CHAPTER I

INTRODUCTION

The term *epilepsy* refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures. The term *seizure* refers to a transient alteration of behavior due to the disordered, synchronous, and rhythmic firing of populations of brain neurons. Seizures can be "nonepileptic" when evoked in a normal brain by treatments such as electroshock or chemical convulsants or "epileptic" when occurring without evident provocation. (McNamara, 2001)

Each year, 120 per 100,000 people in the United States come to medical attention because of a newly recognized seizure. At least 8% of the general population will have at least one seizure in a lifetime. However, it is possible to have a seizure and not have epilepsy. Recurrence of a first unprovoked seizure within 5 years ranges between 23% and 80%. Children with an idiopathic first seizure and a normal electroencephalogram (EEG) have a particularly favorable prognosis. Some seizures may occur as single events resulting from withdrawal of central nervous system (CNS) depressants (eg., alcohol, barbiturate, and other drugs) or during acute illnesses (such as meningoencephalitis) or toxic conditions (e.g., uremia or eclampsia). Some patients will have seizures only associated with fever. These febrile seizures do not epilepsy.

Epilepsy is a chronic disorder, indicating recurrent seizures. The age-adjusted incidence of epilepsy is 44 per 100,000 person-years. Each year, about 125,000 new epilepsy cases occur; of these, 30% are in people under the age of 18 at time of diagnosis. There is bimodal distribution in the occurring in newborn and young children and the

second peak occurring in patients older than age 65. The relatively high frequency of epilepsy in the elderly is now being recognized. At least 10% of patients in long-term care facilities are tacking at least one antiepileptic drug (AED). At this time, it is unknown if these AEDs are used for seizures or other conditions. The seizure type and the cause of the seizure change with age.(Graves, and Garnett, 2002)

The International League Against Epilepsy (ILAE) has proposed two major schemes for classification of seizures and epilepsies: the International Classification of Epileptic Seizures and the International Classification of the Epilepsies and Epilepsy Syndromes. (Adams, Victor and Ropper, 1997; Graves and Garnett, 1999; Kadir and Chadwick, 1999)

The International Classification of Epileptic Seizures combines the clinical description with certain seizures. Seizures are divided into two main groups according to the aura of the brain in which the abnormal discharge originates. If it involves initial activation of both hemispheres of the brain simultaneously, the seizures are termed generalized. If a discharge starts in a localized aura of the brain, they are termed partial or focal seizure (Table 1).

Partial seizures are classified as simple when consciousness is undisturbed. The symptoms (aura) often experienced prior to a generalized tonic-clonic seizure may be a simple partial seizure that secondarily generalized. Partial seizure with a loss or alteration of consciousness is described as complex partial. With complex partial seizures, the patient may have automatism, periods of memory loss, or aberrations of behavior. A partial seizure that becomes generalized is referred to as a secondarily generalized seizure.

Table 1. International classification of epileptic seizures

I. Partial seizures (seizures begin locally)
   A. Simple (without impairment of consciousness)
      1. With motor symptoms
      2. With special sensory or somatosensory symptoms
      3. With psychic symptoms
   B. Complex (with impairment of consciousness)
      1. Simple partial onset followed by impairment of consciousness-with or without automatisms
      2. Impaired consciousness at onset-with or without automatisms
   C. Secondarily generalized (partial onset evolving to generalized tonic-clonic seizures)

II. Generalized seizures (bilaterally symmetrical and without local onset)
   A. Absence
   B. Myoclonic
   C. Clonic
   D. Tonic
   E. Tonic-clonic
   F. Atonic
   G. Infantile spasms

III. Unclassified seizures

IV Status epilepticus

Generalized seizures are of two types-convulsive and nonconvulsive. The common convulsive type is the tonic-clonic (grand mal) seizure. Less common is a purely tonic, or clonic generalized. The classic nonconvulsive generalized seizure is the brief lapse of consciousness or absence (petit mal); included also under this heading are minor motor phenomena such as brief myoclonic or atonic.

The International Classification of Epilepsies and Epilepsy Syndromes adds components such as age of onset, intellectual development, findings on neurologic examination, and results of neuroimaging studies to more fully define epilepsy syndromes (Table 2). Syndromes can include one or many different seizure types (e.g., Lennox Gastaut syndrome). The syndromic approach includes seizure type and possible etiologic classifications (idiopathic, symptomatic, or unknown). Idiopathic describes syndromes that are presumably genetic but also those in which no underlying etiology is documented or suspected. A family history of seizures is commonly present, and neurologic function is essentially normal except for the occurrence of seizures. Symptomatic cases involve evidence of brain damage or a known underlying cause. A cryptogenic syndrome is assumed to be symptomatic of an underlying condition that cannot be documented. Unknown or undetermined is used when no cause can be identified. This syndromic classification is more important for prognostic determinations than a classification based simply on seizure type. The syndrome classification scheme requires more information and, in return, provides a more powerful tool for comprehensive clinical management. A patient's epilepsy is classified based on seizure type (generalized versus partial) and syndromic type (idiopathic, symptomatic, cryptogenic).

Table 2. International classification of epilepsies and epilepsy syndromes.

