for Review.

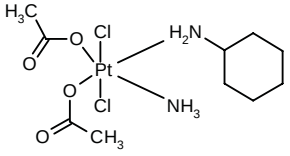
Additional Reference

Liu, J. et al. *Effects of synthetic (-)-huperzine A on cholinesterase activities and mouse water maze performance.* Acta Pharmacol Sin 1998, 19(5): 413.

JM-216
Satraplatin

Antineoplastic
Platinum Complex

EN: 185356



$C_6H_{13}N.C_4H_6Cl_2O_4Pt.H_3N$

Johnson Matthey; Bristol-Myers Squibb

An *in vivo* study using a human non-small cell lung carcinoma cell line (H460) implanted in nude athymic mice showed that JM-216 (150 mg/kg p.o.) enhanced the effects of radiation (10 Gy) given 1 h later. Growth delay of tumors was potentiated in animals receiving JM-216 plus radiation (12.5 ± 1.4 d) as compared to JM-216 (3.5 ± 0.4 d) or radiation (6.1 ± 0.3 d) alone (1).

The pharmacokinetic profile of total and ultrafiltrable plasma platinum was assessed in 14 patients with advanced cancer who received JM-216 (10-50 mg/m^2/day p.o.) for 14 days. The chemotherapeutic agent produced predictable total levels of platinum accumulation in plasma (2).

In a phase I trial, 19 patients received 50 cycles of JM-216 (150-350 mg/m^2 b.i.d.) to examine an alternative and possibly better-tolerated schedule. The study stopped before reaching the maximally tolerated dose due to nonlinear pharmacokinetics. Grade 3 and 4 myelosuppression was seen at 250-350 mg/m^2. The pharmacokinetics of JM-216 was confirmed to be nonlinear and

variable. A daily x 5 schedule was deemed optimal for phase II trials (3).

A phase I trial was performed to determine the maximum tolerated dose of oral JM-216 (10 mg/d or 10 or 20 mg 3x/wk) given 1-3 h before radiation (60 Gy/6 wk) in 20 patients with non-small cell lung cancer (NSCLC) or head and neck squamous cell carcinoma (SCHN). JM-216 at 10 mg/day was well tolerated in NSCLC patients, although 2/2 SCHN patients developed grade 3 nausea, vomiting and diarrhea, requiring dose changes to 10 mg every other day in both groups of patients. With 10 mg 3x/wk, no dose-limiting toxicities (DLT) were observed in the SCHN cohort while 1 patient with NSCLC had grade 3 SGOT elevations. With 20 mg 3x/wk, no DLT were observed in the SCHN cohort, although 1/3 patients with NSCLC had grade 4 nausea/vomiting. It was concluded that JM-216 at 20 mg 3x/wk with radiation (70 Gy) was well tolerated in SCHN patients (4).

A phase I study of paclitaxel (150, 175 or 200 mg/m^2 1-h infusion on day 1) followed by JM-216 (10-60 mg/m^2/d p.o. on days 1-5) with cycles repeated every 21 days attempted to determine the maximum tolerated doses for the combination treatment in 37 patients with advanced refractory malignancies. Dose-limiting toxicity was febrile neutropenia requiring hospitalization and grade 3 thrombocytopenia with doses of 80/175 mg/m^2 JM-216/paclitaxel. Mild to moderate nausea and vomiting, asthenia, alopecia, myalgias/arthralgias (similar to effects seen with paclitaxel alone), paresthesias, anorexia and malaise were also reported. After 3-12 cycles, several patients had stable disease although no objective responses were observed. The recommended phase II dose remains to be determined (5).

Satraplatin is the new proposed international nonproprietary name for JM-216 (6).

1. Mohr, P.J. et al. *Enhancement of radiation effects in vivo by the orally active platinum drug JM216.* Proc Amer Soc Clin Oncol 1999, 18: Abst 1754.

2. Vouillamoz-Lorenz, S., Decosterd, L.A., Bauer, J., Buclin, T., Lejeune, F. *A phase I pharmacokinetics (PK) study of the oral platinum (Pt) analog JM216 administered once a day over 14 days.* 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 500.

3. Beale, P. et al. *Phase I study of oral JM216 given twice daily.* Cancer Chemother Pharmacol 1998, 42(2): 142.

4. Cmelak, A.J. et al. *Phase I study of JM-216 with concurrent radiation in non-small cell lung cancer and squamous cell head and neck cancer.* Proc Amer Soc Clin Oncol 1999, 18: Abst 1520.

5. Jones, S.F. et al. *Phase I study of JM-216 in combination with paclitaxel in patients with advanced malignancies.* Proc Amer Soc Clin Oncol 1999, 18: Abst 831.

6. *Proposed international nonproprietary names (Prop. INN): List 80.* WHO Drug Inf 1998, 12(4): 274.

Original monograph - Drugs Fut 1993, 18: 551.

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Fokkema, E. et al. *Correlation between JM216, JM118 and cisplatin-induced platinum-DNA-adduct levels in a panel of human tumor cell lines with different sensitivities to cisplatin.* Proc Amer Assoc Cancer Res 1999, 40: Abst 1948.

Leyland-Jones, B. et al. *Genomic imbalances associated with acquired resistance to platinum analogues.* 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 563.

Perego, P. et al. *Regulation of sensitivity to cisplatin and platinum-containing drugs by repair and checkpoint control genes in Schizosaccharomyces pombe.* 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 517.

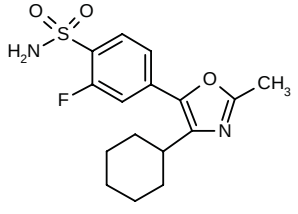
Sessa, C. et al. *Phase I clinical and pharmacokinetic study of the oral platinum analogue JM216 given daily for 14 days.* Ann Oncol 1998, 9(12): 1315.

Van de Vaart, P.J.M. et al. *The oral platinum analogue JM216 is a radiosensitizer.* 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 520.

JTE-522

Antiinflammatory
COX-2 Inhibitor

EN: 239031



$C_{16}H_{19}FN_2O_3S$ **Japan Tobacco; R.W. Johnson**

JTE-522 was tested *in vitro* and *in vivo* to clarify a relationship between expression of COX-2 and liver metastasis of colon cancer and to assess its potential therapeutic effect. Highly metastatic cell lines showed a high frequency of expression of COX-2 mRNA as compared to poorly or nonmetastatic cell lines. JTE-522 showed inhibitory effects on liver metastasis *in vivo* (1).

JTE-522 inhibited human recombinant COX-2 with an IC_{50} of 0.085 μM, while human COX-1 was unaffected even at concentrations of up to 100 μM. The inhibition of COX-2 was highly selective, time-dependent, irreversible and more potent than that observed with other known inhibitors. LPS-induced PGE_2 production in human peripheral blood mononuclear cells was inhibited with an IC_{50} of 15.1 nM, while inhibition of calcium ionophore-induced TxB_2 production in washed human platelets was less potent (2).

Based on the results of a study in mice bearing colon 26 tumors and treated with the selective COX-2 inhibitor JTE-522, a team of independent investigators concluded that COX-2 inhibitors are potentially useful in preventing colorectal tumorogenesis, as well as hematogenous metastasis of colon cancer (3).

JTE-522 (10 mg/kg q12h) was shown to have antihypertensive activities in a study in which treated rats subjected to one-kidney, one-clip renovascular hypertension exhibited significant attenuations in the increase in blood pressure. These results indicate that prostaglandins from COX-2 may be involved in renovascular hypertension (4).

1. Tatematsu, H. et al. *Experimental prevention of liver metastasis of colon cancer by inhibition of COX-2.* Proc Amer Assoc Cancer Res 1999, 40: Abst 2635.

