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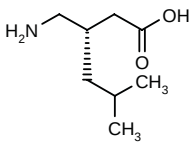
Pregabalin

Prop INN

Antiepileptic

CI-1008
PD-144723

(+)-4-Amino-3(*S*)-isobutylbutyric acid
3(*S*)-(Aminomethyl)-5-methylhexanoic acid



$C_8H_{17}NO_2$ Mol wt: 159.2300

CAS: 148553-50-8

EN: 194644

Synthesis

Pregabalin can be obtained by several different ways:

1) The reaction of 4-methylpentanoic acid (I) with $SOCl_2$ in refluxing chloroform gives the acyl chloride (II), which is condensed with the chiral oxazolidinone (III) by means of BuLi in THF, yielding the corresponding *N*-acyl derivative (IV). The regioselective alkylation of (IV) with benzyl bromoacetate (V) by means of LDA in THF affords the (*S*)-adduct (VI) with >95% ee purity. The elimination of the chiral auxiliary with LiOH and H_2O_2 gives the glutaric acid monoester (VII), which is reduced with BH_3/SMe_2 in THF, yielding compound (VIII). The reaction of (VIII) with tosyl chloride in pyridine yields the tosylate (IX), which is treated with sodium azide in DMSO, affording the azide (X). Finally, this compound is reduced and debenzylated with H_2 over Pd/C in THF (1-3). Scheme 1.

2) The reaction of 4-methylpentanoic acid (I) with $SOCl_2$ in refluxing chloroform gives the acyl chloride (II), which is condensed with the chiral oxazolidinone (III) by means of BuLi in THF, yielding the corresponding *N*-acyl derivative (IV). The regioselective alkylation of (IV) with *tert*-butyl bromoacetate (XI) by means of LDA in THF affords the (*S*)-adduct (XII). The elimination of the chiral auxiliary with LiOH and H_2O_2 gives the glutaric acid monoester (XIII), which is reduced with BH_3/SMe_2 in THF, yielding compound (XIV). The reaction of (XIV) with tosyl chloride in pyridine yields the tosylate (XV), which is treated with sodium azide in DMSO, affording the azide (XVI). The hydrolysis of the *tert*-butyl group of (XVI) affords the free acid (XVII), which is reduced with H_2 over Pd/C (2). Scheme 2.

3) The reaction of diethyl malonate (XVIII) with 3-methylbutanal (XIX) by means of dipropylamine in acetic acid gives the corresponding 2-(3-methylbutylidene)malonate derivative (XX), which is treated with KCN to yield the corresponding addition compound (XXI). The decarboxylative hydrolysis of (XXI) with KOH affords 3-cyano-5-methylhexanoic acid (XXII), which is reduced with H_2 over Ni to yield racemic pregabalin (XXIII). Finally, this racemate is submitted to optical resolution with (*S*)-(+)-mandelic acid (3, 4). Scheme 3.

4) The deamination of L-leucine (XXIV) with $NaNO_2$, NaBr and H_2SO_4 gives 2(*S*)-bromo-4-methylpentanoic acid (XXV), which is esterified with *tert*-butyl acetate and BF_3.AcOH to yield the *tert*-butyl ester (XXVI). The condensation of (XXVI) with the sodium salt of diethyl malonate affords the substituted malonic ester (XXVII), which is selectively hydrolyzed at the *tert*-butyl ester group with formic acid, giving the monoacid (XXVIII). The decarboxylative reduction of (XXVIII) with BH_3 and SMe_2 provides 3(*S*)-isobutylbutano-4-lactone (XXIX). Lactone (XXIX) is submitted to ring opening by treatment with trimethylsilyl iodide in ethanol, yielding 3(*S*)-(iodomethyl)-5-methylhexanoic acid ethyl ester (XXX). The reaction of (XXX) with sodium azide yields azide (XXXI), which is hydrolyzed with KOH in ethanol/water to afford the free acid (XVII). Finally, this compound is reduced to pregabalin by treatment with H_2 over Pd/C (2). Scheme 4.

5) The condensation of 3-methylbutanal (XIX) with cyanoacetic acid ethyl ester (XXXII) (5) or cyanoacetamide (XXXIII) (2, 5) by means of dipropylamine in refluxing hexane, followed by treatment with refluxing 6N HCl, gives 3-isobutylglutaric acid (XXXIV). This compound is converted into the corresponding anhydride (XXXV) by treatment with refluxing acetic anhydride. The reaction of the anhydride (XXXV) with NH_4OH affords the glutaramic

