Dual inhibitors of c-MET and EGFR in triple negative breast cancer: pharmacophore modeling and molecular dynamics based *in silico* drug repositioning

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Table S1. pharmacophore model hypothesis and validation of c-Met active site

No.	Hypothesis	Phase Hypo Score	EF1%	BEDROC160.9	ROC
1	ARR_4	0.15	44.6	0.73	0.9
2	ARR_3	0.15	21.7	0.35	0.87
3	ARR_1	0.16	2.41	0.03	0.84
4	ARR_6	0.13	1.81	0.03	0.83
5	ARR_5	0.13	3.01	0.04	0.81
6	ARR_2	0.16	7.84	0.16	0.81
7	AAAR_5	0.13	1.21	0.03	0.71
8	AAR_2	0.15	7.23	0.14	0.7
9	AAR_1	0.15	0.6	0.01	0.66
10	AAAR_2	0.14	5.42	0.1	0.64
11	AARR_2	0.15	4.82	0.06	0.63
12	AAR_3	0.13	0.6	0.02	0.59
13	AAAR_7	0.12	1.21	0.02	0.58
14	AAR_4	0.13	1.81	0.02	0.57
15	AAAR_1	0.14	3.01	0.05	0.56
16	AARR_1	0.15	1.81	0.05	0.54
17	AAAR_6	0.13	0	0	0.51
18	AAAR_8	0.12	2.41	0.03	0.36
19	AAAR_4	0.14	3.62	0.05	0.27
20	AAAR_3	0.14	0	0	0.24

- (A) acceptor, (R) aromatic Ring

Table S2 pharmacophore model validation of EGFR

No.	Hypothesis	Phase Hypo Score	EF1%	BEDROC160.9	ROC
1	ADHHRRR_1	0.36	27.09	0.5	0.81
2	ADHHRRR_2	0.36	26.54	0.49	0.81
3	ADHHRRR_4	0.36	21.01	0.41	0.8
4	ADHHRRR_3	0.36	20.64	0.41	0.8
5	DDHHRRR_2	0.36	24.7	0.46	0.78
6	DDHHRRR_1	0.36	23.78	0.45	0.78
7	AHHRRR_2	0.31	21.56	0.42	0.75
8	AHHRRR_1	0.31	21.38	0.43	0.75
9	DHHHRRR_1	0.36	19.72	0.39	0.74
10	HRR_2	0.21	20.46	0.38	0.71
11	HRR_1	0.21	20.46	0.38	0.71
12	DHHRRR_2	0.31	17.14	0.35	0.69
13	DHHRRR_1	0.31	17.32	0.35	0.69
14	ADHHRR_2	0.31	20.09	0.4	0.68
15	ADHHRR_1	0.31	20.27	0.41	0.68
16	DDHHHRR_3	0.36	14.01	0.29	0.66
17	DDHHRR_4	0.32	13.27	0.26	0.65
18	DDHHRR_3	0.32	12.9	0.26	0.65
19	DDHHHRR_1	0.36	15.67	0.31	0.65
20	DDHHHRR_2	0.36	19.72	0.39	0.64
21	DDHHRR_2	0.32	16.96	0.34	0.6
22	DDHHRR_1	0.32	15.85	0.33	0.6
23	DHR_2	0.21	15.67	0.31	0.54
24	DHR_1	0.21	15.48	0.31	0.54
25	DHRR_2	0.24	16.59	0.34	0.54
26	DHRR_1	0.24	15.48	0.34	0.54
27	AHHRR_4	0.28	10.69	0.21	0.47
28	AHHRR_3	0.28	10.51	0.22	0.47
29	AHHRR_2	0.28	9.22	0.19	0.47
30	AHHRR_1	0.28	9.03	0.19	0.47
31	AHR_2	0.22	7.93	0.16	0.46
32	AHR_1	0.22	7.74	0.16	0.46
33	DHHRR_4	0.28	7.74	0.18	0.43
34	DHHRR_3	0.28	7.93	0.18	0.43
35	DHHRR_2	0.28	8.48	0.19	0.37
36	DHHRR_1	0.28	8.66	0.19	0.37
37	AHR_4	0.22	4.61	0.11	0.37
38	AHR_3	0.22	4.24	0.1	0.37
39	DDHHR_2	0.27	7.56	0.16	0.34
40	DDHHR_1	0.27	7.37	0.16	0.34

41	AHH_2	0.21	3.5	0.09	0.17
42	AHH_1	0.21	3.5	0.08	0.17
43	DHHR_4	0.24	5.34	0.12	0.14
44	DHHR_3	0.24	5.34	0.12	0.14
45	HHRR_2	0.24	7.56	0.16	0.13
46	HHRR_1	0.24	7.93	0.16	0.13
47	AHHR_2	0.24	5.53	0.11	0.08
48	AHHR_1	0.24	5.53	0.11	0.08
49	DHHR_2	0.24	3.69	0.08	0.06
50	DHHR_1	0.24	3.69	0.08	0.06

- (A) acceptor, (D) donor, (H) hydrophobic, (R) aromatic Ring

Table 3 c-MET pharmacophore-base virtual screening result

Number	Name	MMGBSA dG Bind (Kcal/mol)	Docking score	Glide energy
1	HEXACHLOROPHENE	-113.148	-10.1075	-46.1203
2	TEPOTINIB	-101.176	-11.7964	-69.1832
3	CRIZOTINIB	-99.4024	-12.6876	-47.2851
4	M TRICLABENDAZOLE	-94.9676	-9.85421	-51.5517
5	PASIREOTIDE	-93.793	-11.1342	-73.6724
6	CAPMATINIB	-88.8805	-11.6765	-56.9207
7	ENTRECTINIB	-88.5362	-9.65654	-56.936
8	TIRBANIBULIN	-87.2709	-8.83672	-51.4543
9	DACOMITINIB	-86.7629	-8.88709	-50.3116
10	VALRUBICIN	-81.411	-9.15353	-54.1269
11	M ENTRECTINIB	-78.1147	-11.4692	-49.9739
12	CARVEDILOL	-76.906	-9.4777	-52.6916
13	ONDANSETRON	-76.6241	-8.895	-45.0792
14	RIBOFLAVIN	-75.4588	-8.89034	-50.062
15	METHOTREXATE	-71.7786	-9.73011	-57.3134
16	PROPAFENONE	-71.5292	-10.0798	-48.2777
17	PRAZEPAM	-71.478	-9.3127	-29.9864
18	CHLORTHALIDONE	-69.1597	-11.5382	-39.6589
19	ASENAPINE	-69.0769	-8.90922	-29.0476
20	ZAFIRLUKAST	-67.1374	-9.14132	-62.3164
21	RALOXIFENE	-67.0197	-9.36132	-49.7611
22	DULOXETINE	-66.8535	-9.41139	-38.5964
23	VERICIGUAT	-66.7119	-9.59905	-50.6856
24	BEROTRALSTAT	-66.2648	-8.94213	-57.3349
25	PHENPROCOUMON	-66.1197	-10.6175	-37.175

26	MEBENDAZOLE	-65.4817	-10.5771	-40.4654
27	DICUMAROL	-64.5484	-8.83195	-28.309
28	M DOXEPIN	-64.2645	-8.92276	-27.9244
29	M FLURAZEPAM	-64.1209	-9.025	-33.533
30	CARBENICILLIN INDANYL	-63.6009	-9.93823	-45.5001
31	TOLCAPONE	-63.5186	-9.76391	-37.1588
32	HALAZEPAM	-63.4648	-9.18727	-31.5926
33	TEMAZEPAM	-62.7762	-9.20468	-42.078
34	ESLICARBAZEPINE ACETATE	-62.4287	-8.90296	-42.1344
35	METYRAPONE	-60.786	-9.25183	-35.6945
36	SAFINAMIDE	-59.9711	-9.66733	-43.0401
37	RIBOFLAVIN PHOSPHATE	-58.964	-8.94926	-32.7545
38	VEMURAFENIB	-57.7897	-9.39765	-42.2414
39	AZELASTINE	-57.0146	-9.48456	-42.1496
40	CLONAZEPAM	-56.4232	-8.83197	-35.4621
41	IMIQUIMOD	-56.4223	-9.23784	-32.6754
42	PEMIROLAST	-55.5068	-8.94433	-37.869
43	DOLUTEGRAVIR	-54.255	-9.0325	-36.7375
44	PHENYL AMINOSALICYLATE	-51.9899	-9.00876	-36.3829
45	SULFOXONE	-46.8798	-9.53568	-53.0929
46	FLUOXETINE	-45.337	-9.34561	-30.6715
47	DIPHENIDOL	-45.0924	-9.00331	-32.0155
48	M PICOSULFATE	-43.765	-10.634	-26.3706
49	IDELALISIB	-19.6456	-10.033	-33.4141

