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MONOGRAPH

PERAMPANEL

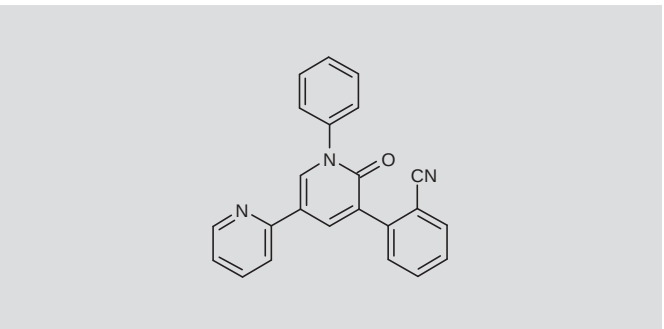
Prop INN; USAN

AMPA Receptor Antagonist
Antiepileptic Agent

E-2007
ER-155055-90

2-(6′-Oxo-1′-phenyl-1′,6′-dihydro-2,3′-bipyridin-5′-yl)benzonitrile
5′-(2-Cyanophenyl)-1′-phenyl-2,3′-bipyridyl-6′(1′*H*)-one
3-(2-Cyanophenyl)-1-phenyl-5-(2-pyridyl)-1,2-dihydropyridin-2-one

InChI: 1S/C23H15N3O/c24-15-17-8-4-5-11-20(17)21-14-18(22-12-6-7-13-25-22)16-26(23(21)27)19-9-2-1-3-10-19/h1-14,16H



$C_{23}H_{15}N_3O$

Mol wt: 349.3847

CAS: 380917-97-5

EN: 314603

SUMMARY

Glutamate is the principal excitatory neurotransmitter that acts through ionotropic and metabotropic glutamate receptors. The ionotropic glutamate receptors, namely NMDA (N-methyl-D-aspartate), AMPA (2-amino-3-[5-methyl-3-oxo-1,2-oxazol-4-yl]propanoic acid) and kainate, play an important role in the pathophysiology of epilepsy. NMDA/kainate receptor antagonists have proven effective in various preclinical studies. However, these molecules are associated with severe side effects, which in turn limit their use in the clinical setting. AMPA receptors on the other hand are non-NMDA glutamate receptors that maintain fast excitatory synaptic neurotransmission and possess a superior safety profile compared to NMDA/kainate receptor antagonists. AMPA receptor antagonists have shown anticonvulsant activity in animal models of epilepsy. There has been a recent breakthrough in understanding the role of AMPA receptors in the pathophysiology of epilepsy. Perampanel, an orally acting, potent, non-competitive AMPA receptor antagonist, has shown promising results in both preclinical and clinical studies in epilepsy. The agent is awaiting approval from the EMA and the FDA for use in the management of epilepsy. The present review attempts to discuss the pharmacological and clinical profile of perampanel.

Key words: AMPA receptors – Perampanel – E-2007 – ER-155055-90 – Epilepsy

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SYNTHESIS*

Perampanel can be prepared by the following methods:

Selective bromide displacement in 2,5-dibromopyridine (I) with NaOMe in refluxing MeOH affords 5-bromo-2-methoxypyridine (II) (1), which alternatively can be obtained by bromination of 2-methoxypyridine (III) with elemental bromine in the presence of NaOAc in EtOAc at 50 °C (2). Metalation of 5-bromo-2-methoxypyridine (II) with BuLi in THF at –75 °C followed by addition of trimethyl borate and aqueous acidic hydrolysis leads to (6-methoxy-3-pyridyl)boronic acid (IV). Subsequent Suzuki coupling of boronic acid (IV) with 2-bromopyridine (V) in the presence of $Pd(OAc)_2$, PPh_3 and K_2CO_3 in DME/H_2O at reflux provides 6-methoxy-3,2′-bipyridine (VI) (1). In an alternative method, bipyridine (VI) can be obtained by metalation of 5-bromo-2-methoxypyridine (II) with BuLi in THF at –75 °C followed by condensation with 2-(phenylsulfonyl)pyridine (VII) (2). Hydrolysis of 6-methoxy-3,2′-bipyridine (VI) by means of aqueous HCl at reflux yields 5-(2-pyridyl)-2-pyridone (VIII) (1, 2). In a related method, Stille coupling of 5-bromo-2-methoxypyridine (II) with (2-pyridyl)tributyltin (IX) in the presence of $Pd(Ph_3)_4$ in DMF at 120 °C followed by methoxy group hydrolysis with concentrated HBr at 110 °C leads to 5-(2-pyridyl)-2-pyridinone (VIII) (1). *N*-Arylation of pyridone (VIII) with either phenylboronic acid (X) (1) or its trimeric anhydride 2,4,6-triphenylboroxine (XI) (3) in the presence of $Cu(OAc)_2$ in pyridine/DMF under air blowing conditions gives 1-phenyl-5-(2-pyridyl)-2-pyridinone (XII), which is brominated using NBS in DMF (1) or EtOAc (3) to yield the 3-bromopyridone derivative