I. Localization-related (focal, partial) epilepsies and syndromes

A. Idiopathic (with age-related onset)

1. Benign childhood epilepsy with centro-temporal spike
2. Childhood epilepsy with occipital paroxysms
3. Primary reading epilepsy

B. Symptomatic

1. Chronic progressive epilepsia partialis continua of childhood
2. Syndromes characterized by seizures with specific modes of precipitation

C. Cryptogenic

II. Generalized epilepsies and syndromes

A. Idiopathic

1. Benign neonatal familial convulsions
2. Benign neonatal convulsions
3. Benign myoclonic epilepsy in infancy
4. Childhood absence epilepsy (pyknolepsy)
5. Juvenile absence epilepsy
6. Juvenile myoclonic epilepsy
7. Epilepsy with grand mal (GTCS) seizures on awakening
8. Other generalized idiopathic epilepsies not defined above
9. Epilepsies with seizures precipitated by specific modes of activation

B. Cryptogenic or symptomatic

1. West syndrome
2. Lennox-Gastaut syndrome

Table 2. (continued) International classification of epilepsies and epilepsy syndromes.

3. Epilepsy with myoclonic-astatic seizures
4. Epilepsy with myoclonic absence

C. Symtomatic

1. Nonspecific etiology
   a. Early myoclonic encephalopathy
   b. Early infantile epileptic encephalopathy
   c. Other symptomatic generalized epilepsies not defined above
2. Specific syndromes

III. Epilepsies and syndromes undetermined whether focal or generalized

A. With both generalized and focal seizures

1. Neonatal seizures
2. Severe myoclonic epilepsy in infancy
3. Epilepsy with continuous spike-waves during slow wave sleep
4. Acquired epileptic aphasia
5. Other undetermined epilepsies not defined above

B. Without unequivocal generalized of focal features

IV. Special syndromes

A. Situation-related seizures

1. Febrile convulsions
2. Isolated seizures or isolated status epilepticus
3. Seizure occurring only when there is an acute metabolic or toxic event

The treatment of epilepsy usually involves long-term treatment that may represent a dramatic change in the patient's life. The aim of the treatment is to prevent the recurrence of seizures with the minimum effective dose of an appropriate antiepileptic drug, resulting in improvement in the quality of life of patients. Of course, the ultimate aim of treatment will be no seizures and no drugs. Unfortunately, this may not be readily achievable for many patients with chronic epilepsy. (Kadir and Chadwich, 1999)

Antiepileptic drug therapy is the mainstay of epilepsy treatment. Today, there are numerous antiepileptic drugs (AEDs) including established AEDs (e.g., phenytoin (1), carbamazepine (2), clonazepam (3), ethosuximide (4), phenobarbital (5), sodium valproate (6)) and dimethadione (7)) and new AEDs (e.g., felbamate (8), gabapentin (9), lamotrigine (10), oxcarbazepine (11), tiagabine (12), topiramate (13), vigabatrin (14) and zonisamide 15)) that have been launched since 1989. It is important to select an appropriate AED for the individual patient. The choice of antiepileptic drug should be based on the seizure classification, the age and sex of the patient, concurrent medical conditions, potential adverse effects, and the pharmacokinetic features of each drug. Table 3 gives the main indications for the AEDs currently available. (Dhillon and Sander, 1999)

Although, the older established AEDs are still widely prescribed, there is a significant group of patients that is resistant to those available therapeutic agents, or suffer from a range of side effects. New AEDs seem to show improved efficacy and side-effect profiles, but patients with intractable epilepsy remain untreated. There is clearly a need for improved medications; therefore, an enormous effort has been exerted towards this goal over the last several years.

Table 3. AEDs for different seizure types

Seizure type	First-line treatment	Second-line treatment
Partial seizures		
Simple partial,	Carbamazepine	Vigabatrin
Complex partial,	Phenytoin	Phenobarbital
Secondarily generalized	Valproate	Gabapentin
	Lamotrigine	Topiramate
Generalized seizures		
Tonic-clonic,	Valproate	Vigabatrin
Tonic,	Carbamazepine	Phenobarbital
Clonic	Phenytoin	
	Lamotrigine	
Absence	Ethosuximide	Clonazepam
	Valproate	Lamotrigine
Atypical absences,	Valproate	Phenobarbital
Atonic	Clonazepam	Lamotrigine
	Clobazam	Carbamazepine
		Phenytoin
Myoclonic	Valproate	Phenobarbital
	Clonazepam	

