Drugs of the Future 1998, 23(2): 205-245

Information Update

Volume 1-22, Number 2

Estimated developmental phase for this month's updated products:

Preclinical

KRN-7000 (immunostimulant; Kirin Brewery)

Phase I

Cerebrocrast (neuroprotectant, cognition enhancer; Latvian State Pharm. Co.)
Recombinant methioninase (antineoplastic; AntiCancer)

Phase II

BAY-12-8039 (fluoroquinolone antibacterial; Bayer)
Ifetroban sodium (antithrombotic; Bristol-Myers Squibb)
Iroplact (heparin inactivator, angiogenesis inhibitor, antineoplastic; Repligen)
KT-6149 (antineoplastic; Kyowa Hakko)
Levetiracetam (anticonvulsant; UCB)
NK-611 (antineoplastic, podophyllotoxin derivative; Nippon Kayaku, Asta)
SCH-56592 (antifungal; Schering Corp.)

Phase III

Colforsin dapropate (treatment of heart failure, adenylate cyclase activator; Nippon Kayaku)
Eptastigmine tartrate (cognition enhancer, acetylcholinesterase inhibitor; Mediolanum)
Fampridine (agent for multiple sclerosis; Elan, Acorda Ther., Axogen, Athena Neurosciences)
Fedotozine tartrate (gastrointestinal motility modulator, treatment of irritable bowel syndrome; Jouveinal, Glaxo Wellcome, Nippon Shinyaku, Warner-Lambert)
Lazabemide hydrochloride (antiparkinsonian, cognition enhancer; Roche)
Leminoprazole (gastric antisecretory, H^+/K^+-ATPase inhibitor; Nippon Chemiphar, Kyorin)
Pamicogrel (platelet antiaggregatory, cyclooxygenase inhibitor; Kanebo, Torii)
Perospirone hydrochloride (antipsychotic; Sumitomo)
Piritrexim (antineoplastic, dihydrofolate reductase inhibitor; Glaxo Wellcome, Ilex Oncology)
Pranidipine (antihypertensive, calcium channel blocker; Otsuka)
S-12968 (antihypertensive; Servier)
Sildenafil (treatment of erectile dysfunction, phosphodiesterase V inhibitor; Pfizer)
SNX-111 (neuronal injury inhibitor, calcium channel blocker; Neurex, Medtronic, Warner-Lambert)
Taltirelin (CNS stimulant, TRH analog; Tanabe Seiyaku)

Registered/Year

Clopidogrel hydrogensulfate (platelet antiaggregatory; Sanofi, Bristol-Myers Squibb, Daiichi Seiyaku)/1997

Launched/Year

Amphotericin B lipid complex (liposomal antifungal; The Liposome Co., Esteve, Wyeth-Ayerst)/1995
Copolymer-1 (agent for multiple sclerosis; Teva, Yeda, Hoechst Marion Roussel)/1996
Ebrotidine (gastric antisecretory, H_2-receptor antagonist; Ferrer)/1997
Olanzapine (antipsychotic; Lilly, Gador)/1996
Omeprazole (gastric antisecretory, H^+/K^+-ATPase inhibitor; Astra, Haessle)/1988
Selegiline hydrochloride (antiparkinsonian, cognition enhancer; Chinoin)/1981

Amphotericin B Lipid Complex
Abelect™

Liposomal Antifungal

EN: 127055

The Liposome Co.; Esteve; Wyeth-Ayerst

Data from various phase I and II pharmacokinetic and efficacy studies indicate that the improved toxicity profile of the injection formulation of amphotericin B lipid complex (Abelcet®), compared with the conventional micellar dispersion formulation, may be due to its faster clearance and larger volume of distribution (1).

In a randomized, open-label study in patients with visceral leishmaniasis infection unresponsive to or relapsing after conventional pentavalent antimony therapy, a 5-day course of therapy with amphotericin B lipid complex (1, 2 or 3 mg/kg/day as 2-h infusion) resulted in definitive clinical and parasitologic responses in 55 of 60 patients assessed 6 months after treatment (2).

A 6-week study in pediatric cancer patients with hepatosplenic candidiasis demonstrated that treatment with amphotericin B lipid complex (2.5 mg/kg/day) was safe and effective, resulting in complete or partial resolution of physical findings and lesions in 5 of 6 patients (3).

The Liposome Company has received marketing approval in Switzerland for Abelcet® (amphotericin B lipid complex injection) for the first-line treatment of candidiasis and severe systemic fungal infections in patients who have not responded to or are intolerant of conventional therapy. Abelcet® has been approved for marketing for a variety of first- and second-line indications in 16 countries, including the U.S., France, Italy, Spain and the U.K. Marketing applications have been filed and are under review in a number of other countries. The launch of this drug in the countries of approval is anticipated during the latter part of 1997 (4).

Abelcet® has been granted marketing approval as first-line treatment of candidiasis and for the treatment of severe systemic fungal infections in patients who were unresponsive to or are intolerant of conventional therapy in Italy and Austria (5).

Amphotericin B lipid complex injection (Abelcet®) has been approved by French regulatory authorities. The initial indication for the drug is the second-line treatment of patients with aspergillosis who have not responded to conventional antifungal therapy and the first-line treatment of patients with aspergillosis whose renal function precludes the use of amphotericin B (6).

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4. *Abelcet earns regulatory approval in Switzerland.* Prous Science Daily Essentials May 16, 1997.

5. *The Liposome Company granted first line approval for Abelcet® in Italy and Austria - First-line indication for candidiasis.* The Liposome Company, Inc. Press Release 1997, January 8.

6. *The Liposome Company, Inc. granted marketing approval for Abelcet® in France.* The Liposome Company,Inc. Press Release 1997, March 3.

Original monograph - Drugs Fut 1995, 20: 129.

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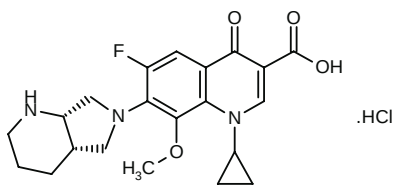
BAY-12-8039 *Fluoroquinolone Antibacterial*

EN: 240775



$C_{21}H_{24}FN_3O_4.HCl$ **Bayer**

The *in vitro* activity of BAY-12-8039, compared to other antimicrobial agents, against 410 clinically significant anaerobic isolates was comparable to that of metronidazole, 16-fold greater than those of cefoxitin, ofloxacin and ciprofloxacin, 32-fold greater than that of cefotetan and at least 128-fold greater than that of penicillin G. Overall, BAY-12-8039 inhibited 91 and 96% of isolates at 2 and 4 μg/ml, respectively (1).

An *in vitro* study against aerobic and anaerobic bacteria isolated from animal and human bite wound infections showed that BAY-12-8039 was active against all Gram-positive and Gram-negative aerobic isolates at ≤ 1.0 μg/ml and most of the anaerobic isolates at ≤ 0.5 μg/ml. Ciprofloxacin, levofloxacin, ofloxacin and sparfloxacin had similar activities against the aerobic strains but were less active against the aerobes (2).

A study comparing the *in vitro* activity of BAY-12-8039 with those of ciprofloxacin, clinafloxacin, levofloxacin, ofloxacin, sparfloxacin and trovafloxacin showed that BAY-12-8039 and clinafloxacin were the most active compounds tested against *Streptococcus pneumoniae* (MIC_{90}s = 0.06 μg/ml), followed by trovafloxacin and sparfloxacin (MIC_{90}s = 0.12 μg/ml). The activity of BAY-12-8039 was similar to the other fluoroquinolones against *Haemophilus influenzae* and *Moraxella catarrhalis* (3).

BAY-12-8039 and 11 other antibiotics were tested for their activity against 371 isolates of Gram-positive cocci. The results showed that BAY-12-8039 was the most effective among the quinolones tested against pneumococci (MIC_{90} = 0.1 mg/l), streptococci (MIC_{90} = 0.2 mg/l) and methicillin-susceptible staphylococci (MIC_{90} = 0.1 mg/l) (4).

In vitro studies showed that BAY-12-8039 was very active against infections caused by Gram-positive rods, particularly *Corynebacterium JK*, *Listeria* and *Actinomycetes*, with respective MIC_{90} values of 2, 0.5 and 0.2 mg/l (5).

The postantibiotic effect (PAE) of BAY-12-8039 against both Gram-positive and Gram-negative organisms was shown to be concentration-dependent and similar to that of other fluoroquinolones. The PAE ranged from 0-2.2, 1.2-3.1 and 1.4-3.3 h at concentrations equivalent to 1, 4 and 10 x MIC, respectively (6).

The *in vitro* activity of BAY-12-8039 against 360 clinical isolates of anaerobic bacteria was determined using the agar dilution method. The MIC values were in the range of 0.125-1.0 mg/l against anaerobic cocci and *Bacteroides fragilis*, 0.25-1.0 mg/l against *Clostridium perfringens* and *Fusobacteria*, 1.0-2.0 mg/l against *C. difficile*, and 0.125-0.25 mg/l against *Bacteroides*, *Porphyromonas* and *Prevotella* species (7).

Results of *in vitro* studies against 820 bacterial strains showed that BAY-12-8039 was 2- to 16-fold more active than ciprofloxacin and ofloxacin against enterococci, staphylococci, streptococci, anaerobes and common nonfermenters (except *Pseudomonas aeruginosa*), and was less active than ciprofloxacin and comparable to ofloxacin against *Enterobacteriaceae* and *Pseudomonas aeruginosa* (8).

BAY-12-8039 was shown to be active *in vitro* against 70 penicillin-sensitive and -resistant strains of *Streptococcus pneumoniae* (MIC_{50}/MIC_{90} = 0.125/0.25 mg/l for both groups). In a rabbit model of *S. pneumoniae*

meningitis, BAY-12-8039 (10 mg/kg/h i.v. for 12 h) was as effective as ceftriaxone in reducing bacterial titers in the CSF. Adjunctive treatment with dexamethasone (1 mg/kg q6h) had only marginal effects on the bactericidal activity and CSF penetration of BAY-12-8039 (9).

Time-kill studies demonstrated that BAY-12-8039 had excellent bactericidal activity at serum C_{max} concentrations achieved after oral dosing, being more active than cefuroxime and clarithromycin against β-lactamase-positive *Moraxella catarrhalis* and penicillin-resistant *Streptococcus pneumoniae*. BAY-12-8039 also had faster killing rates than the other two compounds against beta-lactamase-positive and -negative *Haemophilus influenzae* (10).

BAY-12-8039 was shown to be more active than ciprofloxacin, ofloxacin and levofloxacin against strains of *Staphylococcus aureus* (MIC_{90} = 0.125 μg/ml), *Streptococcus pyogens* (MIC_{90} = 0.25 μg/ml), *S. pneumoniae* (MIC_{90} = 0.5 μg/ml) and viridans group streptococci (MIC_{90}s = 0.5 and 0.25 μg/ml), as active as ciprofloxacin against *M. catarrhalis* (MIC_{90} = 0.125 μg/ml), and 4-fold less active than ciprofloxacin against *H. influenzae* (MIC_{90} = 0.063 μg/ml). Furthermore, BAY-12-8039 was bactericidal at concentrations of 2, 4 and 8 times the MIC, indicating that it would be useful in the eradication of respiratory tract pathogens (11).

In time-kill kinetic studies using both clinical isolates and laboratory strains, BAY-12-8039 was shown to have activity against both Gram-positive and Gram-negative bacteria under both aerobic and anaerobic conditions, as well as against anaerobes with concentration-dependent bactericidal activity and a neglible inoculum effect (12).

In vitro, BAY-12-8039 was shown to be more active than ciprofloxacin and ofloxacin, equipotent to trovafloxacin and less active than clinafloxacin against 218 strains of Gram-positive and Gram-negative anaerobes. Of all anaerobes tested, 83% and 99.5% were inhibited by BAY-12-8039, with MIC_{90} values of ≤ 1 mg/l and ≤ 4 mg/l (13).

BAY-12-8039 exhibited excellent concentration-dependent and inoculum-independent bactericidal activity against Gram-positive, Gram-negative and anaerobic microorganisms. In addition, a significant concentration-dependent postantibiotic effect was observed against both Gram-positive and Gram-negative bacteria (1.4-3.3 hours at 10 times the MIC). The results suggest that the compound should be evaluated further for the treatment of mixed aerobic and anaerobic infections (14).

In an experimental meningitis model in rabbits, BAY-12-8039 (40 mg/kg i.v. bolus x 2) was more effective than vancomycin (20 mg/kg i.v. bolus x 2) against penicillin-resistant *Streptococcus pneumonia*, with significantly higher reductions in CSF bacterial concentrations at 3 and 5 h postinfusion (–3.99 ± 1.30 vs. –2.10 ± 1.07 at 3 h and –5.15 ± 1.40 *vs.* –3.36 ± 1.09 at 5 h, respectively). BAY-12-8039 readily entered the CSF, reaching peak values within 15-30 min after infusion (15).

Results of absorption studies of unlabeled and [^{14}C]-labeled BAY-12-8039 administered as single doses in rats, monkeys, dogs and minipigs (3-10 mg/kg) and in humans (100 mg p.o.) demonstrated high to moderate (52-91%) oral bioavailability of the unchanged compound (dog > human > rat > minipig, monkey) and moderate colonic (rat, minipig) and rectal (dog, rat) bioavailability. The rate of absorption within 2 h after oral administration was rapid (rat < dog < monkey, human) (16).

Distribution studies in male and female rats of single intravenous and oral doses of [^{14}C]-BAY-12-8039 (4.6 or 5 mg/kg) showed high tissue affinity and rapid and homogeneous distribution of radioactivity from blood to organs and tissues after both routes of administration. After oral dosing, the maximum equivalent concentrations of radioactivity were up to 5.5-fold higher in most organs and tissue than in plasma. Elimination of radioactivity up to 24 h postdosing was similar in tissues and plasma. Penetration of radioactivity across the placental barrier was low to moderate, and secretion of radioactivity and unchanged drug into the milk was very low (17).

Results of an open, randomized, crossover study in 6 male subjects demonstrated that food did not influence either the pharmacokinetics of BAY-12-8039 (200 mg p.o.). nor its *in vitro* antimicrobial activity (18).

Once-daily oral doses of 600 mg BAY-12-8039 were shown to be safe and well tolerated in a double-blind, randomized, placebo-controlled study in healthy male volunteers. There were no relevant changes in vital signs, EEG, ECG or laboratory parameters (19).

