Supplementary Information

Identification and characterization of binding thermodynamics and kinetics of inhibitors targeting FGFR1 via molecular modelling and ligand Gaussian accelerated molecular dynamics Simulations

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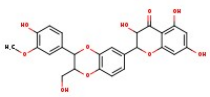
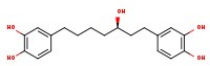
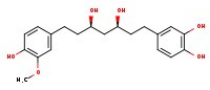
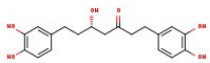
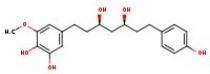
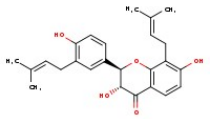
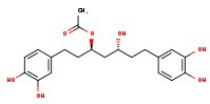
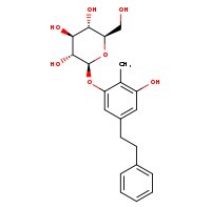
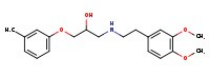
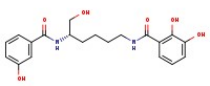
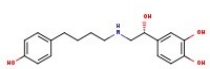
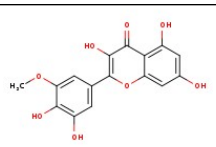
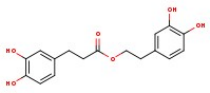
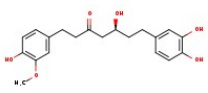
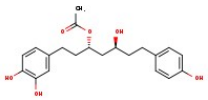
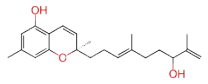
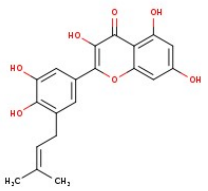
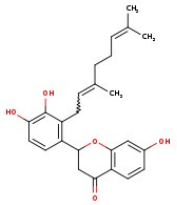
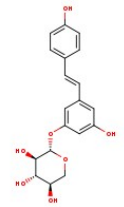
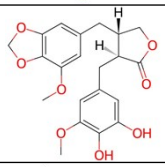
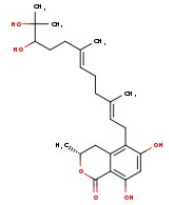
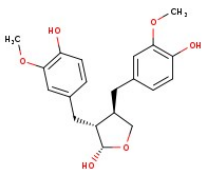
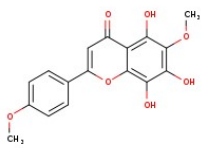
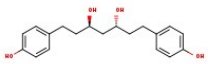
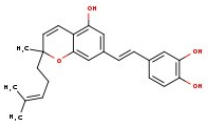
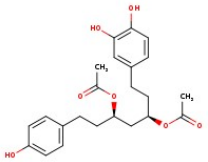
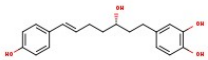
Table S1: List of top hit compounds with their Glide XP-Docking scores in kcal/mol, obtained from the virtual screening workflow and ADMETlab 2.0.

Compounds			Physiochemical property			Glide-XP
Name/ID	Pubchem CID	Structure	MW	Volume	TPSA	Docking score
HMDB0030583 (Silibinin)	5213		482.4	459.7	155.1	-14.8
NPC120982 (Rubranol)	10088141		332.16	348.2	101.15	-13.93
NPC343720	11995071		362.1	374.2	110.3	-13.92
NPC34634 (Hirustanonol)	9928190		346.1	354.3	118.2	-13.91
NPC470213	53387512		362.1	374.2	110.3	-13.71
HMDB0029532 (3-hydroxy glabrol)	480854		408.4	435.5	87	-13.81
NPC109371	54577120		390.1	397.7	127.4	-13.70
NPC134260	11560189		390.1	391.8	119.6	-13.51
HMDB0015409 (Bevantolol)	2372		345.4	367.7	59.9	-12.91
NPC477839	118735510		388.1	391.0	139.1	-12.82
HMDB0015234 (Arbutamine)	60789		317.3	333.1	92.9	-12.81
NPC133953 (Laricitrin)	5282154		332.0	308.8	140.5	-12.81
NPC472271	58446617		318.1	319.7	107.2	-12.71

NPC65935	56675574		360.1	371.6	107.2	-12.41
NPC470214	54577124		374.1	388.9	107.2	-12.40
NPC120638 (Daurichromene A)	10043035		342.2	382.5	49.6	-12.31
HMDB0039732 (Uralenol)	5315126		370.4	366.6	131.3	-12.30
HMDB0040317	131752791		408.8	435.5	86.9	-12.10
NPC121376	44559506		360.1	354.5	119.6	-12.0
NPC174512	11625522		402.1	389.4	103.6	-11.81
NPC473023	122184714		432.2	460.7	107.2	-11.60
NPC181079	45481967		360.1	365.7	88.3	-11.51
HMDB0037096 (Pilosin)	12085264		330.2	317.3	109.3	-11.41

NPC91461	11034432		316.1	339.4	80.9	-11.12
NPC474481 (Pawhuskin B)	11199792		378.1	409.4	69.9	-11.10
NPC86198	54577121		416.1	429.6	113.2	-11.10
NPC147634	49831709		314.1	336.7	80.9	-11.0

