SUPPLEMENTARY INFORMATION ON AChE MODELS FOR BINDING SITE

INTERACTIONS

Note on AO and AP

AO is AChE orthologous whereas AP is AChE paralogous. Some insects have the AP AChE in addition to the AO AChE. Mutations in either AO or AP can lead to resistance. *Drosophila melanogaster* has only AO (or rather AO in other insects seems to be defined as orthologous relative to the one known *Drosophila melanogaster* AChE).

The *Drosophila melanogaster* structure is PDB 1DX4. Reference:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2144661/
Protein Sci. 2000 June; 9(6): 1063–1072.
PMCID: PMC2144661
Three-dimensional structures of *Drosophila melanogaster* acetylcholinesterase and of its complexes with two potent inhibitors.
M. Harel, G. Kryger, T. L. Rosenberry, W. D. Mallender, T. Lewis, R. J. Fletcher, J. M. Guss, I. Silman, and J. L. Sussman.

The human structure is PDB 1F8U. Note this structure is actually the E202Q mutant mutated back to E for the docking.
http://www.ncbi.nlm.nih.gov/pubmed/11053835?dopt=Abstract
Acta Crystallogr D Biol Crystallogr. 2000 Nov;56(Pt 11):1385-94.
Structures of recombinant native and E202Q mutant human acetylcholinesterase complexed with the snake-venom toxin fasciculin-II.
G. Kryger, M. Harel, K. Giles, L. Toker, B. Velan, A. Lazar, C. Kronman, D. Barak, N. Ariel, A. Shafferman, I. Silman, J. L. Sussman.

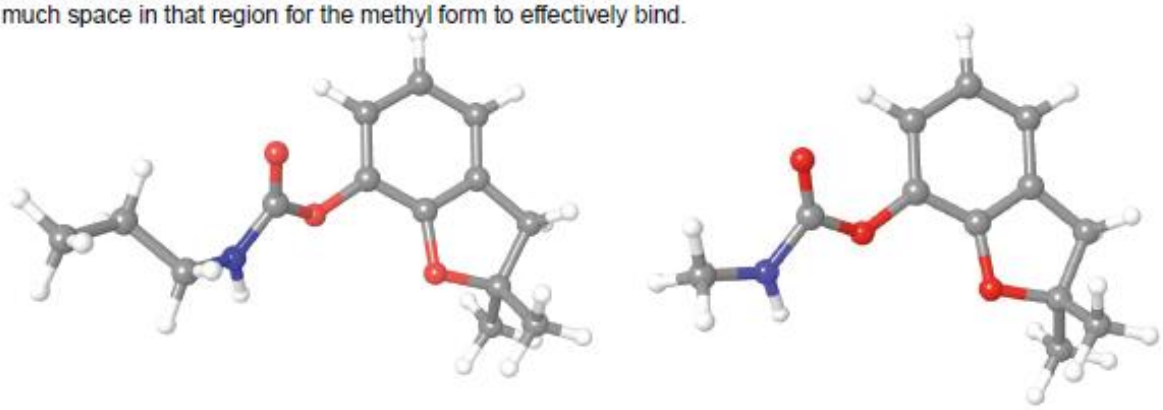
The green rice leafhopper (*Nephottetix cincticeps)* structure is Uniprot D2KTL8 built as a homology model on 1DX4 (Using the Prime algorithm from Schrodinger).
This is explictly labeled as "AO" as part of the gene name.

The African malaria mosquito (*Anopheles gambiae)* structure is PDB 2AZG which is a homology model from Pang, Y.-P. discussed in Current Drug Targets, 2012, 13, 471-482
Novel and viable acetylcholinesterase target site for developing effective and environmentally safe insecticides
Y.-P. Pang, S. Brimijoin, D. W. Ragsdale, K. Y. Zhu and R. Suranyi
This is an AP-AChe and it is this and related AP-Ache's that have the CYS referred to in Fig 2D etc.

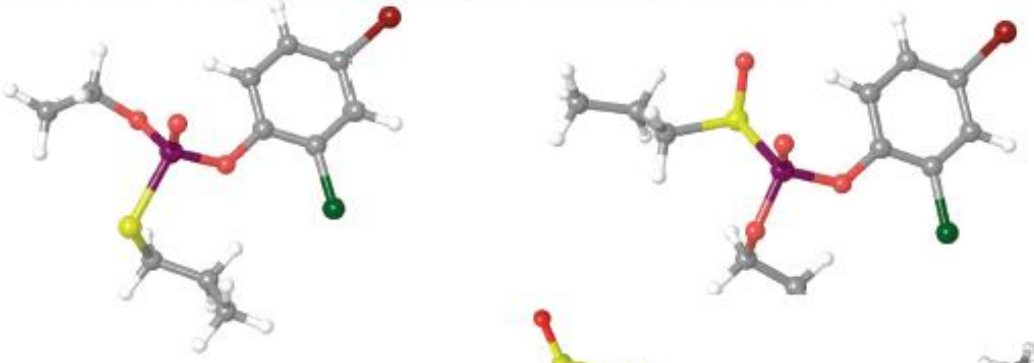
SUPPLEMENTARY INFORMATION ON BINDING SITE INTERACTIONS IN FIG 2

A. Fenitroxon docks better in *Drosophila* than in human AChE by more than 1 kcal/mol in relative binding energy. The nitro moiety of fenitroxon cannot be in plane with the aromatic ring due to steric interactions with the adjacent methyl moiety. None-the-less, the fenitroxon aromatic stacks cleanly in the *Drosophila* AChE whereas the corresponding pocket in human AChE is much more crowded and an alternate and less stable binding mode is adopted as a result.

B. Carbofuran in both the *N*-methyl and *N*-propyl form can have favorable hydrophobic interactions with the *Nephotettix* wild type Phe (290 in *Torpedo* numbering) whereas the resistant mutant F290V leaves too much space in that region for the methyl form to effectively bind.



C. Profenofos *R*-enantiomer (left) and *S*-enantiomer as a sulfoxide (right) are both active in insect. Note the phosphate orientation of each as the leaving group differs in the two forms.



D. AMTS13 docks well in *Anopheles* AChE with the thio sulfonate in range to react with the Cys near the AChE throat and the quaternary ammonium in the binding pocket.