CHAPTER I

INTRODUCTION

The term epilepsy is a collective designation for a group of central nervous system (CNS) disorders having in common the repeated occurence of sudden and transitory episodes seizures) of abnormal phenomena of motor (convulsion), sensory, autonomic, or psychic origin. The seizures are nearly always correlated with abnormal and excessive discharges in the brain, which can be recorded on an electroencephalogram(EEG)(Rall and Schleifer, 1990).

Most estimation on the prevalence of epilepsy falls within the narrow range of between three and six cases/1,000 population. However, much lower(1.5/1,000) or higher(15-30/1,000) prevalence figures have been reported also (Chan, 1992). The disease is more common in children than in adults (Rall and Schleifer, 1990).

The International League Against Epilepsy(ILAE), through its Commission on Classification and Terminology, adopted an International classification of epileptic seizures (ICES) in 1981. The classification is based on clinical manifestation together with ictal and interictal EEGs. They are divided into 3 groups, namely partial

seizures, generalized seizures, and unclassified seizures.

Partial seizures have clinical or EEG evidence of a local onset. The abnormal discharge usually arises in a portion of one hemisphere and may spread to other parts of the brain during a seizure. Partial seizures are subdivided into 3 types:(a)simple partial seizures, (b) complex partial seizures and (C) partial seizures leading secondarily to generalized seizures.

Generalized seizures have no evidence of localized onset, the clinical manifestations and abnormal electrical discharge give no clue to the locus of onset of the abnormality. Generalized seizures are subdivided into 6 types:(a) absence seizures, (b) atypical absence seizures, (c) clonic seizures, (d) tonic seizures, (e) tonic-clonic seizures (grand mal), and (f) atonic seizures (Chan,1992).

The cellular mechanisms which underline epileptic seizures are at present not fully understood. Because of the diversity of seizure types, there are likely to be more than one neurophysiological and biochemical mechanism for seizure disorders(Chan, 1992;Palmer and McTavish,1993).

However, it has been shown that convulsions arise when there is an imbalance in two principal neurotransmitters in the brain ; L-glutamic acid, an

excitatory neurotransmitter, and gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. The concentration of these two amino acids are regulated by two pyridoxal 5'-phosphate-dependent enzymes; L-glutamic acid decarboxylase, which converts glutamate to GABA and GABA aminotransferase, which degrades GABA to succinic semialdehyde. When the concentration of GABA diminishes below a threshold level in the brain, convulsion begins.

Symptomatic epilepsy can result from brain tumors, syphilis, cerebral arteriosclerosis, multiple sclerosis, Buerger's disease, Pick's disease, Alzheimer's disease, sunstroke or heat stroke, acute intoxication, lead poisoning, head trauma, vitamin B_6-deficiency, hypoglycemia and labor (Nanavati and Silverman, 1989).

Recent research has implicated excitatory amino acids, such as L-glutamate, in the aetiology of epilepsy. These amino acids are the main neurotransmitters involved in mediating synaptic excitatory in the CNS. There are 5 specific receptors to which excitatory amino acids bind: N-methyl-D-aspartate (NMDA), quisqualate (AMPA), kainate, L-APA, and metabotropic receptors. At present it is the NMDA and AMPA receptors which are believed to be important in the initiation and propagation of seizures (Palmer and McTavish, 1993).

Nowaday, many drugs have been used to control seizures in epileptic patients. They belong to several chemical ,structural types which are barbiturates(I), hydantoins(II), oxazolidine-2,4-diones (III), succinimides (IV), benzodiazepines (V), acylureas (VI), amides (VII), sulfonamides (VIII), dibenzazepines (IX), and valproic acid (X)(Figure 1) (Mercier, 1973).

The ideal antiepileptic drugs would obviously suppress all seizures without causing any unwanted effects. Unfortunately, the drugs used currently not only fail to control seizure activity in some patients, but they frequently cause side effects that range in severity from minimal impairments of the CNS to death from aplastic anemia or hepatic failure. There is still a demand for new antiepileptic drugs with more selective anticonvulsant effects and less toxicity.

A large number of promising drugs are currently preclinical and clinical evaluated , and several of these will undoubtedly become meaningful additions to the neurologist's pharmacological armamentarium. These drugs are organized according to presumed mechanism of action as described below.

