Electronic Supplementary Material (ESI) for RSC Advances.

SUPPORTING INFORMATION

Computational analysis revealed K634 and T681 mutations modulate 3D-structure of PDGFR-β leading to sunitinib resistance

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Fig. S1

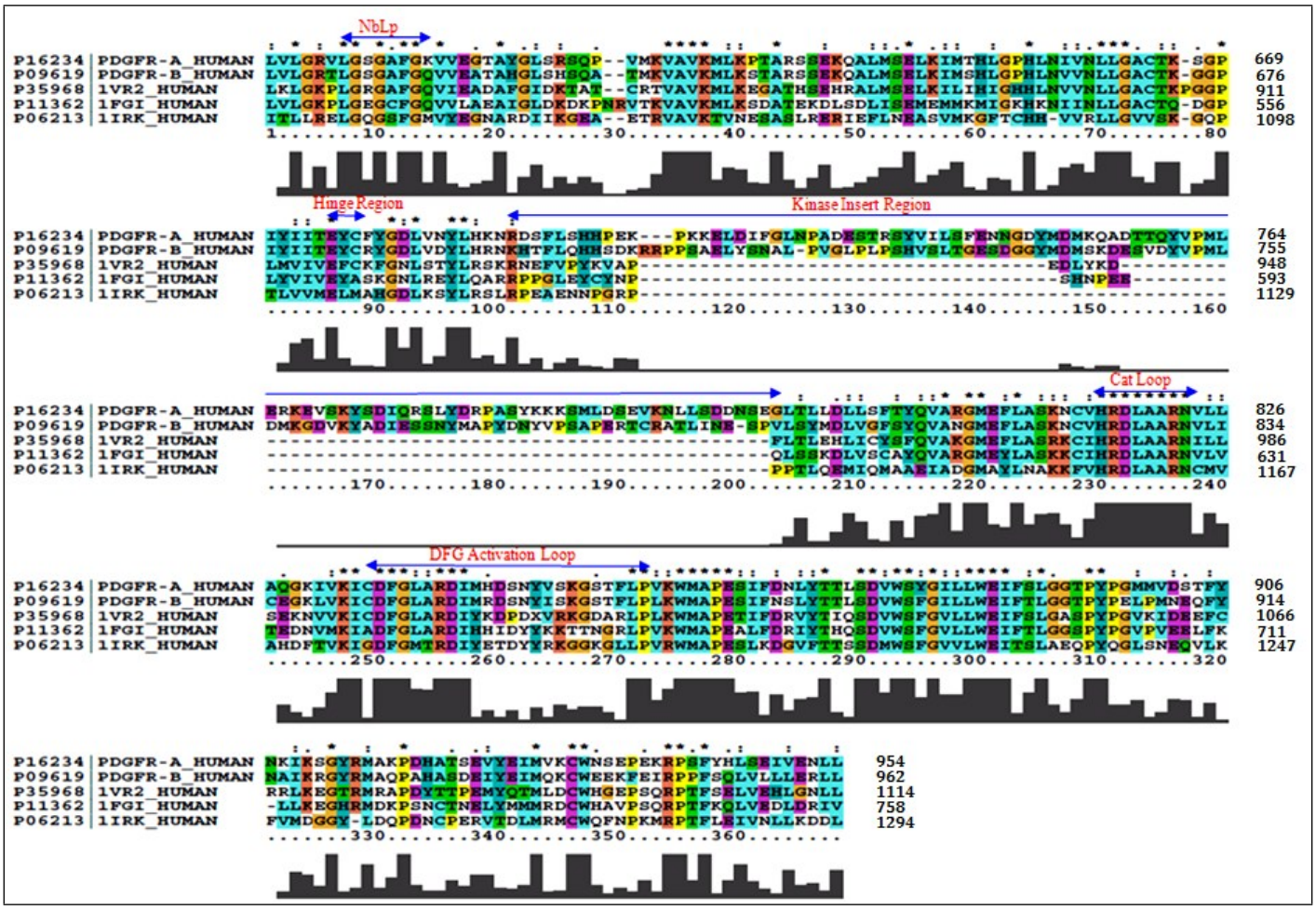

Fig. S1 Sequence alignment for PDGFR-β subtype receptor using Clustal-X 2.0 showed 80% sequence homology with PDGFR-α and PDGFR-β respectively. Red labeling showed highly Conserved regions, which are nucleotide binding loop (NbLp), Hinge region, Kinase insert region, and DFG (Asp-Phe-Gly) region. Symbol (*) showing conserved residues, and (:) showing semi-conserved residues.