Acceptable ranges- Molecular Weight, (0-500) g/mol; Vol_{vdW}: van der Waals volume; TPSA: Topological Polar Surface Area, (0-140)

Compound name	Logp	Logs	No. of H-bond Acceptors	No. of H-bond donors	Caco2 permeability	MDCK permeability	HIA
Silibinin	2.01	-4.79	10	5	-6.25	9.5e-06	0.30
Rubranol	2.94	-3.27	5	5	-5.18	1.8e-05	0.95
NPC343720	2.14	-3.07	6	5	-5.25	7.1e-06	0.98
Hirustanonol	1.40	-1.87	6	5	-5.20	1.1e-05	0.99
NPC470213	2.18	-3.12	6	5	-5.33	6.8e-06	0.85
3-hydroxy glabrol	4.02	-3.13	5	3	-4.85	1.7e-05	0.05
NPC109371	2.36	-2.73	7	5	-5.25	1.1e-05	0.95
NPC134260	1.85	-3.25	7	5	-5.47	1.8e-05	0.80
Bevantolol	2.71	-3.02	5	2	-4.90	3e-05	0.01
NPC477839	1.44	-2.38	8	6	-6.07	3.5e-06	0.25
Arbutamine	0.87	-3.15	5	5	-5.18	1e-05	0.42
Laricitrin	2.12	-3.73	8	5	-5.29	8.6e-06	0.05
NPC472271	2.17	-2.83	6	4	-4.89	1.6e-05	0.92
NPC65935	1.65	-2.24	6	4	-4.91	1.3e-05	0.52
NPC470214	2.71	-2.78	6	4	-4.80	1.4e-05	0.93
DaurichromeneA	4.84	-3.65	3	2	-4.75	2.9e-05	0.04
HMDB0040317	4.95	-3.74	5	3	-4.77	1.6e-05	0.02
Uralenol	4.08	-3.45	7	5	-5.13	1.1e-05	0.03
NPC121376	2.00	-2.55	7	5	-5.94	5.3e-06	0.23
NPC174512	2.73	-4.28	8	2	-4.74	2.2e-05	0.03
NPC473023	4.53	-3.28	6	4	-4.91	2.6e-05	0.04
NPC181079	2.43	-3.48	6	3	-4.80	1.1e-05	0.02
Pilosin	3.29	-3.72	7	3	-4.97	1.3e-05	0.01
NPC91461	2.71	-3.65	4	4	-4.90	4.9e-06	0.17
Pawhuskin B	4.61	-3.07	4	3	-5.01	2.1e-05	0.02
NPC86198	3.00	-3.11	7	3	-2.77	2.8e-05	0.02
NPC147634	3.15	-3.11	4	4	-1.44	1.2e-05	0.03

Table S2- The drug-likeliness properties calculated using the ADMETlab 2.0.

Lipinski's rule of 5 helps in distinguishing between drug-like and non-drug-like molecules.

LogP: logarithm of n-octanol/water distribution coefficient (log mol/L); optimal value ≤ 5 in Lipinski rule.

LogS: logarithm of aqueous solubility (log mol/L); optimal value – 4 to 0.5

No. of H-bond Donor ≤5

No. of H-bond Acceptor ≤10

Caco2: Human colon adenocarcinoma cell line; Caco2 permeability > -5.15 log unit signifies high Caco-2 permeability.

MDCK permeability: Madin-Darby Canine Kidney cells permeability; apparent permeability coefficient > 20 cm/s: high permeability; value in the range of 2-20 cm/s: moderate permeability; < 2 cm/s: low permeability.

HIA: Human intestinal absorption; the output values estimate the likelihood of being HIA+ (HIA+ indicates < 30% human intestinal absorption); drug selection is categorized based on the output values: 0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor.

Table S3- Toxicity prediction of all screened molecules using ADMETlab 2.0.

