

List of Tables

Table S1: List of known RET inhibitors with its inhibitory activity.

Table S2: Calculated global descriptors of hybrid molecules using LACV3P++** energy level.

Table S3: Hydrogen bond interaction involved between the ligand molecules and the receptor.

Table S4: In silico sensitivity analysis of control and hybrid molecules against LC-2/ad cell line.

List of Figures

Figure S1: 3D visualization of bound protein ligand complexes: (a) RET-pralsetinib, (b) RET-LF1, (c) RET-LF2 and (d) RET-LF88 complex.

Figure S2: The synergistic docking of parental compounds where C1, C2, C3 and C4 denotes Luminespib, Pralsetinib, Dovitinib and LOXO-292 respectively. White circle indicates the binding position of compound 1 and the blue circle represents the respective binding mode of the 2nd compound.

Table S1: List of known RET inhibitors with its inhibitory activity.

S. No	Compound Name	PubChem ID	Class of the compound	IC ₅₀ (nM)
1	Pralsetinib	129073603	Not Classified	0.4
2	LOXO-292	134823904	Not Classified	1
3	Luminespib	135539077	Benzenoids	1.34
4	Sitravatinib	25212148	Not Classified	1.5
5	Lenvatinib	9823820	Quinolines	1.5
6	RXDX-105	56846693	Not Classified	3
7	Vandetanib	3081361	Diazanaphthalenes	4
8	Alectinib	49806720	Indoles	4.8
9	Crizotinib	11626560	Pyridines	5
10	Sunitinib	5329102	Indoles	6.66
11	Sorafenib	216239	Organooxygen compounds	7.33
12	Regorafenib	11167602	Organooxygen compounds	8.82
13	AD80	71578106	Pyrazoles	9
14	Cabozantinib	25102847	Organooxygen compounds	11
15	Apatinib	11315474	Not Classified	13
16	Ponatinib	24826799	Benzenoids	25.8
17	Nintedanib	135423438	Indoles	34
18	Dovitinib	135398510	Diazinanes	200

Table S2: Calculated global descriptors of hybrid molecules using LACV3P++** energy level.

S. No.	Control and Linked Fragments	Ionization		Electron		Hardness (η)	Softness (S)	Chemical Potential (χ)
		Potential (IP)	Affinity (EA)					
1	Pralsetinib	8.320	0.876		3.720	0.268	4.590	
2	LF1	8.022	-0.092		4.060	0.246	3.970	
3	LF2	8.954	0.800		4.080	0.245	4.880	
4	LF21	6.057	0.447		3.108	0.321	2.950	
5	LF27	6.067	-0.160		2.630	0.380	3.437	
6	LF88	8.368	0.807		3.960	0.252	4.410	

Table S3: Hydrogen bond interaction involved between the ligand molecules and the receptor.

S. No.	Control and Linked Fragment	Interacting Residues	Interaction Distance (Å)
1	Pralsetinib	ALA807 ... N	1.97
		NH ... ALA807	2.55
		SER811 ... N	2.21
2	LF1	OH ... ALA807	2.23
3	LF2	NH ... ALA807	2.06
		ALA807 ... O	2.05
4	LF88	N ... ALA807	3.83
		NH ... ALA807	2.70
		NH ... ASN879	2.47

Table S4: In silico activity prediction of control and hybrid molecules against LC-2/ad cell line.

