Drugs of the Future 1998, 23(12): 1339-1359
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CCC: 0377-8282/98

Information Update

Volume 1-22, Number 12

Estimated developmental phase for this month's updated products:

Phase I

CD-832.HCl (antihypertensive, calcium antagonist, antianginal; Taisho)
LY-246736 dihydrate (treatment of IBS, treatment of nonulcer dyspepsia; Lilly, Robert Lab., Adolor)

Phase II

Batimastat (antineoplastic, prevention of pterygia recurrence, angiogenesis inhibitor, matrix metalloproteinase inhibitor; British Biotech, InSite Vision)
Etomoxir (treatment of heart failure; Byk Gulden)
KW-2189 (antineoplastic antibiotic; Kyowa Hakko, Janssen, Natl. Cancer Inst.)
p24-VLP (anti-HIV, AIDS vaccine; British Biotech)
SR-48692 (antipsychotic, neurotensin receptor antagonist; Sanofi)

Phase III

Deramciclane fumarate (anxiolytic, antiepileptic, GABA reuptake inhibitor; Egis, Orion, Japan Tobacco)
Gestodene (progestogen, contraceptive, treatment of osteoporosis; Schering AG)
Ilomastat (treatment of corneal wounds, matrix metalloproteinase inhibitor, angiogenesis inhibitor; Ligand, Sankyo, Univ. Florida)
Linetastine (antiallergic/antiasthmatic, leukotriene synthesis inhibitor; Terumo)
Maxacalcitol (treatment of hyperparathyroidism, antipsoriatic; Chugai, Schering-Plough)
Nemorubicin (antineoplastic antibiotic; Pharmacia & Upjohn)
Pibutidine hydrochloride (gastric antisecretory, H_2-receptor antagonist; Taisho, Ikeda Mohando)
Sanfetrinem cilexetil (trinem; Glaxo Wellcome)
SB-207266A (treatment of IBS, 5-HT_4-receptor antagonist; SmithKline Beecham)
Toborinone (treatment of heart failure, phosphodiesterase III inhibitor; Otsuka)

Launched/Year

Doxazosin (antihypertensive, treatment of BPH, α_1-adrenoceptor antagonist; Pfizer, Italfarmaco, Almirall Prodesfarma)/1988
Fasudil hydrochloride (vasodilator, calcium antagonist; Asahi Chem.)/1995
Fluconazole (antifungal, treatment of opportunistic infections; Pfizer)/1988
Lercanidipine hydrochloride (antianginal, antihypertensive, calcium antagonist; Recordati, Byk Gulden, Uriach, Zeneca, Rotta, Zambon, Tsumura, Napp)/1997
Levovist® (imaging agent; Schering AG, Tanabe)
Miglitol (antidiabetic, α-glucosidase inhibitor; Bayer, Pharmacia & Upjohn, Sanwa, Sanofi)/1998
Remifentanil hydrochloride (opioid analgesic, μ-opioid agonist; Glaxo Wellcome)/1996
Risperidone (antipsychotic; Janssen, SmithKline Beecham, Organon, Janssen-Kyowa, Scios)/1993
Tiagabine (antiepileptic, GABA reuptake inhibitor; Novo Nordisk, Sanofi, Abbott)/1996
Zidovudine (anti-HIV, reverse transcriptase inhibitor; Glaxo Wellcome, Verex Lab.)/1987

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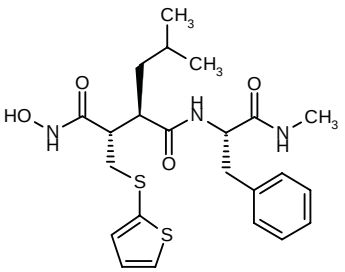
Batimastat

Antineoplastic
Prevention of Pterygia Recurrence
Angiogenesis Inhibitor
Matrix Metalloproteinase Inhibitor

EN: 193260



$C_{23}H_{31}N_3O_4S_2$ **British Biotech; InSite Vision**

The effects of batimastat on bone metastasis of murine melanoma B16F1 and human breast cancer MDA-231 were investigated *in vitro* and *in vivo*. Batimastat inhibited the degradation of osteoblast matrix induced by tumor cells *in vitro* and inhibited tumor growth, necrosis and cachexia *in vivo* in mice bearing B16F1 tumors (1).

The effects of batimastat and captopril alone and in combination were evaluated on murine Lewis lung carcinoma *in vitro* and *in vivo*. The combination was superior to either drug alone in reducing both tumor weight (25%, 33% and 51% reduction on batimastat, captopril and combination, respectively) and lung metastases (29%, 26% and 80% reduction on batimastat, captopril and combination, respectively); survival time was also prolonged (2).

The inhibitory effects of BB-94 on the intrinsic invasive potential of matrilysin-transfected Du-145 cells were evaluated *in vitro*. BB-94 effectively inhibited cellular invasion of matrigel and murine diaphragm, indicating that it may effectively limit tumor growth and reduce the invasion of carcinomas (3).

The effects of batimastat, given concomitantly or subsequent to cisplatin, were investigated in nude mice bearing human ovarian carcinoma HOC22 and HOC8 xenografts. Delayed tumor growth and increased survival time was observed in mice with early-stage tumors. Complete inhibition of the growth and spread of the tumors was observed in mice treated with batimastat (60 mg/kg i.p. every other day x 8) concomitantly with cisplatin (4 mg/kg i.v. every 7 days x 3), and all animals were alive after 200 days. Potentiation of the antitumor activity of cisplatin by batimastat was dose-dependent and was observed in animals with both advanced and late-stage tumors. Subsequent treatment with batimastat was also associated with a significant improvement in survival (4).

BB-94 instilled into the peritoneal cavity after paracentesis in 23 patients with malignant ascites was well tolerated without producing serious adverse events or toxicities. High plasma concentrations were observed 1 h following administration and plasma levels above IC_{50} were detected 28 days after treatment. The results from the study support further evaluation of BB-94 in the treatment of malignant ascites (5).

A phase I/II trial of batimastat was conducted in patients with malignant ascites. Results showed that the drug was well-absorbed via intraperitoneal route and produced few side effects. About half of the subjects responded to treatment, thus warranting further investigation (6).

InSite Vision began a new phase II clinical study using ISV-120, a DuraSite-based formulation of batimastat, for the prevention of recurrent pterygia (7).

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5. Beattie, G.J., Smyth, J.F. *Phase I study of intraperitoneal metalloproteinase inhibitor BB94 in patients with malignant ascites*. Clin Cancer Res 1998, 4(8): 1899.

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7. *InSite Vision: Q3 1997 highlights*. Prous Science Daily Essentials Nov 6, 1997.

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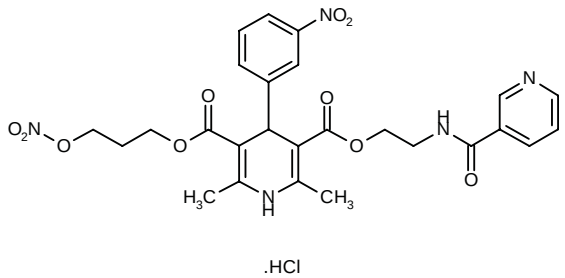
InSite Vision updates investors at H&Q conference. Prous Science Daily Essentials Feb 10, 1998.

CD-832.HCl

Antihypertensive
Calcium Antagonist
Antianginal

EN: 162640



.HCl

$C_{26}H_{27}N_5O_{10}$.HCl **Taisho**

CD-832 blocked both the KCl- and norepinephrine-induced contractions of isolated rabbit aorta. This effect was potentiated by zaprinast and inhibited by methylene blue (1).

The effects of zaprinast and methylene blue on the chronotropic effects of CD-832 were evaluated in isolated guinea pig atria in the presence and absence of isoproterenol. Neither compound had any effect on the dose-response curve of CD-832 in the absence of isoproterenol, while in the presence of isoproterenol, zaprinast produced a 3-fold leftward shift of the curve and methylene blue produced a rightward shift of equal magnitude. Isoproterenol together with the nitric oxide donor SIN-1 reduced the beating rate, while SIN-1 in the absence of isoproterenol produced no chronotropic effects. The results suggest that the effects of CD-832 in the presence of β-adrenergic stimulation are produced through a NO-cGMP-mediated pathway (2).

