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Gaussian field-based 3D-QSAR and molecular simulation studies to design potent pyrimidine-sulfonamide hybrids as selective BRAF^{V600E} inhibitors

Ankit Kumar Singh[1†], Jurica Novak[2,3,4†], Adarsh Kumar[1], Harshwardhan Singh[1], Suresh Thareja[1], Prateek Pathak[5], Maria Grishina[5], Amita Verma[6], Jagat Pal Yadav[6,7], Habibullah Khalilullah[8], Vikas Pathania[9], Hemraj Nandanwar[9], Mariusz Jaremko[10], Abdul-Hamid Emwas[11], and Pradeep Kumar[1*]

[1]Department of Pharmaceutical Sciences and Natural Products, Central University of Punjab, Ghudda, Bathinda, 151401, India; ankitsinghpbh12195@gmail.com (A.K.S.); adarshkumar5198@gmail.com (A.K.); harshwardhansingh371995@gmail.com (H.S.); suresh.thareja@cup.edu.in (S.T.); pradeepyadav27@gmail.com, pradeep.kumar@cup.edu.in (P.K.)

[2]Department of Biotechnology, University of Rijeka, Rijeka, 51000, Croatia; jurica.novak@biotech.uniri.hr (J.N.)

[3]Center for Artificial Intelligence and Cybersecurity, University of Rijeka, Rijeka, 51000, Croatia; jurica.novak@biotech.uniri.hr (J.N.)

[4]Scientific and Educational Center 'Biomedical Technologies' School of Medical Biology, South Ural State University, RU-454080, Chelyabinsk, Russia; jurica.novak@biotech.uniri.hr (J.N.)

[5]Laboratory of Computational Modeling of Drugs, Higher Medical and Biological School, South Ural State University, Chelyabinsk, Russia, 454008, Russia; patkhakp@susu.ru (P.P.); grishinama@susu.ru (M.G.)

[6]Bioorganic and Medicinal Chemistry Research Laboratory, Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Prayagraj, 211007, India; amita.verma@shiats.edu.in (A.V.); j.p.yaduvansi@gmail.com, (J.P.Y.)

[7]Department of Pharmacology, Kamla Nehru Institute of Management and Technology, Faridipur, Sultanpur, 228118, India j.p.yaduvansi@gmail.com, (J.P.Y.)

[8]Department of Pharmaceutical Chemistry and Pharmacognosy, Unaizah College of Pharmacy, Qassim University, Unayzah, 51911, Saudi Arabia; h.abdulaziz@qu.edu.sa (H.K.)

[9]Clinical Microbiology & Bioactive Screening Laboratory, Council of Scientifc & Industrial Research -Institute of Microbial Technology, Sector -39A, Chandigarh, 160036, India; vikasp2311@gmail.com (V.P.); hemraj@imtech.res.in (H.N.)

[10]Smart-Health Initiative (SHI) and Red Sea Research Center (RSRC), Division of Biological and Environmental Sciences and Engineering (BESE), King Abdullah University of Science and Technology (KAUST), Thuwal 23955-6900, Saudi Arabia; mariusz.jaremko@kaust.edu.sa (M.J.)

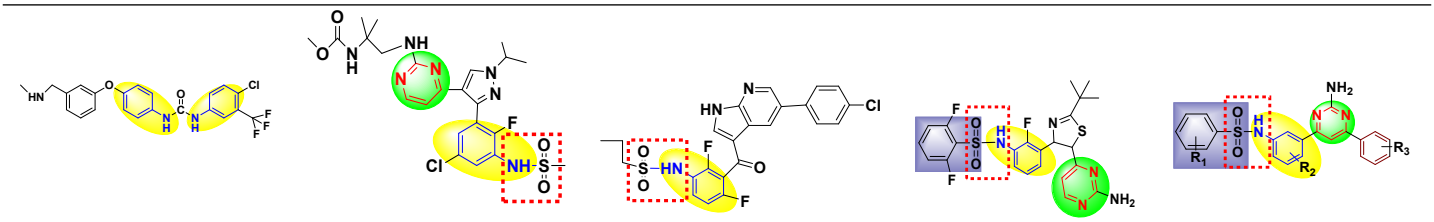
[11]Core Labs, King Abdullah University of Science and Technology (KAUST), Thuwal 23955-6900, Saudi Arabia; abdelhamid.emwas@kaust.edu.sa (A.H.E.)