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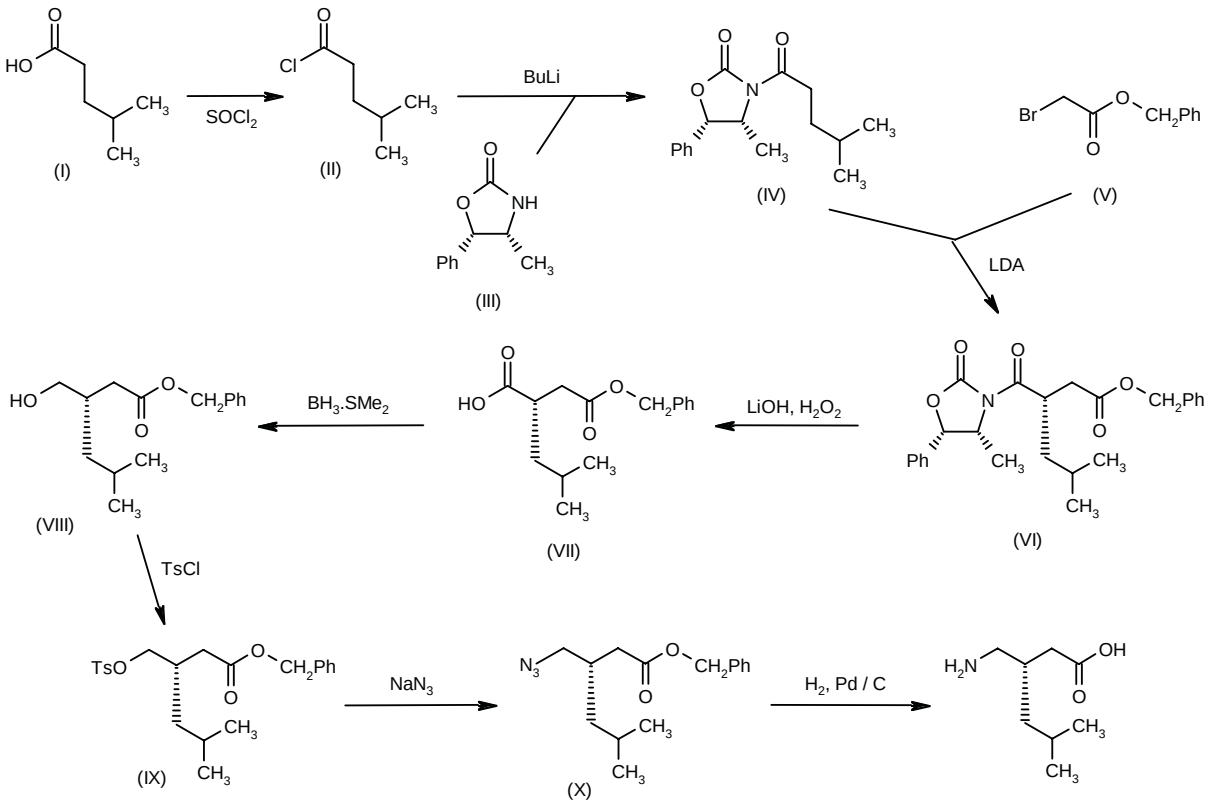