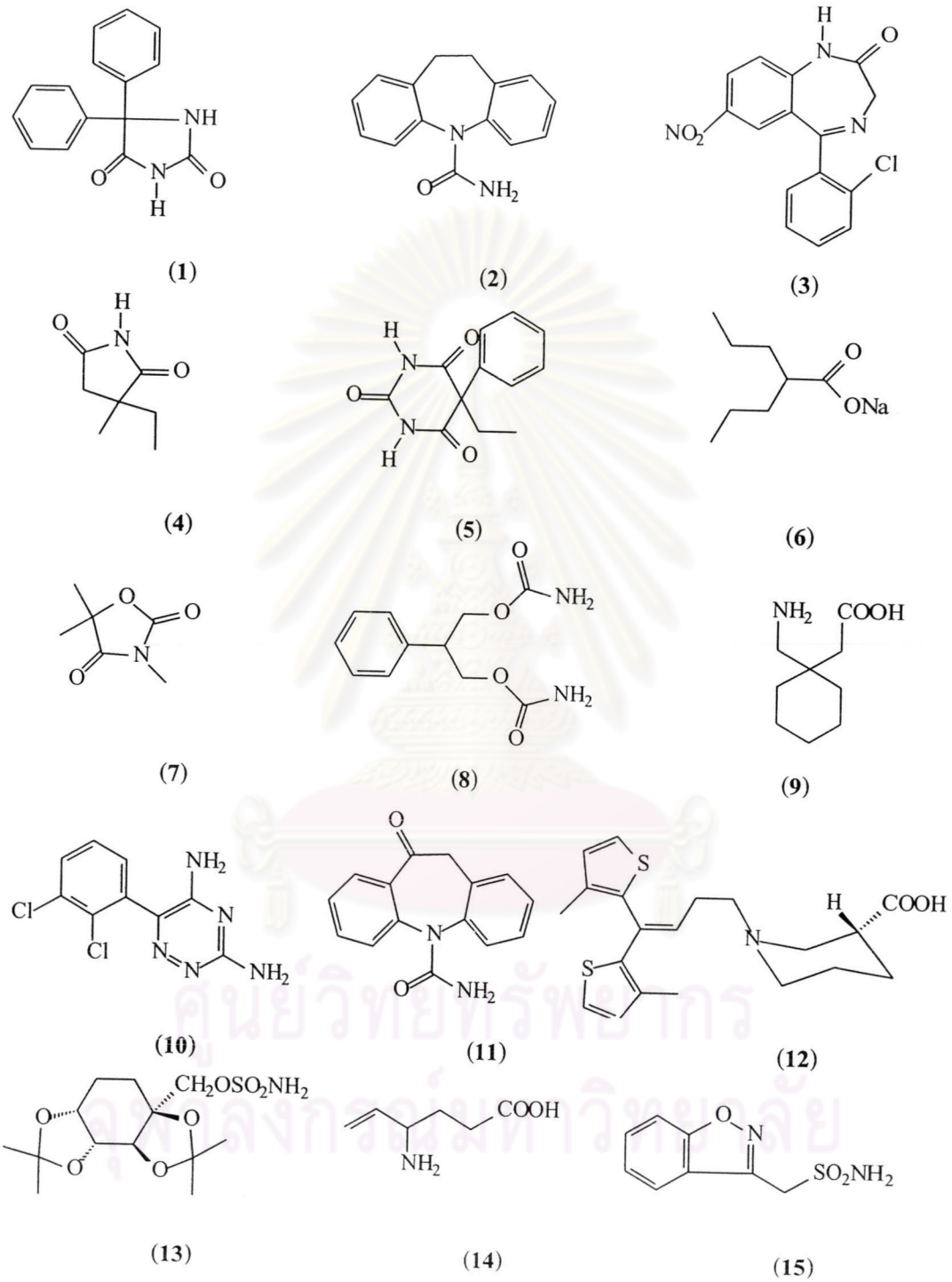


Figure 1. The chemical structures of some antiepileptic drugs (**1-15**).

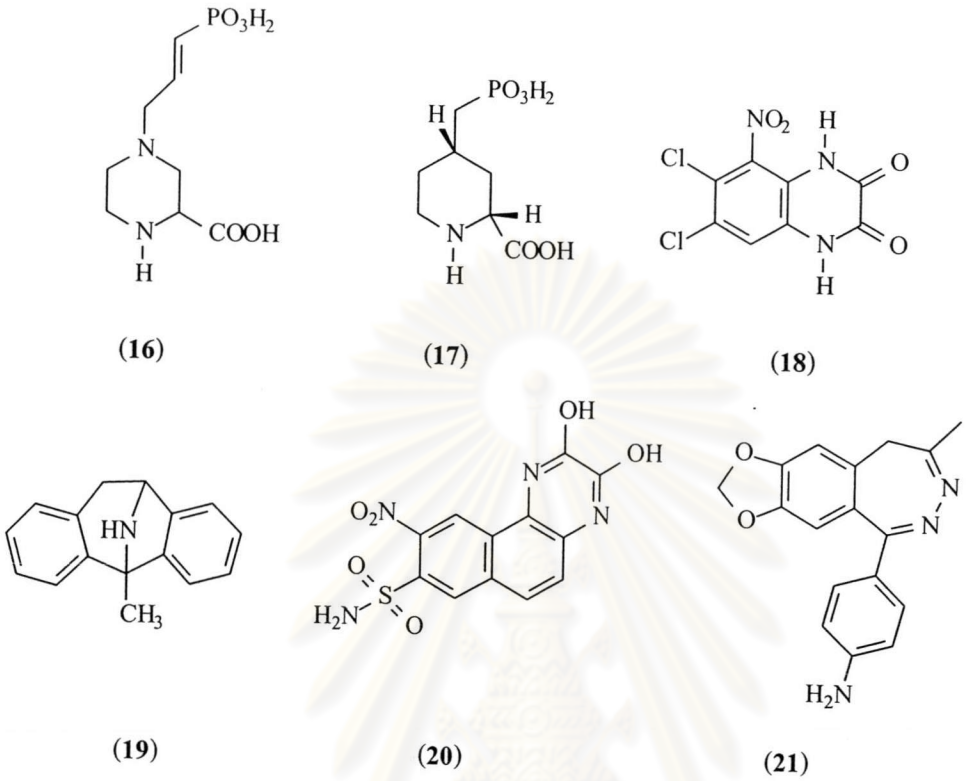


Figure 2. The chemical structures of some anticonvulsants (16-21).