[†] **Equal contribution**

*** Correspondence: *Dr. Pradeep Kumar**: pradeepyadav27@gmail.com, pradeep.kumar@cup.edu.in

Supplementary Figure & Table

1. Supplementary Figure SI(1-7)



Sorafenib	Encorafenib	Vemurafenib	Dabrafenib	Designed compound

Pyrimidine moiety N-Phenyl ring Benzene Sulphonyl Sulphonamide

Figure SI1. Rationality of designed compound based on FDA-approved BRAF inhibitors.

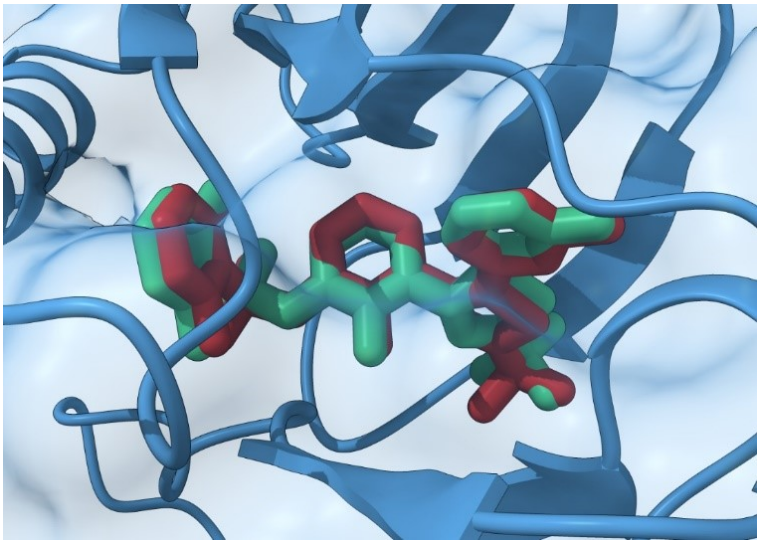


Figure SI2. Overlay of experimental (red) and docked (medium sea green) structures of dabrafenib inside BRAF kinase protein pocket.

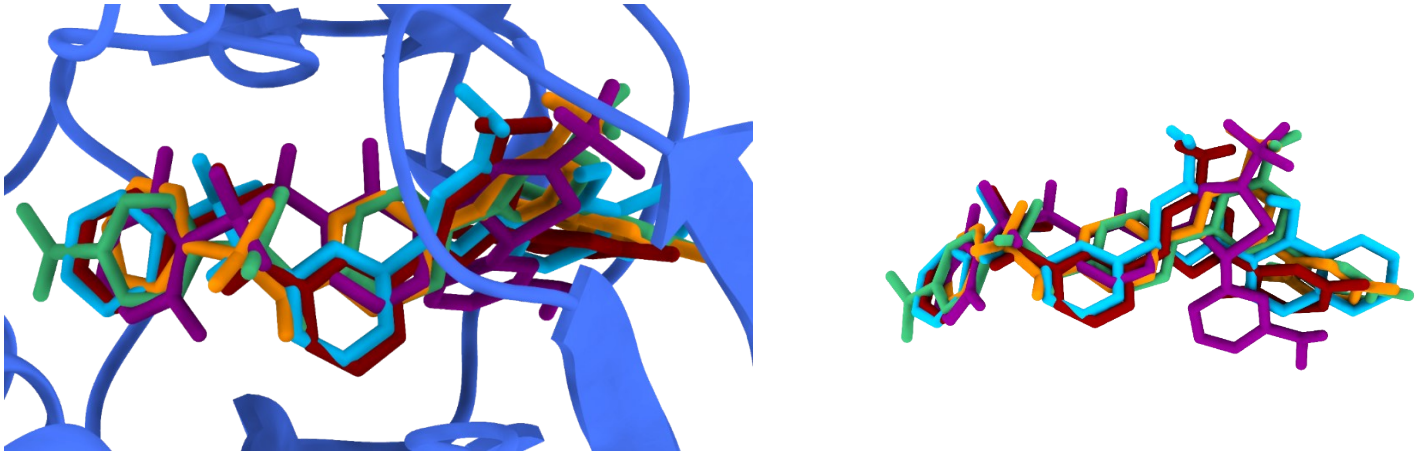


Figure SI3. Binding poses of T109 (red), T126 (orange), T160 (sea green), T183 (sky blue) and reference drug dabrafenib (magenta) as determined by molecular docking to the BRAF kinase protein pocket

