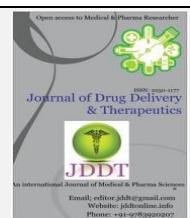


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Review Article

Epilepsy: The next generation drugs

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ABSTRACT

Epilepsy is a disease characterized by spontaneous recurrence of unprovoked seizures. Seizures and epilepsy are different disorders, and the terms should not be used interchangeably. It is not accurate to refer to seizures as epilepsy, although "seizure disorder" refers to epilepsy. Seizures are common and are treated in all branches of medicine. Approximately 10% of the population will have one or more seizures during their lifetime. Seizures are symptoms that occur in acute illness, i.e., provoked seizures, or in epilepsy, ie, unprovoked seizures. Antiepileptic drugs (AEDs) are pharmacologic agents used to reduce the frequency of epileptic seizures. "Antiepileptic" drug is a misnomer, because these drugs are effective as symptomatic treatment of seizures, i.e., the symptoms of epilepsy, not as treatment of epilepsy itself. Recent discoveries in molecular biology and genetics have elucidated a genetic basis for some epilepsy syndromes, which will lead to new treatments. This review include new AEDs viz; Ganaxolone, Eslicarbazepine acetate, Fluorofelbamate, Huperzine A, Carisbamate (RWJ-333369), Brivaracetam (ucb 34714), 2-Deoxy-D-glucose, Retigabine, T2000 , T2007, Valrocemide, Tonabersat (SB-220453), YKP3089, Propyl isopropyl acetamide, JZP-4, ICA-105665, NAX-5055, Perampanel and Valpromide.

Keywords: Epilepsy, Anti-epileptic drugs, Seizures

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INTRODUCTION

Epilepsy affects approximately 50 million people worldwide, with an annual incidence of 50 to 70 cases per 100,000 population ¹. Epilepsy is a common chronic neurologic disorder that affects 1% to 3% of the population, and almost two million people in the United States alone ². Seizures are more common than is generally appreciated; almost 10% of the population will have at least one seizure during their lifetime ³. Epileptic syndromes are defined by many factors, including type of seizure, age at onset of seizures, family history, and findings at physical examination, ictal and interictal electroencephalography (EEG), and neurologic imaging. Overall, complex partial seizures are the most common seizure type across age groups. Generalized seizures are more common in children, and partial seizures are more common in adults. Incidence of partial seizures remains constant at 20 per 100,000 populations from infancy until age 65 years, when it increases sharply. Incidence of generalized tonic-clonic seizures is high at age 1 year (15 per 100,000 population), then declines until age 10

to 14 years and remains at that rate until it again rises at age 65 years. Incidence of absence seizures is 11 per 100,000 populations from age 1 to 10 years, with uncommon onset after age 14 years. Myoclonic seizures are common during the first year of life, but decline after that ⁴⁻⁶.

Epilepsy is a disease characterized by spontaneous recurrence of unprovoked seizures. Seizures and epilepsy are different disorders, and the terms should not be used interchangeably. It is not accurate to refer to seizures as epilepsy, although "seizure disorder" refers to epilepsy. Seizures are symptoms, whereas epilepsy is a disease characterized by recurrent seizures. Seizures can result from diseases with the enduring tendency to seizures characteristic of epilepsy.

During the last decade, the two mainstays of epilepsy treatment, epilepsy surgery and antiepileptic drug (AED) therapy, have made great advances, resulting predominantly from advances in imaging techniques and the development of new AEDs. New AEDs have been developed to provide

drugs with fewer side effects and greater efficacy than those currently available. We review some of the recent drugs which acquired a well renowned position for the treatment of epilepsy. In this article, we review the mechanisms of action, efficacy, pharmacokinetic properties, and adverse reactions of the new AEDs.

Ganaxolone

IUPAC Name: 3 α -hydroxy-3 β -methyl-5 α -pregnan-20-one.

It is 3 β -methyl analog of the neurosteroid allopregnanolone, a metabolite of progesterone. Like other related neurosteroids, ganaxolone is not believed to have nuclear hormone activity and cannot be biotransformed to metabolites with such activity. A new submicron particulate formulation enhances bioavailability of ganaxolone compared to the oral suspension used in earlier studies ⁷.

