CHAPTER I

INTRODUCTION

Epilepsy is a general term for a group of disorders characterized by recurrent seizures. A seizure is defined as a sudden, transient disturbance in cognitive, motor, sensory, or autonomic function that is accompanied by an abnormal, excessive electrical discharge in the brain. Convulsive seizures that involve involuntary muscle contractions are more common than non-convulsive seizures. (Albers and Peroutka, 1992)

Approximately 50 million people worldwide are subject to epilepsy, making this condition the second leading neurological disorder after stroke. Over two-thirds of all epileptic seizures begin in childhood, and this is the age period when seizures assume then widest arrays of the forms. Indeed, in the practice of pediatric neurology, epilepsy is the most common disorder. The incidence increases again after age of 60, with a peak incidence in persons more than 70 years of age. (Adams, Victor, and Ropper, 1997)

Seizures may result from primary or acquired disturbances of central nervous system (CNS) function. In infant and children, seizures may cause by perinatal insults, congenital or development defects, cerebrovascular disease, metabolic disorders, head injuries, infection or fever. In adolescents and adults, important causes include head trauma, neoplasms, vascular lesions, infections and drug or alcohol abuse. In adult and elderly patients, degenerative processes and cerebrovascular disease are important causes of seizures. In most patients, seizures occur in the absence of any diagnosable condition. (Ambre et al., 1995)

Identification of the cause of seizures is of primary importance in the determination of subsequent management. If precipitating factors are identified that are amenable to therapeutic intervention, (e.g., metabolic disorders, hypertensive encephalopathy, or drug overdose), then specific treatment modalities should be instituted to correct the underlying cause. (Alldredge, 1996)

Whereas an etiologic diagnosis of seizures is needed to establish whether chronic antiepileptic drug therapy is necessary, the classification of epileptic seizures by their clinical and electrophysiologic manifestations is necessary to determine which antiepileptic drug is most likely to be effective. Currently, the International League Against Epilepsy classified seizures into two general categories: partial and generalized. (Commission on Classification and Terminology of the International League Against Epilepsy, 1981) (See table 1.)

Partial seizures arise from a specific abnormal location in the brain usually an area damaged by a known pathologic condition, e.g., trauma, tumor, infect, or hemorrhage. Electroencephalography (EEG) of patients with partial seizures often reveals a localized abnormality overlying the seizure focus. Partial seizures are differentiated according to whether or not consciousness is impaired during the event. Complex partial seizures are associated with impairment of consciousness; simple partial seizures are not. These seizures arise most commonly from the temporal lobe and are often associated with unusual symptoms such as hallucination and "psychic phenomena". Both simple and complex partial seizures may spread to involve both hemispheres of the brain and become "secondarily generalized" with convulsions of all extremities and loss of consciousness.

In generalized seizures, epileptic activity is initiated simultaneously in both hemispheres. Generally, consciousness is lost or impaired and motor manifestations

are bilateral. Frequently, no pathologic process is discovered among patients with generalized seizures, suggesting a hereditary cause. Electroencephalographic abnormalities are typically bilateral and generalized. Generalized seizures can be divided into two types–convulsive and nonconvulsive. The common convulsive type is the tonic-clonic (grand mal) seizure. The less common is a purely tonic, or clonic, or tonic-clonic generalized seizure. 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, atonic, or tonic seizures and atypical absence attacks. (Ambers and Peroutka, 1992)

Apart from this epileptic seizure classification, an additional classification specifies epileptic syndromes, which refer to a clustering of signs and symptoms that regularly occur together; the seizure type(s), etiology (idiopathic or symptomatic), precipitating factors, hereditary components, associated clinical features (e.g., mental impairment), and natural history (e.g., age of onset, chronicity, severity), are considered in this classification. (See table 2.)

Idiopathic epilepsies have no definable cause; they often are familial, and onset is age-related. Benign familial neonatal convulsions and juvenile myoclonic epilepsy are two of the idiopathic epilepsy with putative gene assignments, although genetic heterogeneity may exist. In general, idiopathic epilepsies are more likely than symptomatic epilepsies to be associated with normal development, responsiveness to antiepileptic drugs, and remission. Symptomatic epilepsies and syndromes are caused by diagnosable CNS disorders, although, in some patients with presumed symptomatic epilepsy, the underlying cause remains obscure (cryptigenic). In these epilepsies, the interictal EEG is more likely to be abnormal, the prognosis is less favorable, and the response to antiepileptic drugs is variable. (Albers and Peroutka, 1992)

Table 1. International Classification of Epileptic Seizures

I.	Generalized seizures (bilaterally symmetrical and without local onset)
	A. Tonic, clonic, or tonic-clonic(grand mal)
	B. Absence (petit mal)
	1. Simple-loss of consciousness only
	2. Complex-with brief tonic, clonic, or automatic movements
	C. Lennox-Gastaut syndrome
	D. Juvenile myoclonic epilepsy
	E. Infantile spasms (West syndrome)
	Atonic (astatic, akinetic) seizures (sometimes with myoclonic jerks)
II.	Partial or focal seizures (seizures beginning locally)
	A. Simple(*without* loss of consciousness)
	1. Motor (tonic, clonic, tonic-clonic; jacksonian; benign childhood epilepsy; epilepsis partialis continua)
	2. Somatosensory or special sensory (visual, auditory, olfactory, gustatory, vertiginous)
	3. Autonomic
	4. Psychic
	B. Complex (*with* impaired consciousness)
	1. Beginning as simple partial seizures and progressing to impairment of consciousness
	2. With impairment of consciousness at onset
III.	Special epileptic syndromes
	A. Myoclonus and myoclonic seizures
	B. Reflex epilepsy
	C. Acquired aphasia with convulsive disorder
	D. Febrile and other seizures of infancy and childhood
	E. Hysterical seizures

Table 2. Classification of epilepsies and epileptic syndromes

I. LOCALIZATION-RELATED (FOCAL, LOCAL, PARTIAL) EPILEPSIES AND SYNDROMES
A. Idiopathic (with age-related onset)
1. Benign childhood epilepsy with centrotemporal spike (Rolandic)
2. Childhood epilepsy with occipital paroxysms
3. Primary reading epilepsy
B. Symptomatic
1. Chronic progressive epilepsia partialis continua of childhood (Kojewnikow's syndrome)
2. Syndromes characterized by seizures with specific modes of precipitation (e.g., reflex, startle epilepsy)
3. Temporal lobe epilepsies
4. Frontal lobe epilepsies
5. Parietal lobe epilepsies
6. Occipital lobe epilepsies
C. Cryptogenic
II. GENERALIZED EPILEPSIES AND SYNDROMES
A. Idiopathic (with age-related onset-listed in order of age)
1. Benign neonatal familial convulsions
2. Benign neonatal convulsions
3. Childhood absence epilepsy (pyknolepsy)
4. Juvenile myoclonic epilepsy (impulsive petit mal of Janz)
5. Epilepsy with grand mal (GTCS) seizures on awakening
6. Epilepsies with seizures precipitated by specific modes of activation
B. Cryptogenic or symptomatic (in order of age)
1. West syndrome (infantile spasms, Blitz-Nick-Salaam Krampfe)
2. Lennox-Gastaut syndrome
3. Epilepsy with myoclonic-asthetic seizures
4. Epilepsy with myoclonic absences
C. Symptomatic
1. Nonspecific etiology
a. Early myoclonic encephalopathy
b. Early infantile epileptic encephalopathy with suppression burst
2. Specific syndromes
Epileptic seizures may complicate many disease states.
Diseases in which seizures are apresenting or predominant feature are included in this category.
III. EPILEPSIES AND SYNDROMES UNDETERMINED WHETHER FOCAL OR GENERALIZED
A. With both generalized and focal seizures
1. Neonatal seizures
2. Severe myoclonic epilepsy of infancy
3. Epilepsy with continuous spike waves during slow-wave sleep
4. Acquired epileptic aphasia (Landau-Kleffner syndrome)
B. Without unequivocal generalized or focal features
Ali cases with generalized tonic-clonic seizures in which clinical and EEG findings do not permit classification as clearly generalized or localization-related, such as in many cases of sleep-grand mal
IV. SPECIAL SYNDROMES
A. Situation seizures
1. Febrile convulsions
2. Isolated seizures or isolated status epilepticus
3. Seizures occurring only when there is an acute metabolic or toxic event associated with factors such as alcohol, drugs, eclampsia, nonketotoc hyperglycemia