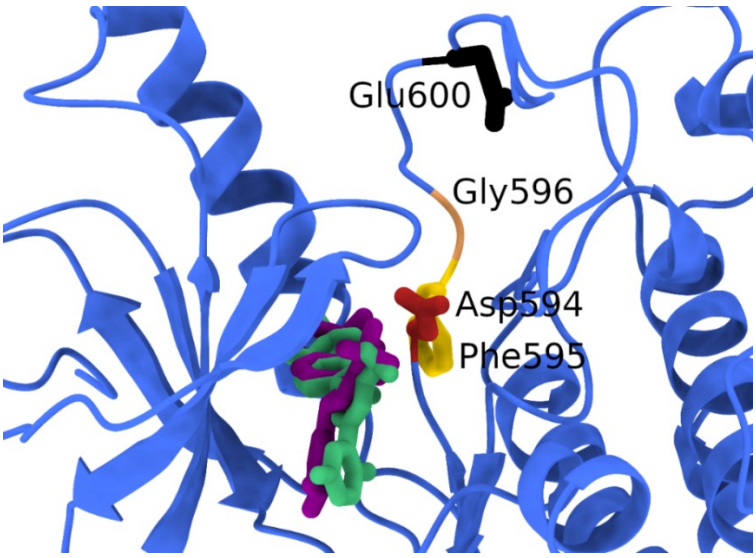


Figure SI4. Glu600 (black) is more than 14 Å apart from docked T160 (sea green) and dabrafenib (magenta) to BRAF

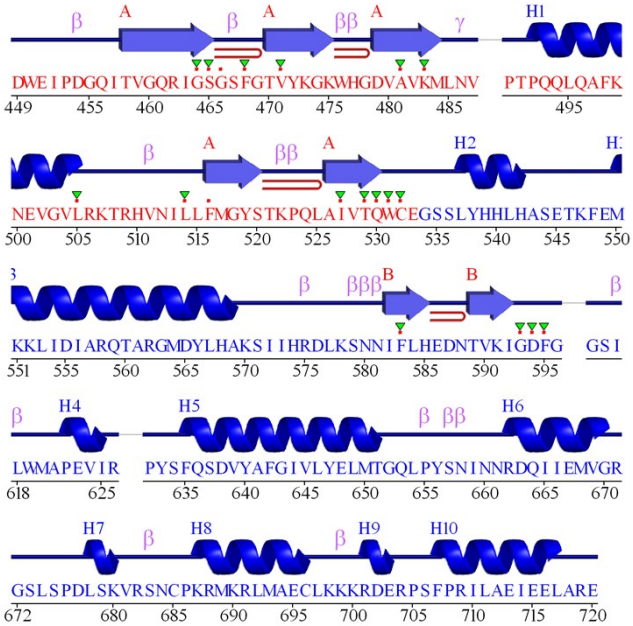


Figure SI5. Secondary structure of the BRAF kinase protein (pdb ID 4XV2). Figure is generated using PDBsum web server.[83]

