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Generating an efficient BACE1 inhibitor for the treatment of Alzheimer's disease based on AI-powered ADMET analysis, Molecular docking and Molecular dynamics studies

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Alzheimer's disease (AD) is an early stage of dementia due to neurodegenerative disorder that affects the cognitive functions, memory patterns, and learning skills. BACE1 (beta-site amyloid precursor protein cleaving enzyme 1) is a crucial protein involved in the progression of AD. There are many clinical trials being carried out targeting BACE1 for the treatment of AD. However, they critically face limitations to succeed as approved drugs. Hence, this work is aimed to identify novel BACE1 inhibitors using AI-driven drug development processes. Using WADDAICA tool, 300 similar ligands based on the structural features of Atebecestat, AZD3839, LY2811376 are generated and then ADMET analysis was done. The molecular docking studies with BACE1 protein complexes (PDB ID: 7DCZ, 4B05, 4YBI) were helpful to identify 3 ligands as promising BACE1 inhibitors having low-binding energy, and by conducting 100 ns molecular dynamic simulation study, a minimal fluctuations was demonstrated with the considerable duration. Finally, an efficient BACE1 inhibitor M6 {O=C(N(C1CC1)Cc1cccc(c1)c1cccnc1)c1cccc(c1)n1nncc1} with good binding affinity, potency (-7.83 Kcal/mol, 1.83 μM), and high BBB permeability for the treatment of AD is sub-selected from the huge volume of chemical spaces, which will be helpful to narrow down the time factor and can pave ways for subsequent in-vitro studies.

Keywords: BACE1, Molecular docking, Molecular dynamics simulation, Pharmacokinetics

Supplementary Figures

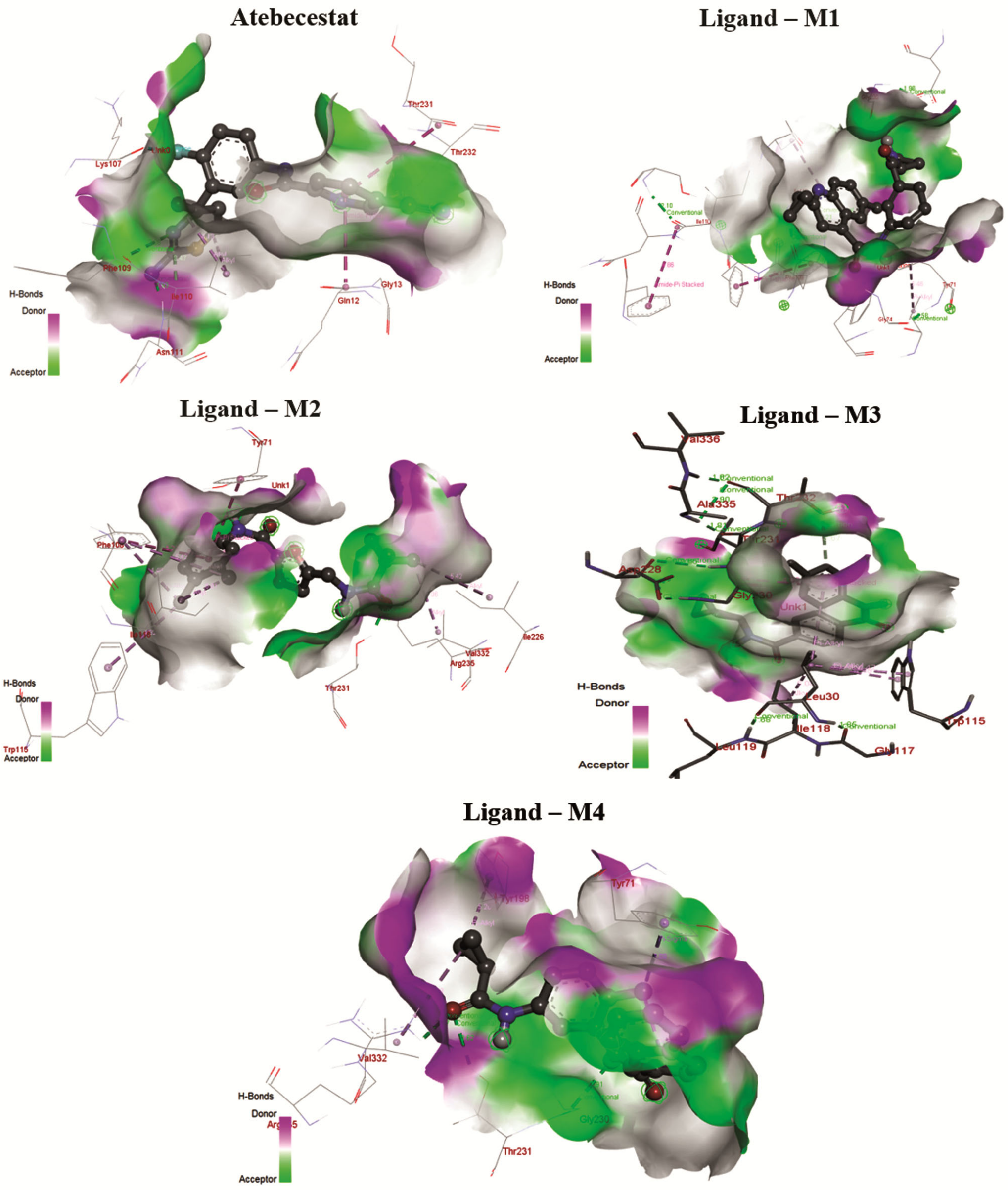
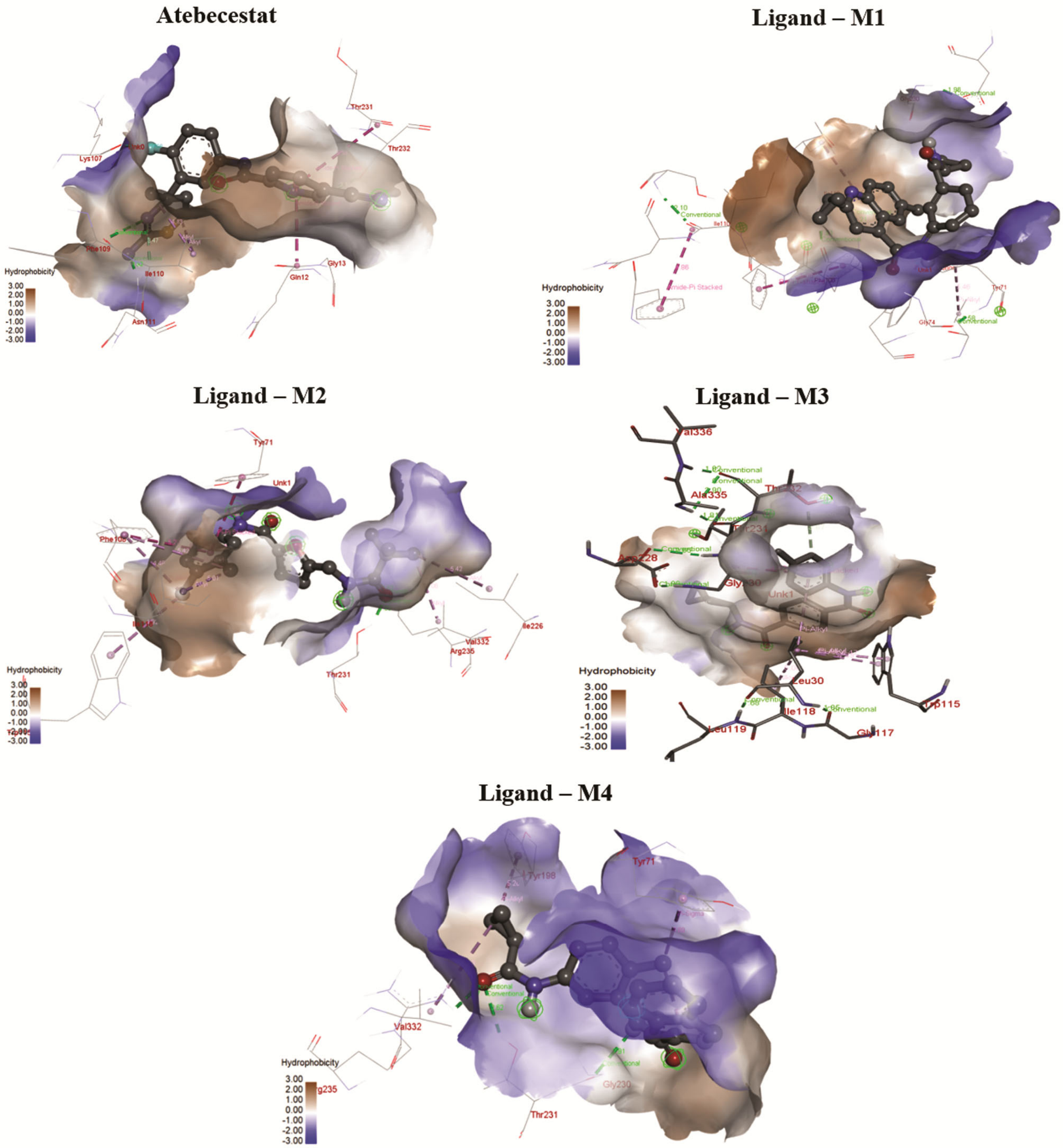


