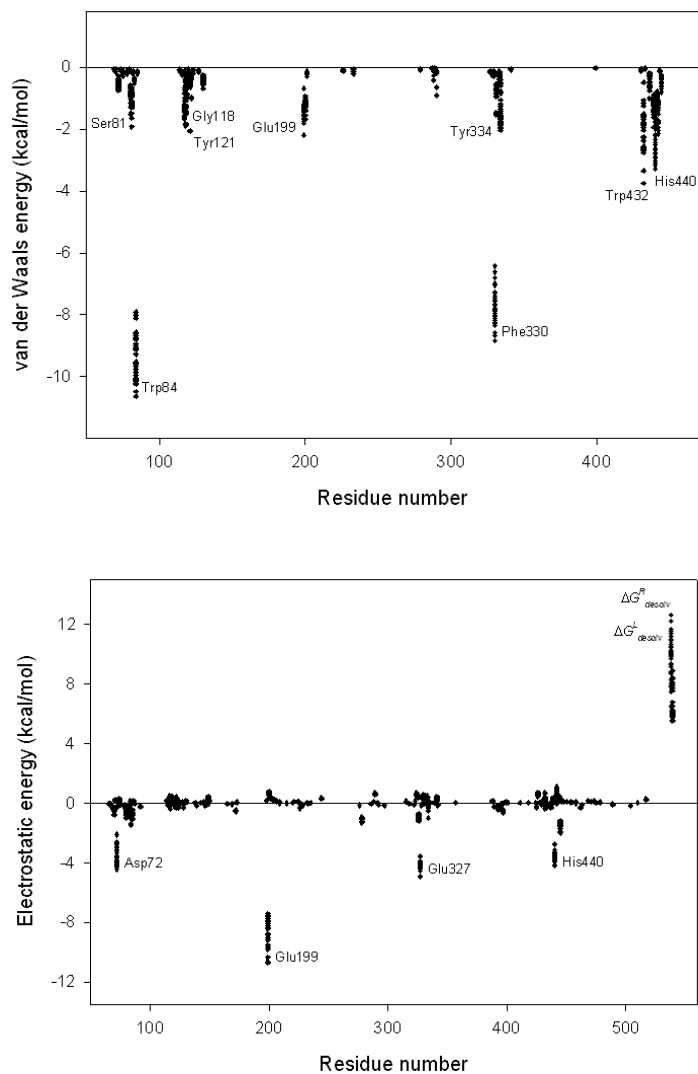


## **SUPPORTING INFORMATION**

**Title:** Modulation of Binding Strength in Several Classes of Active Site Inhibitors of Acetylcholinesterase Studied by Comparative Binding Energy (COMBINE) Analysis

**Authors:** Sonsoles Martín-Santamaría, Jordi Muñoz-Muriedas, F. Javier Luque, and Federico Gago



**Figure 1.** Interaction energy variables that enter the PLS analysis leading to the COMBINE model for the whole set of AChE inhibitors studied. Each diamond represents a value from the energy matrix. On the horizontal axis, the variables are ordered sequentially and correspond to van der Waals (top) and electrostatic (bottom) interactions between the ligands and the protein residues.

CLUSTAL FORMAT for T-COFFEE Version\_1.41, SCORE=69, Nseq=3, Len=614  
http://igs-server.cnrs-mrs.fr/~cnotred/Projects\_home\_page/t\_coffee\_home\_page.html