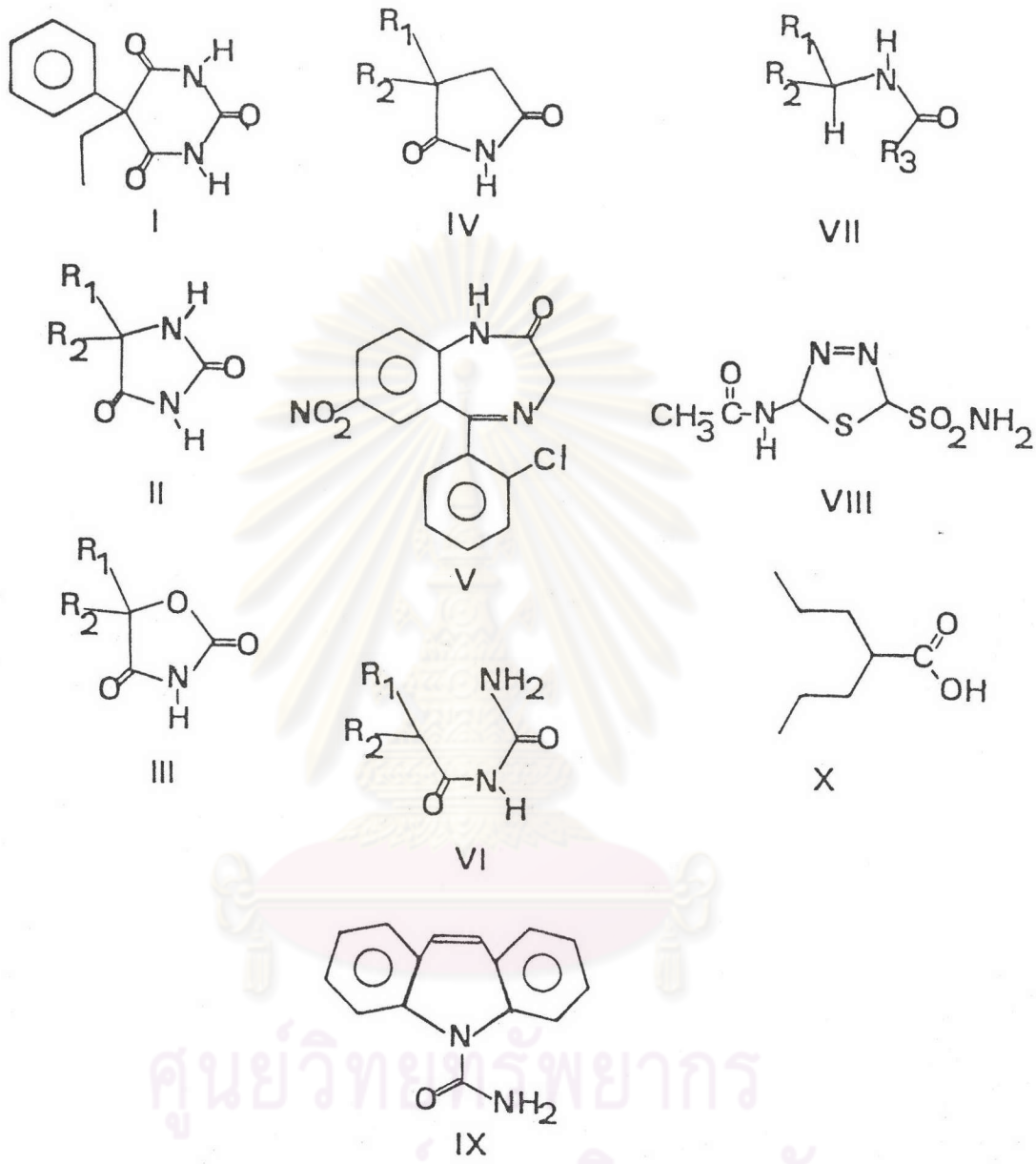


Figure 1. The chemical structures of some types of anticonvulsant agents

A. Drugs whose anticonvulsant profile are similar to phenytoin.

Examples of such compounds include Zonizamide (XI), Denzimol(XII), Nafimidone(XIII), CGS 18416A(XIV), Lamotrizine (XV) , Ralitoline (XVI) , Topiramate(XVII), Flunarizine (XVIII), and Oxacarbarzepine (XIX) (Figure 2) (Rogawski and Porter, 1990).

Topiramate , a sulfamate substituted monosaccharide is structurally distinct from other anticonvulsant drugs. The compound has a reasonably high potency in the maximal electroshock test but is negatively less toxic. Because of the structural complexity of Topiramate, its "half-structures" derivatives had been synthesized, such as McN-5762(XX). This compound also showed significant activity. The SAR required for anticonvulsant activity of these sulfamate derivatives are an lipophilic attachment. Since the sulfamate functionality appears to be important for anticonvulsant activity, and since there are anticonvulsant sulfonamides, such as acetazolamide (VIII) which inhibit the enzyme carbonic anhydrase (CA), these sulfamate derivatives were also tested for their ability to inhibit carbonic anhydrase. The results demonstrate that Topiramate is a relatively weak inhibitor of erythrocyte CA , while McN-5762 is a moderately potent inhibitor (Maryanoff et al., 1987).

