

Industrial process for preparation of Levetiracetam.

Dr.Krishna sarma.Pathy

Levetiracetam belongs to the class of compounds used in the treatment of epilepsy so it has huge demand in market and it is worth to develop the product.

INTRODUCTION

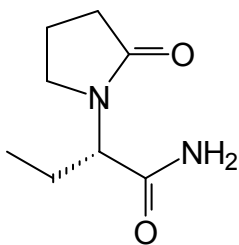
Levetiracetam (Keppra) was approved by the United States Food and Drug Administration in 1999. The exact mechanism by which levetiracetam exerts its antiseizure effects is not completely understood, although it is a different class of drug from other anti-seizure. It is well tolerated in human patients with minimal side effects.

In dogs, levetiracetam is well absorbed after oral administration, is not significantly bound to protein, and is excreted in the urine with minimal liver metabolism. The elimination half-life in dogs is 3.3 hours (compared to 7.7 hours in people). Safety studies in laboratory dogs showed minimal adverse effects even at high doses (UCB Pharma, Inc. Data on file.)

There are no published studies evaluating levetiracetam in dogs with idiopathic epilepsy, but several veterinary schools are currently conducting a clinical trial of levetiracetam in dogs with idiopathic epilepsy uncontrolled with phenobarbital and bromide.

A white to off-white crystalline powder with a faint odour and bitter taste. Crystals from ethyl acetate, M.p. 117°. It is very soluble in water (104 g/100 mL); freely soluble in chloroform (65.3 g/100 mL) and methanol (53.6 g/100 mL); soluble in ethanol (16.5 g/100 mL); sparingly soluble in acetonitrile (5.7 g/100 mL); practically insoluble in *n*-hexane.

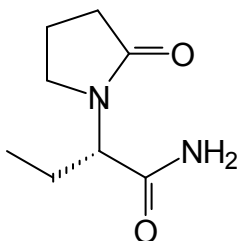
This is a chiral compound with the structural features as drawn below:



The process adopted is as per synthesis description provided in the innovator's patents No.EP163036 & US4943639.

This report compiles the information to depict the course of development from literature search through arriving at the standard laboratory procedure (SLP) and further upto the six month accelerated stability data for the SLP samples.

- a. Name : Levetiracetam
- b. Molecular weight : 170.21
- c. Structure :



- d. Nomenclature : (α S)- α -Ethyl-2-oxo-1-pyrrolidineacetamide

Proprietary name. Keppra

(α S)- α -Ethyl-2-oxo-1-pyrrolidineacetamide

2. CAS—102767-28-2

Majority of the synthesis routes involved:

- a. Use of chiral starting material i.e. (S)-alpha-2-amino butyramide on which the pyrrolidinone ring was built.
- b. Preparation of Racemic acid, resolution of the acid and then conversion of the desired enantiomer into Levetiracetam.

We obviously had to either adopt the synthesis route described by the innovator or to innovate a Patentable synthesis route. It would not be out of place to have it on record that we attempted to arrive at a Patentable route, gathered some initial results and described them in an Indian provisional patent (application date 17.02.2005). In the weeks to come though we were unable to conclude the novel route and eventually the application was abandoned.

During the exercise of synthesis route selection, we attempted to synthesize (S)-alpha-2-amino butyramide. We also attempted to source it from the global intermediate market. Both these attempts did not culminate into useful leads. Incidentally we had a base patent route in working at the bench (EP 0162036), which was then taken up for further development.

In this route, the Racemic Levetiracetam acid is produced by the reaction of pyrrolidinone with alpha-bromobutyrate followed by hydrolysis. The resolution followed by amide formation then furnishes the Levetiracetam.

Gas Chromatography.

System GB—RI 1629.

Column: (analytical) DB-FFAP megabore (30 m × 0.53 mm i.d., 1 μm film thickness); (pre-column) deactivated fused silica (1 m × 0.53 mm i.d.). Column temperature: 70° to 190° (40°/min); 190° to 250° (5°/min), held 2 min. Carrier gas: helium, flow rate 30 mL/min. IS: UCB -G025,. Detection: nitrogen–phosphorus. Retention time(s): levetiracetam, 14.0 min; IS, 11.5 min [T. A. C. Vermeij and P. M. Edelbroek, *J. Chromatogr.*, 1994, **662**; *Biomed. Appl.*, 134–139].

