CHAPTER I

INTRODUCTION

Epilepsy is a collection of seizure disorders which has been defined as a symptom of excessive temporary neuronal discharge, characterized by discrete recurrent episodes of seizures in which there is a disturbance of movement, sensation, behavior, perception and consciousness. It has been estimated that from one-half to one percent of the world population is affected by some form of epilepsy (Daniels and Jorgensen, 1982). More than half of the people suffering from epilepsy have more than one type of seizures (Penry and Newmark, 1979). Seizures are divided fundamentally into two groups : partial and generalized seizures (Goodman and Gilman, 1990).

Partial seizures have clinical or EEG evident 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. Generalized seizures have no evident of localized onset, the clinical manifestations and abnormal electrical discharge give no clue to the locus of onset of abnormality. Partial seizures are also divided into three groups : (a) simple partial seizures, (b) complex partial seizures, and (c) partial seizures secondarily generalized. The generalized seizures include

: (1) generalized tonic-clonic seizures, (2) absence seizures (petit mal), (3) myoclonic seizures, (4) atonic seizures, (5) clonic seizures, and (6) tonic seizures.

The classification of epileptic syndromes has been recently published. The first major division of epileptic syndromes is the same as that for seizures, i.e., into partial epilepsies or the generalized epilepsies. Each of these is further subdivided into idiopathic or symptomatic and then according to age of onset (Rogawski and Porter, 1990).

The cause of epileptic syndromes is imperfectly understood, many hypotheses have been proposed. Several investigators believed that the abnormal function of some neurotransmitters in brain can cause seizures. The concentrations of excitatory and inhibitory neurotransmitters L-glutamate and γ-aminobutyric acid (GABA), respectively, are regulated in central nervous system (CNS) principally by two PLP-dependent enzymes L-glutamic acid decarboxylase, the enzyme that catalyzes the conversion of L-glutamic acid to GABA and GABA aminotransferase, the enzyme that degrades GABA to succinic semialdehyde. Convulsive states have been observed in systems where GABA is prevented from functioning normally, either by the lowering of its concentration in the CNS below a certain level or by blocking its effect (Silverman and Nanavati, 1990). Other

authors stated some seizures were the result of a dietary deficiency of vitamin B_6, or involvement of acetylcholine, noradrenaline, hydroxytryptamine, and dopamine in brain (Spinks and Waring, 1963; Meldrum, 1975).

The methods widely used to evaluate anticonvulsant activity are the maximal electroshock seizure test (MES) and the pentylenetetrazole test. The maximal electroshock test evaluates the ability of drugs to prevent electrically induced tonic hindlimb extension in mice and rats. Efficacy in this method has been shown to correlate with ability to prevent partial and generalized tonic clonic seizures in man, and it is often stated that this model evaluates the capacity of a drug to prevent seizure spread. Drugs that are active in the maximal electroshock test often have a phenytoin-like effect on voltage dependent Na^+ channels. On the other hand, the pentylenetetrazole test as most commonly performed evaluates the ability of potential antiepileptic drugs to prevent clonic seizures and may correlate with activity against absence seizures.

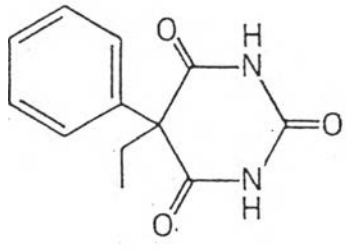
Antiepileptic therapy with organic compound began in 1912 when Hauptmann reported on the clinical effectiveness of phenobarbital. Prior to this the only effective treatment for epilepsy involved the use of bromide ion. However, bromide has a very low therapeutic index, and serious toxicity is often encountered with

plasma concentrations that are required for adequate seizure control (Jones and Woodbury, 1982).

Nowadays, many drugs have been used to control seizures in epileptic patients i.e. barbiturates (I), hydantoins (II), oxazolidine 2,4-diones (III), succinimides (IV), benzodiazepines (V), acylureas (VI), amides (VII), sulfonamides (VIII), dibenzazepines (IX) and valproate (X) (Figure 1).