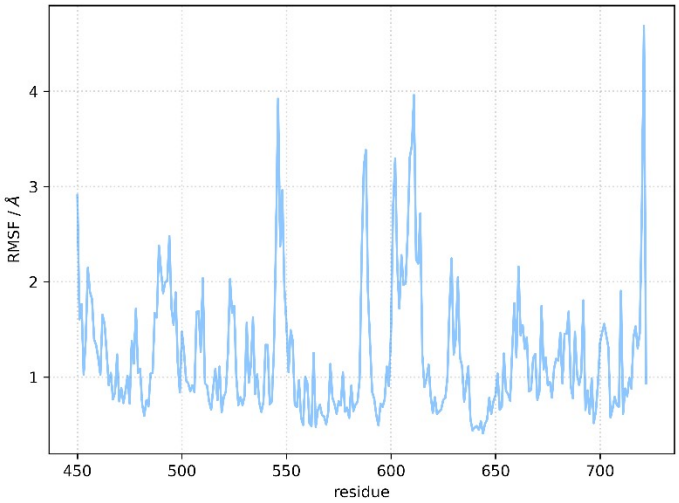


Figure SI6. Root mean square fluctuations per residue of the DAB:hBRk complex.

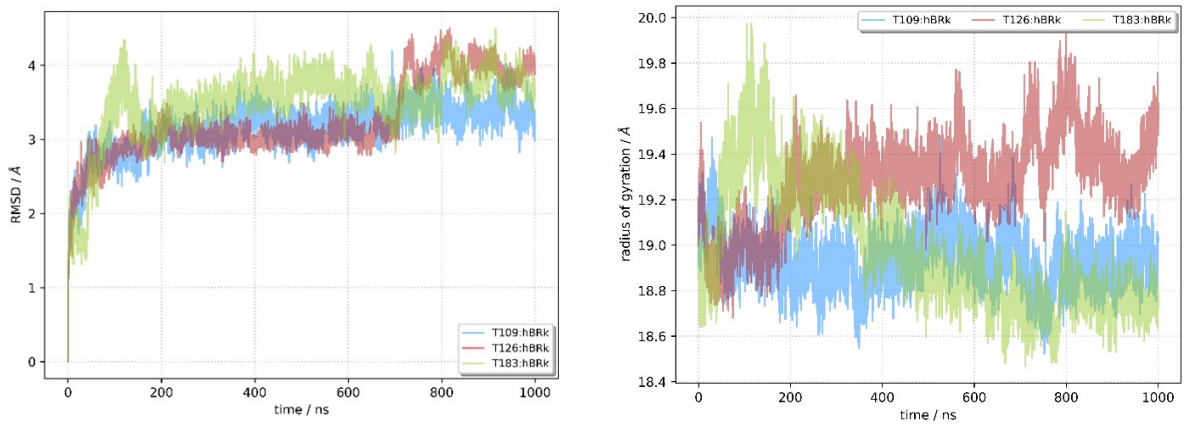


Figure SI7. Molecular dynamics trajectory analysis for T109:hBRk, T126:hBRk, and T183:hBRk complex. RMSD (left) and RoG (right)

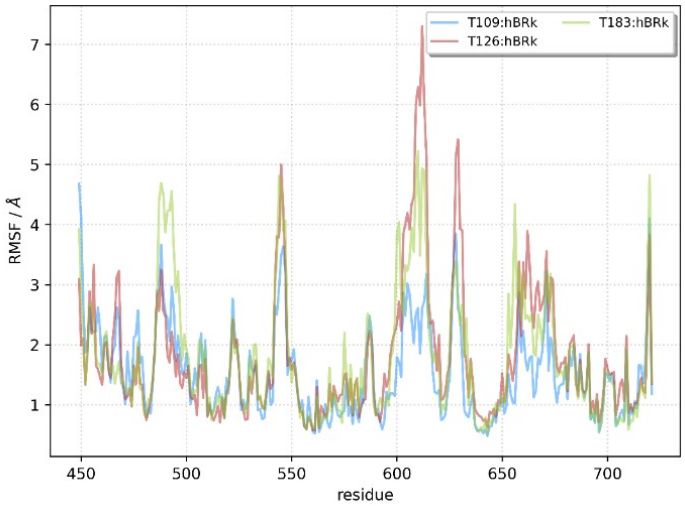


Figure SI8. Root mean square fluctuations per residue of the T109: hBRk, T126: hBRk, and T183: hBRk complex

2. Supplementary Table SI(1-10)

Table SI1. Different derivatives of new designed pyrimidine-sulfonamide hybrid compounds

