CHAPTER I

INTRODUCTION

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Epilepsy is one of the most common neurologic disorders, with a prevalence of approximately 1%, second only to stroke (Lloyd and Gillenwater, 1994). It has been defined as a chronic neurologic condition characterized by recurrent spontaneous seizures not caused by active cerebral disease. Seizure are sudden, involuntary, time-limited alterations in behavior associated with excessive discharges of cerebral neuron, in which there is a disturbance of movement, sensation, behavior, perception, and/or consciousness (Clark,1984).

Epileptic seizure can be characterized by specific Electroencephalogram (EEG) patterns and behavioral events during the seizures. The most widely used classification system is the International Classification of Epileptic Seizures (ICES) introduced in 1981 by the International League Against Epilepsy.

I . Partial seizures (seizures beginning locally)

A. Simple partial seizures (consciousness not impaired ; SPS)

1. With motor symptoms

2. With somatosensory or special sensory symptoms

3. With autonomic symptoms
4. With psychic symptoms

B. Complex partial seizures (with impairment of consciousness ; CPS)

1. Beginning as simple partial seizures and progressing to impairment of consciousness
   a. Without automatisms
   b. With automatisms
2. With impairment of consciousness at onset
   a. With no other features
   b. With features of simple partial seizures
   c. With automatisms

C. Partial seizures (simple or complex) , secondarily generalized

II. Generalized seizures (bilaterally symmetric, without localized onset)

A. Absence seizures
   1. True absence ("petit mal")
   2. Atypical absence

B. Myoclonic seizures

C. Clonic seizures

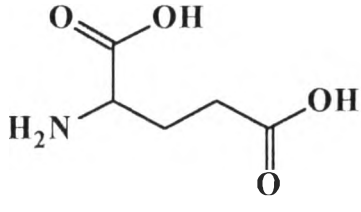
D. Tonic seizures

E. Tonic-clonic seizures ("grand mal")(GTC)

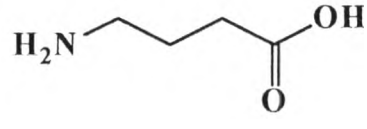
F. Atonic seizures

III. Unclassified seizures

Symptomatic epilepsy can result from specific physiological phenomena such as brain tumors, syphilis, cerebral arteriosclerosis, multiple sclerosis, Buerger's disease, Pick's disease, Alzheimer's disease, sunstroke, acute intoxication, lead poisoning, head trauma, vitamin B6 deficiency, hypoglycemia, and labor. The biochemical mechanism leading to central nervous system electrical discharges and epilepsy are unknown, but there may be multiple mechanism involved, However, it had been shown that convulsions arise when there is an imbalance in two principal neurotransmitters in the brain, L-glutamic acid, an excitatory neurotransmitter, and γ-aminobutyric acid (GABA), an inhibitory neurotransmitter (Nanvati and Silverman, 1989).



L-Glutamic acid



GABA

Anticonvulsant drugs are used in prevention and control of epileptic seizure. An ideal antiepileptic drug should completely suppress seizures in dosage that does not cause sedative or other undesirable side effects. Its onset of action should be rapid and should have a long duration of action for prevention of recurrent seizures (Vida,1989).

The first drug which was a meaningful contribution to controlling the disorder was potassium bromide, introduced by Locock in 1857. Bromides were the only useful therapy until the development of

the barbiturates in the next century. After phenobarbital was introduced in 1912, many analogues of phenobarbital and many other anticonvulsants were synthesized (Bleck and Klawans, 1992). Nowadays, there are many antiepileptic drugs, used for controlling many types of seizures, which can be classified by their structures as follows (Figure 1) :

1. Barbiturates : Phenobarbital (I), Mephobarbital (II), Metharbital (III)
2. Deoxybarbiturate : Primidone (IV)
3. Hydantoins : Phenytoin (V), Mephenytoin (VI), Ethotoin (VII)
4. Oxazolidinediones : Trimethadione (VIII), Dimethadione (IX)
5. Succinimides : Phensuximide (X), Methsuximide (XI), Ethosuximide (XII)
6. Urea and monoacylureas : Phenacemide (XIII), Carbamazepine (XIV)
7. Benzodiazepine : Clonazepam (XV), Diazepam (XVI), Clorazepam (XVII)
8. Branch chain carboxylic acid : Valproic acid (XVIII)
9. Sulfonamide : Acetazolamide (XIX)

