Supplementary Table I - Obtained QSAR models:

Model 1: pIC50 = -7.7006 + 0.0682 (AATS8i) + 11.2360 (AVP-1) + 0.4122 (MoRSEE17) + 0.4250 (GATSe7)

n_{tr} = 38	n_{pred} = 09	R^2 = 0.6898	R^2adj = 0.6510	R^2–R^2adj = 0.0388	LOF = 0.2304
$RMSE_{tr}$ = 0.2304	MAE_{tr} = 0.1978	RSS_{tr} = 1.9642	CCC_{tr} = 0.8164	s = 0.2478	F = 17.7909
Q_{2LOO} = 0.5779	$Q2_{LMO}$ = 0.5434	R^2_{Yscr} = 0.1104	Q^2_{Yscr} = −0.1947	$RMSE_{cv}$ = 0.2689	MAE_{cv} = 0.2303
$PRESS_{cv}$ = 2.6788	CCC_{cv} = 0.7553	R^2ext = 0.7895	MAE_{ext} = 0.2112	$PRESS_{ext}$ = 0.1830	$RMSE_{ext}$ = 0.4013
CCC_{ext} = 0.8017	Q^2_{F1} = 0.7350	Q^2_{F2} = 0.7214	Q^3_{F3} = 0.7394		

Model 2: pIC50 = -8.2543 + 0.0718 (AATS8i) + 12.11910 (AVP-1) + 0.4828 (MoRSEE17) + 0.3563 (GATSe7)

n_{tr} = 37	n_{pred} = 09	R^2 = 0.6932	R^2_{adj} = 0.6560	R^2-R^2_{adj} = 0.0372	LOF = 0.2311
$RMSE_{tr}$ = 0.2311	MAE_{tr} = 0.1962	RSS_{tr} = 2.0301	CCC_{tr} = 0.8188	s=0.2480	F=18.6405
Q^2_{LOO} = 0.5894	$Q2_{LMO}$ = 0.5613	R^2_{Yscr} = 0.1097	Q^2_{Yscr} = -0.1851	$RMSE_{cv}$ = 0.2674	MAE_{cv} = 0.2270
$PRESS_{cv}$ = 2.7168	CCC_{cv} = 0.7614	R^2_{ext} = 0.7895	MAE_{ext} = 0.2131	$PRESS_{ext}$ = 0.1779	$RMSE_{ext}$ = 0.4089
CCC_{ext} = 0.8017	Q^2_{F1} = 0.7350	Q^2_{F2} = 0.7214	Q^2_{F3} = 0.7394		

Supplementary Table II SWISS ADME:

Molecule	Molecular weight (Daltons)	Heavy atoms	Aromatic Heavy atoms	Rotatable bonds	H-bond acceptors	H-bond donors	Molecular Refractivity
23	286.39	20	11	4	2	1	86.12
63	300.42	21	11	5	2	1	90.93
123	345.41	23	16	5	4	1	92.06
147	373.47	25	16	5	4	1	101.99
149	371.48	25	16	5	4	2	104.06
183	349.45	25	17	5	3	1	104.16
145	461.6	32	22	8	4	1	133.01
154	493.6	34	22	10	6	1	136.07
172	349.45	25	17	6	3	1	104
178	351.42	25	17	5	4	2	101.21
186	365.45	26	17	5	4	2	106.18
194	487.57	35	23	10	6	1	138.19

TPSA	Consensus log P	ESOL Class	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor
70.23	3.74	Moderately soluble	High	Yes	No	Yes	Yes
70.23	4.16	Moderately soluble	High	Yes	No	Yes	Yes
111.36	4.06	Moderately soluble	High	No	No	Yes	Yes
111.36	4.73	Moderately soluble	Low	No	No	Yes	Yes
131.59	4.09	Moderately soluble	Low	No	No	Yes	Yes
83.12	4.29	Moderately soluble	High	No	No	Yes	Yes
120.59	5.6	Poorly soluble	Low	No	Yes	No	Yes
139.05	4.94	Poorly soluble	Low	No	No	No	Yes

83.12	4.28	Moderately soluble	High	No	No	Yes	Yes
103.35	3.65	Moderately soluble	High	No	No	Yes	Yes
103.35	4.01	Moderately soluble	High	No	No	Yes	Yes
110.81	4.86	Poorly soluble	Low	No	No	No	Yes

CYP2C9 inhibitor	**CYP2D6 inhibitor**	**CYP3A4 inhibitor**	**Lipinski violations**	**Bioavailability Score**	**Synthetic Accessibility**
Yes	No	Yes	0	0.55	3.37
Yes	No	Yes	0	0.55	3.48
Yes	No	Yes	0	0.55	3.31
Yes	No	Yes	0	0.55	3.5
Yes	No	Yes	0	0.55	3.56
Yes	No	Yes	0	0.55	3.53
Yes	No	Yes	0	0.55	3.92
Yes	No	Yes	0	0.55	4.05
Yes	No	Yes	0	0.55	3.5
Yes	No	Yes	0	0.55	3.39
Yes	No	Yes	0	0.55	3.55
Yes	No	Yes	0	0.55	4.09

Supplementary Table III Protox II ADME:

ADMET predicted profile --- Classifications	**Value**	**Probability**	**Value**	**Probability**	**Value**	**Probability**
PARAMETER	Compond 1		Compound 2		Compond 3	
Molecular Weight	286		300		345	
AlogP	4		4.4		4.7	
H-Bond Acceptor	4		4		6	
H-Bond Donor	1		1		1	
Rotatable Bonds	4		5		5	
Applicability Domain	In domain		In domain		In domain	

Human Intestinal Absorption	+	0.961	+	0.961	+	0.958
Caco-2	+	0.684	+	0.801	+	0.654
Blood Brain Barrier	+	0.973	+	0.979	+	0.974
Human oral bioavailability	+	0.643	+	0.7	+	0.743
Subcellular localzation	Mitochondria	0.608	Mitochondria	0.658	Mitochondria	0.663
OATP2B1 inhibitior	-	1	-	0.859	-	0.713
OATP1B1 inhibitior	+	0.938	+	0.927	+	0.936
OATP1B3 inhibitior	+	0.948	+	0.945	+	0.947
MATE1 inhibitior	-	0.96	-	0.96	-	1
OCT2 inhibitior	-	0.85	-	0.775	-	0.925
BSEP inhibitior	+	0.661	+	0.769	+	0.837
P-glycoprotein inhibitior	-	0.743	-	0.69	-	0.672
P-glycoprotein substrate	-	0.943	-	0.857	-	0.821
CYP3A4 substrate	-	0.573	-	0.565	+	0.528
CYP2C9 substrate	-	0.6	-	0.6	-	0.6
CYP2D6 substrate	-	0.887	-	0.887	-	0.882
CYP3A4 inhibition	-	0.683	-	0.641	-	0.607
CYP2C9 inhibition	+	0.844	+	0.646	+	0.725
CYP2C19 inhibition	+	0.778	+	0.849	+	0.78
CYP2D6 inhibition	-	0.918	-	0.826	-	0.896
CYP1A2 inhibition	+	0.949	+	0.95	+	0.956
CYP inhibitory promiscuity	+	0.905	+	0.911	+	0.931
UGT catelyzed	-	0	-	0	-	0
Carcinogenicity (binary)	-	0.771	-	0.771	-	0.771
Carcinogenicity (trinary)	Danger	0.438	Warning	0.363	Non-required	0.43
Eye corrosion	-	0.991	-	0.988	-	0.985
Eye irritation	-	0.894	-	0.936	-	0.967
Ames mutagenesis	-	0.74	-	0.68	-	0.64
Human either-a-go-go inhibition	+	0.658	+	0.729	+	0.754
micronuclear	+	0.82	+	0.8	+	0.91
Hepatotoxicity	+	0.825	+	0.775	+	0.85
Acute Oral Toxicity (c)	IV	0.772	III	0.677	III	0.534
Estrogen receptor binding	+	0.699	+	0.772	+	0.932