Column: 6-TBDMS-2,3–perme-β-cyclodextrin (20% w/w) in SE52 fused–silica capillary (10 m × 0.25 mm i.d., 0.5 μm film thickness). Column temperature: 110°, held 2 min; to 170° (10°/min), held 5 min. Injector temperature: 210°. Carrier gas: helium, linear velocity, 40 cm/s. IS: N-dimethylvalproyl glycinamide. Detection: tandem mass spectrometry (SIM, m/z: 69, 98, 126 for levetiracetam; m/z: 129, 157, 186 for IS). Retention time(s): (S)-levetiracetam, 8.6 min; (R)-levetiracetam, 8.8 min; IS, 10.3 min [N. Isoherranen et al., *J. Chromatogr. Biomed. Sci. Appl.*, 2000, **745**, 325–332].

High Performance Liquid Chromatography.

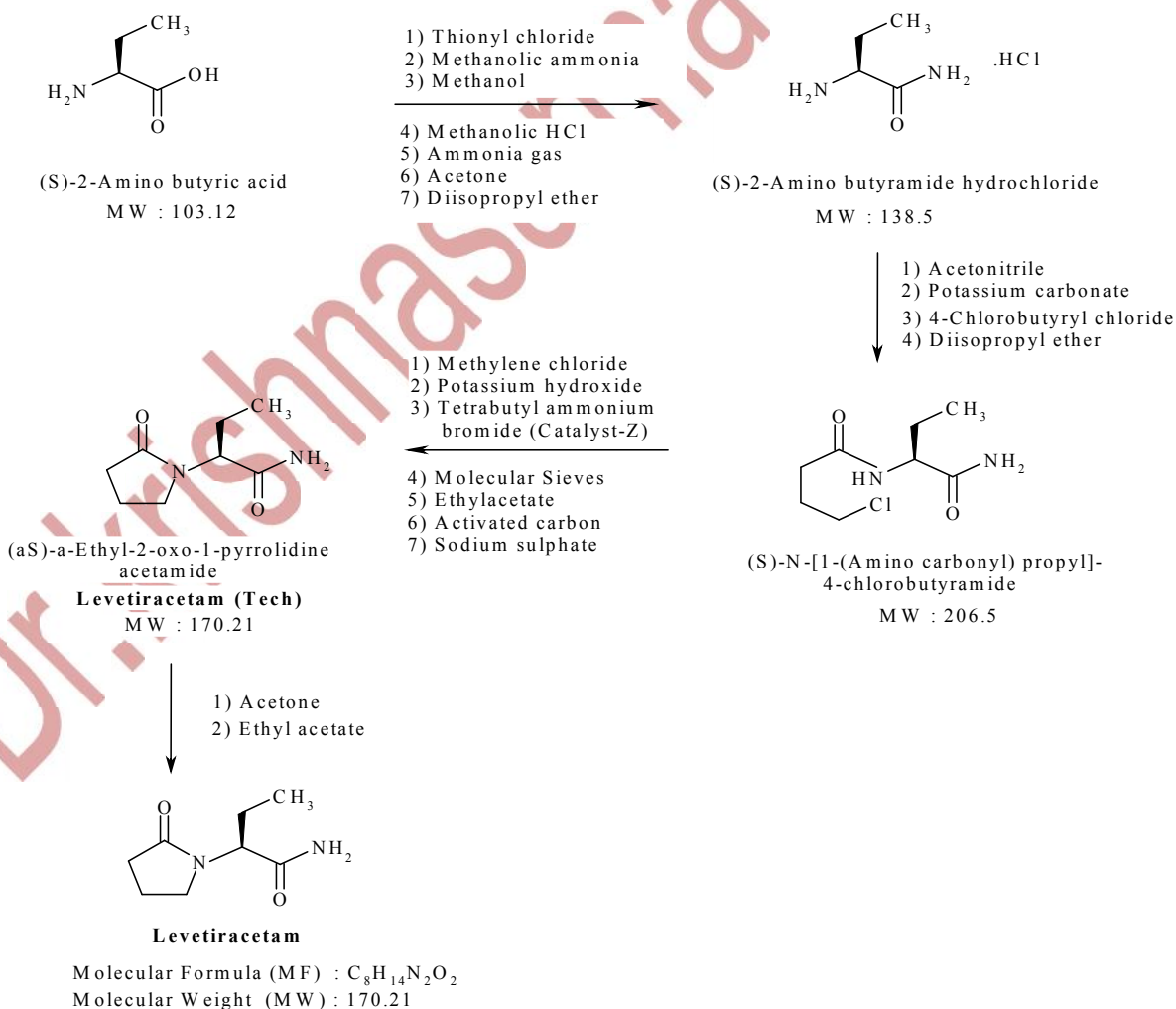
Column: (analytical) 60 RP-select B (LiChrospher, 250 × 4 mm i.d., 5 μm); (pre-column) 60 RP-select B (4 × 4 mm i.d., 5 μm). Mobile phase: acetonitrile:phosphate buffer (50 mM, pH 5.6) (15:85), flow rate 0.8 mL/min. IS: UCB-17025. UV detection (λ=220 nm).

