Supplementary Material

Synthesis, *in vitro* activity, and molecular docking of caffeic acid and resveratrol multi-target derivatives against Alzheimer's disease-related enzymes

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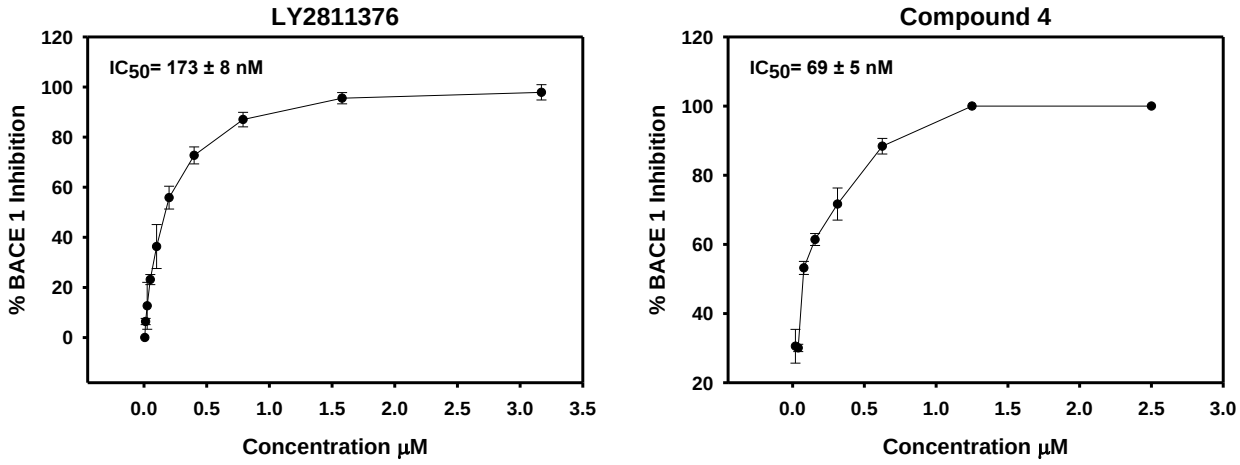


Figure S1. Dose-response curves and IC_{50} in the BACE 1 inhibitory assay for compound **4** and LY2811376. The assay was performed as directed by manufacturer's protocol (see experimental section for more details).

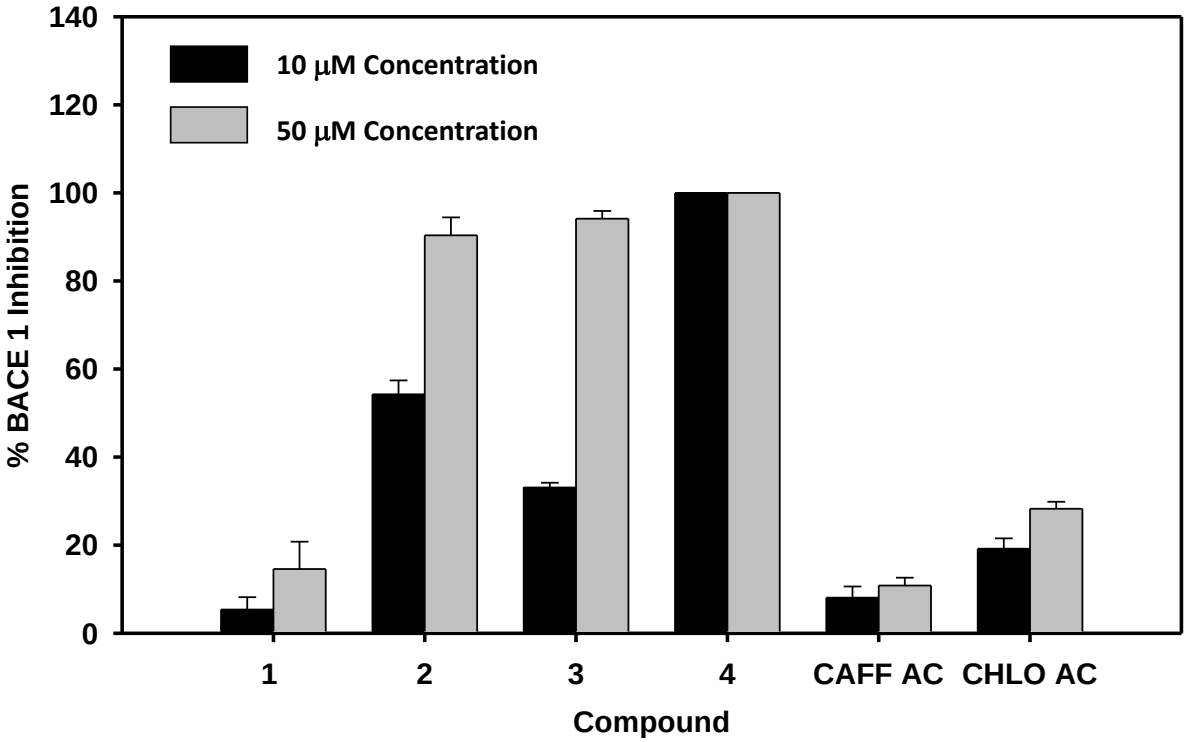


Figure S2. One-concentration FRET experiment of BACE 1 inhibition activity for compounds **1-4,** caffeic acid (CAFF AC) and chlorogenic acid (CHLO AC). The assay was performed as directed by manufacturer's protocol (see experimental section for more details).