(XIII). Finally, this compound is subjected to Suzuki coupling with 2-(2-cyanophenyl)-1,3,2-dioxaborinane (XIV) by means of $Pd(OAc)_2$, PPh_3, CuI and K_2CO_3 in DME (3). Scheme 1.

In a different synthetic strategy, Suzuki coupling of 5-bromo-6-methoxy-3,2′-bipyridine (XV) with 2-(2-cyanophenyl)-1,3,2-dioxaborinane (XIV) using $Pd(PPh_3)_4$ and Cs_2CO_3 in DMF at 140 °C gives 3-(2-cyanophenyl)-5-(2-pyridyl)-2-methoxypyridine (XVI), which undergoes methoxy group hydrolysis by means of $ClSiMe_3$ and NaI in acetonitrile to produce the pyridone derivative (XVII). Finally, subsequent *N*-arylation of pyridone (XVII) with phenylboronic acid (X) in the presence of $Cu(OAc)_2$ and Et_3N in CH_2Cl_2 furnishes perampanel (1). Scheme 1.

BACKGROUND

Epilepsy is a severe neurological disorder that affects nearly 50 million people worldwide. According to the World Health Organization (WHO), approximately 30% of patients with epilepsy are known to suffer from intractable (hard to control) epilepsy and continue to have seizure attacks despite the availability of different antiepileptic drug molecules (4). Seizures can vary from small jerks to violent tonic–clonic convulsions.

Glutamate and GABA (γ-aminobutyric acid) are the two primary neurotransmitters involved in the pathophysiology of epilepsy. GABA is an inhibitory neurotransmitter in the adult brain and glutamate is responsible for the excitatory response. In the normal brain, there is a delicate balance between GABAergic and glutamatergic neurotransmission. Various antiepileptic drugs work by enhancing GABAergic neurotransmission in the brain. On the other hand, there are very few antiepileptic molecules based on our understanding of the glutamatergic theory of epilepsy. We now need to explore effective and safe antiepileptic agents based on our knowledge describing the role of glutamate and glutamatergic synapses in the pathophysiology of epilepsy. These novel molecules may be useful drugs for treating epileptic patients suffering from pharmacoresistance.

Glutamate is an excitatory neurotransmitter in the body that acts on glutamatergic receptors (5). These receptors are further divided into two subclasses, namely: 1) ionotropic ligand-gated ion channels; or 2) metabotropic G protein-coupled receptors (5, 6). Glutamate plays a major role in the neurobiology of various central nervous system disorders, including Parkinson's disease, Huntington's disease, major depression, epilepsy and schizophrenia (7). The ionotropic glutamate receptors are further divided into three subforms, namely, NMDA (*N*-methyl-D-aspartate), AMPA (2-amino-3-[5-methyl-3-oxo-1,2- oxazol-4-yl]propanoic acid) and kainate (8). Glutamate and its receptors are involved in the neuropathology of epilepsy. Exogenous administration of ionotropic glutamatergic ligands such as NMDA, AMPA or kainate is known to produce severe convulsions in rodents (9). On the other hand, blockers of these receptors may be protective in epilepsy. For example, Young et al. reported that acute or subchronic administration of MK-801, a non-competitive NMDA receptor blocker, is effective in reducing the afterdischarges in fully amygdaloid kindled rats (10). These molecules, however, failed to enter the clinic, probably due to their poor adverse event profile outcome.

