Article

Development of Potential Multi-Target Inhibitors for Human Cholinesterases and Beta-Secretase 1: A Computational Approach

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SUPPLEMENTARY MATERIAL

Figure S1. RMSF analysis by means of principal components analysis (PCA) for ZN1733 in complex with AChE (A), BuChE (B), and BACE-1 (C). The blue highlighted area corresponds to regions with more fluctuations.

Figure S2. 2D Chemical structures of AChE, BuChE and BACE-1 inhibitors used to build triple pharmacophore models with their biological activity data [90–96]. The data was obtained from published literature and the activity units were kept as presented in the original material.

Figure S3. 2D Chemical structures of AChE, BuChE and BACE-1 inhibitors used to pharmacophore model validation and their biological activity data [90–96]. The data was obtained from published literature and the activity units were kept as presented in the original material.

Figure S1. RMSF analysis by means of principal components analysis (PCA) for ZN1733 in complex with AChE (A), BuChE (B), and BACE-1 (C). The blue highlighted area corresponds to regions with more fluctuations.

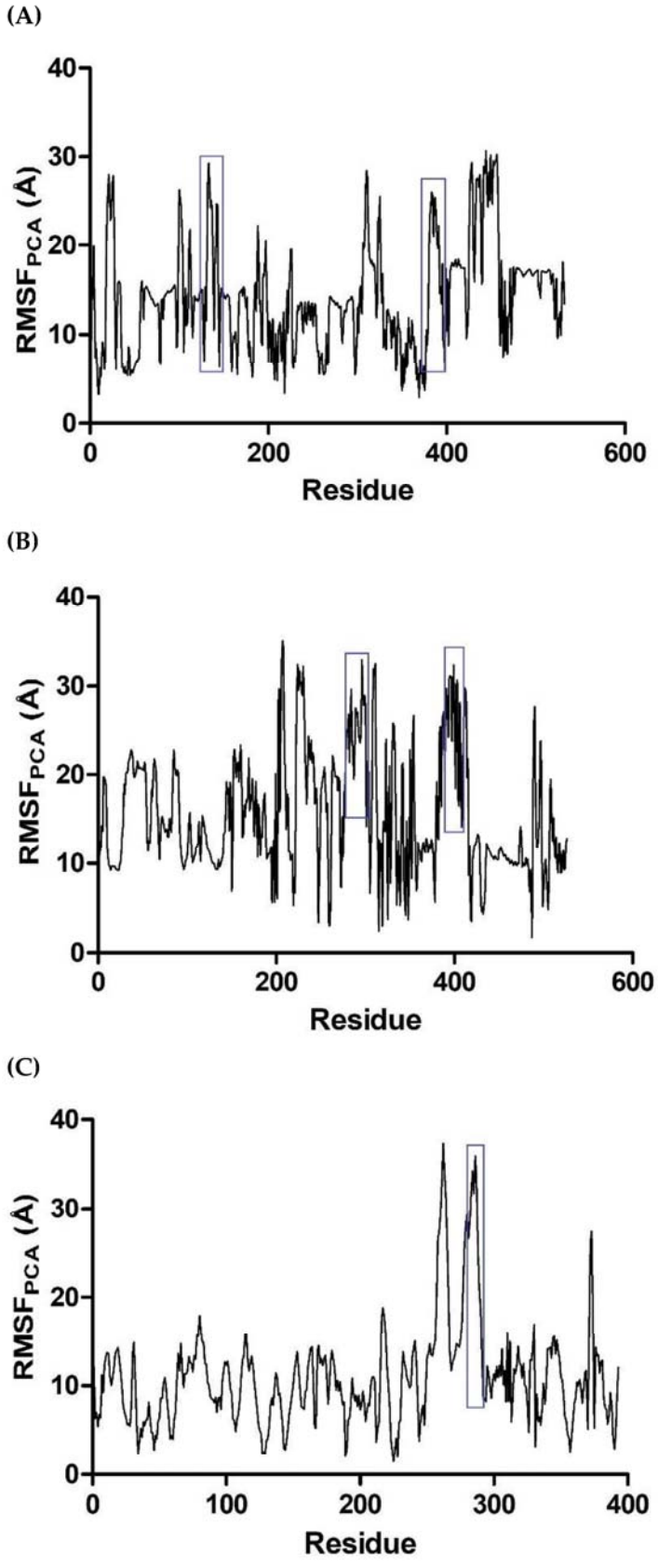
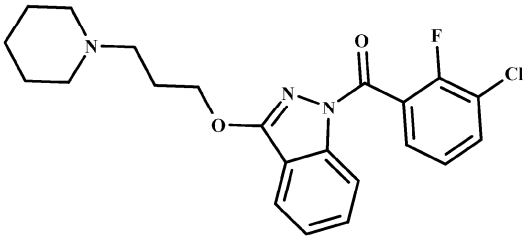
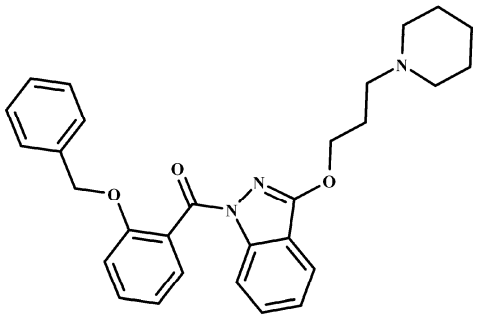
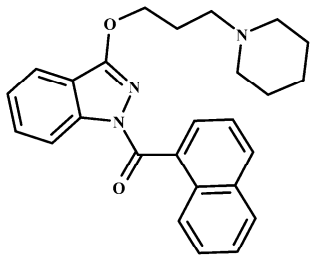
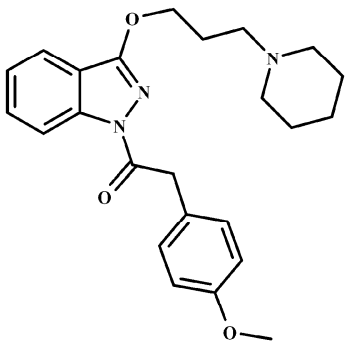