Ganaxolone is a positive allosteric modulator of GABA_A receptors with potency and efficacy comparable to those of its endogenous neurosteroid analog allopregnanolone ⁸. Ganaxolone has protective activity in diverse rodent seizure models, including clonic seizures induced by pentylenetetrazol (PTZ) and bicuculline, limbic seizures in the 6 Hz model, and amygdale and cocaine-kindled seizures ^{9,10}.

In addition to the anticonvulsant activity, there is evidence that neurosteroids can retard the development of spontaneous recurrent seizures in some animal models of epileptogenesis, and therefore they have antiepileptogenic actions in such models ¹¹.

Ganaxolone has been tested in more than 900 subjects in Phase I and Phase II studies and was found to be generally safe and well-tolerated across the dose range used (for Phase II studies, up to 1875 mg/day in adults and up to 54 mg/kg/day in pediatric subjects), with divided daily dosing. The new studies show that ganaxolone at a dose of 1500 mg/day is efficacious, safe and well-tolerated as adjunctive therapy for partial seizures for adults, with no evidence of significant toxicities or weight gain in the Phase II program.

Eslicarbazepine acetate

IUPAC Name: (S)-(-)-10-acetoxy-10,11 dihydro-5H-dibenz[b,f]azepine-5-carboxamide

Eslicarbazepine acetate is a third-generation, singleenantiomer (with one chiral center) member of the long-established family of first-line dibenz[b,f]azepine AEDs. Eslicarbazepine acetate was designed with the aim of improving efficacy and safety in comparison with the structurally related drugs carbazepine and oxcarbazepine. Eslicarbazepine acetate formerly known as BIA 2-093, is a novel CNS-active compound. Eslicarbazepine acetate shares with carbazepine and oxcarbazepine the basic chemical structure of a dibenzazepine nucleus with the 5-carboxamide substituent, but is structurally different at the 10,11-position ¹².

Mechanistically, Eslicarbazepine acetate behaves as a potent blocker of voltage-gated sodium channels through interference with site 2 of the channel, and does not bind to receptors for benzodiazepines, gamma amino butyric acid (GABA) and glutamate ^{13,14}. Eslicarbazepine is the main active metabolite of eslicarbazepine acetate and represents about 95% of the total systemic drug exposure following oral administration of eslicarbazepine acetate. Single and multiple ascending dose studies in healthy male volunteers showed that Eslicarbazepine acetate is rapidly converted to the active metabolite or 10,11 dihydro-10-hydroxy-

5Hdibenz[b,f]azepine-5 carboxamide. The precise mechanism of action of eslicarbazepine acetate is not known. *In vitro* electrophysiological studies indicate that both eslicarbazepine acetate and eslicarbazepine competitively interact with site 2 of the inactivated state of a voltage-gated sodium channel, preventing its return to the active state and repetitive neuronal firing. Eslicarbazepine acetate inhibits release of the neurotransmitters or neuromodulators glutamate, GABA, aspartate and dopamine in rat striatal slices ¹⁵.

Fluorofelbamate

IUPAC Name: 2-phenyl-2-fluoro-1,3 propanediol dicarbamate

Fluorofelbamate is an analogue of felbamate designed to have the same broad spectrum anticonvulsant activity as felbamate without the serious adverse effects of the latter. In particular, the presence of a fluorine atom in the 2-position of the propanediol chain in the Fluorofelbamate molecule is intended to prevent the production of atropaldehyde, the reactive toxic metabolite of felbamate ¹⁶.

Preliminary evidence suggests that Fluorofelbamate acts, at least in part, by decreasing responses to GABA, kainate and N-methyl-D-aspartate (NMDA), and by reducing voltage-dependent sodium currents ¹⁷. Other actions are likely to contribute to its pharmacological effects in animal models. Fluorofelbamate shows protective activity against ischemia- and hypoxia-induced neuronal damage in a variety of models *in vivo* and *in vitro* ¹⁸.

