Adaptable Small Ligand of CYP1 Enzymes for Use in Understanding the Structural Features Determining Isoform Selectivity

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Supporting Information

ABSTRACT: Although several families of compounds have been identified as scaffolds for inhibitors of the CYP1 family, the isoform selectivity determining structural features has not been fully clarified at the molecular interaction level. We studied the CYP1 isoform selectivity for stilbenoid inhibitors using integrated induced fit docking and molecular dynamics simulations. The hydrophobic interactions with the specific phenylalanine residues in the F helix are correlated with inhibitory potency in the CYP1 family. Through this study, we found that the adaptable, small, and semirigid ligand is a promising starting point for the development of isoform-selective inhibitors and investigation of selectivity-determining features.

KEYWORDS: Cytochrome P450, trans-Stilbenoids, Isoform selectivity, Molecular dynamics

The discovery of isoform-selective inhibitors is an important issue in the development of novel therapeutics or chemical tools for biological studies.^{1,2} However, this task is not trivial mainly because of the structural similarity among the binding sites of isoforms.^{3,4} The design of isoform-selective inhibitors is more complicated, especially when different isoforms share many substrates or when isoforms do not have strong preferences for specific substrates. Both of these issues are the case for cytochrome P450 (CYP), which is a superfamily of hemoprotein enzymes that catalyze the oxidation of a wide diversity of endogenous and exogenous compounds.^{5,6}

Among cytochrome P450 enzymes, subfamily 1 (CYP1) has been of great interest because of its association with cancer.^{7,8} These enzymes catalyze the metabolic activation of procarcinogens to reactive metabolites. In addition, these enzymes are responsible for the metabolic deactivation of many anticancer agents, such as paclitaxel, doxorubicin, and mitoxantrone.⁹ Thus, the inhibition of CYP1 enzymes has become the target for chemoprevention and treatment of CYP1-mediated drug resistance. As a consequence, several families of compounds have been identified including stilbenoids and flavonoids.^{10–12}

The representative human CYP1 family members are CYP1A1, CYP1A2, and CYP1B1. The amino acid sequence homology between CYP1A1 and CYP1A2 is 80%.¹³ Although the amino acid sequence homology between CYP1As and CYP1B1 is relatively low (lower than 40%),^{14,15} there is

substantial substrate overlap. The preferred substrates for CYP1 enzymes are planar hydrophobic molecules such as polycyclic aromatic hydrocarbons (PAHs).^{16,17} The X-ray structures of all members of CYP1 have been determined in complex with the inhibitor alpha-naphthoflavone (ANF).^{15,18,19} The overall structures and active site topologies of CYP 1s are very similar to each other. The shape and size of the active site are more similar for CYP1A1 and CYP1B1 than for CYP1A1 and CYP1A2, despite the higher sequence homology between the latter two isozymes.¹⁹ Within the narrow planar active sites of the three isozymes, ANF occupies the same plane. However, its orientations are different; the orientations of ANF in CYP1A1 and CYP1A2 are essentially the same, whereas in CYP1B1, its structure is flipped by 180° along the ligand long axis. This is an interesting feature for understanding the functional diversity and variability of these isozymes and might be a key in designing selective inhibitors.

In our previous studies, we discovered potent and selective CYP1B1 inhibitors belonging to the stilbenoid family and have acquired considerable information on the structure–activity relationships of CYP1 enzyme inhibitors.^{20,21} It was found that the potency and isoform selectivity of inhibitors were very

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Table 1. Inhibitory Activities of ANF and Stilbenoid Analogues 1–3 against CYP1A1, CYP1A2, and CYP1B1 Enzymes^a

Compd	IC ₅₀ (nM) ^b			Ratio		
	1A1	1A2	1B1	1A1/1B1	1A1/1A2	1A2/1B1
ANF ^c	55	75	13	4.2	0.7	5.8
1	300 ± 20	3100 ± 880	6 ± 2	50.0	0.1	516.7
2	61 ± 21	11 ± 2	2 ± 1	30.5	5.5	5.5
3	41 ± 11	1.5 ± 1	4 ± 2	10.3	27.3	0.4