Dysfunction of inhibitory influences is considered important for the development and spread of epileptiform activity. Gamma–aminobutyric acid (GABA) is believed to be the major inhibitory neurotransmitter in the mammalian CNS and, indeed, antagonists of the GABA receptor are potent convulsants in experimental models of epilepsy.

Recently, the role of excitatory amino acids in the CNS, in particular glutamate, has been studied most intensely. Ionotropic glutamate receptors include N-methyl-D-aspartate (NMDA) and non-NMDA types (e.g., kainate, AMPA). Activation of a second class of glutamate receptors (metabotropic), which is G protein linked, also may increase neuronal excitability, at least in the hippocampus. NMDA receptors gate a high conductance ion channel (Ca^{2+}, Na^{+}, K^{+}) that is blocked in a voltage-dependent manner by Mg^{2+}; glycine increases the affinity of NMDA receptors for glutamate and is required for activation.

Activation of kainate, AMPA, as well as NMDA receptors also produces depolarization that is sufficient to open voltage-dependent Ca^{2+} channels. Entry of Ca^{2+} is believed to be critical for synaptic plasticity. Activation of the NMDA receptor system occurs when synaptic inhibition is depressed. The NMDA receptor-mediated excitatory postsynaptic potential (EPSP) has a long duration, which promotes high-frequency neuronal firing. Similar response in target neurons may encourage the spread of epileptiform activity.

In animal model of absence seizures, thalamocortical circuits are involved in the genesis of the spike-and-wave discharge. This oscillatory pattern is generated during a state of diffuse cortical hyperexcitability and is synchronized by thalamic nuclei. Thalamic bursts seem to depend on deinactivation of the low-threshold (T) calcium current and may involve activation of $GABA_B$ receptors. (McNamara, 1996)

Antiepileptic drug therapy is the mainstay of epilepsy treatment. The goals are to reduce the frequency of recurrent seizures and to minimize the adverse effects associated with antiepileptic drug therapy. Specific therapeutic end points must be individualized for each patient. The choice of antiepileptic drug should be base on the seizure classification, the age and sex of the patient, concurrent medical conditions, potential adverse effects, and the pharmacokinetic features of the individual drugs. When these factors are considered and the guiding principles of antiepileptic drug therapy are followed, good to excellent seizure control can be attained in most patients.

Monotherapy is preferred to polytherapy with antiepileptic drugs because of the lower cost associated with the medication and blood level monitoring, reduced potential for adverse reactions, and improved medication compliance with a more simplified drug administration schedule. If seizures are not controlled at adequate plasma concentrations of the initial agents, substitution of a second drug is preferred to the concurrent administration of another agent. However, multiple-drug therapy may be required, especially when two or more types occur in the same patient. (Alldredge, 1996)

Measurement of drug concentrations in plasma greatly facilitates optimizing antiseizure medication, especially when therapy is initiated, after dosage adjustments, in the events of therapeutic failure, when toxic effects appear, or when multiple-drug therapy is insulted. However, clinical effects of some drugs do not correlate well with their concentrations in plasma, and recommended concentrations are only guidelines for therapy. The ultimate therapeutic regimen must be determined by clinical assessment of effect and toxicity. (McNamara, 1996)

Table 3 lists the preferred antiepileptic drugs for the treatment of different seizure types.

Table 3. Antiepileptic drugs of choice based on seizure classification.

	Partial seizure	Generalized tonic-clonic seizures	Absence seizures	Myoclonic seizures
Drug of choice	Carbamazepine Phenytoin	Valproate Carbamazepine Phenytoin	Ethosuccimide Valproate	Valproate
Alternatives				
Primary	Valproate Gabapentin Lamotrigine Vigabatrin Phenobarbital Primidone	Phenobarbital Primidone	Clonazepam	Clonazepam
Secondary	Clorazepate Felbamate		Acetazolamide	

From a structure standpoint, the various drugs used in treating epilepsy may be categorized as follows (McNamara, 1996):

.. Barbiturates and related drugs

e.g. - phenobarbital (I)

- mephobarbital (II)

- primidone (III)

2. Hydantoins

    e.g. - phenytoin (IV)

    - mephenytoin (V)

    - ethotoin (VI)

3. Succinimides

    e.g. - ethosuccimide (VII)

    - methsuccimide (VIII)

    - phensuccimide (IX)

4. Oxazolidinones

    e.g. - trimethadione (X)

    - dimethadione (XI)

5. Benzodiazepines

    e.g. - clonazepam (XII)

    - diazepam (XIII)

    - clorazepate (XIV)

6. Iminostilbene

    e.g. - carbamazepine (XV)

7. Branched-chain carboxylic acid

    e.g. - valproic acid (XVI)

8. Phenyltriazine

    e.g. - lamotrigine (XVII)

9. Cyclic analogue of GABA

e.g. - gabapentin (XVIII)

10. Miscellaneous anticonvulsants

e.g. - phenacemide (XIX)

- acetazolamide (XX)

The chemical structures of these agents are presented in figure 1.