Huperzine A

Huperzine A is a sesquiterpene Lycopodium alkaloid isolated from Chinese club moss (*Huperzia serrata*), also known as the Chinese folk medicine *Qian Ceng Ta*. Traditionally used in China for swelling, fever and inflammation, blood disorders and schizophrenia. Huperzine A is used in China for the treatment of Alzheimer's disease. It is classified as a dietary supplement by the FDA. Huperzine A was active against subcutaneous pentylenetetarzol- but not maximal electroshock-induced-induced seizures following p.o. administration to Swiss-Webster mice, with peak anticonvulsant activity at 1 h ¹⁹. At doses of 1, 2, and 4 mg/kg, a maximum of 62.5% protection was observed. Huperzine A is a potent, highly specific and reversible inhibitor of acetylcholinesterase, with comparable potency to physostigmine, galantamine, donepezil and tacrine ²⁰. Huperzine A also produces dose dependent increases of norepinephrine and dopamine in rat cortex when administered i.p. or locally. A study of neuro-protective, antiepileptogenic, and anticonvulsant effects of huperzine A in a rodent model of traumatic brain injury is in progress.

Carisbamate (RWJ-333369)

IUPAC Name: S-2-O-carbamoyl-1-o-chlorophenyl- ethanol

Carisbamate (RWJ-333369) is a novel anticonvulsant, with one chiral center, initially developed by SK Biopharmaceuticals, under development for the treatment of epilepsy. It shows a broad spectrum of activity in preclinical models of epilepsy and has demonstrated a favorable efficacy and tolerability profile in a Phase II clinical trial. Phase III clinical trials are in progress. Carisbamate has been found to possess potent and a broad spectrum of activity in a battery of acute rodent seizure models ²¹. At 10 and 30 mg/kg i.p., carisbamate significantly reduced the frequency of spontaneous recurrent seizures in the kainate post-status epilepticus model of temporal lobe epilepsy, and compared to topiramate was able to completely suppress spontaneous

recurrent seizures in a larger proportion of rats in the study 22.

Brivaracetam (ucb 34714)

Brivaracetam (ucb 34714) is a novel chiral (with two chiral) high-affinity synaptic vesicle protein 2A (SV2A) ligand which also displays inhibitory activity at neuronal voltage-dependent sodium channels 23. The function of SV2A is not well established; however, a strong functional correlation between SV2A binding affinity and anticonvulsant potency in animal models of both focal and generalized epilepsy has been established 24. Brivaracetam is currently in Phase III development for epilepsy.

Preclinical studies have shown that brivaracetam is more potent and efficacious than levetiracetam in animal models of seizures and epilepsy 25. Two Phase III, double-blind, randomized, multicenter, historical-controlled trials (N01276, NCT00698581 and N01306, NCT00699283) are ongoing to evaluate the efficacy and safety of brivaracetam (50 mg/day) as conversion to monotherapy in patients with uncontrolled focal epilepsy.

2-Deoxy-D-glucose

2-Deoxy-D-glucose, a glucose analogue differing from normal glucose only by removal of a single hydroxyl group at the 2 position, is a glycolytic inhibitor with novel anticonvulsant and disease-modifying antiepileptic properties. 2-Deoxy-D-glucose is preferentially delivered to brain regions in response to energy demand by an exquisitely regulated system of neurovascular coupling involving vascular cells, perivascular neurons, and astrocytes which precisely increases regional blood flow and glucose supply within seconds and within a few hundred microns in neural circuits experiencing increased activity 26, as occurs during seizures. 2-Deoxy-D-glucose, after activity-dependent uptake into cells through glucose transporters, undergoes phosphorylation by hexokinase at the 6 position to 2-deoxy-D-glucose-6-phosphate. 2 Deoxy-D-glucose-6-phosphate is transiently “trapped” in cells. Glycolytic inhibition by 2-deoxy-D-glucose is a novel anticonvulsant mechanism with both acute and chronic actions. The chronic antiepileptic actions of 2-deoxy-Dglucose against progression of kindled seizures have been associated with its actions as a glycolytic inhibitor acting to repress expression of brain-derived neurotrophic factor (BDNF) and receptor tyrosine protein kinase B (TrKB). Preclinical toxicology and pharmacokinetic studies are planned in anticipation of filing of an IND with the FDA. Because 2-deoxy-D-glucose undergoes rapid absorption and uptake after oral and parenteral administration but has a relatively short half-life, a slow-release formulation is currently in development.