Fig. S2

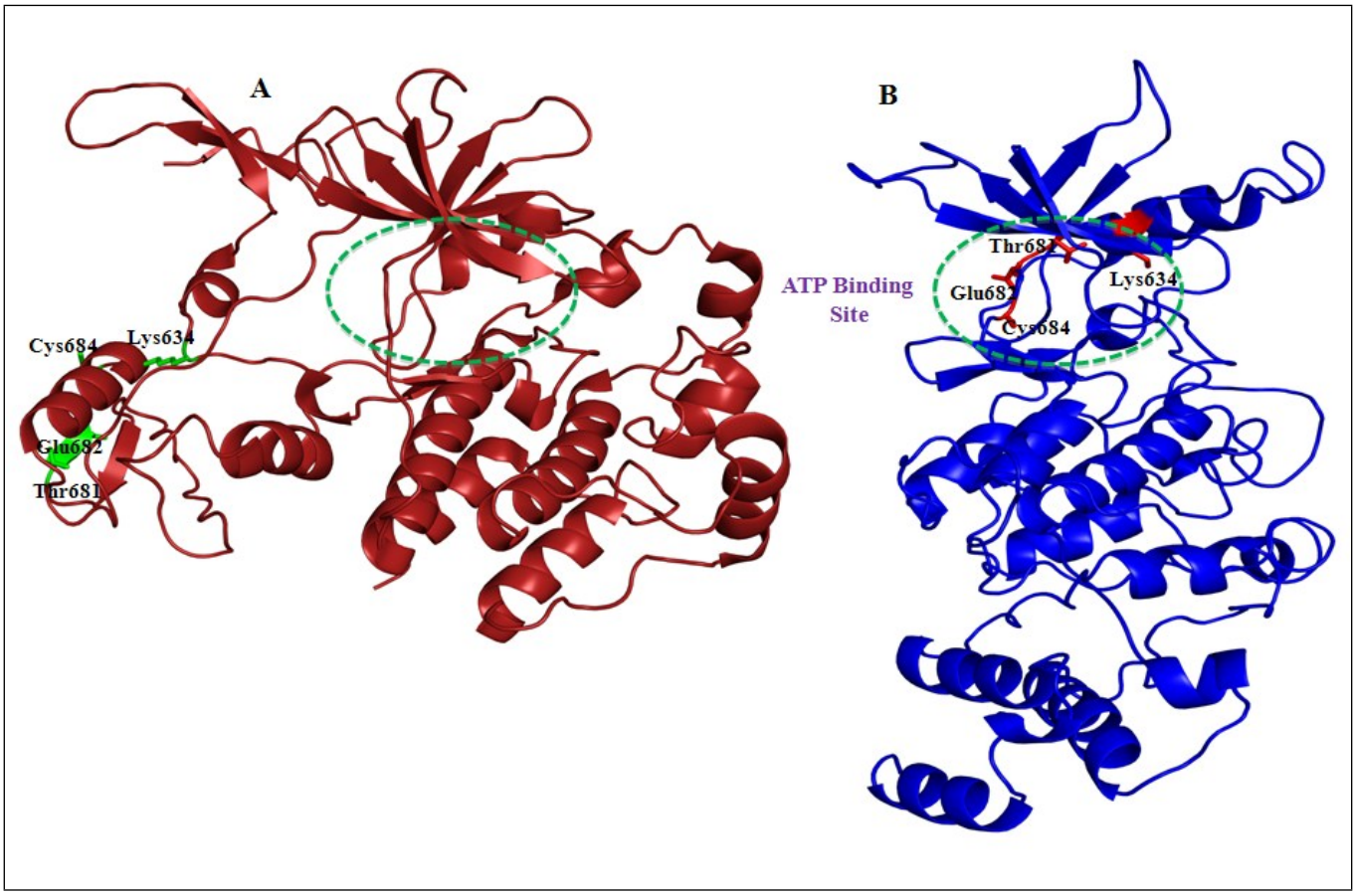

Fig. S2 Comparison of ATP binding site encircled in green dotted lines between the reported structure (Red Cartoon) and predicted structure (Blue Cartoon) of PDGFR-β.

