CHAPTER I

INTRODUCTION

The term epilepsy is used collectively to include a group of syndromes of central nervous system (CNS) disorders characterized by sudden, transitory, and recurring seizures involving one or more of the following systems: motor (convulsion), sensory, autonomic, or psychic. Most investigators do not include single isolated seizures in the definition of epilepsy. Abnormal and excessive discharges in the electroencephalogram (EEG) nearly always accompany the seizures. Synonyms of the term epilepsy are convulsive disorders and seizures disorders (Chan, 1992).

Shorvon (1990) has reported incidence and prevalence studies of epilepsy from many countries but comparisons are often difficult because investigators have adopted different definitions of epilepsy, case-ascertainment methods, and classification schemes; selection bias is also important. Nevertheless, most studies have found incidence rates of 20-70/100,000 per year and point prevalence rates of 4-10/1,000 in the general population. Incidence varies considerably with age; rates are greatest in early childhood, reach a nadir in early adult life, and rise again in elderly people. Prevalence rates show a similar but less pronounced age-related pattern. Most studies show a slight excess of epilepsy among males. Another interesting statistic is the lifetime (or total) prevalence, which is the measure of the number of people in a

population who have ever had epilepsy; estimates vary from 2 to 5% of the population. Thus perhaps as many as 1 in 20 of the population will have had an epileptic seizure at some point in their lives and 1 in 200 will have epilepsy. These calculations indicate that epilepsy is the most prevalent serious neurological condition.

Efforts to classify epilepsy and epileptic seizures have been made for centuries. The objectives of modern-day classifications are to aid research, treatment, and teaching, and to facilitate communication (Gastaut and Zifkin, 1992). In 1969, the International Leaque Against Epilepsy (ILAE) attempted to introduce a scheme for universal application. This scheme, revised in 1981 (by Commission on Classification and Terminology of ILAE) and widely adopted, is a classification of seizure type (table 1) in which EEG data are taken into account whereas aetiology, age, and anatomical site are ignored. In this scheme, seizures are divided into three groups : partial (focal); generalised; and unclassifiable. Partial seizures are those in which epileptic activity is confined to a focal area of the brain, whereas generalised seizures are those in which epileptic discharges involve both cerebral hemispheres widely and simultaneously from the onset of the seizure. In case of unclassified epileptic seizures, this type of seizures includes all seizures that cannot be classified because of inadequate or incomplete data and some that defy classification in hitherto described categories.

Partial seizures are further divided into simple partial and complex partial catagories, according to the preservation or alteration of consciousness. The epileptic activity of partial seizures (simple or complex) may spread to become generalised, in which case the seizure is said to be secondarily

Table 1. ILAE classification of seizure type.

I. Partial seizures.

A. Simple partial seizures.

(1) With motor signs.

(2) With somatosensory or special sensory hallucinations.

(3) With autonomic symptoms and signs.

(4) With psychic symptoms.

B. Complex partial seizures.

(1) Simple partial onset followed by impairment of consciousness.

(2) With impaired consciousness at onset.

C. Partial seizures evolving to secondary generalised seizures.

(1) Simple partial seizures evolving to generalised.

(2) Complex partial seizures evolving to generalised.

(3) Simple partial seizures evolving to complex partial seizures evolving to generalised.

II. Generalised seizures.

A. (1) Absence seizures.

(2) Atypical absence.

B. Myoclonic seizures.

C. Clonic seizures.

D. Tonic seizures.

E. Tonic-clonic seizures.

F. Atonic.

III. Unclassifiable epileptic seizures.

generalised. Generalised seizures are classified into tonic-clonic (grand mal), absence (petit mal), myoclonic, atonic, and clonic seizures. Subdivisions of the classification are shown in table 1.

More recently, in recognition of the fact that a seizure-type classification does not account for other aspects of the heterogeneity of epilepsy, the ILAE devised a new scheme - the Classification of the Epilepsies and Epileptic Syndromes and Related Seizure Disorders (1989) - which is now also widely used and is an attempt to categorise the epilepsies more comprehensively (Commision on Classification and Terminology of ILAE, 1989).

This classification (table 2) takes into account seizure type, EEG, and prognostic, pathophysiological, and aetiological data. It retains the division of epilepsy into generalised and partial (now called localisation-related) categories, with each category subdivided into symptomatic and idiopathic varieties. Two new categories are added - epilepsies and syndromes undetermined, whether focal or generalised, and special syndromes. This scheme is complex and may well confuse non-taxonomists, but it is a serious attempt to incorporate more than simple seizure type data into a comprehensive classification.

Because of the diversity of seizure types, it would be a gross oversimplification to suggest a single mechanism or cause for epilepsy. There is likely to be more than one neurophysiological and biochemical mechanism for seizure disorders. The primary seizure focus may originate of be triggered by factors such as congenital defects, hypoxia at birth, local biochemical changes, neoplasm, head trauma, ischemia, or endocrine disorders (Chan, 1992).

Table 2. ILAE classification of the epilepsies and epilepsy syndromes and related seizure disorders.

1. *Localisation-related (local, focal, partial) epilepsies and syndromes.*
   - 1.1 Idiopathic (with age-related onset).
     - Benign childhood epilepsy with centro-temporal spike.
     - Childhood epilepsy with occipital paroxysms.
     - Primary reading epilepsy.
   - 1.2 Symptomatic.
     - Chronic progressive epilepsia partialis continua.
     - Syndromes characterised by seizures wirh specific modes of precipitation.
       - Temporal lobe epilepsies.
       - Frontal lobe epilepsies.
       - Parietal lobe epilepsies.
       - Occipital lobe epilepsies.
   - 1.3 Cryptogenic.
2. *Generalised epilepsies and syndromes.*
   - 2.1 Idiopathic (with age-related onset).
     - Benign neonatal familial cunvulsions.
     - Benign neonatal convulsions.
     - Benign myoclonic epilepsy in infancy.
     - Childhood absence epilepsy.
     - Juvenile absence epilepsy.
     - Juvenile myoclonic epilepsy.
     - Epilepsy with grand mal seizures (GTCS) on awakening.
     - Other generalised idiopathic epilepsies.
     - Epilepsies with seizures precipitated by specific modes of activation.
   - 2.2 Cryptogenic or symptomatic.
     - West syndrome.
     - Lennox-Gastaut syndrome.
     - Epilepsy with myoclonic-astatic seizures.
     - Epilepsy with myoclonic absences.

Table 2 (continued). ILAE classification of the epilepsies and epilepsy syndromes and related seizure disorders.

2.3 Symptomatic.

2.3.1 Non-specific aetiology.

Early myoclonic encephalopathy.

Early infantile epileptic encephalopathy with suppression burst.

Other symptomatic generalised epilepsies.

2.3.2 Specific syndromes.

Epileptic seizures complicating other disease states.

3. Epilepsies and syndromes undetermined whether focal or generalised.

3.1 With both generalised and focal seizures.

Neonatal seizure.

Severe myoclonic epilepsy of infancy.

Epilepsy with continuous spike waves during slow wave sleep.

Acquired epileptic aphasia.

Other undetermined epilepsies.

3.2 Without unequivocal generalised or focal features.

4. Special syndromes.

4.1 Situation-related seizures.

Febrile convulsions.

Isolated seizures or isolated status epilepticus.

Seizures occurring only with acute metabolic or toxic events.

The cellular mechanisms which underlie epileptic seizures are at present not fully understood; however, defects in inhibitory or increased sensitivity in excitatory neurotransmission may be involved (Palmer and McTavish, 1993). In a mentally alert subject, a normal electroencephalographic (EEG) tracing registers as diffuse, unsynchronised electrical activity. Seizure activity begins when a small number of neurons depolarise simultaneously. As initial depolarisation is calcium- and sodium-dependent (figure 1), blockade of ion channels inhibits influx of these ions, thus stabilising the neuron and preventing depolarisation.