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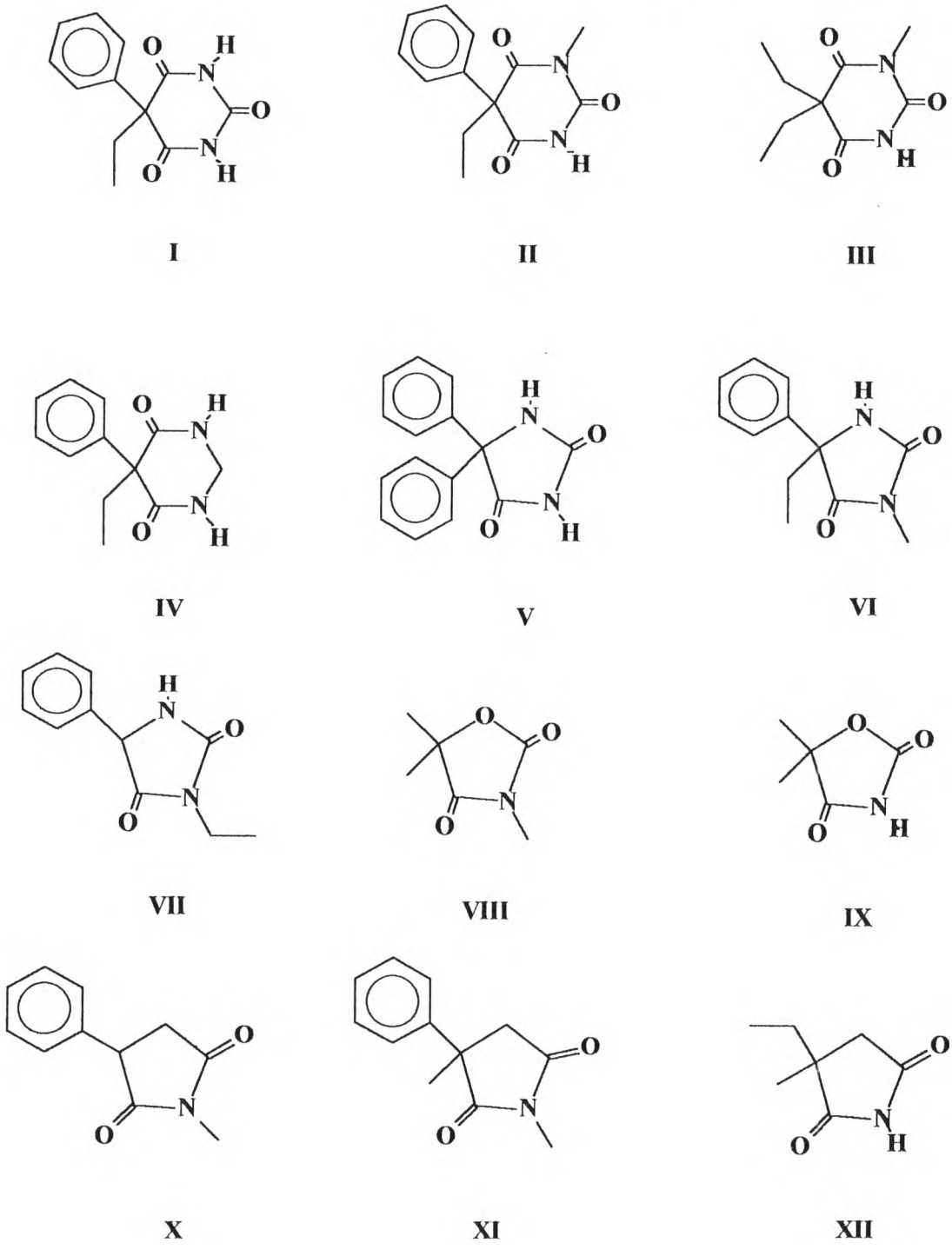
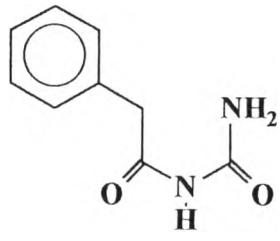


Figure 1 Example of chemical structure of antiepileptic drugs



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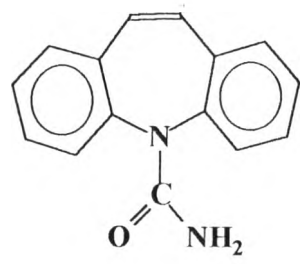

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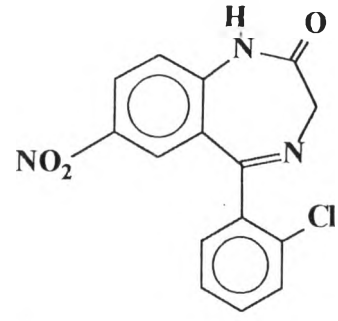

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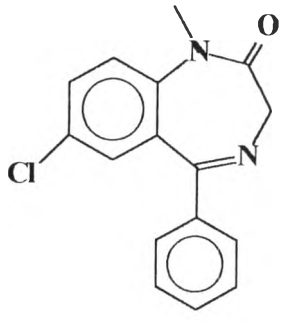

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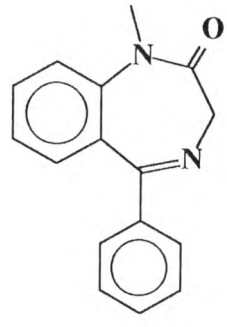

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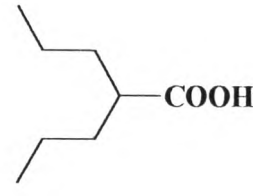

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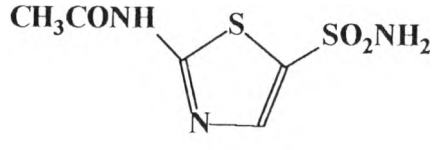


XIX

Figure 1 (continue.) Example of chemical structure of antiepileptic drugs

The mechanism of action of antiseizure drugs falls into three major catagories. The first mechanism occurs in drugs which are effective against generalized tonic-clonic and partial seizures, such as phenytoin and carbamazepine. These drugs appear to reduce sustained high-frequency repititive firing of action potentials by delaying recovery of sodium channels from activation. The second mechanism appears to involve enhanced γ-aminobutyric acid (GABA) -mediated synaptic inhibition, an effect mediated by an action presynaptically of some drugs and post-synaptically of others. This mechanism is founded in drugs which are effective against myoclonic seizure such as benzodiazepines and barbiturates. The final mechanism which occurs in drugs effective against a less common form of epileptic seizure, absence seizures, such as ethosuximide and trimethadione, appears to reduce low-threshold (T-type) calcium channel current (McNamara, 1996).