Despite the fact that firstly detection of new AEDs was more or less by serendipity, so drug development moved on very slowly. In 1969, the Epilepsy Branch of the National Institutes of Health (NIH) established the first approach applied in the search for new AEDs in the US. NIH initiated the Drug Development Program, representing collaboration between academia and the pharmaceutical industry. By 1993, the collaboration had resulted in the screening of more than 15,000 compounds several of which have been developed and marketed as new AEDs. (Sabers and Gram, 1996)

A second approach, which has proved successful, is to undertake structural variation of known AEDs, modifying the chemical structure with the aim of improving

efficacy and/or decrease toxicity. Well-established AEDs such as oxcarbazepine is the result of such an approach.

Finally, what has been termed rational drug development has emerged, base on the increased knowledge of basic pathophysiological events responsible for epilepsy, as well as better understanding of the basic mechanisms of drug activity.

Insights into mechanisms of seizures suggest that an abnormality of potassium conductance, a defect in the voltage-sensitive ion channel, or a deficiency in the membrane adenosine triphosphatase (ATPase) linked to ion transport may result in neuronal membrane instability and a seizure. Selected neurotransmitters (e.g., glutamate, aspartate, acetylcholine, norepinephrine, histamine, corticotropin-releasing factor, purines, peptides, cytokines, and steroid hormones) enhance the excitability and propagation. A deficiency of inhibitory neurotransmitters such as γ-aminobutyric acid (GABA) or an increase in excitatory neurotransmitters would promote abnormal neuronal activity. Normal neuronal activity also depends on an adequate supply of glucose, oxygen, sodium, potassium, chloride, calcium, and amino acids. Systemic pH is also a factor in precipitating seizures. The different kinds of epilepsies probably arise from different physiologic abnormalities. (Graves and Garnett, 1999)

Control of abnormal neuronal activity with AEDs is accomplished by elevating the threshold of neurons to electrical or chemical stimuli or by limiting the propagation of the seizure discharge from its origin. Raising the threshold most likely involves stabilization of neuronal membranes, whereas limiting the propagation involves depression of synaptic transmission and reduction of nerve conduction. The present understanding of the mechanisms by which AEDs exert therapeutic benefits may be summarized as follows:

a) By inhibiting excessive neuronal firing.

b) By inhibiting excitatory mechanisms.

c) By potentiating inhibitory mechanisms.

a) By inhibiting excessive neuronal firing.

Neuronal activity depends on voltage-dependent ion channels, with Na^+, K^+, and Ca^{2+} channels determining the features of the action potential.

The sodium channels can exist in three conformational states: active, resting and inactivated. In general, after the neuronal cell membrane is depolarized, the permeability to sodium ion increases, with sodium ions entering the cells followed by a return to the normal state in a rate- and voltage-dependent manner. The established first choice AEDs – phenytoin and carbamazepine exert their effects by stabilizing the inactive forms of the voltage-dependent Na^+ channel (VGSC) and retarding its rate of recovery from inactivation. More over, high concentrations of valproate can also prolong inactivation of Na^+ channels. Many of the newer drugs, including felbamate, gabapentin, topiramate and lamotrigine exhibit significant inhibitory activity at VGSC in addition to other modes of action (Figure 3 and 5). (Edafiogho and Scott, 1996; McNamara, 1996; Meldrum 1996; White, 1997; Cosford, McDonald and Schweiger, 1998)

Recent evidence points to a significant role for neuronal voltage-gate calcium channels as molecular targets for the treatment of epilepsy. Several AEDs including valproate, ethosuximide, dimethadione and zonisamide are antagonists of T-type calcium

channel current (Figure 4). Lamotrigine has recently been shown to inhibit N-type. (James, 1996; Cosford et al., 1998)

A potentiation of K^+-mediated currents has often been considered as a mechanism of AED action, but no antiepileptic effect of any established AEDs can confidently be attributed to this mechanism. (Meldrum, 1996)

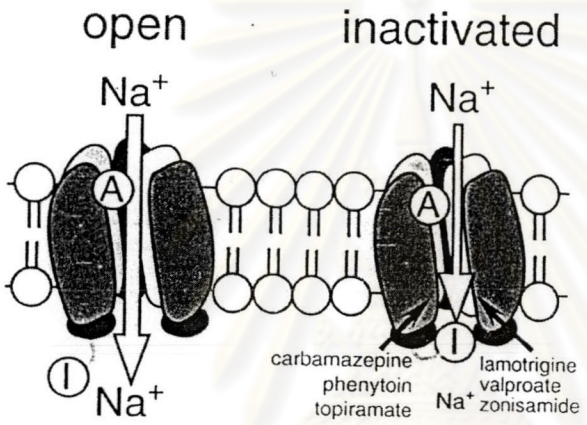


Figure 3. Antiseizure drug-enhanced Na^+ channel inactivation.