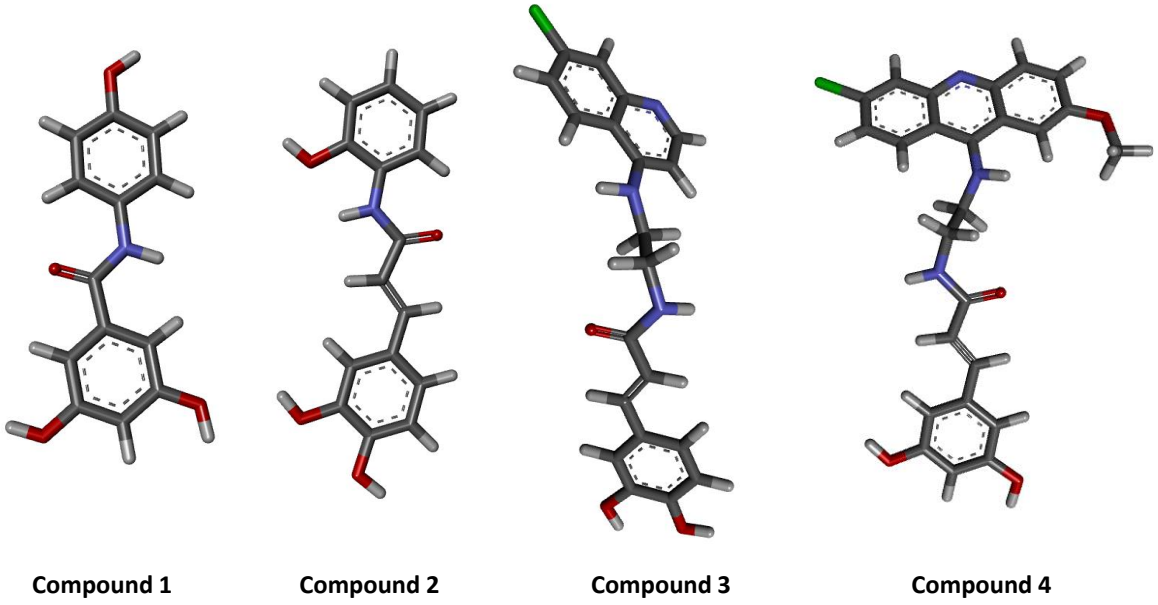


Figure S3. Gaussian 03W optimized structures of compounds **1-4**. All structures were treated with a 6-31G basis set implementing the BL3YP DFT method as described in the Experimental section.

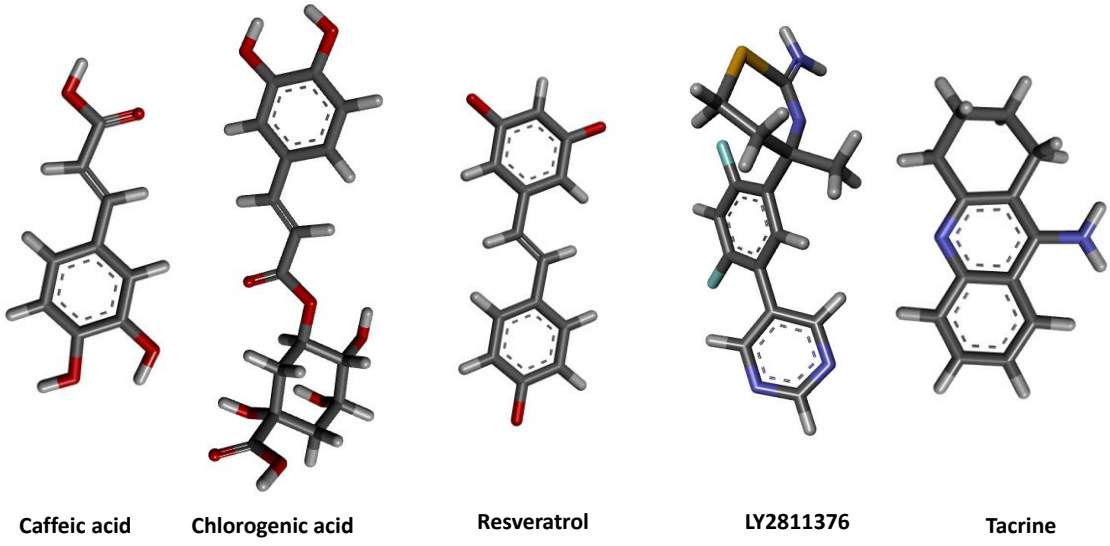


Figure S4. Gaussian 03W optimized structures of controls: caffeic acid, chlorogenic acid, resveratrol, LY2811376 and tacrine. All structures were treated with a 6-31G basis set implementing the BL3YP DFT method as described in the Experimental section.