Compound name	HERG blocker	Hepatotoxicity	Liver injury	Ames Toxicity	Rat oral toxicity	Skin sensitization	Carcinogenicity	Respiratory toxicity
Silibinin	0.05	0.05	0.90	0.30	0.20	0.25	0.35	0.08
Rubranol	0.01	0.06	0.05	0.60	0.08	0.95	0.09	0.07
NPC343720	0.07	0.20	0.01	0.15	0.05	0.98	0.02	0.25
Hirustanonol	0.03	0.29	0.07	0.75	0.08	0.95	0.03	0.04
NPC470213	0.11	0.25	0.08	0.07	0.06	0.96	0.02	0.05
3-hydroxy glabrol	0.02	0.45	0.06	0.05	0.13	0.55	0.03	0.03
NPC109371	0.02	0.39	0.07	0.58	0.03	0.97	0.15	0.05
NPC134260	0.14	0.03	0.04	0.38	0.01	0.02	0.01	0.04
Bevantolol	0.01	0.30	0.05	0.03	0.02	0.45	0.01	0.05
NPC477839	0.06	0.27	0.40	0.04	0.04	0.80	0.08	0.07
Arbutamine	0.31	0.27	0.04	0.35	0.95	0.98	0.05	0.28
Laricitrin	0.16	0.05	0.95	0.32	0.08	0.96	0.02	0.01
NPC472271	0.03	0.02	0.25	0.03	0.78	0.29	0.03	0.02
NPC65935	0.03	0.03	0.26	0.04	0.56	0.93	0.53	0.01
NPC470214	0.09	0.27	0.04	0.26	0.02	0.94	0.53	0.82
Daurichromene A	0.14	0.53	0.03	0.04	0.03	0.84	0.04	0.02
HMDB0040317	0.11	0.63	0.27	0.03	0.04	0.92	0.03	0.35
Uralenol	0.23	0.22	0.92	0.52	0.62	0.95	0.15	0.22
NPC121376	0.33	0.61	0.04	0.35	0.02	0.94	0.52	0.62
NPC174512	0.14	0.23	0.23	0.03	0.03	0.92	0.51	0.17
NPC473023	0.07	0.25	0.26	0.03	0.02	0.71	0.01	0.72
NPC181079	0.33	0.26	0.25	0.22	0.03	0.91	0.15	0.12
Pilosin	0.24	0.22	0.92	0.61	0.22	0.93	0.29	0.21
NPC91461	0.27	0.15	0.03	0.02	0.04	0.95	0.23	0.72
Pawhuskin B	0.31	0.62	0.01	0.06	0.23	0.96	0.62	0.12
NPC86198	0.03	0.82	0.85	0.27	0.02	0.97	0.35	0.03
NPC147634	0.13	0.03	0.25	0.07	0.07	0.91	0.62	0.67

The results suggest the likelihood of the ligands being active/harmful in the relevant evaluations; drug selection with less toxicity/harmful effect is categorized based on the output values: 0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor.

Table S4: Average protein-ligand hydrogen bond interaction profile in Ponatinib, Bevantolol, 3-hydroxy glabrol, Daurichromene A and Pawhuskin B during the 200 ns simulation run.

Binding couples		Molecular dynamics	
Acceptor	**Donor**	**Distance (Å)**	**Occupancy (%)**
Ponatinib			
Lig@O1	**Asp_179@N1**	**2.82**	**22.51**
Glu_69@OE1	**Lig@N2**	**2.83**	**30.82**
Glu_69@OE2	**Lig@N2**	**2.83**	**26.55**
Bevantolol			
Glu_75@OE2	**Lig@N1**	**2.72**	**72.27**
Glu_75@OE2	**Lig@O2**	**2.60**	**44.23**
Glu_69@OE1	**Lig@N1**	**2.75**	**27.37**
Glu_69@OE1	**Lig@O2**	**2.60**	**21.34**
ALA_184@O1	**Lig@N1**	**2.73**	**21.30**
3-hydroxy glabrol			
Lig@O3	**Ala108@N**	**2.86**	**62.37**
Glu106@O	**Lig@O4**	**2.79**	**64.57**
Asp185@OD1	**Lig@O1**	**2.64**	**17.20**
Leu28@O	**Lig@O2**	**2.74**	**16.89**
Asp185@OD1	**Lig@O1**	**2.65**	**16.22**
Glu75@OE1	**Lig@O1**	**2.69**	**12.93**
Daurichromene A			
Asp_185@O	**Lig@O3**	**2.75**	**51.43**
Pawhuskin B			
Glu_106@O	**Lig@O3**	**2.77**	**56.11**
Glu_75@OE1	**Lig@O2**	**2.67**	**32.24**
Glu75@OE2	**Lig@O2**	**2.67**	**15.43**

Table S5: Overview of the network parameters assessment of apo and the analyzed complexes.

Parameter	Apo	Ponatinib	Bevantolol	3-hydroxy glabrol
No. of linked nodes	**289**	**290**	**298**	**294**
No. of links	**311**	**316**	**370**	**342**
No. of hubs	**37**	**32**	**57**	**50**
No. of linked mediated hubs	**138**	**137**	**206**	**178**
No. of Communities	**11**	**9**	**7**	**10**
No. of nodes involved in communities	**39**	**45**	**97**	**72**
No. of links involved in communities	**44**	**55**	**146**	**98**

Table S6: Glide docking scores of the top two Bevantolol analogues.

Ligand name	SMILES	Docking score (kcal/mol)	Mol. Wt (Da)
ANLG-1	**CO[C@H]2CCC(CCNC[C@@H](O)COC1CCC[C@@H](C)C1)C[C@H]2CO**	**-13.72**	**357.29**
ANLG-2	**CCC1CCC(CCNC[C@@H](O)CO[C@@H]2CCCC(C)C2)CC1O**	**-13.56**	**341.29**

Table S7. Decomposition of total binding free energy of most favourable and unfavourable residues.