Fig. S3

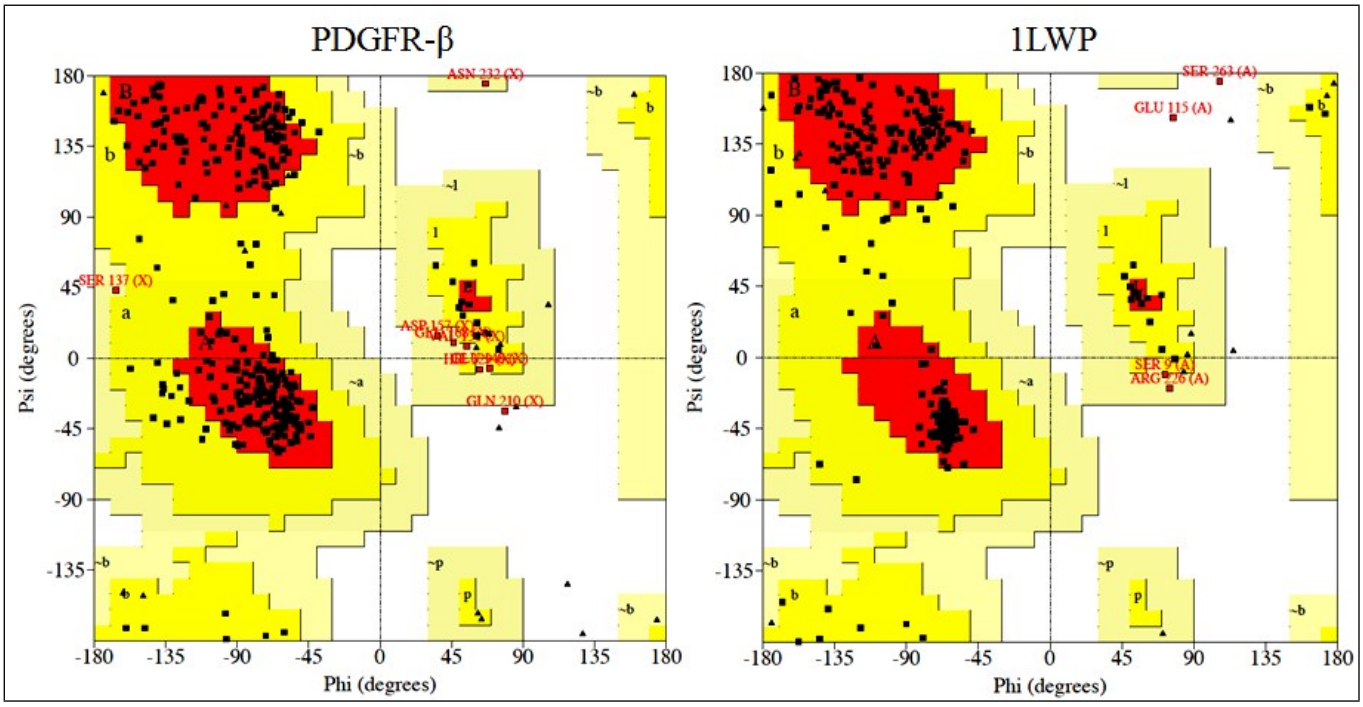

Fig. S3 Ramachandran plot of both the PDGFR-β and earlier predicted model 1LWP; Amino acid residues represented with black dots, most favorable region denoted with red color. Additional allowed, generously allowed and disallowed regions were showed as yellow, pale yellow and white respectively.

Table S1. Ramachandran Plot statistics.