2. Wakitani, K. et al. *Profile of JTE-522 as a human cyclooxygenase-2 inhibitor.* Jpn J Pharmacol 1998, 78(3): 365.

3. Tomozawa, S. et al. *Inhibition of colorectal cancer metastasis by a selective COX-2 inhibitor.* Proc Amer Assoc Cancer Res 1999, 40: Abst 3483.

4. Hayashi, I. et al. *Antihypertensive effect of a cyclooxygenase-2 inhibitor on renovascular hypertension.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst P-257.

Original monograph - Drugs Fut 1998, 23: 598.

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Nakamoto, K. et al. *Effect of JTE522, a COX-2 selective inhibitor, on development of gastric ulcer induced by ischemic reperfusion in Wistar rats.* 18th Meet Jpn Soc Clin Pharmacol Ther (Dec 11-12, Tokyo) 1997, Abst O-166.

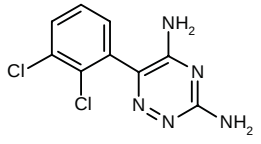
Tatematsu, H. et al. *Effect of COX-2 inhibition on liver metastasis in colorectal cancer.* Jpn J Cancer Res 1998, 89(Suppl.): Abst 413.

Tomozawa, S. et al. *Inhibition of colon cancer metastasis by a selective COX-2 inhibitor.* Jpn J Cancer Res 1998, 89(Suppl.): Abst 1876.

Lamotrigine
Labileno®
Lamictal®

Anticonvulsant
Glutamate Release Inhibitor

EN: 100324



$C_9H_7Cl_2N_5$ **Glaxo Wellcome; DuPont Pharm.; Faes**

The U.S. FDA approved lamotrigine (Lamictal®) for a new indication as add-on treatment of generalized seizures associated with Lennox-Gastaut syndrome (LGS), one of the most difficult-to-control forms of epilepsy in children and adults. The approval is based on a double-blind, placebo-controlled study in 169 patients with LGS. In that study, lamotrigine or placebo was added to the patients' current antiepileptic drug regimen. The patients treated with lamotrigine showed a significant reduction in the frequency of all major seizure types as compared to patients on placebo (32% *vs.* 9%). The frequency of drop attacks and tonic-clonic seizures decreased significantly in the lamotrigine group (34% and 36% reduction, respectively) as compared to the placebo group (9% decrease and 10% increase, respectively). Adverse events included pharyngitis, infections and rash. In addition to the original tablet form containing 25, 100, 150 or 200 mg of active ingredient, a new dispersible form of Lamictal® is also available in 5- and 25-mg tablets; these new tablets can be chewed, swallowed whole or dissolved in liquid for administration by bottle or spoon in patients who have difficulty in taking medication (1, 2).

Health Canada has approved Lamictal® for use in combination with other therapies for the treatment of Lennox-Gastaut syndrome (LGS). Lamictal® has been demonstrated to provide patients with greater control of the wide range of LGS-related seizures, which may permit reduction in the number of medications needed by some patients. Lamictal® has been available in Canada since 1994 as add-on therapy for the management of adult patients with epilepsy who are not satisfactorily controlled by conventional therapies. This therapeutic is now approved as monotherapy following polytherapy in adults, as well as add-on therapy in children and adults with LGS (3).

A recent multicenter, randomized, double-blind, placebo-controlled trial has determined the analgesic efficacy and safety of lamotrigine in patients with painful HIV-associated distal sensory polyneuropathy. The dose was slowly titrated over 7 weeks from 25 mg/day up to 300 mg/day in this 14-week study. Thirteen of 42 patients withdrew before completing dose titration: 11 on lamotrigine and 2 on placebo; dropouts on lamotrigine were attributed to rash in 5 patients and reasons unrelated to the study drug in the other 6 patients. Lamotrigine was significantly superior to placebo at the end of the study as assessed by the primary outcome measure of change in average pain on the Gracely scale, with a significantly greater reduction in pain from baseline. Subgroup analysis showed that this improvement was significant only in patients who had not been exposed to neurotoxic antiretroviral agents, but not in patients receiving neurotoxic antiretroviral therapy. No significant differences between groups were noted in concomitant analgesic use. A larger trial thus appears to be warranted in order to confirm these preliminary results and determine the optimal dose (4).

1. *Lamotrigine approved for new indication in the U.S.: Lennox-Gastaut syndrome.* DailyDrugNews.com (Daily Essentials) Sept 2, 1998.

2. *Expanded indications, new formulation of Lamictal now available in U.S.* DailyDrugNews.com (Daily Essentials) Dec 21, 1998.

3. *Lamictal approved in Canada for Lennox-Gastaut syndrome.* DailyDrugNews.com (Daily Essentials) June 15, 1999.

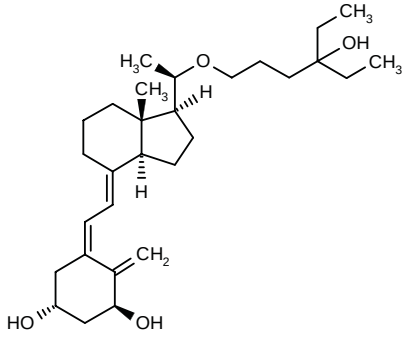
4. Simpson, D.M. et al. *Lamotrigine in the treatment of HIV-associated painful sensory polyneuropathy: A placebo-controlled study.* Neurology 1999, 52(6, Suppl. 2): Abst P03.003.

Original monograph - Drugs Fut 1986, 11: 456.

Lexacalcitol
KH-1060

Immunomodulator
Vitamin D Analog

EN: 166325



$C_{29}H_{48}O_4$ **Leo**

The immunomodulatory effects of KH-1060 have been assessed in an experimental model of skin transplantation in mice. Treated mice received a dose of 0.4 μg/kg/day i.p. starting 3 days before and for 7 days after grafting. As compared to controls, KH-1060-treated mice showed decreased expression of the surface markers I-A(k), CD54 and CD18 on monocytes, indicating an effect on antigen-presenting cells (APCs). Decreased expression of lymphocyte CD25 was also observed, and an increase in lymphocyte CD2 and natural killer cell activity in KH-1060-treated animals indicated a possible alternative mechanism compensating for APC suppression (1).

Ten patients were administered either KH-1060 ointment (1 μg/g) or vehicle only for 8 weeks to establish the drug's effect on the epidermal cell characteristics of chronic idiopathic lichen planus. Treatment with KH-1060 significantly decreased the percentage of cells in S- and G_2M-phase and the percentage of vimentin-positive cells. The percentage of keratin 10-positive cells was not affected (2).

1. Bertolini, D.L. et al. *Immunomodulatory effects of vitamin D analog KH1060 on a experimental skin transplantation model.* 15th Int Congr Nephrol (May 2-6, Buenos Aires) 1999, Abst 451.

2. Glade, C.P., Van der Vleuten, C.J.M., Van Erp, P.E.J., De Jong, E.M.J.J., Van de Kerkhof, P.C.M. *The epidermis of chronic idiopathic lichen planus during topical treatment with the vitamin D-3 analogue KH-1060.* Clin Exp Dermatol 1998, 23(1): 14.

Original monograph - Drugs Fut 1995, 20: 567.

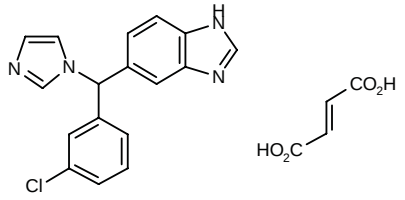
Additional Reference

Saito, Y. et al. *Vitamin D_3 analogue KH1060 with TPA synergistically induces mature macrophages in human myeloblastic leukemia ML-1 cells.* Jpn J Cancer Res 1998, 89(Suppl.): Abst 1188.