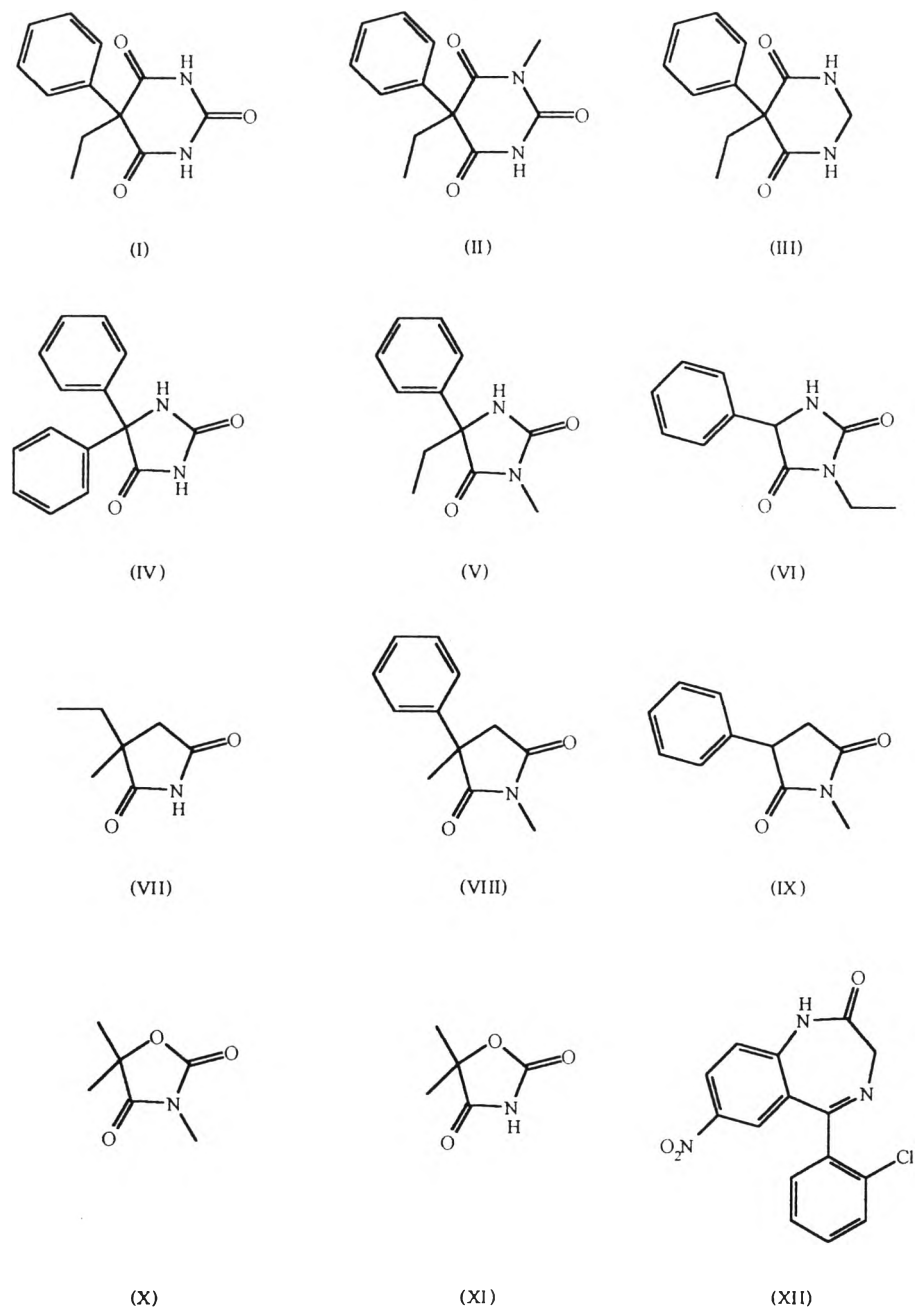


Figure 1. The chemical structures of some antiepileptic drugs.

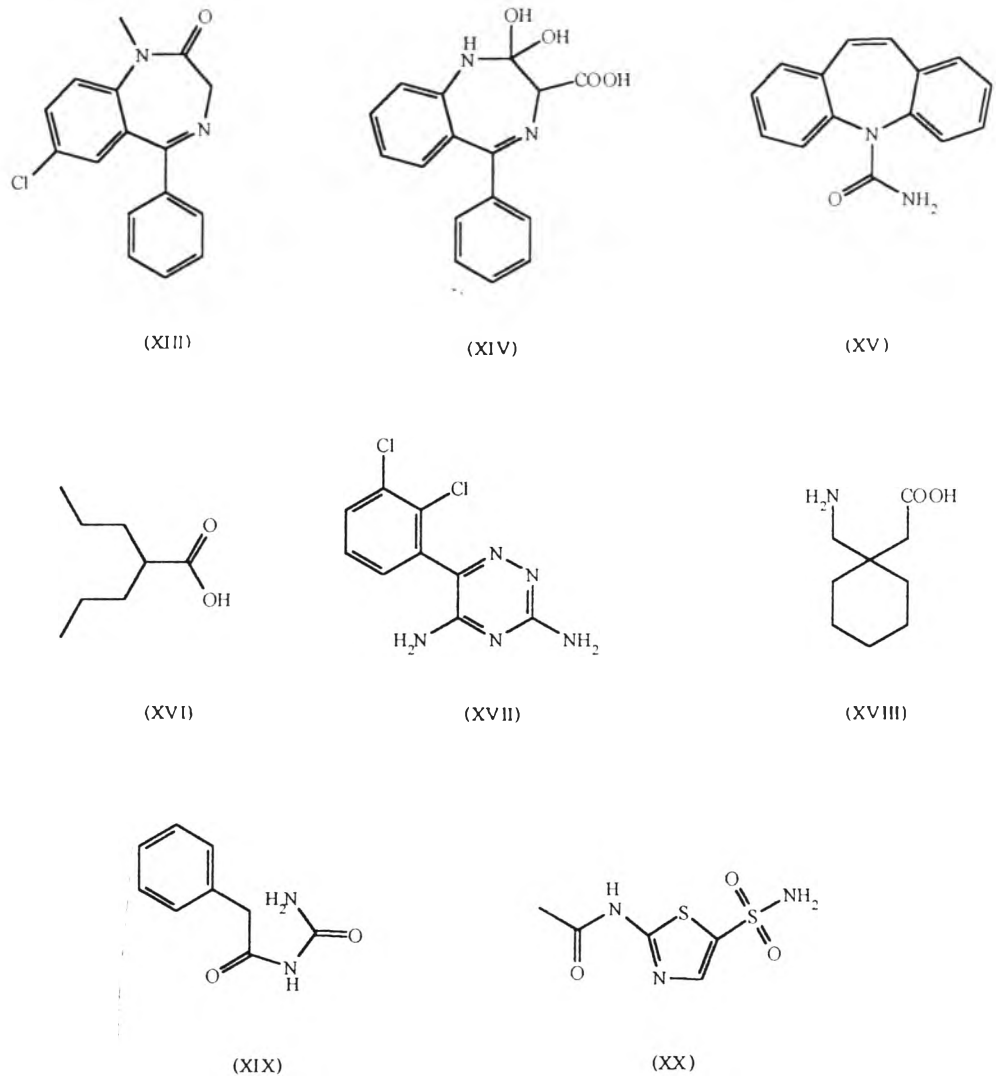


Figure 1. (continued) The chemical structures of some antiepileptic drugs.

The first effective antiepileptic drugs were the result of advances in the understanding of the neuropathological basis of epilepsy, the accidental and serendipitous discovery, advance in synaptic chemistry and the development of animal models for testing putative agents. The isolation of bromine in 1826 and the synthesis of urea in 1826 led to the laboratory synthesis of the first modern antiepileptic drugs, namely potassium bromide and phenobarbital. However, both drugs were associated

with significant adverse effects, particularly sedation, and the use of potassium bromide has essentially been abandoned.

The 25 years following the serendipitous discovery of phenobarbital was devoided of pharmacological advances in the treatment of epilepsy. The next major advance occurred in 1938 with the introduction of phenytoin. This discovery was very important because it was the result of efficacy testing in animal models of epilepsy, and unlike phenobarbital, phenytoin was not sedative and had a wider spectrum of activity. The impetus generated by the discovery of phenytoin and later trimethadione resulted in the laboratory screening of thousands of candidate drugs.

