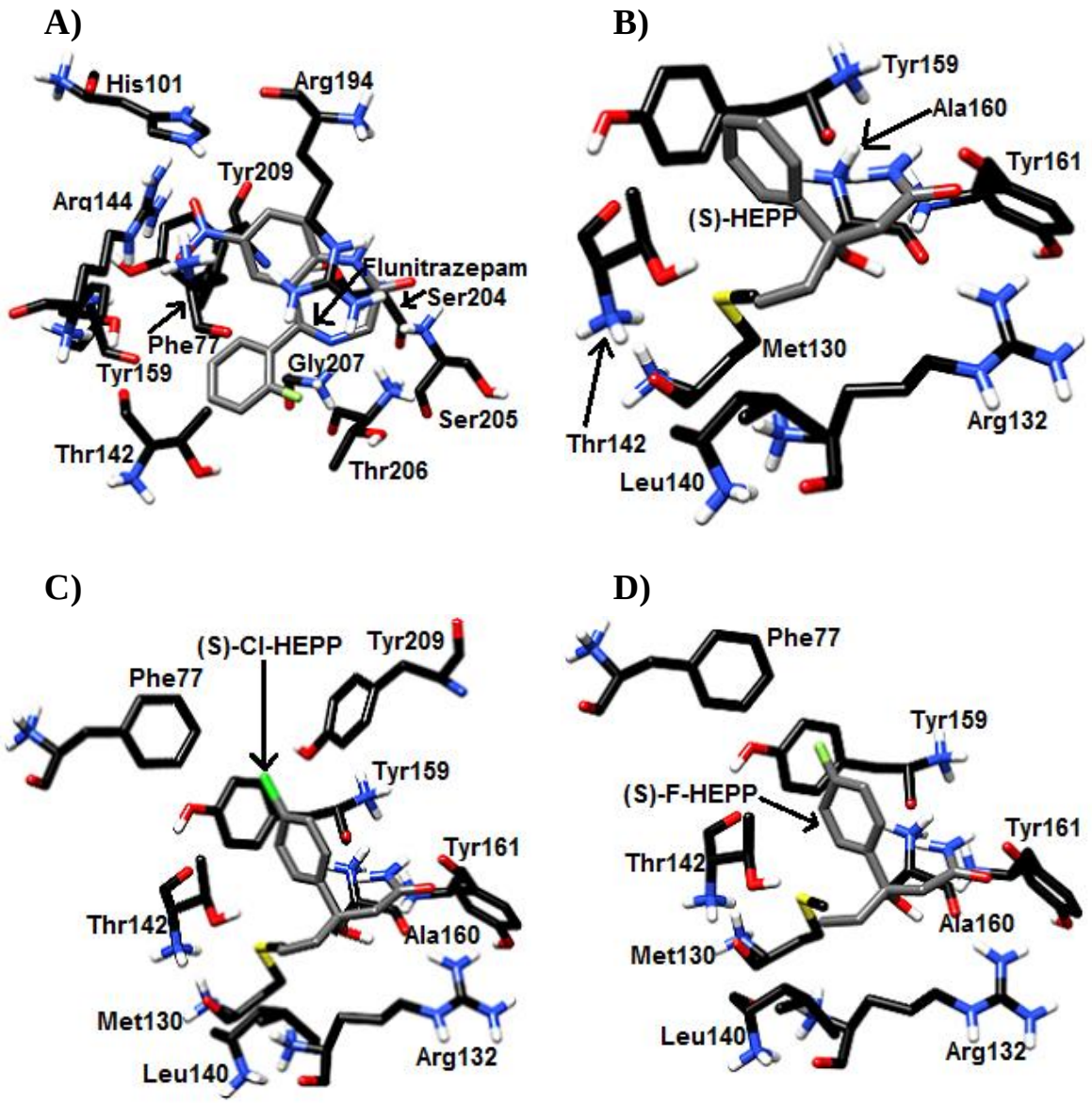
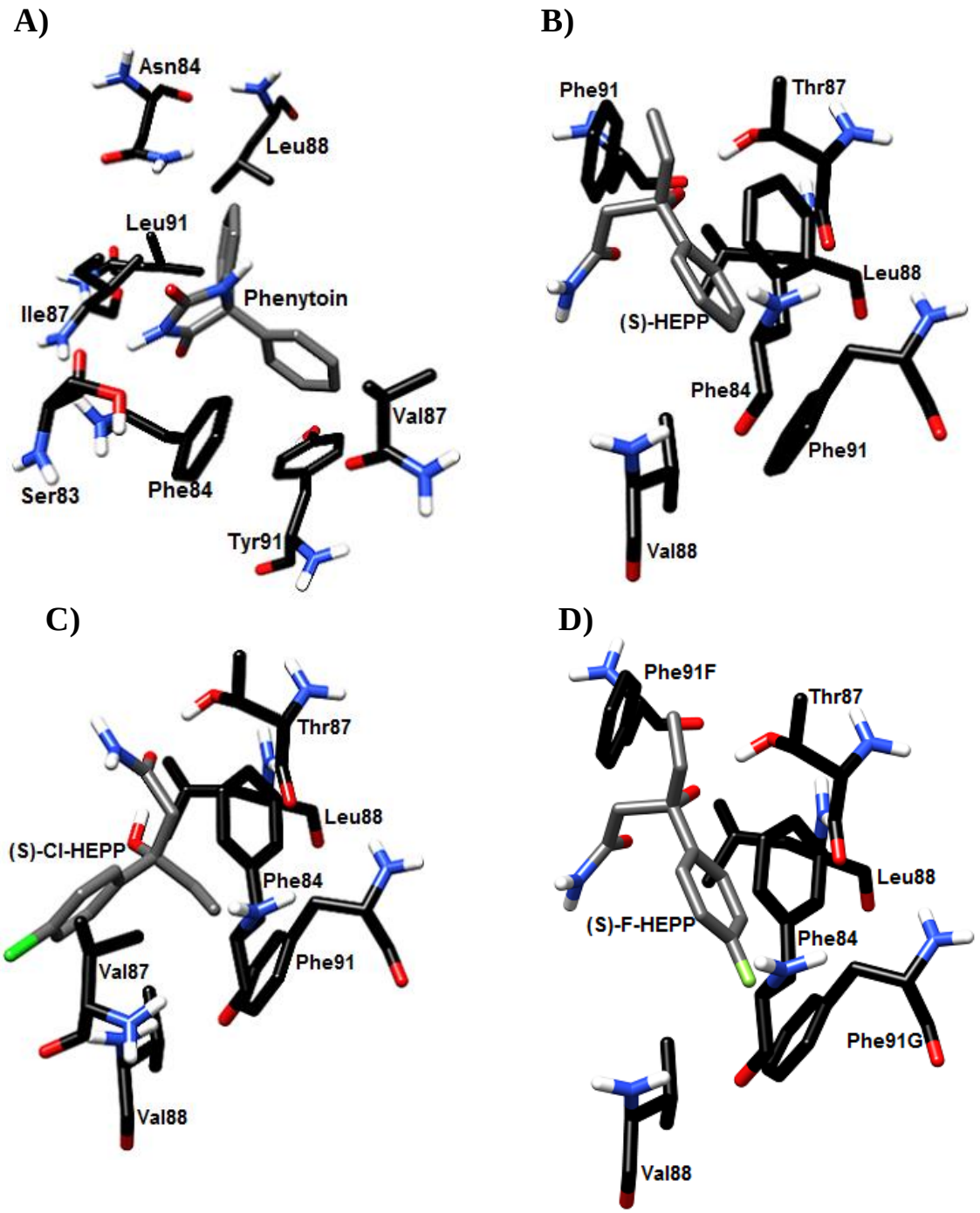


Supplementary Figure 1: Binding of flunitrazepam, (S)-HEPP, (S)-Cl-HEPP, and (S)-F-HEPP on the benzodiazepine binding site of $GABA_A$ receptor.



Supplementary Figure 2: Docking of phenytoin, HEPP and tested ligands on sodium channel Nav1.2.

Supplementary Table 1. Amino acids reached by the tested compounds to produce the interaction described in Figures 4 and Supplementary Fig. 1, and the binding free energies of HEPP, F-HEPP, and Cl-HEPP in docking studies on $GABA_A$ receptor.

Compound	Flunitrazepam	(R)-HEPP	(R)-Cl-HEPP	(R)-F-HEPP	(S)-HEPP	(S)-Cl-HEPP	(S)-F-HEPP
ΔG	-7.42	-5.28	-5.81	-5.3	-5.52	-6.08	-5.59
Amino acids of interaction	Phe77		Phe77	Phe77		Phe77	Phe77
	His101						
		Met130	Met130	Met130	Met130	Met130	Met130
		Arg132	Arg132	Arg132	Arg132	Arg132	Arg132
		Leu140	Leu140	Leu140	Leu140	Leu140	Leu140
	Thr142	Thr142	Thr142	Thr142	Thr142	Thr142	Thr142
	Arg144						
	Tyr159	Tyr159	Tyr159	Tyr159	Tyr159	Tyr159	Tyr159
		Ala160	Ala160	Ala160	Ala160	Ala160	Ala160
				Tyr161	Tyr161	Tyr161	Tyr161
	Arg194						
	Ser204						
	Ser205						
	Thr206						
	Gly207		Gly207				
	Tyr209		Tyr209			Tyr209	

(R)-HEPP: (R)-3-hydroxy, 3-ethyl, 3-phenylpropionamide,); (R)-Cl-HEPP: (3R)-3-hydroxy, 3-ethyl, 3-(4'-chlorophenyl) propionamide; (3R)-F-HEPP: (3R)-3-hydroxy, 3-ethyl, 3-(4'-fluorophenyl)propionamide; (S)-HEPP: (3S)-3-hydroxy, 3-ethyl, 3-phenylpropionamide; (S)-Cl-HEPP: (3S)-3-hydroxy, 3-ethyl, 3-(4'-chlorophenyl) propionamide; (3S)-F-HEPP: (3S)-3-hydroxy, 3-ethyl, 3-(4'-fluorophenyl)propionamide.

Supplementary Table 2: The amino acids reached by the tested compounds to produce the interaction described in Figures 5 and Supplementary Figure 2, and the binding free energies of HEPP, F-HEPP, and Cl-HEPP in docking studies on sodium channel Nav1.2.

Compound	Phenytoin	(R)-HEPP	(R)-Cl-HEPP	(R)-F-HEPP	(S)-HEPP	(S)-Cl-HEPP	(S)-F-HEPP
ΔG	-6.01	-4.47	-4.6	-4.37	-4.43	-4.47	-4.42
Amino acids of interaction	Chain E Ser83* Phe84* Ile87 Leu91 Chain F Asn84 Leu88* Chain G Chain H Val87* Tyr91	Chain E Phe84 Ile87 Asn88 Leu91 Chain F Chain G Chain H Val87 Val88	Chain E Chain F Chain G Thr87 Leu88 Phe91 Chain H Phe84 Val87 Val88	Chain E Chain F Phe91 Chain G Thr87 Leu88 Phe91 Chain H Phe84 Val88	Chain E Chain F Phe91 Chain G Thr87 Leu88 Phe91 Chain H Phe84 Val88	Chain E Chain F Chain G Thr87 Leu88 Phe91 Chain H Phe84 Val87 Val88	Chain E Chain F Phe91 Chain G Thr87 Leu88 Phe91 Chain H Phe84 Val88

(R)-HEPP: (R)-3-hydroxy, 3-ethyl, 3-phenylpropionamide,); (R)-Cl-HEPP: (3R)-3-hydroxy, 3-ethyl, 3-(4'-chlorophenyl) propionamide; (3R)-F-HEPP: (3R)-3-hydroxy, 3-ethyl, 3-(4'-fluorophenyl)propionamide; (S)-HEPP: (3S)-3-hydroxy, 3-ethyl, 3-phenylpropionamide; (S)-Cl-HEPP: (3S)-3-hydroxy, 3-ethyl, 3-(4'-chlorophenyl) propionamide; (3S)-F-HEPP: (3S)-3-hydroxy, 3-ethyl, 3-(4'-fluorophenyl)propionamide.
*Amino acids relevant in the phenytoin binding [36].