AMPA receptors are non-NMDA ionotropic glutamate receptors that play a major role in the pathophysiology of epilepsy. AMPA receptor antagonists possess a better safety profile compared to NMDA receptor antagonists (11). AMPA receptor antagonists are broadly classified into two subcategories: 1) competitive AMPA receptor blockers, which compete with the endogenous ligand, namely glutamate, at the glutamate binding sites; or 2) non-competitive or allosteric modulators, which act at a different site than glutamate and can modify the receptor function despite the presence of an endogenous ligand molecule (12).

NBQX was the first competitive AMPA receptor antagonist to be discovered. NBQX is systemically active and possesses mixed activity at AMPA and kainate receptors. It has been shown to be effective in animal models of neurological disorders (13, 14). Following the discovery of competitive AMPA receptor antagonists, there have been further advancements in the understanding of AMPA receptor physiology. Furthermore, molecules belonging to the 2,3-benzodiazepine class were discovered to be non-competitive AMPA receptor antagonists (15). GYKI-52466 is the prototypical non-competitive AMPA receptor antagonist molecule. Further discoveries led to more potent non-competitive AMPA receptor antagonists, such as talampanel, CP-465022 and perampanel. Here, the activity of perampanel is described in detail.

PRECLINICAL PHARMACOLOGY

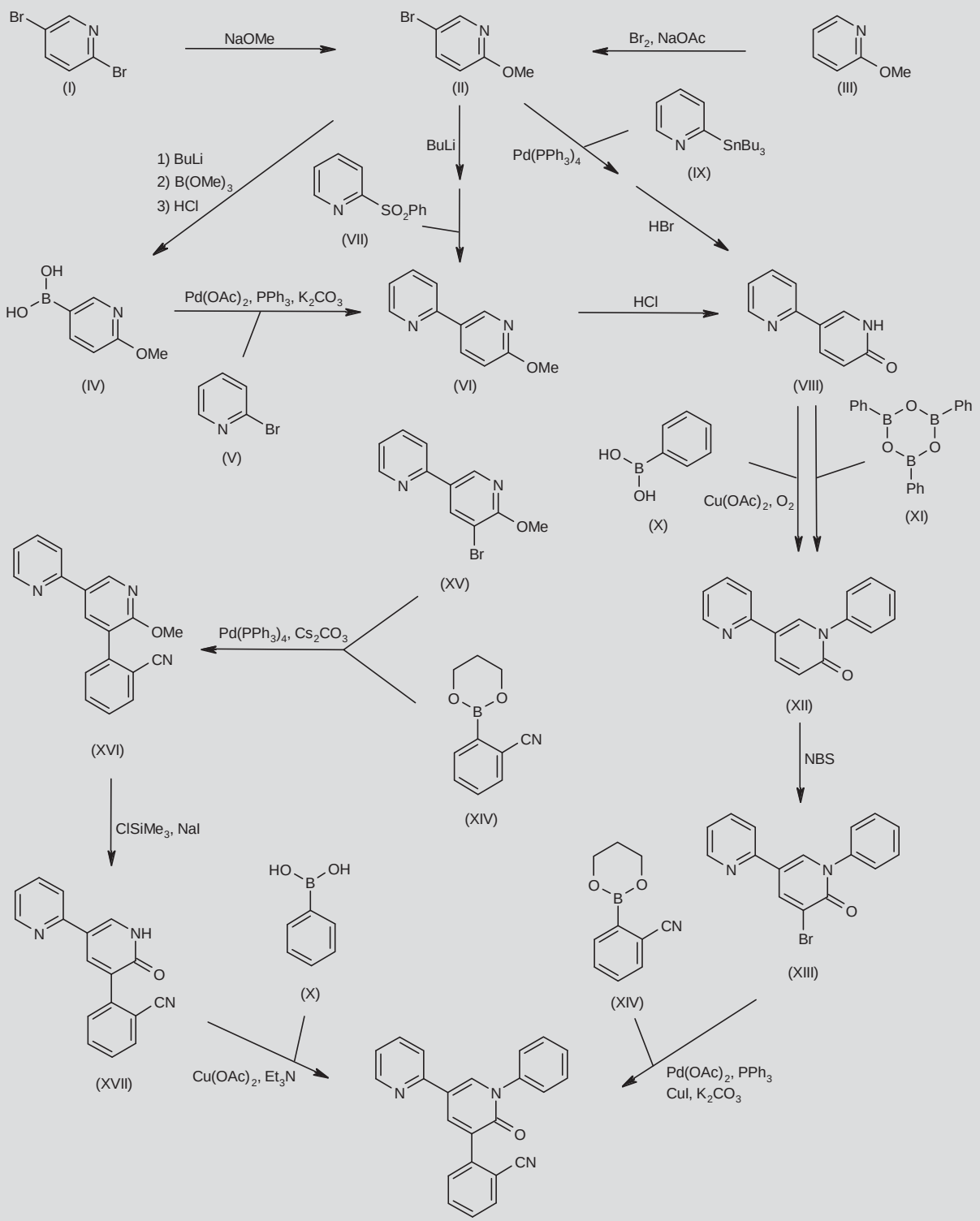
Perampanel is an orally active, non-competitive, selective inhibitor of the AMPA receptor that was discovered by Eisai research laboratories in London and Ibaraki, Japan. The compound has shown antiepileptic activity in both preclinical and clinical studies.