Figure S2. 2D Chemical structures of AChE, BuChE and BACE-1 inhibitors used to build triple pharmacophore models with their biological activity data [90–96]. The data was obtained from published literature and the activity units were kept as presented in the original material.

4 	AChE % Inhibition (10 μM) = 48 BuChE IC_{50} = 0.80 ± 0.04 μM BACE-1 % Inhibition (10 μM) = 34 ± 1
9 	AChE%Inhibition (10 μM) = 31 BuChE IC_{50} = 2.5 ± 0.001 μM BACE-1%Inhibition(10 μM) = 38.4 ± 1.11
12 	AChE%Inhibition (10 μM) = 43 BuChE IC_{50} = 0.007 μM BACE-1%Inhibition(10 μM) = 42 ± 2
16 	AChE%Inhibition (10 μM) = 43 BuChE%%Inhibition (10 μM) = 42 BACE-1%Inhibition (10 μM) = 60 ± 8

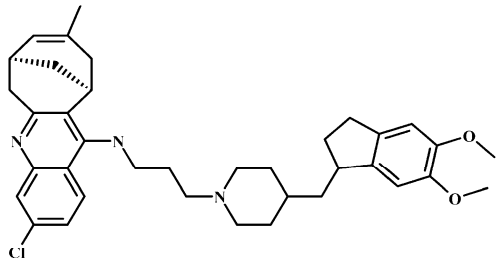
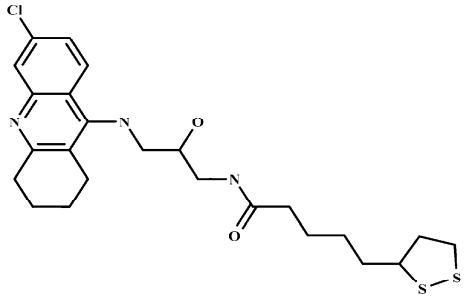
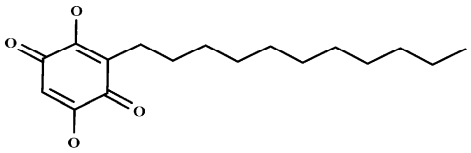