The current and very exciting phase of antiepileptic drug development is the result of our improved understanding of the mechanisms underlying epileptogenesis and is based on developing 'designer drugs' which act in a specific way to interfere with known mechanisms involved in neuronal excitability. Some of these rationally developed antiepileptic drugs are now entering the market. In the course of this process, the mechanism of action of older drugs has been clarified. (Patsalos and Sander, 1994)

Nowadays, there are four targets of action addressed for both clinically available and newer antiepileptic drugs.

1. Sodium channels

Voltage-gated sodium channels are responsible for action potential generation and propagation under normal conditions as well as during seizures. The sodium channels can exist in three conformational states: active, resting, and inactivated. At resting membrane potential, most channels are closed, but they activate within a few hundred microseconds in response to membrane depolarization, resulting

in sodium flux through the open channel pore, and then convert to non-conducting inactivated state within a few milliseconds. Channels almost never open from the inactivated state. However, repolarization of the membrane rapidly converts them back to the resting state, from which they can open in response to a subsequent depolarization.

The antiepileptic drugs; phenytoin and carbamazepine are known to bind with higher affinity to sites near or at inactivated sodium channels and to retard the rate of recovery of the channels from the inactivated state. Sodium channels are the likely molecular targets of a number of important antiepileptic agents, including several promising new compounds, for instance, valproate, lamotrigine, topiramate (XXI), felbamate (XXII), oxcarbazepine (XXIII), dezinamide (XXIV), and fosphenitoin (XXV). (See figure 2) (Avoli, 1997 and Prous, 1994)

2. Excitatory transmitters

It has been demonstrated that glutamate levels are elevated prior to the onset and during the expression of seizures in patients with partial complex epilepsy. Moreover, epileptiform discharges in animal models are readily abolished by excitatory amino acid receptor antagonists. Hence an alternative approach to modulation of GABA-mediated mechanisms in order to control seizures may reside in a reduction of synaptic excitation.

This excitation is mainly due to activation of ionotropic amino acid receptors, NMDA and AMPA/kainate. Data obtained from animal models indicate that NMDA antagonists prevent the occurrence of generalized tonic-clonic and partial seizures and protect against the induction of kindling. Moreover, recent experimental evidence indicates that modulation of metabotropic glutamate receptors also produces an anticonvulsant action. (Avoli, 1997)

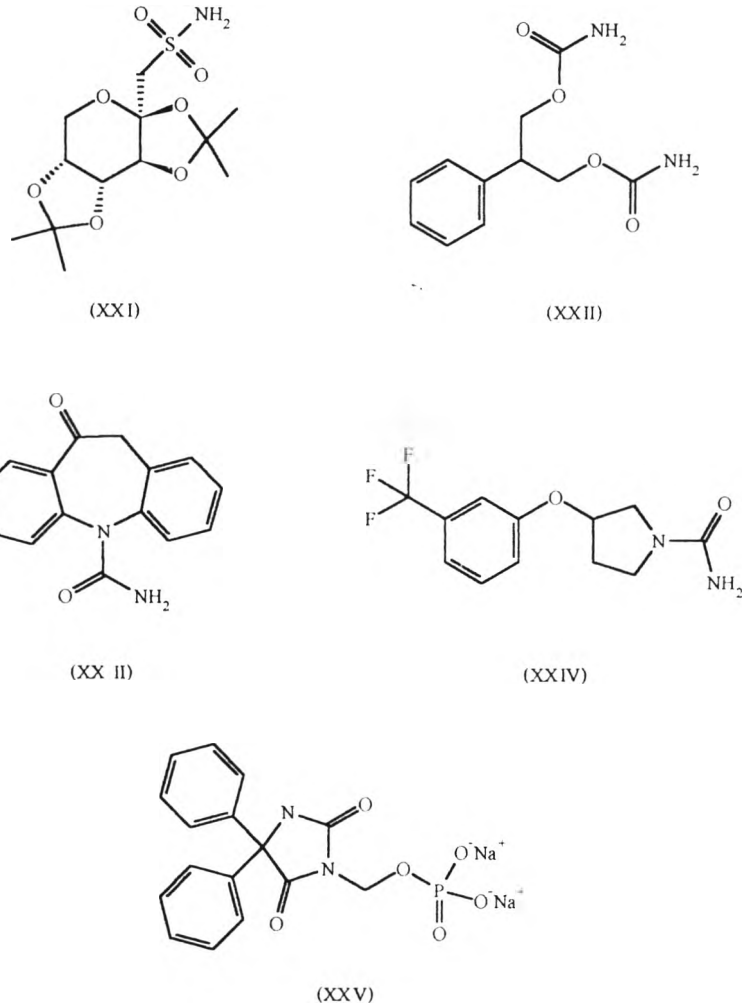


Figure 2. Some anticonvu sant agents acting at sodium channels

NMDA receptor antagonists have been shown to be effective anticonvulsants in various animal mode s of epilepsy, such agents have the potential in seizure disorders. These compounds comprise two groups. (Rogawski and Porter, 1990; Prous, 1994)

a) the competitive antagonists of the NMDA recognition site

- straight chain analogues of glutamate with the

ω-carbonyl group replaced by a phosphoric acid moiety e.g., APH (XXVI), and APV (XXVII)

- cyclic (conformationally restricted) analogues of APV and APH, e.g. CPP (XXVIII), and CGS 19755 (XXIX)
- structurally restricted cyclic derivatives of APH, e.g., NPC-12626 (XXX), and PD-145950 (XXXI)
- orally active competitive antagonists of the NMDA receptor-channel complex e.g., CGP 37849 (XXXII), CGP 39551 (XXXIII), and D-CPP-ene (XXXIV)

b) the non-competitive antagonists of the NMDA receptor-channel complex e.g., phencyclidine (XXXV), MK-801 (XXXVI), ketamine (XXXVII), and dextromethorphan (XXXVIII) (See figure 3)

3) Inhibitory synaptic processes

Gamma-aminobutyric acid (GABA) is major inhibitory neurotransmitter in the mammalian brain. Enhancement of GABA-mediated inhibition would be expected to produce an anticonvulsant effect Pharmacological methods of enhancing GABA-mediated inhibition are:

a) GABA agonists

GABA penetrates the blood-brain barrier poorly, thus, analogues of GABA have been developed to enhance GABA activity. These include the isoxazole muscimol (XXXIX) and the $GABA_A$ receptor agonist THIP (XL), both of which exert their specific action on postsynaptic GABA receptors. GABA also acts postsynaptically ($GABA_B$). This site is sensitive to baclofen (XLI), progabide (XLII), a schiff base of GABA, and CGP-36742 (XLIII). (See figure 4)