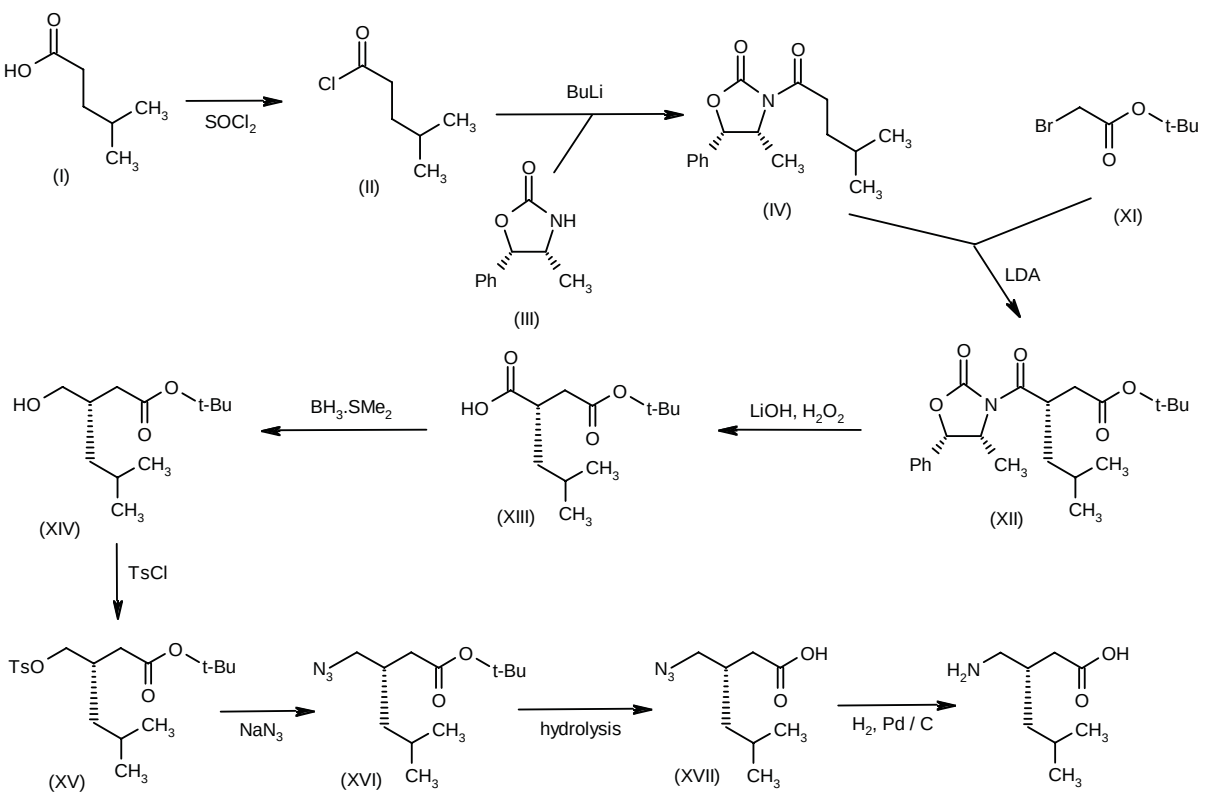
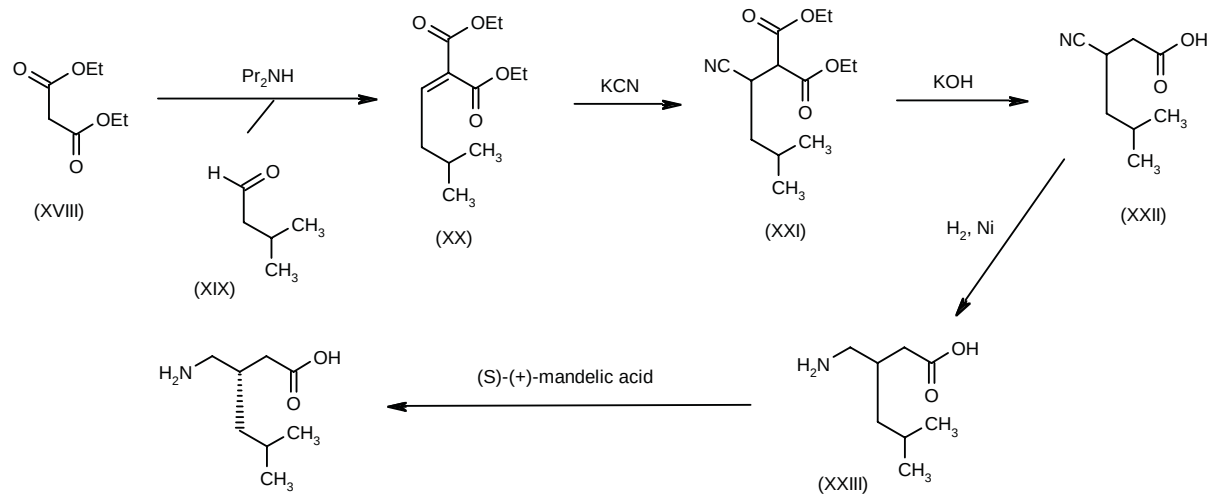
Scheme 1: Synthesis of Pregabalin