A clinically apparent seizure occurs when the abnormal impulse propagates from its point of origin to adjacent and/or distant areas of the brain. γ -Aminobutyric acid (GABA), the major inhibitory neurotransmitter in human brain, suppresses distribution of the impulse by causing neuronal chloride and potassium channels to open, thereby inducing membrane hyperpolarisation A defect in the activity of GABA may therefore result in enhanced propagation of the epileptiform discharge.

Increased activity of excitatory neurotransmitters, such as glutamate and possibly aspartate, may also contribute to the spread of epileptic activity. Glutamate appears to be the excitatory neurotransmitter implicated most in the enhanced propagation of the epileptic impulse. Glutamte is active at several postsynaptic receptor sites, namely the N-methyl-d-aspartate (NMDA) receptor, the d-Amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor, the kainate receptor, and the quisqualate receptor. After binding to the NMDA receptor, glutamate induced intermittent bursts of neuronal firing similar to those seen in an epileptic focus. Antagonists of the NMDA receptor have been

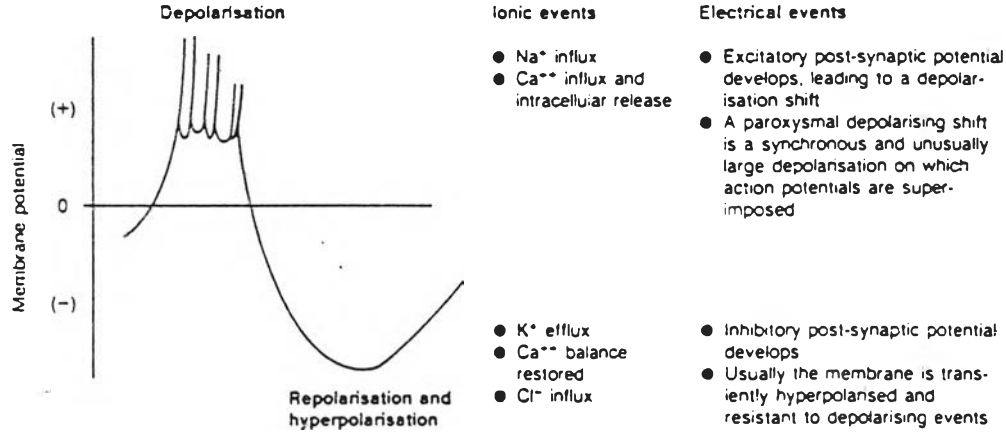


Figure 1. Electrical and ionic events related to neuronal activation/inhibition.

effective antiepileptics in animal models. Thus, it is at this receptor that glutamate is thought to exert its convulsant effects.

Antiepileptic drugs may therefore suppress seizure activity by any or a combination of the following mechanisms:

- stabilisation of the neuronal membrane through effects on ion flux;
- enhancement of the effects of inhibitory neuro-transmitters, e.g. GABA;
- inhibition of excitatory neurotransmitters such as glutamate. (Goa et. al, 1993)

The primary use of anticonvulsant drugs is in the prevention and control of epileptic seizures. The ideal antiepileptic drug, among other things, should completely suppress seizures in doses that do not cause sedation or other undesired central nervous system toxicity. It should be well tolerated and highly effective against various types of seizures, and devoid of undesirable side effects on vital organs and functions. Its onset of action should be rapid after parenteral injection for control of *status epilepticus*, and it should have a long duration of effect after oral administration for prevention of recurrent seizures (Vida, 1989).

The antiepileptic drugs used nowaday belong to several chemical classes (Rall and Schleifer, 1990). Most of the drugs introduced before 1965 are closely related in structure to the barbiturates such as phenobarbital (I), the oldest member of this therapeutic class. These include the hydantoins e.g. phenytoin (II), the deoxybarbiturates e.g. primidone (III), the oxazolidinediones e.g. phenacemide (IV), the succinimides e.g. ethosuccimide (V), and the acylureas

e.g. phenacemide (VI) as shown in figure 2. The agents introduced after 1965 include benzodiazepines e.g. diazepam (VII), an iminostilbene e.g. carbamazepine (VIII), a branched-chain carboxylic acid e.g. valproic acid (IV) (A reappraisal of its pharmacological properties and clinical efficacy in epilepsy is reviewed by Davis et al. (1994).), and sulfonamides e.g. acetazolamide (X) as illustrated in figure 2. The mechanisms of action of these drugs are delineated by Woodbury et al. (1983) and Chapman et al. (1982). In addition, The structure-activity relationships of drugs in each group have also been depicted by Mercier (1973).

For the available anticonvulsant agents, a surprising lack of efficacy for many seizure types and/or tolerance development leads to polytherapy and/or increased dosage regimens, often with the emergence of undesirable side effects or toxicity (Martin and Tegeler, 1988). The vast majority of patients with epilepsy depend on medical therapy, or medications, for control of their seizures (Millchap, 1972). Although antiepileptic drugs are effective in most patients, a sizable minority of patients, 20-25% of the total number, respond poorly and are chronically refractory to medications. Although a limited number of such patients may be candidates for surgical intervention, most patients with refractory epilepsy must look to new, more effective medications for relief of their seizures. The actual number of patients with uncontrolled epilepsy is quite remarkable (Porter, 1990 b).

Another problem found in anticonvulsants used at present is their toxicity. Although the antiepileptic drugs are prescribed for their beneficial effects, they still have the potential for causing toxicity. Antiepileptic drugs can affect the central nervous system, the peripheral nervous system, and other