Notwithstanding, the present antiepileptic drugs available today provide partial control for only about 70-80% and complete control for not more than 50% of the affected population (Jones and Woodbury, 1982). In addition, most antiepileptic drugs suffer from a broad range of undesirable side effects such as sedation, teratogenicity, cognitive disorder, blood dyscrasia and hepatotoxicity. Failure to achieve control of seizures is frequently due to use-limiting side effects seen with increasing doses of the drugs before a satisfactory therapeutic dose is reached. There is still a demand for new antiepileptic drugs with more selective anticonvulsant effects and less toxicity.

Numerous compounds are reported each year as anticovulsant agents. For example, vigabatrin (γ-vinyl-GABA, XI), a specific gamma aminobutyric acid aminotransferase inhibitor, is a mechanism based enzyme



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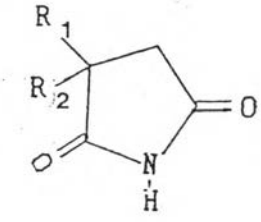

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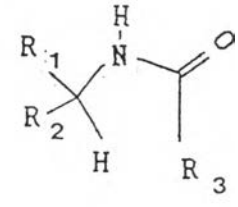

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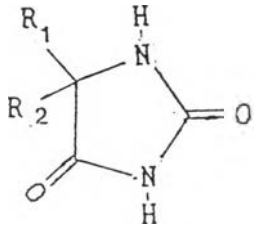

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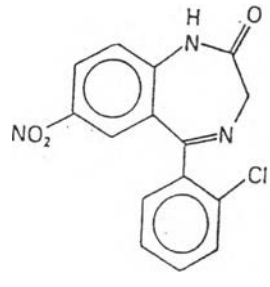

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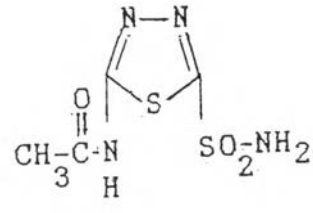

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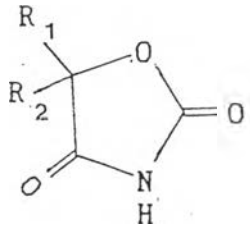

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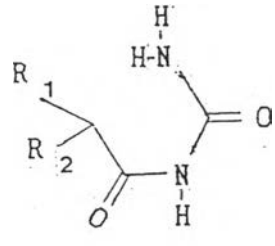

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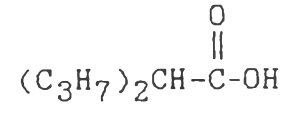

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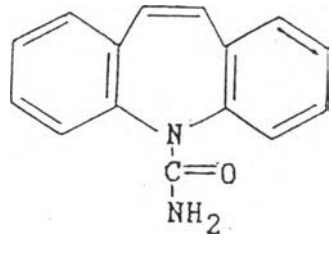
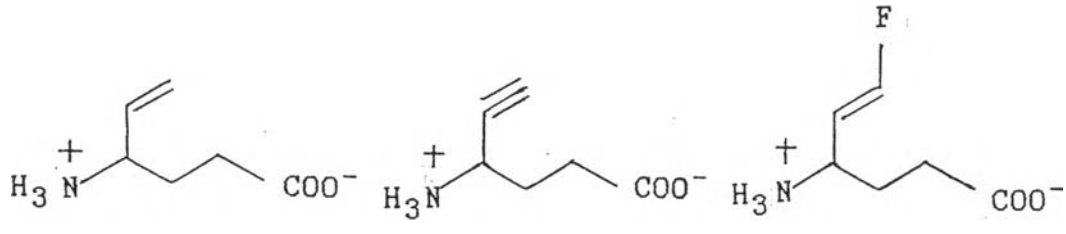


IX

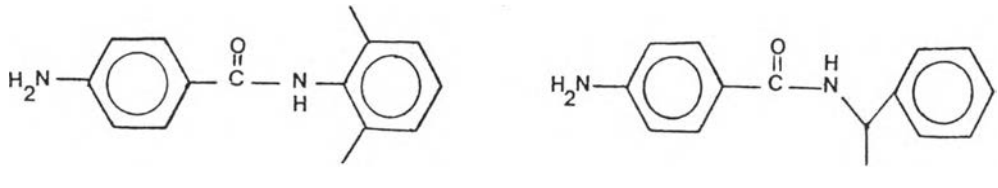
Figure 1 The chemical structures of some types of anticonvulsant agents.