Retention time(s): levetiracetam, 5.4 min; IS, 6.8 min [N. Ratnaraj *et al.*, *Ther. Drug Monit.*, 1996, **18**, 154–157].

Column: RP 3ODS2 (Spherisorb, 150 × 4.6 mm i.d.). Mobile phase: (A)—acetonitrile; (B)—water. Elution programme: (A:B) (6:94) initial, to (20:80) in 5 min, to (40:60) in 1 min, hold for 10 min, to (6:94) in 1 min, hold for 4 min, flow rate 1.0 mL/min. IS: UCB-G025,. Diode-array detection ($\lambda=205$ nm). Retention time(s): levetiracetam, 6.4 min; IS, 7.8 min [T. A. C. Vermeij and P. M. Edelbroek, *J. Chromatogr.*, 1994, **662**; **Biomed. Appl.**, 134–139].

Mass Spectrum.

Principal ions at m/z 126, 98, 41, 69, 58, 55, 127, 44.



(S)-2-Aminobutyric acid is reacted with thionyl chloride in presence of methanol gives (S)-2-Aminobutyric acid methylester which is reacted with ammonia and methanolic hydrochloric acid gives (S)-2-Aminobutyramide Hydrochloride.

(S)-2-Amino butyramide Hydrochloride is condensed with 4-Chlorobutryl chloride in presence of potassium carbonate in acetonitrile to give (S)-N-[1-(Amino carbonyl)propyl]-4-chlorobutyramide which on cyclisation in presence of potassium hydroxide in methylene chloride gives Levetiracetam (Tech).

Levetiracetam (Tech) is purified in acetone and ethylacetate to give Levetiracetam.

Polymorphism:

Levetiracetam exist in different polymorphism. Patent No. WO2004/083180 A1 three novel crystalline form of levetiracetam (form 1, 2, 3).

According to one aspect of the present invention, there is provided a novel crystalline Form I of levetiracetam characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 10.1, 15.1, 18.6, 20.4, 20.6, 22.2, 23.4, 23.9, 24.5, 26.9, 30.4, 31.0, 36.9, 45.6 degrees.

According to another aspect of the present invention, there is provided a novel crystalline Form II of levetiracetam characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 10.1, 14.9, 15.1, 18.5, 20.1, 20.5, 22.2, 23.3, 23.8, 24.4, 26.8, 28.9, 30.0, 30.5, 35.7, 36.3 degrees.

According to another aspect of the present invention, there is provided a novel crystalline Form III of levetiracetam characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 14.9, 20.6, 30.0, 30.6

Stage 1 :

Raw materials:

Sl. No.	Name of chemicals	Unit	Quantity
1	2-Pyrrolidinone	gm	200.0 gm
2	Ethyl-2-bromo butyrate	gm	460.0 gm
3	Sodium Hydride (60.0 %)	gm	95.0 Gm
4	Toluene	ml	1200.0
5	Methanol	ml	40.0
6	DM water	ml	400.0 ml
7	NaOH soln.	ml	125 + 330.0 ml
8	Conc. HCl	ml	270.0 ml
9	Ethyl Acetate	ml	600.0

Process :

In 3Ltr RBF fitted with thermometer pocket and stirrer. Charge 1200.0 ml toluene at 25-30°C Charge 95.0 gm 60.0 % Sodium hydride at 25-30°C under nitrogen atmosphere. Heat reaction mass to 45°C. Start addition of 200.0 gm 2-Pyrrolidinone slowly in 1 1/2-2 hrs. at 45-50°C. Maintain reaction mass to 45-50°C for 30.0 min. Start addn. of 460.0 gm ethyl-2-bromo butyrate in 4-5 hrs. at 45-50°C. Maintain reaction mass to 45-50°C for 30 min.

