

Probing the binding sites, global energy and molecular interactions between ponatinib, cabozantinib and sunitinib anticancer drugs with vascular endothelial growth factor

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ABSTRACT: Global Energy, binding sites and molecular interactions between ponatinib, cabozantinib and sunitinib anticancer drugs with vascular endothelial growth factor was probed to find the best binding energy at the active site. The structures of ponatinib, cabozantinib and sunitinib were drawn and constructed using window based program of ArgusLab and ACDlab ChemSketch softwares. Docking studies were performed using the Patchdock and Firedock online software packages. The protein data bank (PDB) file of the crystal structure of vascular endothelial growth factor (VEGF) was subjected to refinement protocols. The interactive docking method was carried out for all the conformers of each compound in the selected active site. The docked compound was assigned a score according to its fit in the ligand binding pocket (LBP) and its binding mode. The docked complexes were interpreted using Molecular Molegro viewer software. The best binding energy (minimum energy) is -18.12 Kcal/mol, -21.63 Kcal/mol and -14.00 Kcal/mol for ponatinib, cabozantinib and sunitinib respectively. The negative value of the binding energy shows that ponatinib, cabozantinib and sunitinib can selectively inhibit vascular endothelial growth factor (VEGF).

Key words: Cabozantinib, molecular interaction, ponatinib, sunitinib, vascular endothelial growth factor.

INTRODUCTION

Ponatinib was designed using ARIAD's computational and structure-based drug design platform to inhibit the enzymatic activity of BCR-ABL protein with very high potency and broad specificity. Ponatinib was intended to target not only native BCR-ABL, but also its isoforms that carry mutations that confer resistance to treatment with existing tyrosine kinase inhibitors, including especially the T315I mutation for which no effective therapy exists (Zhou et al., 2011). The road to discovery can be linked to ponatinib [AP23464], one of the first of Ariad's ATP competitive dual Src/Abl inhibitors. AP23464 was identified using structure based drug design and focused synthetic libraries of trisubstituted purine analogs. The

substance potently inhibits on nanomolar scale, Src and Bcr-Abl kinases including many common imatinib resistant Bcr-Abl mutations. AP23464 does not inhibit the T315I mutation whereas AP24534 (ponatinib) does (O'Hare et al., 2009). Ponatinib (trade name Iclusig previously AP24534) is an oral drug developed by ARIAD Pharmaceuticals for the treatment of chronic myeloid leukemia (CML) and Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL). It is a multi-targeted tyrosine-kinase inhibitor (Huang et al., 2010). Some forms of CML, those that have the T315I mutation are resistant to current therapies such as imatinib. Ponatinib has been designed to be effective against

these types of tumors (O'Hare et al., 2009). The United States Food and Drug Administration approved the drug as for use in December 2012 but temporarily suspended sales on 31 October 2013 because of "the risk of life-threatening blood clots and severe narrowing of blood vessels (FDA, 2013; Grady, 2013). This suspension was partially lifted on Dec. 20, 2013 with ponatinib being issued revised prescribing information, a new Black Box Warning and a "Risk Evaluation and Mitigation Strategy" in place to better evaluate the risks and benefits of using the drug. Ponatinib was approved by the US FDA on December 14, 2012 for patients with resistant or intolerant CML and Ph+ ALL based on results of the PACE phase II trial reported days earlier at the annual ASH meeting (Gever, 2012). Based on these additional studies, the FDA granted in 2016 full approval and label update to ponatinib (Iclusig) for patients with chronic phase, accelerated phase or blast phase chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia for whom no other tyrosine kinase inhibitor therapy is indicated. Approval was also granted for T3151-positive and T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (<http://www.onclive.com>). The United States Food and Drug Administration issued a partial clinical hold on new trial enrolment for Iclusig on October 9, 2013 due to an increased number of blood clots observed in patients taking the drug (Carroll, 2013).

