Drugs of the Future 2004, 29(10): 992-997
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CCC: 0377-8282/2004

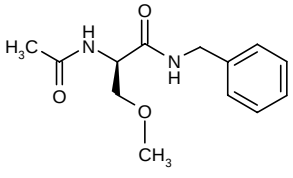
Lacosamide

Prop INN

Antiepileptic Drug
Treatment of Neuropathic Pain
NMDA Glycine-Site Antagonist

Erlosamide (former INN)
Harkoseride
ADD-234037
SPM-927

2(*R*)-Acetamido-*N*-benzyl-3-methoxypropionamide
N-Acetyl-*O*-methyl-D-serine benzylamide



$C_{13}H_{18}N_2O_3$

Mol wt: 250.2962

CAS: 175481-36-4

EN: 278582

Abstract

Lacosamide is a novel, glycine-site NMDA receptor antagonist in development for the treatment of both epilepsy and neuropathic pain. It effectively controlled seizures in a rat experimental status epilepticus model, and also produced dose-dependent reductions in acute and chronic pain in this species. A phase II clinical study of lacosamide as adjunctive therapy demonstrated a median percent reduction in partial seizures of 31.8% over a 4-week maintenance period, with one-third of patients experiencing at least a 50% reduction in seizure frequency. Another phase II study, and an extension study of 24 weeks' duration, also demonstrated clinically relevant reductions in seizure frequency and 50% response rates in up to 54% of patients. Lacosamide has also shown efficacy in the treatment of diabetic neuropathy, and has been reasonably well tolerated in clinical studies, with CNS effects being the most commonly reported. No interactions with other antiepileptic drugs have been observed. Lacosamide entered phase III clinical trials in the second quarter of 2004.

Synthesis

Lacosamide can be obtained by several related ways:

1) Reaction of D-serine (I) with benzyloxycarbonyl chloride and MgO in ethyl ether/water gives *N*-(benzyloxycarbonyl)-D-serine (II), which is treated with methyl iodide and Ag_2O in acetonitrile to yield *N*-(benzyloxycarbonyl)-*O*-methyl-D-serine methyl ester (III). Hydrolysis of compound (III) with K_2CO_3 in MeOH/water affords the free acid (IV), which is treated with benzylamine (V), isobutyl chloroformate and NMM to provide N^1-benzyl-N^2-(benzyloxycarbonyl)-*O*-methyl-D-serinamide (VI). The deprotection of amide (VI) at the α-amino group with H_2 over Pd/C in methanol gives N^1-benzyl-*O*-methyl-D-serinamide (VII), which is finally treated with Ac_2O and DMAP in pyridine (1-3). Scheme 1.

2) Esterification of D-serine (I) with methanol and HCl gives D-serine methyl ester (VIII), which is condensed with benzylamine (V) to yield N^1-benzyl-D-serinamide (IX). Acylation of amide (IX) with acetic anhydride affords N^2-acetyl-N^1-benzyl-D-serinamide (X), which is finally methylated with methyl iodide and Ag_2O (1, 2, 4). Scheme 2.

3) Acylation of D-serine (I) with Ac_2O in AcOH gives *N*-acetyl-D-serine (XI), which is condensed with benzylamine (V) by means of isobutyl chloroformate to yield N^2-acetyl-N^1-benzyl-D-serinamide (X). Finally this compound is methylated with methyl iodide and Ag_2O (1, 2). Scheme 3.

4) Reaction of D-serine (I) with benzyloxycarbonyl chloride and MgO gives *N*-(benzyloxycarbonyl)-D-serine (II), which is condensed with benzylamine (V) by means of isobutyl chloroformate and NMM to yield N^1-benzyl-N^2-(benzyloxycarbonyl)-D-serinamide (XII). Alkylation of amide (XII) with methyl iodide and Ag_2O affords the *O*-methylated amide (V), which is finally *N*-deprotected with H_2 over Pd/C and acylated with Ac_2O as before (5). Scheme 4.