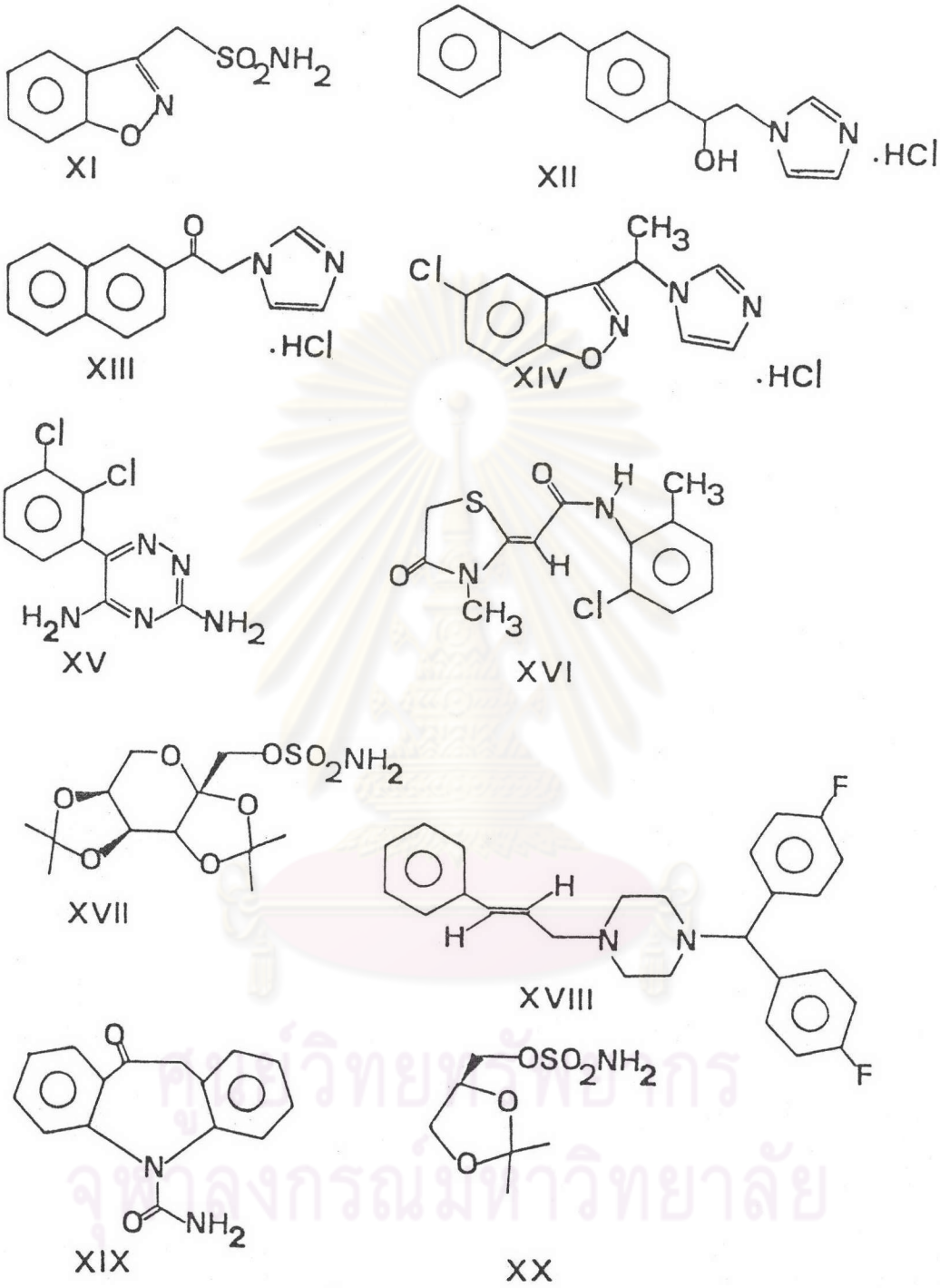


Figure 2. The chemical structures of drugs whose anticonvulsant profile is similar to phenytoin.

Since the only well-documented biochemical effect of acetazolamide is inhibition of CA , it has been demonstrated that the mechanism of its anticonvulsant action (as well as the other sulfonamide CA inhibitors) is through inhibition of this enzyme in the brain. The consequence of inhibition of brain CA is carbon dioxide accumulation, which appears to cause the anticonvulsant effect of this drug (Woodbury, 1980).