In a double-blind, randomized, placebo-controlled study in 7 healthy male volunteers, BAY-12-8039 (800 mg) administered as a single oral dose exhibited linear pharmacokinetics, reached peak concentrations (4.7 mg/l) at 2-4 h postdosing and had a long half-life (about 15 h). In addition to its favorable pharmacokinetic profile, the drug was safe and well tolerated (20).

A placebo-controlled study in 15 healthy male and female volunteers showed that the pharmacokinetic parameters of BAY-12-8039 (400 mg p.o.) administered once daily for 10 days were consistent with linear kinetics and that plasma concentrations exceeded MIC for *Streptococcus pneumoniae* throughout the dosing period. Adverse events did not differ significantly between treatment groups, and no clinically relevant changes in vital signs, ECG, hematology or blood chemistry were observed. Based on these results, the 400-mg dose appears to be sufficient for treating *S. pneumoniae* infections (21).

In an open-label, randomized, crossover study in 12 healthy male volunteers, combined administration of BAY-12-8089 (200 mg p.o. b.i.d.) and theophylline (400 mg p.o. b.i.d.) did not influence the pharmacokinetics of either drug after single dose or in the steady state, indicating that no dosing adjustments are necessary for theophylline (22).

In a randomized, open, crossover study in 12 healthy male volunteers, the pharmacokinetics of BAY-12-8039 (400 mg p.o.) were shown not to be influenced by concomitant administration of ranitidine (150 mg b.i.d.), indicating that dosing adjustments for BAY-12-8039 are not necessary (23).

Results of a randomized, noncontrolled, single-dose study in 12 healthy volunteers showed that when BAY-12-8039 (400 mg) was coadministered with Maalox® the drug's extent and rate of absorption were reduced, but when it was given 4 or 2 h prior to Maalox® administration there was no significant effect on absorption. These results indicate that doses of BAY-12-1089 should be staggered when given together with antacids (24).

A double-blind, randomized, placebo-controlled study in 24 healthy male subjects evaluating single escalating doses of BAY-12-8039 (100, 200 and 400 mg as a 30-min i.v. infusion) demonstrated that the drug was very well tolerated up to the 400-mg dose. Pharmacokinetics were linear over the dose range studied and best fit a three-compartment model, with rapid distribution. The drug's favorable tissue penetration, $t_{1/2}$ and plasma concentrations above the MICs allow for a once-daily dosing regimen (25).

The results of a double-blind, randomized, crossover study in 12 healthy male volunteers administered a single oral dose of BAY-12-8039 (400 mg), with and without concomitant treatment with probenecid (500 mg b.i.d. p.o. for 2 days), showed that probenecid had no significant influence on the plasma kinetics or renal elimination of BAY-12-8039. The drug was safe and well tolerated, and no clinically relevant changes in laboratory parameters or drug-related adverse events were reported (26).

The safety and tolerability of BAY-12-8039 have been assessed in a double-blind, randomized, placebo-controlled trial in 130 healthy volunteers administered single doses of 50-800 mg and multiple doses of 600 mg once daily for 10 days. Adverse effects appearing more frequently with BAY-23-8039 were nausea, soft/loose stools and meteorism/gas, and those appearing more frequently on placebo were headache and the common cold. No significant changes in vital signs, hematology, blood chemistry or ECG were observed (27).

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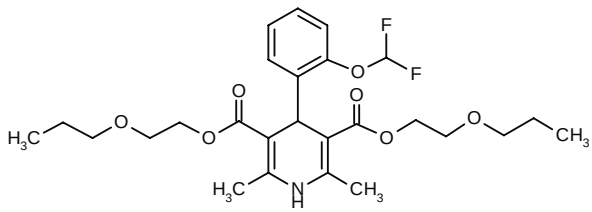
Cerebrocrast
IOS-1.1212

Neuroprotectant
Cognition Enhancer

EN: 131740



$C_{26}H_{35}F_2NO_7$ **Latvian State Pharm. Co. (LV)**

A study in adult rats with hypoxia-induced neurodeficiency showed that a single dose of cerebrocrast (100 mg/kg i.p.) increased exploratory activity, accelerated food-motivated learning, improved sensory attention and normalized emotional responses to negative stimuli. In addition to these enhancing effects, the drug also restored brain serotonin and noradrenaline concentrations altered by hypoxia (1).

Cerebrocrast (1 mg/kg p.o. b.i.d.) administered for 7 days in rabbits with experimentally induced subarachnoidal extravasation was shown to have antispastic and cerebroprotective effects (2).

Results of a single-blind, placebo-controlled, phase I trial in 30 healthy male and female volunteers demonstrated that cerebrocrast infusion (0.2, 1.0 and 2.0 mg i.v.) caused a decrease in systolic and diastolic blood pressure and blood flow velocities, and a slight increase in heart rate. EEG measurements also revealed an increase in brain electrical activity (3).

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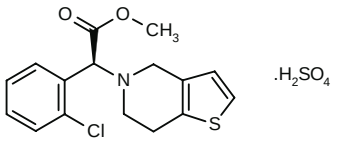
Clopidogrel Hydrogensulfate
Plavix® *Platelet Antiaggregatory*

EN: 142672



$C_{16}H_{16}ClNO_2S.H_2SO_4$ **Sanofi; Bristol-Myers Squibb; Daiichi Seiyaku**

In an *ex vivo* arteriovenous shunt thrombosis model in pigs, clopidogrel (5 mg/kg i.v.) was shown to reduce ADP-induced platelet aggregation and prolong bleeding time under conditions of high-risk stenting (1).

In studies in pigs, single bolus intravenous injections of aspirin (15 mg/kg) and clopidogrel (2.5 and 5 mg/kg) were shown to prolong bleeding time, while neither compound had any effect on blood cell count or coagulation parameters. Aspirin, but not clopidogrel, inhibited arachidonic acid- and collagen-induced platelet aggregation, whereas clopidogrel, but not aspirin, inhibited ADP-induced platelet aggregation. No antithrombotic activity was observed for aspirin *ex vivo*; however, clopidogrel induced a significant decrease in thrombus volume. These results indicate that both drugs have separate anti-aggregation and antithrombotic functions (2).

In a pharmacokinetics study in 12 healthy male subjects, after a single oral dose of clopidogrel (50-150 mg), the carboxylic acid metabolite SR-26334 exhibited a linear pharmacokinetic profile over the entire dose range, thus allowing the use of the metabolite's parameters to assess absorption interaction of the parent compound (3).

A retrospective analysis of studies comparing long-term administration of clopidogrel (75 mg/day) with aspirin (325 mg/day) in patients with atherosclerotic vascular disease showed a relative risk reduction of 8.7% in favor of clopidogrel among all patients, including those with recent myocardial infarction, stroke or peripheral arterial disease (4).

Results of a multicenter, dose-ranging study in 150 ambulatory atherosclerotic patients showed that once-daily doses of clopidogrel (10, 25, 50, 75 or 100 mg) dose-dependently inhibited ADP-induced platelet aggregation and bleeding time prolongation. The drug was well tolerated and no hematological adverse events were reported (5).

The FDA's Cardiovascular and Renal Drugs Advisory Committee recommended approval of clopidogrel bisulfate (Plavix®) for the prevention of vascular ischemic events in patients with a history of symptomatic atherosclerotic disease (6).

Bristol-Myers Squibb and Sanofi have submitted regulatory applications seeking marketing approval for clopidogrel (Plavix™) in the U.S. and Europe (7).

Sanofi and Bristol-Myers Squibb have received FDA approval to market clopidogrel bisulfate (Plavix®) for the reduction of atherosclerotic events in patients with atherosclerosis documented by recent myocardial infarction, recent stroke or established peripheral arterial disease (8).

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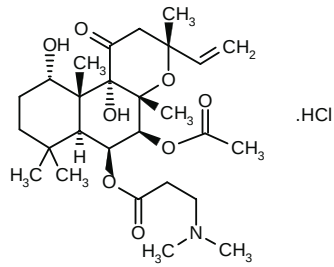
Colforsin Dapropate *Treatment of Heart Failure*
Adenylate Cyclase Activator

EN: 133606



$C_{27}H_{43}NO_8.HCl$ **Nippon Kayaku**

NKH-477 has been evaluated for potential antidepressant activity in the forced swimming test in rats. Dose-dependent decreases in immobility were observed in animals treated with forskolin (0.01- 0.1 mg/kg i.p.) and NKH-477 (0.01-0.5 mg/kg i.p.), with maximal effects being observed at doses much lower than those for amitriptyline (0.05 mg/kg *vs.* 15 mg/kg). NKH-477 induced less sedation than forskolin and was also active in this test after chronic oral administration (1).

A multicenter, dose-finding trial of NKH-477 (0.25, 0.5 and 0.75 μg/kg/min i.v.) in 62 patients with acute heart failure indicated that the optimal dose for clinical improvement and overall safety was 0.5 μg/kg/min. The most frequent drug-related adverse events were palpitation, flush, headache and arrhythmias (2).

Results from a multicenter, randomized, placebo-controlled study in patients with acute heart failure demonstrated that intravenous NKH-477 (0.5 or 0.2 μg/kg/min for 30 min), compared with placebo, produced statistically significant improvement in hemodynamic, subjective and objective symptoms, with the higher dose being significantly more effective than the lower dose. Both doses were well tolerated (3).

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Copolymer-1 Glatiramer Acetate Copaxone®

Agent for Multiple Sclerosis

EN: 199999

Teva; Yeda; Hoechst Marion Roussel

In rats with experimentally induced allergic encephalomyelitis, orally administered copolymer-1 was found to be at least as effective as myelin basic protein (MBP) in decreasing the incidence and severity of the disease. In *ex vivo* assays, oral copolymer-1 was more effective than oral MBP in inhibiting the proliferative responses of lymph node cells and in reducing the secretion of IL-2 and IFN-γ by lymph node cells (1).

An assessment of quality of life in multiple sclerosis patients showed that daily treatment with copolymer-1 not only reduced the frequency of relapses but also helped stabilize patient activity of daily living, including social functioning, depression, fatigue, home management and ambulation (2).

A 6-month, open-label study in 61 patients with multiple sclerosis indicated that continuous treatment with copolymer-1 may decrease the likelihood of developing optic neuritis. In the study, none of the 41 patients having no prior history of optic neuritis developed the disorder following drug treatment, and only 3 of 20 patients having at least one previous episode of optic neuritis showed a recurrence (3).

The results of a 12-month clinical and immunological follow-up study in 10 patients with relapsing multiple sclerosis suggested that the beneficial effects of copolymer-1 treatment, *i.e.*, significant reduction in exacerbation rate and stabilization of disability, were probably due to changes in the activation of T-cell subsets and a shift from proinflammatory to antiinflammatory cytokine profile (4).

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Ebrotidine
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Gastric Antisecretory
H_2-Receptor Antagonist

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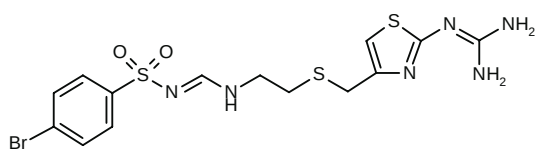

$C_{14}H_{17}BrN_6O_2S_3$ **Ferrer**

The synthesis of ebrotidine as originally published in this journal has been reported (1).

A method for the quantitative determination of ebrotidine in the presence of its principal precursors and degradation products (FI-3354, FI-3564, FI-3591, FI-3641 and FI-3645) has been developed. A solution of the analytical problem was solved in methanol and injected into a Merck-Hitachi HPLC chromatograph using a 25 x 0.4 cm Spherisorb CN 10µ column. An L-3000 photodiode detector in the 245 nm range was used for the quantification. The mobile phase was acetonitrile/sodium dihydrogen phosphate solution (2).

The mechanism of action for the gastroprotective effects of ebrotidine (1-100 mg/kg) against lesions induced by acid-dependent and acid-independent irritants was suggested to involve enhancement of gastric microcirculation, rather than inhibition of gastric acid secretion (3).

Binding studies showed that ebrotidine had greater affinity for guinea pig cerebellum and brain cortex membrane histamine H_2-receptors than ranitidine and cimetidine (K_i = 127.5, 190.0 and 246.1 nM, respectively). However, none of the compounds showed affinity for H_1-receptors (K_i > 5000 mM) (4).

In an *in vitro* study, ebrotidine was shown to be effective against 9 strains of *Helicobacter pylori* (MIC = 75 µg/ml on solid media) and at 100 µg/ml enhanced the activity of erythromycin (3 times), tetracycline (1.1 times) and amoxicillin (3 times), whereas ranitidine was ineffective against *H. pylori* (MIC > 1000 µg/ml) and failed to enhance the activity of the antibiotics at 500 µg/ml (5).

In 3 different experimental models of indomethacin-induced gastroduodenal lesions in rats (pylorus-ligated rats, fasted rats and healing rats), ebrotidine (50 and 100 mg/kg) was found to be as effective as omeprazole (8 mg/kg) and more effective than ranitidine (50 and 100 mg/kg) in the overall prevention and healing of lesions (6).

Ebrotidine administered to rats was shown to dose-dependently inhibit histamine- and pentagastrin-induced acid secretion (ED_{50} = 0.21 and 0.44 mg/kg i.v., respectively) and decrease total acid contents of the stomach (ED_{50} = 7.5 mg/kg p.o.). Serum gastrin levels were significantly increased within 2 and 5 h following single doses of both ebrotidine and ranitidine (100 mg/kg each). Levels returned to normal values 8 h after administration of ebrotidine and after 24 h for ranitidine. Both drugs caused significant increments in plasma gastrin levels, although the effect was more marked with ranitidine than ebrotidine (7).

In rats with ethanol-induced mucosal damage, ebrotidine was shown to dose-dependently inhibit gastric lesions and significantly reduce the number of deep and superficial ulcers (ED_{50} = 26.54 mg/kg), whereas cimetidine, ranitidine and famotidine were ineffective (8).

Daily oral doses of ebrotidine (10 or 35 mg/kg for 17 days) in rats were shown to significantly increase the amount of gastric glandular mucosa, suggesting that the drug's protective effect is due to an increased secretion of mucopolysaccharides (9).

Based on the increase of ethanol-induced lesions and the decrease in gastroprotective action caused by *N*-nitro-L-arginine (10 mg/kg i.v.), L-arginine (200 mg/kg i.v.) and *N*-ethylmaleimide (50 mg/kg s.c.), a study in rats determined that endogenous nitric oxide and sulfhydryl compounds play a crucial role in the gastroprotective activity of ebrotidine (10).