Liarozole Fumarate
Liazal®

Antineoplastic

EN: 209703



$C_{17}H_{13}ClN_4.C_4H_4O_4$ **Janssen**

The effect of prior hormone therapy on second-line treatment was assessed in 321 prostate cancer patients. In a multicenter, phase III study, patients with progressive disease after antiandrogen deprivation were randomized to liarozole (2 x 300 mg/d) or cyproteronacetate (2 x 100 mg/d). Liarozole significantly affected prostate specific antigen (PSA). The PSA response rate and the time to PSA progression were not related to prior first-line therapy and/or antiandrogen withdrawal (1).

Seven patients with extensive plaque psoriasis were given liarozole 75 mg b.i.d. for at least 2 months. PASI scores decreased significantly. Overall, liarozole reduced aspects of cutaneous inflammation and epidermal proliferation while promoting differentiation. At 4 weeks, effects were observed on epidermal expression of ICAM-1 and CD11b-positive cell population (2).

1. Rassweiler, J.J. *The impact of previous hormone therapy on PSA response to liarozole in prostate cancer patients failing first-line androgen ablation.* J Urol 1998, 159(5, Suppl.): Abst 495.

2. Van Pelt, J.P.A., De Jong, E.M.G.J., Bakker, E.S.M., Van de Kerkhof, P.C.M. *Effects of systemic treatment with liarozole on cutaneous inflammation, epidermal proliferation and differentiation in extensive plaque psoriasis.* Skin Pharmacol Applied Skin Physiol 1998, 11(2): 70.

Original monograph - Drugs Fut 1994, 19: 552.

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Kuijpers, A.L.A. et al. *The effects of oral liarozole on epidermal proliferation and differentiation in severe plaque psoriasis are comparable with those of acitretin.* Br J Dermatol 1998, 139(3): 380.

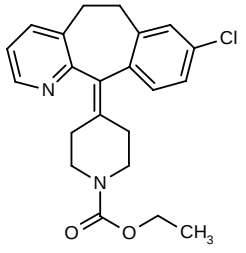
Nagae, H. et al. *Chemopreventive efficacy of liarozole, an inhibitor of retinoic acid metabolism, on N-butyl-N-(4-hydroxybutyl) nitrosamine-induced carcinogenesis in rat urinary bladders.* 94th Annu Meet Am Urol Assoc (May 1-6, Dallas) 1999, Abst 452.

O'Byrne, K.J. et al. *Phase II study of liarozole in advanced non-small cell lung cancer.* Eur J Cancer 1998, 34(9): 1463.

Loratadine
Claritin-D®

Antihistaminic

EN: 090791



$C_{22}H_{23}ClN_2O_2$ **Schering-Plough**

Two hundred and twenty children with otitis media and effusion (OME) were randomized to once-daily loratadine syrup (5 mg if ≤ 30 kg or 10 mg if > 30 kg) in a double-blind, placebo-controlled study to assess the effects of the drug on the evolution of OME. In addition, all subjects received amoxicillin-clavulanic acid (40-80 mg/kg/d x 14 d) and betamethasone (0.12 mg/kg/d x 10 d). Children who received loratadine showed significantly greater improvement of hearing at 1 month and a significant decrease in the use of concomitant antibiotics and corticosteroids as compared to those on placebo. Thus, loratadine plus standard therapy may afford significant long-term benefits in treating children with OME (1).

Synergistic efficacy has been described for montelukast sodium and loratadine in the treatment of patients with allergic rhinitis. Two parallel studies involving 16 patients each were conducted for a total of 12 weeks. Patients in one study received loratadine (10 mg/d p.o.) monotherapy, while those in the other study received the same dose of loratadine plus montelukast (20 mg/d p.o.). The severity and duration of allergic rhinitis decreased in 75% and 87% of the patients receiving monotherapy and combination therapy, respectively. Although monotherapy with loratadine was undeniably effective in treating allergic rhinitis, the 2-drug combination was even more effective, perhaps due to synergistic effects (2).

The efficacy of monotherapy and combination therapy with montelukast and loratadine in the treatment of seasonal allergic rhinitis was evaluated in 460 males and females. Administration of montelukast with loratadine at doses of 10 mg each improved nasal and eye symptoms, as well as nighttime symptoms, as compared to treatment with placebo. The combination therapy demonstrated rapid onset and synergistic effects as compared to monotherapy and treatment with placebo (3).

1. Garabedian, E.N. et al. *Effect of loratadine (L) syrup in the treatment of otitis media with effusion (OME): Randomized double-blind placebo (P) controlled trial.* J Allergy Clin Immunol 1999, 103(1, Part 2): Abst 976.

2. Nsouli, S.M. *Combination loratadine (LR) and montelukast (ML) in the treatment of allergic rhinitis.* Annu Meet Am Coll Allergy Asthma Immunol (Nov 6-11, Philadelphia) 1998, Abst P26.

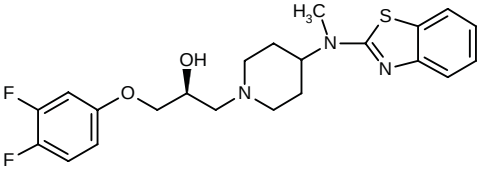
3. Malmstrom, K. et al. *Concomitant montelukast and loratadine provide rapid significant improvement in seasonal allergic rhinitis compared with loratadine alone.* Eur Respir J 1998, 12(Suppl. 28): Abst P1853.

Original monograph - Drugs Fut 1987, 12: 544.

Lubeluzole
Prosynap®

Neuroprotectant
Glutamate Release Inhibitor

EN: 211576



$C_{22}H_{25}F_2N_3O_2S$ **Janssen; Kyowa Hakko**

Janssen has confirmed that the development of lubeluzole, a neuroprotective agent which was being studied in clinical trials for the treatment of stroke, has been discontinued (1).

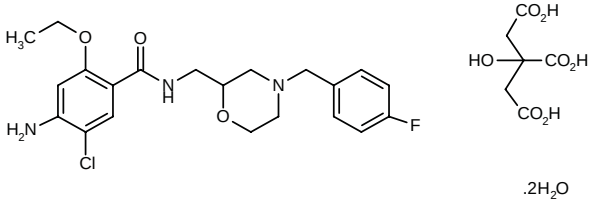
1. *Janssen confirms lubeluzole no longer under development.* DailyDrugNews.com (Daily Essentials) March 3, 1999.

Original monograph - Drugs Fut 1997, 22: 629.

Mosapride Citrate
Gasmotin®

Prokinetic
Treatment of GERD

EN: 137933



$C_{21}H_{25}ClFN_3O_3.C_6H_8O_7.2H_2O$ **Dainippon; AstraZeneca; Dae Wong**

The pharmacological effects of mosapride citrate were examined with results showing that the agent dose-dependently enhanced gastric emptying of liquid or solid meals in rats with effects more potent that metoclopramide and as potent as cisapride. The agent stimulated antral and duodenal motility in a manner similar to cisapride in conscious dogs. Electrically stimulated

contractions of isolated guinea pig ileal longitudinal muscle preparations were enhanced with the agent and this effect was antagonized by tropisetron. Action potential duration in guinea pig papillary muscle was not prolonged by mosapride, in contrast to cisapride which exhibited dose-dependent effects. Mosapride also inhibited [^{3}H]-GR-113808 binding to 5-HT_4 receptor in guinea pig ileum and striatum with no observed affinity for dopamine D_2 receptors, in contrast to cisapride and metoclopramide (1).

Mosapride citrate (Gasmotin®) has been launched in Japan for the treatment of gastroesophageal reflux disease. It is supplied as 2.5- and 5-mg tablets and as powder, 10 mg/g (2, 3).