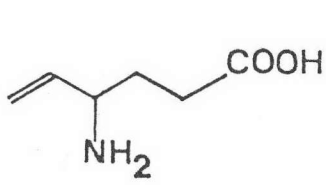
B. Drugs which enhance GABA-mediated inhibition in CNS.

It has been shown that convulsions arise when there is an imbalance in two principal neurotransmitters in the brain ; L-glutamic acid , an excitatory neurotransmitter and GABA, an inhibitory neurotransmitter. When the concentration of GABA diminishes below a threshold level in the brain,the convulsions begin. Since L-glutamic acid is converted to GABA by L-glutamic acid decarboxylase (GAD) and GABA is then degraded to succinic semialdehyde by GABA aminotransferase (GABA-T), the brain GABA concentration can be increased by drugs that inactivate GABA-T. These compounds are for example , Vigabatrin (XXI), and Stiripentol (XXII). Vigabatrin is a specific, enzyme-activated inhibitor of the GABA catabolic enzyme ,GABA-T. The drug becomes covalently linked to GABA-T at its active site and thereby causes an irreversible inhibition of the enzyme. Another approach

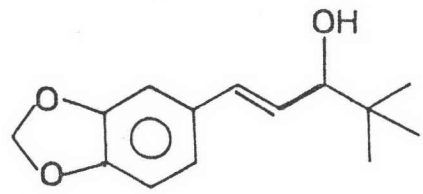
for increasing the brain GABA concentration is to use drugs that act as agonist of the GABA receptor-Cl-channel complex, such as Progabide(XXIII), and SL-75102 (XXIV) (Figure 3). Both compounds are highly specific for the GABA receptor system and do not significantly influence GABA synthesis , metabolism and uptake (Nanavati and Silverman, 1989;Rogawski and Porter, 1990).

C. Drugs that block excitatory amino acid receptors.

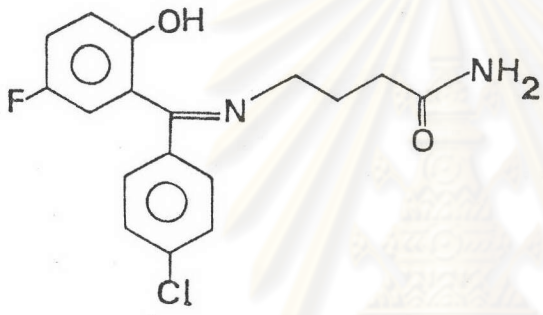
Recent advances in the physiology and pharmacology of excitatory amino acid transmitter systems have highlighted the potential of excitatory amino acid receptors as a target for anticonvulsant drugs. The amino acids glutamate and aspartate have long been known to excite neurons and cause convulsive activity when applied to the cerebral cortex. It has been possible to classify excitatory amino acid receptors , using these pharmacological tools, into three subtypes, identified by the agonists that selectively activate them: quisqualate, kainate and NMDA.It is now apparent that the NMDA receptor plays a critical role in many types of seizures. Observations suggested that antagonists of the NMDA receptor could have potential utility in treatment of epilepsy. Drugs antagonising NMDA receptors can be classified into 2 types :(a) competitive antagonists, eg.



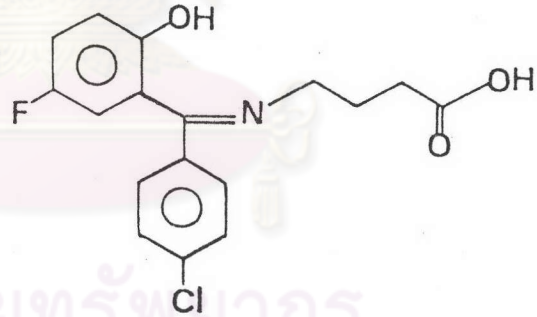
XXI



XXII



XXIII



XXIV

Figure 3. The chemical structures of drugs which enhance GABA-mediated inhibition in CNS.

APV(XXV) , CGS37849 (XXVI) , CPP(XXVII) , and NPC 12626 (XXVIII) , and (b) noncompetitive antagonists , eg. Phencyclidine (XXIX) , ketamine (XXX), and MK-801 (XXXI) (Figure 4).

D. Drugs with a novel spectrum of anticonvulsant activity.

Examples of such compounds include Felbamate (XXXII), LY201116 (XXXIII), and D-19274(XXXIV) (Figure 5).

Another approach for developing drugs is the design of prodrugs. The term prodrug refers to a pharmacologically inactive compound that is converted to an active drug either by a metabolic biotransformation or a nonenzymatic process. Design of prodrugs has been utilized to overcome many problems of drugs such as solubility, absorption and distribution, instability, toxicity or duration of actions (Silverman, 1992).