Table S1. Predicted binding affinities, non-covalent interactions and RMSD value of the re-docking of co-crystallized LY2811376 to the active site of BACE 1 via Vina.

LY2811376 COCRYSTAL RUN#	Binding Affinity Kcal/mol BACE 1	Hydrogen Bond	Hydrophobic Interactions	Aromatic Interacting Residues	Electrostatic Interactions	Halogen Interactions	RMSD
1	**-8.3**	**Asp32, Asp228**	--	--	--	--	0.5892
2	**-8.3**	**Asp32, Asp228**	--	--	--	--	0.5842
3	**-8.3**	**Asp32, Asp228**	--	--	--	--	0.5932
4	**-8.3**	**Asp32, Asp228**	--	--	--	--	0.5936
5	**-8.3**	**Asp32, Asp228**	--	--	--	--	05929
AVG	**-8.3**					**AVG**	**0.5906**

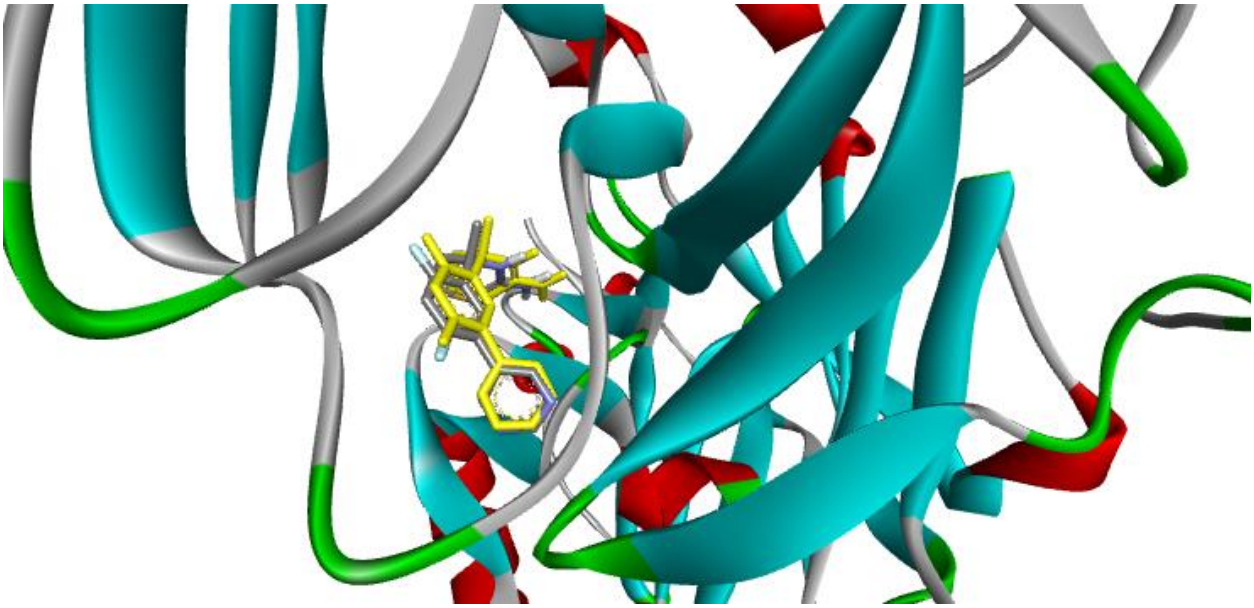


Figure S5. Native co-crystal LY2811376 in yellow superimposed with best pose of the re-docked structure predicted by Vina.