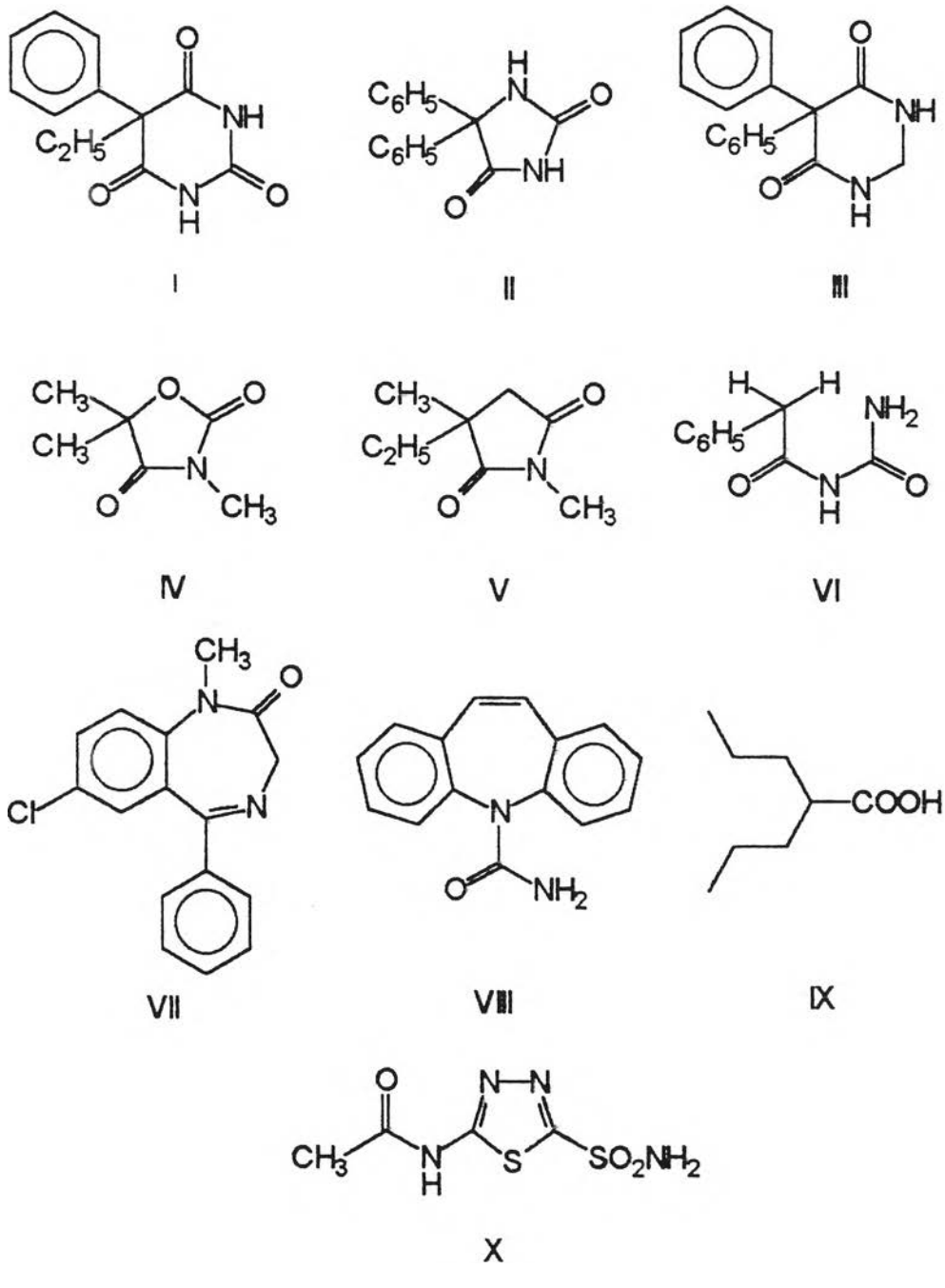


Figure 2. The chemical structures of some common used anticonvulsant drugs.

organ systems. The most noticeable side effect of the antiepileptic medications on the central nervous system is sedation: a feeling of sleepiness, drowsiness, or fatigue, which may be accompanied by increasing time spent sleeping. Other effects are cognitive effects (e.g. memory impairment, slowing of performance), emotional changes (e.g. irritability, aggressiveness, hyperacidity in children), cerebellar disorders (e.g. feeling of disequilibrium, ataxia), and extrapyramidal effects (e.g. dyskinesia, dystonia). The effect on the peripheral nervous system, that is peripheral neuropathy, can be observed in patients with the chronic use of phenytoin. Many organs can also be affected by anticonvulsants. Skin rashes are the most dramatic manifestation of toxicity of antiepileptic drugs. Other toxic effects are associated with hematological system, endocrine system, immunological system. In addition, function abnormalities can be found in many organs such as heart, liver, lung, kidney, and pancreas etc (Leppik, 1992).

Though there are lots of antiepileptic drugs launched in the market, none possesses the ideal properties. Therefore, it is reasonable to search for new types of chemicals that are suitable as the ideal anticonvulsants.

In the past two decades, several more rational approaches have been developed that may provide a higher yield of more effective and more targeted drugs for epilepsy (Porter, 1990 a). A large number of promising compounds are currently undergoing preclinical and clinical evaluation (Martin and Tegeler, 1988; Hrib and Martin, 1989), and several of these will undoubtedly become meaningful additions to the neurologist's pharmacological armamentarium. The antiepileptic drugs under devlopmental stage can be classified according to presumed mechanism of action into 4 groups, as followed.

A. Drugs whose anticonvulsant profile is similar to phenytoin (Rogawski and Porter, 1990).

Like phenytion, these drugs can protect against maximal electroshock seizures but fail to affect clonic seizures induced by pentylenetetrazol. The proposed mechanism of anticonvulsant action is that the drugs can decrease neuronal excitability secondarily to blocking Na^+ or Ca^{2+} channels. The samples of drugs in this group are zonisamide (XI) (Peters and Sorkin, 1993), denzimol (XII), nafimidone (XIII), CGS 18416A (XIV), lamotrigine (XV) (Goa et al., 1993), ralitoline (XVI), topiramate (XVII), flunarizine (XVIII), and oxcarbazepine (XIX) (figure 3).

B. Drugs that act by enhancing GABA-mediated inhibition.

GABA is the most comprehensively studied inhibitory neurotransmitter in the CNS (Robert, 1974). It is involved in the central regulation of a variety of physiological processes. Furthermore, it appears to play a role in the pathophysiology of epilepsy (Krogsgaard-Larsen et al., 1983). Impairment of GABA-mediated inhibition can induced either focal or generalized seizures. This is seen with compounds blocking the synthesis of GABA (i.e. glutamic acid decarboxylase inhibitors such as isoniazid and 4-deoxypyridoxine) and with compounds blocking its postsynaptic action. The reviews about GABA agonists and antagonists including a summary knowledge about the GABA receptors have been discussed by Krogsgaard-Larsen and Christensen (1980); and also Krogsgaard-Larsen (1981).

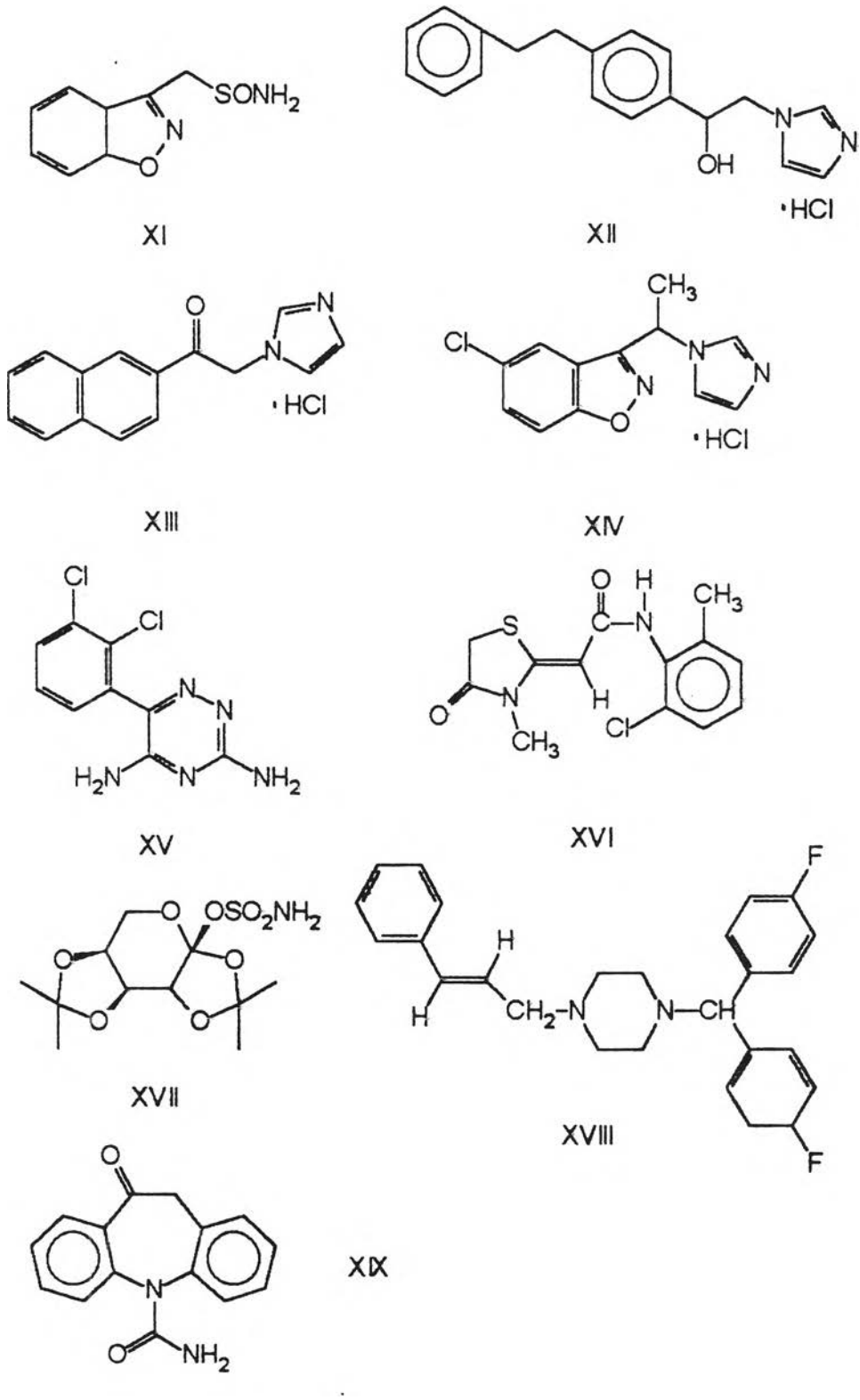


Figure 3. The chemical structures of drugs that have anticonvulsant profile like phenytoin.

