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MONOGRAPH

BRIVARACETAM

Rec INN; USAN

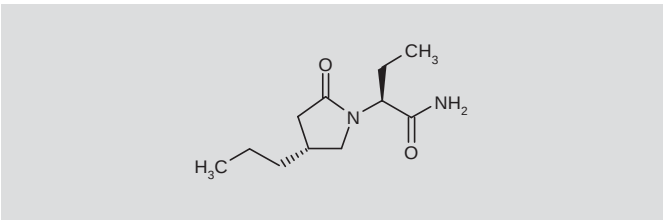
SV2A Ligand
Antiepileptic Drug

UCB-34714
Rikelta™

2(*S*)-[2-Oxo-4(*R*)-propylpyrrolidin-1-yl]butyramide

(α*S*,4*R*)-α-Ethyl-2-oxo-4-propyl-1-pyrrolidineacetamide

InChI: 1S/C11H20N2O2/c1-3-5-8-6-10(14)13(7-8)9(4-2)11(12)15/h8-9H,3-7H2,1-2H3,(H2,12,15)/t8-,9+/m1/s1



$C_{11}H_{20}N_2O_2$
Mol wt: 212.2887
CAS: 357336-20-0
CAS: 357335-87-6 (racemate)
EN: 321316

SUMMARY

Brivaracetam is a racetam derivative with anticonvulsant properties. It binds to synaptic vesicle glycoprotein 2A (SV2A) to produce its clinical effect. Brivaracetam is believed to have broad antiseizure activity, a relatively benign adverse event profile and good tolerability. Brivaracetam undergoes complete absorption after oral administration, with time to peak plasma concentrations of 0.5-1.75 h. It has been reported to interact with and moderately decrease the levels of carbamazepine, phenytoin and oral contraceptives. Recent phase III trials with this molecule have yielded contrasting results and future studies looking at this potential broad-spectrum anticonvulsant will determine its place in the clinician's armamentarium.

SYNTHESIS*

Brivaracetam can be synthesized following several different strategies:

Condensation of 2(*S*)-aminobutyramide (I) with Meldrum's acid derivative (II) in refluxing acetonitrile affords a mixture of two pyrrolidonecarboxylic acid regioisomers, (III) and (IV), which, without isolation, are subjected to decarboxylation in methyl isobutyl ketone at 120 °C, and then separated by column chromatography (1). Scheme 1.

Alternatively, 2(*S*)-aminobutyramide (I) –obtained by basification of either its tartrate salt with NH_4OH/*i*-PrOH or its hydrochloride salt with NH_3/*i*-PrOH (2)– is reductively condensed with 5-hydroxy-4-propyl-2-furanone (V) by means of $NaBH_4$ and NaOH in H_2O/toluene, yielding the dihydropyrrol-2-one (VI) (3). Transfer hydrogenation of compound (VI) with ammonium formate and Pd/C in H_2O at 50 °C provides the diastereomeric mixture of pyrrolidinones (VII) (3), which are finally separated by column chromatography (2, 4, 5) or recrystallization (5). Scheme 1.

The intermediate dihydropyrrolone (VII) is alternatively obtained by direct condensation of furanone (V) with 2(*S*)-aminobutyramide (I) in the presence of H_2 and Pd/C in AcOH/*i*-PrOH (2) or by cyclization of aminoamide (I) with 3-(iodomethyl)hexanoyl chloride (VIII) by means of KOH and tetrabutylammonium bromide in CH_2Cl_2 (4). Scheme 1.

Amide (VII) is also prepared from 2-(2-oxo-4-propylpyrrolidino)-butyric acid (IX) via activation as the corresponding mixed anhydride with ethyl chloroformate and Et_3N in THF, followed by quenching with liquid ammonia (5). Scheme 1.

Similarly, alkylation of optically pure 4(*R*)-propyl-2-pyrrolidinone (X) with racemic methyl 2-bromobutyrate (XI) in the presence of NaH in THF affords pyrrolidinone butyrate methyl ester (XII) as a diastereomeric mixture. Subsequent ammonolysis of ester (XII) with aqueous ammonia gives the corresponding mixture of amides (XIII) separated using column chromatography (6). Scheme 1.

