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Role of polarization in ligand docking and binding affinity prediction for inhibitors of dengue virus

Kshatresh Dutta Dubey · Amit Kumar Chaubey · Rajendra Prasad Ojha

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Abstract Molecular docking methodology is useful in predicting comparative binding affinity of library of different ligands whose co-crystal structure in complex form is already known. However, scope of this methodology is not reliable for cross docking of different ligands due to incorrect prediction of binding pose if co-crystal structure is unknown**.** In the present work, we have studied the ligand polarization due to protein environment during the docking of seven ligands in envelope protein of dengue virus. We have used six kinase inhibitors which are active for dengue virus as well and a detergent molecule whose crystal structure is already known. We observed major change in docking scores due to polarization of ligands. The charges of the ligands were calculated by ab initio methods for the accuracy of our results. We observed increased hydrogen bonding due to polarization in protein environment. These results are more significant for inhibitors containing electronegative elements like chlorine and fluorine.

Keywords Charge transfer · Kinase inhibitors · Envelope protein · Protein–ligand interaction

Introduction

Computer simulation algorithms are a major source for study of biological systems via molecular mechanics model. The force field used in these algorithms plays a crucial role in accuracy and robustness of this technique. The concept of fixed point charge is the foundation of many widely used force field methods like OPLS (Jorgenson *et al.*, 1983, 1996), AMBER (Cornell *et al.*, 1995), and CHARMM (Mackerell *et al.*, 1998) etc. These force fields use charges derived by empirical methods which does not account role of polarization of ligand in specific environments. However, it is clear that accurate reproduction of the rigorously correct quantum mechanical potential energy surface requires the incorporation of electronic polarization into force field (Friesner, 2006). Consequently, the introduction of explicit polarization into molecular mechanics models has been a major objective of the computational chemists and biologists. Here, we have investigated the role of polarization of ligand in protein environments for Dengue virus for different type of inhibitors.

Dengue virus (DENV) is a major public health problem in tropical and sub tropical area with up to 100 millions infected annually (Deen *et al.*, 2006; Mackenzie *et al.*, 2004; Malavige *et al.*, 2004). DENV is the member of the flaviviruses, which (including West Nile virus (WNV), Yellow fever virus (YFV), Japanese Encephalitis virus (JEV), and tick borne encephalitis virus (TBEV) etc.) are associated with human disease. The dengue viral genome is a single stranded positive sense RNA of about 11 Kb in length. The genomic RNA encodes a single polyprotein that is co- and post translationally processed by both viral and cellular protease into three structural proteins, the Capsid (C), pre-membrane (PreM), and envelope (E) proteins. Infection by dengue virus is initiated by fusion between viral membrane and the host membrane. The envelope E protein mediates the fusion process in a pH dependent manner. Hence, envelope protein may be a target for a drug that blocks the entry of dengue virus. The E protein of dengue virus consists of three domains: a central

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domain I, extended finger like domain II, and immunoglobin like domain III. Domain II contains a hydrophobic stretch of amino acids, referred as the fusion peptide which is exposed during conformational change on acidic environment and initiates the fusion process (Yennamali *et al.*, 2009; Bressanelli *et al.*, 2004; Stiasny and Heinz, 2006; Mukhopadhyay *et al.*, 2005; Kielian, 2006; Zhang *et al.*, 2004; Qi *et al.*, 2008). The crystal structure of pre- and post fusion forms of a truncated version of the E protein is known (Modis *et al.*, 2003, 2004). In pre-fusion form, the dengue E protein is arranged into dimer while in the post fusion, due to acidic environment, it reorients itself into trimeric forms. During the transition from dimer to trimer, domain III rotates and shifts toward the fusion peptide by 39°. It is seen that residue 83–100 behaves as a hinge region for the rotation and shifting. Fortunately, a small ligand-binding pocket is also observed between these hinge regions (Modis *et al.*, 2003). Hence, any drug/inhibitor which binds in this region may block the transition from dimer to trimer formation which is necessary stage of viral entry. Therefore, this hinge region is a hot spot for inhibition of dengue virus.

