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Full Length Research Paper

In silico identification of BIM-1 (2-methyl-1H-indol-3-yl) as a potential therapeutic agent against elevated protein kinase C beta associated diseases

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Protein kinase C beta is involved in apoptosis, transcription regulation, B-cell activation, regulation of the B-cell receptor signalosome and B-cell survival by regulating BCR-induced NF-kappa-B activation. Increased activation of PKC-βI along with overproduction of diacylglycerol (DAG) and vascular endothelial growth factor (VEGF) participate in pathogenesis of various aliments like asthma, cancer propagation, cardiovascular disorders, diabetes, tumor formation, AIDS and neurological disturbances. Inhibiting elevated activation of PKC-βI, after identification of most appropriate inhibitor, could serve as a potential therapeutic option for the treatment of several diseases. Its computational modeling is important to study interactions with various other signaling proteins. The aim of study was to investigate computational model of protein kinase C- βI and inhibitory potential of BIM-1 (2-methyl-1H-indol-3-yl), balanol-1 and staurosporine-1 to protein kinase C- βI. Model of protein kinase C - βI was built with the assistance of Modeller software. Known structure of PKC-βII was compared with modeled protein. Template (PDB ID: 2I0E) was searched from PSI Blast and structural analysis was performed by using 3D Coffee. Quality of model was dependent on template and sequence alignment. Amidst the five generated models, quality factor of best selected model via ERRAT was obtained as 88.923. Using Auto Dock Tools, selected values were docked individually. After analysis of results in PyMOL 1.3 and SPDBV v4.02 viewer; on the basis of highest value of affinity (-8.6 kcal/mol), lower distance from root-mean-square deviation (RMSD) l.b (1.379) along-with four polar contacts with PKC-βI that is, [Glu101 (O-H=2.1 Å), Val103 (O-N=2.9 Å, O-O=3.3 Å) and Thr84 (O-O=3.1 Å)], BIM-1 was selected to the best inhibitor. This approach holds a great promise for understanding of PKC- βI inhibitors and consequently its role in therapeutics.

Key words: Protein kinase C, protein kinase C beta, *in silico*, therapeutic agent, PRKCB1, PRKCB2, BIM-1 (2-methyl-1H-indol-3-yl), balanol-1 and staurosporine-1.

INTRODUCTION

Protein kinase C (PKC) are frequently studied, multigene family of related serine/threonine kinases, activated by lipid secondary messenger diacylglycerol, constituting approximately 2% of the genome (Saeed et al., 2011).

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Protein kinase C, beta (PRKCB) is thought to be associated with various processes such as regulation of the B-cell receptor (BCR) signalosome, apoptosis and transcription regulation. PRKCB plays vital role for B-cell activation and B-cell survival by regulating BCR-induced NF-kappa-B activation. This molecule serves as the receptor for phorbol esters (a class of tumor promoters) (P05771 KPCB_HUMAN; Uniprot). It has also been reported by various studies conducted on mice that these kinases may also regulate neuronal functions and after

onset of stress these kinases correlate fear induced conflict behavior (PRKCB; *Homo sapiens*; NCBI gene database). These molecules are calcium-activated and phospholipid-dependent. PRKCB plays prominent role for homeostasis of triglycerides as well. This protein contains one AGC-kinase C-terminal domain, C2 domain and protein kinase domain; and contains two phorbol-ester/DAG-type zinc fingers (P05771 KPCB_HUMAN; Uniprot). Some of the alternative names for this protein include; PKCB; PRKCB1; PRKCB2; MGC41878 and PKC-beta (PRKCB; *Homo sapiens*; NCBI gene database).

PKC family contains single polypeptide kinases which are made up of a regulatory region (N-terminal region) and catalytic region (C-terminal region). The regulatory region is almost 20 to 40 kDa, whereas catalytic region is 45kDa. There are 11 isozymes of PKC which are classified into three groups. Among these groups, first exhibits; α, two alternatively spliced variants βI and βII and γ. The second group includes; δ, ε, η, θ, and μ. Whereas third group illustrates least understood; ζ and λ. Conventional isozymes include four conserved domains: C1 to C4. Biochemical analysis showed that, C1 domain includes Cys-rich motif and provides binding site for diacylglycerol or phorbol ester. C2 domain provides Ca -binding site, and recognition site for acidic lipids. C3 domain provides ATP-binding and C4 domain attributes substrate-binding properties (Saeed et al., 2011; Steinberg, 2005). There are two main groups of protein kinase C (PKC); serine/threonine -specific kinases, and tyrosine -specific kinases which constitute 80 and 20% respectively (Manning et al., 2002).