Residue	G_{vdw}	G_{elec}	G_{polar}	$G_{non-polar}$	G_{bind}
Ponatinib					
Glu531	-2.56	-0.75	3.79	0	1.98
Ile545	-2.06	-0.07	0.41	0	-1.72
Asp641	-1.15	-6.67	10.25	0	2.43
Bevantolol					
Lys520	-0.77	24.34	-20.60	0	2.97
Glu537	-1.90	-51.34	45.43	0	-7.41
Asp647	-3.30	-45.57	44.64	0	-4.22
3-hydroxy glabrol					
Val498	-2.02	-0.24	0.35	0	-1.91
Glu537	-0.11	-0.24	0.51	0	0.14
Leu636	-2.07	-0.31	0.36	0	-2.02

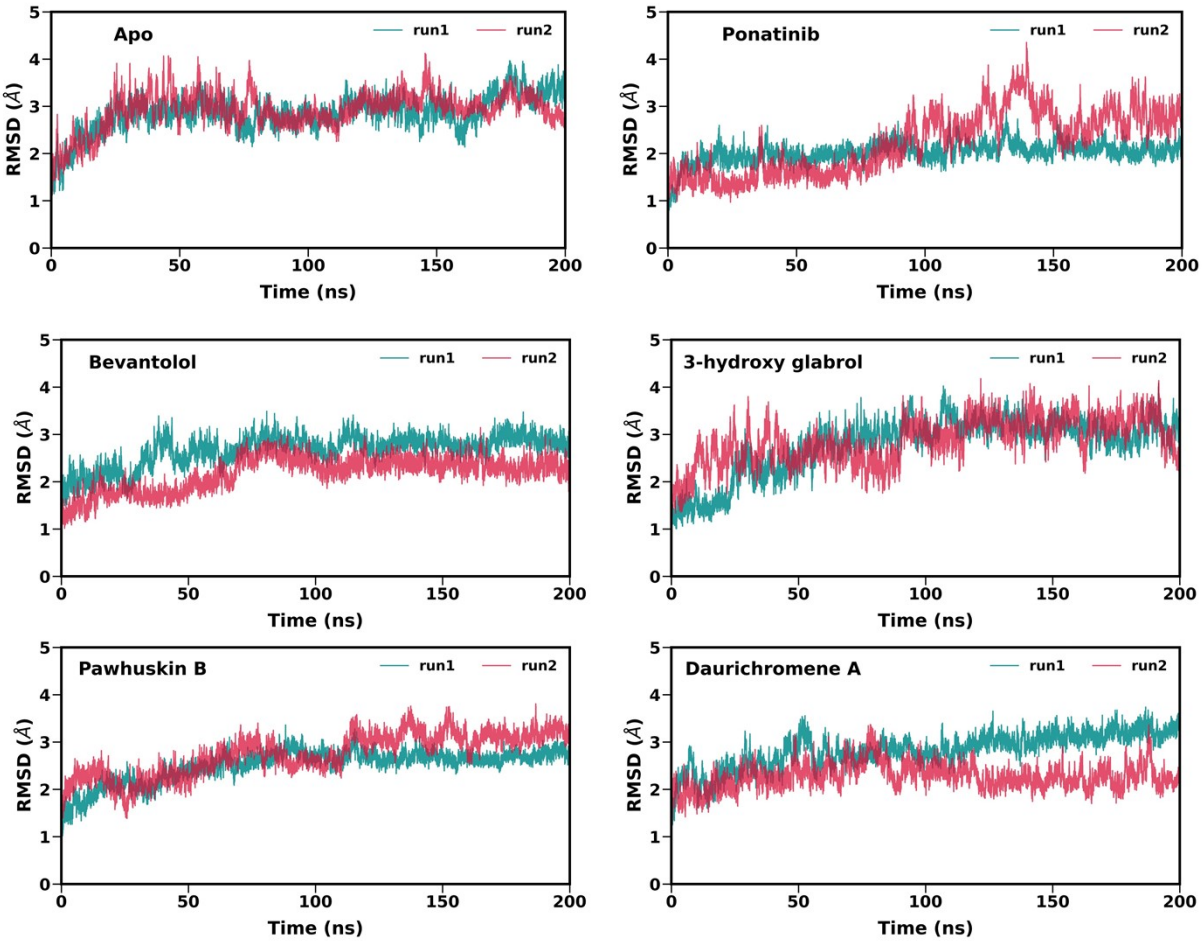


Figure S1: Time evolution of Cα atom RMSD of all the systems investigated in this study.

