3936812 PYPE/M : MAJOR : PHARMACEUTICAL CHEMISTRY; M.Sc. in Pharm. (PHARMACEUTICAL CHEMISTRY)
KEY WORDS : CHROMAN / COUMARIN / NICOTINIC / ANTIRADICAL / PRODRUG / LIPID PEROXIDATION / LOCOMOTOR / WATER MAZE

ORAWAN MONTHAKANTIRAT : SYNTHESIS AND ANTIRADICAL ACTIVITY OF PRODRUGS OF CHROMAN AMIDE AND COUMARIN AMIDE. THESIS ADVISORS ; OPA VAJRAGUTA, Ph.D., PENCHOM PEUNGVICHA, Ph.D. 136 p. ISBN 974-662-480-6

Structure modification of the cerebroprotective antiradicals through prodrug approach was carried out in this study. These aims were to improve the drug delivery to the target organ by increasing lipophilicity and protecting the active hydroxy functional group. Three new compounds (**12P**, **16P**, **18**) were designed and synthesized. **12P** and **16P** were the prodrugs of chroman amide (**12**) and coumarin amide (**16**) while **18** was the new hydroxynicotinyl amide. The O-acetyl group was the pro-moiety or carrier of the prodrugs which served to protect the active group to be delivered to the target organ. *Ex vivo* antilipid peroxidation activity of prodrugs **12P** and **16P** were significantly greater than those of the respective parents while the *in vitro* inhibition of prodrugs were found to be lower or no action. These indicated that the prodrugs with protected active group effectively reached the brain, the target site, but *in vitro*, the prodrugs were unable to release their parents or released them slowly. Compound **18** showed substantial *ex vivo* inhibition despite very low *in vitro* inhibition.

Neuropharmacology of the synthesized antiradicals was investigated in mice in two models. In the first model, all test compounds (50-100 mg/kg, i.p.) showed significant suppression on the hypermotility induced by methamphetamine 18.16%-63.83% suppression. The prodrugs were more potent than their respective parents. The suppression demonstrated the enhancement of brain delivery and the antagonism against aberrant dopamine release. Compounds **16P** and **18** were the promising candidates since they did not reduce locomotor activity in normal conditions, as did other tested compounds. In the second model, water maze model, **12P** (200 mg/kg) and **18** (100 mg/kg) as well as tacrine (3 mg/kg), a reference drug, significantly reduced the learning and memory impairment induced by scopolamine. The neuropharmacological results support the additional role of antiradicals in the modulation of brain neurotransmitters in the aberrant condition.