PRKCB gene encodes for 671 amino acid protein. It has been reported that the most likely location of PRKCB is chromosome 16p11.2 (Francke et al., 1989). The genomic structure of PRKCB revealed that this gene consists of 18 exons which span for 375 kb, with exclusively large intron of over 150 kb, between exons two and three. The length of these exons range from 32 to 174 bp (Greenham et al., 1998). It has been reported that protein kinase C-beta, got activated in the cell due to oxidative conditions. Activation induces p66 (SHC) phosphorylation, and triggers accumulation of mito-chondrial protein after its recognition by prolyl isomerase PIN1. Once it got imported, p66 (SHC) causes changes in mitochondrial calcium ion responses and its 3D structure, which ultimately results into apoptosis (Pinton et al., 2007). Metzger et al. (2010) reported that PRKCB is associated with androgen-dependent kinase signaling which ultimately leads to writing of new chromatin mark H3T6ph, that consequently hamper removal of active methyl from H3K4 during adrenergic receptor (AR) -stimulated gene expression (Metzger et al., 2010). Experimental studies conducted on mice concluded that, in antigen receptor-mediated signal transduction, two isoforms [PKC-beta-I (PRKCB1) and PKC-beta-II (PRKCB2)] play vital role for B-cell activation and are functionally associated with bruton tyrosine kinase (Leitges et al., 1996). Cogram et al. (2004) reported prominent role of PRKCB1 and PRKCG in mediating the prevention of neural tube defects in mouse due to inositol (Cogram et al., 2004).

Activation of PKC-βI is mainly dependent on phosphorylation at three distinct conserved residues; T500, T642 and S661. The complete activity of holo-enzyme depends upon presence of three different cofactors; diacylglycerol (DAG), phosphatidylserine (PS) and calcium. Appropriate binding of ATP binding within catalytic domain plays vital role in proper phosphorylation of specific substrates (Ramesh Saxena et al., 1994). Increased activation of PKC-βI along with increased production of diacylglycerol (DAG) and vascular endothelial growth factor (VEGF) participate in pathogenesis of numerous diseases like diabetes, tumor formation, cancer propagation, AIDS, cardiovascular disorders, neurological disturbances and asthma (Vineet et al., 2008). This might be due to increased permeability of endothelial cells of blood vessels and abnormal signaling of growth factors (Idris and Donnelly, 2006). ATP analogue, competitive inhibitors of PRKCB1, can speci-fically inhibit kinase activity of enzyme by binding within its ATP binding cleft. Inhibiting elevated activation of PKC-βI, after identification of most appropriate inhibitor, could serve as a potential therapeutic option for the treatment of several diseases.

In this report, we computationally modeled the catalytic domain of PKC-βI (by using PKC-βII as a template PDB ID: 2I0E) along with three different inhibitors namely: BIM-1 (2-methyl-1H-indol-3-yl), balanol-1 and staurosporine-1, in order to check the most potent inhibitor for PKC-βI. Up-to-date no crystal structure of PRKCB1 is known, but three dimensional structure of PRKCB2 has been determined. As these molecules (PRKCB1 and PRKCB2) are 94% identical to each other, therefore the structure of PRKCB2 can be used to model PRKCB1's structure (Ramesh et al., 1994). *In silico*, docking is essential to detect range of amino acids within the protein kinase, interacting with three different inhibitors molecule. Inner details regarding affinity and binding of inhibitors within cleft of protein kinase will become fruitful in inactivation of protein kinases, leading to inhibition of various cellular mechanisms. Com-putational analysis concluded BIM-1 as the most appropriate inhibitor against elevated protein kinase C, beta associated ailments.

MATERIALS AND METHODS

Study setting

In silico, study was conducted on PKC-βI and PKC-βII with the aim to identify docking of different inhibitors namely: BIM-1 (2-methyl-1H-indol-3-yl), balanol-1 and staurosporine-1, at appropriate position at the facilities provided by NUST Center of Virology and

Table 1. Summary of successfully produced models.

File name	Mol pdf	DOPE score	GA341 score
PKCb1.B99990001.pdb	2011.13135	-39657.49609	1.00000
PKCb1.B99990002.pdb	1951.12256	-39975.96875	1.00000
PKCb1.B99990003.pdb	1934.44543	-39647.96484	1.00000
PKCb1.B99990004.pdb	2001.21509	-39879.07813	1.00000
PKCb1.B99990005.pdb	1916.31055	-40116.76563	1.00000

Immunology, Islamabad.

Data collection

Structure of protein kinase C beta –I was modeled and compared with known protein kinase C beta –II. For this purpose, Modeler 9.9 software was used to model PKC-βI and Auto Dock Tools were used to dock given inhibitors into PKC-βI (Modeler version 9.9 ; AUTODOCK VINA: version 1.0 beta 04). Best conformation model and docking results were obtained by "Swiss PDB Viewer" (SPDBV Version 4.02).