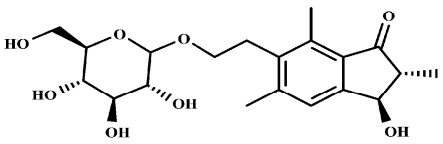
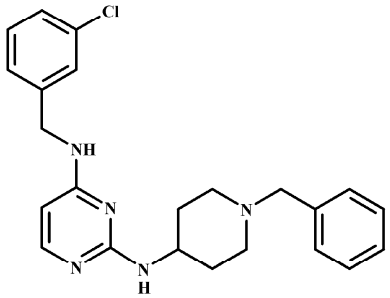
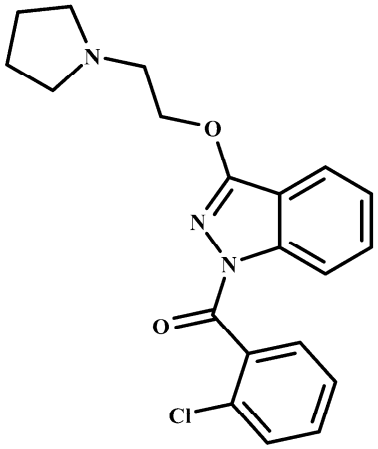
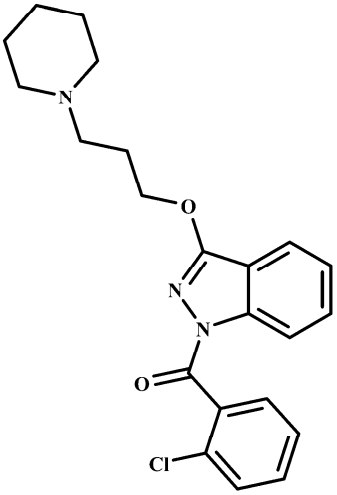
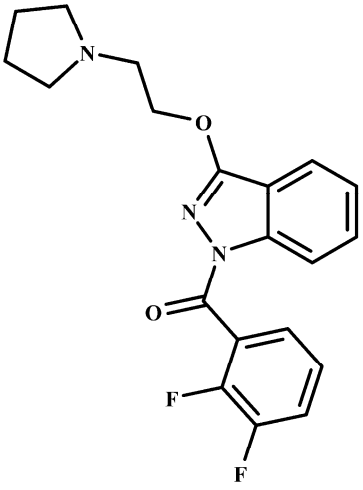
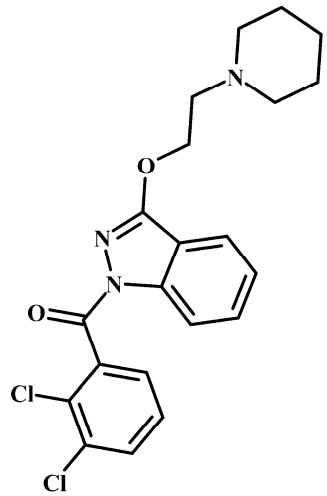
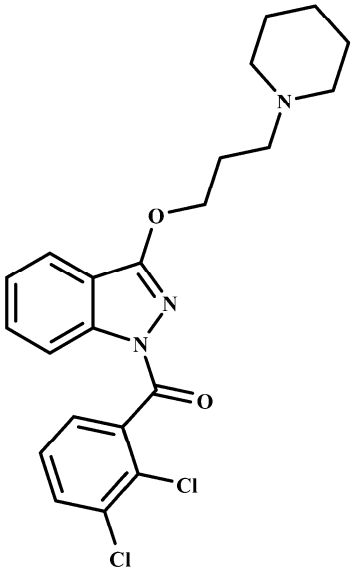
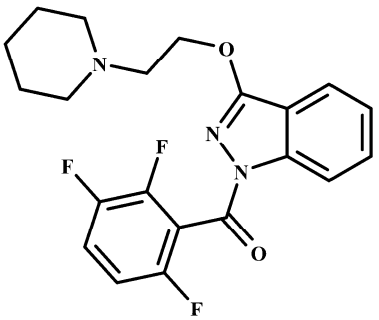
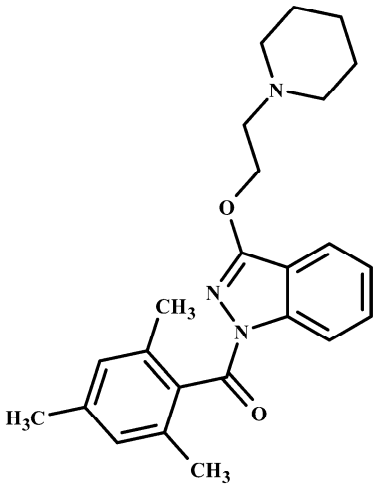
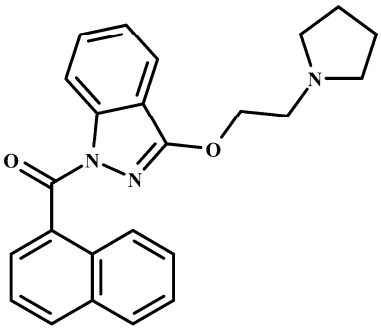
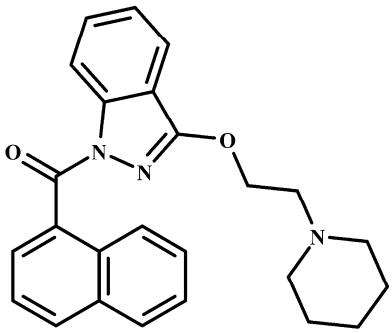
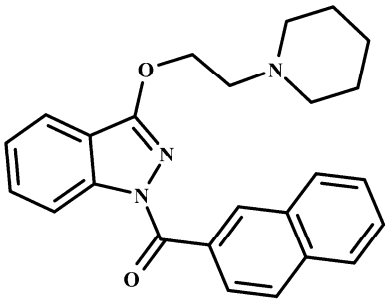
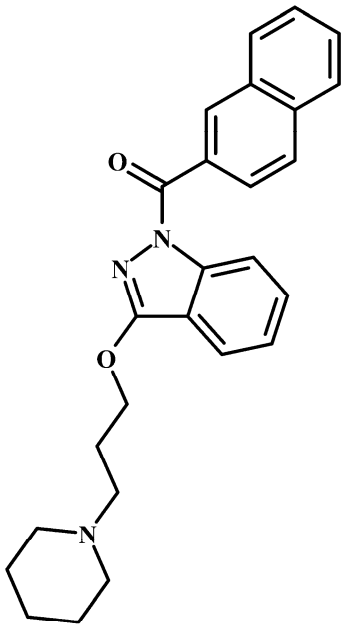
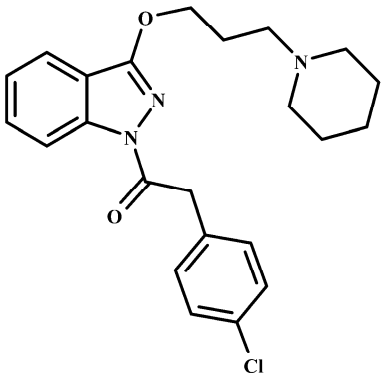
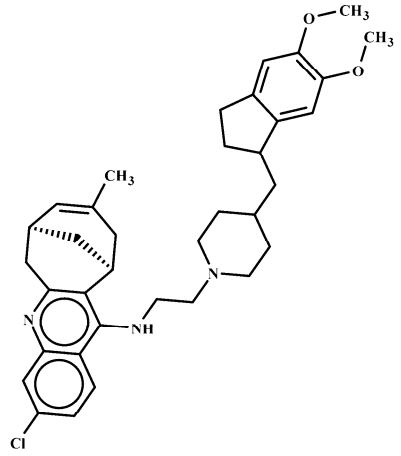
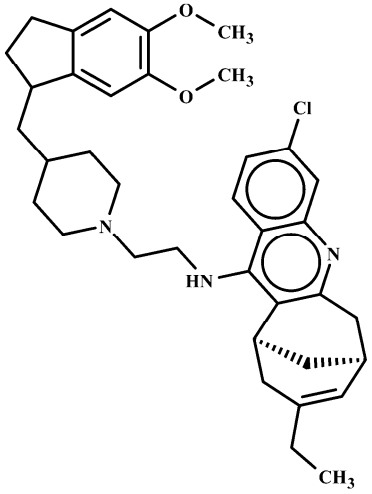
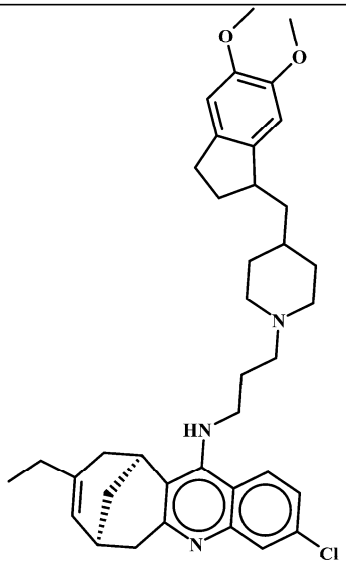
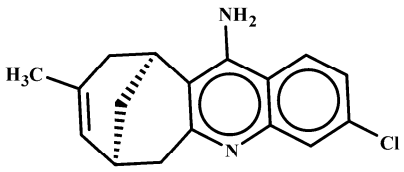
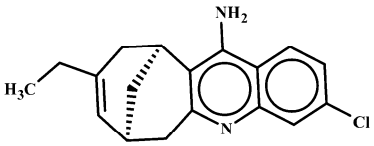
