Drugs of the Future 1999, 24(9): 999-1045

CCC: 0377-8282/99

Information Update

Volume 1-23, Number 9

Estimated developmental phase for this month's updated products:

Phase I

Annamycin (antineoplastic; Aronex)
DMP-851 (anti-HIV; DuPont Pharm.)

Phase II

AIT-082 (cognition enhancer; NeoTherapeutics)
Atiprimod hydrochloride (immunomodulator; AnorMED)
Bryostatin 1 (antineoplastic; CRC Technology, Arizona State Univ.)
CMI-392 (antipsoriatic, treatment of atopic dermatitis; LeukoSite)
Mivobulin isethionate (antineoplastic; Warner-lambert, Natl. Cancer Inst.)
Murabutide (immunomodulator; Choay, Institut Pasteur)
OM-89 (immunomodulator; OM)
OPC-31260 (vasopressin V_2 antagonist; Otsuka)

Phase III

9-Aminocamptothecin (antineoplastic, DNA topoisomerase I inhibitor; Research Triangle Inst., Natl. Cancer Inst., Idec, Pharmacia & Upjohn)
Aripiprazole (antipsychotic; Otsuka, Bristol-Myers Squibb)
Brain-derived neurotrophic factor (treatment of ALS and neuropathies; Regeneron, Amgen, Sumitomo)
Edatrexate (antineoplastic; SRI)
MDL-100907 (antipsychotic; Hoechst Marion Roussel) (discontinued)
Norastemizole (antihistamine, treatment of allergic rhinitis; Sepracor)
Osutidine (antiulcer, histamine H_2 antagonist; Toyama)
Pegylated recombinant megakaryocyte growth and development factor (antineoplastic, hematopoietic; Amgen, Kirin Brewery) (discontinued)
Ranolazine (antianginal; Roche Bioscience, Kissei, CV Therapeutics, Innovex)
Rasagiline (antiparkinsonian, cognition enhancer, MAO-B inhibitor; Teva)
Sitafloxacin hydrate (quinolone antibacterial; Daiichi Pharm., Beijing General)

Preregistered

Lafutidine (gastric antisecretory, histamine H_2 antagonist; Fujirebio, Taiho, Salix)

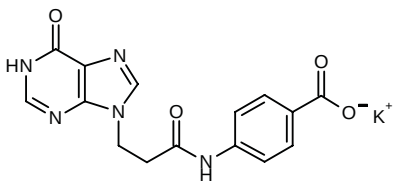
Launched/Year

Atorvastatin calcium (hypolipidemic, HMG-CoA reductase inhibitor; Warner-Lambert, Pfizer, Yamanouchi, Syncro)/1997
Buspirone hydrochloride (treatment of ADHD; Bristol-Myers Squibb, Sano)/1985
Cefteram pivoxil (cephalosporin; Toyama, Showa)/1987
Etanercept (antiarthritic, TNF-α antagonist, Immunex, Wyeth-Ayerst)/1998
Fadrozole hydrochloride (antineoplastic; Novartis)/1995
Fluvastatin sodium (hypolipidemic, HMG-CoA reductase inhibitor; Novartis, Tanabe, AstraZeneca)/1994
Glimepiride (antidiabetic; Hoechst Marion Roussel)/1995
Granisetron hydrochloride (antiemetic, 5-HT_3 antagonist; SmithKline Beecham)/1991
Imiquimod (immunomodulator, treatment of genital warts; 3M Pharm., Daiichi Pharm.)/1997
Memantine hydrochloride (treatment of neurogenic pain, treatment of diabetic neuropathy)/1982
Olopatadine hydrochloride (treatment of allergic rhinitis, ophthalmic antiallergic; Kyowa Hakko, Alcon)/1997
Palivizumab (anti-RSV; MedImmune, Abbott)/1998
Prednisolone farnesylate (antiarthritic, corticosteroid; Taiho, Kuraray, Dainippon)/1998
Quinupristin/Dalfopristin (streptogramin; Rhône-Poulenc Rorer)/1999
Reteplase (thrombolytic; Biovail, Roche, Centocor)/1996
Rosiglitazone maleate (antidiabetic; SmithKline Beecham, Bristol-Myers Squibb)/1999
Tirofiban hydrochloride (platelet antiaggregatory, gpIIb/IIIa receptor antagonist; Merck & Co., Banyu)/1998
Troglitazone (antidiabetic; Sankyo, Warner-Lambert, Glaxo Wellcome)/1997
Venlafaxine (antidepressant; Wyeth-Ayerst, Scios, Almirall Prodesfarma)/1994
Voglibose (antidiabetic; Takeda)/1994

AIT-082
Leteprinin Potassium
Neotrofin®

Cognition Enhancer

EN: 204883



$C_{15}H_{12}KN_5O_4$

NeoTherapeutics

Results from studies in rat hippocampal neurons and astrocytes indicated that, in addition to its long-term effects on neurotrophic factors, AIT-082 appears to enhance neuronal cell excitability acutely and may also influence ion channels, membrane potential and intracellular ion concentrations (1).

The neuroprotective effects of AIT-082 against NMDA *in vitro* and *in vivo* were suggested to involve an increase in the local release of adenosine and neurotrophic factors from astrocytes (2).

AIT-082 appeared to promote cholinergic sprouting in the ventral dentate gyrus of the hippocampus following unilateral entorhinal cortex lesions in rats (3).

In cultured developing mouse hippocampal neurons, AIT-082 was found to promote neuritogenesis, and also promoted neurite recovery following exposure to glutamate (4).

In mice, AIT-082 was shown to rapidly enter the brain following a single i.p. dose and to rapidly increase levels of nerve growth factor mRNA in cortex and hippocampus. It remained in the brain for only a few minutes and thus does not accumulate, which may account for the absence of side effects associated with its administration (5).

Studies in young and aged mice indicated that the memory-enhancing effects of AIT-082 are independent of corticosteroid hormones. The compound was shown to improve existing memory deficits in aged animals and to delay the onset of age-induced memory deficits. Reversal of amnesia induced by a variety of agents was also observed with AIT-082. Other behavioral effects of the compound included a short-lasting analgesic effect and short-lasting improvement in rotarod performance, which may be dependent on corticosteroid hormones. No anxiolytic activity was observed (6).

Preliminary results from a phase I double-blind, placebo-controlled, single-dose, escalation study with AIT-082 has shown a possible beneficial effect of the agent on memory and speed of processing. In 9 healthy elderly volunteers receiving AIT-082 (0.6, 2, 6 and 20 mg/kg/week p.o.) for 5 weeks, no serious side effects were reported and the drug was well tolerated. The time to peak concentration was 90 min with an elimination half-life of approximately 15 h. Improvements in performance were observed in the Number Comparison test, Symbol Digit test, Trails A and other neuropsychological tests (7).

Treatment with AIT-082 has been shown to produce a statistically significant positive effect on memory function in healthy elderly volunteers. In this double-blind, placebo-controlled phase Ib study, the compound was well tolerated and produced no serious adverse events at doses of up to 2000 mg/day for 7 days. This is the first demonstration of memory improvement and safety with AIT-082 following multiple dosing over a short period of time, and builds on the results obtained in phase I trials evaluating single doses of the compound in healthy volunteers and patients with Alzheimer's disease (8).

AIT-082 produced a positive effect on behavioral function memory improvement in a phase II clinical study involving patients with Alzheimer's disease. This double-blind, placebo-controlled phase IIa study at 13 clinical centers in the U.S. enrolled 74 patients with mild to moderate AD for 28 days of treatment. AIT-082 was safe and well tolerated at once-daily doses of 50-500 mg (9).

A new phase IIb study designed to establish the therapeutic oral dose of AIT-082 for the treatment of Alzheimer's disease was initiated in the Republic of South Africa and later expanded to Canada and Australia. Other countries will be added upon regulatory approvals. The phase IIb study represents the first clinical testing of AIT-082 outside North America. This double-blind, placebo-controlled trial is designed to study the effects of 3 doses of AIT-082 over the course of 90 days of treatment in as many as 400 patients with mild to moderate Alzheimer's disease. The efficacy measures employed in the study were selected to detect the types of cognitive and behavioral changes which may occur in patients with Alzheimer's disease (10, 11).

Results from a phase IIa, placebo-controlled clinical trial of AIT-082 in 75 patients with mild to moderate Alzheimer's disease have been reported. The double-blind trial evaluated the subjects after the 28-day treatment period, then again 28 days after discontinuing treatment. Improvements were observed in cognitive functioning and behavior in patients treated with AIT-082. Of the patients receiving the 150-mg dose of the drug, 72% showed an improvement in total ADAS-cog scores, a measure of cognitive functioning, and significant positive differences were noted on the Global Behave-AD test as well. Furthermore, the CIBIC-plus, a measure of overall disease severity, demonstrated a marked improvement in the drug-treated groups, both at the end of treatment and 28 days after discontinuing treatment. AIT-082 (Neotrofin®) is under development by NeoTherapeutics for nerve repair and regeneration, with Alzheimer's disease as its first intended clinical indication. Preclinical studies have shown that the compound can control the production of multiple natural neurotrophic factors and restore function in animal models of aging, brain injury and spinal cord injury (12).

Leteprinim potassium is the new proposed international nonproprietary name for AIT-082 (13).

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6. Ritzmann, R.F., Lim, M., Glasky, M.S., Glasky, A.J. *The effects of AIT-082 on memory in young and aged mice.* Soc Neurosci Abst 1998, 24(Part 2): Abst 770.5.

7. Grundman, M. et al. *A phase I study of AIT-082 in healthy elderly volunteers.* Soc Neurosci Abst 1998, 24(Part 1): Abst 477.15.

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11. *NeoTherapeutics begins Neotrofin clinical trials in Canada and Australia.* DailyDrugNews.com (Daily Essentials) March 16, 1999.

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Original monograph - Drugs Fut 1997, 22: 945.

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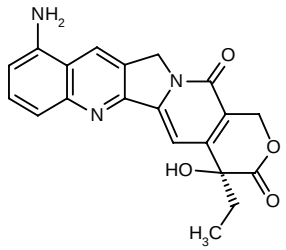
9-Aminocamptothecin *Antineoplastic*
IDEC-132 *DNA Topoisomerase I Inhibitor*

EN: 184764



$C_{20}H_{17}N_3O_4$

Research Triangle Inst.; Natl. Cancer Inst. (US); Idec; Pharmacia & Upjohn

A study has demonstrated that DNA damage induced by camptothecin is different in malignant and healthy cells. Normal peripheral blood mononuclear cells from patients treated with camptothecin showed downregulation of topoisomerase I. Cellular extracts from 3/4 leukemic patients treated with a 72 h infusion of 9-AC showed unchanged topoisomerase I levels but significantly reduced topoisomerase II levels (1).

9-Aminocamptothecin specifically inhibits topoisomerase I but is poorly soluble in water. However, an oral PEG-1000 formulation of 9-AC has recently been demonstrated to have a bioavailability of about 48%. In order to further examine the pharmacokinetics of this formulation, a phase I and pharmacological study was conducted in 30 patients with malignant solid tumors refractory to standard forms of therapy. The study explored the maximum tolerated dose, toxicity profiles, pharmacokinetic/dynamic relationships and preliminary antitumor activity of 9-AC as hard gelatin capsules employing PEG-1000 as excipient. Patients received 21-day treatment cycles consisting of oral PEG-1000 9-AC at doses of 0.25-1.1 mg/m^2 once daily for 7 or 14 days. Plasma sampling was performed on day 1 and on day 6 or 8 of the first course, and analysis was performed by high-performance liquid chromatography. The 27 evaluable patients received a total of 89 courses. Myelosuppression and diarrhea were dose-limiting at 1.1 mg/m^2/day for 14 days. The plasma AUC of 9-AC varied considerably among patients, but intrapatient variability was minimal. The percent decrease in white blood cell count correlated significantly with the AUC of 9-AC lactone. Partial response was observed in 1 patient with metastatic colorectal cancer and disease stabilization was achieved in an additional 6 patients. Based on these findings, a dose of 0.84 mg/m^2/day is recommended for use in phase II trials. Moreover, due to the important interpatient variation in AUC found in this study, a pharmacokinetically guided phase II study may be advisable (2, 3).

Modest single-agent activity of 9-AC was demonstrated in a phase II study involving 58 previously untreated patients with stage IIIB or stage IV non-small cell lung

cancer administered the agent (1416 or 1100 μg/m^2/day i.v. for 3 days) every 14 days with G-CSF (5 μg/kg/day s.c.) given on day 5 after completion of 9-AC. Of 54 patients evaluated, 5 had a partial response (9-28 weeks). Median time to disease progression was 2.3 months. A 30% 1-year survival rate was obtained with 27 second-line chemotherapy patients achieving a rate of 56.7%. Adverse effects with the higher dose included grade 4 neutropenia (6/13) and thrombocytopenia (5/13); these toxicities were observed in 12/45 and 3/45 patients, respectively, with the lower dose (4, 5).

A phase II trial showed that 5-day continuous infusion of 9-AC (480 μg/m^2/day) per week for 3 weeks repeated every 4 weeks had no antitumor activity in 18 patients with advanced colorectal cancer. One patient died from nonneutropenic sepsis at week 4. No partial or complete responses were observed and grade 3 and 4 toxicities included diarrhea (3), granulocytopenia (5), nausea (2) and vomiting (2). Mean nadir absolute granulocyte count was 2.3 on day 10. Eight patients received an escalated dose of 600 μg/m^2/day and had nadir absolute granulocyte counts of 1.5 on day 22. Median number of courses was 2 and median time to disease progression was 8 weeks (6, 7).

The pharmacokinetics of 9-AC (0.42 mg/m^2/day i.p. every other day x 6) or topotecan (1.5 mg every day x 5) were examined in a phase I trial with results presented from 3 patients. The i.p. AUC values for 9-AC and topotecan were about 10- (835 *vs.* 117 ng/ml·h) and 20-fold (2142 *vs.* 92 ng/ml.h) higher than the plasma AUC values, respectively. Rapid elimination from the peritoneal cavity was observed for both (about 17 h) and peak plasma levels for 9-AC (5-9 ng/ml) and topotecan (10-13 ng/ml) occurred between 0.4-2 h. Plasma decays with i.p. administration were similar to those observed with agents given i.v. Tolerance with i.p. administration was excellent with no systemic effects observed (8).

A phase II and pharmacokinetic study examined 9-AC as a 72-h infusion (14-day cycles) in 28 patients with recurrent or persistent epithelial ovarian cancer previously treated with DDP and/or paclitaxel and with good end organ function. Patients who received 1-2 prior therapies received 47 μg/m^2/h and those with 3 or more were given 35 μg/m^2/h; all patients were administered G-CSF (5 μg/kg for 8 days) starting 24 h after 9-AC. Mean total drug levels were 173.4 and 123.9 nmol/l in 24 patients given 47 or 35 μg/m^2, respectively. Six partial responses (21.4%) with PFS periods of 3, 6, 8, 10, 11 and 12 months were observed, with 50% of all patients (including those resistant to DDP, paclitaxel or both) showing some clinical improvement with treatment (9).

The pharmacokinetics and oral bioavailability of 9-AC PEG-1000 capsules (1.5 mg/m^2 p.o. on day 1 and 1 mg/m^2 i.v. on day 8 or *vice versa*) were evaluated in 12 patients with solid tumors in a randomized study. Plasma lactone and carboxylate forms of 9-AC rapidly reached equilibrium with the active lactone < 10% of the total drug at the terminal disposition phase. Peak levels of 9-AC occurred at 1.2 h and a bioavailability of 48.6 ± 17.6% was obtained, showing significant systemic exposure and indicating the possibility of chronic oral treatment (10).

Linear and dose-independent pharmacokinetics were obtained for 9-AC (0.25-1.5 mg/m^2 p.o.) administered to 29 patients with solid tumors after 68 courses. The AUC increased from 6.88 ± 4.76 to 30.2 ± 14.2 ng·h/ml with small intrapatient variability; intrapatient variability in peak levels was also small, indicating that repeated prior exposure to 9-AC did not cause drug accumulation or alterations in kinetics. Interpatient variability was high and predictable from serum albumin levels. Saliva was found to be an unreliable matrix for pharamcokinetic analysis since concentration ratios were highly variable and patient-dependent. The mean AUC of 9-AC was significantly correlated with myelotoxicity grade and percent decrease in leukocyte, neutrophil and platelet counts (11).

A phase I trial of 9-AC (0.9-1.8 mg/m^2/day i.v. 10-min infusion x 5 every 3 weeks) in 18 chemotherapy naive patients with solid tumors concluded that the recommended dose for phase II studies was 1.3 or 1.5 mg/m^2/day. Neutropenia was the main toxicity observed and the maximum tolerated dose was 1.8 mg/m^2 with a dose-limiting toxicity of neutropenic sepsis. Anemia, nausea/vomiting, alopecia and asthenia were also observed. Plasma 9-AC was greater than 10 nM for up to 24 h postdosing in the majority of patients (12).

A phase II study examined the tolerability and efficacy of 9-AC treatment (35 μg/m^2/h x 72 h every 14 days) as second-line therapy for ovarian cancer in 46 patients. Doses of 9-AC were reduced to 5 μg/m^2/h for grade 4 neutropenia or thrombocytopenia lasting for > 72 h. Maximum toxicities observed in 43 patients were grade 3 (30%) and 4 (28%) neutropenia, grade 3 (14%) and 4 (5%) thrombocytopenia; grade 2 (45%), 3 (26%) and 4 (7%) anemia; grade 3 (16%) and 4 (7%) nausea and vomiting; grade 3 infection (12%); and grade 3 diarrhea and constipation. Of the 38 evaluable patients for response, 5 partial responses, 13 stable diseases and 9 progressions were seen in patients with measurable disease with an overall response rate of 19%; 1 partial response, 1 stable disease and 9 progressions were observed in patients with nonmeasurable disease (13).

A phase I dose escalation study of a colloidal dispersion formulation of 9-AC as a treatment for 39 patients with refractory or relapsed acute leukemia, acute lymphocytic leukemia or blastic phase of chronic myelogenous leukemia has shown that the MTD was 1.4 mg/m^2/course as a 7-day continuous infusion; this dose was 3- to 4-fold higher than infusions (3-day) administered for solid tumors. Treatment with 9-AC resulted in antileukemic activity (marrow hypoplasia) in 46% of the patients on day 14. The dose-limiting toxicity was severe mucositis seen in 3/6 patients treated with 1.6 mg/m^2/day. At the MTD, 3/10 patients had grade 4 mucositis and 1/0 had grade 3 diarrhea. No complete or partial remissions were observed out of 37 evaluable patients (14).

Idec has terminated its 9-AC development program due to the results of a phase II trial in 8 types of solid tumors. However, the company will continue to discuss

  CCC: 0377-8282/99

with Pharmacia & Upjohn the ongoing supply of 9-AC to support the National Cancer Institute's development program (15).

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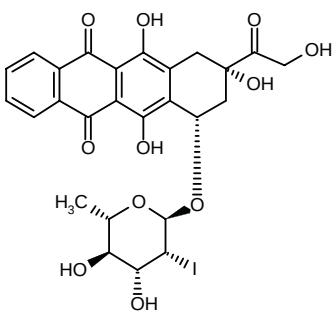
Annamycin
Annamycin LF
AR-522

Antineoplastic

EN: 110329



$C_{26}H_{25}IO_{11}$

Aronex

Results from preclinical and clinical pharmacokinetic and metabolism studies of annamycin in rats and humans have been summarized and compared to those from studies using doxorubicin and epirubicin. Although the metabolites of annamycin may be unique, metabolism of annamycin appears to be a combination of phase I and II reactions typical of doxorubicin and epirubicin (1).

Aronex has initiated a phase I/II clinical trial of annamycin in patients with refractory or relapsed

leukemia. Designed to treat a wide range of multidrug-resistant cancers without the cardiotoxicity associated with the anthracyclines currently on the market, annamycin will be tested in patients with refractory or relapsed acute myelogenous leukemia, acute lymphocytic leukemia or blast crisis of chronic myelogenous leukemia. The trial is designed to document the antitumor activity and define the maximum tolerated dose of the compound (2).

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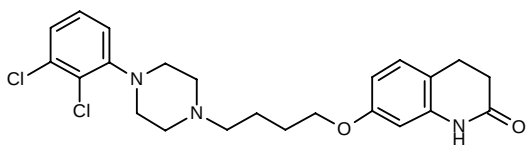
Aripiprazole

Antipsychotic

EN: 162295



$C_{23}H_{27}Cl_2N_3O_2$ **Otsuka; Bristol-Myers Squibb**

A more complete synthesis of aripiprazole has been published: The condensation of 7-hydroxy-1,2,3,4-tetrahydroquinolin-2-one (I) with 1,4-dibromobutane (II) by means of K_2CO_3 in hot DMF gives 7-(4-bromobutoxy)-1,2,3,4-tetrahydroquinolin-2-one (III), which is then condensed with 1-(2,3-dichlorophenyl)piperazine (IV) by means of NaI and triethylamine in refluxing acetonitrile (1). Scheme 1.

The results of a pharmaco-EEG study evaluating the clinical effects of aripiprazole in healthy volunteers have been published. The compound, administered at doses of 1 or 2 mg, showed an EEG profile similar to that of low-dose risperidone, consisting of an increase of fast alpha activity without a concomitant decrease in delta activity. At the dose of 4 mg, aripiprazole produced neuroleptic-like changes in the EEG (2).

Bristol-Myers Squibb and Otsuka have established a development, commercialization and collaboration agreement for aripiprazole. The new compound has a unique mechanism of action and has the potential to help expand the options for safely and effectively treating schizophrenia and possibly other forms of mental illness. Aripiprazole was discovered by Otsuka and represents a new generation of antipsychotics with a unique pharmacological profile. In extensive clinical trials, the compound appears to show efficacy with an excellent tolerability profile. Under the terms of the agreement, BMS will market and promote aripiprazole, in collaboration with Otsuka and under Otsuka's trademark, in the U.S. and the E.U. Outside these markets, excluding Japan and some Asian and Middle East countries, BMS will have an exclusive license to develop and market the drug (3).

