

SEMINAR ANNOUNCEMENT

PhD Thesis Defence Seminar

Pharmacophoric Models of Sodium Channel Antagonists

by

Mr. Poon Thong Yuen
Department of Pharmacy
National University of Singapore

on

Date: Saturday, 10th July 2004
Time: 1000 – 1100 hrs
Venue: Pharmacy Tutorial Room (S4-05-16)

Synopsis:

A pharmacophoric model, which consists of one H-bond donor (D), one H-bond acceptor (A) and one hydrophobic group (H), was derived from five good neuronal (type II) sodium channel blockers. The A-H, A-D and D-H distances are $4.02 \pm 1.26 \text{ \AA}$, $5.65 \pm 1.26 \text{ \AA}$, and $3.27 \pm 1.26 \text{ \AA}$ respectively.

The model was validated and subsequently adapted into a screening process which identified the 4,6-diamino-1,2-dihydro-2,2-substituted-1-phenyl-1,3,5-triazines (phenyldihydro-1,3,5-triazines) as good sodium channel blockers while the benzyloximes were predicted to be weak blockers. Synthesis and testing of the compounds in the [³H]-batrachotoxin (BTX) assay verified the predictions. The most active compounds in the phenyldihydro-1,3,5-triazines series (compound **34**) and benzyloxime series (compound **51**) have IC₅₀ values of $4.0 \pm 0.5 \mu\text{M}$ and $0.44 \pm 0.02 \text{ mM}$ respectively.

The phenyldihydro-1,3,5-triazines did not possess epileptic protection in the Maximal Electroshock (MES) assay but were found to have analgesic properties in the hot-plate assay, while the benzyloximes displayed epileptic protection in the MES assay, and one compound possesses slight analgesic properties.

Keywords: sodium channels, pharmacophore, triazines, benzyloximes, BTX.

ALL ARE WELCOME