CHAPTER I

INTRODUCTION

Epilepsy is one of the most common neurological disorder. The word epilepsy comes from the Greek: a 'phenomenon in which man appeared to be seized by forces from without' (Wilder and Bruni, 1981).

The term epilepsies is a collective designation for a group of central nervous system (CNS) disorders having in common the repeated occurrence 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).

The terminology of epilepsy has evolved over many years as scientific knowledge has increased. The word epilepsy itself has many meanings, even today some would restrict its use to the supposedly idiopathic or primary disorder of generalized seizures without evidence of focal onset. The term grand mal describes the major generalized convulsion, which is characterized by loss of consciousness followed by a sequence of tonic and clonic convulsive activity. Grand mal seizures are now known as generalized tonic-clonic seizures. The term petit mal, formerly used to describe absence attacks, which occur primarily in children and are associated with an electroencephalogram (EEG) pattern of 3 per sec spike and wave discharge, has given way to the new terminology of absence seizures. Automatisms, psychic seizures, limbic seizures, and psychomotor attacks are older terms that implicate temporal lobe or limbic system localization, they are known as complex partial seizures.

The term aura is used to indicate a warning of an oncoming seizure. Indeed, from anatomic and physiological standpoints, the aura represents the seizure onset and may be the most important part of the seizure, the symptoms and signs of the seizure may reflect the function

of the part of the brain in which it originates. The aura may entirely represent a simple partial seizure, which is recognized by current classification.

Premonitory or prodromal symptoms are less clearly defined, and little physiological or biochemical information is available as to their exact meaning. However, patients and observers of patients can sometimes predict when seizures will commence. Mothers may report that children become irritable, dull or withdrawn, patients may have headaches, malaise, and sensations of impending doom hours before the seizure occurs.

In the past, seizures were named on the basis of precipitating factors. These types of seizures are rare. The most common, which occurs in patients who are sensitive to light, often can be precipitated with photic stimulation, it is known as photic epilepsy. Similar seizures may be induced by viewing television, riding under trees in bright sunlight, or other visual stimuli. Musicogenic epilepsy is the term for seizures precipitated by music or particular sounds. Rarely, seizures may be precipitated by reading or by attempting to solve arithmetic problems. These types of attacks have been called reading epilepsy and epilepsia arithmatica. If a patient runs during a seizure, he may be described as having cursive epilepsy, if he laughs, he may be said to have gelastic seizures (Wilder and Bruni, 1981).

Although a completely satisfactory seizure classification is not available, the Classification of Epileptic Seizures of the International League Against Epilepsy is the most wildly accepted. The main feature of this classification is the distinction between seizures that are generalized from the beginning and those that are partial or focal at the onset and become generalized secondarily. The classification categorizes epileptic seizures as partial, generalized, and unclassified (Wilder and Bruni, 1981; vida, 1989; Rall and Schleifer, 1990; Garnett, 1993), as summarized below.

    I. Partial seizures.(Focal, Local seizures)
        A. Simple partial seizures. (conciousness not impaired)
            1. With motor signs.
            2. With somatosensory or special-sensory symptoms.
(simple hallucinations, e.g., tingling, light flashes, buzzing)

      3. With autonomic symptoms or signs.

      4. With psychic symptoms. (disturbance of higher cortical function)

      B. Complex partial seizures. (generally with impairment of consciousness, may sometimes begin with simple symptomatology)

      1. Simple partial onset followed by impairment of consciousness.

      2. With impairment of consciousness at onset.

      C. Partial seizures evolving to generalized tonic-clonic seizures.

      1. Simple partial seizures evolving to generalized tonic-clonic seizures.

      2. Complex partial seizures evolving to generalized tonic-clonic seizures.

      3. Simple partial seizures evolving to complex partial seizures evolving to generalized tonic-clonic seizures.

      II. Generalized seizures. (convulsive or nonconvulsive)

      A.1. Absence seizures.

      A.2. Atypical seizures.

      B. Myoclonic seizures.

      C. Clonic seizures.

      D. Tonic seizures.

      E. Tonic-Clonic (grand mal) seizures.

      F. Atonic seizures.

      G. Infantile spasms.

      III. Unclassified epileptic seizures.

      IV. Addendum. (Status epilepticus or prolonged partial or generalized seizures without recovery between attacks)

      All form of epilepsy originate in the brain. It is believed to be the result of changes in neuronal activity. These changes, such as an excessive neuronal discharge, may in turn be brought about by a disturbance of physicochemical function and electrical activity of the brain. The cause of this abnormality, however, is not clearly understood (Vida, 1989; Rall and Schleifer, 1990).

The most important property of the nerve cell is its excitability. It responds to excitation by generating an action potential, which may lead to repeated discharges. All normal neurons may be come epileptic if subjected to excessive excitation. An abnormality of potassium conductance, a defect in the voltage-sensitive calcium channels, or a deficiency in the membrane ATPases linked to ion transport may result in neuronal membrane instability and a seizure. The normal firing of neurons is controlled by excitatory and inhibitory neurotransmitters. Acetylcholine, norepinephrine, histamine, and corticotropin-releasing factor enhance the excitability and propagation of neuronal activity, whereas gamma-aminobutyric acid (GABA) and dopamine inhibit neuronal activity and propagation. Normal neuronal activity also depends on an adequate supply of glucose, oxygen, sodium, potassium, calcium and amino acids. Systemic pH is also a factor in precipitating seizures. They may be primary defects in the GABAergic inhibitory system or in the sensitivity or arrangement of the receptors involved in excitatory neurotransmission that result in a seizure (Garnatt, 1993).

Epilepsy is a chronic disorder. In selected patients surgery may offer a cure. Although drug therapy can often control the manifestations of the disease, antiepileptic drugs do not cure epilepsy. The proper treatment of epilepsy begins with a careful classification of the seizure type and selection of the most effective antiepileptic drugs. The first treatment goal is to control or reduce the frequency of seizures, allowing the patient to live an essentially normal life. Ideally, seizure frequency should be reduce to zero (Garnett, 1993).

Over the centuries, many substances have been used with the aim of controlling epilepsy. In 1857 the antiepileptic efficacy of bromide was introduced by Locock and for half a century, potassium bromide was the mainstay of treatment for epilepsy, until it was replaced by phenobarbital in 1912 when Hauptmann tried this sedative in epilepsy. Phenytoin was first introduced for the treatment of epilepsy in 1938 and represented a major pharmacological advance in the treatment of neurological disease. Phenytoin is still one of the most widely used anticonvulsants. By manipulating the cyclic ureide moiety from which phenytoin and phenobarbital are derived, additional barbiturates and hydantoins as well as oxazolidinediones and succinimides were provided over the next two decades. In the nineteen-sixties the anticonvulsant activity of carbamazepine and valproate were recognized, while diazepam become a

drug of first choice for the treatment of status epilepticus. In the ninteen-seventies valproate and three new benzodiazepines were marketed. From 1975 to 1984 no new antiepileptic drugs were marketed (Swinyard, 1980; Sneader, 1985; Vida, 1989).

The available antiepileptic drugs belong to several chemical structural types which are the barbiturates e.g. phenobarbital (I), the hydantoins e.g. phenytoin (II), the deoxybarbiturates e.g. primidone (III), the oxazolidinediones e.g. trimethadione (IV), the succinimides e.g. ethosuccimide (V), the acylureas e.g. phenacemide (VI), the benzodiazepines e.g. diazepam (VII), an iminostibene that is carbamazepine (VIII), a branched-chain carboxylic acid that is valproic acid (IX), and the sulfonamides e.g. acetazolamide (X) (Rall and Schleifer, 1990) as illustrated in Figure 1. The mechanism of action of these eight classes of chemical compounds to block seizures are devided into three classes; by enhancing sodium channel inactivation, by enhancing GABAergic inhibition or by blocking T calcium current. The mechanism of action of these drugs are described by Rogawski and Porter (1990). The structure-activity relationships of drugs in each group have also been depicted by Mercier (1973).