The crystal structure of a detergent β-OG complex with dengue E protein is known and several other inhibitors are also suggested as target for this binding site. In the present study, we did computational docking of some known kinase inhibitors in the pre-fusion structure of dengue virus. A recent study of the Chu and Yang 2007 reveals that some inhibitors of c-Src family kinase also inhibit the dengue virion. In the study of Chu and Yang, it is proposed that those inhibitors that inhibit active and inactive both forms of kinase, are also effective for inhibition of dengue virus. We took dasatinib (Tokarski *et al.*, 2006), nilotinib (Rix *et al.*, 2007), PHA (Carpinelli *et al.*, 2007), PD3, PD5, and PD17 (Dar *et al.*, 2008) for the present study. 3-D structures of these inhibitors are shown in Fig. 1. The pH dependence of dengue E virus plays a crucial role for its mechanism; we prepared all inhibitors on low pH environments.

Methodology

Classical docking

The initial structure of dengue E virus was imported from protein data bank (PDB code loan) (Modis *et al.*, 2003). The imported structure has missing hydrogens, which was corrected by protein preparation wizard of maestro software (Maestro, 2008). The entire system was minimized till RMSD of 0.30 Å. The ligand dasatinib, nilotinib, PHA, PD3, PD5, PD17, and β-OG were obtained from the different crystal structure. Prior to docking, all ligands were subjected to a minimization of 1,500 cycles of conjugate gradient in low pH environments. After the protein and ligand preparation, the entire system was proceeded for docking calculations. Glide 5.0 (2008) was used for all docking calculations. Glide uses a hierarchical scoring and scaling method, details of the theory can be found in references (Friesner *et al.*, 2004; Halgren *et al.*, 2004; Taylor *et al.*, 2002; Sotriffer *et al.*, 2002; Dubey *et al.*, 2010).

QM-polarized ligand docking

The QM-polarized ligand docking protocol aims to improve the partial charges on the ligand atoms in a docking by replacing them with charges derived from quantum mechanical calculations. In this hypothesis, a QM/MM model for the ligand charges are employed in docking calculations rather than usual fixed charges assigned by the OPLS-AA force field (Cho *et al.*, 1995). Ligand is treated as QM region and DFT method is used in quantum chemical calculations. The applications and details of QM/MM method can be found in a recent article of Shaik *et al.* (2010). Sometimes, the treatment of polarization charge method adapts incorrect pose having lower energy than co-crystal structure (experimental crystal structure). To overcome this problem, an unbiased algorithm that can be executed without any knowledge of co-crystal ligand pose, is used in QM-polarized ligand docking protocol (Kaminiski *et al.*, 2002, 2004; Kaminiski 2005). This protocol retains five poses rather than retaining only one pose. QM/MM calculations are performed on the five retained poses. Charges for the ligand are extracted, and redockings with each of these charge sets is performed. Finally, the total protein ligand interaction energies (Coulomb + van der Waals) of the best scoring pose from each of the five docking are compared and the lowest total energy structure among them is selected as the final prediction for the structure of the protein ligand complex. In this way, the polarization of the charge on the ligand by receptor is accounted for, and redocking of the ligands with these new charges can result in improving docking accuracy. The whole process is divided into three procedures. In the first step, initial docking is done using empirical charge model and docking score of each ligand is calculated for this model. In the present study, we have used OPLS force field (Jorgenson *et al.*, 1983, 1996), whose energy equation is given by

$$E = E_{\text{bond}} + E_{\text{bend}} + E_{\text{tors}} + E_{\text{non-bond}}$$

where first term of the right hand side represents energy due to stretching of bonds, second term represents bending energy in bonds, third term represents energy due to torsional or dihedral angle and the last term represents the