Perampanel blocked the AMPA-induced increase in $[Ca^{2+}]_i$ with an IC_{50} of 93 nM in rat cortical neurons, and at a very high concentration (30 mM) it inhibited the NMDA-induced increase in $[Ca^{2+}]_i$ by 18%. This study demonstrated that perampanel is a selective AMPA receptor antagonist and has very little or no activity on NMDA receptors. Perampanel is a non-competitive antagonist of AMPA receptors, as GYKI-52466 and CP-465022 displaced [^{3}H]-perampanel binding to rat forebrain membranes. Furthermore, glutamate, an endogenous ligand, and NBQX, a competitive AMPA receptor antagonist, did not affect [^{3}H]-perampanel binding to rat forebrain membranes (16).

Perampanel is active in various animal models of seizures. The ED_{50} values for perampanel in maximal electroshock, audiogenic and pentylenetetrazol-induced seizure models were 1.6 (95% confidence interval [CI]: 1.3-1.9), 0.47 and 0.94 mg/kg, respectively, when tested in mice. The molecule was found to be more potent compared to carbamazepine and sodium valproate, two standard antiepileptic agents (16). The latency to AMPA (0.4 mM by intracerebroventricular [i.c.v.] infusion) seizure occurrence was enhanced by perampanel at 2 and 4 mg/kg orally (p.o.). Also, the latency to NMDA (0.08 mM by i.c.v. infusion) seizures was enhanced by perampanel at 8 mg/kg p.o. (17).

Perampanel affects motor coordination in mice with a TD_{50} value of 1.8 mg/kg (95% CI: 1.4-2.8). Based on this value, the protective index (TD_{50}/ED_{50}) was found to be 1.1, 3.8 and 1.9, respectively, in maximal electroshock, audiogenic and pentylenetetrazol-induced seizure models (16).

Scheme 1. Synthesis of Perampanel



When tested in an amygdala seizure test model, it was found that perampanel 10 mg/kg administered 1 hour before the test significantly increased the afterdischarge threshold in amygdala kindled rats. Also, perampanel at doses of 5 and 10 mg/kg p.o. reduced seizure severity, afterdischarge duration and motor seizure duration in amygdala kindled rats (16).