By the assistance of model building techniques, protein kinase C beta- I model was built. For this purpose sequence of its catalytic domain was acquired from Swiss Prot. Template was searched from PSI blast. Template protein was selected on the basis of 100% sequence homology and most appropriate resolution of 2.6 Å using PSI blast. Required structural alignment was done by using 3D Coffee. It was believed that the choice of templates and the quality of the sequence alignment would determine quality of our model. Jalview software (Version 2.6.1) was used to obtain the alignment file in PIR format (ALI-file). ALI-file was modified according to the pair wise alignment of 2I0E FASTA sequences, both from SPDBV and PDB server using EMBOSS software (Jalview: version 2.6.1 ; EMBOSS database). In order to run modeler, essentials include; protein kinase C beta- I PDB files as templates, Alignment File in PIR format (ALI- FILE) and Python Script (PY FILE). Five PDB output files were generated using Modeler, B99990001, B99990002, B99990003, B99990004 and B99990005.

Comparison of results was done, the model exhibiting high value for GA341 score, lower for molpdf and DOPE score would be the best model (Table 1). "B99990005.pdb" satisfied the above mentioned criteria. The next task was to evaluate interactions utilizing "ERRAT". For this purpose best model was uploaded to ERRAT which assesses the amino acid environment in protein structures and classifies the atoms in a protein structure as carbon (C), nitrogen (N) and oxygen/sulphur (O). ERRAT accurately identifies incorrectly folded regions in protein models.

Initially protein PDBQT file was created and non polar hydrogen bonds were added. Affinity calculations were carried out via grid widget in AutoDock. The Auto Dock tools add charges automatically, assign atom types and merge hydrogen atoms. It is the grid box which provides search space for docking. X, Y and Z centers were selected accordingly; grid box should cover the protein pocket and also its corresponding neighboring amino acid residues. Hence it was adjusted such that the selected portion efficiently docks at appropriate pocket where ligand could bind efficiently. The values of X center (35.5), Y center (55.5) and Z center (25.5) were adjusted along with number of points in X dimensions (28), Y dimensions (30) and Z dimensions (32). The spacing value was adjusted to 1 Å. Later on, the ligand file BIM-1 was opened in Auto Dock software. On loading, Auto Dock computed gasteiger charges, 26 non-polar hydrogen atoms, 20 aromatic carbons and four rotatable bonds. Torsion was defined by detecting root, which is the rigid part of the ligand and remains fixed. Torsion widget helped to find rotatable and non-rotatable bonds. BIM-1 has 14 rotatable bonds and no non-rotatable bonds; including amide bond. After calculating rotatable bonds, file was saved as PDBQT.

The command prompt yielded nine different conformations of the ligand. The PDBQT file was opened in PyMOL 1.3, in order to find best output results. The best confirmation was selected based on highest binding affinity value (it can also be selected on the basis of root mean square value from a reference structure given in log file generated by the Auto Dock). Visual observance in PyMOL 1.3 helped to find a conformation that could properly bind to cleft. The same procedure was applied on the other two ligands; balanol-1 and staurosporine-1. In case of balanol-1, on loading it, Auto Dock Tool computed gasteiger charges, 10 non-polar hydrogens, 20 aromatic carbons and 2 rotatable bonds. No changes were made to the rotatable bonds. Using command prompt, again PDBQT of balanol-1 was generated and visualized under the PyMOL 1.3 viewer. In case of staurosporine-1; on loading it, Auto Dock Tool computed gasteiger charges, 24 non-polar hydrogens, 20 aromatic carbons and four rotatable bonds. In order to get the exact confirmation, changes were made to this ligand in such a way that one rotatable bond (between C; 9 and N; 4) was changed to non-rotatable one, as this has no effect on its activity. By making use of command prompt, PDBQT file of staurosporine-1 was generated and visualized under the PyMOL 1.3 viewer.

RESULTS

The PKC-ßI model was compared with the template PKC-ßII (PDB ID: 2I0E). ERRAT results were obtained for identifying the most appropriate PKC-ßI file. After selection of the protein file, the following graphical representation was obtained (Figure 1). After analysis it was revealed that modeled protein kinase c isoform-β1 (PKCb1.B99990005.pdb) was most suitable one selected for docking with the specific inhibitors.

Structural analysis of PKC-ßI

The structures of PKC-ßI and PKC-ßII were superimposed in SPDBV v4.02 and the PKC-ßI structure was analyzed using PKC-ßII as a template. This superimposition revealed that PKC-ßI contained the conserved catalytic C domain (Gly 106- Lys 300) comprising of α-helices αD, αE, αF, αG, αH and αI as well as the regulatory N (Leu19- Glu101) domain consisting of β-sheets: β1, β2, β3, β4, β5 and α-helices: αA, αB and αC; both joined via a linker region (Tyr102- Gly105). PKC-ßI contained three phosphorylation sites required for