The biosynthesis of GABA occurs only in the neurons, since it cannot penetrate the blood-brain barrier, and no peripheral precursor is known. γ -Aminobutyric acid is formed by the decarboxylation of L-glutamate, catalyzed by glutamic acid decarboxylase (GAD). This reaction is irreversible. The cofactor of GAD is pyridoxal phosphate (vitamin B_6). Since GAD is the rate-determining enzyme, GABA metabolism can be regulated by the manipulation of this enzyme, the manipulation of pyridoxal, or both. GABA can be deactivated and recycled by the transamination reaction with α-ketoglularate to yield glutamate. This transamination is catalyzed by the enzyme GABA transaminase (GABA-T), which is widely distributed. Therefore, free GABA cannot be found anywhere except in the brain. The transaminase enzyme also depends on pyridoxal phosphate as a cofactor. (See figure 4).

The neuronal activity of GABA shows two different inhibitory mechanisms. The first is the partial (presynaptic) depolarization of an excitatory neuron, which causes a decrease in neurotransmitter release when this neuron receives an electrical impulse. The second mechanism is the conventional hyperpolarization of an excitatory neuron by increase Cl^- ion flux, which makes the neuron unable to fire when it receives a normal impulse (Nogrady, 1988).

The approach to the design of novel anticonvulsant drugs arose in the 1970s as a result of increasing awareness of the role of intrinsic GABAergic inhibitory circuit in preventing the spread of seizure discharges. The mechanisms and chemicals that enhance GABA-mediated inhibition are described as below (Meldrum, 1992). (See also figure 5.)

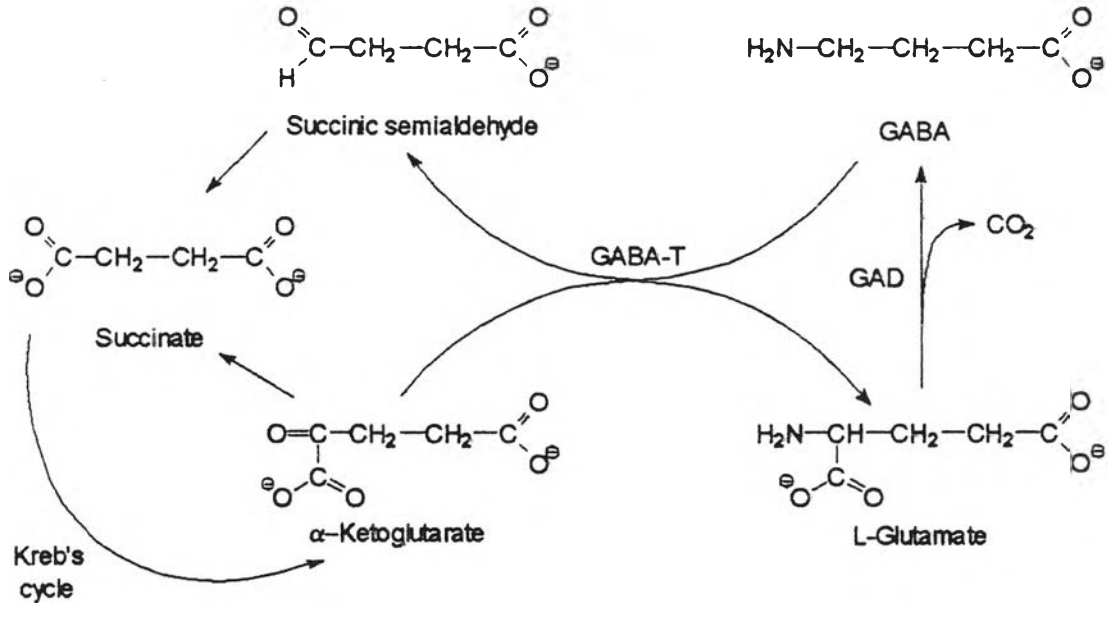


Figure 4. γ-Aminobutyric acid (GABA) metabolism.

1. GABA, GABA agonists, and GABA prodrugs.

e.g. liposome-entrapped GABA, muscimol (XX), THIP (gaboxadol) (XXI), cetyl GABA, pivaloyl GABA, benzoyl GABA, C-18 glyceryl lipid esters of GABA (Jacob et al.,1987), progabide (XXII) (Kaplan and Raizon, 1980; Wick et al., 1985), and SL 75102 (XXIII) (Kaplan and Raizon, 1980).

2. Enhanced GABA synthesis and/or synaptic release.

e.g. baclofen (XXIV), vigabatrin (γ-vinyl-GABA, and DL-4-aminohex-5-enoic acid) (XXV) (Grant and Heel, 1991).

3. GABA-transaminase inhibition.

e.g. L-cycloserine, ethanolamine-O-sulfate, γ-acetylenic GABA (XXVI), vigabatrin (XXV), gabaculine (XXVII), and stiripentol (XXVIII). Fore more details, the review about mechanistic classification of GABA aminotransferase inactivators is reported by Nanavati and Silverman (1989).

4. GABA uptake inhibition.

e.g. nipecotic acid (XXIX), THPO (XXX), SKF 100330A (1-(4,4-diphenyl-3-butenyl)-1,2,5,6-tetrahydro-3-pyridine carboxylic acid hydrochloride) (XXXI), stiripentol (XXVIII), CI-966 (XXXII), NNC-711 (XXXIII) (Suzdak et al., 1992), and tiagabine ((R)-1-(4,4-bis(3-methyl-2-thienyl)-3-butenyl)-3-piperidine carboxylic acid hydrochloride) (XXXIV).

5. Action at GABA/Benzodiazepine allosteric site.

e.g. 1,4-benzodiazepines (e.g. clonazepam (XXXV)), 1,5-benzodiazepines (e.g. clobazam (XXXVI)), flumazenil (XXXVII),