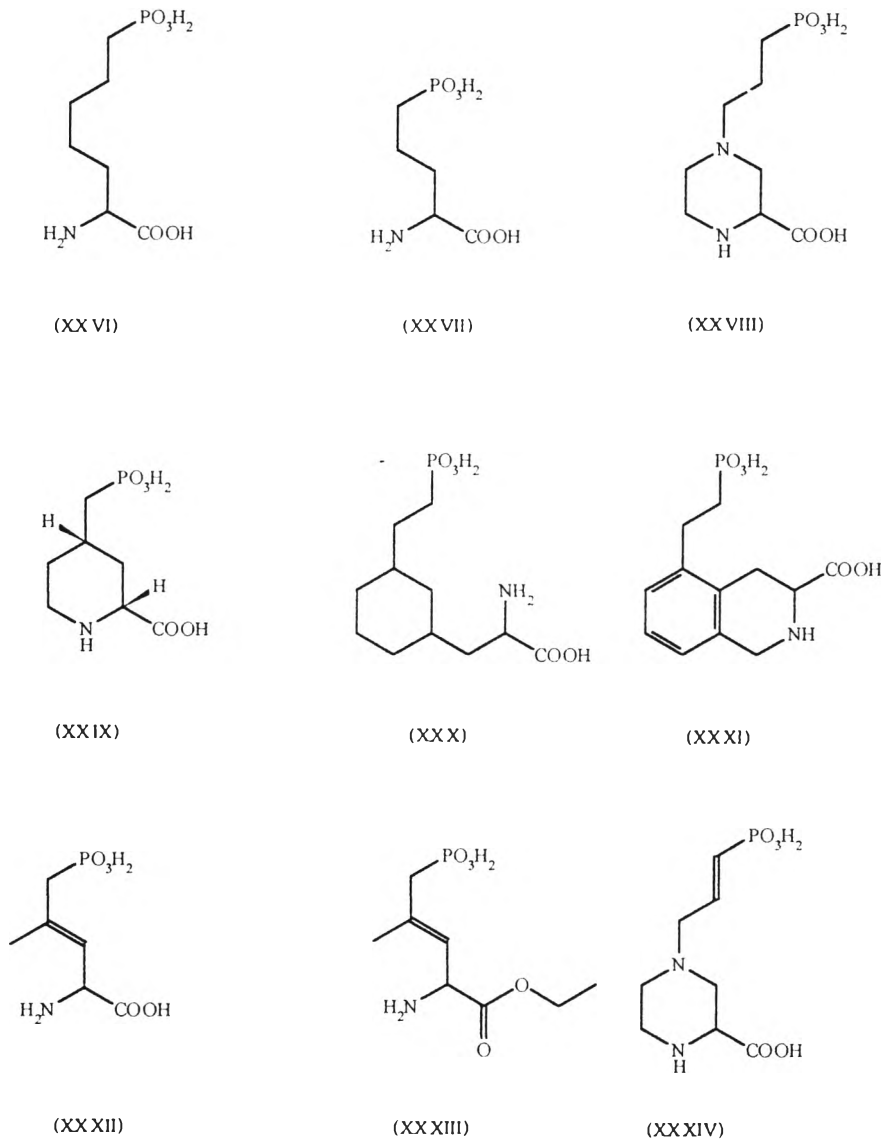
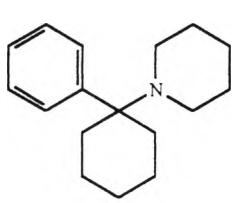


Figure 3. Chemical structures of some competitive and noncompetitive NMDA receptor antagonists



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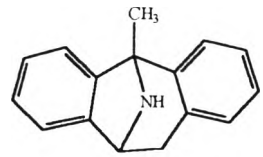

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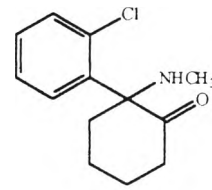

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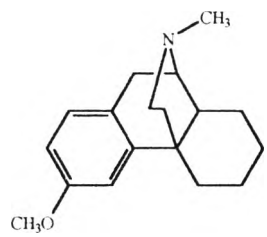


(XXXVIII)

Figure 3. (continued) Chemical structures of some competitive and noncompetitive NMDA receptor antagonists

b) GABA uptake inhibitors

Synaptically released GABA is inactivated by reuptake into nerve terminals or into glial cells. This process can be inhibited by tiagabine (XLIV), the lipophilic GABA uptake inhibitor derivative that increases synaptic GABA levels and potentiates the amplitude and duration of GABA-midiated inhibitory post synaptic potentials.

c) GABA transaminase inhibitors

An approach that represents an alternative strategy to direct potentiation of postsynaptic $GABA_A$ receptor function is to increase GABA availability. Vigabatrin (Gamma-vinyl GABA, XLV) elevates brain GABA levels by inhibiting GABA transaminase, which is the main degradative enzyme for GABA.

d) Allosteric enhancement

The benzodiazepine receptor is an allosteric site that interacts with the GABA recognition site and the effect is to increase the number of chloride channels opened by a given concentration of GABA. The compounds that display anticonvulsant activity at the site are the 1,4-benzodiazepines, clobazam and desmethylclobazam (XLVI) (see figure 4) (Edafigho and Scott, 1996)

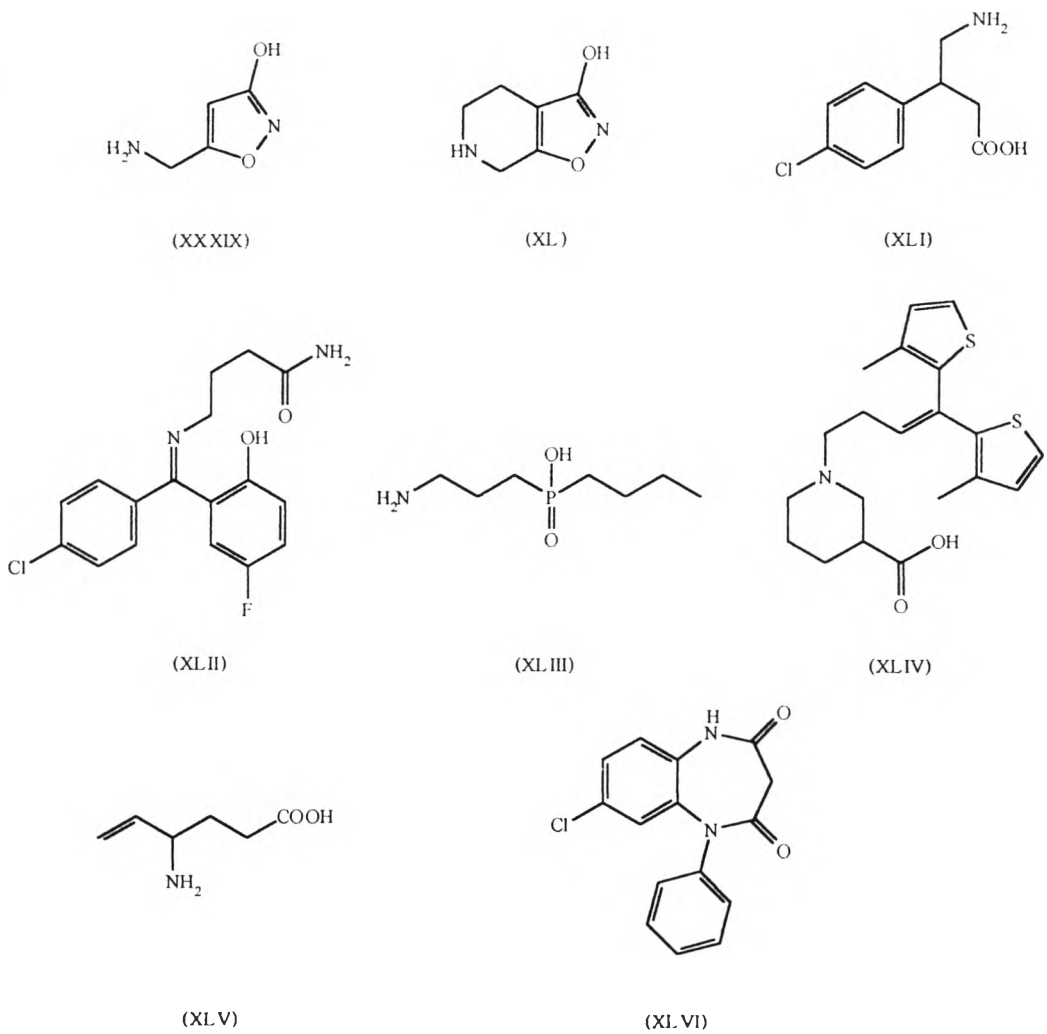


Figure 4. Chemical structures of anticonvulsant agents acting at inhibitory synaptic processes.