The pharmacokinetics of ebrotidine was studied in rats and dogs. In rats, the drug (10 mg/kg p.o. or i.v) was rapidly absorbed (C_{max} = 0.498 μg/ml, t_{max} = 30 min) with an abosolute bioavailability of 22%, a clearance of 29 ml/min.kg and volume of distribution of 1852 ml/kg. In dogs, the drug (150 mg p.o. and 25 mg i.v.) was also rapidly absorbed (C_{max} = 2.17 μg/ml, t_{max} = 2 h) with an absolute bioavailability of 29-64%, a clearance of 600 ml/h.kg and volume of distribution of 1000 mg/kg (11).

Acute toxicity studies of ebrotidine determined the lethal doses for mice (LD_{50} = 366 mg/kg i.p. and 107 mg/kg i.v.) and rats (LD_{50} = 316 mg/kg i.p. and 100 mg/kg i.v.). The lethal doses for oral administration were indeterminable (12).

A subacute toxicity study of ebrotidine (50, 200 and 500 mg/kg) in Sprague-Dawley rats and Beagle dogs for 4 and 7 weeks, respectively, showed that the higher dose produced a higher liver weight and decreased hematocrit and red blood cells in rats. The drug was more toxic in dogs than in mice, producing single increments of transaminase, alkaline phosphatase and lactated dehydrogenase, and in some cases death. These effects were similar to those found with cimetidine and ranitidine treatment. The 50-mg/kg dose was well tolerated in both species (13).

A chronic toxicity study of ebrotidine in rats (50, 200 and 500 mg/kg p.o. for 6 months) and dogs (50, 200 and 400 mg/kg p.o. for 12 months) determined the maximum toxic effect-free dose to be 50 mg/kg for both species. Adverse events in both groups included occult blood feces, lower weight gain and alkaline phosphatase increment. Rats also experienced lower food consumption and proteinase decrease while dogs experienced erosion of the intestinal mucosa and in some cases, at the higher dose, death (14).

Reproductive toxicity studies of ebrotidine in rats (50, 200 and 500 mg/kg p.o.) and rabbits (25, 100 and 200 mg/kg) determined the maximum toxic effect-free dose for both species to be 25 mg/kg. The results showed that the drug did not interfere with gametogenesis, organogenesis, fertility, postnatal development or lactation in F0 or F1 offspring. Treatment-related effects included lower weight gain in the parents and fetuses of rats, slower bone calcification, and a slight increase in embryonic mortality in rabbits (15) .

Carcinogenicity studies of ebrotidine in mice (50, 200 and 500 mg/kg p.o. for 18 month) and rats (50, 200 (150), 300 and 500 mg/kg p.o. for 24 months) determined that the drug does not induce neoplastic or preneoplastic effects in either species at doses up to 500 mg/kg. However, this dose decreased survival rate in mice, decreased weight gain in rats and increased the frequency of lipoid pneumonia and kidney calculi in rats (16).

The effect of ebrotidine on enteroendocrine cell populations was studied in mice (500 mg/kg for 18 months) and male rats (500 mg/kg p.o. for 60 days). The results indicate that the drug did not produce any significant differences in the density of gastric mucosa antral G-cells in rats or enterochromaffin-like cells in mice (17).

A study comparing ebrotidine (500 mg/kg), ranitidine (500 mg/kg), cimetidine (500 mg/kg) and omeprazole (43.5 mg/kg) administered orally for 60 days in male rats determined that, of the antisecretory agents, ebrotidine produced the lowest hypergastrinemic effect and the fastest recovery of baseline gastrin levels (18).

Based on results from the Ames, sex-linked lethal mutation, chromosomal aberration, micronucleus and sister chromatid exchange frequency tests it was determined that ebrotidine does not produce mutagenic or clastogenic effects (19).

A tolerability and pharmacokinetics study of ebrotidine in 16 healthy subjects determined that the drug was well tolerated following single oral doses up to 1600 mg and multiple oral doses of 800 mg/12 h for 12 days. Peak plasma concentrations occurred 2-3 h after oral dosing and elimination half-life was 9-14 h. No clinically relevant adverse events were observed (20).

A randomized, single-blind, pharmacokinetic study of ebrotidine (150, 300 and 500 mg p.o. b.i.d. for 7 doses) in 8 healthy volunteers determined the drug was rapidly absorbed (t_{max} ~ 2 h), with steady-state concentrations obtained in 24-48 h and a terminal elimination half-life of at least 7 h. The drug was well tolerated with no clinically significant dose-related adverse events (21).

Pharmacokinetic studies of single and multiple doses of ebrotidine (150-800 mg p.o.) administered to healthy volunteers determined the t_{max} (2 h), C_{max} (364-1168 ng/ml), AUC_{0-12h} (1427-5997 ng.h/ml, for the 150-800 mg doses) and elimination half-life (13.9-20.3 h, for 400, 600 and 800 doses). Following multiple dosing no accumulation was observed and 10-24% of the dose was excreted in the urine, primarily as the drug's main metabolite, ebrotidine sulfate (22).

A study in 18 healthy volunteers showed that ebrotidine (800 mg/day p.o.) prevented indomethacin-induced gastric lesions indicating that the drug is a noncompetitive inhibitor of carbonic anhydrase I and II (23).

A phase II, multicenter, double-blind, placebo-controlled study of ebrotidine (200, 400, 600 and 800 mg/day for 4 days) in 110 patients with duodenal ulcer demonstrated that the 400-800 mg doses, as compared to placebo, produced a significantly higher healing rate (90-95% *vs.* 55%) and produced significantly less ulcer-related pain and symptoms. The results showed that a daily dose of 400 mg is safe and effective in the treatment of duodenal ulcers (24).

A double-blind, placebo-controlled, parallel group study comparing ebrotidine (800 mg) with cimetidine (800 mg) showed that ebrotidine, as compared to placebo, significantly increased gastric pH levels during the post-administration, postprandial and nocturnal periods. Cimetidine produced similar results and there was no significant difference between treatment groups (25).

Results of a double-blind, randomized, parallel group study comparing ebrotidine (400 mg/day) to ranitidine (300 mg/day then 150 mg/day) for 8 weeks in 250 patients showed that the drugs were equally effective and

safe for the healing and prevention of relapse of duodenal ulcers (26).

In a randomized, multicenter, double-blind, 8-week study, a single daily dose of ebrotidine (400 mg/day) was shown to be as effective as ranitidine (300 mg/day p.o.) in healing rates in nonsmokers with endoscopically confirmed duodenal ulcer. However, in smokers, ebrotidine produced significantly higher healing rates than ranitidine. There was no difference between smokers and nonsmokers in the ebrotidine-treated group and alcohol intake showed no significant effect on healing rates (27).

A study comparing ebrotidine (400 or 800 mg/day p.o.) to ranitidine (150 or 300 mg/day p.o.) in 30 patients with rheumatic disease and piroxicam-induced gastric lesions showed that ebrotidine at 800 mg was more effective than ranitidine, at either dose, at preventing mucosal gastric lesions (28).

A phase II, double-blind, randomized, 8-week trial compared the efficacy of ebrotidine (400 mg) and ranitidine (300 mg), when combined with amoxicillin (750 mg t.i.d.) and metronidazole (500 mg t.i.d.) for 14 days, in the eradication of *Helicobacter pylori* in 30 patients with duodenal ulcer. Results showed that both treatments were equally effective in the elimination of *H. pylori* (over 80% eradication in both groups), in ulcer healing rate (86.7% at 4 weeks for both groups) and improvement of clinical symptoms (29).

A phase III, randomized, double-blind, parallel group trial comparing single doses of ebrotidine (800 mg/day) to ranitidine (300 mg/day) in 50 patients with benign gastric peptic ulcer showed that both drugs significantly improved healing rates and decreased ulcer diameter at week 6, but at week 12 ebrotidine was significantly better in the intention-to-treat analysis and in the per protocol analysis (96 and 98% *vs.* 88 and 87.5%, respectively). Ebrotidine also showed higher overall improvement of symptoms. The treatments were well tolerated with no significant adverse events reported (30).

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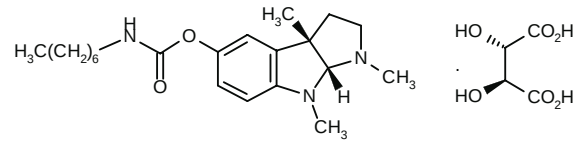
Eptastigmine Tartrate

Cognition Enhancer
Acetylcholinesterase Inhibitor

EN: 146545



$C_{21}H_{33}N_3O_2.C_4H_6O_6$ **Mediolanum**

Behavioral studies in aged male rats demonstrated that repeated administration of eptastigmine (0.6 mg/kg/day s.c. for 15 days) increased cortical acetylcholine levels and prevented age-associated impairment in spatial memory, whereas it had only a partial effect on nonspatial memory impairment (1).

Results of a double-blind, randomized, placebo-controlled, multicenter study of eptastigmine (20 mg b.i.d. or t.i.d. for 4 weeks) in 103 patients with probable Alzheimer's disease suggested that the significant improvement observed in patient performance on all tests and scales was associated with the drug's moderate inhibition of acetylcholinesterase levels (2).

Results of a 2-year, open-label extension study in 26 patients with probable Alzheimer's disease demonstrated significantly lower deterioration rates in patients treated with eptastigmine (10 mg t.i.d.) as compared to placebo-treated patients (3).

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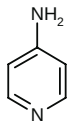
Fampridine
Neurelan®

Agent for Multiple Sclerosis

EN: 182600



$C_5H_6N_2$

Elan; Acorda Ther.; Axogen; Athena Neurosciences

Findings from a study using malignant astrocytoma cell lines U87 and A172 showed that 4-aminopyridine dose-dependently inhibited proliferation and blocked the outward rectifier potassium channel in both cell types. The drug also induced apoptosis in U87 cells with wild-type p53 but not in A172 cells with mutant p53 (1).

In experimental studies using demyelinated axons, clinical doses of 4-aminopyridine were found to increase synaptic transmission, motor neuron excitability and muscle twitch tension, but to have no effect on the number of axons conducting through a demyelinated lesion. These results indicate that the drug's beneficial effects in multiple sclerosis are due to mechanisms not involving demyelinated axons (2).

In a guinea pig model of chronic spinal cord injury, low concentrations of 4-aminopyridine (0.5 and 1 μM) caused an increase in the amplitude of the action potential, while high concentrations (1 and 10 mM) suppressed action potential conduction (3).

4-Aminopyridine (1-2 mg/kg) was shown to improve motor unit performance in dogs with hereditary canine spinal muscular atrophy. The effect was more pronounced in older animals with failing motor units than in older and younger symptomless animals (4).

Results of an open-label study in 17 healthy patients with traumatic spinal cord injury demonstrated that a single dose of 4-aminopyridine (10 mg p.o.), administered in an immediate-release formulation, provided a sustained, clinically and statistically significant improvement in pulmonary function (5).

Results from studies in 10 thermosensitive multiple sclerosis patients showed that a single oral dose of 4-aminopyridine (5-25 mg) induced reductions in P100 latencies on visual evoked potentials and in N9-N19 interval on somatosensory evoked potentials (SEP). The drug also induced an increase in N19 amplitude on SEP (6).

Results of a study in 19 patients with spinal cord injury demonstrated that 4-aminopyridine (10 mg p.o.) reduced motor-evoked potentials but did not alter peripheral reflex activity, indicating that the improvements in neuromuscular functioning were mediated through enhancement of central motor conduction (7).

A double-blind, placebo-controlled, crossover trial evaluating the clinical efficacy of sustained-release 4-aminopyridine (17.5 mg b.i.d for 1 week) in 10 multiple sclerosis patients with stable motor deficits showed that the drug improved timed gate, timed stair climbing, maximum voluntary isometric contraction, manual muscle testing and grip strength. No serious side effects were reported (8).

Acorda Therapeutics and Elan have signed an agreement to collaborate on the latter's oral sustained-release formulation of fampridine for the treatment of spinal cord injury (SCI). Pursuant to the agreement, Elan has granted Acorda exclusive worldwide rights to develop and market the product for SCI. Elan, in addition to having taken an equity stake in Acorda, will develop the product for multiple sclerosis and other non-SCI markets (9).

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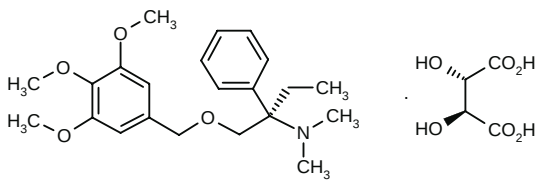
Fedotozine Tartrate

Gastrointestinal Motility Modulator
Treatment of Irritable Bowel Syndrome

EN: 163822



$C_{22}H_{31}NO_4.C_4H_6O_6$ **Jouveinal; Glaxo Wellcome; Nippon Shinyaku; Warner-Lambert**

Results of *in vitro* experiments performed on dorsal root ganglion neurons have shown that the increases in intracellular calcium as a response to mechanical stimulation were dose-dependently inhibited by fedotozine (1-100 nM), whereas the increases in response to capsaicin and caffeine were not affected by the drug (1).

Results of a study in rats showed that local or systemic (s.c.) administration of fedotozine (30, 300 and 600 μg/rat) and (–)-U-50488 (30,60 and 100 μg/rat) dose-dependently inhibited formalin-induced visceral pain in the colonic wall. The antinociceptive effect was more potent for both compounds via local rather than systemic administration (2).

Studies in conscious hydrated rats demonstrated that fedotozine, in contrast to several other reference κ agonists and morphine, had no effect on water diuresis. The drug also had no effect on urine output when administered in the lateral ventricle of the brain, nor did it alter the diuretic effects of U-50,488h. These findings indicate that fedotozine is an atypical κ agonist since it lacks activity on receptor subtypes regulating diuresis (3).

A randomized, placebo-controlled study in healthy volunteers showed that fedotozine (30 mg t.i.d. for 7 days), as compared to placebo, significantly increased discomfort threshold (14.4 ± 0.92 *vs.* 12.0 ± 1.13 mmHg), but did not modify gastric compliance or somatic sensitivity. Gastric distension-induced inhibition of the RIII reflex was also reduced by fedotozine (4).

A meta-analysis of 3 multicenter, randomized, double-blind, placebo-controlled phase IIb and III studies of fedotozine (30 mg t.i.d. for 6 weeks) in 658 patients with functional dyspepsia demonstrated that the drug was significantly more effective than placebo on both the overall dyspepsia intensity score and on 4 of 5 dyspeptic symptoms (5).