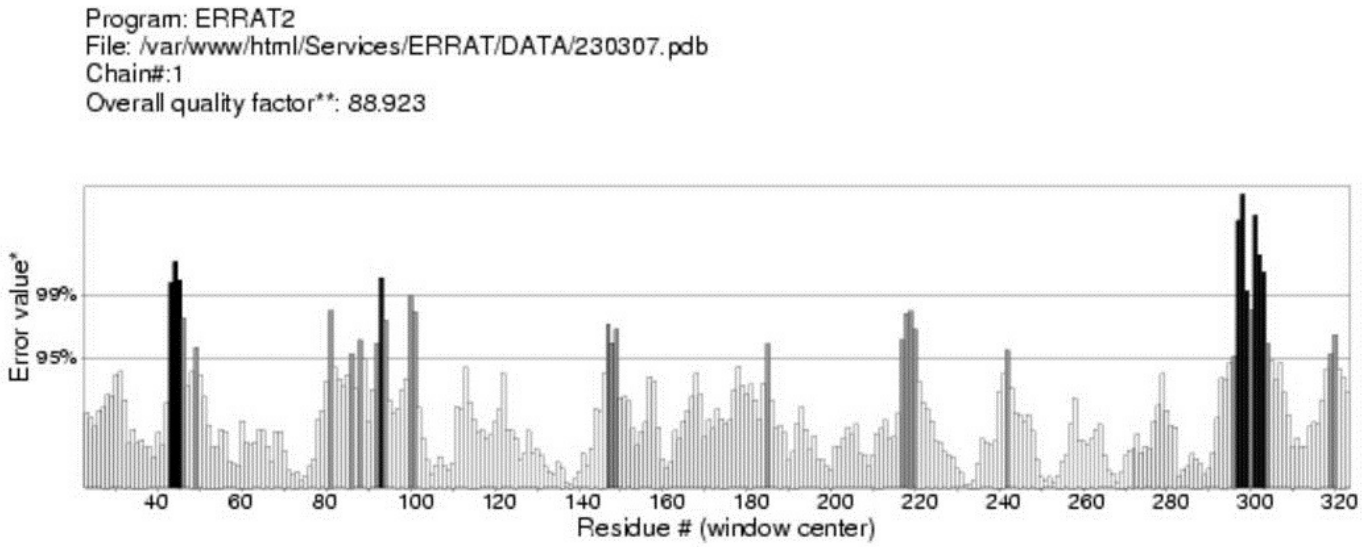


Figure 1. Graphical representation by ERRAT. Here in this graph, on the error axis two lines are drawn to indicate the confidence with which it is possible to reject regions that exceed the error value. Overall quality factor was 88.923, for which the calculated error value falls below 95% rejection limit.

activation and working of the enzyme which include; Thr180, Val319 and Ala338 present on activation loop (Asp164- Glu191), turn motif (Lys304- Phe328) and hydrophobic motif (Gln334- Gly339) respectively. A glycine-rich loop (Gly29- Lys35) connecting β1 and β2 strands was also present. A unique alpha helix (named αA) which to-date was found in PKC-βII only, was present in PKC-βI (Figure 2) as well (Phe310-Arg316). Additionally, a unique alpha helix (Asn335-Glu336) was discovered to be present in PKC-ßI, but not in PKC-ßII (Grodsky et al., 2006). The key catalytic residues in PKC-ßI conserved in all protein kinases were Lys51, Asp164, Asp146 and Asn151.

Comparisons of docking results

BIM-1 (2-methyl-1H-indol-3-yl)

Results obtained using Auto Dock tools provide a log file, giving different conformations of the inhibitor BIM-1 (Figure 3) according to the binding affinity and root-mean-square deviation (RMSD) value. Log file provided us with nine conformations of BIM-1. The first four conformations were selected on the basis of high binding affinity and low RMSD value. The selected conformations were visualized in PyMOL 1.3 and polar interactions between the chosen conformations and the modeled protein (PKC-ßI) were computed and visualized. First conformation (-9.0 Kcal/mol) showed only one polar interaction with PKC ßI (Asp150). Second conformation (-8.6 Kcal/mol) exhibited a total of four polar interactions with the modeled protein (including a hydrogen bond with Glu101, two polar contacts with Val103 and one with Thr84), while the third conformation (-8.4 Kcal/mol) had three polar interactions (one with Asp150 and two with Val103). On the other hand, the fourth conformation (-8.3 Kcal/mol), of BIM-1 displayed three polar contacts (two with Asp164 and one with Val103).