Androgen receptor binding	+	0.64	+	0.711	+	0.758
Thyroid receptor binding	+	0.744	+	0.845	+	0.519
Glucocorticoid receptor binding	-	0.53	+	0.629	+	0.902
Aromatase binding	+	0.759	+	0.803	+	0.851
PPAR gamma	+	0.618	+	0.681	+	0.7
Honey bee toxicity	+	0.605	-	0.517	-	0.649
Biodegradation	-	0.85	-	0.85	-	0.925
crustacea aquatic toxicity	-	0.57	-	0.61	-	0.56
Fish aquatic toxicity	+	0.818	+	0.852	+	0.963
ADMET predicted profile --- Regressions	**Value**	**Unit**	**Value**	**Unit**	**Value**	**Unit**
Water solubility	-3.303	logS	-3.526	logS	-3.616	logS
Plasma protein binding	0.568	100%	0.584	100%	0.78	100%
Acute Oral Toxicity	2.524	kg/mol	2.587	kg/mol	2.156	kg/mol
Tetrahymena pyriformis	0.923	pIGC50 (ug/L)	0.999	pIGC50 (ug/L)	0.659	pIGC50 (ug/L)
Hepatotoxicity	**Active**	**0.59**	**Inactive**	**0.56**	**Active**	**0.61**
Carcinogenicity	**Active**	**0.5**	**Active**	**0.52**	**Inactive**	**0.52**
Immunotoxicity	**Inactive**	**0.97**	**Inactive**	**0.54**	**Inactive**	**0.83**
Mutagenicity	**Inactive**	**0.55**	**Inactive**	**0.59**	**Inactive**	**0.53**
Cytotoxicity	**Inactive**	**0.78**	**Inactive**	**0.69**	**Inactive**	**0.68**

Value	**Probability**	**Value**	**Probability**	**Value**	**Probability**
Compond 4		Compond 5		Compond 6	
373		371		349	
5.3		4.9		5.1	
6		7		5	
1		2		1	
5		5		5	
In domain		In domain		In domain	
+	0.958	+	0.955	+	0.9627
+	0.513	+	0.516	+	0.5993
+	0.975	+	0.968	+	0.9729
+	0.743	+	0.671	+	0.7

Mitochondria	0.671	Mitochondria	0.716	Mitochondria	0.6851
-	0.856	-	0.567	-	0.7081
+	0.947	+	0.898	+	0.9504
+	0.945	+	0.942	+	0.9467
-	1	-	0.92	-	0.96
-	0.875	-	0.875	-	0.8
+	0.872	+	0.802	+	0.9424
-	0.571	-	0.63	+	0.6592
-	0.771	-	0.719	-	0.8841
+	0.5	+	0.564	-	0.5
-	0.6	-	0.6	-	0.789
-	0.882	-	0.881	-	0.8865
-	0.537	+	0.729	-	0.6089
+	0.68	+	0.747	+	0.7012
+	0.759	+	0.666	+	0.8839
-	0.899	-	0.867	-	0.8527
+	0.925	+	0.758	+	0.8787
+	0.927	+	0.775	+	0.9256
-	0	+	0.8	-	0
-	0.771	-	0.757	-	0.7714
Danger	0.397	Non-required	0.367	Danger	0.5749
-	0.987	-	0.991	-	0.9925
-	0.945	-	0.937	-	0.9469
-	0.6	-	0.62	-	0.73
-	0.391	-	0.472	+	0.6736
+	0.87	+	0.88	+	0.83
+	0.825	+	0.825	+	0.8
III	0.595	III	0.704	III	0.7686
+	0.92	+	0.925	+	0.9173
+	0.77	+	0.762	+	0.7992
+	0.828	+	0.701	+	0.7731
+	0.693	+	0.779	+	0.6976
+	0.833	+	0.841	+	0.8071
+	0.76	+	0.705	+	0.7978
-	0.541	+	0.638	-	0.5571
-	0.925	-	0.9	-	0.9

-	0.61	-	0.61	-	0.56
+	0.971	+	0.938	+	0.8723
Value	**Unit**	**Value**	**Unit**	**Value**	**Unit**
-4.088	logS	-3.764	logS	-3.905	logS
1.026	100%	0.903	100%	0.731	100%
2.149	kg/mol	2.192	kg/mol	2.337	kg/mol
0.678	pIGC50 (ug/L)	0.873	pIGC50 (ug/L)	0.844	pIGC50 (ug/L)
Active	**0.69**	**Inactive**	**0.54**	**Active**	**0.55**
Active	**0.5**	**Active**	**0.52**	**Active**	**0.53**
Active	**0.62**	**Active**	**0.55**	**Active**	**0.51**
Inactive	**0.55**	**Inactive**	**0.57**	**Inactive**	**0.52**
Inactive	**0.71**	**Inactive**	**0.65**	**Inactive**	**0.79**

Value	**Probability**	**Value**	**Probability**	**Value**	**Probability**
Compond 7		Compond 8		Compond 9	
462		494		349	
6.7		6.1		5.1	
7		9		5	
1		1		1	
8		10		6	
In domain		In domain		In domain	
+	0.9638	+	0.9638	+	0.9625
-	0.6605	-	0.6645	+	0.6411
+	0.9769	+	0.9722	+	0.9763
-	0.5	+	0.5286	+	0.6
Mitochondria	0.8206	Mitochondria	0.7442	Mitochondria	0.6699
-	0.7148	-	1	-	0.7114
+	0.9257	+	0.9268	+	0.9356
+	0.9398	+	0.9399	+	0.9456
-	1	-	1	-	0.96
-	0.65	-	0.825	-	0.8
+	0.9768	+	0.9653	+	0.8981
+	0.7557	+	0.8572	-	0.482
-	0.7891	-	0.7094	-	0.7883
+	0.5779	+	0.6109	+	0.5322
-	0.6	-	0.6	-	0.5942

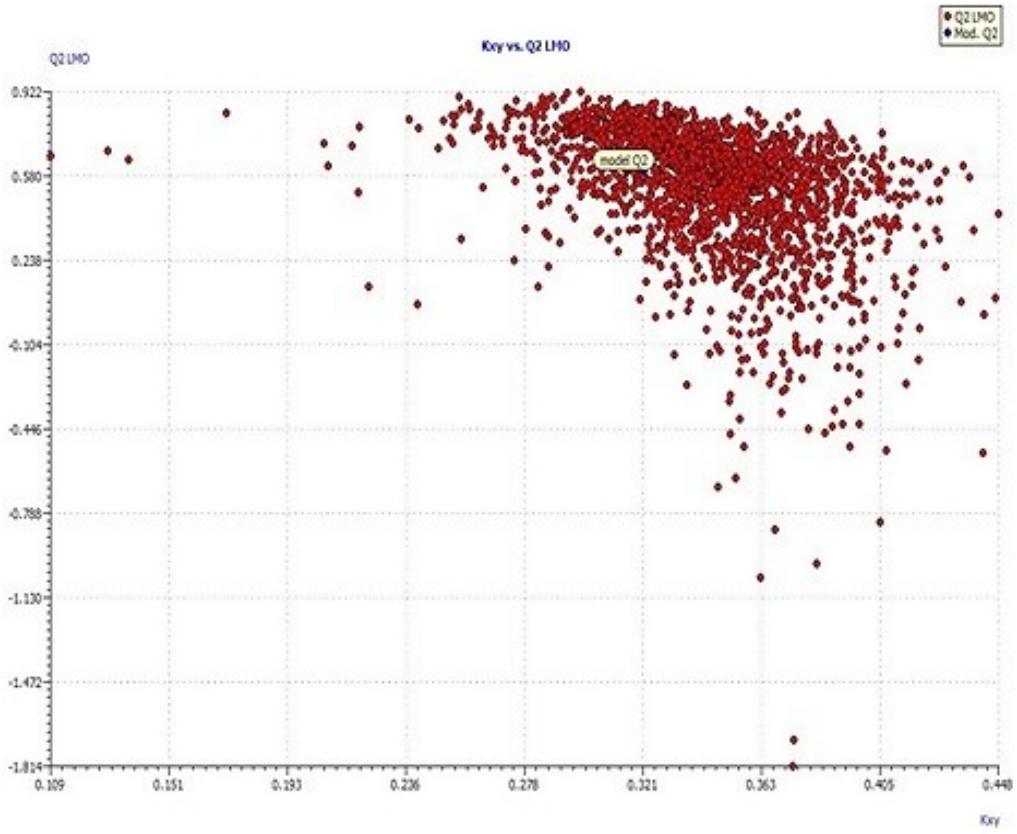
-	0.8727	-	0.8727	-	0.8724
+	0.8006	+	0.8503	-	0.7079
+	0.8399	+	0.6975	+	0.6767
+	0.9292	+	0.8775	+	0.8968
-	0.7007	-	0.8133	-	0.8013
+	0.9058	+	0.8064	+	0.9132
+	0.9789	+	0.9533	+	0.9475
-	0	-	0	-	0
-	0.8031	-	0.8031	-	0.8571
Danger	0.3617	Non-required	0.3773	Danger	0.4261
-	0.9906	-	0.9893	-	0.9921
-	0.9509	-	0.9487	-	0.9514
-	0.68	-	0.7	-	0.73
+	0.8999	+	0.8772	+	0.9645
+	0.79	+	0.85	+	0.86
+	0.825	+	0.85	+	0.925
III	0.7117	III	0.6233	III	0.7156
+	0.8869	+	0.8851	+	0.9386
+	0.8805	+	0.884	+	0.8396
+	0.7752	+	0.75	+	0.7441
+	0.7686	+	0.8394	+	0.8069
+	0.7135	+	0.5225	+	0.785
+	0.8322	+	0.7327	+	0.828
+	0.5821	+	0.6226	-	0.6079
-	0.925	-	0.85	-	0.975
-	0.57	-	0.51	-	0.54
+	0.9785	+	0.9719	+	0.8932
Value	**Unit**	**Value**	**Unit**	**Value**	**Unit**
-4.775	logS	-4.281	logS	-3.92	logS
0.941	100%	1.004	100%	0.624	100%
2.799	kg/mol	2.352	kg/mol	2.271	kg/mol
1.043	pIGC50 (ug/L)	1.181	pIGC50 (ug/L)	1.009	pIGC50 (ug/L)
Active	**0.55**	**Active**	**0.58**	**Active**	**0.61**
Active	**0.54**	**Active**	**0.52**	**Active**	**0.51**
Inactive	**0.77**	**Active**	**0.52**	**Active**	**0.79**