Long-term treatment with fedotozine (30 mg t.i.d. for 1 year) in 506 patients with functional dyspepsia and irritable bowel syndrome demonstrated improvement or resolution of symptoms in 84% and 87% of cases, respectively, as well as improvement in patients' quality of life. Laboratory tests, ECG/EEG, biochemical and hematological parameters were normal. The most frequent adverse events were constipation, abdominal pain, headache and nausea (6).

In a double-blind, placebo-controlled multicenter trial 333 patients were randomized to treatment with fedotozine (30 mg t.i.d.) or placebo for a period of 6 weeks. Overall intensity of dyspepsia symptoms improved significantly in the fedotozine group as compared to the placebo group, as did epigastric pain, nausea and a patient global score representing the average of five symptoms. Postprandial fullness improved, although not to a significant extent, whereas slow digestion and the inability to finish a meal were unaffected. A tendency toward improved irritable bowel syndrome symptoms was also observed in patients administered the active drug. Fedotozine demonstrated excellent safety (7).

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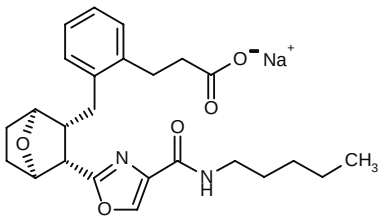
Ifetroban Sodium

Antithrombotic

EN: 203961



$C_{25}H_{31}N_2NaO_5$ **Bristol-Myers Squibb**

Results of a placebo-controlled, double-blind study in 24 healthy male subjects showed that a single dose of ifetroban (250 mg p.o.), compared to aspirin (325 mg p.o.), potently inhibited arachidonic acid- and collagen-induced *ex vivo* platelet aggregation (1).

In a pharmacokinetics study of ifetroban (250 mg) in healthy elderly and young subjects of both sexes, greater mean AUC and C_{max} values and lower mean total body clearance values were found in elderly males and females as compared to their younger counterparts. No gender-related differences were observed and treatment was well tolerated by all subjects (2).

A study in aspirin-free patients with intermittent claudication showed that ifetroban (50, 150 and 250 mg) strongly inhibited arachidonic acid- and U-46,619-induced *ex vivo* platelet aggregation, partially inhibited collagen-induced aggregation and had no effect on ADP (3).

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Original monograph - Drugs Fut 1994, 19: 107.

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EN: 182667

$C_{346}H_{585}N_{97}O_{102}S_5$ **Repligen**

Recombinant platelet factor 4, administered either as a 30-min infusion (0.3-3.0 mg/kg) or as a 6-h infusion (3.0 mg/kg), was evaluated in a phase I trial in patients with metastatic colorectal cancer who had failed treatment with 5-FU. Mild leg twitching in 2/3 patients administered the 6-h infusion was the only toxicity observed, and several patients experienced a mild increase in fibrinogen level. The drug was well tolerated at the dosing regimens studied, although no clinical responses were observed in the 11 evaluable patients (1).

Results of a preliminary phase I/II study in 4 evaluable patients with recurrent high-grade glioma, all having had prior surgery and radiation, demonstrated that localized injections of recombinant platelet factor 4 (2.5 and 5.0 mg, 3 times weekly) were feasible and nontoxic, although all patients had disease progression (2).

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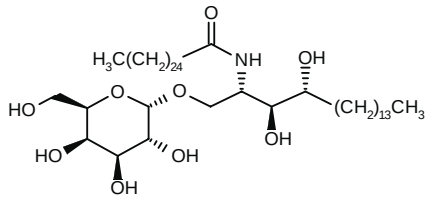
KRN-7000
AGL-582

Immunostimulant

EN: 222499



$C_{50}H_{99}NO_9$ **Kirin Brewery**

A single injection of dendritic cells pretreated with KRN-7000 (100 ng/ml) was shown to inhibit tumor growth and prolong survival periods in mice inoculated with colon-26 and EL-4 liver cancer cell lines. The antigen-presenting cell function of dendritic cells derived from murine bone marrow cells and Langerhans cells was also enhanced by drug pretreatment (1).

KRN-7000 was shown to be more effective than mitomycin C, doxorubicin, cisplatin and 5-FU and comparable to IL-12 in inhibiting hepatic metastasis in mice (2).

Dendritic cells stimulated with KRN-7000 inhibited liver metastasis, suggesting the potential of the compound for dendritic cell therapy (3).

In a study in NK-deficient mice with B16 liver and lung metastases, treatment with KRN-7000 resulted in marked suppression of tumor growth, prolonged survival times and cures in 20% of mice. Furthermore, the cured mice rejected rechallenge with B16 cells, indicating that KRN-7000 induces tumor immunity (4).

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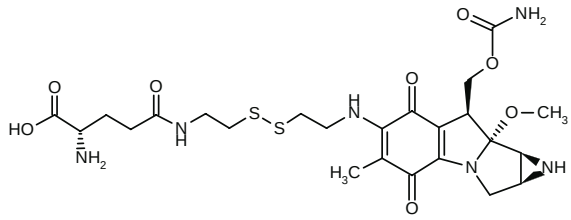
KT-6149
KW-2149
E-90/007

Antineoplastic

EN: 142017



$C_{24}H_{34}N_6O_8S_2$ **Kyowa Hakko**

Findings from a study using human and mouse serum demonstrated that the cytotoxicity of KW-2149 is mediated via extracellular metabolism in serum and differs between species of origin and batches of serum (1).

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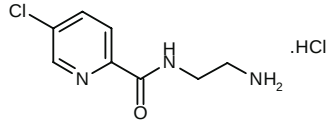

$C_8H_{10}ClN_3O.HCl$ **Roche**

The pharmacokinetics and pharmacodynamics of lazabemide (100-350 mg p.o.) administered as single or multiple doses were evaluated in a placebo-controlled, double-blind study in 30 healthy subjects. The drug produced a rapid, reversible and dose-dependent inhibition of monoamine oxidase B activity in platelets; the effect lasted for 16 and 36 h with the 100- and 350-mg doses, respectively. All doses of the drug were well tolerated, with headache being the most frequent adverse event at higher doses (1).

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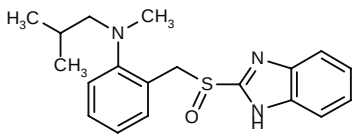
H^+/K^+-ATPase Inhibitor

EN: 175342



$C_{19}H_{23}N_3OS$ **Nippon Chemiphar; Kyorin**

Leminoprazole pretreatment of cultured rabbit gastric mucosal cells for 2 and 4 h was shown to have cytoprotective effects against indomethacin-induced cell damage. Induction of protein synthesis by exposure to leminoprazole was suggested to contribute to the drug's cytoprotective action (1).

In studies in Heidenhain pouch dogs, locally applied leminoprazole dose-dependently inhibited histamine-stimulated gastric secretion for at least 7 h. Degradation products of leminoprazole did not have any effect when applied to the pouch and the surface of the gastric mucosa was not damaged by the drug (2).

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Original monograph - Drugs Fut 1996, 21: 155.

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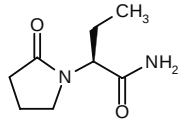
Levetiracetam

Anticonvulsant

EN: 113936



$C_8H_{14}N_2O_2$ **UCB**

Neurochemical studies in mouse brain demonstrated that single doses and twice-daily doses of levetiracetam (0-300 mg/kg i.p.) for 5 days had no effect on GABA, glutamate and glutamine concentrations, nor on GABA-transaminase and glutamic acid decarboxylase activities. These results suggest that the drug's anticonvulsant action is not mediated via the GABAergic system (1).

Results of electrophysiological studies of levetiracetam (10 μM) in rat hippocampal slice preparations demonstrated that the drug did not alter the components of normal synaptic transmission; however, it did inhibit bicuculline- and NMDA-induced epileptiform bursting in a manner similar to that of other antiepileptogenic drugs (2).

Results from a study in primary cultures of rat cortical astrocytes indicated that a 1-h exposure to levetiracetam (10-1000 μM) had no effect on the transport or metabolism of GABA, supporting the hypothesis that the GABA system is not involved in the drug's mechanism of action (3).

In behavioral studies in normal and amygdala-kindled rats, high doses of levetiracetam (up to 1700 mg/kg i.p.) produced mild sedation and ataxia but did not induce psychomimetic effects. Furthermore, in corneally-kindled mice, the drug's TD_{50} and ED_{50} values (2223 and 7.3 mg/kg, respectively) against secondarily generalized motor seizures gave a therapeutic ratio of 305, which compared favorably to those for established antiepileptic drugs. The unique pharmacological and safety profile of the drug in these animal models indicates its potential in the treatment of partial epilepsy in humans (4).

The effects of a single dose of levetiracetam (1000 mg) on sleep were studied in 12 normal healthy volunteers using a placebo-controlled, double-blind, crossover design. Results showed that the drug significantly increased stage 2 sleep and REM latency, but had no significant effect on slow wave sleep. Patients reported deeper sleep and fewer number of awakenings, but more difficult and slower waking in the morning (5).

In an early phase II trial in patients with photosensitive epilepsy, single (250, 500, 750 or 1000 mg) or multiple (250 mg b.i.d. for 3-5 days) oral doses of levetiracetam dose-dependently suppressed or abolished IFS-evoked photoparoxysmal EEG responses in 9 of 12 patients. No pharmacokinetic interactions with other antiepileptic drugs or serious side effects were observed (6).

Evidence from 2 double-blind, placebo-controlled, dose-ranging studies in 618 patients with partial epilepsy showed that add-on treatment with levetiracetam (1, 2 and 3 mg/day) resulted in statistically significant reductions in the frequency of seizures for all doses compared to placebo, with the higher doses being more effective than the lower dose (7).

Results from a double-blind, placebo-controlled, crossover study in 16 patients with a history of stable partial epilepsy while on carbamazepine monotherapy showed that a single dose of 1000 mg levetiracetam significantly increased total time spent in stage 2 sleep, significantly decreased total time spent in stage 4 sleep and had no effect on REM sleep. Although there were no significant changes in objective sleep continuity measures, the drug did improve some measures of subjective sleep quality, such as feeling more drowsy at bedtime, less restlessness and fewer awakenings during the night (8).

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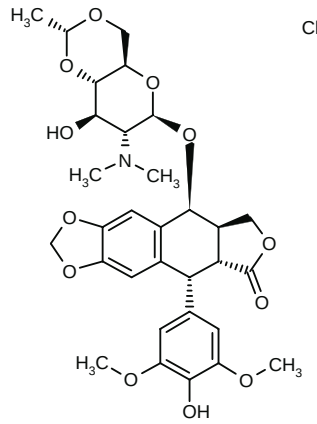
NK-611

Antineoplastic
Podophyllotoxin Derivative

EN: 126573



Chiral

$C_{31}H_{37}NO_{12}$

Nippon Kayaku; Asta

In a clinical and pharmacokinetic phase I trial of increasing doses of NK-611 (5, 10, 12.5 and 15 mg/day p.o.) in 16 evaluable cancer patients, the maximum tolerated dose was determined to be 12.5 mg/day administered for 21 consecutive days. The main hematologic toxicity was granulocytopenia, and mild nonhematological toxicities consisted of grade 1 nausea and grade 2 alopecia. A dose of 10 mg/day was recommended for phase II clinical studies (1).

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Yamada, H. et al. *Efficacy of new water-soluble analogue of etoposide, NK 611, on hepatocellular and biliary duct carcinoma cell lines in vitro.* Proc Amer Assoc Cancer Res 1997, 38: Abst 149.

Olanzapine

Antipsychotic

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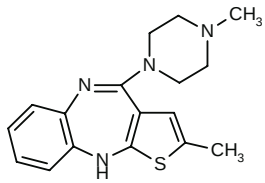
EN: 177756



$C_{17}H_{20}N_4S$

Lilly; Gador

The synthesis of some metabolites of olanzapine have been described (1):

1) Synthesis of 4'-*N*-desmethyl olanzapine: The condensation of 2-fluoronitrobenzene (I) with 3-cyano-5-methylthiophene-2-amine (II) by means of LiOH in DMSO gives the expected secondary amine (III), which is cyclized by means of $SnCl_2$ in ethanol yielding 2-methyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepine-4-amine (IV). Finally, this compound is condensed with piperazine (V) in toluene/DMSO affording the metabolite 2-methyl-4-(1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine. (Scheme 1).

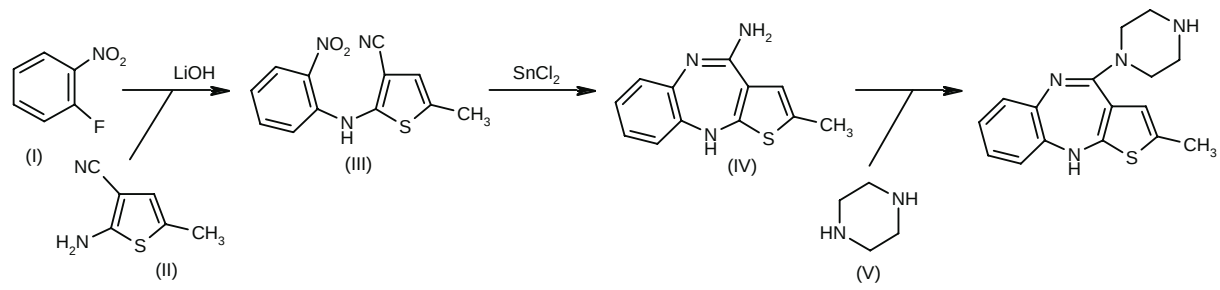
2) Synthesis of olanzapine 4'-*N*-oxide: The condensation of 2-fluoronitrobenzene (I) with 3-cyano-5-methylthiophene-2-amine (II) by means of LiOH in DMSO gives the expected secondary amine (III), which is cyclized by means of $SnCl_2$ in ethanol yielding 2-methyl-10*H*-thieno[2,3-*b*][1,5]-benzodiazepine-4-amine (IV). The condensation of (IV) with *N*-methylpiperazine (V) in toluene/DMSO affords 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*]-[1,5]benzodiazepine (olanzapine) (VI), which is finally oxidized with *m*-chloroperbenzoic acid (m-CPBA) in dichloromethane to give the metabolite 2-methyl-4-(4-methyl-4-oxidopiperazinyl-1-yl)-10*H*-thieno[2,3-*b*]-[1,5]benzodiazepine. (Scheme 2).