Dainippon has signed a license agreement with Dae Wong for Gasmotin® in Korea. Dae Wong plans to introduce the product in Korea within the next year (4).

1. Yoshida, N. *Pharmacological effects of the gastroprokinetic agent mosapride citrate.* Folia Pharmacol Jpn 1999, 113(5): 299.

2. *New peristaltic stimulant on the way to market in Japan.* DailyDrugNews.com (Daily Essentials) July 9, 1998.

3. *First launch for Dainippon's prokinetic agent.* DailyDrugNews.com (Daily Essentials) Oct 2, 1998.

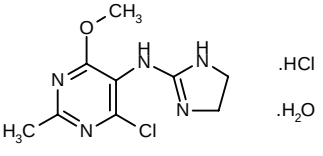
4. *Dainippon establishes Korean partnership for mosapride citrate.* DailyDrugNews.com (Daily Essentials) June 2, 1999.

Original monograph - Drugs Fut 1993, 18: 513.

Moxonidine Hydrochloride Hydrate
Cynt®

Antihypertensive
Imidazoline I_1 Agonist

EN: 090787



$C_9H_{12}ClN_5O.HCl.H_2O$ **Lilly; Solvay**

Lilly, together with its collaborative partner Solvay, announced the initiation of MOXCON, a large, randomized, global phase III trial designed to evaluate the safety and efficacy of the antihypertensive agent moxonidine hydrochloride hydrate for the treatment of congestive heart failure (CHF). The MOXCON trial will evaluate the ability of moxonidine to treat CHF by modulating sympathetic overactivity. Moxonidine is currently marketed in more than 20 countries for the treatment of hypertension. It is not approved in the U.S. for any indication (1).

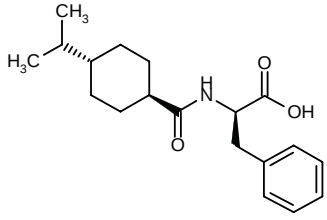
1. *MOXCON study will test the efficacy of SIRAs in treating heart failure.* DailyDrugNews.com (Daily Essentials) Aug 27, 1998.

Original monograph - Drugs Fut 1987, 12: 553.

Nateglinide
A-4166
Fastic®
Starlix®
Starsis®

Antidiabetic

EN: 127137



$C_{19}H_{27}NO_3$ **Ajinomoto; Yamanouchi; Novartis**

The association between the rapid onset and shorter duration of action of A-4166 in sulfonylurea receptor binding kinetics was evaluated *in vitro* using membranes from RIN-5F cells and recombinant cells expressing human SUR1. The order of displacement of radiolabeled glibenclamide in both cell lines was, from high to low: glibenclamide, glimepiride, repaglinide, glipizide, A-4166, L-isomer of radiolabeled glibenclamide and tolbutamide. A-4166 did not affect dissociation kinetics of radiolabeled glibenclamide, an observation consistent with the hypothesis that A-4166 binds competitively to the glibenclamide binding site on SUR1 receptors (1).

The effects of A-4166 (50 mg/kg gavage) on glucose and lipid metabolism were compared with those of glibenclamide (1 mg/kg gavage) in rats. A-4166 significantly lowered blood glucose level 1 h following meal intake at week 3, and a trend towards higher pancreatic insulin content was observed in A-4166-treated rats. The results indicate that postprandial glucose control by A-4166 may improve glucose and lipid metabolism in NIDDM (2).

In a study in cynomolgus monkeys, nateglinide and repaglinide displayed significantly different pharmacokinetic profiles. Nateglinide stimulated early insulin secretion, which returned to baseline within 60 min, while insulin levels rose more slowly with repaglinide and remained significantly above baseline 3.5 h after dosing (3).

In a placebo-controlled comparative study designed to compare mealtime glucose regulation using single oral doses of nateglinide (120 mg) and repaglinide (0.5 or 2.0 mg) in healthy humans, peak postmeal insulin levels were obtained earlier with nateglinide than with repaglinide. Nateglinide blunted the mealtime glucose excursion more effectively than repaglinide; the latter was associated with persistent insulin elevation 4 h after a meal in spite of maintaining glucose concentrations below 70 mg/dl. From 1.5 h onward, insulin levels after nateglinide were similar to placebo (4).

In a placebo-controlled study in 10 subjects with type II diabetes, administration of nateglinide (30, 60 or 120

mg t.i.d.) 10 min before each meal for 7 days resulted in significant, dose-related decreases in glucose and increases in insulin at multiple time points over a 24-h period. In a subgroup of patients receiving a fourth dose of 120 mg nateglinide before a bedtime snack, 24-h glucose exposure was reduced even further. Nateglinide was safe and well tolerated, with no episodes of hypoglycemia reported (5).

The prandial effects of 4 doses of nateglinide and placebo were assessed in 243 type II diabetic subjects in a double-blind, randomized, 12-week, parallel-group study with Sustacal® challenge. At week 12, nateglinide was shown to lower blood glucose by restoring prandial insulin secretion and reduced meal-related glucose fluctuations (6).

The effects on glycemic control of 4 doses of nateglinide (30, 60, 120 and 180 mg) and placebo before main meals were assessed in 289 diabetic patients in a double-blind, randomized, 12-week, parallel-group study with Sustacal® challenge. At the doses tested, nateglinide dose-dependently reduced fasting and postprandial hyperglycemia by improving prandial insulin secretion. All doses were well tolerated (7).

At its meeting last month, the CPAC's Committee on Drugs recommended approval of the fast- and ultra-short-acting insulin secretagogue nateglinide in Japan. Pending final approval, the compound will be marketed for the treatment of noninsulin-dependent diabetes under the trade names Starsis® (Yamanouchi) and Fastic® (Ajinomoto). The compound is supplied as 30- and 90-mg tablets. Nateglinide has been licensed to Novartis as Starlix® for development worldwide except Japan, Korea, Taiwan, the U.K. and Israel (8).

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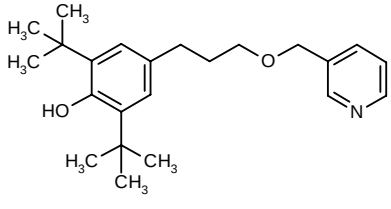
Nicanartine

Hypolipidemic
Antioxidant

EN: 199112



$C_{23}H_{33}NO_2$ **Merz**

The efficacy of treatment with nicanartine in a rabbit model of restenosis has been described. Rabbits with induced preinterventional plaques in the right carotid artery and subjected to balloon angioplasty were administered nicanartine 120 mg/kg. A significant reduction in the number of cells undergoing DNA synthesis and intimal macrophages was observed 7 days after treatment, indicating a decrease in proliferative responses. A trend toward reduced plaques was observed in treated animals. Thus, it appears that following interventional procedures, treatment with nicanartine could be an option for individuals with coronary artery disease (1).

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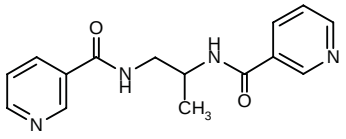
Nicaraven
Antevas®

Neuroprotectant

EN: 090263



$C_{15}H_{16}N_4O_2$ **Chugai**

Evaluation of nicaraven in combination with spinal hypothermia for the prevention of neuronal degeneration in rats following spinal trauma showed that intravenous administration of the drug attenuates glutamate release, without producing synergistic effects (1).

Nicaraven (35, 175, 350 and 1750 μM) was shown to dose-dependently inhibit platelet aggregation in 10 healthy volunteers and 10 patients with cerebral thrombosis. ADP- and collagen-induced aggregation were significantly inhibited by the agent at doses of 350 μM or higher and 1750 μM, respectively, in healthy subjects and both aggregation rates were inhibited by 1750 μM in patients (2).