The primary target for ponatinib is a BCR-ABL, an abnormal tyrosine kinase that is the hallmark of CML and Ph+ ALL. CML is characterized by an excessive and unregulated production of white blood cells by the bone marrow due to a genetic abnormality that produces the BCR-ABL protein, O'Hare et al (2009). Cabozantinib, marketed under the trade name Cabometyx among others, is a small molecule inhibitor of the tyrosine kinases c-Met and VEGFR2, and has been shown to reduce tumor growth, metastasis and angiogenesis. It was discovered and developed by Exelixis Inc and was granted orphan drug status by the U.S. Food and Drug Administration (FDA) in January 2011 (Exelixis, 2011). Cabozantinib is approved by the U.S. FDA for medullary thyroid cancer (FDA approves Cometriq, 2012) and advanced renal cell carcinoma in people who have received prior anti-angiogenic therapy (FDA Approval Announcement, 2016). It is currently undergoing clinical trials for the treatment of prostate, bladder, ovarian, brain, melanoma, breast, non-small cell lung, pancreatic, and hepatocellular cancers. In October 2011, cabozantinib met its primary endpoint in a phase 3 clinical trial (EXAM) conducted by Exelixis investigating its effect on progression-free survival in medullary thyroid cancer. A new drug application was submitted in the first half of 2012 (Thyroid cancer, 2011) and on November 29, 2012 cabozantinib in its capsule formulation was granted marketing approval by the U.S. FDA under the name

Cometriq for treating patients with medullary thyroid cancer (FDA approves Cometriq, 2012). Approval for its tablet formulation was granted for treating people with kidney cancer on April 25th, 2016 (<http://www.accessdata.fda.gov/drugsatfda>). Grapefruit and grapefruit juice should be avoided as they may increase the concentration of the drug in the blood (Cometriq prescribing, 2015). It is not yet known if cabozantinib is safe and effective in children. It is undergoing clinical trials for the treatment of prostate, ovarian, brain, melanoma, breast, non-small cell lung, hepatocellular and kidney cancers (Cabozantinib - List Results, 2013). Phase 3 study of cabozantinib versus everolimus in people with advanced clear renal cell carcinoma that worsened after VEGFR-target therapy, found benefit with cabozantinib (Choueiri et al., 2015). Sunitinib (marketed as Sutent by Pfizer and previously known as SU11248) is an oral, small-molecule, multi-targeted receptor tyrosine kinase (RTK) inhibitor that was approved by the FDA for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST) on January 26, 2006. Sunitinib was the first cancer drug simultaneously approved for two different indications (US Food and Drug Administration ,2006)]. Sunitinib inhibits cellular signaling by targeting multiple receptor tyrosine kinases (RTKs). These include all receptors for platelet-derived growth factor (PDGF-Rs) and vascular endothelial growth factor receptors (VEGFRs), which play a role in both tumor angiogenesis and tumor cell proliferation. The simultaneous inhibition of these targets therefore reduces tumor vascularization and triggers cancer cell apoptosis and thus results in tumor shrinkage. Sunitinib also inhibits CD117 (c-KIT) (Hartmann and Kanz, 2008), the receptor tyrosine kinase when improperly activated by mutation drives the majority of gastrointestinal stromal cell tumors (Quek and George, 2009). It has been recommended as a second-line therapy for patients whose tumors develop mutations in c-KIT that make them resistant to imatinib, or patients who cannot tolerate the drug (Blay and Reichardt, 2009; Gan et al., 2009). In addition, sunitinib binds RET, CD114 and CD135 receptors. The fact that sunitinib targets many different receptors, leads to many of its side effects such as the classic hand-foot syndrome, stomatitis, and other dermatologic toxicities. Thus, the objective of this research is to probe the binding sites, global energy and molecular interactions between ponatinib, cabozantinib and sunitinib anticancer drugs with vascular endothelial growth factor.