The effects of CD-832 (0.3, 1 and 3 μg/kg/min i.v.) on intracranial pressure, vertebral blood flow and common carotid blood flow were evaluated in anesthetized dogs. CD-832 had no significant effects on any of the parameters, suggesting that it may be a useful agent for the treatment of hypertension or angina pectoris (3).

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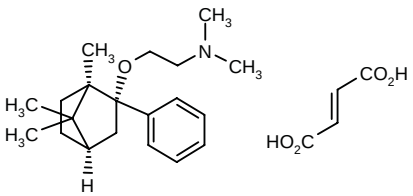
Deramciclane Fumarate

Anxiolytic
Antiepileptic
GABA Reuptake Inhibitor

EN: 144469



$C_{20}H_{31}NO.C_4H_4O_4$ **Egis; Orion; Japan Tobacco**

Deramciclane blocked 5-HT_{2C} receptor-mediated phosphoinositide hydrolysis (IC_{50} = 168 nM) and reduced the basal rate of phosphoinositide hydrolysis by 33% in the choroid plexus. Single doses of deramciclane 0.5 and 10 mg/kg produced receptor occupancy of 45 and 79%, respectively. Prolonged treatment of the choroid plexus with similar doses of deramciclane did not alter the binding of agonist DOI or the antagonist mesulergine to 5-HT_{2C} receptor. Evaluation of 5-HT_{2A} receptor binding showed that deramciclane occupied 78% of the receptor binding sites but produced no notable effects on agonist binding following prolonged exposure (1).

Radiolabeled deramciclane was used to determine the absorption profile of the drug in rats, dogs and rabbits, and in isolated intestinal loops of rats. The drug was readily absorbed after oral administration in animals, with a t_{max} of 1 h in rats and rabbits and 6 h in dogs. No absorption was observed during 2 h in stomachs isolated from all three species, and gastric juice did not decompose the compound. The drug was mainly excreted through bile, with a higher intensity in rats than in dogs. Plasma drug concentrations in female rats were higher than in male rats (2).

Distribution and pharmacokinetics of deramciclane were evaluated in rats following single and repeated oral administrations. The drug was rapidly absorbed from the gastrointestinal tract with concentration-time curves describing a two-compartment open model. The intact molecule was detected in brain tissue. The concentrations of deramciclane in the hypophysis were 2-fold higher than those observed in the plasma and brain tissue, with no significant differences in concentrations observed in the left and right regions of the brain (3).

The results of a pharmacokinetic study of single oral doses of deramciclane fumarate (1, 3, 6 and 10 mg/kg) in rats indicated that the elimination half-life was not dose-dependent. Furthermore, the relationship between doses and AUC values was not linear, possibly due to the saturation of one or more of the biotransformation pathways (4).

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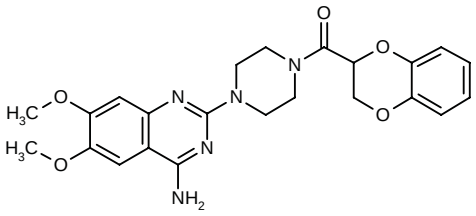
Original monograph - Drugs Fut 1990, 15: 1174.

Doxazosin
Cardura®

Antihypertensive
Treatment of BPH
α_1-Adrenoceptor Antagonist

EN: 090854



$C_{23}H_{25}N_5O_5$

Pfizer; Italfarmaco; Almirall Prodesfarma

In a 16-week double-blind, placebo-controlled study, 163 hypertensive benign prostatic hyperplasia (BPH) patients were divided into severe, intermediate or mild disease groups and 82 normotenisve BPH patients were separated according to baseline American Urological Association (AUA) BPH severity score and modified Boyarsky symptom bothersomeness score; both groups were administered doxazosin. Treatment significantly improved baseline maximum and mean urinary flow and Boyarsky scores. No differences were observed in AUA scores between disease severity groups, suggesting doxazosin therapy may be effective in BPH regardless of the degree of disease severity (1).

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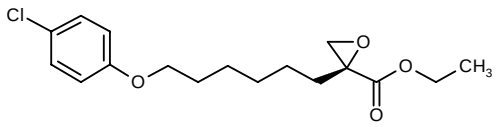
Etomoxir

Treatment of Heart Failure

EN: 100320



$C_{17}H_{23}ClO_4$ **Byk Gulden**

The effects of long-term etomoxir treatment in rats with experimental infarction were evaluated. Animals received etomoxir (10 mg/kg/day) or ramipril (1 mg/kg/day) after induced myocardial infarction. Six weeks later, a reduction in the increase in left ventricular end-diastolic pressure (LVEDP) was observed and infarct size was significantly reduced in etomoxir-treated rats; although hypertrophy decreased in ramipril-treated animals, no effect on LVEDP was detected. The authors speculate that the decrease in infarct size observed with etomoxir treatment may be due to improvement in contractile function of injured myocytes, in addition to an increase in calcium in sarcoplasmic reticulum (1).

The potential clinical utility of etomoxir has been evaluated in 9 patients with NYHA II-III chronic heart failure in an open pilot study. Patients received compound (80 mg/day) for 3 months in addition to standard therapy with ACE inhibitors, diuretics, digitalis or β-blockers. All showed clinical improvement at the end of the treatment period, as manifested by increases in cardiac output and stroke volume and decreases in pulmonary capillary wedge pressure and Pa(mean) during maximum exercise, and by increases in left ventricular ejection fraction. Although not placebo-controlled, the findings in this small group of patients indicate that etomoxir may be useful in the treatment of chronic heart failure (2, 3).

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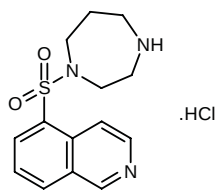
Fasudil Hydrochloride
Eril®
Fasdil®

Vasodilator
Calcium Antagonist

EN: 154989



$C_{14}H_{17}N_3O_2S.HCl$ **Asahi Chem.**

Fasudil hydrochloride was evaluated for inhibition of HIV-1 replication *in vitro*. In a monocytic cell line infected with HIV-1 strains U1 or OM10.1, fasudil at noncytotoxic

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concentrations blocked TNF-α-induced NF-κB-dependent replication of both strains of the virus, although it was more active against U1. These results indicate that fasudil inhibits TNF-α-induced HIV-1 replication by blocking the signal transduction pathway responsible for NF-κB activation (1).

Fasudil hydrochloride was shown to inhibit vascular smooth muscle cell migration *in vitro* and to significantly reduce neointimal formation in rabbit carotid artery after balloon injury (2).

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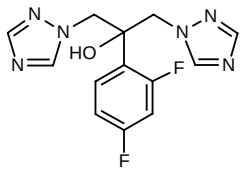
Fluconazole
Diflucan®
Triflucan®

Antifungal
Treatment of Opportunistic Infections

EN: 108008



$C_{13}H_{12}F_2N_6O$ **Pfizer**

The effects of continuous and intermittent therapy with fluconazole on recurrent and developed fluconazole resistance were studied in HIV-positive patients with CD4 cell count <350 x 10^6/l and oropharyngeal candidiasis. Twenty subjects were given 200 mg/day and 48 received intermittent therapy at the time of symptomatic relapses. Oral samples were taken weekly (during infection episodes) and quarterly. A 4-fold increase in MIC to at least 16 μg/ml, the emergence of new resistant species or a significant rise in the proportion of resistant isolates determined the development of resistance. Patients under continuous therapy showed lower relapse rates, more sterile cultures and slightly greater microbiological resistance than those on intermittent therapy. Although resistance occurred in both treatment regimens, therapeutic responses were excellent (1).

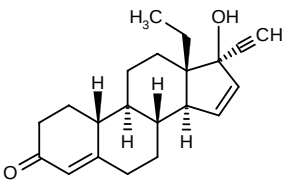
1. Revankar, S.G. et al. *A randomized trial of continuous or intermittent therapy with fluconazole for oropharyngeal candidiasis in HIV-infected patients: Clinical outcomes and development of fluconazole resistance*. Am J Med 1998, 105(1): 7.

Original monograph - Drugs Fut 1985, 10: 982.

Gestodene

Progestogen
Contraceptive
Treatment of Osteoporosis

EN: 137511



$C_{21}H_{26}O_2$ **Schering AG**

The effects of gestodene and norgestimate on lipid and lipoprotein parameters were evaluated on days 2, 11 and 21 of the third, sixth and twelfth treatment cycles in 46 female subjects. No deleterious effects on lipoprotein metabolism were observed, indicating that both compounds can be classified as estrogenic formulations with respect to their effect on lipid metabolism (1).