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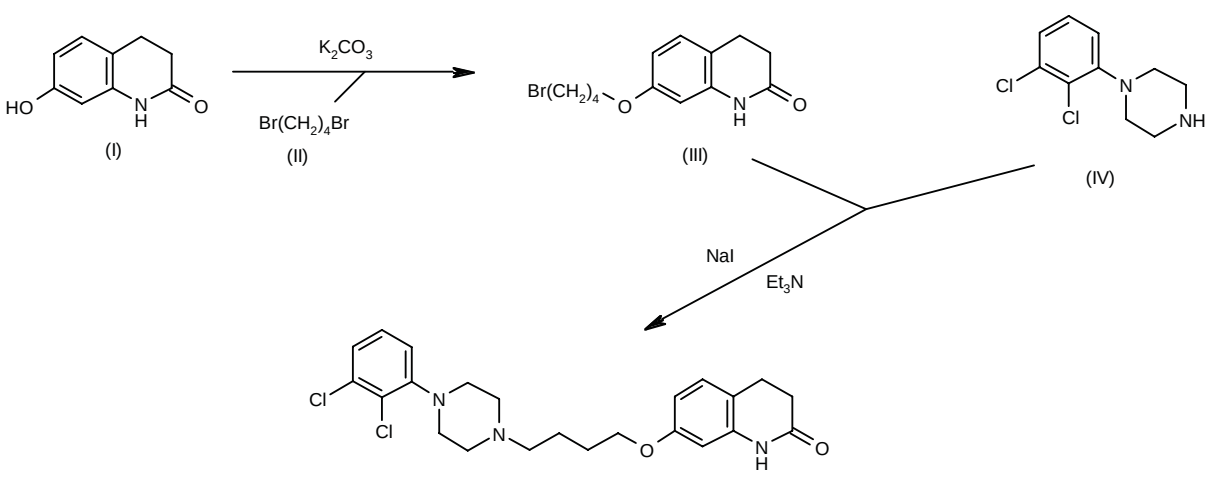
Scheme 1: Synthesis of Aripiprazole



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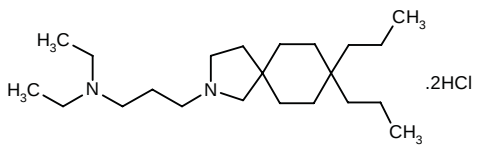
Atiprimod Hydrochloride *Immunomodulator*
SK&F-106615

EN: 203907



$C_{22}H_{44}N_2.2HCl$ **AnorMED**

The effects of atiprimod (20 mg/kg/day for 15 days) on rat alveolar macrophage function and immunocompetence was examined in *Candida albicans*-infected mice. *Ex vivo* dose-dependent candidacidal activity was observed in alveolar macrophage from treated and untreated rats at 1 h after exposure to the agent *in vitro*; superoxide dismutase inhibited atiprimod candidacidal activity. Particulate superoxide production or phagocytosis were not affected by the agent although a decrease in the ability of alveolar macrophage to concentrate acridine orange, indicating an increase in lysosomal pH, was observed. Free radical-mediated killing of *Candida* in the presence of H_2O_2, iron and iodide was also observed in a call free system (1).

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Original monograph - Drugs Fut 1995, 20: 893.

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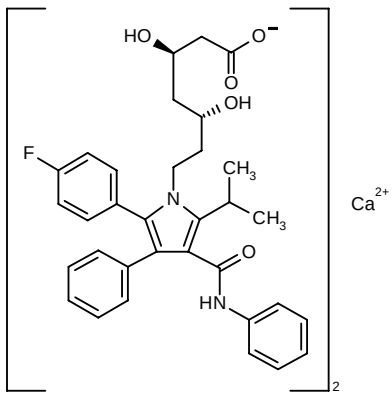
Atorvastatin Calcium *Hypolipidemic*
Lipibec® *HMG-CoA Reductase Inhibitor*
Lipitor®
Sortis®
Torvast®

EN: 180072

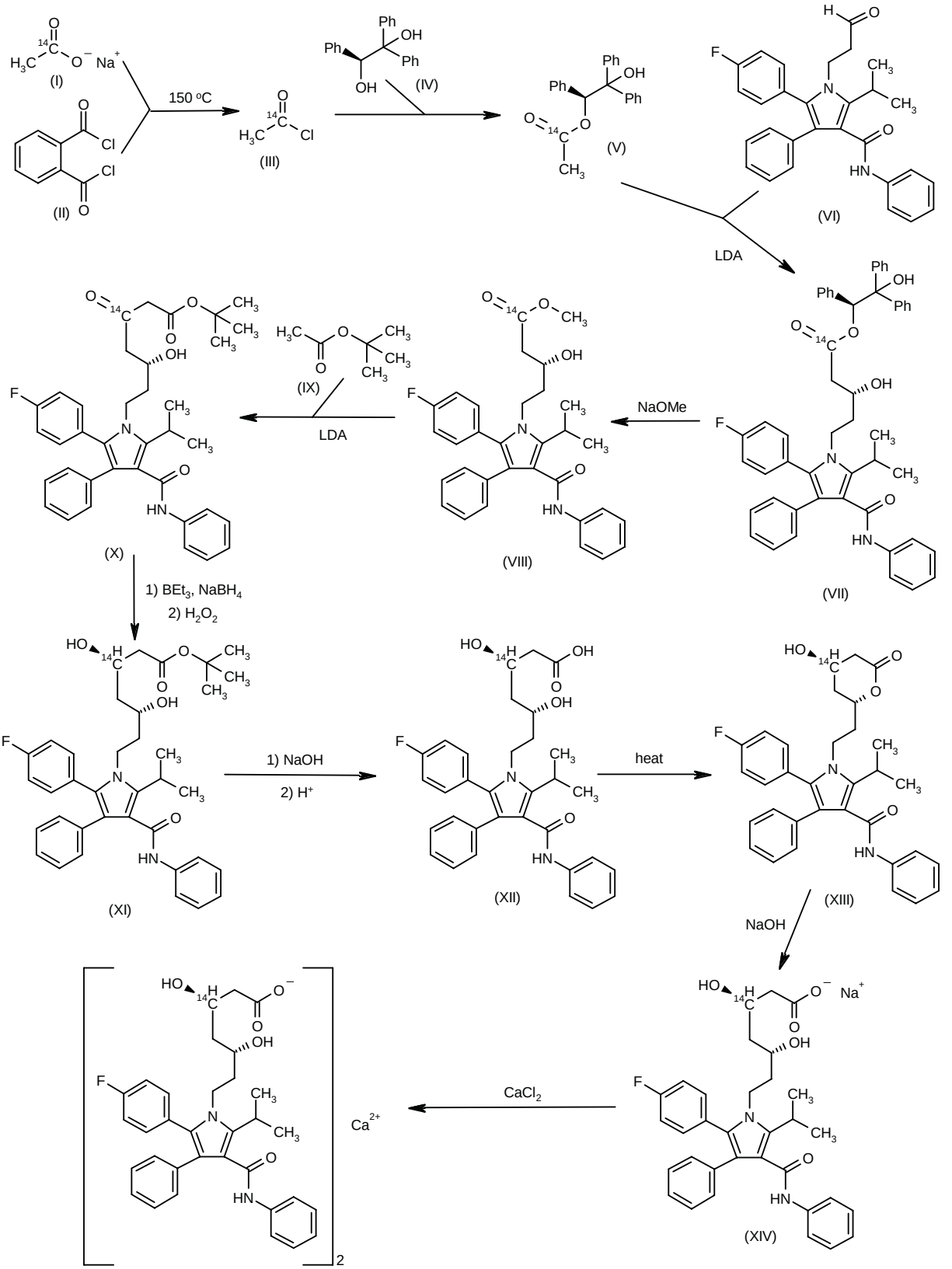


$C_{66}H_{68}CaF_2N_4O_{10}$ **Warner-Lambert; Pfizer; Yamanouchi; Syncro**

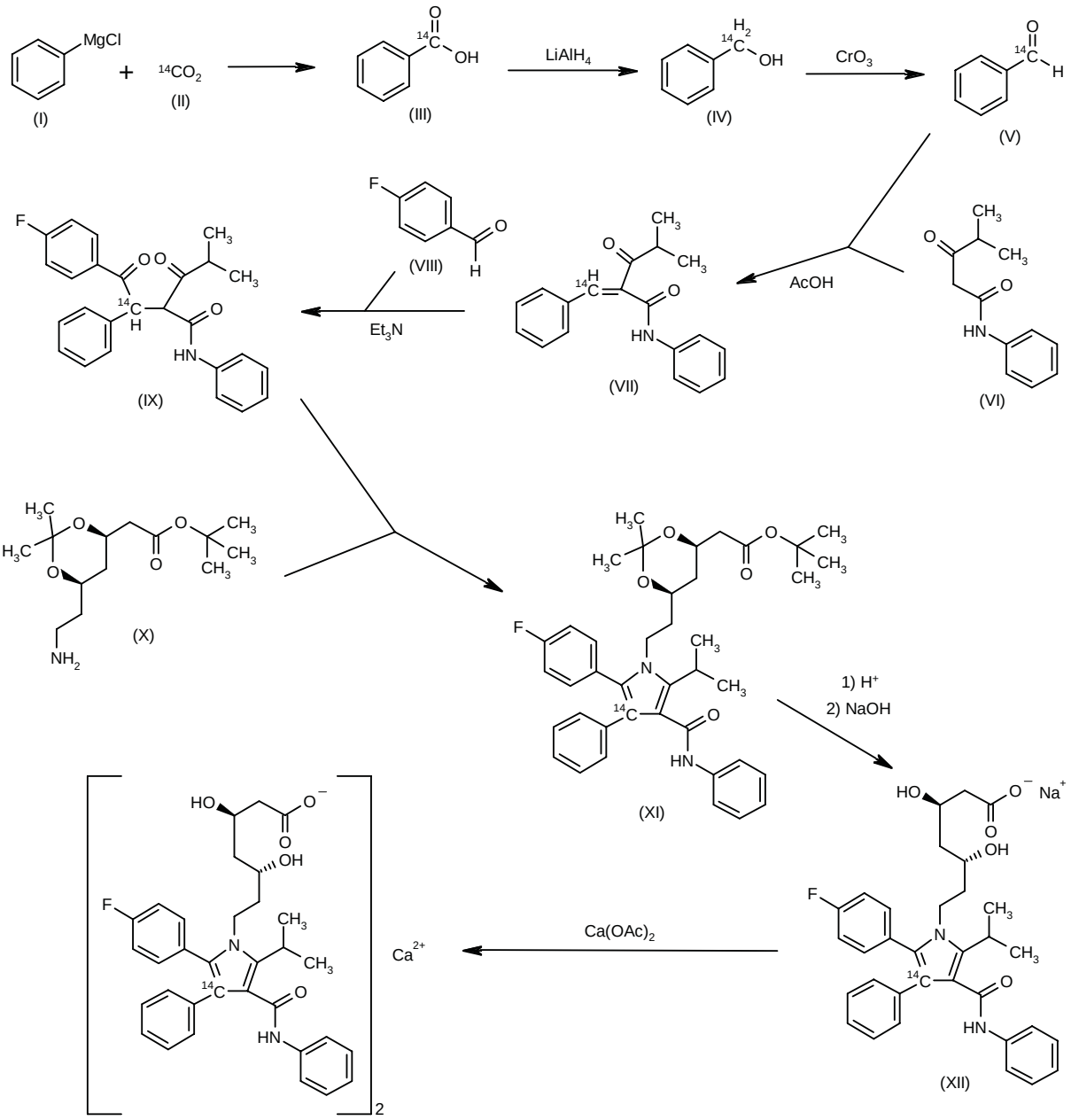
The synthesis of atorvastatin [^{14}C]-labeled on the side chain has been described: The reaction of [^{14}C]-labeled sodium acetate (I) with phthaloyl chloride (II) in refluxing xylene gives the acyl chloride (III), which is treated with 1,2,2-triphenyl-1(*S*),2-ethanediol (IV) in dichloromethane, yielding the expected monoacetate (V). The condensation of (V) with the pyrrolepropionaldehyde (VI) by means of lithium diisopropylamide (LDA) in THF affords the chiral β-hydroxyester (VII), which is transesterified with sodium methoxide in methanol, providing the corresponding methyl ester (VIII). The condensation of (VIII) with *tert*-butyl acetate (IX) by means of LDA in THF gives the β-oxo-δ-hydroxyester (X), which is regioselectively reduced to the dihydroxyester (XI) by means of BEt_3, $NaBH_4$ and H_2O_2 in THF. The hydrolysis of (XI) with NaOH in THF/water, followed by acidification yields the free acid (XII), which is heated in refluxing toluene in a Dean-Stark trap to provide lactone (XIII). The reaction of (XIII) with NaOH in THF/methanol gives the corresponding sodium salt, which is finally treated with $CaCl_2$ in the same solvent (1). Scheme 2.

The synthesis of ring-labeled [^{14}C]-atorvastatin has been described: The Grignard reaction of phenylmagnesium chloride (I) with [^{14}C]-labeled CO_2 (II) in THF/ethyl ether gives the benzoic acid (III), which is reduced with $LiAlH_4$ in ethyl ether to the benzyl alcohol (IV). The oxidation of (IV) with pyridinium dichromate affords the benzaldehyde (V), which is condensed with the isobutyrylacetamide (VI) by means of β-alanine in acetic acid, yielding a mixture of the *cis*- and *trans*-benzylidene derivatives (VII). The condensation of (VII) with 4-fluorobenzaldehyde (VIII) by means of triethylamine and a thiazolium bromide catalyst affords the 1,4-dione (IX), which is

Scheme 2: Synthesis of Side Chain-Labeled [1^{4}C]-Atorvastatin Calcium



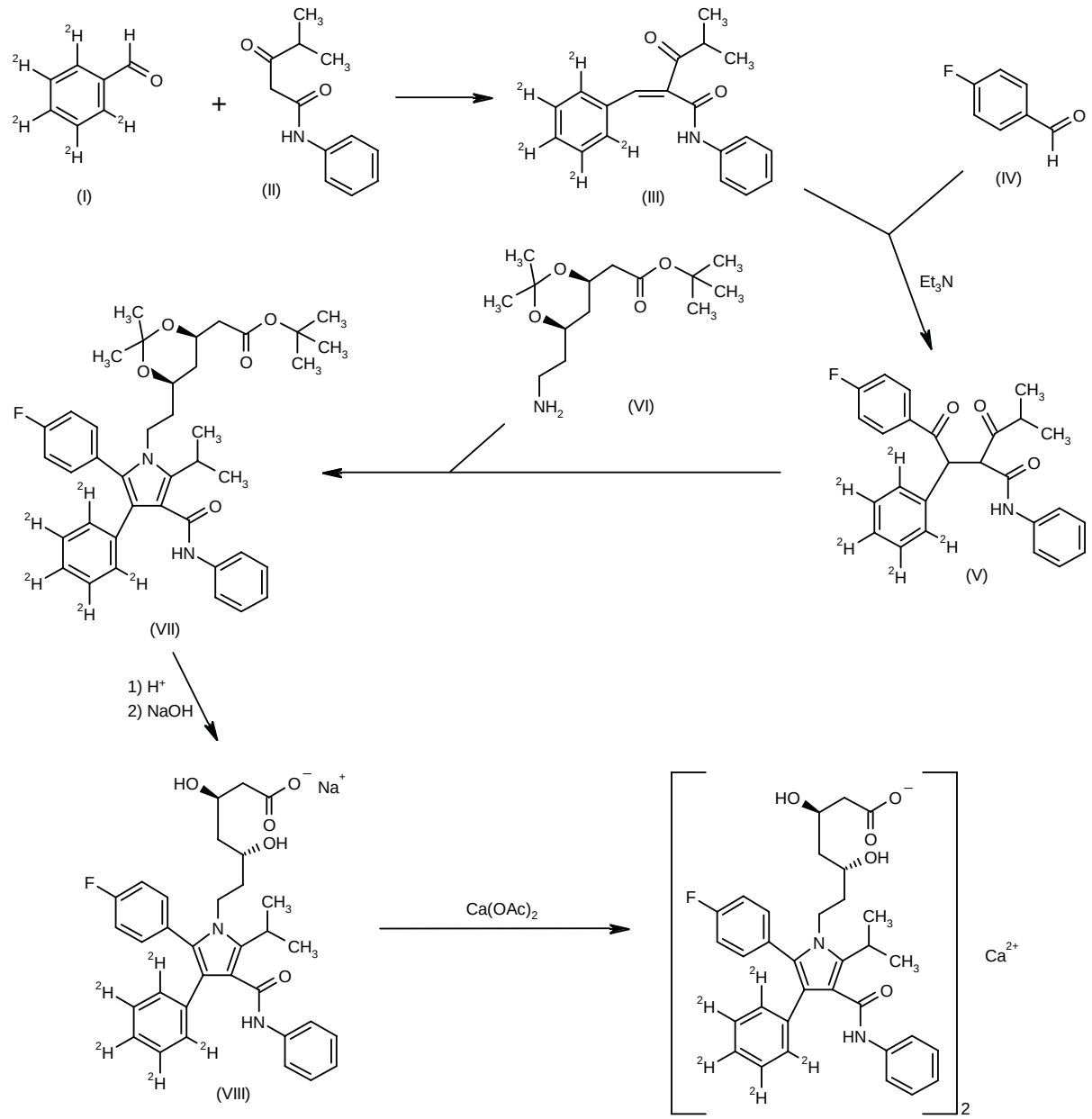
Scheme 3: Synthesis of Ring-Labeled [^{14}C]-Atorvastatin Calcium



cyclized with the chiral amino ester (X) in hot heptane/toluene/THF to provide the protected pyrroloheptanoic ester (XI). The deprotection of (XI) in acidic medium, followed by the hydrolysis of the ester group with NaOH, affords the sodium salt (XII), which is finally treated with calcium acetate in THF/water (2). Scheme 3.

The synthesis of deuterium-labeled atorvastatin has been described: The condensation of pentadeuterium-labeled benzaldehyde (I) with the isobutyrylacetamide (II) by means of β-alanine in acetic acid yields a mixture of *cis*- and *trans*-benzylidene derivatives (III). The condensation of (III) with 4-fluorobenzaldehyde (IV) by means of triethylamine and a thiazolium bromide catalyst affords the 1,4-dione (V), which is cyclized with the chiral amino ester (VI) in hot heptane/toluene/THF to provide the protected pyrroloheptanoic ester (VII). The deprotection of (VII) in acidic medium, followed by the hydrolysis of the ester group with NaOH, affords the sodium salt (VIII), which is finally treated with calcium acetate in THF/water (3). Scheme 4.

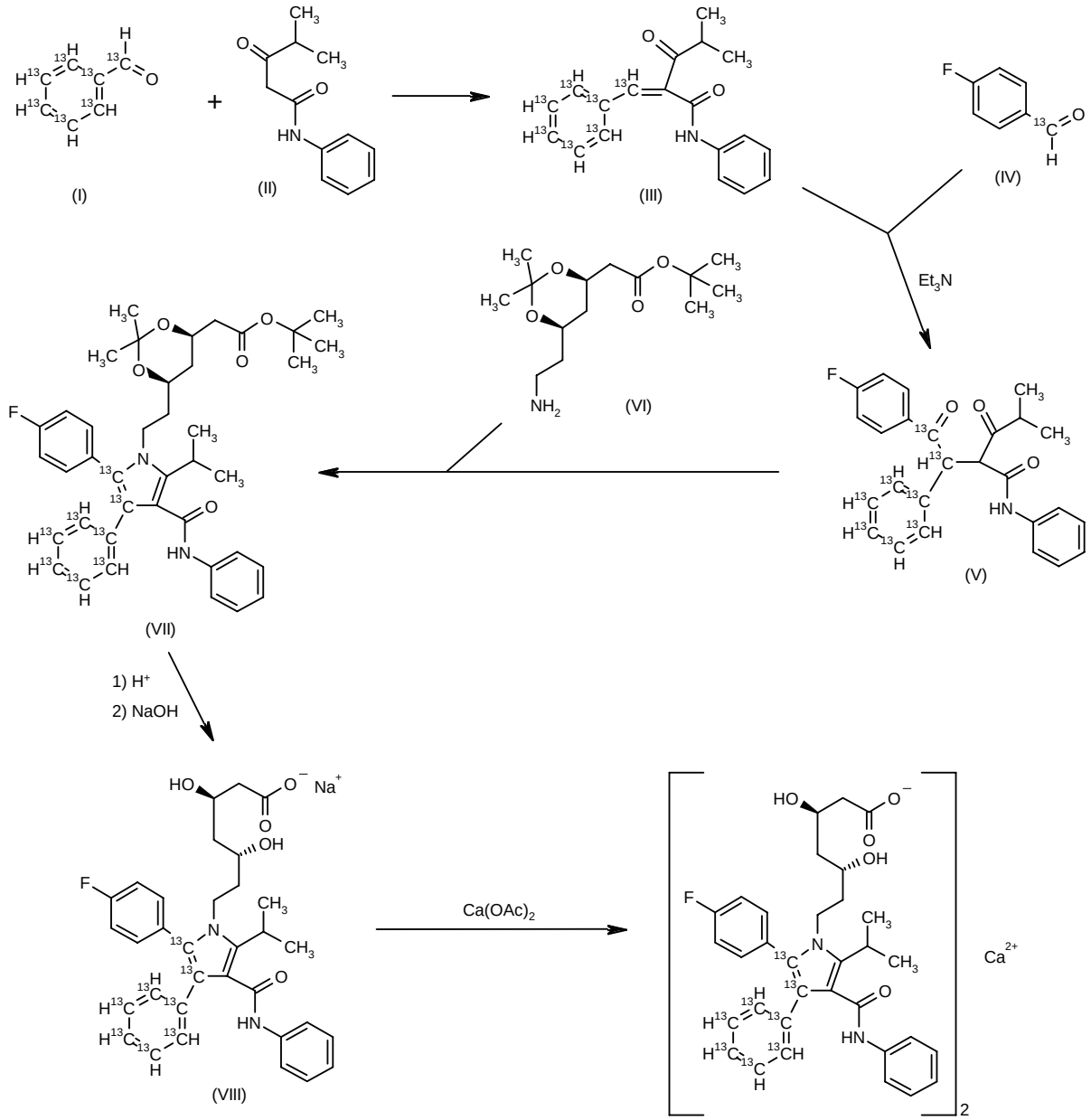
Scheme 4: Synthesis of Deuterium-Labeled Atorvastatin Calcium



The synthesis of [^{13}C]-labeled atorvastatin has been described: The condensation of hepta [^{13}C]-labeled benzaldehyde (I) with the isobutyrylacetamide (II) by means of β-alanine in acetic acid yields a mixture of *cis*- and *trans*-benzylidene derivatives (III). The condensation of (III) with carbonyl [^{13}C]-labeled 4-fluorobenzaldehyde (IV) by means of triethylamine and a thiazolium bromide catalyst affords the 1,4-dione (V), which is cyclized with the chiral amino ester (VI) in hot heptane/toluene/THF to provide the protected pyrroloheptanoic ester (VII). The deprotection of (VII) in acidic medium, followed by the hydrolysis of the ester group with NaOH, affords the sodium salt (VIII), which is finally treated with calcium acetate in THF/water (3). Scheme 5.