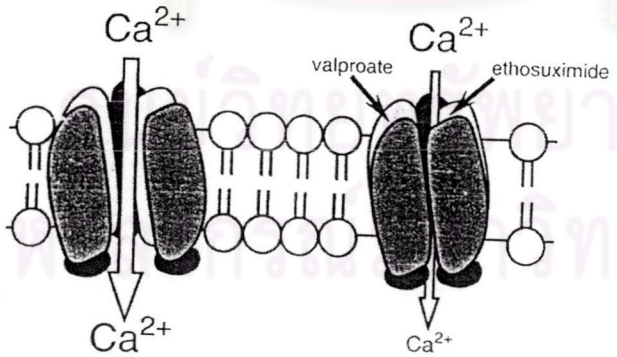


Figure 4. Antiseizure drug-induced reduction of current through T-type Ca^{2+} channels.

b) By inhibiting excitatory mechanisms.

The acidic amino acids glutamate and aspartate are thought to be the major fast excitatory neurotransmitters in the mammalian central nervous system (CNS). It is believed that there are five subtypes of receptors for the excitatory amino acids (EAAs). The three major subtypes of EAA receptor that have been identified are classified as *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), and kainate receptors. The AMPA and kainate receptors are usually referred to as the non-NMDA receptors for EAAs. (Edafiogho and Scott, 1996)

At the excitatory synapse, once released from the presynaptic terminal, glutamate can bind to both NMDA and non-NMDA receptors. Glycine is required as a co-agonist at the NMDA receptor, which is coupled to an associated ion channel permeable to Na^+, K^+ and Ca^+ (Figure 5). (White, 1997)

The NMDA receptor complex possesses multiple modulatory sites that are targeted by several new generation-AEDs. Drugs can decrease NMDA function competitively by binding to the NMDA receptor (e.g., D-CPPene (16) or CGS-19755 (17)) or the strychnine-insensitive glycine receptor (e.g., ACEA 1021 (18) and felbamate) or noncompetitively by binding to a site within the open channel (e.g., dizocipine (19), felbamate).

Glutamate can also activate an ion channel coupled to the non-NMDA AMPA/Kainate receptor that is permeable to Na^+ and K^+. Activation of the non-NMDA receptor by glutamate provides sufficient depolarization to relieve the Mg^{2+}-dependent block of the NMDA receptor. Drug can block non-NMDA responses competitively (e.g.,

NBQX (20)) or noncompetitively (GYKI 52466 (21)). Kainate-evoked currents can also be blocked by topiramate.

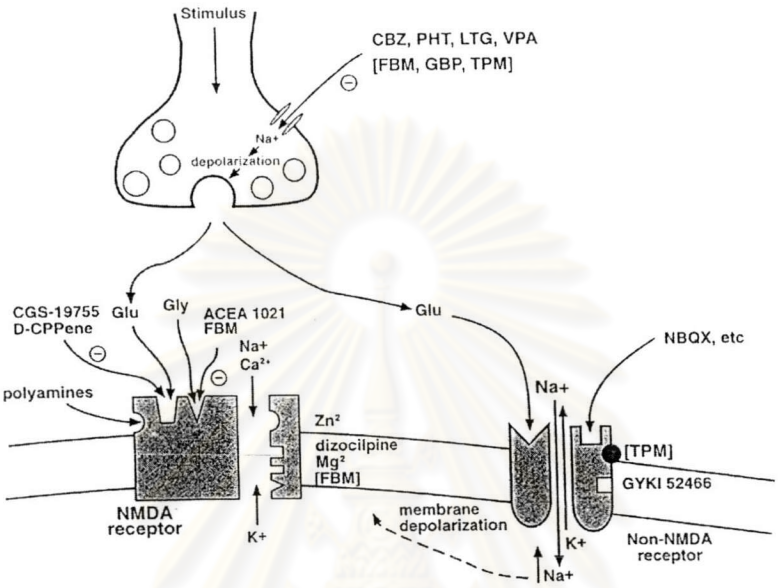


Figure 5. Proposed mechanisms of action of some AEDs mediated by glutamate at the excitatory synapse. (CBZ, carbamazepine; FBM, felbamate; GBP, gabapentin; Glu, glutamate; Gly, glycine; LTG, lamotrigine; PHT, phenytoin; TPM, topiramate; VPA, valproate)

c) By potentiating inhibitory mechanisms.