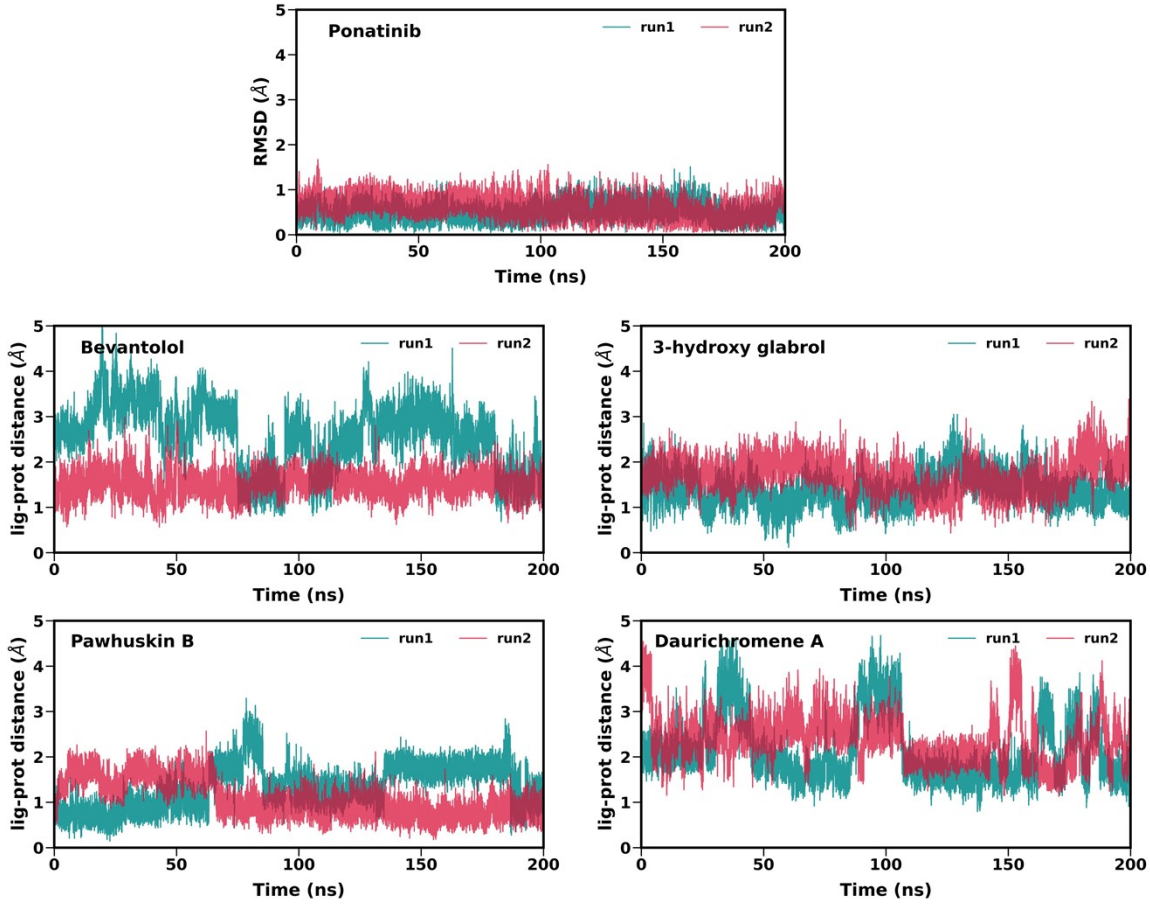


Figure S2: Time evolution of ligand-protein distance in all the complex systems.