Check TLC.

Mobile Phase :

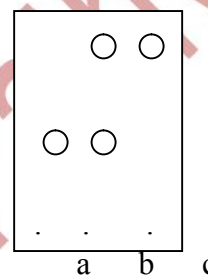
Chloroform : Methanol/ Iodine vapours

9 : 1

a) 2-Pyrrolidinone & MDC (1 : 1)

b) CO Spot

c) RM 5.0 ml + 3.0 ml water + 3.0 ml ethyl acetate



Check absence of 2-Pyrrolidinone

Cool reaction mass to 0-5°C. Add 40.0 ml methanol in reaction mass at 0-5°C in 30.0 min. Reaction mass stir for 15-20 min. at 0-5°C. Start addition of 400.0 ml D. M. water in 30.0 min. at 0-5°C. Reaction mass heat to 60°C. Start addition of (125 gm + 330 ml) NaOH soln. at 60°C in 30.0 min. After addition reaction mass heat to 80°C. Maintain reaction mass 80-85°C for 3.0 hrs.

Check TLC

Mobile Phase :

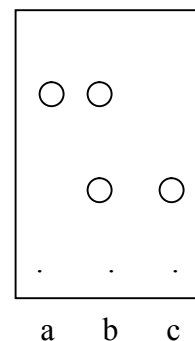
Chloroform : Methanol / Iodine vapour

9 : 1

a) Stage 1 ester

b) CO Spot

c) RM acidify to pH 1.0 5.0 ml + 3.0 ml water + 3.0 ml ethyl acetate



Check absence of Ester

If TLC Complies. Reaction mass cool to 25-30°C and kept for layer separation for 20-30min. Separate layer and take toluene layer for recovery. Take Aq. Layer and cool to 0-5°C. Adjust pH 1.0-2.0 by 270.0 ml conc. HCl at 0-5°C. Maintain reaction mass at 0-5°C for 30.0 min. Filter reaction mass at 0-5°C. Suck dry and wash with 60.0 ml water at 0-5°C. Suck dry and unload. Wt. of wet cake : 380.0 gm

Purification :

In 2Ltr RBF fitted with thermometer pocket and stirrer Charge ethyl acetate 600.0 ml at 25-30°C. Add above 380.0 gm wet cake at 25-30°C. Heat reaction mass to reflux and maintain for 10-15 min. Cool reaction mass to 5-10°C. Maintain reaction mass at 34-38°C for 60.0 min. Filter reaction mass at 34-38°C. Suck dry and wash with 30.0 ml ethyl acetate at 30 °C.

Suck dry and unload.

Wt. of Wet cake : 370.0 gm

Dry at 60-65 °C

Wt. of Dry material : 300.0 gm(LV stage 1)

Stage 2 Process :

In 3Ltr RBF fitted with thermometer pocket and stirrer Charge 1500.0 ml toluene at 25-30°C. Charge 500.0 gm LV stage 1 at 25-30°C. Heat reaction mass to 50°C. Start addn. of alpha MBA + TEA (150 + 170 gm) in 210 ml toluene. Heat reaction mass to 60°C. Maintain reaction mass to 2.0 hrs at 60-65°C. Cool reaction mass to 10-15°C during cooling Seed with 1.0 gm DRS passing quality at 40°C. Maintain reaction mass for 1.0 hrs at 10-15°C. After maintaining the reaction mass Filter the reaction mass at 10-15°C. Suck dry and unload the wet cake. Wash with 50 ml toluene at 10-15°C. Suck dry and unload the wet cake.

Wet wt. 388 gm(LV stage2)

Purification of LV stage2 in Acetone :

- 1) Charge (4.0 time of above wet cake) 1552.0 ml acetone at 25-30°C.
- 2) Charge wet cake in reactor at 25-30°C.
- 3) Stir the slurry for 15.0 min.
- 4) Heat the reaction mass for reflux and maintain 30 min.
- 5) Cool reaction mass to 10°C.
- 6) Maintain slurry for 1.0 hr. at 10-15°C.
- 7) Filter the slurry at 10°C.
- 8) Suck dry and wash with 100 ml acetone at 10°C.
- 9) Suck dry and unload wet cake.