Fig. S1 — Electrostatic (H-bond) interactions of M1-M4 drug-like ligands and Atebecestat with amino acid residues in the binding pocket of protease (7DCZ)


Atebecestat

Ligand – M1

Ligand – M2

Ligand – M3

Ligand – M4

Fig. S2 — Hydrophobic interactions of M1-M4 drug-like ligands and Atebecestat with amino acid residues in the binding pocket of protease (7DCZ)

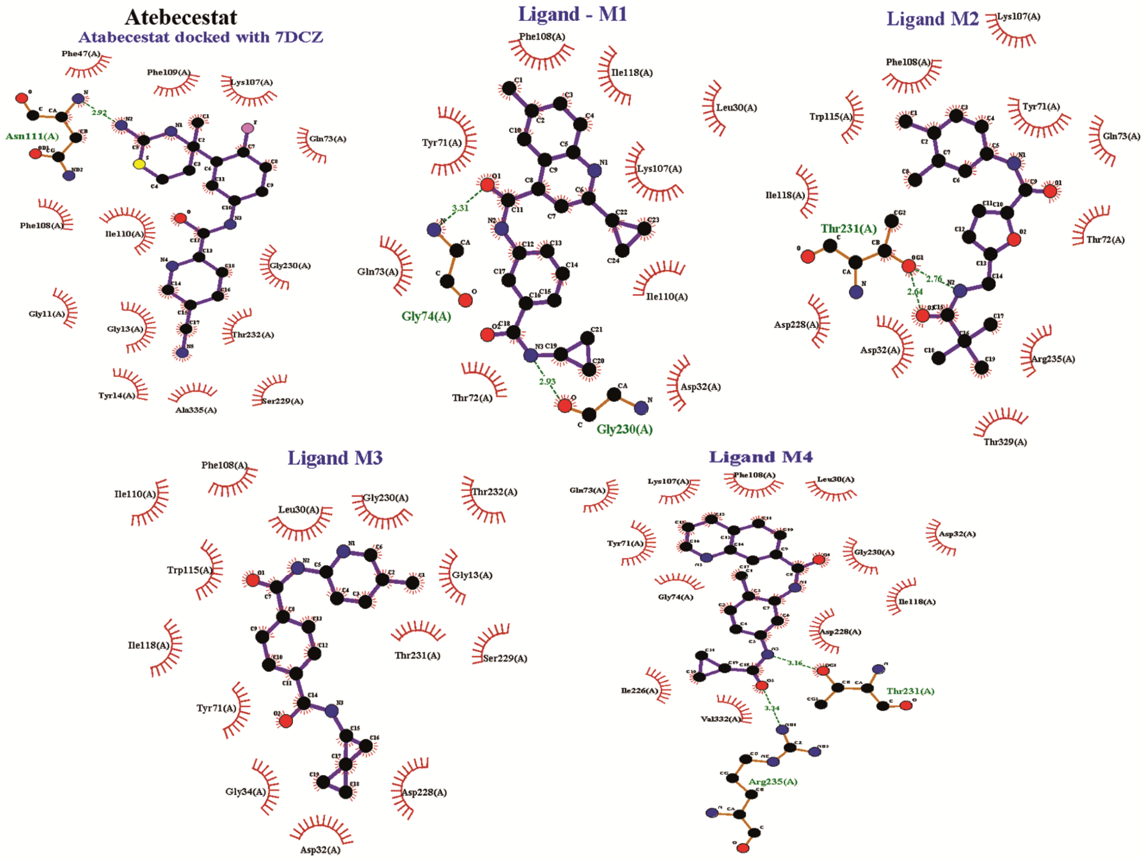


Fig. S3 — LigPlot of M1-M4 drug-like ligands and Atebecestat with 7DCZ

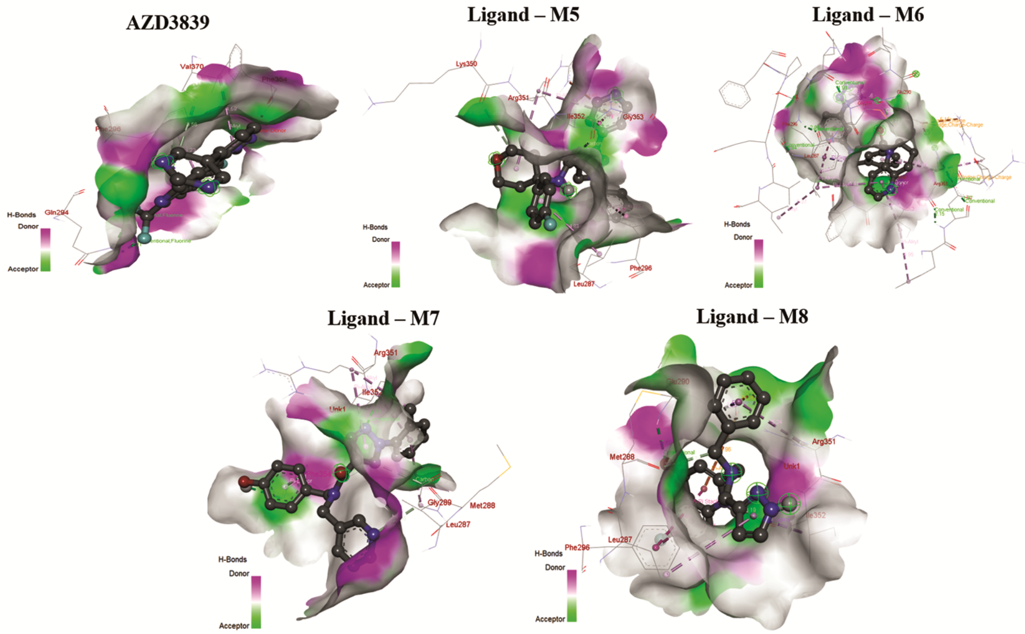
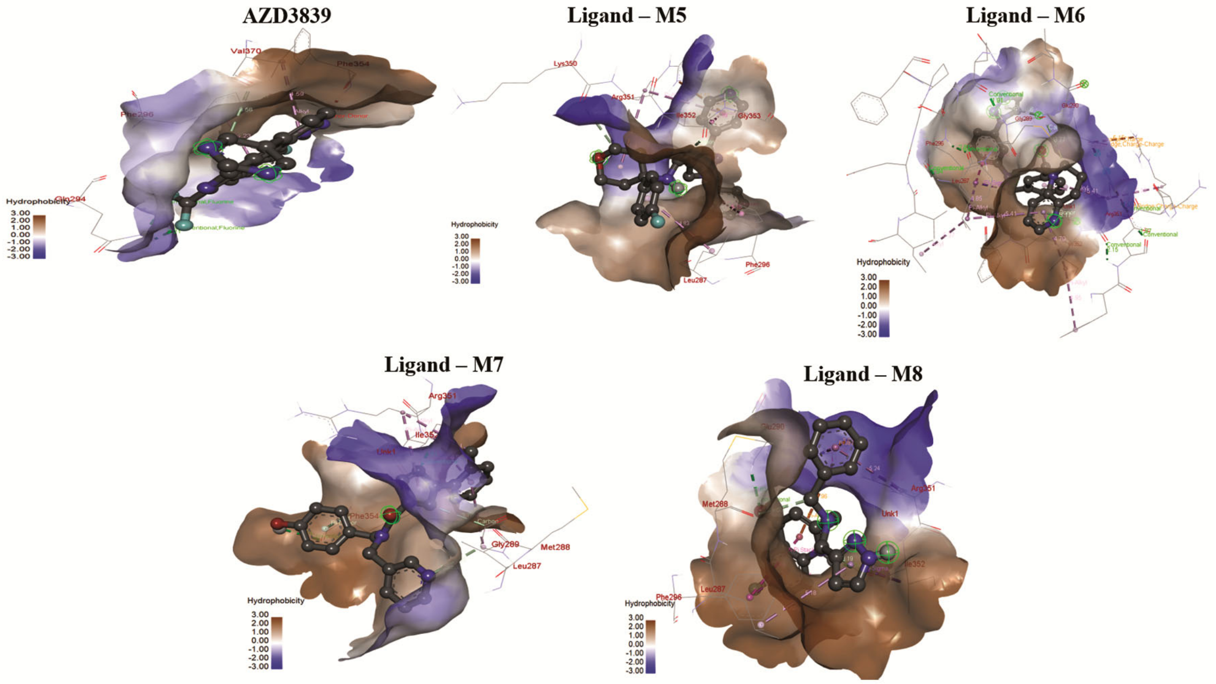


Fig. S4 — Electrostatic (H-bond) interactions of M1-M4 drug-like ligands and AZD3839 with amino acid residues in the binding pocket of protease (4B05)



AZD3839

Ligand – M5

Ligand – M6

Ligand – M7

Ligand – M8

Fig. S5 — Hydrophobic interactions of M5-M8 drug-like ligands and AZD3839 with amino acid residues in the binding pocket of protease (4B05)