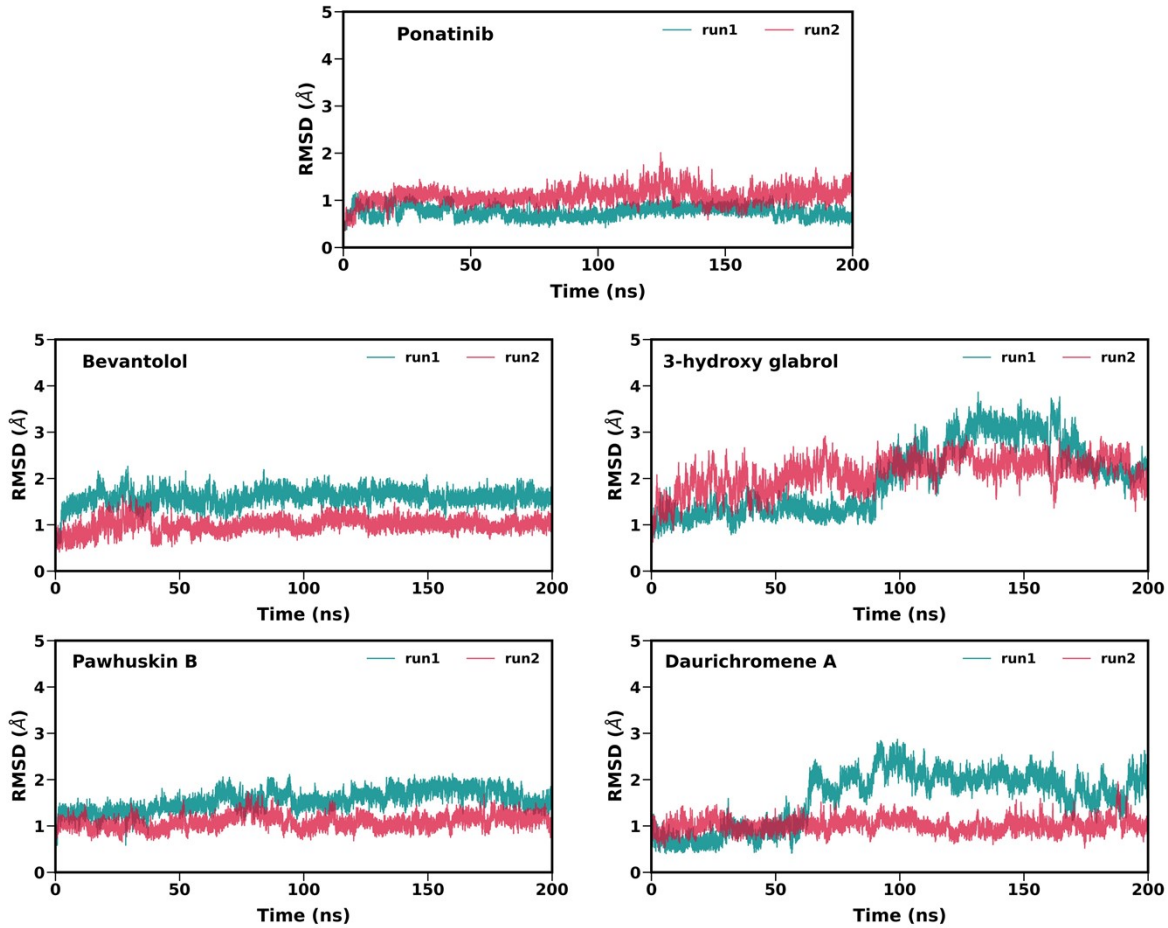


Figure S3: Time evolution of binding pocket RMSD throughout the 200 ns simulation in all the complex systems.

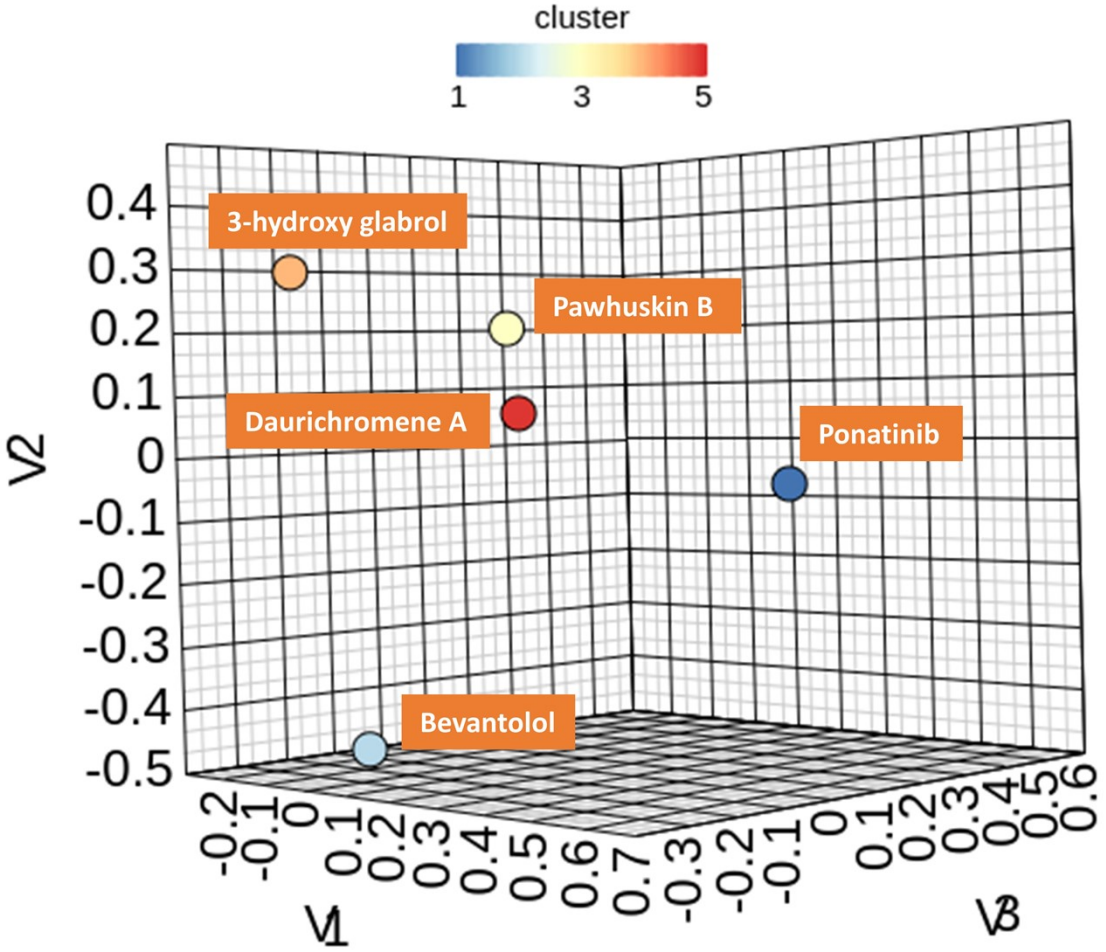


Figure S4: Multidimensional (3D) scaling of selected compounds show high structural diversity. The axes (V1, V2 and V3) defines chemical space in three directions.