^aEnzyme activities were measured by following the procedure described in ref 20. ^bThe IC₅₀ values are the means ± range of two separate experiments determined using a quadratic expression by nonlinear regression methods with GraphPad Prism software (San Diego, CA). ^cTaken from ref 23.

sensitive to the substitution patterns on the *trans*-stilbene template. Based on our previous SAR results and the X-ray structural information on CYP 1s, we explored the crucial selectivity-determining structural features of stilbenoid CYP1 inhibitors through computational modeling studies. We anticipate that an improved understanding of isoform selectivity at the molecular interaction level will lead to the discovery of more drug-like isoform-selective CYP inhibitors. We herein present our studies on this topic.

In our previous studies, we found that 2,4,3',5'-tetramethoxystilbene (**1**, Table 1) is a highly potent and selective competitive inhibitor of CYP1B1.^{20,22} We also found that when its 2,4-dimethoxyphenyl ring was substituted by a 2-thiophenyl group (**2** in Table 1), the inhibitory potentials were increased, but selectivity was reduced.²⁰ Compound **1** showed 50-fold and 520-fold selectivities against 1B1 over 1A1 and 1A2, respectively, while compound **2** exhibited 30-fold and 5-fold selectivities. We attributed the lower isoform selectivity of inhibitor **2** to its smaller molecular size. The molecule volume of **2** is only 201 Å³, which is smaller than that of **1** and other isozyme-selective stilbenoid inhibitors and is much less than 50% of the volume of CYP1 active site cavities (441–524 Å³).¹⁹ In this study, we used this small and less selective CYP inhibitor **2** as a starting point of investigation. We envisioned that incorporation of appropriate functional groups into the core structure of **2** would grant a change in isoform selectivity and allow the identification of the selectivity-determining structural features.

With such an aim in mind, a 3,5-dimethoxyphenyl group of **2** was modified by adding various substituents. Most analogues of this kind did not show substantial selectivity and potency. However, a compound with an imidazole moiety (**3**, Table 1) showed a remarkably potent inhibition against CYP1A2 (IC₅₀ = 1.5 nM) and a good selectivity over 1A1 (27-fold). The selectivity between 1A2 and 1B1 was not high, but interestingly, the isoform preference was different compared to mother compound **2**.

Computational modeling studies were performed with three compounds, **1**, **2**, and **3**, to explore the selectivity-determining structural features of the stilbenoid CYP1 inhibitors. First, to gain information on the binding pose, a docking study was carried out using the induced fit docking (IFD) protocol in the Schrödinger Suite 2017-4²⁴ and the X-ray crystal structures of CYP 1s. The X-ray crystal structures of CYP1A1 (PDB code: 4I8V),¹⁹ CYP1A2 (PDB code: 2HI4),¹⁸ and CYP1B1 (PDB

code: 3PM0)¹⁵ were obtained from the Protein Data Bank site (<http://www.rcsb.org/>).

The predicted binding poses of the inhibitors are shown in Figure 1. Compound **1**, the CYP1B1-selective inhibitor, fit the

Figure 1. Proposed binding pose of compounds **1** (orange stick), **2** (blue stick), and **3** (green stick) on CYP1A1 (blue surface model), CYP1A2 (green surface model), and CYP1B1 (red surface model). The binding site cavities of CYP 1s are represented by transparent solid-style models derived from ANF-complexed X-ray structures. The heme is shown as sticks colored by atom type.

active binding site of CYP1B1 very well. In CYP1B1, the binding pocket near the heme is sufficiently large to accommodate the 3,5-dimethoxyphenyl group of **1**, and the binding cavity near the entrance is also sufficiently large to accommodate the 2,4-dimethoxyphenyl group without obvious steric clashes. In CYP1A1, the binding pocket is shorter in length, and the pocket near the heme is narrower than that of CYP1B1. This difference might be why the 3,5-dimethoxyphenyl ring of **1** was docked in a tilted mode directly above the heme prosthetic group, thus avoiding the steric clashes at the binding pocket of CYP1A1. The best docking pose of **1** in the active site of CYP1A2 suffered from severe steric clashes due to the compact and narrow active site, which well explains the low affinity of CYP1A2 for compound **1**.