Retigabine

IUPAC Name: *N*-[2-amino-4-(4-fluorobenzylamino)-phenyl]-carbamic acid ethyl ester

Retigabine is a unique antiepileptic compound that was identified during screening at the National Institutes of Health in 1991, and is currently being developed by Valeant Pharmaceuticals, USA. Early investigations showed that retigabine could activate a voltage-sensitive, neuron-specific outward potassium current that was later identified as the M-current mediated by KCNQ (Kv7) channels. Upon activation by excitatory input, the M-current opposes subsequent depolarizing inputs, reducing the likelihood of raising the membrane potential above the action potential threshold. Retigabine reduces neuronal excitability by primarily enhancing the activity of the KCNQ2/KCNQ3

(Kv7.2/Kv7.3) Secondary mechanisms of action include potentiation of GABA-evoked currents in cortical neurons via activation of GABA_A receptors containing β_2 or β_3 subunits. Channels 27. A Phase II, multicenter, randomized, double blind, placebo controlled dose-ranging trial (Study 205) evaluated retigabine 600, 900, or 1200 mg/day as adjunctive therapy in adults with partial-onset seizures. Two recently completed double-blind, placebo controlled Phase III studies have confirmed the dose dependent efficacy of 600–1200 mg/day retigabine and demonstrated that 600–900 mg/day is an appropriate initial target dose range for retigabine as adjunctive therapy in adults with partial-onset seizures.

T2000

IUPAC Name: 1,3-dimethoxymethyl-5,5- diphenylbarbituric acid

T2000 is a member of the barbiturate class of drugs. T2000 is a prodrug and is rapidly metabolized to monomethoxymethyl-5,5-diphenylbarbituric acid (MMMDPB) and 5,5 diphenylbarbituric acid. Earlier studies performed on isolated neural systems in *aplysia* and the hippocampus of the rat have shown that 5,5-diphenylbarbituric acid, the major metabolite of T2000, suppresses neural repetitive firing in both systems at concentrations lacking significant effects on GABA neurotransmission. These effects may be attributable to enhancement of outgoing membrane potassium current. Studies of 5,5 diphenylbarbituric acid on cat motor nerve terminal function show a suppression of repetitive discharges similar to the effects of phenytoin, a compound which acts on sodium channels in the nerve membrane. T2000 is being investigated for the treatment of essential tremor, myoclonus dystonia and epilepsy.

T2007

IUPAC Name: Sodium 5,5-diphenylbarbiturate

T2007 is a member of the barbiturate class of drugs. T2007, the sodium salt of 5,5 diphenylbarbituric acid, a new barbiturate salt, is presently under development by Taro Pharmaceuticals for treatment of epilepsy and essential tremor. T2007 and prodrugs of DBP like T2000 (1, 3-dimethoxymethyl-5,5-diphenylbarbituric acid), retain useful pharmacological activities at dosages that are not accompanied by sedation

Valrocemide

IUPAC Name: N-valproyl glyciamide

Valrocemide was selected from a series of N-valproyl derivatives of GABA and glycine because of its favorable pharmacokinetic and anticonvulsant activity profiles in preclinical screening models²⁸. In mice and rats, Valrocemide protects against seizures induced by maximal electroshock test (MES), pentylenetetrazol (PTZ), bicuculline (BIC) and picrotoxin (PIC). In healthy subjects, VLR exhibits linear pharmacokinetics after single oral doses ranging between 250 and 4000 mg and multiple doses ranging between 250 and 1000 mg three times daily²⁹⁻³¹. Recently, a new controlled-release formulation of valrocemide has been developed and in a crossover study conducted in 18 healthy subjects was found to produce equivalent AUC exposure to an immediate release formulation of valrocemide, with a relative bioavailability of 88% (90% CI, 81–96%).