The synthesis of [^{13}C,^{15}N]-labeled atorvastatin has been described: The condensation of hepta [^{13}C]-labeled benzaldehyde (I) with the isobutyrylacetamide (II) by means of β-alanine in acetic acid yields a mixture of *cis*- and *trans*-benzylidene derivatives (III). The condensation

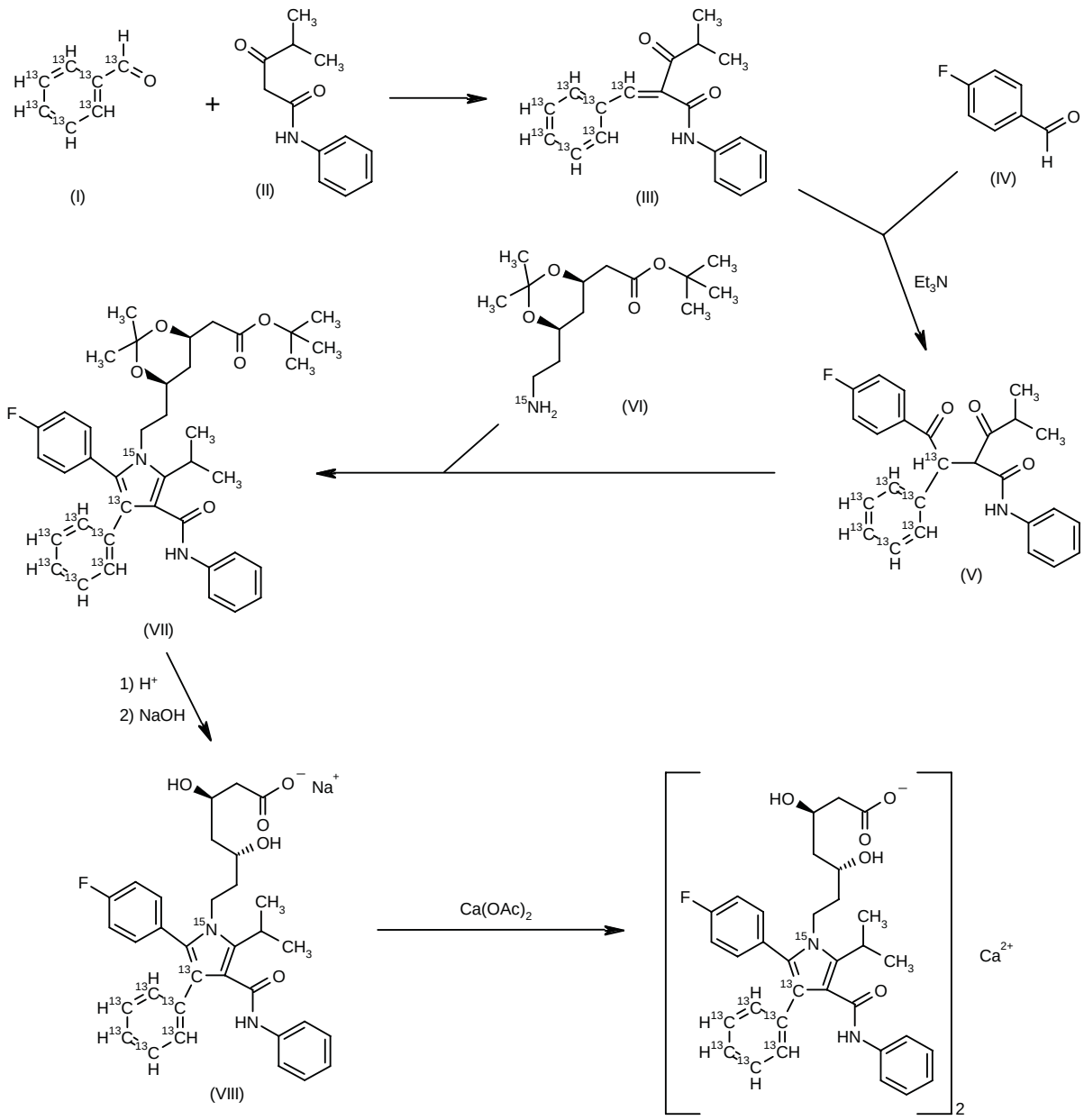
Scheme 5: Synthesis of [^{13}C]-Labeled Atorvastatin Calcium



of (III) with 4-fluorobenzaldehyde (IV) by means of triethylamine and a thiazolium bromide catalyst affords the 1,4-dione (V), which is cyclized with the chiral [^{15}N]-labeled amino ester (VI) in hot heptane/toluene/THF to provide the protected pyrroloheptanoic ester (VII). The deprotection of (VII) in acidic medium, followed of the hydrolysis of the ester group with NaOH, affords the sodium salt (VIII), which is finally treated with calcium acetate in THF/water (3). Scheme 6.

A recent study has reviewed the pharmacological effects (other than lipoprotein modulation) of the HMG-CoA reductase inhibitors atorvastatin, pravastatin, cerivastatin, simvastatin and lovastatin. All agents improved endothelium-dependent vasodilation, and vascular smooth muscle proliferation was inhibited by all agents except pravastatin, with cerivastatin exhibiting the highest potency. Atorvastatin had no effect on platelet-thrombus formation, fibrinogen levels or plasminogen activator inhibitor-1 levels (4).

Scheme 6: Synthesis of [^{13}C,^{15}N]-Labeled Atorvastatin Calcium



Yamanouchi filed for Japanese marketing approval of atorvastatin calcium for the treatment of hyperlipidemia. Clinical trials in Japan have reflected an efficacy profile similar to that in U.S. studies, in which atorvastatin consistently demonstrated efficacy superior to that of other statins (5).

Atorvastatin calcium has been launched by Syncro in Argentina under the trade name Lipibec®. The compound is supplied as coated tablets, 10 and 20 mg (6).

Warner-Lambert has signed a letter of intent with Pfizer to continue and expand their highly successful copromotion of atorvastatin calcium (Lipitor®). The companies will continue their collaboration for a total of 10 years and plan to explore potential Lipitor® line extensions and product combinations and other areas of mutual interest (7).

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  CCC: 0377-8282/99

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Brain-Derived Neurotrophic Factor

BDNF *Treatment of ALS and Neuropathies*
rhBDNF

EN: 198453

Regeneron; Amgen; Sumitomo

The effect of BDNF (0.1, 1, 10, 100 pg/ml) on the survival rate of isolated rat retinal ganglion cells was examined *in vitro* using flow cytometry. Results showed that the agent dose-dependently improved survival (1).

Results from an *in vitro* and *in vivo* study suggest that BDNF mediates glucagon secretion of pancreatic α-cells via the TrkB receptor. Immunohistochemistry using the anti-TrkB antibody showed that glucagon secretion of BDNF (10 ng/ml for 7 days)-treated isolated mouse pancreatic islets was significantly reduced (121 ± 27 *vs.* 179 ± 22 pg/islet); insulin secretion and insulin and glucagon contents of islets were unaffected. Plasma glucagon levels of mice treated for 7 days (10 mg/kg/day s.c.) were slightly less than controls (65.4 ± 22.7 *vs.* 73.4 ± 32.8 pg/ml) and plasma glucose levels tended to be greater (-26.4 ± 17.8 *vs.* -15.2 ± 20.9 mg/dl). Plasma glucose levels of wild, hetero and homo newborns of BDNF-knockout mice were < 19, 25 ± 7 and 31 ± 8 mg/dl, respectively (2).

The neuroprotective effects of BDNF were demonstrated in rat eyes injected intravitreally with NMDA or kainic acid to induce glutamate receptor-mediated neuronal death. Although intravitreal BDNF (≥ 1 mcg) did not affect the increase in glutamate levels following retinal injury, morphometric analysis showed that the agent rescued inner retinal cells from death (3).

A study using the rat model of retinal ischemia-reperfusion injury showed that intravitreal BDNF (5 μg) suppressed cell death of injured retinal ganglion cells, possibly through suppression of caspase-2 expression. Retinal ganglion cell death during ischemic-reperfusion injury was found to be related to c-Jun and caspase-2 but not caspase-1 and caspase-3 expression (4).

The protective effects of BDNF were demonstrated in a model of mild experimental glaucoma. Rats were injected with 5% Fluorogold and intraocular pressure was increased in the left eye 3 days later via cauterization. Rats were treated with 1-3 injections of BDNF (5 μg/2 μl) 5, 19 and 33 days after surgery. BDNF rescued many but not all damaged retinal ganglion cells, possibly due to increases in nitric oxide synthase which inactivates the agent (5).

The effects of BDNF (0.5 or 1 μg intravitreal) and neurotrophin-4 (0.5 μg intravitreal) were compared on the survival of axotomized retinal ganglion cells of adult cats. Both agents resulted in longer survival of ganglion cells and protected against the degeneration of β cells (6).

BDNF was shown to regulate glucose metabolism through insulin action in db/db mice. Obese mice treated with BDNF (20 mg/kg/day s.c. for 2 weeks) had significantly reduced glucose levels as compared to controls (219.8 ± 57.1 *vs.* 489.8 ± 89.3 mg/dl) and phosphorylation of the insulin receptor in muscle and liver was also observed in treated animals. In the STZ-induced diabetic mouse model, although BDNF did not reduce blood glucose, it enhanced the hypoglycemic action of insulin with levels of 196.0 ± 60.7 mg/dl obtained with combination treatment as compared to 363.5 ± 91.2, 437.6 ± 44.6 and 459.9 ± 64 mg/dl for insulin and BDNF alone and controls, respectively (7).

Recombinant human BDNF (100 μg/day) was shown to accelerate colonic but not gastric or small bowel transit at 24 and 48 h in a 6-week, randomized, double-blind, placebo-controlled trial in 40 healthy subjects. Evaluation of 30 subjects also showed an increase in stool frequency in patients treated with BDNF as compared to placebo (8).

BDNF continues to progress in clinical trials and is being developed for intrathecal and subcutaneous administration in the treatment of amyotrophic lateral sclerosis. In Japan, the product is licensed to Sumitomo (9).

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ischemia-reperfusion injury. Invest Ophthalmol Visual Sci 1999, 40(4): Abst 2533.

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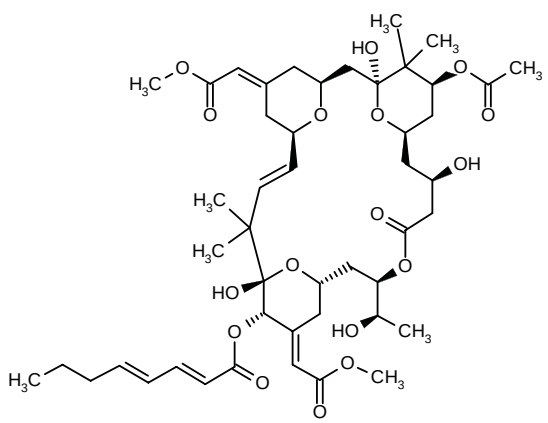
Bryostatin 1

Antineoplastic

EN: 165188



$C_{47}H_{68}O_{17}$

CRC Technology; Arizona State Univ. (US)

A study examining the compatibility and stability of bryostatin 1 infusion devices showed that bryostatin 1-PET formulation diluted (1 and 10 μg/ml) with benzyl alcohol preserved saline in polypropylene (PP) but not polyvinyl chloride (PVC) bags can be used for long-term i.v. administration. In PP bags, bryostatin 1 content when diluted with saline or preserved saline was unchanged after 28-day storage at room temperature while concentrations decreased in PVC bags. In addition, diethylhexylphthalate leakage into solution dependent on bryostatin 1 concentration was first observed on the second day of storage with PVC bags and peaked on day 6 (1).

Bryostatin 1 treatment of a human acute lymphoblastic leukemia cell line (Reh) decreased Bcl-2 mRNA expression and enhanced Bcl-2 degradation via activation of the ubiquitin pathway. Cells were incubated with bryostatin 1 (1-10 nM) for 3 h resulting in a 50% decrease in Bcl-2 protein 24 h later; after 24 h, Bcl-2 mRNA expression returned to normal. Immunoprecipitation and immunoblotting revealed that Bcl-2 was ubiquinated in bryostatin 1-treated cells leading to an 80% decrease in the protein by 120 h. Lactacystin inhibited the bryostatin 1 decrease in Bcl-2 (2).

Sixteen patients with malignant melanoma received bryostatin 25 μg/m^2/wk over 1 h for 3 courses followed by a rest week. Main toxicities were grade 2-3 myalgia, grade 2 phlebitis, fatigue and vomiting. Fourteen patients had progressive disease and 1 had stable disease for 9 months. Bryostatin is apparently ineffective in treating metastatic melanoma (3).

An ongoing, randomized phase II study examined the efficacy of bryostatin 1 given over 24 h/week x 3 (25 μg/m^2/day i.v.) or over 72 h/2 weeks (40 μg/m^2/day i.v.) with courses repeated every 4 weeks in 42 patients with melanoma. Out of the 15 evaluable patients given the 72-h infusion, 1 minor and 1 partial response were observed and out of 12 patients receiving the 24-h infusion, 1 patient had a minor response. No myelosuppression was observed. Adverse grade 3-4 toxicities in the 24- and 72-h infusion groups after 27 and 42 courses, respectively, included myalgia (74 and 98%), nausea/vomiting (52 and 17%), fatigue (44 and 71%), constipation (22 and 21%), skin rash (22 and 45%), fever (22 and 5%), headache (19 and 29%), diarrhea (15 and 19%) and anorexia (11 and 19%) (4).

Bryostatin given either as a weekly 24-h (25 μg/m^2) or a biweekly 72-h (120 μg/m^2) infusion was shown not to be effective for the treatment of advanced metastatic melanoma in a randomized phase II study in 17 patients. The 24-h infusion was better tolerated with 92% of the 12 evaluable patients achieving 90% or more of the planned dose intensity as compared to 73% of the 15 evaluable patients receiving the 72-h infusion. Three patients experienced severe side effects and 2 were removed from therapy due to toxicities in the 72-h infusion group. Myalgia was the most common adverse effect with grade 1-2 experienced by 33% in the 24-h group and 67% in addition to grade 3 (4) and grade 4 (1) in the 72-h group. Mild to moderate nausea, diarrhea and headache were observed in both groups and minimal hematological or biochemical toxicities were observed. One partial response for 24 weeks was seen in the 24-h group and 2 patients in each group had stable disease with a duration of 9-23 and 15-36 weeks with the 24-h and 72-h infusions, respectively. The study was terminated early due to the lack of required responses (5).

A phase I study examined the efficacy and tolerability of bryostatin 1 (10, 15, 20, 25 and 30 mg/m^2 as 24-h infusion) with cisplatin (50 or 75 mg/m^2 as 1-h infusion) treatment every 21 days in 17 patients with melanoma. No grade 3 or 4 toxicities or cumulative myalgia were observed. Grade 2 adverse effects observed were related to cisplatin and included nausea (5), vomiting (4), anorexia (3), musculoskeletal pain (2), fatigue (1), erythema (1), arrhythmia (1) and incoordination (1). Of 13 evaluable patients, 1 had a partial response lasting 2 months (6).

In a randomized phase II trial, the efficacy of combination therapy with bryostatin 1 and all-*trans* retinoic acid was shown in 16 patients with myelodysplastic syndromes and acute myeloid leukemia. Treatment with all-*trans* retinoic acid (75 mg/m^2 b.i.d. p.o. days 1-8 and 15-22) and bryostatin 1 (60 μg/m^2 30 min i.v. or 40 μg/m^2/day 72 h i.v.) was well tolerated with 3 patients developing shortness of breath and facial flushing 2 min into the second 30-min bryostatin 1 infusion. Minor responses were seen in 3 patients with reductions in marrow blasts and increases in ANC and platelet counts. PKCβ levels of peripheral blood mononuclear cells from patients were reduced after bryostatin 1 treatment, indicating enzyme activation (7).

A phase I study demonstrated the tolerability of weekly 1-h infusions of paclitaxel (80 mg/m^2) with escalating doses of bryostatin 1 (starting at 15 μg/m^2) 24 h later for 3-week cycles with 1 rest week in 18 patients with advanced solid tumors. Myalgia, the dose-limiting toxicity with 25 μg/m^2/week bryostatin 1 in single agent trials, was limited to grade 1 and 2 in this study even with dose escalations to 45 μg/m^2/week. Two DLTs were observed including 1 patient with chronic atrial fibrillation who developed new tachyarrhythmia with 15 μg/m^2 bryostatin 1 and another who had an ANC of 1.2 and grade 3 leukopenia despite bryostatin 1 dose reductions. The pharmacokinetics of paclitaxel were unchanged with increasing doses of bryostatin 1. A partial response in liver and nodal metastases was seen in 1 patient with recurrent esophageal adenocarcinoma and 1 minor response was observed in a pancreatic cancer patient (8).

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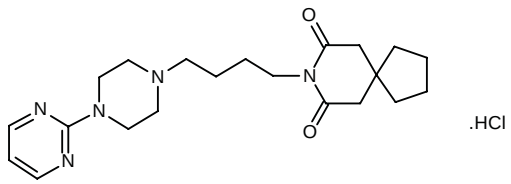
Buspirone Hydrochloride *Treatment of ADHD*
BuSpar® (transdermal)

EN: 115228



$C_{21}H_{31}N_5O_2.HCl$ **Bristol-Myers Squibb; Sano**

The tolerability and pharmacokinetics of a new transdermal patch formulation of buspirone hydrochloride (BuSpar®) and of its major metabolite (1-pyrimidinylpiperazine) were evaluated in healthy volunteers. Subjects received a 40-cm^2 patch containing 4.8 mg buspirone or placebo according to a double-blind, randomized, parallel, placebo-controlled design. Steady-state pharmacokinetics of both buspirone and its metabolite were attained on day 3, and C_{max} and AUC_{0-24} of both parent drug and metabolite increased in a dose-proportional manner. Plasma parent drug and metabolite concentrations declined upon removal of the patches, giving $t_{1/2}$ values of 7 and 14 h, respectively. The patches were safe and well tolerated by healthy subjects, and a dose of 120 cm^2 was selected for phase II and phase III studies (1).

Preliminary results have been reported from the first phase III trials on transdermal buspirone for anxiety and depression, under development by Sano in collaboration with Bristol-Myers Squibb. In the anxiety trial in 170 patients, no statistically significant differences were observed between active treatment and placebo. Transdermal buspirone was associated with minimal side effects. In the depression trial in 158 patients, changes in several parameters after 4 weeks of treatment showed nearly statistically significant differences between active treatment and placebo, and at 8 weeks, statistically significant improvement was observed in one of the patient-rated scales after active treatment (2, 3).

The FDA has notified Sano that a single, adequate and well-controlled trial is sufficient to establish the effectiveness of the transdermal buspirone patch for the treatment of anxiety. Normally, the FDA requires more than one study to establish the efficacy of a drug. The transdermal formulation is currently in phase III for the treatment of anxiety and attention deficit hyperactivity disorder (ADHD) (4, 5).

1. Fulmor, I.E. et al. *Tolerability and pharmacokinetics of fixed doses of buspirone administered transdermally to healthy subjects.* 100th Annu Meet Amer Soc Clin Pharmacol Ther (March 18-20, San Antonio) 1999, Abst PII-83.

2. *BMS, Sano to collaborate on transdermal BuSpar development.* DailyDrugNews.com (Daily Essentials) Aug 30, 1996.

3. *Preliminary analysis of pivotal trials on transdermal buspirone announced.* DailyDrugNews.com (Daily Essentials) Jan 29, 1997.

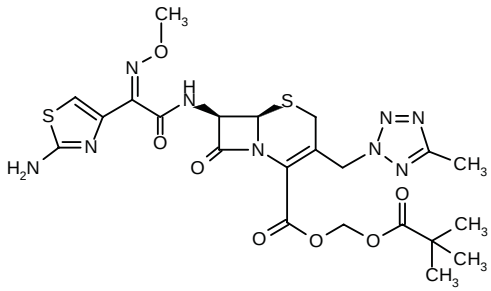
4. *Transdermal buspirone pivotal trials.* DailyDrugNews.com (Daily Essentials) Feb 21, 1997.

5. *Single efficacy trial for transdermal buspirone required by FDA.* DailyDrugNews.com (Daily Essentials) June 25, 1997.

Original monograph - Drugs Fut 1976, 1: 409.

Cefteram Pivoxil *Cephalosporin*
Tomiron®

EN: 100078



$C_{22}H_{27}N_9O_7S_2$ **Toyama; Showa**

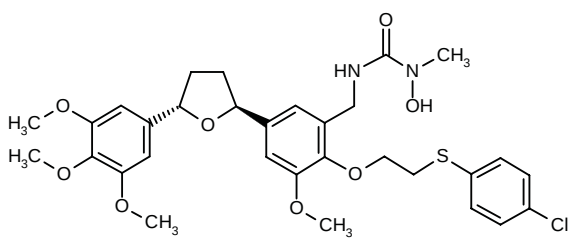
Toyama and Showa have signed a comarketing agreement for cefteram pivoxil (Tomiron[R]) as a treatment for periodontitis. The compound gained approval for this indication in 1991 (1).

1. *Toyama, Showa expand periodontis collaboration.* DailyDrugNews.com (Daily Essentials) Jan 14, 1999.

Original monograph - Drugs Fut 1986, 11: 732.

CMI-392 *Antipsoriatic*
Treatment of Atopic Dermatitis

EN: 206965



$C_{31}H_{37}ClN_2O_8S$ **LeukoSite**

LeukoSite signed a definitive agreement to acquire CytoMed, Inc. and two of its compounds, one of which is CMI-392. CMI-392 is formulated as a topical product that blocks two biochemical pathways implicated in inflammation. The compound is currently undergoing phase II studies in adults with psoriasis and in children with atopic dermatitis (1).

1. *LeukoSite acquires CytoMed programs in asthma and inflammation.* DailyDrugNews.com (Daily Essentials) Jan 20, 1999.

Original monograph - Drugs Fut 1996, 21: 933.

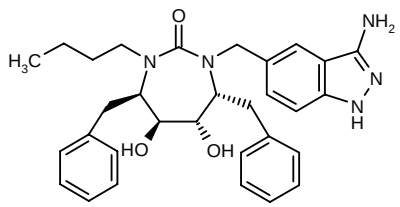
Additional Reference

Chorghade, M.S. et al. *Process improvements in the commerical production of CMI-392.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst ORGN 017.

DMP-851

Anti-HIV

EN: 249846



$C_{31}H_{37}N_5O_3$ **DuPont Pharm.**

The synthesis of DMP-851 has been performed as follows: The oxidation of *N*-(benzyloxycarbonyl)-D-phenylalaninol (I) with NaOCl catalyzed by 2,2,6,6-tetramethyl-1-piperidinyloxyl free radical (TEMPO) and NaBr in water gives the corresponding aldehyde (II), which is dimerized by means of Coulton's reagent (VCl_3/Zn/THF) to the pinacol (III). The silylation of (III) with triethylsilyl chloride and imidazole in DMF yields the silylated diol (IV), which is submitted to hydrogenolysis with H_2 over Pd/C in toluene, affording the free diamine (V). The cyclization of (V) with carbonyldiimidazole (CDI) in toluene followed by desilylation with 1N HCl gives (4*R*,5*S*,6*S*,7*R*)-4,7-dibenzyl-5,6-dihydroxyperhydro-1,3-diazepin-2-one (VI), which is treated with 2,2-dimethoxypropane (VII) and *p*-toluenesulfonic acid in DMF, yielding the corresponding acetonide (VIII) [Pierce, M.E. *et al.* J Org Chem 1996, 61(2): 444]. The methylation of (VIII) with methyl triflate in refluxing dichloroethane affords the cyclic isourea (IX), which is alkylated with butyl iodide/NaH in DMF, giving the *N*-monobutyl derivative (X). A new alkylation of (X) with 3-cyano-4-fluorobenzyl bromide (XI) in refluxing acetonitrile yields the disubstituted cyclic urea (XII), which is finally treated with hydrazine in refluxing butanol to generate the indazole ring and treated with HCl in methanol to eliminate the acetonide group (1, 2). Scheme 7.