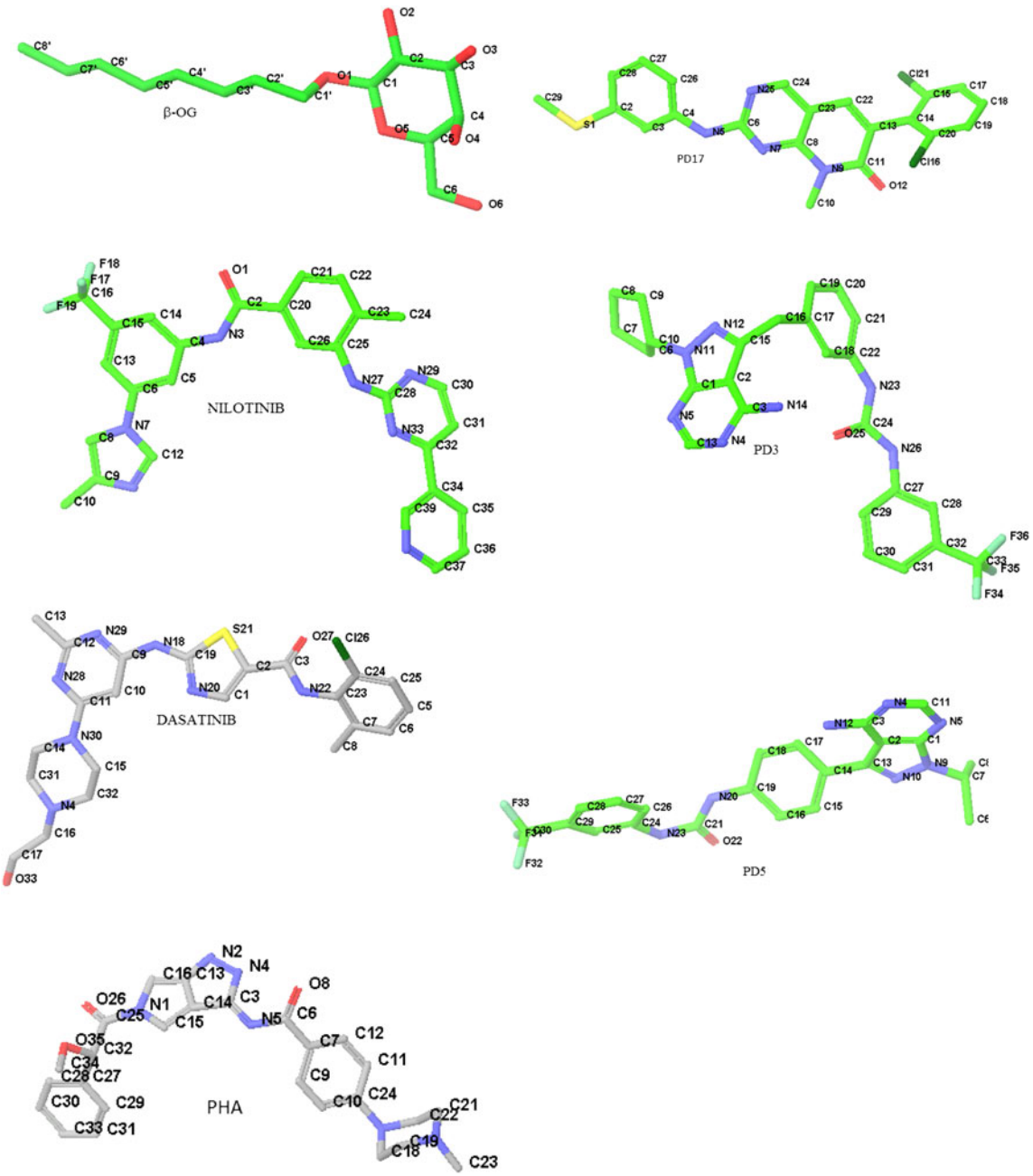

Fig. 1 Chemical structures of all inhibitors. Name of the atoms are shown according to the PDB data

non-bonded interactions like van der Waals and Lennard-Jones potentials. In the second step, the ligand partial charge is calculated using ab intio QM method. In the process, we used 6-31G* basis set, B3LYP density function, and ultrafine accuracy level. In the third step, each ligand was redocked in DENV receptor using new partial charges calculated by QM methods. Finally, the docked structures are ranked according to the Glide score obtained after QM-polarized docking. For the polarized ligand, we have used some additional terms in force field equation rather than an empirical formula (Friesner, 2006). This energy equation is

$$E = E_{\text{bond}} + E_{\text{bend}} + E_{\text{tors}} + E_{\text{non-bond}} + E_{\text{q/q}} + E_{\text{q/u}} + E_{\text{u/u}} + E_{\text{pol}}.$$