Valproic acid is one of the most widely used anticonvulsant drugs since it has a broad spectrum of anticonvulsant activity. Additionally it is well tolerated in man and toxic side effects are rare in clinical practice. However since valproic acid is an organic acid, it can cause gastric irritation if it is orally administered. To overcome such undesired effect, valproic

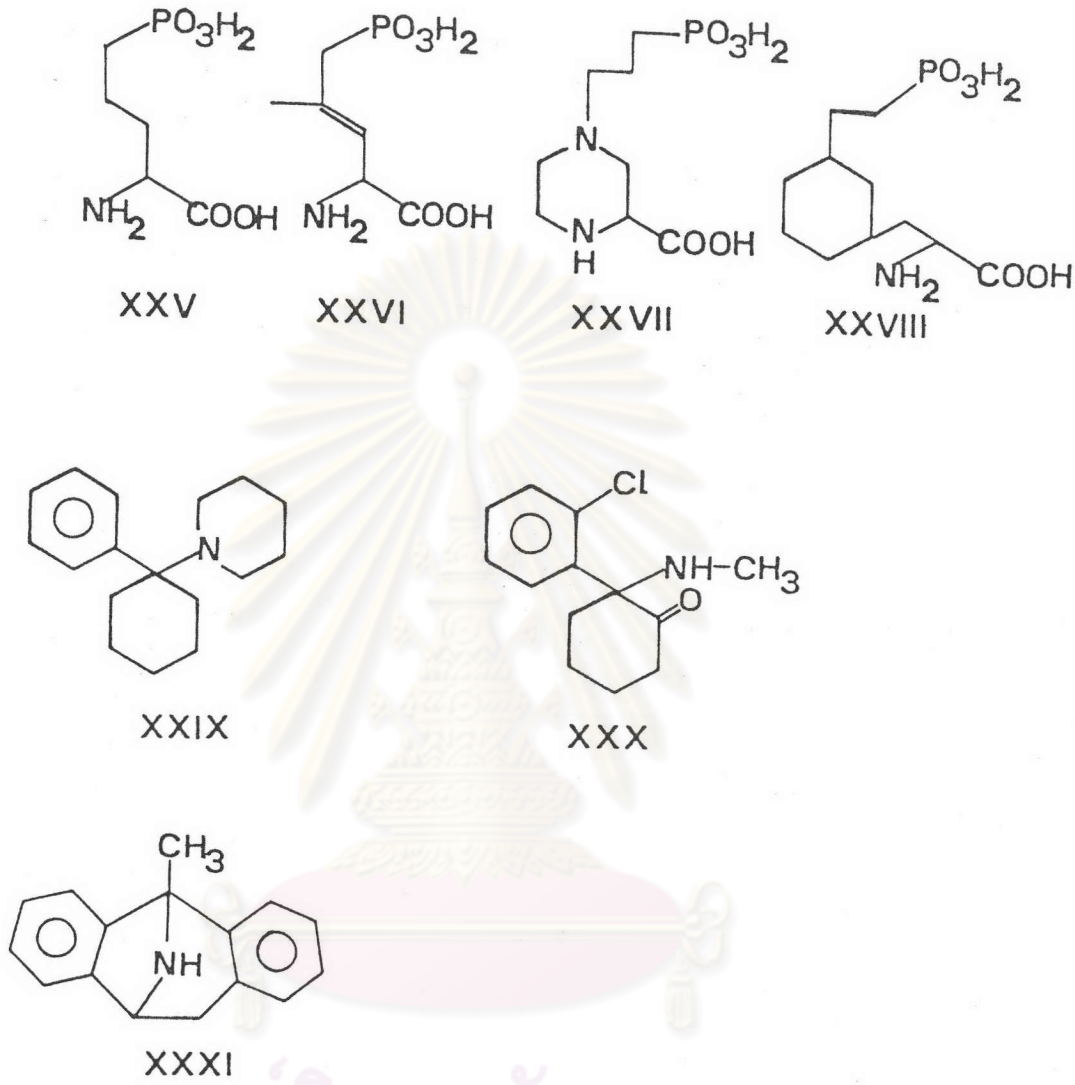


Figure 4. The chemical structures of drugs that block excitatory amino acid receptors.