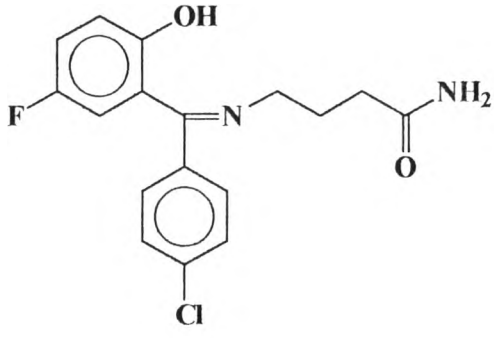
From modern knowledge of putative pathophysiological epileptogenic mechanisms, many novel agents have been developed. For example, it has been known that the antiepileptic drugs in common clinical use such as benzodiazepines, barbiturates and valproate exert their anticonvulsant action by enhancing GABA-mediated inhibition in the CNS. This recognition has led to the rational development of several potentially useful new drugs that also enhance central inhibition through an interaction with the GABA system in many ways. The most direct way is using drugs which can enter the brain and can be converted to GABA or compounds structurally related to $GABA_A$ receptor agonist activity or to analogues of other endogenous inhibitory substances, such as glycine

or taurine (Figure 2). One of the successful results of this approach is progabide (XX), a GABA analogue with $GABA_A$ agonist activity, which is converted to two additional GABA agonists (SL 75012 (XXI) and GABAamide) and ultimately to GABA itself. Other examples are milacemide (XXII), a glycine prodrug, and taltrimide (XXIII), an analogue of taurine (Porter and Rogawski, 1993).

Inhibition of GABA catabolic enzyme, GABA transaminase (GABA-T), which enhances the synaptic availability of GABA by preventing its breakdown to glutamate and succinic semialdehyde (Figure 3) is one of the alternative ways. GABA-T inhibitor such as vigabatrin (XXIV) is among the most promising of the new antiepileptic drugs.

Blockage of GABA uptake into neurones or glia is another way to enhance the GABA levels. Nipecotic acid and guavacine, two conventional GABA uptake blockers, have anticonvulsant activity, but these drugs do not penetrate the blood-brain barrier. Therefore, several nipecotic acid derivatives have been developed such as CI-966 (XXV) and tiagabine (XXVI).

Apart from enhancement of inhibition, blockage of the synaptic excitation mediated by N-methyl-D-aspartate-type (NMDA) glutamate receptors is another particularly promising avenue for anticonvulsant drug development. Drugs antagonizing NMDA receptor can be classified into 2 types, competitive (Figure 4) and non-competitive antagonists (Figure 5). The first potent and selective competitive antagonist of the NMDA



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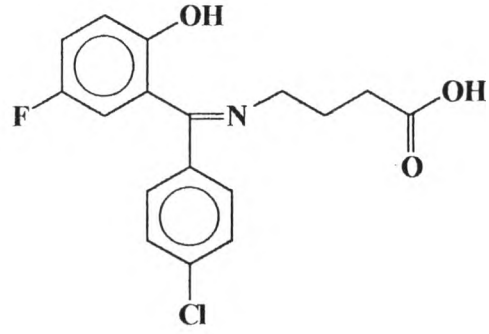
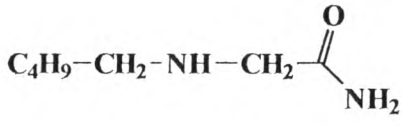


XXI



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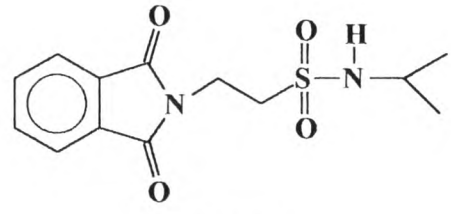

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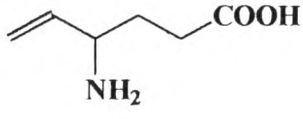

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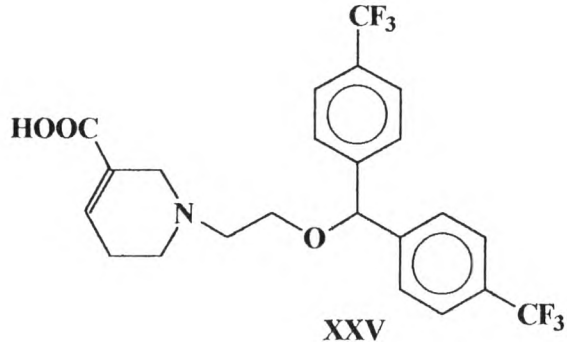

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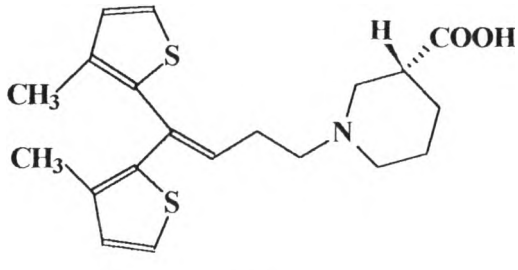


XXVI

Figure 2 Chemical structure of some drugs enhancing GABA level

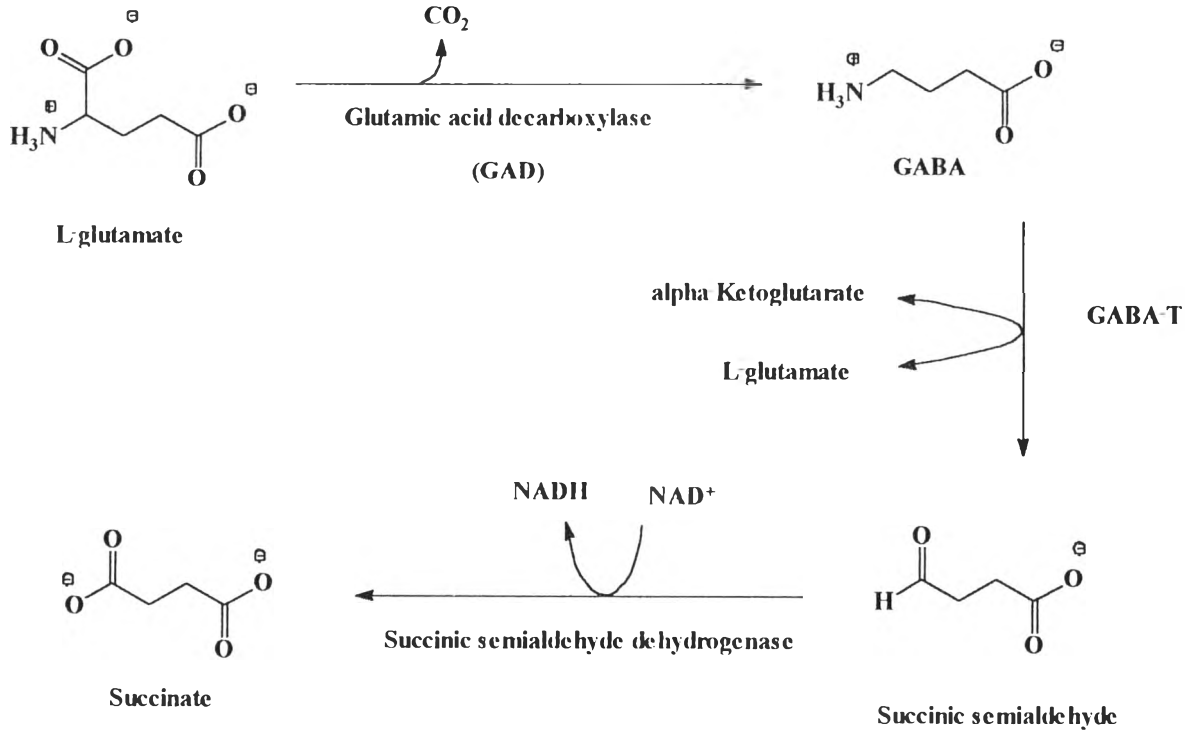
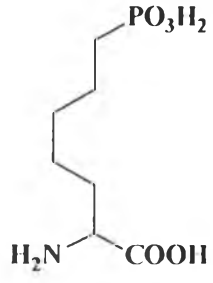


Figure 3 Metabolic pathway of L-Glutamate

recognition site to be described are straight-chain analogs of glutamate with the ω-carboxyl group replaced by a phosphonic acid moiety, such as 2-amino-7-phosphonoheptanoic acid (APH, XXVII) and 2-amino-5-phosphonovaleric acid (APV, XXVIII), that competitively block the glutamate recognition site of the NMDA receptor-channel complex. But these compounds are less active than phenytoin or phenobarbital following systemic administration, due to their limited blood-brain barrier penetration, and are inactive orally. To overcome this problem, cyclic analogues of APV and APH, CPP (XXIX) and CGS 19755 (XXX), respectively, were synthesized. Recently, another analogue of APH, NPC 12626 (XXXI), has been described. Despite their high anticonvulsant potencies, all of the competitive NMDA receptor antagonists have the unfortunate problem of causing behavioral side effects that are related specifically to their effects, including disruption of motor performance and impairment of memory. There is a new series of orally active competitive NMDA receptor antagonists which has recently been described, such as CGP 37849 (XXXII), a 3-unsaturated derivative of APV, and its carboxyethylester, CGP 39551 (XXXIII), and the dextrorotatory enantiomer of the 1- unsaturated derivative of CPP, D-CPP-ene (XXXIV).

The potent non-competitive antagonists are phencyclidine (XXXV) and ketamine (XXXVI), the dissociative anesthetics, and dibenzocycloalkenimine dizocilpine (MK-801, XXXVII). Of particular interest in this group is ADCI (XXXVIII) , a carboxamide analogue of



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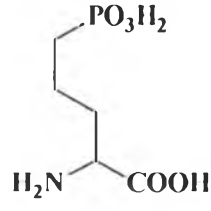

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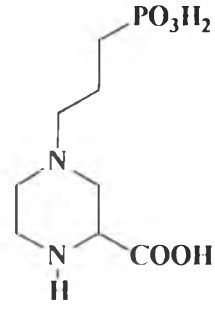

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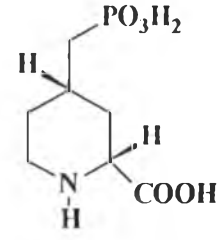

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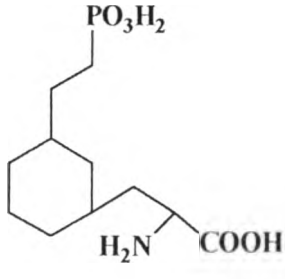

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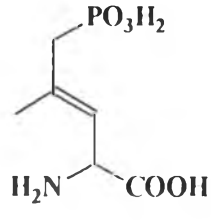

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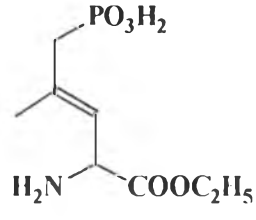

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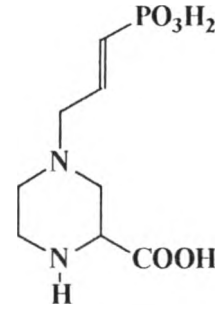
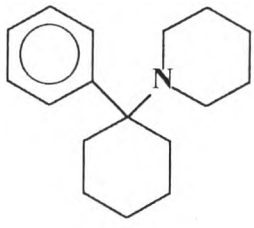


XXXIV

Figure 4 Chemical structure of sone competitive NMDA receptor antagonists



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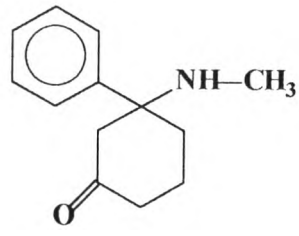

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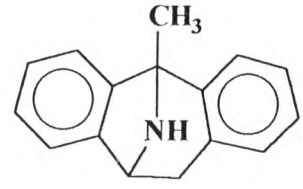

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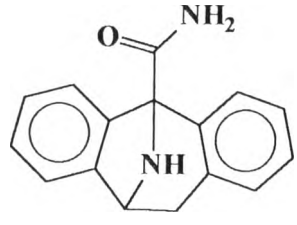


XXXVIII

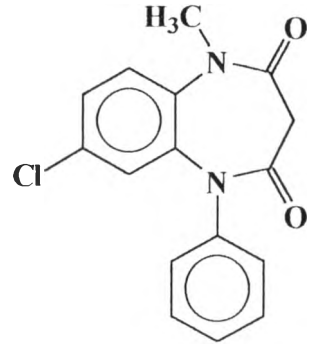
Figure 5 Chemical structure of some non-competitive NMDA receptor antagonists

dizocilpine, which has a therapeutic index comparable to that of carbamazepine.

Moreover, there are several other sites on the NMDA receptor channel complex at which pharmacologically antagonists can inhibit NMDA receptor-mediated responses and these could potentially serve as targets of anticonvulsant drugs, including the strychnine-insensitive glycine coagonist site and the polyamine modulatory site. A number of more or less selective glycine site antagonists have been described including 7-chlorokynurenic acid, cycloleucine, quinoxaline analogues, 5-substituted indole-2-carboxylic acids and 1-aminocyclobutane-1-carboxylic acid. In addition, HA-966 (1-hydroxy-3-amino-2-pyrrolidone) has recently been identified as a partial agonist at the glycine site. Antagonists of the polyamine site include ifenprodil, an antiischemic drug, and its analog SL 82.0715.

In addition to this approach, there are many novel drugs that have been developed. Some analogues acts by binding to benzodiazepine receptors, such as clobazam (XXXIX), and flumazenil (XL) (Figure 6).

There is a large number of anticonvulsant drugs under development that have spectrum of activity in animal seizure models that is similar to that of phenytoin including zonisamide (XLI), denzimol (XLII), nafimidone (XLIII), CGS 18416A (XLIV), lamotrigine (XLV), ralitoline (XLVI), topiramate (XLVII), flunarizine (XLVIII), oxcarbazepine (XLIX), and remacemide (L) (Figure 7). It is conceivable



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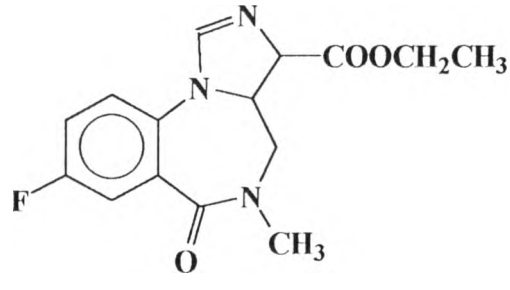
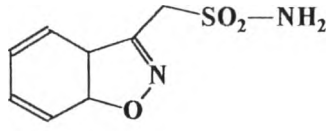
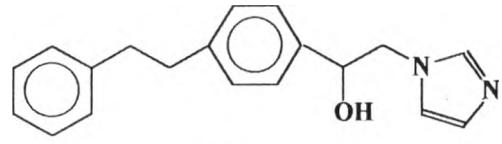


XL

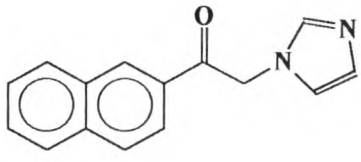
Figure 6 Chemical structure of some drugs act by binding to benzodiazepine receptors



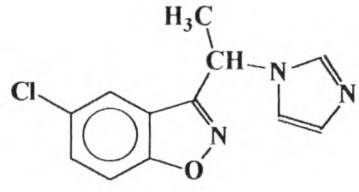
XLI



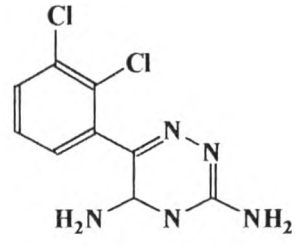
XLII



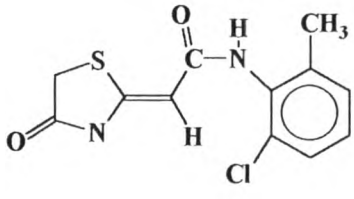
XLIII



XLIV



XLV



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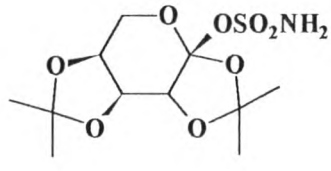

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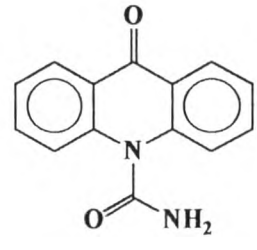

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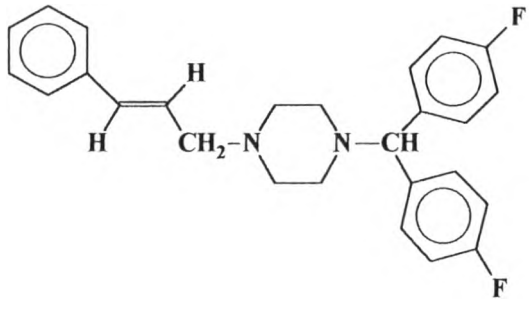

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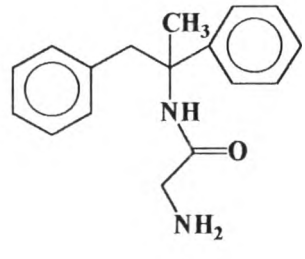


L

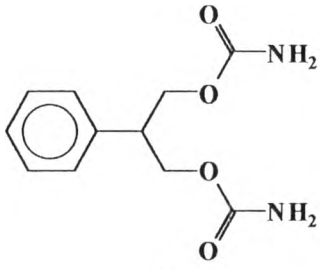
Figure 7 Chemical structure of some ansticonvulsansts having spectrum activity similar to phenytoin

that these compounds could act on Na^+ channels in a way similar to that of phenytoin, although this will need to be verified experimentally.

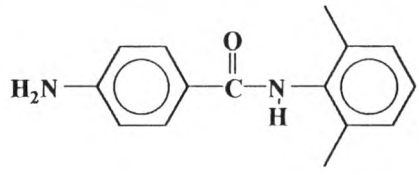
Moreover, there are many drugs which have novel spectrum of anticonvulsant activity (Figure 8) e.g. felbamate (LI), LY 201116 (LII), Gabapentin (LIII), Eterobarb (LIV), U-54494A (LV), D-19274 (LVI), AHR 12245 (LVII), CI-218872 (LVIII), zopiclone (LIX), zolpidem (LX), and CGS -9896 (LXI).

Although there are many antiepileptic drugs, the research for new active compounds remains, since available antiepileptic drugs are effective in only 60-80% of patients. In addition, most marketed anticonvulsants suffer from a broad range of undesirable side effects such as sedation, teratogenicity, cognitive dulling, blood dyscrasia, and hepatotoxicity. Failure to achieve control of seizures is frequently due to use-limited side effects with increasing dosage of the drugs before satisfactory therapeutic dose is reached (Pacia, 1990).

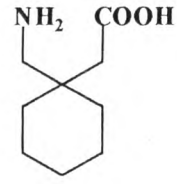
Valproic acid (2-propylpentanoic acid) is one of the most interesting drugs. Its chemical structure is simple and it has broad spectrum of action which includes tonic-clonic, partial complex and absence seizure (Palaty, and Abbott, 1995). However, anticonvulsant potency is considered to be less than those of phenobarbital, phenytoin, and carbamazepine. In addition, the use of valproate in the treatment of epilepsy associate with two major side-effect, teratogenicity and hepatotoxicity (Bialer, 1993).



LI



LII



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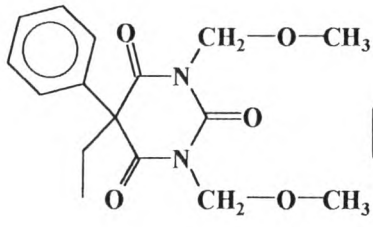

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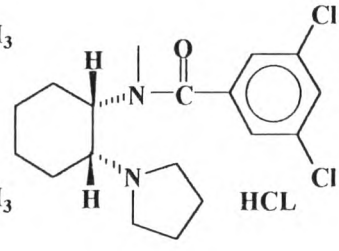
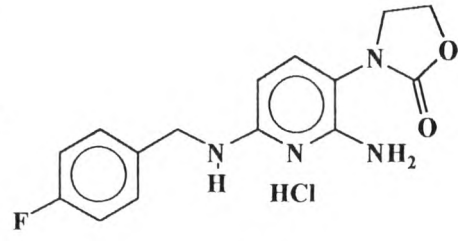
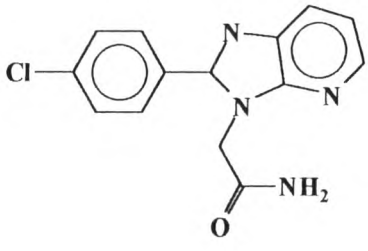


LV



LVI



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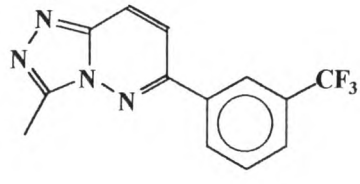
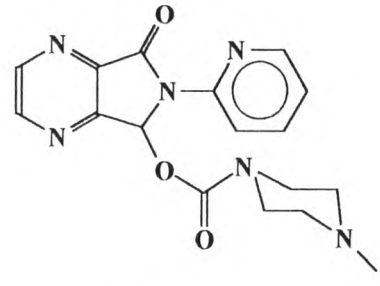
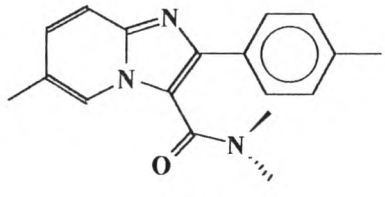


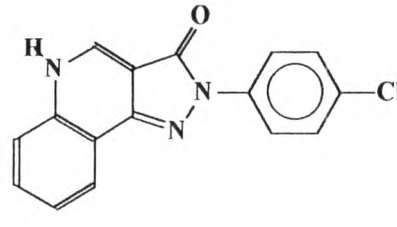
LVIII



LIX



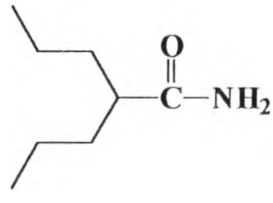
LX



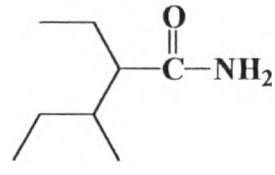
LXI

Figure 8 Chemical structure of some drugs with novel spectrum of anticonvulsant activity

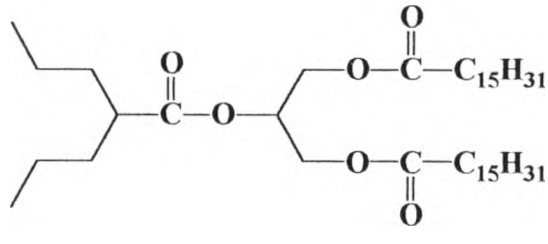
Many derivatives and prodrugs of valproate had been synthesized. For example, valpramide (LXII), a primary amide of valproic acid, has been used in several European countries as an antiepileptic and antipsychotic agent. Valnoctamide (LXIII), an isomer of valpramide, has also been used as anxiolytic drug and it also possess anticonvulsant activity (Hay-Yehia, 1990). Ester of valproate, such as 1,3-dihexadecanoylamino-2-valproyl-propane-2-ol (LXIV), is another form of prodrugs which was developed in order to reduce the side effects of valproic acid (Mergen, 1991).



(LXII)



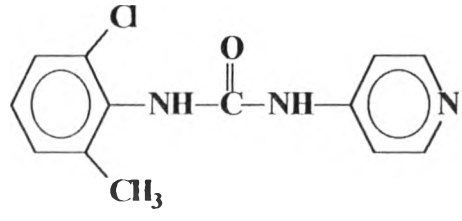
(LXIII)



(LXIV)

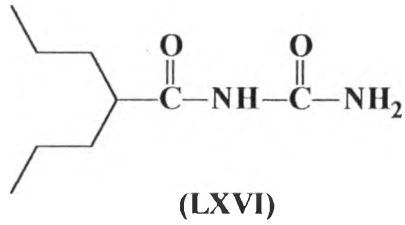
In 1990, Pavia discovered potent anticonvulsant effect of a series of N-phenyl-N′-(4-pyridinyl)urea. N-(2-Chloro-6-methyl)phenyl-N′-(4-pyridinyl)urea (LXV) was most active compound in this series. It

was effective against seizure induced by maximum electroshock but did not protect mice from clonic seizure produced by pentylenetetrazole. This profile suggests that LXV would be a useful treatment aganist generalized tonic-clonic and partial seizures (Pavia, 1990).



(LXV)

In 1992, W. Janwitayanuchit (Wichan Janwitayanuchit, 1992) had synthesized valproylurea (LXVI). The compound has been evaluated for the anticonvulsant activity with standard MES and PTZ test medel. The study revealed that LXVI possesses good potective activity and low toxicity (Thongchai Sooksawate, 1995). Moreover, LXVI was proved to be less hepatotoxic than valproic acid (Watcharaporn Patchamart, 1996).



(LXVI)

In 1996, P. Rodesittisuk (Pornchai Rodesittisuk, 1996) had synthesized the valproylurea analogues (LXVII) which also proved to possess good activity.