Tonabersat (SB-220453)

IUPAC Name: (3S-cis)-N-(6-Acetyl-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1 benzopyran-4-yl)-3-chloro-4-fluorobenzamide

Tonabersat, formerly known as SB-220453, is a chiral (with two asymmetric centers) novel benzoylaminobenzopyran compound with potent anticonvulsant activity. Tonabersat selectively and specifically binds a unique stereo selective site in the CNS, thought to be at the neuronal gap junction. As such, tonabersat represents a 'first-in-class' neurotherapeutic that does not act via any established anticonvulsant mechanisms. In a number of animal seizure models, tonabersat, at doses of 1-10 mg/kg orally, exhibited activity comparable in efficacy and potency with current AEDs. The pain associated with migraine headache is believed to be associated with activation of the trigeminal vascular system. Stimulation of the fifth cranial (trigeminal) nerve results in a reproducible increase in carotid blood flow and a concomitant reduction in carotid vascular resistance. The effects of tonabersat on trigeminal nerve stimulation were investigated in the anaesthetised cat. Continuous i.v. administration of tonabersat at 3.4 or 11.5 mol/h produced a dose-dependent and time-related reduction in the effects of trigeminal nerve stimulation³².

YKP3089

YKP3089 is a novel compound with broad-spectrum anticonvulsant activity under clinical development at SK Life Science. YKP3089 protects against MES induced seizures in mice with an ED₅₀ of 9.8 mg/kg i.p., and in rats with an ED₅₀ of 1.9 mg/kg p.o. In the sc Met seizures model, YKP3089 given ip inhibited the clonic seizures in mice and rats, with ED₅₀ values of 28.5 and 13.6 mg/kg, respectively. YKP3089 was also effective against seizure induced by picrotoxin with an ED₅₀ of 34.5 mg/kg in mice. YKP3089 was effective in reducing significantly the expression of stage 5 seizures in the hippocampal kindled rat (ED₅₀ = 16.4 mg/kg). YKP3089 was effective in the mouse 6 Hz psychomotor seizure model at 22, 32 and 44 mA, with ED₅₀ values of 11.0, 17.9 and 16.5 mg/kg, respectively. YKP3089 also protects against lithium-pilocarpine-induced intractable seizures in rats (ip) (ED₅₀ = 7.0 mg/kg)³³.

Propylisopropyl acetamide (PID)

PID is a chiral (with one chiral center) CNS-active constitutional isomer of valpromide, the CNS-active corresponding amide of valproic acid³⁴. PID is not metabolized in animals to its corresponding acid (propylisopropylacetic acid) and therefore can be regarded as a metabolically stable constitutional valpromide isomer.

JZP-4

IUPAC Name: [3-(2,3,5-trichloro-phenyl)-pyrazine-2,6-diamine]]

JZP-4, is a novel, potent sodium and calcium channel blocker, structurally related to lamotrigine and endowed with broad spectrum anticonvulsant activity. The anticonvulsant profile of JZP-4 was established in a battery of well defined seizure and epilepsy models, with tests performed by the Anticonvulsant Screening Project at the National Institute of Neurological Disorders and Stroke (NINDS) and internally. The results from these studies suggest that JZP-4 possesses a broad-spectrum of activity³⁵. JZP-4 has inhibitory effects on both sodium and calcium channels, which collectively represent its presumed mechanism of action. JZP 4's antiepileptic properties are currently being evaluated in proof-of-concept study in humans. Single oral doses of JZP-4 ranging from 50 to 200 mg are compared to a single oral dose of Lamotrigine (325 mg) in their ability to decrease cortical excitability following transcranial magnetic stimulations in healthy male volunteers³⁶.

ICA-105665

ICA-105665 is a chemically novel (although its chemical structure has not yet been disclosed) highly selective opener of neuronal KCNQ (Kv7) potassium channels. The activity of ICA-105665 has been tested in a range of seizure and epilepsy models at Icagen and by the Anticonvulsant Screening Project of the National Institute of Neurological Disorders and Stroke. The primary effect of this compound is to shift the voltage-dependence of KCNQ2/Q3 channel activation to more negative potentials. As a result, KCNQ2/3 current is enhanced at voltages near the threshold for activation at which this channel typically has significant effects on membrane excitability (Table 3). This functional increase in KCNQ2/3 current is expected to be greater for neurons with more depolarized resting membrane potentials and/or high firing rates. ICA-105665 has been tested for its ability to reduce the photoparoxysmal EEG response in epilepsy patients with photosensitivity using well established standardized methods³⁷.