The ideal antiepileptic drugs would completely suppress all clinical and electroencephalographic evidence of the patient's epilepsy while producing no immediate or delayed side effect (Ritter et al.,1995). This ideal does not exist in the available antiepileptic drugs. None has been capable of achieving total seizure control in all patients. A careful diagnosis of the seizure type, a careful selection of drug along with monitoring of its concentration in the blood, and the ensuing individualized attention to the patient's overall needs can lead to optimal results (Glaser, 1980). Polytherapy is often necessitates by the lack of complete control of seizures or tolerance development by the selected anticonvulsant. Currently marketed antiepileptic drugs are associated with a wide range of side effects and the complete suppression of seizures must be balanced against side effects, especially as treatment may be very prolong (Garnett,1993). Therefore, a need for new drugs that are the ideal antiepileptic drugs which may be more effective than those current antiepileptic drugs and devoid of their side effects currently exists.
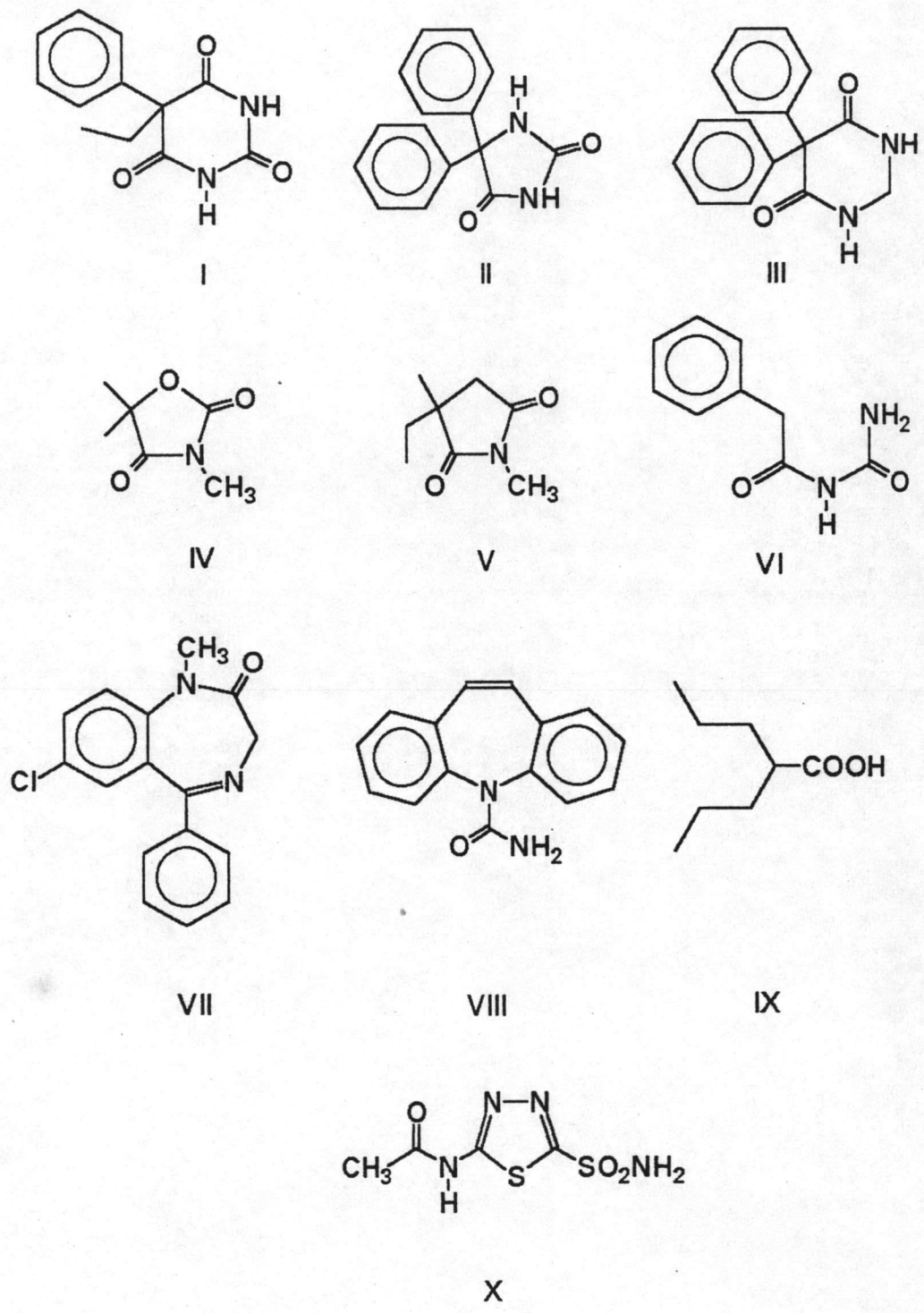
Figure 1. Types of chemical structures of anticonvulsant agents.

Since both the primary pathology of epilepsy and precise mechanisms by which the available antiepileptic drugs act are not well understood, the development of new agent remains a challenging problem.

The past decade has witnessed a resurgence of interest in the development of new anticonvulsant drugs, and research has been extended to novel structural types and focused on the molecular and cellular events responsible for the disorder. Several promising new compounds have marketed and progressed to various stages of clinical development.

Major approaches to the design of novel antiepileptic drugs include the continuing exploitation of mechanistic approaches based on GABA and new advances in the pharmacology of excitatory amino acid antagonists.

The former approach arose since several antiepileptic drugs, including benzodiazepines, valproic acid, and barbiturates were believed to work, at least in part, by enhancing GABA-mediated inhibition. As a result, much interest has recently been focused on the various potential pharmacological approaches to the enhancement of GABAergic function in humans, for example, by the direct agonism of GABA receptors, the inhibition of the uptake of GABA into neuronal and glial cell bodies, or by the inhibition of enzymatic breakdown of GABA (Krogsgaard-Larsen, 1981).

GABA agonists XII, XIII, XIV, and XV were developed by conformation restriction of various parts of the molecule of GABA (XI) and bioisosteric replacements of the functional groups of this amino acid. Muscinol (XVI), a constituent of the mushroom *Amanita muscaria*, has extensively used as a lead for the design of different classes of GABA analogues. The 3-hydroxyisoxazole structure of muscinol can be replaced by 3- hydroxyisoxazoline to give dihydromuscinol (DHM, XVII) which is a potent GABA agonist, and it also interacts with the GABA uptake system (Krogsgaard-Larsen et al., 1986). Conversion of muscinol into gaboxadol (THIP, XVIII) and the isomeric compound 4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine-3-ol (THOP) effectively seperated GABA agonist and GABA uptake inhibitor, THIP being a
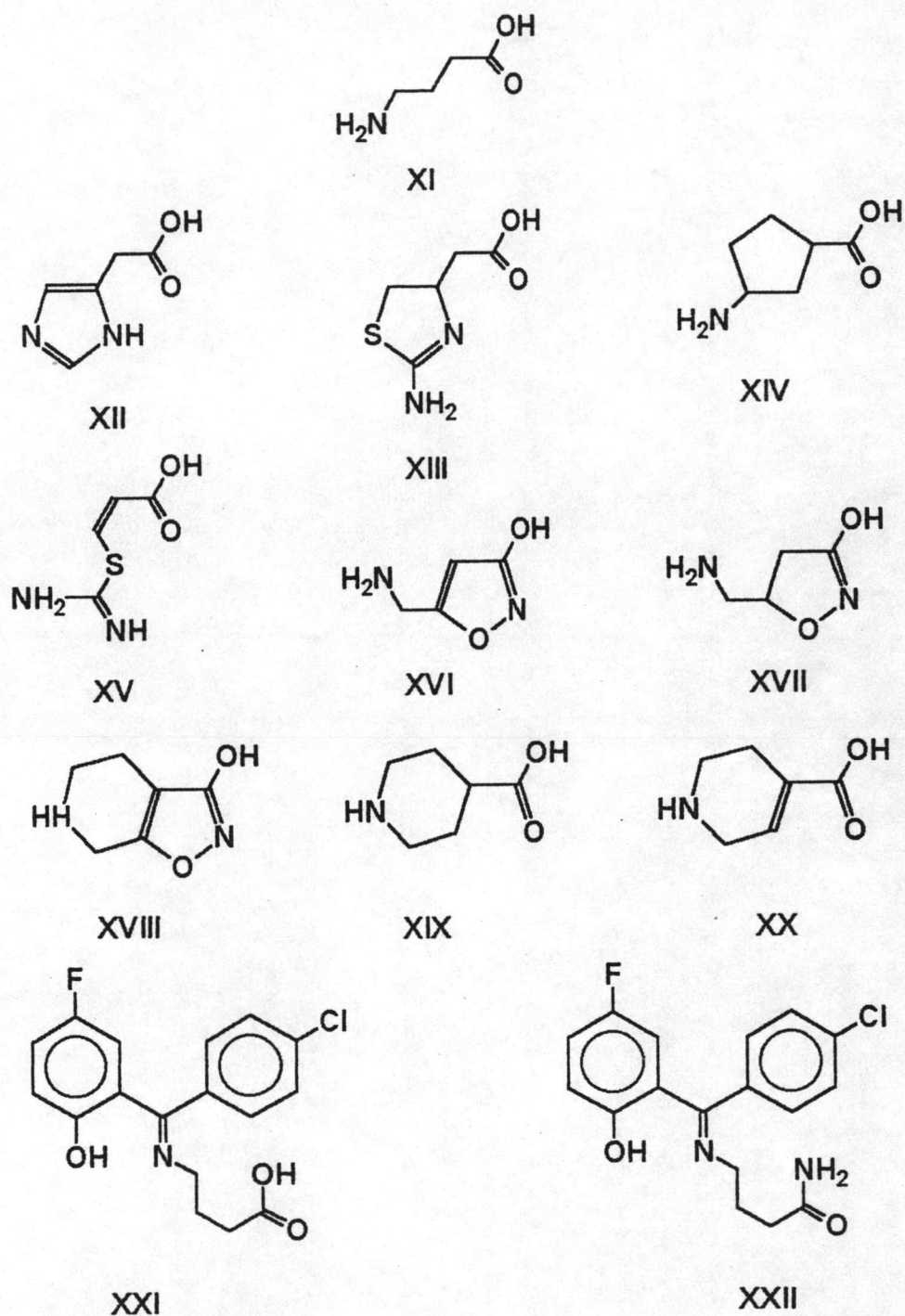
Figure 2. The chemical structures of GABA, GABA agonists and GABA prodrugs.

GABA agonist and THOP a GABA uptake inhibitor (Krogsgaard-Larsen et al., 1994).

Using THIP as a lead, a series of specific monoheterocyclic GABA agonist, including isoguvacine (XIX), and isonipecotic acid (XX) were developed.

In addition to these GABA agonists, a number of GABA prodrugs were developed which are the benzophenone imine derivatives of GABA such as SL75,102 (XXI) and progabide (XXII), cetyl GABA, pivaloyl GABA, benzoyl GABA (Meldrum, 1992), and diacylglycerol-GABA adducts (Jacob et al., 1985, 1987, 1990).