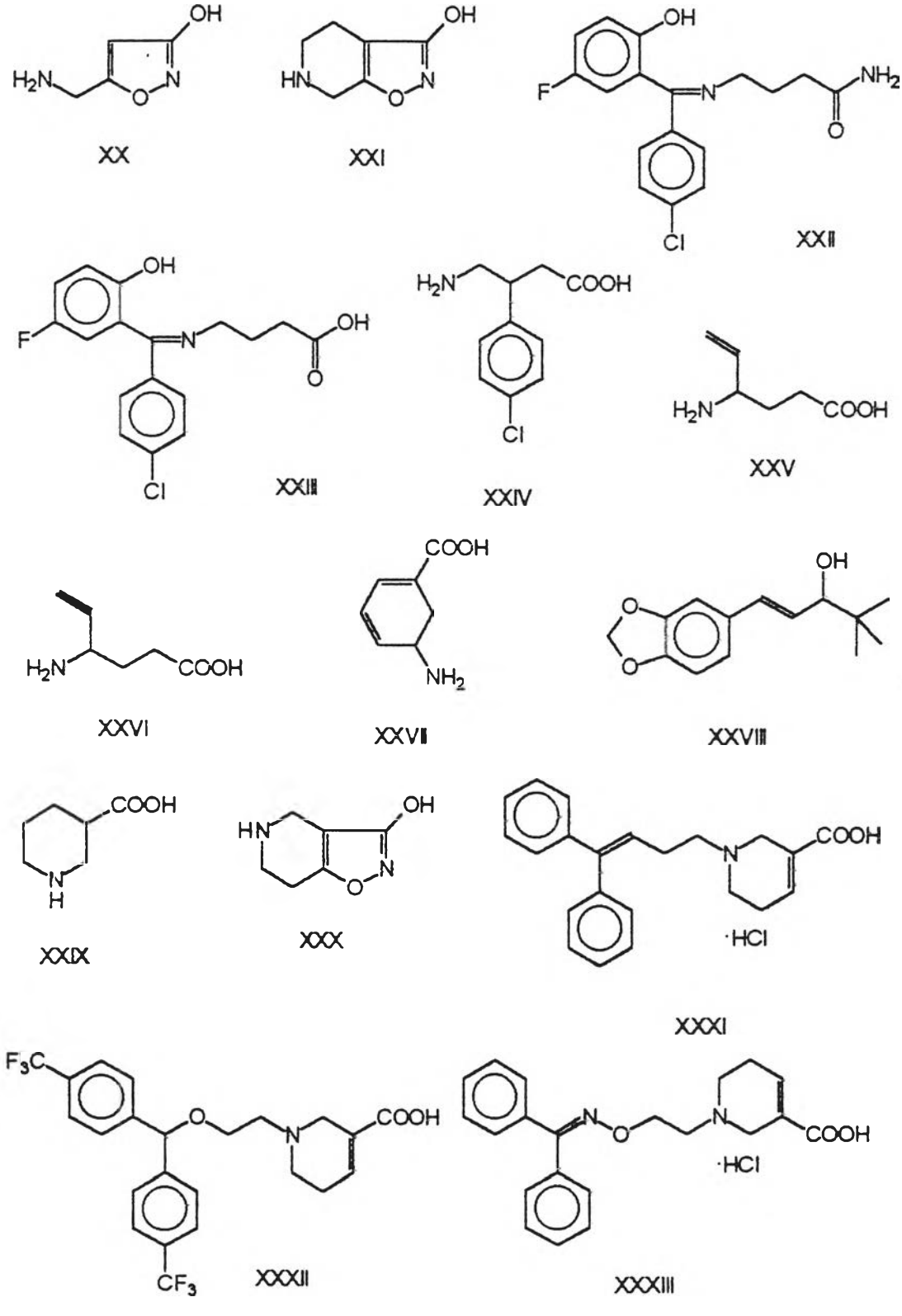


Figure 5. The chemical structures of drugs that enhance GABA-mediated inhibition.

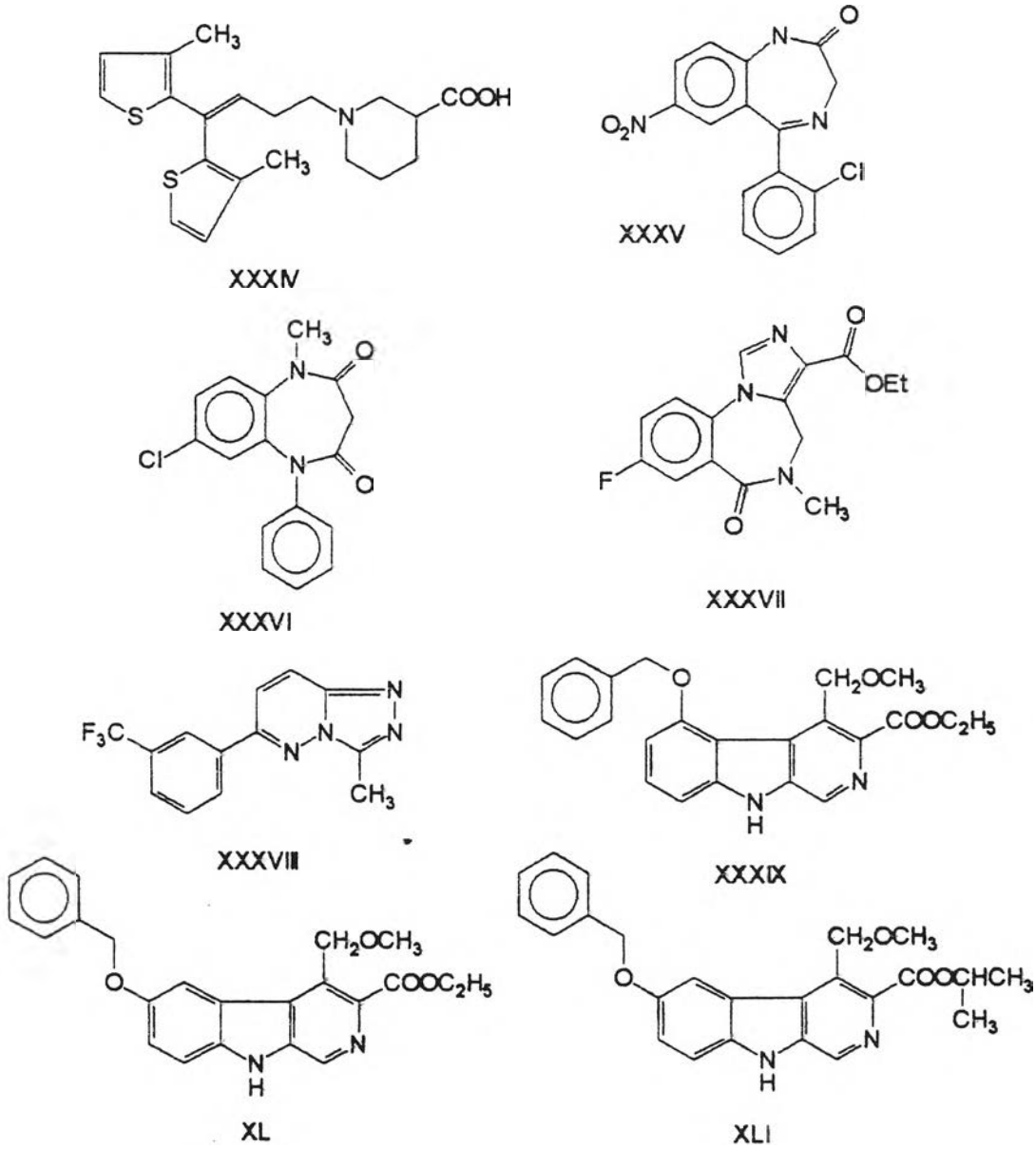


Figure 5 (continued). The chemical structures of drugs that enhance GABA-mediated inhibition.

triazolopyridazines (e.g. Cl 218-872 (XXXVIII)), and β-carbolines (e.g. ZK 91296 (XXXIX), ZK 93423 (XL), and ZK 112119 (abecarnil) (XLI)).

6. Action at Chloride ionophore/ picrotoxinin/ barbiturate site.
   e.g. barbiturates.

C. Drugs that decrease excitatory amino acid transmission.

Recent advances in the physiology and pharmacology of excitatory amino acid transmitter systems have highlighted the potential of excitatory amino acid receptors as a target for anticonvulsant drugs (Lehmann et al., 1987; Johnson, 1989; Johnson and Bigge, 1991). The amino acids, glutamate and aspartate, have long been known to excite neurons and cause convulsive activity when applied to the cerebral cortex. It has been possible to classify excitatory amino acid receptors into three subtypes, identified by the agonists that selectively activate them : quisqualate [now more properly referred to by the more specific agonist AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid)], kainate, and NMDA. It is now apparent that the NMDA receptor plays a critical role in many types of seizures, and there is a growing body of data that implicates NMDA receptors in the development of some forms of epilepsy (Rogawski , 1992).

Thus, pharmacological agents diminishing excitatory transmission may possess antiepileptic properties. Possible pharmacological approaches to decrease excitatory transmission are delineated as below (Meldrum, 1992). (For chemical structures of drugs in this group, see figure 6.)

1. Inhibition of glutaminase.

   e.g. azaserine, DON.

2. Presynaptic effects on release.

   e.g. - adenosine (A1) receptor activators : 2-chloro adenosine, cyclohexyladenosine, and phenylisopropyladenosine.

   - $GABA_B$ agonists : baclofen.

   - benzodiazepines.

3. Postsynaptic antagonists.

   a. non-selective antagonists.

   b. NMDA antagonists.

