Comparative Computational Studies on Selective CytochromeP450 1B1 Inhibitors

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Abstract: *Selective inhibitors of CYP isoforms gaining importance in the treatment of cancers caused by hormonal imbalance. Metabolites of estradiol and polyaromatic hydrocarbons generated due to CYP1B1 activity were reported to be oncogenic. The selective CYP1B1 inhibitors could have the potential therapeutic utility in controlling the cancer due to these oncogens. Due to the CYP isoforms high sequence similarity the design of selective CYP inhibitor is difficult. Recently our group has reported two novel chemical classes (scaffolds) that are specific towards CYP1B1. The chemical architecture of these compounds should give valuable information for its selectivity and potency against CYP1B1. Overlay of our compounds and ANF by Shape and electrostatic based similarity and molecular docking displayed different orientations. Moreover the study has shown the overlay of three atom bridge of selective inhibitor superimposed on –O-CH- linking aryl groups rather than –CO-CH=CH- of ANF. Molecular docking simulation revealed that the selective inhibitors are either establishing H-bonding interaction with Asp333 or π-π staking interaction Phe231 and Phe268. Molecular docking simulation has provided much more information rather than simple shape and electrostatic based similarity study. Crucial H-bonding interactions and π-π staking interactions responsible for selectivity towards CYP1B1 were identified. Two atom linker between the aryl groups matter, cyclization simply ensures the planarity of ANF and quinazolines.*

Keywords: *CYP1B1, Selective inhibitors, Similarity search, Docking, Druggability, ADME.*

Introduction

Cytochrome P450 (CYP) enzymes are present in various organs of the human body, comprise of a large family of detoxification enzymes. The cytochrome P450 1B1 isoform (CYP1B1) is a heme-thiolate monooxygenase which causes the hydroxylation of steroids, estrogens and fatty acids. Unlike other CYPs, CYP1B1 is not present in normal healthy tissues but significant expression of the protein has been reported in most hormonal cancers including that of the ovary, prostate, uterus, mammary, pituitary, regardless of the cancer's genetic origin. Recent studies revealed that CYP1B1 plays a major role in the genesis of hormone-mediated prostate and breast cancers [14-16]. In both cancerous and precancerous cells of mammary, prostate and ovarian tissues, the regio-specific metabolism of estradiol by CYP1B1 produces '4-hydroxy estradiol (4-OHE_2)', while CYP1A1 and CYP1A2 produces '2-hydroxy estradiol (2-OHE_2)'. Amongst these two metabolites 4-OHE_2 has been reported to

initiate the oncogenesis [32]. In cancerous cells these metabolites 2-OHE_2 and 4-OHE_2 undergo further oxidation to form tumor initiator quinones, 2,3-estradiol quinone and 3,4-estradiol quinone. 2,3-estradiol quinone forms the stable adduct with DNA which do not suppose to have mutations. Whereas 3,4-estradiol quinone forms the de-purinating adducts which bind to DNA and tubuline leading to genotoxic mutations [3-5, 10, 18, 21, 22, 33]. Therefore, the rate and extent of CYP1B1 expression in endometrium, mammary and ovarian tissues can be considered as potential biomarker for hormonal oncogenesis [5, 13, 15, 28, 29].

For the treatment of hormonal cancers, selective inhibitors of CYP1B1 will have potential benefits in comparison with a pan inhibitor of CYP as pan inhibitors may adversely impact the metabolism of many other xenobiotics [12]. But designing a selective inhibitor of CYP1B1 is a challenging job as active sites of CYP1 family enzymes have ≤ 40% sequence similarity. So it is quite difficult to design a highly specific and selective inhibitor against these iso-enzymes [17, 30].

Recently our group has reported CYP profiling of two different novel classes of compounds and identified potent and highly selective inhibitors of CYP1B1 in each class [26, 27]. We understand the importance of analyzing the structural features that are responsible for the selectivity of these compounds towards CYP1B1. Findings may help us in devising lead optimization strategy by retaining selectivity. Many different computational tools are available to predict the enhanced potency and selectivity of newly designed inhibitors [8, 20, 24, 25], but we came across very few literatures on the application of such tools in the design of selective inhibitors of CYP1B1. Two potent actives from both the classes (BNUB-10 and BNUA-21) were selected for the study. They belong to two different chemical scaffolds and similar biological activity reveals that they share some similarity in their chemical architecture and are complementary to active site of CYP1B1 [31]. With this background, objective of the current study is to access the shape and electronic similarity [1] between potent actives from both the classes (BNUB-10 and BNUA-21) along with the few other inhibitors reported in the literature, Alphanaphthaflavone (ANF) [2, 11] (Fig. 1).