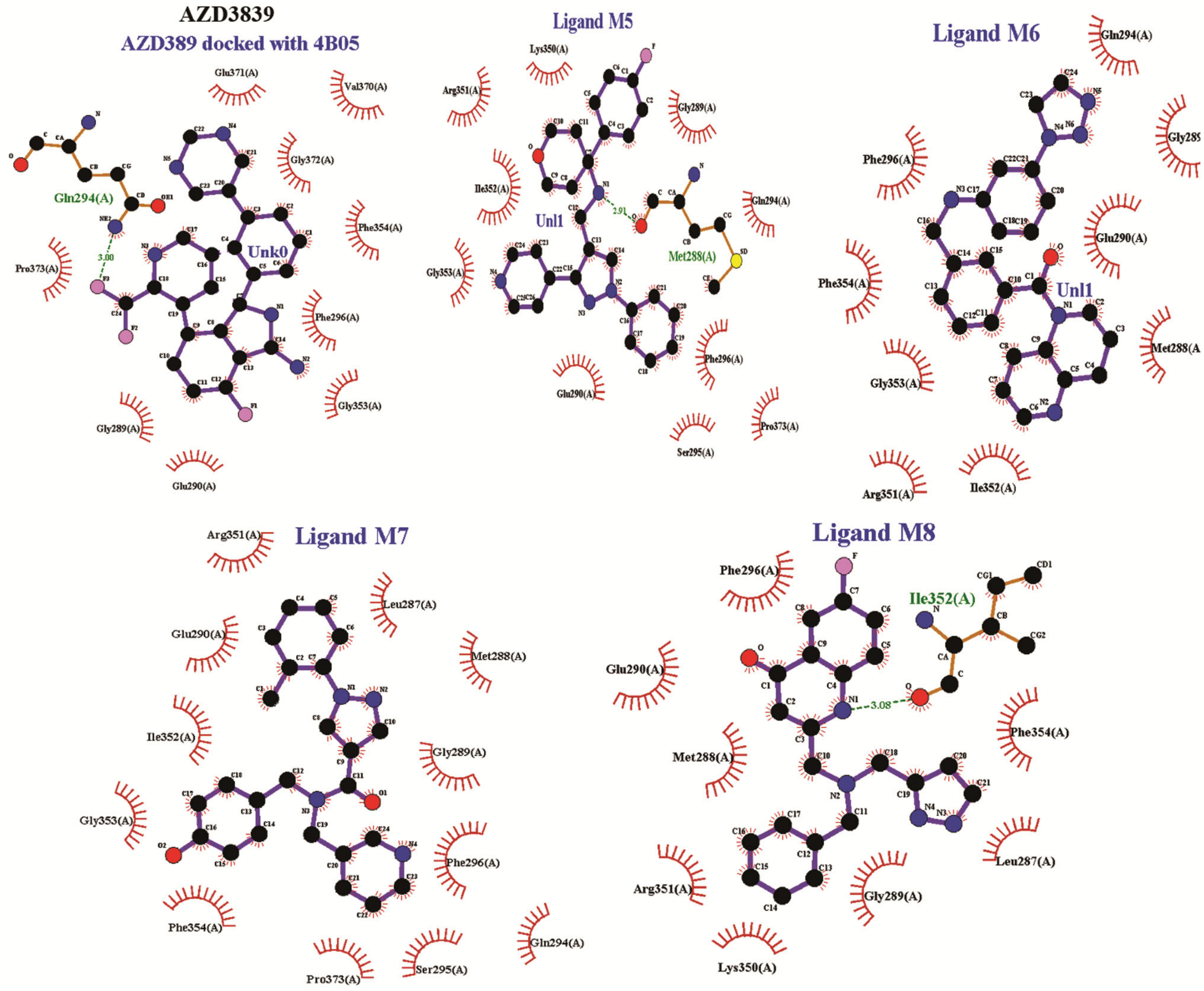
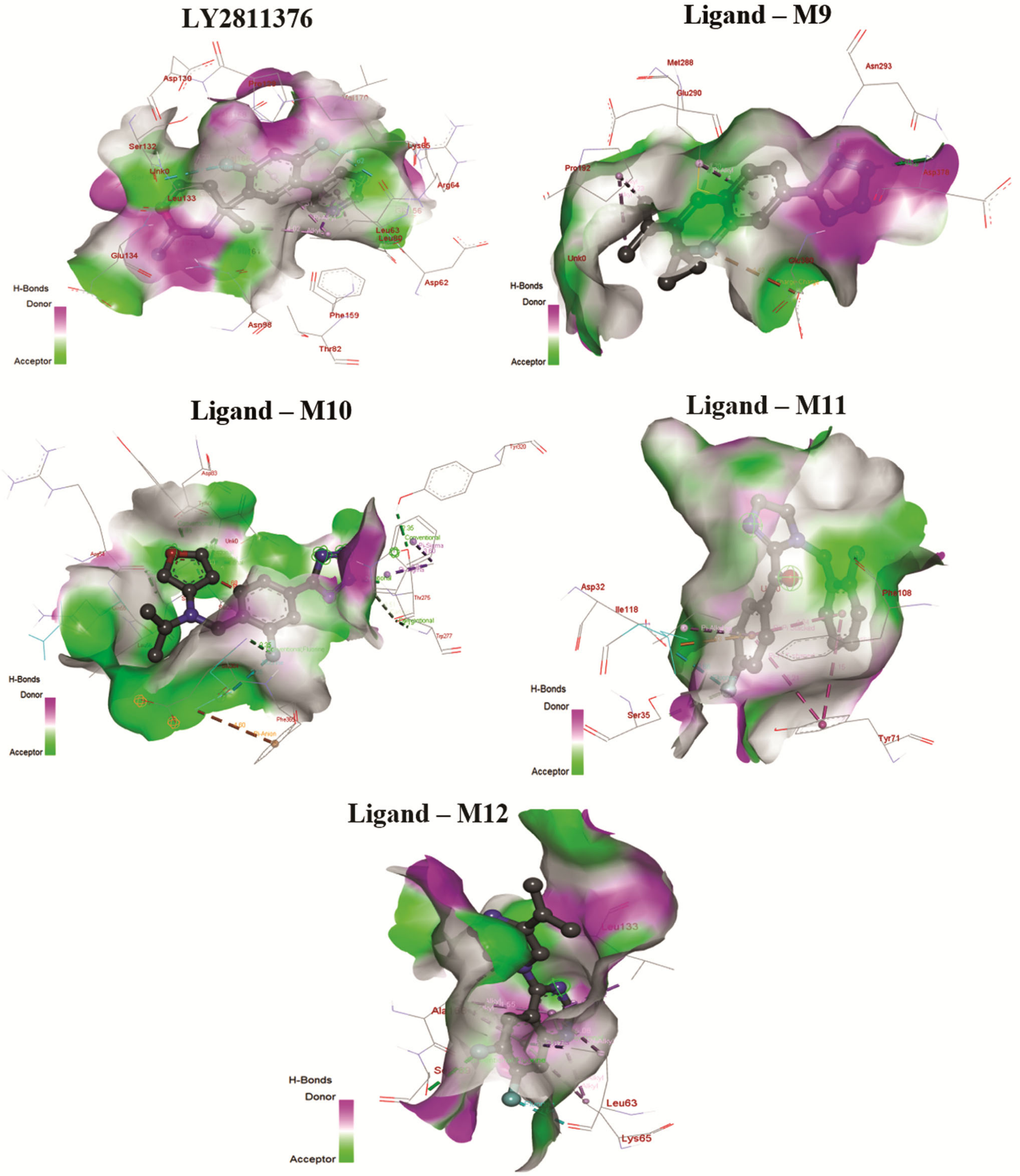