	Plot statistics	
	PDGFR-β	**1LWP**
Residues in most favoured regions [A,B,L]	89.0%	88.3%
Residues in additional allowed regions [a,b,l,p]	8.8%	10.4%
Residues in generously allowed regions [~a,~b,~l,~p]	1.6%	0.6%
Residues in disallowed regions	0.6%	0.6%
	100.0%	100.0%
Total number of residues	**363**	**363**

Fig. S4

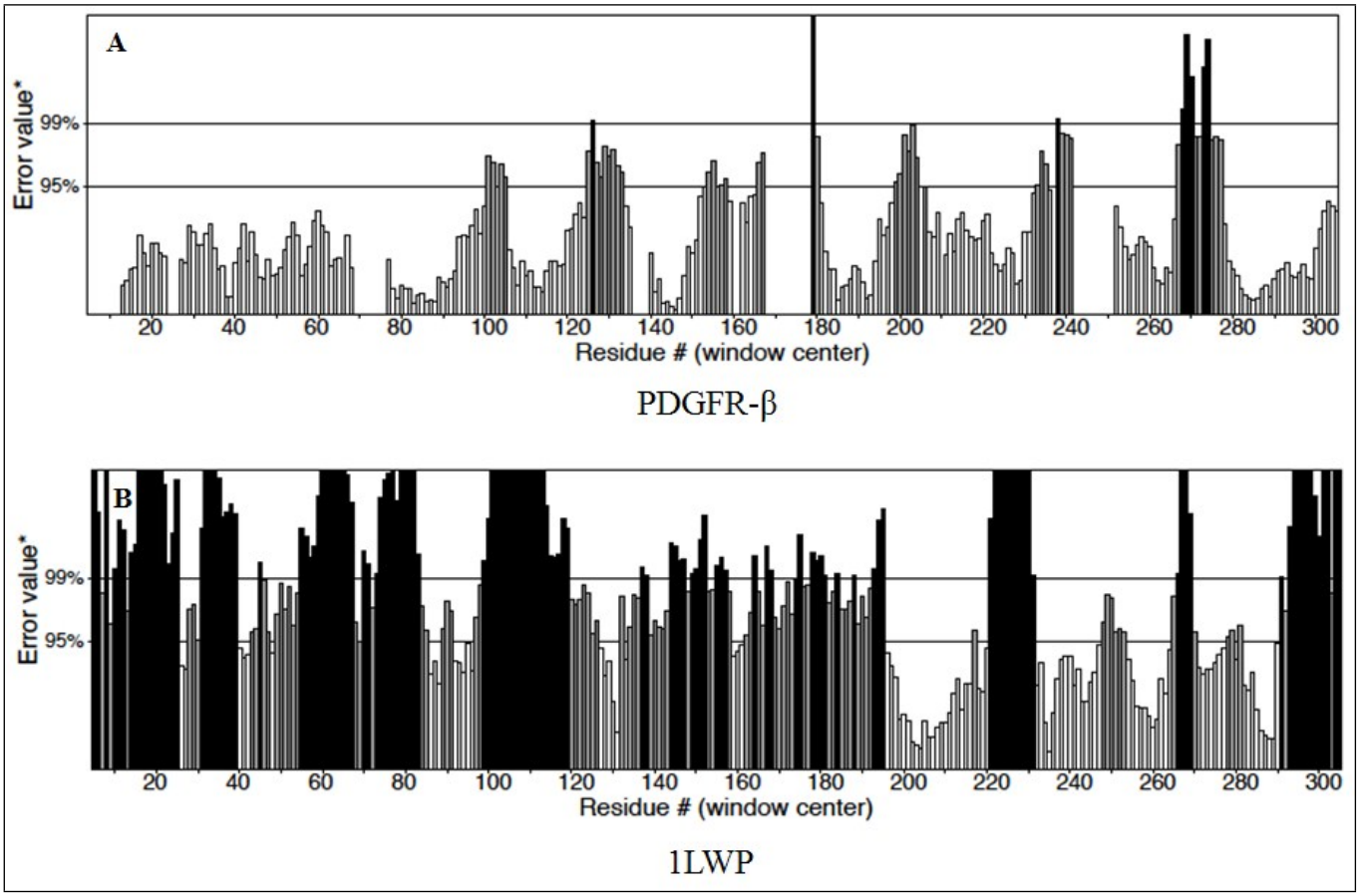

Fig. S4 ERRAT2 plot determines "overall quality factor" for non-bonded atomic interactions and gives the measure of the structural error at each amino acid residues in the 3D structure model. Ideally this error should be below 95% cut-off value.

