CHAPTER I

INTRODUCTION

Epilepsy, affects approximately 1% of the worldwide population and the second most common neurologic disorder after stroke, is used collectively (Chan, 1992) to include a group of syndromes of central nervous system (CNS) disorder characteristized by sudden, transitory, and recurring seizure involving one or more of the following system: motor (convulsion), sensory, automatic, or psychic. Most investigators do not include single isolated seizures in the definition of epilepsy. Abnormal and excessive discharges in the electroencephalogram (EEG) nearly always accompany the seizures. Synonyms of the term epilepsy are convulsion disorders and seizure disorders.

The International League Against Epilepsy (ILAE), through its Commission on Classification and Terminology, adopted an international classification of epilepsy seizures (ICES) in 1981. Seizures are classified on the basis of distinctive behavioral features as well as on ictal and interictal electroencephalographic (EEG) findings and are divided broadly into three groups (Ambre, 1994): partial (focal), generalized, and unclassified epileptic seizures.

- Partial seizures arisen part of one cerebral hemisphere and are often accompanied by focal EEG abnormalities. They are subdivided according to whether consciousness is maintained (simple) or impaired (complex).

- Generalized seizures are characterized by impaired consciousness with clinical or EEG evidence indicating movement of both hemisphere initially; they are classified as nonconvulsion or convulsion subtypes.

- Unclassified seizures include neonatal seizures that differ greatly from those in older patients and often represent the initial

symptom of a serious neurologic disorder. A range of behavior (including apnea and autonomic phenomena) may be seizures, but not all are reflected in the EEG findings. Thus, neonatal seizures may be difficult to diagnose and classify.

In 1989, a more complete description of the various types of seizure has been provided. The commission on Classification and Terminology of the ILAE classified the epilepsies on the basis of seizure type (localization-related or generalized) and seizure etiology (idiopathic or symptomatic).

Epilepsies and epileptic syndromes were classified into four types:

- Localization-related (focal, local, partial) epilepsies and syndromes.

A. Idiopathic (with age-related onset).

1. Benign childhood epilepsy with centrotemporal spike (Rolandic).
2. Chlidhood epilepsy with occipital paroxysms.
3. Primary reading epilepsy.

B. Symptomatic.

1. Chronic progressive epilepsia partialis continua of childhood (Kojewnikow's syndrome).
2. Syndrome characterized by seizures with specific modes of precipitation (eg. reflex, startle epilepsy).
3. Temporal lobe epilepsies.
4. Frontal lobe epilepsies.
5. Parietal lobe epilepsies.
6. Occipital lobe epilepsies.

C. Cryptogenic.

- Generalized epilepsies and syndromes.

A. Idiopathic (with age-related onset-listed in order of age).

1. Benign neoatal familial convulsions.
2. Benign neonatal convulsions.
3. Childhood absence epilepsy (pyknolepsy).
4. Juvenile myoclonic epilepsy (impulsive petit mal of Janz).
5. Epilepsy with gran mal (GTCS) seizures on awakening.
6. Epilepsies with seizures precipitated by specific modes of activation.

B. Cryptogenic or symptomatic (in order of age).

1. West syndrome (infantile spasms, Blitz-Nick-Salaam Krampfe).
2. Lennox-Gastaut syndrome.
3. Epilepsy with myoclonic-astatic seizures.
4. Epilepsy with myoclonic absense.

C. Symptomatic.

1. Nonspecific etiology.

a. Early myoclonic encephalopathy.
b. Early infantile epileptic encephalopathy with suppression burst.

2. Specific syndromes.

Epileptic seizures may complicate many disease states. Diseases in which seizures are a presenting or predominant feature are included in this category.

- Epilepsies and syndromes undetermined whether focal or generalized.

A. With both generalized and focal seizures.

1. Neonatal seizures.
2. Severe myoclonic epilepsy of infancy.
3. Epilepsy with continuous spike waves during slow-wave sleep.
4. Acquired epileptic aphasid (Landau-Kleffner syndrome)

B. Without unequivocal generalized or focal features.

All cases with generalized tonic-clonic seizures in which clinical and EEG findings do not permit classification as clearly generalized or localization-related, such as in many cases of sleep-grand mal.

- Special syndromes.

A. Situation-related seizures.

1. Febrile convulsions.
2. Isolated seizures or isolated status epilepticus.
3. Seizures occurring only when there ia an acute metabolic or toxic event associated with factors such as alcohol, drugs, eclampsia, nonketotic hyperglycemia.

There were many reasons that used to explain the pathology of epilepsy, and two of these included:

- Specific physiological phenomena such as brain tumors, cerebral arteriosclerosis, multiple sclerosis, Buerger's disease, Pick's disease, Alzheimer's disease, sunstroke or heat stroke, acute intoxication, lead poisoning, head trauma, vitamin B6 deficiency and hypoglycemia.

- Imbalance in two principal neurotransmitters in the brain, L-glutamic acid (GLU), an excitatory neurotransmitter, and gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. (Rall and Schleifer, 1990; Edafiogho, Hinko, Farrar et al., 1992) When the

concentration of GABA diminishes below a threshold level in the brain, the convulsion is occured.

There are many common drugs used in the treatment of convulsion. They may be categorized, from a structural standpoint (Johnson, 1992;), as follow (See figure 1):

1. Barbiturates

   e.g. - Phenobarbital (I)
   - Mephobarbital (II)
   - Metharbital (III)

2. Hydantoins

   e.g. - Phenytoin (IV)
   - Mephenytoin (V)
   - Ethotoin (VI)

3. Oxazolidinediones

   e.g. - Trimethadione (VII)
   - Paramethadione (VIII)

4. Succinimides

   e.g. - Phensuxinimide (IX)
   - Methsuxinimide (X)
   - Ethosuximide (XI)

5. Benzodiazepines

   e.g. - Clonazepam (XII)
   - Diazepam (XIII)

6. Urea and monourea

   e.g. - Phenacemide (XIV)
   - Carbamazepine (XV)

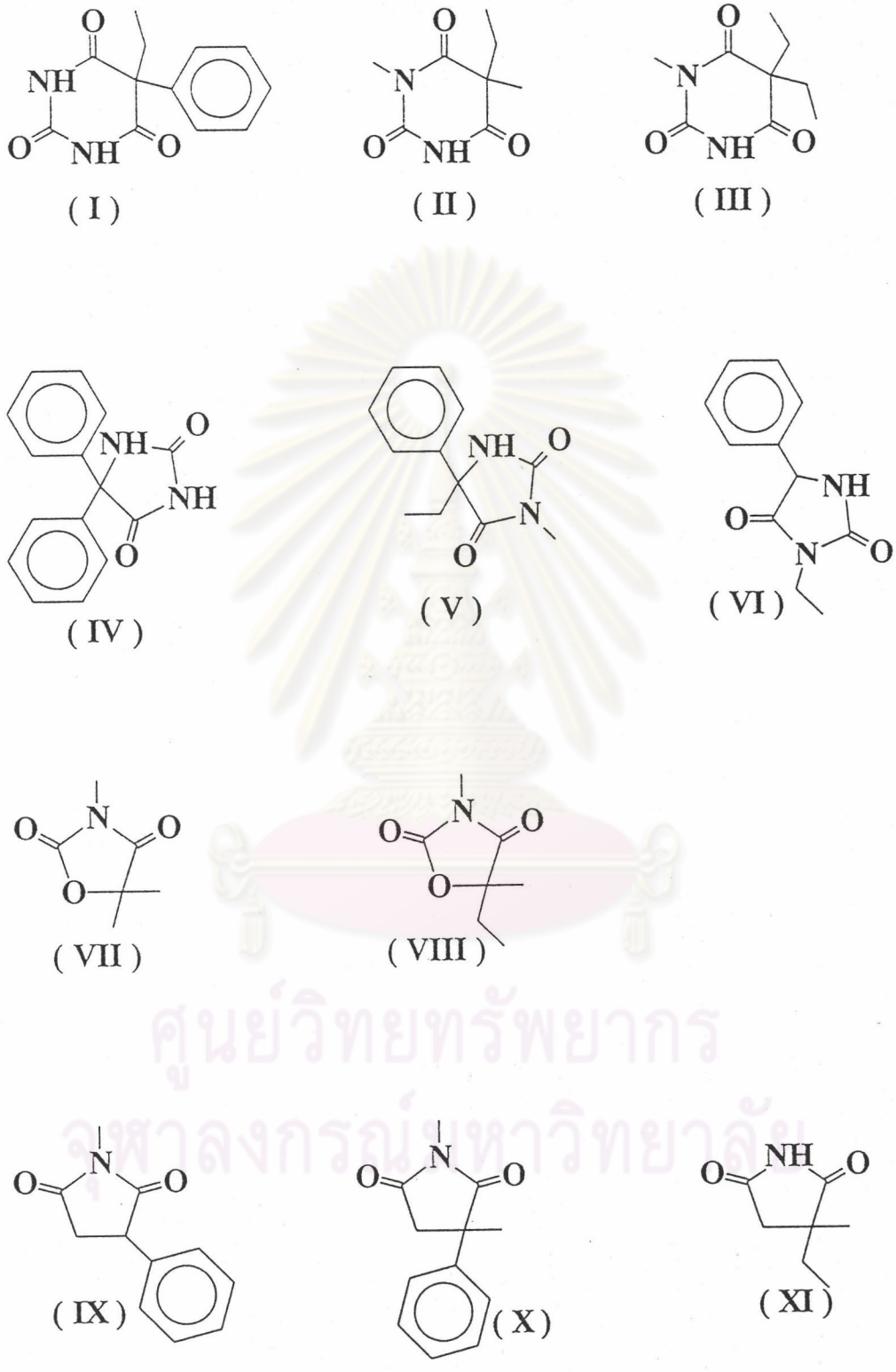
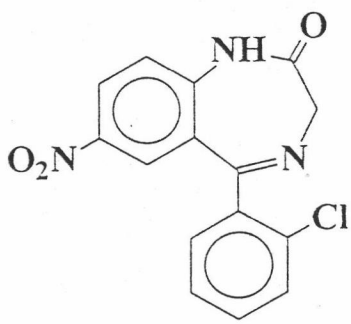


Figure 1. The chemical structures of some common drugs that used in the treatment of convulsion.



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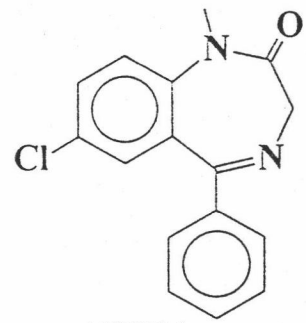

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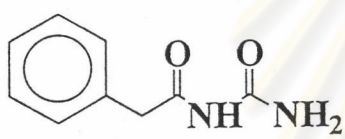

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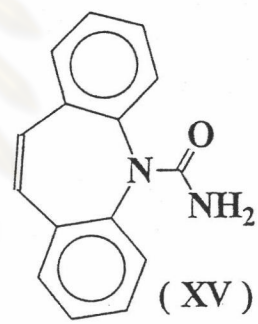

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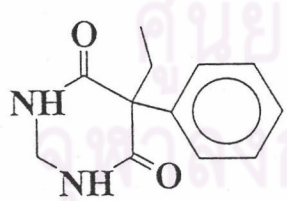

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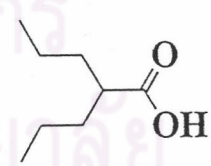

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Figure 1. (Continued). The chemical structures of some common drugs that used in the treatment of convulsion.

7. Miscellaneous

e.g. - Primidone (XVI)
- Valproic acid (XVII)

Nowadays, there are several new antiepileptic drugs undergoing extensive clinical investigation. Some drugs have already been approved and others are at the awaiting approval in a number of countries. And these drugs are organized according to presumed mechanism of action as described below:

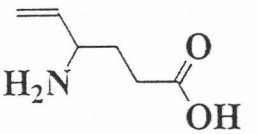
1) Drugs which enhance GABAnergic transmission.

Gamma-aminobutyric acid (GABA) is a major inhibitory transmitter in the cerebral nervous system (CNS). Impaired GABAnergic function appears to contribute to seizure susceptibility, and enhancement of GABA-mediated inhibition has an anticonvulsant effect. These compounds are for example, Vigabatrin (XVIII), and aminooxyacetic acid (AOAA) (XIX) (See figure 2). They enhance GABAnergic transmission by elevating GABA level via irreversible inhibition of GABA transaminase (GABA-T), GABA-degrading of mammalian enzyme. See metabolic pathway of GABA in figure 3.

The antiepileptic action of vigabatrin has been demonstrated in various animal models of epilepsy. The drug has both antiepileptogenic and antiseizure properties in the kindling model, and recently it has also been shown to protect hippocampal structure and function in the perforant pathway stimulation model of epilepsy. Vigabatrin induces a dose-related increase in free and total GABA in the cerebrospinal fluid (CSF).

2) Drugs whose anticonvulsant profile are similar to phenytoin.

These drugs include Zonizamide (XX), Denzimol (XXI), Nafimidone (XXII), Lamotrizine (XXIII), Flunarizine (XXIV), Ralitoline (XXV), Topiramate (XXVI) (Rogawski and Porter, 1990), and Oxcarbarzepine (XXVII) (Kalviainen, Keranen and Riekkinen, 1993) (See figure 4).



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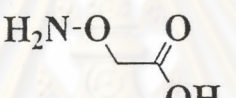

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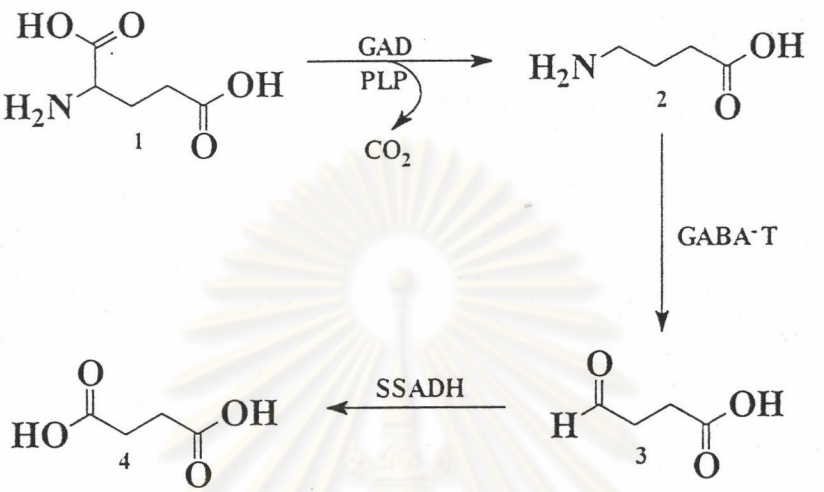
Figure 2. The chemical structures of drugs which enhance GABAinergic transmission.



1 = L-glutamic acid

2 = gamma-aminobutyric acid

3 = succinic semialdehyde

4 = succinic acid

PLP = pyridoxal-5'-phosphate dependent enzyme

GAD = L-glutamic acid decarboxylase

GABA-T = gamma-aminobutyric acid transferase

SSADH = succinic semialdehyde dehydrogenase

Figure 3. Metabolic pathway of GABA.

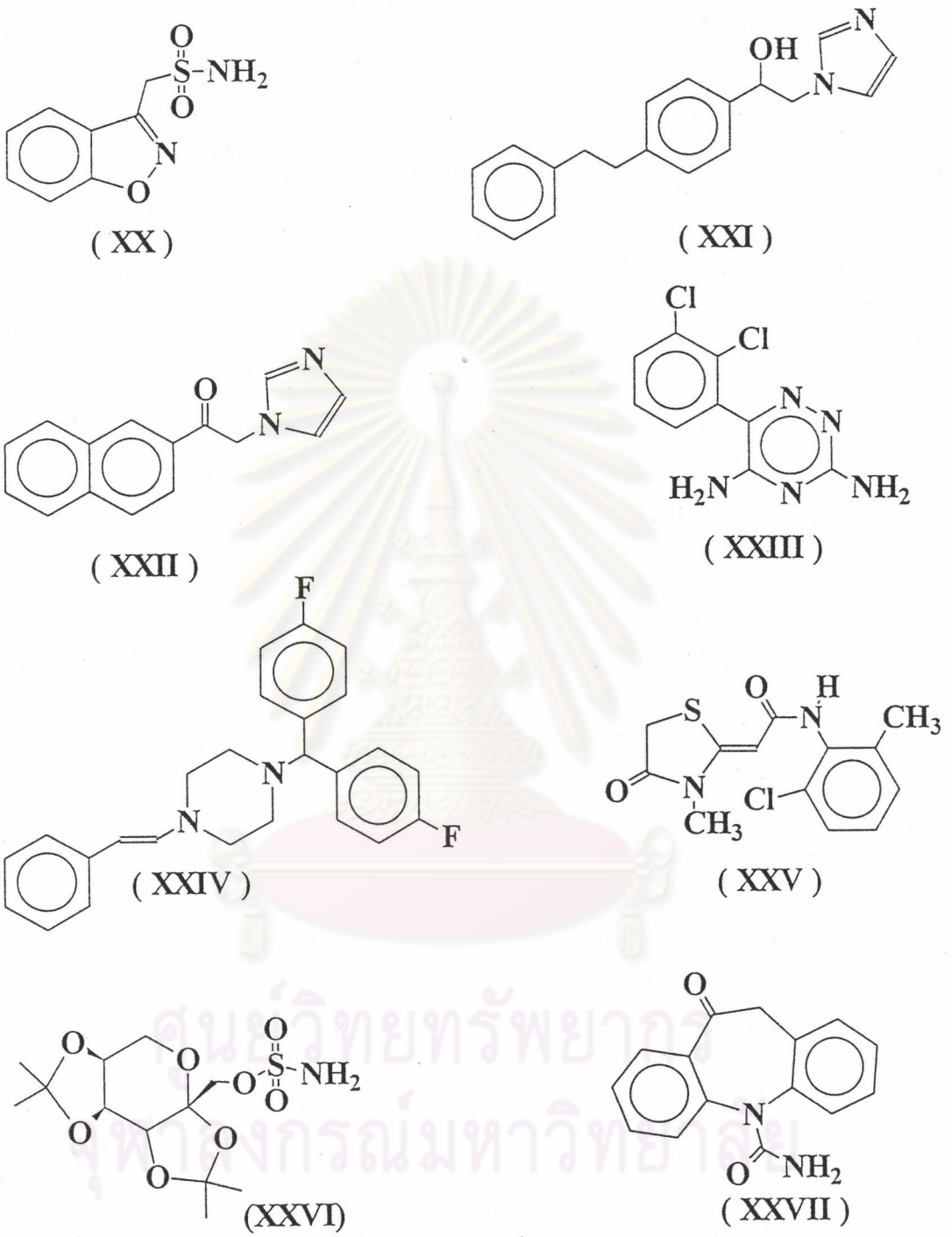


Figure 4. The chemical structures of drugs whose anticonvulsant profiles are similar to phenytoin.

Oxcarbarzepine is a keto derivative of carbamazepine. In experimental models of epilepsy, the antiepileptic profile and potency of oxcarbazepine as well as its main human metabolite, 10,11-dihydro-10-hydroxy-carbazepine (HYCZ), is similar to those of carbamazepine and phenytoin. The antiepileptic efficacy of oxcarbazepine in humans is most probably attributable to HYCZ (Kalviainen, Keranen and Riekkinen, 1993).

3) Drugs as neuronal ionotropic excitatory amino acid receptor antagonist.

Excitatory amino acid antagonists may have important therapeutic potential in the treatment of several neurodegenerative disorder diseases. At least three ionotropic glutamate receptors have been identified by classical methodology. These ionotropic receptors are named for the agonists which activated them: *N*-methyl-D-aspartic acid (NMDA), 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA) , and kainic acid (KA).

The NMDA receptor, one type of neuronal ionotropic excitatory amino acid receptor. More specifically, it is an integral membrane protein comprised of recognition domains for glutamate and several endogenous coagonist and modulatory substances, including glycine and polyamines. Activation of NMDA receptors by neurotransmitter glutamate is resulting in membrane depolarization and neuroexcitation.

The discovery in recent years of several modulatory sites on the NMDA receptor complex has been followed by the identification of a wide array functional antagonists that block NMDA receptor responses via a specific action at these various target sites.

Drugs, NMDA receptor antagonists, can classify into four types as follow (See figure 5):

1. Competitive NMDA recognition site antagonists.

e.g. CGS-37849 (XXVIII), CPPene (XXIX), CGS-19755 (XXX), LY-274614 (XXXI) (Oinstei et al., 1989; Hutchison et al., 1982; Bigge et al., 1989).

2. Uncompetitive NMDA antagonists.

e.g. Dizocilpine (MK-801) (XXXII), CPC (XXXIII), PPA (XXXIV), ADCI (XXXV) (Rogawski, 1992), and Dextromethophan (XXXVI) (Calderon et al., 1991).

3. Glycine site antagonists.

e.g. 5,7-DCKA (XXXVII), MDL-29-951 (XXXVIII), L-687,414 (XXXIX), 6,7-DCQX (XL), L-701,273 (XLI) (Foster and Kemp, 1989).

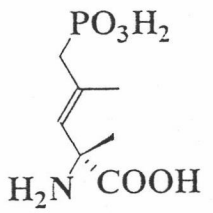
4. Polyamine site antagonists.

e.g. Ifenprodil (XLII) (Chenard et al., 1991).

4) Drugs with a novel spectrum of anticonvulsant action.

Although much of the available literature pertains to either the facilitation of inhibitory GABAergic system or inhibition of excitatory amino acid neurotransmitter, anticonvulsant activity can be mediated by many mechanism.

Nowadays, there are many drug possessing a novel spectrum of anticonvulsant activity (Brodie and Porter, 1990). These drugs include, CL-218,872 (XLIII), Zopiclone (XLIV), Zolpidem (XLV), CGS-9896 (XLVI) (Tomczuk et al., 1991), LY-201116 (XLVII), LY-201979 (XLVIII), LY-201409 (XLIX), Felbamate (L), Gabapentin (LI), D-19274 (LII) (Robertson et al., 1991), MK1-203 (LIII), MK1-907



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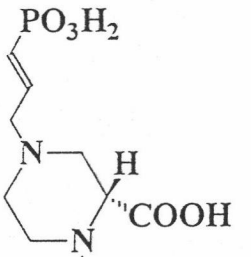

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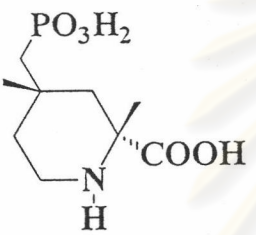

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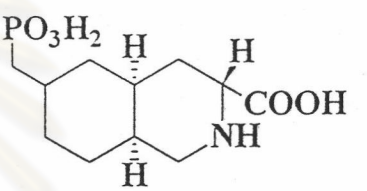

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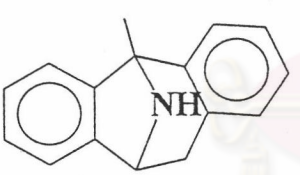

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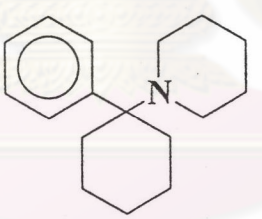

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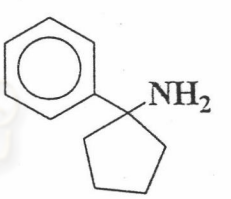

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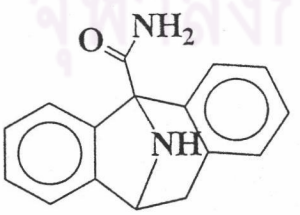

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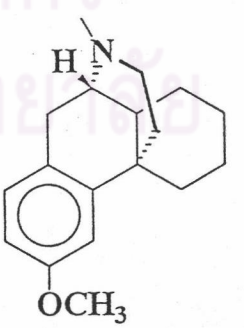

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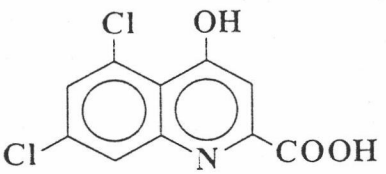
Figure 5. The chemical structures of drugs, NMDA receptor antagonists.



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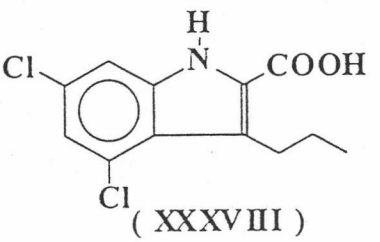

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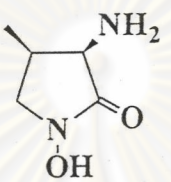

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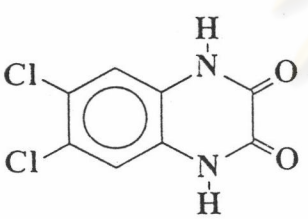

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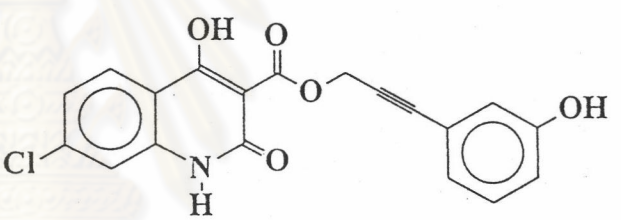

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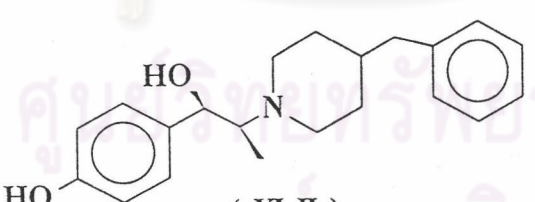

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Figure 5. (Continued). The chemical structures of drugs, NMDA receptor antagonists.

(LIV), AHR-12245 (LV) (Edafiogho, Hinko, Chang et al., 1992), Carbetapentane (LVI) (Calderon et al., 1991) (See figure 6).

Valproic Acid.

Valproic acid was discovered to have anticonvulsant properties serendipitously. In 1962, Pierre Eymard, a research student at the University of Lyon, had synthesized series of derivatives of khellin and used valproic acid as a solvent in pharmacological testing. The solution had found to have anticonvulsant activity. Shortly after this, H. Meunier used valproic acid for dissolve his compound and found that his dissolved compound had anticonvulsant properties. Meunier realized this could not be mere coincidence. So he immediately tested the valproic acid and discovered it was an anticonvulsant. After detailed studied by Carraz and his colleagues, valproic acid was subjected to extensive clinical investigation before its sodium salt, Epilim, was marketed in 1967. Since then it has been used widely in Europe, but it did not gain FDA approval for the treatment of absence seizures in United State. Until 1978, it was approved as an adjunctive therapy for other types of seizures occurring in conjugation with absence seizures (Sneader, 1985).

Valproate, sodium salt of valproic acid, has a broad spectrum of antiepileptic activity. It is useful particularly for absence seizure, especially in case where ethosuximide proves to be ineffective. It is also the drug of choice against myoclonic seizure, coexisting absence and tonic-clonic seizures, as well as atonic seizures, although the latter seizures are relatively intractable to treatment (Smith and Reynard, 1992). Other indications for valproic acid include treatment of partial seizures, febrile seizures, primary and secondary generalized tonic-clonic seizures. Better results tend to be obtained when valproate is used as the only drug rather than in polydrug therapy.

Valproate is rapidly absorbed after oral administration. Salts of valproic acid are converted into valproic acid in the digestive tract. The time required for absorption is 30 min. to one hour for the tablet form or the solution, but is much longer (2-8 hours) for the enteric coated tablet.

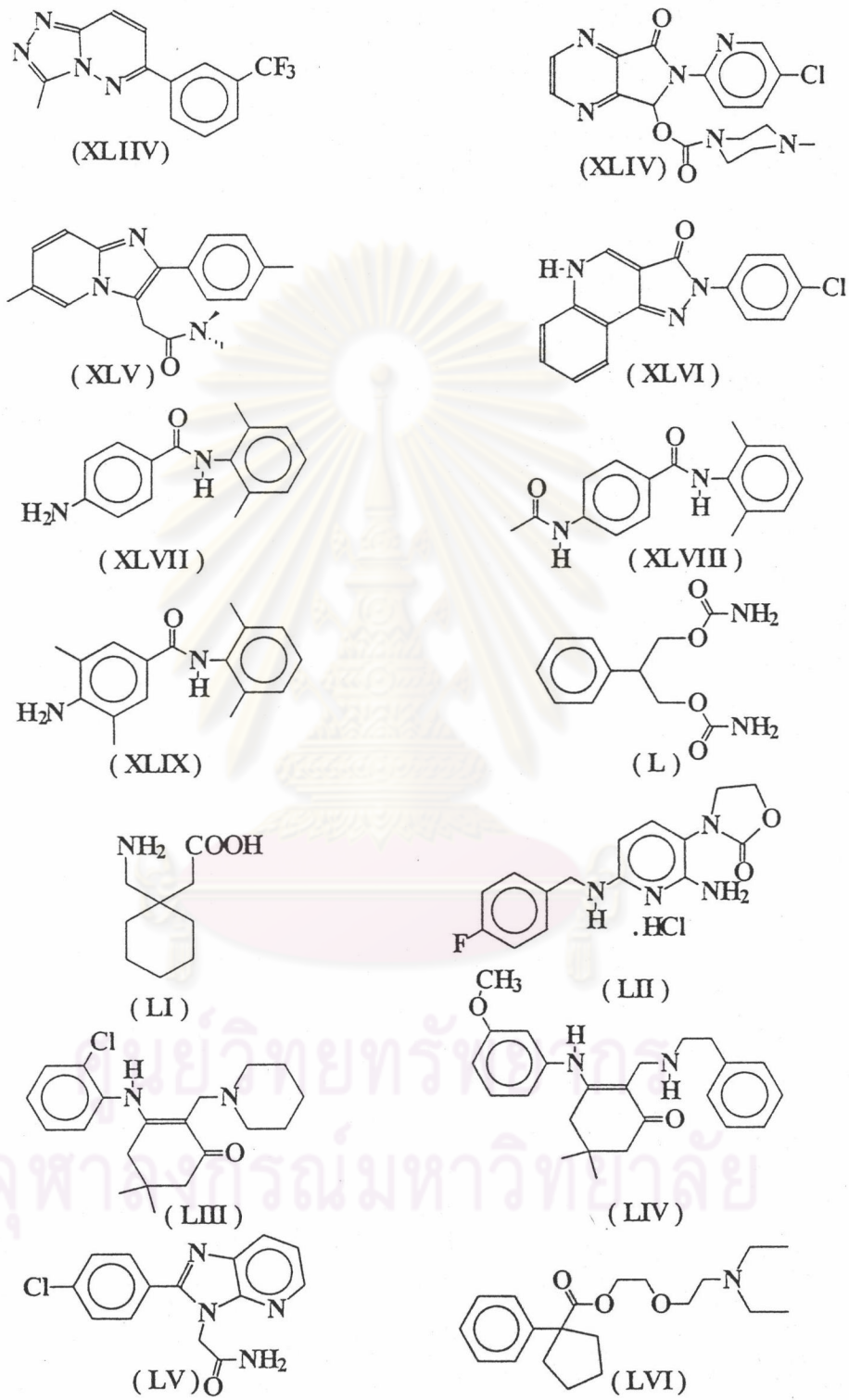


Figure 6. The chemical structures of drugs with a novel spectrum of anticonvulsant action.

The distribution of valproate is primarily limited to the blood and extracellular fluid. Penetration of the drug into tissue is very limited. The apparent volume of distribution of valproate is between 0.1 and 0.4 l/kg. The half-life of valproate appears to be 15-17 hours, and is independent of the dose administered.

About 90% of valproate is bound to plasma protein, mainly to albumin. Protein binding of valproate results in a longer retention of the drug, and its temporary inactivation. Only free valproate is available for pharmacological activity, since only the free form diffuses into the brain. Valproate can be displaced from its protein binding sites by substances which complete for the same sites. These include fatty acid, bilirubin, uric acid, and drugs such as aspirin, clofibrate, and phenylbutazone.

Valproate is almost completely metabolized before excretion, only 1-3% of the administered dose being found as unchanged drug in the urine. Four metabolic pathways have been found for valproate: glucuronidation, β-oxidation, ω-oxidation, and ω-1 oxidation (Chapman et al., 1982) (See figure 7).

The main metabolic route of valproate is glucuronidation. The conjugated drug is rapidly excreted in the urine. The glucuroconjugated ester of valproate is not very stable, and it partially hydrolyzed in basic solutions, and completely by β-glucuronidase. Another metabolic routes, ω- and ω-1 oxidation, of valproate appear to be of less importance than glucuronidation and β-oxidation.

The mechanism of action of valproate does not clear (Abrams, 1983). But there are three different hypothesis proposed for the mechanism of the anticonvulsant action of valproate as follow (Ward et al., 1983):

- Valproate increases GABA concentration in the brain. Both by increasing of activity of L-glutamic acid dehydrogenase (GAD) and by inhibiting of gamma-aminobutyric acid transaminase (GABA-T) and thereby acts by enhancing inhibition.

- Vaproate has a direct effect on membranes to decrease excitability of neurons.

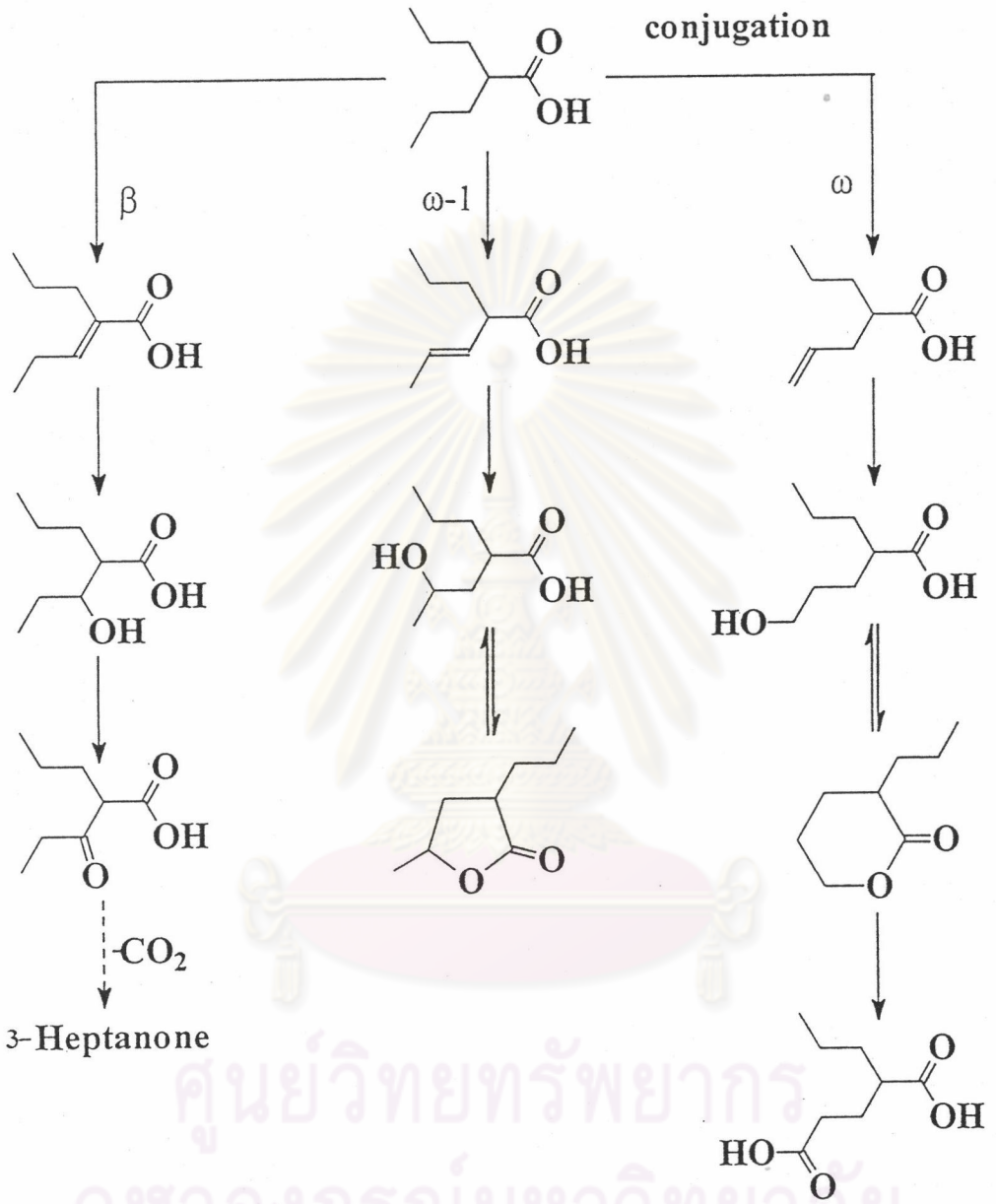


Figure 7. Metabolic pathways for valproate.

- Valproate potentiates the GABA receptor such that, in the presence of this drug, a given release of GABA exerts a greater inhibitory action on the postsynaptic membrane.

The incidence of minor side effects has been reported; include nausea, diarrhea, vomiting, fatigue, abdominal cramps, and heartburn. The most occur transiently during the early phase of therapy. These effect can be minimized by using enteric-coated tablets and administering the drug with or after a meal. Sedative is uncommon with valproate alone but may be striking when valproate is add to phenobarbital. Other reversible adverse effects seen in a small number of patients, include weight gain, increase appetite, hair loss, ataxia, tremor, and rash.

Aminooxyacetic Acid (AOAA).

In 1961, DaVanzo et al., reported that compound U-7524, aminooxyacetic acid (AOAA), has anticonvulsant activity (DaVanzo, Greig, and Cronin, 1961); against electrically-, chemically-, and kindling-induced seizures (Kuriyama, Robert, and Rubinstein, 1966).

They found that the 4-fold increase in the level of GABA in the brain of mice observed 6 hours after AOAA administered (Wood and Peesker, 1973) that agree closely with the value obtained previously (Kuriyama et al., 1966). In agreement with the earlier work of Baxter and Robert (1961) the present results indicate that elevation in GABA level was caused by a preferential inhibition of GABA-degrading enzyme, gamma-aminobutyric acid (GABA-T). The inhibition of mammalian enzyme by AOAA cannot be reversed (Wallach, 1961).

The major disadvantage of AOAA is its ability to induce convulsion at high dose. Tapia R., found that the inhibition of the GABA synthesizing enzyme, L-glutamic acid dehydrogenase (GAD), activity was observed when the high level of AOAA was used (Loscher, 1979).

To decrease the side effect, convulsion, from high dose of AOAA the prodrugs of AOAA were synthesized. The prodrugs would

be hydrolyzed to obtain sufficient quantities of AOAA to elicit only anticonvulsant activity in the brain (Edafiogho, et al., 1992).

This research was aimed to synthesize novel imidooxy liked compounds, containing 2-propylpentamidooxy moiety. The derivatives as *O*-alkyl, or *O*-acyl-2-propylpentanohydroxamate were synthesized as follow : (See figure 8)

R = H (CU-763-1201)

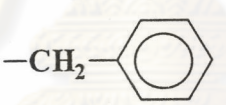
Na (CU-763-1202)

R = Alkyl; $-CH_2-C(=O)-O-CH_2CH_3$ (CU-763-1203)

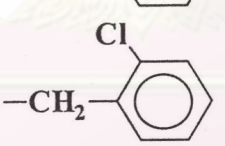
$-CH_3$ (CU-763-1204)

$-CH_2-CH_3$ (CU-763-1205)

$-CH_2-CH_2-CH_3$ (CU-763-1206)



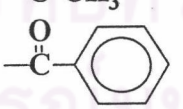
(CU-763-1207)



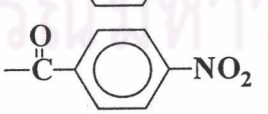
(CU-763-1208)

R = Acyl; $-C(=O)-O-CH_2CH_3$ (CU-763-1209)

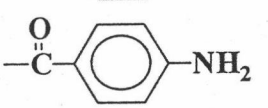
$-C(=O)-CH_3$ (CU-763-1210)



(CU-763-1211)



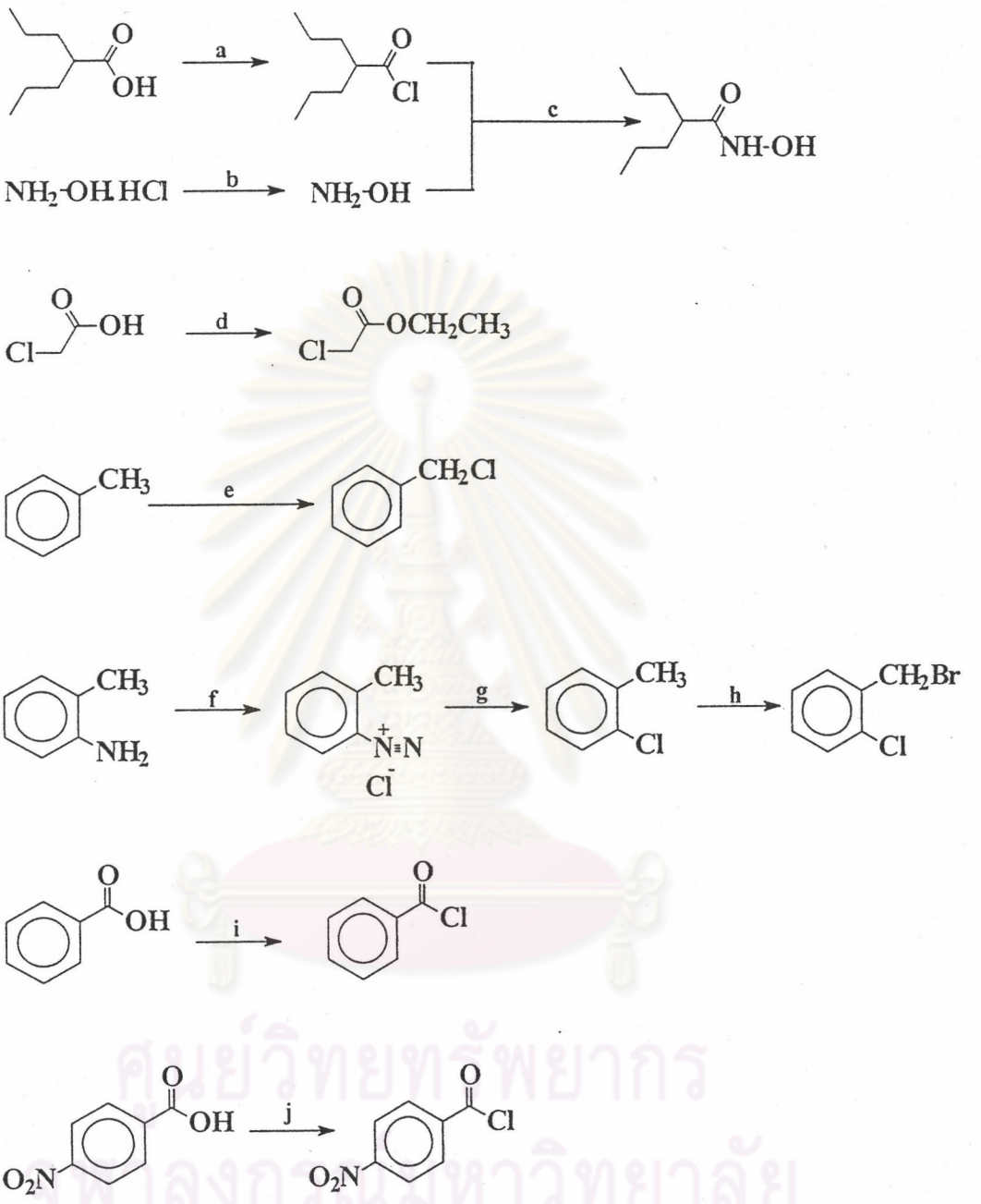
(CU-763-1212)



(CU-763-1213)

Figure 8. The chemical structures of target compounds in this research.

The synthetic approach for all compounds is shown in figure 9.



a)$SOCl_2$,Reflux , b) Na_2CO_3 ,10 % H_2O in THF, c) Na_2CO_3 ,15 °C, d) EtOH, H_2SO_2, Reflux, e) SO_2Cl_2, Benzoyl peroxide, f) HCl, HNO_2, 0-5 °C, g) CuCl, HCl, h) NBS, Benzoyl peroxide, i) PCl_5, Δ, j) PCl_5, Δ

Figure 9. The synthetic approach of target compounds in this research.

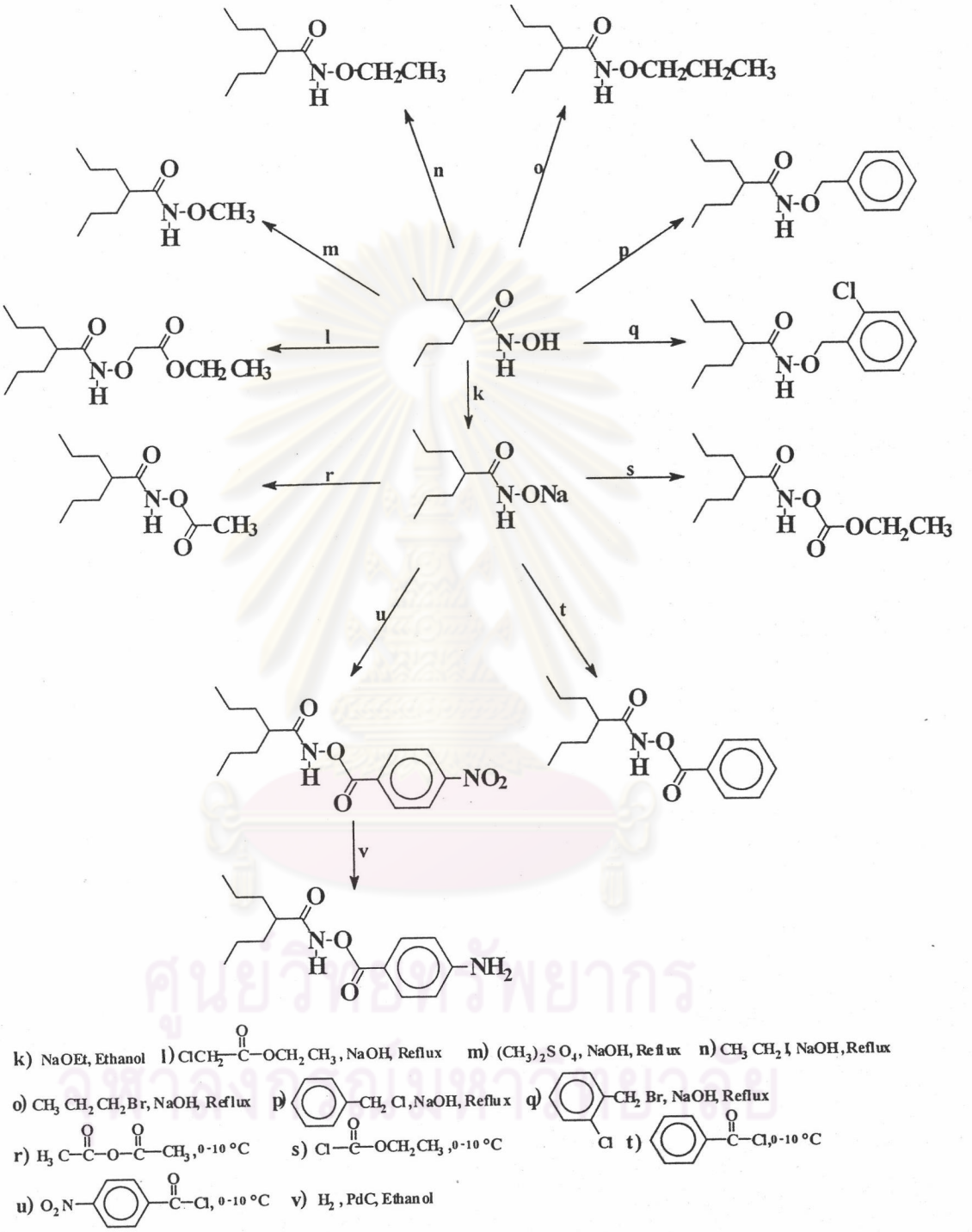


Figure 9. (Continued). The synthetic approach of target compounds in this reseach.