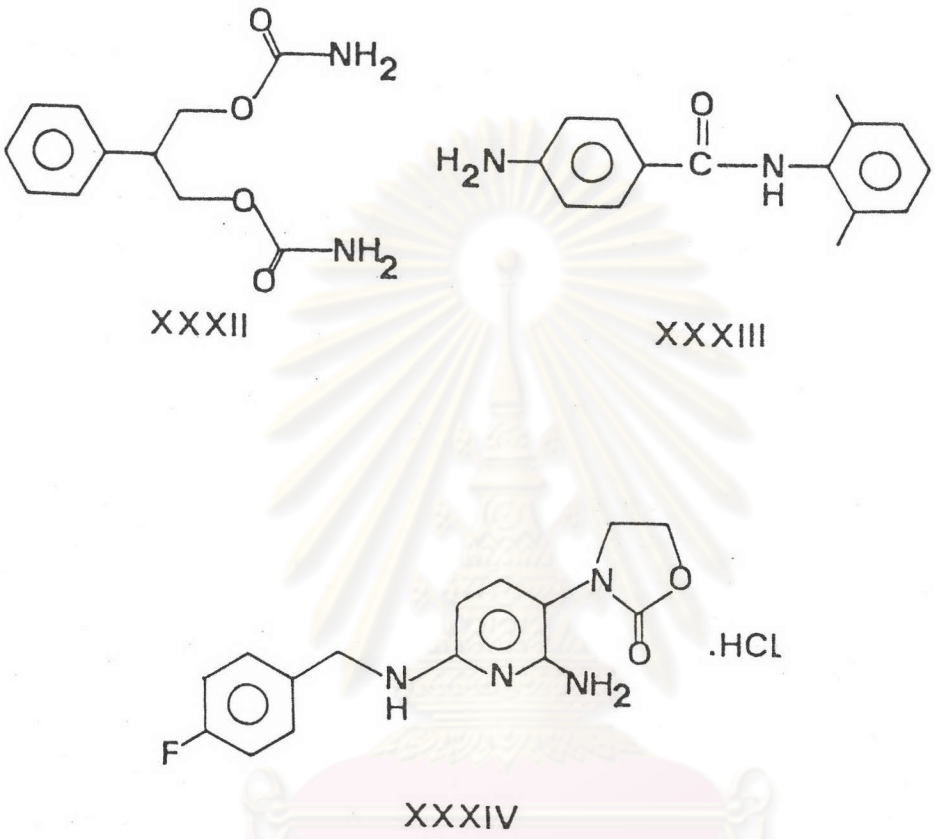


Figure 5. The chemical structures of drugs with a novel spectrum of anticonvulsant activity

acid can be prepared in prodrug form. If 2-propylpentanoic acid (valproic acid) is prepared in the form of 2-propylpentanal , it can possibly be designed in many prodrug forms such as Schiff base , oximes , acetals, oxazolidines and thiazolidine (Figure 6) (Silverman, 1992).

There had been an investigation indicating that 2-propylpentanal acetals (XXXV-XXXVII) (Figure 7) were metabolically converted to valproic acid. Proposed pathway for the enzymatic oxidation of 2-propylpentanal diethylacetal (XXXVI) is shown in Figure 8 (Vicchio and Callery, 1989).

Since aliphatic acetals are structurally resemble to cyclic acetals, prodrug of valproic acid in cyclic acetal form such as [2-(1-propylbutyl)-1,3-dioxolan-4-yl]methanol (XXXVIII) (Figure 9) may also be candidate substrate for similar oxidation reaction (Vicchio and Callery, 1989). Moreover, this would be benificial to its anticonvulsant activity since there had been an investigation indicating that compounds of 2-substituted-4 -hydroxymethyl-1,3-dioxolane (XXXIX) (Figure 9) possessing muscle relaxant activity when large doses were administered. Small doses, such compounds protected animals from the effect of lethal doses of strychnine and metrazol (pentylenetetrazol). The paralizing action appeared to be optimum if a total of 6-8 carbons was attached at position

