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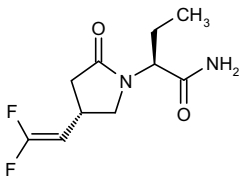
# Seletracetam

*Antiepileptic Drug*

Prop INN; USAN

## UCB-44212

2(*S*)-[4(*S*)-(2,2-Difluorovinyl)-2-oxopyrrolidin-1-yl]butyramide



$C_{10}H_{14}F_2N_2O_2$
Mol wt: 232.2272

CAS: 357336-74-4

EN: 357513

**Abstract**

Levetiracetam (Keppra®; UCB) is currently the most promising agent for the treatment of refractory partial-onset seizures in adults. Seletracetam, a levetiracetam analogue, was designed to optimize the efficacy and safety profile of levetiracetam. Preclinical studies demonstrated that seletracetam was effective in rodent seizure models. Both preclinical and phase I clinical studies showed that seletracetam was active as an antiepileptic, safe and well tolerated. Phase II clinical studies of seletracetam as add-on therapy were carried out in adult patients with refractory partial-onset seizures, and it demonstrated promising efficacy, reducing seizure frequency by approximately 40% from baseline. The studies also showed that seletracetam was well tolerated over the dose range tested (20-160 mg/day). Phase III clinical trials are expected to open for recruitment soon.

### Synthesis

Seletracetam can be prepared by two different ways:

The condensation of dimethyl itaconate (I) with *tert*-butyl L-2-aminobutyrate (II) in refluxing MeOH produces the pyrrolidinone (III) as a mixture of diastereoisomers at the methoxycarbonyl group. After reduction of the methyl ester (III) to the primary alcohol (IV) by means of $NaBH_4$ in EtOH, oxidation with $CrO_3$ in pyridine/$CH_2Cl_2$ affords aldehyde (V). Subsequent reaction of (V) with dibromodifluoromethane and hexamethylphosphorous triamide gives the difluorovinyl *tert*-butyl ester (VI), which is then cleaved by treatment with trifluoroacetic acid to yield the carboxylic acid (VII), which is activated as the mixed anhydride (VIII) with ethyl chloroformate and $Et_3N$ in cold $CH_2Cl_2$. The title carboxamide is finally obtained by treatment of anhydride (VIII) with ammonia in $CH_2Cl_2$, followed by chromatographic separation of the obtained diastereomeric mixture (1). Scheme 1.

In an alternative method, alkaline hydrolysis of 4,4,4-trifluoro-2-butenyl acetate (IX) in the presence of benzyl triethylammonium chloride, followed by treatment of the intermediate alcohol (X) with *p*-toluenesulfonyl chloride, gives the trifluorobutenyl tosylate (XI). Subsequent condensation of tosylate (XI) with L-2-aminobutyramide (XII) yields the allylic amine (XIII), which is then heated with neat dimethyl malonate (XIV), giving the malonamide (XV). Cyclization of (XV) in the presence of DBU affords the difluorovinyl pyrrolidinone (XVI) as a mixture of four diastereoisomers. Hydrolysis of the methyl ester (XVI), followed by re-crystallization from MeOH, provides the 4(*S*),3(*R,S*)-pyrrolidone (XVII), which finally undergoes decarboxylation in boiling methyl isobutyl ketone to furnish the title compound (2). Scheme 2.

### Background

Antiepileptic drug (AED) development has progressed dramatically during the past decade. International authorities have approved 10 new AEDs since 1993. Although the majority of the larger pharmaceutical companies have slowed down their direct investment in AED development, there is still a promising array of new chemical entities in the development pipeline with different mechanisms of action. A number of these represent improvements on currently available drugs, such as levetiracetam, valproate, carbamazepine, felbamate and benzodiazepine-like drugs (3).