The Meldrum's acid derivative (II) is prepared by the following method. Sharpless asymmetric dihydroxylation of 1-pentene (XIV) by means of AD-mix-β in *tert*-butanol/water produces (*R*)-1,2-pentanediol (XV), which is treated with $SOCl_2$ in chloroform to generate the cyclic sulfite (XVI). This compound, without isolation, is oxidized with $RuCl_3$ and $NaIO_4$ to afford the cyclic sulfate (XVII), which is then condensed with dimethyl malonate (XVIII) by means of NaH in

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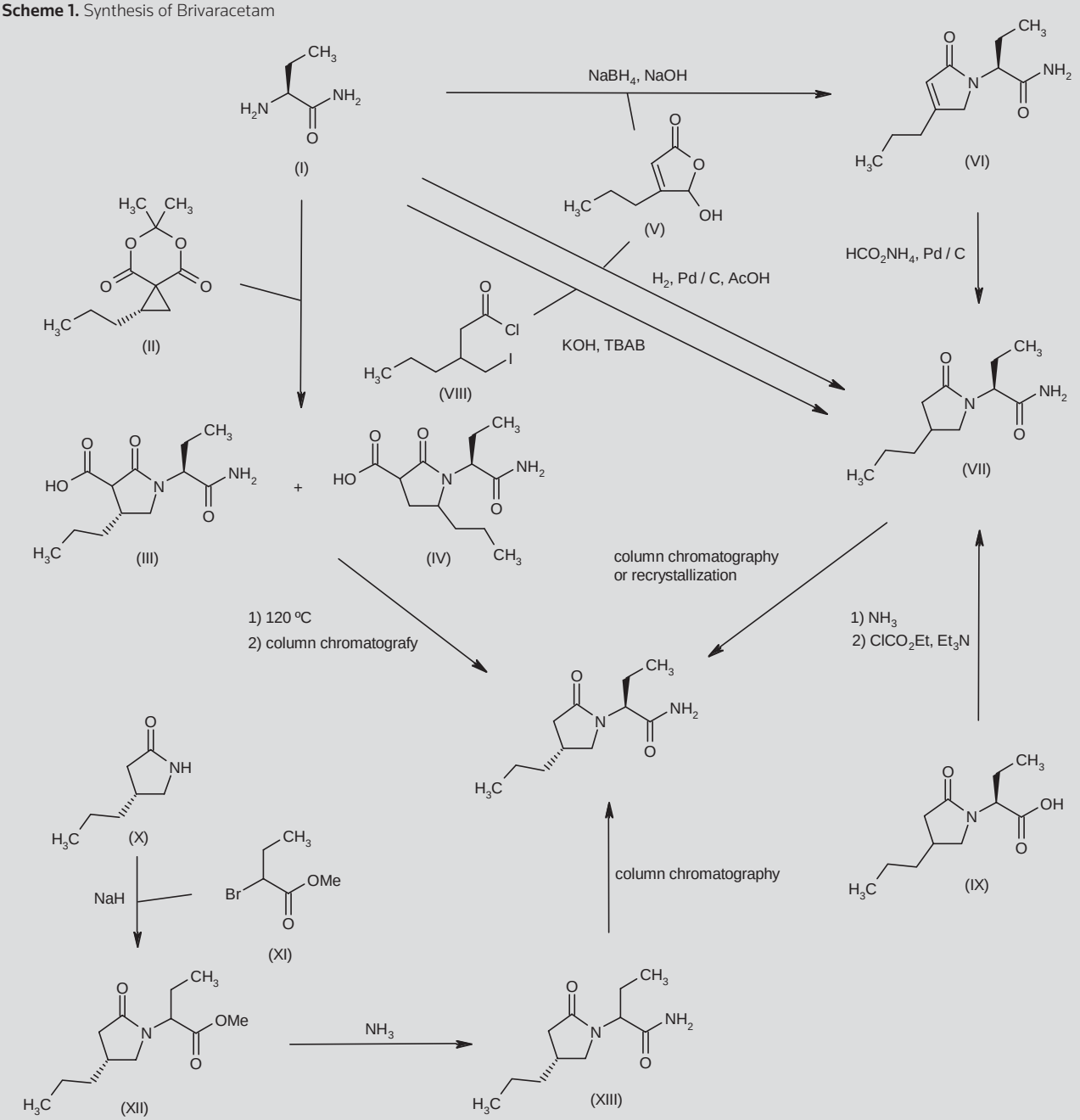
*Synthesis prepared by R. Pandian, J. Bolós and R. Castañer. Thomson Reuters, Provença 388, 08025 Barcelona, Spain.