MATERIALS AND METHODS

The structures of ponatinib, cabozantinib and sunitinib (Figures 1, 2 and 3) were drawn and constructed using window based program of Arguslab (Thompson, 2007)

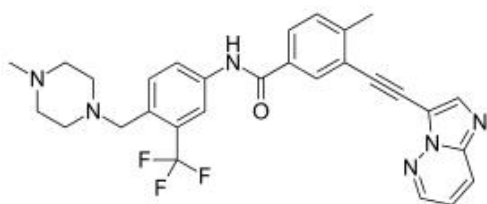


Figure 1. Chemical structure of Ponatinib,

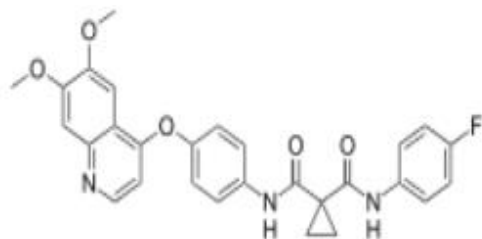


Figure 2. Chemical structure of Cabozantinib.

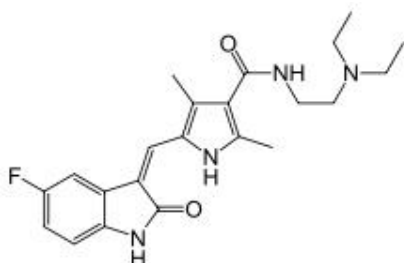


Figure 3. Chemical structure of Sunitinib.

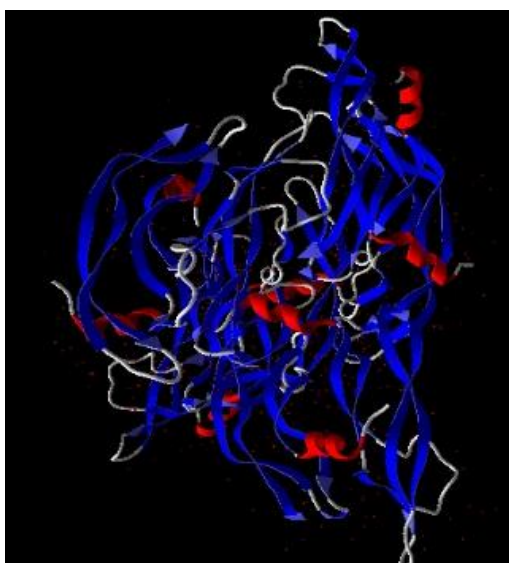


Figure 4. The crystal structure of vascular endothelial growth factor (VEGF) refined to 1.93 Å resolution.

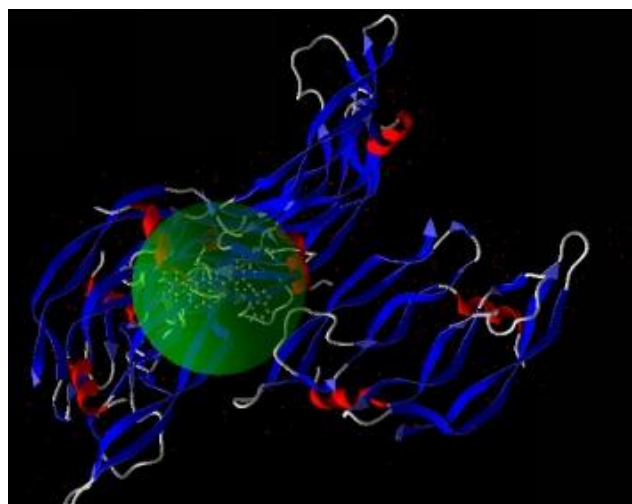


Figure 5a. Ponatinib docked with vascular endothelial growth factor (VEGF).

and ACDlab /ChemSketch softwares (Advanced Chemistry Development, 2008). Docking studies were performed using the Patchdock and Firedock online software packages (Mashiach, 2008; Andrusier, 2007; Duhovny, 2002). The protein data bank (PDB) files of the crystal structure of vascular endothelial growth factor (VEGF) refined to 1.93 (Mashiach, 2008). A resolution having PDB entry number 2VPF was downloaded from the protein data bank website. Regularization and optimization for protein and ligand were performed. Determination of the essential amino acids in binding site was carried out. The interactive docking method was carried out for all the conformers of each compound in the selected active site. The docked compound was assigned a score according to its fit in the ligand binding pocket (LBP) and its binding mode. The docked complexes were interpreted using Molecular Molegro viewer software (Molegro Molecular Viewer, 2012).