Active	0.51	Inactive	0.56	Inactive	0.55
Inactive	0.66	Inactive	0.69	Inactive	0.74

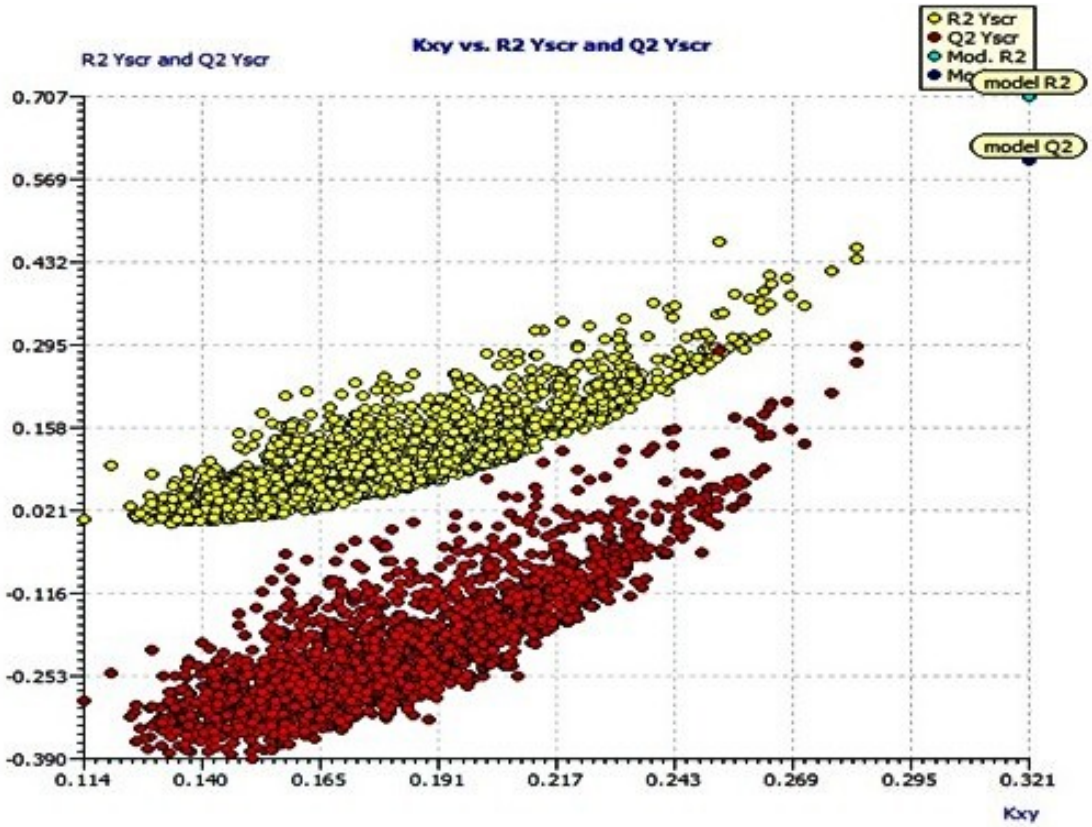
Value	Probability	Value	Probability	Value	Probability
Compond 10		Compond 11		Compond 12	
351		365		365	
4.5		4.8		4.8	
6		6		6	
2		2		2	
5		5		5	
In domain		In domain		In domain	
+	0.9568	+	0.9568	+	0.9568
+	0.5916	+	0.5	+	0.5
+	0.9715	+	0.9715	+	0.9715
+	0.5429	+	0.5857	+	0.5857
Mitochondria	0.7303	Mitochondria	0.7015	Mitochondria	0.7015
-	0.7063	-	0.5659	-	0.5659
+	0.9481	+	0.9038	+	0.9038
+	0.9434	+	0.9413	+	0.9413
-	0.92	-	0.92	-	0.92
-	0.825	-	0.825	-	0.825
+	0.8646	+	0.9085	+	0.9085
-	0.6164	-	0.4442	-	0.4442
-	0.8329	-	0.7841	-	0.7841
+	0.5348	+	0.575	+	0.575
-	0.7934	-	0.7934	-	0.7934
-	0.8808	-	0.8808	-	0.8808
+	0.6514	+	0.7574	+	0.7574
+	0.7049	+	0.7684	+	0.7684
+	0.7853	+	0.8054	+	0.8054
-	0.7626	-	0.7897	-	0.7897
+	0.6606	+	0.6144	+	0.6144
+	0.7544	+	0.7788	+	0.7788
-	0.6	+	0.6	+	0.6
-	0.7571	-	0.7571	-	0.7571
Danger	0.4279	Danger	0.4579	Danger	0.4579
-	0.9922	-	0.9919	-	0.9919

-	0.9443	-	0.9534	-	0.9534
-	0.65	-	0.62	-	0.62
-	0.4425	-	0.585	-	0.585
+	0.89	+	0.87	+	0.87
+	0.775	+	0.775	+	0.775
III	0.6652	III	0.6656	III	0.6656
+	0.8973	+	0.9385	+	0.9385
+	0.9155	+	0.8307	+	0.8307
+	0.7879	+	0.7456	+	0.7456
+	0.7828	+	0.8015	+	0.8015
+	0.8156	+	0.8049	+	0.8049
+	0.8215	+	0.7983	+	0.7983
-	0.5307	+	0.5248	+	0.5248
-	0.95	-	0.9	-	0.9
-	0.64	+	0.51	+	0.51
+	0.9071	+	0.9159	+	0.9159
Value	**Unit**	**Value**	**Unit**	**Value**	**Unit**
-3.963	logS	-4.197	logS	-4.197	logS
0.747	100%	0.861	100%	0.861	100%
2.58	kg/mol	2.311	kg/mol	2.311	kg/mol
0.789	pIGC50 (ug/L)	0.96	pIGC50 (ug/L)	0.96	pIGC50 (ug/L)
Active	**0.63**	**Inactive**	**0.59**	**Active**	**0.57**
Active	**0.59**	**Active**	**0.52**	**Inactive**	**0.5**
Active	**0.97**	**Active**	**0.96**	**Inactive**	**0.78**
Inactive	**0.54**	**Inactive**	**0.5**	**Inactive**	**0.52**
Inactive	**0.68**	**Inactive**	**0.73**	**Inactive**	**0.71**