Scheme 1. Synthesis of Brivaracetam



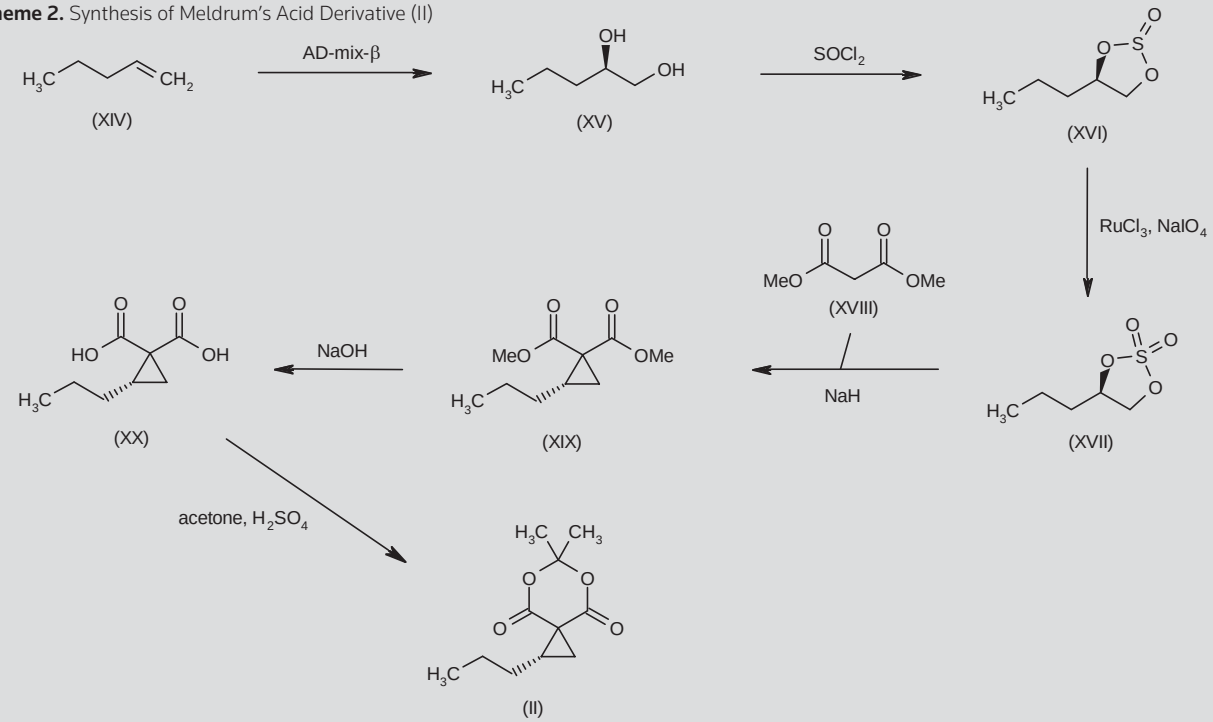
dimethoxyethane to provide the spirocyclopropane (XIX). Hydrolysis of the ester groups of (XIX) by means of aqueous NaOH gives the corresponding diacid (XX), which is reacted with acetone in the presence of H_2SO_4 to yield the target dioxane dione (II) (1). Scheme 2.

The synthetic precursors of pyrrolidinone (VII) are prepared as follows:

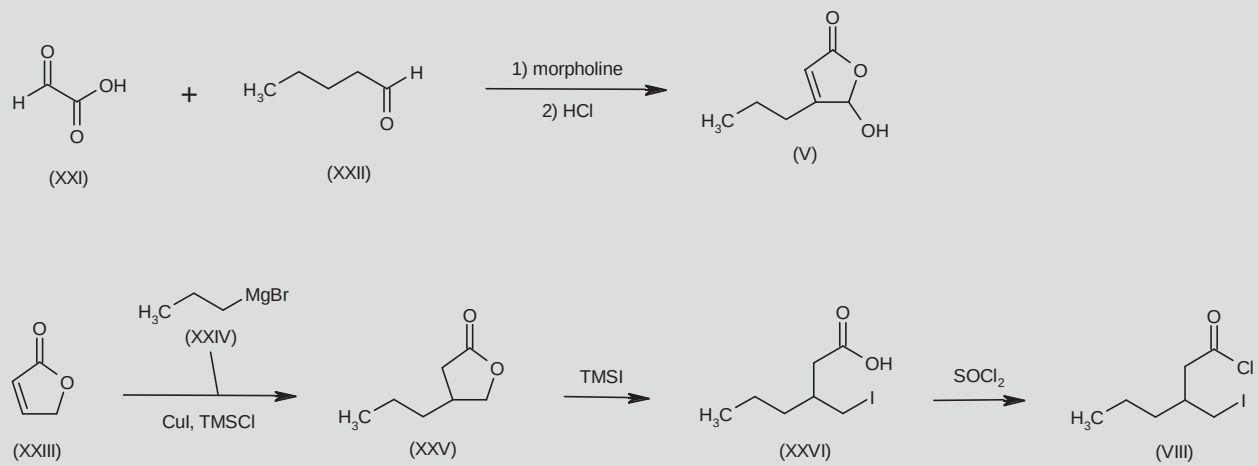
5-Hydroxy-4-propyl-2-furanone (V) is obtained by aldol condensation of glyoxylic acid (XXI) with valeraldehyde (XXII) in the presence of morpholine in heptane, followed by cyclization of the intermediate aldehyde acid under acidic conditions (2). Scheme 3.