The first three terms are the valence (bonded) terms and they have standard molecular mechanical form and taken directly from the classical OPLS force field. The last four terms represent the fixed charge (q), fixed dipole (u), and polarization (pol) electrostatic interactions. Finally, the

non-bonded interaction usual Lennard-Jones 6–12 potential and a more flexible functional form are employed. The detailed descriptions are discussed elsewhere (Kaminiski *et al.*, 2004; Kaminiski, 2005). In the present study, we have used same grid parameter for classical and QM-polarized docking. The QM/MM calculations are performed by Qsite 5.0. In Qsite, the MM parts are calculated by Impact (Schrodinger Inc.) and the QM part is treated with Jaguar (Schrodinger Inc). In the calculations, we have used Gaussian charge distribution to represent the potential at the boundaries of the QM region while the MM point charges for the rest of the MM region. All calculations are performed in the gas phase, therefore, the discussion of solvation parameters are irrelevant in our calculations.

Results

The 3-D ribbon diagrams of the crystal structure of dengue E virus with different docked inhibitors are shown in Fig. 2. Figure 2a represents the initial crystal structure

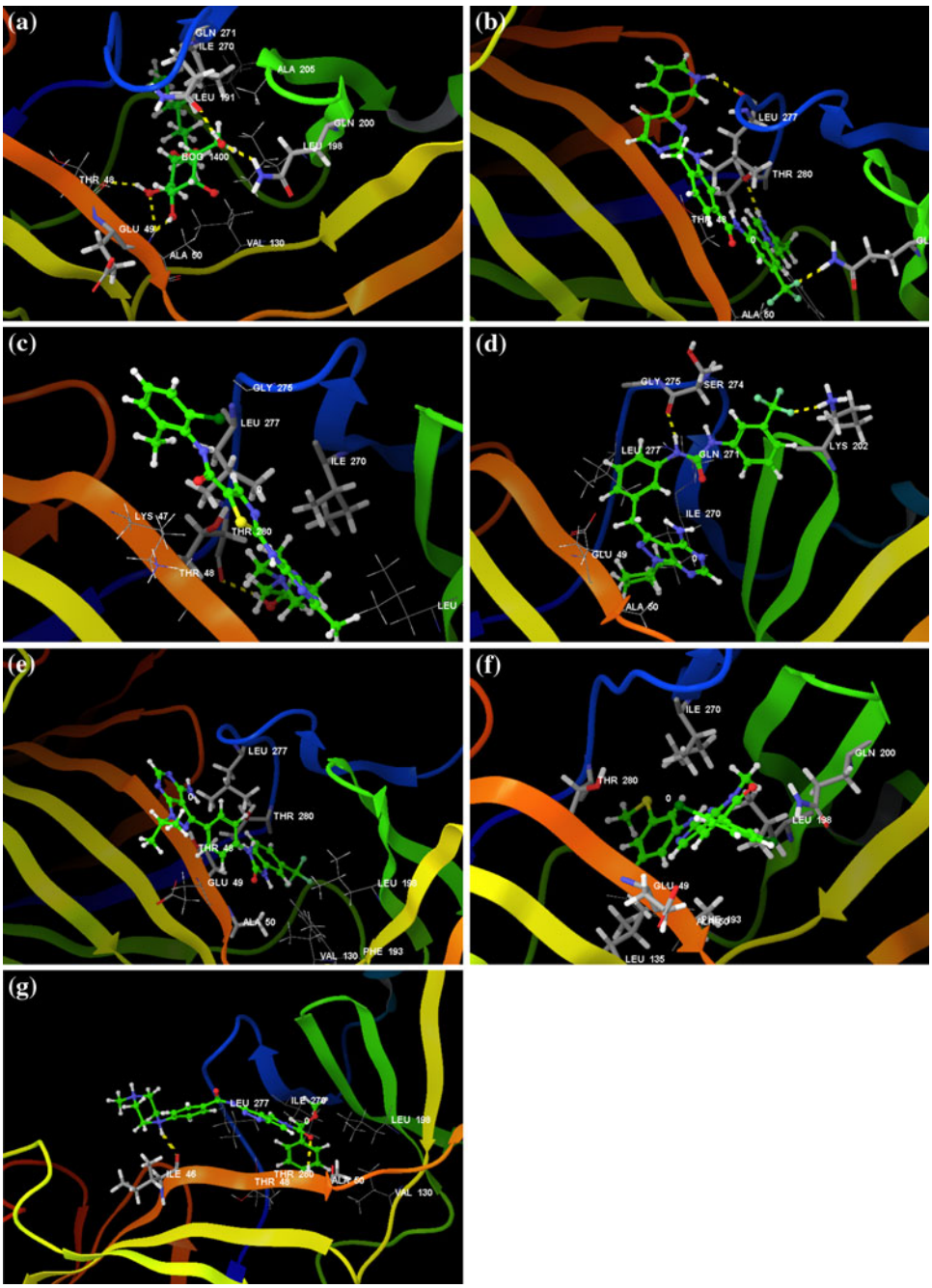

Fig. 2 Structure of docked system where all inhibitors are shown in ball and stick representation. Residues interacting with target receptor are represented by tube. **a** Binding of *β*-OG, **b** Binding of nilotinib, **c** Binding of dasatinib, **d** Binding of PD3, **e** Binding of PD5, **f** Binding of PD17, **g** Binding of PHA

bound with detergent β-OG, which is modeled by maestro visualization package. From the figure, we see that β-OG fits between the space formed between the domain I and domain II. The aliphatic chain of β-OG is oriented toward the domain Ist and hydrophobic (aromatic) group lies toward domain II. In the best-docked pose, it forms hydrogen bonds with Thr 48, Ala 50, Gln 200, and Gln 271. Residue Ala 50 forms two hydrogen bonds with detergent β-OG. At the first glance of the β-OG molecule, we see that hydrophobic group of this ligand shows main interactions with the receptor that indicates the importance of hydrophobicity for good potential drug for this receptor. Table 1 represents docking score and other energy terms in the binding of ligand with target receptor. The