In Silico Design, Molecular Docking and Synthesis of Novel [1,1-Biphenyl]-4-Carbonitril Schiff Base Derivatives as Cholinesterase Inhibitors

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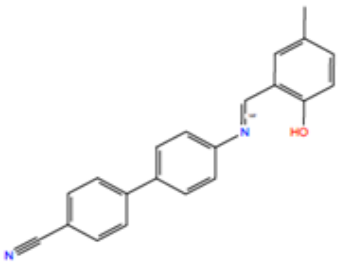
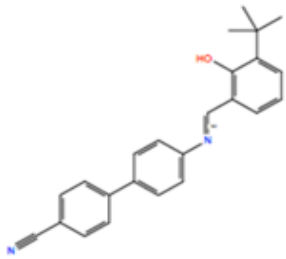
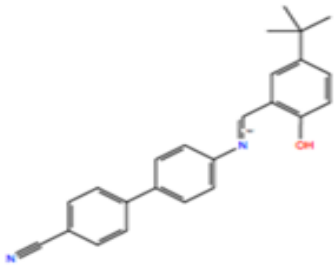
N1	N2	N3
		

Figure (1) structure of newly synthesized compounds

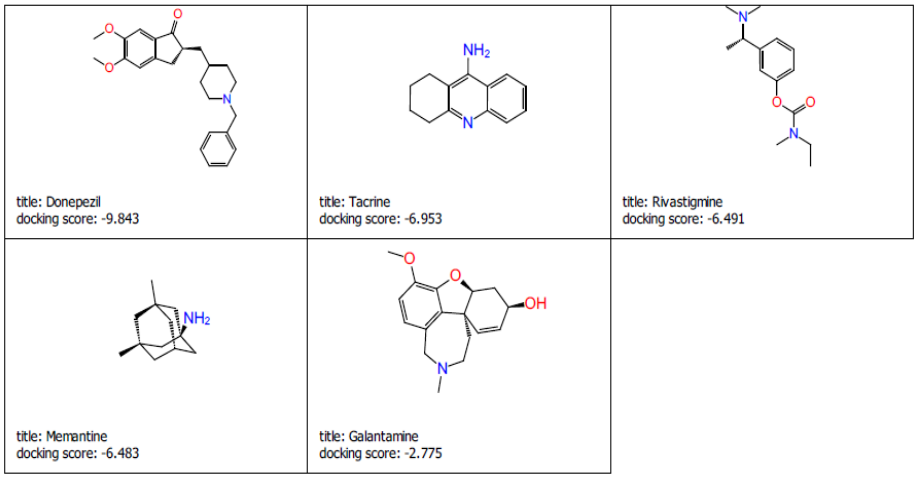


Figure (2) A List of docking binding values and chemical structure of acetylcholinesterase Inhibitors.

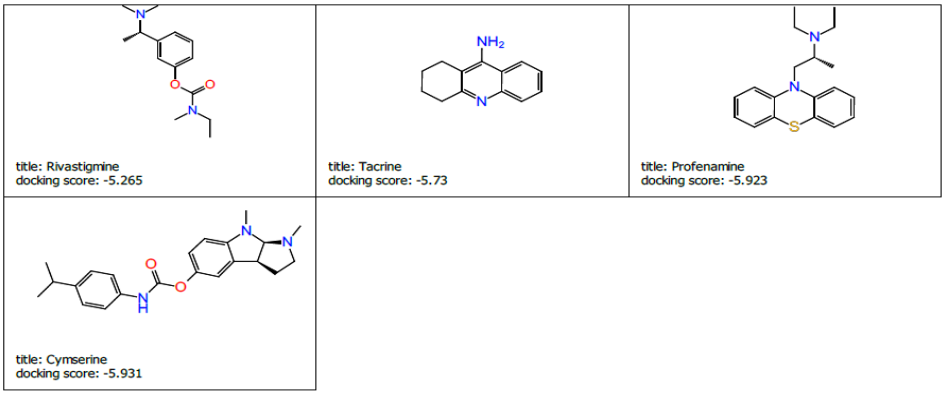


Figure (3) A List of docking binding values and chemical structure of butyrylcholinesterase Inhibitors.