Preparation of iodoacyl chloride (VIII) starts with the conjugate addition of propylmagnesium bromide (XXIV) to 2-furanone (XXIII) in the presence of CuI and TMSCl in ethyl ether to produce 4-propylbutyrolactone (XXV), which undergoes lactone ring opening by means of iodotrimethylsilane in CH_2Cl_2, affording 3-(iodomethyl)hexanoic

Scheme 2. Synthesis of Meldrum's Acid Derivative (II)



Scheme 3. Synthesis of Synthetic Precursors of (VII)



acid (XXVI), and finally, chlorination of acid (XXVI) with $SOCl_2$ in benzene (4). Scheme 3.

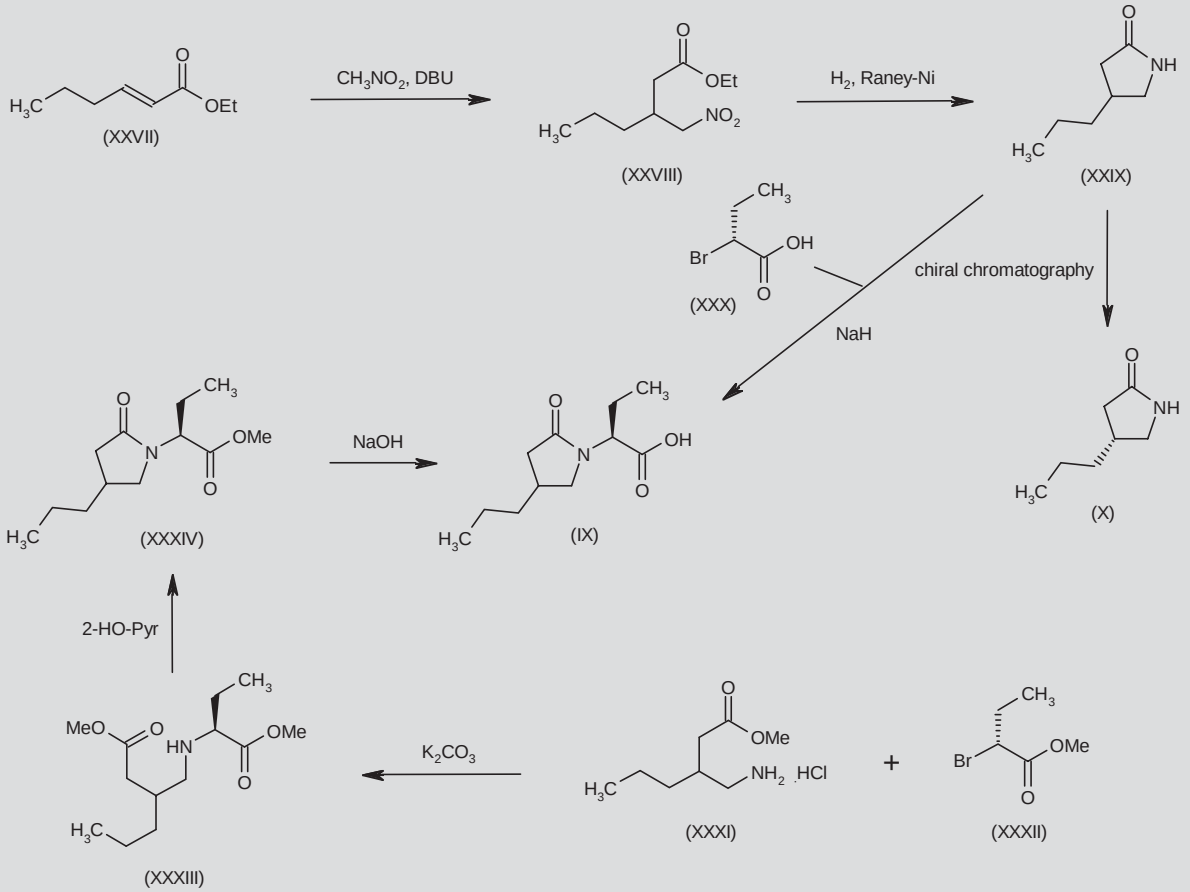
Pyrrolidone intermediates (IX) and (X) are prepared as follows:

Conjugate addition of nitromethane to 2-hexenoic acid ethyl ester (XXVII) by means of DBU gives ethyl 2-(nitromethyl)hexanoate (XXVIII), which by nitro group reduction with H_2 and Raney-Ni in MeOH at 55 °C cyclizes to the racemic lactam (XXIX). Resolution of compound (XXIX) using chiral column chromatography results in the optically pure (*R*)-enantiomer (X) (6). Scheme 4.

The intermediate pyrrolidinone butyric acid (IX) can be obtained by *N*-alkylation of 4-propyl-2-pyrrolidinone (XXIX) with (*R*)-2-bromobutyric acid (XXX) in the presence of NaH in THF (5). Scheme 4.

In an alternative procedure, alkylation of ethyl 4-amino-3-propylbutyrate hydrochloride (XXXI) with methyl (*R*)-2-bromobutyrate

Scheme 4. Synthesis of Intermediates (IX) and (X)



(XXXII) by means of K_2CO_3 in acetonitrile gives the amino diester (XXXIII), which cyclizes to the pyrrolidinone (XXXIV) by heating in toluene at 80 °C in the presence of a catalytic amount of 2-hydroxypyridine. Finally, saponification of methyl ester (XXXIV) using aqueous NaOH then affords the corresponding carboxylic acid (IX) (5). Scheme 4.

BACKGROUND

Epilepsy is believed to affect around 1% of the population. While antiepileptic drugs (AEDs) have been the mainstay of treatment, their use can sometimes be limited by suboptimal efficacy and a variety of adverse effects. Poorly controlled epilepsy can be associated with increased mortality, injuries and psychosocial limitations (7). Synaptic vesicle glycoprotein 2A (SV2A) is a glycoprotein found abundantly in the membranes of synaptic vesicles of neurons (8). Its role in epilepsy was discovered during the search for the mechanism of action of levetiracetam, a derivative of piracetam. Levetiracetam was approved by the FDA in 1999 and has been used for the treatment of partial seizures with or without generalization, generalized tonic–clonic seizures and juvenile myoclonic epilepsy. When introduced, it was clearly evident that it differed in its mechanism of action from other available anticonvulsants.

Further studies led to the identification of SV2A as a binding site for levetiracetam (9). SV2A binding facilitates the release of neurotransmitters by preparing synaptic vesicle fusion and exocytosis (10). The physiology of SV2A function and its role in epilepsy are still not fully clear, but mice with *SV2A* gene knockout have been reported to have abnormal neurotransmission, develop seizures and die within the first 3 weeks of life (11). Animal models with heterozygosity for SV2A have shown lowered seizure threshold and an increased susceptibility to corneal kindling (12).

Brivaracetam is a racetam derivative with anticonvulsant properties. It is one of the recently developed designer medications which are the result of ongoing efforts to address some of the shortcomings of existing AEDs. Brivaracetam is the 4-*n*-propyl analogue of levetiracetam, which is believed to act by binding to SV2A. A positive correlation between binding affinity for SV2A and antiseizure activity has been demonstrated in animal models with a number of levetiracetam analogues. Brivaracetam was chosen for further trials because of its broad antiseizure activity, a relatively benign adverse

event profile and good tolerability in preclinical studies. Following successful phase I and II trials, this molecule has undergone and is undergoing phase III trials.