Table 4 EGFR pharmacophore-base virtual screening result

Number	Name	MMGBSA dG Bind (Kcal/mol)	Docking score	Glide energy
1	COBICISTAT	-111.8847622	-7.976882967	-65.24533701
2	BREMELANOTIDE	-109.0832434	-8.83930296	-82.35648537
3	LANREOTIDE	-108.9720011	-8.696933872	-82.68727303
4	SARALASIN	-106.0756078	-10.32767813	-84.88412094
5	PASIREOTIDE	-103.933776	-8.461799626	-87.40173244
6	ERLOTINIB	-102.8207575	-10.49881075	-58.32833481
7	AMPHOTERICIN B	-102.0083692	-9.227351036	-70.12491226
8	RITONAVIR	-100.432119	-8.063881863	-75.13867855
9	ANGIOTENSIN II	-97.08430091	-11.36072455	-90.97228622
10	OXYTOCIN	-95.27331343	-8.072898001	-75.14519882
11	DACOMITINIB	-94.05902222	-9.228156293	-53.19803667
12	SELPERCATINIB	-92.94007877	-7.773381954	-57.50364208

13	DESLANOSIDE	-91.72318869	-7.732376427	-60.40616035
14	AFATINIB	-90.75074083	-9.82760251	-57.31923389
15	ICOMTINIB	-90.60937593	-9.117567796	-46.54690838
16	SINCALIDE	-89.61580444	-8.475270446	-88.41709709
17	VALRUBICIN	-88.46690838	-8.106946764	-59.26667786
18	CANAGLIFLOZIN	-87.47979514	-7.969282841	-49.71697807
19	OSIMERTINIB	-87.31188282	-8.182380066	-53.84221077
20	SETMELANOTIDE	-86.54171478	-8.561830042	-76.67557907
21	TRAVOPROST	-86.46834304	-7.794164957	-50.48788548
22	SERTACONAZOLE	-86.26365295	-8.154896618	-42.26012397
23	GEFITINIB	-85.11110502	-8.294864547	-46.11164284
24	M FIDAXOMICIN	-84.91824415	-9.243739396	-61.97245979
25	OCTREOTIDE	-82.22650987	-9.081564314	-84.35085297
26	DESMOPRESSIN	-82.14994151	-7.627600218	-78.46639633
27	OLODATEROL	-81.44960446	-7.758166271	-48.76274395
28	IXAZOMIB	-80.30047283	-8.431593893	-50.24266434
29	ECONAZOLE	-79.97031509	-7.634420222	-44.12808692
30	EMPAGLIFLOZIN	-79.91250682	-8.978106311	-50.35771179
31	ERTUGLIFLOZIN	-79.46949357	-8.033418649	-50.24038696
32	LAROTRECTINIB	-79.47491552	-8.220617	-50.16515875
33	SELUMETINIB	-77.86457063	-9.280087318	-51.11791086
34	PEXIDARTINIB	-77.16376258	-8.358510518	-45.75952339
35	PITAVASTATIN	-77.11764822	-8.632883297	-47.93113804
36	LAPATINIB	-77.04849233	-8.046506427	-56.61333919
37	HYDROXYCHLOROQUINE	-76.37939638	-8.019644708	-37.39989996
38	M SELUMETINIB	-75.91977467	-8.549359981	-48.99003696
39	PLAZOMICIN	-75.47260511	-8.363491922	-57.04883385
40	DAPAGLIFLOZIN	-74.49088974	-8.075306783	-50.39474678
41	FENOLDOPAM	-72.83264489	-8.516723004	-34.35267067
42	BORTEZOMIB	-72.6139127	-8.136782142	-53.10796928
43	BINIMETINIB	-72.40349303	-8.787672571	-50.09866142
44	DOCETAXEL	-71.92674407	-7.867561698	-58.42463207
45	IDARUBICIN	-70.74819383	-7.963606869	-53.76989174
46	EZETIMIBE	-70.61299726	-7.810521292	-43.17826748
47	ESTETROL	-68.3399576	-7.961487054	-38.75888538
48	SACUBITRIL	-68.29263184	-8.269772287	-47.37074089
49	CRIZOTINIB	-67.49959519	-10.78915313	-45.30870056
50	ROSUVASTATIN	-66.7910999	-8.209282505	-47.39077997
51	OMADACYCLINE	-66.2954344	-7.602046971	-38.16872978
52	WARFARIN	-66.00394913	-7.656521728	-41.11967039
53	CEFOPERAZONE	-65.71877405	-8.325124185	-69.53261042

54	ARBUTAMINE	-65.47037292	-8.079256015	-43.62244034
55	ATORVASTATIN	-64.64547348	-7.611603783	-51.82890272
56	PRALATREXATE	-64.59931054	-7.568376666	-56.067626
57	REGADENOSON	-64.26434974	-7.934380892	-54.4534111
58	CHLOROQUINE	-64.19082407	-8.00233595	-34.40816665
59	PHENPROCOUMON	-64.02186948	-7.607243222	-33.30106926
60	EPIRUBICIN	-64.00040011	-7.928747887	-57.68253136
61	APOMORPHINE	-63.81873803	-7.898668281	-32.39686489
62	M AMODIAQUINE	-63.3886118	-8.8407572	-42.32088518
63	CANGRELOR	-62.20120826	-8.408537228	-63.51173592
64	MEBENDAZOLE	-61.95913863	-7.581162226	-36.42149496
65	RIBOFLAVIN	-61.53852146	-9.768021113	-51.4049263
66	TADALAFIL	-61.49903723	-7.940735817	-31.92233968
67	METHACYCLINE	-61.11560515	-7.792014848	-46.65385818
68	TOLCAPONE	-60.95863285	-7.896705338	-36.77293456
69	ERAVACYCLINE	-59.36395404	-8.117702737	-53.65415382
70	DABIGATRAN	-58.07413961	-7.755062958	-53.71243477
71	CERIVASTATIN	-57.92761423	-7.879352339	-46.05922318
72	OXYTETRACYCLINE	-57.71911568	-7.969929483	-48.08411407
73	M REMDESIVIR	-57.63974881	-8.817434312	-36.11153984
74	MASOPROCOL	-57.52373866	-9.310321122	-35.24548817
75	VALGANCICLOVIR	-56.85275931	-8.020737212	-48.0977807
76	RIBOFLAVIN PHOSPHATE	-55.80884545	-8.404988443	-49.53312206
77	CRISABOROLE	-53.5106133	-8.143863446	-32.8743372
78	CLADRIBINE	-52.59113705	-8.392390387	-34.20452642
79	TRIAMTERENE	-52.38548341	-8.886456723	-32.49963605
80	SULFAPHENAZOLE	-52.02587905	-8.016733319	-37.24487448
81	CLOFARABINE	-51.94497088	-7.685688932	-33.64342761
82	SULFADOXINE	-48.54466733	-7.821031995	-38.59629107
83	ADENOSINE	-47.59422827	-9.583722275	-36.02366257
84	VIDARABINE	-46.34919229	-9.005628955	-41.20659637
85	LEVOMEFOLATE	-44.063244	-8.040880749	-43.04594088
86	FLUDARABINE	-40.61962167	-7.716735678	-38.65628529
87	M PENCICLOVIR	-37.95043983	-7.817235006	-49.87418365