Balanol-1

Balanol-1, a potent inhibitor of PKC-βI, binds to its ATP binding domain and inhibits its activity. The competition between ATP and balanol-1 for binding with the ATP binding domain indicates that balanol-1 has 3000 times more affinity than ATP (Koide et al., 1995; Juliana et al., 1999). The provided ligand was an analogue of BIM-IV and a study on its analogues indicates that for inhibition of PKC-βI, amide linkage of benzamido functional group is important. Secondly, a free four hydroxyl group in benzamido region of balanol is required for potential inhibition of PKC-βI. Thirdly, the conformation of benzamide plays an important role in PKC-βI inhibition (Vineet et al., 2008). The docking results provided us with nine conformations of balanol-1; out of which we selected the best four for further analysis owing to their higher binding affinities and lower RMSD value. The four conformations and the modeled protein PKC-ß1 were analyzed in PyMOL 1.3 for their polar interactions. It was observed that the first conformation had three polar interactions with PKC-βI that is, two with Glu101 and one with Thr84 and had binding affinity of -8.4 Kcal/mol. In the case of second conformation (binding affinity -8.4 Kcal/mol), three polar interactions existed between the modeled protein PKC-ßI and balanol-1 (two interactions with Glu101 and one with Thr84). Whereas the third

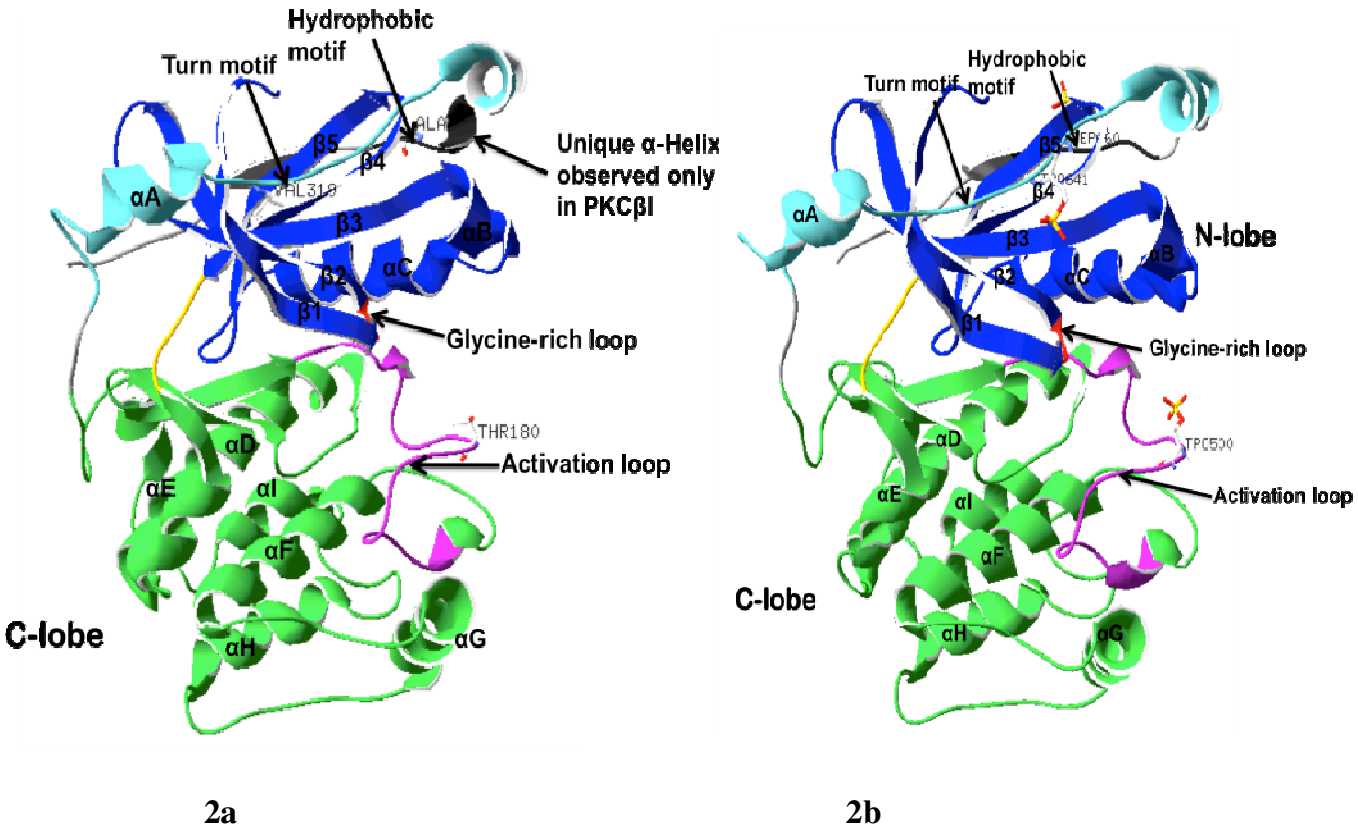


Figure 2. Analysis of structure. 2a; Catalytic domain of PKC β-I. The N-lobe is given in dark blue and C-lobe in green. The glycine rich loop is highlighted in red, activation loop in pink and phosphorylated residues are given in stick representation. A unique α-helix is shown in black. 2b; Catalytic domain of PKC β-II. The N-lobe is given in dark blue and C-lobe in green. The glycine rich loop is highlighted in red, activation loop in pink and phosphorylated residues are given in stick representation.