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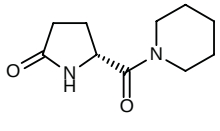
NS-105
Fasoracetam

Cognition Enhancer

EN: 135479



$C_{10}H_{16}N_2O_2$ **Nippon Shinyaku**

Average daily administration of NS-105 at dose ranges of 80-200 mg/kg and 310-810 mg/kg in rhesus monkeys and rats showed no evidence of reinforcing effects or potential for physical dependence (1).

Fasoracetam is the new proposed international nonproprietary name for NS-105 (2).

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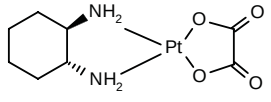
Oxaliplatin
Eloxatin®
Transplatin®

Antineoplastic
Platinum Complex

EN: 108094



$C_6H_{14}N_2.C_2O_4Pt$ **Lilly; Sanofi-Synthélabo**

Sanofi and Lilly are forming a U.S.-based joint venture for the regulatory submission, launch and commercialization of oxaliplatin under development by Sanofi. A submission to the FDA seeking approval of oxaliplatin in combination with 5-FU as a first-line treatment for all forms of advanced metastatic colorectal cancer is planned for the third quarter of 1999 (1).

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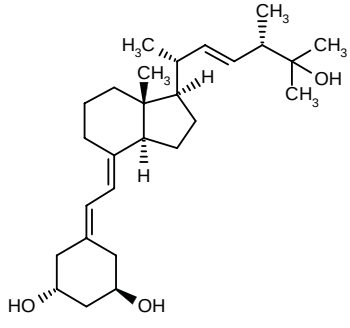
Paricalcitol
Paracalcin
ABT-358
Zemplar®

Treatment of Thyroid Disease

EN: 248876



$C_{27}H_{44}O_3$ **Abbott**

In a double-blind, multicenter study, 78 patients with end-stage renal disease on hemodialysis were randomized to paracalcitol (0.12 ± 0.01 μg/kg i.v. infusion) or placebo. A decrease of 30% or more in serum intact parathyroid hormone (iPTH) for 4 consecutive weeks was observed in 68 and 8% of patients on paracalcitol and placebo, respectively. At 12 weeks of treatment, the serum iPTH level decreased in the paracalcitol and placebo groups by 389 and 87 pg/ml, respectively. A reduction in serum alkaline phosphatase was observed in 31.8% of patients taking paracalcitol and in 8.3% of those patients on placebo. The few hypercalcemic episodes that occurred were all associated with a >70% reduction in PTH levels. Overall, paracalcitol safely and effectively suppressed iPTH levels in hemodialysis patients (1).

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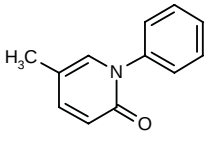
Pirfenidone
Deskar®

Antifibrotic

EN: 090236



$C_{12}H_{11}NO$ **Marnac; Shionogi; Synexus**

The antifibrotic effect of pirfenidone was shown to involve suppression of bleomycin-induced inflammatory responses and downregulation of bleomycin-induced overexpression of lung procollagen I and II genes. Hamsters were fed a pirfenidone (0.5%)-containing or a control diet 2 days prior to bleomycin (7.5 U/kg/5 ml) or saline intratracheal instillation and throughout the experiment. Bleomycin + pirfenidone-treated animals exhibited a gradual decrease in lung malondialdehyde levels from 10-21 days and decreased lung prolyl hydroxylase activity as compared to control bleomycin-treated animals. Pirfenidone also significantly decreased transcription of procollagen I at day 14 (1).

The efficacy of pirfenidone in the reversal of diabetes- or hypertension-induced fibrosis was evaluated in rats. Treatment of diabetic and hypertensive rats with pirfenidone 200 mg/kg reduced the deposition of collagen and did not affect functional parameters such as increased diastolic stiffness or vasoconstrictor response to noradrenaline, demonstrating the drug's efficacy in the reversal of cardiac fibrosis (2).

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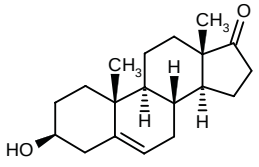
Prasterone

Immunosuppressant
Treatment of SLE
Antiallergic/Antiasthmatic

EN: 213244



$C_{19}H_{28}O_2$ **Genelabs; Jenapharm; Mipharm; Pharmadigm**

Gene expression of cytochrome P450 17 α-hydroxylase (P450c17) and dehydroepiandrosterone (DHEA) production were examined in an *in vitro* study using highly purified neonatal rat astrocytes, oligodendrocytes and neurons in an attempt to identify the cellular pathway by which DHEA is synthesized in the brain. Results showed that cerebral cortex astrocytes expressed P450c17 and dose-dependently metabolized pregnenolone, testosterone or estradiol to DHEA and produced androstenedione from progesterone. Cortical neurons had lower levels of P450c17 mRNA transcript and produced less DHEA from pregnenolone and androstenedione; oligodendrocytes neither expressed P450c17 nor produced DHEA. Hypothalamic astrocytes produced 3 times more

DHEA than cortical astrocytes and also dose-dependently produced DHEA from testosterone and estradiol with the metabolism of estradiol to DHEA 3 times more active than in cortical astrocytes (1).

DHEA was shown to retard the development of early nephropathy in obese Zucker rats which possibly resulted from more causes than just inducing smaller gains in body weight (2).

The efficacy of DHEA 5 mg/kg/day in the prevention of age-related cognitive and immune decline was evaluated in female rats. Rats receiving active treatment demonstrated a higher exploratory activity and reduced emotional reaction in open field. Short-term memory in social recognition tests also improved, although no differences were observed in cellular immune response or brain monoamine turnover (3).

Evaluation of DHEA treatment in genetically obese rats showed that administration of the compound for 10 days produced reductions in body weight and plasma insulin levels and increased the glucose disposal rate. Serum concentrations of tumor necrosis factor-alpha decreased. The results suggest that dehydroepiandrosterone may ameliorate insulin resistance in this study model (4).

DHEA was tested to see whether it would affect renal catecholamines in male Zucker rats. Rats ate chow containing 0.6% DHEA. Serotonin renal levels were elevated in obese rats; DHEA and a calorie-restricted diet lowered serotonin compared to that seen in lean rats. This effect may be due to the compound's salutary effect on renal function (5).

The activities of daily living and muscle strength improved and myotonia decreased in 11 patients with myotonic dystrophy who received DHEA sulfate (200 mg/d x 8 wk). In addition, 4 patients with cardiac involvement showed improved conduction block and premature beats (6).

The effects of 100 mg DHEA administered for 6 months were assessed in 19 healthy nonobese men and women (50-65 years). This trial revealed that a daily oral 100-mg dose of DHEA for 6 months elevated circulating DHEA and DHEA sulphate (DS) concentrations and the DS/cortisol ratio. No serious adverse events were reported. Women showed biotransformation to potent androgens near or just above levels seen in younger women. Men had decreased fat body mass and greater muscle strength. Differences in response to DHEA may reflect gender-specific responses to the drug and/or confounding factors in women such as estrogen replacement therapy (7).

Ten healthy men were treated for 18 months with at least 50 mg/day of DHEA. No changes were seen regarding prostatic specific antigen or serum testosterone (8).

The pharmacokinetics and biotransformation of orally administered DHEA (50 or 100 mg) were investigated in 9 healthy female volunteers with transient suppression of adrenal androgen secretion due to dexamethasone (0.5 mg q.i.d. x 4 d). The 50 mg dose of DHEA appeared to be an adequate dose in females with adrenal insufficiency (9).