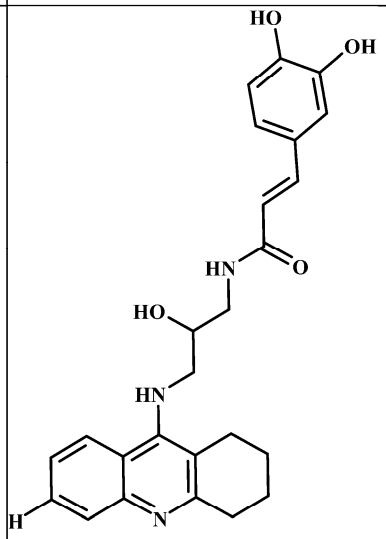
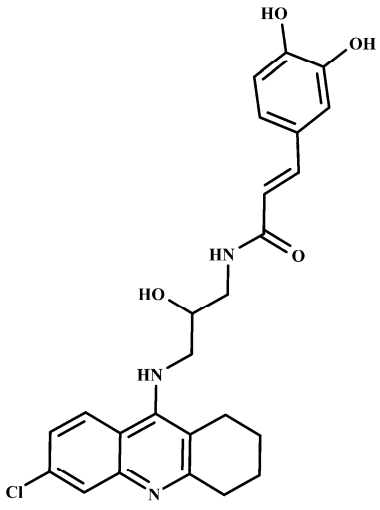
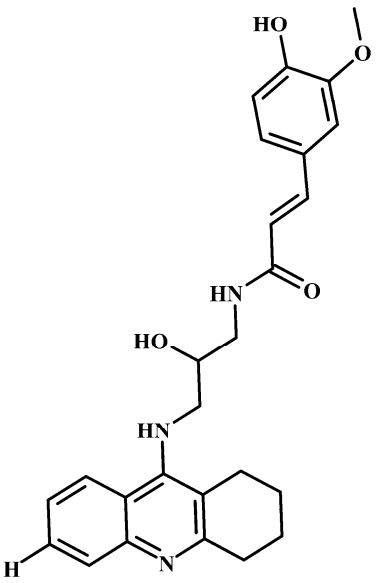
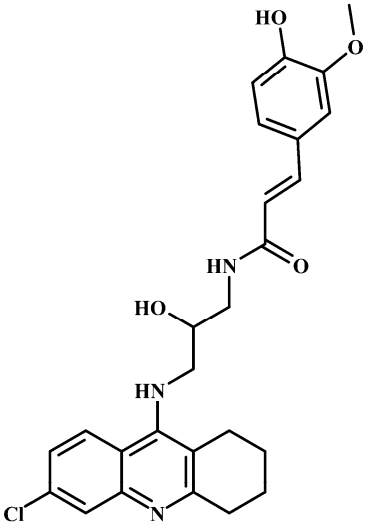
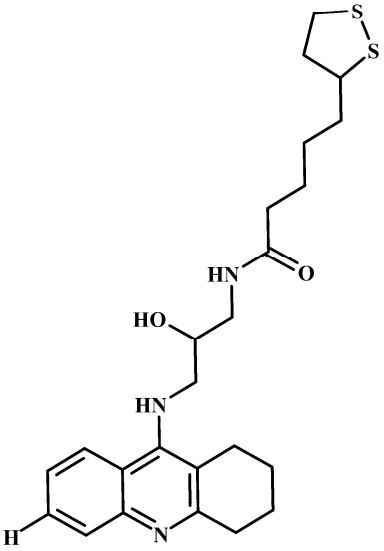
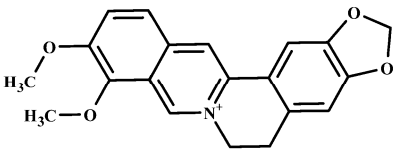
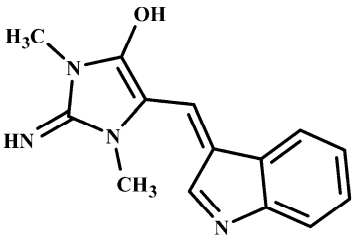
18	
	AChE IC_{50} = 0.003 μM BuChE IC_{50} = 0.349 ± 0.02 μM BACE-1%Inhibition(5μM) = 30,8 ± 4,1
28	
	AChE IC_{50} = 0.04 μM BuChE IC_{50} = 1.03 μM BACE-1%Inhibition (10 μM) = 46.78 ± 3.12
30	
	AChE%Inhibition (10 μM) = 70.15 BuChE%%Inhibition (10 μM) = 77.15 BACE-1%Inhibition (10 μM) = 77.61 ± 3.78
40	
	AChE IC_{50} = 5.29 ± 0.82 μM BuChE IC_{50} = 3.77 ± 0.38 μM BACE-1 IC_{50} = 9.74 ± 1.9 μM
44	
	AChE IC_{50} = 7.70 ± 0.77 μM BuChE IC_{50} = 2.50 ± 0.23 μM BACE-1 IC_{50} = 1.70 ± 0.15 μM