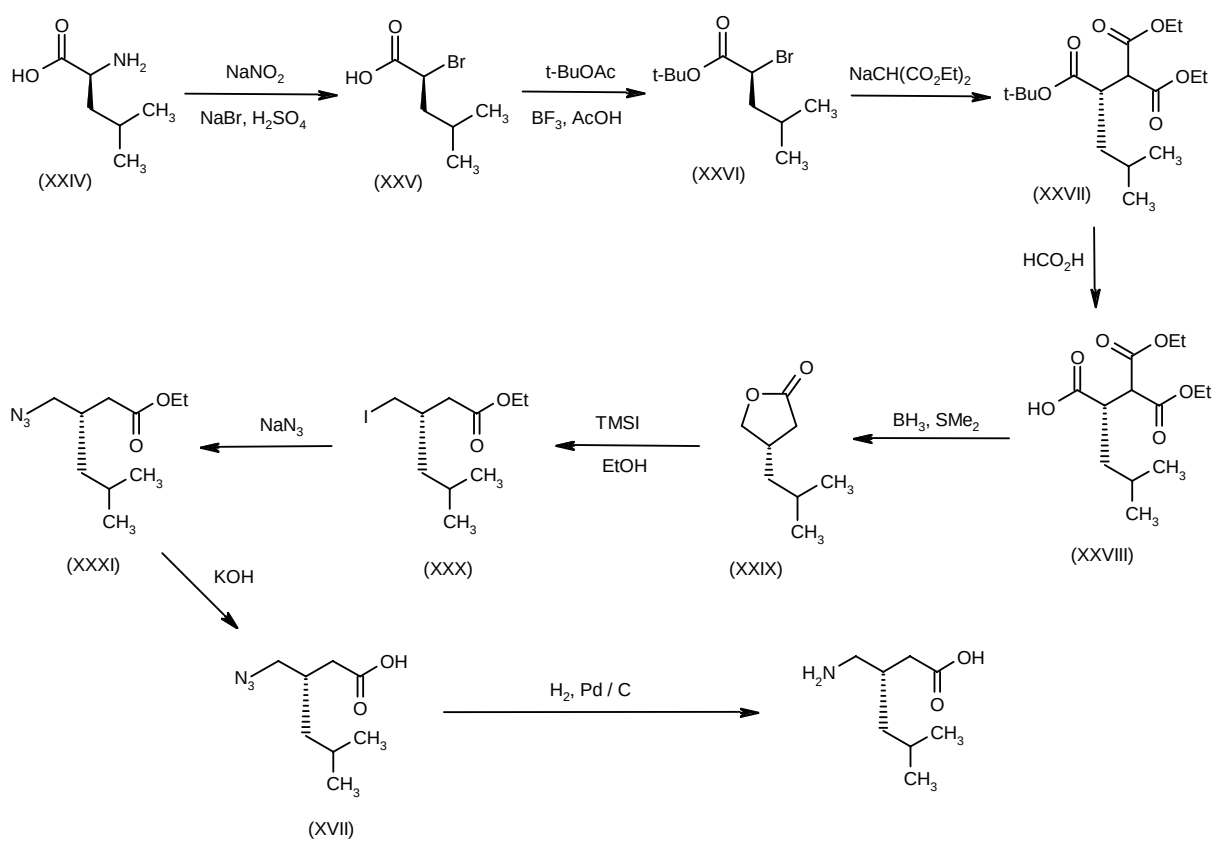
Scheme 2: Synthesis of Pregabalin



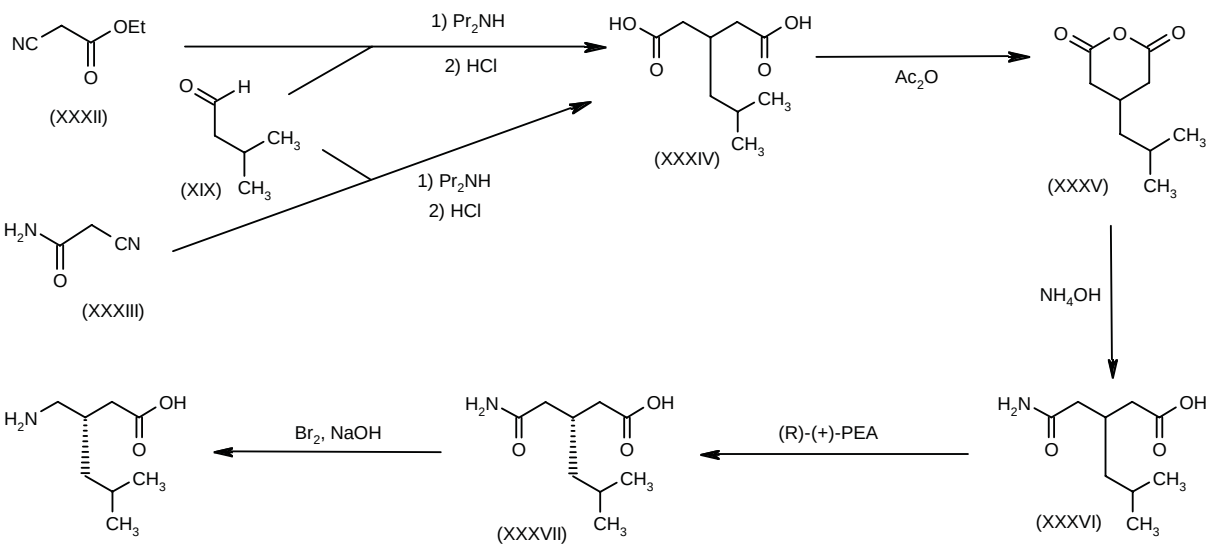
Scheme 3: Synthesis of Pregabalin



Scheme 4: Synthesis of Pregabalin



Scheme 5: Synthesis of Pregabalin



amide (XXXVI), which is submitted to optical resolution with (*R*)-(+)-1-phenylethylamine, yielding the (*S*)-enantiomer (XXXVII). Finally, this compound is submitted to a Hoffmann degradation with Br_2/NaOH (2, 5). Scheme 5.

Introduction

Over 4000 years have elapsed since epileptic disease was mentioned in the Babylonian civil code of Hammurabi and early Hebrew scripts. Over the centuries, many substances and concoctions have been used with the aim of controlling epilepsy. The antiepileptic efficacy of bromide was documented in 1857, and for half a century potassium bromide was the leading treatment for epilepsy until it was replaced in 1912 by phenobarbital.