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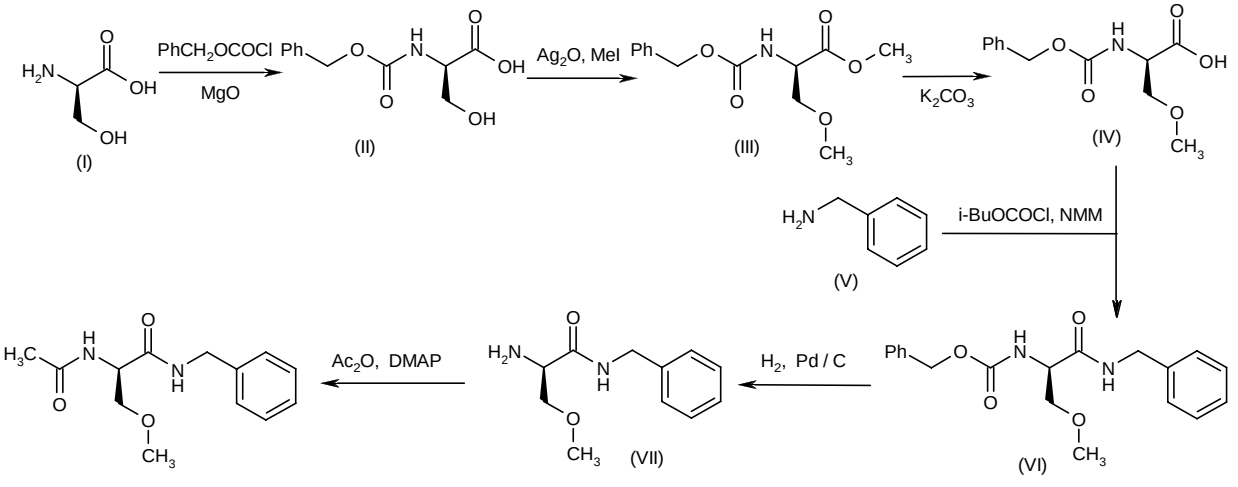
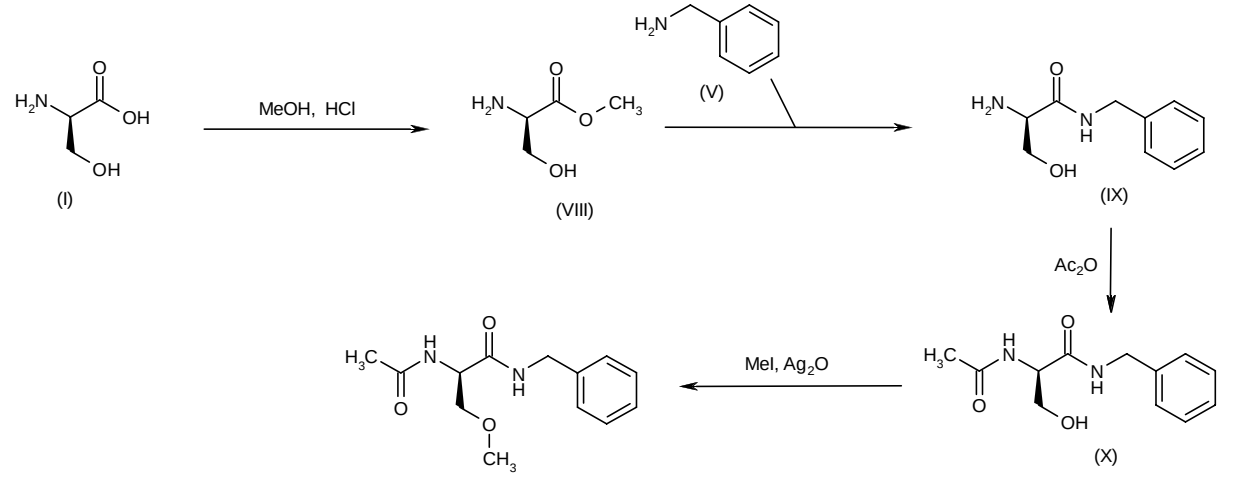
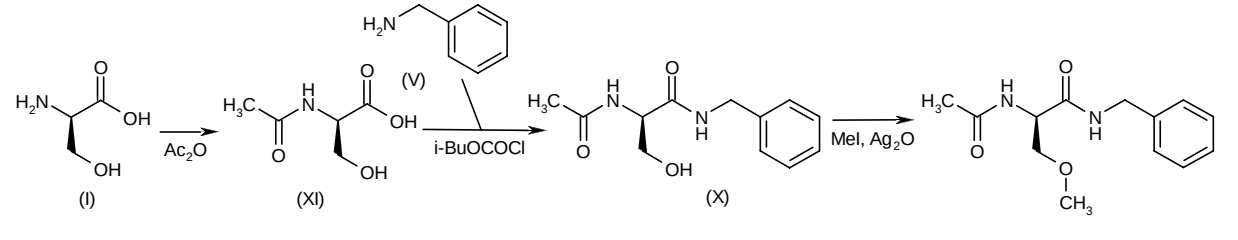
Scheme 1: Synthesis of Lacosamide