RESULTS AND DISCUSSION

The crystal structure of vascular endothelial growth factor (VEGF) refined to 1.93 Å resolution is shown in Figure 4. Ponatinib, cabozantinib and sunitinib docked with vascular endothelial growth factor (VEGF) are shown in Figures 5a, 6a and 7a respectively. Interactions of ponatinib, cabozantinib and sunitinib with vascular endothelial growth factor (VEGF) are presented in Figures 5b, 6b and 7b respectively. Global energy predictions for ponatinib, cabozantinib and sunitinib with vascular endothelial growth factor (VEGF) complexes were reported in Tables 1 to 3 respectively.

Ponatinib docked with vascular endothelial growth factor (VEGF) is shown in Figure 5a. Hydrogen bonding

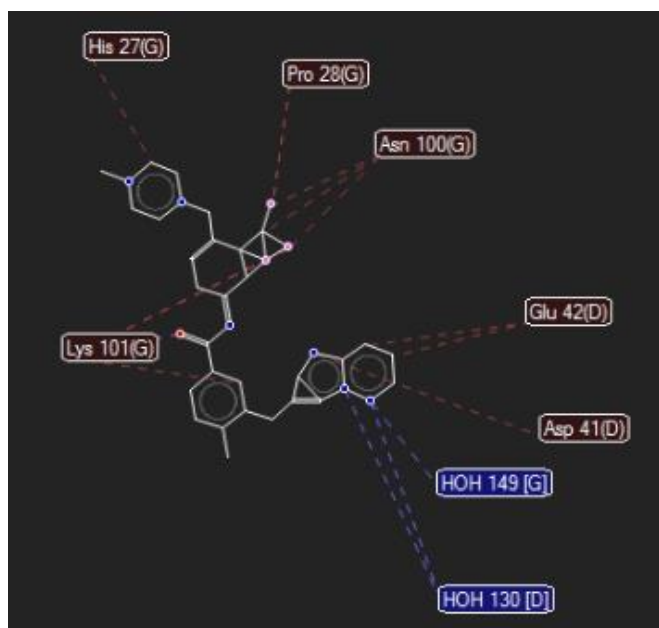


Figure 5b. Interactions of ponatinib with vascular endothelial growth factor (VEGF).

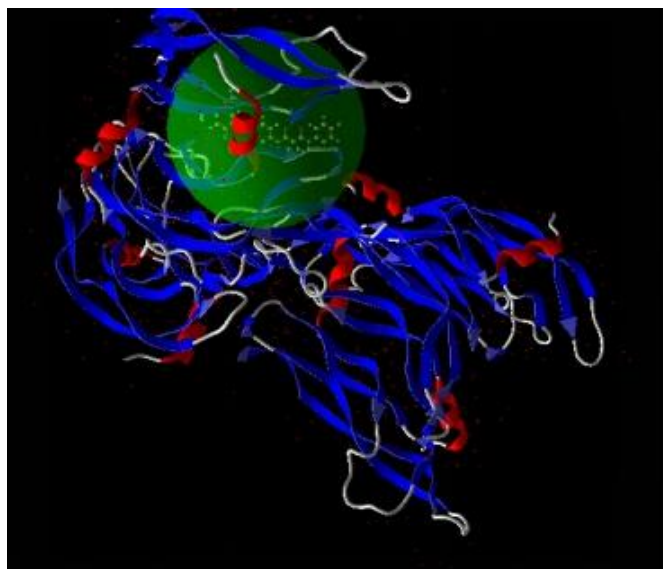


Figure 6a. Cabozantinib docked with vascular endothelial growth factor (VEGF).