1. Rodgers, J.D., Lam, P.Y.-S., Johnson, B.L. et al. *Design and selection of DMP 850 and DMP 851: The next generation of cyclic urea HIV protease inhibitors.* Chem Biol 1998, 5(10): 597

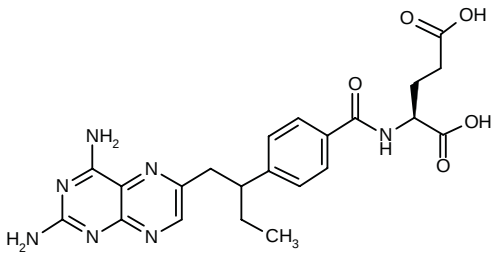
2. Rodgers, J.D., Lam, P.Y.-S. (The DuPont Pharmaceutical Co.). *(4R,5S,6S,7R)-Hexahydro-1-[5-(3-aminoindazole)methyl]-3-butyl- 5,6-dihydroxy-4,7-bis[phenylmethyl]-2H-1,3-diazepin-2-one, its preparation and its use as HIV protease inhibitors.* WO 9820009.

Original monograph - Drugs Fut 1998, 23: 987.

Edatrexate

Antineoplastic

EN: 108334



$C_{22}H_{25}N_7O_5$ **SRI**

The toxicity and maximum tolerated dose of edatrexate in combination with carboplatin were assessed in 46 chemotherapy-naive patients with advanced solid tumors. The combination was safe and well tolerated. Probably due to prophylactic ice chip cryotherapy, no dose-limiting mucositis was observed, thus permitting dose escalation of edatrexate. The phase II recommended dose of this combination is 110 mg/m^2 edatrexate with ice chip cryotherapy (1).

A phase II study of edatrexate (80 mg/m^2/week for 4 weeks every 5 weeks) in 25 patients with relapsed or refractory germ cell tumors showed that the agent had no antitumor activity. Of the 23 evaluable patients, 56% had grade 3-4 toxicities including stomatitis and malaise/fatigue/lethargy and 2 patients had grade 4 anemia and anemia and thrombocytopenia, respectively (2).

1. Edelman, M.J. et al. *Phase I trial of edatrexate plus carboplatin in advanced solid tumors: Amelioration of dose-limiting mucositis by ice chip cryotherapy.* Invest New Drugs 1998, 16(1): 69.

2. Meyers, F.J. et al. *Phase II trial of edatrexate in relapsed or refractory germ cell tumors: A Southwest Oncology Group study (SWOG 9124).* Invest New Drugs 1999, 16(4): 347.

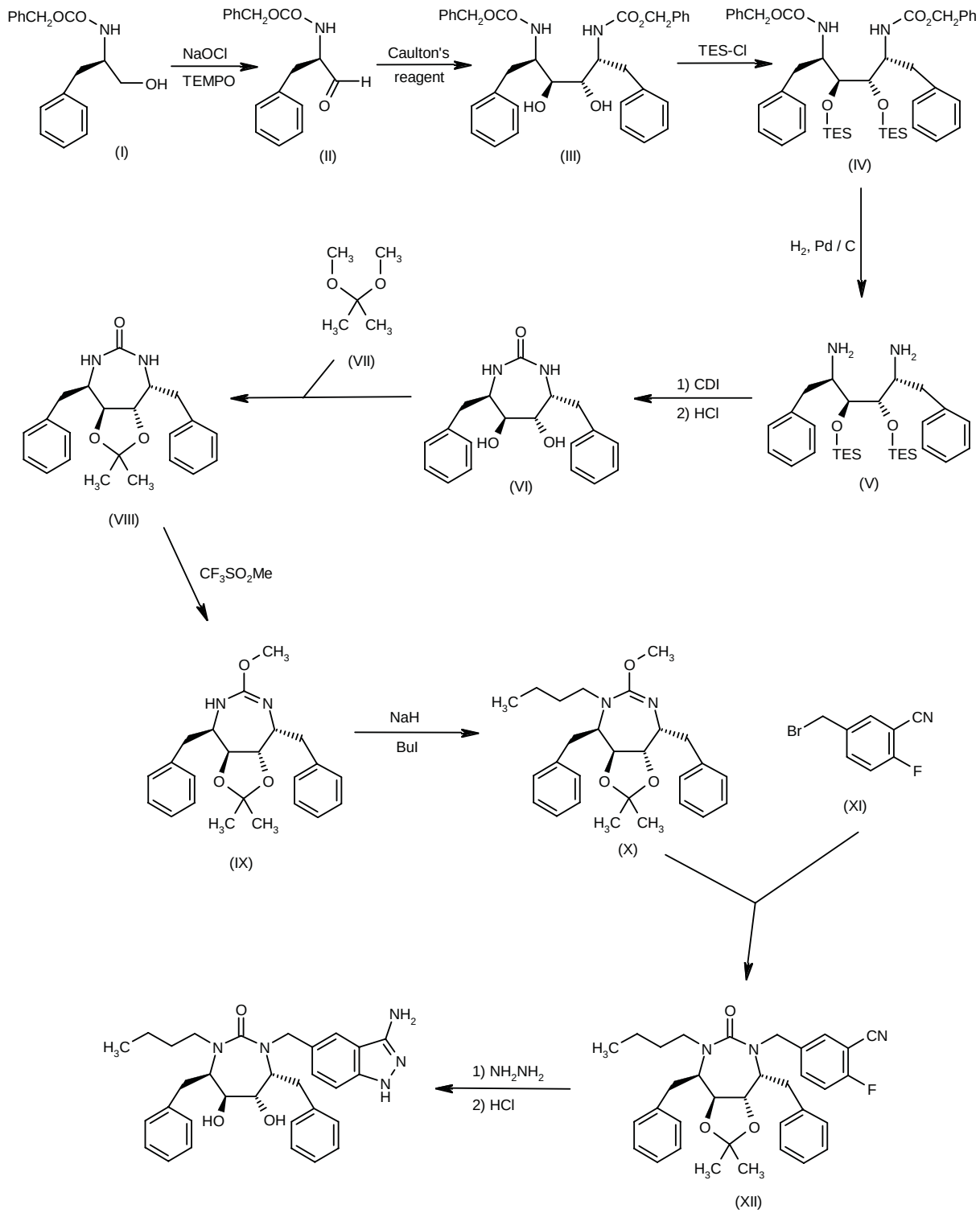
Original monograph - Drugs Fut 1989, 14: 849.

Additional References

D'Andrea, G. et al. *Phase I study of escalating doses of edatrexate in combination with placlitaxel in patients with metastatic breast cancer.* Clin Cancer Res 1999, 5(2): 275.

Rigas, J.R. et al. *Phase I study of the sequential administration of edatrexate and paclitaxel in patients with advanced solid tumors.* Ann Oncol 1999, 10(5): 601.

Scheme 7: Synthesis of DMP-851



  CCC: 0377-8282/99

Etanercept
Enbrel®
TNFR:Fc
TNR-001

Antiarthritic
TNF-α Antagonist

EN: 213242

Immunex; Wyeth-Ayerst

Results of a double-blind, randomized, placebo-controlled, multidose phase I safety study in 47 heart failure patients demonstrated that etanercept was well tolerated and the incidence of adverse events was similar in all treatment groups. The 47 patients were NYHA class III-IV and were randomized to be treated for 3 months with twice-weekly injections of either etanercept 5 or 12 mg/m^2 or placebo. At 3 months, measurements of clinical activity suggested consistent improvement for patients on active drug in NYHA classification, left ventricular ejection fraction, quality of life and clinical composite score. In addition, there appeared to be a positive dose response in each of the categories (1).

In a 24-week randomized, double-blind, placebo-controlled study, 89 rheumatoid arthritis (RA) patients receiving methotrexate (10-25 mg/week) were given etanercept (25 mg twice weekly s.c.) or placebo. Treatment was well tolerated with only mild injection site reactions attributed to etanercept. Rapid and sustained improvement was observed with treatment in 71% and 39% of the etanercept-treated patients compared to 27% and 3% in the placebo group meeting ACR criteria for 20% and 50% improvement, respectively (2).

In a multicenter, double-blind study, 234 patients suffering from RA for a mean of 11.5 years were randomized to etanercept (10 or 25 mg s.c. injection) twice weekly or placebo. A significant increase in the 20% and 50% ACR response rates was observed in the active group as compared to placebo. The drug was generally well tolerated with the most common side effects being mild injection site reactions and upper respiratory symptoms (3).

The long-term (up to 2 years) safety and efficacy of etanercept (25 mg twice/week s.c.) were examined in an open-label study in 105 patients with active RA who previously failed therapy with 1-4 DMARDs; oral corticosteroid (up to 10 mg/day) and/or oral analgesic therapy was permitted. Adverse effects were as expected and incidence of mild injection site reactions was low. No increase in malignancies or new autoimmune diseases were observed. Rapid clinical response was observed within 2 weeks and was sustained with treatment. Improvements in Paulus 50% and 70% responses, tender and swollen joint count, patients and physician global assessments, morning stiffness and CRP at 24 months were observed in 65, 39, 87, 84, 50, 67, 83 and 62% of treated patients, respectively (4).

Twice-weekly treatment with etanercept (10 or 25 mg s.c.) for 6 months did not have any adverse effects on immunocompetence, based on several indicators of immune function, in a subgroup of 49 patients participating in a phase III trial (5).

A placebo-controlled phase III trial in 234 patients failing on 1-4 DMARDs has compared etanercept 10 and 25 mg in terms of improvements in physical functioning and well-being. Both doses were statistically superior to placebo for all outcomes (6).

Based on findings obtained in 2 multicenter, randomized, placebo-controlled, double-blind trials in patients with active RA, a clear dose-response relationship was observed with etanercept (0.25, 2 and 16 mg/m^2 and 10 and 25 mg). Based on 3-month ACR response data, the dose of 25 mg s.c. twice weekly was considered to be optimum for the treatment of RA (7).

The efficacy of etanercept (10, 20, 25 or 50 mg/week) for the treatment of RA was assessed by ultrasonographic measurement in 13 drug-treated patients and 6 patients given placebo. Significant decreases in ESR, Health Assessment Questionnaire, VAS and physician and patient global assessment were observed in etanercept-treated patients. The ratios of pulsativity and resistivity indices significantly increased by 91% and 27%, respectively, indicating increased peripheral resistance in the synovium and regressed inflammatory state with treatment (8).

The efficacy and safety of etanercept have been established in elderly (> 65 years) patients, who represent a significant proportion of RA sufferers. Improvements in disease activity among elderly patients were consistent with those seen in younger patients, and the safety profile was also favorable in this population. 20% and 50% ACR responses were obtained in 48% and 39%, respectively, of younger patients at the highest dose level, and in 63% and 55% of elderly patients, respectively, at the same dose. Mild injection-site reactions were the most frequently reported side effect in both age groups (9).

Sixty-nine patients (aged 4-17 years) with polyarticular course juvenile RA were enrolled in a 2-part safety and efficacy study. During the first part of the trial, open-label etanercept (0.4 mg/kg s.c.) was administered twice weekly for 90 days. A single NSAID and low-dose prednisone were also permitted. At the end of the treatment period, 51 patients (74%) met the clinical response criteria, defined as at least 30% improvement in at least 3 of 6 JRA core set variables and no more than 1 variable worsening by 30% or more. During the second part of the study, the 51 responding patients were randomized to treatment with the same dose of etanercept or placebo for a period of 4 months or until disease flare. In the active treatment group, the average time to symptom worsening was 116 days compared to just 28 days for patients on placebo. Overall, 80% of the etanercept group had at least 30% improvements in disease activity and impact, and more than 40% had at least 70% improvements.

Injection-site reactions and mild to moderate upper respiratory tract infections were the most frequent side effects but did not result in discontinuation of the study drug (10).

In 2 double-blind, multicenter trials, 80 patients with severe RA refractory to multiple previous DMARD treatments were administered TNF-55-IgG1 (40-940 mg cumulative). In 11 patients who continued therapy for 3 years, there was an 81% reduction in swollen joint count, less morning stiffness, less pain and a reduction in steroids. Overall, the drug was safe and effective for long-term treatment in this indication (11).

Etanercept (25 mg s.c. twice/week for up to 1 year) was shown to be well tolerated and safe in an open-label ongoing trial in 106 patients with active RA; concurrent NSAID but not DMARD therapy was allowed. At 2 weeks and 12 months, 70% and 91% of the patients showed 20% improvement in tender joint count and 57% and 91% had improved swollen joint counts. No antibodies to etanercept were detected and adverse effects were as expected. Infrequent mild injection-site reactions were observed (12).

The Wyeth-Ayerst division of American Home Products has submitted an MAA to the European Medicines Evaluation Agency (EMEA) for etanercept (Enbrel®) for the treatment of active RA. The MAA submission is based on phase III clinical data demonstrating a marked reduction in the number of painful and swollen joints in etanercept-treated patients with severe disease failing to respond to conventional therapies; measurements of health-related quality of life, including functionality, mental health and vitality, also improved with drug treatment (13).

Etanercept (Enbrel®) has been approved for marketing in the U.S. The drug is indicated for the reduction in signs and symptoms of moderately to severely active RA in patients who have an inadequate response to one or more DMARDs, and can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone. Immunex and Wyeth-Ayerst will market the drug in North America and other Wyeth-Ayerst affiliates will market it elsewhere. Enbrel™ is supplied as sterile lyophilized powder for reconstitution and parenteral (s.c.) administration in single-use vials containing 25 mg etanercept (14).

The FDA has issued a new warning about safety concerns associated with the use of Enbrel®. New postmarketing reports indicate that certain patients receiving the drug have developed serious infections, including sepsis, and that several of these patients have died from the infections. Immunex is alerting physicians to the new safety concerns, reminding them of the current label warning and informing them that the labeling has been revised to incorporate the new information. The warning related to sepsis has been expanded to include patients with any active infection, including chronic or localized infections. In addition, it is now recommended that patients who develop a new infection while being treated with the drug be closely monitored. It is further recommended that physicians exercise caution when considering prescribing Enbrel® to patients with a history of recurring infections or with underlying conditions such as advanced or poorly controlled diabetes that may predispose them to infection. The FDA has requested that Immunex perform additional studies to assess the risk of serious infection related to Enbrel® therapy (15).

Positive results have been reported in early, active RA for etanercept. In a phase III pivotal study in 633 RA patients with early, active disease, etanercept was compared to methotrexate using 2 primary endpoints: 1) structural damage to joints, measured over a 1-year period using the Modified Sharp Scoring Method and 2) the signs and symptoms of RA, evaluated by percent improvement over 6 months. All of the patients in the study had RA for less than 3 years and had never been treated with methotrexate. The participants were randomized to etanercept (10 or 25 mg twice/week s.c.), methotrexate (up to 20 mg once/week p.o.) or placebo for 12 months. Treatment with etanercept was found to slow disease progression and reduce signs and symptoms. Mild to moderate reactions at the site of injection were the most common side effects reported. The data from this study have not yet been reviewed by the FDA but are included as part of an application submitted for regulatory approval (16, 17).

The FDA has approved Enbrel® in the U.S. for the treatment of moderately to severely active polyarticular course juvenile RA in patients who show inadequate response to one or more DMARDs, an indication for which the medication has also received orphan drug designation. The dose of Enbrel® for juvenile RA patients is 0.4 mg/kg, with a maximum dose of 25 mg, administered twice weekly as s.c. injections 72-96 h apart (18).

Genentech and Immunex have signed a license agreement granting rights to Immunex under Genentech's immunoadhesin patent portfolio for Enbrel®. Immunex will pay Genentech an initial license fee and royalties on sales of Enbrel® in exchange for a worldwide, coexclusive license covering p75TNFR:Fc fusion proteins. Enbrel® is the first product that uses immunoadhesin technology to be approved by the FDA for medical use (19).

1. Bozkurt, B. et al. *Results of a multidose phase I trial with tumor necrosis factor receptor (p75) fusion protein (etanercept) in patients with heart failure.* J Am Coll Cardiol 1999, 33(2, Suppl. A): 184A.

2. Weinblatt, M.E., Kremer, J.M., Bankhurst, A.D., Bulpitt, K.J., Fleischmann, R.M., Fox, R.I., Jackson, C.G., Lange, M., Burge, D.J. *A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate.* New Engl J Med 1999, 340(4): 253.

3. Moreland, L.W., Schiff, M.H., Baumgartner, S.W. et al. *Phase III trial of DMARD failing rheumatoid arthritis patients with TNF receptor p75 Fc fusion protein (TNFR:Fc, Enbrel™).* J Invest Med 1998, 46(3): 228A.

  CCC: 0377-8282/99

4. Moreland, L.W. et al. *Long-term safety and efficacy of etanercept (Enbrel™) in DMARD refractory rheumatoid arthritis (RA).* 14th Eur Leag Against Rheum Congr (June 6-11, Glasgow) 1999, Abst 409.

5. Moreland, L.W. et al. *Effects of TNF receptor (p75) fusion protein (TNFR:Fc; Enbrel™) on immune function.* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 158.

6. Moreland, L. et al. *Functioning and well-being of DMARD-failed rheumatoid arthritis in patients receiving p75 TNFR:Fc (Enbrel™).* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 159.

7. Moreland, L.W. et al. *Optimal dose of TNF receptor p75 Fc fusion protein (TNFR:Fc, Enbrel™).* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 157.

8. Rogind, H. et al. *Ultrasonographic changes in relation to clinical observations after treatment of rheumatoid arthritis (RA) with Enbrel™ (TNFα receptor, TNR).* 14th Eur Leag Against Rheum Congr (June 6-11, Glasgow) 1999, Abst 410.

9. Baumgartner, S.W. et al. *Response of elderly patients to TNF receptor p75 Fc fusion protein (TNFR:Fc; Enbrel™).* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 160.

10. Garrison, L. et al. *Safety and efficacy of tumor necrosis factor receptor p75 Fc fusion protein (TNFR:Fc; Enbrel™) in polyarticular course juvenile rheumatoid arthritis.* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 584.

11. Sander, O., Rau, R. *Treatment of refractory rheumatoid arthritis with a tumor necrosis factor α receptor fusion protein (TNFR55-IgG1) - A monocentric observation in 80 patients.* Z Rheumatol 1998, 57(5): 307.

12. Moreland, L.W., Baumgartner, S.W., Tindall, E.A. et al. *Longterm treatment of DMARD failing rheumatoid arthritis patients with TNF receptor p75 Fc fusion protein (TNFR:Fc; Enbrel™).* J Invest Med 1998, 46(3): 229A.

13. *European filing announced for Enbrel.* DailyDrugNews.com (Daily Essentials) Nov 11, 1998.

14. *FDA approves, Immunex launches breakthrough treatment for RA.* DailyDrugNews.com (Daily Essentials) Nov 3, 1998.

15. *Enbrel warning related to infections issued by FDA and Immunex.* DailyDrugNews.com (Daily Essentials) May 13, 1999.

16. *Enbrel shows positive results in early, active RA.* DailyDrugNews.com (Daily Essentials) May 18, 1999.

17. *New label sought for Enbrel in early, active RA.* DailyDrugNews.com (Daily Essentials) July 16, 1999.

18. *FDA approves Enbrel for JRA.* DailyDrugNews.com (Daily Essentials) June 2, 1999.

19. *Genentech and Immunex reach license agreement for immunoadhesin technology.* DailyDrugNews.com (Daily Essentials) June 10, 1999.

Original monograph - Drugs Fut 1998, 23: 951.

Additional References

Goldenberg, M.M. *Etanercept, a novel drug for the treatment of patients with severe, active rheumatoid arthritis.* Clin Ther 1999, 21(1): 75.

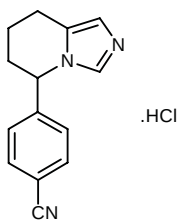
Keystone, E.C. *The role of tumor necrosis factor antagonism in clinical practice.* J Rheumatol 1999, 26(Suppl. 57): 22.

Moreland, L.W. *Inhibitors of tumor necrosis factor for rheumatoid arthritis.* J Rheumatol 1999, 26(Suppl. 57): 7.

Moreland, L.W. et al. *Etanercept therapy in rheumatoid arthritis - A randomized, controlled trial.* Ann Intern Med 1999, 130(6): 478.

Fadrozole Hydrochloride *Antineoplastic*
Arensin®
Afema®

EN: 151483



$C_{14}H_{13}N_3.HCl$ **Novartis**

The synthesis of [^{14}C]-fadrozole hydrochloride has been described: The reaction of 4-bromotoluene (I) with [^{14}C]-copper cyanide in hot DMF gives [^{14}C]-4-methylbenzonitrile (II), which is brominated with *N*-bromosuccinimide (NBS) and benzoyl peroxide/hυ in CCl_4 to yield the corresponding bromomethyl derivative (III). The condensation of (III) with *N,N*-dimethyl-4-[3-(trimethylsilyloxy)-propyl]imidazole-1-carboxamide (IV) by means of ammonia, followed by desilylation with HCl, affords labeled 4-[5-(3-hydroxypropyl)imidazol-1-ylmethyl]benzonitrile (V). The reaction of (V) with $SOCl_2$ in dichloromethane gives the corresponding chloropropyl derivative (VI), which is finally cyclized by means of potassium *tert*-butoxide in THF and treated with dry HCl in ethanol/ethyl acetate to obtain the corresponding hydrochloride (1). Scheme 8.

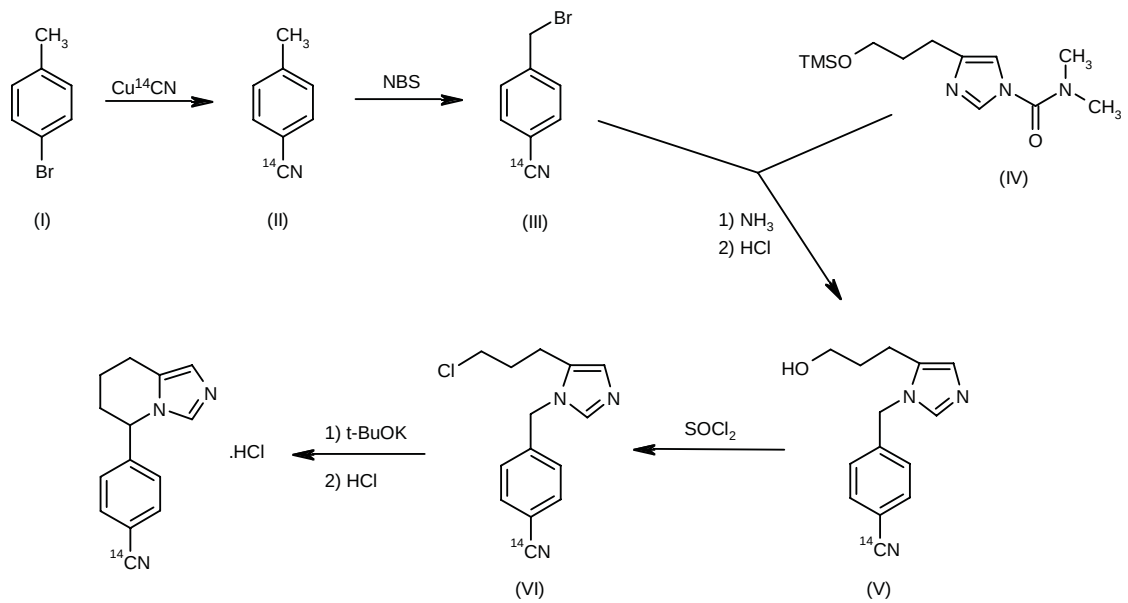
1. Markus, B., Allentoff, A.J., Desai, M., Chaudhuri, N.K., Duelfer, T. *Synthesis of ^{14}C-labelled CGS 16949A (fadrozole HCl), a potent aromatase inhibitor.* J Label Compd Radiopharm 1997, 39(11): 885.