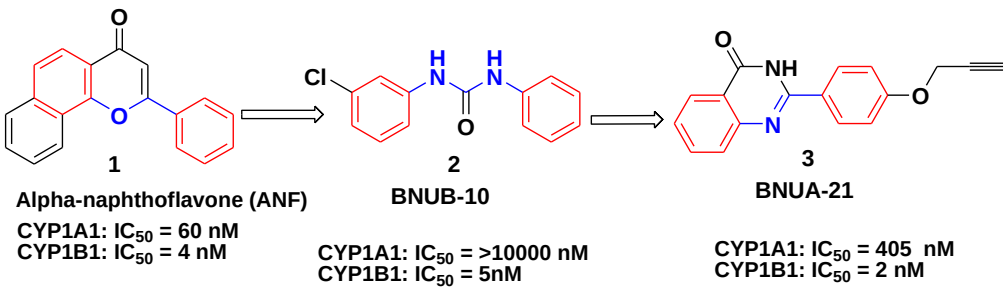


Fig. 1 Potent CYP1B1 inhibitors used for computational studies

Further, evaluation of druggability of the target protein and Absorption, Distribution, Metabolism and Excretion (ADME) properties of the novel compounds were also carried out that in turn may help us in lead optimization strategy to be implemented in due course of research on these compounds.

Materials and methods

Shape and electrostatic analysis was performed by using vROCS (3.2.1.4) and EON (2.1.0.5) of OpenEye toolkit [19]. Molecular docking and Site map analysis were done using Glide and SiteMap module on Maestro-9.2 (Schrödinger LLC suite) [23], respectively, running on RHEL5 operating system installed on DELL Precision T3400 machine (*n*-series, Intel core 2

Quad processor, 8GB RAM, 500GB HDD). Ligands were sketched using build panel and prepared for docking using Ligprep module implemented in Maestro-9.2. The X-ray crystal structure of CYP1B1 co-crystalized with ANF (PDB ID: 3PM0) [31] was downloaded from www.rcsb.org. For validation of software the co-crystallized ligand was extracted and redocked into the active site. Protein was prepared for docking through Protein preparation wizard and Grid was constructed using Glide → Grid generation wizard by specifying the center of the ligand as center of the grid. Docking was performed using Glide → Ligand docking with XP protocol. The docked conformers were analyzed through XP-visualizer. Default parameters were employed during all the computational studies.

Shape and electrostatic study

Shape and electrostatic similarity study has been carried out keeping ANF as query (a standard molecule with known activity). ANF is non-selective inhibitor of CYP family. For this study its bioactive conformation has been retrieved from CYP1B1-ANF complex (PDB ID: 3PM0). Conformers of BNUB-10 and BNUA-21 were generated using Omega-2.4.3. The generated conformers were then used to evaluate the shape based similarity using vROCS. The output of vROCS was then further subjected to evaluation of electrostatic based similarity using EON.

Molecular docking study

The compounds were also subjected to docking using Glide module implemented in Maestro-9.2. X-ray crystal structure of CYP1B1 complexed with ANF (PDB ID: 3PM0) has been used for the purpose. Protein preparation wizard and Ligprep utility in Maestro were used for preparing the protein and ligands (ANF, BNUB-10 and BNUA-21). Glide grid generation tool was used to generate the grid keeping co-crystallized ligand as center of the grid. XP protocol has been employed to run Glide Ligand Docking. Docked molecules were analyzed using Glide → XP visualizer. Complex of all the ligands with CYP1B1 has been generated for further Sitemap analysis.

Site map analysis

All the three complexes prepared at the end of docking simulation were used to evaluate the druggability of the target protein using Sitemap tool implemented in Maestro-9.2 [7, 9]. The hydrophobicity, hydrophilicity, H-bond donor and acceptor properties generated for each complex were then used to judge the druggability of the target protein on a predefined value of 0-2.

In silico ADME prediction

Pharmacokinetic properties (ADME) are the crucial part of new drug development procedure as many molecules were withdrawn from the market due to their poor pharmacokinetic profile. Hence all the three ligands were evaluated for their favorable pharmacokinetic property using QikProp v3.4 module implemented in Maestro-9.2.