Analogously, a series of cyclic amino acids derived from THOP (XXIII) including nipecotic (XXIV) and guvacine (XXV) was developed as GABA uptake inhibitors, but they are fully zwitterionic at physiologic pH, which explains their very poor penetration of the blood brain barrier. In an effort to overcome this problem, A group at SmithKline and French Laboratories examined the effect of adding lipophilic side chains to the nitrogen atom of various GABA uptake inhibitors. Surprisingly, the addition of 4,4-diphenyl-3-butenyl side chains to nipecotic acid and guvacine to give SKF 89,976A (XXVI) and SKF 100,330A (XXVII), respectively resulted in a 20-fold increase in potency when test in brain synaptosomes (Ali et al., 1985). Since this report, other groups have synthesized similar derivatives such as CI-966 (XXVIII) (Pavia et al., 1992), tiagabine (XXIX) (Andersen et al., 1993), 4,4-diphenyl-3-butenyl analogue of THPO (XXX) (Krogsgaard-Larsen et al., 1994), and (S)-1-[2-[tris(4-methoxyphenyl)methoxy]ethyl]-3-piperidinecarboxylic acid (XXXI) (Dhar et al., 1994).

Inhibitors of GABA transminase, the enzyme initiating the further metabolism of GABA via GABA shunt (Figure 4), showed anticonvulsants acitivity in many animal models of epilepsy and one such compound, γ-vinyl GABA or Vigabatrin (XXXII) are now approved for clinical use in the U.K. (Meldrum, 1992). The review about proposed inactivation mechanism of this compound and other GABA transminase inhibitors is described by Nanavati and Silverman (1989).

The later approach to the design of novel anticonvulsant drugs developed in the early 1980s following the description of potent selective
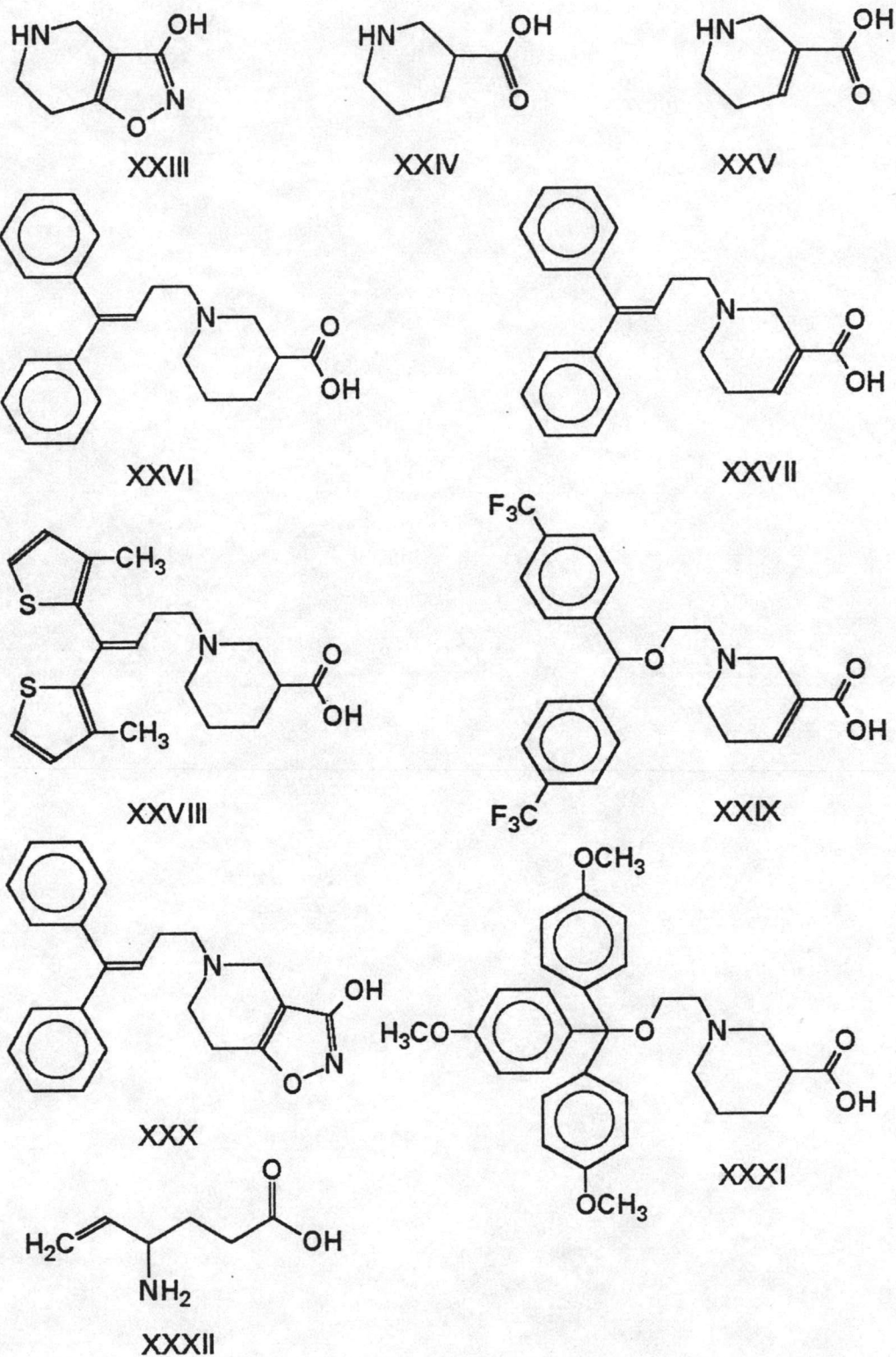
Figure 3. The chemical structures of GABA reuptake inhibitors and vigabatrin (XXXII).
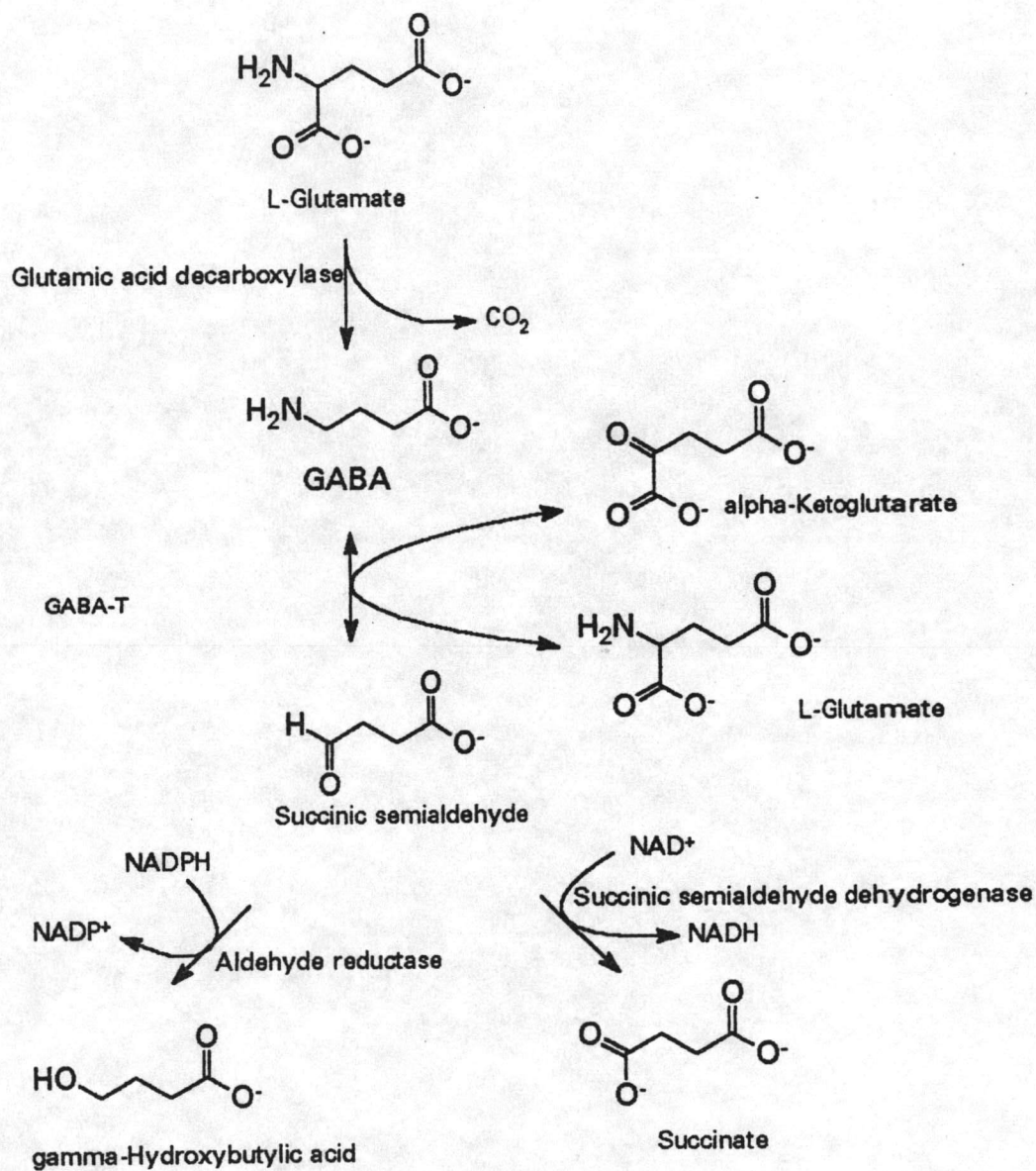
Figure 4.   GABA metabolism.

antagonists of the postsynaptic excitatory action of glutamate and the discovery of the anticonvulsant effect of selective inhibitors acting on the N-methyl-D-aspartate (NMDA) receptor.

The excitatory amino acid, 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 the NMDA receptor has been the most studied. Excess activity at this receptor has deleterious effects on CNS function. Antagonists of the NMDA receptor could thus have potential utility in a number of CNS disorder, most notably in the treatment of epilepsy. Drugs antagonising NMDA receptors can be classified into 2 types, the competitive antagonists, and the noncompetitive antagonists.