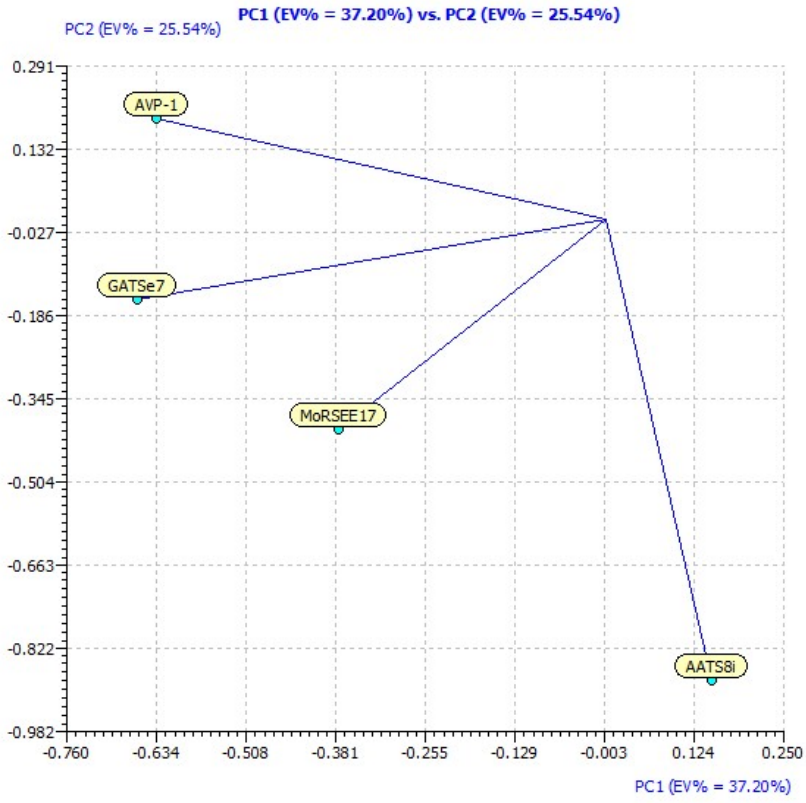
Supplementary figure 1 model 3 LMO plot



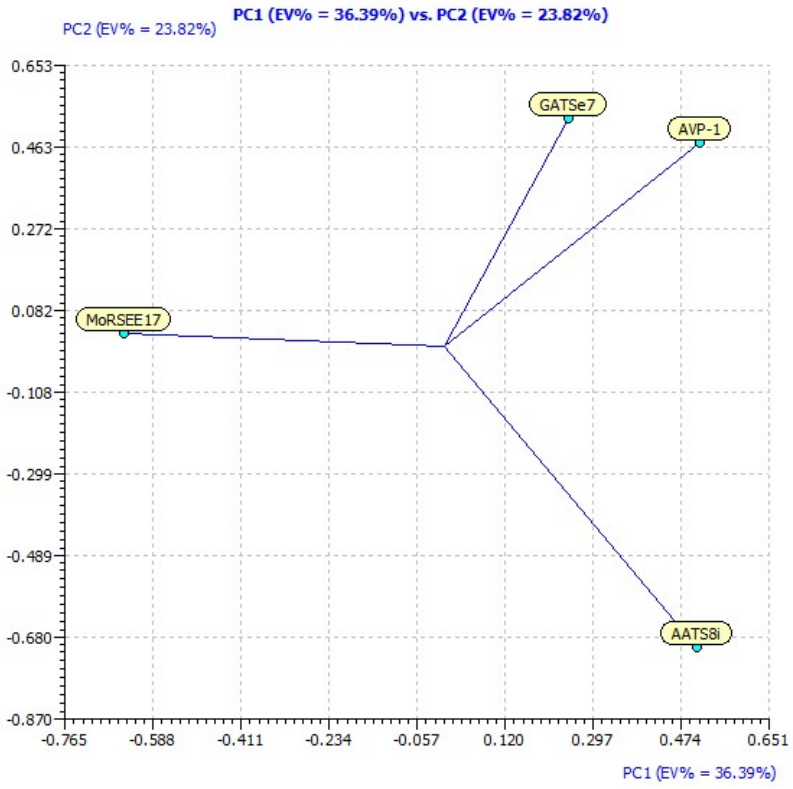
Supplementary figure 2 model 3 Y-scrambles plot



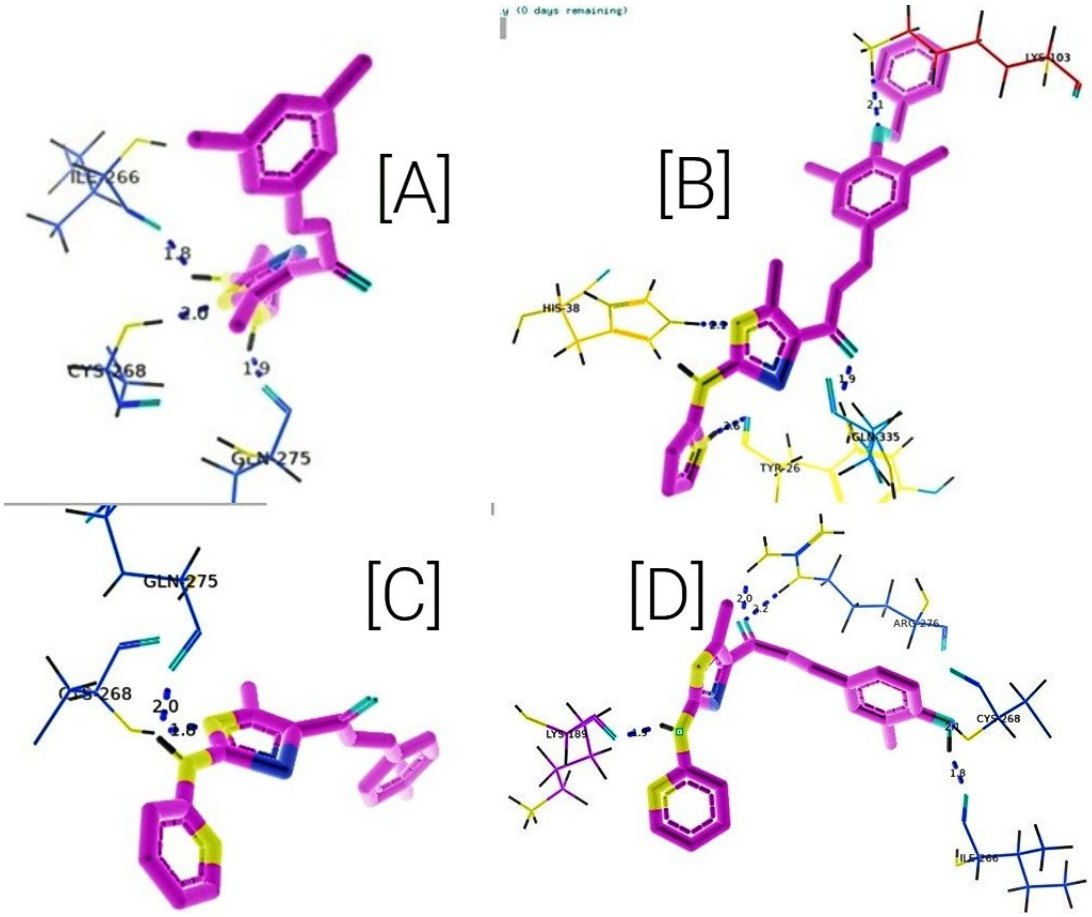
Supplementary figure 3 PCA loading plot model 3 with descriptor names



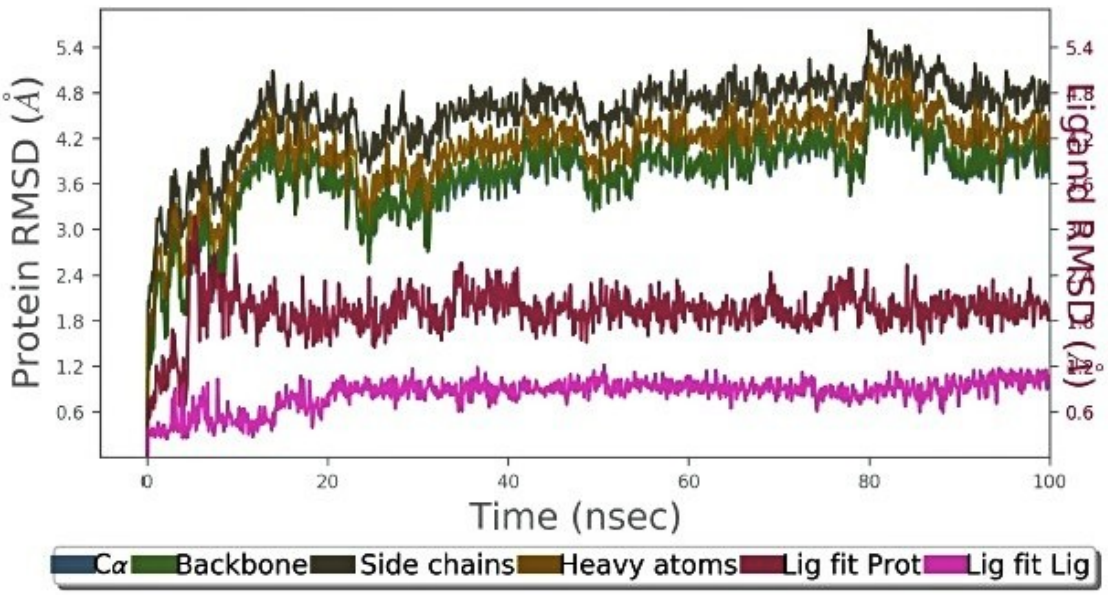
Supplementary figure 4 loading plot for designed and dataset compounds