Results and discussion

Shape and electrostatic studies

The rational in comparing shape and electrostatic properties is that it is primary topological determinants of molecule, which can be considered for better fitness and binding in the active pocket of protein or enzyme. For these purpose the bioactive conformation of ANF, a pan CYP inhibitor has been used as a query. ANF was extracted from X-ray crystal structure of

CYP1B1 with ANF (PDB ID: 3PM0) and used as query to run shape based as well as electrostatic based similarity search using vROCS and EON (OpenEye Tools), respectively. The results are analyzed using VIDA (OpenEye Tools). The shape and electrostatic potentials for BNUB-10 (Fig. 2C) were found to be 0.554 and 0.231, and similarly for BNUA-21 (Fig. 2D) the values were 0.690 and 0.020, respectively indicating good correlation between BNUB-10 and ANF, and BNUA-21 and ANF.

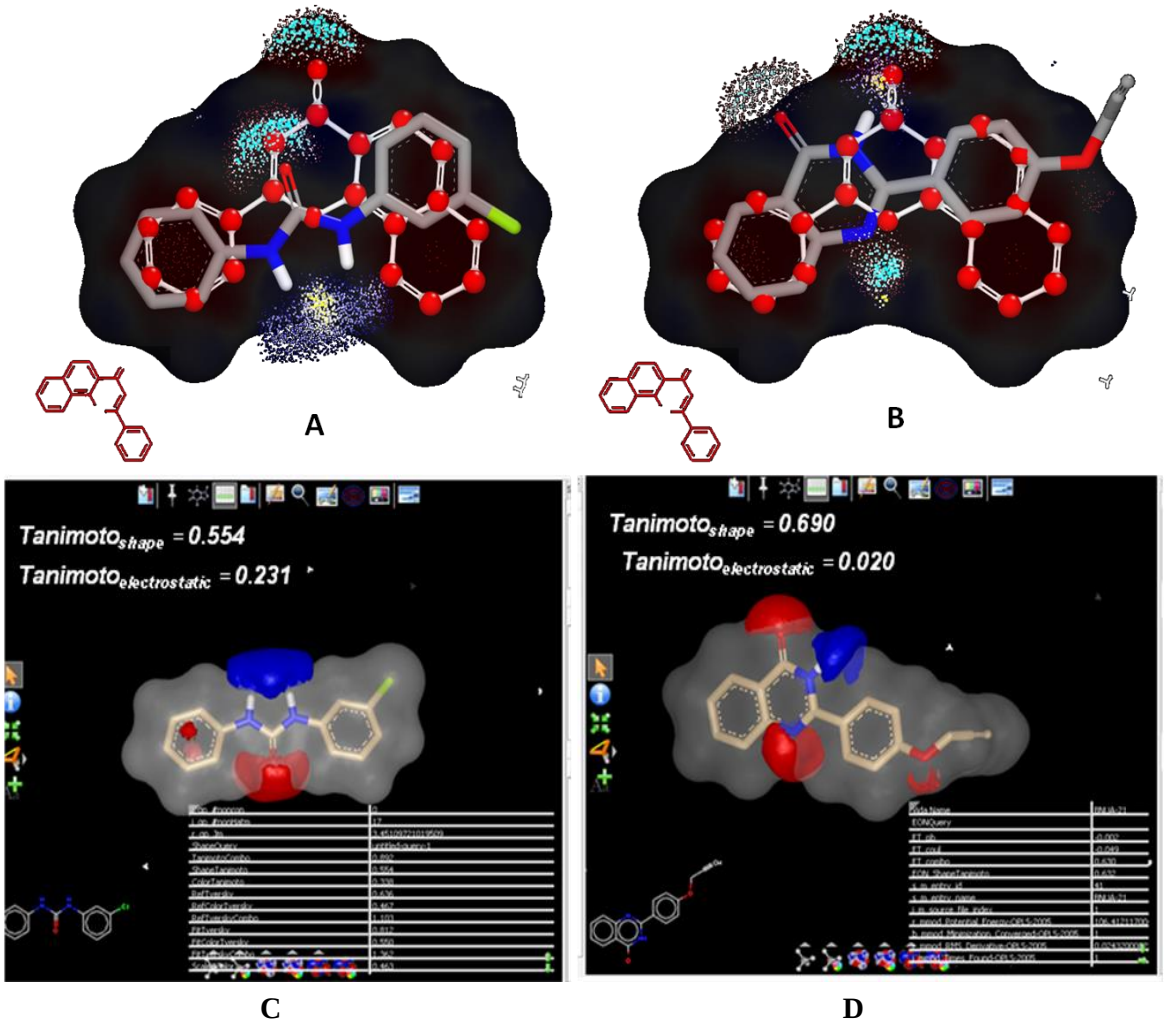


Fig. 2 A) Overlap structure of ANF (red color, ball and stick model) and BNUB-10 (silver color, stick model); B) Overlapping of ANF and BNUB-21 (silver color stick model): blue color denotes electropositive areas and red color indicates electronegative area; C) The display of shape and electrostatic potentials for BNUB-10; D) BNUA-21 with that of ANF in their neutral form.