NAX-5055

Neuropeptides are potent modulators of neuronal excitability. The endogenous neuropeptide galanin is widely expressed in the CNS and has been recognized as a potential anticonvulsant agent. NAX 5055 is one of the prototype compounds that have been extensively evaluated. In proof of-principle studies, NAX 5055 has validated the technology platform by demonstrating long-lasting and dose-dependent activity in the 6 Hz seizure model following i.v., i.p. s.c. and oral administration³⁸. NAX 5055 also exhibited potent efficacy in other models of epilepsy and pain.

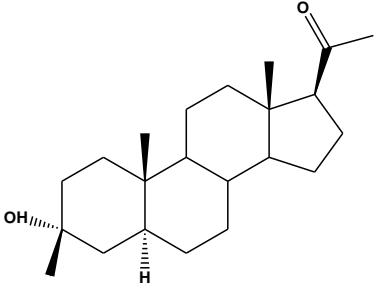
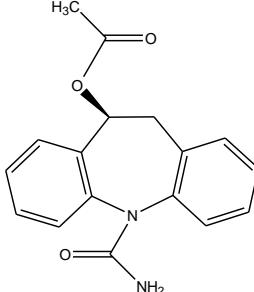
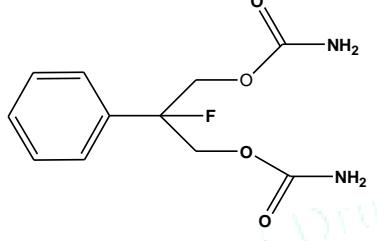
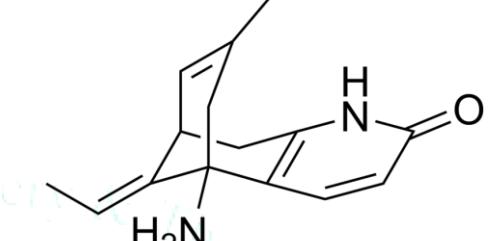
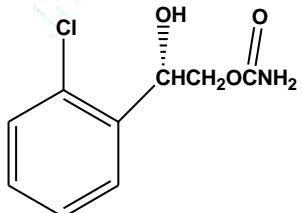
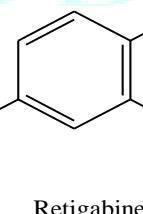
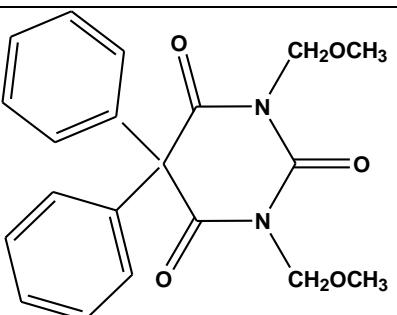
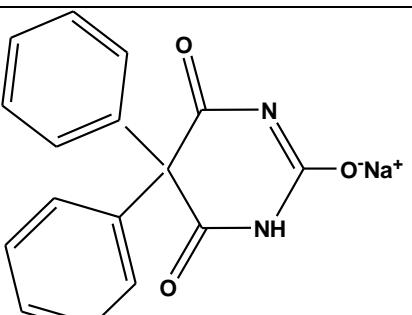
Perampanel (E2007)