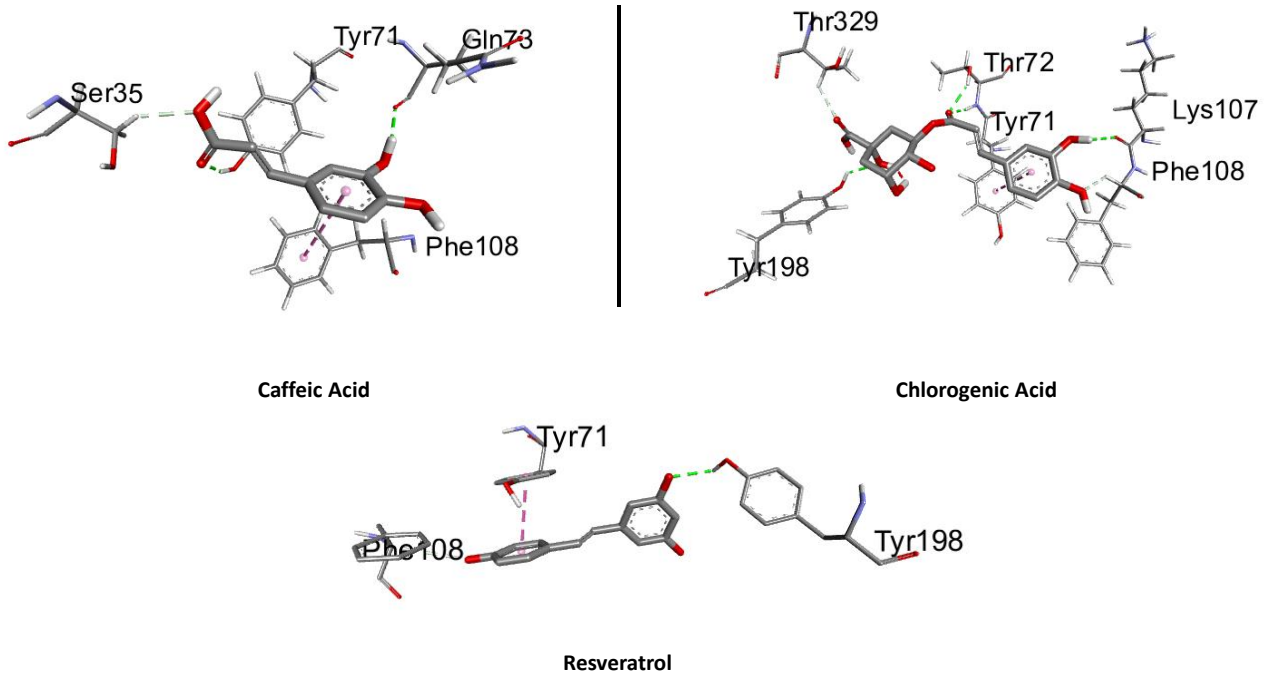


Figure S6. Representation of noncovalent interactions between caffeic acid, chlorogenic acid, and resveratrol with BACE 1 catalytic site residues. Green colored dashed lines represent hydrogen bonds, orange dashed lines represent electrostatic π-anion interactions, and purple lines represent hydrophobic interactions (π-π interactions, π-sigma, π-alkyl, alkyl interactions).

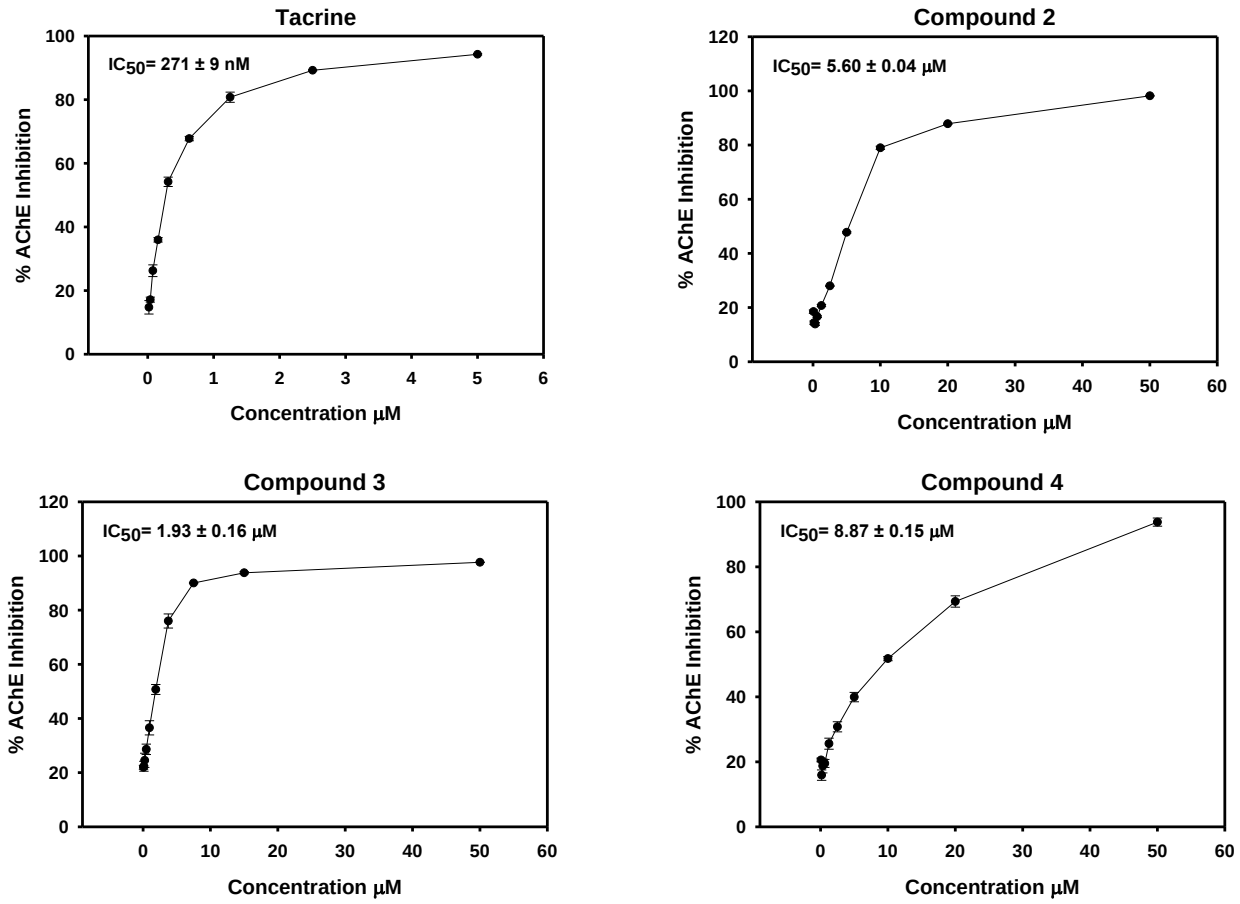


Figure S7. Dose-response curves and IC_{50} in the AChE inhibitory assay for compounds **2**, **3** and **4** as well as tacrine. The assay was performed as directed by manufacturer's protocol (see experimental section for more details).