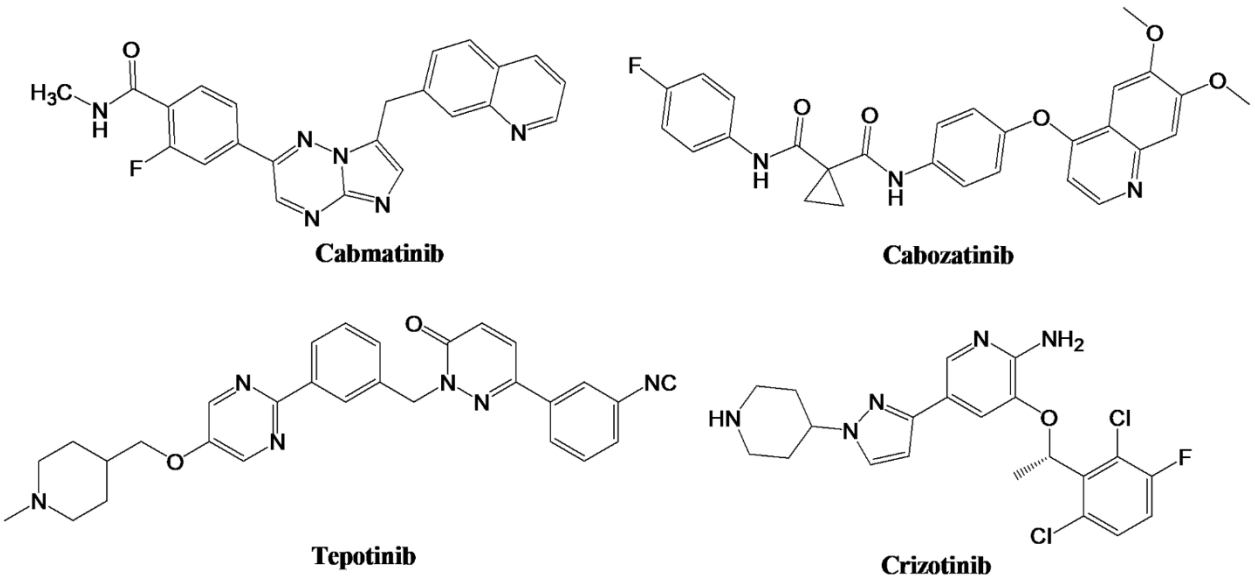
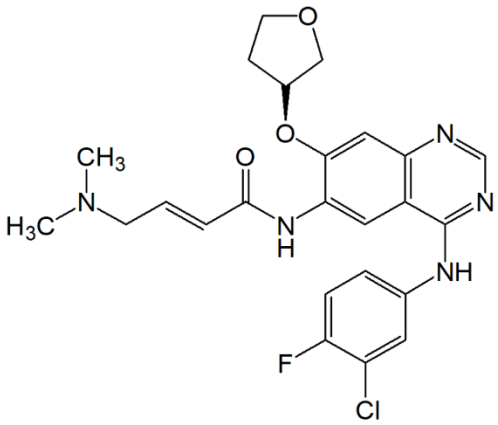
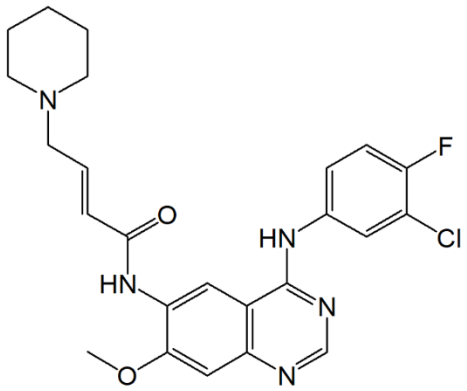


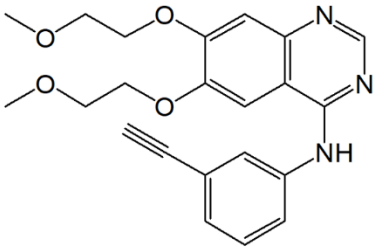
Figure 1. 2D representation of c-MET FDA-approved inhibitors



Afatinib



Dacomitinib



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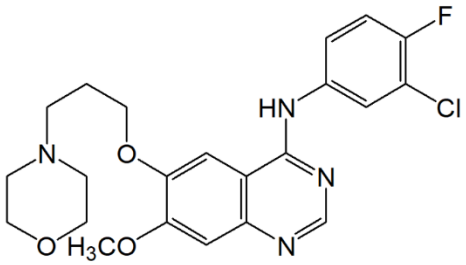
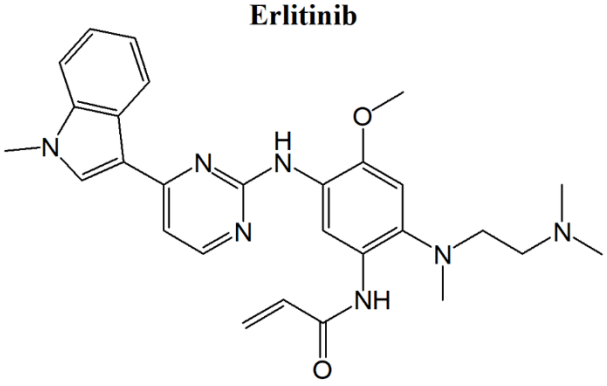
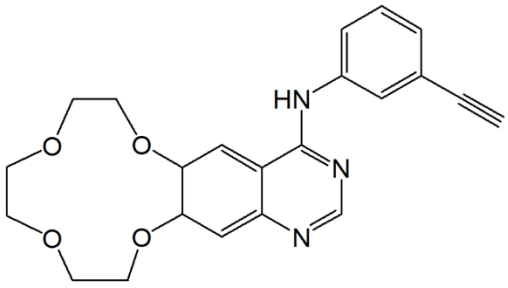


Gefitinib



Osimertinib



Icontinib

Figure 2. 2D representation of EGFR FDA-approved inhibitors

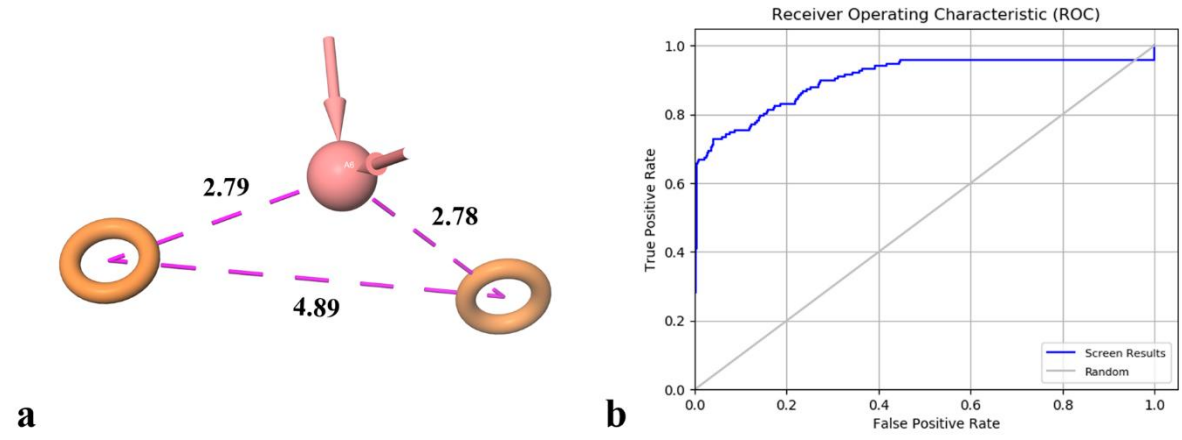


Figure 3. 3D representation of the highest ranked pharmacophore hypothesis of c-MET, ARR_4. This figure shows the ARR_4 inter-site positions (acceptor pink, aromatic ring orange) and distances in angstroms (a), along with the relative ROC (b)