3) Synthesis of 2-hydroxymethyl olanzapine: The condensation of 2-fluoronitrobenzene (I) with 3-cyanothiophene-2-amine (II) by means of LiOH in DMSO gives the expected secondary amine (III), which is formylated with DMF by means of $POCl_3$ yielding the aldehyde (IV). The reductocyclization of (IV) with $SnCl_2$ in ethanol affords 4-amino-10*H*-thieno[2,3-*b*]-[1,5]benzodiazepine-2-carbaldehyde (V), which is reduced with $NaBH_4$ in ethanol to the corresponding hydroxymethyl derivative (VI). Finally, this compound is condensed with *N*-methylpiperazine (VII) in toluene/ DMSO to give the metabolite 2-(hydroxymethyl)-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*]-[1,5]benzodiazepine. (Scheme 3).

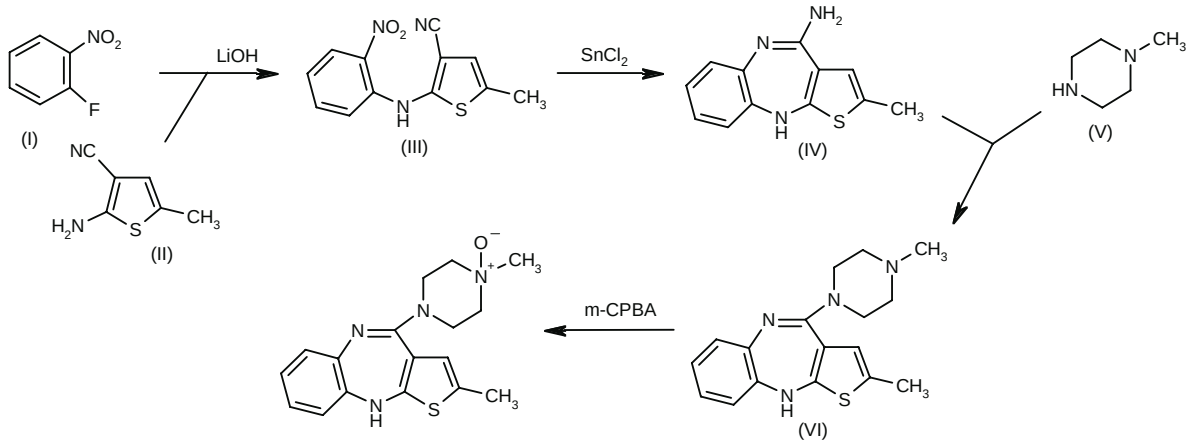
An international, double-blind, randomized study comparing Lilly's olanzapine (Zyprexa™) with risperidone for the treatment of schizophrenia was reported on May 20th at the American Psychiatric Association annual meeting in San Diego. This 28-week trial, conducted by Lilly, involved 339 patients who received either olanzapine or risperidone in doses of 10-20 mg/day and 4-12 mg/day, respectively. Results indicated that the drugs had comparable safety profiles; however, a statistically significantly greater number of olanzapine patients showed at least a 40% and 50% improvement in the severity of positive and negative symptoms on the Positive and Negative Symptom Scale (PANSS) after 28 weeks. In addition, olanzapine demonstrated statistically significantly greater improvements on the Scale of the Assessment of Negative Symptoms (SANS) and in depressive symptoms, as indicated by change in the PANSS depressive score. The estimated rate of relapse at 28 weeks was 12% and 32% for olanzapine and risperidone, respectively. Following 28 weeks of treatment, patients receiving risperidone were more likely to report extrapyramidal side effects than olanzapine-treated patients. Both groups reported comparable improvements in their total Heinrichs-Carpenter Quality of Life Scale score; however, the olanzapine group demonstrated a statistically significantly greater long-term improvement in interpersonal relations (2).

In an international, multicenter, double-blind trial in 2996 patients with schizophrenia, schizophreniform or

Scheme 1: Synthesis of 4'-*N*-Desmethylolanzapine



Scheme 2: Synthesis of Olanzapine 4'-*N*-Oxide



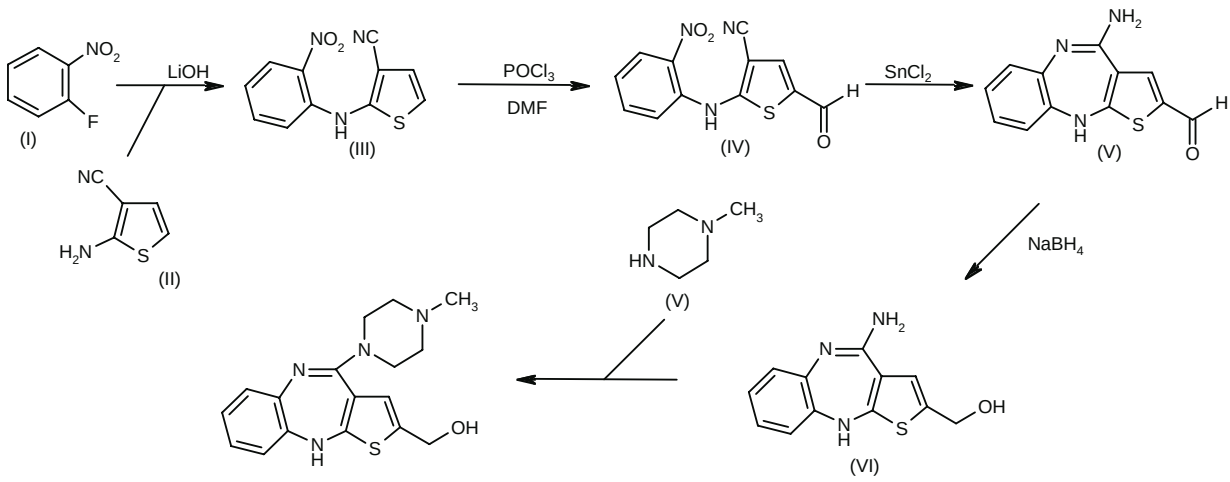
schizoaffective disorders, olanzapine was shown to be statistically significantly superior to haloperidol in regard to overall improvement on the Brief Psychiatric Rating Scale, mean change in positive and negative symptoms, comorbid depression, extrapyramidal symptom profile, effect on prolactin levels, response rate and safety profile (3).

The 6-week acute-phase results of an international double- blind study comparing three dose ranges of olanzapine (5 ± 2.5, 10 ± 2.5 and 15 ± 2.5 mg/day) with a fixed dose of olanzapine (1.0 mg/day) and haloperidol (15 ± 5 mg/day) in 431 schizophrenic patients showed that the high-dose olanzapine group, compared to the fixed-dose group, had statistically significantly greater improvement in overall psychopathology and positive psychotic symptoms. Compared with the haloperidol group, all olanzapine-treated patients had a lower incidence of treatment-emergent acute extrapyramidal syndromes and only minimal increases in prolactin concentrations (4).

Results of studies in 24 male volunteers with chronic or subacute schizophrenic disorder and dysfluency treated with olanzapine showed that speech fluency may be a useful criteria in selecting among different neuroleptics rather than requiring treatment failure with typical neuroleptics (5).

Results of two large studies on the effectiveness of long-term maintenance therapy with olanzapine have been reported. In the first study comparing fixed doses of

Scheme 3: Synthesis of 2-Hydroxymethyl Olanzapine



olanzapine (5, 10 or 15 mg) with haloperidol (10 mg) and placebo, the percent of patients not relapsing was significantly higher in the olanzapine-treated group (71.5%) compared to the placebo group (32.8%). In the second study comparing olanzapine 5-20 mg with haloperidol 5-20 mg, the results demonstrated the superiority of olanzapine in terms of percent of patients not relapsing (80.9% *vs.* 72.2%), as well as in improvement of quality of life (6).

Results of an international, multicenter, double-blind trial in 300 patients with schizoaffective disorder showed that a single oral dose of olanzapine (5-20 mg) produced a significantly greater improvement in BPRS total, PANSS total, PANSS negative, CGI severity and MADRS total scores than a single dose of haloperidol (5-20 mg) (7).

A study of the disposition and biotransformation of olanzapine (12.5 mg) administered as a single oral dose in 6 healthy male volunteers showed that the drug was extensively metabolized by *N*-glucuronidation, allylic hydroxylation, *N*-oxidation and *N*-dealkylation. *N*-glucuronidation was the primary pathway contributing to drug-related circulating species and excretory products in the feces and urine (8).

A study evaluating the effect of fluvoxamine (50-100 mg/day for 11 days) on the pharmacokinetics and pharmacodynamics of olanzapine (2.5-7.5 mg for 8 days) in 10 healthy male smokers showed that fluvoxamine increased olanzapine's mean C_{max} (84%) and AUC_{0-24} (119%), and decreased clearance (50%) and bioavailability (45%). Fluvoxamine also decreased the C_{max} (64%) and AUC_{0-24} (77%) of olanzapine's primary metabolite, *N*-desmethyl olanzapine. The results indicate that fluvoxamine significantly reduces olanzapine clearance by inhibiting CYP1A2 first-pass metabolism (9).

Results of an open-label study of olanzapine (5-25 mg/day for 18 weeks) in 3 patients unresponsive to clozapine or who discontinued treatment due to leukopenia showed that olanzapine reduced the total PANSS score and appeared to be safe and well tolerated, with no hematological side effects being reported (10).

A double-blind, randomized study of olanzapine (10-20 mg/day) and risperidone (4-12 mg/day) in 297 patients with schizophrenia, schizophreniform disorder and schizoaffective disorder showed that both drugs were equally efficacious. However, olanzapine was significantly superior in reducing mood symptoms, improving clinical response and preventing relapse. Olanzapine was also superior to risperidone regarding adverse events such as extrapyramidal symptoms, sexual dysfunction and prolactin level (11).

A multicenter, open-label study of olanzapine (5-25 mg/day for 18 weeks) in 45 evaluable patients unresponsive to clozapine treatment showed that olanzapine produced reductions of 14.2% and 14.7% in PANSS- and BPRS-total scores, respectively. The drug appeared to be safe and well tolerated (12).

Analysis of three placebo-controlled, long-term studies comparing the efficacy of olanzapine (to 20 mg/day) with haloperidol (to 20 mg/day) in 904 patients with schizophrenia, schizophreniform disorder or schizoaffective disorder determined that the incidence of newly emergent tardive dyskinesias was significantly less in the olanzapine-treated group (13).

The unblinded results of a 10-week clinical trial of olanzapine (25 mg/day) *versus* chlorpromazine (1200 mg/day) in 81 patients with treatment-resistant schizophrenia showed that 10% of the patients had responded to treatment at the time of reporting (14)

The results of 4 double-blind, pivotal clinical studies comparing olanzapine to haloperidol and/or placebo indicated that olanzapine is as effective as haloperidol for treating the positive symptoms of schizophrenia and more effective than haloperidol for treating the negative symptoms (15).

A review of the clinical data in 2500 patients with schizophrenia has demonstrated the overall safety and very low discontinuation rate associated with olanzapine treatment. Somnolence, weight gain and transaminase elevations were the most frequently reported treatment-related adverse events (16).

An analysis of the direct or indirect effects of treatment on negative symptoms of schizophrenia has been performed using results from a previous, 52-week, double-blind, randomized trial comparing olazapine, haloperidol and placebo in 335 schizophrenic patients. The results showed significantly greater direct and indirect effects on negative symptoms for high-dose olanzapine (17).

Results of a multicenter, double-blind, parallel-group study comparing olanzapine and risperidone in 339 patients with schizophrenia and other psychotic disorders demonstrated that both drugs were safe and effective, although olanzapine was significantly more efficacious than risperidone in treating negative symptoms, overall response rate and maintaining response at 28 weeks. There were significantly fewer adverse events and a significantly lower incidence of extrapyramidal side effects, hyperprolactinemia and sexual dysfunction with olanzapine (18).

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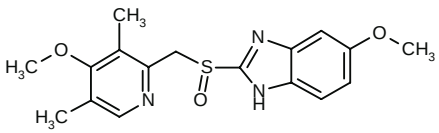
Omeprazole

Gastric Antisecretory
H^+/K^+-ATPase Inhibitor

EN: 090859



$C_{17}H_{19}N_3O_3S$ **Astra; Haessle**

Results of a randomized, double-blind, controlled study in 107 evaluable patients with benign gastric ulcer associated with *H. pylori* infection demonstrated that eradication treatment with omeprazole (40 mg once daily for 8 weeks) and amoxycillin (750 mg b.i.d. during weeks 7 and 8) resulted in lower rates of gastric ulcer recurrence over 1 year, although healing rates were not significantly higher (1).

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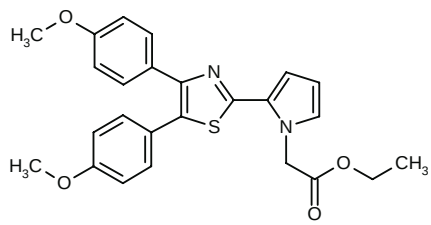
Pamicogrel

Platelet Antiaggregatory
Cyclooxygenase Inhibitor

EN: 118825



$C_{25}H_{24}N_2O_4S$ **Kanebo; Torii**

Findings from recent studies indicate that the inhibitory effects of KBT-3022 on platelet activation may be due to inhibition of cyclooxygenase by the drug's main metabolite, desethyl KBT-3022 (1).

Studies using a rat model of photochemically induced arterial thrombosis suggested that the potent antithrombotic effect of desethyl KBT-3022, the main metabolite of KBT-3022, was due, in part, to its ability to inhibit thrombin-induced platelet aggregation (2).

The pharmacokinetics and pharmacology of KBT-3022 have been assessed in guinea pigs. After both i.v. and oral administration, KBT-3022 was rapidly metabolized to the corresponding acid, C_{max} and AUC values for the metabolite increasing proportionally to dose over the range 5-20 mg/kg. Following oral administration of [^{14}C]-labeled KBT-3022, levels of radioactivity in platelets were much higher than in plasma, and the difference was even more marked for the metabolite. Almost complete inhibition of TxB_2 production was observed for at least 48 h after oral administration of KBT-3022 at doses of 1 and 5 mg/kg, the duration of the effect being longer after the higher dose (3).

In a guinea pig model of arterial thrombosis, pretreatment of the saphenous artery with KBT-3022 (0.1, 0.3, 1 and 3 mg) 3 h prior to thrombus induction was shown to concentration-dependently prolong time to thrombotic occlusion and inhibit collagen-induced platelet aggregation in whole blood *ex vivo*. The antithrombotic potency of KBT-3022 was 300 and 1000 times greater than that of aspirin and ticlopidine, respectively (4).