4) Calcium channels

Some antiepileptic drugs reduce the flow of Ca^{2+} through T-type Ca^{2+} channels, thus reducing the pacemaker current that underlies the thalamic rhythm in spikes and wave seen in generalized absence seizures. These are valproate, dimethadione, and ethosuccimide. (McNamara, 1996)

Other anticonvulsants with precise mechanism of action are uncertain, but that have progressed to clinical trials include CGP-33101 (XLVII), levetiracetam (XLVIII), losigamone (XLIX), F-721 (L), PD-144723 (LI), RWJ-37947 (LII), NNC-138119 (LIII), and RWJ-37868 (LIV) (Prous, 1994) (See figure 5)

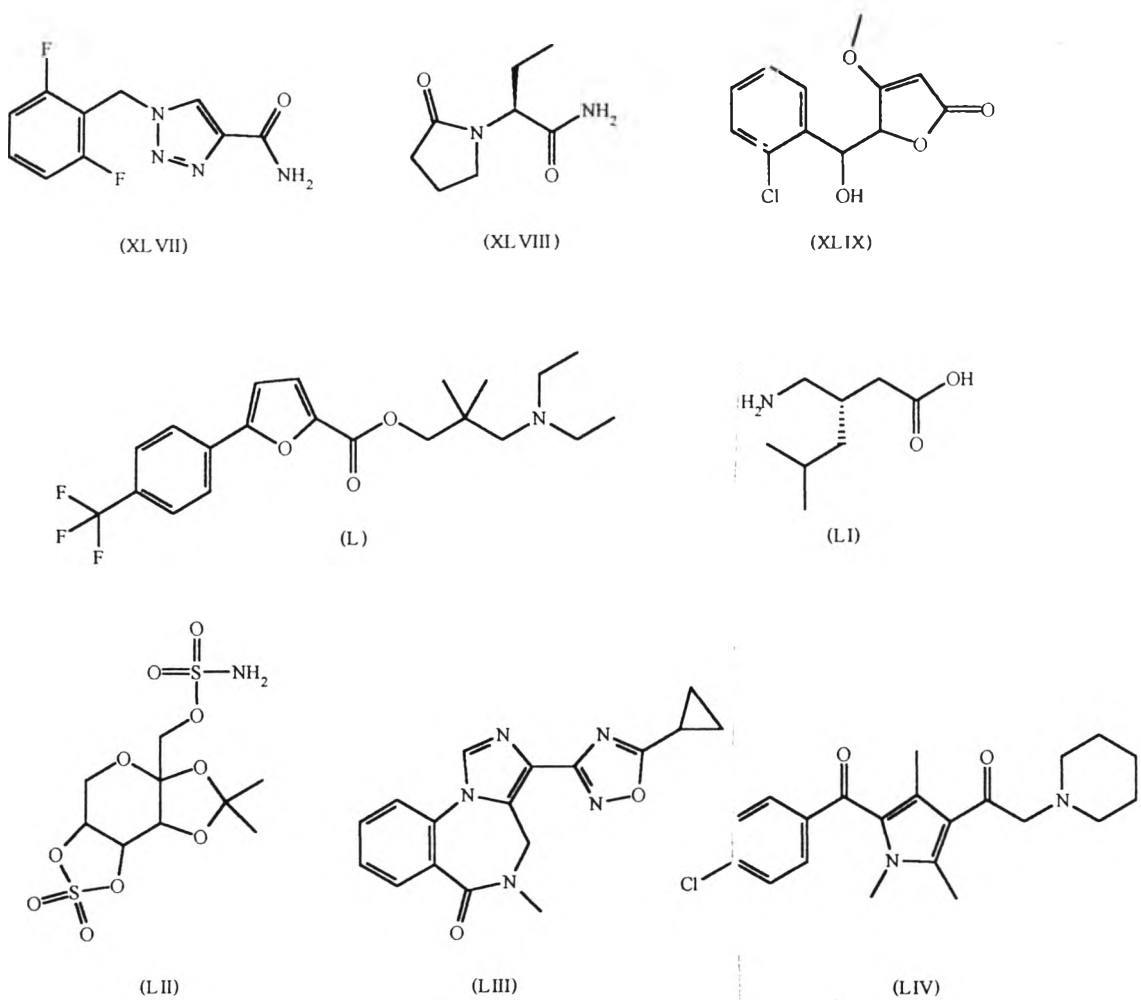


Figure 5. Chemical structures of antiepileptic drugs under development.

It is estimated that 25% of the epileptic population have seizures that are not responsive to presently available medical therapies. Despite the optimal use of available antiepileptic drugs, many patients with epilepsy fail to experience seizure control and others do so only at the expense of significant toxic side effects. Estimates suggest that available medication controls the seizures in only 50% of patients or decreases the incident in only 75% of patients. Only a small number of these drug-resistant patients may be candidate for surgical intervention, making the field of anticonvulsant drug discovery a high priority.

Valproic acid is one of the four major antiepileptic drugs. While it has a broad antiepileptic spectrum of activity, two serious (although rare) side effects, teratogenicity and hepatoxicity, have been associated with the drug therapy. Comparative analysis of the anticonvulsant potency and safety margin, utilizing the classical rodent models, shows that valproic acid is less potent than the other three antiepileptics: phenobarbital, phenytoin, and carbamazepine. Consequently, there is a substantial need to develop improved derivatives of valproic acid.

Valpromide or dipropylacetamide (LV, figure 6), a primary amide of valproic acid, is widely used in several European countries, both as an antiepileptic and as an antipsychotic drug. Among the series of valproic acid analogues tested in mice for anticonvulsant activity, valpromide was found to be the most potent, being two to five times more potent than valproic acid. However, valpromide exerted a more significant sedative side effect. (Haj –Yehia and Bialer, 1989)

In addition, valpromide was shown to be much less teratogenic in mice than valproic acid. Radatz, Ehlers, Yagen, Bialer, and Nau (1998) concluded that the amidation of a carboxylic group and / or β–substitution in the molecule of a valproic acid analogue greatly reduces its teratogenic properties.