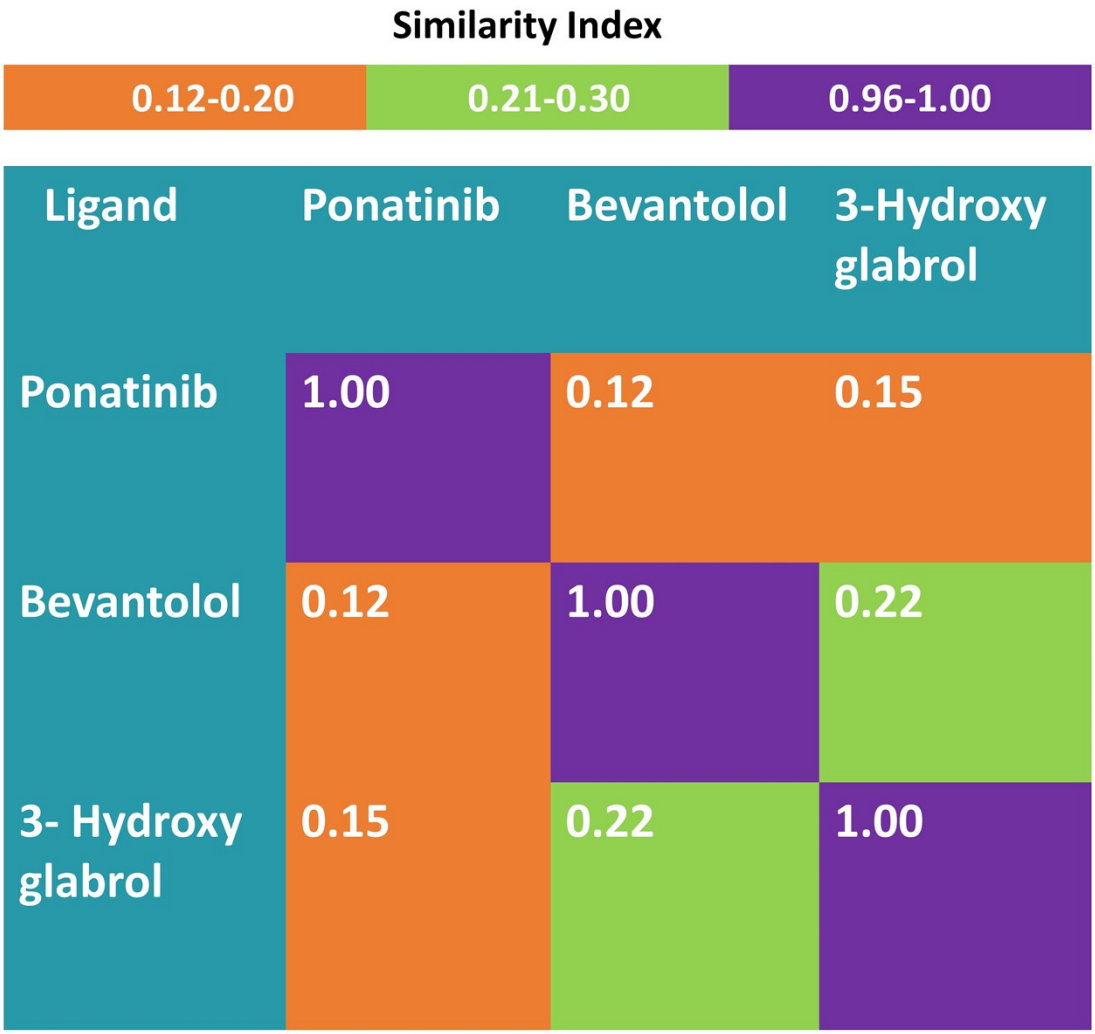


Figure S5: Structural similarity measurement among the selected compounds with control (Ponatinib) determined by the Maximum Common Substructure (MCS) Tanimoto index.

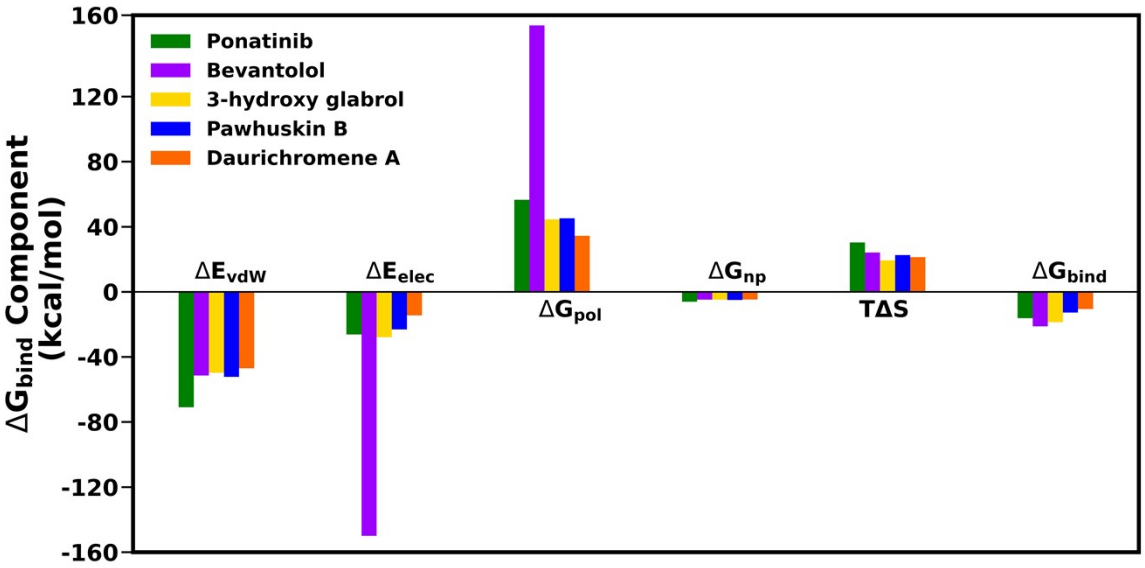


Figure S6: Graphical representation of binding free energy components for all the complex systems.