and steric interactions were observed in ponatinib ligand map (Figure 5b). Hydrogen bonding occurred with Lys 101(G), HOH 147(G) and HOH 130(D). The strength of the bonds were -2.40, -0.20 and -1.68 Kcal/mol respectively. These interactions were quite favourable due to negative free energy and suitable bond lengths. Steric interactions occurred with Gln 42(D), Asp 41(D), Asp 100(G), Lys 101(G), His 27(G), Pro 28(G) and Asn

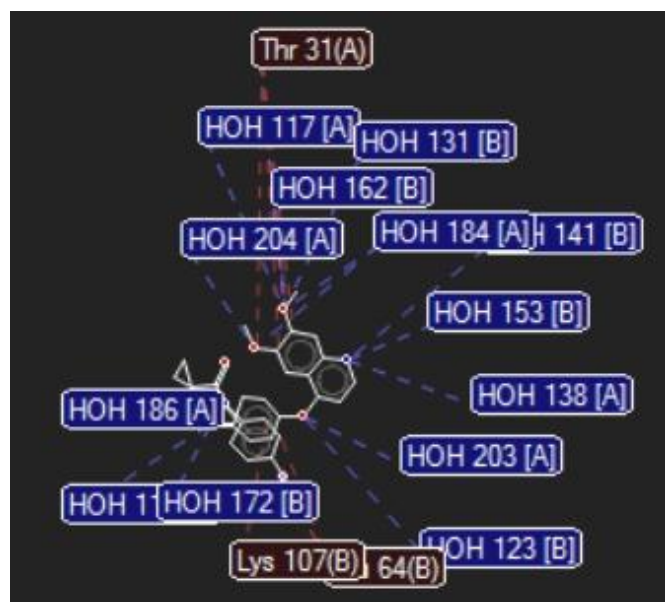


Figure 6b. Interactions of cabozantinib with vascular endothelial growth factor (VEGF).

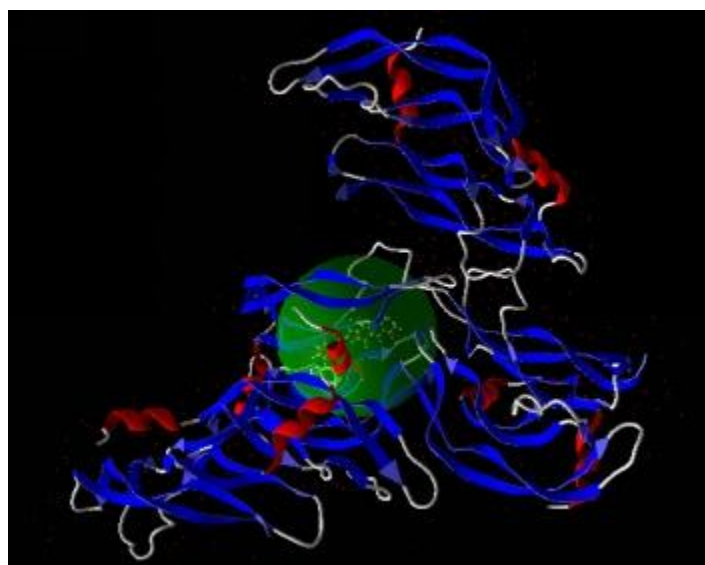


Figure 7a. Sunitinib docked with vascular endothelial growth factor (VEGF).