Fig. S6 — LigPlot of M5-M8 drug-like ligands and AZD3839 with 4B05



LY2811376

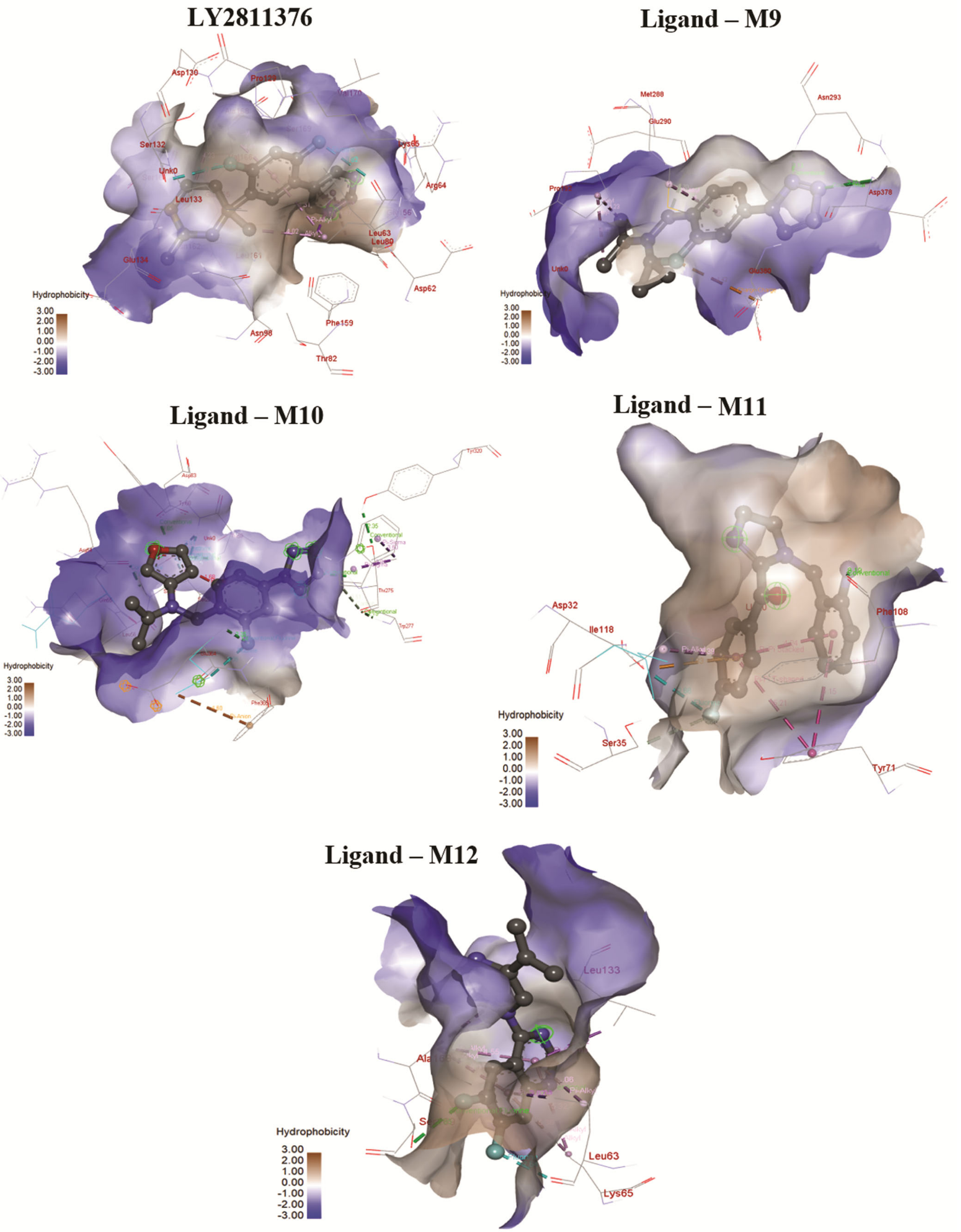
Ligand – M9

Ligand – M10

Ligand – M11

Ligand – M12

Fig. S7 — Electrostatic (H-bond) interactions of M9-M12 drug-like ligands and LY2811376 with amino acid residues in the binding pocket of protease (4YBI)



LY2811376

Ligand – M9

Ligand – M10

Ligand – M11

Ligand – M12

Fig. S8 — Hydrophobic interactions of M9-M12 drug-like ligands and LY2811376 with amino acid residues in the binding pocket of protease (4YBI)