Columbic energy for the β-OG is −11.56 kcal/mol while the van der Waal energy is −28.08 kcal/mol. Among all other energy terms, van der Waal has the highest contribution in the binding. If we compare van der Waal energies of other ligands, β-OG has smallest value, which arises due to smaller size. The electrostatics energy is highest for β-OG that implies good bonded interactions like hydrogen bonds.

The docking score for nilotinib, which is a src kinase inhibitor, also shows good docking score that implies better binding mode than β-OG. Nilotonib occupies different place rather than β-OG. Due to bigger size, nilotinib occupies more space in binding site and shows high van der Waals energy terms. It forms three hydrogen bonds with Gln 200, Leu 277, and Thr 280. The smaller Columbic energy than β-OG may be explained due to lack of two hydrogen bonds relative to β-OG. However, it occupies more space in binding site, so, it may inhibit DENV target stronger than β-OG. The bounded interaction of nilotinib with the receptor is shown in Fig. 2b.

Dasatinib gets docking score of −5.46 and forms one hydrogen bonds with Thr 280. The electrostatic energy is significantly better than PD3 and PD5, and the van der Waals energy is main binding term. It also favors to interact with residues of domain I as PHA. The lipophilic contacts and phobic attractions are better than PD3 and PD5. The binding mode of dasatinib is shown in Fig. 2c.

The binding mode of PD3 with target receptor is shown in Fig. 2d. It implies that PD3 has different orientation in binding site. Maximum part of this inhibitor is oriented toward domain II and covers maximum part of the binding site. It forms two hydrogen bonds with Lys 202 and Ser 273. The Columbic interaction energy for PD3 is −5.66 kcal/mol, which is less than nilotinib. Again, the van der Waal contribution (−40.51 kcal/mol) is maximum among other energy terms and it is higher than β-OG molecules due to its larger size.

PD5 has docking score of −5.63, which is slightly higher than PD3. The electrostatic interaction for PD5 is low because it does not form any hydrogen bond with the target receptor. The van der Waal interaction term is also less than PD3, but, due to lipophillic contact and phobic attraction terms of −2.5 kcal/mol, which is greater than PD3, it gains good docking score over PD3. PD5 fits in the space formed between domain I and domain II.