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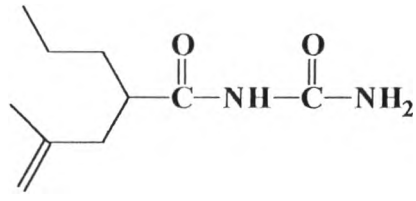
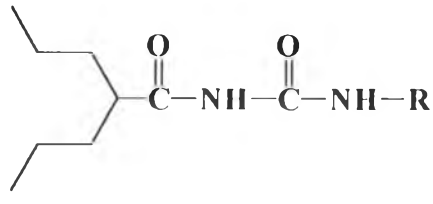
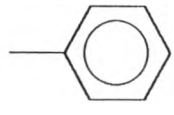
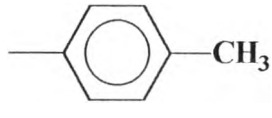


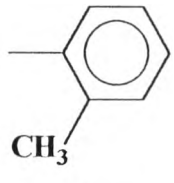
LXVII

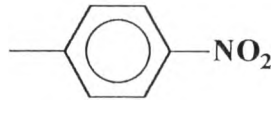
This research aimed to synthesized N-(2-propylpentanoyl)-N′-arylurea. The aryl moiety (R) in the target compound represent each aryl part of the diarylurea in LXV. The structures can be shown as follows :

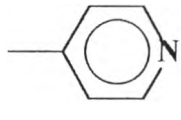


R =  **CU -763-13-05**

 **CU -763-13-06**

 **CU -736-13-07**

 **CU -763-13-08**

 **CU -763-13-09**

The synthetic approach for the target compounds can be shown in Figure 9. The valproyl chloride, which can be synthesized by the conventional method from valproic acid, can be converted to either the acylisothiocyanate or acylisocyanate. In former case, the acid chloride was allowed to react with potassium thiocyanate to form the isothiocyanate which is then reacted with the amine. Oxidation of the thiocarbonyl in the thiourea derivative should yield its corresponding urea. In latter case, the acylisocyanate can be formed by reacting acid chloride with potassium cyanate. Addition of amine should yield the urea derivative.

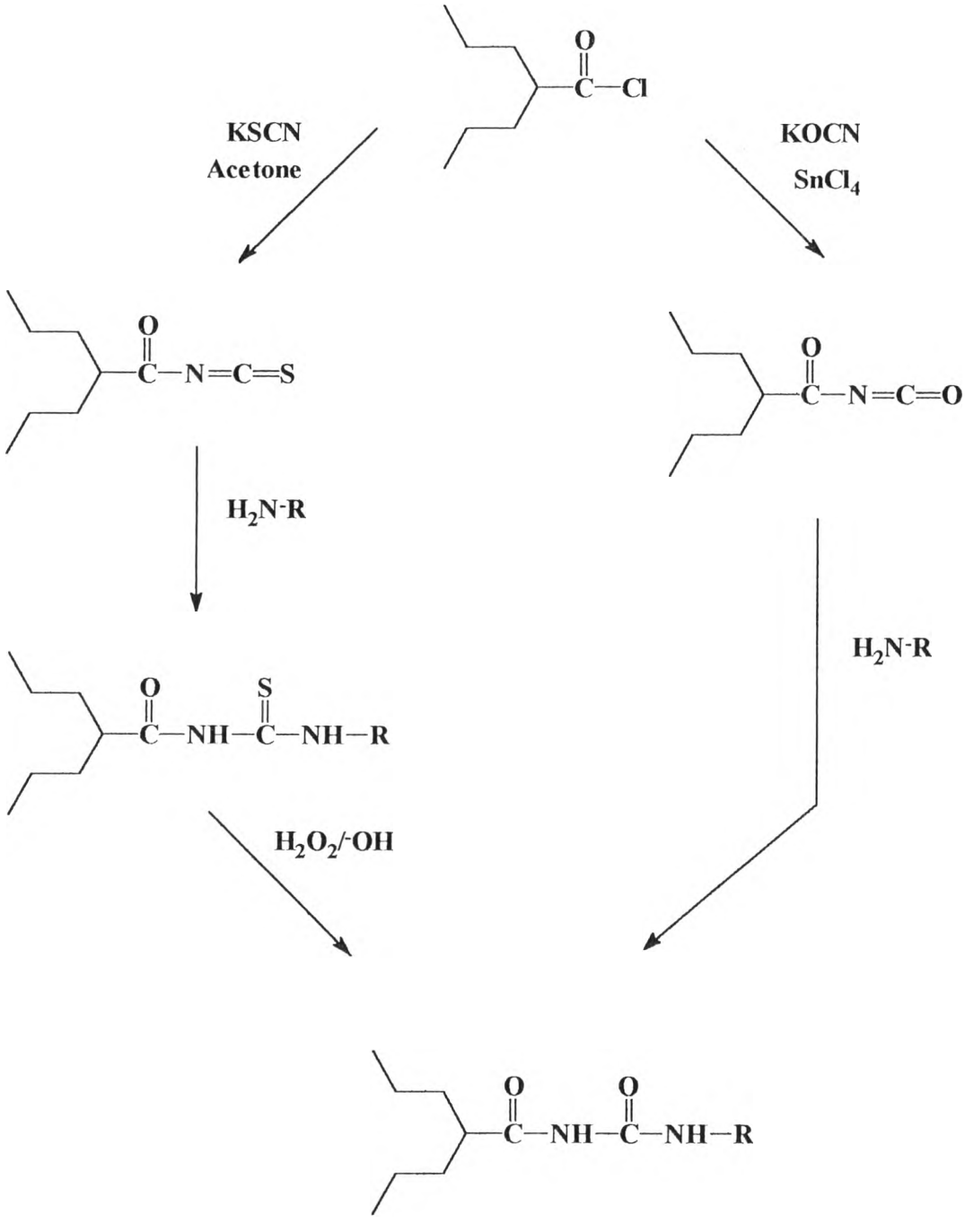


Figure 9 Synthetic approach of N-acyl-N′-arylurea