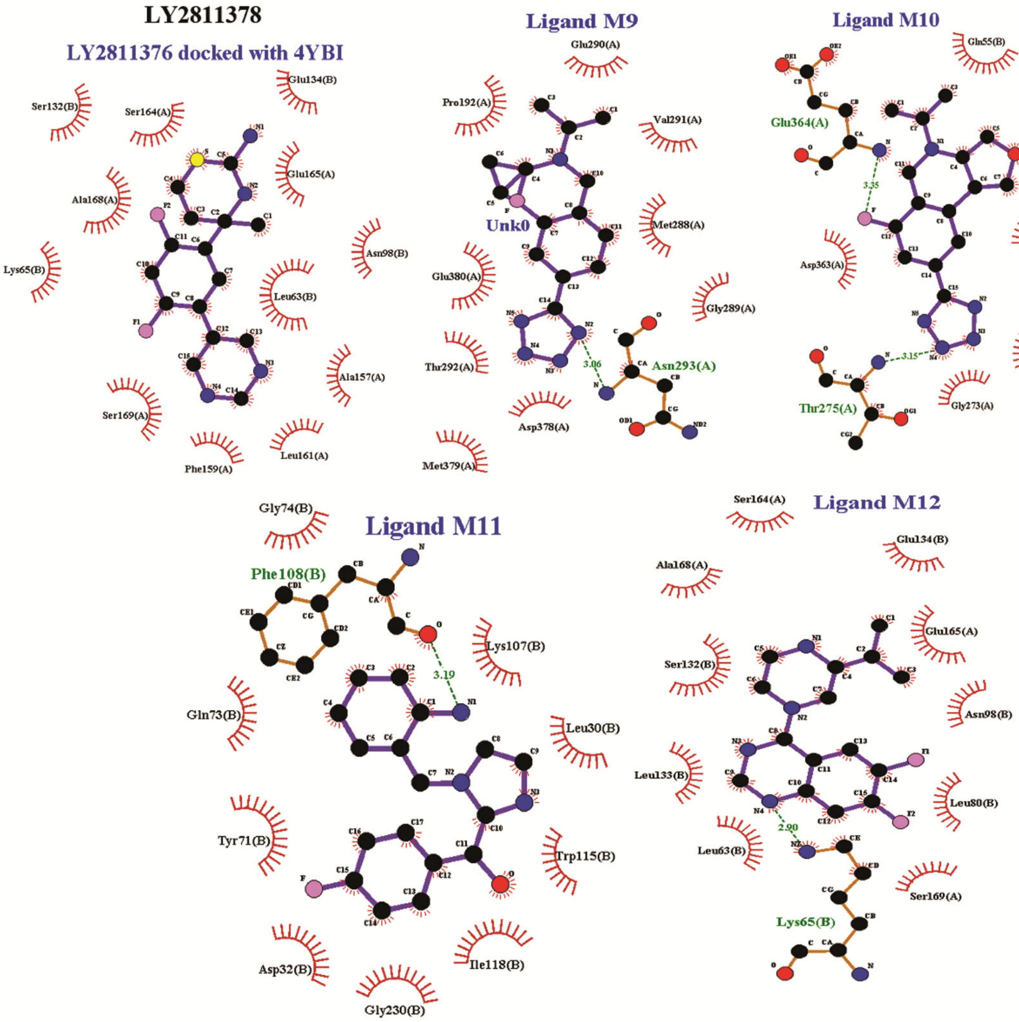
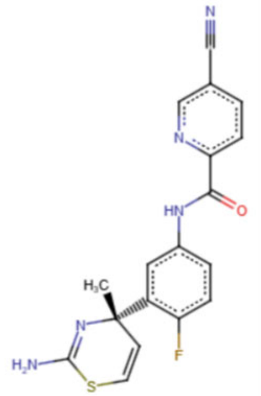
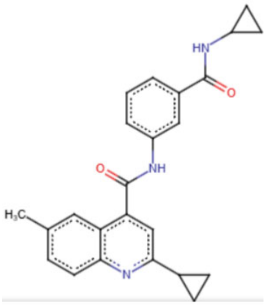
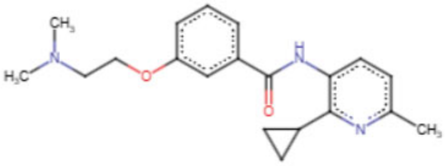
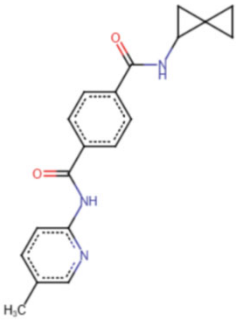
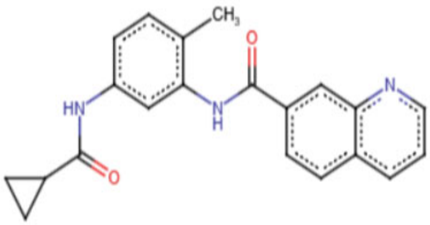
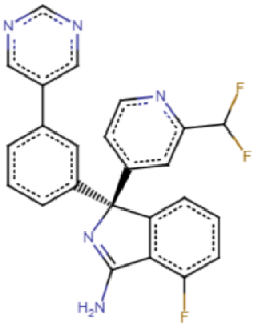
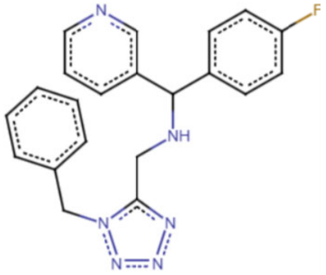
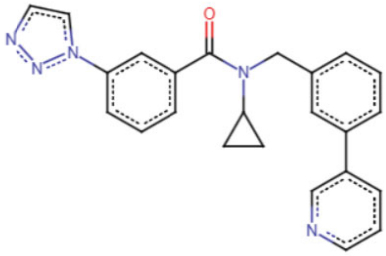
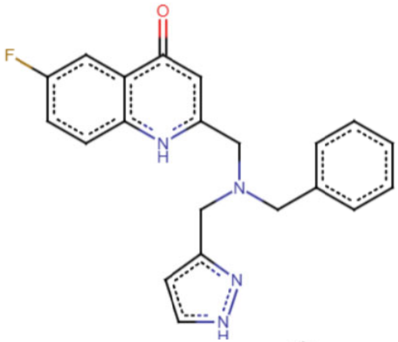
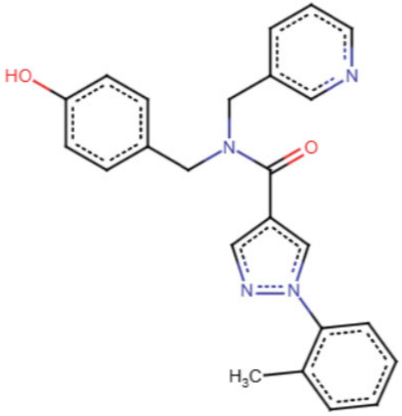