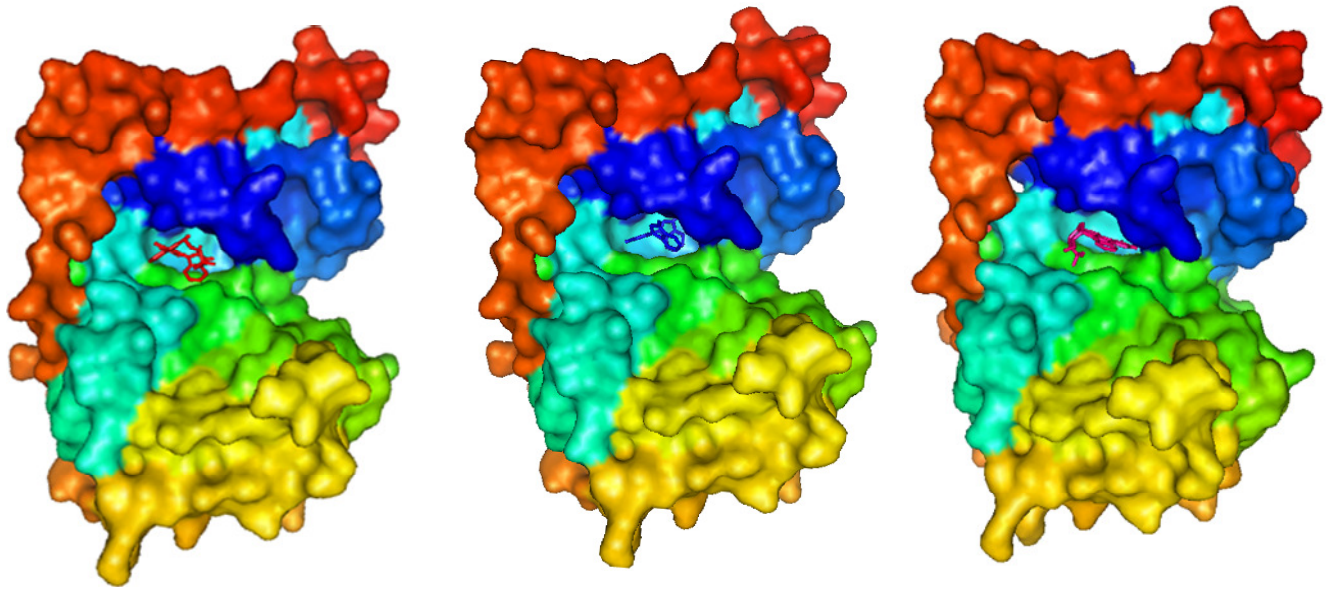


Figure 3. Analysis of docking. 3a, Docking of 2-methyl-1H-indol-3-yl-BIM-1 into the cleft of PKC β-I; 3b, docking of balanol-1 into the cleft of PKC β-I; 3c, docking of staurosporine-1 into the cleft of PKC β-I.