Original monograph - Drugs Fut 1989, 14: 843.

Additional Reference

Allentoff, A.J. et al. *Palladium-catalyzed aryl cynations in radiosynthesis: Synthesis of ^{14}C-labeled fadrozole, a potent aromatase inhibitor.* 218th ACS Natl Meet (Aug 22-26, New Orleans) 1999, Abst MEDI 49.

Scheme 8: Synthesis of [^{14}C]-Fadrozole Hydrochloride

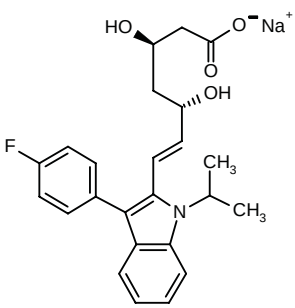


Fluvastatin Sodium

Lescol®
Canef®

Hypolipidemic
HMG-CoA Reductase Inhibitor

EN: 129568



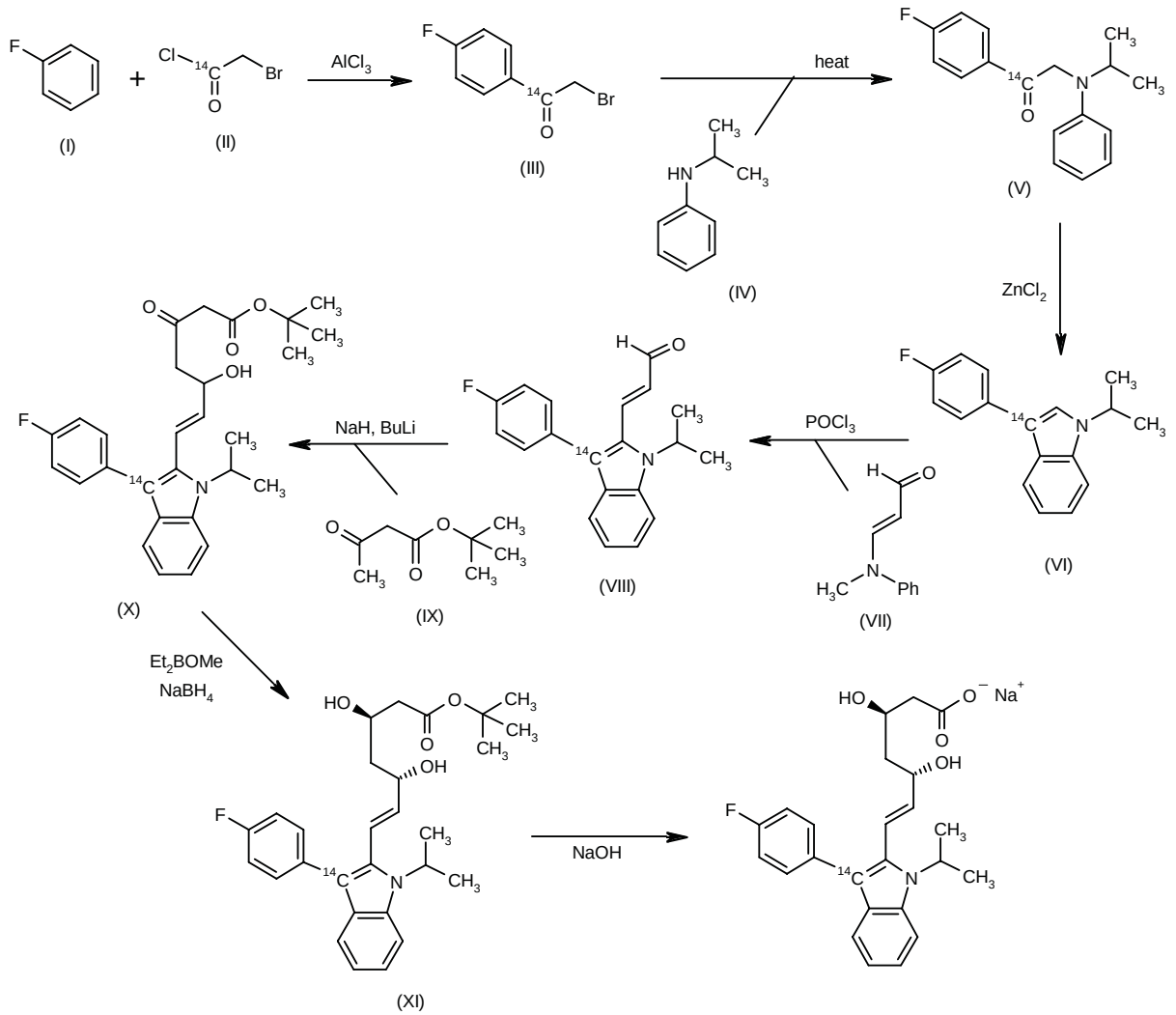
$C_{24}H_{25}FNNaO_4$ **Novartis; Tanabe; AstraZeneca**

A synthesis of [^{14}C]-labeled fluvastatin has been described: The acylation of fluorobenzene (I) with [^{14}C]-bromoacetyl chloride (II) by means of $AlCl_3$ gives the expected phenacyl bromide (III), which is condensed with *N*-isopropylaniline (IV) in hot ethanol, yielding the tertiary amine (V). The cyclization of (V) by means of anhydrous $ZnCl_2$ in refluxing ethanol affords the indole (VI), which is alkylated with 3-(*N*-methyl-*N*-phenylamino)acroleine (VII) by means of $POCl_3$ in refluxing acetonitrile, giving 3-[3-(4-fluorophenyl)-1-isopropylindol-2-yl]acroleine (VIII). The reductocondensation of (VIII) with *tert*-butyl acetoacetate (IX) by means of NaH and BuLi in THF yields 7-[3-(4-fluorophenyl)-1-isopropylindol-2-yl]-5-hydroxy-3-oxo-6-heptenoic acid *tert*-butyl ester (X), which is further reduced with $NaBH_4$ and diethyl(methoxy)borane in THF to the dihydroxy compound (XI) as a mixture of the two *syn*-enantiomers (XI). Finally, this compound is hydrolyzed with NaOH in methanol to the expected sodium salt (1). Scheme 9.

The angiographic progression and the benefits of fluvastatin were evaluated in patients participating in the Lipoprotein and Coronary Atherosclerosis Study (LCAS). These patients had LDL cholesterol levels that were mildly or moderately elevated, and many also had low levels of HDL cholesterol. A baseline HDL cholesterol level of < 0.91 mmol/l was observed in 68 of the 339 patients with biochemical and angiographic data from the study. Among the patients from the placebo group, those with low HDL cholesterol showed significantly more angiographic progression than those with higher HDL cholesterol levels. Of the patients receiving fluvastatin, progression was significantly reduced in those with low levels of HDL cholesterol. Furthermore, the treatment effect of fluvastatin on minimum lumen diameter was significantly greater in patients with low HDL cholesterol levels than in those with high levels. Event-free survival was greater in patients with low HDL cholesterol levels who received fluvastatin than in those who received placebo. These findings underline the importance of raising HDL cholesterol levels in patients with CAD, although the primary focus of therapy should be to reduce LDL cholesterol levels (2).

Novartis has begun recruiting patients for a landmark study under the acronym FAME (Fluvastatin Assessment of Morbi-mortality in the Elderly), designed to determine

Scheme 9: Synthesis of [^{14}C]-Fluvastatin Sodium



the effects of cholesterol-lowering therapy with fluvastatin sodium on the primary prevention of heart attack and stroke in elderly patients with hypercholesterolemia. FAME is a prospective, double-blind, randomized, parallel-group, placebo-controlled, 6-year study and will involve approximately 5400 men and women aged 70-85 years with primary hypercholesterolemia. Fifty percent of the study participants will be women; postmenopausal women are at increased risk for cardiovascular disease, and FAME is expected to provide much needed information about this population. The study will be conducted at approximately 70 centers in France, Italy, Spain and Belgium. Subjects will be administered the investigational extended-release 80-mg Lescol XL® tablets once daily, and the primary objective will be an evaluation of the effects of treatment on time to first major cardiovascular event (cardiovascular death, nonfatal myocardial ischemia or nonfatal stroke). FAME will also measure the effects of treatment on the incidence of all-cause mortality, cardiovascular death, nonfatal MI, nonfatal stroke, revascularization procedures and peripheral artery intervention (3).

The FDA has approved a new indication for Lescol(R): it can now be used to decrease triglycerides and apolipoprotein B in patients with mixed dyslipidemia (both elevated cholesterol and triglycerides). The new indication is based on the results of a pooled analysis of 12 placebo-controlled trials in over 1600 patients with hypercholesterolemia and mixed dyslipidemia, which showed significant reductions in triglycerides, apolipoprotein B, LDL cholesterol and total cholesterol, as well as variable increases in HDL cholesterol. In addition to the new indication, the FDA has also cleared revised labeling for the drug based on safety data from a pooled analysis. The

agency now recommends fewer liver function tests for patients taking Lescol®. Liver function monitoring is required for all HMG-CoA reductase inhibitors, although the frequency of testing varies among drugs. According to the revised labeling for Lescol®, monitoring is now recommended only before initiation of therapy and at 12 weeks following initiation of therapy or an increase in dose; if results are normal, no further testing is required, although it is still recommended that any liver function abnormality be closely monitored (4).

1. Tang, Y.S., Jones, L., Sunay, U.B. *Synthesis of carbon-14 labeled fluvastatin (Lescol®).* J Label Compd Radiopharm 1998, 41(1): 1.

2. Ballantyne, C.M., Herd, A.J., Ferlic, L.L., Dunn, J.K., Farmer, A., Jones, P.H., Schein, J.R., Gotto, A.M. *Influence of low HDL on progression of coronary artery disease and response to fluvastatin therapy.* Circulation 1999, 99(6): 736.

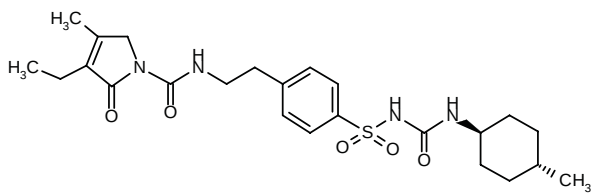
3. *FAME study will evaluate effects of lipid lowering in the elderly.* DailyDrugNews.com (Daily Essentials) Nov 10, 1998.

4. *FDA okays new indication and minimal liver function testing for Lescol.* DailyDrugNews.com (Daily Essentials) March 12, 1999.

Original monograph - Drugs Fut 1991, 16: 804.

Glimepiride *Antidiabetic*
Amaryl®

EN: 109856



$C_{24}H_{34}N_4O_5S$ **Hoechst Marion Roussel**

Glimepiride, a first-line treatment for type II diabetes, has received FDA approval for second-line combination use with the type II diabetes drug metformin (1).

1. *FDA approves new therapy for type II diabetes.* DailyDrugNews.com (Daily Essentials) March 10, 1999.

Original monograph - Drugs Fut 1992, 17: 774.

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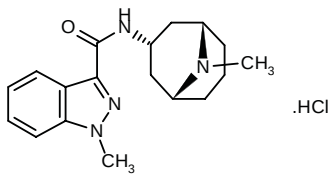
Profozic, V. et al. *Pharmacokinetics and safety of glimepiride in type II diabetics with liver impairment.* Diabetes 1999, 48(Suppl. 1): Abst 1578.

Stehouwer, M.H.A. et al. *Glimepiride and insulin multicenter study in NIDDM (GIM Study): Hypoglycaemic events and perceived barriers to good glycaemic control.* 34th Annu Meet Eur Assoc Study Diabetes (Sept 8-12, Barcelona) 1998, Abst 966.

Granisetron Hydrochloride *Antiemetic*
Kytril® *5-HT_3 Antagonist*

EN: 130362

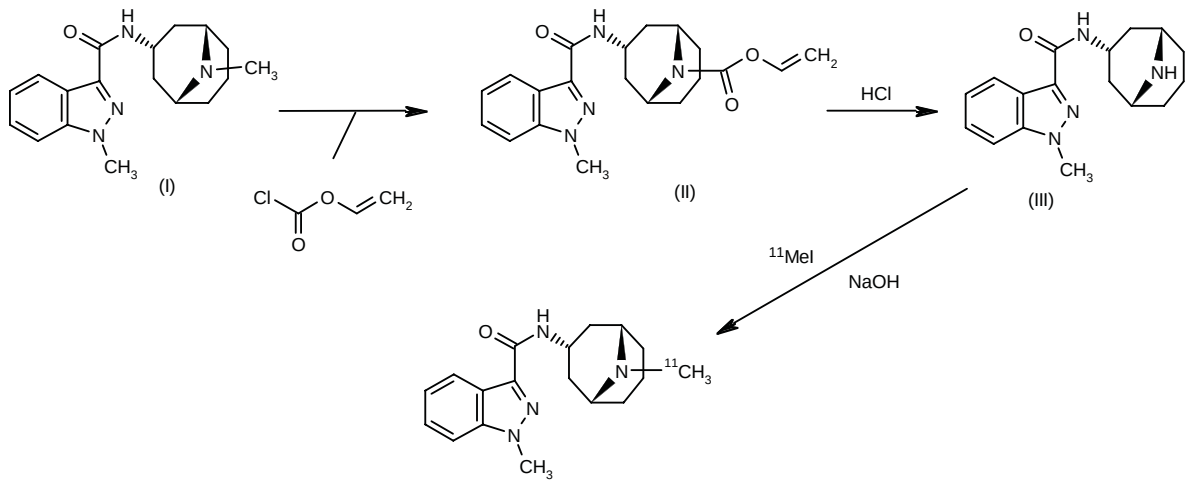


$C_{18}H_{24}N_4O.HCl$ **SmithKline Beecham**

A synthesis of [^{11}C]-granisetron has been published: The desmethylation of granisetron (I) with vinyl chloroformate in refluxing dichloroethane gives the intermediate vinyl ester (II), which is decarboxylated with dry HCl in dichloromethane, yielding desmethylgranisetron (III). Finally, this compound is methylated with [^{11}C]-methyl iodide and NaOH in DMF at 145 °C (1). Scheme 10.

The FDA has approved Kytril® tablets for the prevention of nausea and vomiting associated with radiation, including total-body irradiation (TBI) and fractionated abdominal radiation. Kytril® tablets (2 mg once daily) are currently indicated for the prevention of nausea and vomiting associated with emetogenic cancer therapies including high-dose cisplatin. The decision to approve Kytril® for this indication was based on review of data from two U.S. clinical trials. The first trial was a double-blind, randomized study in which 18 patients undergoing TBI for bone marrow transplantation received Kytril® tablets. TBI consisted of 11 fractions of radiation over 4 days. Patients were given Kytril® tablets (2 mg) 1 h prior to the first daily fraction of radiation. Over the entire 4-day dosing period, 22% of patients treated with Kytril® did not experience vomiting or receive rescue antiemetics, compared to 0% of patients in a historical negative control group. In addition, patients who received Kytil® tablets also experienced significantly fewer emetic episodes during the first day of radiation and over the 4-day treatment period compared to patients in the historical control group. The median time to first emetic episode was 36 h for patients who received Kytril® tablets. The most frequently reported adverse events were headache, diarrhea and asthenia. The second trial was a double-blind, randomized study of patients receiving fractionated upper abdominal radiation.

Scheme 10: Synthesis of [^{11}C]-Granisetron



Kytril® tablets were given 1 h prior to radiation, composed of up to 20 daily fractions. Patients treated with Kytril® had a significantly longer time to the first episode of vomiting relative to those patients who received placebo and a significantly longer time to the first episode of nausea. The most frequently reported adverse events were diarrhea, asthenia and constipation. In these two studies, the adverse events reported by patients receiving Kytril® and concurrent radiation were similar to those reported by patients receiving Kytril® prior to chemotherapy. Overall, however, headache was less prevalent among patients with radiation-induced nausea and vomiting (2).

1. Vandersteene, I., Audenaert, K., Slegers, G., Dierckx, R.A. *Synthesis of [^{11}C]granisetron, a possible positron emission tomography ligand for 5-HT$_3$ receptor studies.* J Label Compd Radiopharm 1998, 41(3): 171.

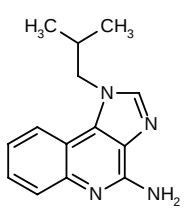
2. *FDA approves SB's Kytril for prevention of radiation-induced nausea and vomiting.* DailyDrugNews.com (Daily Essentials) July 29, 1999.

Original monograph - Drugs Fut 1989, 14: 875.

Imiquimod
Aldara®

Immunomodulator
Treatment of Genital Warts

EN: 111924



$C_{14}H_{16}N_4$

3M Pharm.; Daiichi Pharm.

A double-blind, randomized, placebo-controlled study has assessed the clinical efficacy and tolerability of imiquimod 1% cream in 60 male patients with their first episode of culture-confirmed genital herpes. The patients were instructed to apply the medication to their lesions twice daily for 5 consecutive days/week. Treatment was associated with marked clinical benefit, providing both a significantly shorter mean duration of healing (5.2 days *vs.* 14 days with placebo) and more healed patients (23/30 [76.7%] *vs.* 2/30 [6.7%] on placebo). A mild burning sensation was reported by 2 patients on imiquimod and 4 showed a transient increase in body temperature with mild headache and malaise; these effects resolved within 24 h. No patient discontinued treatment and 4/23 healed patients relapsed after 9 months (1).

The mechanism of action of topical imiquimod cream 5% was evaluated in a double-blind, placebo-controlled study in patients with genital warts treated three times daily for up to 16 weeks. All 16 imiquimod-treated patients and 1/3 placebo patients showed at least a 75% reduction in total wart area. Using wart biopsies and polymerase chain reaction methods, imiquimod was shown to significantly increase interferon-α, interferon-γ and 2',5'-oligoadenylate synthetase mRNA, and showed a tendency to increase TNF-α and IL-12 p40. The significant increase in CD4 mRNA and the tendency for an increase in CD8 mRNA observed in imiquimod-treated patients suggested activation of cell-mediated immune responses. In addition, treatment with imiquimod was associated with a significant decrease in human papillomavirus viral load, as well as decreases in the expression of markers of cell proliferation and increases in the expression of keratinocyte differentiation markers and tumor suppressor genes (2).

Imiquimod has been launched in Germany (Aldara® 5% cream) for the topical treatment of genital and perianal warts/condylomata acuminata. The drug was first launched in the U.S. and is also available in the U.K. (3, 4).

1. Syed, T.A., Ahmadpour, O.A., Ahmad, S.A., Shamsi, S. *Treatment of genital herpes in males with imiquimod 1% cream - A randomised, double-blind, placebo-controlled study.* Clin Drug Invest 1998, 16(3): 187.

2. Arany, I. et al. *Enhancement of the innate and cellular immune response in patients with genital warts treated with topical imiquimod cream 5%.* Antivir Res 1999, 43(1): 55.

3. *3M launches revolutionary new treatment for external genital and perianal warts in U.K.* DailyDrugNews.com (Daily Essentials) Oct 15, 1998.

4. *Another market introduction for imiquimod.* DailyDrugNews.com (Daily Essentials) Dec 15, 1998.

Original monograph - Drugs Fut 1989, 14: 870.

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Czelusta, A.J. et al. *A guide to immunotherapy of genital warts - Focus on interferon and imiquimod.* Biodrugs 1999, 11(5): 319.

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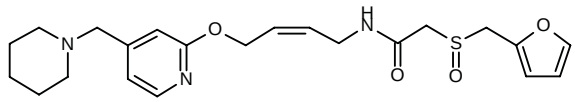
Trofatter, K.F. *Imiquimod in clinical practice.* Eur J Dermatol 1998, 8(Suppl. 7): 17.

Lafutidine
Protecadin®

Gastric Antisecretory
Histamine H_2 Antagonist

EN: 145925



$C_{22}H_{29}N_3O_4S$ **Fujirebio; Taiho; Salix**

A new synthesis of lafutidine has been described: The condensation of 2-bromopyridine-4-carbaldehyde ethylene ketal (I) with 4-(2-tetrahydropyranyloxy)-2(*Z*)-buten-1-ol (II) by means of NaOH, K_2CO_3 and tetrabutylammonium bisulfate in refluxing toluene gives the corresponding substitution product (III), which by treatment with pyridinium *p*-toluenesulfonate (PPTS) in hot ethanol yields the 2(*Z*)-butenol (IV). The reaction of (IV) with $SOCl_2$ and then with potassium phthalimide (V) affords the substituted phthalimide (VI), which by treatment with hydrazine hydrate in refluxing methanol gives the 2(*Z*)-butenamine (VII). The condensation of (VII) with 2-(2-furylmethylsulfinyl)acetic acid 4-nitrophenyl ester (VIII) in THF yields the expected amide (IX), which is treated with *p*-toluenesulfonic acid in refluxing acetone/water to eliminate the ethylene ketal protecting group, yielding the aldehyde (X). Finally, this compound is reductocondensed with piperidine (XI) by means of $NaBH_4$ in ethanol. Description: Crystals, m.p. 92.7-94.9 °C (1). Scheme 11.

Salix Pharmaceuticals signed a letter of intent with Fujirebio to negotiate a license agreement under which Salix would obtain exclusive rights to lafutidine, a novel antiulcer treatment currently being developed by Fujirebio in Japan. Salix would receive rights to the drug throughout the world, excluding Japan, Taiwan, Korea, Brazil and Argentina (2).

1. Hirakawa, N., Matsumoto, H., Hosoda, A., Sekine, A., Yamaura, T., Sekine, Y. *A novel histamine 2 (H_2) receptor antagonist with gastroprotective activity. II. Synthesis and pharmacological evaluation of 2-furfuryl-thio and 2-furfurylsulfinyl acetamide derivatives with heteroaromatic rings.* Chem Pharm Bull 1998, 46(4): 616.

2. *Salix negotiates lafutidine license agreement with Fujirebio.* DailyDrugNews.com (Daily Essentials) Feb 18, 1999.

Original monograph - Drugs Fut 1994, 19: 835.