At the initiation of these studies the most potent competitive NMDA antagonists known were 2-amino-5-phosphonopentenoic acid (XXXIII) and 2-amino-7-phosphono heptanoic acid (XXXIV), discovered by Watkins. On developing, many potent competive NMDA antagonists were discovered such as the piperazine analogue of 2-amino-7-phosphonoheptanoic, the 4-(3-phosphonopropyl)piperazine-2-carboxylic acid (XXXV), and its unsaturated analogue (XXXVI); the unsaturated analogue of 2-amino-5-phosphono pentenoic acid, CGS 37,849 (XXXVII), and its ethyl ester CGS39,551 (XXXVIII); the piperidine analogue of 2-amino-5-phosphonopentenoic acid, CGS 19,755 (XXXIX) (Hutchison et al., 1989; Meldrum, 1992).

The potent noncompetitive NMDA antagonists are two dissociative anesthetics, phencyclidine (XL), and ketamine (XLI) and the related compound dibenzocycloalkenimine MK-801 (dizocilpine, XLII). They show significant anticonvulsant activity in rodent models of epilepsy. Based on structure of dizocilpine, ADCI (XLIII), a compound having the basic dibenzocycloheptene-5,10-imine ring structure of dizocilpine with a carbamyl group (as in carbamazepine) substituted at the 5-position was synthesized and found to be an effective anticonvulsant in the mouse (Rogawski snd porter, 1990).

In recent years, a number of modulatory sites have been identified on the NMDA receptor-cation channel complex, the neurotransmitter (glutamate) recognition site, at which competitive
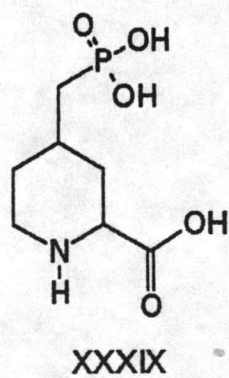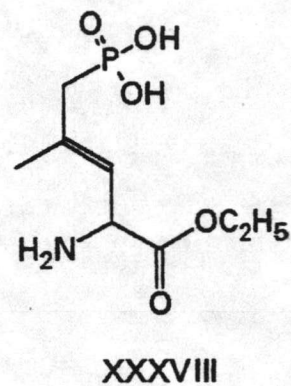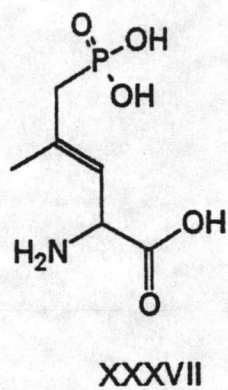
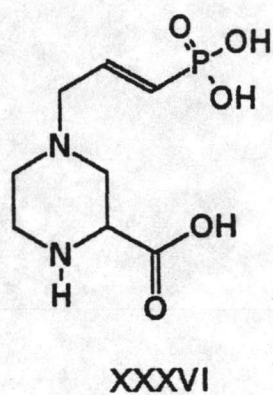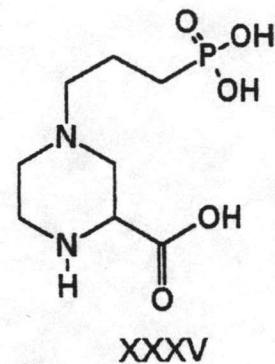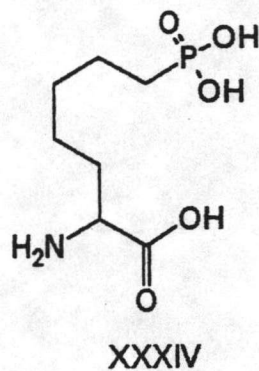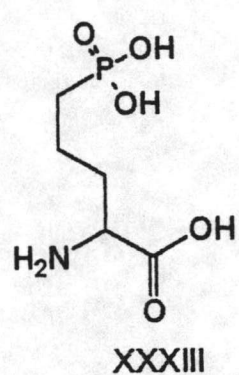XXXIII

XXXIV

XXXV

XXXVI

XXXVII

XXXVIII

XXXIX

Figure 5. The chemical structures of competitive NMDA
antagonists.

antagonists bind; the ion channel, which noncompetitive antagonists, dizocilpine blocks; the polyamine binding site; and a site that binds glycine, which has been show to be necessary for receptor activation. Several types of compound are known to inhibit the binding of glycine to this site, including kynurenic acid derivatives, such as compound XLIV; 2-carboxytetrahydroquinolines, such as L-689,560 (XLV); 3-acyl-4-hydroxyquinolin-2-(1*H*)-ones, such as L-701,723 (XLVI); and 3-nitro-3,4-dihydro-2-(1*H*)quinolones, such as L-698,554 (XLVII) and showed anticonvulsant activity in rodent model (Rowley et al., 1993; Carling et al., 1993).

In addition to these approaches, there are many novel anticonvulsant drugs that are developed. Some are the analogues of the currently marketed anticonvulsant drugs e.g. oxcarbazepine (XLVIII), an analogue of carbamazepine; clobazam (XLIX), a 1,5-benzodiazepine; enterobarb (L), a barbiturate; felbamate (LI), a dicarbamate that is structurally similar to the antianxiety agent meprobamate; and gabapentin (LII), a conformationally restricted analogue of GABA but does not interact with GABA receptors (the mechanism of its anticonvulsant activity is unknown).

Some have novel structural types such as the benzisoxazole derivative, zonisamide (LIII) and CGS18,416A (LIV); the imidazole derivatives, denzimol (LV) and nafimidone (LVI); a phenyltriazine lamotrigine (LVII); a thiazolidinone ralitoline (LVIII); a sulfamate-substituted monosaccharide topiramate (LIX); an aminobenzamide LY201,116 (LX); a benzamide U-54,494A (LXI); a pyridine-oxazolidinone D-19,274 (LXII); a imidazopyridine AHR12,245 (LXIII); a derivative of glycine milacemide (LXIV); a lipophilic derivative of taurine taltrimide (LXV); and stiripentol (LXVI) (Rogawski and porter, 1990).