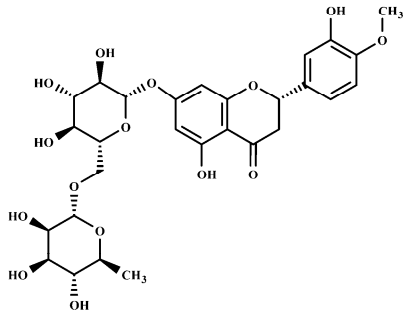
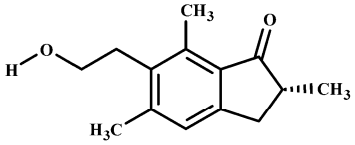
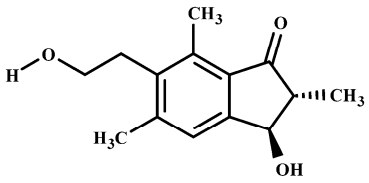
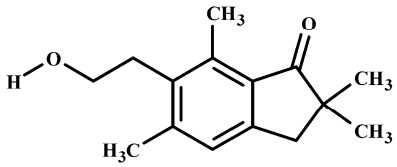
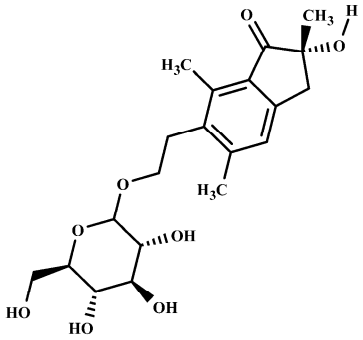
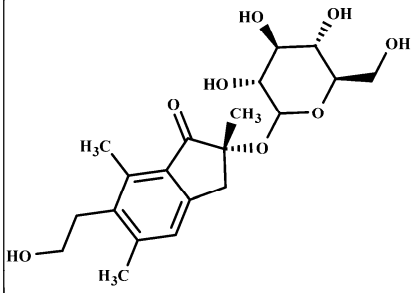
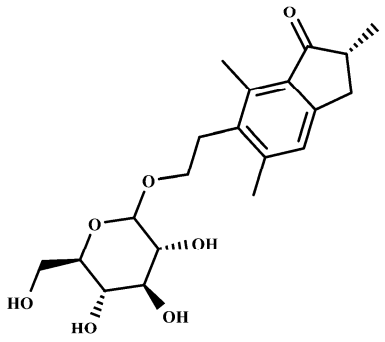
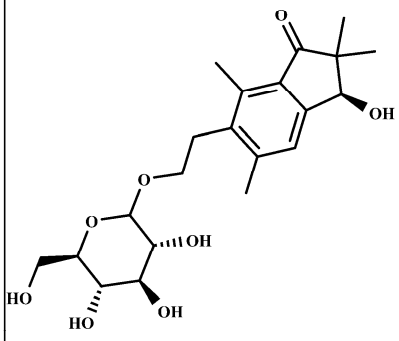
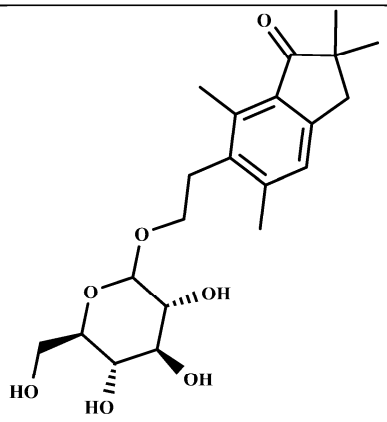
Figure S3. 2D Chemical structures of AChE, BuChE and BACE-1 inhibitors used to pharmacophore model validation and their biological activity data [90–96]. The data was obtained from published literature and the activity units were kept as presented in the original material.