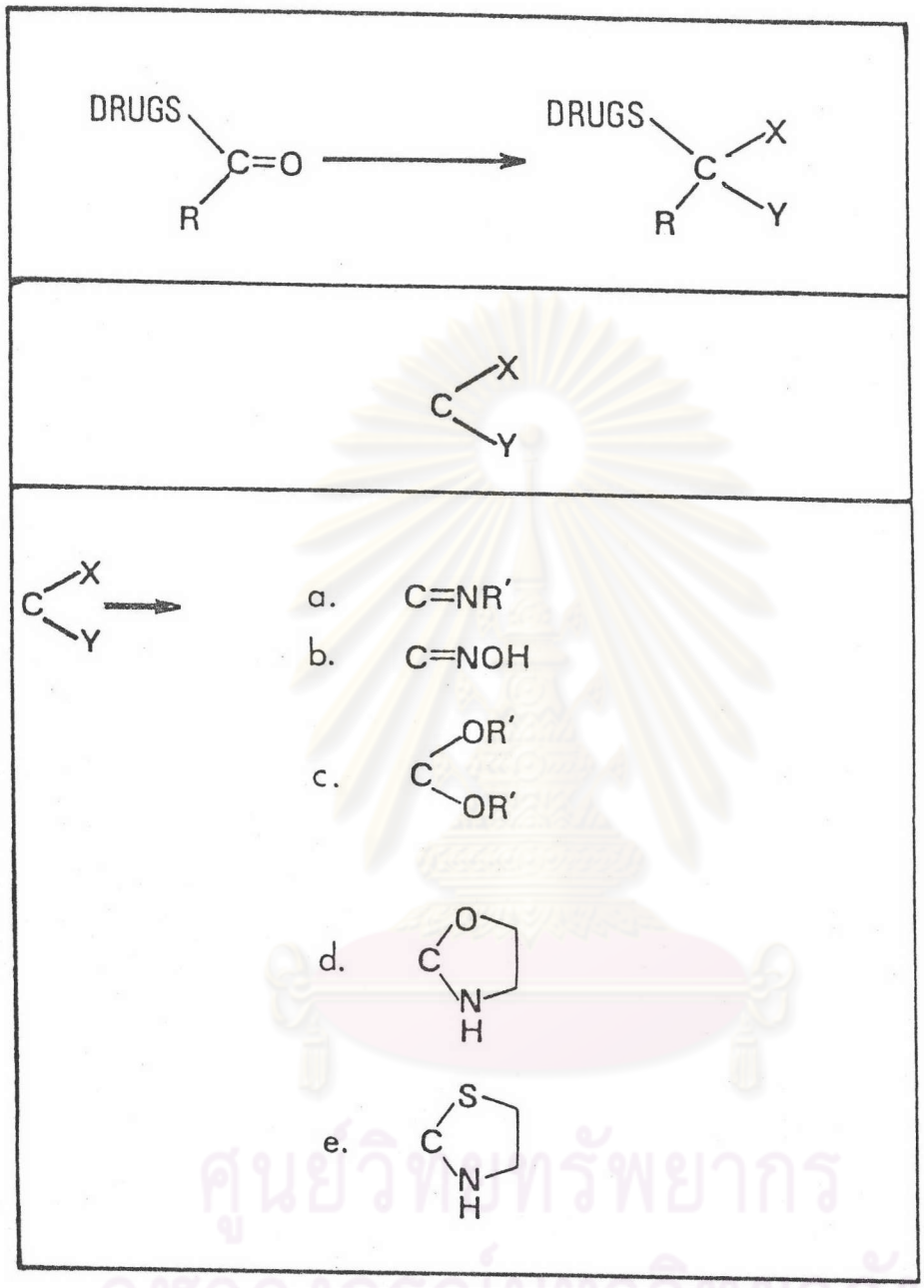
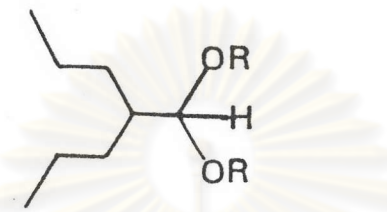