   1. competitive NMDA recognition site antagonist : APV (XLII), APH (XLIII), CPP (XLIV), CPP-ene (XLV), CGP 37849 (XLVI), CGP 39551 (XLVII), CGS 19755 (XLVIII), and NPC 12626 (XLIX).

   2. noncompetitive NMDA recognition site antagonists : phencyclidine (L), ketamine (LI), MK-801 (LII), and dextromethorphan (LIII).

   3. glycine antagonists : HA 966 (LIV), 7-chloro- kynurenic acid (LV), and 5,7-dichlorokynurenic acid (LVI).

   4. polyamine site antagonists : ifenprodil (LVII).

   c. non-NMDA (kainate, quisqualate) antagonists : DNQX (LVIII), and CNQX (LIX).

4. Enhancing glutamate reuptake.

5. Long term down regulation of receptors.

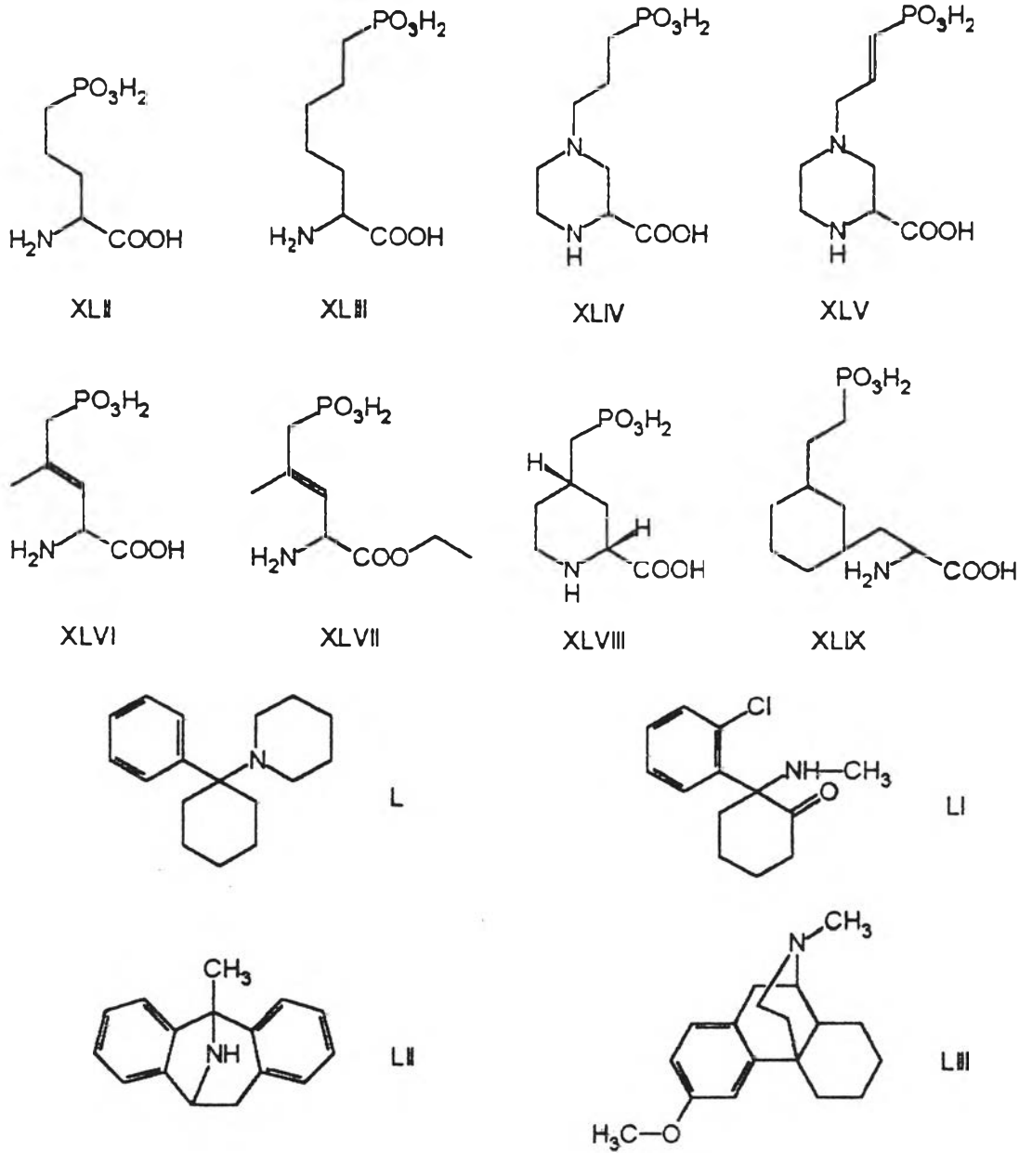


Figure 6. The chemical structures of drugs that diminish excitatory amino acid transmission.

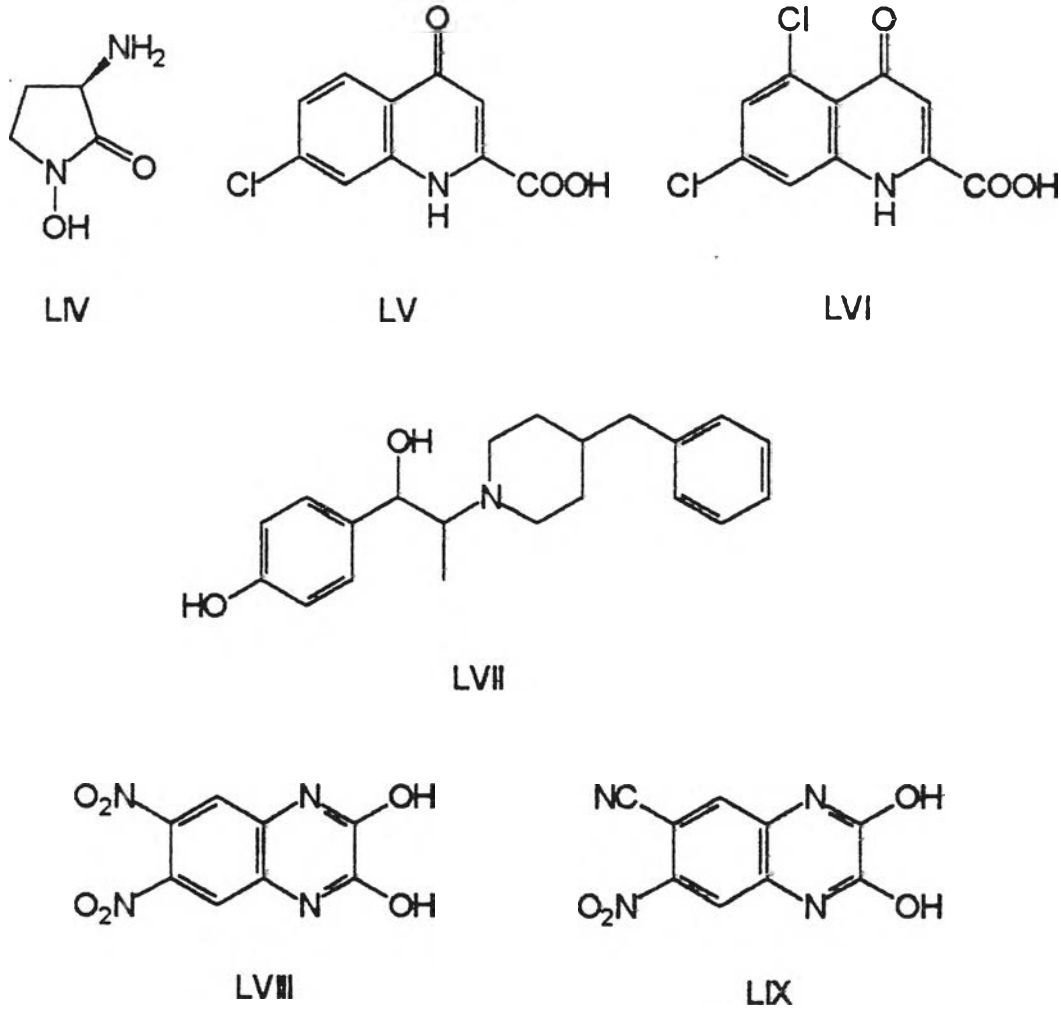


Figure 6 (continued). The chemical structures of drugs that diminish excitatory amino acid transmission.