inactivator (Nanavati and Silverman, 1989). The irreversible inhibition of GABA-T by vigabatrin results in a prolonged elevation in brain GABA levels. Other compounds (XII, XIII) that inactivated GABA-T in the same manner as that of vigabatrin were illustrated (Nanavati and Silverman, 1989).



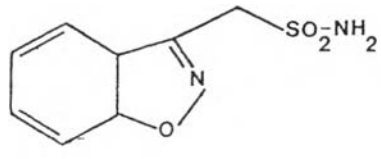
XI XII XIII

Clark et al. (1986) reported the extensive structure activity studies of aminobenzamide derivatives on the anticonvulsant activity. Of the compounds examined, the two compounds (XIV, XV) were proved to be the most potent in the maximal electroshock test

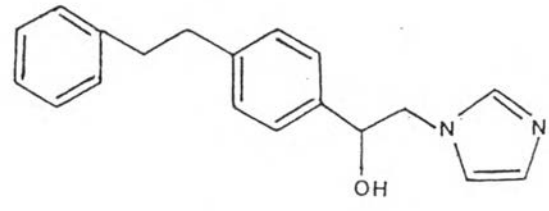


XIV XV

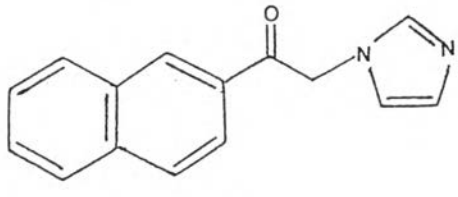
Zonisamide (XVI), denzimol (XVII), nafimidone (XVIII), lamotrigine (XIX), ralitoline (XX), topiramate (XXI) and oxacarbazepine (XXII) were reported as anticonvulsant agents that having a similar profile of anticonvulsant activity to phenytoin in protection against maximal electroshock seizures test (Rogawski and Porter, 1990).



XVI



XVII



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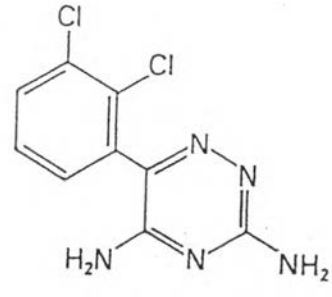

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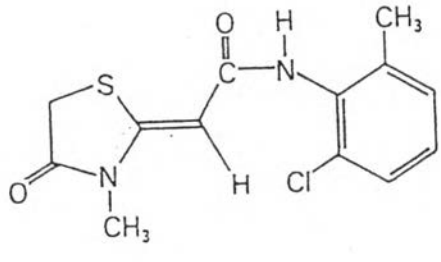

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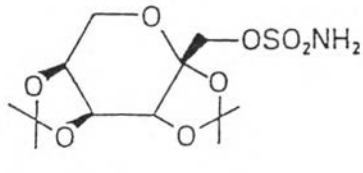
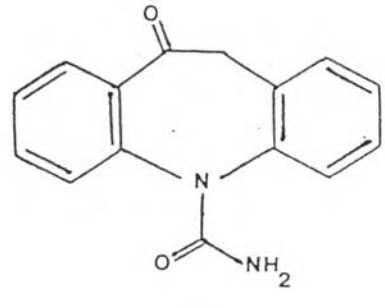
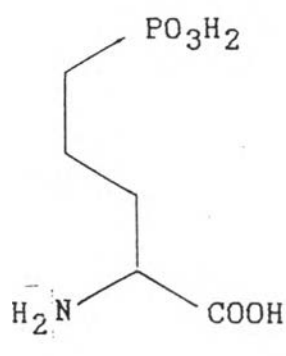