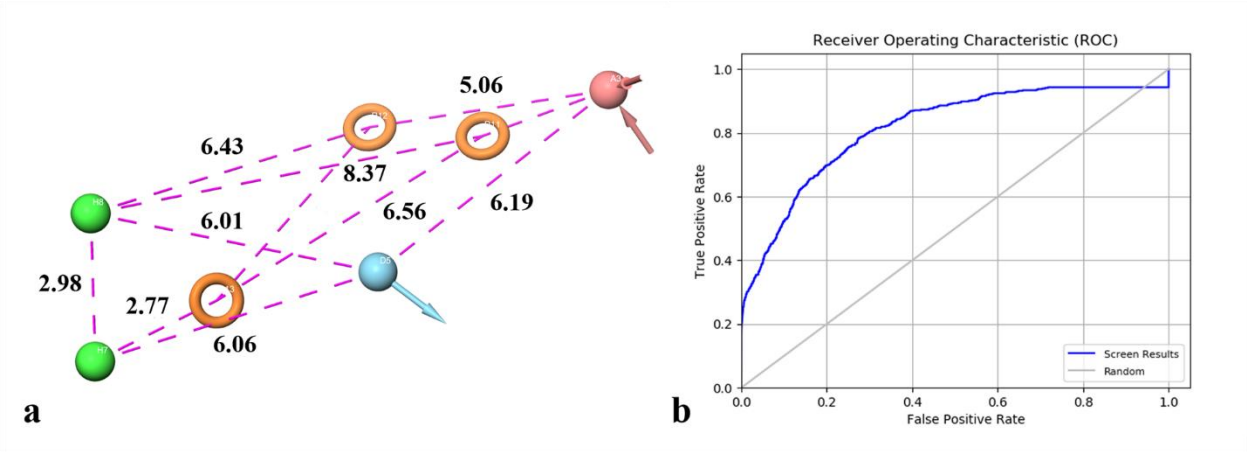


Figure 4. ADHHRRR_1 is the highest ranked pharmacophore hypothesis for selected EGFR. This figure presents the ADHHRRR_1 inter-site position (acceptor pink, aromatic ring orange, donor blue, and hydrophobic green) and distances in angstroms (a). Furthermore, (b) exhibits the ROC curve for this pharmacophore hypothesis.

Table 5. The binding energy calculation, residues and type of interactions over the c-MET active site through induced fit docking procedure

No.	Name	MM-GBSA ΔG_{Bind} (Kcal/mol)	Interaction over c-MET active site		
			H-Bond	Hydrophobic	Electrostatic

1	Crizotinib	-99.4024	Met1160, Asp1222, Tyr1159, Pro1158, Lys1161	Tyr1230, Ala1221, Ala1226, Val1092, Lys1110, Leu1157, Leu1140, Met1211, Ile1084, Ala1108	-
2	Pasireotide	-93.793	Arg1086, Met1160, His1162, Asp1164, Glu1233, Ile1084, Gly1163, Pro1158	Ile1084, Tyr1159, Tyr1230, Ala1108 Val1092	-
3	Dacomitinib	-86.7629	Met1160, Tyr1159, Arg1208	Met1211, Tyr1230, Arg1086, Ala1108, Ile1084, Val1092, Tyr1159, Ala1221, Leu1157, Met1160	-
4	Valrubicin	-81.411	Val1083	Ala1221, Met1211, Tyr1230	-
5	Riboflavin	-75.4588	Met1160, Ile1084, Arg1208, Asp1164	Leu1140, Leu1157, Met1211, Tyr1230, Ile1084, Val1092, Ala1108	-
6	Phenprocoumon	-66.1197	Met1160, Pro1158	Tyr1230, Tyr1159, Ala1226, Val1092, Lys1110, Leu1157, Ala1108, Met1160, Met1211, Ala1221, Ile1084	-
7	Mebendazole	-65.4817	Met1160, Ile1084, Lys1161	Tyr1230, Tyr1159, Ile1084, Ala1108, Val1092, Ala1221, Ala1226	-
8	Tolcapone	-63.5186	Met1160, Pro1158, Gly1085, Tyr1159	Met1211, Tyr1230, Ala1221, Ala1226, Leu1140, Ile1084, Val1092, Ala1108	Tyr1159

Table 6. The binding energy calculation, residues and type of interactions over the EGFR active site through induced fit docking procedure

No.	Name	MM-GBSA ΔG_{Bind} (Kcal/mol)	Interaction over EGFR active site		
			H-Bond	Hydrophobic	Electrostatic
1	Pasireotide	-103.9337	Cys797, Asp855, Asn842, Asp800 Val717- Glu804, Phe795, Leu718, Gly796	Leu718, Gly719, Arg841, Val717- Val726- Ala743, Leu844, Lys745	
2	Dacomitinib	-94.0590	Met793, Gly719- Gln791	Leu718, Lys745, Leu788, Ala743, Met793, Leu844,	-
3	Valrubicin	-88.4669	Lys745, Cys797, Asp800, Gly719, Met793	Lys745, Val726, Leu844, Leu747	Asp855
4	Crizotinib	-67.49959	Met793, Asp800, Gln791, Leu718	Ala743, Val726, Lys745, Leu718, Leu844	-
5	Phenprocoumon	-64.0219	-	Lys745, Val726, Ala743, Leu844, Leu718,	-
6	Mebendazole	-61.9591	Met793, Gly796, Pro794	Leu718, Ala743, Leu844, Val726	-
7	Riboflavin	-61.5385	Met793, Cys797, Leu718- Leu792	Leu718, Leu747, Lys745, Val726, Ala743, Leu844,	-