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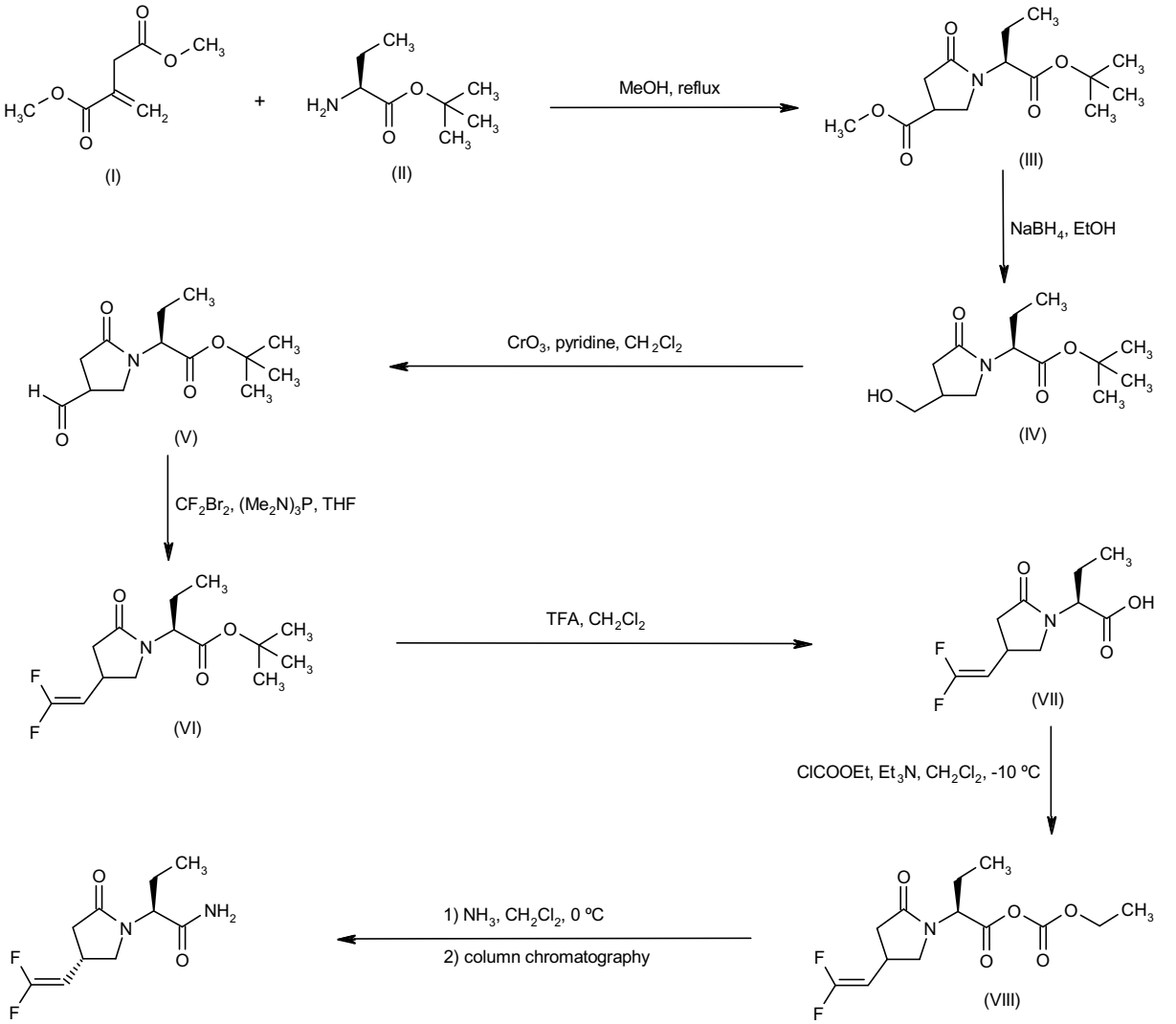
**Scheme 1: Synthesis of Seletracetam**




Levetiracetam (Keppra®; UCB) has demonstrated remarkable antiepileptic efficacy and good tolerability in clinical studies, and it is currently the most promising chemical agent for the treatment of refractory partial-onset seizures in adults. Recently, synaptic vesicle protein of type 2A (SV2A) was recognized as the target of levetiracetam, and a strong correlation between the affinity of a compound for SV2A and its ability to protect against seizures was observed in a mouse model of epilepsy. To discover ligands with strong affinities for SV2A, over 1,000 molecules have been studied. Among all the molecules tested, seletracetam (UCB-44212) showed exceptional pharmacological characteristics, including high affinity and selectivity for SV2A both *in vivo* and *in vitro* and was selected for further development (3, 4). Phase III clinical trials of seletracetam are planned.