Figure 6. Prodrug analogs of carbonyl compounds



	R
XXXV	CH_3
XXXVI	CH_2CH_3
XXXVII	$CH(CH_3)_2$

Figure 7. Acetals of 2-propylpentanal

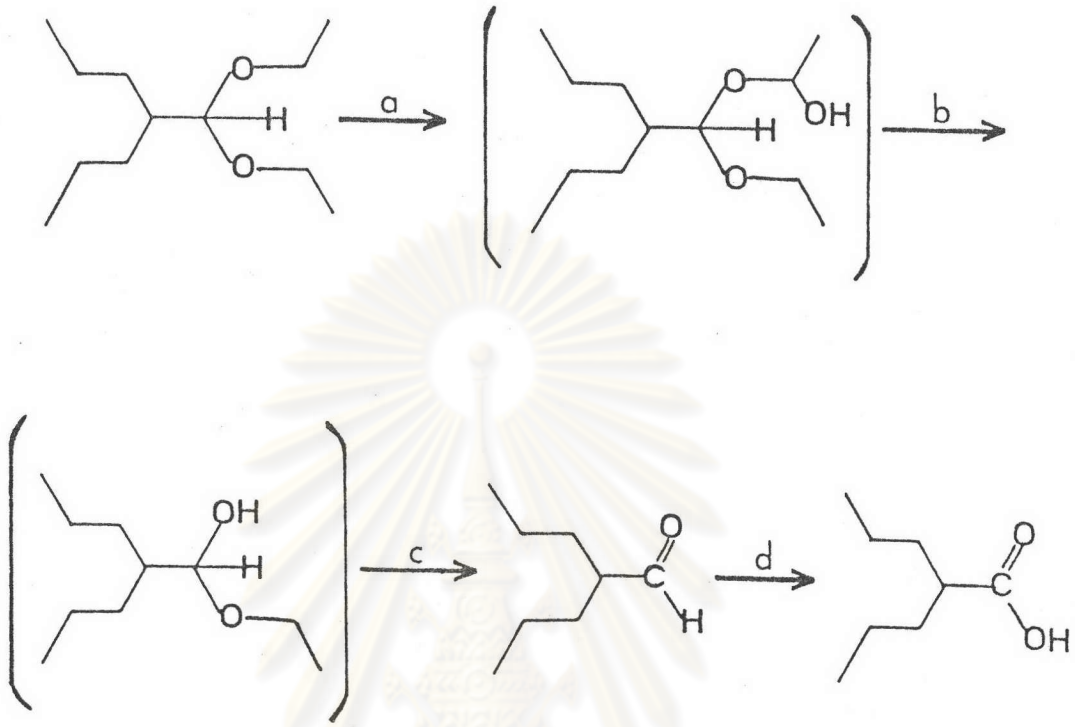
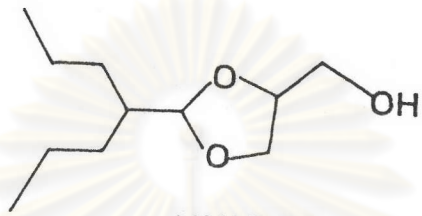
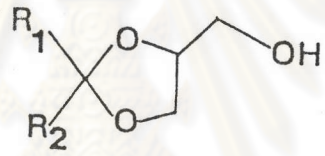


Figure 8. Proposed pathway for the enzymatic oxidation of 2-propylpentanal diethyl acetal.
a, Cyt-P450; b, nonenzymatic elimination of acetaldehyde; c, nonenzymatic elimination of ethanol; d,aldehyde dehydrogenase or aldehyde oxidase. Brackets indicate chemically unstable hemiacetal intermediates.



XXXVIII



XXXIX

Figure 9. Structures of 2-substituted-4-hydroxymethyl-1,3-dioxolanes

2 of compound XXXIX,comparing with compound XXXVIII, which has a total of 7 carbons attached at position 2 (Berger, Boekelheide and Tarbell, 1948; Boekelheide et al., 1949; Donahoe and Kimura, 1968).

When the hydroxyl group of compound XXXVIII is replaced by a sulfamate group, it gives an alkyl sulfamate derivative, [2-(1-propylbutyl)-1-3-dioxolan-4-yl]methyl sulfamate (XL) which is structurally resemble to McN-5762 (XX) which possesses a significant anticonvulsant activity.

Considering the chemical structure of compound XL , it is expected to possess a promising anticonvulsant activity since it contains 3 pharmacophores , namely valproic acid, 2-substituted-4-hydroxymethyl-1,3-dioxolane and alkyl sulfamate , each individually possesses anticonvulsant activity (Figure 10).

This research was aimed to synthesize [2-(1-propylbutyl)-1,3-dioxolan-4-yl]methyl sulfamate.

The synthetic approach for [2-(1-propylbutyl)-1,3-dioxolan-4-yl]methyl sulfamate is shown in Figure 11.

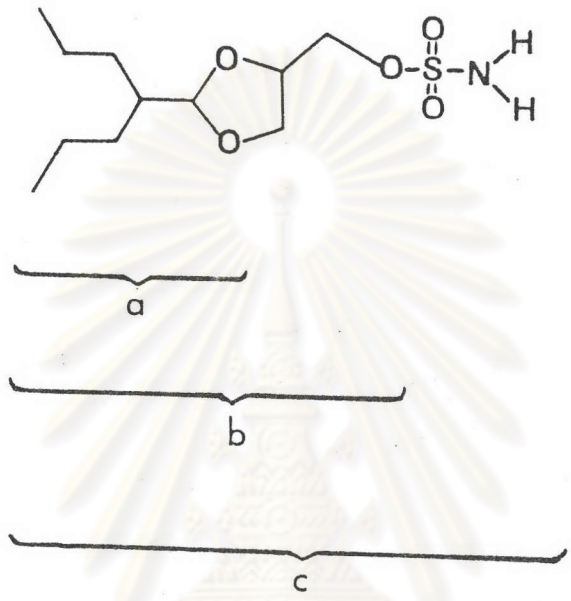


Figure 10. Structure of [2-(1-propylbutyl)-1,3-dioxolan-4-yl]methyl sulfamate containing three pharmacophores; a, valproic acid; b,2-substituted-4-hydroxymethyl-1,3-dioxolane; c,alkyl sulfamate, each individually possesses anticonvulsant activity.