Figure 2. Molecular dynamics simulation study and interaction profile analysis of compound 1 (orange ball and stick) in (a) CYP1A1 (blue stick residues), (b) CYP1A2 (green stick residues), and (c) CYP1B1 (red stick residues). A portion of the F-helix is displayed in the ribbon model, and heme is represented as a cpk model colored by atom type. Dashed pink lines represent hydrophobic interactions between enzyme and ligand. Contact histograms for the (d) CYP1A1, (e) CYP1A2, and (f) CYP1B1 enzymes with compound 1 are represented by a colored stacked bar plot between 40 and 100 ns of the MD simulation. Only H-bonding (yellow-green colored bar) and representative hydrophobic interactions (lavender colored bar) are presented for clarity. The specific π - π stacking interactions of the 2,4-dimethoxyphenyl group in 1 with Phe224 (in CYP1A1), Phe226 (in CYP1A2), and Phe231 (in CYP1B1) are displayed by the blue-colored stacked bars.

Figure 3. Molecular dynamics simulation study and interaction profile analysis of compound 2 (blue ball and stick) in (a) CYP1A1 (blue stick residues), (b) CYP1A2 (green stick residues), and (c) CYP1B1 (red stick residues). A portion of the F-helix is displayed in the ribbon model, and heme is represented as a cpk model colored by atom type. Dashed pink lines represent hydrophobic interactions between enzyme and ligand. Contact histograms for the (d) CYP1A1, (e) CYP1A2, and (f) CYP1B1 enzymes with compound 2 are represented by a colored stacked bar plot between 40 and 100 ns of the MD simulation. Only H-bonding (yellow-green colored bar) and representative hydrophobic interactions (lavender colored bar) are presented for clarity. The specific π - π stacking interactions of the 3,5-dimethoxyphenyl group in 2 with Phe224 (in CYP1A1), Phe226 (in CYP1A2), and thiophene ring with Phe231 (in CYP1B1) are displayed by the blue colored stacked bars.

The nonselective CYP1 inhibitor 2 also fit in the binding pocket of CYP1B1 very well in a similar binding mode as 1. The 3,5-dimethoxyphenyl group was positioned above the heme, and the thiophene ring was located near the entrance. However, in CYP1A1 and CYP1A2, the bulkier 3,5-dimethoxyphenyl group of 2 was located near the entrance to avoid steric repulsion that would otherwise be encountered at the narrow pocket near the heme. The 3,5-dimethoxy phenyl group experienced more steric clash in the binding pocket of CYP1A1 compared to that in the pocket of CYP1A2, which explicates the lower potency of 2 toward CYP1A1 than toward the other CYP 1s.

The predicted binding pose of inhibitor 3 was different from those of the smaller inhibitors 1 and 2 due to the presence of the imidazole moiety. In all CYP 1s, the imidazole ring was located near the heme to coordinate to the heme iron, and the thiophene ring was positioned on the upper side of the binding cavity. In particular, the thiophene ring of 3 in CYP1A2 protruded out of the binding pocket because of the narrow and short cavity, thereby resulting in the imidazole ring posed directly above the heme to provide the optimal distance and angle for an imidazole–heme coordination. This atypical binding mode accounted for the remarkably potent inhibitory activity of 3 against CYP1A2. When compound 3 was bound in

Figure 4. Molecular dynamics simulation study and interaction profile analysis of compound **3** (green ball and stick) for (a) CYP1A1 (blue stick residues), (b) CYP1A2 (green stick residues), and (c) CYP1B1 (red stick residues) enzyme. A portion of the F-helix is displayed in the ribbon model, and heme is represented as a cpk model colored by atom type. Dashed pink lines represent hydrophobic interactions between enzyme and ligand. The distance between the nitrogen atom of imidazole and the iron of heme for each CYP1 enzyme is represented. Contact histograms for the (d) CYP1A1, (e) CYP1A2, and (f) CYP1B1 enzymes with compound **3** are represented by a colored stacked bar plot between 40 and 100 ns of the MD simulation. Only H-bonding (yellow-green colored bar) and representative hydrophobic interactions (lavender colored bar) are presented for clarity. The specific π - π stacking interactions of the thiophene ring in **3** with Phe224 (in CYP1A1), Phe226 (in CYP1A2), and Phe231 (in CYP1B1) are displayed by the blue colored stacked bars.

the active site of CYP1B1, the pocket was adequately filled without obvious steric clashes. This feature might be one of the reasons for the high inhibitory activity of **3** against CYP1B1. On the other hand, in CYP1A1, the thiophene ring of **3** experienced steric clash in the relatively smaller pocket of CYP1A1, and this might decrease its affinity to CYP1A1.

To better understand the protein–ligand interaction features between stilbenoid inhibitors and CYP 1s as well as the molecular basis for specificity, we performed molecular dynamics (MD) simulations using Desmond v4.8 software.^{25,26} The CYP1–inhibitor complexes obtained from the above docking studies were used as starting structures for the MD simulations.

Figure 2a–c presents the binding pose of stilbenoid inhibitor **1** in CYP 1s, and Figure 2d–f shows the interactions during MD simulation. Our MD simulation study suggested that the CYP1B1 isoform preference of compound **1** could be attributed to the interactions between the 2,4-dimethoxyphenyl group and Phe231 in the F helix (Figure 2c and 2f). It has been reported that the F helix in CYP 1s plays an important role in ligand binding and is involved in the determination of substrate specificity for CYP1A subfamily enzymes.^{15,27} Moreover, hydrophobic interactions with the phenylalanine residue in the F helix have been suggested as a crucial factor for the activity of CYP1 inhibitors.^{27–29} We observed a high degree of π - π stacking interaction of the 2,4-dimethoxyphenyl group with Phe231 and an additional interaction with Phe268. In contrast, when compound **1** bound to CYP1A1 or CYP1A2, relatively weak π - π stacking interactions were observed between the 2,4-dimethoxyphenyl group and the Phe224 or Phe226 residue, respectively.

According to our docking study, the orientations of the 3,5-dimethoxyphenyl group of **2** are different depending on the size and shape of the isoenzyme binding cavity; the orientations of **2** in CYP1A1 and CYP1A2 are the same, whereas in the more spacious CYP1B1, the molecular structure

was flipped along the ligand short axis. This orientation adjustment is possible because of the presence of a relatively small thiophene ring. As a consequence, compound **2** fit the active binding site of all CYP 1s very well but displayed reduced selectivity. Nevertheless, compound **2** has a preference for CYP1B1. Based on the MD simulation, this preference could be explained by hydrophobic interactions between the 3,5-dimethoxyphenyl group of **2** and Phe134, Ala330, and Ile399 in CYP1B1 (Figure 3c and 3f) in addition to the strong π - π stacking interaction of the thiophene ring with Phe231. On the other hand, despite the favorable hydrophobic interactions of the 3,5-dimethoxyphenyl group of **2** with the phenylalanine residue in the F helix of CYP1A1 and CYP1A2, the thiophene ring involved only weak hydrophobic interactions with amino acids located near the heme (Figure 3a–b and 3d–f).

Unlike thiophene stilbenoid **2**, the imidazole moiety-containing derivative **3** displayed a CYP1A2 isoform preference, which is unusual in other classes of CYP1 inhibitors. According to our modeling study of **3**, the orientations of the ligand long axis are essentially the same in all CYP 1s, and the imidazole moiety is located near the heme. Our MD simulation suggested that the CYP1A2 isoform preference might arise from the presence of strong hydrophobic interactions between the thiophene ring and protein residues at the entrance of the binding pocket; the thiophene ring of **3** formed π - π stacking interactions with Phe226 and additional hydrophobic interactions with Val227, Phe260, and Phe319 (Figure 4b and 4e). In addition, cation- π interactions between the imidazole ring and Phe125 also contribute to higher binding affinity for CYP1A2. In contrast, in CYP1A1 and CYP1B1, the thiophene ring formed hydrophobic interactions with only two amino acids (Phe224 and Val 228 for CYP1A1; Phe 231 and Phe 268 for CYP1B1). Although the π - π stacking interaction fractions of **3** were lowest in CYP1B1, compound **3** showed a considerable potency against CYP1B1.