100(G). Global energy predictions for ponatinib - vascular endothelial growth factor (VEGF) complex is shown in Table 1. The docking score has been ranked according to their global energy. The global energy is the binding energy of the solution. The contributions of the van der Waals forces and atomic contact energy (ACE) to the global binding energy have been shown. The best binding energy (minimum energy) is -18.12 Kcal/mol. The negative value of the binding energy shows that the

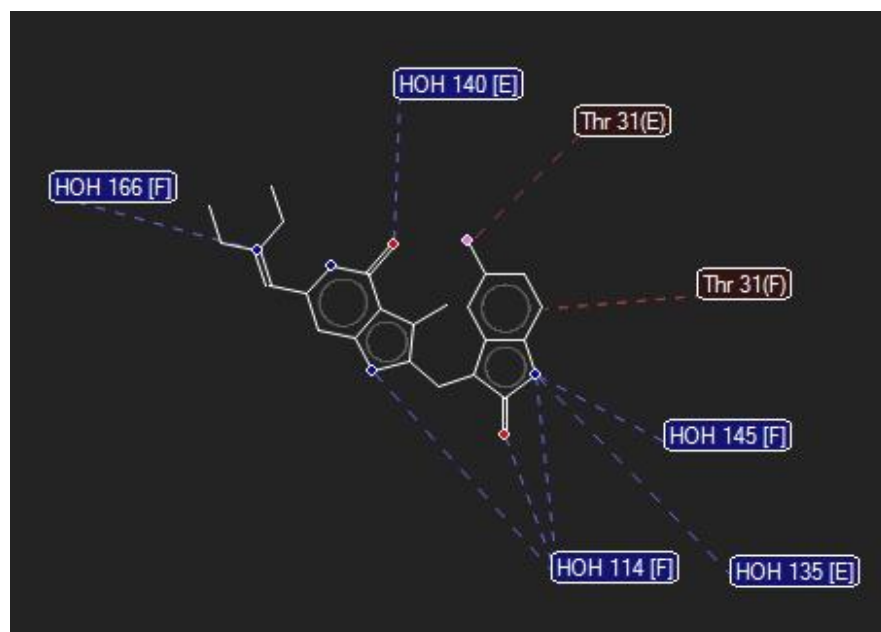


Figure 7b. Interactions of Sunitinib with vascular endothelial growth factor (VEGF).

Table 1. Global energy predictions for ponatinib - vascular endothelial growth factor (VEGF) complex.

Rank	Solution Number	Global Energy Kcal/mol _↓	Attractive VdW Kcal/mol	Repulsive VdW Kcal/mol	ACE Kcal/mol
1	4	-18.12	-16.81	5.00	-0.29
2	10	-4.88	-11.71	2.25	3.58
3	9	-4.07	-2.09	0.61	-1.07
4	6	-3.97	-8.73	5.69	-0.01
5	8	13.31	-9.02	33.09	-1.81
6	2	19.52	-10.76	40.79	-0.04
7	5	72.27	-18.23	147.01	-12.59
8	7	124.55	-11.49	176.22	-1.74
9	1	868.98	-29.60	1182.94	-21.70
10	3	900.74	-15.45	1169.52	-8.58

ponatinib can selectively inhibit vascular endothelial growth factor (VEGF) This is in agreement with the work of Yadav et al . (2017) on molecular docking studies of 3-bromopyruvate and its derivatives to metabolic regulatory enzymes: Implication in designing of novel anticancer therapeutic strategies.

Cabozantinib docked with vascular endothelial growth factor (VEGF) is shown in Table 2. The docking factor (VEGF) is shown in Figure 6a. Hydrogen bonding and steric interactions were observed in cabozantinib ligand map (Figure 6b). Hydrogen bonding occurred with HOH 186(A), HOH 138(A), HOH 141(B), HOH 172(B),HOH 204(A), HOH 162(B), HOH 117(B),HOH 123(B), HOH 203(A), HOH 141(B), HOH 184(A), HOH 131(B), Thr 31(A) and HOH 153(B). The strength of the bonds were -0.03, -2.50,-2.50, -0.69, -1.86, -2.50, -2.50, -