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sp|P04058|ACES_TORCA -----MNLTVTSSLGVLLHLV---VLCQADHDHSELLVNTKSGKVMGTRVPVLSHSI
sp|P23795|ACES_BOVIN -MRPPWCPLHTPSLTPPLLLLLLFLIGGAEAEQPEPELLVMVVRGGRLRGLRMAPRGPV
sp|P22303|ACES_HUMAN MRPPQCLLHTPSLASPLLLLLLWLLGGVGAEGREDAELLVTVRGGRLRGLRKTGGPV
      . . * : ** * : . . . : . . . . . . : * * : . . . :
sp|P04058|ACES_TORCA SAFLGIPFAEPPVGNMRFRRPEPKKPWSGVWNASTYPNNCQYVDEQFPFGFSGSEMWNPN
sp|P23795|ACES_BOVIN SAFLGIPFAEPPVGPVRRFLPEPKRPWPVGLNATAFQSVCYQYVDTLYPGFEGTEMWNPN
sp|P22303|ACES_HUMAN SAFLGIPFAEPPMGPRRFLPEPKQPWSGVVDATTQSVCYQYVDTLYPGFEGTEMWNPN
      *****:* ** *****:* * : : : . * ***** :*:*:*:*****
sp|P04058|ACES_TORCA REMSEDCLYLNIVWVSPRPKSTT-VMVWIYGGGFYSGSSTLDVYNGKYLAYTEEVLVLSL
sp|P23795|ACES_BOVIN REISEDCLYLNWVTPYPRPSSPTPVLVWIYGGGFYSGASSLDVYDGRFLTQAEGTVLVSM
sp|P22303|ACES_HUMAN REISEDCLYLNWVTPYPRPTSP TPVLVWIYGGGFYSGASSLDVYDGRFLVQAERTVLVSM
      *:*:*:*:*:*:* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
sp|P04058|ACES_TORCA SYRVGAFGFLALHGSQEAPGNVGLLDQRMALQWVHDNIQFFGGDPKTVTIFGESAGGASV
sp|P23795|ACES_BOVIN NYRVGAFGFLALPGSREAPGNVGLLDQRLALQWVQENVAAFGGDPTSVTLFGESAGAASV
sp|P22303|ACES_HUMAN NYRVGAFGFLALPGSREAPGNVGLLDQRLALQWVQENVAAFGGDPTSVTLFGESAGAASV
      .***** *:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*:*
sp|P04058|ACES_TORCA GMHILSPGSRDLFRRAILQSGSPNCPWASVSVAEGRRAVELGRNLNC----NLNSDEEL
sp|P23795|ACES_BOVIN GMHLLSPPSRGLFHRAVLQSGAPNGPWATVGVGEARRRATLLARLVGCPPGGAGNDTEL
sp|P22303|ACES_HUMAN GMHLLSPPSRGLFHRAVLQSGAPNGPWATVGMGEARRRATQLAHLVGCPPGGTGGNDTEL
      *:*:* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
sp|P04058|ACES_TORCA IHCLREKKPQELIDVEWNVLPFDSIFRFVFPVIDGEFFPTSLESMLNSGNFKKTKQILLG
sp|P23795|ACES_BOVIN VACLRRAPAQDLVDHEWRVLPQESVFRFSFVFPVVDGDFLSDTPEALINAGDFHGLQVLVG
sp|P22303|ACES_HUMAN VACLRTPAQVLVNHWHVLPQESVFRFSFVFPVVDGDFLSDTPEALINAGDFHGLQVLVG
      : * * * : . * * : : * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
sp|P04058|ACES_TORCA VNKDEGSFLLYGA P G F S K D S E S K I S R E D F M S G V K L S V P H A N D L G L D A V T L Q Y T D W M D D N
sp|P23795|ACES_BOVIN VVKDEGSYFLVYGA P G F S K D N E S L I S R A Q F L A G V R V G V P Q A S D L A A E A V V L H Y T D W L H P E
sp|P22303|ACES_HUMAN VVKDEGSYFLVYGA P G F S K D N E S L I S R A E F L A G V R V G V P Q V S D L A A E A V V L H Y T D W L H P E
      * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
sp|P04058|ACES_TORCA NGIKNRDGLDDIVGDHNVICPLMHFVNKYTKFNGTYLYFFNHRASNLVWPEWGMVIGHY
sp|P23795|ACES_BOVIN DPARLREALSDVVDHNVVCPVAQLAGRLAAQGARVYAYIFEHRASLTSWPLWGMVPHGY
sp|P22303|ACES_HUMAN DPARLREALSDVVDHNVVCPVAQLAGRLAAQGARVYAYVFEHRASLTSWPLWGMVPHGY
      : : * : . * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
sp|P04058|ACES_TORCA EIEFVFG L P L V K E L N Y T A E E E A L S R R I M H Y W A T F A K T G N P N E P H S Q E S - K W P L F T T K E Q K
sp|P23795|ACES_BOVIN EIEFIFGLPLEP SLNYTIEERTFAQRLMRYWANFARTGDPNDPRDPKAPQWPPYTAGAQQ
sp|P22303|ACES_HUMAN EIEFIFGIPLDPSRNYTAEKIFAQRLMRYWANFARTGDPNPRDPKAPQWPPYTAGAQQ
      * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
sp|P04058|ACES_TORCA FIDLNTEPMKVHQRLRVQMCVFNQFLPKLLNATACDGELSSSGTSSSKGIIFYVLF SIL
sp|P23795|ACES_BOVIN YVSLNLRPLEVRRGLRAQACAFWNRFLPKLLSATDTLDEAERQWKAEFHRWSSYMVHWKN
sp|P22303|ACES_HUMAN YVSLDLRPLEVRRGLRAQACAFWNRFLPKLLSATDTLDEAERQWKAEFHRWSSYMVHWKN
      : : * * : . * : * : * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
sp|P04058|ACES_TORCA YLIF-----
sp|P23795|ACES_BOVIN QFDHYSKQDRCS DL
sp|P22303|ACES_HUMAN QFDHYSKQDRCS DL
      : .
```

**Figure 2.** Sequence alignment of *Torpedo californica* (ACES\_TORCA), bovine (ACES\_BOVIN) , and human (ACES\_HUMAN) AChE enzymes, as performed by T-Coffee (Notredame, C.; Higgins, D.; Heringa, J. T-Coffee: A novel method for multiple sequence alignments. *J. Mol. Biol.* **2000**, *302*, 205–217). Phe330 (bold type) in *Torpedo californica* (blue) is replaced in the mammalian enzyme by a Tyr (red).