1. Wiegratz, I., Jung- Hoffman, C., Gross, W., Kuhl, H. *Effect of two oral contraceptives containing ethinyl estradiol and gestodene or norgestimate on different lipid and lipoprotein parameters*. Contraception 1998, 58(2): 83.

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Additional Reference

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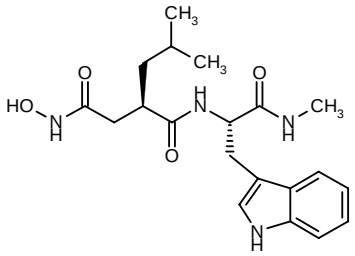
Ilomastat
Galardin™
Galardin MPI™

Treatment of Corneal Wounds
Matrix Metalloproteinase Inhibitor
Angiogenesis Inhibitor

EN: 194637



$C_{20}H_{28}N_4O_4$ **Ligand; Sankyo; Univ. of Florida**

Administration of GM6001 in a rat model of bacterial meningitis induced by *Streptococcus pneumonia* reduced upregulated levels of matrix metalloprotein-9 in cerebrospinal fluid and significantly reduced neuronal injury associated with bacterial meningitis (1).

Ilomastat, being developed by Sankyo under license from Ligand, is in phase II trials in Japan (2).

1. Leib, S.L., Leppert, D., Clements, J., Tauber, M.G. *Matrix metalloproteinase inhibition by GM6001 is neuroprotective in experimental pneumococcal meningitis*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst B-34.

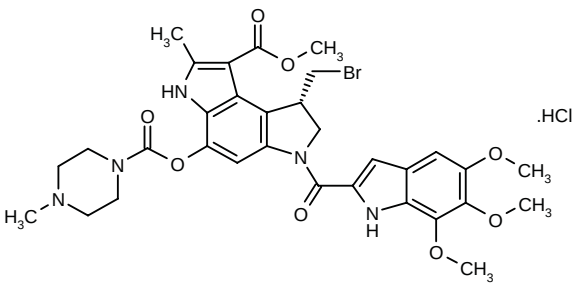
2. *Focus on Sankyo's R&D activities at home and abroad*. Prous Science Daily Essentials Oct 9, 1998.

Original monograph - Drugs Fut 1993, 18: 1109.

KW-2189

Antineoplastic Antibiotic

EN: 171447



$C_{32}H_{36}BrN_5O_8.HCl$ **Kyowa Hakko; Janssen; Natl. Cancer Inst. (US)**

A synthesis of [^{3}H]-KW-2189 has been published: The condensation of duocarmycin B_2 (I) with *tert*-butoxycarbonylpiperazine (II) and 4-nitrophenyl chloroformate by means of triethylamine in dichloromethane gives the expected piperazinecarboxylate (III), which is reduced with $NaBH_4$ in allyl alcohol to yield the hydroxy-derivative (IV). The treatment of (IV) with camphorsulfonic acid (CSA) in hot toluene affords the isomerized compound (V) along with simultaneous deprotection of the piperazine ring. Finally, compound (V) is methylated with tritiated methyl iodide and $NaHCO_3$ in acetone/methanol (1). Scheme 1.

Caffeine was shown to enhance the inhibitory activity of KW-2189 on the growth of human lung cancer cells *in vitro* by blocking the repair of DNA strand breaks induced by the drug. The results indicate that DNA repair is mediated by a caffeine-sensitive mechanism (2).

1. Nagamura, S., Kinugawa, M., Ogasa, T., Saito, H. *The synthesis of [H-3]KW-2189, a novel active antitumor antibiotic*. J Label Compd Radiopharm 1997, 39(6): 471.

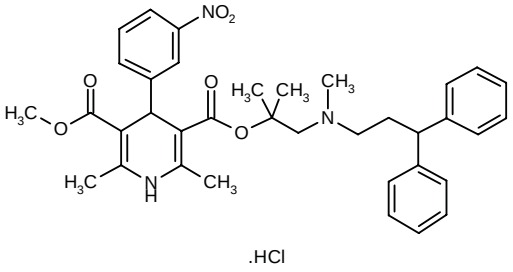
2. Ogasawara, H., Nishio, K., Ishida, T., Arioka, H., Fukuoka,K., Saijo, N. *In vitro enhancement of antitumor activity of a water-soluble duocarmycin derivative, KW-2189, by caffeine-mediated DNA-repair inhibition in human lung cancer cells*. Jpn J Cancer Res 1997, 88(11): 1033.

Original monograph - Drugs Fut 1993, 18: 1112.

Lercanidipine Hydrochloride
Zanedip®
Lercadip®
Lerdip®
Zanidip®

Antianginal
Antihypertensive
Calcium Antagonist

EN: 090990



$C_{36}H_{41}N_3O_6.HCl$ **Recordati; Byk Gulden; Uriach; Napp; Zeneca; Rotta; Zambon; Tsumura**

Two new related ways for the synthesis of lercanidipine have been reported: Scheme 2.

1) The condensation of diketene (I) with the aminoalcohol (II) gives the corresponding acetoacetate ester (III), which is allowed to react with 3-nitrobenzaldehyde (IV) by means of HCl in chloroform yielding the expected benzylidene derivative (V). Finally, this compound is cyclized with methyl 3-aminocrotonate (VI) in refluxing isopropanol.

2) By esterification of 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid monomethyl ester (VIII) with alcohol (II) by means of $SOCl_2$ in DMF/dichloromethane. Description: Crystals, m.p. 185-90 °C (1).

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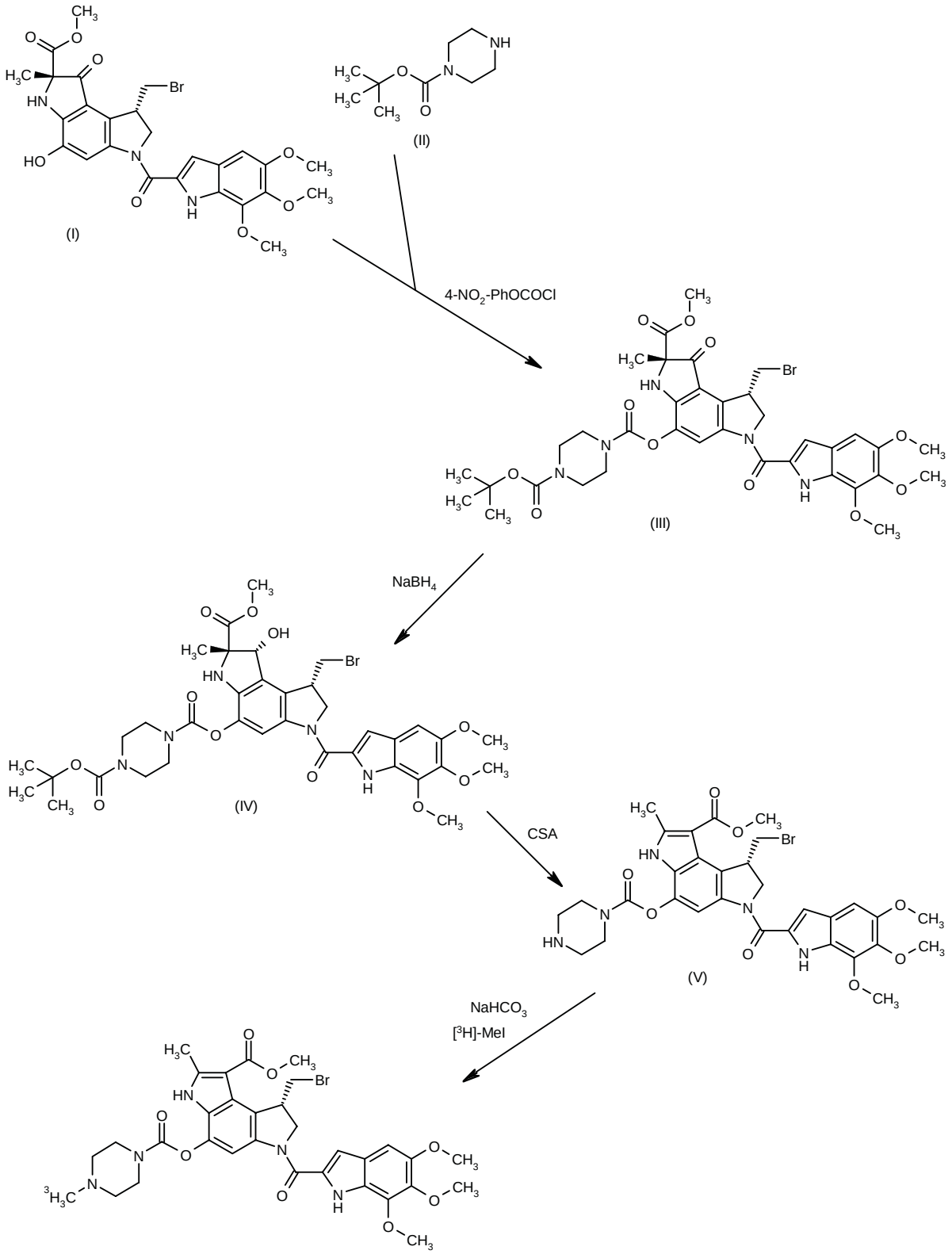
Scheme 1: Synthesis of [^{3}H]-KW-2189