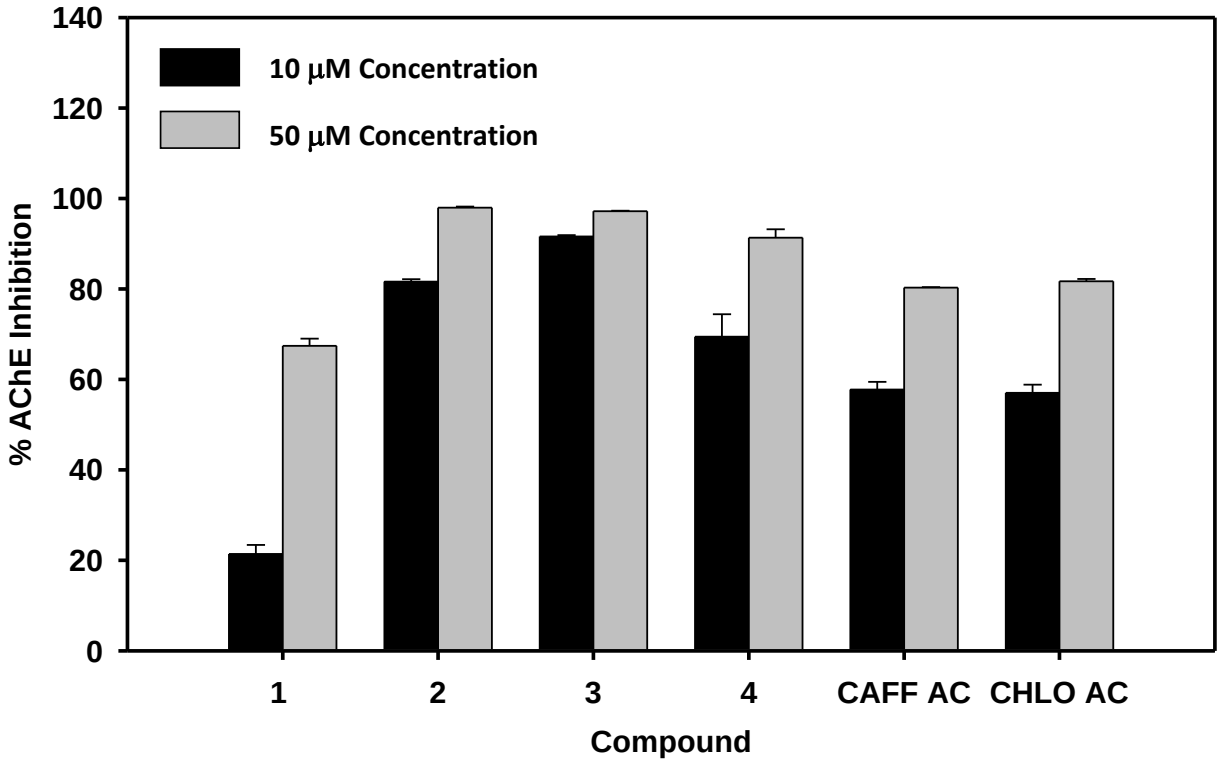


Figure S8. One-concentration AChE inhibition activity for compounds **1-4,** caffeic acid (CAFF AC) and chlorogenic acid (CHLO AC). The assay was performed as directed by manufacturer's protocol (see experimental section for more details).

Table S2. Predicted binding affinities, non-covalent interactions and RMSD value of the re-docking of co-crystallized tacrine to the active site of AChE via Vina.

TACRINE COCRYSTALIZED STRUCTURE RUN#	Binding Affinity Kcal/mol AChE	Hydrogen Bond	Hydrophobic Interactions	Aromatic Interacting Residues	Electrostatic Interactions	RMSD
1	**-9.3**	His447	Trp86, Tyr337, His447, Tyr341	Trp86, Tyr337, Tyr341	--	0.4031
2	**-9.2**	His447	Trp86, Tyr337, His447	Trp86, Tyr337	--	0.3993
3	**-9.3**	His447	Trp86, Tyr337, His447	Trp86, Tyr337	--	0.3993
4	**-9.2**	His447	Trp86, Tyr337, His447	Trp86, Tyr337	--	0.3979
5	**-9.3**	His447	Trp86, Tyr337, His447	Trp86, Tyr337	--	0.3889
AVG	**-9.3**				**AVG**	**0.3977**