There were 4 compounds in the category of amide derivatives of vaproic acid synthesized and proven to have anticonvulsant activity, namely,

- N-(2-propylpentanoyl)urea (LVI), the ureide analogue of valproic acid (Wicharn Janwitayanuchit, 1992; Thongchai Sooksawate,1995)

- N-(2-propylpentanoyl)glycinamide (LVII), the N-(2-propylpentanoyl) derivative of an inhibitory amino acid. (Hadad and Bialer, 1995)

- N-(hydroxymethyl)-2-propylpentamide (LVIII) which was found serendipitously as a by-product from mannich reaction. (Chamnan Patarapanich and Boonyong Tantisira, unpublished data)

- N-(hydroxyethyl)-2-propylpentamide (LIX), a stable valpromide analogue. (Levi, Yagen, and Bialer, 1997) (See figure 6)

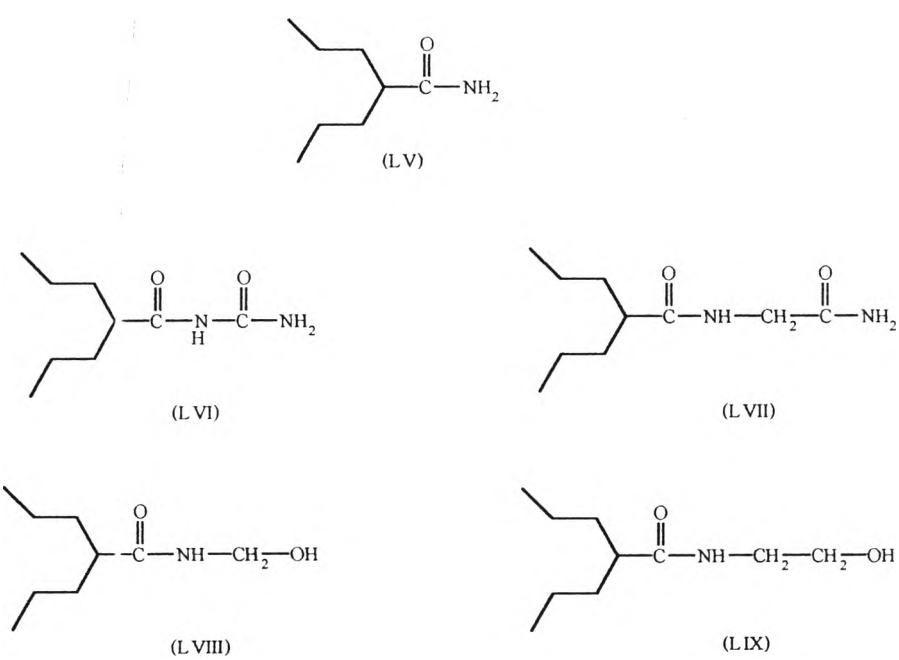
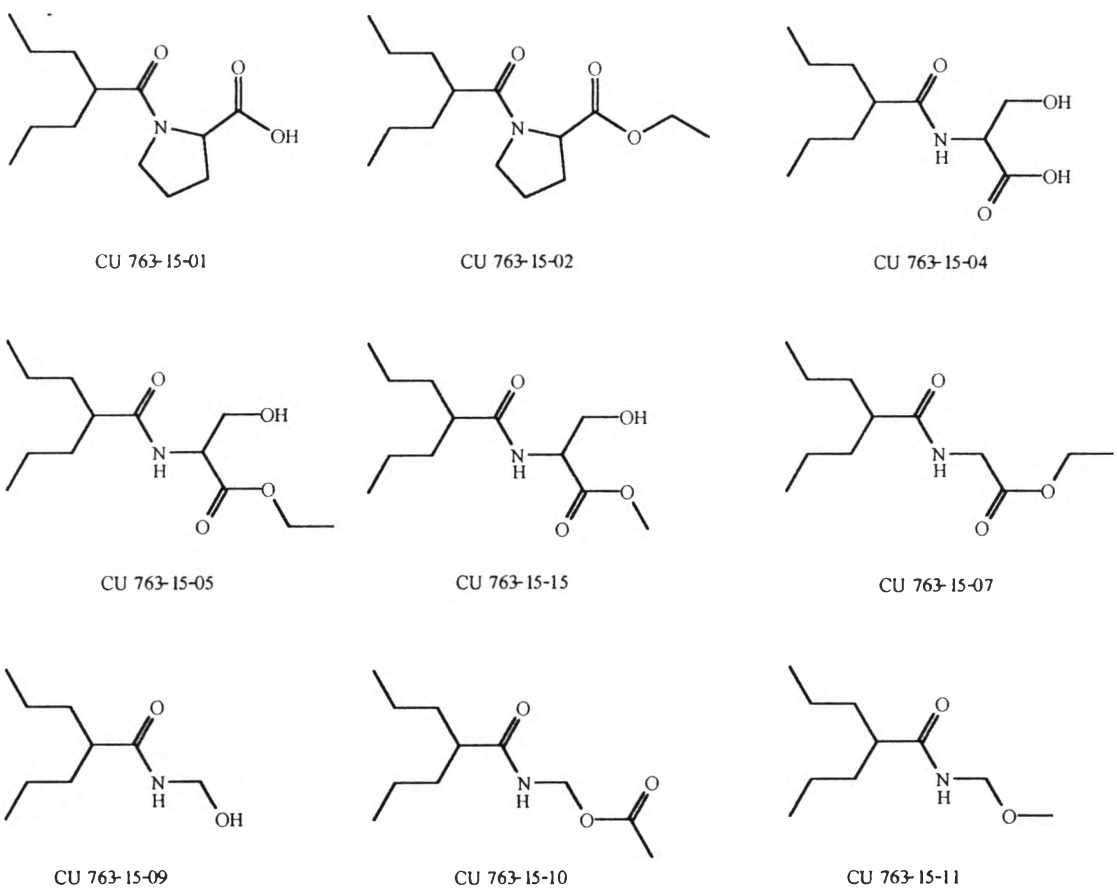


Figure 6. Chemical structures of some derivatives of valproic acid having anticonvulsant activity.

Hydrogen bond donating or accepting group at α or β position to amide nitrogen of 2-propylpentamide seems to correlate with anticonvulsant activity.

This research is aimed to synthesize amide derivatives of valproic acid of which chemical structures relate to this type of compounds proposed to have anticonvulsant activity. The chemical structures are shown as follow. (Figure 7)



(LVIII)

Figure 7. Chemical structures of target compounds in this research.

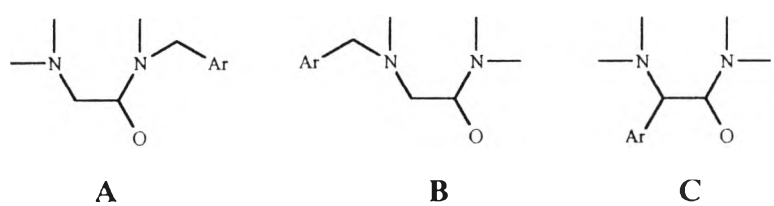
Inspection of chemotherapeutic agents possessing CNS depressant and anticonvulsant activities reveals a common structural pattern. (Figure 8) Three functionalities are prevalent in many of these compounds.

(1) ethylene diamine

(2) an oxygen atom on the carbon of ethylene chain bridging the two amino groups.

(3) an aromatic ring at the α- position to amino residue.

Representatives of this structural design are substituted hydantoins, piperazines, and benzodiazepines. (Cortes, Liao, Watson, and Kohn, 1985; Conley and Kohn, 1987)



A **B** **C**

Figure 8. Structural units present in many anticonvulsants.