Fig. S9 — LigPlot of M9-M12 drug-like ligands and LY2811376 with 4YBI

Supplementary Tables

Table S1 — Chemical Structure and SMILES of 12 validated ligands and their reference drug compounds

Compound	SMILES	Structure
Atebecestat	N#Cc1ccc(nc1)C(=O)Nc1ccc(c(c1)[C@]1(C)C=CSC(=N1)N)F	
M1	Cc1ccc2c(c1)c(cc(n2)C1CC1)C(=O)Nc1cccc(c1)C(=O)NC1CC1	
M2	CN(CCOc1cccc(c1)C(=O)Nc1ccc(nc1C1CC1)C)C	
M3	Cc1ccc(nc1)NC(=O)c1ccc(cc1)C(=O)NC1CC21CC2	
M4	O=C(c1ccc2c(c1)nccc2)Nc1cc(ccc1C)NC(=O)C1CC1	

AZD3839	FC(c1nccc(c1)[C@@]1(N=C(c2c1cccc2F)N)c1cccc(c1)c1cncnc1)F	
M5	Fc1ccc(cc1)C(c1cccnc1)NCc1nnnn1Cc1ccccc1	
M6	O=C(N(C1CC1)Cc1cccc(c1)c1cccnc1)c1cccc(c1)n1nncc1	
M7	Fc1ccc2c(c1)c(=O)cc([nH]2)CN(Cc1cc[nH]n1)Cc1ccccc1	
M8	Oc1ccc(cc1)CN(C(=O)c1cnn(c1)c1ccccc1C)Cc1cccnc1	

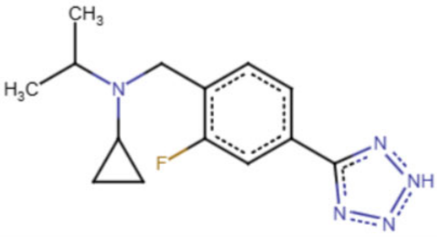
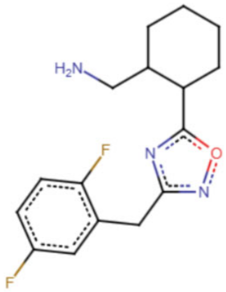
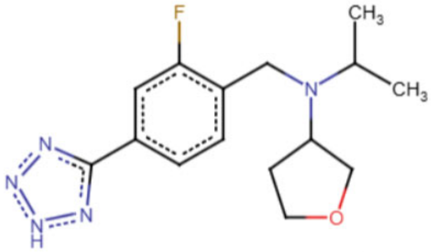
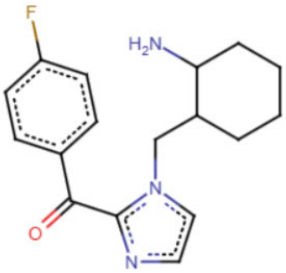
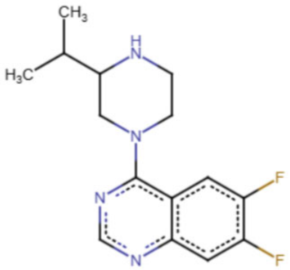
LY2811376	CC(N(C1CC1)Cc1ccc(cc1F)c1n[nH]nn1)C	
M9	NCC1CCCCC1c1onc(n1)Cc1cc(F)ccc1F	
M10	CC(N(C1COCC1)Cc1ccc(cc1F)c1n[nH]nn1)C	
M11	NC1CCCCC1Cn1ccnc1C(=O)c1ccc(cc1)F	
M12	CC(C1NCCN(C1)c1ncnc2c1cc(F)c(c2)F)C	

Table S2 — Analysis of mode of interactions with amino acid residues at active site-gorge of BACE1 enzymes