A prospective study investigating the relationship between cortisol, DHEA sulfate and cognition was conducted in 189 healthy volunteers aged 55-80 years. Findings indicated that basal free cortisol levels were positively related to cognitive impairment, cortisol levels after dexamethasone were associated with cognitive decline and the relationship between DHEA sulfate and cognitive impairment and decline was inverse but not significant (10).

DHEA replacement therapy for 12 months was shown to correct and prevent several problems associated with menopause. Eight of 10 women with a maturation value of 0 showed stimulated vaginal epithelium maturation after treatment; stimulation of maturation was also seen in 3 treated women with intermediate pretreatment maturation values. Hip bone mineral density was significantly increased from 0.744 ± 0.021 to 0.759 ± 0.025 g/cm^2. Significant decreases in plasma bone alkaline phosphatase (20%) and urinary hydroxyproline/creatinine ratio (28%) and a 2.1-fold increase in plasma osteocalcin were observed after DHEA treatment. Endometrial atrophy was unaffected and beneficial effects on well-being and energy were reported (11).

The effects of DHEA treatment in exclusively female AIDS patients were assessed in 29 individuals receiving either 50 mg/day DHEA or a placebo for 6 months. Results showed that DHEA plasma levels were restored to physiological levels after DHEA treatment. Significant increases in body weight and CD4 counts were observed in DHEA-treated patients, as well as improvements in energy, physical and cognitive function, emotional well-being and current health perception. Moreover, increases were observed in the levels of several cytokines such as IL-1ra and TNF-α. No significant differences were observed in IL-α, IL-1β, IL-2, IFN-γ or IL-6 levels, but IGFBP-1 levels significantly decreased in DHEA-treated patients. Viral load tended to increase in the placebo group and decrease in the treated group, but these differences were not significant (12).

The safety and efficacy of DHEA (12 mg/kg i.v.) were examined in a randomized, placebo-controlled study in 9 volunteers with cat hair-induced asthma given the agent 30 min before cat room challenge. Preliminary data showed a mean difference in the change of FEV_1 after treatment of 14% (13).

The results from a study examining the efficacy and safety of DHEA treatment, with emphasis on assessing scores of quality of life, in patients with advanced HIV disease have been reported. Thirty-two HIV-infected patients were administered either 50 mg/d DHEA for 4 months or placebo. Plasma DHEA sulfate levels significantly increased in the DHEA-treated group as compared to the placebo group. Moreover, there was a significant improvement in mental health, as determined by quality-of-life scores taken every month, in the DHEA-treated group. CD4 cell counts did not change during the follow-up and no side effects were observed with drug treatment (14).

DHEA (30 mg for 1 month) supplementation to estrogen replacement therapy in postmenopausal women was shown to induce cytokine production and TH-1 cell subpopulations. The increase in IL-13 production observed after 2 weeks of estrogen treatment was shown to be significantly decreased with DHEA treatment. Estrogen-induced decreases in IFN-γ were further reduced with the drug (15).

DHEA has been designated a fast track product by the U.S. FDA for the treatment of systemic lupus erythematosus. If positive results are obtained from phase III testing, the company plans to begin NDA filing by the end of the year (16).

Pharmadigm has entered an agreement with Mipharm for the European development of Pharmadigm's lead product PB-005, an injectable form of DHEA sulfate for use by hospitals for the management of acute inflammation (17).

Pharmadigm recently completed a double-blind, placebo-controlled phase II trial of PB-005 in an inhaled allergen challenge in acute asthma. Results demonstrated that PB-005 significantly reduced the severity and duration of acute asthmatic episodes, confirming observations in earlier phase II trials of the drug in exercise-induced asthma. PB-007, the company's injectable formulation of DHEA, recently completed preclinical testing in animal models of stroke and heart attack. The company intends to advance PB-007 into human clinical trials to evaluate this product's efficacy in the management of ischemia/reperfusion injury associated with cardiovascular surgery, heart attack and stroke (18).

Results of Neurocrine Bioscience's phase II/III trial with DHEA for the treatment of Alzheimer's disease did not demonstrate a difference in efficacy between patients treated with DHEA *versus* placebo, despite a suggestion of efficacy from a previously completed 60-patient phase II trial. Based on these results, Neurocrine will not pursue further development of DHEA (19).

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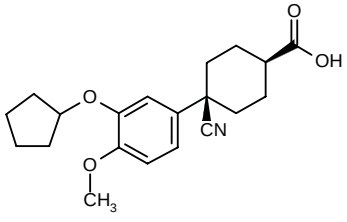
SB-207499
Ariflo™

Antiallergic/Antiasthmatic
PDE IV Inhibitor

EN: 204973



$C_{20}H_{25}NO_4$ **SmithKline Beecham**

SB-207499 potently inhibited inflammatory cytokine production as assessed *in vivo*. SB-207499 was as potent as (*R*)-rolipram but possessed markedly less central nervous system activity. SB-207499 may be an excellent tool for evaluating the antiinflammatory potential of PDE_4 inhibitors (1).

SB-207499 inhibited ovalbumin (OA)-induced contractions in guinea pig isolated tracheal strips (EC_{50} = 1 μM) but had little or no effect on exogenous agonist-induced contractions, indicating that the drug's *in vitro* effects are due to inhibition of mediator release from mast cells. SB-207499 inhibited OA-induced bronchoconstriction in anesthetized guinea pigs (ID_{50} = 1.7 mg/kg i.v. and 17 mg/kg p.o.). At 1, 3 and 6 h after SB-207499 (30 mg/kg p.o.), OA-induced bronchospasm was reduced by 92, 70 and 58%, respectively. House dust mite-induced bronchoconstriction was also inhibited by SB-207499 (ID_{50} = 0.9 mg/kg i.v. and 8.9 mg/kg p.o.). *In vitro*, the agent did not show bronchrelaxant activity although it inhibited leukotriene D_4 (LTD_4)-induced bronchospasm (ID_{50} = 3 mg/kg i.v.). At 1 h before antigen or LTD_4 challenge, SB-207499 (10 or 30 mg/kg p.o.) markedly reduced bronchospasm and eosinophil influx in conscious guinea pigs. These data indicate that SB-207499 has potential in treating asthma and other inflammatory disorders (2).

SB-207499 has been assessed for its ability to inhibit IL-5 production and eosinophil activation. SB-207499 inhibited antigen-induced IL-5 production in human peripheral blood mononuclear cells with an IC_{50} of 1.4 μM. Using eosinophils obtained from guinea pig peritoneal lavage fluid, SB-207499 produced a concentration-dependent increase in cAMP content (IC_{50} = 2.0 μM) and suppressed fMLP-stimulated superoxide production (IC_{50} = 0.8 μM). Antigen-induced eosinophil infiltration into the lungs of guinea pigs was inhibited by 88 ± 33% at a dose of 30 mg/kg p.o. SB-207499 thus appears to block several steps in the recruitment and activation of eosinophils (3).

SB-207499 (3 and 10 mg/kg p.o.) was found to be more effective than RP-73401, rolipram and LAS-31025 in inhibiting histamine- and antigen-induced edema formation in the skin of sensitized guinea pigs (4).

SB-207499 (1-30 mg/kg p.o.) given 1 h before challenge dose-dependently prevented OA-induced bronchospasm and airways eosinophilia in sensitized guinea pigs; greater potency against eosinophilia compared to bronchoconstriction indicated greater efficacy against antigen-induced formation and release of mediators than against preformed mediators. Prednisolone (50 mg/kg p.o.) given 18 and 1 h before challenge inhibited eosinophil infiltration but was ineffective against bronchoconstriction. SB-207499 (30 mg/kg) was more potent than prednisolone (50 mg/kg) in inhibiting LPS-induced neutrophilia, even when the compounds were given 1 and 6 h after LPS. The broad antiinflammatory and bronchodilating effects of SB-207499 appear to be ideal for the treatment of asthma and chronic obstructive pulmonary disease (5).