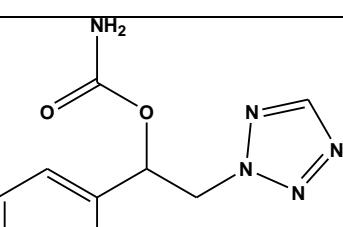
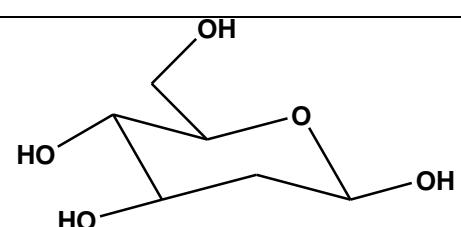
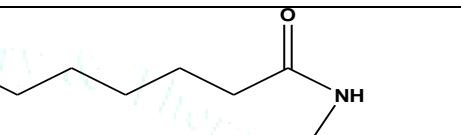
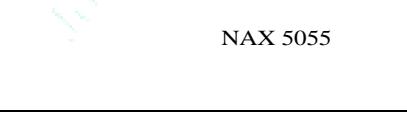
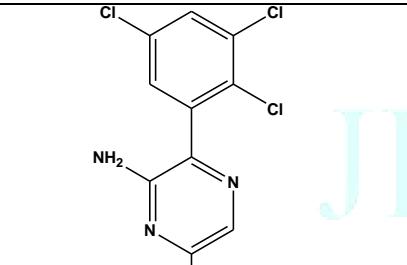
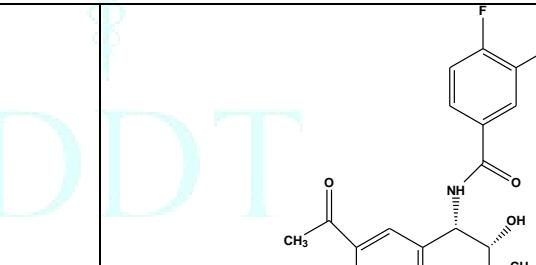
Perampanel (E2007) is an orally active, noncompetitive, and highly selective AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)-type glutamate receptor antagonist currently in Phase III development for epilepsy. Preclinical studies have demonstrated that perampanel attenuates a spectrum of seizure types in rodent models of seizures and epilepsy³⁹. Three Phase III, randomized, placebo-controlled, adjunctive therapy, double-blind, multicenter, multinational studies in patients 12 years of age or older with refractory partialonset seizures are ongoing. These studies (NCT00699582, NCT00699972 and NCT00700310) are designed to evaluate the efficacy and safety of perampanel (2, 4, 8, and 12 mg/day) over a 12-week maintenance period.

Valpromide

Valpromide, the corresponding amide of valproic acid. Valpromide possesses two stereogenic carbons in its structure and has been commercially available as an anxiolytic drug in the form of a racemic mixture (Nirvanil®) in France. A recent study showed that racemic- valpromide (1 mM) drastically inhibits human brain crude homogenate myo-inositol-1-phosphate (MIP) synthase activity. Valpromide was found to reduce the MIP synthase activity by an apparent competitive mode of inhibition at concentrations within the therapeutic range of valproic acid (Ki = 0.18 mM)⁴⁰. These data support the clinical use of valpromide in bipolar disorder. The development of valpromide (as racemate or individual stereoisomer) as a new potentially non-teratogenic and nonhepatotoxic CNS agent that is more potent than valproic acid, may offer a valuable alternative to valproic acid for the treatment of patients with bipolar disorder, epilepsy and neuropathic pain.

Table 1: Chemical structures of antiepileptic drug

 <p>3α-hydroxy-3β-methyl-5 α-pregnan-20-one</p>	 <p>(S)-(-)-10-acetoxy-10,11 dihydro-5H-dibenz[b,f]azepine-5-carboxamide</p>
<p>Ganaxolone</p>	<p>Eslicarbazepine acetate</p>
 <p>2-phenyl-2-fluoro-1,3 propanediol dicarbamate</p>	 <p>Huperzine A</p>
<p>Fluorofelbamate</p>	 <p>S-2-O-carbamoyl-1-o-chlorophenyl- ethanol</p>
<p>Carisbamate (RWJ-333369)</p>	<p>Brivaracetam (ucb 34714)</p>
 <p>Retigabine</p>	 <p>Retigabine</p>
 <p>1,3-dimethoxymethyl-5,5- diphenylbarbituric acid</p>	 <p>Sodium 5,5- diphenylbarbiturate</p>

T2000	T2007
 <p>N-valproyl glycinamide</p>	 <p>Propylisopropyl acetamide</p>
<p>Valrocemide</p>  <p>YKP3089</p>	<p>Propylisopropyl acetamide</p> 
<p>YKP3089</p>	<p>2-Deoxy-D-glucose</p>  <p>6-Hydroxymethyl-tetrahydro-pyran-2,4,5-triol</p>
 <p>NAX 5055</p>	 <p>Sar-WTLNSAGYLLGPKKKK-NH₂</p>
<p>NAX 5055</p>  <p>4-(3-(2,3,5-trichloro-phenyl)-pyrazine-2,6-diamine)</p>	<p>Tonabersat (SB-220453)</p>  <p>[(3S-cis)-N-(6-Acetyl-3,4-dihydro-3-hydroxy-2,2-dimethyl-1H-1 benzopyran-4-yl)-3-chloro-4- fluorobenzamide]</p>

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