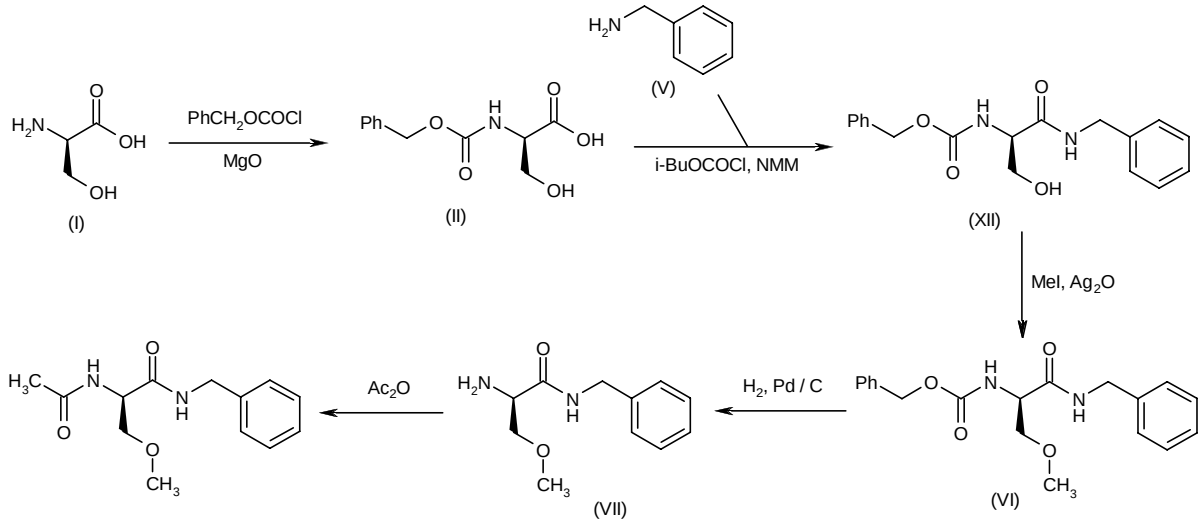
Scheme 2: Synthesis of Lacosamide



Scheme 3: Synthesis of Lacosamide



Scheme 4: Synthesis of Lacosamide



Introduction

Epilepsy results in an individual being susceptible to recurrent unprovoked seizures, defined by a combination of clinical features and abnormal electroencephalogram (EEG) recordings. Epilepsy is one of the most common neurological disorders, and the causes are multifactorial. Appropriate therapy is dependent upon the accurate classification of the disorder and the type of seizure occurring in an individual, and aims to decrease the frequency, duration and severity of seizures. There is strong evidence to implicate alterations in the NMDA glutamate receptor in epilepsy. Glutamate is the principal excitatory amino acid in the central nervous system (CNS) and most excitatory synaptic transmission is mediated via this route. Pain signaling is also mediated via glutamate receptors, and the common alteration in neural function partly explains the accepted finding that many antiepileptic drugs are also effective in neuropathic pain. Neuropathic pain is a chronic form of pain represented by a heterogeneous group of conditions affecting the normal functioning of the peripheral nervous system or the CNS. It is characterized by neuronal hyperexcitability and does not respond well to traditional analgesics. The use of drugs acting on NMDA-site receptors, however, has been limited by either insufficient efficacy or intolerable adverse effects (6-13).

Lacosamide (formerly erlosamide or harkoseride) is a glycine-site NMDA antagonist that belongs to a novel class of functionalized amino acids. The compound is currently in phase III clinical development for the treatment of epilepsy and neuropathic pain.

Pharmacological Actions

Highly potent anticonvulsant activity was demonstrated for lacosamide using the maximal electroshock (MES) seizure test in mice and rats. Following i.p. dosing in mice, the ED_{50} for seizure control was 4.5 mg/kg *versus* 6.5 mg/kg for phenytoin. Following oral administration in rats, the ED_{50} was 3.9 mg/kg (4, 5, 14, 15).