The effects of SB-207499 on the pharmacodynamic response to inhaled salbutamol were evaluated in a double-blind, 3-part crossover study. Healthy male volunteers received SB-207499 (10 mg b.i.d.) or placebo for 5 days; 1 h after dosing on day 5, subjects were administered nebulized salbutamol (2.5 mg) or placebo. The pharmacodynamic results demonstrated that SB-207499 may be coadministered with inhaled salbutamol without potentiating cardiovascular effects (6).

The potential drug interactions following concomitant administration of SB-207499 and theophylline were evaluated in healthy male volunteers. For 28 days, subjects were randomized to receive SB-207499 (10 mg b.i.d.) or placebo with single dose-rising exposure to oral theophylline (60, 120, 180 and 240 mg). Assessments on days 7, 14, 21 and 28 showed no changes in either SB-207499 or theophylline pharmacokinetics. There was no indication of pharmacodynamic or pharmacokinetic interactions with oral theophylline (7).

In a double-blind, parallel-group study, the effects of SB-207499 (10 mg b.i.d.) on the pharmacokinetics of prednisolone (10 mg/d) were examined in 24 subjects administered prednisolone for 14 days together with SB-207499 on day 8 for 7 days. Results indicated that SB-207499 can be safely administered with prednisolone without changing endogenous or exogenous steroid profiles (8).

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Original monograph - Drugs Fut 1998, 23: 607.

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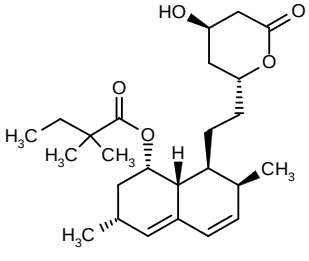
Simvastatin
Zocor®

Hypolipidemic
HMG-CoA Reductase Inhibitor

EN: 122234



$C_{25}H_{38}O_5$ **Merck & Co.; Mediolanum; Amrad**

The FDA approved a new 80-mg tablet of simvastatin (Zocor®), which was shown to lower LDL cholesterol in clinical studies by a mean of 47%. In addition, official prescribing information for the drug was changed to recommend the existing 20-mg tablet as the usual starting dose. Patients who require only a moderate reduction in LDL cholesterol may still be started at 10 mg. In addition to lowering cholesterol, Zocor® 80 mg lowered triglycerides by a median 36% in 189 patients with triglycerides over 200 mg/dl. These results are based on a 24-week trial comparing the efficacy and safety of Zocor® 40 mg and 80 mg in 433 and 664 patients, respectively. Zocor® was well tolerated, with only 1.5% of the patients on the 80-mg strength discontinuing treatment due to drug-related side effects compared to 1.4% given the 40-mg dose. The FDA also approved Zocor® as an adjunct to other lipid-lowering therapies in patients with homozygous familial hypercholesterolemia (1).

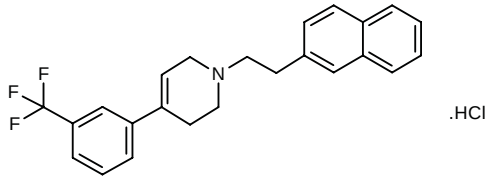
1. *FDA approves new dose range for Zocor.* DailyDrugNews.com (Daily Essentials) July 23, 1998.

Original monograph - Drugs Fut 1988, 13: 531.

SR-57746A
Xaliproden Hydrochloride

Neuroprotectant
Treatment of ALS
5-HT_{1A} Agonist

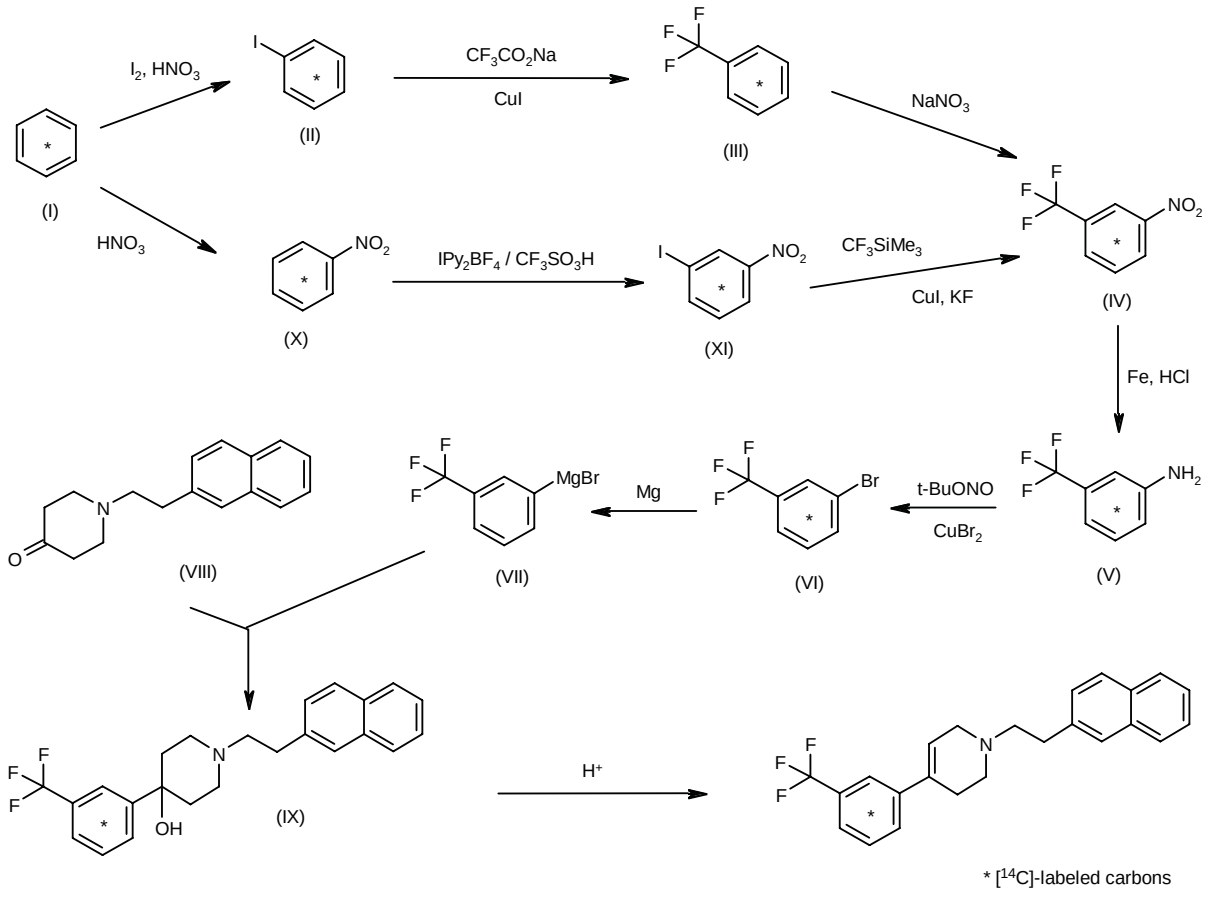
EN: 162594



$C_{24}H_{22}F_3N.HCl$ **Sanofi-Synthélabo**

A synthesis of [^{14}C]-labeled SR-57746A has been described: The iodination of [$^{14}C_6$]-benzene (I) with nitric acid/I_2 gives iodobenzene (II), which is treated with sodium trifluoroacetate and CuI, yielding trifluoromethylbenzene (III). The nitration of (III) with sodium nitrate affords 3-(trifluoromethyl)nitrobenzene (IV), which is reduced with Fe/HCl to the corresponding aniline (V). The reaction of (V) with *tert*-butyl nitrite and $CuBr_2$ provides 3-(trifluoromethyl)bromobenzene (VI), which is treated with Mg in THF, affording the corresponding Grignard reagent (VII). The condensation of (VII) with piperidone (VIII) gives the piperidol (IX), which is finally dehydrated in acidic medium. In order to aviod radioactive contamination during the purification of compounds iodobenzene (II) and trifluoromethylbenzene (III) by liquid chromatography, a safer route using less volatile compounds has been developed: The nitration of [$^{14}C_6$]-benzene (I) with nitric acid gives nitrobenzene (X), which is iodinated with IPy_2BF_4/CF_3SO_3H, yielding 3-iodonitrobenezene (XI). Finally, this compound is trifluoromethylated with CF_3SiMe_3, CuI and

Scheme 7: Synthesis of [^{14}C]-Labeled SR-57746A



KF to provide 3-(trifluoromethyl)nitrobenzene (IV), already reported (1). Scheme 7.