The steps in the synaptic action of GABA which are possible sites of drug intervention include stimulation of GABA release, inhibition of GABA reuptake, reduction of the breakdown of GABA, and modulation of post-synaptic GABA receptor. GABA receptors are comprised of $GABA_A$ receptor and the metabotropic $GABA_B$ receptor. (Cosford, McDonald and Schweiger, 1998)

The $GABA_A$ receptor and its associated allosteric binding sites are coupled to a chloride-permeable ion channel. AEDs can enhance GABA at the postsynaptic receptor by increasing channel opening and burst frequency (e.g., benzodiazepines (such as clonazepam) and topiramate) or by increasing channel open and burst duration (e.g., phenobarbital). AEDs can also enhance GABA-mediated neurotransmission by blocking neuronal and glial reuptake of synaptically released GABA (e.g., tiagabine). Vigabatrine increases GABA levels within neuronal terminals and surrounding glial cells by irreversibly inhibiting GABA aminotransferase (GABA-T), which metabolizes GABA to succinic acid semialdehyde (SSA). Gabapentin has been shown to increase GABA levels within the occipital cortex of patients with epilepsy (Figure 6). (White, 1997)

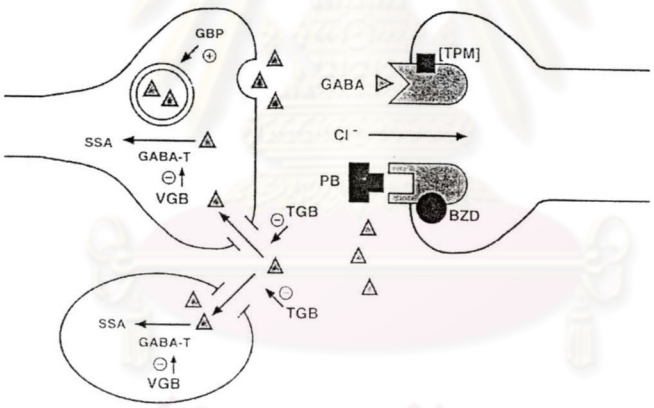
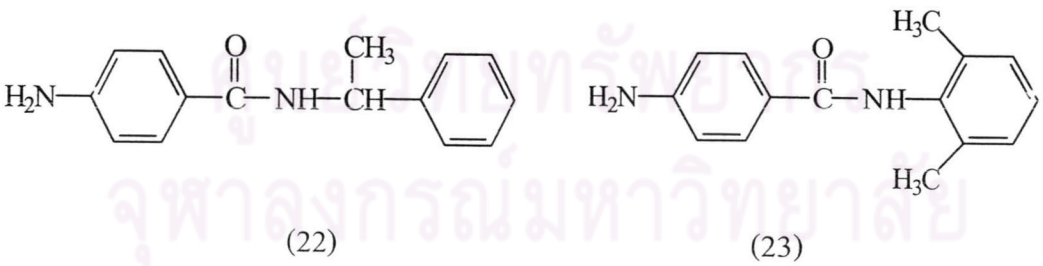


Figure 6. Proposed mechanisms of action of some AEDs at the $GABA_A$ inhibitory synapse. (BZD, benzodiazepine; GABA, γ-aminobutyric acid; GABA-T; GABA aminotransferase; GBP, gabapentin; PB, phenobarbital; TGB, tiagabine; TPM, topiramate; SSA, succinic acid semialdehyde; VGB, vigabatrine;)

The improved understanding of the molecular mechanism lead to discussion of the concepts of drug treatment and drug discovery. Monotherapy (one medication) has been prefered to polytherapy (multiple medications) in the treatment of epilepsy for many years since fewer side effects, fewer drug interations, lower medication costs, and better compliance are expected to present when monotherapy is utilized. Polytherapy will be instituted when the patient cannot be controlled by a single drug. However, with the known mode of action and a very favorable toxicity profiles of many new drugs over the old AEDs, a novel concept of "rational polytherapy" have emerged as an alternative. This concept is based on the assumption that combining some AEDs may result in supra additive (synergistic efficacy) and infra additive (antagonistic) toxicity, resulting in an enhanced efficacy and toxicity profile. However it is important to examine the benefits of this combination therapy. When polytherapy is used, it should satisfactorily embrace the following principles. Firstly, it is best to combine antiepileptic drugs with different mechanism of action than to prescribe combination those have similar mechanism of action. Second, it is best to select antiepileptic drugs with relatively little potential for drug-drug interaction. Third, patients treated with polytherapy demand more intensive monitoring, both clinically and possibly with antiepileptic drug levels. (Sabers and Gram, 1996; Kadir and Chadwich, 1999)

In AEDs development, general researches focus on searching a new drug with less toxic and known mechanism of action. According to the concept of monotherapy, AEDs with multiple modes of action are required to treat various type of seizures. On the other hand, with the concept of rational polytherapy, and advanced knowledge in mechanism of action at molecular level, there is a high possibility that AEDs with highly selective mechanism of action will be developed. (Cosford, et al., 1998)

The 4-aminobenzamides are a chemically novel series of potential antiepileptic drugs. Extensive structure-activity studies have been carried out by Clark and his collaborators on the anticonvalsant activity of aminobenzamides of arylalkylamines and arylamines (Clark et al., 1984; Clark et al., 1985; Clark et al., 1986). The original member of the series, 4-amino-*N*-(α-methylbenzyl)benzamide or LY188544 (22), is a potent maximal electroshock (MES) anticonvalsant in mice and rats, and had some activity against chemically induced seizures such as s.c.Ptz (pentylenetetrazole), s.c.Bic (bicuculine), and s.c.Pic (picrotoxin) (Clark and Davenport, 1987), but untoward toxicological findings precluded development of this compound or either of its enantiomer (Robertson, 1991). Ameltolide, 4-amino-*N*-(2,6-dimethylphenyl)benzamide or LY201116 (23), is the most potent benzamide anticonvalsant studied to date. This compound potently inhibited MES-induced seizures in mice, but was ineffective against a variety of chemically induced seizures. This phenytoin-like profile, coupled with a high protective index, suggests that the compound may be suitable for treatment of generalized tonic-clonic and partial seizures in man, and and clinical studies are in progress. Unfortunately, ameltolide was rapidly inactivated by *N*-acetylation at the 4-amino group (reversible) and subsequent hydroxylation of one of the methyl substituent.