XXI

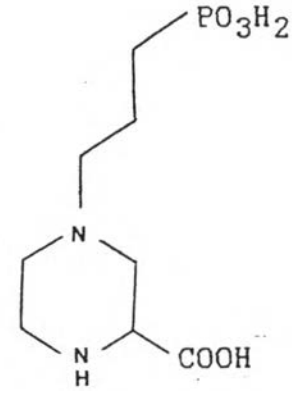


XXII

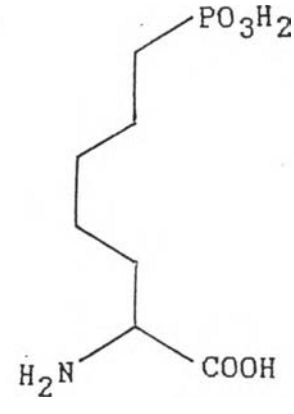
Recent advances in the physiology and pharmacology of excitatory amino acid neurotransmitter systems have highlighted the potential of excitatory amino acid receptors as a target for anticonvulsant drugs. The excitatory amino acids, aspartate and glutamate, mediate their actions via at least three classes of receptors which are generally represented by the prototypical agonists N-methyl-D-aspartic acid (NMDA), quisqualic acid (QUIS), and kainic acid (KA). Of these, NMDA receptor apparently 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 (Hutchison et al., 1989). Compound XXIII, XXIV and XXV were some competitive NMDA recognition site antagonists.



XXIII

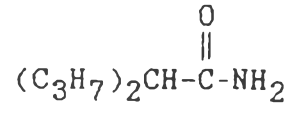


XXIV



XXV

Of all the antiepileptic drugs avialable today, valproic acid is attractive in its broad spectrum activity and its low side effects. Valproic acid exerts moderately anticonvulsant action, however, numerous derivatives have been developed in the hope of potentiation of its action. For instance, the primary amide of valproic acid (valpramide, XXVI) was proven to be about 5 times more active than valproic acid.



XXVI

However, prolonged use of valproic acid has arisen the incidence of rare, but serious, hepatotoxicity and a highly hygroscopic property of valproate, usually used as its sodium salt, renders formulation very difficult.

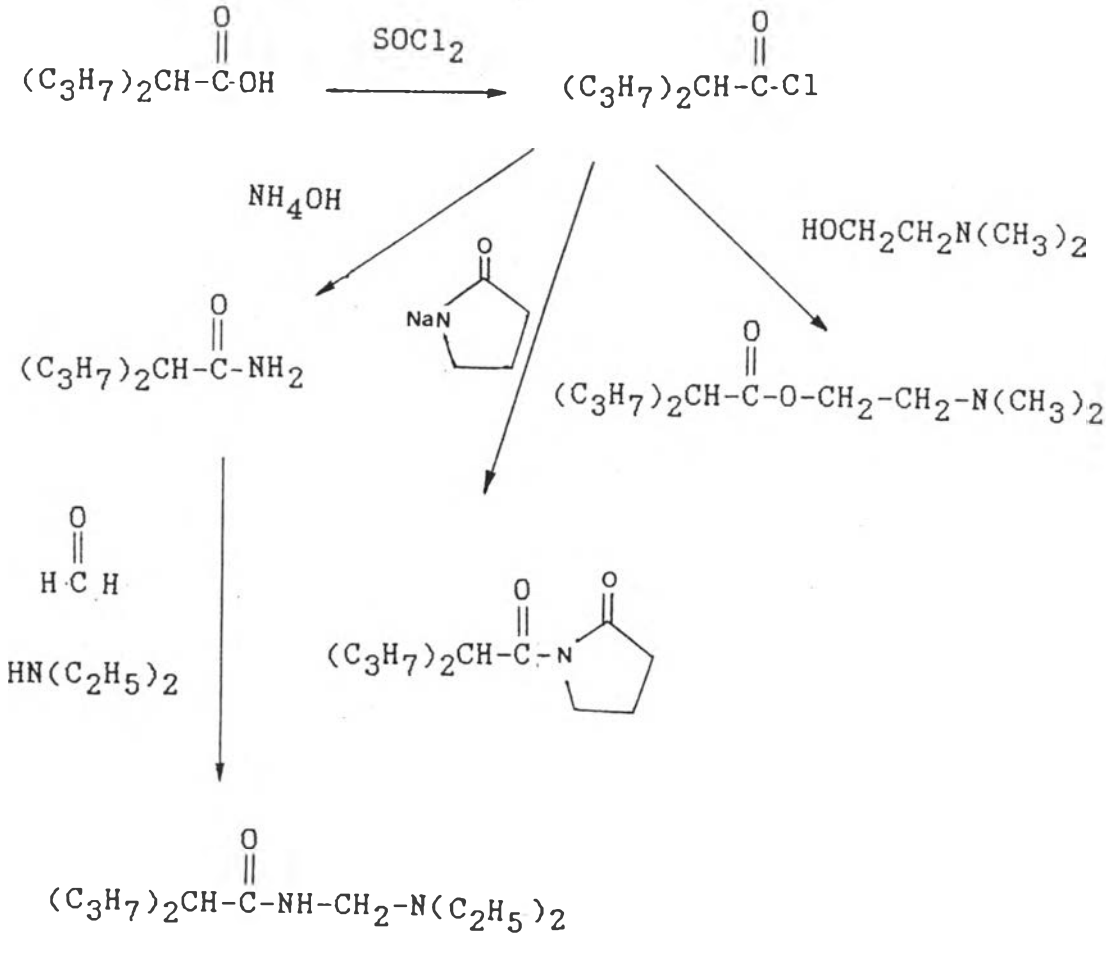
This research was aimed to synthesize valproic acid analogues by modifying on carboxyl group, which were divided into the following 2 types.