This research was aimed to synthesize the compounds having antiepileptic activity by developing the improved derivatives of the excisting antiepileptic drugs. There are four major antiepileptic drugs with wide antiepileptic spectrum of activity which are valproic acid, phenobarbital, phenyltoin and carbamezepine. Valproic acid is the compound selected for the development since it has shown efficacy against a variety of seizure disorder and relatively lacked of toxicity as compared with phenytoin and phenobarbital.
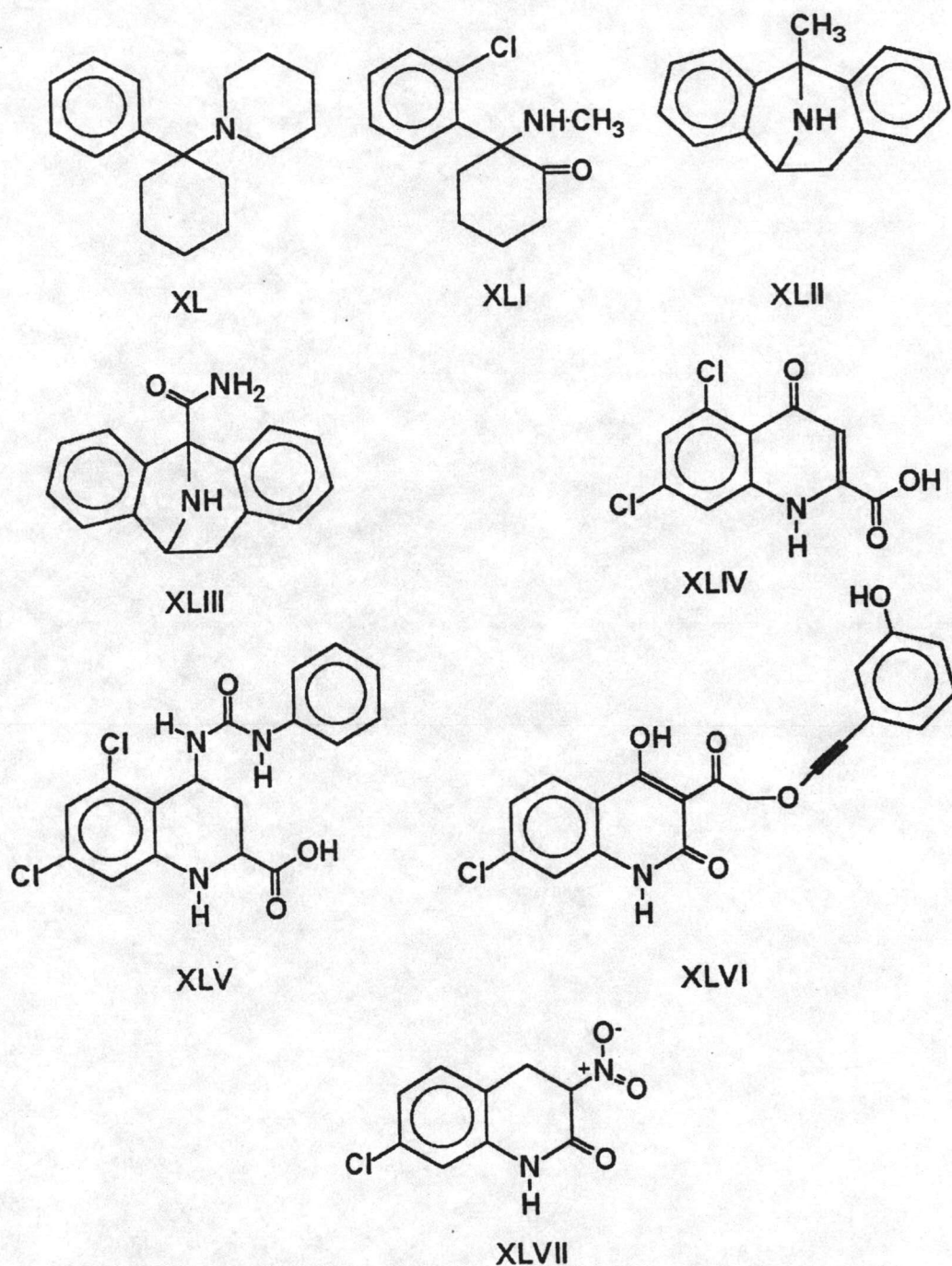
Figure 6. The chemical structures of noncompetitive NMDA
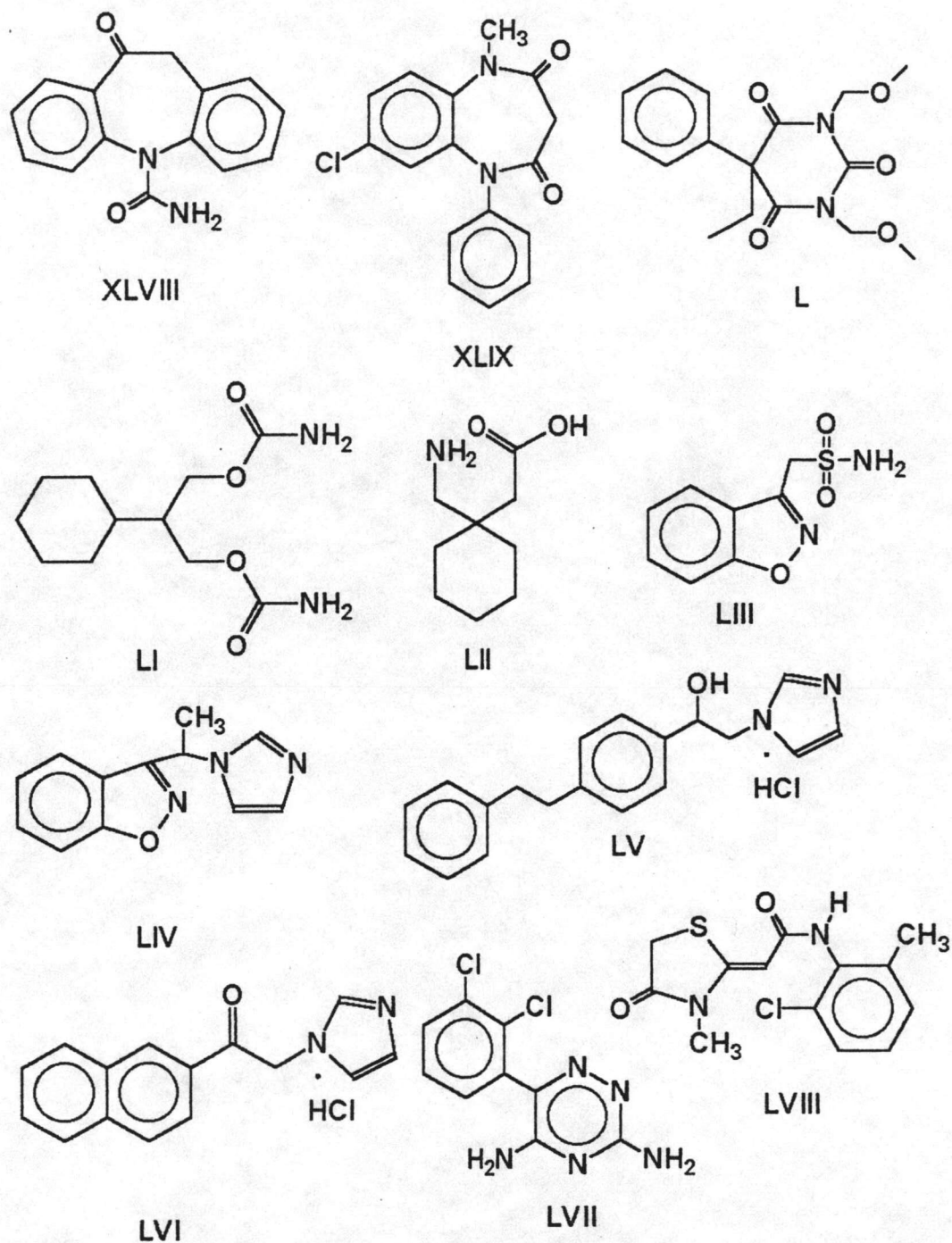antagonists and glycine-site NMDA antagonists

XLVIII

XLIX

L

LI

LII

LIII

LIV

LV

LVI

HCl

LVII

LVIII

Figure 7. The chemical structures of novel anticonvulsant drugs
and analogues of the currently anticonvulsant drugs.
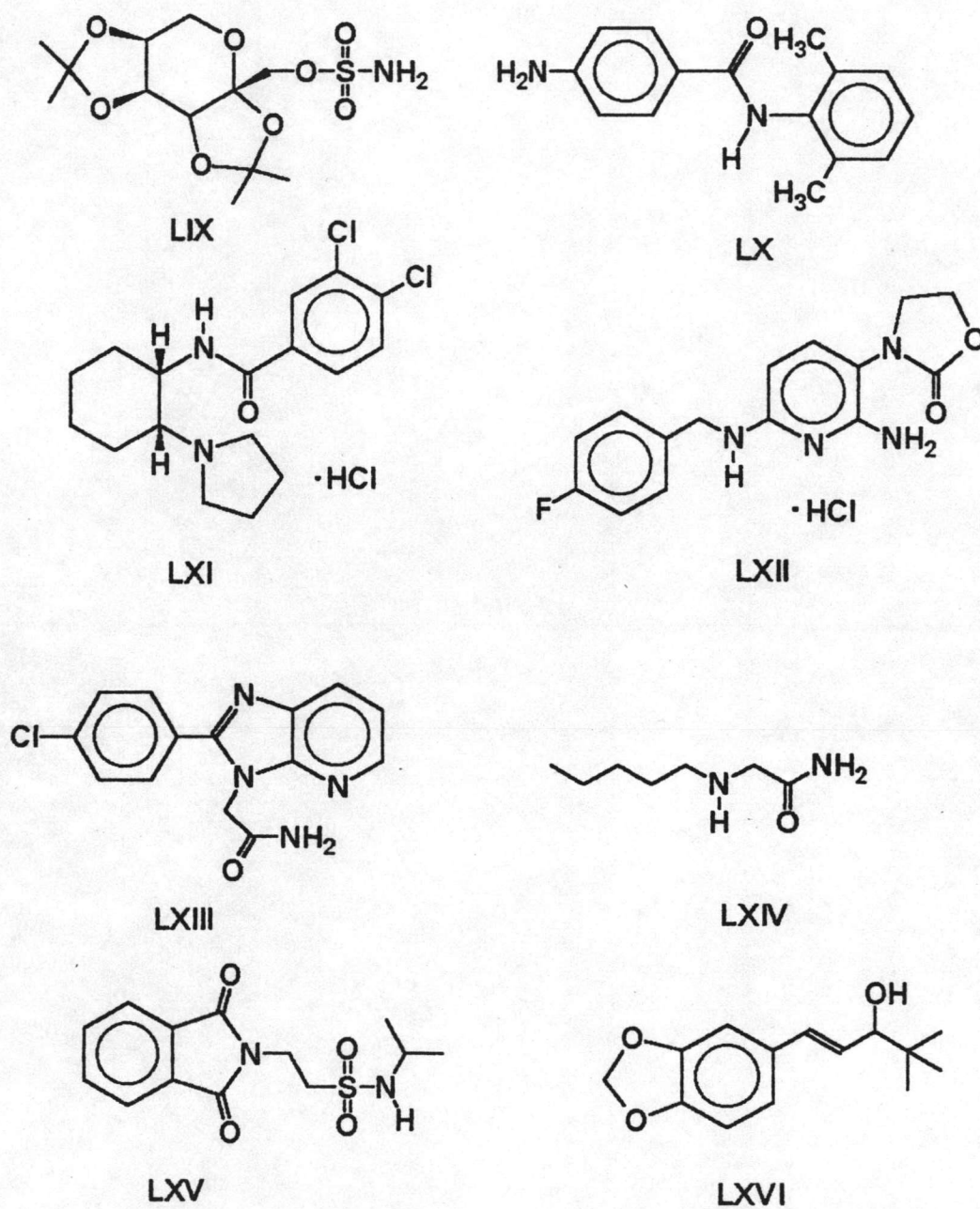
LIX

LX

LXI

·HCl

LXII

·HCl

LXIII

LXIV

LXV

LXVI

Figure 8. The chemical structures of novel anticonvulsant drugs
having novel structural types.

Valproic acid is the drug of first choice for most generalized seizures and it also useful in the treatment of partial seizures. It is the only the antiepileptic drug that is effective against absence and other types of generalized seizures. If febrile seizures are treated prophylactically, valproic acid may be preferable to phenobarbital. It may also be useful in neonatal seizures (Garnett, 1993).

Although the clinical usefulness of valproic acid as an antiepileptic drug is well established (Chapman et al., 1980; Davis et al., 1994), this compound suffers two major drawbacks; the fluctuation in levels of drug in plasma and various side effects.

The plasma concentrations of valproic acid vary considerably during the day, mainly due to two factors.

1. Rapid absorption producing peak concentrations in most patients 1 to 2 hours after a conventional tablet.

2. Rapid elimination, in particular in the presence of other enzyme inducing drugs (this also causes the drug to be administered several times a day).

The most frequently reported side effects are gastrointestinal complaints including nausea, vomiting anorexia and weight gain. Other frequently reported side effects are drowsiness, ataxia and tremor but the most serious side effect of valproic acid are hepatotoxicity and teratogenicity that are rarely reported (Jeavons, 1984; Schmidt, 1984; Garnett, 1993).