PHARMACOKINETICS AND METABOLISM

Two phase I clinical trials were carried out with perampanel. Both trials enrolled healthy male subjects 18-45 years old. The first trial was a single-dose study involving 55 subjects and the second trial was a multiple-dose study involving 32 subjects. The majority of volunteers were Caucasian. It was found that perampanel is rapidly absorbed and the peak plasma concentration varied between 0.25 and 2 hours after administration in the single-dose study. The mean apparent $t_{1/2}$ ranged between 53 and 123 hours. On the multiple-day dosing schedule, steady state was reached at 24 hours and the observed $t_{1/2}$ at steady state was 99.8 hours after 1 mg and 129.5 hours after 4 mg perampanel. In the single-dose trial, perampanel at doses of 2 mg and higher produced sedation as assessed by the Bond and Lader sedation subscale. In the multiple-day dosing study, perampanel only at a high dose (6 mg) was reported to have sedative effects, as assessed by the same test (18).

SAFETY

In a safety assessment, the most frequent adverse events observed were headache, dizziness and fatigue in the single-dose study. There were no serious adverse events with perampanel. In the multiple-dose study, the most frequent adverse events reported were somnolence, dizziness and headache. The volunteers did not show any changes in vital parameters and electrocardiogram after perampanel administration. However, five subjects in the multiple-dose study had a transient elevation of AST (aspartate aminotransferase) and ALT (alanine aminotransferase) from > 1.5 to < 2.5 times the upper limit of normal. In general, most adverse events after multiple dosing were mild (89.7%) or moderate (8.7%) in severity. There were no serious adverse events noted with perampanel at therapeutic doses (18).

CLINICAL STUDIES

Two phase II clinical studies were performed with perampanel in patients with refractory partial-onset seizures (19). The studies were randomized, double-blind and placebo-controlled. The first study (206) involved administration of perampanel at 1 mg/day (0.5 mg twice a day or 1 mg once a day) and titrated to maximum of 4 mg/day (titrated in 1 mg/day increments every 2 weeks to a maximum of 4 mg/day) (19, 20). In the second study (208), perampanel was administered at 2 mg once a day and titrated up to a maximum of 12 mg (2 mg/day increments every 2 weeks to a maximum of 12 mg once a day) (19). The plasma concentration of perampanel in the phase II studies was described by a one-compartment disposition model with first-order absorption and elimination. Perampanel was found to be safe at these doses and adverse events including dizziness, somnolence, gait disturbance and balance disorder were observed in 27.8% of the placebo-treated patients and 32.6% of the perampanel-treated patients (19, 20).

Three phase III studies were carried out under the EXPLORE (EXamining Perampanel Observations from Research Experience) program.

In one phase III study (306), a total of 706 patients were enrolled from 25 countries and received either placebo or 1 of 3 doses of perampanel. Patients were started with a 2-mg dose of perampanel and either remained on the same dose or the dose was increased weekly as 2-mg increments to doses of 4 or 8 mg. Perampanel decreased the median seizure frequency and increased the responder rate in this study. The effect was more significant at 4 and 8 mg compared to the placebo-treated group (21-23).

In another phase III study (304) involving 308 patients from the U.S., Canada and Central/South America, perampanel was found to reduce the seizure frequency at doses of 8 and 12 mg compared to the placebo control group (24).

The third phase III clinical trial (305) demonstrated that perampanel 8 and 12 mg once daily reduced the median seizure frequency by 30.5% and 17.6%, respectively. The study involved a total of 389 subjects with uncontrolled epilepsy who were on 1-3 antiepileptic drugs. Patients were enrolled from the E.U., the U.S., Asia, Australia and South Africa who had uncontrolled epilepsy and were currently taking one to three other epilepsy drugs (25-28).

CONCLUSION

Perampanel is a potent AMPA receptor antagonist that has shown favorable activity in preclinical and clinical studies of epilepsy. Perampanel is awaiting approval from the EMA and the FDA for the treatment of epilepsy. If approved for its use in the clinic, the molecule will be the first of its kind with a unique mechanism of action to manage patients with epilepsy.

SOURCE

Eisai Co., Ltd. (JP).

DISCLOSURES

The author states no conflicts of interest.

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