PD17 shows better docking score than PD3 as well. The electrostatic contribution for PD17, −0.340 kcal/mol, is least among all docked ligands. Since the surface area of PD17 is large, it has good van der Waals contribution. The lipophillic contacts and phobic attraction for PD17 is better than PD3, which may be the reason for good docking score. It acquires the same position as PD5 in binding site. The binding mode of PD5 and P17 is shown in Fig. 2e and 2f.

PHA forms two hydrogen bonds with Ile 40 and Ala 50. The binding interactions of PHA are shown in Fig. 2g. We see that PHA occupies good position in binding site and it covers maximum part of the space between the hinge region formed by domain I and domain II. The most part of the PHA interacts with domain I, the docking score of PHA comes as −6.39 and it also shows polar interaction term in the active site. The lipophillic contacts and phobic attractions are higher than PD3 and PD5. All these energy contributions give docking score to PHA.

Table 1 Docking score of different inhibitors using classical force field model

Ligand	Docking score	E_{Coul}	E_{vdw}	E_{lipo}
β-OG	−5.3	−11.56	−28.08	−2.9
Nilotinib	−7.1	−7.04	−49.10	−2.9
PHA	−6.3	−7.11	−36.64	−2.8
PD3	−5.3	−5.66	−40.51	−2.0
PD5	−5.7	−1.37	−38.32	−2.5
PD17	−5.6	−0.34	−40.26	−2.5
Dasatinib	−5.4	−5.06	−41.99	−2.4

All energies are in kcal/mol

Table 2 Docking score of different inhibitors when they are docked by QM-polarized ligand docking protocol

Ligand	Docking score	E_{Coul}	E_{vdw}	E_{lipo}
β-OG	−5.5	−11.35	−27.24	−3.1
Nilotinib	−6.6	−4.52	−47.62	−3.0
PHA	−5.5	−6.12	−46.76	−2.1
PD3	−3.3	−2.45	−38.55	−2.5
PD5	−2.4	−1.00	−17.87	−2.2
PD17	−6.2	−7.31	−28.59	−2.2
Dasatinib	−6.5	−9.91	−31.85	−2.8