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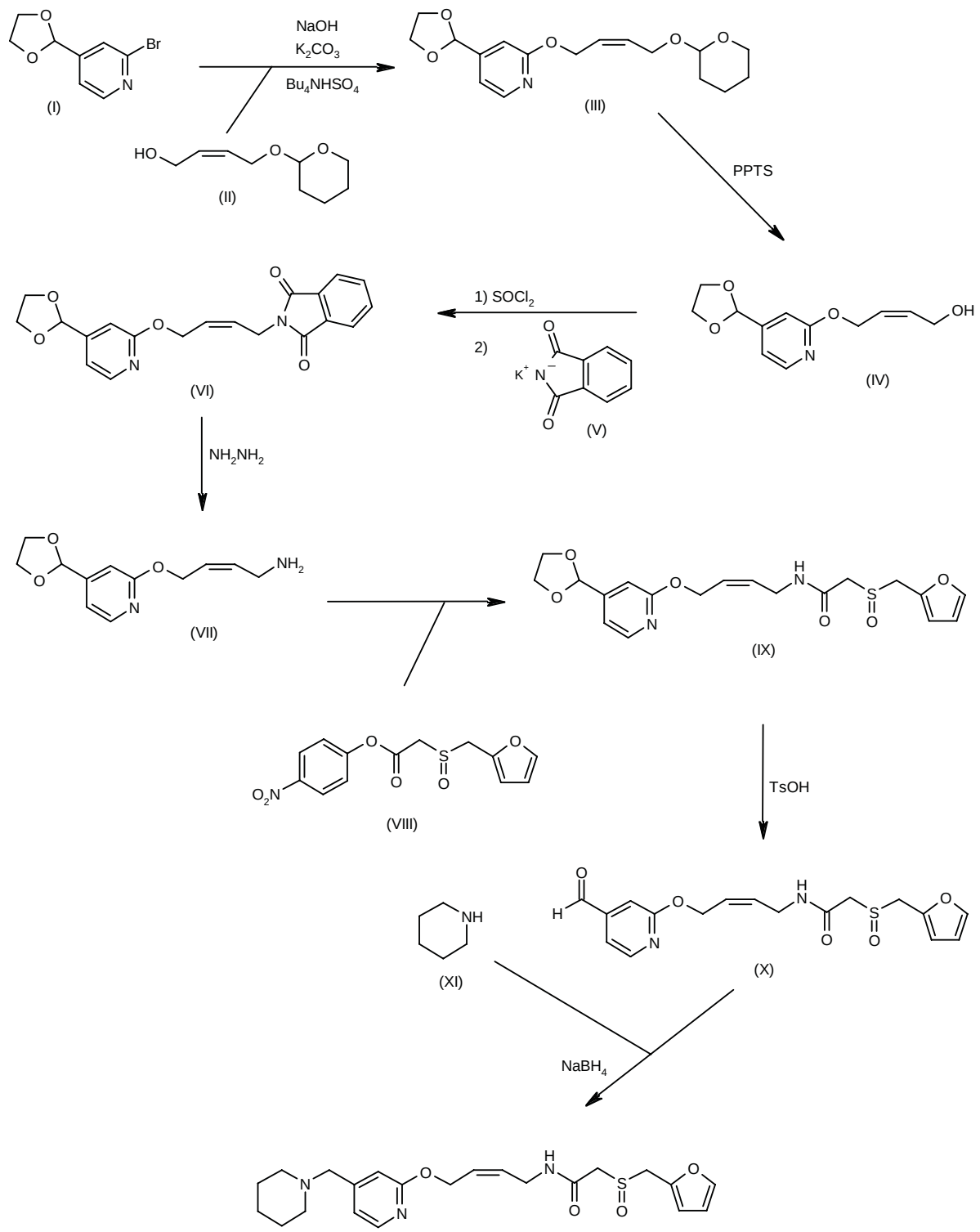
Scheme 11: Synthesis of Lafutidine



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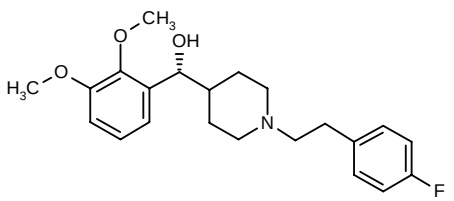
MDL-100907
M-100907

Antipsychotic
5-HT_{2A} Antagonist

EN: 179327



$C_{22}H_{28}FNO_3$ **Hoechst Marion Roussel**

Two double-blind, randomized, placebo-controlled trials were conducted to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of M-100907 in healthy male volunteers. Single oral doses of 9, 18, 36, 72, 108 or 138 mg and multiple oral doses of 3, 9, 18, 36 or 72 mg/day for 7 days were compared to placebo. The effects of the compound on vital signs, physical and laboratory examination did not differ significantly from those of placebo in either the single- or multiple-dose study. The maximum tolerated dose was determined to be 72 mg for either single or repeated dosing (1).

The development of M-100907 has been discontinued for the treatment of acute schizophrenia on the basis of a recent analysis of the results of phase III trials (2).

1. Brunner, F., Bhargava, V., Howard, D., Offord, S.J. *The safety, tolerability, pharmacokinetics, and pharmacodynamics of a selective 5-HT_{2A} antagonist, M100907, following single and multiple oral dosing in healthy volunteers.* Eur Neuropsychopharmacol 1998, 8(Suppl. 2): Abst P.2.091.

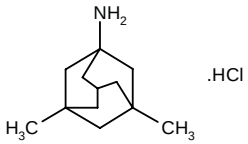
2. *Hoechst Marion Roussel establishes three high-priority compounds during Q2 1999.* DailyDrugNews.com (Daily Essentials) Aug 27, 1999.

Original monograph - Drugs Fut 1998, 23: 955.

Memantine Hydrochloride
Akatinol®

Treatment of Neurogenic Pain
Treatment of Diabetic Neuropathy

EN: 091101



$C_{12}H_{21}N.HCl$ **Neurobiological Technologies; Allergan**

A phase IIb clinical trial to evaluate memantine hydrochloride as a treatment for painful peripheral diabetic neuropathy has been initiated. The trial will evaluate the ability of memantine to relieve chronic pain due to peripheral neuropathy and nerve damage, particularly nocturnal pain that frequently interferes with sleep. This randomized, double-blind, placebo-controlled, dose-ranging trial is expected to enroll around 400 patients at 22 sites throughout the U.S. Subjects will receive daily oral doses of memantine or placebo for 8 weeks, initially a 10-mg daily dose, escalating by 10 mg at weekly intervals to either 20 or 40 mg (1, 2).

1. *Neurobiological Technologies initiates phase IIb trial of memantine.* DailyDrugNews.com (Daily Essentials) Nov 13, 1998.

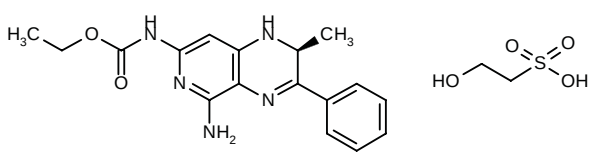
2. *Enrollment completed for phase IIb memantine trial in diabetic peripheral neuropathy.* DailyDrugNews.com (Daily Essentials) Sept 24, 1999.

Original monograph - Drugs Fut 1976, 1: 427.

Mivobulin Isethionate
CI-980
NSC-635370

Antineoplastic

EN: 149879



$C_{17}H_{19}N_5O_2.C_2H_6O_4S$ **Warner-Lambert; Natl. Cancer Inst. (US)**

A study has demonstrated the ability of CI-980 to cross the blood-brain barrier to enter brain tumors in rats. Rats received a bolus of [^{14}C]-CI-980 (50 μCi/rat, 0.92 mg/kg) in the tail vein 11 days after implantation of intracranial 9L-gliosarcomas and were sacrificed 30 or 60 min after dosing. At both time points, respectively, high concentrations of the agent were detected in liver

(1004 ± 4.2 and 390 ± 20 μM), normal brain (535 ± 191 and 324 ± 22 mM) and brain tumor tissue (484 ± 223 and 302 ± 32 μM) as compared to plasma (0.19 and 0.11 μM) and urine (15.71 and 11.2 μM) (1).

A phase II trial has shown that continuous i.v. infusion of CI-980 (4.5 mg/m^2/day) over 3 days repeated every 3 weeks had no antitumor activity against non-small cell lung cancer. Out of 14 patients entered, no objective responses were observed although 8 patients had stable disease for a median of 5 cycles. Median time to disease progression was 2 months, median survival was 33.7 weeks and a 1-year survival rate of 41.7% was projected. Toxicities included myelosuppression, anemia and fatigue (2).

Eighteen patients with previously treated soft tissue sarcomas received CI-980 for a total of 48 cycles of which 42 were administered at a dose level of 4.5 mg/m^2/day for 3 days. Grade 3-4 neutropenia complicated 20 cycles; 2 cycles were complicated by FUO. No CNS toxicities were reported. CI-980 was well tolerated in this phase II study but was inactive against soft tissue sarcomas (3).

CI-980 (4.5 mg/m^2/day i.v. 72-h continuous infusion every 21 days) was shown to be ineffective in a phase II trial in 21 chemotherapy- and immunotherapy-naive patients with disseminated malignant melanoma. The overall response rate was 0% and 15 patients died with a median overall survival of 8 months. Hematologic toxicities included 5 cases of grade 4 granulocytopenia, 2 cases of grade 3 nausea/vomiting and 3 cases of grade 3 weakness/fatigue. It was concluded that the agent does not warrant further investigation in these patients (4).

Results from a National Central Nervous System Consortium phase II evaluation of CI-980 in 24 patients showed no significant activity of the agent against recurrent or progressive malignant gliomas. Six patients in the phase I arm received 3 escalating doses (10.5, 12.0 and 13.5 mg/m^2 infusions over 72 h every 3 weeks) and 18 patients were given the maximum dose for each cycle. The phase II arm was stopped due to no complete or partial responses. Median survival was 38 weeks and mean time to progression was 6.4 weeks. Of 24 patients, 7 had stable disease with a median time to response of 6 weeks, a 7-week duration of response and a 19-week time to progression. Grade 3-4 granulocytopenia was the dose-limiting hematologic toxicity. Other adverse effects included mild hepatic toxicity, nausea, headache and fatigue; 3 episodes of neurologic toxicity (*i.e.*, moderate cerebellar dysfunction) were observed with 1 patient discontinuing despite stabilization of tumor (5).

1. Portnow, J. et al. *The intracerebral distribution study of CI-980: A new agent being studied in patients with glioblastoma multiforme.* Proc Amer Soc Clin Oncol 1999, 18: Abst 565.

2. Vokes, E.E., Arrieta, R., Lad, T., Masters, G.A., Hoffman, P.C., Ansari, R., Schumm, P., Golomb, H.M. *A phase II trial of CI-980 in advanced non-small cell lung cancer.* 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 380.

3. Patel. S.R. et al. *Phase II study of CI-980 (NSC 635370) in patients with previously treated advanced soft-tissue sarcomas.* Invest New Drugs 1998, 16(1): 87.

4. Whitehead, R.P. et al. *Phase II trial of CI-980 in patients with disseminated malignant melanoma: A Southwest Oncology Group study.* Proc Amer Soc Clin Oncol 1999, 18: Abst 2138.

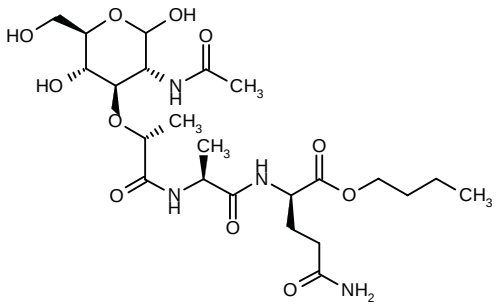
5. Kunschner, L.J. et al. *Lack of efficacy of CI-980 (NSC#635370) for the treatment of recurrent or progressive malignant gliomas: A National Central Nervous System Consortium phase II evaluation of CI-980.* Neurology 1999, 52(6, Suppl. 2): Abst S28.004.

Original monograph - Drugs Fut 1997, 22: 980.

Murabutide

Immunomodulator

EN: 090445



$C_{23}H_{40}N_4O_{11}$ **Choay; Institut Pasteur**

The efficacy of murabutide on the inhibition of HIV replication in monocyte-derived macrophages (MDMs) and dendritic cells (DCs) was assessed. Auctely infected MDMs and DCs with M-tropic HIV-1 isolates were maintained with or without the presence of murabutide. The addition of the compound to infected MDMs and DCs produced 60-100% inhibition of viral replication in cultures from 10 different donors. Murabutide demonstrated potent HIV-suppressing activity in reservoir cells and continues to be evaluated as adjunct antiretroviral therapy (1).

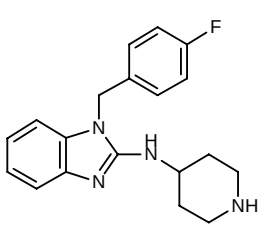
1. Bahr, G., Darcissac, E., Grau, O., Truong, M.J., Dewulf, J., Debard, C., Capron, A. *Inhibition of HVI-1 replication in reservoir cells by the safe immunomodulator murabutide.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 22424.

Original monograph - Drugs Fut 1986, 11: 750.

Norastemizole

Antihistamine
Treatment of Allergic Rhinitis

EN: 209628



$C_{19}H_{21}FN_4$ **Sepracor**

A 28-day study compared astemizole and norastemizole (2 mg/kg i.p. b.i.d.) in rats. Significant weight gain (89.5 g) was observed with astemizole as compared to norastemizole (43.9 g) and the vehicle (41.2 g). Although sporadically higher daily food consumption was observed in astemizole-treated animals, comparable consumption was observed in all groups at day 29 indicating that weight gain occurred even with similar caloric intake between groups. Oral toxicological studies in mice, rats and dogs treated for 28 days, 6 months and 1 year, respectively, also showed that norastemizole did not cause weight gain (1).

Johnson & Johnson has elected not to exercise its option to copromote Sepracor's norastemizole. Sepracor will continue to fund clinical development and marketing of the drug, which is in phase III trials for the treatment of seasonal and perennial allergic rhinitis. The company's development program remains on track for NDA filing by the end of 2000 (2).

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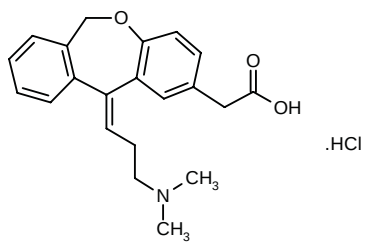
2. *Johnson & Johnson withdraws from norastemizole collaboration.* DailyDrugNews.com (Daily Essentials) May 18, 1999.

Original monograph - Drugs Fut 1998, 23: 966.

Olopatadine Hydrochloride
Patanol®

Treatment of Allergic Rhinitis
Ophthalmic Antiallergic

EN: 141324



$C_{21}H_{23}NO_3.HCl$ **Kyowa Hakko; Alcon**

The safety and efficacy of olopatadine hydrochloride were evaluated in a randomized, placebo-controlled trial in 98 subjects with a recent history of allergic conjunctivitis. Conjunctival allergen challenge tests were performed on the first 2 visits to establish allergen and concentration producing allergic conjunctivitis, as well as at several time points up to 8 h after instillation of 1 drop of olopatadine (0.01, 0.05, 0.1 or 0.15%) in one eye and placebo in the other during the next 3 visits. All concentrations of olopatadine showed clinically and statistically significant superiority over placebo as regards the ability to prevent ocular itching at all evaluations and ocular redness at most evaluations, immediately and for up to 8 h following drug instillation. The concentration of 0.1% was the most effective. No drug-related side effects were observed. The rapid onset and long duration of action of olopatadine in this study suggest the feasibility of twice-daily dosing (1).

A randomized, blinded, parallel-group study has compared the efficacy of olopatadine hydrochloride plus loratadine to that of loratadine monotherapy in reducing ocular itching associated with allergic conjunctivitis. Drugs were instilled 8 h before allergen challenge. In subjects with antigen-induced allergic conjunctivitis, the combination therapy was significantly more effective than loratadine monotherapy at 3, 7 and 10 min postallergen challenge. Duration of ocular itching was also significantly shorter with the combination than with loratadine alone at the 3- and 10-min time points (2).

1. Abelson, M.B. *Evaluation of olopatadine, a new ophthalmic antiallergic agent with dual activity, using the conjunctival allergen challenge model.* Ann Allergy Asthma Immunol 1998, 81(3): 211.

2. Abelson, M.B., Lanier, B.Q. *Evaluation of Patanol and Claritin for allergic conjunctivitis using the conjunctival antigen challenge.* Annu Meet Am Coll Allergy Asthma Immunol (Nov 6-11, Philadelphia) 1998, Abst P28.

Original monograph - Drugs Fut 1993, 18: 794.

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Kaise, T. et al. *Mechanism of the inhibitory effect of KW-4679 on nasal mucosal swelling induced by antigen-antibody reaction in guinea pigs.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst O-10.

OM-89
Subreum®

Immunomodulator

EN: 122672

OM

In an *in vitro* study, the proliferation of lymphocytes in response to OM-89 was evaluated in cells from spleen and lymph nodes of sensitized and orally treated mice. Specific proliferative responses could be effectively induced in animals sensitized by the appropriate methods, but not in orally treated mice. Thus, it appears that OM-89, rather than shifting the balance from Th1 to Th2 responses, causes the induction of a novel set of regulatory T-cell clones called Tr1 cells. The Tr1 cells proliferate only minimally in response to antigen, but produce high levels of IL-10. This mechanism of action, unknown until now, appears to contribute to the immunomodulatory activity of OM-89 (1).

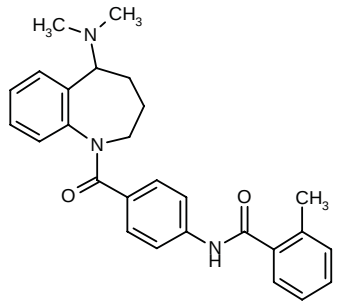
1. Phipps, P.A. *Induction of Tr1 cells: A possible mechanism in the therapeutic action of OM-89.* 9th Int Conf Inflamm Res Assoc (Nov 1-5, Hershey) 1998, Abst A2.

Original monograph - Drugs Fut 1994, 19: 845.

OPC-31260

Vasopressin V_2 Antagonist

EN: 172879



$C_{27}H_{29}N_3O_2$ **Otsuka**

The effects of OPC-31260 in a rat model of subarachnoid hemorrhage have been evaluated. Significant water retention was seen after water loading in the subarachnoid hemorrhage model, with increased water and sodium content in the brain and elevated plasma vasopressin levels. The administration of OPC-31260 prevented water retention and the accumulation of water and sodium in the brain, although plasma vasopressin levels increased further as a result. Cerebral edema induced by subarachnoid hemorrhage decreased significantly upon oral administration of OPC-31260. Thus, vasopressin appears to play an important role in the development of antidiuresis and altered brain water and electrolyte balance resulting from subarachnoid hemorrhage, and the protective effects of OPC-31260 stem from its action on renal tubular function (1).

Long-term oral administration of OPC-31260 in Sprague-Dawley rats with adriamycin-induced progressive water retention was shown to improve the survival rate via continuous aquaretic action, despite an increased level of plasma vasopressin (2).

The effects of OPC-31260 were evaluated in a genetic mouse model of progressive polycystic kidney disease (PKD) in PCY mice from early (4 weeks) to late stages (29 weeks). These mice showed elevated renal vasopressin V_2 receptor and aquaporin 2 and 3 (AQP2 and AQP3) mRNA expression, as well as reduced urine osmolality and aldose reductase mRNA expression in cystic kidneys. Urinary cAMP was also increased. Treatment of mice (from 4-24 weeks of age) with OPC-31260 (0.05-0.1% in the feed) induced a reduction in renal cystic enlargement and significantly reduced the increase in cAMP and the overexpression of the collecting duct genes involved in urine concentration (V2, AQP2 and AQP3). In addition to the beneficial effects of OPC-31260, the results also indicate that stimulation of overexpressed V_2 receptors and cAMP are involved in the progressive enlargement of cystic collecting ducts in PKD (3).

OPC-31260 was assessed for its effect on hemodynamics in the early and late phase after myocardial infarction in rats. In the early phase, OPC-31260 (30 mg/kg/day p.o.) was given on days 1-5 postoperatively. Hemodynamics were measured on day 5, in the late phase weeks 10-11 and at the end of 11 weeks. Results showed that OPC-31260 decreased left ventricular end-diastolic pressure and central venous pressure in both the early and late phases (4).

The therapeutic activity and diagnostic potential of OPC-31260 were evaluated in patients with progressive cirrhosis. Eight patients with biopsy-proven cirrhosis and ascites or peripheral edema were given a single oral dose (30 mg) of OPC-31260, and aquaretic responses in patients were compared to those in 6 healthy volunteers. Urinary excretion at 0-2 h increased significantly and urine osmolality at 2-4 h decreased significantly in cirrhosis patients. Free water clearance in patients increased from -0.48 ± 0.14 ml/min at baseline to +0.19 ± 0.21 ml/min at 0-4 h postdosing; this increase was only half as great as that in healthy volunteers. Urinary excretion of sodium increased 2-fold in healthy subjects following administration of OPC-31260, while this parameter was unchanged in cirrhotic patients. Urinary excretion of vasopressin increased 2- to 3-fold with respect to baseline in healthy subjects and tended to increase in patients with cirrhosis. No increase was observed in urinary excretion of PGE_2, and only slight increases were seen in serum sodium and plasma vasopressin levels in both subject groups. These findings indicate that OPC-31260 may be useful in treating impaired water handling in patients with cirrhosis, and support further clinical evaluation (5).

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Original monograph - Drugs Fut 1993, 18: 802.

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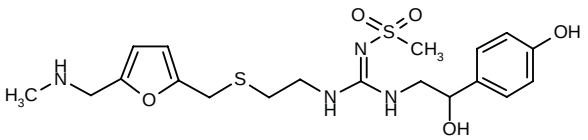
Sato, K. et al. *Vasopressin receptor in vascular fundus of canine femoral arteries.* Folia Pharmacol Jpn 1999, 113(3): Abst 54.

Osutidine

Antiulcer
Histamine H_2 Antagonist

EN: 159328



$C_{19}H_{28}N_4O_5S_2$ **Toyama**

The antagonistic properties of T-593 on [^{14}C]-aminopyrine accumulation in isolated canine gastric mucosal cells were assessed and compared to those of ranitidine and famotidine. T-593 showed insurmountable antagonism and it slowly associated and dissociated with the receptor. (–)-(S)-T-593 was identified as causing H_2-receptor antagonism (1).

The mucosal protective effects of T-593 (3-30 mg/kg p.o.) were shown to be partially mediated via endogenous nitric oxide (NO) and improvements in gastric mucosal blood flow in a study in rats. A dose-dependent reduction in aspirin/HCl-induced gastric mucosal lesions was observed in the treated group. Pretreatment with L-NAME attenuated the effects of the agent and L-arginine antagonized the L-NAME effects. T-593 was also shown to inhibit the aspirin/HCl-induced decreases in gastric mucosa total NO synthase activity and blood flow, with the effects of T-593 on blood flow antagonized by L-NAME pretreatment (2).

T-593 was evaluated for its inhibitory activity on histamine-induced gastric acid secretion in anesthetized rats. The compound was 3.5-fold more potent than ranitidine in inhibiting the formation of indomethacin-induced gastric lesions in rats but was 4-fold less potent than famotidine. T-593 was as effective as famotidine in healing acetic-acid induced gastric ulcers in the presence and absence of indomethacin and was 10- and 2-fold more potent than ranitidine and famotidine, respectively, in protecting against hemorrhagic shock-induced lesions with prior dosing of histamine. The antiulcer activity of T-593 appears to be a result of its dual inhibition of gastric acid secretion and protection of the gastric mucus membrane (3).

The effect of T-593 on the recurrence and relapse of cryocautery-induced gastric ulcer was investigated in the rat and its action was compared to that of famotidine and ranitidine. T-593 promoted ulcer healing and was associated with a lower recurrence and/or relapse rate than seen with conventional H_2-antagonists, thereby demonstrating potential for clinical therapy (4).

The antiulcer effects of T-593 were evaluated in 6 types of gastric ulcer, reflux esophagitis and 3 types of duodenal ulcer models in rats and compared to those of ranitidine and famotidine. T-593 dose-dependently inhibited ulceration in these models and had greater antiulcer effects than ranitidine and famotidine in the reserpine model. Both T-593 and famotidine sped up the healing of chronic gastric and duodenal ulcers induced by acetic acid or cryocautery, and prevented ulceration in reflux esophagitis and in acute duodenal ulcers. The potent antiulcer effects of T-593 may contribute to its antisecretory and mucosal protective effects (5).