Table 1. 2D and 3D docking results of Schiff base compounds N1–N3 inside the AChE active site (PDB ID: 1EVE)

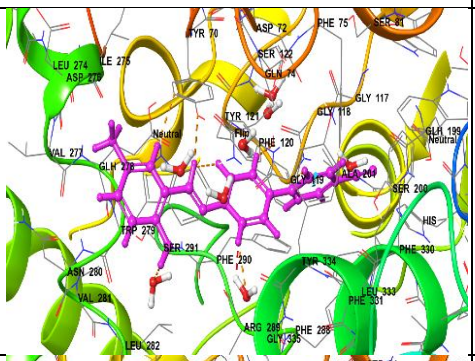
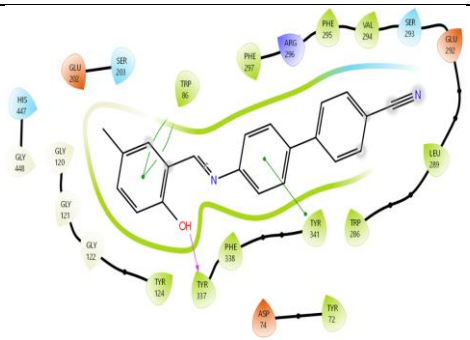
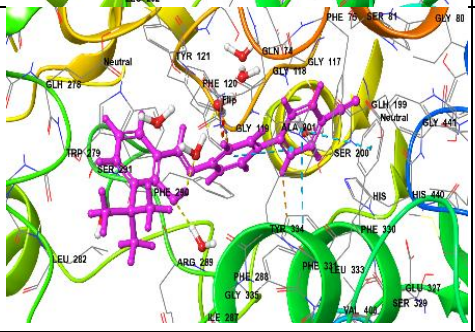
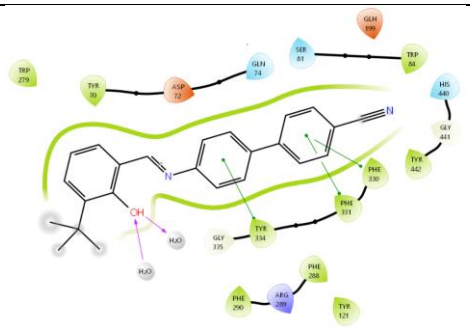
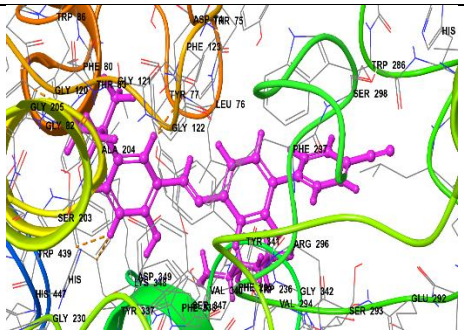
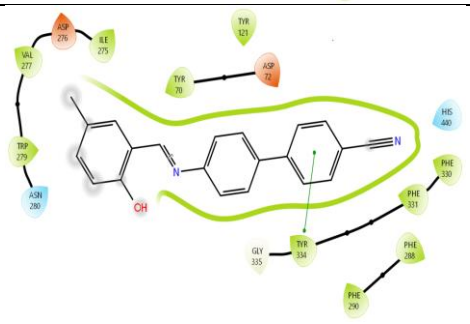
Com.	3D view of compounds inside active site	2D view of compounds inside active site	Docking Score in kcal/mol	RMSD
N1			-8.719	94.565
N2			-9.637	96.207
N3			-8.302	96.008

Table 2. 2D and 3D docking results of Schiff base compounds N1–N3 inside the AChE active site (PDB ID: 4EY7)