I. Synthesis of potential prodrugs of valproic acid

II. Synthesis of monoureide analogues of valproic acid

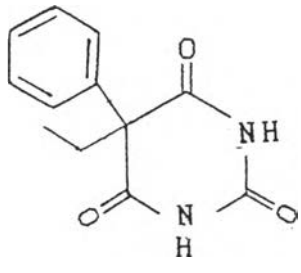
In general, compounds containing carboxyl groups can be prepared in various forms of prodrug (Bundgaard, 1985). Here, three forms (ester, amide and mannich base of valproic acid) were synthesized in the expectancy of reduction of gastric irritation and other adverse reactions of its parent drug.

The synthetic approach for potential prodrugs of valproic acid can be represented by following scheme I.

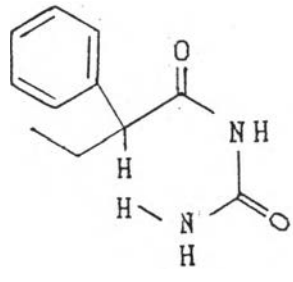


Scheme I Synthesis of prodrugs of valproic acid.

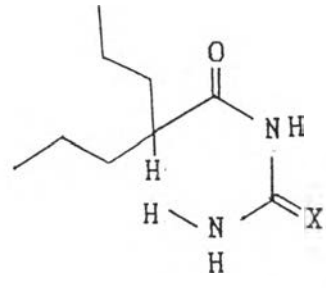
The successful use of phenobarbitone (XXVII) in treatment of epilesy, encouraged chemists to attempt to design active compounds modelled on the partial structure of the barbiturate ring. The discovery of activity in phenacemide (XXVIII), acyclic structure which embodied a major part of the phenobarbitone molecule, prompted the idea to synthesize monoureide analogues with 5-di-propyl side chain (XXIX), which resemble the partial structure of valproic acid.



XXVII

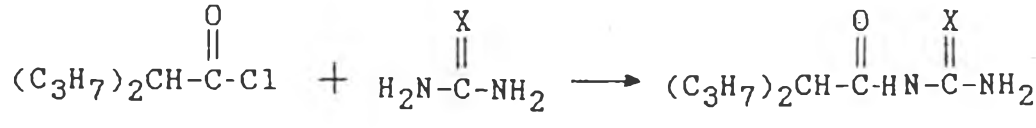


XXVIII



XXIX

The target compounds can be synthesized according to scheme II.



Scheme II Synthetic approach for monoureide analogues of valproic acid.