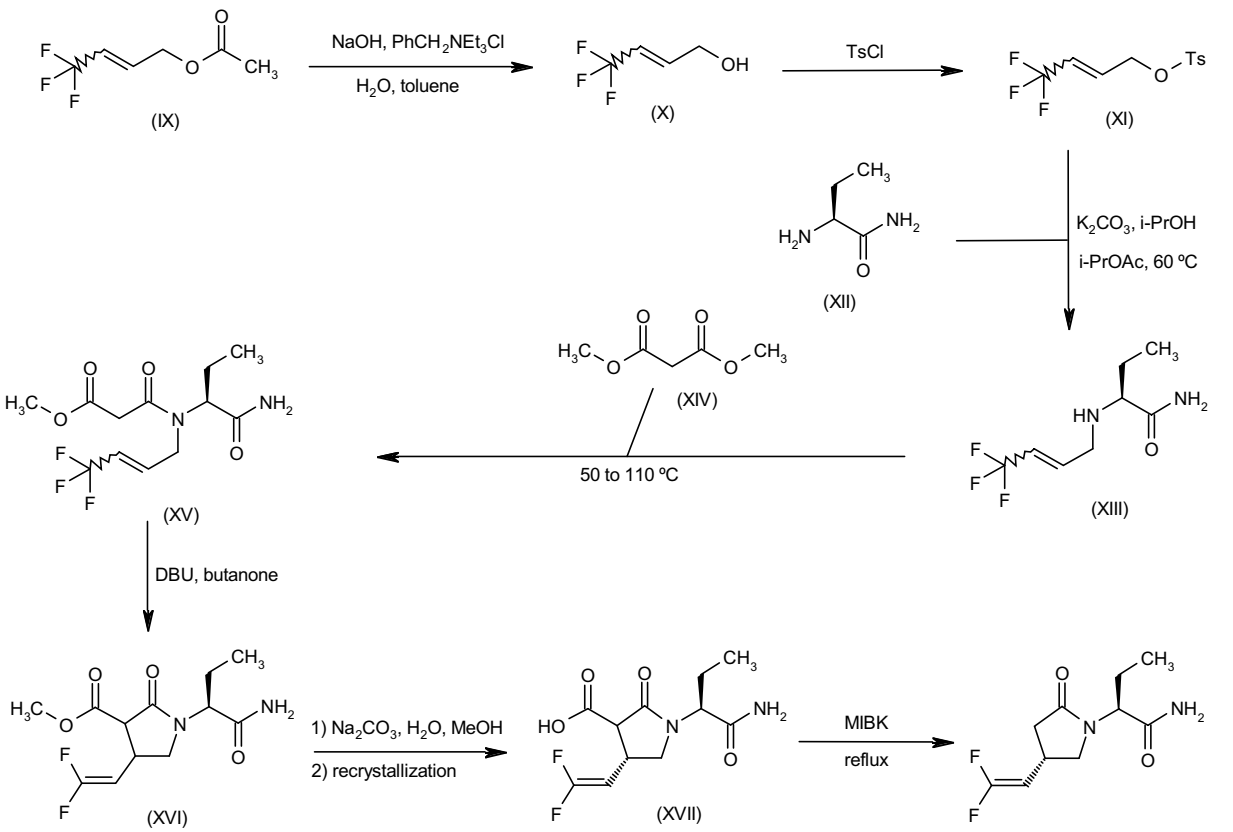
## Preclinical Pharmacology

The affinity of seletracetam for SV2A ($pK_i$ = 7.1) is 10-fold higher than that of levetiracetam ($pK_i$ = 6.1) and early preclinical studies showed that seletracetam has a higher potency than levetiracetam in rodent models of epilepsy (5-12).

*In vitro* studies using cultured hippocampal neurons showed that seletracetam had no direct effect on GABA-, glycine-, kainate- or AMPA-gated currents at up to 100 μM, but that it potently blocked the inhibitory effect of zinc and β-carboline on glycine-gated currents (5).

The effect of seletracetam on epileptiform responses was studied in *in vitro* models of epilepsy. Epileptiform responses were induced in rat hippocampal slices by either perfusion with a high $K^+$/low $Ca^{2+}$ fluid (HKLCF) or

**Scheme 2: Synthesis of Seletracetam**




by the addition of bicuculline methiodide. In both models, seletracetam inhibited the epileptiform responses with higher potency and efficacy than levetiracetam. Seletracetam (1-10 μM; maximal effect at 3.2 μM) significantly decreased the HKLCF-induced increase in population spike amplitude and the number of repetitive population spikes. Seletracetam also inhibited bicuculline-induced population spikes, with a maximal effect at 10 μM. Maximal effects of levetiracetam have been reported at 32 μM (6, 7, 12).