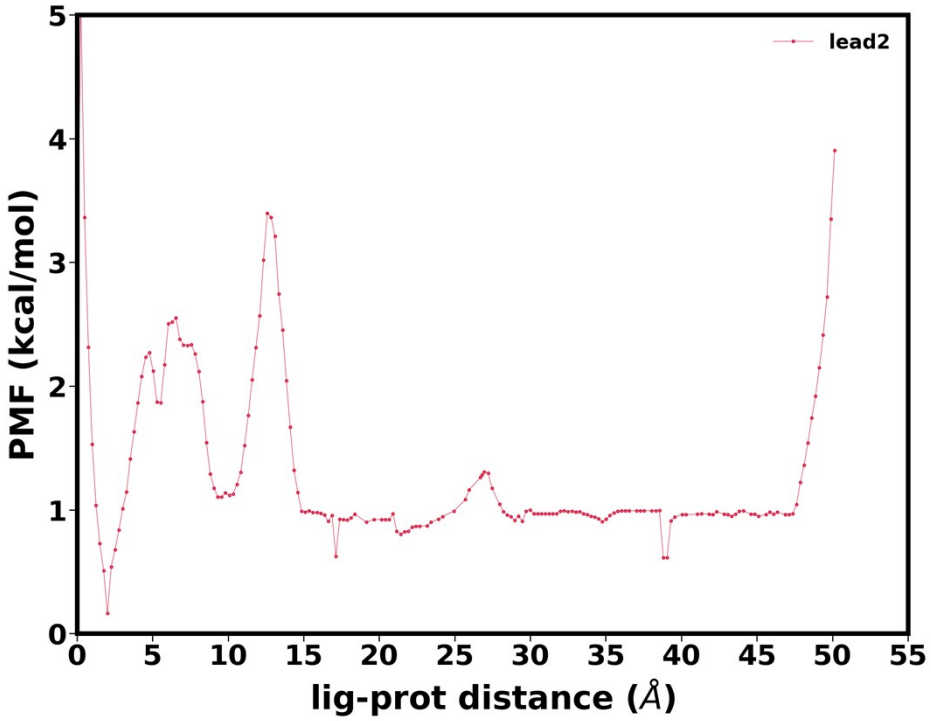


Figure S7: 1D-PMF profile of FGFR1-ligand complex with reaction coordinate ligand-protein distance.

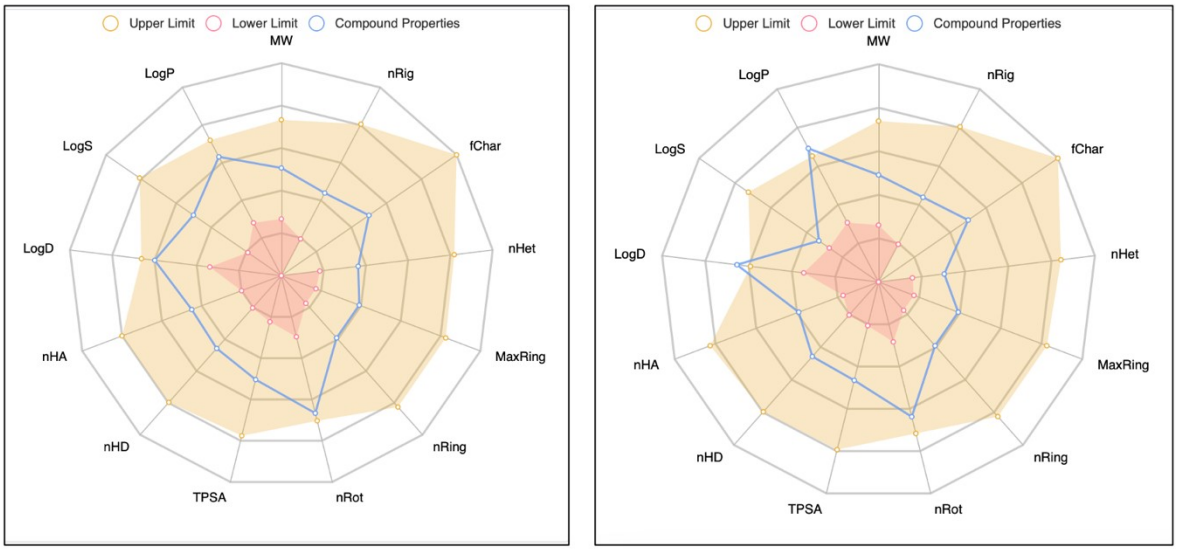


Figure S8: ADMET profile of bevantolol analogue ANLG-1 and ANLG-2 obtained from ADMETlab 2.0.