In a rat model of aspirin-insensitive arterial thrombosis, both desethyl KBT-3022 (up to 1 mg/kg i.v.), the main active metabolite of KBT-3022, and BM-10505 dose-dependently prolonged the time to achieve thrombotic occlusion. Furthermore, desethyl KBT-3022, unlike BM-10505 and aspirin, concentration-dependently inhibited thrombin-induced platelet aggregation (5).

The pharmacokinetics of KBT-3022 after intravenous and oral administration have been determined in mice, rabbits, dogs and rats (6).

Results of metabolism studies of oral KBT-3022 in rats, mice, dogs and humans indicated that the metabolism in humans most closely resembles that in mice (7).

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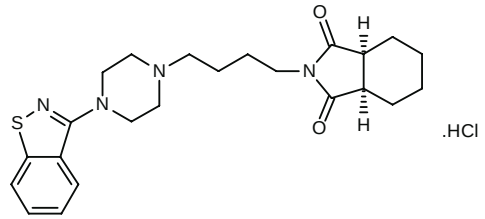
Perospirone Hydrochloride *Antipsychotic*

EN: 161247



$C_{23}H_{30}N_4O_2S.HCl$ **Sumitomo**

In CHO cells expressing human dopamine D_{2L} and $D_{4.4}$ receptors, perospirone markedly inhibited the specific binding of [^{3}H]-spiperone to both receptors, with respective K_i values of 0.24 and 0.83 nM. Perospirone also concentration-dependently antagonized dopamine-induced inhibition of adenylate cyclase activity in D_{2L} and $D_{4.4}$ cells, with EC_{50} values of 3.4 and 15 nM, respectively (1).

Results of studies on the central actions of perospirone showed that the drug inhibited 5-HT_2 receptor-mediated behavior, antagonized 5-HT-induced potentiation of platelet aggregation *in vitro* and inhibited D_2 receptor-mediated behavior in rats. These effects were not influenced by age, gender or repeated drug administration. When coadministered with other drugs, perospirone potentiated the D_2 antagonist action of haloperidol and the inhibitory effects of cimetidine on gastric acid, while augmenting the anticonflict action of diazepam (2).

Receptor binding studies of the 11 major metabolites of perospirone showed that all of them had lower affinities for D_2 and 5-HT_2 receptors than the parent drug. ID-15036, the 1-hydroxylated metabolite, showed the highest binding affinities, followed by the 4-hydroxylated metabolites, ID-20234 and ID-20235 (3).

A toxicity study of SM-9018 in mice and rats gave LD_{50} values of 660 and 720 mg/kg in male and female mice, respectively, 1240 and 870 mg/kg p.o. in male and female rats, respectively and 28-40 and 33 mg/kg i.v. in male and female rats, respectively (4).

Results of a toxicity study in male and female Sprague-Dawley rats administered repeated oral doses of SM-9018 (0.2, 1, 5 and 25 mg/kg for 12 months) determined the no-observed adverse effect dose to be 0.2 mg/kg (5).

Reproductive and developmental studies in male and female rats determined that the no-observed adverse effect doses of SM-9018 for male and female general toxicity were 1 and 0.5 mg/kg, respectively. The no-observed adverse effect doses for male and female reproductive performance were determined to be 30 and 0.1 mg/kg,

respectively, and 3 mg/kg for development of the next generation (6).

Results of a fertility study of SM-9018 (10 and 30 mg/kg) administered to female rats 14 days before mating and 14 days following recovery showed that the effects of the drug on food consumption, body weight, spontaneous activity, frequency of estrous, number of implantation sites and live fetuses were reversible upon cessation of treatment (7).

A teratogenicity study of daily oral doses of SM-9018 (1.0, 3.0, 10 mg/kg) in rats during fetal organogenesis determined that the maternal no-observed adverse effect dose was 1.0 mg/kg and for gestation, parturition, lactation, fetus and offspring the no-observed effect dose was 10 mg/kg (8).

Reproductive and developmental toxicity studies of daily oral SM-9018 (0.2, 1 and 5 mg/kg) in pregnants rats during the perinatal and lactation periods showed that the maternal no-observed adverse effect dose was below 0.2 mg/kg; the dose for no-observed adverse effect for dams and offspring was 1.0 mg/kg (9).

Studies in orally or intramuscularly sensitized guinea pigs showed that SM-9018 did not have antigenic potential (10).

Disposition studies in rats showed that after single oral doses of radiolabeled SM-9018 (10 mg/kg) there were no apparent sex differences in serum concentration and excretion of radioactivity. C_{max} and AUC of serum radioactivity were higher in fasted rats compared to fed rats. *In vitro* plasma protein binding ratios were more than 92%, with the drug binding to both human serum albumin and α_1-acid glycoprotein (11).

Studies of repeated administration of SM-9018 (10 mg/kg/day p.o. for 14 days) in rats showed that the drug was rapidly absorbed and excreted, with no significant accumulation being observed (12).

Studies on the disposition of SM-9018 (1, 10 and 100 mg/kg) administered as a single dose to fasted and fed male rats showed that food intake delayed absorption of the drug, resulting in a lower C_{max} of serum radioactivity, although absorption ratio, metabolism and excretion were unaffected (13).

The metabolic profile of [^{14}C]-labeled SM-9018 was investigated in rats after single dose administration (10 mg/kg p.o.) (14).

The effects of aging and hepatic or renal dysfunction on the disposition of SM-9018 have been studied in 20-month old rats, CCL_4-treated rats and partially nephrectomized rats (15).

Disposition studies of radiolabeled SM-9018 (1.5 mg/kg i.v.) and its hydroxide metabolite, ID-15036 (1.5 mg/kg i.v.) in rats showed that cleavage of the butylene chain was one of the major metabolic pathways of both compounds (16)

The transfer to fetus and milk of single oral doses (10 mg/kg) of SM-9018 has been evaluated. Results showed that radioactivity concentration in the fetus at 30 min was 22% of that in maternal serum on day 13 of pregnancy. In lactating rats, concentrations in milk at 30 min reached a maximum of 111 ng/ml (17).

Studies in rats have shown that SM-9018 administered as single (10 and 100 mg/kg/day p.o.) and repeated (10 mg/kg/day p.o. x 14 days) doses had no effects on hepatic drug metabolizing enzyme activities measured at 24 h postdosing. However, repeated doses of 100 mg/kg/day caused significant decreases in body weight, liver weight, liver weight to body weight ratio and microsomal protein content at 24 h postdosing but not at 168 h postdosing (18).

An evaluation of the effects of perospirone (0.3-3 mg/kg p.o.) on conditioned fear stress-induced freezing behavior in rats showed that the drug significantly and dose-dependently attenuated freezing behavior, while clozapine (1-30 mg/kg p.o.), risperidone (0.03-1 mg/kg p.o.), ritanserin (0.1-1 mg/kg p.o.) and ketanserin (0.3-1 mg/kg p.o.) reduced behavior in a U-shaped manner. Neither haloperidol (0.1-3 mg/kg p.o.), chlorpromazine (3-100 mg/kg p.o.), thioridazine (3-100 mg/kg p.o.), mosapramine (3-100 mg/kg p.o.) nor tiapride (30-1000 mg/kg p.o.) were effective. The results indicate that perospirone is effective in the treatment of mood disturbances associated with schizophrenia and has a broader efficacy profile as compared with conventional antipsychotic drugs (19).

Results of a study comparing perospirone with haloperidol showed that both drugs dose-dependently inhibited SKF-38393-induced vacuous chewing movement in rats, although perospirone was about 30 times less potent. These findings may be related to the 5-HT_2 blocking activity of perospirone (20).

Toxicity studies of SM-9018 in male and female cynomolgus monkeys administered a single oral dose (500, 1000 and 2000 mg/kg in males and 2000 mg/kg in females) or multiple daily doses (1, 5 and 25 mg/kg for 13 weeks or 0.2, 1.0 and 5 mg/kg for 52 weeks) showed that the single lethal dose of the drug was ~ 2000 mg/kg. The no-observed adverse effect level of repeated oral doses for 52 weeks was 0.2 mg/kg (21).

A teratogenicity study of daily oral doses of SM-9018 (2.5, 10 and 40 mg/kg) in rabbits during fetal organogenesis determined the maternal no-observed adverse effect dose to be 2.5 mg/kg. The no-observed adverse effect dose for lethality, teratogenicity and fetal development was 40 mg/kg (22).

Oral administration of SM-9018 in rats and intravenous and oral administration in rhesus monkeys was shown to produce acute central nervous depression. However, the drug had no direct effects on suppression of barbital withdrawal signs in monkeys or physical dependence producing potential in rats, indicating that it is not likely to cause dependence (23).

Metabolism studies of SM-9018 in rats and cynomolgus monkeys determined that ID-15036 is the primary metabolite of the drug. Metabolic pathways consisted mainly of hydroxylation of the 1, 2-cyclohexanedicarboximide, oxidative cleavage of the C-N bond between the piperazine ring and the butylene chain, *S*-oxidation of the isothiazole ring and reductive cleavage of the N-S bond on the isothiazole ring followed by *S*-methylation (24).

Disposition studies of radiolabeled SM-9018 in fed and fasted cynomolgus monkeys showed that after oral administration of a 10 mg/kg solution there was no significant difference between fasted and fed monkeys in regard to C_{max}, AUC, t_{max} or $t_{1/2}$ values. After administration of an 8 mg tablet, there was no significant difference in t_{max} or $t_{1/2}$ of the drug or its metabolite between fasted and fed monkeys; however, fed monkeys had a significantly lower serum C_{max} and AUC than fasted monkeys. With both treatments, urinary excretion occurred more slowly in fed monkeys and the serum ratio between the drug and its primary metabolite (ID-15036) indicated that transformation of the drug occurs faster in fed monkeys (25).

Electrophysiological studies in rabbits and cats showed that perospirone is weaker than chlorpromazine and haloperidol in slowing spontaneous EEG and has no effect on EEG recruiting response, EEG arousal response, spinal reflex activities and hippocampal afterdischarge (26).

The efficacy and safety of perospirone hydrochloride have been compared to those of mosapramine in a double-blind, randomized trial in 161 schizophrenic patients. Doses of 12-48 mg/day perospirone and 75-300 mg/day mosapramine were administered for 8 weeks. Both compounds showed comparable efficacy, except for a more marked week-to-week reduction in energy and anxiety-depression cluster scores on perospirone. Extrapyramidal side effects were reported in 46% and 56% of those on perospirone and mosapramine, respectively (27).

In an early phase II study, the clinical efficacy and safety of perospirone were evaluated in 72 patients with schizophrenia. Drug administration began at a dose of 12 mg/day, and was adjusted to as high as 48 mg/day for a total of 8 weeks. Final global inprovement was moderate or better in 49%, and improvement was slight or better in 69%. Notable side effects occurred in 56% of the patients studied, and included akathisia, dysarthria, salivation, tremor, insomnia and somnolence. Perospirone was considered to have superior clinical efficacy and safety as compared to other available antipsychotic agents (28).

The results of a late phase II study of perospirone hydrochloride indicate that the optimal dose is in the range of 12-48 mg/day, and that the compound at a dose of 4 mg is nearly equivalent to 1 mg haloperidol. Perospirone appeared to be especially useful for improving negative symptoms of schizophrenia, and to be more effective than antipsychotic drugs currently in use (29).

The efficacy and safety of long-term (6 months or more) administration of perospirone were evaluated in 55 schizophrenic patients in a late phase II study. Final global improvement rating showed significant improvement, moderate improvement and slight improvement in 24%, 69% and 89% of those treated, respectively. Aggravation occurred in 2% of the patients tested. The vast majority of patients had no side effects or continued treatment in spite of side effects. Extrapyramidal symptoms occurred in 56% of those treated, but most symptoms either disappeared or could be resolved by administering antiparkinsonian drugs. The antipsychotic efficacy of perospirone was found to be maintained with long-term treatment, with a very low incidence of severe side effects (30).

A fine granule formulation of perospirone hydrochloride (8-48 mg/day) was administered daily to 42 patients for 8 weeks. The optimal dose for this formulation was comparable to that which had been determined for the tablet formulation, and clinical efficacy and safety of perospirone were found to be superior to those of other antipsychotic agents (31).

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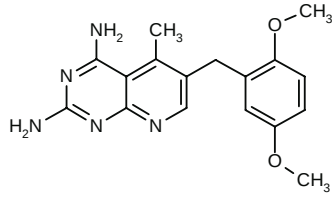
Piritrexim

Antineoplastic
Dihydrofolate Reductase Inhibitor

EN: 090468



$C_{17}H_{19}N_5O_2$ **Glaxo Wellcome; Ilex Oncology**

In a phase II trial in 13 evaluable patients with advanced transitional cell cancer of the bladder who had failed first-line chemotherapy, treatment with oral piritrex-

im (25 mg t.i.d. for 5 days weekly for 3 weeks, then 50 mg t.i.d.) resulted in 3 partial responses (lasting 2, 8 and 14 months), 5 stable diseases and no complete responses. Myelosuppression was the major dose-limiting toxicity (1).

Ilex Oncology and MPI Development have formed a limited partnership with the goal of developing piritrexim. Ilex has licensed development and marketing rights for piritrexim to the joint venture in exchange for a licensing fee, milestone payments and royalties (2).

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Pranidipine
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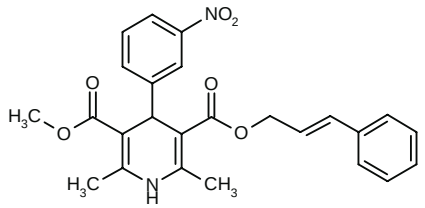
Antihypertensive
Calcium Channel Blocker

EN: 162312



$C_{25}H_{24}N_2O_6$ **Otsuka**

Results of a study comparing intravenous bolus injections of pranidipine (10 and 30 μg/kg), nifedipine (30 and 100 μg/kg) and amlodipine (1000 and 3000 μg/kg) in anesthetized rats demonstrated that both doses of pranidipine caused a significant dose-dependent decrease in mean circulatory filling pressure, whereas this effect was not observed with nifedipine at either dose or with the low dose of amlodipine (1, 2).

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Recombinant Methioninase
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AC-9301
NSC-686747

Antineoplastic

EN: 219531

AntiCancer

Data from an *in vitro* study using various human tumor cell lines and normal cell strains demonstrated that treatment with recombinant methioninase (0.125-4 U/ml) strongly inhibited tumor cell growth (IL_{50} = 0.25 U/ml), while having no effect on normal cell strains up to 4 U/ml. The mechanism of action for the enzyme's inhibitory effects on tumor cells was suggested to involve apoptosis (1).