In a rat experimental status epilepticus model, cobalt-lesioned rats were treated with lacosamide 1.25-120 mg/kg after the second generalized tonic-clonic seizure. The ED_{50} was 45.4 mg/kg. Seizure control was achieved quickly and maintained for 90 min; it was dose- and concentration-dependent with minimal variability. Pharmacokinetic evaluation indicated that lacosamide demonstrated rapid absorption from the peritoneal space, a long elimination half-life and rapid penetration into the brain. Very few side effects were observed at doses below 80 mg/kg (16, 17).

The effect of lacosamide on neuropathic pain-like behaviors was also investigated in rats. Spinal cord and infraorbital nerve injury were induced using a photochemical method. Mechanical and cold allodynia-like behaviors were alleviated in a dose-dependent manner following single doses of lacosamide of 10-20 mg/kg. Motor impairment or strong sedation was not observed. Chronic administration of the drug at a dose of 20 mg/kg twice daily totally reversed the allodynia-like state, without any evidence of tolerance. A higher dose of 30 mg/kg also reduced facial mechanical hypersensitivity in rats with infraorbital nerve injury (18).

Lacosamide was also investigated at doses of 5, 10, 20 and 40 mg/kg administered i.p. in well-defined rat models of acute and chronic pain. The most sensitive tests were those of prolonged inflammatory pain (the

formalin test) and chronic neuropathic pain (mechanical allodynia). Lacosamide produced dose-dependent reductions in nociceptive behavior in these models starting at a dose of 10 mg/kg. At doses of 20 mg/kg and above, chronic neuropathic pain (thermal hyperalgesia) and acute inflammatory mechanical hyperalgesia (paw pressure test) were also significantly reduced (19, 20).

Toxicity

The hepatic effects of lacosamide were investigated in rats following daily doses of 3.9 mg/kg (the MES ED_{50}) or 100 mg/kg for 7 days. At the higher dose, lacosamide increased the activity of the liver transferases glutathione *S*-transferase and UDP-glucuronosyltransferase by 47% and 54%, respectively. There was no increase in serum alanine aminotransferase activity. No influence on cytochrome P-450 concentration was observed, in contrast to carbamazepine (21).

Pharmacokinetics and Metabolism

The pharmacokinetics and safety and tolerability profile of orally administered lacosamide were evaluated in a dose-escalating single-dose trial, a multiple-dose trial and a food interaction trial in healthy subjects. In the single-dose trial, doses of 400, 600 and 800 mg lacosamide were administered to 16 subjects, and doses of 300 or 500 mg lacosamide twice daily for 14 days were administered to 33 subjects in the multiple-dose trial. Both trials were conducted under randomized, double-blind, placebo-controlled designs. Lacosamide was rapidly absorbed, with dose-proportional plasma concentrations, and pharmacokinetics were comparable after single and multiple dosing. Following doses of 400 and 600 mg lacosamide, the peak plasma concentrations (C_{max}) were 8.7 and 14.3 μg/ml, respectively. The corresponding values for the AUC were 143 and 231 μg·h/ml, respectively. The terminal half-life of approximately 13 h supported a once- or twice-daily treatment regimen. Concomitant food intake had no effect on the pharmacokinetic parameters of lacosamide. The drug was safe and generally well tolerated, with no effect on vital signs, ECG parameters or clinical laboratory values. The most frequently reported adverse events were CNS-related, with 7 of 11 subjects in the multiple-dose study requiring a dose reduction from 500 mg to 400 mg lacosamide (22).

Clinical Studies

Possible drug interactions between lacosamide and the antiepileptic drugs valproic acid and carbamazepine were investigated in 4 open-label, randomized, multiple-dose trials in healthy subjects. No evidence for a drug-drug interaction between these compounds was observed; the 90% confidence intervals of the AUC and C_{max} point estimates were within the bioequivalence ranges of 80-125%. The rate and extent of absorption of each drug were unchanged following administration alone or in combination (23).