Further *in vitro* experiments were performed to elucidate the mechanisms of antiepileptic activity of seletracetam. In one study, the effect of seletracetam on high-voltage-activated (HVA) calcium ($Ca^{2+}$) currents and the spontaneous epileptiform repetitive paroxysmal depolarization shift induced by reducing the $Mg^{2+}$ concentration and by adding bicuculline and 4-aminopyridine was studied in rat cortical neurons using whole-cell patch-clamp techniques. It reduced HVA currents with an $IC_{50}$ of 271 ± 2.1 nM, with maximum inhibition (43.13 ± 4.6%) observed at 10 μM. Seletracetam (0.03-300 μM) also reduced paroxysmal depolarization shifts in a concentration-dependent manner. Seletracetam reduced the concomitant increase in intracellular calcium concentration ($[Ca^{2+}]_i$) by up to 75%, with a peak effect at 30 μM (8). The effect of seletracetam on neuronal tetrodotoxin-sensitive $Na^{2+}$ currents was also studied in rat hippocampal neurons. It showed no inhibition of neuronal sodium currents at up to 100 μM (9).

Seletracetam displayed potent antiepileptic activity in several animal models, giving $ED_{50}$ values of 0.31, 0.17 and 0.15 mg/kg i.p., respectively, in corneally kindled mice, audiogenic seizure-prone mice and Genetic Absence Epilepsy Rats from Strasbourg (GAERS); it also protected against seizures in hippocampal kindled rats, with a minimum effective dose of 0.23 mg/kg p.o. On the other hand, $TD_{50}$ values in the rotarod test in corneally kindled rats and GAERS were 325 and 449 mg/kg i.p., respectively (7, 11).

The anticonvulsant activity of seletracetam was also studied in adult male rats using a model of self-sustaining status epilepticus (SSSE) induced by 30-min intermittent stimulation of the perforant path. Seletracetam at doses of 300, 200 and 100 mg/kg i.v. dose-dependently reduced seizure duration from 32.2 min in control animals and 32 min in animals administered levetiracetam (500 mg/kg i.v.) to 3.5, 11 and 25 min, respectively. At the highest dose, seletracetam demonstrated stronger seizure pro-

tection than previously reported for diazepam (10 mg/kg i.v.) and comparable to that previously reported for phenytoin (50 mg/kg i.v.) (10).

The ability of seletracetam to reduce dyskinesia after L-DOPA monotherapy was evaluated in the MPTP-lesioned marmoset model of Parkinson's disease. Seletracetam (1, 3, 10 and 30 mg/kg) was given orally in combination with L-DOPA (13.9 mg/kg) and demonstrated a comparable antiparkinsonian effect to L-DOPA monotherapy, while it significantly reduced dyskinesia at the two higher doses compared to L-DOPA monotherapy (13). Similar results were obtained using a higher dose of L-DOPA (76 ± 7 mg/kg) (14).

## Pharmacokinetics and Metabolism

The pharmacokinetics of seletracetam were investigated in a randomized, double-blind, placebo-controlled phase I study in healthy male volunteers administered single doses of 2-600 mg. The study demonstrated that seletracetam was rapidly absorbed and had linear pharmacokinetics; a half-life of 8 h was reported. Co-administration with a high-fat meal reduced the $C_{max}$ but not the AUC. Seletracetam was mainly eliminated via the urine (60% of dose in 48 h) as both the unchanged compound and a carboxylic acid metabolite (15).

## Safety

To study the safety of seletracetam in humans, single (2-600 mg) and multiple doses (40-400 mg/day for 2 weeks) were administered to healthy male volunteers in randomized, double-blind, placebo-controlled trials. No serious adverse events were observed in the studies. The most frequent side effects, including dizziness, drowsiness, euphoria and feeling drunk, were mild or moderate. The side effects generally appeared shortly after the first dose and lasted for less than 12 h. No treatment-related changes in clinical laboratory tests, vital signs or electrocardiograms, nor significant changes in physical or neurological function, were observed (15, 16).

## Clinical Studies

The efficacy and safety of seletracetam as an add-on therapy in the treatment of adult patients with refractory partial-onset seizures receiving up to three AEDS were assessed in two open-label, multicenter, dose-escalation phase II studies. In one study, seletracetam was given to patients who were experiencing partial-onset seizures while receiving levetiracetam as one of the concomitant drugs. Seletracetam was given to the patients at doses of 10, 20, 40 and 80 mg b.i.d. In both studies, promising efficacy was observed, with seletracetam reducing seizure frequency by approximately 40% from baseline. The studies also suggested that seletracetam was well tolerated over the dose range evaluated (17-19).

Two phase III trials in patients with epilepsy are expected to start patient recruitment soon (20).

## Source

UCB (BE).

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