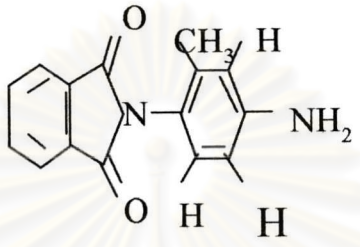
Chapter I

Introduction

Of the countless neurological diseases and disorders that have been identified, few are as pervasive and common as epilepsy (Bazil and Pedly, 1998; Kocki et al., 2003).This a major health problem affecting about 0.5 - 1% of the population worldwide (Bazil and Pedly, 1998; Kocki et al., 2003).

The principal goal of therapy with an antiepileptic drug, (AED) is to keep the patient free of seizures without interfering with normal brain function. In anticonvulsant drug development, a 50% decrease in seizure frequency is often accepted as evidence of clinical efficacy (Weiser, 1993). The most satisfactory endpoint of efficacy, however, is total remission of seizures with no impairment in quality of life. Because 20-30% of epileptic patients never become seizure free with drug therapy and up to 40% of individuals suffer from intractable, pharmacoresistant epilepsy (Kwan and Brodie, 2000) this means that approximately twelve million people worldwide have never had completely successful drug therapy for their seizures. In addition to the problem of pharmacoresistance, treatment with several AEDs may lead to considerable undesired effects, most commonly to neurotoxic and idiosyncratic reactions (Brodie, 2001). Therefore, in difficult-to-control cases, new therapeutic strategies with better safety, lesser toxicity and higher efficacy are needed urgently, justifying the continuous search for novel antiseizure medication.

In 2000, N-(4-Amino-2-Methylphenyl)phthalimide, (AMP) was discovered by Mr. Wanchai Pleumpanupat. It was a derivative of phthalimide (Pleumpanupat, 2000). AMP was effective in the Maximum Electroshock Seizure models, (MES). Comparatively, AMP was more potent than VPA in the MES model (Pleumpanupat, 2000).



N-(4-Amino-2-Methylphenyl)phthalimide (Pleumpanupat, 2000)

Efficacy in the MES model correlates with efficacy in suppressing tonic-clonic generalized seizures. In contrast, Pentylenetetrazole test, (PTZ) examines the ability of a compound to raise seizure threshold and is predictive of drug efficacy in the absence of seizure (Rogawski and Porter, 1990; White et al, 1997; Loscher, 1998). Furthermore, it has been suggest that these two tests may actually evaluate the effect of drugs on two separate anatomical structures (Browing, 1992). Both of the tests are recommended as primary screening tests in Antiepileptic Drug Development (ADD) program which was established in the U.S.A. in 1974 by collaborations between government, pharmaceutical industry and academia (White et al., 1998). Thus, this study aims to evaluate anticonvulsant activity, expressed as the median effective dose (ED_{50}), of AMP in both the MES and PTZ models in parallel with its toxicity in a battery of toxicity testing as suggested in the ADD program (Cereghino and Kupferberg, 1993). Furthermore a possible

effect of AMP on the levels of cortical excitatory and inhibitory amino acid neurotransmitters of freely moving rats would also be investigated.