Phenytoin was first introduced for the treatment of epilepsy in 1938 and represented a major pharmacological advance in the treatment of neurological disease. Phenytoin is still one of the most widely used anticonvulsants. By manipulating the cyclic urea moiety from which phenytoin and phenobarbital are derived, additional barbiturates and hydantoins, as well as diones and succinimides, were synthesized over the next 20 years. In the 1960s, carbamazepine and valproate sodium were marketed, while diazepam became the drug of choice for the treatment of status epilepticus. In the 1970s, valpromide and 3 new benzodiazepines (clobazam, clonazepam and lorazepam) were introduced for clinical use.

Recognizing the need for new, more effective and safer anticonvulsant drugs, the Epilepsy Branch of the National Institute of Neurological Disorders and Stroke (NINDS) of the NIH, established the Anticonvulsant Development Program in 1975. This program has screened over 15,000 new chemical entities for antiepileptic activity. From 1975-1984, no new antiepileptic drugs were marketed. Progabide, a GABA prodrug, was marketed in France in 1985 and during the next 5 years, 4 new anticonvulsant drugs (vigabatrin, zonisamide, oxcarbazepine and lamotrigine), as well as a delayed-release formulation of valproate semisodium, were introduced.

During the past decade, renewed interest in the development of novel anticonvulsant drugs has resulted in the introduction of 2 new compounds in the U.S. in 1993: gabapentin (Neurontin®; Warner-Lambert) and felbamate (Felbatol®; Carter-Wallace). Antiepileptic drugs in clinical use are listed in Table I and those in clinical trials and preclinical testing are listed in Tables II and III, respectively.

Molecular targets for anticonvulsant drug development mainly include voltage-sensitive sodium channels, benzodiazepine/barbiturate sites at the γ-aminobutyric acid (GABA) type A receptors, GABA-metabolizing enzymes, excitatory amino acids and adenosine. GABA is the most important inhibitory neurotransmitter within the central nervous system, and exogenous administration of GABA directly into the brain of a convulsing animal fully stops seizures. However, GABA does not cross the blood-brain barrier and cannot be used in therapeutics.

GABA acts on $GABA_A$ and $GABA_B$ receptors. The former are coupled to a chloride channel and include a benzodizepine-binding site that modulates chloride conductance upon stimulation by GABA or GABA agonists (muscimol, isoguavacine). $GABA_B$ receptors are coupled to a $G_{i/o}$ protein. GABA has been used as a chemical

Table I: Drugs used for the treatment of epilepsy (Prous Science Ensemble database).

Year of Introduction	Compound (Trade Name)	Manufacturer	Mechanism of Action
1912	Phenobarbital (Luminal)	Sanofi Winthrop	Barbiturate, $GABA_A$ receptor function enhancer
1938	Phenytoin sodium (Dilantin; Epanutin)	Parke-Davis	Thought to limit neuronal firing by stabilizing neuronal membrane
1952	Primidone (Mysoline)	Zeneca; Wyeth-Ayerst	Phenobarbital prodrug
1956	Acetozolamide (Diamox)	Lederle	Carbonic anhydrase inhibitor
1957	Clometiazole edisylate (Heminevrin)	Astra	Sedative
1958	Ethosuximide (Zarontin)	Parke-Davis	Thought to reduce threshold calcium currents
1963	Carbamazepine (Tegretol)	Novartis	Thought to limit neuronal firing by estabilizing neuronal membrane
1965	Diazepam (Valium)	Roche	Benzodiazepine; $GABA_A$ receptor function enhancer
1967	Valproic acid (Convulex)	Pharmacia & Upjohn	GABA release enhancer
1971	Lorazepam (Ativan)	Wyeth-Ayerst	Benzodiazepine; $GABA_A$ receptor function enhancer
1973	Clonazepam (Klonopin; Rivopril)	Roche	Benzodiazepine; $GABA_A$ receptor function enhancer
1975	Clobazam (Frisium)	Hoechst	Benzodiazepine; $GABA_A$ receptor function enhancer
1989	Divalproex sodium[+] (Depakote)	Abbott	GABA release enhancer
1989	Sodium valproate (Epilim)	Sanofi Winthrop	GABA release enhancer and metabolism inhibitor
1989	Vigabatrin (Sabril)	Hoechst	GABA analog; GABA transaminase inhibitor (the enzyme responsible for catabolism of GABA)
1989	Zonisamide (Excegram; Zenegram)	Dainippon; Elan	Not yet established
1990	Lamotrigine (Lamictal)	Glaxo Wellcome	Neuronal membrane stabilizer; glutamate release inhibitor
1990	Oxcarbazepine (Trileptal)	Novartis	10-Keto analog of carbamazepine
1993	Felbamate (Felbatol)	Wallace	Glycine site NMDA modulator
1993	Gabapentin (Neurontin)	Parke-Davis	GABA analog; mechanism of action not yet established a though it appears to potentiate intracellular GABA
1995	Topiramate (Tomamax; Topamax)	Janssen-Cilag; Ortho-McNeil	Sodium channel blocker
1996	Fosphenytoin sodium (Cerebyx)	Warner-Lambert	Disodium phosphate ester prodrug of phenytoin
1996	Tiagabine HCl (Gabitril)	Abbott; Cephalon; Sanofi Winthrop; Novo Nordisk	GABA uptake inhibitor
1999	Diazepam (Diastat)	Draxis; Elan	Benzodiazepine; $GABA_A$ receptor function enhancer; rectal gel