(22) (23)

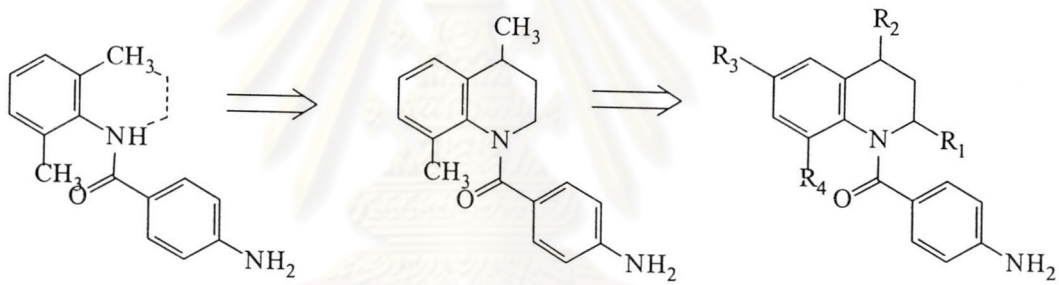
Figure 7. The chemical structure of potent anticonvulsant 4-aminobenzamides derivatives (LY188544 (22) and LY201116(23)).

Structure-activity relationship (SAR) studies reveal that the addition of two or one ortho methyl group on anilide phenyl ring of 4-amino-*N*-phenylbenzamide yields a more potent anticonvulsant than unsubtituted 4-amino-*N*-phenylbenzamide, respectively (Clark, 1985). In addition, molecular modeling and crystallographic studies show that the conformations of 4-amino-*N*-phenylbenzamide are determined by the number of ortho methyl substituents and by a preference for orientation of the ortho substituent toward the NH group of the central amide. The preferred conformation for binding mode is assumed to be that adopted by the 2,6-dimethyl compound, ameltolide, which places one methyl group above and one below the molecular plane formed by the central amide and the aminophenyl ring. The active conformation facilitates the formation of strong intermolecular hydrogen bonds to the central amide region(Duke, and Codding, 1992).

Rigid analogues of ameltolide, *N*-(*p*-aminobenzoyl)-4,8-dimethyl-1,2,3,4-tetrahydroquinoline (XXIV) and *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydriquinoline derivatives (XXV) were synthesized by Sathit Niratisai (1994) and Tanarat Kietsakorn (2000), respectively(See Fifure8). CU-17-06, some of this series, *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydro-4-methylisoquinoline was investigated for anticonvulsant effect. From pharmacological study, CU-17-06 was less potent than ameltolide (ED_{50} = 77.62 mg/kg and 1.08 mg/kg, respectively). In term of safety, CU-17-06 seems to be rather safe as indicated by no lethality observed in the dose up to 1,000 mg/kg where as ameltolide demonstrated the LD_{50} of 63 mg/kg (Rodpaewpaln, 2003).

Because of the optimal anticonvulsant activity of 4-amino-*N*-(α-methylbenzyl)benzamide (XXII), a new analogue of this compound was designed by ring closure, as same as the rigid analogue of ameltolide, to give *N*-(*p*-aminobenzoyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (XXVI) (see Figure 8). The target molecule was

fixed to be in active conformation for binding receptor, the N-C bond of *N*-(α-methylbenzyl) group can not rotate around amide bond. To extend structure-activity relationship (SAR), the variation of methyl substituent along positions 1 and/or 3 of tetrahydroisoquinoline nucleus will affect the conformational orientation and the binding mode of molecule (steric effect). Increasing lipophilicity of compound by adding alkyl chain and alkyl group may affect the penetration of compound through blood brain barrier, easier than parent compoud. In addition, the position of nitrogen atom on tetrahydroisoquinoline ring can be also studied to compare with that of tetrahydroquinoline ring.



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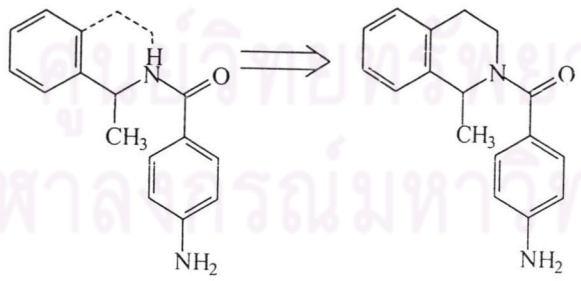
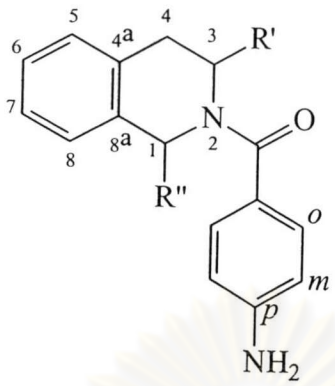