D. Drugs with a novel spectrum of anticonvulsant activity.

Although much of the available literature pertains to either the facilitation of inhibitory GABAergic systems or the inhibition of excitatory amino acid neurotransmission, anticonvulsant activity can be mediated by many mechanisms. Nowaday, there are many drugs possessing a novel spectrum of anticonvulsant activity (Brodie and Porter,1990). The samples of these drugs are felbamate (LX), gabapentin (LXI), U-54494A (LXII), D-19274 (LXIII), AHR-12245 (LXIV), and ameltolide (LY 201116) (LXV). (See figure 7.) However, the mechanisms of action of the mentioned drugs were still obscured.

Design of a new analogue of ameltolide.

Among novel anticonvulsants under preclinical and clinical trials, the 4-aminobenzamides are an interesting chemically novel series of potential antiepileptic drugs. One of the most potent drugs in this series is ameltolide (4-Amino-N-(2,6-dimethylphenyl)benzamide, or LY201116). This compound is a selective anticonvulsant in the maximal electric shock test in mice. There is a great interest that the ED_{50} values of this compound is much smaller than any other anticonvulsants used at present. In addition, it is expected to possess the same mechanism of action by blocking sodium conductance channels as phenytoin and carbamazepine. Thus, due to its high potency, this drug and its analogues may be used as a model in investigating the pharmacophore that can interact with the sodium channels in the molecular level.

The 4-aminobenzamides have spawned several interesting antiepileptic drug candidates. Extensive structure-activity studies have been carried out by

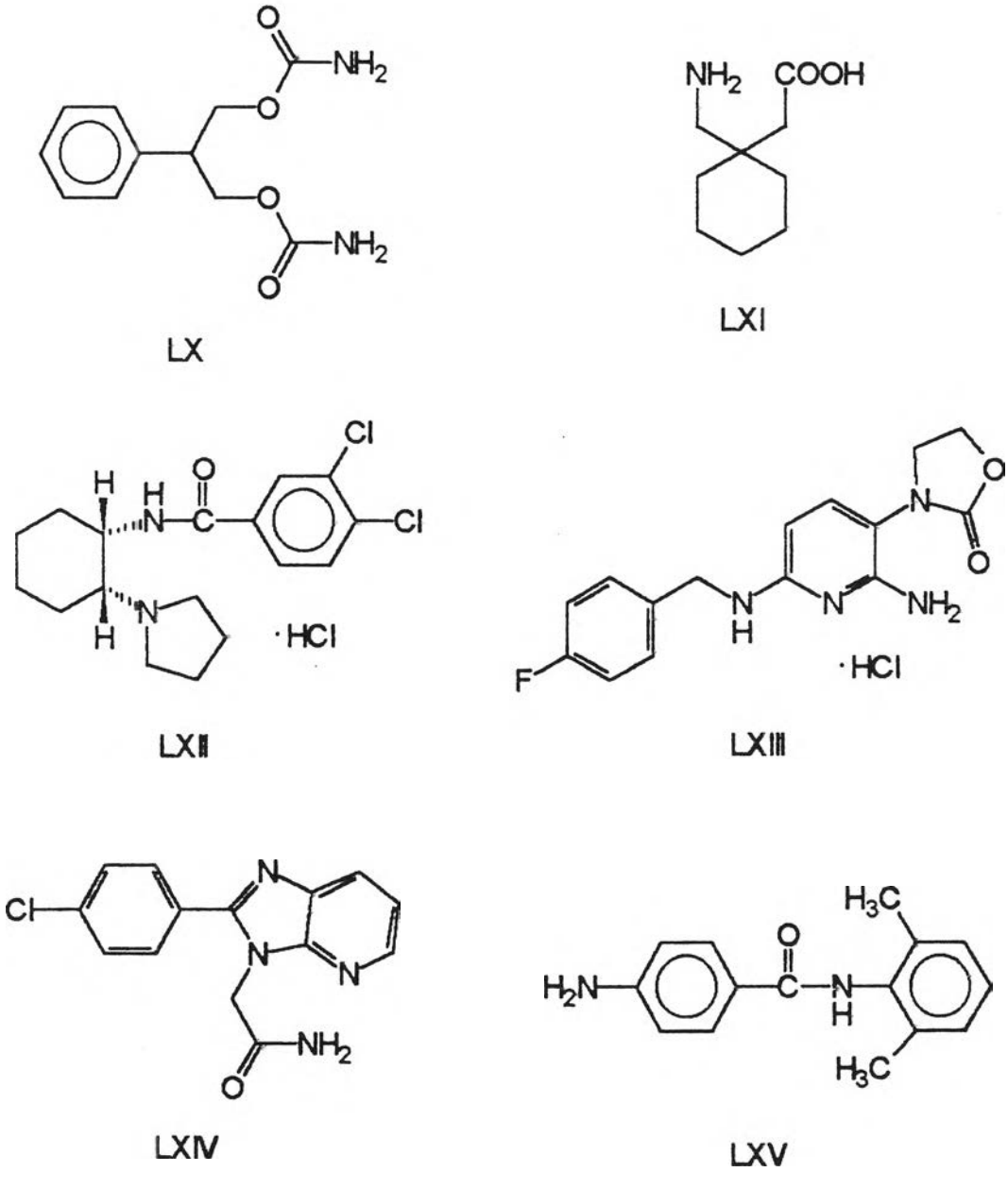


Figure 7. The chemical structures of drugs with a novel spectrum of anticonvulsant activity.

Clark and his collaborators on the anticonvulsant 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-(1-phenylethyl)benzamide (LXVI, figure 8), is a potent maximal electroshock (MES) selective anticonvulsant in mice and rats (Clark and Davenport, 1987), but untoward toxicological findings precluded development of this compound or either of its enantiomers (Robertson, 1991). Ameltolide, 4-Amino-N-(2,6-dimethylphenyl) benzamide or LY201116 (XLV), is the most potent benzamide anticonvulsant 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 clinical studies are in progress. Recent studies have revealed that ameltolide is inactivated by metabolism to the N-acetyl analogue, 4-(Acetylamino)-N-(2,6-dimethylphenyl) benzamide, but this metabolic pathway appears to be reversible in a variety of species. Moreover, further biotransformation studies in rats unveiled that hydroxylation of N-acetyl metabolite occurred in addition to metabolic N-acetylation (Parli et al., 1987; Potts et al., 1989). One expected position for hydroxylation would be on the two aromatic methyl substituents (LXVII), a well-precedented metabolic pathway (Testa and Jenner, 1976). Pharmacological studies demonstrated that hydroxylation of one of the methyl substituents leads to a substantial decline in the potency of ameltolide as an anticonvulsant in mice (Robertson, 1991).

