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PREECHA BOONCHOONG : DESIGN AND SYNTHESIS OF COUMARIN AMIDES AS ANTIRADICAL AGENTS. THESIS ADVISOR : OPA VAJRAGUPTA, Ph.D., YUVADEE WONGKRAJANG, M.S. 158 P. ISBN 974-661-791-5

In searching for new types of antiradical agents, a series of coumarin amides (**14-16**) and chroman amides (**17**) were designed and synthesized. Their structures were modified by varying the chemical function of both sides of amide. The selected nucleus in acid part was 7-hydroxycoumarin and the amine parts were 1-diphenylmethylpiperazine, tryptamine and 2-amino-6-methoxy quinoline. Four new compounds were tested for antilipid peroxidation activity *in vitro* using thiobarbituric acid method. Coumarin amides showed inhibitory activity with IC_{50} of 109-286 μM while chroman **17** was the most active with IC_{50} of 0.17 μM. *Ex vivo* antilipid peroxidation activity in both normal mice and mice with head injuries were investigated. Significant inhibition was not found in coumarin amides even at high dose of 200 mg/kg regardless of *in vitro* inhibition. Chroman amide **17**, however, shows significant inhibition in *ex vivo* of 23.80 % at a dose 100 mg/kg. ESR spin trapping method was performed to investigate the scavenging ability against $^{\bullet}OH$ radical by using α-pheny-*tert*-butylnitrone (PBN) as spin trap. All of chroman and coumarin amides suppressed the $^{\bullet}OH$ generation resulting in the decrease of signal area of PBN/$^{\bullet}OH$ adduct, suggested that both chroman and coumarin amides were antiradical. The difference between the *in vitro* results (antilipid peroxidation and ESR) and *ex vivo* results arised from the poor accessibility of coumarin amides in brain due to the non-hindered hydroxy and low log P. The quantitative structure-activity relationships (QSAR) of 13 previous compounds (**1-13**) were studied by classical QSAR and 3D-QSAR (Apex-3D and CoMFA) techniques. The derived 5 QSAR models gave predictive cross-validated r^2_{cv} of 0.597-0.978. The predictive power of the models was tested by the four new compounds (**14-17**). The predicted values from all models were in agreement with the experimental values in some extent. Apex-3D models yielded the best prediction; the activity of **17** was predicted to be as potent as in the experiment. The classical QSAR models indicated that antilipid peroxidation was attributed to the electronic C_{O1} and E_{LUMO}, steric MR and hydrophobic log P. The predicted activity of **17** from CoMFA was much lower than the experimental value. This deviation occurred according to the missing of hydrophobic field in standard CoMFA study. Thus, the structure/physicochemical properties for good bioavailability activity should also be taken into consideration for drug design.