(28) (29)

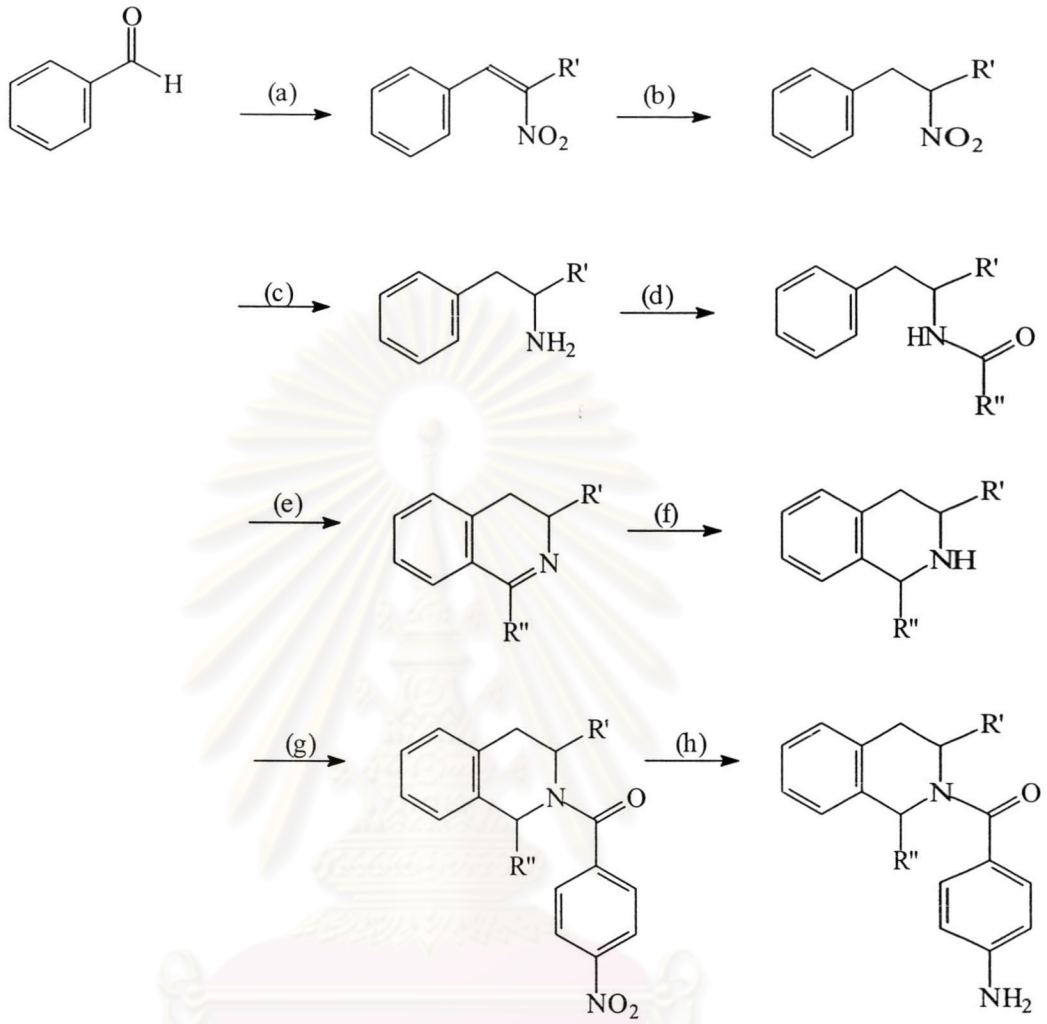
Figue 8. The design of rigid analogues by ring closure from their parent compounds.



Compound	R′	R″
(30)	H	CH_3
(31)	H	H
(32)	CH_3	H
(33)	CH_3	CH_3

Figure 9. The chemical structures of target derivatives of *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline.

This research was aimed to synthesize four *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline derivatives (30-33) (see Figure 9). The synthetic approach of *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline derivatives is shown in Figure 10.



(a) i.CH_3NO_2, NaOH, MeOH/ (20%) HCl sol^n, 0-5°C (R′= H); ii. $EtNO_2$, $NH_4(CH_3COO)$, glacial acetic acid, reflux, 24 hrs (R′= CH_3); b) $NaBH_4$, $CHCl_3$, iso-PrOH, 0°C,1-2 hrs; (c) H_2, Pd/C, glacial acetic acid, absolute EtOH, 60 psi (Parr apparatus); (d) i. $(CH_3CO)_2O$, TEA, THF, reflux, 1 hr (R″= CH3); ii.HCOOH, ref, 1 hr (R″= H); (e) $POCl_3$ and/or P_2O_5, toluene or xylene, reflux, 2-3 hrs. (f) $NaBH_4$, MeOH, 0°C; (g) p-nitrobenzoylchloride, K_2CO_3, THF, reflux, 1 hr; (h) H_2, Pd/C, CH_2Cl_2.

Figure 10. The synthesis approach of the target derivatives of *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline.