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ORIGINAL PAPER

Comparing the electronic properties and docking calculations of heme derivatives on CYP2B4

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Abstract Cytochrome P-450 is a group of enzymes involved in the biotransformation of many substances, including drugs. These enzymes possess a heme group (**1**) that when it is properly modified induces several important physicochemical changes that affect their enzymatic activity. In this work, the five structurally modified heme derivatives **2–6** and the native heme **1** were docked on CYP2B4, (an isoform of P450), in order to determine whether such modifications alter their binding form and binding affinity for CYP2B4 apoprotein. In addition, docking calculations were used to evaluate the affinity of CYP2B4 apoprotein-heme complexes for aniline (A) and *N*-methyl-aniline (NMA). Results showing the CYP2B4 heme **4**- and heme **6**-apoprotein complexes to be most energetically stable indicate that either hindrance effects or electronic properties are the most important factors with respect to the binding of heme derivatives at the heme-binding site. Furthermore, although all heme-apoprotein complexes demonstrated high affinity for both A and NMA, the CYP2B4 apoprotein-**5** complex had higher affinity for A, and the heme **6** complex had higher affinity for NMA. Finally, surface electronic properties (SEP) were calculated in order to explain why certain arginine residues of CYP2B4 apoprotein interact with polarizable functionalities, such as ester groups or sp^2 carbons, present in some heme derivates. The main physicochemical parameter involved in the recognition process of the heme derivatives, the CYP2B4 apoprotein and A or NMA, are reported.

Keywords Cytochrome P450 · DFT · Docking · Heme derivatives · HOMO-LUMO orbitals

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Introduction

Cytochrome P450 (P450) enzymes comprise a superfamily of heme-thiolate proteins are widely distributed across all taxonomic kingdoms [1]. The common catalytic function of these enzymes is the two-electron reduction of molecular oxygen to yield water and reactive oxygen species (ROS). The ROS is often subsequently inserted into one of many endogenous or exogenous substrates to form hydroxylated products [2, 3]. The two electrons necessary for P450 activity are supplied by oxidation of NADPH via the P450 reductase enzyme or cytochrome b_5 [4]. Several factors,

such as the heme iron's spin-state, the extent of heme molecule's planarity, and the hydrophobicity, hindrance and electrostatics surrounding the heme, influence the efficiency of electron transport [5–8]. Introducing appropriate chemical functionality at heme positions C-2, C-4, C-6 and C-7 modulates the heme iron's electron density, which in turn modifies these physicochemical properties. The resulting structural modifications can also alter the proteins's redox properties [9–11]. The scope and limitations of these redox changes have been experimentally evaluated for some proteins such as myoglobin and hemoglobin [9–11]. Similar findings have not been previously reported for P450 microsomal isoforms, despite the enzyme's relevance with respect to the biotransformation of drugs. Accordingly, docking simulations were conducted to evaluate the affinity of heme derivatives for these enzymes. Specifically, the CYP2B4 apoprotein [12–14] and heme (**1**) and its derivatives **2–6** (Table 1) were selected for this study [15]. The latter was taking into account the CYP2B4 apoprotein active site and the electron-withdrawing or donating effects of the groups placed at C-2, C-4, C-6 and C-7 heme positions [16–19].

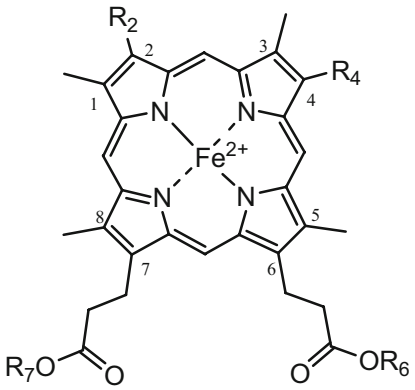
In this work, the authors used computation methods to examine the physicochemical parameters involved in the recognition of heme derivatives by CYP2B4 apoprotein. Calculations were also performed to determine the affinity of the various heme-apoprotein complexes for two well-known CYP2B4 substrates, aniline (A) and *N*-methyl-aniline (NMA). The ultimate aim of this study was to determine whether the nature of the functional groups tethered to the heme core plays a significant role during the recognition process between enzyme and substrate.

Method of calculation

Coordinates for a three-dimensional structure of heme **1** and the residues comprising the CYP2B4 heme binding site were taken from the appropriate published crystal structure (PDB code: 2bdm). This structure was then used to obtain HOMO-LUMO energies at the B3LYP/6–31G* level using Gaussian 98 software [20]. For the iron atom, all theoretical calculations were performed using a LANL2 pseudopotential [15, 21]. The structures of both, A and NMA were optimized using the aforementioned DFT level. The surface electrostatic potential (SEP) of certain amino acid residues forming the CYP2B4 heme binding site were also calculated. Our group recently reported DFT-optimized geometries and HOMO-LUMO energies for **1–6** [15], and these previous findings were used to carry out docking simulations.

To identify the recognition site mediating binding between CYP2B4 apoprotein and its ligands (both hemes and substrates), docking simulations were conducted using two different 3-D structures of CYP2B4 (PDB codes: 2bdm

Table 1 Structure of heme (**1**) and its derivatives (**2–6**)



Heme	R_2	R_4	R_6	R_7
1	$CHCH_2$	$CHCH_2$	H	H
2	H	$CHCH_2$	H	H
3	$CHCH_2$	H	H	H
4	$COCH_3$	$COCH_3$	H	H
5	$CHCH_2$	$CHCH_2$	*p*-nitrophenoxy	*p*-nitrophenoxy
6	$CHCH_2$	$CHCH_2$	*p*-aminophenoxy	*p*-aminophenoxy

and 1po5). These two crystal structures differ slightly because 1po5 is the structure of the pure protein, while 2bdm is a co-crystal of CYP2B4 apoprotein with its substrate ligands [22]. Before attempting any docking simulations, all partial atomic charges (Gasteiger-Marsili formalism), all of the ligand's rotatable bonds, and all CYP2B4 atoms' Kollman charges were assigned using AutoDock Tools [23]. Missing residues and hydrogen atoms were similarly built back into the model with the same software.

For docking studies, the AutoDock (3.0.5) program was chosen because its algorithm allows for full flexibility of small ligands [23]. A GRID-based procedure was employed to prepare the structural input and to define the binding sites [24]. A rectangular lattice ($126\times126\times126$ Å^3) with points separated by 0.375 Å was superimposed upon the entire protein structure.

All docking simulations were conducted using the hybrid Lamarckian genetic algorithm, with an initial population of 100 randomly placed individuals and a maximum of 1.0×10^8 energy evaluations. All other parameters were maintained at their default settings. Resulting docked orientations within a root-mean square deviation of 0.5 Å of each other were clustered together. The lowest energy cluster returned for each ligand was subjected to further analysis.

First, A and NMA were docked onto CYP2B4 (pdb code: 2bdm and 1po5), as control experiments. Next, heme **1** was withdrawn from its binding site yielding the CYP2B4 apoprotein. Subsequently, heme **1** and its derivatives **2–6** were individually re-docked onto the apoprotein. The lowest energy coordinates resulting from the docking simulations, which were identified with AutoDock Tools, were then used to define five new CYP2B4 apoprotein-heme complexes (Fig. 1). Finally, A and NMA were once again docked onto these complexes (Fig. 1). The docked heme-apoprotein complexes were visualized using the visual molecular dynamics (VMD) viewer [25].

Results and discussion

Computational tools allow several chemical and biological properties to be directly calculated with a high degree of accuracy [26]. Such tools have also enabled the study of several physicochemical properties of amino acids and protein prosthetic groups, such as HOMO-LUMO energies [15, 27, 28] and SEP [29]. Along with docking calculations, these computations are able to predict both the binding mode and the binding the affinity between a protein and its ligands [30].

The optimized geometry and electronic properties of **1** and its derivatives **2–6** (Table 1) were determined from previous efforts [15] in order to explain the possible relationship between these parameters and the catalytic activities of P450 enzymes [31, 32]. Thus, the authors docked a set of heme derivatives, conveniently modified at C-2, C-4, C-6 and C-7 carbons [15], onto CYP2B4 apoprotein, which allow predictions of drug biotransformations [33]. These docking experiments employed crystal structures for two different conformations of the CYP2B4 protein (2bdm and 1po5). It is well known that the heme binding site is conserved, whereas that the extent of the protein's conformational changes upon ligand binding [22].

Gibbs free energy changes (ΔG) of −13.39 and −15.79 kcal mol^{-1} (Table 2) were obtained when heme **1** was docked onto 2bdm and 1po5, respectively. These values confirm that the molecule has sufficient affinity for both protein conformations. These results are in agreement with experimental data previously reported for other heme proteins [10]. Similarly, the heme's spatial coordinates are identical to those of heme groups from both parent crystal structures [18]. In contrast, the positions of the amino acid residues within the heme binding site of the docked structure are different from those in the 2bdm and 1po5 structures. In order to maintain the heme at its original position and to conserve its catalytic properties, it is therefore necessary to account for the interactions between the heme derivative and its amino acid neighbors.

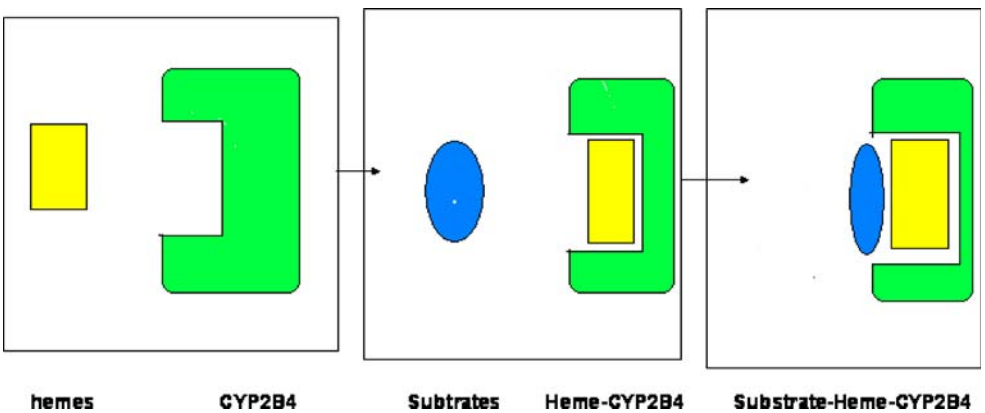


Fig. 1 Scheme of steps to be followed for obtaining five new CYP2B4 apoprotein-heme complexes by docking

Table 2 Docking results for heme and CYP2B4 substrates on different CYP2B4 apoprotein-heme complexes

	Heme on CYP2B4 apoprotein, ΔG (kcal mol^{-1})		NMA on CYP2B4 apoprotein-heme complexes, ΔG (kcal mol^{-1})		A on CYP2B4 apoprotein-heme complexes, ΔG (kcal mol^{-1})	
	2bdm	1po5	2bdm	1po5	2bdm	1po5
Native	–	–	–5.60	–5.42	–5.53	–5.27
1	–13.39	–15.79	–4.69	–5.28	–4.98	–5.07
2	–13.61	–14.55	–4.72	–4.66	–5.02	–4.75
3	–13.67	–15.40	–5.23	–4.48	–4.97	–4.45
4	–13.65	–15.75	–5.62	–4.78	–5.40	–4.86
5	–14.02	–16.29	–4.66	–4.78	–5.04	–4.85
6	–16.96	–16.44	–5.47	–5.59	–5.87	–5.27

The above calculations considered only electronic effects resulting from varying porphyrin functionality in a simulated vacuum and neglected the other physicochemical properties of the binding site, such as hindrance, electrostatic charge, and solvation [24, 34–38].

The negative ΔG values depicted in Table 2 showed that all heme derivatives had roughly the same affinity for the 2bdm and 1po5 apoproteins with the exception of **6**, which was bound more tightly to both structures. This higher affinity was attributed to electrostatic and π-cationic interactions between the *p*-nitrophenoxy groups at the heme R_6 and R_7 positions and the NH_3^+ moieties of Arg residues 98, 125, and 434 side chains. Interestingly, despite structural dissimilarity at the R_6 and R_7 positions, hemes **1** and **6** docked onto the 2bdm apoprotein in the exact same orientation. Docking orientations still differed for the 1po5 apoprotein. These observations may explain the differences in terms of HOMO-LUMO densities [15, 39] to explain the binding affinity between the two parent apoprotein structures (Figs. 2 and 3). On the other hand, the heme derivative **2** has high HOMO density at the C-4 carbon due to the electron-withdrawing effects of the R_4 vinyl group [15]. When docked onto the 1po5 apoprotein (Fig. 3), the C-R_4 moiety interacts with amino acid residues Leu 441 and Ala 442 in the same manner as the C-R_4 moiety of **1** (Fig. 3). The dangling *p*-nitrophenoxy group changes its orientation relative to heme **1**, but the free energies of binding still remain similar. In contrast, heme derivative **3** lacks the electron-withdrawing functionality at C-4 (R_4=H), so there is a correspondingly high HOMO density on the heme iron atom [15]. This causes **3** to adopt a different orientation with respect to heme derivate **1**, although binding affinity is once again similar (Table 2). These data support the hypothesis that the chemical nature of the C-R_4 functional group and the locant are important factors for orienting the heme derivatives within their binding site.

The high affinity of heme **6** for both subtypes of apoprotein was initially attributed to the high HOMO density on the sp^2 carbons of the heme propionic group [15], which interacted favorably with positively charged arginine residues in the binding site. Subsequent SEP calculations for this structure verified this hypothesis by showing that electrostatic forces oriented anionic regions of the heme, such as the propionic group, toward cationic arginine residues in the active site [40], (Fig. 4). Further screening of the electrostatic surface was conducted for the other complexes in order to explain differences in the binding modes and binding affinities between the 2bdm and 1po5 apoprotein structures [41]. The results suggested that Arg residues 98, 125, and 438 engaged in favorable cation-π interactions with the *p*-nitrophenoxy moieties (R6 and R7) of heme **6**. It was therefore likely that this positively charged region of the protein has sufficiently high LUMO energies to make additional HOMO-LUMO interactions between groups. These results could explain how heme binding is affected by the presence of electron-withdrawing substituents (**4**, **5**). Increases in the sp^2 carbon's LUMO density reflect the different modes of heme binding to the apoprotein (Figs. 2 and 3). Understanding and predicting HOMO-LUMO energies played an important role in elucidating how the different heme derivatives interacted with CYP2B4 apoprotein. Such calculations could eventually help design and/or identify new heme derivatives with increased P450 activities. In these experiments, it was clear that both hindrance effects and electronic properties were important for controlling the binding of different heme derivatives at the protein binding site. This is exemplified by heme derivative **5**, which possessed slightly higher binding affinity but remarkably different docking orientation compared to heme **1**. This is because hemes **5** and **6** have substantial structural additions that increase their molecular volumes and cause changes in their electronic properties, which are reflected in the frontier orbital calculations and docking simulations [15].

Both derivatives **5** and **6** were recognized in the same place but bound with distinct orientations and through a different set of interactions. Heme **6** had higher binding affinity than heme **5** for both the 2bdm and the 1po5 CYP2B4 apoproteins. As evident in Figs. 2 and 3, all hemes examined docked onto the apoprotein at the usual

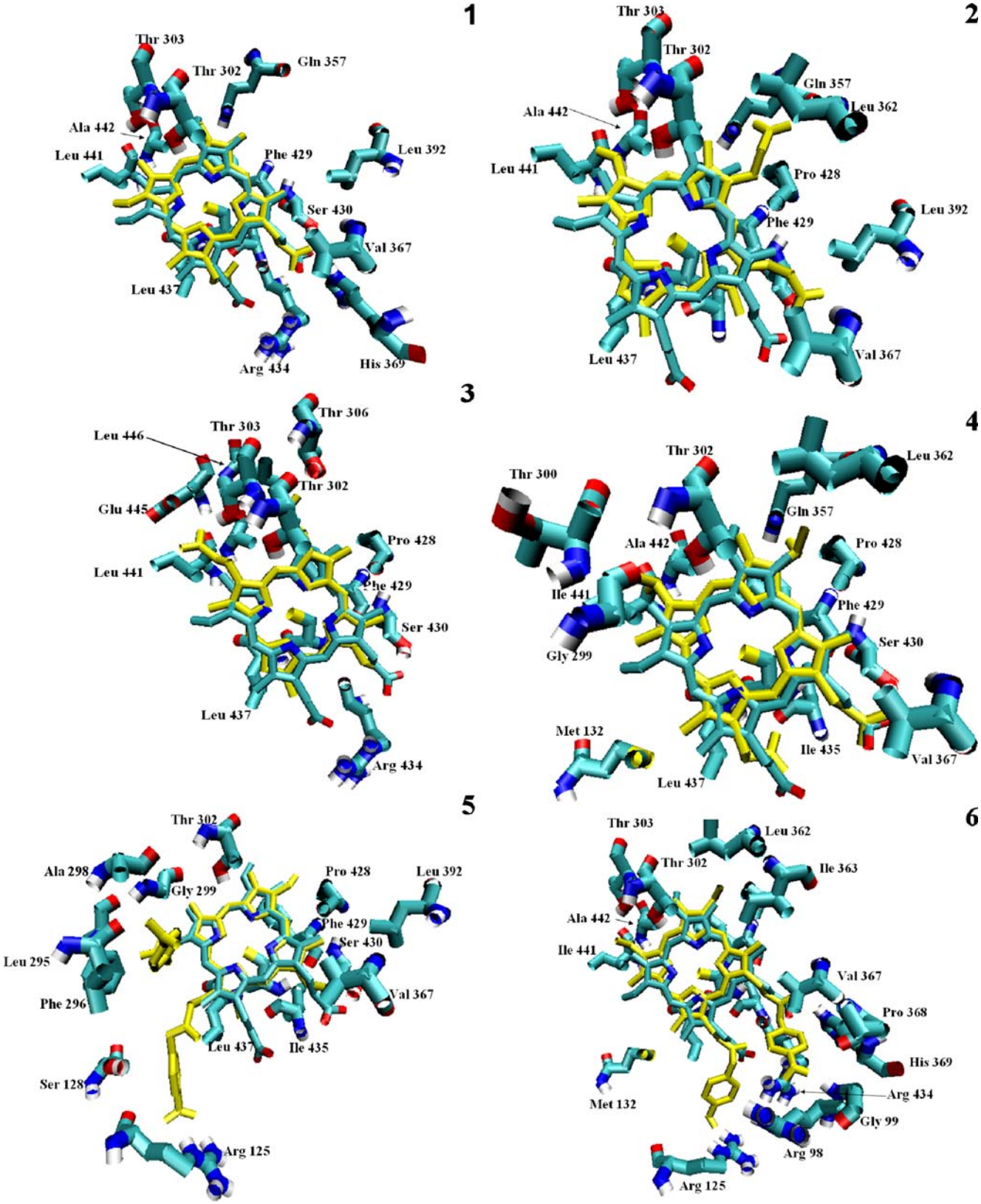
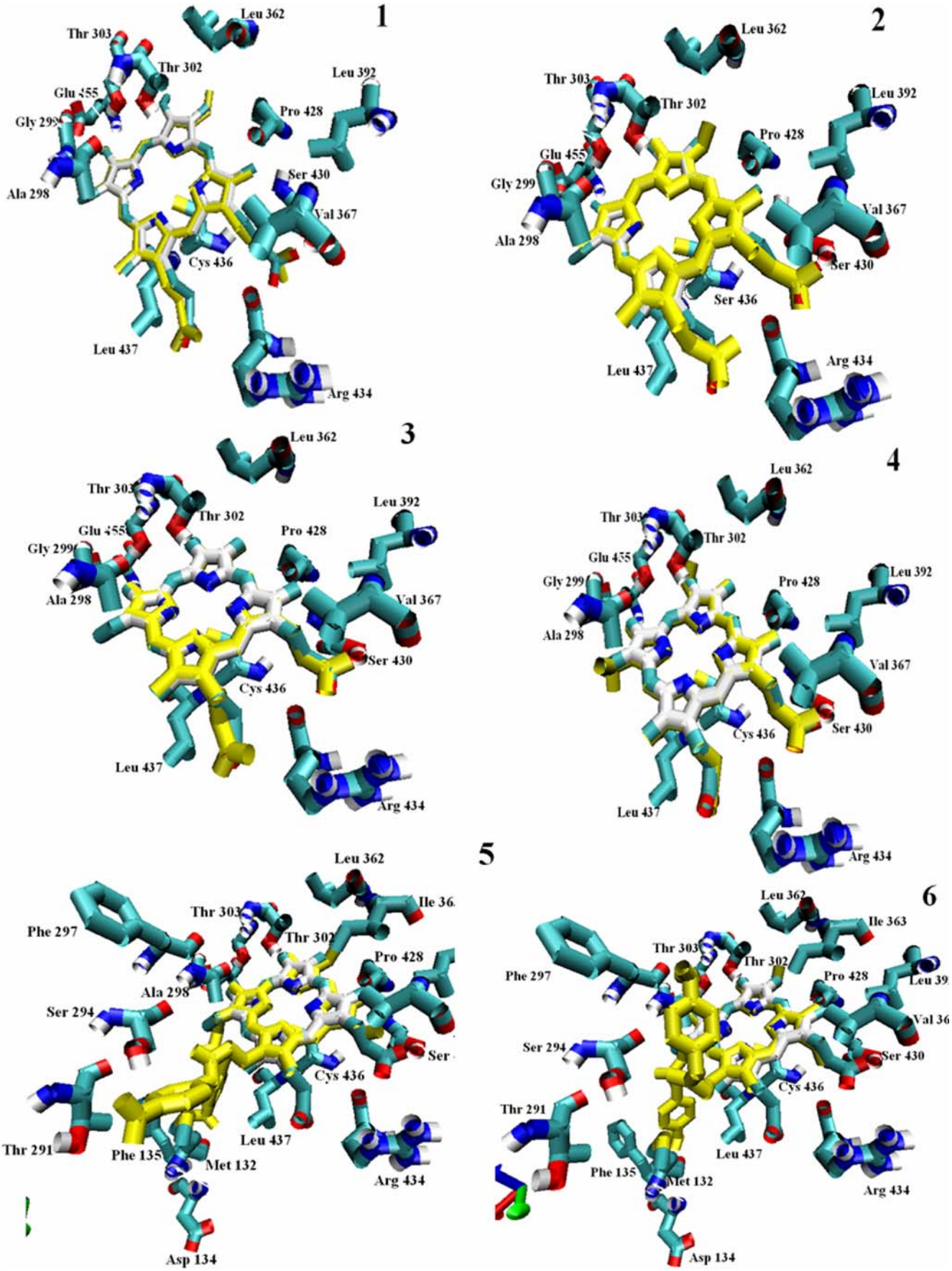


Fig. 2 Docking of the heme derivatives (blue) on CYP2B4 (pdb code: 2bdm)


1
Leu 362
Thr 303
Thr 302
Leu 392
Glu 455
Pro 428
Gly 299
Ser 430
Ala 298
Val 367
Cys 436
Leu 437
Arg 434
2
Leu 362
Thr 303
Thr 302
Leu 392
Pro 428
Glu 455
Gly 299
Val 367
Ala 298
Ser 430
Ser 436
Leu 437
Arg 434
3
Leu 362
Thr 303
Thr 302
Leu 392
Glu 455
Pro 428
Gly 299
Ala 298
Val 367
Ser 430
Cys 436
Leu 437
Arg 434
4
Leu 362
Thr 303
Thr 302
Glu 455
Gly 299
Pro 428
Leu 392
Ala 298
Val 367
Cys 436
Ser 430
Leu 437
Arg 434
5
Leu 362
Ile 36
Thr 303
Phe 297
Thr 302
Pro 428
Ala 298
Ser 294
Ser
Cys 436
Thr 291
Leu 437
Phe 135
Met 132
Arg 434
Asp 134
6
Leu 362
Ile 363
Thr 303
Phe 297
Thr 302
Pro 428
Leu 39
Ser 294
Val 36
Ser 430
Cys 436
Thr 291
Leu 437
Phe 135
Met 132
Arg 434
Asp 134

◀ **Fig. 3** Docking of the heme derivatives (blue) on CYP2B4 (pdb code: 1po5)

heme binding site in close spatial proximity to the following residues: Ile 179, Ala 442, Thr 302, Phe 429, Cys 436, Ile 363, His 369, Ser 430, Arg 98, Val 367, Arg 434, Trp 121, Ile 114, Arg 125, Leu 437, Gly 438, Ala 298, and Ile 441. This same set of conserved residues is located near the heme group in three different CYP2B4 crystal structures (PDB code: 2bdm, 1po5 and 1suo) [22]. The experimental data [10], the DFT calculations performed on heme derivatives [15] and the aforementioned docking simulations all suggested that chemical modification of the heme group might possibly change a P450 isoform's catalytic behavior. When electron-donating groups are bonded at the R6 and R7 positions, as was the case for heme derivative 6, the observed computational results were in agreement with previous reports concerning other heme proteins.

After performing docking simulations for all heme-apoprotein complex pairs, the well-established CYP2B4 substrates A and NMA were docked on the original 2bdm and 1po5 structures in order to determine their binding sites [42]. Addition or removal of a prosthetic group to increase enzyme activity could be difficult but would yield important results [10]. A prosthetic group with lower affinity for the apoprotein could bind more tightly to its substrate through a retroelectron donation effect [43]. This may explain why the heme **4**-apoprotein complex, which possesses greater electron-donating capacities, demonstrated higher affinity for A and NMA.

The docking results showed that A was recognized by two favorable interactions. The first was located close to the C-2 vinyl group, and the second occurred over the heme iron (Fig. 5). These findings were attributable to favorable interactions between aniline's high HOMO density (Fig. 6) and the heme iron's high LUMO density, which was a direct consequence of the electron-withdrawing effects of the porphyrin vinyl group. Thus, A and NMA docked at the same site as was observed in the original CYP2B4, and these data are in good agreement with experimental reports [42].

Docking simulations predicted that the heme **4**- and heme **6**-apoprotein complexes demonstrated the highest affinity for A and NMA. These prosthetic groups have excess HOMO density on their heme sp^2 carbons, which interact with the LUMO density of NMA. This substrate is probably less polar than A, because A has an unprotected amino group capable of engaging in nucleophilic attack [44]. Heme derivatives **4** and **6**, which have greater affinity for A and NMA, demonstrate the importance of a prothetic group's electronic properties.

Unfortunately, the affinity of A for the heme **4**–apoprotein complex disagreed with previous experimental reports for CYP450nor [18]. These errors could have stemmed from simplifications in the computational model. For example, protein movement was not considered in the docking simulations performed, but it remains an important factor affecting the catalytic activity of CYP2B4. Alternatively, CYP2B4 and CYP450nor do have some significant structural differences [45].

Docking simulations and frontier orbital calculations did not allow for the elucidation of the catalytic mechanism. Nevertheless, the fact that heme could be incorporated into CYP2B4 apoprotein but had no preference for either of the

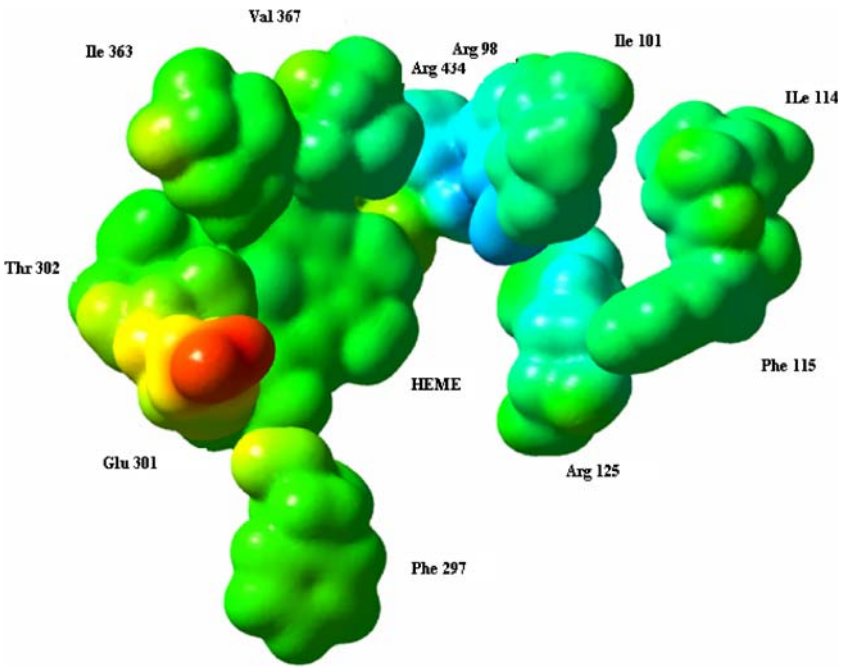


Fig. 4 Heme and amino acids which recognize the substrates depicted as surface electrostatic properties showing high positive charges at Arg residues (blue color)

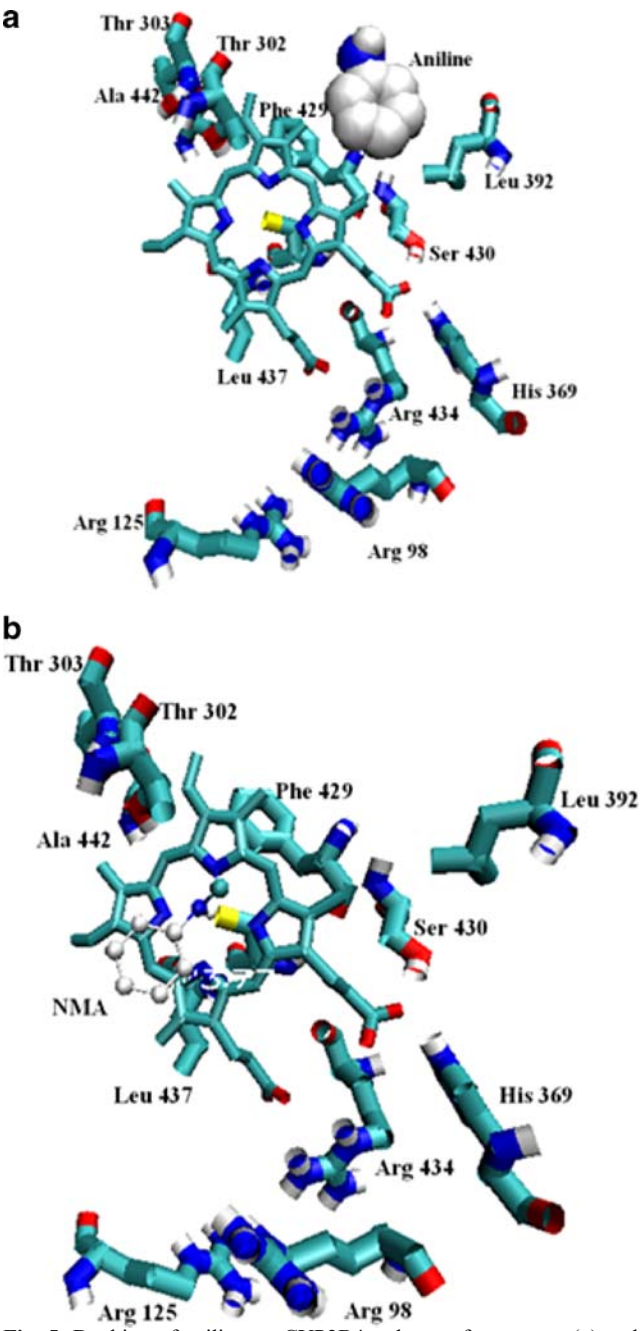


Fig. 5 Docking of aniline on CYP2B4 at lowest free energy (**a**) and over heme group (**b**)

two different substrates (Table 2) indicated the iron atom's HOMO density was greater in heme **4** than in heme **2**. This effect could be explained in terms of retroelectron donation in which a molecule's HOMO or LUMO densities change after engaging in other HOMO-LUMO interactions [43]. The propionic groups located at the C-6 position of heme **4** had the greatest HOMO and LUMO densities [15], and the corresponding densities at the heme's iron atom were modified slightly. Thus, substrate recognition was better for heme derivative **4** than for heme **2** (Table 2).

Conclusions

In this work, different heme derivatives were docked onto two conformations of CYP2B4 apoprotein derived from the two PDB files, 2bdm and 1po5. The results demonstrated that HOMO-LUMO densities play an important role in directing the molecular recognition between the heme and apoprotein.

The heme derivatives possessing electron-donating functionalities had higher affinity for apoprotein and were bound to the same location as the heme in the native-state protein. The affinity between the different heme-apoprotein complexes and the substrate was somewhat varied. The well-known CYP2B4 substrates A and NMA explored in this study altered their binding behavior in response to the heme derivative present. Hemes with electro-donating functionality had higher affinity for A and NMA because this increases LUMO density. Aniline is more polar than NMA, and so its affinity for the heme **6** complex, which has electron-donating groups to increase its heme HOMO density, was greater. A similar phenomenon might also

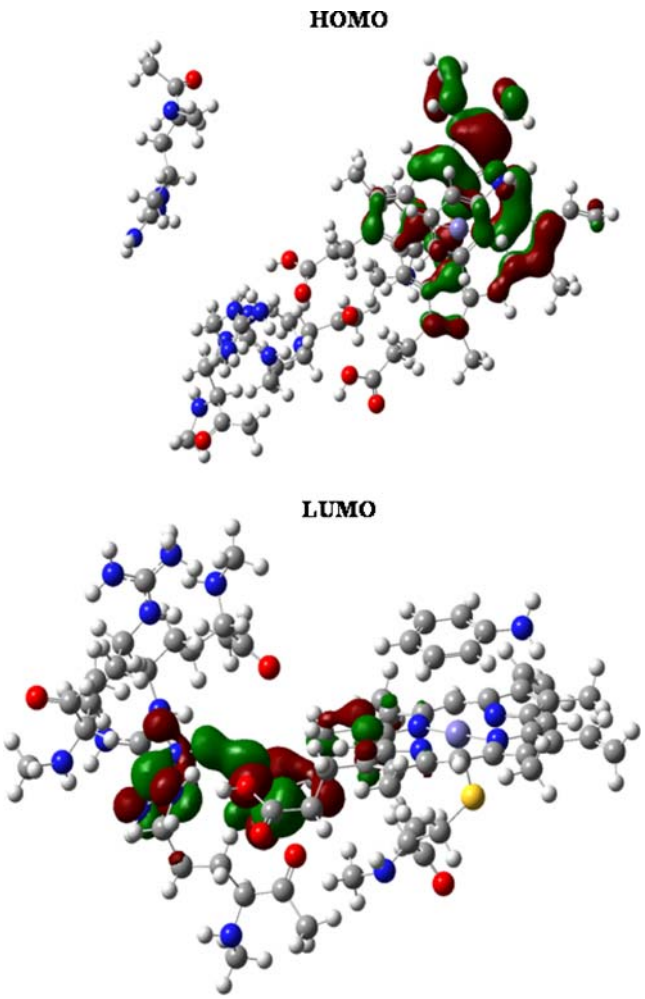


Fig. 6 HOMO (up) and LUMO (low) 3D shapes for 1, arginine residues and aniline, obtained from docking simulations with $\Delta G = -4.42$ kcal mol^{-1}

explain the results for heme **1**. Its electron-donating character was predicted to create favorable interactions with the positive charges of the apoprotein's arginine residues, and this hypothesis was corroborated by SEP calculations.

These results suggested that there was an interaction between the heme LUMO and the substrate HOMO. To further explore this hypothesis, a more diverse set of heme derivatives might be tested. In addition, heme-apoprotein complexes corresponding to derivatives **2**, **3**, **5**, and **6** could be synthesized and evaluated experimentally.

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