No.	R_1	R_2
T101	H	H
T102	H	2-Cl
T103	H	4-Cl
T104	H	3-Br
T105	H	4-Br
T106	H	4-NO_2
T107	H	2,4-Cl
T108	H	2,6-Cl
T109	H	2,5-F
T110	H	4-OCH_3
T111	H	2,4-OCH_3
T112	H	2,5-OCH_3
T113	H	3-OH
T114	H	4-OH
T115	H	2-OH
T116	H	2-OH,3,5-I
T117	H	3,4-OCH_3
T118	H	H
T119	H	2-Cl
T120	H	4-Cl
T121	H	3-Br
T122	H	4-Br
T123	H	4-NO_2
T124	H	2,4-Cl
T125	H	2,6-Cl
T126	H	2,5-F
T127	H	4-OCH_3
T128	H	2,4-OCH_3
T129	H	2,5-OCH_3
T130	H	3-OH
T131	H	4-OH
T132	H	2-OH
T133	H	2-OH,3,5-I
T134	H	3,4-OCH_3
T135	NO_2	H
T136	NO_2	2-Cl
T137	NO_2	4-Cl
T138	NO_2	3-Br
T139	NO_2	4-Br
T140	NO_2	4-NO_2
T141	NO_2	2,4-Cl
T142	NO_2	2,6-Cl
T143	NO_2	2,5-F
T144	NO_2	4-OCH_3
T145	NO_2	2,4-OCH_3
T146	NO_2	2,5-OCH_3
T147	NO_2	3-OH
T148	NO_2	4-OH
T149	NO_2	2-OH
T150	NO_2	2-OH,3,5-I
T151	NO_2	3,4-OCH_3
T152	NO_2	H
T153	NO_2	2-Cl
T154	NO_2	4-Cl
T155	NO_2	3-Br
T156	NO_2	4-Br
T157	NO_2	4-NO_2
T158	NO_2	2,4-Cl
T159	NO_2	2,6-Cl
T160	NO_2	2,5-F
T161	NO_2	4-OCH_3
T162	NO_2	2,4-OCH_3
T163	NO_2	2,5-OCH_3
T164	NO_2	3-OH
T165	NO_2	4-OH
T166	NO_2	2-OH
T167	NO_2	2-OH,3,5-I
T168	NO_2	3,4-OCH_3

No.	R_1	X
T169	NO_2	1-Quinoline
T170	NO_2	1-Pyrrole
T171	NO_2	2-Thiophene
T172	NO_2	3-Thiophene
T173	NO_2	1-Naphthol
T174	NO_2	Quinoline
T175	NO_2	Pyrrole
T176	NO_2	2-Thiophene
T177	NO_2	3-Thiophene
T178	NO_2	1-Naphthol
T179	H	Quinoline
T180	H	Pyrrole
T181	H	2-Thiophene
T182	H	3-Thiophene
T183	H	1-Naphthol
T184	H	Quinoline
T185	H	Pyrrole
T186	H	2-Thiophene
T187	H	3-Thiophene
T188	H	1-Naphthol

Table SI2. Molecular docking results for a series of designed compounds and selected marketed drugs against BRAF kinase with V600E mutation.

Compounds	Energy (kcal mol^{-1})
Dabrafenib	-12.7
T109	-12.3
T183	-12.1
T160	-12.1
T126	-12.1
T131	-11.9
T102	-11.9
T104	-11.9
T121	-11.9
T155	-11.9
T119	-11.8
T164	-11.8
T107	-11.8
T124	-11.8
T114	-11.8
T148	-11.8
T184	-11.8
T179	-11.8
T165	-11.8
T158	-11.7
T101	-11.7
T113	-11.7
T153	-11.7
T118	-11.6
T143	-11.6
T152	-11.6
T135	-11.6
T174	-11.5
T130	-11.5
T103	-11.5
T110	-11.5
T120	-11.5
T133	-11.4
T150	-11.4
T144	-11.4
T112	-11.4
T116	-11.4
T154	-11.4
T139	-11.4
T178	-11.4
T106	-11.3
T177	-11.3
T122	-11.3
T129	-11.3
T167	-11.3
T105	-11.3
T156	-11.3
T169	-11.3
T137	-11.2
T175	-11.2
T176	-11.2
T166	-11.2
T159	-11.2
T132	-11.2
T138	-11.2
T157	-11.1
T108	-11.1
T111	-11.1
T187	-11.1
T188	-11.1
T173	-11.1
T127	-11.1
T180	-11.1
T125	-11.1
T185	-11.1
T168	-11
T117	-11
T136	-11
T161	-11
T163	-11
T181	-11
T186	-11
T162	-11
T145	-10.9
T123	-10.9
T147	-10.8
T128	-10.8
T134	-10.8
T115	-10.8
Encorafenib	-10.7
T149	-10.7
T171	-10.6
T141	-10.6
T172	-10.6
Vemurafenib	-10.5
T170	-10.3
T182	-10.2
Sorafenib	-10.2
T140	-10.2
T151	-10.1
T146	-9.9
T142	-9.5

