**Tacrine-sugar mimetic conjugates as enhanced cholinesterase inhibitors**

Quelli Larissa Oliveira de Santana,\textsuperscript{a,b} Tereza C. Santos Evangelista,\textsuperscript{a,b} Petra Imhof,\textsuperscript{c} Sabrina Baptista Ferreira,\textsuperscript{b} José G Fernández-Bolaños,\textsuperscript{d} Magne O. Sydnes,\textsuperscript{a} Óscar Lopéz,\textsuperscript{d} and Emil Lindbäck \textsuperscript{*a}

\textsuperscript{a}Department of Chemistry, Bioscience and Environmental Engineering, Faculty of Science and Technology, University of Stavanger, NO-4036 Stavanger, Norway.

\textsuperscript{b}Department of Organic Chemistry, Chemistry Institute, Federal University of Rio de Janeiro, UFRJ, 21949-900 Rio de Janeiro, RJ, Brazil

\textsuperscript{c}Departamento de Química. Friedrich-Alexander University (FAU) Erlangen-Nürnberg Computer Chemistry Center Nägebsachstrasse 25 91052 Erlangen Germany.

\textsuperscript{d}Orgánica, Facultad de Química, Universidad de Sevilla, c/Profesor García González 1, 41012, Seville, Spain

**List of content**

Docking and Molecular dynamics simulation studies.................. 2

NMR spectra................................................................. 6
Docking and Molecular dynamics simulation studies

Figure S1: Superposition of Ache from *Torpedo californica* in ligand-bound (pdb ID 1ut6, gold) and apo-(pdb ID 1qt1, brown) form with Ache from *Electrophorous Electricus* (pdb ID 1c2b, silver). The ligand N-9-(1',2',3' Tetrahydroacridinyl)-1,8- diaminooctane of the 1ut6 structure is shown in black. Important active site residues are labelled.
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Figure S2: Binding poses for the different ligand models. For each model, one docking pose with the tacrine moiety at the CAS (Pose 1) and one with the iminosugar at the CAS (Pose 2) are shown. The estimated binding affinities of the respective two poses differ by only 0.4 - 1.0 kcal/mol.
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Figure S3: Median structures as most representative snapshots of the protein-ligand complexes. Residues Trp86 and Trp286 (el. ectricus numbering) of the CAS and PAS, respectively, are highlighted in magenta. Oxygen atoms of water molecules around the ligands are shown as red spheres.

The snapshots from the MD simulations (see Figure S3) show the ligands accommodated in the protein such that with one end (sugar or tacrine) is bound at the CAS, i.e. close to Trp 86, and the other (tacrine or sugar) in the PAS, close to Trp 286. The two poses can clearly be distinguished from which part is
bound to which site, that is Pose 1 has the tacrine moiety at the CAS and in Pose 2 it is the iminosugar that is placed at the CAS.
$^1$H-NMR of compound 17 (CDCl$_3$, 400.13 MHz)
$^{13}$C-NMR of compound 17 (CDCl$_3$, 100.61 MHz)
$^1$H-NMR of compound 18 (CDCl$_3$, 400.13 MHz)
$^{13}$C-NMR of compound 18 (CDCl$_3$, 100.61 MHz)
$^1$H-NMR of compound 19 (CDCl$_3$, 400.13 MHz)
$^{13}$C-NMR of compound 19 (CDCl$_3$, 100.61 MHz)
$^1$H-NMR of compound 21 (CDCl$_3$, 400.13 MHz)
$^{13}$C-NMR of compound 21 (CDCl$_3$, 100.61 MHz)
$^1$H-NMR of compound 22 (CDCl$_3$, 400.13 MHz)
$^{13}$C-NMR of compound 22 (CDCl$_3$, 100.61 MHz)
$^1$H-NMR of compound 24a (CDCl$_3$, 400.13 MHz)
$^{13}$C-NMR of compound 24a (CDCl$_3$, 100.61 MHz)
$^1\text{H-NMR of compound } 24\text{b (CDCl}_3, 400.13 \text{ MHz)}$
$^{13}\text{C}-\text{NMR}$ of compound 24b (CDCl$_3$, 100.61 MHz)
$^1$H-NMR of compound 24c (CDCl$_3$, 400.13 MHz)
$^{13}$C-NMR of compound 24c (CDCl$_3$, 100.61 MHz)
$^1$H-NMR of compound 24d (CDCl$_3$, 400.13 MHz)
$^{13}$C-NMR of compound 24d (CDCl$_3$, 100.61 MHz)
$^1$H-NMR of compound 25 (CDCl$_3$, 400.13 MHz)
$^{13}$C-NMR of compound 25 (CDCl$_3$, 100.61 MHz)
$^1$H-NMR of compound 12a (CD$_3$OD, 400.13 MHz)
$^{13}$C-NMR of compound 12a (CD$_3$OD, 100.61 MHz)
$^1$H-NMR of compound 12b (D$_2$O, 400.13 MHz)
$^{13}$C-NMR of compound 12b (D$_2$O, 100.61 MHz)
$^1$H-NMR of compound 12c (CD$_3$OD, 400.13 MHz)
$^{13}$C-NMR of compound 12c (CD$_3$OD, 100.61 MHz)
$^1$H-NMR of compound 12d (CD$_3$OD, 400.13 MHz)
$^{13}$C-NMR of compound 12d (CD$_3$OD, 100.61 MHz)
$^1$H-NMR of compound 6HCl (D$_2$O, 400.13 MHz)
$^{13}$C-NMR of compound $6\text{HCl}$ (D$_2$O, 100.61 MHz)
$^1$H-NMR of compound 27a (CDCl$_3$, 400.13 MHz)
\(^{13}\)C-NMR of compound 27a (CDCl\(_3\), 100.61 MHz)
$^1$H-NMR of compound 27b (CDCl$_3$, 400.13 MHz)
$^{13}$C-NMR of compound 27b (CDCl$_3$, 100.61 MHz)
$^1$H-NMR of compound 27c (CDCl$_3$, 400.13 MHz)
$^{13}$C-NMR of compound 27c (CDCl$_3$, 100.61 MHz)
$^1$H-NMR of compound 13a (D$_2$O, 400.13 MHz)
$^{13}$C-NMR of compound 13a (D$_2$O, 100.61 MHz)
$^1$H-NMR of compound 13b (D$_2$O, 400.13 MHz)
$^{13}$C-NMR of compound 13b (D$_2$O, 100.61 MHz)
$^1$H-NMR of compound 13c (D$_2$O, 400.13 MHz)
$^{13}$C-NMR of compound 13c (D$_2$O, 100.61 MHz)