Osutidine has undergone extensive toxicological testing in animals. General pharmacological studies in several animal species following i.v. or oral administration demonstrated no significant effects for T-593 except at high doses (1000 mg/kg p.o. and 10-30 mg/kg i.v.) (6).

Single-dose toxicity studies of osutidine were performed in rats and beagle dogs. Oral and subcutaneous LD_{50} values in rats were over 5 g/kg in both sexes, and intravenous LD_{50} values were 83.9 mg/kg and 86.4 mg/kg, respectively, in males and females. Similarly, in dogs, the oral LD_{50} value was > 5 g/kg and the i.v. LD_{50} was 60-100 mg/kg (7).

The results from 12-month repeated-dose toxicity studies in rats given oral doses of osutidine (100, 500 and 2000 mg/kg/day) indicated a nontoxic dose of 500 mg/kg/day. The only effects observed were a suppression in body weight gain in females at the highest dose and an increase in cecum weight in both sexes at 500 and 2000 mg/kg/day. These effects disappeared during a 1-month recovery period (8).

Twelve-month repeated-dose toxicity studies of oral osutidine (50, 200 and 500 mg/kg/day) have also been conducted in beagle dogs. No deaths and no abnormalities in general signs, body weight, food consumption, urinalysis, hematological and blood chemistry examinations, ECG, ophthalmological examination, macroscopic or histological analysis were observed. The nontoxic dose was determined to be at least 500 mg/kg/day (9).

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2. Marubuchi, S. et al. *Implication of endogenous nitric oxide in gastric mucosal protective effect of T-593, a novel anti-ulcer agent, in rats.* Jpn J Pharmacol 1999, 79(2): 195.

3. Shibata, H., Kusayanagi, Y., Arai, H., Hashiba, K., Yamamoto, Y., Onoda, M. *Synthesis and antiulcer activity of N-2-(2-hydroxy-2-phenyl)ethyl-N''-(methanesulfonyl)guanidine analogue of ranitidine. Development of a new antiulcer agent T-593.* Yakugaku Zasshi 1998, 118(3): 88.

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5. Arai, H. et al. *Effects of T-593, a novel anti-ulcer agent, on various experimental models of ulcers in rats. Possible implication of gastric mucosal blood flow.* Jpn Pharmacol Ther 1998, 26(11): 33.

6. Furuhata, K., Terashima, N., Ono, S., Tanaka, K., Fukuda, H., Nagasawa, H., Nojima, N., Arai, H. *General pharmacological studies of osutidine (T-593), a novel antiulcer agent.* Pharmacometrics 1998, 55(4): 119.

7. Nagai, A., Shibata, T., Nagasawa, M., Kizawa, K., Kawamura, Y., Kodama, T. *Single dose toxicity studies of osutidine (T-593), a novel antiulcer agent, in rats and dogs.* Pharmacometrics 1998, 55(4): 139.

8. Nagai, A., Miyazaki, M., Sanzen, T., Nagasawa, M., Nozawa, I., Kawamura, Y., Kodama, T. *Twelve-month oral repeated dose toxicity study of osutidine (T-593), a novel antiulcer agent, in rats.* Pharmacometrics 1998, 55(4): 149.

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Original monograph - Drugs Fut 1993, 18: 809.

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Palivizumab
MEDI-493
Synagis®

Anti-RSV

EN: 218833

MedImmune; Abbott

The safety and pharmacokinetics of MEDI-493 (15 mg/kg) were evaluated in 2 phase I studies. In the first trial, 5 autologous and 1 allogenic hematopoietic stem cell transplantation patients at risk for respiratory syncytial virus (RSV) infection were found to have peak MEDI-493 levels of 345-505 μg/ml 30 min following infusion and serum levels above 40 μg/ml were maintained for 22.4 days in 83% of the patients. The second trial involved 13 allogenic and 2 autologous patients with RSV upper respiratory infection or RSV pneumonia also treated with aerosolized ribavirin. Peak MEDI-493 levels were 102-572 μg/ml following infusion and a mean half-life of 10.7 days was obtained. Serum levels above 40 μg/ml were maintained for 7 and 21 days in 100% and 73% of the patients, respectively. All patients with RSV upper respiratory tract infections recovered and 83% with RSV pneumonia survived the 28- day study period. MEDI-493 was well tolerated in both studies with no adverse effects observed (1).

The safety and pharmacokinetics of MEDI-493 were reported from a phase I/II multicenter, open-label, dose-escalating study involving 41 children born prematurely (up to 6 months old) and 24 children with bronchopulmonary dysplasia (up to 24 months old) given 1-5 monthly i.m. injections (5, 10 and 15 mg/kg). The results obtained were similar to those reported after i.v. administration of the agent. Mean serum MEDI-493 levels were 91.1 μg/ml at 30 days and the 15 mg dose maintained trough levels of 70 μg/ml. Treatment was well tolerated with only 3 cases of adverse effects related to the agent. RSV was only observed in 2 patients receiving the 5 mg/kg dose (2).

Data from IMpact-RSV, a pivotal multicenter, randomized, 1500-patient study of palivizumab have been reported. Results showed that monthly prophylaxis with palivizumab (15 mg/kg i.m.) was associated with a 55% reduction in the incidence of hospitalization of premature infants for RSV as compared to placebo. Palivizumab prophylaxis resulted in a 78% reduction in RSV-related hospitalizations in children without bronchopulmonary dysplasia (BPD) and a 39% reduction in hospitalizations in children with BPD. Furthermore, children randomized to palivizumab had significantly fewer days of RSV hospitalization as compared to placebo (36.4 *vs.* 62.6 days/100 children, respectively). The study established that palivizumab protects against serious RSV disease in high-risk children regardless of BPD status, gestational age or weight and provided the first demonstration of the effectiveness of a monoclonal antibody in preventing an infectious disease in humans (3, 4).

Abbott and MedImmune have submitted a Marketing Authorization Application for palivizumab (Synagis®) with the European Agency for Evaluation of Medical Products for review. The U.S. FDA has approved the drug which is available by prescription from Abbott's Ross Products Division and MedImmune. Synagis® is supplied as a sterile lyophilized powder in single-use vials containing 100 mg for i.m. injection (5).

The European Union's Committee for Proprietary Medicinal Products has adopted a positive opinion on Synagis®. If approved, the drug will be the only preventive treatment for RSV in pediatric patients under 2 years of age who suffer from lung problems due to chronic bronchopulmonary dysplasia or prematurity. Synagis™ has been approved in Argentina, Australia, Brazil, Columbia, Kuwait, Mexico and the U.S. (6, 7).

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2. Saez Llorens, X. et al. *Safety and pharmacokinetics of an intramuscular humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia.* Pediatr Infect Dis J 1998, 17(9): 787.

3. *Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants.* Pediatrics 1998, 102(3): 531.

4. *IMpact-RSV trial results announced at international congress.* DailyDrugNews.com (Daily Essentials) Aug 26, 1998.

5. *Synagis submitted for review by EMEA: Product now available in U.S.* DailyDrugNews.com (Daily Essentials) Aug 17, 1998.

6. *CPMP adopts positive opinion on Synagis for RSV prevention.* DailyDrugNews.com (Daily Essentials) May 26, 1999.

7. *Abbott makes major strides in R&D during Q2.* DailyDrugNews.com (Daily Essentials) July 27, 1999.

Original monograph - Drugs Fut 1998, 23: 970.

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Pegylated Recombinant Megakaryocyte Growth and Development Factor

Pegacaristim *Antineoplastic*
PEG-rHuMGDF *Hematopoietic*
MGDF®

EN: 229057

Amgen; Kirin Brewery

The *in vitro* effects of PEG-rHuMGDF have been evaluated alone and in combination with various hematopoietic growth factors (G-CSF, GM-CSF, SCF, IL-3, IL-6 and EPO) in bone marrow obtained from patients with aplastic anemia and healthy volunteers. Twelve of the 19 patients with anemia responded to treatment with PEG-rHuMGDF; of these, 9 responded further with the addition of other growth factors. The highest responses were obtained with the combinations PEG-rHuMGDF + SCF and PEG-rHuMGDF + SCF + IL-3 + EPO (1).

An *in vivo* study using normal and myelosuppressed mice showed that a single injection (10 or higher μg/kg) of PEG-rHuMGDF dose-dependently increased platelet production on day 3 (peak on days 5-6) and marrow megakaryocyte production on day 1 (peak on day 3); no increase in mean platelet volume was observed *in vitro* after incubation with PEG-rHuMGDF. A dose of 100 μg/kg did not increase marrow megakaryocyte colony-forming units although the frequency of high ploidy megakaryocytes and large marrow megakaryocytes increased. At 24-48 h, an increase in the percentage of megakaryocytes in mitosis was observed with the 1000 μg/kg dose (2).

Pegacaristim is the new proposed international nonproprietary name for peglycated recombinant megakaryocyte growth and development factor (3).

Amgen has discontinued development of PEG-rHuMGDF due to evidence of neutralizing antibodies in a few patients in cancer clinical trials and other subjects in platelet donor clinical trials (4, 5).

1. Brereton, M.L. et al. *The in vitro effect of pegylated recombinant human megakaryocyte growth and development factor (PEGrHuMGDF) on megakaryopoiesis in patients with aplastic anaemia.* Br J Haematol 1999, 104(1): 119.

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3. *Proposed international nonproprietary names (Prop. INN): List 80.* WHO Drug Inf 1998, 12(4): 272.

4. *Amgen discontinues clinical testing of PEG-rHuMGDF for one of two indications.* DailyDrugNews.com (Daily Essentials) Aug 21, 1998.

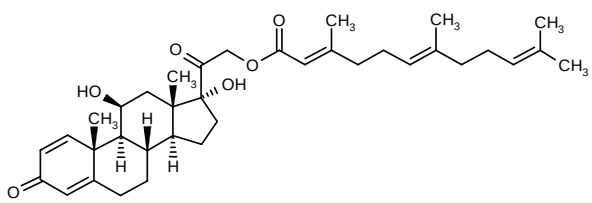
5. *Development of MGDF discontinued at Amgen.* DailyDrugNews.com (Daily Essentials) Sept 14, 1998.

Original monograph - Drugs Fut 1997, 22: 987.

Prednisolone Farnesylate

Farnerate Gel® *Antiarthritic*
Farnezone Gel® *Corticosteroid*

EN: 154424



$C_{36}H_{50}O_6$ **Taiho; Kuraray; Dainippon**

Prednisolone farnesylate has been launched in Japan for the treatment of pain associated with rheumatoid arthritis. The product is marketed by Taiho under the trade name Farnerate Gel® and by Dainippon (manufactured by Kuraray) under the name Farnezone Gel®. In both cases it is supplied as 25- and 50-g tubes containing 14 mg/g of the active ingredient (1).

1. *New arthritis Rx now available in Japan.* DailyDrugNews.com (Daily Essentials) Sept 30, 1998.

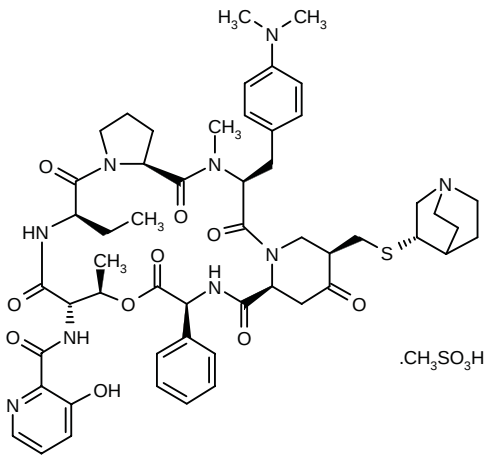
Original monograph - Drugs Fut 1993, 18: 805.

Quinupristin/Dalfopristin *Streptogramin*
Synercid®

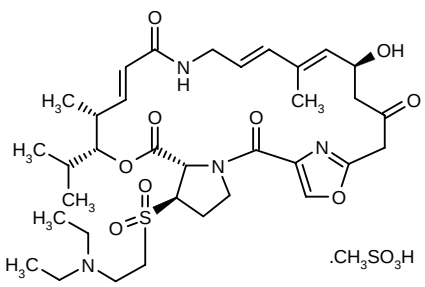
EN: 166760

Defined mixture of pure and synergistic mesilate salts of quinupristin and daldopristin in a ratio 30/70 in %, w:w.

Quinupristin Mesilate
EN: 138965



Dalfopristin Mesilate
EN: 166761



Rhône-Poulenc Rorer

The MICs of quinupristin/dalfopristin were compared to vancomycin, erythromycin, clindamycin, ciprofloxacin and gentamicin against 50 staphylococcal strains including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus* and coagulase-negative staphylococci. Title compound was the most active against methicillin-sensitive and -resistant staphylococci with only *S. haemolyticus* showing an MIC of 4 mg/ml. The MIC for vanomycin was < 2 mg/ml with all strains. Erythromycin was effective against 35% and 60% of *S. aureus* and coagulase-negative staphylococci, respectively, and 38.7% and 70% were susceptible to clindamycin and ciprofloxacin and 51.5% and 60% susceptible to gentamicin, respectively (1).

Against 18 Gram-positive cocci, quinupristin/dalfopristin showed postantibiotic effects (PAEs) and postantibiotic sub-MIC effects of > 2 h. Mean pneumococcal and staphylococcal PAEs were 2.8 and 4.7 h, respectively. Shorter PAEs were found with constitutively as compared to inducibly macrolide-resistant staphylococci. Mean PAEs for vancomycin-susceptible and -resistant *Enterococcus faecium* were 8.5 and 2.6 h, respectively (2).

In a rabbit model of *Streptococcus pneumoniae* meningitis, treatment with quinupristin/dalfopristin resulted in an attenuated inflammatory response and a reduction in the concentration of neuron-specific enolase in the cerebrospinal fluid (CSF). Although ceftriaxone (10 mg/kg/h) exhibited greater bactericidal activity, significantly lower concentrations of proinflammatory cell wall components, lipoteichoic and teichoic acids (133-193 ng/ml *vs.* 455 ng/ml at 14 h postinfection), and TNF activity (0.1-0.2 U/ml *vs.* 30 U/ml at 14 h postinfection) in CSF were observed in quinupristin/dalopristin-treated rabbits. Neuron-specific enolase was also significantly reduced in animals treated with quinupristin/dalfopristin as compared to the ceftriaxone group (3.6-4.6 μg/l *vs.* 17.7 μg/l at 24 h postinfection) (3).

A study has shown the efficacy of quinupristin/dalfopristin (7.5 mg/kg every 8 or 12 h) as a treatment for patients with renal failure and multiresistant *S. epidermidis* or *S. aureus* or vancomycin-resistant *E. faecium* infections. Treatment was well tolerated with 6/7 patients cured of infections within 10-34 days. Myalgias without increases in creatinine kinases were observed in 2 patients receiving treatment every 8 h. No accumulation of the parent compound or principal metabolites was observed (4).

Quinupristin/dalfopristin was clinically effective in a study showing bacteriologic activity in Gram-positive infections in 54 neutropenic patients with leukemia treated with the drug (7.5 mg every 8 or 12 h). Bacteriologic responses were observed in 75% of patients with vancomycin-resistant *E. faecium*. Clinical success defined as improvement or clearance of infection which correlated to neutrophil recovery was observed in 52% of the patients. Adverse effects included myalgia (9.3%) and arthralgia (16.7%) (5).

Quinupristin/dalfopristin in combination with ciprofloxacin for 11 days was shown to be effective in a case of severe endocarditis due to multiresistant *S. haemolyticus*, *S. epidermidis*, *E. faecium* and *E. faecalis*. The patient, intolerant to previous therapy with imipenem + gentamicin, flucloxacillin + teicoplanin or clindamycin + fosfomycin, was afebrile within 1 week after administration of title compound (7.5 mg/kg t.i.d.) + ciprofloxacin (400 mg t.i.d.). Valve vegetation disappeared within 2 weeks and blood cultures were negative (6).

The pharmacokinetics of quinupristin/dalfopristin (7.5 mg/kg i.v.) were examined in 8 noninfected continuous ambulatory peritoneal dialysis patients and 8 healthy volunteers. The combination treatment was well tolerated

and only mild adverse effects were observed which resolved prior to trial discharge. No differences in C_{max}, AUC, distribution volume, rate of total body clearance or $t_{1/2}$ in plasma values for the two antibiotics were observed between groups. No differences in C_{max}, t_{max}, AUC or $t_{1/2}$ were observed for cysteine, the glutathione conjugate of quinupristin or the pristinamycin IIA metabolite of dalfopristin. Parent and metabolite concentrations of dialysate measured up to 6 h postdose were below MIC values and dialysis clearance was not significant. The results indicate that i.v. administration of these agents would not be sufficient for treatment of peritonitis due to peritoneal dialysis (7).

Quinupristin/dalfopristin (Synercid®) has been launched in the U.K. for use in patients with nosocomial pneumonia, skin and soft tissue infections and clinically significant infections due to *E. faecium* when there is no other active antibacterial agent. Synercid® is supplied as powder for solution for infusion in single-use vials containing 150 mg quinupristin and 350 mg dalfopristin as the mesilate salts (8, 9).

The FDA has approved Synercid® for the treatment of bloodstream infections due to vancomycin-resistant *E. faecium* (VREF) and skin and skin structure infections caused by methicillin-susceptible *S. aureus* or *Streptococcus pyogenes*. Approval of this indication was based on the drug's ability to clear VREF from the bloodstream, with clearance of bacteremia considered to be a surrogate endpoint. There are no results from well-controlled clinical trials that confirm the validity of this surrogate marker. However, a study to verify the clinical benefit of therapy with Synercid® on traditional clinical endpoints is under way (10).

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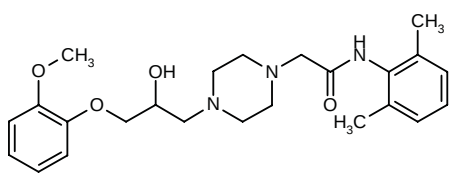
Ranolazine

Antianginal

EN: 101796



$C_{24}H_{33}N_3O_4$

Roche Bioscience; Kissei; CV Therapeutics; Innovex

The potent antianginal effects of ranolazine were shown in a study in rats and dogs. Intraduodenal administration of the agent (10, 30 or 50 mg/kg) or atenolol (10 mg/kg) to anesthetized dogs with 2-min coronary ligation during electrical pacing significantly attenuated ST-T wave elevation; the effects of ranolazine were sustained for 3 h. Although decreases in diastolic blood pressure, heart rate and the first derivative of left ventricular pressure were observed with atenolol treatment, no changes in hemodynamic parameters were noted with ranolazine. Oral administration of title compound (10, 30 or 50 m/kg) to rats dose-dependently attenuated epinephrine-induced elevations in ST-segment depression. However, ranolazine at oral doses of 10 and 30 mg/kg had no effects on vasopressin (0.2 IU/kg i.v.)-induced elevations in ST-segment depression, indicating that the agent does not have protective effects against vasospasm-induced angina pectoris (1).

CV Therapeutics has initiated its first pivotal phase III trial for ranolazine in Canada, Czech Republic and Poland. These new clinical trial centers complement the U.S. centers currently enrolling patients nationwide and will study ranolazine when used in combination with other antianginals for the treatment of chronic stable angina (2).

CV Therapeutics has initiated its second pivotal phase III clinical trial for ranolazine. The CARISA (Combination Assessment of Ranolazine In Stable Angina) trial is a randomized, double-blind, placebo-controlled trial of ranolazine used in combination with other antianginal drugs. The primary endpoint of this 450-patient trial will be duration of exercise on a treadmill. Results from the CARISA trial, along with the MARISA trial involving monotherapy with ranolazine in 175 patients, will be filed as part of CV Therapeutics' New Drug Application submission to the FDA (3, 4).

Results from a randomized, double-blind, placebo-controlled, crossover study of 3 dose levels of immediate-release ranolazine demonstrated that the drug may increase exercise time in chronic stable angina patients, and clarifies divergent findings from earlier studies. The study assessed the potential antianginal action of ranolazine IR using treadmill exercise testing, generally considered the standard method for evaluating antianginal treatments. Data from the study indicate that at peak ranolazine plasma concentrations, all ranolazine dosing regimens tested may increase the following treadmill exercise parameters in patients with angina: duration of exercise, time to onset of angina and time to 1-mm S-T segment depression. Furthermore, these exercise parameters may increase in patients receiving beta-blockers in combination with ranolazine, as well as in those receiving calcium antagonists in combination with ranolazine. The results also indicate that there may be no change in heart rate or blood pressure among any of the dosing regimens. Ranolazine is presently being investigated in phase III clinical trials subject to a U.S. IND and applicable foreign authority submissions. CV Therapeutics has not yet submitted an NDA to the FDA or equivalent application to any other regulatory agencies for ranolazine. In addition, ranolazine has not yet been determined to be safe or effective in humans for its intended use. CV Therapeutics has arranged to have Innovex commercialize ranolazine in the U.S. upon approval (5).

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  CCC: 0377-8282/99

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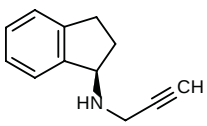
Rasagiline

Antiparkinsonian
Cognition Enhancer
MAO-B Inhibitor

EN: 174550



$C_{12}H_{13}N$

Teva

The neuroprotective effects of early rasagiline (0.2 and 1 mg/kg) treatment were suggested to be through maintenance of cholinergic neuronal transmission in a study using mice with closed head injury. Animals treated 5 min after injury exhibited significantly accelerated recovery of motor function and spatial memory and a 40-50% reduction in cerebral edema. Treatment with scopolamine prevented all the neuroprotective effects except edema. Recovery of spatial function was also accelerated when rasagiline (1 mg/kg) was injected daily from day 3 after injury, although motor function was unaffected (1).

The safety and efficacy of rasagiline mesilate as an adjunct to levodopa was determined in a multicenter, double-blind, randomized, placebo-controlled, parallel-group trial in 70 patients with Parkinson's disease. The dose was titrated from 0.5 mg/day up to 2 mg/day over 12 weeks. All doses of rasagiline had beneficial effects in fluctuating patients as seen by decreases in the total Unified Parkinson's Disease Rating Scale (UPDRS) score (23.2% *vs.* 8.5% on placebo); these effects persisted until 6 weeks after discontinuing treatment. Very good safety and tolerability were reported, adverse effects being indistinguishable from those on placebo. All doses of the active compound provided almost complete inhibition of MAO-B (2).

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Reteplase
Rapilysin®
Retavase®

Thrombolytic

EN: 172244

Biovail; Roche; Centocor

Crystaal, a division of Biovail, has announced the availability of reteplase (Retavase®), an easy-to-administer and fast-acting emergency treatment for heart attacks. Retaplase is a fibrin-specific thrombolytic agent indicated for use in the management of acute myocardial infarction in adults. The compound restores blood flow to the heart by breaking up and dissolving blood clots in the coronary artery and is most effective when used within 6 h after the onset of heart attack symptoms. Retaplase offers quicker administration time because no dose calculations are required and 2 doses are administered by syringe at 30-min intervals. Key findings from the RAPID II trial demonstrated that retaplase opened the arteries in a higher proportion of patients than the standard medication at 90 min. More patients also had blood flow restored at both 60 and 90 min compared to the current standard therapy. Reteplase was developed by Boehringer Mannheim prior to its merger with Roche. Centocor acquired U.S. and Canadian rights from Roche last year and subsequently sublicensed the product to Biovail for Canada (1-3).