[+]Also for the treatment of bipolar disorder and prophylaxis of migraine.

Table II: Antiepileptic drugs in clinical trials (Prous Science Ensemble database).

Compound	Phase	Manufacturer	Mechanism of Action
Leviracetam	NDA filed	UCB	Not yet established
Losigamone	Phase III	Schwabe	May be mediated by stimulation of $GABA_A$ receptor-regulated chloride channels
Pregabalin	Phase III	Warner-Lambert	GABA analog
Remacemide	Phase III	AstraZeneca	NMDA antagonist
Rufinamide	Phase III	Novartis	Appears to act by limiting the frequency of firing of sodium (+)-dependent action potentials in neurons
Ganaxolone	Phase II	CoCensys	Epalon compound, synthetic analog of a metabolite of progesterone
Retigabine	Phase II	Asta Medica	Not fully understood; potassium channel opener
Talampanel	Phase II	Lilly	AMPA antagonist
TV-1901	Phase II	Teva	Valproylglycinamide
DP-VPA	Phase I	D-Pharm	Phospholipid-based valproic acid prodrug
GP-3269	Phase I	Gensia Sicor	Adenosine kinase inhibitor
GW-273293	Phase I	Glaxo Wellcome	Sodium channel inhibitor; follow-up to lamotrigine
Harkoseride	Phase I	Harris FRC; Univ. Houston	Glycine site NMDA antagonist
NPS-1776	Phase I	NPS	Not yet established
SKP-509	Phase I	SK	Not yet established
TV-141	Phase I	Teva	Undisclosed

Table III: Mechanisms of action of antiepileptic drugs in preclinical and biological testing (Prous Science Ensemble database).

Compound	Manufacturer	Mechanism of Action
WO 9923073+	Novartis	Glutamate release inhibitor
WO 9900389	Ortho-McNeil	$GABA_A$ ligand
WO 9931075+	Warner-Lambert	Gabapentin analog
ABS-103R	American Biogenetic Sciences	Single isomer valproic acid analog
AWD-131-138	Asta Medica	Not yet established
BM-401	Catholic Univ. Louvain	Pharmacological profile similar to that of phenytoin
CGP-79397	Novartis; Sibia Neurosciences	Excitatory amino receptor ligand
CO-101244	Warner-Lambert; CoCensys	NMDA antagonist
Conantokin-G and derivatives+ (US 5830998)	Bearsden Bio; Cognetix; Medtronic	Marine Conus snail peptide; NMDA receptor modulator
CP-465022	Pfizer	AMPA receptor antagonist
DPB/DMMDPB	Taro	Members of the barbiturate family
GP-3269	Metabasis Therapeutics	Adenosine-regulating agent; adenosine kinase inhibitor
LU-73068	Knoll	Glutamate receptor antagonist
NeuroCell™-FE	Diacrin	Porcine neural cell product for transplantation into patients
PPG	Novartis; Sibia Neurosciences	Group III mGluR agonist
(–)-RPR-118723	Rhône-Poulenc Rorer	Glycine site NMDA antagonist

+Representative compound from current literature and patents.

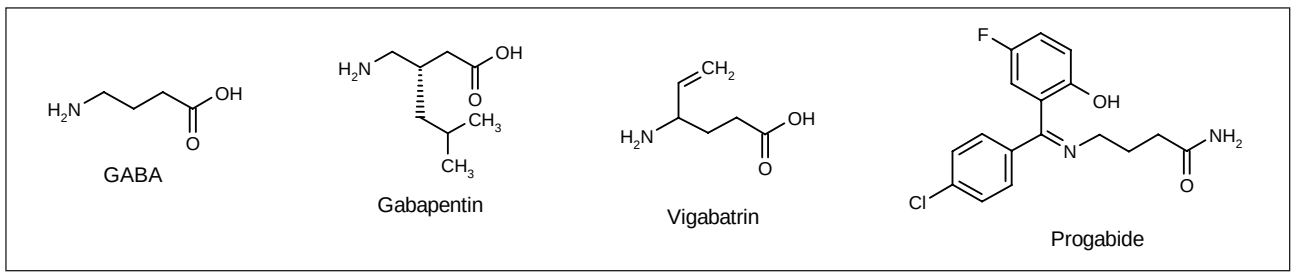


Fig. 1. Chemical structures of GABA analogs in use as anticonvulsant drugs.

template for a number of inhibitory compounds putatively useful for the treatment of convulsant diseases. Several 3-substituted GABA analogs have been developed for the treatment of epilepsy, including gabapentin, vigabatrin and progabide (Fig. 1).