Wt. of wet cake 309.0 gm

- 10) Use wet cake directly for next stage. **LV stage2**

Purification of Stage 2 :

Sr. No.	Raw material	M. wt.	Qty. /kg	Remarks
1	1 st purify Stage 2	292.4	309.0 wet	
2	Mixed Solvent (Toluene : Ethanol 9:1)		(778.5 + 86.5 ml) 865 ml	To dissolve stage 2
			185 ml	To wash
3	Pure st2	292.4	410-425.0 gm	

- 1) Add 865.0 ml mixed solvents (778.5ml toluene and 86.5 ml ethanol) in 2.0 lit 3N RBF
- 2) Add 309 gm wet cake at 25-30°C.
- 3) Heat slurry to 80°C.
- 4) Maintain for 30 min. at 80-85°C. Clear solution obtained
- 5) Cool to 10 ± 2°C and kept for 1.0 hr
- 6) Filter and suck dry and wash with 185 ml mixed solvent (166.5 ml toluene and 18.5 ml ethanol)
- 7) Suck dry and unload wet cake.
- 8) Dry at 65 ± 5°C
- 9) Dry wt. : 210.0 gm

Check SOR if SOR should be NMT 40 ± 1.5° if not OK repeat purification one more time.

Stage 3 :

Take 1.0 lit. 3 neck RBF fitted with stirrer and thermometer pocket. Take 225.0 ml water at 25-30°C. Charge 180.0 gm Stage 2 purified at 25-30°C. Cool reaction mass to 0-5°C. Adjust pH 12-13 by adding (27 gm NaOH and make up to 90 ml) 30% NaOH solution at 0-5°C in 30 min. Stir reaction mass for 30.0 min. & raise temp. 25-30°C Charge 193.5 ml toluene in reaction mass at 25-30°C. Stir reaction mass for 15.0 min. Settle the reaction mass at 25-30°C. Separate the organic layer. Collect Aq. Layer and extract with 2X 90.0 ml toluene. Keep Organic Layer. for Alpha methyl benzyl amine recycling.

Collect Aq. Layer, cool 0-5°C and adjust pH 2.0 by 30.0% HCl at 0-5°C. In slurry add 288.0 ml MDC. Stir reaction mass for 30.0 min. Settle the reaction mass for 30.0 min.

Separate the layers. Collect Organic Layer. Aq. Layer extract with 2 X 144.0 ml MDC Collect and combine Organic Layer. Distill MDC at 45-50°C and degas under vacuum below 35°C. In residue add 270.0 ml toluene Heat slurry to 70-80°C and maintain 15-30 min.

Cool reaction mass to 0-5°C. Maintain reaction mass to 0-5°C for 1.0 hr.

Filter slurry at 0-5°C. Suck dry and wash with 120 ml of toluene at 0-5°C.

Dry at 60-65°C.

Wt. of dry material 90.0 gm

Stage 4 :

Take 1.0 lit. 3 neck RBF fitted with stirrer and thermometer pocket. Take 222.0 ml MDC. Charge 37.0 gm Stage3 (S acid) at 25-30°C. Stir reaction mass for 30.0 min. Cool the reaction mass to -25 to -30°C. Charge simultaneously 28.0 gm ethyl chloroformate and 23.0 gm triethyl amine. After addition stir reaction mass for 30.0 min. at -25 to -30°C. Cool reaction mass to -35°C. Start purging of ammonia gas for 2-3 hrs. at -35°C. Check completion of reaction by HPLC. After reaction completion Stop ammonia purging and add 1.85 gm Soda ash. Raise temp. to 20°C. Filter the slurry at 20-25°C. Wash cake with 2X 18.5 ml MDC. Collect filtrate and distill out MDC under vacuum. In residue add 185.0 ml ethyl acetate and heat to reflux 70-75°C. Add 1.85 gm Carbon and soda ash 1.85 gm. Clarify through Hyflow and wash with 9.5 ml ethyl acetate. Collect filtrate and cool to 25-30°C. Filter the slurry. Suck dry and wash with 18.5 ml ethylacetate. Suck dry and unload the wet cake.

Dry at 60-65°C under vacuum

Wt. of dry material 24 -26.0 gm