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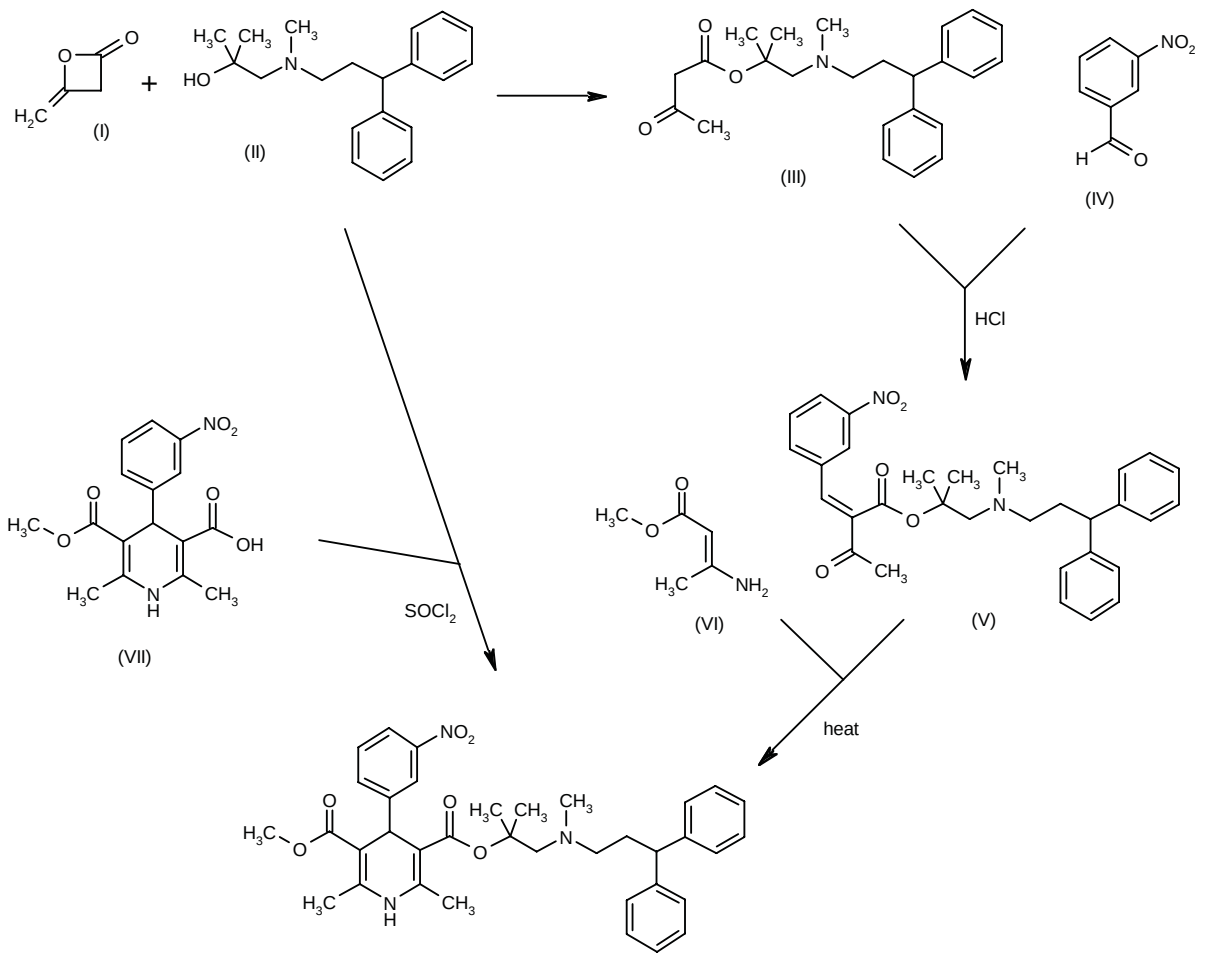
Scheme 2: Synthesis of Lercanidipine



In vitro studies in rabbit and rat tissues showed that lercanidipine possesses markedly high vascular selectivity as compared to other calcium antagonists (2).

The effects of lercanidipine and other 1,4-dihydropyridine calcium entry blockers on cerebral, renal, coronary and peripheral blood flow were compared in anesthetized dogs. Results showed that lercanidipine has preferential cerebral and coronary vasodilating activity and possesses comparable or superior activity to other calcium antagonists on regional blood flow. Onset of vasodilation is slower than with the other 1,4-dihydropyridines (3).

The overall safety and tolerability of lercanidipine in elderly hypertensive patients has been confirmed in over 1799 patients. The incidence of side effects was similar in young and elderly hypertensive patients, and the overall incidence of side effects in patients treated with 10 or 20 mg/day lercanidipine was similar to that for placebo (4).

Results from double-blind, comparative clinical studies in 889 patients with mild to moderate essential hypertension indicate a response rate on lercanidipine 10 mg once daily of 58-89%. Two long-term studies in 399 patients showed maintenance of the antihypertensive effect for the entire study period. Treatment with lercanidipine was associated with a very low incidence of side effects, similar to placebo treatment (5).

Napp has introduced lercanidipine hydrochloride (Zanidip®) in the U.K. for the treatment of mild to moderate hypertension. It is available as tablets of 10 mg (6).

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Levovist®
SHU-508-A
SH/TA-508
Echoscope®

Imaging Agent

EN: 201522

Schering AG; Tanabe

Rabbits treated with SH/TA-508 (0.08 or 0.4 g/kg i.v.) exhibited slight or marked transient increases, respectively, in pulmonary arterial pressure. When 0.8 g/kg was administered in rabbits, blood PCO_2 transiently increased while PO_2 decreased. No damage to the blood-brain barrier was observed when doses of 0.02 g/kg and 100 mg/ml were injected into the rat internal carotid artery, demonstrating that the drug was well tolerated (1).

The effects of peripheral venous injections of Levovist® (200 and 400 mg/ml) on pulsed-wave Doppler flow quality of the transthoracic (TTE) and transesophageal (TEE) recorded pulmonary venous flow were examined in 26 patients. Levovist® improved the quality of pulmonary venous flow Doppler signal recorded by TTE, with quality and quantity comparable to the signal recorded by TEE (2).

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2. Lambertz, H., Schuhmacher, U., Tries, H.P., Stein, T. *Improvement of pulmonary venous flow Doppler signal after intravenous injection of Levovist*. J Amer Soc Echocardiogr 1997, 10(9): 891.

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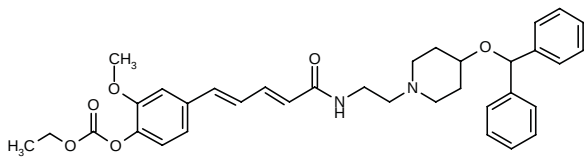
Linetastine

Antiallergic/Antiasthmatic
Leukotriene Synthesis Inhibitor

EN: 134775



$C_{35}H_{40}N_2O_6$

Terumo

In passively sensitized guinea pigs with allergic rhinitis, TMK-688 (1 and 3.2 mg/kg p.o.) inhibited increased intranasal resistance following antigen challenge. TMK-688 significantly inhibited the increase in immunoreactive LTB_4 and LTC_4 in nasal lavage fluid following antigen challenge at the higher dose, and tended to inhibit it at the lower one. Leakage of a brilliant blue dye following antigen challenge from the bloodstream into the nasal cavities was also inhibited significantly by this compound (1).