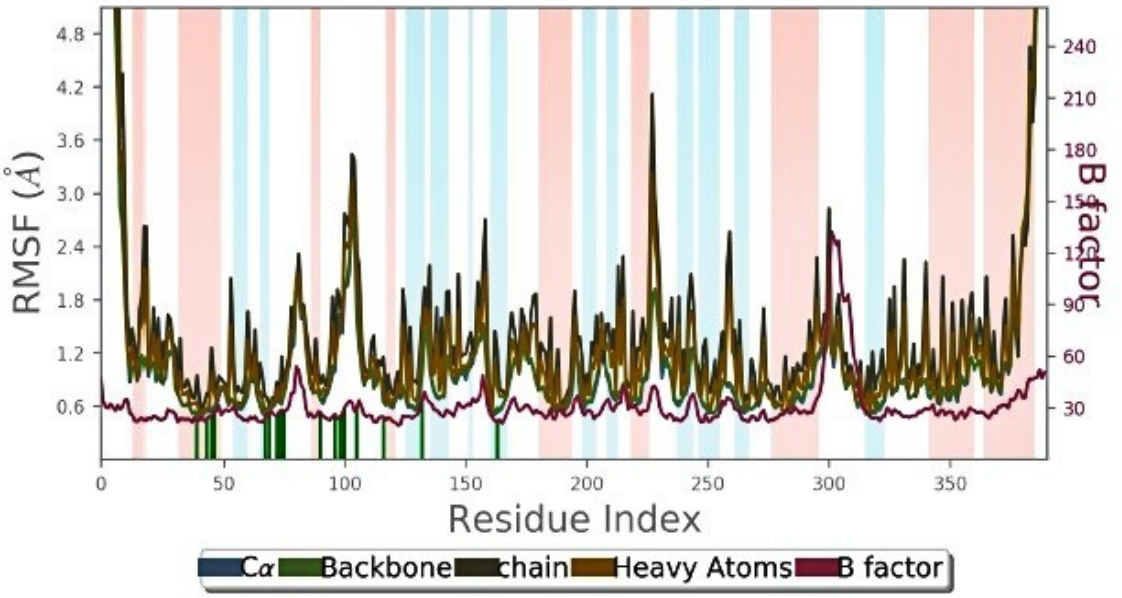
Supplementary figures 5a to 5d docking images combined



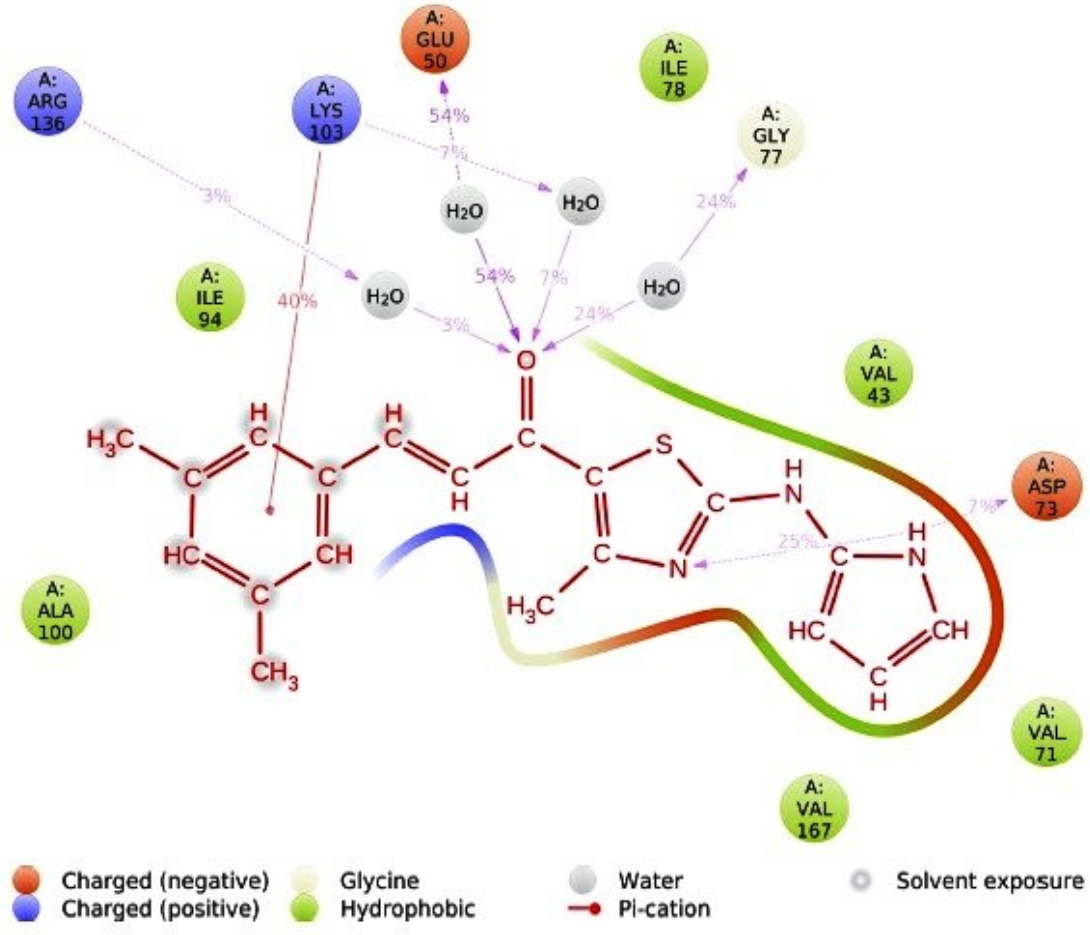
Supplementary Fig 6a RMSD graph of ligand 143 with 6J90



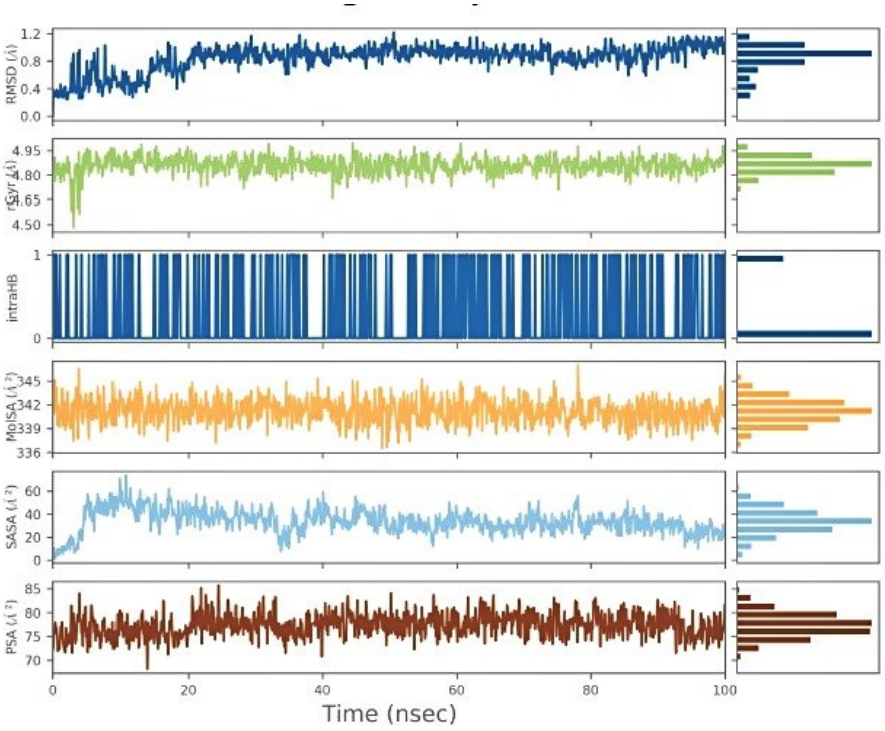
Supplementary Fig 6b RMSF graph ligand 143 with 6J90