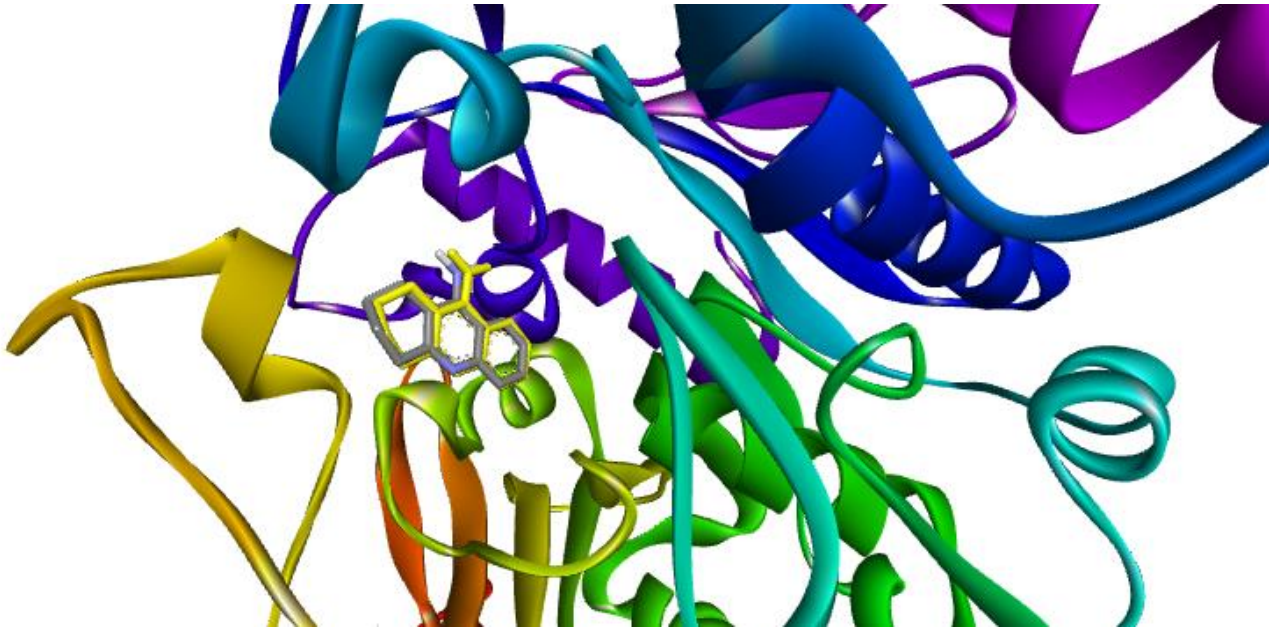


Figure S9. Native co-crystal tacrine in yellow superimposed with best pose of the re-docked structure predicted by Vina.