It was expected that urea bridge (red color items in given formula Ar-NH-CO-NH-Ar) present in BNUB-10 will superimpose with the three carbon α, β unsaturated carbonyl portion (-CO-CH=CH-) of ANF. But the resultant overlay of BNUB-10 (a diphenyl urea derivative) revealed that the three atom bridge (-NH-CO-NH) between the two aryl rings overlapping with the two atom bridge (-O-CH-) of ANF. Moreover the phenyl ring carrying chloro substitution was found to overlap with naphthyl portion of ANF (Fig. 2A). In case of BNUA-21 the quinazoline portion was expected to exactly superimpose with the coumarine portion of ANF. Surprisingly, BNAU-21 displayed a reversed orientation by having the

benzene ring superimposed over pyranone ring of ANF (Fig. 2B). It is understood that two atom bridging between the two aryl group matters rather than three atom linker and the aryl group with bulkier substitutions rather determines the orientation of the molecule.

Molecular docking studies

Molecular docking study has also been carried out using the X-ray crystallographic structure of CYP1B1 with ANF (PDB ID: 3PM0). The software validation was done by redocking of ANF at its original position in its co-crystalline structure. The root mean square deviation (RMSD) value was found to be 0.01871. As various conformers were generated during ligand preparation that results in several docked poses of each molecule. Here we consider the high docking score for each docked molecule. The highest docking scores were found to be -9.650, -7.737 and -8.415 for ANF, BNUA-21 and BNUB-10, respectively. The scores shown by the molecules were found to be very close to reference molecule ANF. Analysis of the docked conformers revealed a surprising fact that both BNUB-10 and BNUA-21 overlaid over ANF in a reverse orientation than the one observed in case of shape and electrostatic based overlay (Fig. 3A and B, respectively).

Pocket environment and interaction of ligand with the residues in the pocket determines their orientation inside the pocket. The phenyl rings carrying the electronegative substituents were found to position themselves near the iron. ANF, a pan CYP inhibitor has been found to exhibit hydrophobic interaction only, while BNUB-10 displays two H-bonding interaction with Asp333. No such H-bonding interaction was observed in case of BNUA-21, but it displays a π-π stacking interaction with Phe231 and Phe268. We suppose any one of these two interactions should be there for a molecule to show selectivity towards CYP1B1.

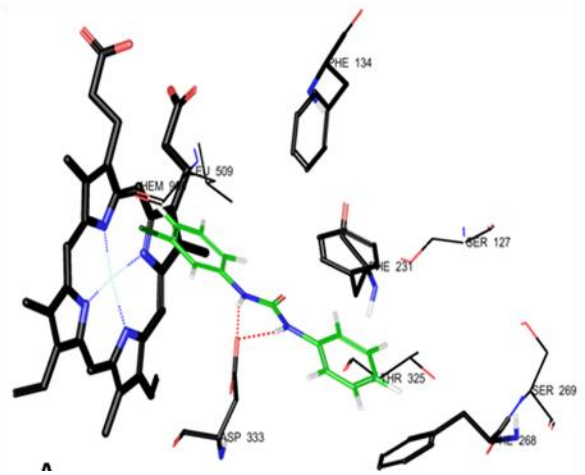
Site map analysis

Site map tool in Maestro-9.2 is used to predict whether a protein can be a druggable target. For validation of druggability of active site of CYP1B1 enzyme (PDB ID: 3PM0) we used three potent CYP1B1 inhibitor. ANF (50 nm) and BNUB-10 (5 nm) were employed to justify the binding analysis of active pocket of CYP1B1. The results were summarized in Table 1.