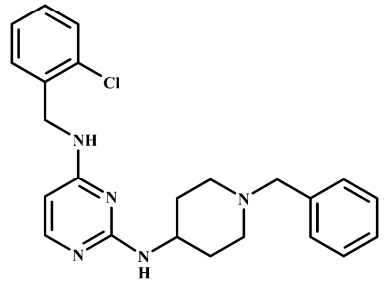
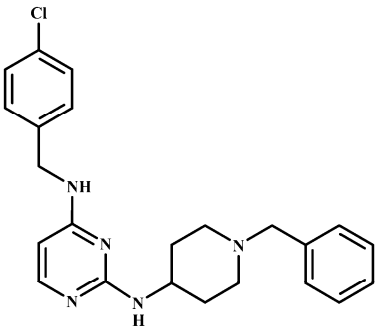
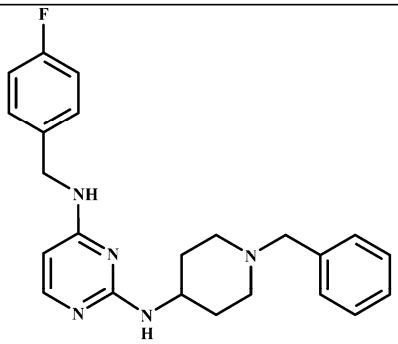
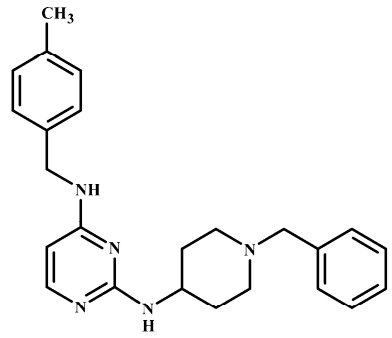
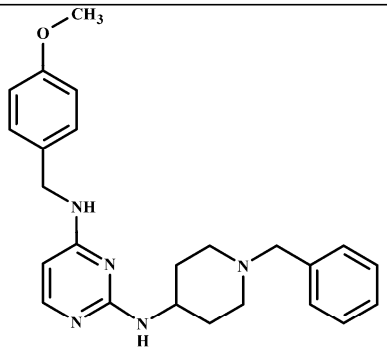
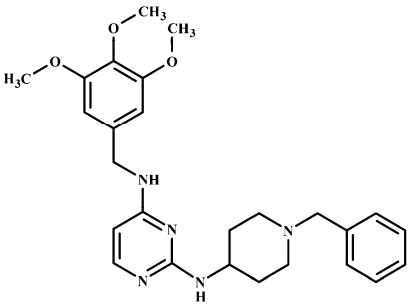
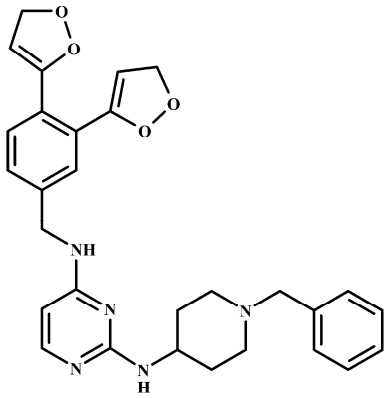
1	**2**	**3**
		