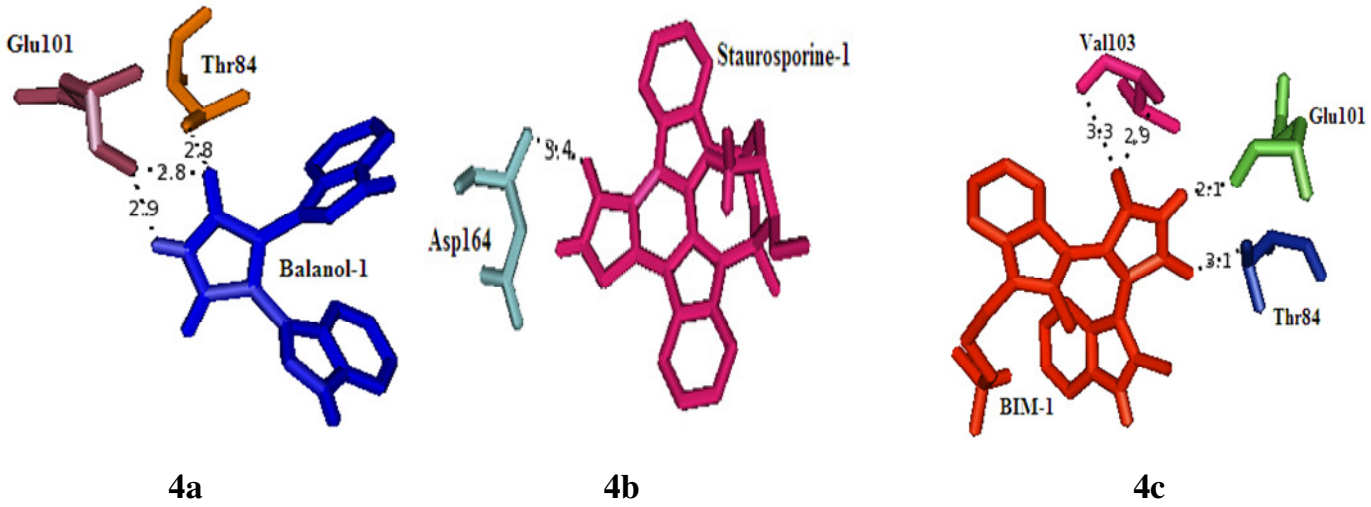


Figure 4. 4a; Four polar interactions between BIM-1 and PKC ßI including Glu 101(H-O=2.1 Å), Val 103 (O-N=2.9 Å, O-O=3.3 Å) and Thr 84 (O-O=3.1 Å); 4b, three polar interactions between balanol-1including two with Glu 102 (H-O=2.9Å, O-O=2.8Å) and one with Thr 84(O-O=2.8 Å); 4c, only one polar interaction between staurosporine-1 and PKC ßI that was with Asp 164 (O-N=3.4 Å).

conformation exhibited only one polar contact with PKC-βI that is, with Glu101 and had a binding affinity of -8.4 Kcal/mol. Interaction with Glu101 was also observed in fourth conformation (binding affinity of -8.3 Kcal/mol).

Staurosporine-1

Staurosporine-1 is a non-selective ATP competitive inhibitor of kinases including PKC-βI (Seynaeve et al., 1994). The analysis was to be done on the derivative of staurosporine named 7-hydroxystaurosporine (UCN-01) with an additional hydroxyl group on lactam ring and molecular weight of 482.53 g/mol (David et al., 2003 ; Wolfarm web resource: 7-hydroxystaurosporine). About nine conformations were identified out of which top four were selected on the basis of highest binding affinity and lower RMSD value. Making use of PyMOL 1.3, the polar interactions were identified and it was observed that the first two conformations (-10.0 Kcal/mol and -9.6 Kcal/mol respectively) of staurosporine did not show any kind of interaction with PKC-βI whereas the third conformation (-8.5 Kcal/mol) displayed a polar contact with Asp164. The fourth conformation (-8.3 Kcal/mol) had a polar interaction with Glu101.

Polar interactions between PKC β-I and selected inhibitors

Since for every given inhibitor and its interaction with PKC-β1, various conformations were generated by Auto Dock Tools and on the basis of log file, four conformations of each inhibitor were analyzed using PyMOL 1.3. Among these, the best conformation for each ligand was chosen on the basis of binding affinity, RMSD value and polar interactions. It was analyzed that BIM-1 showed a binding affinity of 8.6 Kcal/mol and 1.379 RMSD values. Thus about 8.6 Kcal/mol of energy is released upon interaction BIM-1 with PKC-ßI. There were four polar interactions between BIM-1 and PKC-ßI including Glu101 (H-O=2.1 Å), Val103 (O-N=2.9 Å, O-O=3.3 Å) and Thr84 (O-O=3.1 Å) (Figure 4a). On the other hand, the binding affinity of balanol-1 was -8.4 Kcal/mol and its RMSD value was 3.209. Three polar interactions, two with Glu101 (H-O=2.9Å, O-O=2.8Å) and one with Thr84 (O-O=2.8 Å) of PKC-ßI were observed (Figure 4b). The IC-50 value of balanol-1 was found to be 500 nM for PKC-βI. Whereas the interaction of staurosporine-1 with PKC-ßI exhibited binding affinity of about 8.5 Kcal/mol and its RMSD value came out to be 1.186. It presented only one polar interaction with PKC-ßI that was with Asp164 (O-N=3.4 Å) (Figure 4c). A comparison between different inhibitors with respect to association with PKC-βI is shown in Table 2.

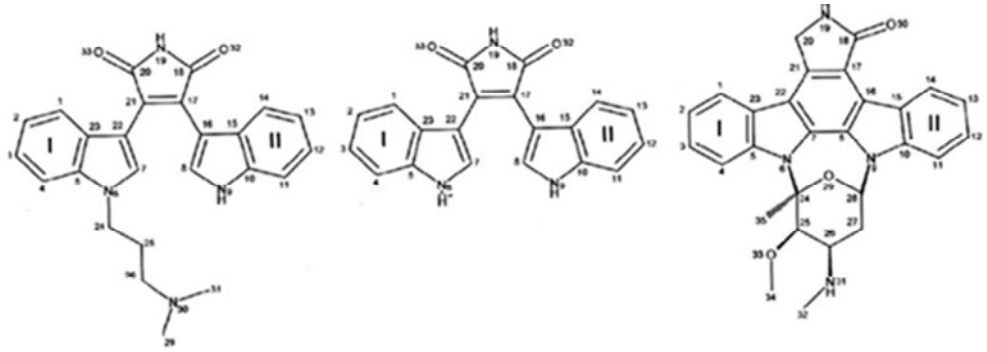
DISCUSSION

Lack of a three dimensional structure for PKC βI was compensated by building a theoretical model of catalytic site of PKC βI via assistance of PKC βII (PDB ID: 2I0E) as the template. The modeled protein is similar to its template with RMSD of 0.31 Angstrom; measured by SPDV. As over expression of PKC beta has been associated with various clinical ailments, several ATP competitive inhibitors have been analyzed for their inhibitory activity as potential therapeutic agents. Our study includes three ATP competitive inhibitors BIM-1, balanol-1 and staurosporine. All three share basic

Table 2. Comparison among inhibitors with respect to association with PKC-βI.