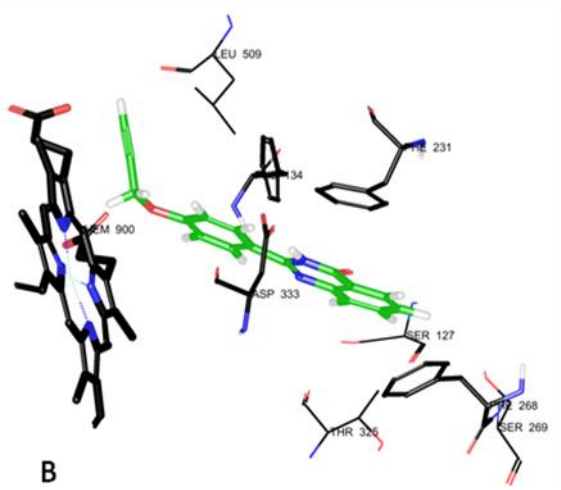
Table 1. SiteMap property values and DScore ranks for the potent CYP1B1 inhibitors

Entry	ANF	BNUB-10	BNUA-21
IC_{50}, nm (CYP1B1) [a]	50	5	2
Category	2	2	2
DScore	1.404309	1.382313	1.400733
SiteScore	1.313017	1.299781	1.310601
Size	116	117	125
Enclosure	0.971348	0.970455	0.970364
Exposure	0.309524	0.295181	0.313187
Hydrophilic	0.363495	0.429324	0.372653
Hydrophobic	5.153594	4.923842	4.838209

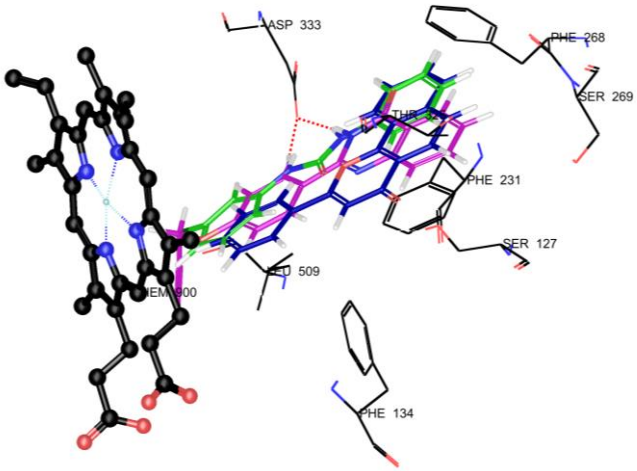
[a] IC_{50} values were determined in Sacchrosomes™ and it represents mean and standard deviations from three independent experiments [26, 27].



A)



B)



C)

Fig. 3 3D interaction diagram of: A) BNUB-10; B) BNUA-21 at active site of CYP1B1 enzyme and showing the interactions with amino acid residues (PDB ID: 3PM0); C) interactions of all three molecules aligned at active site of CYP1B1; (blue color ANF, green color BNUB-10 and pink color BNUA-21).

The DScore values indicated that all molecules have identical score, which falls under the category of druggable site as reported by the Cheng and co-workers [6]. DScore as reported earlier, it is calculated based on the sitescore, size, hydrophilicity, hydrophobicity, enclosure, exposure and H-bond donor and acceptor values. The Fig. 4A comprises of the BNUB-10 binding site map in active pocket of CYP1B1 while Fig. 4B is for BNUA-21 and Fig. 4C shows the all three molecule interactions.