8	Tolcapone	-60.9586	Met793, Gln791	Lys745, Met766, Leu788, Leu718, Ala743, Leu844	-

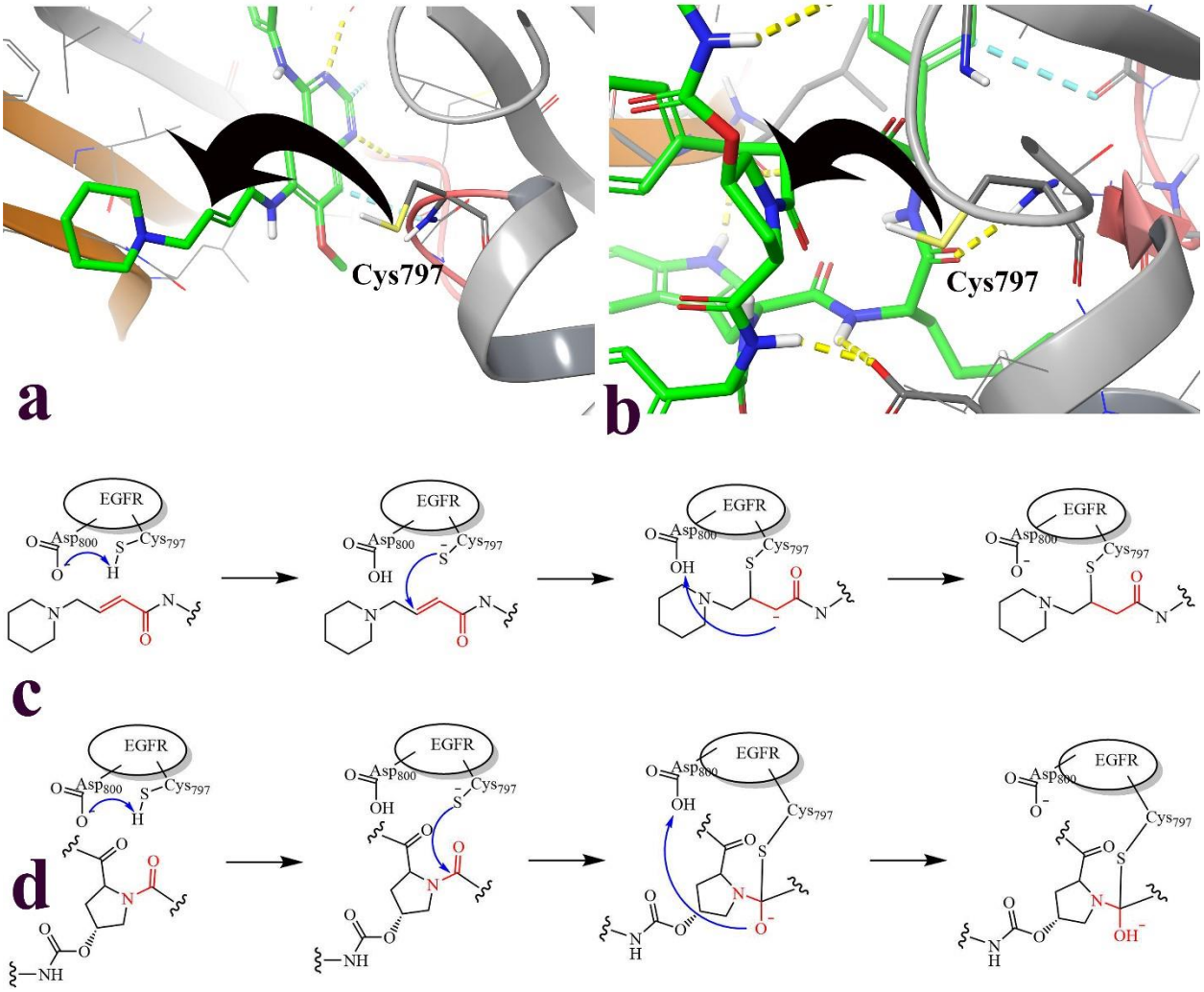
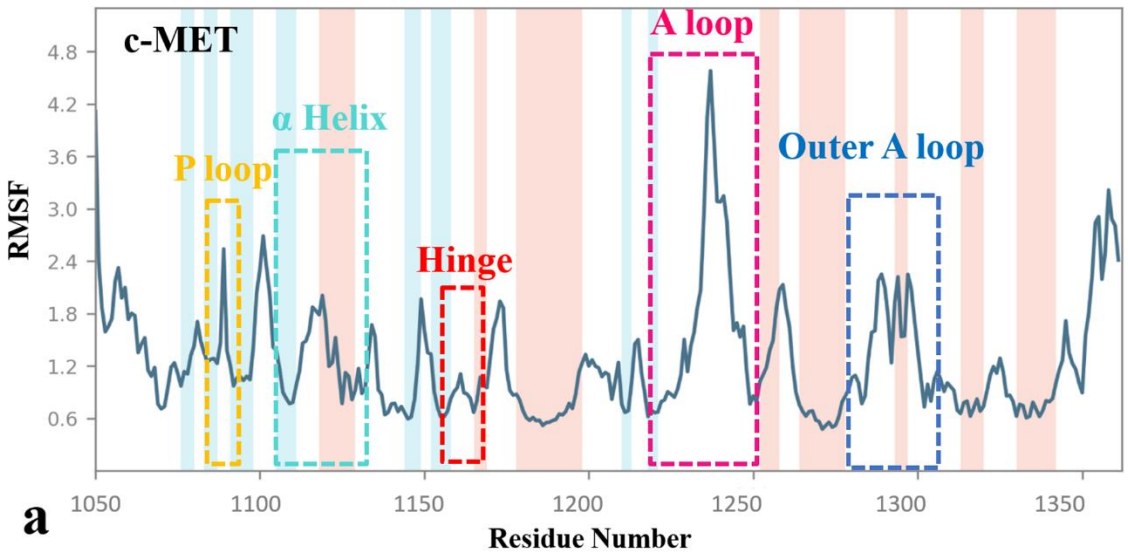
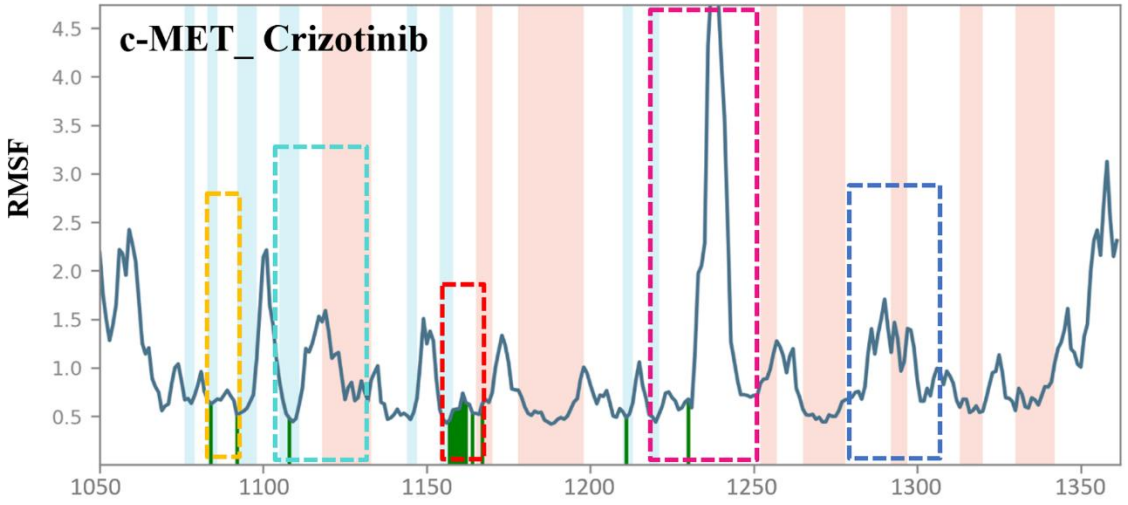


Figure 5. 3D representation of spatial arrangement of the (piperidin-1-yl) but-2-enoyl tail of dacomitinib (a) and the modified L-hydroxy proline moiety of pasireotide (b) around the Cys797 of the kinase hinge region (the nucleophile and the probable electrophilic center defined by the head and tail of the black arrows). The detailed mechanism of the proposed nucleophilic-electrophilic reaction possibility by dacomitinib and pasireotide represented in part (c) and (d), respectively.


c-MET
A loop
α Helix
P loop
Outer A loop
Hinge
RMSF
4.8
4.2
3.6
3.0
2.4
1.8
1.2
0.6
1050
1100
1150
1200
1250
1300
1350
Residue Number