In a study using Yoshida sarcoma cells, a reduction in levels of methionine in tumor cells treated with recombinant methioninase was associated with enhancement of the antitumor activity of 5-FU (2).

Recombinant L-methioninase has been reported to be more active against leukemia cells than against solid tumors *in vitro* (3).

A new model in Yoshida sarcoma bearing rats demonstrated that continuous infusion of recombinant methioninase (3000 U/day for 5 days) inhibited tumor growth as well as lymph node metastases (4).

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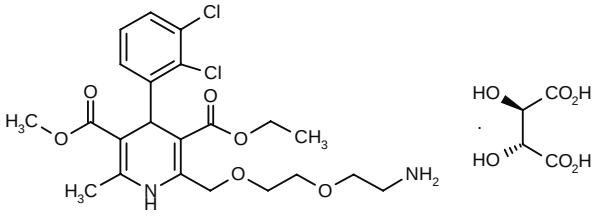
S-12968

Antihypertensive

EN: 172165



$C_{22}H_{28}Cl_2N_2O_6.C_4H_6O_6$ **Servier**

A synthesis of S-12968 has been published (1):

The cyclization of 4-[2-(2-phthalimidoethoxy)ethoxy]-3-oxobutyric acid ethyl ester (I) with 2-(2,3-dichlorobenzylidene)-3-oxobutyric acid 2-cyanoethyl ester (II) and ammonium formate in hot ethanol gives the protected racemic 1,4-dihydropyridine (III), which is submitted to a chiral preparative HPLC to obtain the (*R*)-(–)-enantiomer (IV). The deprotection of (IV) with aqueous methylamine affords (*S*)-(–)-2-[2-(2-aminoethoxy)ethoxymethyl]-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-monoethyl ester (V). Finally, this compound is methylated with diazomethane in ethyl ether/methanol. Scheme 4.

The starting compounds, the phthalimido derivative (I) and the dichlorobenzylidene derivative (II) have been obtained as follows:

1) The condensation of 2-[2-(2-chloroethoxy)-ethoxy]ethanol (VI) with potassium phthalimide (VII) in refluxing DMF gives the expected phthalimido derivative (VIII), which is oxidized with the Jones reagent in acetone yielding 2-[2-(2-phthalimidoethoxy)ethoxy]acetic acid (IX). The condensation of (IX) with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (X) by means of carbonyldiimidazole (CDI) and pyridine in dichloromethane affords 2,2-dimethyl-5-[2-[2-(2-phthalimidoethoxy)ethoxy]acetyl]-1,3-dioxane-4, 6-dione (XI), which is finally treated with refluxing ethanol to obtain the phthalimido derivative (I) used as starting material. Scheme 5.

2) The condensation of Meldrum's acid (X) with acetic acid (XII) by means of CDI and pyridine as before gives 5-acetyl-2,2-dimethyl-1,3-dioxane-4,6-dione (XIII), which is submitted to ring opening with 3-hydroxypropionitrile (XIV) in refluxing toluene yielding 2-cyanoethyl acetoacetate (XV). Finally, the condensation of (XV) with 2,3-dichlorobenzaldehyde (XVI) by means of piperidine and hexanoic acid in refluxing benzene affords the dichlorobenzylidene derivative (II) used as the second starting compound. Scheme 4.

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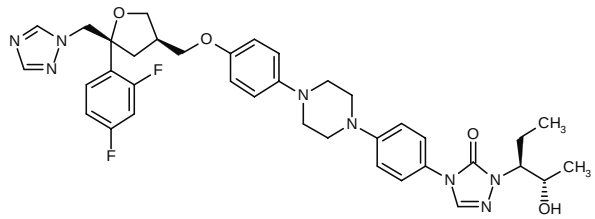
SCH-56592

Antifungal

EN: 226562



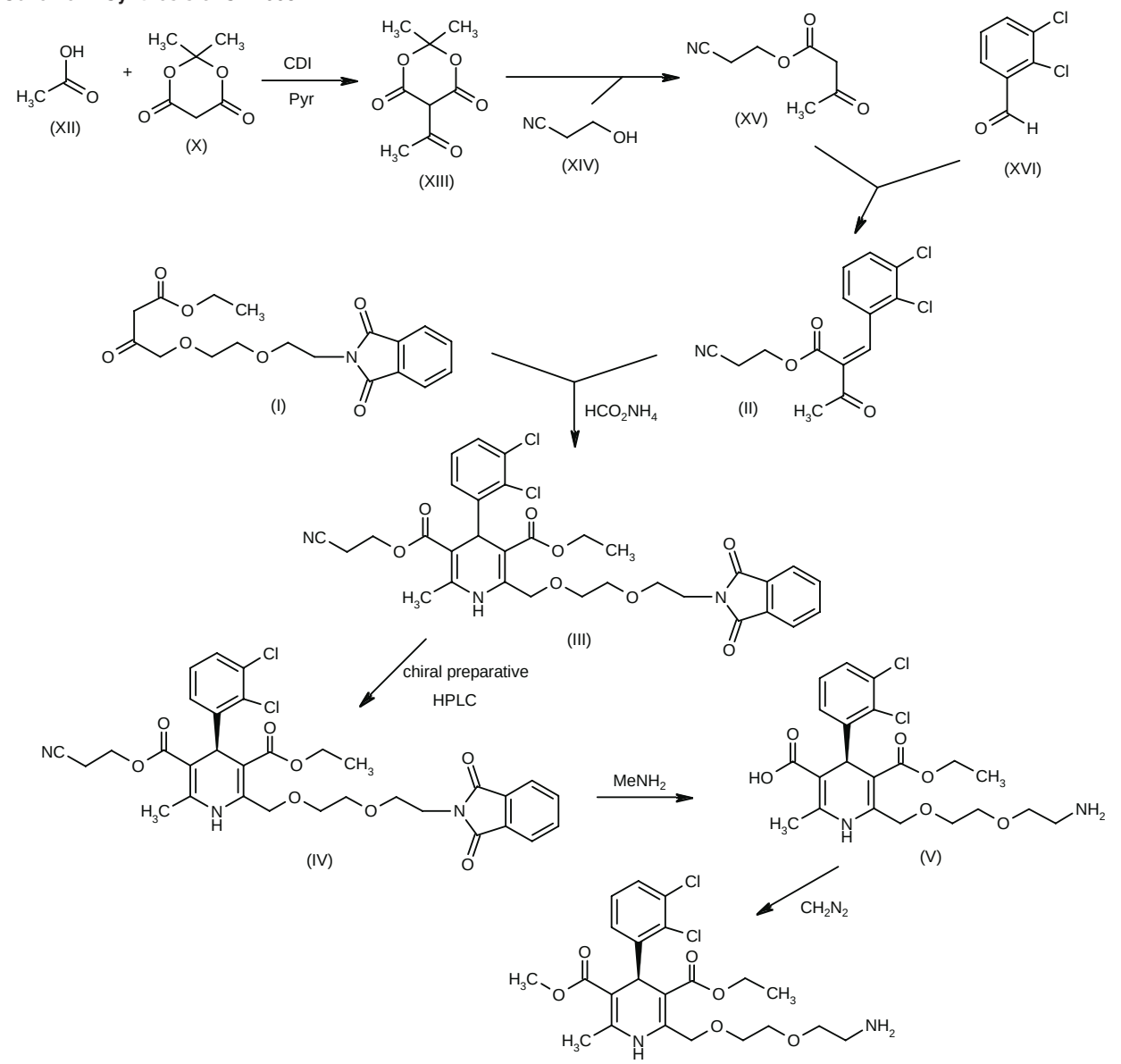
$C_{37}H_{42}F_2N_8O_4$ **Schering Corp.**

A new synthesis of SCH-56592 has been described: The reaction of (*S*)-ethyl lactate (I) with pyrrolidine (II) gives 1-[(*S*)-lactoyl]pyrrolidine (III), which is benzylated as usual with benzyl chloride yielding the benzyl ether (IV). The reaction of (IV) with ethylmagnesium bromide in THF affords 2(*S*)-benzyloxy-3-pentanone (V), which is reduced with $LiBH_4$ in dimethoxyethane giving 2(*S*)-benzyloxy-3(*RS*)-pentanol (VI). The reaction of (VI) with 4-chlorobenzenesulfonyl chloride (VII) yields the corresponding sulfonate (VIII), which is treated with hydrazine in ethanol to afford a diastereomeric mixture of hydrazines that is resolved with L-dibenzoyltartaric acid giving the (*S*,*S*)-enantiomer (IX). The formylation of (IX) with refluxing ethyl formate yields the chiral formyl hydrazide (X), which is cyclized with *N*-[4-[4-[4-(trimethylsilyloxy)phenyl]piperazin-1-yl]phenyl]carbamic acid phenyl ester (XI) affording the triazolone (XII). Finally, this compound is condensed with the chiral tetrahydrofuran derivative (XIII) by means of NaOH in DMSO, and debenzylated by hydrogenation with H_2 over Pd/C in formic acid (1). Scheme 6.

An *in vitro* study comparing the antifungal activities of SCH-56592, amphotericin B and itraconazole against 60 clinical isolates of *Aspergillus* showed that SCH-56592 was very active against all species and at lower concentrations than amphotericin B and itraconazole, with respective minimum fungicidal concentrations of 3.64, 10.3 and 15.09 μg/ml (2).

The results of *in vitro* and pharmacokinetic studies in mice, dogs and monkeys, in which the physical and

Scheme 4: Synthesis of S-12968



chemical properties of capsule, tablet, liquid and injectable formulations of SCH-56592 were evaluated for their suitability in clinical trials, have been reported (3).

The *in vitro* activity of SCH-56592 against 404 clinical isolates of *Candida* species was found to be 2- to 32-fold greater than that of amphotericin B and flucytosine, equivalent to that of itraconazole and equal to or 8-fold greater than that of fluconazole (4).

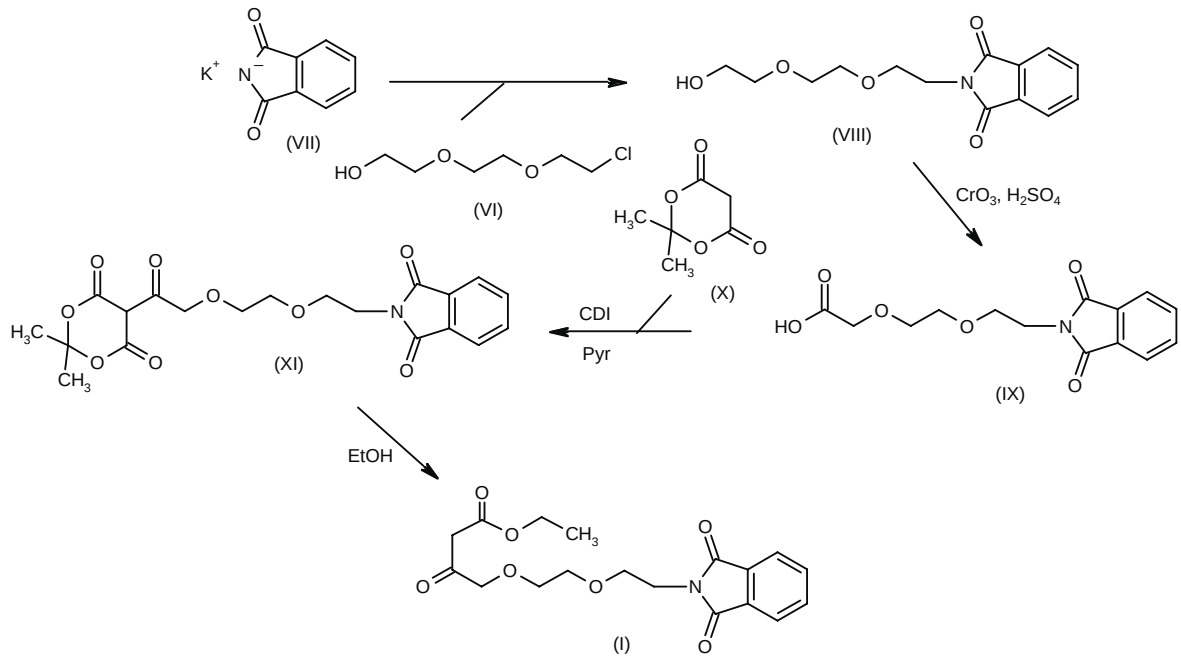
In vitro studies evaluating the effects of various assay conditions on the antifungal activities of SCH-56592 and itraconazole against various pathogenic yeasts indicated that variations in concentration and type of solubilizing agent produced significant differences in the MICs of both drugs (5).

Results of interaction studies of SCH-56592 with *Candida albicans* multidrug efflux transporters and various cytochrome P450 forms suggest that the drug is relatively insensitive to mutations in CYP51A1 (6).

In vitro studies against clinical isolates of 3 different *Fusarium* species (*F. solani*, *F. oxysporum* and *F. moniliforme*) demonstrated interspecies variability in susceptibility to SCH-56592, whereas amphotericin B susceptibility was comparable for all 3 species (7).

SCH-56592 (5, 10 and 25 mg/kg/day for 10 days) was shown to be highly effective against *Aspergillus fumigatus* infection in immunocompromised mice. Survival rates against an itraconazole-susceptible isolate were 90-100% for all 3 doses, and against an itraconazole-resis-

Scheme 5: Synthesis of Intermediate (I)



tant isolate were 20, 60 and 100%, respectively, for the 5, 10 and 25 mg/kg doses (8).

In a murine model of systemic coccidioidomycosis, the fungicidal activity *in vivo* of SCH-56592 (0.5, 2, 10 or 25 mg/kg/day p.o.) was ≥ 200-fold as potent as fluconazole (10 or 100 mg/kg/day p.o.) and ≥ 50-fold as potent as itraconazole (10 or 100 mg/kg/day p.o.) in reducing CFU in the spleen, lung and liver. SCH-56592 cured 1/9, 6/10 and 9/9 mice given doses of 2, 10 and 25 mg/kg, respectively, while neither fluconazole nor itraconazole cured any survivors (9).

In an immune-depleted murine model of pulmonary histoplasmosis, treatment with SCH-56592 (1 mg/kg/day) resulted in a significant reduction in fungal burden and 100% survival in a lethal model (10).

Oral administration of SCH-56592 once daily for 3-4 days was shown to be effective in inhibiting systemic and pulmonary fungal infections in normal and immunocompromised guinea pigs (11).

In a murine model of experimental infection due to *Leishmania donovani*, treatment with SCH-56592 (30 mg/kg/day p.o. for 14 days) was effective in reducing the parasite burden in liver and spleen tissues (12).

