CHAPTER I

INTRODUCTION

Depression is a heterogeneous disorder. It is characterized by a disturbance of mood associated with alteration in behavior, energy, appetite, sleep and weight (Neal, 1994). A depressive person becomes persistently sad and unhappy. Although depression can cause people to kill themselves, in general the prognosis is good. The primary aim of treatment is to prevent harm and to relief distress. In cases of mild depression, psychotherapy alone can be effective, but in moderate to severe depression, pharmacotherapy with an antidepressant medication is indicated, regardless of whether the patient is referred for psychotherapy (Majeroni and Hess, 1999). Traditionally the antidepressant drugs are categorized by their chemical structure (e.g. tricyclic) or their predominant pharmacological action (e.g. monoamine oxidase inhibitor or selective 5-HT reuptake inhibitor). All the antidepressants are equally effective. There is no convincing evidence that any one drug is any faster acting, or any better or any worse than any other in relieving the symptoms of depression. The major difference between agents is in their side effect profile, toxicity in overdose and also variations in the cost of different agent (Pratt, 1994). At present, the cause of depression and the mechanisms of action of antidepressants are unknown. Research on antidepressant drugs has led to the 'monoamine hypothesis' - that depression resulted from a decrease in the activity of central noradrenergic and/or serotonergic system (Neal, 1994).

There are many models relevant to depressive disorder. Models are animal preparations that attempt to mimic a human condition, including human psychopathology (Gayer and Markou, 1995). No experimental model exists at present for such depressive states in animal (McKinney and Bunny, 1969; Thiebot *et al*, 1992). One of the most widely used animal models of depression is the behavioral despair test (Forced swimming test). This model was developed to predict the efficacy of

antidepressants. The forced swimming test is particularly simple and cheap for screening new molecules (Burin,1990). The majority of antidepressants,including tricyclic (e.g. amitriptyline, imipramine), MAO inhibitors (e.g. clorgyline, tranylcypromine), and newer antidepressants (e.g. trazodone, nomifensin) decrease the total immobility time in this test (Persolt *et al*, 1979; Borsini, Lecci, Mancinelli, de Aranno, and Meli, 1987; Trullas, Folio, Young, Miller, Boje, Skolnick, 1991; Simiand *et al*, 1992; Manisto, Lang, Rauhala, and Vasar, 1995; Redrobe, MacSweeney, and Bourin, 1996). The measurement of locomotor activity and Rota-rod test were the models which help to indicate that the improved performance of animals (decreased immobility time) is not due to the increased motor activity or defect in motor coordination or fatigue resistance.

The synthesized chemicals in this study are 5-hydroxymethyl-8-methyl-2-pentyl-4*H*-dioxino[4,5-c]pyridine hydrochloride (CU 763-14-07) and 2-hexyl-5-hydroxymethyl-8-methyl-4*H*-dioxino[4,5-c]pyridine hydrochloride (CU 763-14-10). Previous studies reported that both of them inhibit MAO from rat liver mitochondria (Ratanachol, 1997; Wongsomnuk, 1998). For reason that agents which exhibit inhibition of monoamine oxidase enzyme may possess antidepressant activity (e.g. Phenelzine, tranylcypromine, clorgyline, pargyline), therefore studying and investigation on pharmacological properties of CU 763-14-07 and CU 763-14-10 may provide data which are beneficial to the development of effective antidepressants in the future. The purposes of the present study were to investigate the potential antidepressant activity of the test substances on the animal models. The present study also determines the preliminary effects of CU 763-14-07 and CU 763-14-10 on the central neurotransmitter system. It is probable that these test substances, which inhibit MAO activity *in vitro*, may be effective in animal model of depression through this mechanism.