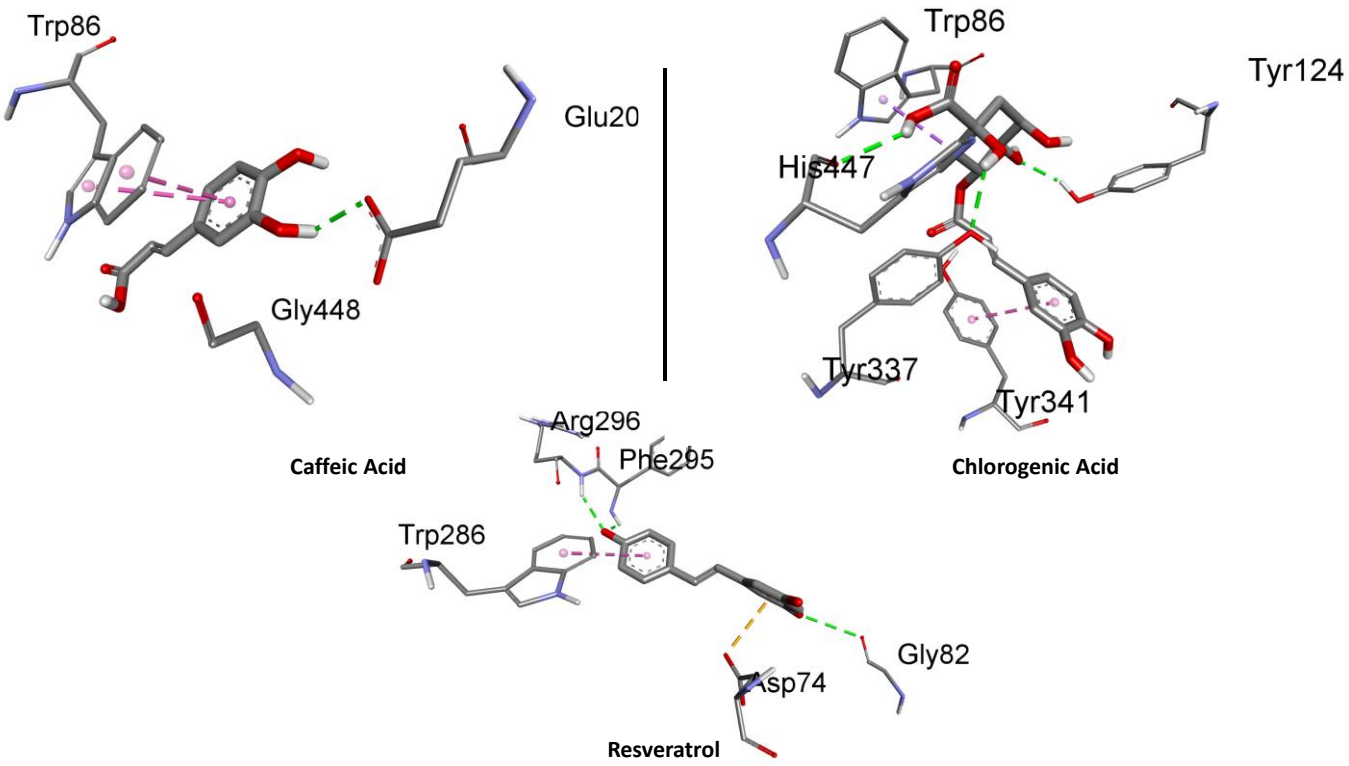
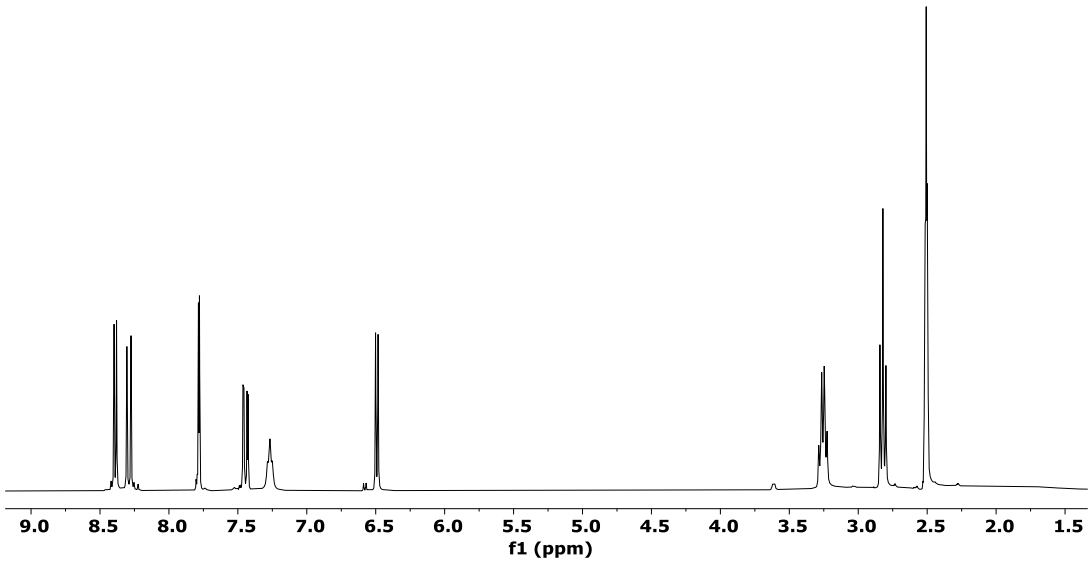
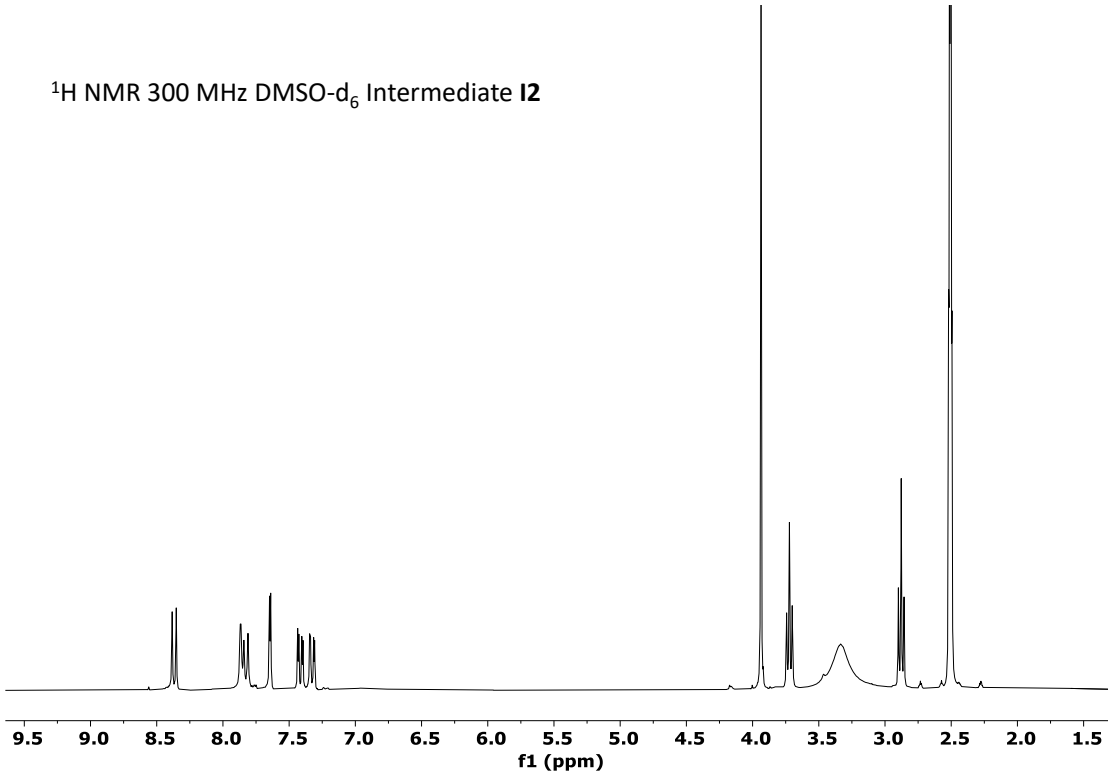