Fig. S5

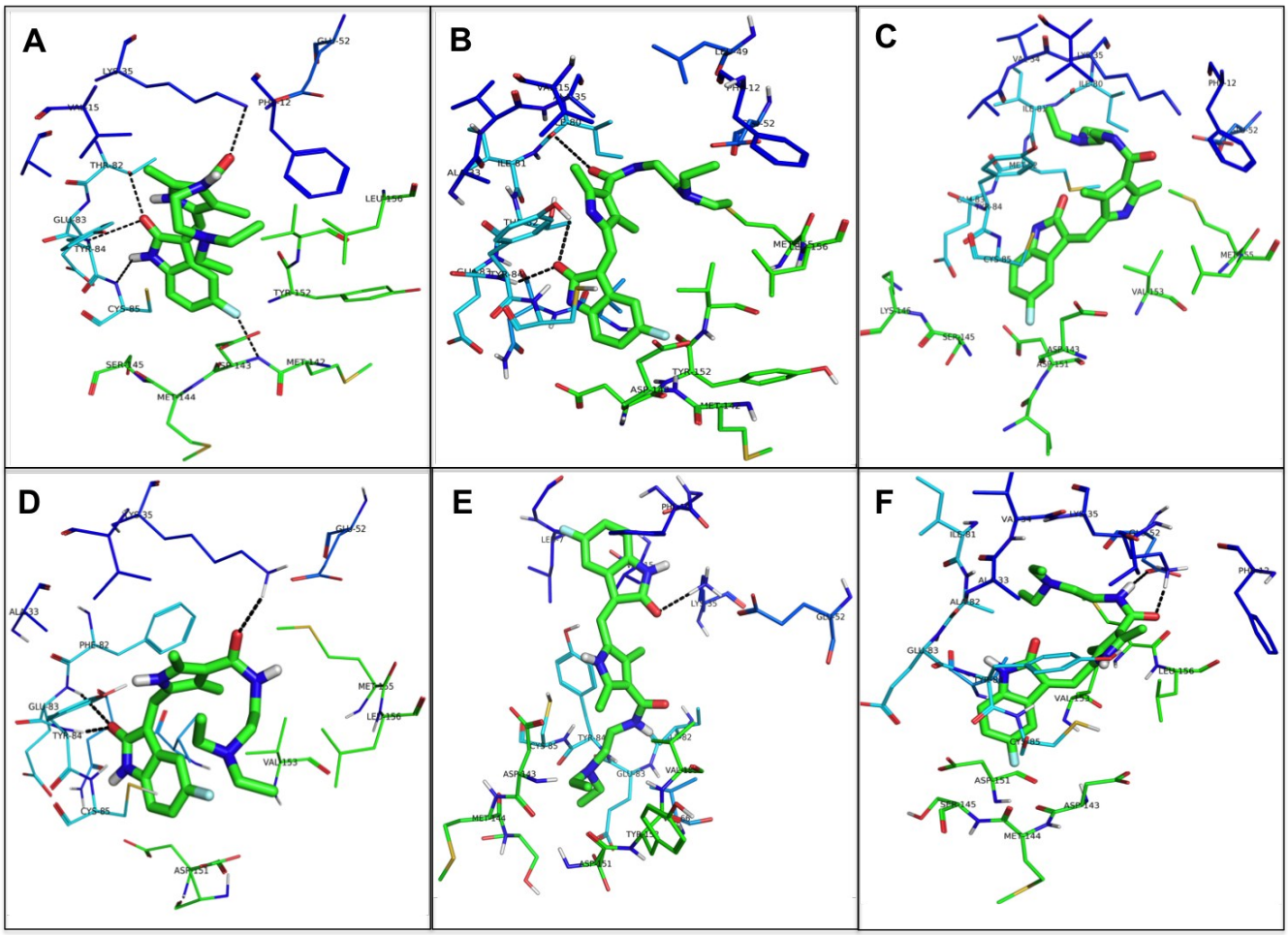

Fig. S5 Comparison of variation in surrounding amino acid residues of (A) Wild type, (B) K634A, (C) T681M, (D) T681F, (E) T681I and, (F) T681A.