AChE IC50 = 9.7 ± 0.8 μM BuChE IC50 = 1.3 ± 0.5 μM BACE-1 %Inhibition (10 μM) = 9 ± 3	AChE IC50 = 9.7 ± 0.3 μM BuChE IC50 = 0.07 ± 0.01 μM BACE-1 %Inhibition (10 μM) = 12 ± 4	AChE IC50 = 11 ± 1 μM BuChE IC50 = 11 ± 1 μM BACE-1 %Inhibition (10 μM) = 14 ± 2
5	**6**	**7**
		
AChE IC50 = 10.5 ± 0.5 μM BuChE IC50 = 0.6 ± 0.3 μM BACE-1 %Inhibition (10 μM) = 18.1 ± 0.4	AChE IC50 = 17 ± 2 μM BuChE IC50 = 0.080 ± 0.003 μM BACE-1 %Inhibition (10 μM) = 45.1 ± 0.9	AChE IC50 = 9.4 ± 0.6 μM BuChE IC50 = 9.4 ± 0.2 μM BACE-1 %Inhibition (10 μM) = 14.3 ± 0.9

8	10	11
		
AChE IC50 = 11.6 ± 0.7 µM BuChE IC50 = 0.29 ± 0.03 µM BACE-1 %Inhibition (10 µM) = 12 ± 2	AChE %Inhibition (10 µM) = 35 BuChE IC50 = 0.15 ± 0.03 x 10-3 µM BACE-1 %Inhibition (10 µM) = 20 ± 4	AChE %Inhibition (10 µM) = 37 BuChE IC50 = 0.26 ± 0.07 x 10-3 µM BACE-1 %Inhibition (10 µM) = 11 ± 3
13	**14**	**15**
		
AChE %Inhibition (10 µM) = 43 BuChE IC50 = 4.0 ± 0.3 µM BACE-1 %Inhibition (10 µM) = 50 ± 5	AChE %Inhibition (10 µM) = 33 BuChE IC50 = 2.1 ± 0.3 µM BACE-1 %Inhibition (10 µM) = 38 ± 3	AChE %Inhibition (10 µM) = 43 BuChE %Inhibition (10 µM) = 46 BACE-1 %Inhibition (10 µM) = 50 ± 2

17	19	20
		
hAChE IC50 = 0.013 µM BuChE IC50 = 0.303 ± 0.012 µM BACE-1 %Inhibition (10 µM) = 24.6 ± 3	AChE IC50 = 0.029 ± 0.002 µM BuChE IC50 = 0.419 ± 0.017 µM BACE-1 %Inhibition (5 µM) = 12.5 ± 0.7	AChE IC50 = 0.0004 µM BuChE IC50 = 0.194 ± 0.009 µM BACE-1 %Inhibition (5 µM) = 14.9 ± 3.9
21	**22**	**23**
		