PRECLINICAL PHARMACOLOGY

While the pharmacodynamics of brivaracetam are still under investigation, various mechanisms of action have been postulated and some of these have been established (Fig. 1). Like levetiracetam, brivaracetam is a selective SV2A ligand, but it is much more potent in this regard (13), showing 13 times higher affinity for SV2A compared to levetiracetam (4). Brivaracetam has an additional chiral center substituted in the 4-position in the 2-pyrrolidinone ring, giving it two stereoisomers, and this stereoselectivity is most likely associated with the enhanced binding affinity (4). Interestingly, and unlike levetiracetam, it also inhibits the peak amplitude of voltage-dependent inward Na^+ currents (14), but lacks levetiracetam-like effects on voltage-gated Ca^{2+} and K^+ currents (15, 16). It opposes the action of negative modulators of $GABA_A$ and glycine receptors such as zinc and β-carbolines at concentrations tenfold lower than those of levetiracetam. Brivaracetam is also believed to decrease NMDA-mediated glutamate release (17). The above differences might explain the broader anticonvulsant effect of brivaracetam in both preclinical and clinical studies (18).

In both in vitro and in vivo preclinical studies, brivaracetam has demonstrated potent suppression of seizure activity (19). In contrast to levetiracetam, brivaracetam showed antiseizure activity in both the maximal electroshock and subcutaneous pentylenetetrazol models of epilepsy; it was also effective against generalized motor seizures in hippocampal-kindled rats and the genetic absence epilepsy rat from Strasbourg (20). In audiogenic seizure-prone and corneally kindled mouse models of epilepsy, brivaracetam was 10 times more potent than levetiracetam (21). In combination with diazepam, it controlled seizure activity in animal models of drug-resistant self-sustaining status epilepsy (4).

Brivaracetam has also undergone preclinical trials for other potential uses, including neuropathic pain and essential tremor. In rat models of mononeuropathic and diabetic pain brivaracetam performed better than gabapentin (22). The antitremor efficacy of brivaracetam was comparable to that of carbamazepine and gabapentin at nonsedative doses (23). As a derivative of the nootropic agent piracetam, brivaracetam has shown procognitive effects in animal models.

PHARMACOKINETICS AND METABOLISM

The pharmacokinetic properties of brivaracetam have been evaluated in preclinical studies using animal models. These studies indicated high oral bioavailability.

A total of 71 healthy volunteers participated in double-blind, randomized, placebo-controlled phase I trials investigating the pharmacokinetics, safety and tolerability of brivaracetam (24, 25). Of these, 27 received a single dose of 10-1400 mg of brivaracetam, 36 volunteers received 200-800 mg/day in divided doses for 2 weeks and 8 received a single dose of 150 mg in the fasting state and after a high-fat meal in order to estimate food effects. Brivaracetam was rapidly and completely absorbed after oral administration, with the time to maximum concentrations (t_{max}) being 0.5-1.75 h (comparable to the t_{max} of 0.5 h in animal studies). Food interferes with absorption and delays peak plasma concentrations (C_{max}), but does not affect the AUC. It is weakly bound to plasma proteins and has a low first-pass metabolism, with a half-life of about 7-8 h (24). Brivaracetam is mainly metabolized by hydrolysis via a non-cytochrome P450 pathway, although oxidation by the CYP2C8 isoform of cytochrome P450 pathway is also involved. Its metabolites are inactive and elimination is completed by the renal system (26). Approximately 8% of the total drug is excreted unchanged in the urine. It has been reported that the pharmacokinetics of brivaracetam are largely unchanged in the elderly and in individuals with renal impairment.

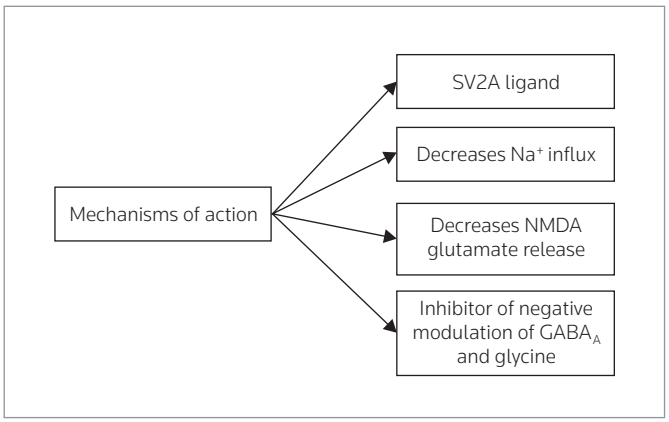


Figure 1. Potential mechanisms of action of brivaracetam.