The effects of SR-57746A were assessed in a murine model of progressive motor neuronopathy. This autosomal recessive mutation results in caudio-cranial degeneration of motor axons which permits the animal to be used to investigate therapeutic strategies for treating motor neuron diseases like amyotrophic lateral sclerosis. When given to mutant mice, SR-57746A delayed the progression of motor neuron degeneration (2).

SR-57746A was shown to be a survival factor for neurons *in vivo*, indicating that it may be a potential treatment for damaged motor neurons. Rats were treated with the agent for 14 days following postnatal unilateral section of the sciatic nerve resulting in 50% survival of motor neurons in the spinal L4 lumbar segment. Motor neuron death was rescued by treatment on both the axotomy and nonaxotomy side, although neuronal diameter was not preserved (3).

Xaliproden hydrochloride is the new proposed international nonproprietary name for SR-57746A (4).

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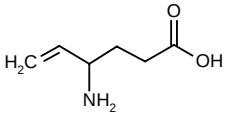
Vigabatrin *Anticonvulsant*
Sabril® *Treatment of Alcohol Withdrawal Syndrome*
Sabrilex®

EN: 090252



$C_6H_{11}NO_2$ **Hoechst Marion Roussel; Novartis**

Vigabatrin (1, 3 or 6 g) was assessed as add-on therapy in a multicenter, double-blind, dose-finding study enrolling 174 patients with uncontrolled complex partial seizures with or without secondary generalization. Vigabatrin significantly and dose-dependently reduced the median frequency of seizures per month as compared to placebo; therapeutic success was observed in 24, 51 and 54% of patients taking 1, 3 and 6 g of vigabatrin, respectively, which was significantly superior to placebo (7%). While the 3- and 6-g doses were the most effective as add-on therapy to reduce seizure frequency, the incidence of adverse events (fatigue, drowsiness, dizziness) associated with the 6-mg dose may limit its utility (1).

The potential use of vigabatrin in the treatment of alcohol withdrawal syndrome in comparison to oxazepam was evaluated in a double-blind, randomized, 7-day trial in 38 inpatients. CIWA-A scores decreased on days 2, 3, 5 and 7 as compared to day 1 in both treatment groups, with no statistically significant difference between groups. Thus, vigabatrin may represent an interesting treatment option for alcohol withdrawal syndrome, with the advantage of being a drug with no known abuse potential (2).

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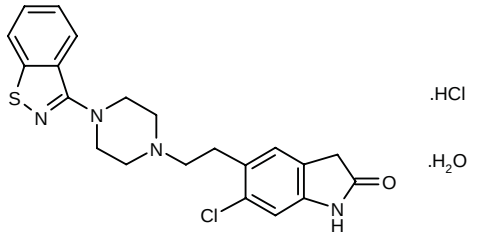
Ziprasidone Hydrochloride *Antipsychotic*
Zeldox® *Dopamine D_2 Antagonist*
5-HT_{2A} Antagonist

EN: 199378



$C_{21}H_{21}ClN_4OS.HCl.H_2O$ **Pfizer**

The activity of ziprasidone as tested in two *in vivo* models showed that the compound behaves as a 5-HT_{1A} agonist *in vivo* due to its ability to inhibit raphe cell firing and to selectively increase PFC dopamine release. By activating the 5-HT_{1A} receptors, ziprasidone may prove beneficial and advantageous in treating schizophrenia (1).

The interaction of ziprasidone with a variety of human receptors was evaluated and its profile was compared with that of other antipsychotics including olanzapine, risperidone, quetiapine, clozapine and haloperidol. Ziprasidone's greater serontonergic pharmacology and its selective effects on the 5-HT/NE transporter along with its high affinity for D_2 receptors indicate that the drug will be an effective antipsychotic with possible efficacy for affective symptoms and a low propensity to cause extrapyramidal side effects (EPS) (2).

Children and adolescents with Tourette's syndrome received either placebo or ziprasidone (5 mg/d starting dose, raised 5 mg b.i.d. every 3-4 d up to 40 mg/d). At the studied dose range, ziprasidone reduced the symptoms of Tourette's syndrome, was well tolerated and was associated with a lower risk of EPS (3).

Thirty-eight hospitalized patients received a 2-mg intramuscular dose of ziprasidone while 41 patients received a 20-mg dose. These patients with psychosis and acute agitation experienced a rapid and substantial reduction in agitation for at least 4 h after dosing; no extreme sedation was observed. Ziprasidone 20 mg was very well tolerated (4).

The tolerability and safety of fixed-dose, intramuscular ziprasidone was compared to that of flexible-dose, intramuscular haloperidol in a randomized, open-label study. For 3 days, 306 psychotic patients received ziprasidone (5, 10 or 20 mg q.i.d.) or haloperidol (10-40 mg b.i.d. or q.i.d.). After intramuscular treatment, patients were administered oral ziprasidone (40-200 mg/d) or haloperidol (inital dose equal to last i.m. dose) for 4 days. Intramuscular ziprasidone and the switch to oral therapy were well tolerated and showed possible tolerability advantages over rapid-acting intramuscular antipsychotics (5).

The population pharmacokinetics of ziprasidone was assessed in healthy and schizophrenic subjects. Data were collected from 483 subjects to expand understanding of the agent's two-compartment model. Ziprasidone showed dose-related increases in exposure which were related to body size. Gender, age, liver and renal function did not alter ziprasidone's pharmacokinetic parameters (6).

A total of 294 chronically ill, stable schizophrenic patients received ziprasidone (40, 80 or 160 mg/d) or placebo for 1 year in a prospective, randomized, double-blind study. Ziprasidone was effective in long-term treatment, prevented acute exacerbation, was very well tolerated (especially with movement disorders and weight gain) and improved global functioning (7).

The population pharmacokinetics of multiple-dose intramuscular ziprasidone (5, 10 and 20 mg q.i.d. for 3 d) were assessed using a model made from single-dose studies in healthy volunteers. Peak exposure was shown to be 30 min with dose-dependent increases in exposure but no drug accumulation (8).

A population pharmacokinetic method was used in the phase I development of rapid-acting intramuscular ziprasidone (5, 10 or 20 mg q.i.d. for 3 d) to assess its safety profile in 18 schizophrenic patients. Ziprasidone had predictable, linear pharmacokinetics in which therapeutic plasma levels were reached quickly (9).

Following a decision by the FDA to not approve Pfizer's NDA for ziprasidone hydrochloride (Zeldox®) without additional clinical data, the company has decided on a new development strategy. Pfizer had been informed that additional clinical data was required to answer questions regarding the observation of a slight increase in the cardiovascular QTc interval in patients treated with the drug, an effect which is also seen with many other antipsychotics. The company is designing a new study to address this question and plans to refile in late 1999. In the meantime, ziprasidone introductions in any other markets will be put on hold until the new study has been completed (10, 11).

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