a


c-MET_ Crizotinib
RMSF
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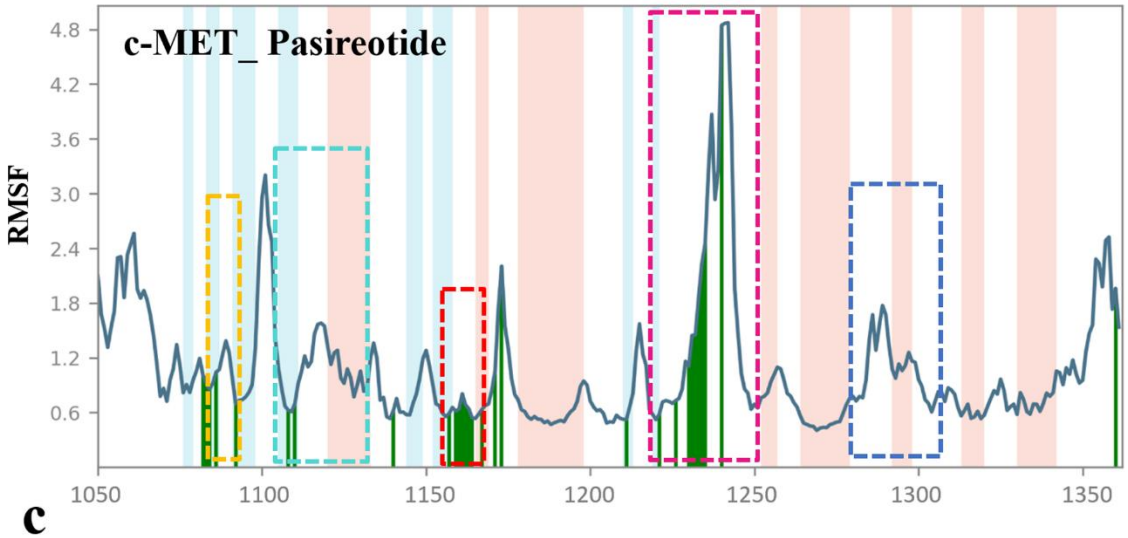
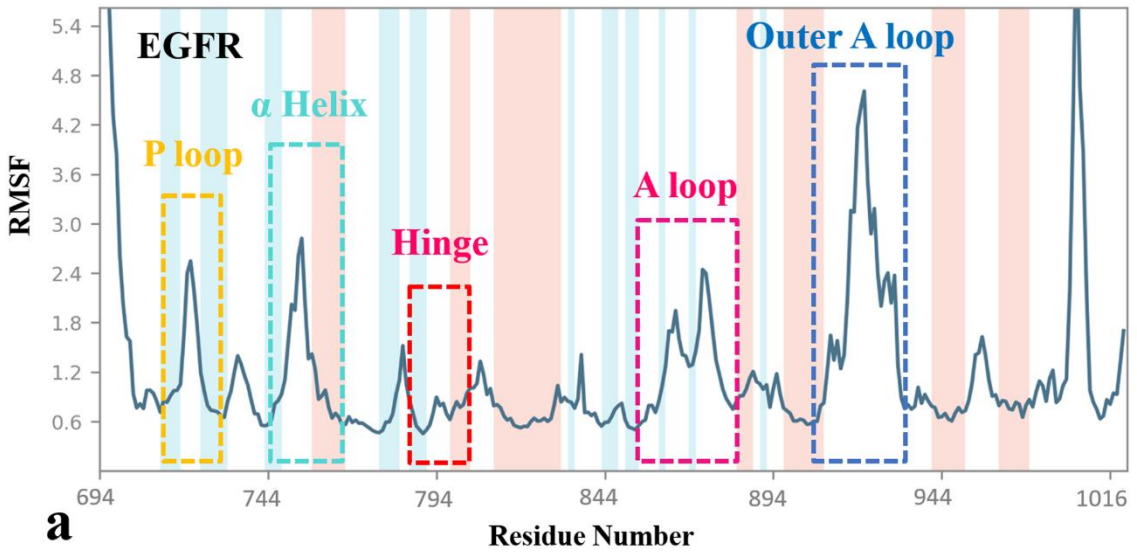
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1050
1100
1150
1200
1250
1300
1350

b

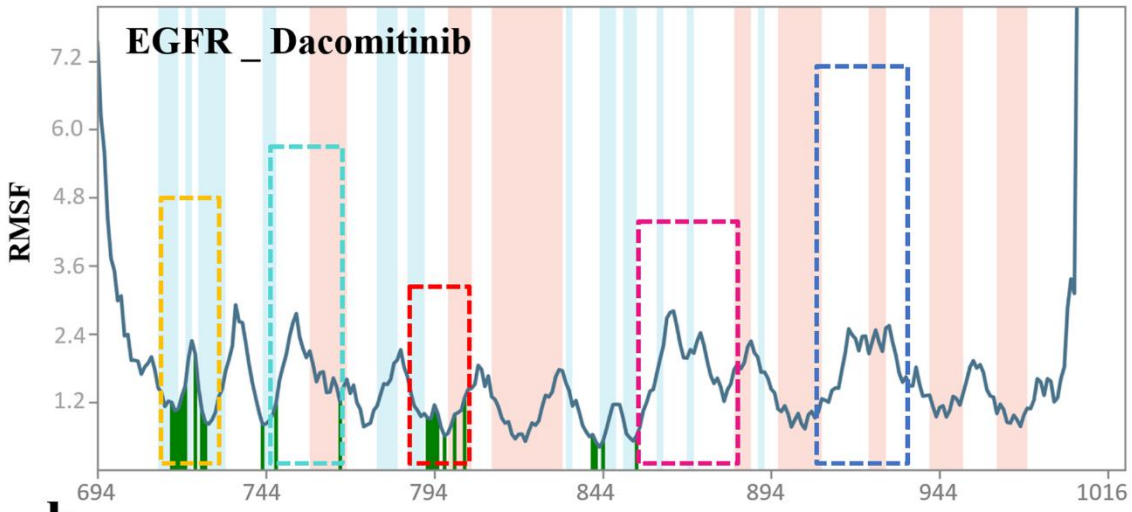

c-MET_ Pasireotide
RMSF
4.8
4.2
3.6
3.0
2.4
1.8
1.2
0.6
1050
1100
1150
1200
1250
1300
1350

c

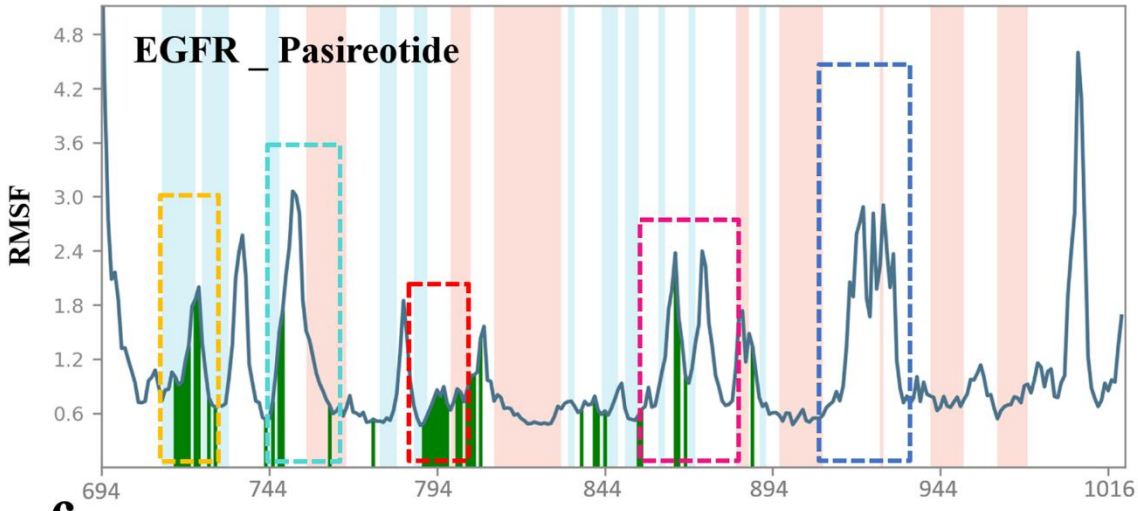
Figure 6. RMSF plot of c-MET residue in non-bonded-state (a) in complexed with crizotinib (b) and in complex with pasireotide (c) over 80 ns MD simulation time. α-helical and ß-strand regions are highlighted by pink and blue backgrounds, respectively.


EGFR
Outer A loop
α Helix
P loop
A loop
Hinge
RMSF
5.4
4.8
4.2
3.6
3.0
2.4
1.8
1.2
0.6
694
744
794
844
894
944
1016
Residue Number

a


EGFR _ Dacomitinib
RMSF
7.2
6.0
4.8
3.6
2.4
1.2
694
744
794
844
894
944
1016

b


EGFR _ Pasireotide
RMSF
4.8
4.2
3.6
3.0
2.4
1.8
1.2
0.6
694
744
794
844
894
944
1016

c

Figure 7. RMSF plot of EGFR kinase domain residue in non-bonded-state (a) in complexed with dacomitinib (b) and in complex with pasireotide (c) over 80 ns MD simulation time. α-helical and ß-strand regions are highlighted by pink and blue backgrounds, respectively.

