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Design of novel carbamate acetylcholinesterase inhibitors based on the multiple binding sites of acetylcholinesterase

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Abstract:
This work describes the design, synthesis, AChE inhibitory activity, and structure-activity relationship of compounds related to a recently discovered series of AChE inhibitors: phthalimide alkyloxyphenyl *N*-methylcarbamates. The influence of structural variations on inhibitory potency was carefully investigated by modifying different alkyloxy chain lengths and positions between phthalimide and phenyl *N*-methylcarbamate. The biological properties of the series were investigated in some detail by considering their activity on isolated enzymes. All of the newly synthesized derivatives, when tested on isolated AChE from the brain of the housefly (*Musca domestica*), were more active than phenyl *N*-methylcarbamate. In particular, compound **I1** displayed the best AChE inhibition (352-fold higher than phenyl *N*-methylcarbamate, and 29-fold higher than metolcarb), which suggested that the phthalimide group of **I1** bound strongly to the residues lining the gorge, and phenyl *N*-methylcarbamate bound at the catalytic sites.

Keywords:
carbamate insecticides, acetylcholinesterase, multiple binding sites, inhibitory activity, structure-activity relationship

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