All energies are in kcal/mol

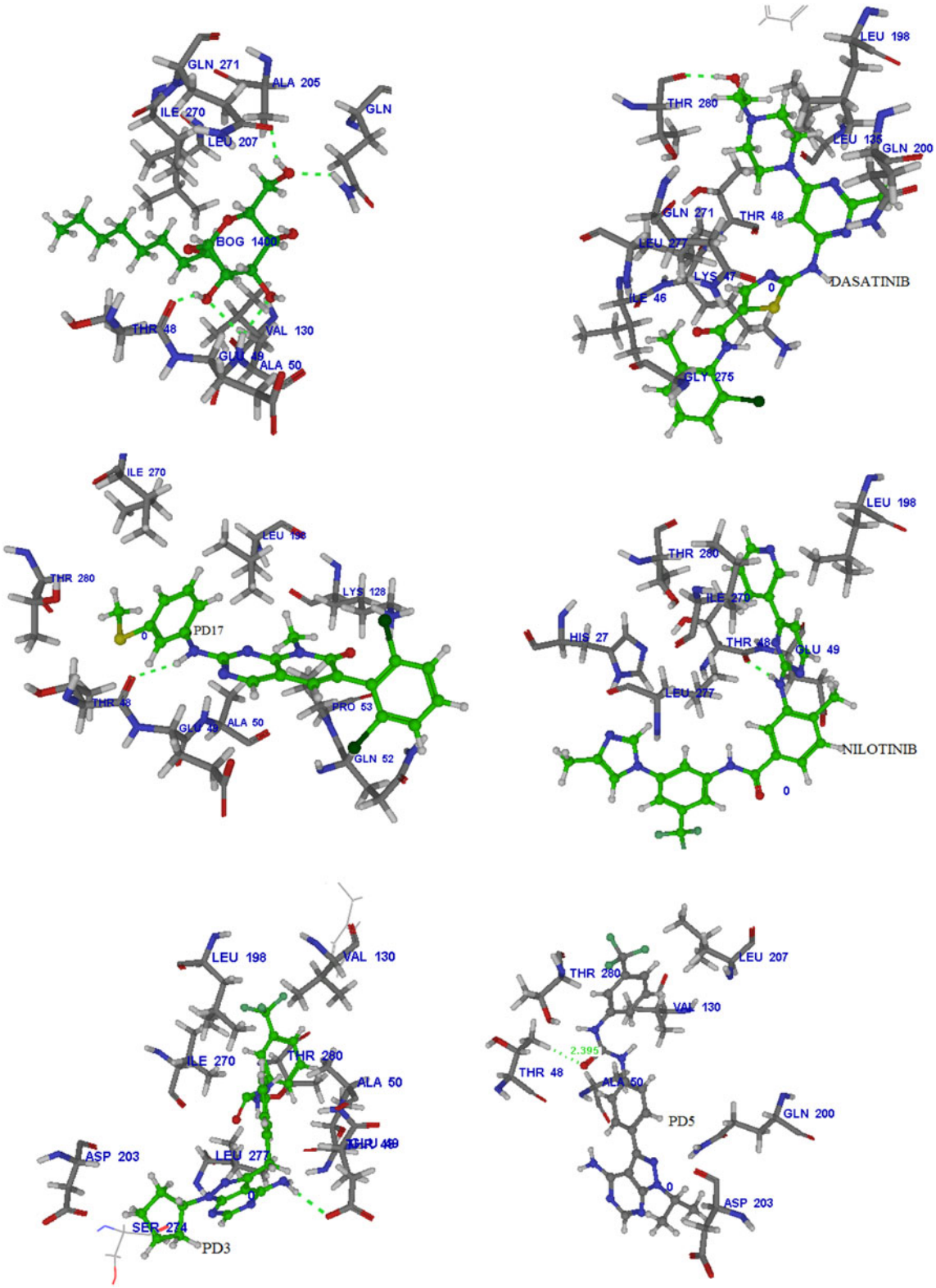

Fig. 3 The binding mode of inhibitors docked by QM-polarized ligand docking. Inhibitors are shown in ball and stick model while those residues which interacts with inhibitors arte shown by tube. Hydrogen bonds are shown by *dotted lines*

QM-polarized docking results

The ligand charge was calculated using ab initio method and redocked into the same receptor to study the polarization and charge effect due to protein environments. Table 2 shows the results of QM-polarized ligand docking. From Table 2, we notice changing in docking scores and other binding terms for all ligands. Docking of β-OG generates 385 different poses. The docking score of the best pose is −5.52, which is slightly better than classical docking results. Since the Columbic and van der Waal contributions are almost same as previously docked results, QM-polarized methods do not have considerable effect for this particular ligand. Table 2 signifies a foremost change in docking score of nilotinib after QM-polarized docking method. Nilotinib gets docking score of −6.64 among 383 different possible poses that is less than previously docked result. It adopts different orientations on QM charge treatment, and forms single hydrogen bond with Thr 48. PD3 shows a radical change in docking score. In the latter case, docking score of −3.37 is less than previously docked system. The decrements in van der Waal and electrostatic contributions are also apparent from the Table 2. The orientation of PD3 also changes on QM charge treatment. In QM-docked structure, it forms hydrogen bond with Thr 280 instead of Lys 202 and Ser 273. Likewise, docking score of PHA and PD5 decrease too. For PHA, the increase of van der Waal interaction term implies that it occupies more surface area of binding cavity but there are weaker bonding interactions due to less electrostatic energy. However, the van der Waals and electrostatic energy for PD5 decrease. The QM charge effect is prevalent for PD17 as it is obvious from the docking score after QM-polarized ligand docking. We get docking score of PD17 as −6.24, which is large with respect to previously docked position. The Columbic interaction, which occurs due to bonded interaction, is relatively high. PD17 shows a change in van der Waals relative to the previous docked form. It forms a hydrogen bond with Tyr 48 which was not clear in classical docking results. The hydrogen bonding and different poses of all ligands after QPLD method is shown in Figs. 2 and 3.