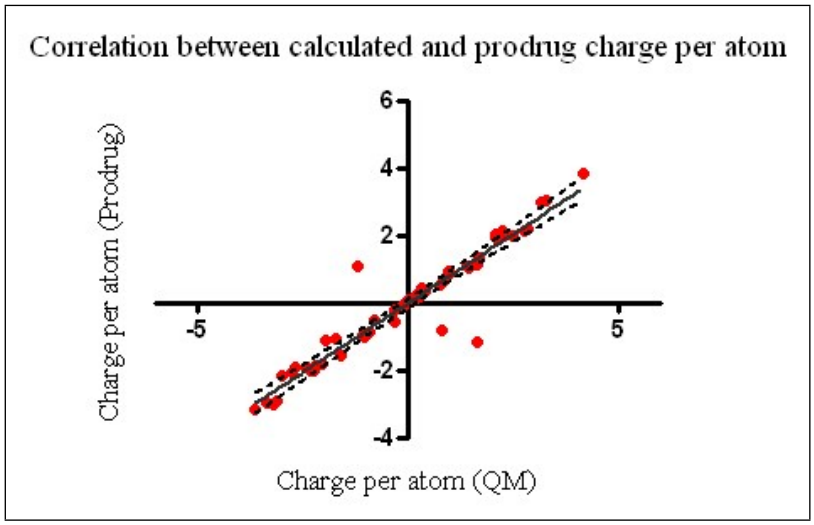

Fig. S6 Correlation plot between ligand charges that were predicted by PRODRG2 and MO chemical quantum calculation. The plot showed correlation value (r2 = 0.89).

Table S2. Identification of ten conformations on the basis of docking energies.

S.No	Rank	Run	Conf: ΔG	Residues	No. Of Interactions
1	**1**	**22**	**-12.94**	**K634, T681, Y683, C684, D742**	**5**
2	3	28	-10.15	G739, M741, D742	3
3	4	9	-10.10	Y683, M741	2
4	5	15	-9.94	Y683, D742	2
5	6	7	-9.85	D688, M741	2
6	7	48	-9.79	D688, D742	2
7	8	34	-9.65	D688, D742	2
8	6	13	-9.15	G739, Y762	2
9	6	5	-8.95	E682, Y683	2
10	6	23	-8.86	K634, D742	2

Table S3. Amino acid residues involved in hydrogen bonding interactions present only in the Catalytic loop region of PDGFR-β.

Protein Model	Residue No.	Chain	Residue No.	Distance (Å)	Distance Type
Wild Type (WT)	Cys843	A	Leu839	3.2	Side-Main
	Phe845	A	Ile842	3.1	Main-Main
	Gly846	A	Leu817	2.9	Main-Main
	Leu847	A	Leu817	2.9	Main-Main
	Arg853	A	Cys835	2.9	Side-Main
	Arg853	A	Glu836	2.6	Side-Main
	Asn856	A	Glu836	3.0	Side-Side
	Tyr857	A	Arg853	3.3	Main-Main
	Ile858	A	Asp854	3.3	Main-Main
	Ser859	A	Asn856	3.1	Main-Main
	Lys860	A	Tyr857	2.9	Main-Main
	Gly861	A	Tyr857	2.9	Main-Main
K634A (MT)	Asp844	A	Val840	2.9	Main-Main
	Ala848	A	Pro774	2.9	Main-Main
	Arg849	A	Leu847	2.8	Side-Main

	Asn856	A	Arg853	2.9	Main-Main
	Asn856	A	Arg853	2.8	Side-Main
	Tyr857	A	Arg854	3.2	Main-Main
	Ile858	A	Asp855	3.1	Main-Main
	Ser859	A	Ser855	2.8	Main-Main
	Lys860	A	Tyr857	3.1	Main-Main
	Ser862	A	Glu836	2.8	Side-Main
	Thr863	A	Asn831	2.9	Main-Side
	Thr863	A	Asn831	2.7	Side-Side
T681M (MT)	Cys843	A	Leu839	3.4	Side-Main
	Asp844	A	Val840	2.9	Main-Main
	Phe845	A	Ile842	3.0	Main-Main
	Gly846	A	Ile842	3.0	Main-Main
	Leu847	A	Phe845	3.1	Main-Main
	Arg849	A	Leu732	2.9	Side-Main
	Met852	A	Asp850	2.9	Main-Main
	Ile858	A	Asp854	2.7	Main-Main
	Ser859	A	Asn856	2.9	Main-Main
	Lys860	A	Asn831	2.6	Side-Side
	Lys860	A	Glu836	2.6	Side-Main
	Lys860	A	Glu836	2.7	Side-Side
	Lys860	A	Asn856	3.0	Main-Main
	Lys860	A	Tyr857	3.1	Main-Main
	Gly861	A	Tyr857	3.2	Main-Main
	Thr863	A	Asn793	3.1	Side-Side
T681F (MT)	Asp844	A	Lys841	3.3	Main-Main
	Arg849	A	Asp850	2.7	Side-Side
	Ile851	A	Leu847	3.2	Side-Main
	Arg853	A	Ala848	2.8	Side-Main
	Asn856	A	Arg853	2.9	Main-Main
	Tyr857	A	Arg853	2.9	Main-Main
	Ile858	A	Asp854	2.9	Main-Main
	Ser859	A	Asn856	2.7	Side-Main
	Lys860	A	Tyr857	3.4	Main-Main
	Lys860	A	Glu836	2.6	Side-Side
	Gly861	A	Tyr857	2.8	Main-Main
T681I (MT)	Cys843	A	Met852	3.0	Side-Main
	Asp844	A	Lys841	2.8	Main-Main