Structure-activity relationship (SAR) studies on the benzamide framework reveal that the addition of two *o*-methyl groups (XLV) yields an even more MES-potent anticonvulsant than the unsubstituted 4-amino-N-

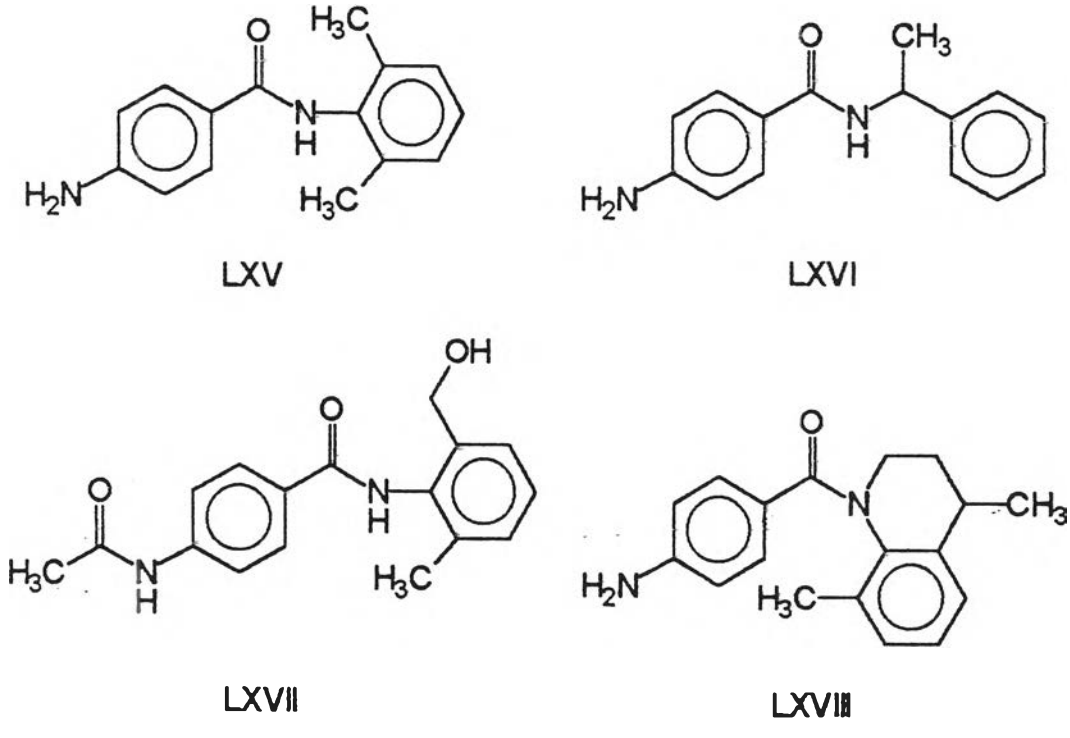


Figure 8. The chemical structures of 4-aminobenzamide derivatives.

phenylbenzamide. The superior activity of ameltolide (XLV) is not simply a result of two methyl substituents being present, but is closely related to the positions of these groups on the phenyl ring. As a result, the conformation restricted by the two *o*-methyl groups should plays an important role in determining the activeness of the compound (Duke and Codding, 1992).

In this research, a new analogue of ameltolide was designed to improve the potential as anticonvulsant. First, the parent ameltolide could be converted to a drug with a longer duration of action by protecting it from metabolic attack. A vulnerable group in a parent drug can be sterically hindered to a metabolic process by introduction of alkyl groups in its vicinity (Smith, 1988). Therefore, replacing one of the *o*-methyl groups (primary carbon) on the phenyl ring by a branched alkyl group (tertiary carbon) should increase the steric hindrance at this position and protect this vulnerable group from the attacking metabolizing enzyme.

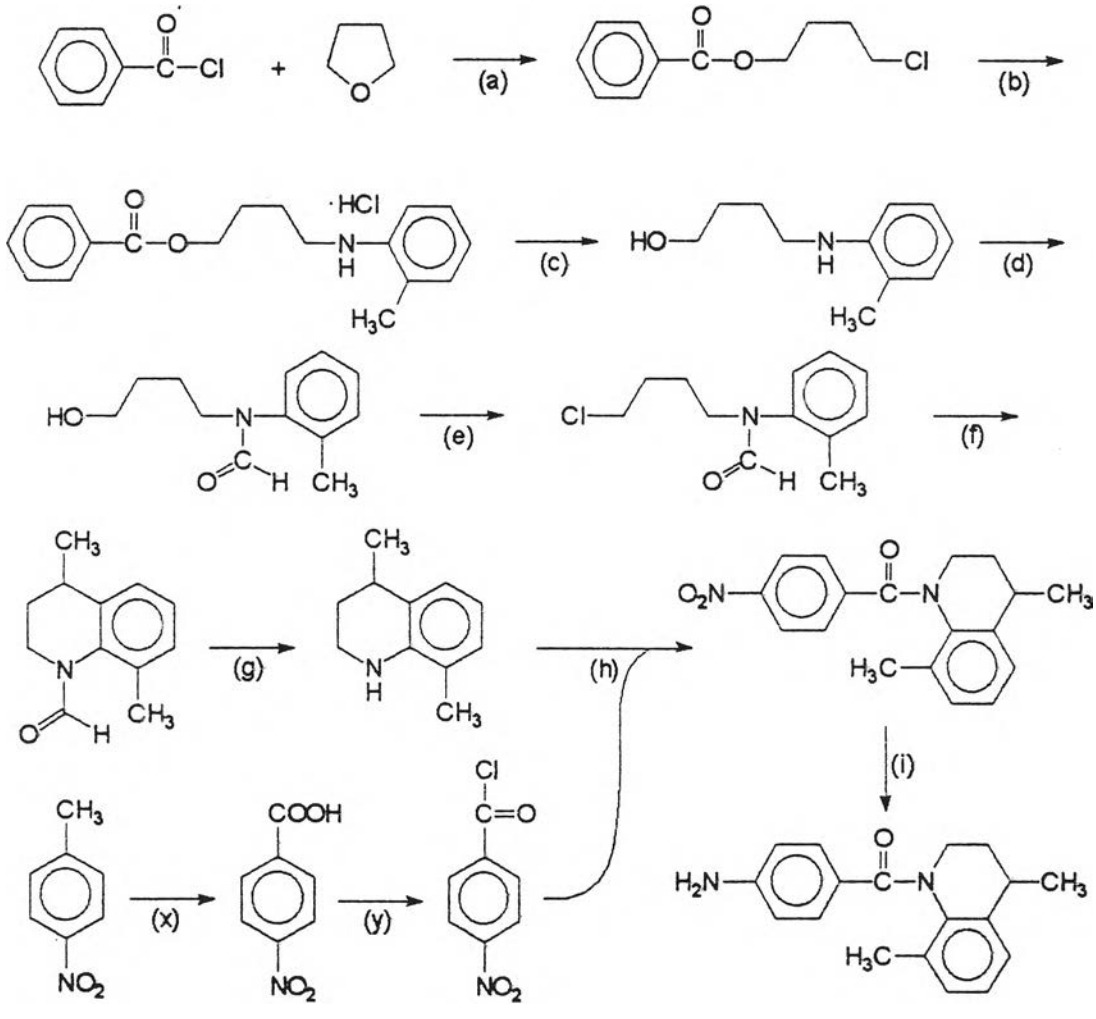
Second, linking the *o*-position of the phenyl ring with nitrogen of the amide bond by the alkyl chain can yield a rigid analogue. This rigid compound will prevent the rotation around the nitrogen-phenyl single bond ,which could occurred in the parent compound. Such rigid structure can assist in studying the conformation of compounds in this class that will fit with the receptor.

Finally, antiepileptic drugs traditionally act directly on the brain, after crossing the blood-brain barrier (BBB). The penetration of drugs across the BBB is dependent on the physicochemical characteristics of their molecules including lipid solubility (Pop et al., 1991). The alkyl chain added to the parent molecule may increase the lipophilicity; thus, it is expected that the designed

molecule will have better ability to penetrate into brain.

This research was aimed to synthesize N-(*p*-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline (LXVIII).

The synthetic approach of N-(*p*-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline is shown in figure 9.



(a) $ZnCl_2$, reflux; (b) *o*-toluidine, in sealed tube, 125°-130°c, 6 hrs; (c) aqueous NaOH-ethanol, reflux, 3hrs; (d) HCOOH, reflux, 3 hrs; (e) $SOCl_2$, 40°-50°c, 3 hrs; (f) $AlCl_3$, CS_2; (g) aqueous NaOH-ethanol, reflux, 3 hrs; (h) K_2CO_3, benzene, reflux, 12 hrs; (i) H_2, Pd/C, Parr apparatus, 3 hrs; (x) $Na_2Cr_2O_7$, H_2SO_4, heat; (y) PCl_5, heat.

Figure 9. The synthetic approach of N-(*p*-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline.