CHAPTER II

HISTORICAL

Clark and co-workers firstly reported anticonvulsant activity of several benzamides in 1984. Some of them produced a high activity against maximal electroshock (MES) induced seizure (Clark *et al.*, 1984, 1985). In this chapter, the historical aspects of 4-aminobenzamide series and its active compounds, 4-amino-*N*-(α-methylbenzyl)benzamide or LY188544 (22), and 4-amino-(2',6'-dimethylphenyl)benzamide or LY201116 (23), are reviewed. These compounds are prototype of rigid analogues, *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline derivatives and *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroquinoline, respectively, the former is the target compounds in this research.

Structure-Activiy Relationships of 4-Aminobenzamides

1. The effects of substitution with alkyl- and arylakyl groups at the amide nitrogen (see Figure 11).

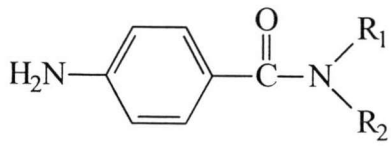
The unsubstituted 4-aminobenzamide (**34**) showed some slight activity against subcutaneous metrazole (scMet) induced seizures and no activity against maximal electroshock (MES) induced seizures at 600 mg/ kg. The *N*-methyl amide (**35**) exhibited anti-MES activity at 600 mg/kg, while compounds **36-41** are effective against MES at 100 mg/Kg. These compounds (**35-41**) are effective against scMet at less than toxic doses. The toxic effects of the *N*-*n*-alkylbenzamides (**35-40**) appeared to increase with the chain length. This trend continued through the highest homologue, *n*-hexyl amide. The *N*-cyclohexylbenzamide (**41**) is more potent against MES and scMET than the *n*-hexyl amide

(**40**) or the other *n*-alkyl amides. Compound **41** also exhibited much less toxicity than even the n-propyl amide (**37**). The activity profile of the *N*,*N*-di-*n*-propyl amide **42** is similar to that for **41**.

The initial anticonvulsant evaluation was extended to the compounds containing an aromatic ring (**43-49 and 22**) on the nitrogen of amide. These results indicated that one additional aromatic ring produced optimal activity. The N-benzyl amide (**44**) showed anti-MES activity with greater potency than any of the N-alkyl amides. However, the addition of a second phenyl group as in (**49**) drastically decreased the anticonvulsant effects. Compounds **43**, **44** and **22** display maximum anti-MES activity, with compound **22** appearing to be the most potent. A substantial drop in activity was observed when the *N*-α-methylbenzyl group of **22** was replaced by the isomeric β-phenylethyl group (**45**) or the *N*-benzyl-*N*-methyl derivative (**48**). (Clark *et al.*, 1984)

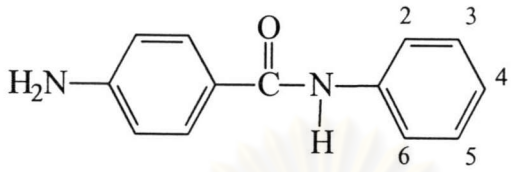
2. The effects of substitution of additional groups on the *N*-phenyl ring (see Figure 12).

Compound **43** possessed activity against MES- and scMet-induced convulsions in the 50 mg/kg dose range. Compounds **23, 43 and 50-60** all showed activity against MES-induced convulsions at 300 mg/kg 30 min after administration with most compounds maintaining minimal anti-MES activity at least 4 hrs after administration. Several compounds showed activity against scMet-induced convulsions at 30 min; however, the activity essentially disappeared at 4 hrs. Each of the monomethylated anilides **50-52** exhibited convulsant activity similar to **43**.



Compound	R_1	R_2
34	H	H
35	CH_3	H
36	CH_2CH_3	H
37	$CH_2CH_2CH_3$	H
38	$CH_2CH_2CH_2CH_3$	H
39	$CH_2CH_2CH_2CH_2CH_3$	H
40	$CH_2CH_2CH_2CH_2CH_2CH_3$	H
41	cyclohexyl	H
42	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$
43	C_6H_5	H
44	CH_2-C_6H_5	H
22	$CH(CH_3)$-C_6H_5	H
45	CH_2CH_2-C_6H_5	H
46	$CH(CH_3)CH_2$-C_6H_5	H
47	$CH_2CH(CH_3)$-C_6H_5	H
48	CH_2-C_6H_5	CH_3
49	$CH(C_6H_5)_2$	H

Figure 11. The chemical structures of 4-amino-*N*-substituted benzamides.



compound	substituent position				
	2	3	4	5	6
43	H	H	H	H	H
50	CH_3	H	H	H	H
51	H	CH_3	H	H	H
52	H	H	CH_3	H	H
53	CH_3	CH_3	H	H	H
54	CH_3	H	CH_3	H	H
55	CH_3	H	H	CH_3	H
23	CH_3	H	H	H	CH3
56	H	CH_3	CH_3	H	H
57	H	CH_3	H	CH_3	H
58	$CH(CH_3)_2$	H	H	H	H
59	$CH(CH_3)_2$	H	H	H	CH_3
60	$CH(CH_3)_2$	H	H	H	CH_2CH_3

Figure 12. The chemical structures of substituted 4-aminobenzanilde.

Compounds **53-57** represented all the possible dimethylated anilides, and these compounds continued to show good anti-MES activity with compound **23** being the most effective. The profile of anticonvulsant activity for **23** was characterized by marked ability to modify the maximal electroshock pattern and inability to elevate the metrazole seizure threshold. The compounds **58-60** all possessed an ortho-isopropyl group and represented diverse activity and toxicity profiles. The screening results did not allow for any clearcut conclusions concerning structure-activity relationships; however, the anti-MES activity was observed in all compounds (Clark *et al.*, 1985).

3. The effects of the addition methylene group between the amidecarbonyl and the aromatic ring of aminobenzoyl moiety (see Figure 13).

The addition of a methylene group in the phenyl acetamides **(62)** relative to the benzamides **(61)** significantly decreased anticonvulsant activity. The decreased activity was likely the result of different electronic and conformation factor (Clark *et al.*, 1986).

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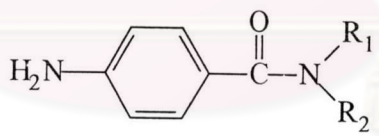

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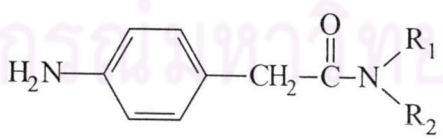

Figure 13. The chemical structure of 4-amino-*N*-substitutedbenzamide (**61**) and 4-amino-*N*-substitutedphenylacetamide (**62**).

4. The effects of the amino substitution pattern of the aminobenzoyl moiety (see Figure 14).

The location of amino group in the aminobenzoyl moiety is important for activity, with the 4-aminobenzanilides (**63**) showing the highest potency and the 2-aminobenzanilides (**65**) the least. In general, the anticonvulsant activity of the aminobenzanilides corresponds to the ring substitution pattern of 4-amino (**63**) > 3-amino (**64**) > 2-amino (**65**). Nevertheless, the 2,6-dimethylaniline derivative (**23**) was still the most potent anti-MES agent in each series (Clark *et al.*, 1986).

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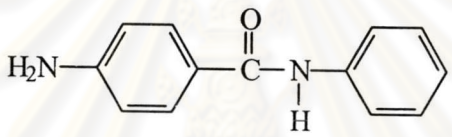

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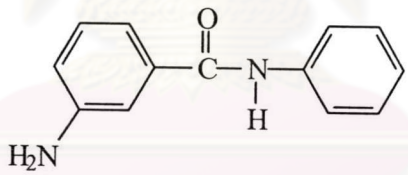

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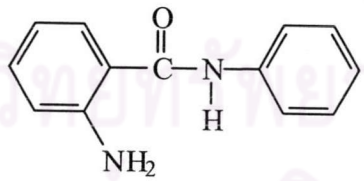

Figure 14. The chemical structures of aminobenzanilide derivatives.

5. The effects of substitution on the aminobenzoyl moiety of 4-amino-*N*-(2',6'-dimethylphenyl)benzamide (see Figure 15).

In order to sterically preclude or diminish the rate of metabolic *N*-acetylation, analogues of ametolide (**23**), possessing either one (**66**) or two (**67**) methyl groups ortho to the 4-amino substituent, were synthesized. Both compounds antagonized MES-induced seizures after administration to mice. Compound **66** was still rapidly metabolized by *N*-acetylation. However, compound 67 provided exceptionally high and long-lived plasma concentrations of parent drugs; no N-acetyl metabolite could be detected. While 23 and 66 showed no pharmacologically relevant effects on hexobarbital-induced sleeping time in mice, 67 is a potent, dose-dependent potentiator of sleeping time. Oral administration of 375 mg/kg led to a 61% increase in sleeping time relative to the control values. Thus, 67 represents one of the most potent potentiators of hexobarbital-induced sleeping time described to date (Robertson *et al.*, 1987 and 1988)

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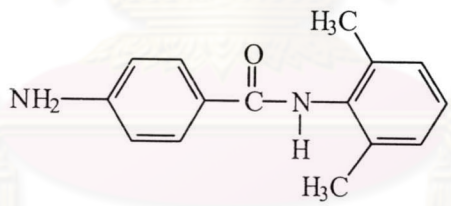

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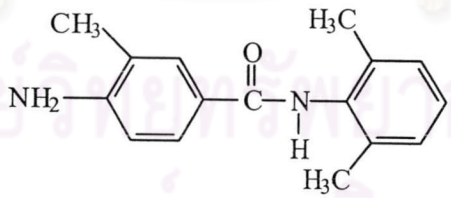

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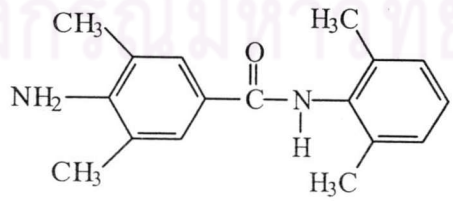

Figure 15. The chemical structures of 4-aminobenzamides with/without substituent(s) on the aminobenzoyl moiety.

6. The effects of the second amino group on the anilide phenyl ring (see Figure 16).

The introduction of a second amino group on the substituted phenyl ring decreased the anticonvulsant potency after intraperitoneal administration to mice; in contrast, it enhanced the activity after oral administration to rats, probably due to pharmacokinetic factors (Kanyonyo, Poupaert and Lambert, 1998).

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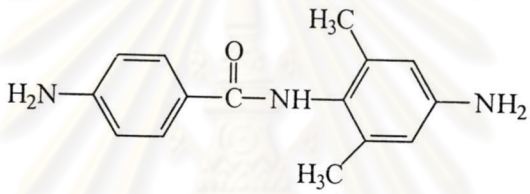
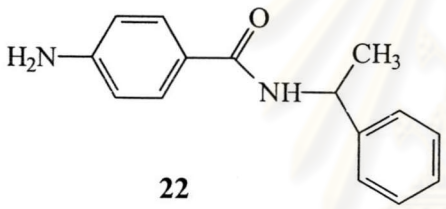


Figure 16. The chemical structure of 4-amino-*N*-(4'-amino-2',3'-dimethylphenyl)benzamide.

Molecular Modeling and Crystallographic Studies of 4-Amino-N-phenylbenzamide Anticonvulsants

The most active compounds (**22**, **23** and **50**) of 4-aminobenzamides (See Figure17), each have a single active crystalline conformation, which has approximately the same angles between the three planes (planes A, B, and C in Figure 18). In summary, a model for the MES-active conformation of these *N*-phenylbenzamide anticonvulsants can be constructed with four major factors: (a.) the *N*-phenyl ring which is nearly perpendicular to the central amide region, thus facilitating the formation of strong intermolecular hydrogen bonds to the central amide region, (b.) an ortho-methyl substituent oriented toward the NH group of the central amide plane, (c.) a hydrogen bond

acceptor in central region on the side of the central plane opposite to the *o*-methyl group, and (d.) an approximately coplanar orientation of the aminophenyl ring to the central amide plane. Whether the substituent methyl groups play any role other than orientation the phenyl ring with respect to the amide region is uncertain; however, given the preferential orientation of a single ortho-methyl group, compound **50**, it was hypothesized that recognized in a hydrophobic pocket at the binding site. In the active conformation of 2,6-dimethyl compound was assumed that it places one methyl group above and one below the molecular plane formed by the central amide and aminophenyl ring (Duke and Codding, 1992).



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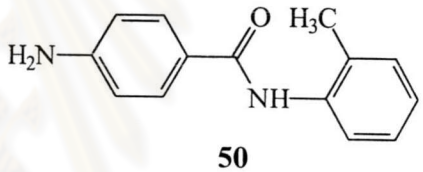

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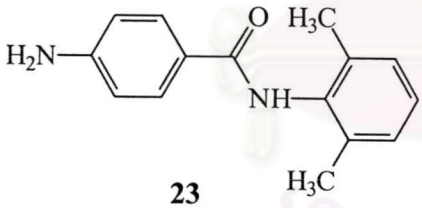

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Figure 17. The chemical structure of the most active compound in 4-amino-*N*-substitutedbenzamide series

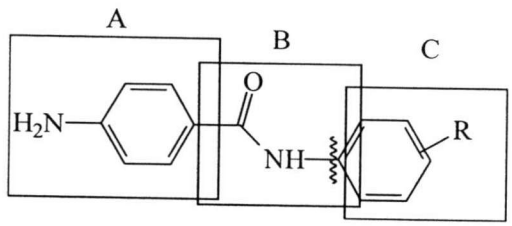

Figure 18. The three planar regions of the 4-amino-*N*-substitutedphenylbenzamide

The Pharmacological Effects of 4-Amino-*N*-(α-methylbenzyl)benzamide and Its Enantiomer

The anticonvulsant profile of LY188544, *S,R*-4-amino-*N*-(α-methylbenzyl)benzamide after peritoneal administration to mice was determined in standard anticonvulsant tests: maximal electroshock (MES), strychnine tonic-extensor, and threshold tests using pentylenetetrazol, picrotoxin, and bicuculine. In this series of tests, LY188544 had good activity in the MES test and some activity in the three threshold tests. The ED_{50} values of LY188544 against MES, s.c.Ptz, s.c.Bic, and s.c.Pic were 18.0, 41.7, 39.1, and 191 mg/kg, respectively. Thus, its profile of activity was most similar to that of phenobarbital, and less similar to that of phenytoin and carbamazepine. After oral administration to mice and rats, LY188544 was effective in the MES (ED_{50} 10.3 mg/kg) test but did not provide complete protection in the threshold pentylenetetrazol test. When the individual stereoisomers, LY188545 (*S* isomer) and LY188546 (*R* isomer), were evaluated after oral administration, LY188545 was 2.2 times more potent than LY188546 against MES-induced seizures (ED_{50} 10.9 and 23.7 mg/kg, respectively). However, when evaluated after intravenous administration, the potency difference was only 1.1 (ED50 7.5 and 8.2 mg/kg, respectively). LY188546 was the least toxic in terms of neurological impairment. All compounds had good protective indexes (ratio between doses for neurological impairment

and doses for anticonvulsant efficacy in the MES test; TD_{50}/ED_{50}). LY188545 and LY188546 potentiated hexobarbital sleeping time after acute administration but not after chronic (4 days) administration. Tolerance did not develop to the effects of LY188546 on MES or neurologic impairment after 4 days administration.

These results suggested that LY188544 is an anticonvulsant with a promising pharmacological profile. Unfortunately, because of untoward toxicological finding of these compounds, the development of LY188544 and its enantiomers were precluded (Leander *et al*, 1988).

Pharmacological Effects of Ameltolide

Ameltolide is a potent and selective anticonvulsant in the maximal electroshock test in mice. The ED_{50} values after oral and intravenous administration were 1.7 mg/kg and 0.51 mg/kg, respectively. For comparison, the oral and intravenous ED_{50} values for the anticonvulsant phenytoin which is selective for the maximal electroshock test were 9.1 and 8.5 mg/kg, respectively. After oral administration, ameltolide had a protective index of 13.5 (Leander *et al.*, 1988). After intraperitoneal to mice, therapeutic indexes (LD_{50}/ anti-MES ED_{50}) for ameltolide, phenytoin, and phenobarbital were 62, 24, and 12, respectively (Robertson *et al.*, 1986). After 4 days of administration, there was no evidence of the development of tolerance to the anticonvulsant effects of ameltolide. The hexobarbital-induced sleeping time was not significantly affected by either acute or chronic administration of ameltolide for 4 days. In combination studies with the anticonvulsants, phenytoin and carbamazepine, which are selective for the maximal electroshock test, ameltolide produced dose-additive effects, suggesting its anticonvulsant action through the same mechanism of action as these prototype anticonvulsants. In addition, ameltolide was

unable to inhibit seizure induced by subcutaneous administration of pentylenetetrazole, bicuculine, picrotoxin, or strychnine to mice. This marked MES-selective profile resembles that of phenytoin.

The anticonvulsant and toxic properties of ameltolide were compared with phenytoin, phenobarbital, ethosuximide, and valproate by Clark (1988). The results indicated that the ameltolide is the most potent anticonvulsant in the maximal electroshock seizure (MES) model. The protective index of ameltolide compared favorably with prototype anticonvulsants, and there appeared to be a good safety margin. The studies suggested that ameltolide be an effective anticonvulsant in human and supported the development of the compound for epileptic treatment.

Correlation Between Experimental Animal Models and Clinical Utility of Active Anticonvulsants

From the hypothesis that the MES test identified agent with activities against general tonic-clonic seizures and complex partial seizure, whereas the s.c.Ptz test identified compounds that are efficacious against generalized absence and myoclonic seizures (White, 1977). Because of its efficacy in the MES test, ameltolide can be predicted to be an effective anticonvulsant for treatment of general tonic-clonic seizures and complex partial seizure, whereas 4-amino-*N*-(*α*-methylbenzyl)benzamide would have broader activities than ameltolide.

Mechanism of Action of 4-Amino-*N*-(α-methylbenzyl)benzamide

As same as phenobarbital, 4-amino-*N*-(α-methylbenzyl)benzamide had good activity in the MES test and some activity in the three threshold tests (s.c.Ptz, s.c.Bic, s.c.Pic). Possibly, the mechanism of action of this compound is similar to that of phenobarbital, its anticonvulsant was involved blockade of sodium channels and enhancement of GABA-mediated inhibitory transmission (Leander *et al.*, 1988; White, 1997).

Mechanism of Action of Ameltolide

Because ameltolide produced dose-additive effects with two prototype anticonvulsants, phenytoin and carbamazepine, which are selective for the maximal electroshock test. These interactions suggested that ameltolide, phenytoin, and carbamazepine produced their selective anticonvulsants in the maximal electroshock test by the same mechanism of action. Perhaps ameltolide produced a membrane-stabilizing effect, as measured by the reduction of sustained repetitive firing, possibly by a use-dependent block of sodium conductance channels, as has been characterized previously for phenytoin and carbamazepine (Leander *et al*, 1988; White, 1997).

Metabolism, Disposition and Pharmacokinetics of Ameltolide in Rats

The metabolism, disposition, and pharmacokinetics of ameltolide have been studied in rats by Potts et al. (1989). ^{14}C-labelled ameltolide was well adsorbed (~94%) from the gastrointestinal tract following oral administration. Of the dose administered, 64.5% was excreted in the urine and 29% in the bile; with the majority being excreted

during the first 24 hrs. Peak plasma levels of ameltolide were observed at 0.75 hr. Its biotransfomation in rats was investigated by quantitating and isolating metabolites from urine and plasma. The major route of metabolism was *N*-acetylation to form 4-acetamido-*N*-(2,6-dimethylphenyl)benzamide (ADMP), and subsequent hydroxylation to form 4-(acetamido)-*N*-(2-hydroxymethyl-6-methylphenyl)benzamide (HADMP). (See Figure 19) Pharmacological studies demonstrated that N-acetylation and hydroxylation of one of the methyl substituent led to a substantial decline in the potency of ameltolide as an anticonvulsant (Robertson et al., 1991). However, in the step that ameltolide was inactivated by metabolism to its *N*-acetyl analogue (ADMP), this metabolic pathway appeared to be reversible to the parent compound in a variety of species (Parli *et al.*, 1987). Two hours after oral dosing with ^{14}C-labelled ameltolide, ADMP and HADMP comprised 92% of the total radioactivity in the plasma. The major urinary metabolite, accounting for 63% of the radioactivity in the urine, was HADMP. The elimination of ameltolide from the systemic circulation following intravenous administration was monophasic, with a terminal half-life of 9.4 min. The volume of distribution was 911 ml/kg and the plasma clearance was 66.9 ml/min/kg (Niratisai, 1994). The primary result indicated that it exhibited anticonvulsant activity against MES test.

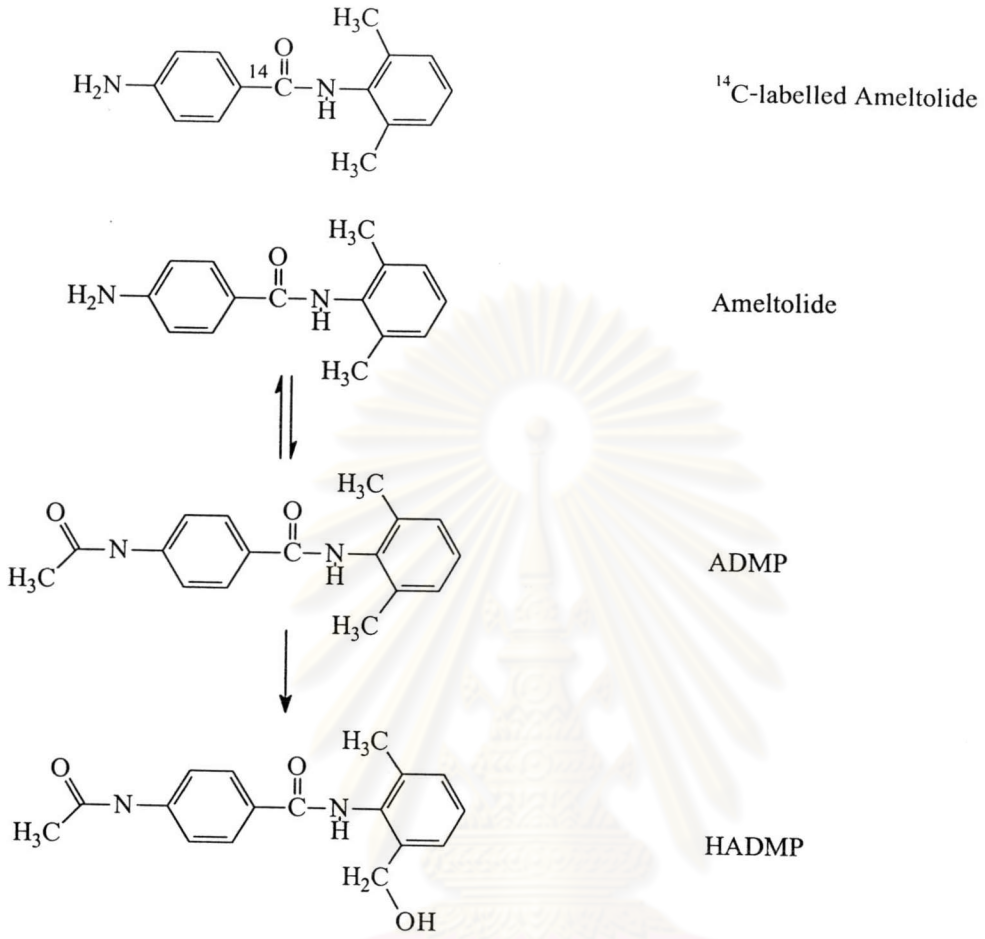

Figure 19. Metabolic pathway of ameltolide.

The Rigid Analogues of Ameltolide, *N*-(*p*-Aminobenzoyl)-1,2,3,4-tetrahydroquinoline derivatives (See Figure 20)

In 1994, *N*-(*p*-aminobenzoyl)-4,8-dimethyl-1,2,3,4-tetrahydroquinoline was firstly designed and synthesized by Sathit Niratisai. Metabolic hydroxylation of one of the methyl substituent on the phenyl ring led to decline the potency of ameltolide, therefore, replacing one of the ortho-methyl groups (primary carbon) on the ortho-phenyl ring by a branched alkyl group (tertiary carbon) should increase the steric hindrance at this position

and protect this vulnerable group from the attacking metabolizing enzyme (A to B). Linking the *o*-position of the phenyl ring with nitrogen of the amide bond by alkyl chain can yield a rigid analogue (B to C). This rigid compound will prevent the rotation around the nitrogen-phenyl single bond and fix compound to be in an active conformation. In addition, the alkyl chain added to the parent molecule may increase the lipophilicity; thus, it is expected that the designed molecules will have better ability to penetrate into brain (Niratisai, 1994).

To extend the structure-activity relationship on *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline pharmacophore, *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline and its derivatives (D) were synthesized by Tanarat Kietsakorn. Introduction of the methyl group along variable positions of 1,2,3,4-tetrahydroisoquinoline nucleus especially at the piperidine ring and C-8 will affect the conformational orientation of compound which may lead to an understanding of an appropiate conformation for target binding site (Kietsakorn, 2000). The anticonvulsant activity of these compounds has still been evaluated.

Some of this series, *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydro-4-methylisoquinoline (CU-17-06), was investigated for anticonvulsant effect. From pharmacological study, CU-17-06 was less potent than ameltolide (ED_{50} = 77.62 mg/Kg and 1.08 mg/Kg, respectively). In term of safety, CU-17-06 seems to be rather safe as indicated by no lethality observed in the dose up to 1,000 mg/Kg where as ameltolide demonstrated the LD_{50} of 63 mg/Kg, which indicate CU-17-06 very low toxicity (Rodpaewpaln, 2003).

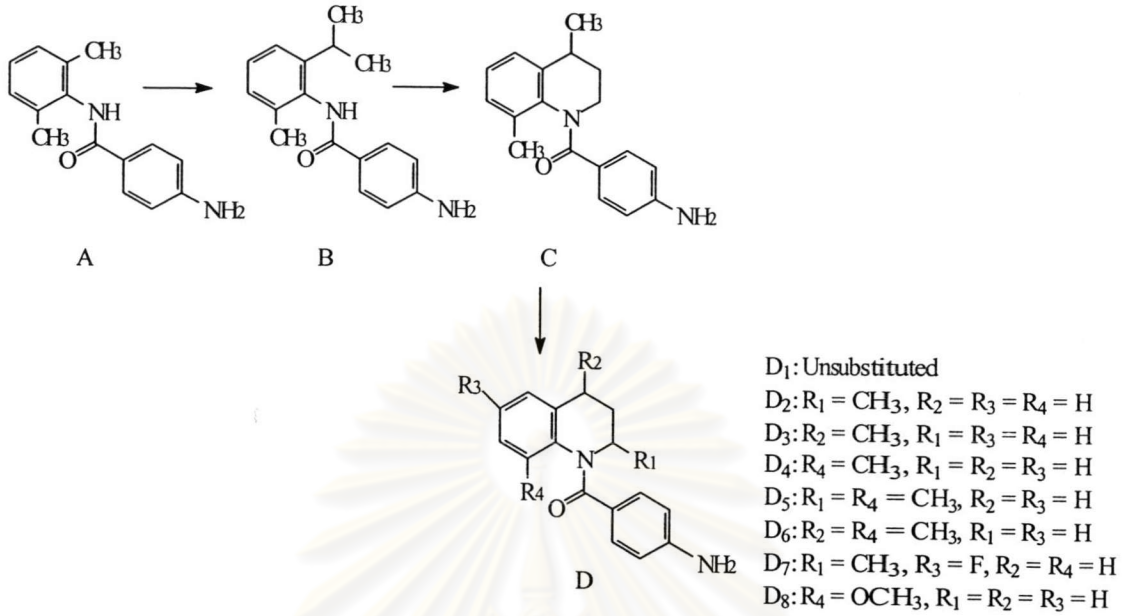

Figure 20. The design of the rigid analogues of ameltolide

General Methods for the Preparations of Intermediates and the Target Derivatives of [*N*-(*p*-Aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline

For the synthesis of the target molecules, there are three main steps. First, the preparation of 1,2,3,4-tetrahydroisoquinolines. Second, the addition of *p*-nitrobenzoyl group on the basic nitrogen of 1,2,3,4-tetrahydroisoquinoline compound. Finally, *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline compounds were reduced to obtain the target compounds, *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinolines. General methods for the syntheses of these types of organic compounds are described as below.

Syntheses of 1,2,3,4-tetrahydroisoquinoline compounds (Claret, 1975; Nose and Kudo, 1983; Carey and Sunberg, 1990; Smith, 2002)

There are several methods for preparing 1,2,3,4-tetrahydroisoquinolines. In the most widely used methods, the final ring-closure completes the heterocyclic ring by intramolecular electrophilic attack at a ring position of an aromatic intermediate. The 'reagent' is a positive carbon center suitably placed on a side-chain *ortho* to the position of ring closure. Thus in the Bischler-Napieralski, Pictet-Gams, and Pictet-Spengler syntheses outlined below, the intermediates can be represented by (I) and ring closure is at bond (a). In the Pomeranz-Fritsch synthesis the intermediates can be represented by (II) and ring closure at bond (b) (See Fiure 21).

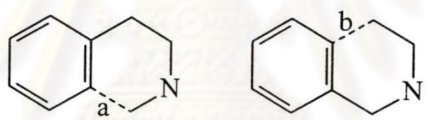

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Figure 21. The representation of intermediates in the synthesis of tetrahydroisoquinoline.

Some types of reaction such as Bischler-Napieralski, Pictet-Gams and Pomeranz-Fritsch syntheses may generate products which are isoquinoline or 3,4-dihydroisoquinoline compounds. These compounds were reduced to give 1,2,3,4-tetrahydroisoquinoline.

a) The Bischler-Napieralski synthesis

It results in the formation of 3,4-dihydroisoquinolines by ring closure of *N*-(2-phenylethyl)amides. The amides are usually formed by the acylation or aroylation of 2-

phenylethylamines. The ring-closure stage is an acid-catalysed, intramolecular, electrophilic, aromatic substitution. Successful reagents include phosphorus pentoxide(P_2O_5 or P_4O_{10}), phosphorus pentachloride (PCl_5), and phosphorus oxychloride ($POCl_3$) in boiling toluene, xylene or decalin (See Figure 22).

The reduction of imine compounds, 3,4-dihydroisoquinoline produce tetrahydroisoquinoline. The reducing methods will be mentioned latter.

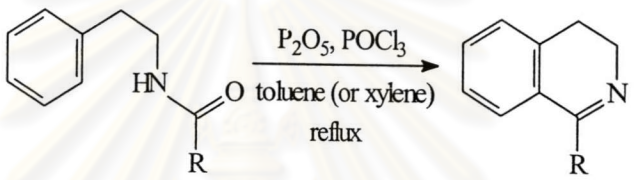


Figure 22. Synthesis of 3,4-dihydroisoquinoline by Bischler-Napieralski reaction

b) <u>The Pictet-Gams synthesis</u>

The *N*-acyl or aroyl derivatives of a 2-hydroxyl- or 2-methoxy-(2-phenylethyl)amine are used for the cyclization to produce the fully aromatic isoquinoline directly. (See Figure 23) The corresponding isoquinolines were reduced by sodium borohydride ($NaBH_4$) - nickelous chloride ($NiCl_2$) reduction to give product, 1,2,3,4-tetrahydroisoquinoline compounds in good yield (See Figure 24).

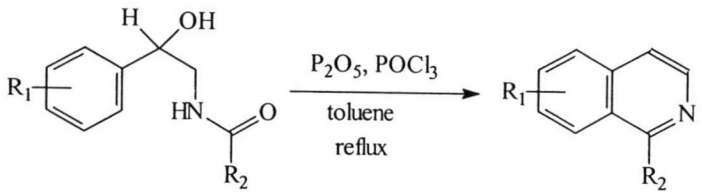


Figure 23. The synthesis of isoquinoline by Pictet-Gams reaction

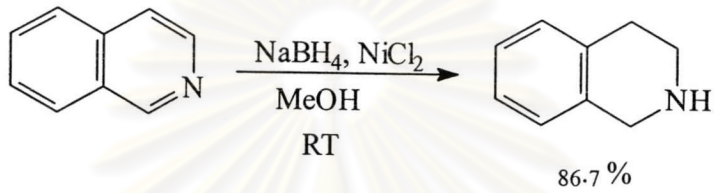


Figure24. The reduction of isoquinoline compound by using sodium borohydride and nikelous chloride to form 1,2,3,4-tetrahydoisoquinoline

c) <u>The Pictet-Spengler synthesis</u>

A suitable intermediate of type (I) can be readily prepared by the condensation of a 2-phenylethylamine with an aldehyde to form an imine ; the ring closure can then be induced by an acid as in the Bishcler-Napiralski synthesis. In this case the ring closure is the result of a Mannich reaction and a tetrahydroisoquinoline is formed (See Figure 25).

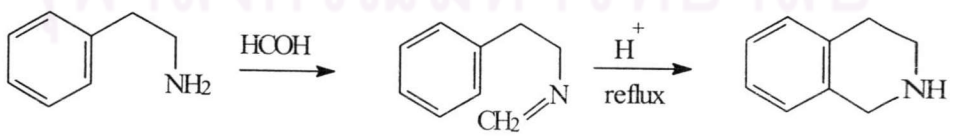
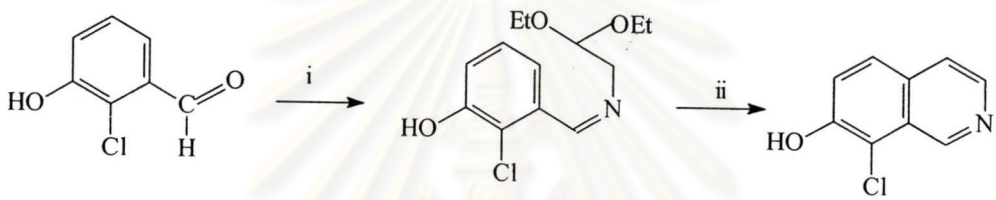


Figure25. The synthesis of 1,2,3,4-tetrahydroisoquinoline by Pictet-Spengler reaction

d) The Pomeranz-Fritsch synthesis

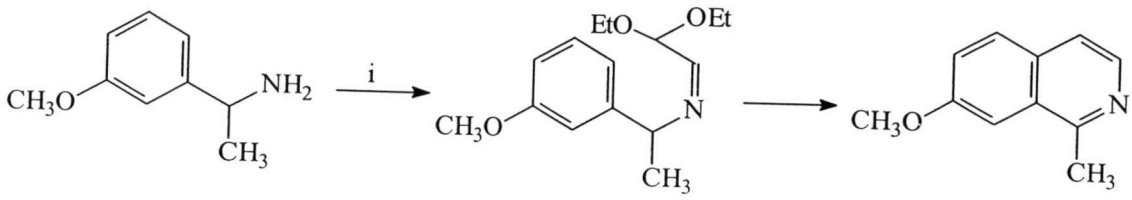
The condensation of benzaldehyde or a substituted benzaldehyde with the acetal of aminoacetaldehyde gives a schiff base (aldimine) with the skeleton structure (II) which can be cyclized with acids to an isoquinoline. The acetal group is necessary to protect the bifunctional aminoaldehyde from polymerization by self condensation; it is sensitive to acid hydrolysis and does not prevent the final ring closure.



i, $H_2NCH_2CH(OEt)_2$, C_6H_6 ; ii, (a) H_2SO_4 (76%), 8 °C, 40 h, (b) NH_4OH; yield 64%

Figure26. The synthesis of isoquinoline by Pomeranz-Fritsch reaction through aldimine intermediate.

The poor yields obtained in the formation of ketimines, as opposed to aldimines, in the first stage of this synthesis makes it unsuitable for the preparation of 1-substituted isoquinolines, but this limitation can be overcome by preparing an isomeric imine from a substituted benzylamine and the hemiacetal of glyoxal. The latter can be obtained from the acetal of acrolein by oxidation and cleavage of the glycol so formed (See Figure 27).

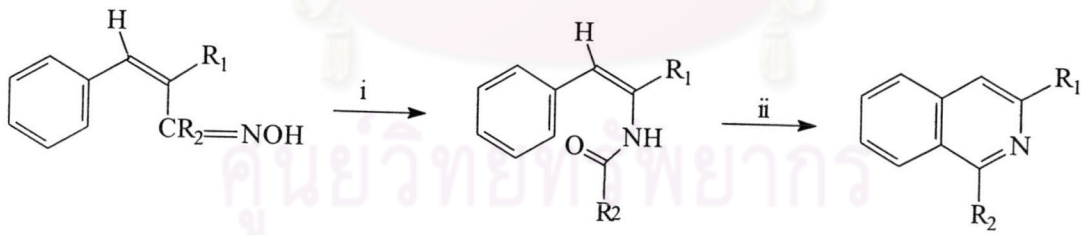


i, $O{=}CHCH(OEt)_2$, piperidine, toluene, reflux; ii, (a) H_2SO_4 (76%), HCl, 10-20 °C, 5.5 days, (b) NaOH; yield 50%

Figure 27. The synthesis of isoquinoline by Pomeranz-Fritsch reaction through ketimine intermediate

e) <u>Syntheses of isoquinolines via the Beckmann rearrangement</u>

The oxime of cinnamaldehyde ($R_1{=}R_2{=}$ H) when submitted to the conditions for the Beckmann rearrangement with phosphorus pentoxide gives isoquinoline, presumably by ring-closure of the N-styrylformamide which would normally result from the Beckmann rearrangement (See Figure 28).



i, P_2O_5, Beckmann rearrangement; ii, $-H_2O$

Figure 28. The synthesis of isoquinoline via the Beckmann rearrangement

Reduction of 3,4-Dihydroisoquinoline to 1,2,3,4-tetrahydroisoquinoline (Potapov, 1967; Carey and Sunberg, 1990; Smith, 2002)

3,4-Dihydroisoquinoline compounds which contain imine (C=N) group were reduced by some type of reductions to form amine compounds.

a) By catalytic hydrogenation

The reduction of 3,4-dihydroisoquinoline compounds was conducted by catalytic hydrogenation over palladium or platinum at room temperature, 4-100 atm. Reduction did not go to completion, a little of starting substance remained.

b) Reduction by hydride donors

Hydride reducing agents such as sodium borohydride ($NaBH_4$) and sodium cyanoborohydride ($NaBH_3CN$) were used to reduce imine compounds to form amine.

The solution of imine compound in methanol with sodium borohydride was stirred at 0°C to give product, amine (See Figure 29).

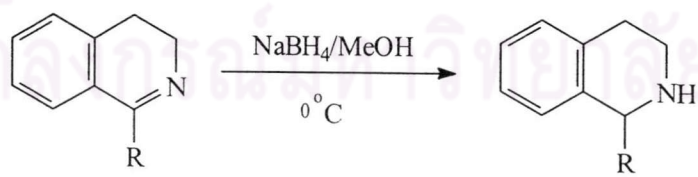


Figure 29. The reduction of 3,4-dihydroisoquinoline by using sodium borohydride.