Pregabalin is the pharmacologically active *S*-enantiomer of 3-aminomethyl-5-methyl hexanoic acid, a 3-alkylated (isobutyl) analog of GABA.

Pharmacological Actions

As with gabapentin, another GABA analog, the mechanism of action of pregabalin is unknown. The drug does not affect sodium and calcium channels or glutamate and GABA release and uptake, and does not show affinity for glutamate, GABA, monoamine, adenosine, acetylcholine or opiate receptors. However, it does displace [^{3}H]-gabapentin from its binding site on the $\alpha_2\delta$-subunit of calcium channels and is suggested to increase neuronal GABA content. In experiments of displacement of [^{3}H]-gabapentin in synaptic plasma membranes from rat neocortex, pregabalin showed an IC_{50} of 37 nM, compared to 80 nM for unlabeled gabapentin. Pregabalin has also been shown to dose-dependently enhance glutamic acid decarboxylase activity (1, 6, 7).

Both pregabalin and gabapentin inhibited potassium-induced noradrenaline release from rat neonatal striatal slices, but only gabapentin had significant effect on electrically evoked neurotransmitter release. Gabapentin, but not pregabalin, inhibited potassium-induced and electrically evoked dopamine release (8).

Pregabalin has shown anticonvulsant activity in many animal models, including maximal electroshock-, pentylenetetrazone-, bicuculline-, picrotoxin- and strychnine-induced seizures, and kindled seizures and seizures in genetically susceptible animals (Table IV). The drug has exhibited a profile similar to that of gabapentin, but active doses have been found to be 3- to 10-fold lower (3, 6). Effect-site concentration analysis in rats submitted to maximal electroshock showed half maximal activities (EC_{50}) at 0.5 and 2.4 μg/ml for pegabalin and gabapentin, respectively, with similar brain concentration to anticonvulsant activity equilibration half-times (32-35 min) (9).

In rodents, pregabalin protected against maximal electroshock-induced tonic seizures with ED_{50} values of 20 mg/kg p.o. in mice and 1.8 mg/kg p.o. in rats, but did not cause ataxia except at high doses (TD_{50} values of

Table IV: Experimental anticonvulsant profile of pregabalin (P) and gabapentin (G) in animal models (Prous Science MFline database).

Test	Model	ED_{50}	Ref.
Maximal electroshock-induced tonic seizures	Mice	P: 20 mg/kg i.v. G: 87 mg/kg i.v.	1, 6, 7
		P: 17 mg/kg p.o. G: 210 mg/kg p.o.	10
Electroshock-induced seizures	Mice	P: 0.7-1.4 mg/kg i.v. G: 13 mg/kg i.v.	6, 10
	Rats	P: 1.8 mg/kg p.o.	10
Pentylenetetrazole-induced seizures	Mice	P: 100 mg/kg p.o. or i.p.	10
Ataxia	Rats	P: 60-260 mg/kg p.o.	10

60-260 mg/kg p.o.). Pregabalin also prevented threshold clonic seizures induced by pentylenetetrazole in rats (ED_{50} = 100 mg/kg p.o. or i.p.) and partly blocked picrotoxin- and bicuculline-induded seizures. In audiogenic seizure prone mice, pregabalin decreased seizure frequency after doses of 3 and 10 mg/kg p.o.

Pregabalin has also been found to be effective in rat models of neuropathic pain, including intrathecal substance P- or NMDA-, carrageenan- and formalin-induced pain, thermal injury and postoperative pain. In these models, pregabalin was at least twice as effective as gabapentin against both thermal and mechanical pain. Furthermore, pregabalin did not induce sedation (3, 11). In streptozocin-treated rats, both pregabalin and gabapentin, but not morphine and amitriptyline, blocked the static and dynamic components of mechanical allodynia. These results suggest that pregabalin and gabapentin may represent a novel class of drugs for the treatment of neuropathic pain, for which conventional analgesics such as morphine and nonsteroidal antiinflammatory drugs show only limited value (12).

In rats, rectal distension induced by inflating a balloon induces abdominal contractions that are enhanced by partial restraint stress or endotoxin. Oral treatment with pregabalin dose-dependently reduced abdominal cramps, suggesting a reduction in basal rectal sensitivity (13). Both pregabalin and gabapentin also dose-dependently inhibited ultraviolet light-induced pain in the Hargreaves test in rats (14). Pregabalin infused into the dorsal horn of the spinal cord through a microdialysis fiber also antagonized kaolin- and carrageenan-induced pain and edema in rat paw tests (15).