According to a spokesperson for Terumo, TMK-688 was evaluated in phase III testing; however, this product is no longer under development (2).

1. Shizawa, T., Maeda, K., Abe, K., Ishii, T., Kamitani, T. *Effects of TMK688, a novel anti-allergic drug, on allergic nasal obstruction and exudative responses in sensitized guinea pigs*. Naunyn-Schmied Arch Pharmacol 1997, 356(6): 815.

2. Prous Science Daily Essentials Jan 14, 1998.

Original monograph - Drugs Fut 1988, 13: 1056.

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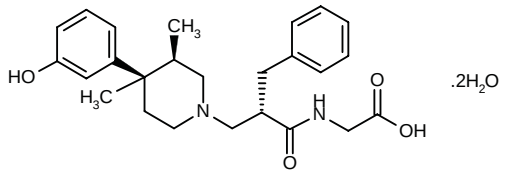
LY-246736 Dihydrate *Treatment of IBS*
ADL-8-2698 *Treatment of Nonulcer Dyspepsia*

EN: 207549



$C_{25}H_{32}N_2O_4.2H_2O$ **Lilly; Robert Lab.; Adolor**

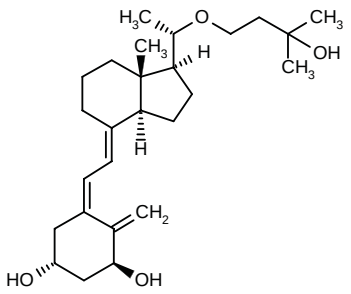
Adolor has obtained a 13-month exclusive worldwide option to Roberts' LY-246736, designated ADL-8-2698 by Adolor, a gastrointestinal agent in phase Ib clinical development for the prevention of opiate-induced constipation. LY-246736 is a potent, orally active and peripherally selective μ-opioid receptor antagonist which completely reversed opioid-induced prolongation of gastrointestinal transit time in preclinical and pilot clinical trials (1).

1. *Adolor in-licenses Roberts compound for narcotic-induced constipation*. Prous Science Daily Essentials Jun 18, 1998.

Original monograph - Drugs Fut 1994, 19: 1078.

Maxacalcitol *Treatment of Hyperparathyroidism* *Antipsoriatic*

EN: 127850



$C_{26}H_{42}O_4$ **Chugai; Schering-Plough**

Daily local injections of 22-oxacalcitriol (250 nmol) decreased the density of neurofibroma cells transplanted subcutaneously into the skin of nude mice. The same effects were observed on neurofibroma cells transplanted into experimental tissue specimens (1).

The ability of maxacalcitol and 1,25-dihydroxyvitamin D_3 to suppress parathyroid hormone (PTH) secretion was assessed and compared in female nude mice with parathyroid tissue transplanted from a patient with severe secondary hyperparathyroidism. Results suggest that maxacalcitol and 1,25-dihydroxyvitamin D_3 suppress PTH secretion in the setting of severe parathyroid hyperplasia only in the presence of normal or high serum calcium levels (2).

Results from a double-blind right and left comparative study in which psoriasis vulgaris was treated and an open trial (involving large skin areas; PASI score >15), determined that the optimal concentration of 22-oxacalcitriol ointment was 25 μg/g and a daily application up to 16 g was deemed safe in terms of serum calcium levels (3).

Schering-Plough and Chugai have signed an agreement giving Schering-Plough exclusive worldwide marketing rights, excluding Japan, to Chugai's maxacalcitol for the topical treatment of psoriasis (4).

Chugai has concluded phase III testing of the vitamin D_3 analog maxacalcitol (OCT) for the indication of secondary hyperparathyroidism, and has filed for approval with the Japanese regulatory authorities. The compound is also being developed for a second indication, psoriasis, through a collaboration with Schering-Plough. OCT ointment is in phase III testing for psoriasis in Japan and the U.K. (5).

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2. Funahashi, H., Tanaka, Y., Imai, T., Wada, M., Tsukamura, K., Hayakawa, Y., Matsuura, N., Kikumori, T., Oiwa, M., Tominaga, Y., Takagi, H. *Parathyroid hormone suppression by 22-oxacalcitriol in the severe parathyroid hyperplasia*. J Endocrinol Invest 1998, 21(1): 43.

3. Nakagawa, H., Ohkido, M., Harada, S., Kawashima, M., Ohkawara, A., Yoshikawa, K., Ozawa, A. *Dose finding studies of a novel vitamin D analogue 22-oxacalcitriol ointment on psoriasis vulgaris*. J Eur Acad Dermatol Venereol 1998, 11(Suppl. 2): Abst FC21-8.

4. *Schering-Plough and Chugai sign marketing agreement for psoriasis drug*. Prous Science Daily Essentials Mar 20, 1998.

5. Prous Science Daily Essentials Sept 10, 1998.

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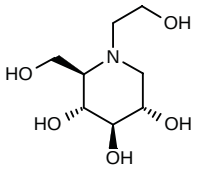
Watanabe, K. et al. *Twelve-month intravenous toxicity study of OCT in rats*. Jpn Pharmacol Ther 1998, 26(Suppl. 1): 81.

Miglitol
Glyset®
Diastabol®

Antidiabetic
α-Glucosidase Inhibitor

EN: 102773



$C_8H_{17}NO_5$

Bayer; Pharmacia & Upjohn; Sanwa; Sanofi

Findings from a bioequivalence study between 2 different miglitol regimens (two 25 mg or one 50 mg tablet) indicated that both administrations inhibited postprandial increase of blood glucose. In addition, ANOVA showed significant differences in 'between subjects' and 'subjects/group' for log C_{max} and log $AUC_{(0-3)}$ and in 'time period' for log $AUC_{(0-3)}$. No significant difference was noted in 'group or sequence' and 'drug'. The 90% CIs of C_{max}-ratio and $AUC_{(0-3)}$-ratio of plasma glucose were 96.5-105.4% and 99.7-102.9%, respectively. Being within the interval of 80-125%, these data indicated that both regimens were bioequivalent (1).

In a long-term double-blind, randomized, placebo-controlled study, 385 diet-treated or diet and sulfonylurea-treated Hispanic patients with NIDDM were administered miglitol (50, 100, 150 or 200 mg t.i.d.) or a placebo for 1 year. Miglitol-treated patients exhibited significant (0.63, 0.73 and 0.82%) reductions in HbA1c levels for 3, 9 and 12 months of treatment, respectively, in addition to decreases in 120 min postprandial glucose and insulin levels and no differences in fasting insulin or lipid levels. The effects were maintained throughout the 1-year treatment period. Decreases in fasting plasma glucose and albumin-to-creatinine ratios almost reached significance. Adverse effects observed in the miglitol-treated group included dose-dependent flatulence and diarrhea (2).

The interactions between miglitol (100 mg t.i.d.) and glyburide (2.5 mg b.i.d.) were evaluated in 28 patients with noninsulin-dependent diabetes mellitus. Miglitol reduced the values of AUC and C_{max} for glyburide by 19 and 16%, respectively. Mean plasma glucose concentrations were 213 mg/dl in patients treated with miglitol and glyburide, as compared to 234 mg/dl in patients treated with glyburide and placebo. Mean C_{max} values for glucose for the respective study groups were 289 and 341 mg/dl, while average insulin concentrations were 47.5 and 53.5 mg/dl. The results indicate that coadministration of miglitol and glyburide have positive synergistic effects on plasma glucose and insulin levels in patients with NIDDM (3).

Miglitol was launched in June 1998 in its first market, Germany, for the treatment of type II diabetes. Known as Diastabol® in Europe and Glyset® in the U.S., the compound was developed and will be manufactured by Bayer, while it will be marketed in all major markets with the exception of North America and Japan by Sanofi. It is approved in tablets of 50 and 100 mg (4, 5).

Pharmacia & Upjohn has been granted marketing rights to Bayer's miglitol for marketing in the U.S., Canada, Australia and New Zealand under the tradename Glyset®. The agreement also includes rights to market miglitol as an over-the-counter drug in the future (6).

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5. *First launch for Bayer's miglitol*. Prous Science Daily Essentials Jun 30, 1998.

6. *P&U to market Glyset in U.S., Canada and several other countries*. Prous Science Daily Essentials Sept 2, 1998.