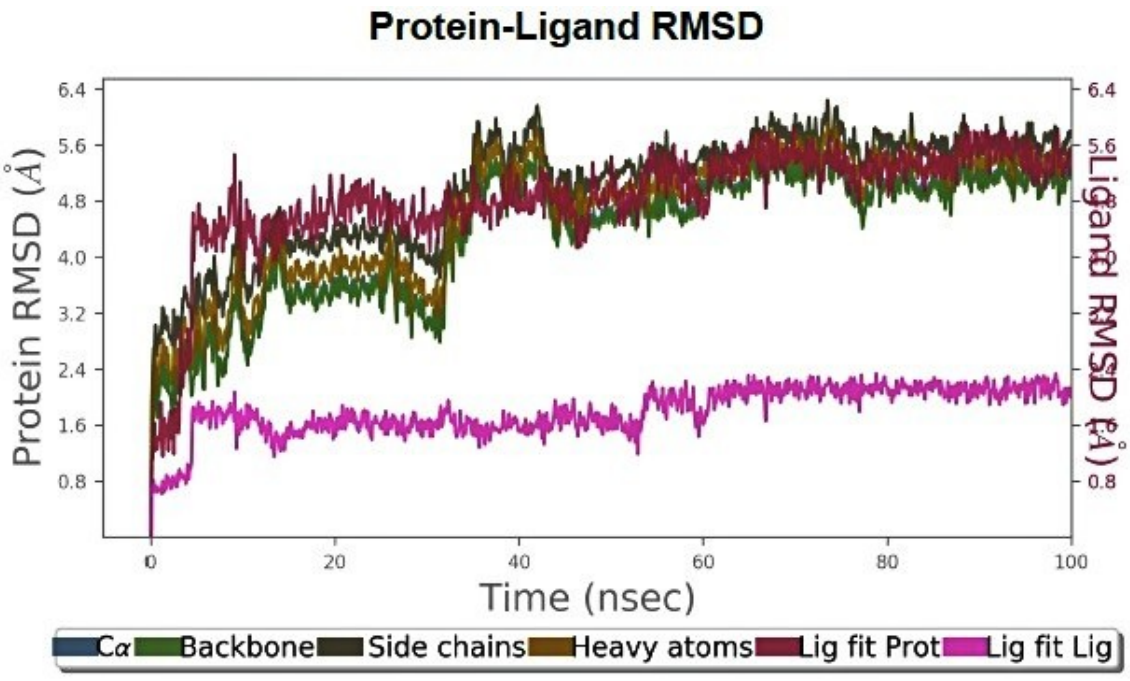
Supplementary Fig 6c Hbond contacts ligand 143 with 6J90



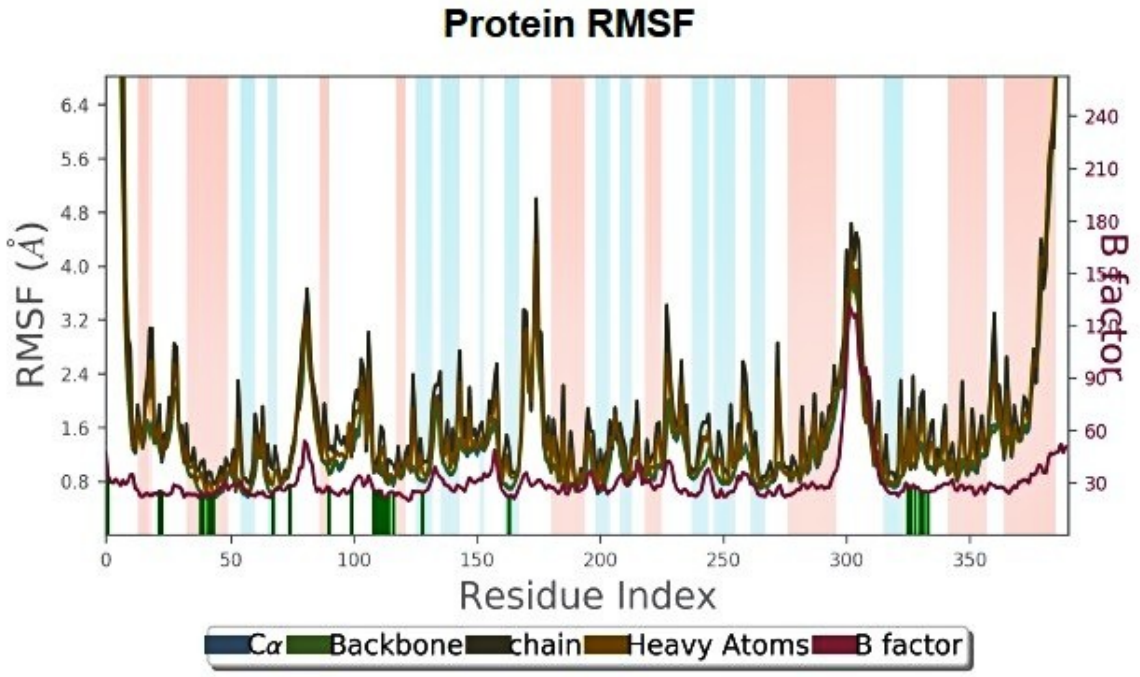
Supplementary Fig 6d Surface analysis ligand 143 with 6J90



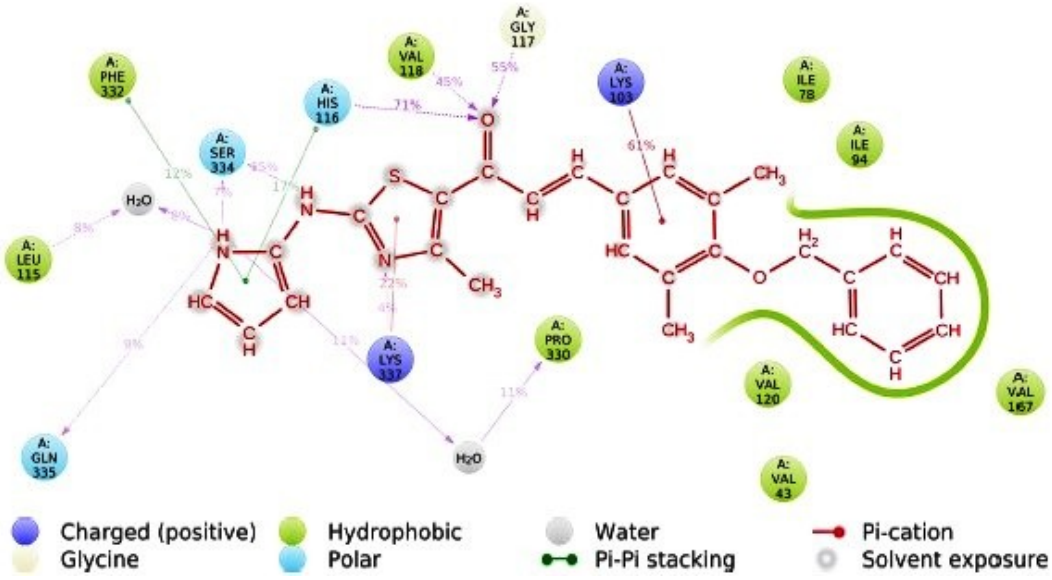
Supplementary Fig 7a RMSD graph of ligand 145 with 6J90



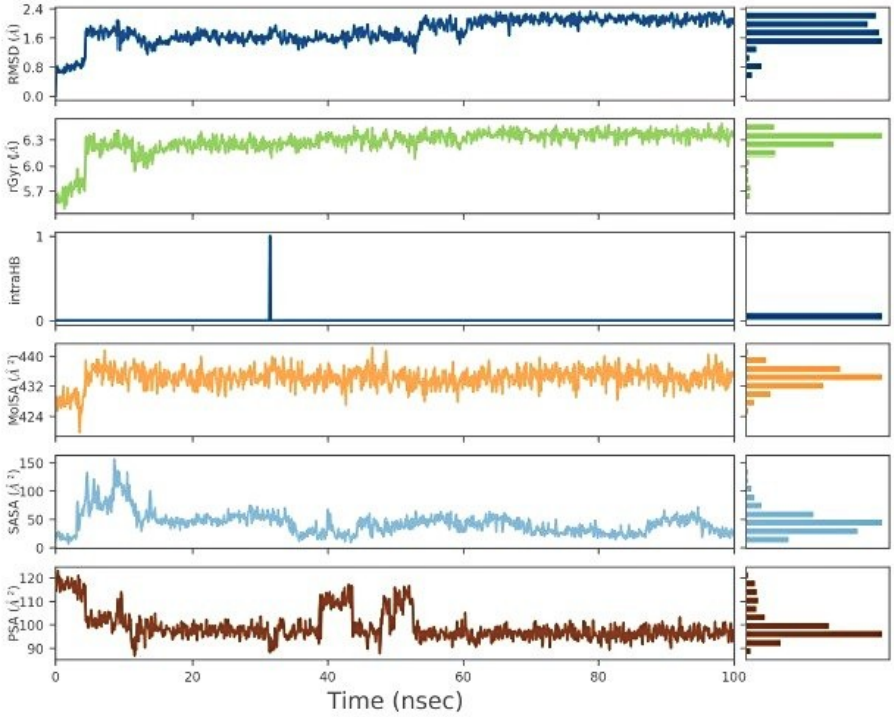
Supplementary Fig 7b RMSF graph ligand 145 with 6J90