AChE IC50 = 0.004 µM BuChE IC50 = 0.247 ± 0.018 µM BACE-1 %Inhibition (5 µM) = 14 ± 0.1	AChE IC50 = 0.0003 µM BuChE IC50 = 0.159 ± 0.01 µM BACE-1 %Inhibition (5 µM) = 21.8 ± 7.2	AChE IC50 = 0.70 µM BuChE IC50 = 1.01 µM BACE-1 %Inhibition (10 µM) = 10.51 ± 2.55

24	25	26
		
AChE IC50 = 0.15 µM BuChE IC50 = 0.36 µM BACE-1 %Inhibition (10 µM) = 13.07 ± 5.81	AChE IC50 = 0.03 µM BuChE IC50 = 0.31 µM BACE-1 %Inhibition (10 µM) = 14.97 ± 1.25	AChE IC50 = 0.02 µM BuChE IC50 = 0.71 µM BACE-1 %Inhibition (10 µM) = 2.57 ± 7.29
27	**29**	**31**
		
AChE IC50 = 0.10 µM BuChE IC50 = 1.18 µM BACE-1 %Inhibition (10 µM) = 24.77 ± 5.46	AChE %Inhibition (10 µM) = 92.05 ± 0.51 BuChE %Inhibition (10 µM) = 21.92 ± 1.82 BACE-1 %Inhibition (10 µM) = 43.42 ± 2.08	AChE %Inhibition (10 µM) = 35.62 ± 2.05 BuChE %Inhibition (10 µM) = 10.55 ± 0.39 BACE-1 %Inhibition (10 µM) = 20.32 ± 4.05

32	33	35
		
AChE IC50 = 22.80 ± 2.78 μM BuChE IC50 = 48.09 ± 0.74 μM BACE-1 IC50 = 16.99 ± 1.25 μM	AChE IC50 = 16.2 ± 1.0 μM BuChE IC50 = 48.1 ± 0.59 μM BACE-1 IC50 = 29.6 ± 3.5 μM	AChE IC50 = 17.8 ± 0.62 μM BuChE IC50 = 55.9 ± 5.6 μM BACE-1 IC50 = 67.1 ± 7.7 μM
36	**37**	**38**
		
AChE IC50 = 46.5 ± 3.4 μM BuChE IC50 = 80.1 ± 6.8 μM BACE-1 IC50 = 80.0 ± 5.9 μM	AChE IC50 = 110.0 ± 3.0 μM BuChE IC50 = 19.4 ± 0.22 μM BACE-1 IC50 = 84.6 ± 6.0 μM	AChE IC50 = 39.3 ± 1.9 μM BuChE IC50 = 119.0 ± 2.5 μM BACE-1 IC50 = 94.4 ± 4.5 μM
39	**41**	**42**
		
AChE IC50 = 2.55 ± 0.23 μM BuChE IC50 – 62.0 ± 0.71 μM BACE-1 IC50 = 18.0 ± 2.8 μM	AChE IC50 = 27.4 ± 1.2 μM BuChE IC50 – 19.3 ± 0.17 μM BACE-1 IC50 = 10.7 ± 1.5 μM	AChE IC50 = 24.1 ± 1.1 μM BuChE IC50 – 5.31 ± 0.19 μM BACE-1 IC50 = 53.3 ± 1.2 μM

43	45	46
		
AChE IC50 = 7.0 ± 0.77 µM BuChE IC50 = 2.40 ± 0.24 µM BACE-1 IC50 = 1.70 ± 0.15 µM	AChE IC50 = 8.80 ± 0.88 µM BuChE IC50 = 2.80 ± 0.28 µM BACE-1 IC50 = 3.20 ± 0.30 µM	AChE IC50 = 7.70 ± 0.70 µM BuChE IC50 = 2.20 ± 0.20 µM BACE-1 IC50 = 0.70 ± 0.05 µM
47	**48**	**49**
		
AChE IC50 = 12.90 ± 0.12 µM BuChE IC50 = 2.50 ± 0.22 µM BACE-1 IC50 = 11.10 ± 0.10 µM	AChE IC50 = 9.40 ± 0.90 µM BuChE IC50 = 4.90 ± 0.50 µM BACE-1 IC50 = 0.60 ± 0.04 µM	AChE IC50 = 10.30 ± 0.10 µM BuChE IC50 = 7.70 ± 0.65 µM BACE-1 IC50 = 8.90 ± 0.90 µM
50		
		
AChE IC50 = 12.60 ± 0.12 µM BuChE IC50 = 3.90 ± 0.40 µM BACE-1 IC50 = 1.40 ± 0.13 µM		