Pregabalin has also been shown to prevent indomethacin-induced gastric damage in rats through a central mechanism, as the effect was more potent when the drug was injected intracisternally than when given orally or intraperitoneally (16).

Pharmacokinetics and Metabolism

Pregabalin is absorbed after oral administration through a large neutral amino acid carrier-mediated intestinal transport mechanism (17). In rats, the pharmacokinetics of pregabalin are dose-proportional, with plasma concentrations decreasing monoexponentially. The drug has a high oral bioavailability (83%), is not significantly metabolized and exhibits maximal effects in the maximum electroshock assay approximately 2-4 h after i.v. dosing (9). Pregabalin showed a similar pharmacokinetic profile in other animals (mice, rabbits and monkeys), with high oral bioavailability and no metabolism (18).

Table V: Summary of pharmacokinetic properties of pregabalin in healthy volunteers (19) [Prous Science PKline database].

Dose	Pharmacokinetic constants
1-300 mg p.o.	F = ≥89.8% t_{max} = 1.3 h C_{max} = 0.04-9.46 μg/ml $AUC_{0-\infty}$ = 0.22-66.3 μg·h/ml $t_{1/2}$ = 4.6-6.8 h UR_{parent} = 89.8%

In a study in healthy volunteers, pregabalin had an oral bioavailability of 90%, reaching dose-proportional peak levels (C_{max}) of 0.04-9.5 μg/ml after 1.3 h at doses of 1-300 mg. It was not metabolized (90% of the parent drug was recovered in the urine) and was excreted with a $t_{1/2}$ of 4.6-6.8 h. Meals delayed t_{max} and C_{max} but had no effect on $t_{1/2}$ (19). The pharmacokinetic properties of pregabalin are summarized in Table V.

Toxicity

Most antiepileptic drugs are contraindicated during pregnancy due to a high risk of fetal/neonatal death and/or malformation. In pregnant rats, pregabalin showed maternal toxicity only at doses over 100 mg/kg, with severity increasing near parturition. No deaths occurred at doses up to 2500 mg/kg. At these doses, delivery impairment and dystocia occurred in 1 animal each. Some postimplantation losses and/or neonatal deaths occurred at doses over 250 mg/kg. Additionally, decreased fetal and offspring body weight, skeletal malformations, delayed acquisition of developmental skills, behavioral changes and impaired reproductive function were observed in offspring (20).

Box 1: Pregabalin versus gabapentin in refractory partial epilepsy (21, 22) [Prous Science CSline database].

Design	Randomized, double-blind, comparative clinical study
Population	Patients with complex partial seizures with or without secondary generalization who were tapered off of all antiepileptic drugs during hospitalization (n = 93)
Interventions	Pregabalin (P), 200 mg t.i.d. x 8 d (n = 42) Gabapentin (G), 100 mg t.i.d. x 8 d (n = 51)
Results	Time to exit[1] (h): P (191) $\geq$ G (88) Study completion rate: P (57.1%) > G (23.5%) [p = 0.003]
Conclusions	Pregabalin exhibited anticonvulsant potential in patients with refractory partial epilepsy with a trend to a better efficacy profile as compared to gabapentin

[1]Exit criteria included a predefined number of seizures, adverse changes in seizure character or medication intolerance.

Clinical Studies

In a phase I, randomized, placebo-controlled, double-blind clinical study in 29 healthy volunteers, pregabalin at doses up to 300 mg was well tolerated. The most commonly reported adverse events included headache, dizziness and nausea, all with mild or moderate intensity. No serious adverse events or clinically significant changes in safety parameters were noted (19).

In a double-blind study, video-EEG monitoring was used for diagnostic or presurgical evaluations in patients with at least 3 complex partial seizures within 72 h or 4 complex partial seizures within 120 h tapered off of all antiepileptic drugs during hospitalization. Subjects were randomized to 200 mg t.i.d. pregabalin or 100 mg t.i.d. gabapentin for up to 8 days. Preliminary results after 49 patients had entered the study showed a completion rate of 51.5%, indicating that inpatient monotherapy is an efficient design for early demonstration of anticonvulsant efficacy of new antiepileptic drugs. No further data on comparative efficacy of pregabalin and gabapentin was available from this trial (21). Upon completion of the trial, 93 patients with complex partial seizures with or without secondary generalization had been enrolled. Median time to exit was 191 h for patients on pregabalin and 88 h for patients on gabapentin, with the proportion of patients completing the trial being 57.1 and 23.5%, respectively. There was a positive trend in favor of pregabalin (22) (Box 1).

Pregabalin is currently in phase II clinical trials to assess its safety and efficacy in patients with refractory partial seizures. Additional trials are planned to study its efficacy as monotherapy for pediatric patients.

Manufacturer

Warner-Lambert Co. (US).

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