	Phe845	A	Lys841	2.9	Main-Main
	Asp850	A	Leu847	2.9	Main-Main
	Ile851	A	Leu847	3.2	Main-Main
	Met852	A	Ile842	2.9	Main-Main
	Ser855	A	Asp854	3.1	Main-Side
	Asn856	A	Arg853	3.0	Main-Main
	Tyr857	A	Arg853	2.8	Main-Main
	Tyr857	A	Ser862	2.7	Side-Side
	Ile858	A	Asp854	2.9	Main-Main
	Ser859	A	Asn856	3.3	Main-Main
	Lys860	A	Tyr857	3.0	Main-Main
	Lys860	A	Glu836	2.8	Side-Side
	Gly861	A	Tyr857	2.9	Main-Main
	Thr863	A	Gly861	3.0	Main-Main
	Thr863	A	Gly861	3.0	Side-Main
	Thr863	A	Asn831	2.9	Main-Side
	Leu865	A	Ala829	3.2	Main-Main
T681A (MT)	Cys843	A	Leu839	2.9	Main-Main
	Cys843	A	Arg853	3.3	Side-Main
	Asp844	A	Val840	2.9	Main-Main
	Phe845	A	Lys841	3.0	Main-Main
	Phe845	A	Ile842	3.1	Main-Main
	Arg853	A	Phe845	2.8	Side-Main
	Arg853	A	Asp850	2.9	Side-Side
	Arg853	A	Asp850	3.0	Side-Side
	Tyr857	A	Asn793	2.7	Side-Side
	Ile858	A	Asp854	2.7	Main-Main
	Ser859	A	Asn856	3.2	Main-Main
	Lys860	A	Asn856	2.9	Main-Main
	Gly861	A	Asn856	2.8	Main-Main

Table S4. Amino acid residues involved in hydrogen bonding interactions present only in the DFG region of PDGFR-β.

Protein Model	Residue No.	Chain	Residue No.	Distance (Å)	Distance Type
Wild Type (WT)	Arg825	A	Gly900	3.1	Main-Main
	Arg825	A	Leu899	2.7	Side-Main
	Leu827	A	The898	2.8	Side-Side
	Ala828	A	Asp826	3.1	Main-Side
	Arg830	A	Asp826	2.7	Side-Side
K634A (MT)	Ala828	A	Asp826	3.1	Main-Side
	Arg830	A	Asn831	2.9	Side-Side
	Asn831	A	Glu836	2.9	Side-Side
T681M (MT)	Arg830	A	Asp931	2.7	Side-Side
	Arg830	A	Asp931	2.7	Side-Side
T681F (MT)	Asp826	A	Asp826	2.6	Main- Side
	Arg830	A	Asn831	2.8	Side-Side
	Arg830	A	Thr863	3.1	Side-Side
	Asn831	A	Glu836	2.9	Side-Side
	Asn831	A	Glu836	2.9	Side-Side
T681I (MT)	Ala828	A	Asp826	3.0	Main-Side
	Arg830	A	Arg922	2.9	Side-Main
	Arg830	A	Arg922	2.8	Side-Main
	Asn831	A	Glu836	2.8	Side-Main
	Asn831	A	Gly861	3.1	Side-Main
T681A (MT)	Ala828	A	Asp826	2.9	Main-Side
	Arg830	A	Arg709	3.2	Side-Main
	Asn831	A	Gly861	2.8	Side-Main