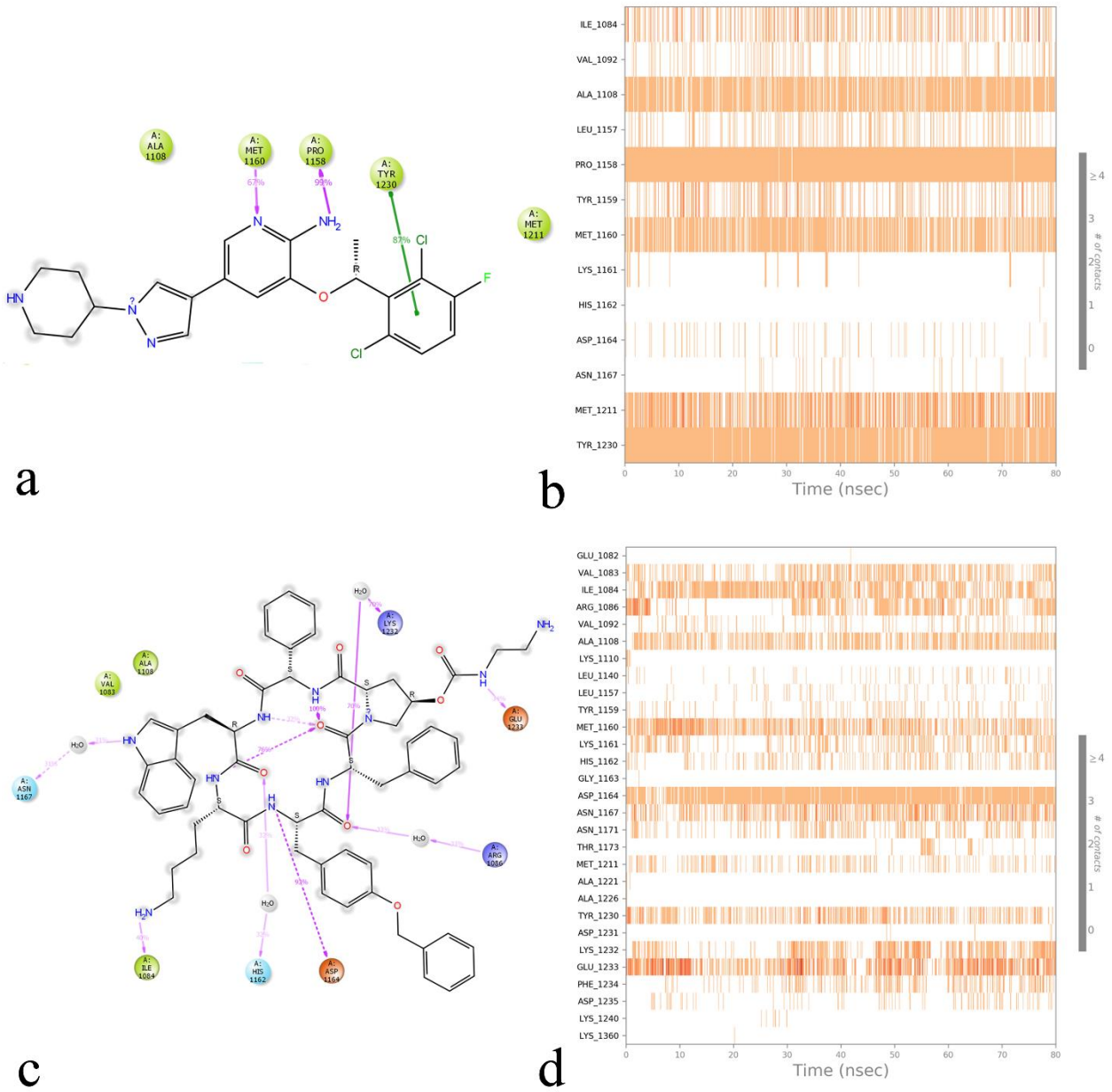


Figure 8. Detailed interactions between crizotinib (a) and pasireotide (c) over c-MET active site residues in the selected trajectory are shown in the schematic which is responsible for over 30% of MD simulation time. The timeline renderings of interacting residues over the whole simulation time of c-MET complexed with crizotinib (b) and pasireotide (d), respectively.