Recognition of these empirical blueprints in anticonvulsant drugs led to the synthesis and investigation of antiepileptic activity of functionalized amino acids which represent type A. These compounds were proven to display potent anticonvulsant activity. (See figure 9)

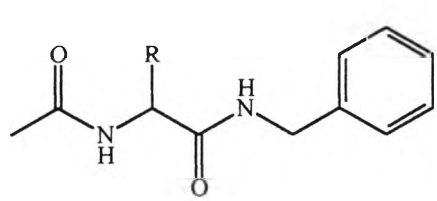


Figure 9. General structure of the functionalized amino acids.

The pronounced activity observed for functionalized amino acids prompts the synthesis of the following 3 amide derivatives of valproic acid. (See figure 10)

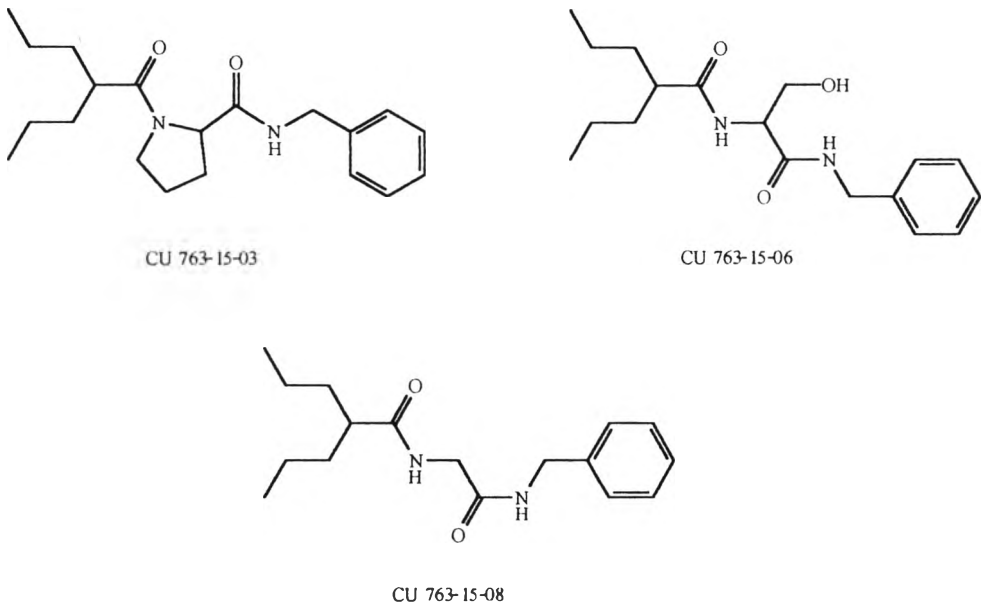
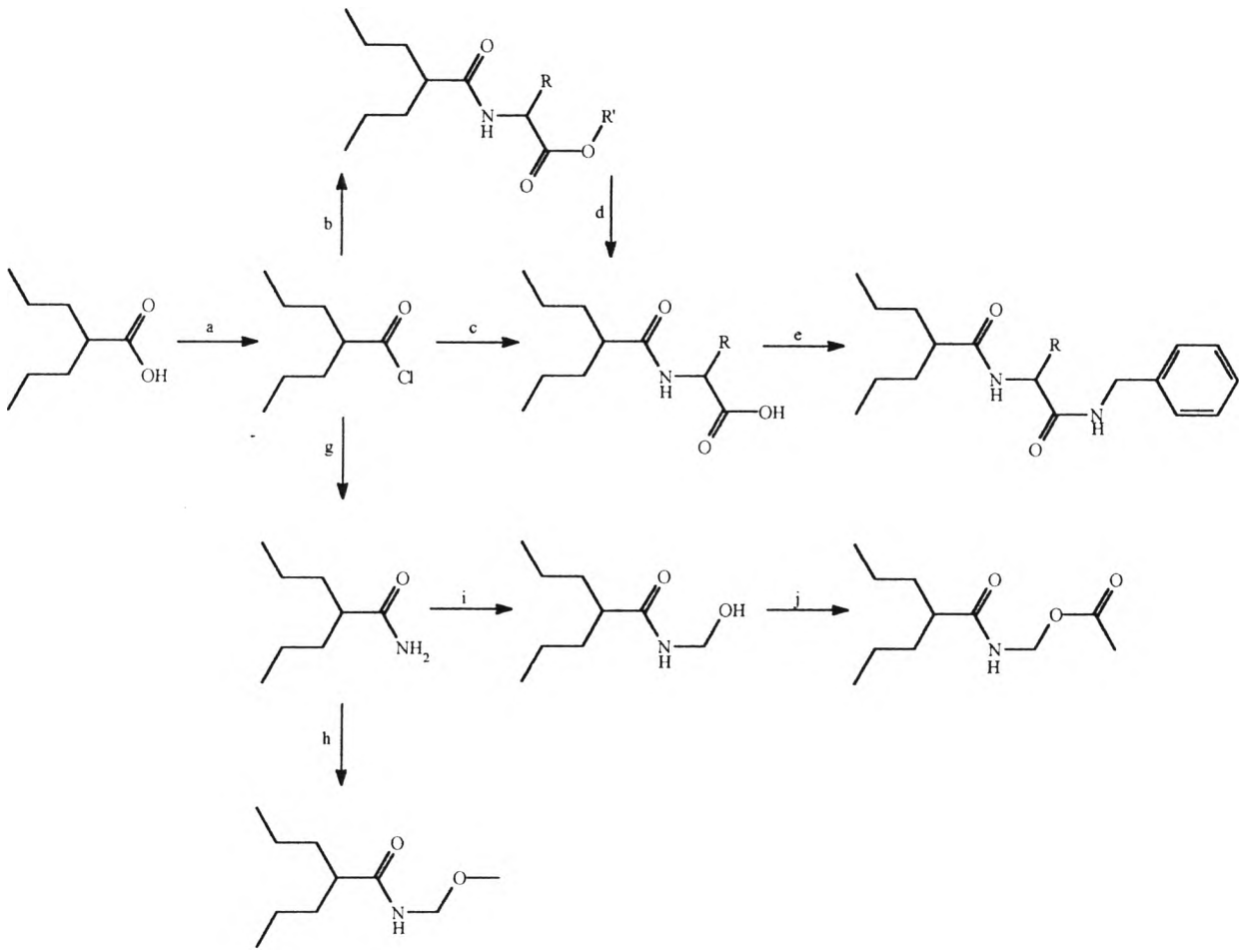


Figure 10. Chemical structures of target compounds in this research.

The synthetic approach for all compounds is shown in figure 11.



a) $SOCl_2$/ reflux

b) HCl H_2N-CHR-COOR'/ TEA/ 0-4° C

c) H_2N-CHR-COOH/ 10% NaOH/ 0-4° C

d) 1N NaOH/ methanol/room temperature

e) H_2N-CH_2-Ph/ DCC

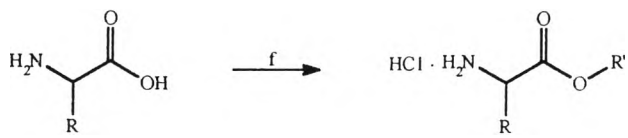
g) NH_4OH/ 0-4° C

h) Cl-CH_2-O-CH_3/ NaH/ 0-4° C

i) 37% formaldehyde/ K_2CO_3

j) acetic anhydride/ pyridine/ reflux

Figure 11. The synthetic approach of target compounds in this research.



f) ethanol or methanol/ $SOCl_2$/ reflux

Figure 11.(continued) The synthetic approach of target compounds in this research.