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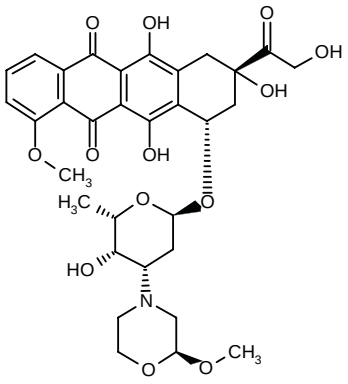
Nemorubicin
FCE-23762
PNU-152243

Antineoplastic Antibiotic

EN: 127052



$C_{32}H_{37}NO_{13}$ **Pharmacia & Upjohn**

In a phase I trial, the *in vitro* myelotoxicity of plasma taken from patients treated with PNU-152243 (0.70, 0.82 or 0.94 mg/m^2 p.o. for 1, 4, 6, 12 or 24 h) was examined using human umbilical cord blood cells (granulocyte precursors [GM-CFC] and erythroid progenitors) and compared to a rat liver microsome activated form (mMMDX) and a pure metabolite (PNU-159682). Toxicity was greater in cells treated with the metabolites and was associated with exposure time. ID_{70}s for inhibition of growth after 24-h exposure to PNU-152243, mMMDX and PNU-159682 were 140, 3 and 0.17 ng/ml, respectively. Results demonstrated that a plasma concentration of PNU-152243 1000 times lower than the active dose *in vitro*, resulted in a myelotoxic effect in GM-CFC suggesting that metabolites, remaining even after the disappearance of PNU-152243 due to longer half-lives, may be responsible for myelotoxicity (1).

The pharmacokinetics of oral PNU-152243 was evaluated in 21 patients. No objective treatment-related responses were observed, and due to the severe gastrointestinal toxicity observed in several cases, further clinical development of the drug was not recommended (2).

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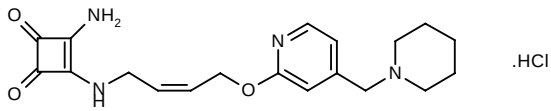
Pibutidine Hydrochloride
IT-066

Gastric Antisecretory
H_2-Receptor Antagonist

EN: 161243



$C_{19}H_{24}N_4O_3$.HCl **Taisho; Ikeda Mohando**

Pibutidine blocked the binding of [^{3}H]-tiotidine in cells transfected with the wild-type H_2 receptor, an effect that was potentiated by preincubation of the cells with the drug and maintained after extensive washing of the cells. A similar effect was observed in cells expressing the canine H_2 receptor with a 190Ala to Thr substitution in the fifth transmembrane domain, although this effect was attenuated after washing of the cells (1).

Evaluation of the effects of IT-066 (0.3-3 mg/kg p.o.) in rat gastric mucosa showed that the drug stimulates nitric oxide production, implicating a role of endogenous NO in the pharmacological actions of the drug (2).

The structure-related H_2 antagonistic activity of IT-066 was investigated in isolated guinea pig atria. The replacement of a pyridine ring with a benzene ring maintained the antagonistic activity of the drug, while oxidation of the piperidine ring completely abolished its antagonistic effects. Replacement of *cis*-2-butene, the connecting carbon chain, with butane, *trans*-butene or 2-butyne abolished the irreversible antagonism of the drug and reduced its potency. These results demonstrate the importance of the piperidine ring and the connecting carbon chain to the antagonistic activity of IT-066 (3).

In a rat model of induced gastric lesions, pibutidine (5 mg/kg p.o.) significantly reduced lesion formation, an effect that was inhibited by the selective inhibition of NO

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synthase and by infusion of the NO scavenger carboxy-PTIO. Indomethacin also reduced the protective effects of pibutidine. The results suggest that endogenous prostaglandins and NO are involved in the mucosal protection produced by pibutidine (4).

The healing effects of pibutidine were demonstrated in rats and Mongolian gerbils with chronic gastric ulcers, with dosing initiated 4 days after ulcer induction and continuing for 1-2 weeks over the dose range of 1-10 mg/kg p.o. b.i.d. Ulcer healing accelerated significantly in animals treated with pibutidine. Ulcer healing was delayed by 3 weeks of indomethacin administration, while pibutidine was able to inhibit this delayed healing. The compound also prevented hydrocortisone-induced ulcer recurrence and increased the mitogenic activity of the gastric juices. In gerbils with ulcers complicated by Helicobacter pylori infection, the coadministration of pibutidine and clarithromycin accelerated ulcer healing (5).

Pibutidine hydrochloride is the new proposed international nonproprietary name for IT-066 (6).

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p24-VLP
Ty.p24.VLP

Anti-HIV
AIDS Vaccine

EN: 196966

British Biotech

The effects of therapeutic immunization with p24-VLP (virus-like particle) and zidovudine (AZT) were assessed on various immunogenic parameters and viral load in a phase II trial enrolling asymptomatic HIV-infected individuals with $CD4^+$ counts > 400 million cells/l. Sixty-one AZT-naive patients were randomized to 6-month treatment with oral AZT (200 mg t.i.d.) plus monthly i.m. injection of alum adjuvant; oral AZT (200 mg t.i.d.) plus monthly i.m. injection of p24-VLP (500 μg) in alum; or oral placebo plus monthly i.m. injection of p24-VLP (500 μg) in alum. There were no significant differences between the three treatment groups in terms of antibody responses to p24, $CD4^+$ or $CD8^+$ cell counts, viral load, T-cell responses to p24, p17, recall antigen or mitogen, or markers of immune activation, in spite of the fact that antibody and proliferative responses to the carrier protein of the vaccine were induced with p24-VLP immunotherapy. p24-VLP was well tolerated, but did not display therapeutic efficacy in this phase II trial (1).

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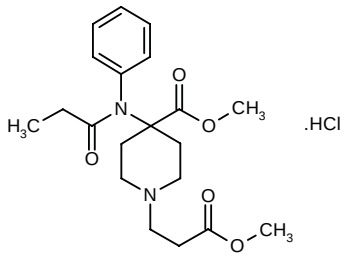
Remifentanil Hydrochloride
Ultiva®

Opioid Analgesic
μ-Opioid Agonist

EN: 185000



$C_{20}H_{28}N_2O_5.HCl$

Glaxo Wellcome

Results of studies in mice administered remifentanil or endomorphin-2 indicate a role for the NMDA receptor, and possibly nitric oxide synthase, in the development of ultra acute antinociceptive tolerance to the two drugs (1).

In a randomized, double-blind clinical study, 80 patients undergoing major abdominal surgery in which propofol and remifentanil infusions were used to induce anesthesia, were administered 20 min prior to the end of surgery and following extubation a bolus of either fentanyl

(0.15 and 0.05 mg), buprenorphine (0.3 and 0.15 mg), morphine (15 and 7 mg) or piritramide (15 and 7 mg). Results showed that administration of the longer acting opioids provided effective immediate control of postoperative pain (2).

In a prospective, randomized, double-blind, placebo-controlled study, 7 healthy subjects were administered an i.v. infusion of either remifentanil (0.75, 1.5 and 3.0 ng/ml), alfentanil (16, 32 and 64 ng/ml) or saline for 120 min and analgesic effects were evaluated by forearm immersion in an ice bath. Dose-dependent decreases in pain intensity and "bothersomeness" ratings were observed in subjects receiving remifentanil and alfentanil with a 20:1 ratio of remifentanil resulting in more analgesia as compared to alfentanil. The potency ratio was determined to be 40:1 with 1.5 ng/ml remifentanil and 64 ng/ml alfentanil (3).

In a phase IV open-label, multicenter SOURCE observational trial, 1961 patients undergoing elective surgery received remifentanil (0.5 in patients older than 65 years of age or 1.0 μg/kg/min i.v.) infusion with a reduction in dose (0.25 μg/kg/min) following intubaton and isoflurane or propofol during maintenance. Remifentanil therapy was concluded to be safe with comparable or fewer adverse effects than those reported from earlier studies (4).