S. No.	Control and linked fragments	IC ₅₀ (log μM)	IC ₅₀ (μM)
1	Pralsetinib	3.294	26.950
2	LF1	3.573	35.623
3	LF2	2.082	8.020
4	LF88	1.521	4.576

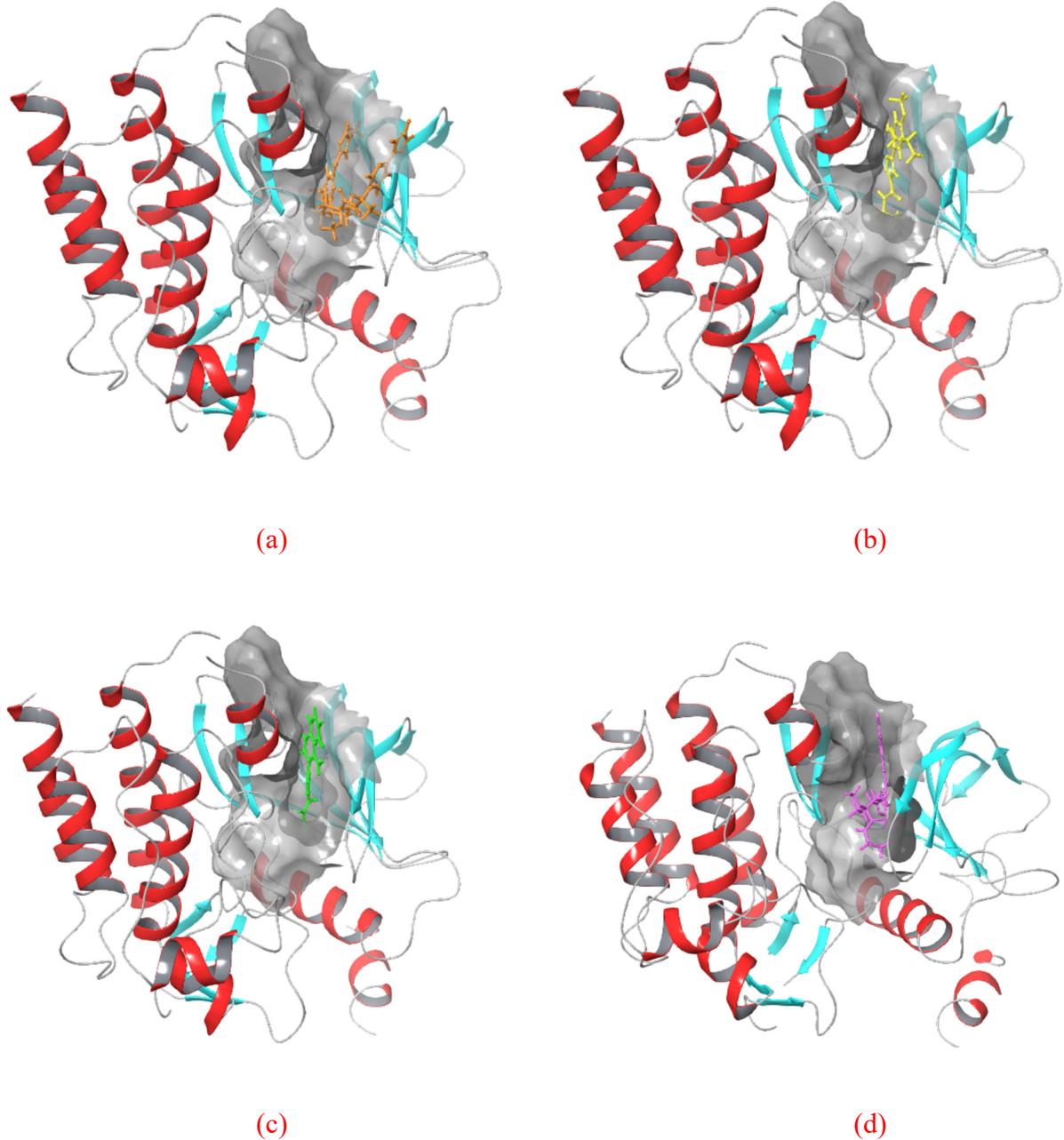
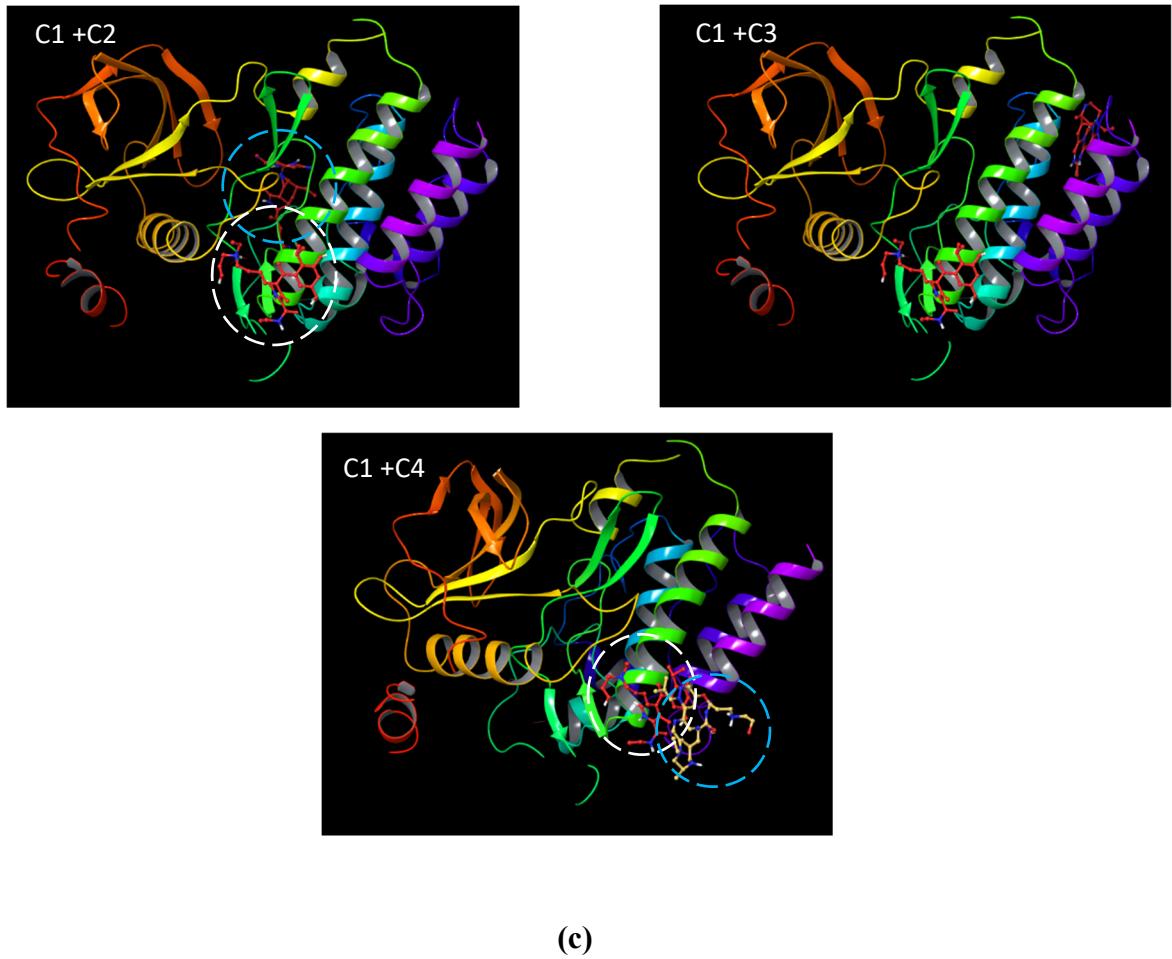


Figure S1: 3D visualization of bound protein ligand complexes: (a) RET-pralsetinib, (b) RET-LF1, (c) RET-LF2 and (d) RET-LF88 complex.



(c)

Figure S2: The synergistic docking of parental compounds where C1, C2, C3 and C4 denotes Luminespib, Pralsetinib, Dovitinib and LOXO-292 respectively. White circle indicates the binding position of compound 1 and the blue circle represents the respective binding mode of the 2nd compound.