1.86, -0.03, -2.50,-1.80, -2.31, -0.04, -1.87 and 1.77 Kcal/mol respectively. These interactions were quite favourable due to negative free energy and suitable bond lengths. Steric in interactions occurred with Lys 107(B), Glu 64(B) and Thr 31(A) respectively. Global energy predictions for cabozantinib - vascular endothelial growth factor (VEGF) complex is shown in Table 2. The docking score has been ranked according to their global energy. The global energy is the binding energy of the solution. The contributions of the van der Waals forces and atomic contact energy (ACE) to the global binding energy have been shown. The best binding energy (minimum energy) is -21.63 Kcal/mol. The negative value of the binding energy shows that the cabozantinib can selectively inhibit vascular endothelial growth factor (VEGF). This is

Table 2. Global energy predictions for cabozantinib - vascular endothelial growth factor (VEGF) complex.

Rank	Solution Number	Global Energy Kcal/mol↓	Attractive VdW Kcal/mol	Repulsive VdW Kcal/mol	ACE Kcal/mol
1	8	-21.63	-12.12	2.69	-5.21
2	9	-13.59	-7.80	2.23	-3.31
3	6	-6.00	-9.94	10.15	-0.27
4	1	-1.02	-0.83	0.24	-0.82
5	2	-0.10	-2.08	0.35	-0.08
6	3	2.10	-1.14	0.00	1.17
7	7	15.29	-21.99	64.21	-3.24
8	4	66.49	-14.69	130.47	-11.13
9	5	628.75	-21.60	834.80	-7.48
10	10	2759.48	-17.25	3515.86	-18.41

Table 3. Global energy predictions for Sunitinib – vascular endothelial growth factor (VEGF) complex.

Rank	Solution Number	Global Energy Kcal/mol↓	Attractive VdW Kcal/mol	Repulsive VdW Kcal/mol	ACE Kcal/mol
1	1	-14.00	-8.78	7.65	-5.37

consistent with the publication of Ahuja and Singh (2016) on *in silico* approach for SAR analysis of the predicted model of DEPDC1B: a novel target for oral cancer.

Sunitinib docked with vascular endothelial growth factor (VEGF) is shown in Figure 7a. Hydrogen bonding and steric interactions were observed in sunitinib ligand map (Figure 7b). Hydrogen bonding occurred with HOH 166(F), HOH 145(F), HOH 140 (E), HOH 135 (E) and HOH 114 (F). The strength of the bonds were -2.35, -0.44, -2.19, -0.98 and -2.14 Kcal/mol respectively. These interactions were quite favourable due to negative free energy and suitable bond lengths. Steric interactions occurred with Thr 31(E) and Thr 31(F). Global energy predictions for Sunitinib - vascular endothelial growth factor (VEGF) complex is shown in Table 3. The docking score has been ranked according to their global energy. The global energy is the binding energy of the solution. The contributions of the van der Waals forces and atomic contact energy (ACE) to the global binding energy have been shown. The best binding energy (minimum energy) is -14.00 Kcal/mol. The negative value of the binding energy shows that the sunitinib can selectively inhibit vascular endothelial growth factor (VEGF). This is in agreement with report of Ikpeazu et al. (2017) on using Patchdock, a molecular docking algorithm based on shape complementarity principles.

Conclusion

The best binding energy (minimum energy) is -18.12 Kcal/mol, -21.63 Kcal/mol and -14.00 Kcal/mol for

ponatinib, cabozantinib and sunitinib respectively. The negative value of the binding energy shows that ponatinib, cabozantinib and sunitinib can selectively inhibit vascular endothelial growth factor (VEGF). Molecular interaction is used in structure-based drug design to predict the binding energy and conformation of ligands complexed to target receptors. Molecular interaction can be seen as “lock and key”. The receptor is seen as the lock while the ligand is the key. This explains the best conformation of the ligand when it binds to the receptor. During molecular interaction, the ligand and the protein try to achieve the “best-fit”.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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