Water-soluble prodrugs of SCH-56592 have been claimed. The prodrugs are readily converted to SCH-56592 *in vivo* and give high serum levels in mice, rats, dogs and monkeys after oral administration, as well as a very long serum half-life and good tissue distribution when given once daily (13).

Pharmacokinetic studies in rats and dogs demonstrated that after oral administration of an aqueous suspension of SCH-56592, absorption of the drug was slow (~ 8 h), distribution into tissues was extensive (V_d = 2.60 and 3.5 l/kg in dog and rat, respectively) and elimination was primarily via the feces. The plasma half-lives were 10-20 h in both species (14).

The safety, tolerability and pharmacokinetics of increasing multiple doses of SCH-56592 (100, 200, 400 and 800 mg/day b.i.d for 14 days) were evaluated in 48 healthy volunteers in a randomized, double-blind, placebo-controlled study. Overall results showed that the drug was well tolerated, with no differences in incidence, type or intensity of adverse events reported between drug- and placebo-treated groups (15).

Results of a randomized, open-label, 4-way crossover, single-dose study in 20 healthy subjects showed that the bioavailability of the suspension formulation of SCH-56592 (200 mg) increased 4-fold with a high-fat meal and 1.5-fold with a nonfat meal compared to the fasted state. The bioavailability of the suspension was about 40% higher compared to the tablet when both formulations were given with a high-fat meal (16)

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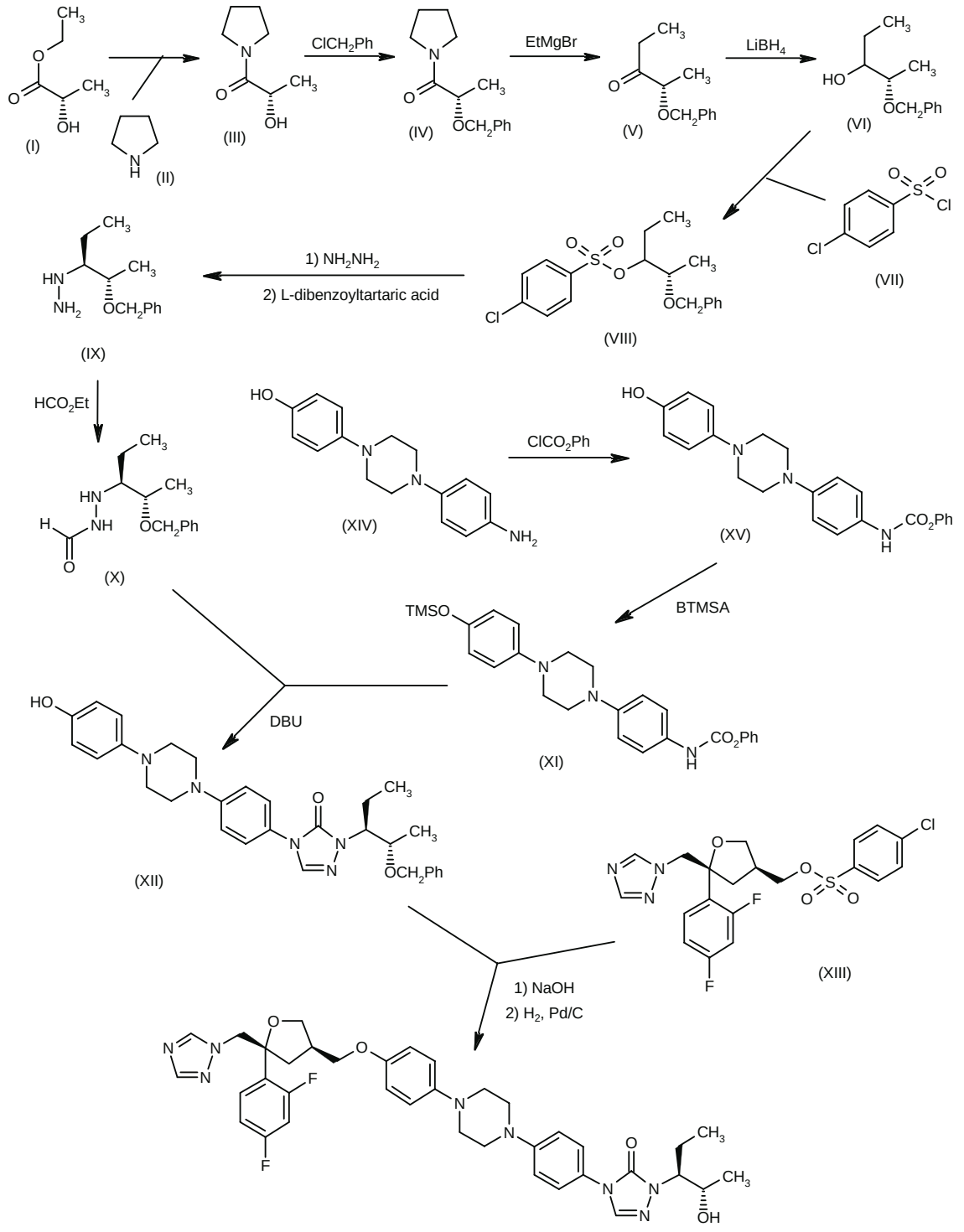
Scheme 6: Synthesis of SCH-56592



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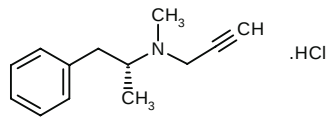

$C_{13}H_{17}N.HCl$ **Chinoin**

Results of a randomized, double-blind, placebo-controlled, multicenter study in 341 moderately impaired patients with Alzheimer's disease showed that selegiline (5 mg b.i.d.) and α-tocopherol (1000 IU b.i.d.), alone or in combination, had definite beneficial effects on functional outcome measures but not on cognition (1).

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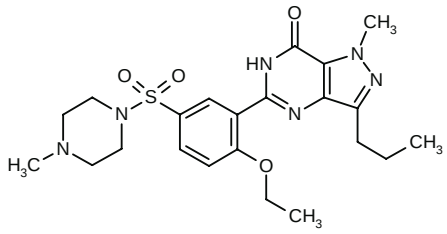

$C_{22}H_{30}N_6O_4S$ **Pfizer**

Recent studies have demonstrated that cultured human corpus cavernosum smooth muscle cells express phosphodiesterase type V activity, which is inhibited by nanomolar concentrations of sildenafil (1).

In a study evaluating the effects of sildenafil on erectile function in anesthetized dogs, increasing doses of sildenafil (1, 3, 10, 30 and 100 μg/kg i.v.) produced a dose-dependent potentiation of electrically stimulated intracavernosal pressure, but had no effect on blood flow to the penis, blood pressure or heart rate (2).

Sildenafil (3, 10, 30, 100 and 300 μg/kg) administered intravenously into the corpus cavernosum of anesthetized dogs produced a dose-related potentiation of sodium nitroprusside-induced intracavernosal pressure, which was maximal at 300 μg/kg (ED_{50} = 16.2 μg/kg) (3).

In an 8-week, double-blind, placebo-controlled study in 416 male outpatients with erectile dysfunction, sildenafil (5, 25, 50 or 100 mg p.o.) administered 1 h before sexual activity was shown to dose-dependently improve the ability to achieve and maintain an erection. Adverse events were generally mild, and included headache, vasodilation, dyspepsia and diarrhea (4).

Results of a double-blind, randomized, placebo-controlled, crossover study in 27 male patients with erectile dysfunction due to spinal cord injury showed that a single oral dose of 50 mg of sildenafil significantly increased penile base rigidity, as compared to placebo (65% *vs.* 8%). No patients withdrew from the study because of adverse events (5).

A 1-year, open-label, extension study of intermittent oral doses of sildenafil (10-100 mg, depending on tolerance and efficacy) in 311 male patients with erectile dysfunction showed that 271 patients benefitted from drug treatment and completed the study, while 13 and 12 patients withdrew due to lack of efficacy and adverse events, respectively. The most frequent adverse events were headache, facial flushing and indigestion (6).

In a 28-day, double-blind, placebo-controlled, dose-response study in patients with erectile dysfunction due to spinal cord injury, daily treatment with single oral doses of sildenafil (50 mg) improved erections in 9/12 patients, whereas only 1/14 placebo-treated patients reported improvement. Sildenafil-treated patients also had significant improvement in sex life satisfaction ratings compared with the placebo group. The drug was well tolerated, with no patients discontinuing treatment due to adverse events (7).

The clinical efficacy of sildenafil has been demonstrated in a group of 27 male patients with erectile dysfunction solely attributable to traumatic spinal cord injury. Patient satisfaction with the treatment was reflected in a questionnaire, in which 9/12 patients on sildenafil reported improved erections as compared to 1/3 patients on placebo (8).

Results of a two-stage, double-blind, placebo-controlled study in 26 men with erectile dysfunction caused by spinal cord injury showed that sildenafil (50 mg once daily as required for 28 days) increased penile rigidity and improved erections in 65% and 75% of patients, respectively (9).

The results of a 6-month, randomized, double-blind, placebo-controlled study in 416 men with erectile dysfunction demonstrated that oral sildenafil (5, 25, 50 or 100 mg), administered 1 h prior to sexual activity, dose-dependently increased the ability to achieve and maintain an erection. The drug was well tolerated, with headache, dyspepsia and flushing being the most common adverse events (10).

In a 1-year, open-label, extension study in 271 male patients with erectile dysfunction, oral sildenafil (10, 25, 50 or 100 mg as required) was shown to be effective and well tolerated. Only 4.2% of patients withdrew due to lack of efficacy and 1% to treatment-related adverse events. Headache, facial flushing and indigestion were the most frequent adverse events reported (11).

The effects of oral sildenafil (25 and 50 mg/day for 10 days) on erectile dysfunction were evaluated in 21 diabetic patients using a double-blind, randomized, placebo-controlled, crossover design. Sildenafil improved the quality of erections in 48% and 52% of patients in the 25-mg and 50-mg groups, respectively, compared to 10% of the placebo patients. Mild and transient headache, indigestion and muscular ache were the most frequently observed adverse events (12).

A 6-month, double-blind, placebo-controlled, dose-escalation study of oral sildenafil (25-100 mg/day as required) in 315 patients demonstrated that the drug was well tolerated and highly effective in treating erectile dysfunction due to organic, psychogenic and mixed causes. Patients and partners rated sildenafil significantly superior to placebo in ability to penetrate and maintain erections, as well as overall satisfaction with intercourse (13).

Results of a 12-week, double-blind, placebo-controlled, randomized study in 111 patients with broad spectrum erectile dysfunction showed that oral sildenafil (25-100 mg depending on response) significantly improved erections compared with placebo (81% *vs.* 18%). Mean scores for frequency of penetration, frequency of maintained erections and satisfaction with sex life were consistently higher in patients treated with sildenafil compared with the placebo-treated group (14).

Pfizer has been notified by the FDA that its NDA for sildenafil citrate (Viagra™), a treatment for erectile dysfunction, will receive priority review status once the application is officially accepted (15).

Pfizer has submitted regulatory applications in the U.S. and Europe seeking approval for sildenafil citrate (Viagra™) for the treatment of male erectile dysfunction (16).

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$C_{102}H_{172}N_{36}O_{32}S_7$

Neurex; Medtronic; Warner-Lambert

In a rat model of experimental allergic neuritis, SNX-111 (0.3 μg) administered as a single bolus intrathecal injection was shown to block mechanical allodynia. The effect was immediate (30 min postinjection) and lasted for more than 24 h (1).

SNX-111 administered by continuous intrathecal infusion (1, 10 and 100 ng/h) or by bolus injection (30-300 ng) was shown to produce potent, dose-dependent antinociceptive effects in rat models of acute, persistent and neuropathic pain (2).

Studies in rats and human brain tissue demonstrated that treatment with SNX-111 significantly improved mitochondrial brain dysfunction, indicating that the drug would be useful for clinical studies in severe head injury (3).

Continuous subacute intravenous infusion of SNX-111 (100 μg/kg/h) for 6 days was shown to cause reversible blockade of mechanical allodynia in rats with experimentally induced painful peripheral neuropathy (4).

In a rat model of acute thermal nociception, SNX-111 (30 ng/h) and morphine (15 μg/h) coadministered as a spinal intrathecal infusion acted synergistically to produce analgesia. However, SNX-111 treatment did not prevent the development of morphine tolerance (5).

Pharmacokinetic studies of SNX-111 administered as a 24-h continuous, constant-rate intravenous infusion in rats and cynomolgus monkeys showed a close correspondence for both species in kinetic parameters, with no consistent gender- or dose-related differences. Steady-state plasma concentrations were achieved within 2-4 h after beginning infusion and the apparent terminal half-lives were 4.61 and 6.48 h for rats and monkeys, respectively (6).

A case study of a male patient with intractable brachial plexus avulsion pain refractory to all medications during 23 years showed that an intrathecal infusion of SNX-111 (2 ng/kg/h) provided 100% pain relief without any adverse effects (7).

An open-label, dose-titration study in patients with chronic pain demonstrated that intrathecally administered SNX-111 had a significant analgesic effect, with 6 of 11 patients reporting marked improvements in pain decrease from baseline and marked reductions in opioid use (8).

Neurex and its development partner Warner-Lambert expect to commence phase III trials on SNX-111 for the treatment of head trauma (9).

Neurex, in conjunction with Warner-Lambert, has announced a pause in patient enrollment in the ongoing clinical trial of intravenous SNX-111 in patients with severe head trauma. Additional clinical data from earlier studies must be analyzed to assess the risk-benefit relationship of administering SNX-111 to patients with severe head trauma. However, phase III testing of this compound for analgesic treatment of malignant and neuropathic chronic pain syndromes will continue, because the dose of SNX-111 used intrathecally for these syndromes is 10,000 times lower than the intravenous doses being given in the head trauma study (10).

Neurex and Warner-Lambert have restarted their pivotal phase II study evaluating SNX-111 in head trauma (11).

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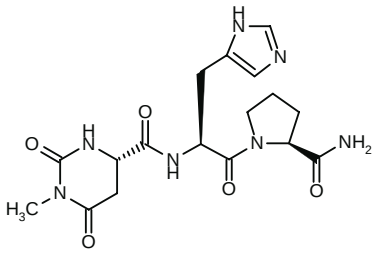

$C_{17}H_{23}N_7O_5$

Tanabe Seiyaku

Data from a clinical study in 3 patients with spinocerebellar degeneration indicated that treatment with TA-0910 enhances norepinephrine turnover in the central nervous system (1).

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