SAFETY

The safety and tolerability of brivaracetam have been evaluated in preclinical studies, indicating low toxicity and no adverse effects on fertility, pregnancy or fetal development. There were also no carcinogenic or mutagenic effects in animal models.

In early clinical trials, brivaracetam at therapeutic doses was well tolerated, with a benign adverse effect profile comparable to that of placebo. Similar to levetiracetam, it also had a good therapeutic index. The most common side effects reported with the use of brivaracetam included somnolence and dizziness, which were transient and disappeared within the first 24 h, indicating a rapid tolerance to adverse effects. Other side effects reported include headache, fatigue, nausea, throat irritation, disturbance of attention and euphoric mood. A dose-dependent increase in side effects has been observed, especially beginning at a dose of 80 mg. However, side effects were rapid in onset and disappeared during the first 24 h (27). No significant abnormalities, including ataxia, were seen on physical examination, psychometric and neurological tests, vital signs, EKG and EEG. Brivaracetam is not proarrhythmic and does not affect cardiac repolarization (28).

CLINICAL STUDIES

The antiepileptic activity of brivaracetam has been investigated in phase II trials (Table I). A subject-blind, placebo-controlled phase II

Table I. *Phase II efficacy studies.*

Reference	Brivaracetam dose	Sample size	Results	Side effects
Kasteleijn-Noist Trenité et al. (29)	10, 20, 40, 80 mg	18 photosensitive epilepsy patients	14 of 18 achieved complete abolishment of photoparoxysmal response	Dizziness, nausea, sedation, dry mouth
French et al. (30)	5, 20, 50 mg	Total, N = 208; placebo, n = 54; brivaracetam 5 mg, n = 50; 20 mg, n = 52; 50 mg, n = 52	Mean reduction in seizures: placebo 21.7%, brivaracetam 5 mg 30%, 20 mg 40%, 50 mg 53%	Similar to placebo
Van Paesschen et al. (31)	50, 150 mg	Total, N = 157; placebo, n = 52; brivaracetam 50 mg, n = 53; 150 mg, n = 52	Mean reduction in seizures: placebo 14.7%, brivaracetam 50 mg 39%, 150 mg 33.3%	Well tolerated, with similar side effects to placebo

trial was conducted in 18 photosensitive epilepsy patients treated with single doses of brivaracetam of 10, 20, 40 and 80 mg (29). Standardized intermittent photic stimulation (IPS) was used to identify the individual standard photosensitivity range (SPR). Single doses of brivaracetam were effective in decreasing IPS-evoked photoparoxysmal encephalogram responses (PPR) and the 80-mg dose was most effective, with a rapid onset and a duration of action lasting up to 60 h following a single dose. Of 18 patients, 14 had complete abolishment of PPR evoked by IPS, and all 18 patients had reductions in SPR.

Two randomized, double-blind, placebo-controlled phase II trials have evaluated brivaracetam as an adjunctive treatment for refractory partial-onset seizures. In the first study, 208 patients with partial seizures on 1-2 anticonvulsants and still experiencing 4 or more partial seizures over a baseline period of 4 weeks were included and randomized to receive brivaracetam or placebo. Add-on brivaracetam was administered at doses of 5, 20 and 50 mg/day. Efficacy was assessed every week for a total of 7 weeks. The response rate (50% reduction in seizure frequency) was 30%, 43% and 53%, respectively, at the above doses, compared to the placebo response rate of 22%. Seizure-free rates were approximately 8% with all three doses, whereas those with placebo were 1.9%. The tolerability and side effect profile was comparable to placebo at all doses of brivaracetam (30). The second study was similar but evaluated the efficacy and tolerability of brivaracetam 50 and 150 mg compared to placebo in 157 patients with partial seizures. Response rate and seizure-free rate were 39% and 9.4%, respectively, with 50 mg/day, 33.3% and 5.9%, respectively, with 150 mg/day and 18.9% and 1.9%, respectively, with placebo. Both doses of brivaracetam were well tolerated, but compared to the 50 mg/day dose of brivaracetam, the 150 mg/day dose did not show greater therapeutic efficacy (31).