Under acidic condition, protonation of nitrogen gives an iminium salt that is then reduced with cyanoborohydride to an amine (See Figure30).

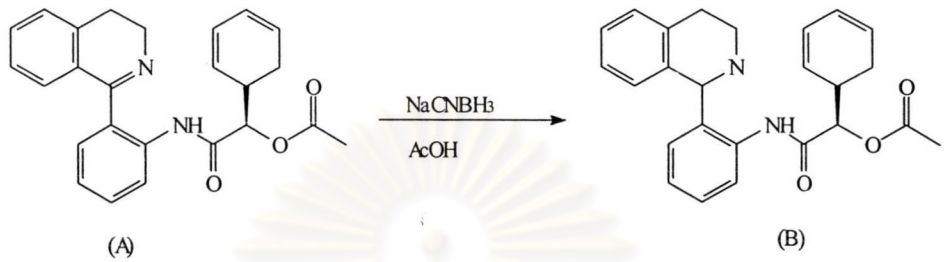


Figure30. The reduction of 3,4-dihroisoquinoline compound by using sodium cyanoborohydride.

Syntheses of amides by *N*-acylation of amine compounds (Morrison and Boyd, 1987; Bruice, 1988; Wade, 1999)

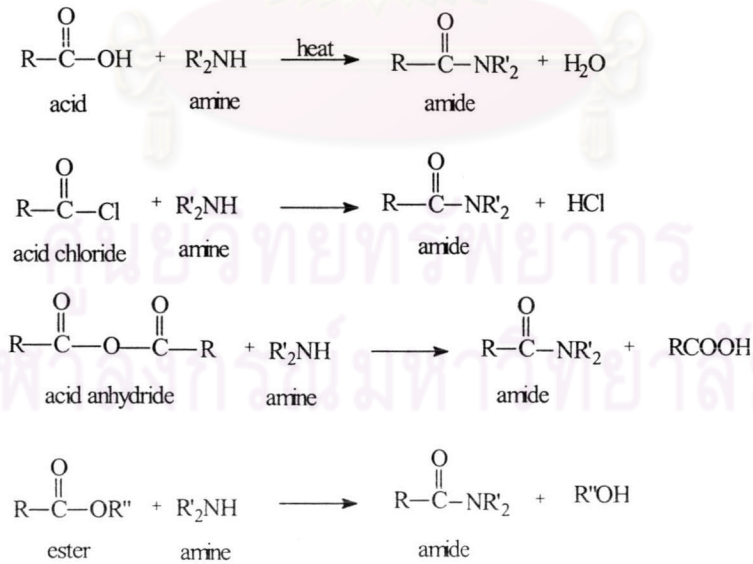


Figure 31. The formation of amides compounds by *N*-acylation of amine

In the laboratory, amides are commonly synthesized by the reaction of an acid chloride (or anhydride) with an amine. The most common industrial synthesis involves heating an acid with an amine to drive off water and promote condensation. Esters react with amines and ammonia also give amides. (See Figure 31)

a) <u>syntheses of amides from acyl halides</u>

The treatment of acyl halides with amines is a very general reaction for the preparation of amides. Acyl chlorides are highly reactive acylating agents and react very rapidly with amines. The reaction of an acyl chloride with ammonia or with a primary or secondary amine or arylamine produces an amide, H^+ and Cl^-. The H^+ generated in the reaction will protonate unreacted ammonia or amine because these protonated compounds are not nucleophiles, they can not react with the acyl chloride. The reaction, therefore, must be carried out with twice as mush ammonia as acyl chloride or else there will be only enough amine to react with of the acyl halides. In some cases aqueous alkali is added to combine with the liberated HCl.

c) <u>Syntheses of amide from acid anhydride</u>.

An acid anhydride reacts with an minne to form an amide. Acid anhydrides undergo the same reaction as acid cholrides, but a little more slowly; where acid chlorides yield a molecule of HCl, anhydrides yield a molecule of carboxylic acid. Two equivalent of an amine, or one equivalent of an amine plus one equivalent of a tertiary amine such as pyridine or tertiary amine, must be employed in the reaction of an amine with an anhydride so that sufficient amine is present to react with the acid produced in the reaction.

d) Syntheses of amides from esters.

The reaction of an ester with an amine is a slow reaction. However, unlike the reaction of an ester with water or an alcohol, the rate of the reaction of an ester with an amine cannot be increased by H^+ or by HO^- or RO^-. Aminolysis of an ester can be driven to completion by using excess amine or by distilling off the alcohol as it is formed.

Reduction of nitro compounds to amine. (March, 1968 ; Morrison and Boyd, 1987)

Like many organic compounds, a nitro compound can be reduced to an amine in two general ways.

a) By catalytic hydrogenation

Hydrogenation of a nitro compound to an amine takes place smoothly when a solution of the nitro compound is shaken with finely divided palladium, platinum or nickel under hydrogen gas. Palladium is the most common hydrogenation catalyst for both aromatic and aliphatic nitro compounds. This method can not be used when the molecule also contains some other easily hydrogenated group, such as a carbon-carbon double bond.

b) By chemical reduction.

Adding hydrochloric acid to a mixture of the nitro compound and a metal, usually granulated tin most often carries out chemical reduction in the laboratory. In the acidic solution, The amine is obtained as its salt; the free amine is liberated by addition of base, and is steam-distillated from the reaction mixture. The crude amine is generally

contaminated with some unreduced nitro compound, from which it can be separated by taking advantage of the basic properties of the amine; the amine is soluble in aqueous mineral acid, while the nitro compound is not.