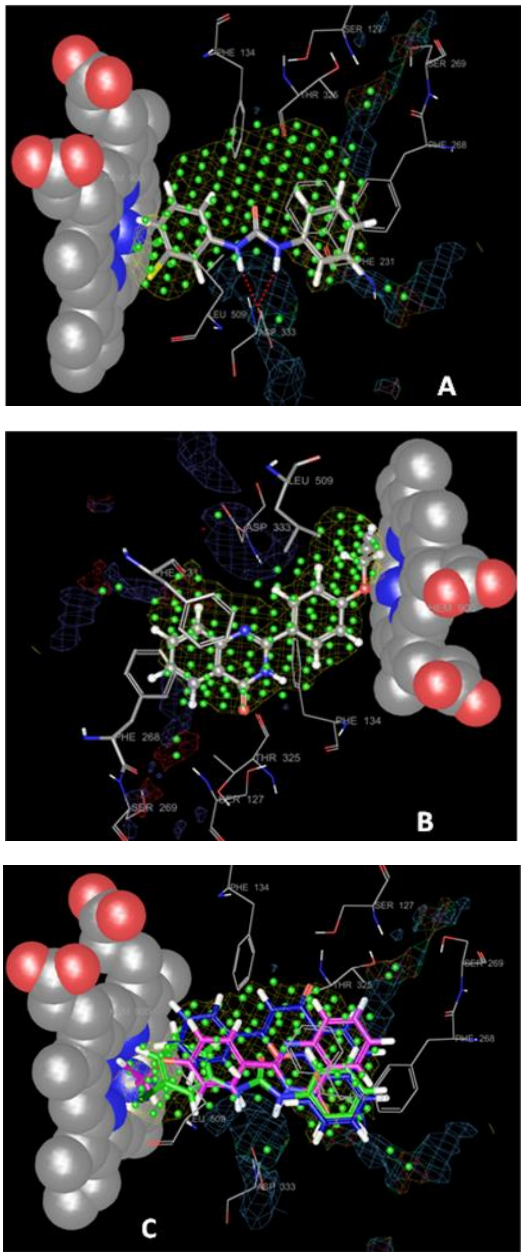


Fig. 4 Binding mode analysis of: A) BNUB-10; B) BNUA-21; C) all the three molecules at active site of CYP1B1 enzyme, ANF (blue color), BNUB-10 (green color) and BNUA-21 (pink color). The various crucial interactions are red color denotes H-bond acceptor, blue color shows H-bond donor, green color represents hydrophilic interaction. Heme is represented by space fill model (in which carbon atom atoms displayed in silver color and nitrogen and oxygen were shown in blue and red color, respectively, H atoms were not shown for clarity).

The 3D graphical contour map displayed the different types of interactions between ANF and receptor site. The red and blue color denotes the H-bond acceptor and H-bond donor properties, yellow region indicates hydrophobic interactions and green is for the hydrophilic interactions. As all three molecules are equipotent CYP1B1 inhibitors and interestingly we got the DScore values also similar 1.404309, 1.382313 and 1.400733 for ANF, BNUB-10 and BNUA-21, respectively. Similarly BNUA-21 was also used for CYP1B1 active pocket assessment. The category as reported by Cheng and co-workers were 0 means difficult, 1 means undruggable and 2 means druggable. This was calculated on the basis of number of site points, the degree of enclosure and hydrophilic score. Moreover, all the DScore values ranging from 1.382 to 1.404 suggested that CYP1B1 active site is druggable inspite of size variations among the molecules.

In silico ADME prediction

In silico ADME calculation has been performed using Qikprop.v3.4 (Maestro-9.2, Schrodinger LLC) to access the drug likeness properties of ligands. Results obtained are shown in Table 2. None of them was found to violate Lipinski Ro5, a parameter used for predicting the oral absorption of the drug molecules. The tool predicted 100% oral absorption for all the three molecules. A poor BBB permeability was predicted for all the three molecules (PlogBB) which implies that there may be no CNS related adverse effects with these molecules.

Table 2. *In silico* ADME calculation for drug like properties of all four molecules

Entry	ANF	BNUB-10	BNUA-21
Lipinski rule of five	0	0	0
Mol, Wt	272.303	246.696	276.294
PLog P, (o/w)[a]	4.159	2.992	3.129
PSA[b]	34.039	46.745	58.186
HBA[c]	2.5	2	4.25
HBD[d]	0	2	1.5
PlogBB[e]	0.072	0.05	-0.551
Oral absorption, %	100	100	100

[a] Predicted octanol/water partition coefficient.
[b] PSA – Polar surface area.
[c] HBA – H-bond acceptor.
[d] HBD – H-bond donor.
[e] Predicted brain/blood partition coefficient (from -3 to 1.2).

Conclusion

Two potent and selective inhibitors of CYP1B1 reported by our group have been considered for evaluation of their shape and electrostatic similarity with a pan CYP inhibitor ANF. Further molecular docking simulation study has also been carried out. The results obtained revealed that the shape and electrostatic based algorithm aligned the molecules considering the unsubstituted phenyl rings at one end and substituted on the other end. Whereas in the molecular docking simulation the active site pocket environment determines their orientation differently considering the other crucial interactions between the protein and ligand.

Further, the Sitemap analysis reveal certain important factors that may help us in designing analogs for Lead optimization purpose:

(i) An electronegative group on a phenyl ring establishing interaction with Heme;

(ii) Less polar bridge with an ability to establish a H-bonding interaction with Asp333;

(iii) Appropriately oriented second phenyl ring to establish π-π interaction for improved potency and selectivity towards CYP1B1.

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