Table SI3. Clustering statistics for T160: hBRk complex

clusters	DBI [a]	PSF [b]	SSR/SST [c]
2	1.85	1074.02	0.097
3	2.25	1274.32	0.203
4	2.48	1108.58	0.250
5	2.31	1076.36	0.301

[a]**DBI** = Davies-Bouldin index**,** [b]**pSF** = pseudo-F statistic, [c]**SSR/SST** = ratio of sum of squares regression and sum of squares error

Table SI4. T160: hBRk conformational occupancy over time (1μs)

cluster	conformation	population	d	csd	RMSD against A
1	A	0.519	2.714	0.332	0
2	B	0.361	2.329	0.238	1.631
3	C	0.120	2.290	0.257	1.938

d = average distance between points in the cluster, **csd** = standard deviation of points in the cluster

Table SI5. Clustering statistics for T109: hBRk complex

Clusters	DBI [a]	PSF [b]	SSR/SST [c]
2	2.25	1632.51	0.140
3	2.13	1237.83	0.198
4	2.32	1103.44	0.249
5	2.52	943.59	0.274

[a]**DBI** = Davies-Bouldin index, [b]**pSF** = pseudo-F statistic, [c]**SSR/SST** = ratio of sum of squares regression and sum of squares error

Table SI6. T109: hBRk conformational occupancy over time (1μs)

Cluster	Conformation	Population	d	csd	RMSD against A
1	A	0.611	2.453	0.265	0
2	B	0.308	2.528	0.288	1.884
3	C	0.080	2.551	0.432	1.998

d = average distance between points in the cluster, **csd** = standard deviation of points in the cluster

Table SI7. Clustering statistics for T126: hBRk complex

Clusters	DBI [a]	PSF [b]	SSR/SST [c]
2	1.77	1843.86	0.156
3	1.70	2449.64	0.329
4	1.58	1768.59	0.347

5	1.96	1629.42	0.395

[a]**DBI** = Davies-Bouldin index, [b] **pSF** = pseudo-F statistic, [c] **SSR/SST** = ratio of sum of squares regression and sum of squares error

Table SI8. T126: hBRk conformational occupancy over time (1μs)

cluster	conformation	population	d	csd	RMSD against A
1	A	0.501	2.619	0.355	0
2	B	0.298	2.729	0.426	2.519
3	C	0.187	2.540	0.401	2.691
4	D	0.014	2.481	0.462	3.077

d = average distance between points in the cluster, **csd** = standard deviation of points in the cluster

Table SI9. Clustering statistics for T183: hBRk complex

clusters	DBI [a]	PSF [b]	SSR/SST [c]
2	1.87	2514.42	0.201
3	1.69	2037.47	0.290
4	1.82	1845.13	0.356
5	1.94	1415.46	0.362

[a] **DBI** = Davies-Bouldin index, [b] **pSF** = pseudo-F statistic, [c] **SSR/SST** = ratio of sum of squares regression and sum of squares error

Table SI10. T183: hBRk conformational occupancy over time (1 μs).

cluster	conformation	population	d	csd	RMSD against A
1	A	0.651	2.632	0.313	0
2	B	0.285	2.870	0.478	2.246
3	C	0.064	2.698	0.580	4.154

d = average distance between points in the cluster, **csd** = standard deviation of points in the cluster