Figure S10. Representation of noncovalent interactions between caffeic acid, chlorogenic acid, and resveratrol with AChE catalytic site residues. Green colored dashed lines represent hydrogen bonds, orange dashed lines represent electrostatic π-anion interactions, and purple lines represent hydrophobic interactions (π-π interactions, π-sigma, π-alkyl, alkyl interactions).

^{1}H NMR 300 MHz DMSO-d_6 Intermediate **I1**



^{1}H NMR 300 MHz DMSO-d_6 Intermediate **I2**



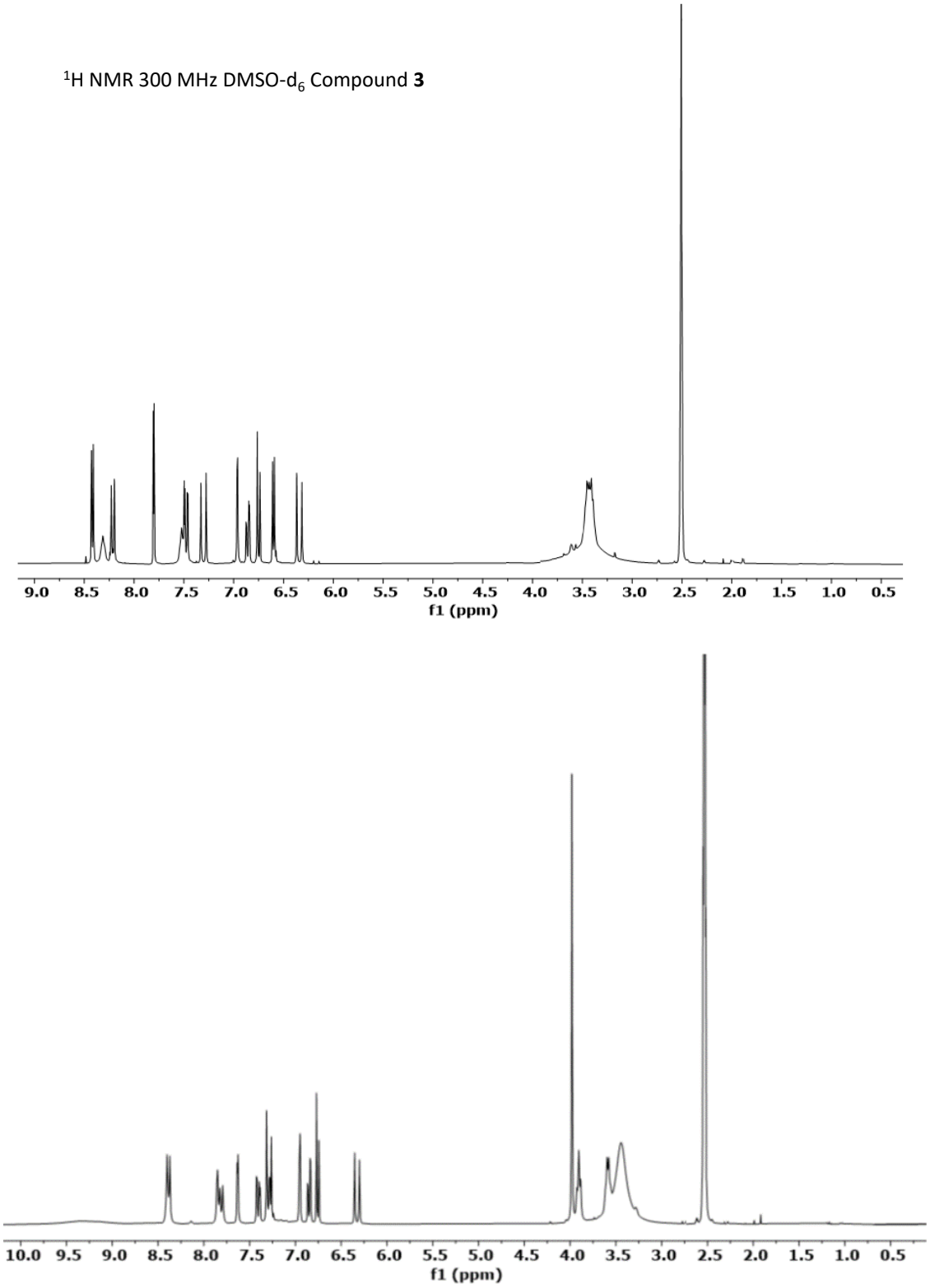


Figure S11. ^{1}H NMR 300 MHz in DMSO-d$_6$ for intermediates **I1** and **I2**, and compounds **3** and **4**. Chemical shifts are expressed in ppm relative to residual proton signals in the deuterated solvents.