In order to minimize these problem, two approaches are generally taken; a pharmaceutical or a chemical approach. In the pharmaceutical approach, the slow-release formulations have been developed as a means of reducing fluctuation in serum concentration and reducing the dosing regimen or frequency of valproic acid. The enteric-coated preparations have been developed which result in the liberation of valproic acid to avoid the local gastric irritation (Zaccara et al., 1988).

In the chemical approach, this can be done by the design of a prodrug or by the synthesis of an analogue. For this reserch, a prodrug design is selected. In the case of valproic acid, prodrugs can minimize side effects such as gastric irritation and solve the pharmaceutical

problem associated with valproic acid (which is a liquid) or a hydroscopic sodium valproate.

A prodrug is pharmaceutically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation within the body in order to release the active drug. The prodrug is synthesized by attachment of a pro-moiety to the molecule of parent compound or otherwise modification the parent compound. The prodrug-drug conversion may take place before absorption (e.g. in the gastrointestinal tract), during absorption, after absorption or at the specific site of drug action in the body, all dependent upon the specific goal for which the prodrug is designed (Bundgaard, 1991).

Usually, the term prodrug implied a covalent link between an active moiety (drug) and a pro-moiety (carrier moiety) (Balant and Doelker, 1995), so it is important to understand the nature of the chemical bond linking the active moiety to its pro-moiety and the nature of the pro-moiety. Knowledge of the nature of the chemical bond may help to explain the nature of the biotransformation process. The study of the fate in the body of the pro-moiety is particularly important from a safety point of view and should be investigated just as thoroughly as the active moiety.

There are several reports on prodrugs of valproic acid including three type of chemical compounds; amide prodrugs of valproate, ester prodrugs of valproate, and 2-propylpentanal acetals (for detail see Chapter II, History).

For 2-propylpentanal acetals, there had been an investigation indicating that these compounds were metabolically converted to valproic acid. Proposed pathway for the enzymatic oxidation of 2-propylpentanal diethylacetal (LXVII) is shown in Figure 9 (Vicchio and Callery, 1989).

On consideration, if dihydroxy or trihydroxy compound is used as pro-moiety, both the ester derivatives of valproate and 2-propylpentanal acetals can be obtained. Pyridoxine (LXVIII) is the compound suitable for the requirement.
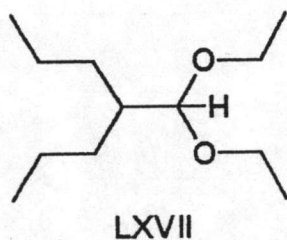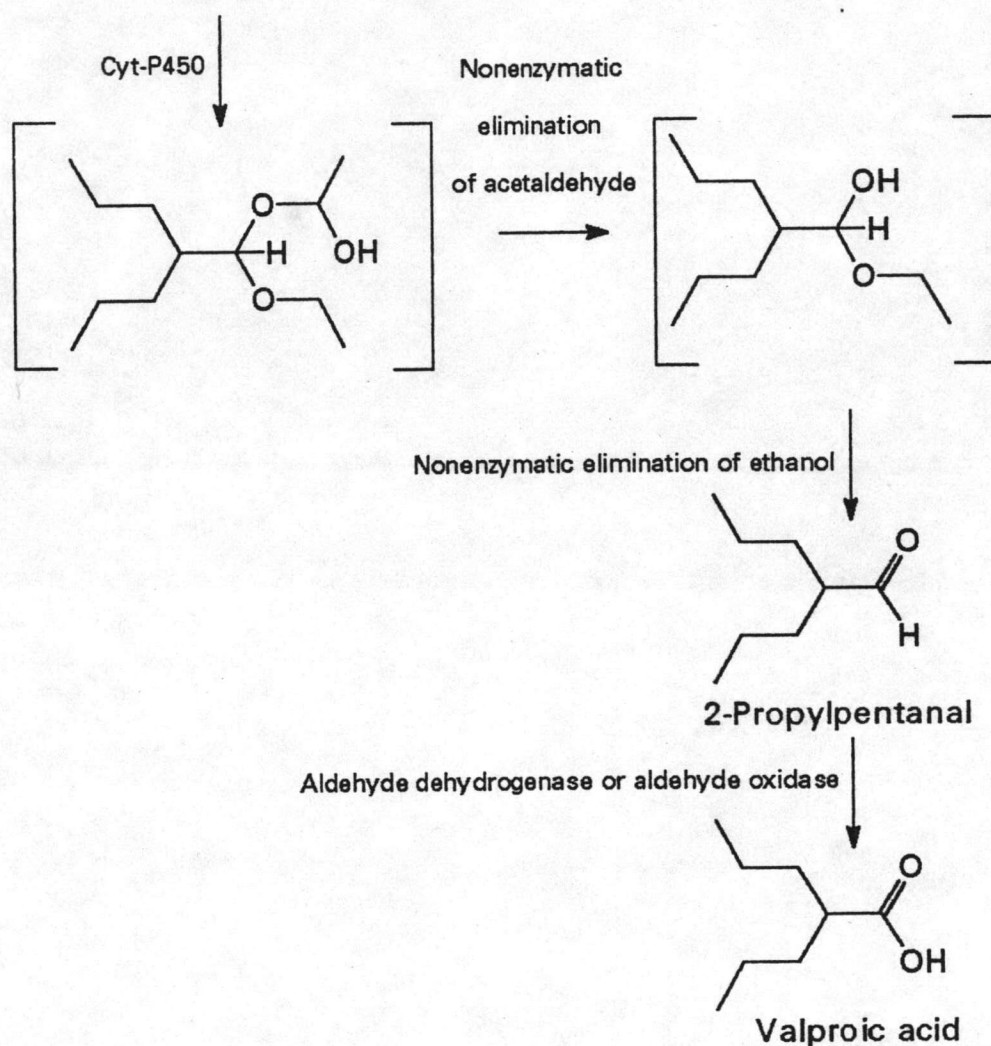
Figure 9. Proposed pathway for the enzymatic oxidation of 2-propylpentanal diethyl acetal. Brackets indicate chemically unstable hemiacetal intermediates. (Vicchio and Callery, 1989)

Pyridoxine is one of the three similar compounds that may be referred to as vitamin B_6, the other two are pyridoxal and pyridoxamine. In the body, all three are converted to pyridoxal-5-phosphate which is the coenzyme for a number extremly important metabolic reaction of the α-amino acid including transmination, racemization, and decarboxylation. Only pyridoxine hydrochloride, however, is used in pharmaceutical preparation, it is the 3-hydroxy-4,5-di(hydroxymethyl)-2-methylpyridine (Aboul-Enein and Loutfy, 1984).

Pyridoxine is a water-soluble vitamin and readily absorbed in the jejunum. It has low acute toxicity and elicits no outstanding pharmacodynamic actions after either oral or intravenous administration (Marcus and Coulston, 1990). Moreover, severe vitamin B_6 deficiencies can lead to epileptic-like convulsive seizures, and the convulsions can be controlled by treatment with pyridoxine. It is believed that the convulsions are due to a belowed normal availability of the CNS neurotransmitter, gamma-aminobutyric acid (GABA), from glutamic acid decarboxylation, which is effected by the coenzyme pyridoxal-5-phosphate (Marcus and Coulston, 1990; Leklem, 1994).

Since aliphatic acetals are structurally resemble to cyclic acetals, prodrug of valproic acid in form of cyclic acetals of pyridoxine may also be candidate substrate for similar oxidation reaction. Pyridoxine is a trihydric vitamin, so there are two possible structures of its cyclic acetals either.

1. the six-membered cyclic acetal, the 5-hydroxymethyl -8-methyl-2-(1-propylbutyl)-4H-dioxino[4,5-c]pyridine or α^4,3-O-(2-propyl pentanylidene)pyridoxine, CU-736-10-01 (LXIX).

2. the seven-membered cyclic acetal, the 9-hydroxy-8-methyl-3-(1-propylbutyl)-4H,9H-dioxepino[5,6-c]pyridine or α^4,α^5-O-(2-propyl pentanylidene)pyridoxine (LXX).

Valproic acid is a drug containing carboxyl group, it also can be converted to prodrug esters from which the active valproic acid are regenerated by esterases. Mono-, di-, trisubstituted esters of pyridoxine have been decided to synthesize in this research including.

1. 3-Hydroxy-4-hydroxymethyl-2-methyl-5-(2-propyl pentanoyl) oxymethylpyridine or pyridoxine-5-valproate, CU-736-10-02 (LXXI).

2. 4,5-Di(hydroxymethyl)-2-methyl-3-(2-propylpentanoyl)oxy

pyridine or pyridoxine-3-valproate, CU-736-10-03 (LXXII).

  3. 5-Hydroxy-2-methyl-3-(2-propylpentanoyl)oxy-4-(2-propyl pentanoyl)oxymethylpyridine or pyridoxine-3,4-divalproate, CU-736-10-04 (LXXIII).

  4. 4-Hydroxymethyl-2-methyl-3-(2-propylpentanoyl)oxy-5-(2-propylpentanoyl)oxymethylpyridine or pyridoxine-3,5-divalproate, CU-736-10-05 (LXXIV).

  5. 2-Methyl-3-(2-propylpentanoyl)oxy-4,5-di[(2-propyl pentanoyl)oxymethyl]pyridine or pyridoxine trivalproate, CU-736-10-06 (LXV).