Ligand	No. of polar interaction	Binding affinity of best conformation	RMSD value
2-methyl-1H-indol-3-yl-BIM-1	4	-8.6kCal/mol	1.379
Balanol-1	3	-8.4kCal/mol	3.209
Staurosporine-1	1	-8.5kCal/mol	1.186

RMSD, Root-mean-square deviation.



5a **5b** **5c**

Figure 5. Structural analysis of the three inhibitors used for docking within the model protein PKC β-I. 5a, BIM-1 (2-methyl-1H-indol-3-yl); 5b, balanol; 5c, staurosporine. The two indole rings present in 5a, 5b and 5c are designated by roman numerals I and II.

symmetric architecture of a maleimide flanked by two indole rings in the case of indolo-carbazole staurosporine, two indole rings are linked to maleimide (the imide ring) forming an extended aromatic and planar system, along with cyclic bonding of the sugar moiety from the two indole nitrogen atoms. Staurosporine is a prototypical ATP-competitive kinase inhibitor in that it binds to many kinases with high affinity, though with little selectivity (Ubersax and Ferrell, 2007). The small molecule crystal structure of balanol-1, a derivative consisting only of the maleimide group and the two indole rings, shows a comparable rotation of one indole as found in our docking studies, indicating an energetically preferred conformation (Kawakami et al., 2002). The carbon atoms of ligand provide hydrophobic interactions including Vander Waal interaction with the carbon atoms in backbone of the amino acids and the hydrophobic side chains while the nitrogen and oxygen atoms of the ligand make polar interactions including hydrogen bonding with the polar residues of active site of protein. Although hydrophobic interactions have an important role in binding to the active site, these bonds are weak as compared to the polar interactions of hydrogen bonding. So therefore, patterns of hydrogen bonding were observed in protein ligand interactions to determine the most potent inhibitor (Figure 5).

Factors that should be kept in mind while designing a therapeutic agent against a protein includes that it should have minimal impact on native protein conformation specially active site architecture, size of the inhibitor should be optimum so that it can fit compactly (Gassel et al., 2004). Furthermore the designed ligand should have high affinity in terms of hydrogen bonds and hydrophobic interactions with the protein along with selectivity. Keeping these parameters in mind the ligand-protein interactions were assessed and best ligand for PKC βI inhibition was decided. Our study proposes that the inhibitory potential of BIM-1 is greater as compared to balanol-1 and staurosporine-1. The binding affinity of BIM-1 was greatest among the three and the number of polar interactions were also maximum that is, four. Due to which greater energy will be released during interaction and higher would be the potency of BIM-1 as compared to others. Moreover it does not disrupt the protein structure as it has a flexible indole ring that orients itself inside the active site pocket. Due to the optimal size and flexibility it also has a maximum occupancy within the active site pocket. Also, the presence of hydrogen bond between BIM-1 and PKC-ßI stabilizes the inhibition, therefore it is suggested that BIM-1 is a relatively stable and potent inhibitor of PKC-ß1 and can be used as an effective therapeutic agent against various ailments in which PKC-ßI is elevated.

Conclusion

PRKCB1 and PRKCB2 are 94% identica l to one another;

therefore the structure of PRKCB2 can be used to model PRKCB1's structure. Till now, no crystal structure of PRKCB1 is known, but three dimensional structure of PRKCB2 has been determined. The aim of this study was to analyze the structure of PKC-βI and further probate its binding with different inhibitors at the accurate site within the cleft. Our results led us to deduce BIM-1 of being the most effective of the selected inhibitors of PKC beta I. Such an inference was drawn upon observing the differences in the hydrogen bonding patterns and energy calculation displayed by each of the mentioned inhibitors when docked with our model protein. Balanol-1 because of its small size and non-specific behavior towards PKC βI and staurosporines' large, rigid structure accounted for an inefficient hydrogen bond pattern and a disrupted a-helical in PKC beta I model, respectively. In contrast, favorable size of BIM-1 allowed it to show greater complementation with the targeted catalytic domain, thereby allowing it to emerge the more potent of the inhibitor than its counterparts in the study. Most importantly, these results suggest BIM-1 of being a preferable candidate for drugs designed against PKC beta I, providing with crucial insights in the field of therapeutics and drug development.

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