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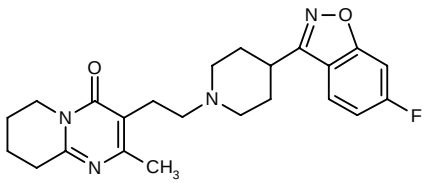
Risperidone
Risolept®
Risperdal®
Belivon®

Antipsychotic

EN: 127142



$C_{23}H_{27}FN_4O_2$

Janssen; SmithKline Beecham; Organon; Janssen-Kyowa; Scios

A 74-year old female patient treated for schizoaffective disorder with risperidone (18 mg/day), fluvoxamine (250 mg/day), procyclidine (5 mg/day) and lorazepam (5 mg/day) exhibiting risperidone-related neuroleptic malignant syndrome (NMS) was administered supportive treatment including vitamins E (1600 IU/day) and B_6 (200 mg/day). Vitamin therapy resulted in a decrease in abnormal involuntary movements score (from 39 to 19), a reduction in psychiatric scaling from 74 to 45 and com-

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plete recovery from NMS, including a decrease in peak plasma clearance from 469 IU/l to normal (35 IU/l) within 5 days (1).

Scios has signed an agreement with Janssen for the copromotion of risperidone (Risperdal®). Risperdal® effectively controls a wider range of psychotic symptoms with fewer side effects than more conventional medications (2).

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2. *Scios and Janssen to copromote Risperdal*. Prous Science Daily Essentials May 18, 1998.

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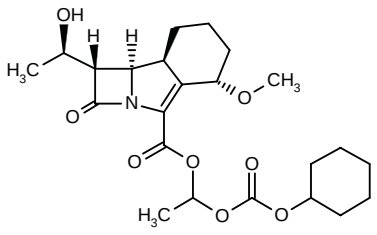
Sanfetrinem Cilexetil

Trinem

EN: 183596



$C_{23}H_{33}NO_8$ **Glaxo Wellcome**

Physiochemical analysis of GV-118819X showed that melting of the compound is irreversible and produces a double peak. Further studies revealed that GV-118819X is a eutectic mixture containing one diastereoisomer in excess, and that the diastereoisomer can be obtained in crystalline form from a melted sample by thermal annealing (1).

A new synthesis of sanfetrinem has been puplished: The condensation of (3*S*,4*R*)-4-acetoxy-3-[1(*R*)-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one (I) with 2-methoxy-2-cyclohexen-1-one (II) by means of lithium bis(trimethylsilyl)amide (LHMDA) in THF gives a mixture of diastereomers that are separated by flash chromatography yielding pure enantiomer (III). The hydrogenation of the double bond of (III) with H_2 over Pd/C in ethyl acetate affords another mixture of diastereomers that are also separated by flash chromatography giving pure enantiomer (IV). The cyclization of (IV) with allyl acrylate (V) by means of triethylamine yields (4*S*,8*S*,9*R*,10*S*)-10-[1(*R*)-hydroxyethyl]-4-methoxy-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic acid allyl ester (VI), the silylated allyl ester of sanfetrinem. Finally, this compound is desilylated by treatment with tetrabutylammonium fluoride (TBAF)/acetic acid in THF and saponified with potassium 2-ethylhexanoate (KEH) (2). Scheme 3.

The antibacterial activity of sanfetrinem was compared with 15 other antimicrobial agents in 218 isolated strains of *Bacteroides fragilis*. The drug produced MIC_{50} and MIC_{90} values of 0.1 and 1 mg/ml, respectively, comparable to the corresponding values for imipenem and meropenem, and lower than values observed with nine other β-lactams. Therefore, sanfetrinem may have clinical value in the treatment and prophylaxis of infections with strains of *Bacteroides fragilis* (3).

Sub-MICs of sanfetrinem were found to significantly increase normal human polymorphonuclear granulocyte (PMNs) phagocytosis and intracellular bactericidal activity against *Klebsiella pneumoniae*. Results suggest that sanfetrinem may directly act on either PMNs or *K. pneumoniae* (4).

The uptake of sanfetrinem by human polymorphonuclear cells (PMNs) was examined *in vitro* with penetration observed at all concentrations tested. Uptake was complete within 5 min and was energy-independent. PMN phagocytosis and intracellular bactericidal activity against ingested *Streptococcus pneumoniae* was also significantly increased following exposure of PMNs to sanfetrinem and PMNs were more effective against streptococci pretreated with sanfetrinem (5).

The pharmacokinetics and inflammatory fluid penetration of sanfetrinem administered as its prodrug GV-118819X (equivalent to 125 and 500 mg of sanfetrinem) were evaluated in 6 healthy volunteers. Peak plasma concentrations of 0.77 and 2.47 μg/ml were reached following administration of 125 and 500 mg doses, respectively, and were observed after 2.8 and 2.67 h, respectively. Peak concentrations in inflammatory exudate were 0.26 and 0.86 μg/ml for the low and high doses, respectively, and were observed after 1.33 and 1.97 h after administration of respective doses. Terminal elimination half-lives in plasma and inflammatory fluid for the low and high doses were 1.33 and 1.97 h, and 1.66 and 1.74 h, respectively. Overall penetration of the drug into inflammatory fluid was estimated to be 51.4 and 47.0% of the 125- and 500-mg doses, respectively, while urine recovery of the 125-mg dose was 18.4% and of the 500-mg dose was 24.15%. The drug's instability in the inflammatory exudate could explain the poor penetration observed in this study (6).

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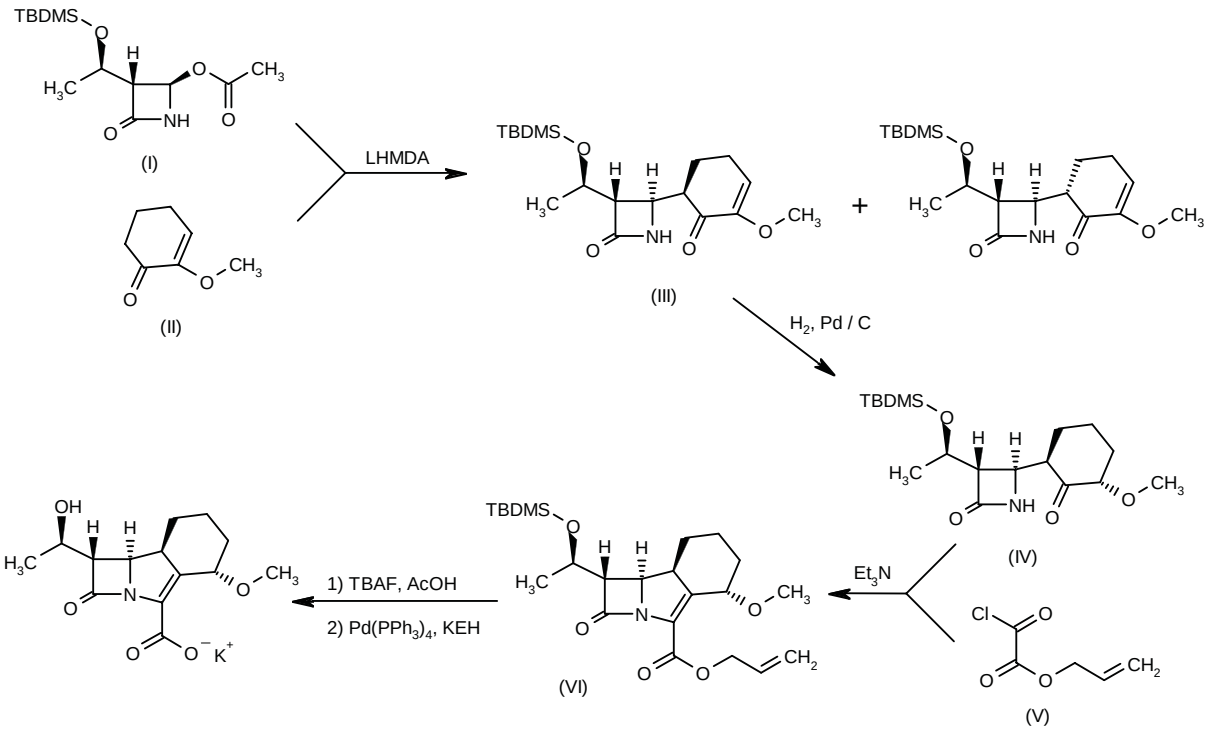
Scheme 3: Synthesis of Sanfetrinem Potassium



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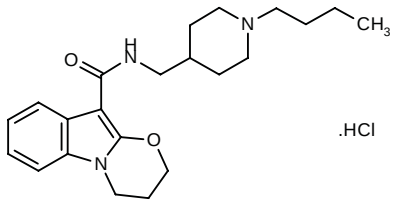
Glaxo Wellcome's R&D pipeline remains full and diverse. Prous Science Daily Essentials Jan 21, 1998.

SB-207266A

Treatment of IBS
5-HT_4-Receptor Antagonist

EN: 229794



$C_{22}H_{31}N_3O_2$.HCl **SmithKline Beecham**

In the absence of exogenous 5-HT, SB-207266 had no effects on normal patterns of intestinal mobility in guinea pigs and mice, while in the presence of 5-HT, the drug antagonized the 5-HT-induced sensitization of the peristaltic reflex and the lowering of peristalsis distension threshold. Oral and subcutaneous administration of SB-207266 in mice blocked 5-HT-induced increments in the rate of defecation, fecal pellet formation and their fluid content. Optimal efficacy was observed at doses of 10 μg/kg s.c. and 1000 μg/kg p.o (1).

The effects of SB-207266A on rectal sensitivity and small bowel transit were studied in 15 patients with

intestinal bowel syndrome (IBS), previously unaffected by rectal hypersensitivity. Subjects received SB-207266A (20 mg once daily) for periods of 10 days with 14-day washout periods in between. Eleven patients on active treatment reported an improvement in their IBS symptoms as compared to 1 patient in the placebo-treated group. SB-207266A significantly increased oracaecal transit but had no significant effects on rectal sensitivity (2).

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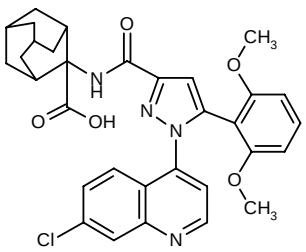
SR-48692

Antipsychotic
Neurotensin Receptor Antagonist

EN: 192167



$C_{32}H_{31}ClN_4O_5$ **Sanofi**

The effects of SR-48692 on renal function and the effects of NO on the diuretic activity of the drug were evaluated in rats. The drug dose-dependently increased urine output and urinary excretion of Na^+, K^+ and Cl^- in fed animals. Neurotensin had no effects on urine output but did reduce the diuretic activity of SR-48692. Inhibition of NO synthase blocked the diuretic activity of SR-48692 but did not affect urine output. Central and systemic administration of SR-48692 not only increased diuresis but also increased urinary excretion of nitrates and nitrites. These results support the association between the activity of neurotensin, arginine-vasopressin and NO production and the regulation of renal excretion of water, Na^+, K^+ and Cl^- (1).

SR-48692 (2.5 μg i.c.v. and 25 μg i.p.) blocked neurotensin-induced gastric mucosal protection in pylorus ligated rats, while doses of 2.5 μg i.p. had no effects. High doses of SR-48692 administered i.p. blocked neurotensin-induced secretory inhibition while i.c.v. administered doses had no effects. The results indicate that the high-affinity neurotensin receptor mediates neurotensin-induced protection against stress-induced injury, as opposed to the neurotensin-induced inhibition of gastrin-stimulated acid secretion (2).

Long-term administration of SR-48692 (1 mg/kg i.p.) to Wistar rats was evaluated for its effects on the activity of mesocortical and mesolimbic dopaminergic systems. The drug selectively modulated the dopaminergic mesolimbic system as compared to the mesocortical pathway, suggesting that it may be effective in the treatment of neuropsychiatric disorders associated with hyperactivity of the mesolimbic dopaminergic system or the hypothalamic-pituitary-adrenal axis (3).

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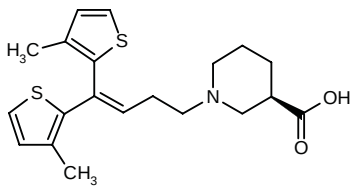
Tiagabine
Gabitril®
Tiabex®

Antiepileptic
GABA Reuptake Inhibitor

EN: 139181



$C_{20}H_{25}NO_2S_2$ **Novo Nordisk; Sanofi; Abbott**

In an open trial, 8 patients of both genders were administered tiagabine (20 mg/day, gradually increased depending on side effects) to test its antimania properties. The drug had no pronounced antimania efficacy as compared to standard regimens of valproate, lithium or neuroleptics. In addition, rapid dosage increases may be associated with severe side effects (1).

In a randomized, multicenter, double-blind, placebo-controlled, dose-response trial involving 297 patients with intractable complex partial seizures, tiagabine (16, 32, 56 mg q.i.d.) was shown to be efficacious and well-tolerated as adjunctive therapy. A clear dose-response relationship was observed. Furthermore, adverse events were dose-related and consisted of dizziness, tremor, abnormal thinking and depressed mood (2).

In a randomized, parallel-group, double-blind study, 40 patients with chronic partial epilepsy on stable antiepileptic drug (AED) monotherapy were switched to tiagabine (slow or fast titration to 10 mg b.i.d. followed by a decrease in AED). A total of 85% of the patients were successfully switched, including 11/14 who experienced dizziness necessitating a change to an open drug switch scheme (5 mg b.i.d. tiagabine). At least 1 side effect was observed in 93% of the patients, with 80% needing treatment for CNS-related side effects. Results also showed that the maintenance dose was 7.5-35 mg/day. Tiagabine monotherapy was found to have a 30% risk at 12 weeks and a 52% risk in the first 48 days for unacceptable seizure control or unacceptable adverse effects, according to Kaplan-Meier estimates of probability time (3).

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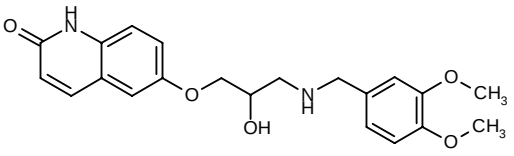
Gabitril introduced in Germany. Prous Science Daily Essentials Jun 23, 1997.

Novo Nordisk licenses tiagabine to Sanofi. Prous Science Daily Essentials Dec 3, 1997.

Toborinone

Treatment of Heart Failure
Phosphodiesterase III Inhibitor

EN: 162135



$C_{21}H_{24}N_2O_5$ **Otsuka**

The effects of toborinone 10 μM on energy metabolism were evaluated in microembolized guinea pig hearts. The drug elevated the rate of increase of left ventricular developed pressure, an index of contractility, by 15%, without changing the heart rate. Changes in creatinine phosphate, ATP, inorganic phosphate and the ratio of creatinine phosphate and inorganic phosphate were not detected. The results indicate that toborinone may be effective in the treatment of ischemic heart failure (1).

In a double-blind, multicenter study, 48 patients with moderate to severe heart failure were administered a 6-h continuous infusion of toborinone (1.25, 2.5, 5.0 or 10 μg/kg/min) or placebo. Clinical improvement in hemodynamic status was observed in 17% of patients receiving placebo and in 25, 58, 92 and 100% of patients receiving 1.25, 2.5, 5.0 and 10 μg/kg/min toborinone infusions, respectively. Mean C_{max} ranged from 166-1554 ng/ml and pharmacokinetic parameters increased in proportion to dose (2).

The myocardial effects of intracoronary administration of OPC-18790 were assessed in 8 heart failure patients who received the drug over 20 min at a dose of 31.25 μg/min followed by a dose of 62.5 μg/min for another 20 min. There was no reduction in preload and afterload, suggesting that OPC-18790 is a modest inotrope. Significant increases were observed in end-systolic elastance at both doses and isovolumic relaxation improved in the absence of a reduction in afterload. Diastolic function improved and was accompanied by significant decreases in right atrial pressure. These responses resulted in lowered left heart filling pressures, improved ventriculoarterial coupling and constant myocardial efficiency without inducing arrhythmias (3).

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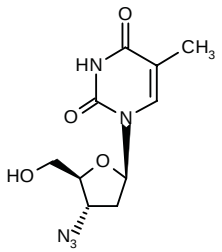
Zidovudine
Retrovir®

Anti-HIV
Reverse Transcriptase Inhibitor

EN: 113563



$C_{10}H_{13}N_5O_4$ **Glaxo Wellcome; Verex Lab.**

Nearly 3000 mother-infant pairs participated in a study to determine if the mode of delivery had any impact on prenatal HIV-1 transmission when mothers were treated with zidovudine (AZT). Among 1917 mothers who did not take AZT during pregnancy, 17.2% transmitted HIV-1 to their infants. Among the 902 mothers who did take the drug, only 0.8% of those undergoing an elective C-section transmitted the virus to their child compared to 6.6% giving birth vaginally and 11.4% undergoing emergency C-section. HIV transmission was 5-fold lower in cases when women took AZT. In those women who did not take AZT, the method of delivery made very little difference in the incidence of HIV transmission (1).

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