  The synthetic approach for these seven compounds is shown in Figure 11-14.
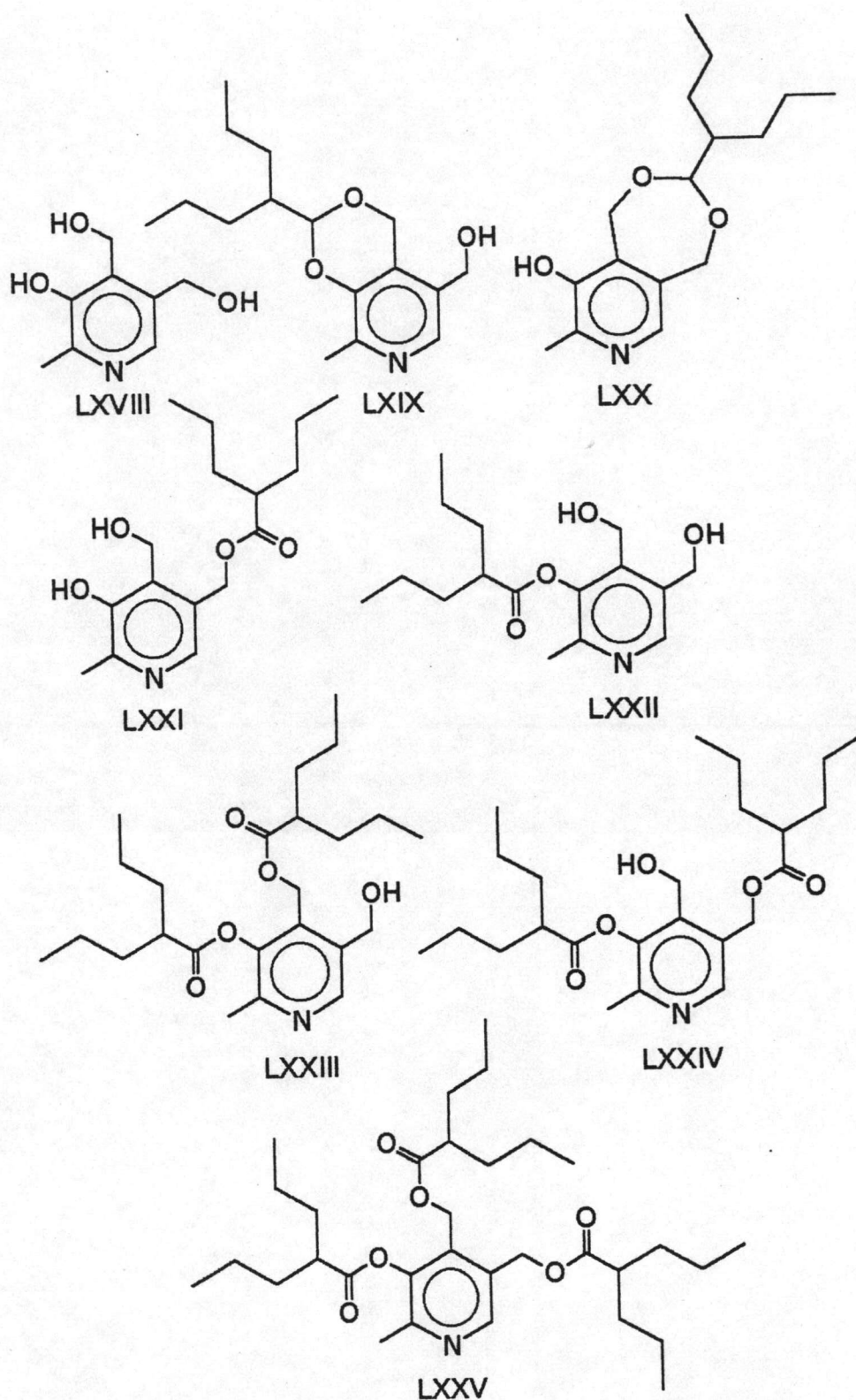
Figure 10. The chemical structures of pyridoxine (LXVIII) and the valproic acid derivatives proposed to synthesize in this research.
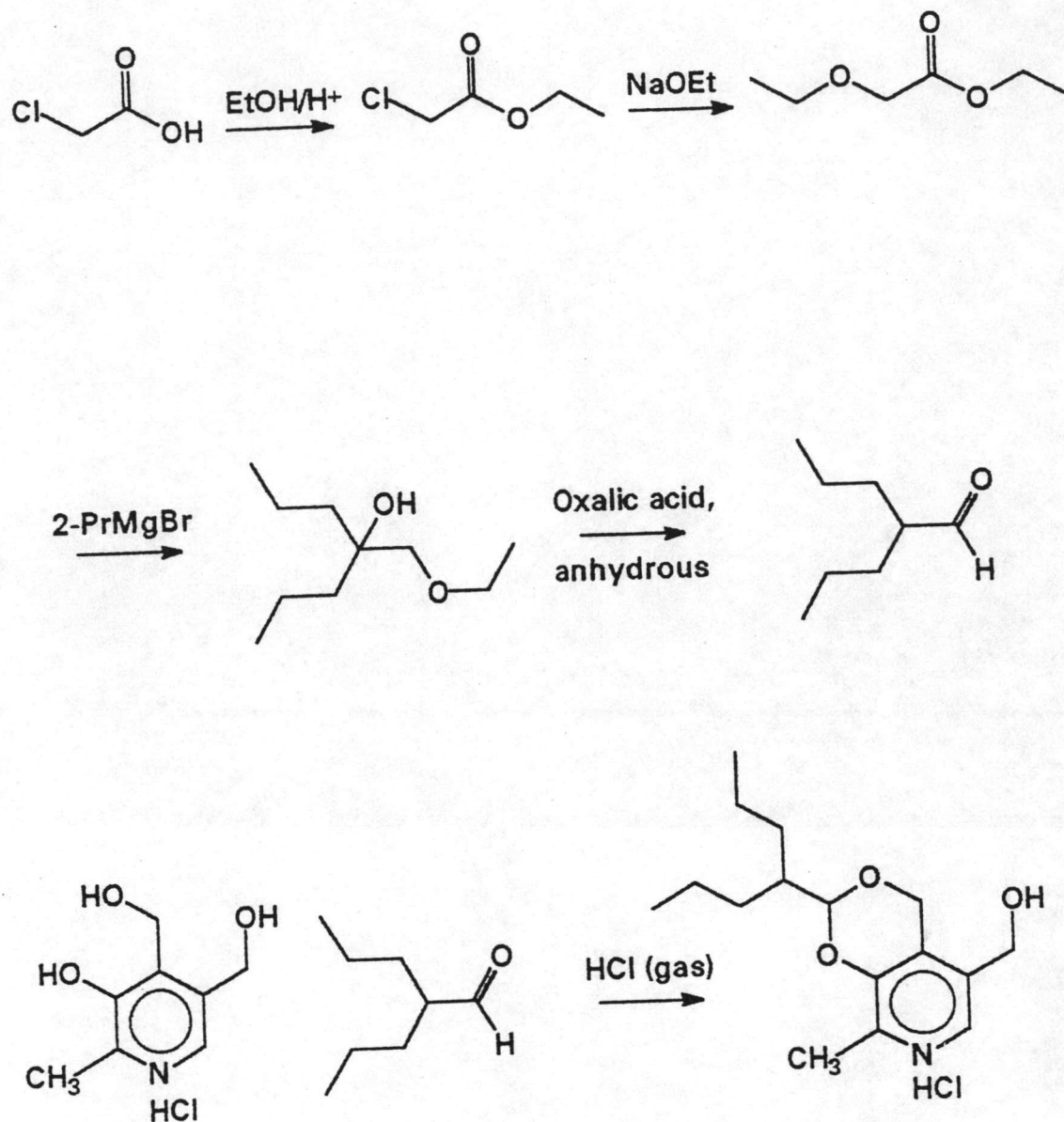
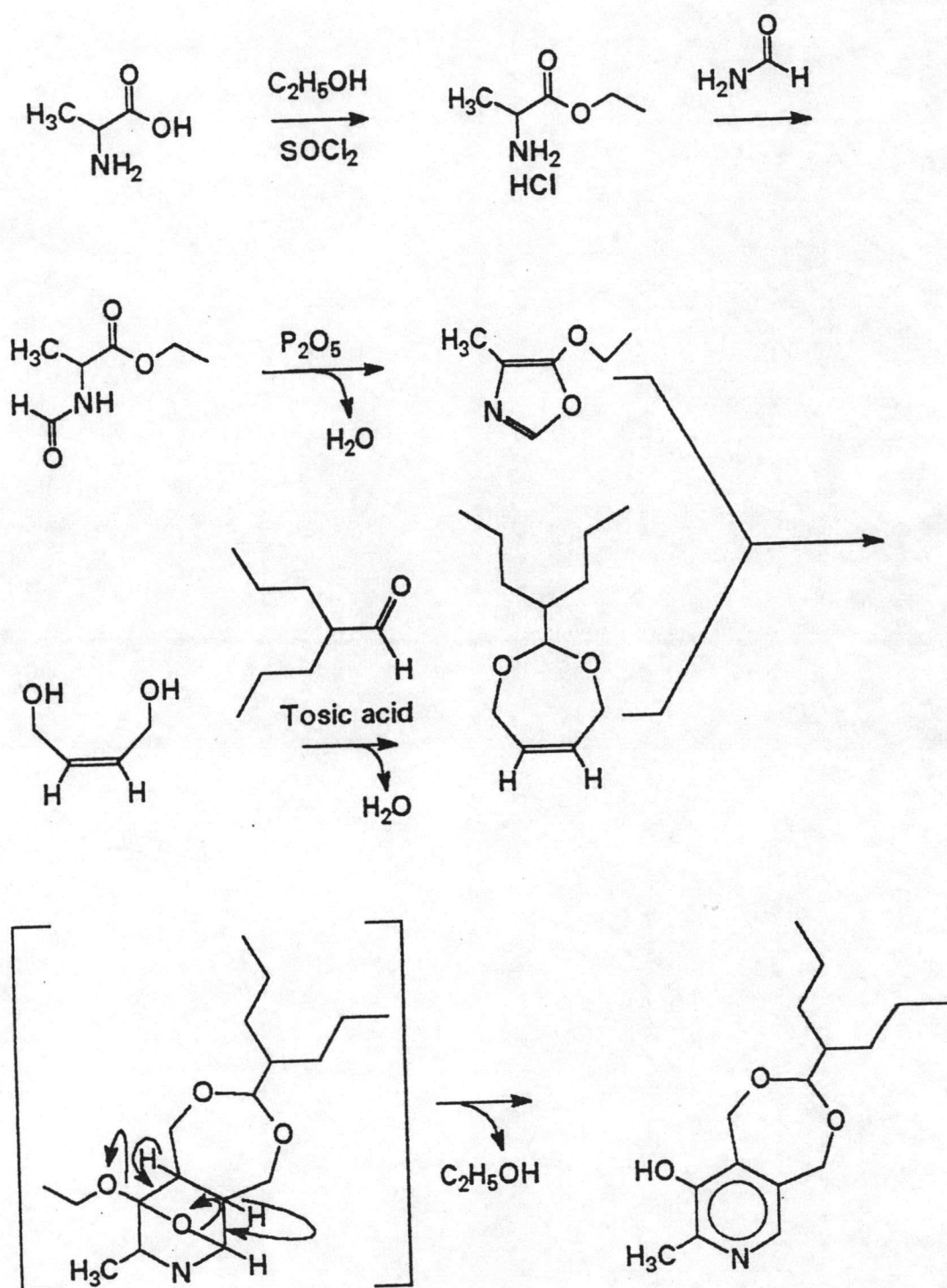Figure 11. The synthetic approach of α^4,3-O-(2-propylpentanylidene) pyridoxine (LXIX).