An open-label, dose-titration study was performed to determine the tolerability and efficacy of lacosamide as adjunctive therapy in patients with partial seizures with or without secondary generalization. Patients were receiving a stable regimen of up to 2 antiepileptic drugs and had 4 or more seizures/month. Following a 4-week baseline period, patients entered a maximum 8-week titration period, during which time lacosamide was increased from 50 mg twice daily to a maximum of 300 mg twice daily on a weekly basis. Patients received the maximum tolerated dose (MTD) during a maintenance period of 4 weeks. A total of 90 patients were evaluable for efficacy. The most common MTD was 600 mg/day (median of 300 mg/day). Lacosamide reduced the incidence of partial seizures, as shown by a median decrease in seizure frequency of 3.88 per 28 days, corresponding to a median percent reduction of 31.8%. One-third of patients had a reduction in seizure frequency of at least 50% and 7 were seizure-free. Plasma concentrations of concomitant antiepileptic drugs remained stable during treatment with lacosamide, indicating that the observed seizure reduction was not due to increased levels of these drugs. The most frequently reported adverse events were CNS-related, and no clinically important changes in vital signs or laboratory parameters were observed. Weekly pharmacokinetic analysis and ECG recordings showed no correlation between ECG parameters and lacosamide plasma concentrations, indicating that lacosamide, at doses up to 600 mg/day, had no clinically important influence on conductivity (P-R interval) and repolarization (Q-T_c interval) of the myocardium (24-27).

Patients who completed open-label primary trials were eligible to enter an open-label extension trial. Of 68 patients enrolled in the extension, data were available from 54 at 24 weeks. The mean age of the patients was 40 years and the median dose of lacosamide was 400 mg/day. The median percentage reduction in seizure frequency for evaluable patients at 24 weeks was 53%, and 54% of these patients had a reduction in seizure frequency of at least 50% compared with baseline of the primary trial. Lacosamide was well tolerated, with only 1 patient discontinuing the trial due to an adverse event (28).

In a multicenter, double-blind, placebo-controlled phase IIb study, 497 patients with partial seizures were randomized to treatment with lacosamide as adjunctive therapy for 12 weeks. The primary endpoints of reduction in seizure frequency and 50% response rate were achieved, and the study demonstrated statistically significant and clinically relevant reductions in seizure frequency. More than 90% of patients who completed the study entered an open-label follow-up (29).

The efficacy of lacosamide in the treatment of neuropathic pain was assessed in a single-center, open-label, dose-escalating study in 25 patients with resistant neuropathic pain of at least 4 months' duration. Patients

completed a dose-escalation phase over 6 weeks, during which the lacosamide dose was increased by 100 mg weekly, if required, to a maximum of 600 mg daily. Treatment was continued in a 4-week maintenance phase, then withdrawn without tapering for a further 2-week assessment period. Mean daily pain scores recorded using an 11-point Likert scale fell by 0.83, and increased by 0.58 upon lacosamide withdrawal. There were decreases in mean scores for shooting pain, paresthesia and allodynia, but less effect on numbness and burning pain. The study indicated that lacosamide may have an analgesic effect in neuropathic pain, although the overall pain reduction was not statistically significant, and approximately 50% of patients discontinued due to adverse events (30, 31).

A randomized, double-blind, placebo-controlled pilot study was conducted in 44 patients with postherpetic neuralgia. Patients were titrated over a 6-week period to a lacosamide dose of either 300 or 600 mg/day, or placebo. A 4-week maintenance period and a dose-tapering phase followed. There were no clinically relevant differences between lacosamide and placebo in changes in the average daily pain score measured using an 11-point Likert scale. Lacosamide was generally well tolerated, with no evidence of effect on Q-T_c intervals during ECG recordings. CNS-related adverse events were more frequently reported at the higher dose level (32).

The analgesic effect and safety of lacosamide were also investigated in patients with neuropathic pain due to diabetic distal sensory polyneuropathy. In this multicenter, randomized, double-blind, placebo-controlled, dose-escalation study, 119 patients received lacosamide at up to 400 mg/day or placebo. Patients were followed during a titration phase, a 4-week maintenance phase, a dose-tapering phase and a follow-up period. There were statistically significant and clinically relevant differences in favor of lacosamide in the mean reduction in overall pain from baseline to the maintenance period, as measured by an 11-point Likert scale. There were also statistically significant differences in the mean reduction in pain interference with sleep/activity, and consistent changes in other secondary efficacy parameters. This study demonstrated the efficacy of lacosamide in diabetic neuropathic pain, and a comparable safety profile to placebo with doses up to 400 mg/day (33, 34).

Lacosamide entered phase III clinical trials in May 2004 (29).

Source

Lacosamide was originally discovered at the University of Houston (US) and licensed to Harris FRC Corp. (US) by Research Corporation Technologies, Inc. (US). Schwarz Pharma AG (DE) has acquired rights from Harris FRC for the development and commercialization of lacosamide worldwide except Japan.

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