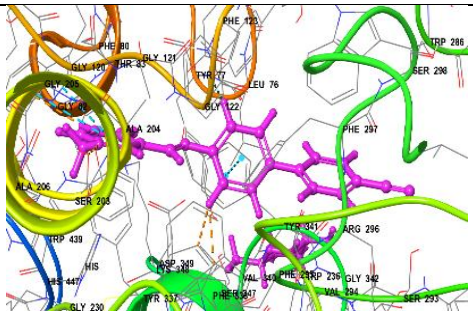
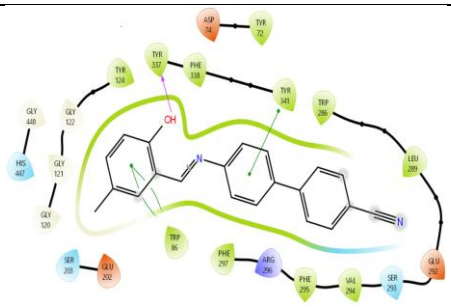
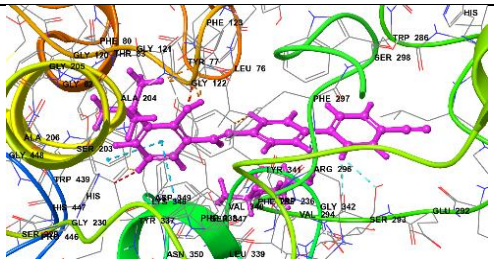
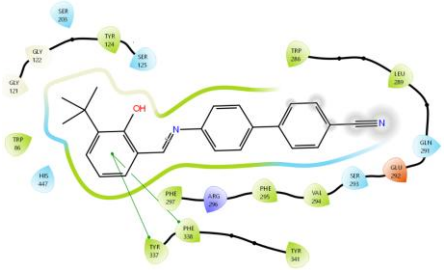
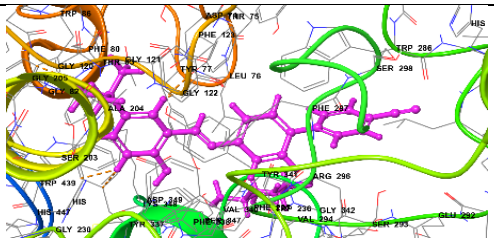
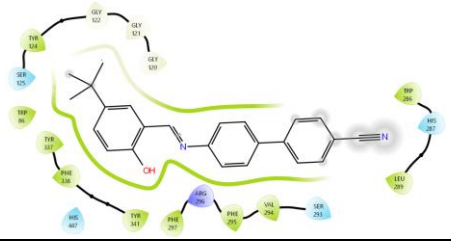
Com.	3D view of compounds inside active site	2D view of compounds inside active site	Docking Score in kcal/mol	RMSD
N1			-9.09	53.158
N2			-9.491	51.698
N3			-8.99	53.229

Table 3. 2D and 3D docking results of Schiff base compounds N1–N3 inside the butyrylcholinesterase (BChE) active site(PDB ID: 6EQP)

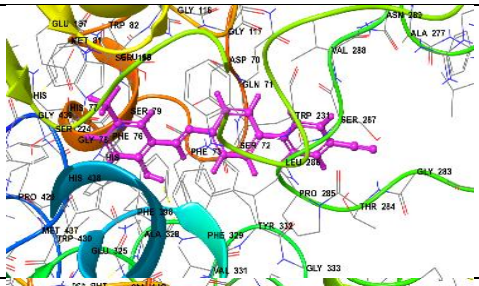
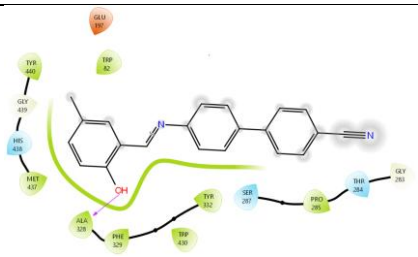
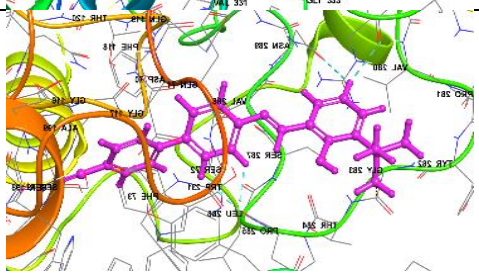
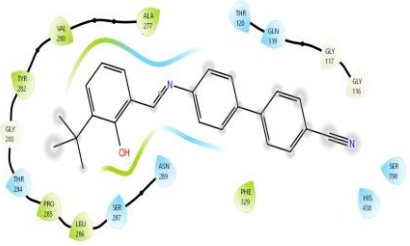
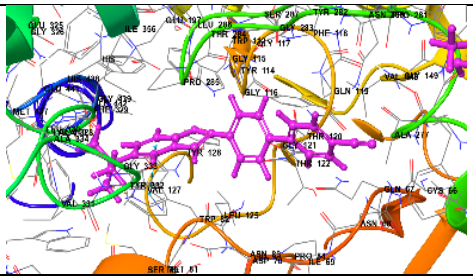
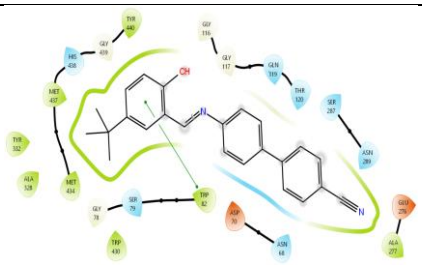
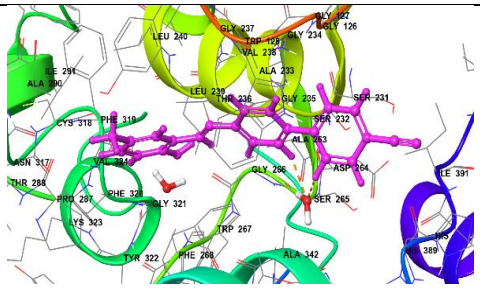
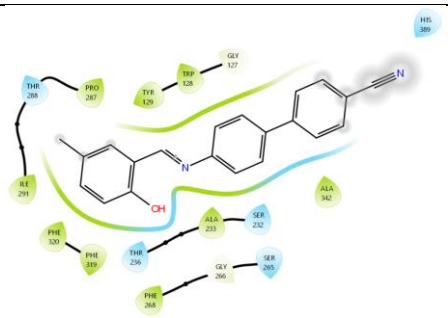
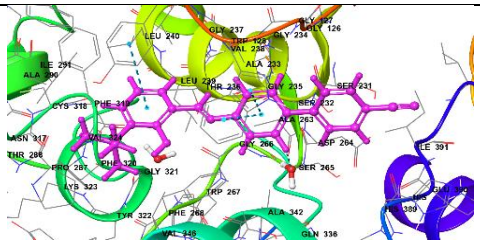
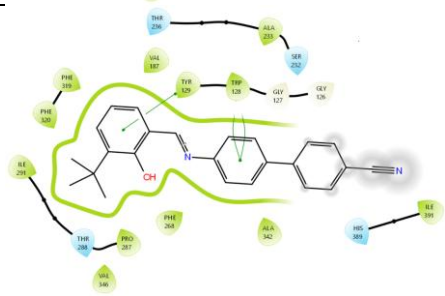
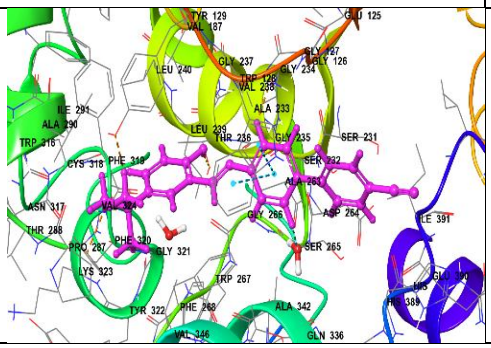
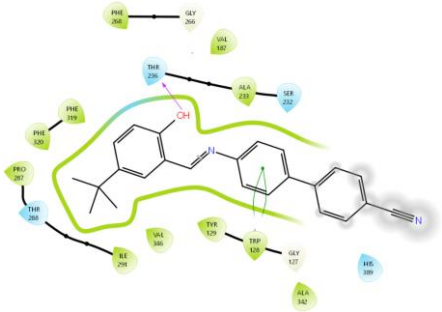
Comp.	3D view of compounds inside active site	2D view of compounds inside active site	Docking Score in kcal/mol	RMSD
N1			-5.593	66.741
N2			-4.054	64.649
N3			-6.341	63.476

Table 4. 2D and 3D docking results of Schiff base compounds N1–N3 inside the Notum fragment active site (PDB ID: 7BDD)

Comp.	3D view of compounds inside active site	2D view of compounds inside active site	Docking Score in kcal/mol	RMSD
N1			-7.297	13.811
N2			-7.598	14.160
N3			-8.081	14.630

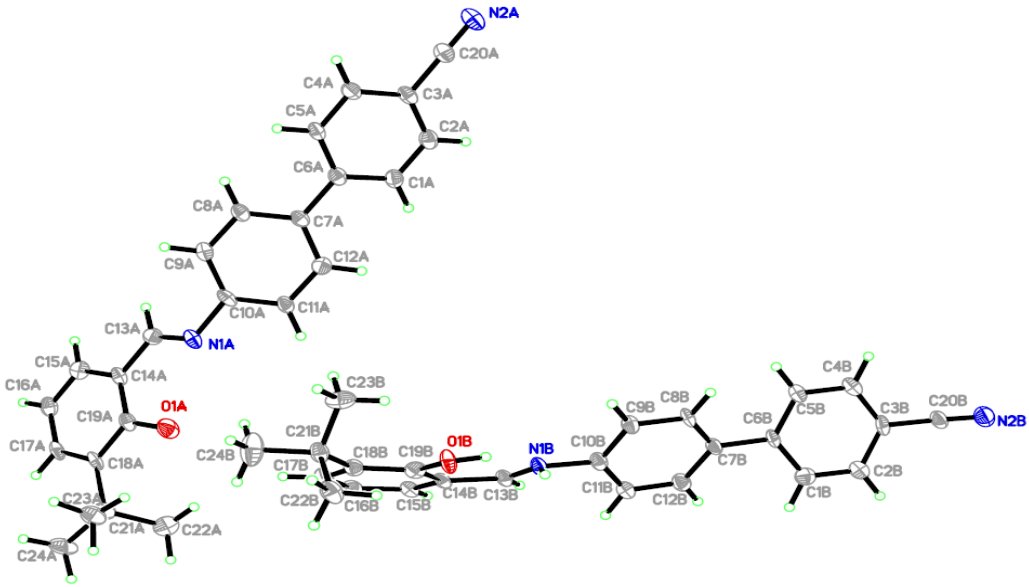


Figure (4) The X-ray crystallographic diagram as single view of compound N3

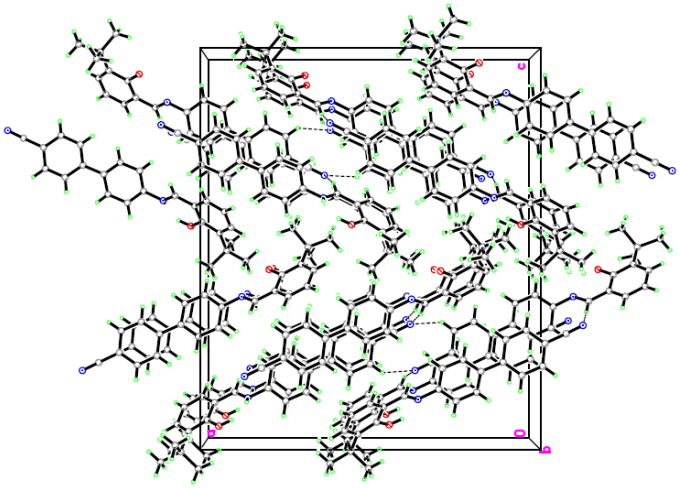


Figure (5) The X-ray crystallographic diagram packed view of compound N3

Table: ^{1}H-NMR Assignment for Compound N1 in DMSO-d_6

Proton Label	δ (ppm)	Multiplicity	J (Hz)	Proton Environment
H-7	8.97	s	—	Azomethine proton (–CH=N–)
H-2″–H-6″	7.94	s	—	Aromatic protons on terminal phenyl ring
H-2', H-6'	7.87	d	8.5	Ortho to –CN on central biphenyl ring
H-3', H-5'	7.54	d	8.5	Meta to –NH on central biphenyl ring
H-6	7.48	d	1.8	Aromatic proton ortho to OH (salicylaldehyde ring)
H-4	7.25	dd	8.3, 1.8	Aromatic proton (salicylaldehyde ring)
H-3	6.89	d	8.3	Aromatic proton (salicylaldehyde ring)
OH	12.69	s	—	Phenolic OH (intramolecular H-bonded)

Table: ^{1}H-NMR Assignment for Compound N2 in DMSO-d_6

Proton Label	δ (ppm)	Multiplicity	J (Hz)	Proton Environment
H-7	9.05	s	—	Azomethine proton (–CH=N–)
H-2″–H-6″	7.94	s	—	Aromatic protons on terminal phenyl ring
H-2', H-6'	7.89	d	8.6	Ortho to –CN on central biphenyl ring
H-3', H-5'	7.89	d	8.5	Meta to –NH on central biphenyl ring
H-6	7.51	d	1.7	Aromatic proton ortho to OH (salicylaldehyde ring)
H-4	7.41	dd	8.3, ~2	Aromatic proton (salicylaldehyde ring)
H-5	6.94	d	8.3	Aromatic proton (salicylaldehyde ring)
OH	14.11	s	—	Phenolic OH (intramolecular H-bonded)
$(CH_3)_3$ (t-Bu)	1.42	s	—	tert-Butyl protons at position 3 of salicylaldehyde ring (9H)

Table: ^{1}H-NMR Assignment for Compound N3 in DMSO-d_6

Proton Label	δ (ppm)	Multiplicity	J (Hz)	Proton Environment
H-7	8.95	s	—	Azomethine proton (–CH=N–)
H-2″–H-6″	7.92	s	—	Aromatic protons on terminal phenyl ring
H-2', H-6'	7.89	d	8.5	Ortho to –CN on central biphenyl ring
H-3', H-5'	7.88	d	8.6	Meta to –NH on central biphenyl ring
H-6	7.71	d	1.7	Aromatic proton ortho to OH (salicylaldehyde ring)
H-4	7.23	dd	8.3, ~2	Aromatic proton (salicylaldehyde ring)
H-3	6.82	d	8.3	Aromatic proton (salicylaldehyde ring)
OH	12.11	s	—	Phenolic OH (intramolecular H-bonded)
$(CH_3)_3$ (t-Bu)	1.33	s	—	tert-Butyl protons at position 5 of salicylaldehyde ring (9H)