Figure 12. The synthetic approach of α^4,α^5-O-(2-propylpentanylidene) pyridoxine (LXX).
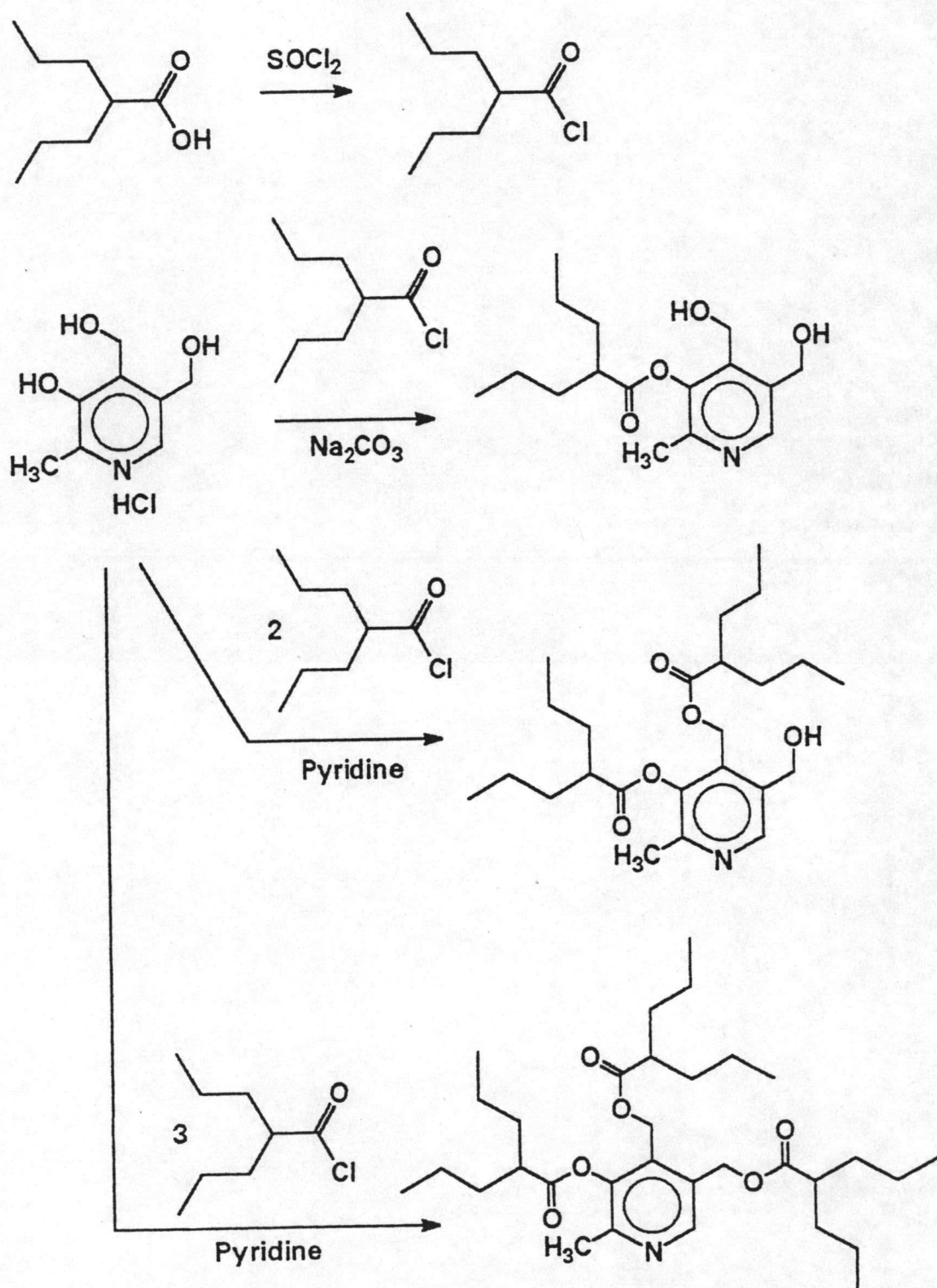
Figure 13. The synthetic approach of pyridoxine-3-valproate (LXXII), pyridoxine-3,4-divalproate (LXXIII) and pyridoxine trivalproate (LXXV).
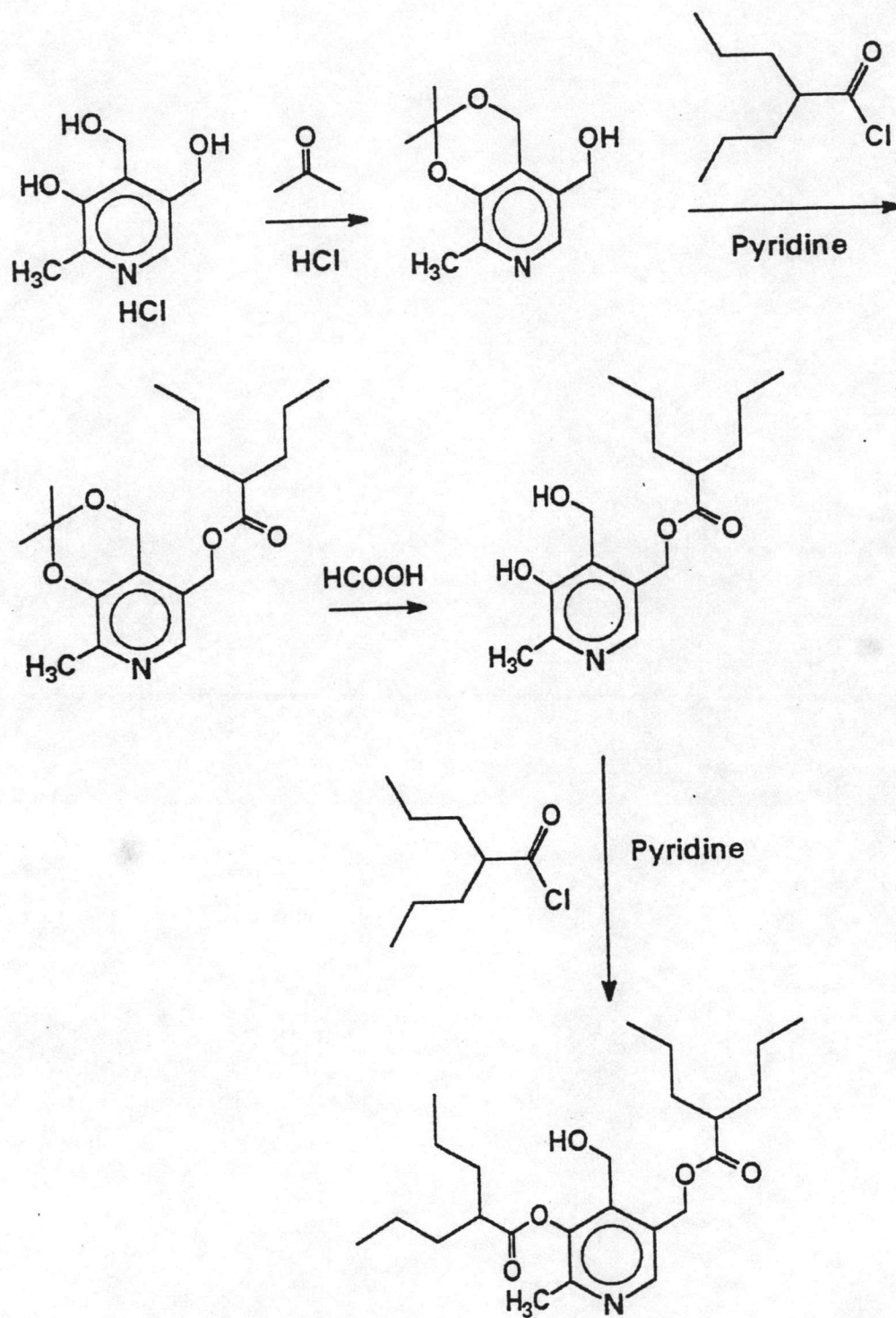
Figure 14. The synthetic approach of pyridoxine-5-valproate (LXXI), pyridoxine-3,5-divalproate (LXXIV).