Results from two recent randomized, double-blind, placebo-controlled phase III trials of brivaracetam were presented at the 63rd Annual Scientific Conference of the American Epilepsy Society. Interestingly enough, both these prospective, multicenter studies had contrasting conclusions (32). While one of these trials suggested that brivaracetam can significantly reduce partial-onset seizures, the other one did not report a statistically significant improvement in the primary efficacy endpoint. Each of these studies included about 400 patients with refractory partial-onset seizures. Investigators randomized roughly 100 participants to each arm of the study. Patients in the American study (N01253) received placebo or brivaracetam 5, 20 or 50 mg twice daily, whereas those in the study performed in Europe and Asia (N01252) received placebo or brivaracetam 20, 50 or 100 mg. The patients were treated for 12 weeks in both studies. The subjects were aged 16-70 years and had two or more partial-onset seizures in the 3 months before screening. These individuals had eight or more seizures during the 8-week prospective baseline and were taking one or two concomitant antiepileptic drugs. Investigators in the American trial observed a reduction in partial-onset seizure frequency per week over placebo on the 50-mg dose, which achieved statistical significance on the primary endpoint. On the other hand, in the European trial, investigators reported that the reduction in seizures was not statistically significant. In the American study, the use of brivaracetam 50 mg was associated with a 12.8% reduction in partial-onset seizures compared to placebo. In contrast, the European study showed that it was associated with only a 6.5% reduction compared with placebo, although the dose of 100 mg was associated with an 11.7% reduction in partial-onset seizures. While the reasons for these contrasting findings are not clear and more studies are clearly needed in this regard, some of the leading researchers in the field have suggested that brivaracetam may fall short of its predecessor, even though it is effective, has few drug interactions and a reasonable safety profile. Thus, the phase III data, while discordant, suggest the need for further research before brivaracetam can be used successfully in the clinic.

Brivaracetam was granted orphan drug status by the FDA in May 2005 for the treatment of symptomatic myoclonus. It also received orphan drug status in Europe in August 2005 for the treatment of progressive myoclonic seizures. Brivaracetam is currently undergoing several phase III trials looking at efficacy, long-term tolerability and side effects in children 16 years or older with epilepsy (ClinicalTrials.gov Identifier NCT00761774, NCT00175916 and NCT00150800). An open-label phase III study examining the effect of brivaracetam on steady-state plasma levels of phenytoin when they are used together in patients with epilepsy has been completed (ClinicalTrials.gov Identifier NCT00426673). A number of phase III studies in adults with partial-onset seizures have also been completed (ClinicalTrials.gov Identifier NCT00490035 and NCT00464269).

In addition, three other interesting studies, a randomized, double-blind, 4-way crossover study compared levetiracetam, lorazepam and placebo, looking at the neurocognitive effects of brivaracetam in healthy volunteers (ClinicalTrials.gov Identifier NCT00736931), an exploratory, double-blind, placebo-controlled study evaluating the efficacy, safety and tolerability of brivaracetam at doses of 200 and 400 mg/day in patients with postherpetic neuralgia (ClinicalTrials.gov Identifier NCT00160667), and two multicenter, randomized, double-blind, placebo-controlled, parallel studies evaluating the efficacy and safety of brivaracetam used as adjunctive treatment in adolescents and adults with Unverricht-Lundborg disease, have been completed (ClinicalTrials.gov Identifier NCT00357669 and NCT00368251).

DRUG INTERACTIONS

At doses that were severalfold higher than the therapeutically recommended dose (400 mg/day and more), brivaracetam was observed to interact with and moderately decrease the levels of carbamazepine (AUC decreased by 13%), phenytoin and oral contraceptives. It only slightly increased the plasma concentrations of carbamazepine-10,11-epoxide (2.5-fold increase in AUC) (33). Hence, when using the "therapeutic range" doses of 5-150 mg/day, no adjustments are recommended when using brivaracetam with other anticonvulsants (34). Interaction with oral contraceptives has no effect on the suppression of ovulation. Although current data suggest that brivaracetam has low toxicity, and no adverse effects on fertility, pregnancy or fetal development, this needs to be explored further and confirmed in long-term studies.

CONCLUSIONS AND FUTURE DIRECTIONS

Brivaracetam reflects the success of research efforts to rationally design molecules to optimize the SV2A binding of levetiracetam. It is a potent SV2A ligand with broad-spectrum antiepileptic activity, a good side effect profile and could offer a much-needed option for the treatment of photosensitive epilepsy, refractory partial-onset seizures and progressive myoclonus. Other potential clinical uses, including positive neurocognitive effects, attenuation of neuropathic pain and tremor, need to be studied further in clinical trials. Recent phase III data, however, have been conflicting and suggested the need for further research in the area.

SOURCE

UCB SA (BE).

DISCLOSURES

The authors state no conflicts of interest.

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