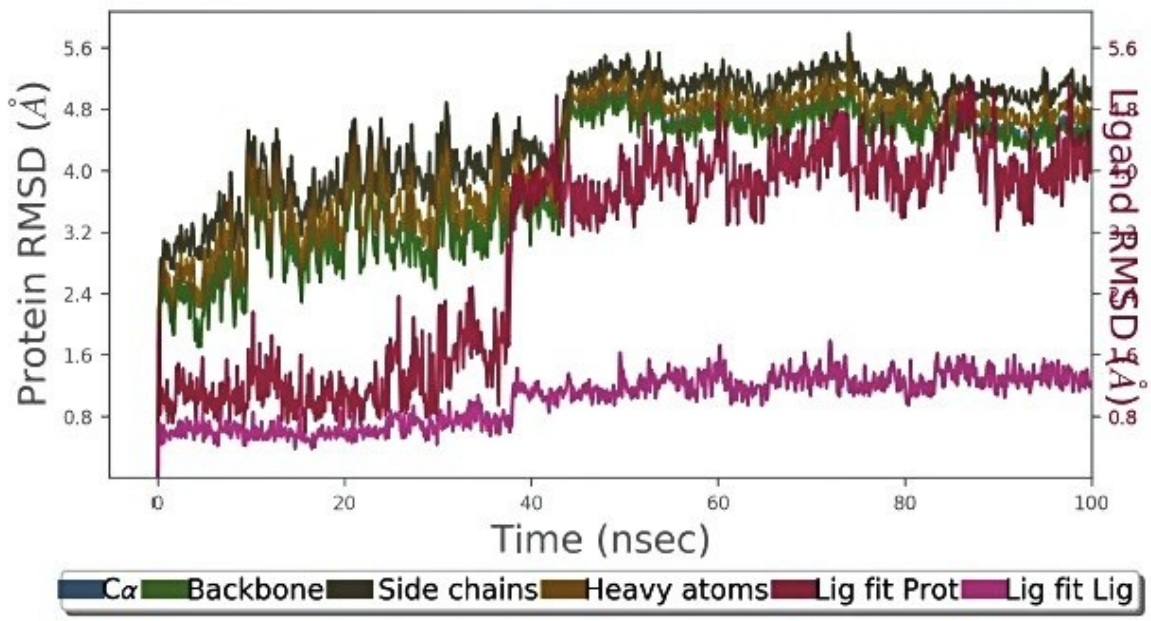
Supplementary Fig 7c Hbond contacts ligand 145 with 6J90



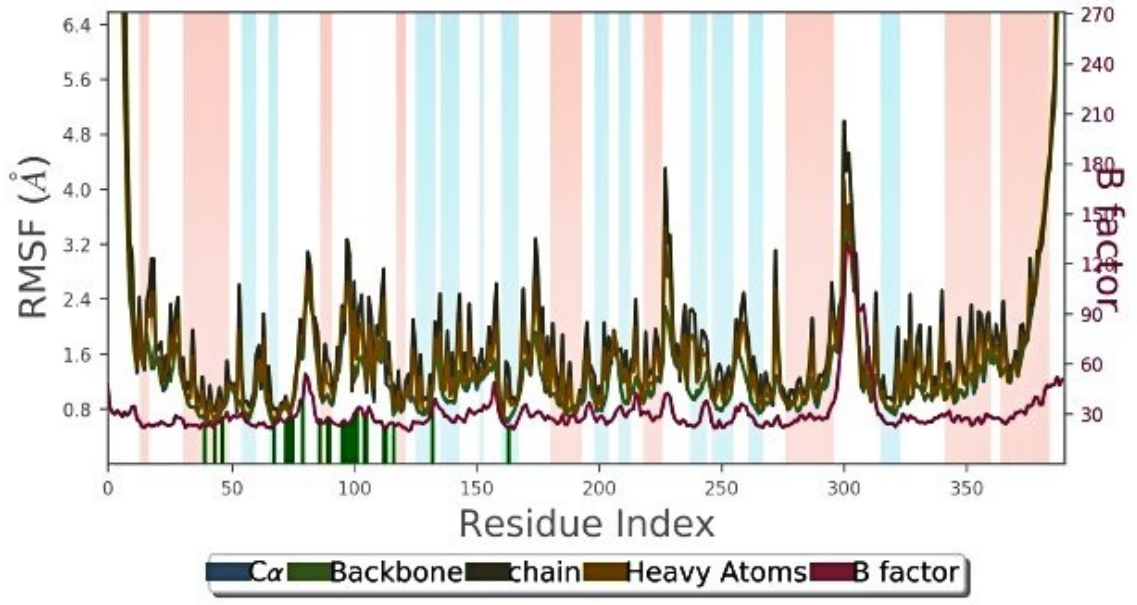
Supplementary Fig 7d Surface analysis ligand 145 with 6J90



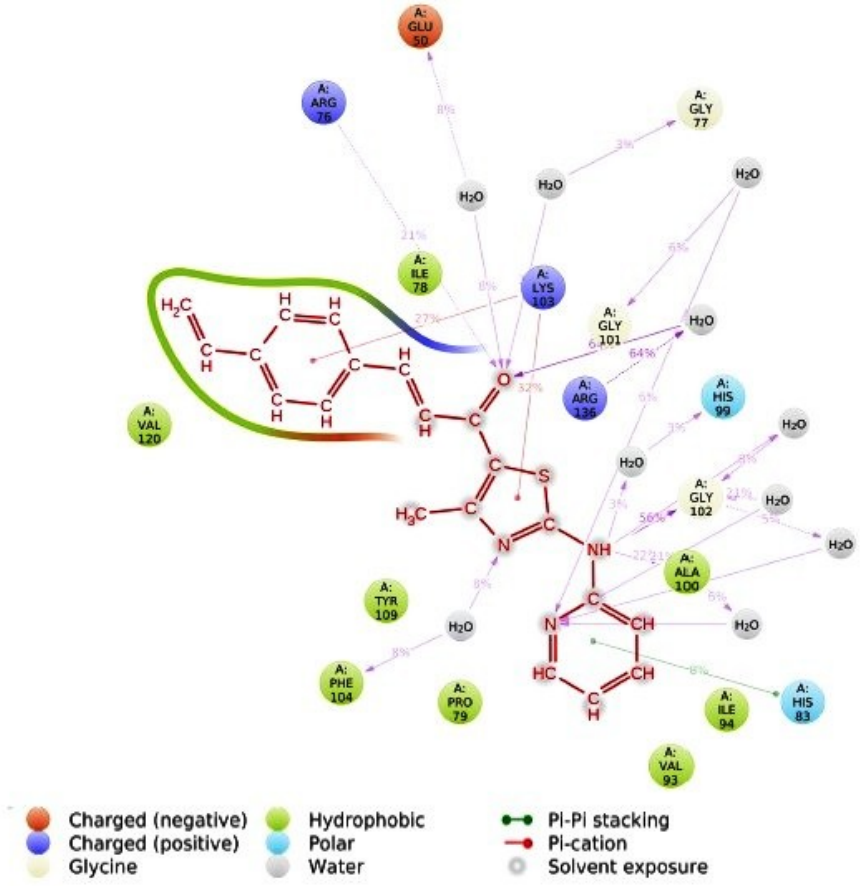
Supplementary Fig 8a RMSD graph of ligand 172 with 6J90