Donor		**Acceptor**		**Distance (Å)**	**Category**	**Type**
		Atebecestat + 7DCZ				
A:ASN111:HN	H-Donor	:Atabec:N	H-Acceptor	1.93	Hydrogen Bond	Conventional Hydrogen Bond
:Atabec:N	H-Donor	A:PHE109:O	H-Acceptor	3.36	Hydrogen Bond	Conventional Hydrogen Bond
A:ILE110:CA	H-Donor	:Atabec:N	H-Acceptor	3.47	Hydrogen Bond	Carbon Hydrogen Bond
:Atabec:C	H-Donor	A:THR232:OG1	H-Acceptor	3.19	Hydrogen Bond	Carbon Hydrogen Bond
A:LYS107:O	Halogen Acceptor	:Atabec:F	Halogen	3.27	Halogen	Halogen (Fluorine)
A:GLN12:C,O;GLY13:N	Amide	:Atabec	Pi-Orbitals	4.11	Hydrophobic	Amide-Pi Stacked
A:THR231:C,O;THR232:N	Amide	:Atabec	Pi-Orbitals	5.14	Hydrophobic	Amide-Pi Stacked
:Atabec:C	Alkyl	A:ILE110	Alkyl	4.13	Hydrophobic	Alkyl
:Atabec	Alkyl	A:ILE110	Alkyl	4.96	Hydrophobic	Alkyl
		AZD3839 + 4B05				
A:GLN294:HE21	H-Donor; Halogen Acceptor	:AZD:F	H-Acceptor; Halogen	2.72	Hydrogen Bond; Halogen	Conventional Hydrogen Bond; Halogen (Fluorine)
A:GLN294:HE22	H-Donor; Halogen Acceptor	: AZD:F	H-Acceptor; Halogen	2.21	Hydrogen Bond; Halogen	Conventional Hydrogen Bond; Halogen (Fluorine)
: AZD:C	H-Donor	A:VAL370:O	H-Acceptor	3.56	Hydrogen Bond	Carbon Hydrogen Bond
A:VAL370	Alkyl	: AZD	Alkyl	4.59	Hydrophobic	Alkyl
A:PHE296	Pi-Orbitals	: AZD	Alkyl	4.23	Hydrophobic	Pi-Alkyl
		LY2811376 + 4YBI				
B:LEU63:O	Halogen Acceptor	:LY281:F	Halogen	3.62	Halogen	Halogen (Fluorine)
B:SER132:O	Halogen Acceptor	: LY281:F	Halogen	3.47	Halogen	Halogen (Fluorine)
B:LEU63:CD2	C-H	: LY281	Pi-Orbitals	3.9	Hydrophobic	Pi-Sigma
A:ALA168	Alkyl	: LY281	Alkyl	4.23	Hydrophobic	Alkyl
: LY281:C	Alkyl	B:LEU63	Alkyl	4.02	Hydrophobic	Alkyl
: LY281	Pi-Orbitals	A:ALA168	Alkyl	4.46	Hydrophobic	Pi-Alkyl
: LY281	Pi-Orbitals	B:LEU63	Alkyl	4.31	Hydrophobic	Pi-Alkyl
: LY281	Pi-Orbitals	A:ALA157	Alkyl	4.87	Hydrophobic	Pi-Alkyl
: LY281	Pi-Orbitals	A:LEU161	Alkyl	5.31	Hydrophobic	Pi-Alkyl
		Ligand M1 + 7DCZ				
A:GLY74:HN	H-Donor	:M1:O	H-Acceptor	2.41	Hydrogen Bond	Conventional Hydrogen Bond
: M1:H	H-Donor	A:GLY230:O	H-Acceptor	1.98	Hydrogen Bond	Conventional Hydrogen Bond
A:PHE108:CA	H-Donor	: M1:O	H-Acceptor	3.66	Hydrogen Bond	Carbon Hydrogen Bond
: M1:C	C-H	: M1	Pi-Orbitals	3.56	Hydrophobic	Pi-Sigma
A:TYR71	Pi-Orbitals	: M1	Pi-Orbitals	5.57	Hydrophobic	Pi-Pi T-shaped
A:PHE108	Pi-Orbitals	: M1	Pi-Orbitals	5.22	Hydrophobic	Pi-Pi T-shaped
A:PHE108	Pi-Orbitals	: M1	Pi-Orbitals	5.52	Hydrophobic	Pi-Pi T-shaped
: M1:C	Alkyl	A:ILE118	Alkyl	4.81	Hydrophobic	Alkyl
: M1	Alkyl	A:ILE110	Alkyl	4.39	Hydrophobic	Alkyl
A:TYR71	Pi-Orbitals	: M1:C	Alkyl	4.09	Hydrophobic	Pi-Alkyl

			Ligand M6 + 4B05			
:M6:C	H-Donor	A:GLY289:O	H-Acceptor	3.77	Hydrogen Bond	Carbon Hydrogen Bond
A:GLU290:HN	H-Donor	: M6	Pi-Orbitals	3.06	Hydrogen Bond	Pi-Donor Hydrogen Bond
A:ILE352:HN	H-Donor	: M6	Pi-Orbitals	3.17	Hydrogen Bond	Pi-Donor Hydrogen Bond
: M6:C	C-H	A:PHE296	Pi-Orbitals	3.89	Hydrophobic	Pi-Sigma
A:PHE296	Pi-Orbitals	: M6	Pi-Orbitals	4.34	Hydrophobic	Pi-Pi Stacked
A:ARG351	Alkyl	: M6	Alkyl	5.41	Hydrophobic	Alkyl
: M6	Pi-Orbitals	A:LEU287	Alkyl	5.41	Hydrophobic	Pi-Alkyl
: M6	Pi-Orbitals	A:ILE352	Alkyl	4.7	Hydrophobic	Pi-Alkyl
: M6	Pi-Orbitals	A:ARG351	Alkyl	4.99	Hydrophobic	Pi-Alkyl
			Ligand M10 + 4YBI			
A:THR275:HN	H-Donor	:M10:N	H-Acceptor	2.58	Hydrogen Bond	Conventional Hydrogen Bond
A:TRP277:HN	H-Donor	A:THR275:O	H-Acceptor	2.13	Hydrogen Bond	Conventional Hydrogen Bond
A:TYR320:HH	H-Donor	A:THR275:OG1	H-Acceptor	2.35	Hydrogen Bond	Conventional Hydrogen Bond
A:GLU364:N	H-Donor; Halogen Acceptor	: M10:F	H-Acceptor; Halogen	3.35	Hydrogen Bond; Halogen	Conventional Hydrogen Bond; Halogen (Fluorine)
B:SER22:HN	H-Donor	B:SER57:OG	H-Acceptor	2.17	Hydrogen Bond	Conventional Hydrogen Bond
B:SER57:HN	H-Donor	B:ARG54:O	H-Acceptor	2.07	Hydrogen Bond	Conventional Hydrogen Bond
B:SER57:HG	H-Donor	B:ASP83:OD2	H-Acceptor	1.85	Hydrogen Bond	Conventional Hydrogen Bond
B:THR59:HN	H-Donor	B:SER57:OG	H-Acceptor	2.46	Hydrogen Bond	Conventional Hydrogen Bond
B:TYR60:HN	H-Donor	B:SER57:O	H-Acceptor	2.47	Hydrogen Bond	Conventional Hydrogen Bond
B:TYR60:HN	H-Donor	B:SER57:OG	H-Acceptor	2.81	Hydrogen Bond	Conventional Hydrogen Bond
A:TRP277:CD1	H-Donor	A:THR275:O	H-Acceptor	3.51	Hydrogen Bond	Carbon Hydrogen Bond
: M10:C	H-Donor	B:SER57:O	H-Acceptor	3.4	Hydrogen Bond	Carbon Hydrogen Bond
A:GLU364:OE2:B	Halogen Acceptor	: M10:F	Halogen	3.05	Halogen	Halogen (Fluorine)
A:GLU364:OE1:B	Negative	A:PHE365	Pi-Orbitals	4.6	Electrostatic	Pi-Anion
A:THR275:CG2	C-H	A:TRP277	Pi-Orbitals	3.91	Hydrophobic	Pi-Sigma
A:THR275:CG2	C-H	A:TRP277	Pi-Orbitals	3.6	Hydrophobic	Pi-Sigma