1. *Biovail subsidiary will market clot buster in Canada.* DailyDrugNews.com (Daily Essentials) Sept 16, 1998.

2. *Centocor will market Retavase exclusively in the U.S. starting in January.* DailyDrugNews.com (Daily Essentials) Dec 4, 1998.

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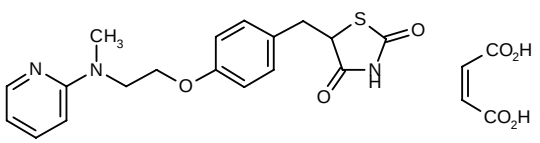
Rosiglitazone Maleate

Antidiabetic

BRL-49653C

Avandia®

EN: 210057



$C_{18}H_{19}N_3O_3S.C_4H_4O_4$

SmithKline Beecham; Bristol-Myers Squibb

Troglitazone was found to be more potent than rosiglitazone and its metabolites as a vasorelaxant in phenylephrine-precontracted rat aorta. The order of potency for vasorelaxation (IC_{50} in μM) was: troglitazone (59) > rosiglitazone (130) > SB-244675 (380) ≥ SB-275286 (390) ≥ SB-237216 (410) ≥ SB-243914 (500) > SB-280789 (650); SB-271528 only achieved 15% relaxation at 1 mM. This rank order is in contrast to the therapeutic potency of the agents in which rosiglitazone is 100-fold more potent than troglitazone. The rank order of potency for half-maximal displacement of nitrendipine in rat cerebral cortical membranes as compared to nifedipine (IC_{50} = 2.8 ± nM) was (IC_{50} in μM): troglitazone (13) > SB-243914 (51) > SB-280789 (110) > rosiglitazone (270) > SB-275286 (290) > SB-244675 (560) > SB-237216 (650); SB-271528 was ineffective up to 100 μM (1).

Rosiglitazone (50 μmol/kg diet) was shown to prevent hypertension *in vivo* and protect against insulin resistance-associated impaired endothelial function *in vitro* in a study using fatty Zucker rats given the agent for 9-12 weeks. Treatment prevented the rise in systolic blood pressure observed in fatty rats (123 ± 1 *vs.* 147 ± 5 and 125 ± 2 mmHg in untreated fatty and lean rats, respectively) and lowered fasting hyperinsulinemia (7.0 ± 1.4 *vs.* 287 ± 6 ng/ml in untreated fatty rats). *In vitro* studies using mesenteric arteries from fatty rats showed that impairment of acetylcholine-induced relaxation of norepinephrine-induced contractions was partially prevented by rosiglitazone (66.5 ± 3 *vs.* 62.4 ± 3.4% untreated fatty rats). Insulin-induced decreases in the contractile responses to norepinephrine observed in lean rats and absent in untreated fatty rats were also partially restored in rosiglitazone-treated fatty rat arteries, possibly explaining the agent's antihypertensive effects (2).

Zucker fatty rats treated with rosiglitazone for a prolonged period produced substantial protection against development and progression of renal injury as well as the adaptive changes to pancreatic islet morphology brought about by sustained hyperinsulinemia (3).

Rosiglitazone dose adjustments were found to be unnecessary in patients with chronic renal impairment in a study in which a total of 57 healthy subjects and patients with mild to severe renal impairment were given rosiglitazone (8 mg p.o.). Treatment was well tolerated with similar $t_{1/2}$ (4-5 h) values obtained for all groups. AUC, C_{max} and fraction unbound were also similar in healthy subjects and patients with mild or moderate renal impairment. Patients with severe renal impairment had about 20% lower AUC and C_{max} values and a 38% greater unbound fraction as compared to healthy subjects. Mean unbound AUC was only slightly increased (10-20%) in patients with renal impairment as compared to healthy individuals (4).

A dose adjustment in rosiglitazone therapy was advised for patients with type II diabetes with moderate to severe hepatic impairment in a recent pharmacokinetic study in which a total of 35 healthy subjects and patients with hepatic impairment were given a single dose of rosiglitazone (8 mg p.o.). Treatment was well tolerated. Total AUC was 34% higher in patients with hepatic impairment and $t_{1/2}$ was prolonged in these individuals (6.0 *vs.* 3.8 h in healthy subjects). Lower albumin levels (3.0 *vs.* 4.3 g/l) were correlated to a 2-fold higher percent of fraction unbound in patients with hepatic impairment (5).

The pharmacokinetics of rosiglitazone (8 mg p.o.) were unaffected by hemodialysis in a study involving 10 chronic hemodialysis patients and 10 healthy subjects. Rosiglitazone was well tolerated and AUC, C_{max} and $t_{1/2}$ values were similar in both groups, indicating that dose adjustment in hemodialysis patients is unnecessary (6).

SmithKline Beecham submitted a Marketing Authorization Application to the European Agency for the Evaluation of Medicinal Products to market rosiglitazone maleate (Avandia®) for the treatment of type II diabetes, either as monotherapy or in combination with other drugs (7).

Rosiglitazone maleate (Avandia®) is now available in the U.S. for the treatment of type II diabetes as both monotherapy and in combination with metformin. The FDA approval was based on a review of data from clinical studies involving more than 5500 patients with type II diabetes. Avandia® recently received marketing approval in Mexico and regulatory applications have been filed with the European Medicines Evalulation Agency and in 13 other markets worldwide. SmithKline Beecham recently entered into a copromotion agreement with Bristol-Myers Squibb for Avandia® (8-13).

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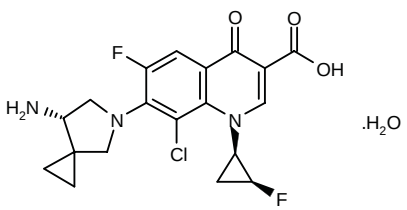
Sitafloxacin Hydrate DU-6859a

Quinolone Antibacterial

EN: 176447



$C_{19}H_{18}ClF_2N_3O_3.H_2O$ **Daiichi Pharm.; Beijing General**

An efficient synthesis of 7(*S*)-(*tert*-butoxycarbonylamino)-5-azaspiro[2.4]heptane (XI), a key intermediate in the synthesis of DU-6859a, via an asymmetric microbial reduction has been described: The reaction of *N*-benzylglycine (I) with *tert*-butoxycarbonyl anhydride gives *N*-benzyl-*N*-(*tert*-butoxycarbonyl)glycine (II), which is condensed with the potassium salt of ethyl hydrogen malonate (III) by means of carbonyldiimidazole (CDI) in THF, yielding 4-[*N*-benzyl-*N*-(*tert*-butoxycarbonyl)amino]-3-oxobutyric acid ethyl ester (IV). The cyclopropanation of (IV) with 1,2-dibromoethane (V) by means of K_2CO_3 in refluxing acetone affords the cyclopropane derivative (VI), which is cyclized by means of trifluoroacetic acid in dichloromethane to give 5-benzyl-5-azaspiro[2.4]heptane-4,7-dione (VII). The enantioselective microbial reduction of (VII) by means of *Phaeocreopsis* spp. JCM 1880 in a complex medium containing glucose and polypeptone yields 5-benzyl-7(*R*)-hydroxy-5-azaspiro-[2.4]heptan-4-one (VIII), which by reaction with triphenylphosphine, diethyl azodicarboxylate and diphenylphosphoryl azide (DPPA) followed by reduction with $LiAlH_4$, is converted into 7(*S*)-amino-5-benzyl-5-azaspiro[2.4]heptane (IX). The protection of (IX) with *tert*-butoxycarbonyl anhydride as usual gives the protected amine (X), which is finally debenzylated by hydrogenation with H_2 over Pd/C in ethanol affording the desired 7(*S*)-(*tert*-butoxycarbonylamino)-5-azaspiro[2.4]heptane (IX) (1). Scheme 12.

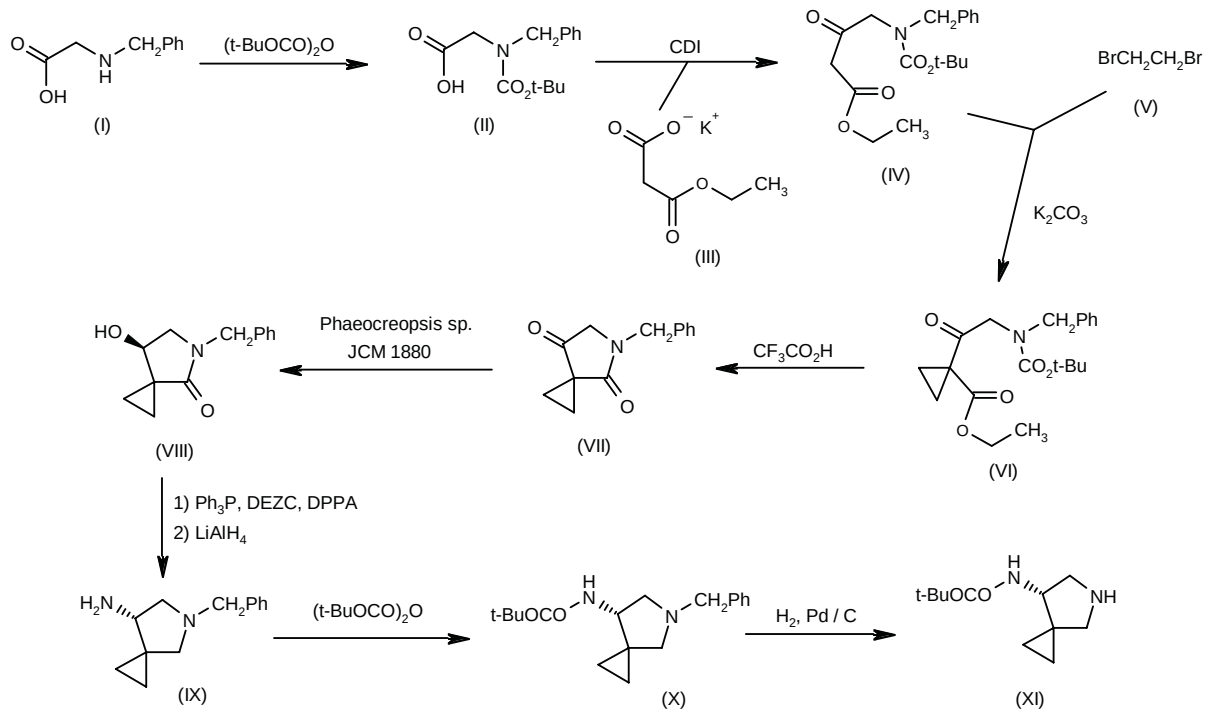
Sitafloxacin has shown potent and broad-spectrum antibacterial activity, particularly against respiratory pathogens. Extensive *in vitro* studies have demonstrated that the new fluoroquinolone compares favorably with other quinolones in terms of activity against Gram-negative aerobic pathogens, Gram-positive cocci and anaerobes (2-4).

The effects of sitafloxacin on DNA gyrase and topoisomerase IV purified from quinolone-susceptible isolates were assessed. Sitafloxacin gave IC_{50} values of 1.5, 1.2, 0.082 and 0.15 μg/ml, respectively, for inhibition of supercoiling activity of DNA gyrase from *S. aureus*, *S. pneumoniae*, *E. coli* and *P. aeruginosa*, and respective values of 0.48 and 1.9 μg/ml against decatenation activity of *S. aureus* and *S. pneumoniae* topoisomerase IV. The compound was more potent than other quinolones such as ciprofloxacin, sparfloxacin and levofloxacin and was also more active against altered DNA gyrase and topoisomerase IV (5).

The inhibitory activity of sitafloxacin on DNA gyrase from *E. coli*, topoisomerase IV from *S. aureus* and topoisomerase II from human placenta were compared. The drug exhibited highest inhibitory activities against bacterial type II topoisomerases and the lowest against human type II topoisomerase. Inhibition of bacterial type II topoisomerases by quinolones was not associated with their inhibition of human topoisomerase II (6).

Good clinical efficacy was reported for sitafloxacin in an early clinical trial in patients with lower respiratory tract infections and its safety and efficacy were subsequently evaluated in patients with mild to moderate pneumonia, chronic lower respiratory tract infections (RTI) and acute RTI. In this multicenter study, sitafloxacin was given at doses of 50 or 100 mg orally twice daily after meals for 3-15 days. An overall clinical efficacy of 87.9% was obtained, with efficacy rates of 95.4%, 83.2%, 91.7% and 80%, respectively, against pneumonia, chronic RTI, acute upper RTI and other RTI; bacterial eradication was obtained in 90% of cases studied. Mild to moderate side effects of diarrhea, soft stools and gastric pain were

Scheme 12: Synthesis of Intermediate (XI) of Sitafloxacin



observed in 11.8% of patients and mild laboratory abnormalities (elevation in GPT and/or GOT and eosinophilia) were observed in 19.9% of patients (7).

Sitafloxacin has been studied in patients with skin infections, giving overall efficacy rates of 70-100%. The results indicated good efficacy in all types of infections, although a rather high incidence of side effects and laboratory abnormalities was reported. Most of the symptoms/changes in values were mild or moderate, however, and sitafloxacin is considered to be a clinically useful antibiotic (8).

Sitofloxacin has shown activity against *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Chlamydia* spp., the causative pathogens of community-acquired pneumonia (9).

Sitafloxacin treatment has been evaluated in numerous clinical conditions, including osteomyelitis, suppurative arthritis, dental and oral surgical infections, infectious enteritis, as well as genitourinary tract, obstetric and gynecological, ocular, surgical and otorhinolaryngological infections (10-17).

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Tirofiban Hydrochloride
Aggrastat®

Platelet Antiaggregatory gpIIb/IIIa Receptor Antagonist

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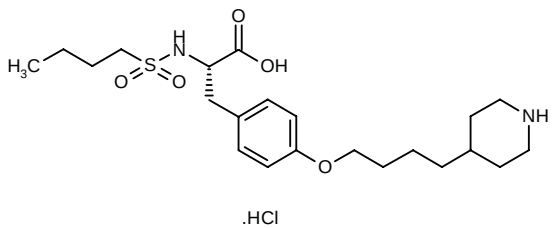

$C_{22}H_{36}N_2O_5S.HCl$ **Merck & Co.; Banyu**

Tirofiban (final concentration, 0.01 M) or saline was added to platelet-rich plasma from 19 patients with diabetes mellitus and 20 healthy volunteers. The plasma was then perfused over a fibronectin-coated slide at a shear rate of 25/s; 8 min later the number of adherent platelets was determined. While no significant difference in adhesion between patient and control groups was observed, tirofiban significantly reduced the number of adhered platelets in both groups (1).

The effects of tirofiban *versus* placebo on adverse cardiac outcome and coronary artery restenosis at 6 months have been assessed. All subjects received either placebo or tirofiban (10 μg/kg i.v. bolus for 3 min) followed by a 36-h infusion (0.15 μg/kg/min). Tirofiban failed to reduce the incidence of restenosis at 6 months (2).

Results from a PRISM-PLUS study have demonstrated that addition of tirofiban to heparin therapy reduced cardiac ischemic complications in diabetic patients with unstable angina/non-Q wave myocardial infarction. Although diabetic patients tended to be older than nondiabetic patients and had prior myocardial infaction, treatment with tirofiban and heparin sustained reductions in major cardiac outcomes in this group (3).

A 43% decrease in the incidence of death and/or myocardial infarction was observed in patients with coronary artery disease who received tirofiban + heparin when compared to patients who were administered heparin alone. In addition, the CRP levels of the 65 patients enrolled in this study increased progressively following development of unstable angina/non-Q wave myocardial infarction; this increase was less for those patients taking tirofiban + heparin at 24 h postdrug discontinuation (4).

Using the results of a PRISM-PLUS trial, a model was created to determine the differences in days of hospitalization in 1563 patients with unstable angina or non Q-wave myocardial infarction treated with heparin alone or in combination with tirofiban. Patients receiving heparin and tirofiban had an average of 0.59 fewer days of hospitalization than patients on heparin alone. Tirofiban-treated patients in intensive care, step-down unit and regular wards had 0.19, 0.16 and 0.24 fewer days of hospitalization, respectively. The results obtained

were not statistically significant but suggest that for every 2 people treated with tirofiban, 1 day of hospital stay is avoided and for every 5 treated with the agent, approximately 1 ICU day is avoided (5).

A review describing the pharmacokinetics and pharmacodynamics of tirofiban in normal volunteers and in patients with coronary artery disease, including patients with renal or hepatic insufficiency has been published. The results of the phase III program studying the efficacy and safety profile of the compound, as well as modalities for its clinical use, are also included in the review (6).

Tirofiban hydrochloride (Aggrastat®) has received regulatory approval from Health Canada. It is the only gpIIb/IIIa receptor antagonist indicated to reduce the rate of deaths, new heart attacks and refractory ischemia in patients with unstable angina. Aggrastat® is administered intravenously for 48-108 h in conjunction with aspirin and heparin and is generally well tolerated. Clinical trials showed a slightly more frequent occurrence of bleeding than with heparin alone (7).

Aggrastat® has recently become available in the U.K. for use in the prevention of early myocardial infarction in patients with unstable angina or non-Q wave myocardial infarction with last episode of chest pain within 12 h and ECG changes and/or elevated cardiac enzymes. It is supplied as 50-ml vials containing a concentrate for solution for infusion of 0.25 mg/ml tirofiban as the hydrochloride monohydrate salt (8).

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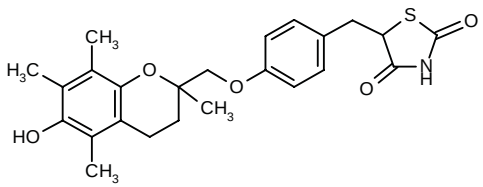
Troglitazone
Rezulin®
Romozin®

Antidiabetic

EN: 105806



$C_{24}H_{27}NO_5S$

Sankyo; Warner-Lambert; Glaxo Wellcome

Warner-Lambert has amended a 400-patient study designed to evaluate the potential of troglitazone for reducing insulin resistance in women with polycystic ovarian syndrome, discontinuing treatment in the approximately 120 patients who have yet to complete the study. The company will evaluate the continued therapeutic effect of troglitazone in this study after treatment is stopped. Also, Warner-Lambert will delay the initiation of a 5-year study to investigate the drug's effect in patients with impaired glucose tolerance, a condition of insulin resistance that precedes type II diabetes. An ongoing 5-year trial in women with a history of gestational diabetes, currently in its fourth year, will continue (1, 2).

Significant new changes are being made to the labeling and recommended uses for troglitazone (Rezulin®) due to further evidence of serious and sometimes fatal liver injury in patients treated with the drug. The indication for Rezulin® should be limited to type II diabetes patients who are not adequately controlled by other therapy. This product should not be used as initial single-agent therapy. Furthermore, prospective patients should have liver chemistries tested before starting therapy, monthly during the first year of therapy and quarterly thereafter. Warner-Lambert will prepare a patient information sheet with FDA-approved information about the safe and effective use of Rezulin®, which will be available to patients through their pharmacists with each prescription of the product. A new indication will also be added to the drug's labeling for its use in combination with sulfonylureas and metformin in patients whose diabetes is not adequately controlled by the combined use of these other drugs alone (3).

The U.K. Medicines Control Agency has rejected Glaxo Wellcome's application to reintroduce troglitazone (Romozin®) for the treatment of type II diabetes in the U.K. Glaxo Wellcome and Sankyo voluntarily suspended marketing of troglitazone in the U.K. following concerns over a significant increase in the number of reported serious hepatic adverse events in patients treated with the product in the U.S. and Japan. Troglitazone is licensed by Sankyo to Glaxo Wellcome for Europe and other countries, including South Africa and Israel. The U.K. is the only country in which Glaxo Wellcome has introduced the drug (4).

1. *New study will assess troglitazone in the prevention of IGT.* DailyDrugNews.com (Daily Essentials) Nov 26, 1998.

2. *Warner-Lambert updates U.S. status of Rezulin.* DailyDrugNews.com (Daily Essentials) Jan 18, 1999.

3. *Labeling and use changes announced for Rezulin.* DailyDrugNews.com (Daily Essentials) June 18, 1999.

4. *Romozin cannot be reintroduced in the U.K., MCA says.* DailyDrugNews.com (Daily Essentials) March 23, 1999.

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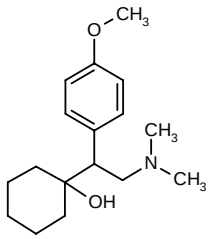
Venlafaxine
Effexor®
Efexor®

Antidepressant

EN: 100721



$C_{17}H_{27}NO_2$

Wyeth-Ayerst; Scios; Almirall Prodesfarma

The FDA has approved a new indication for Wyeth-Ayerst's venlafaxine hydrochloride extended-release capsules (Effexor® XR) for the treatment of generalized anxiety disorder (GAD). Effexor® is the first and only antidepressant proven effective in relieving GAD. The approval was based on the results of 2 short-term, double-blind, placebo-controlled trials involving 782 patients with GAD. The trials were the first to successfully demonstrate the efficacy of an antidepressant in treating patients with GAD who did not have major depressive disorder. In the first study, patients were treated with a daily dose of venlafaxine 75, 150 or 225 mg or placebo for 8 weeks. The second study included patients treated with venlafaxine 75 or 150 mg or placebo for 8 weeks. In both studies, drug-treated patients demonstrated statistically significant reductions in anxiety symptoms compared to the placebo groups based on standard psychiatric measures. The most common adverse events were nausea, dry mouth, insomnia, abnormal ejaculation, anorexia, constipation, nervousness and sweating (1).

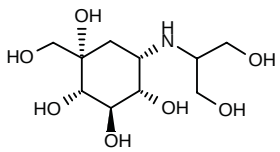
1. *Effexor XR receives FDA approval for treatment of GAD.* DailyDrugNews.com (Daily Essentials) March 15, 1999.

Original monograph - Drugs Fut 1988, 13: 839.

Voglibose
Glustat®
Basen®

Antidiabetic

EN: 116077



$C_{10}H_{21}NO_7$

Takeda

The potential efficacy of voglibose for adjunctive treatment of mild portal-systemic encephalopathy (PSE) in cirrhotic patients was evaluated in a double-blind, randomized, controlled trial in 35 patients who were treated for 2 weeks with voglibose (2 mg t.i.d.) or placebo. Significantly more patients on voglibose (83% *vs.* 35% on placebo) had at least a 40% improvement in the overall PSE index. Furthermore, mean stool pH decreased following treatment with voglibose but not placebo, and a significant improvement was observed in number connection test performance in voglibose-treated patients. Diarrhea was reported by 7 patients in the voglibose group but none on placebo. These findings support the use of voglibose as an adjunctive treatment of PSE, although further clinical studies are necessary (1).

1. Uribe, M. et al. *Beneficial effect of carbohydrate maldigestion induced by a disaccharidase inhibitor (AO-128) in the treatment of chronic portal-systemic encephalopathy - A double-blind, randomized, controlled trial.* Scand J Gastroenterol 1998, 33(10): 1099.

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