Discussion

Result obtained from classical force field docking and QM/MM-polarized ligand docking implies the role of polarization of ligand in protein environment. For detergent like β-OG, polarization does not play a vital role due to the lack of atoms like fluorine, chlorine etc. Other inhibitors contain these elements and they show significant variation in

Table 3 Charges of different inhibitors in both- classical force field method and polarized force field method

For BOG		
Atoms	Charge in FF	Charge PF
O6	−0.68	−0.67
O4	−0.70	−0.68
O3	−0.70	−0.67
O2	−0.70	−0.62
O5	−0.40	−0.50
O1	−0.40	−0.35
For nilotinib		
Atoms	Charge in FF	Charge PF
N	+1.0	−0.62
F17	−0.20	−0.15
F18	−0.20	−0.14
F19	−0.20	−0.18
N7	−1.02	−0.12
N3	−0.39	−0.54
O1	−0.50	−0.52
N27	−0.70	−0.81
N29	−0.84	−0.76
N33	−0.84	−1.00
N38	+1.0	−0.65
For PD17		
Atoms	Charge in FF	Charge PF
O12	−0.50	−0.68
Cl16	−0.18	−0.02
Cl21	−0.18	−0.11
S1	−0.34	−0.15
N5	−0.74	−0.76
N25	−0.84	−0.75
N7	−0.84	−0.86
For PD3		
Atoms	Charge in FF	Charge PF
F36	−0.20	−0.17
F35	−0.20	−0.16
F36	−0.20	−0.14
N23	−0.39	−0.22
N26	−0.39	−0.54
O25	−0.50	−0.54
N14	−0.84	−0.98
N4	−0.84	−0.92
N5	−0.84	−0.90
N12	−0.49	−0.34
N11	−0.12	−0.33

Table 3 continued

For PD5		
Atoms	Charge in FF	Charge PF
F31	−0.20	−0.17
F32	−0.20	−0.15
F33	−0.20	−0.15
N23	−0.39	−0.27
O22	−0.50	−0.34
N20	−0.39	−0.50
N12	−0.84	−0.81
N4	−0.84	−0.85
N5	−0.84	−0.82
N10	−0.49	−0.54
N9	−0.12	+0.08
For dasatinib		
Atoms	Charge in FF	Charge PF
Cl26	−0.18	−0.11
N22	−0.39	−0.42
N20	−0.52	−0.48
S21	−0.03	−0.40
N18	−0.62	−0.40
N24	−0.62	−0.81
N28	−0.84	−0.76
N30	−0.54	−0.18
N4	−0.63	−0.29
O33	−0.68	−0.71

FF Classical force field, *PF* polarized force field

docking score as well as Coulomb and van der Waals energy terms. Examination of the QM/MM docking and classical force field docking results reveals that when polarized charges are employed, a different hydrogen bonding pattern is favored over alternative accessible to ligand in an unconstrained search of the available phase space. The Coulomb energy of the protein ligand interaction is a key component of the scoring function that is used to select the final docked pose; this component changes substantially when polarized, rather than fixed charges are employed. According to the (Cho *et al.*, 1995) the results obtained from the QM-polarized ligand has least root mean square deviation (RMSD) from its co-crystal structure, so hydrogen bonding results from polarized docking may consider as accurate binding pose relative to the classical force field docking. Due to polarization and ab initio calculation of charge, change in electrostatic energy in each ligand is also noticeable.

The role of polarization may also be understood by the charge transfer/induction due to protein environments. To explore the role of charge, we calculated partial charge by two ways. In the first way, charges are calculated without considering polarization effect while in the second case charge is calculated by taking account of polarization effect. Table 3 shows effect of polarization on partial charge of the elements of the ligands. It is clear that effect of polarization is very small for the β-OG due to the small change in charges of this particular ligand. This fact is also supported by docking scores of β-OG by approaching classical force field docking and QM-polarized ligand docking. The variation of charge of all ligand is obvious by the first glance of the Table 3.

Conclusions

The study shows that polarization of ligand in protein environment plays a crucial role during the comparative study of different ligands. Due to the polarization, the distribution of charge on the ligands changes which directly effects the electrostatic interaction between the ligand and the target receptor. This causes major change in binding affinity of ligands which may give wrong speculation of binding potency. The accurate calculation of charge of drug ligand may increase the binding affinity by increasing the electrostatic interactions. The hydrogen bonds in polarized docking are analogous to the hydrogen bonding pattern observed in the crystal structure. This scope is useful for the ligands containing highly electronegative elements like Cl, F, and S but it is not much effective for those inhibitors which have lack of such elements.

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