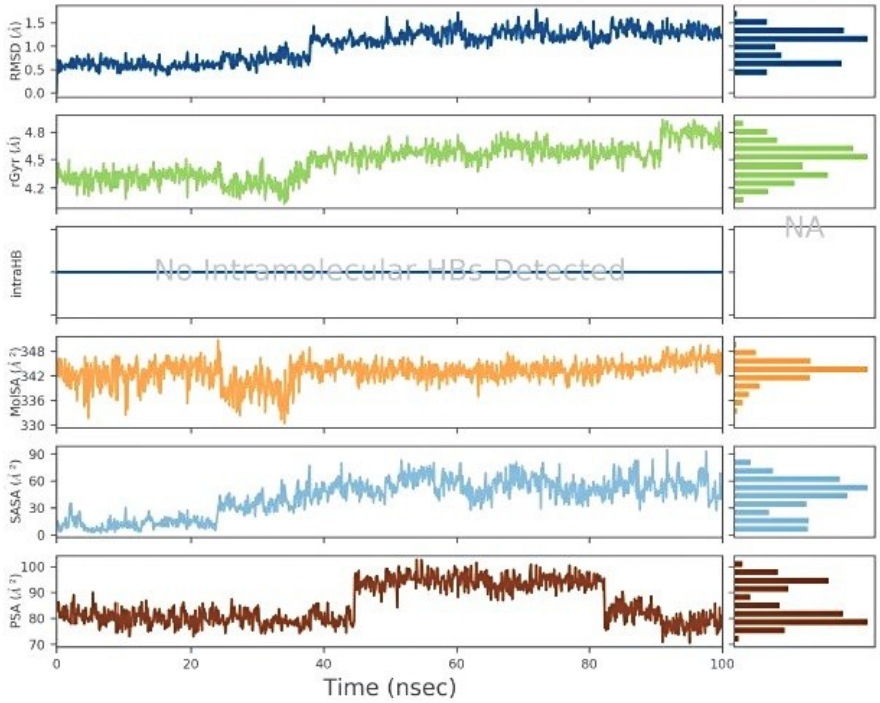
Supplementary Fig 8b RMSF graph ligand 172 with 6J90



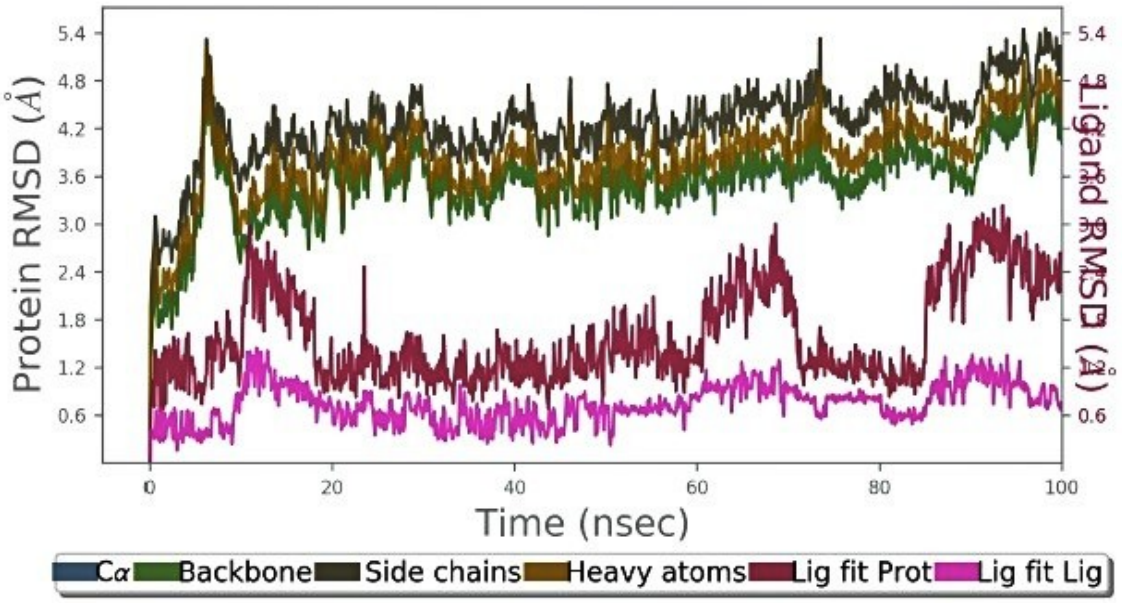
Supplementary Fig 8c Hbond contacts ligand 172 with 6J90



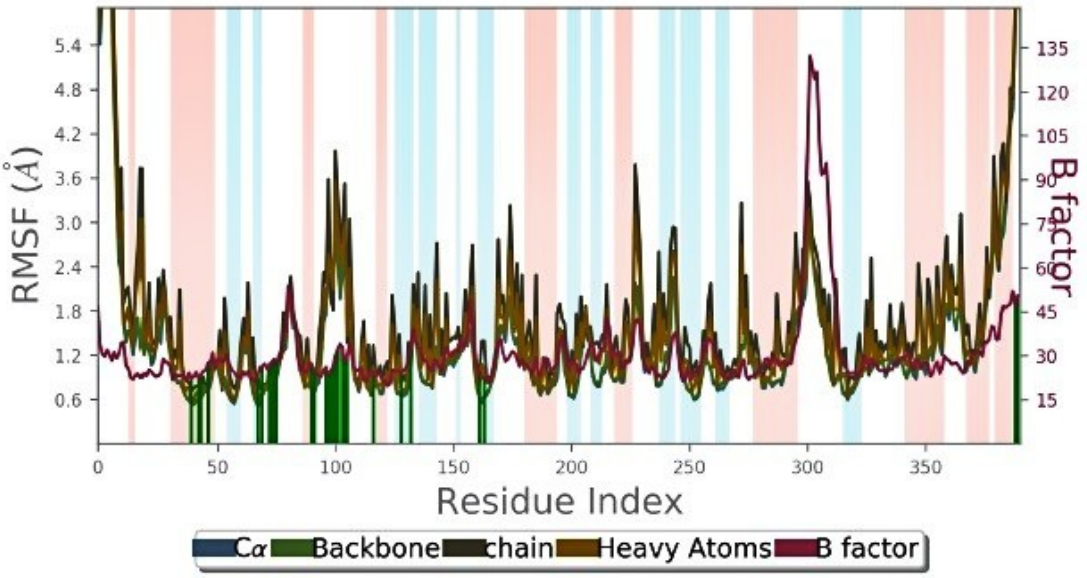
Supplementary Fig 8d Surface analysis ligand 172 with 6J90



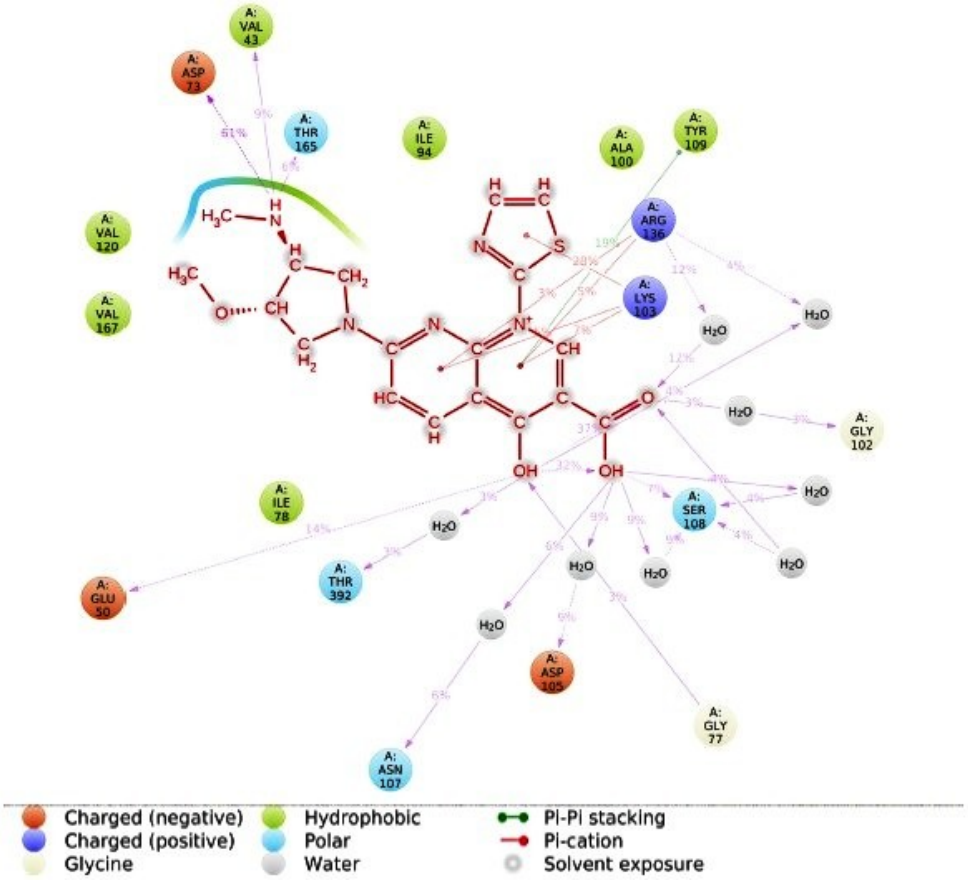
Supplementary Fig 9a RMSD graph of reference compound with 6J90



Supplementary Fig 9b RMSF graph reference compound with 6J90



Supplementary Fig 9c Hbond contacts reference compound with 6J90



Supplementary Fig 9d Surface analysis of reference compound with 6J90