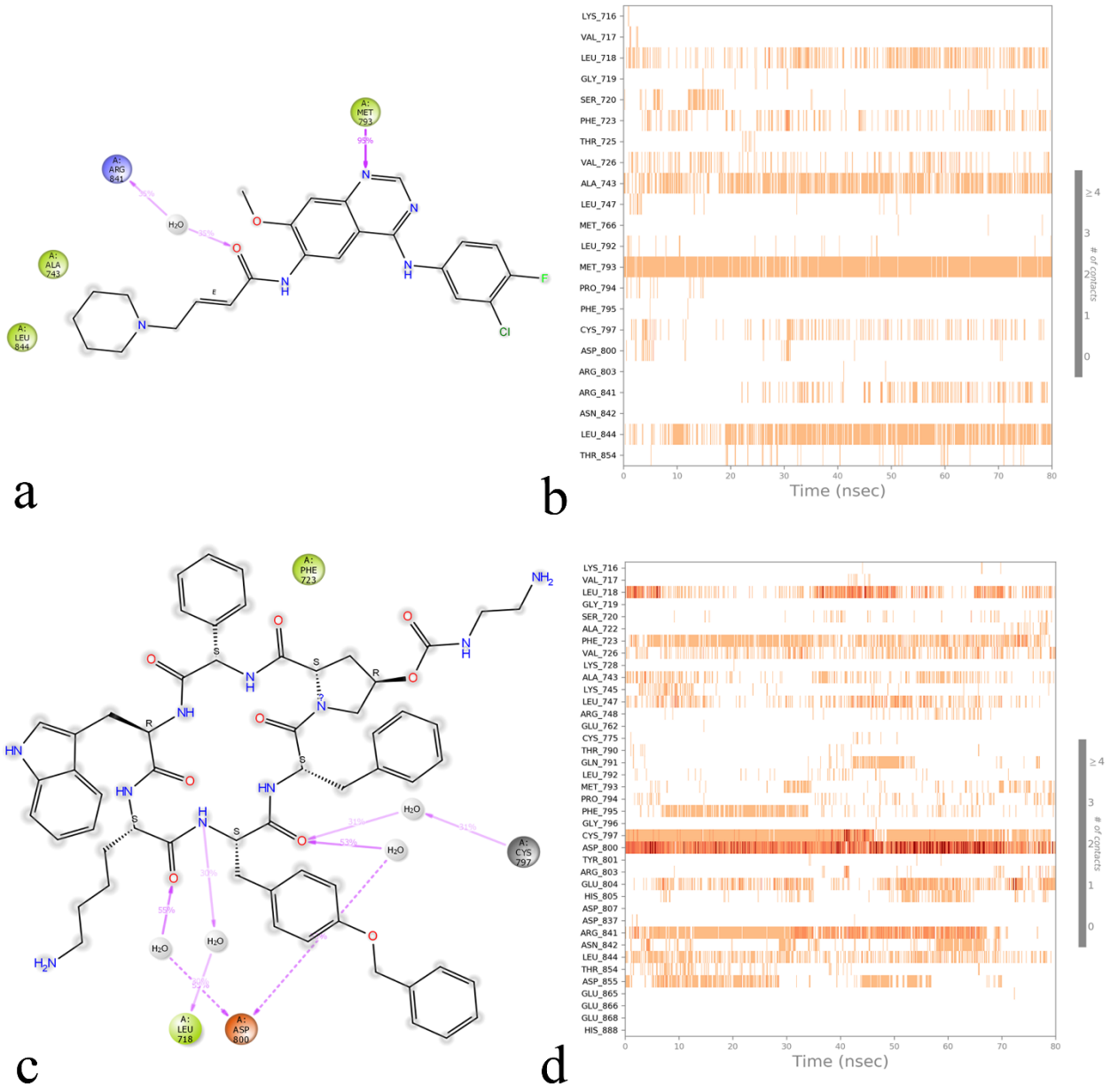
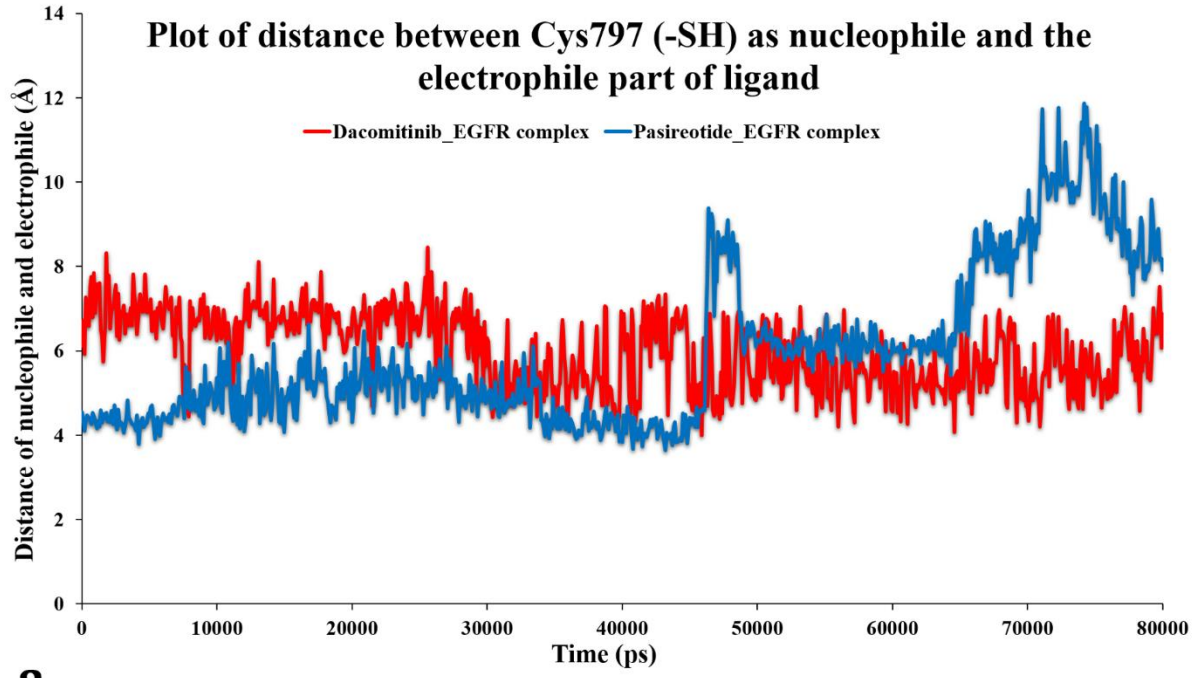
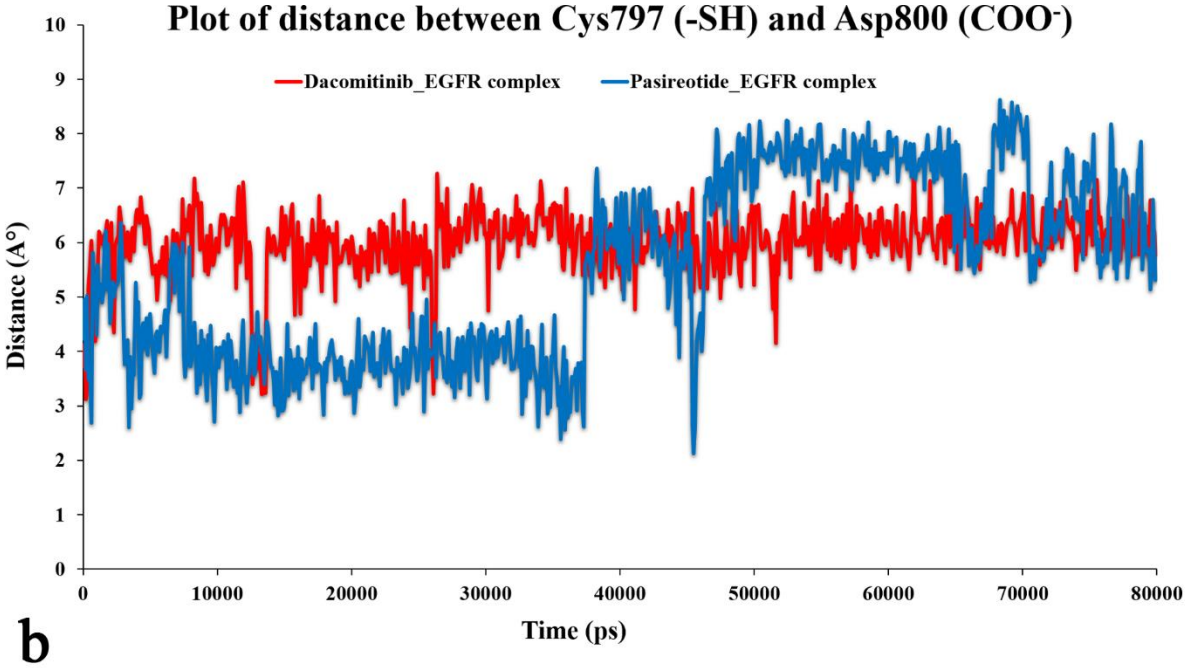


Figure 9. Detailed interactions between dacomitinib (a) and pasireotide (c) over EGFR active site residues in the selected trajectory are shown in the schematic which is responsible for over 30% of MD simulation time. The timeline renderings of interacting residues over the whole simulation time of EGFR complexed with dacomitinib (b) and pasireotide (d), respectively.



a



b

Figure 10. Plot of the distance between Cys797 (-SH) as nucleophile at the hinge region of EGFR kinase domain with the electrophile center of dacomitinib (in red color) and pasireotide (in blue color) (a), and the Plot of the distance between Cys797 (-SH) as nucleophile and Asp800 (COO^-) as base

Table 7 Binding free energy (ΔGbind) values

Complex name	ΔG_{bind} Kcal/mol	Solvation effects Kcal/mol	Van der waals energy Kcal/mol	Electrostatic energy Kcal/mol
c-MET_Pasireotide	-58.22	-1592.92	-2958.971	-1682.530
c-MET_Crizotinib	-77.56	-2136.35	-2958.971	-1682.530
EGFR_Pasireotide	-84.37	-1648.90	-2829.229	-1682.212
EGFR_Dacomitinib	-94.06	-1635.35	-2874.917	-1671.286

Table 8 Proposed potential c-MET and EGFR dual inhibitor, mechanism of action and therapeutic indication. The information is derived from drug bank (https://www.Drugbank.ca).

No.	Name (DB No.)	Mechanism of Action	Indication	FDA-approved year
1.	PASIREOTIDE (DB06663)	Activates somatostatin receptors	treatment of Cushing's disease	2012
2.	VALRUBICIN (DB00385)	it inhibits the incorporation of nucleosides into nucleic acids, causes extensive chromosomal damage, and arrests cell cycle in G2	treatment of BCG-resistant bladder carcinoma	1998
3.	DACOMITINIB (DB11963)	inhibitor of the human epidermal growth factor receptor (EGFR) family (EGFR/HER1, HER2, and HER4) tyrosine kinases.	Treatment of non-small cell lung cancer (NSCLC)	2018
	RIBOFLAVIN (DB00140)	Binds to riboflavin hydrogenase, riboflavin kinase, and riboflavin synthase	used to correct vitamin B2 deficiency	

	CRIZOTINIB (DB08865)	inhibitor of tyrosine kinase, anaplastic lymphoma kinase (ALK), hepatocyte growth factor receptor (HGFR, c-MET), ROS1 (c-ros), and Recepteur d'Origine Nantais (RON)	Treatment of metastatic non-small cell lung cancer (NSCLC) and treatment of systemic anaplastic large cell lymphoma (ALCL)	2011
	MEBENDAZOLE (DB00643)	binding to the colchicine-sensitive site of tubulin, thus inhibiting its polymerization or assembly into microtubules.	treat helminth infections	1974
	PHENPROCOUMON (DB00946)	anticoagulant drug, inhibits vitamin K reductase	prevention and treatment of thromboembolic disease	
	TOLCAPONE (DB00323)	inhibitor of catechol-O-methyltransferase (COMT)	treatment of Parkinson's Disease	1998

1DB no.: Drug Bank Accession Number