This result might be explained by the proximity of the imidazole group to the heme iron (Figure 4c and 4f), which induced tight binding of the ligand to CYP 1s.³⁰

In conclusion, we analyzed the CYP1 isoform selectivity of semirigid stilbenoid inhibitors using integrated IFD and MD simulations to understand the selectivity-determining structural features and further to discover isoform-selective inhibitors. In this work, we initially focused on comparing the binding modes of stilbenoid and its thiophene derivative **2**, which is a smaller and less selective CYP inhibitor. We realized that the π - π stacking interactions with the specific phenylalanine residues in the F helix are correlated with inhibitory potency in the CYP1 family. Due to the presence of a relatively small thiophene ring, the thiophene stilbenoid **2** flips its orientation according to the cavity shapes and electrostatic environments, which suggested the possibility that thiophene stilbenoids and similar semirigid small stilbenoids can serve as common adaptable scaffolds for all CYP1 inhibitors via the incorporation of appropriate functional groups that can interact with certain parts of the binding pocket. The imidazole moiety-attached thiophene stilbenoid derivative **3** anchors to the heme prosthetic group and allows a CYP1A2 isoform preference, which is unusual in other classes of CYP1 inhibitors. Our simulation indicated that the imidazole ring determines the binding orientation of the thiophene stilbenoid and provides additional binding affinity. Through this study, we demonstrated that the small and semirigid ligand could be a promising starting point for the development of isoform-selective inhibitors and the investigation of selectivity-determining features.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmchemlett.8b00409.

Experimental procedures for *trans*-stilbenoids synthesis, computational methods, analytical data of synthetic compounds, details of the RMSD and RMSF as well as figures for MD simulations, and conserved residue information among the CYP1 subfamily (PDF)

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

CYP, cytochrome P450; PAHs, polycyclic aromatic hydrocarbons; ANF, alpha-naphthoflavone; IFD, induced fit docking; MD, molecular dynamics.

■ REFERENCES

- (1) Zhan, P.; Itoh, Y.; Suzuki, T.; Liu, X. Strategies for the Discovery of Target-Specific or Isoform-Selective Modulators. *J. Med. Chem.* **2015**, *58*, 7611–7633.
- (2) Huggins, D. J.; Sherman, W.; Tidor, B. Rational approaches to improving selectivity in drug design. *J. Med. Chem.* **2012**, *55*, 1424–1444.
- (3) Haupt, V. J.; Daminelli, S.; Schroeder, M. Drug Promiscuity in PDB: Protein Binding Site Similarity Is Key. *PLoS One* **2013**, *8*, e65894.
- (4) Govindaraj, R. G.; Brylinski, M. Comparative assessment of strategies to identify similar ligand-binding pockets in proteins. *BMC Bioinf.*, published online March 9, 2018; DOI: 10.1186/s12859-018-2109-2.
- (5) Hasemann, C. A.; Kurumbail, R. G.; Boddupalli, S. S.; Peterson, J. A.; Deisenhofer, J. Structure and function of cytochromes P450: a comparative analysis of three crystal structures. *Structure* **1995**, *3*, 41–62.
- (6) Guengerich, F. P.; Waterman, M. R.; Egli, M. Recent Structural Insights into Cytochrome P450 Function. *Trends Pharmacol. Sci.* **2016**, *37*, 625–640.
- (7) Cui, J.; Li, S. Inhibitors and prodrugs targeting CYP1: a novel approach in cancer prevention and therapy. *Curr. Med. Chem.* **2014**, *21*, 519–552.
- (8) Go, R.-E.; Hwang, K.-A.; Choi, K.-C. Cytochrome P450 1 family and cancers. *J. Steroid Biochem. Mol. Biol.* **2015**, *147*, 24–30.
- (9) McFadyen, M. C.; McLeod, H. L.; Jackson, F. C.; Melvin, W. T.; Doehmer, J.; Murray, G. I. Cytochrome P450 CYP1B1 protein expression: a novel mechanism of anticancer drug resistance. *Biochem. Pharmacol.* **2001**, *62*, 207–212.
- (10) Liu, J.; Sridhar, J.; Foroozesh, M. Cytochrome P450 family 1 inhibitors and structure-activity relationships. *Molecules* **2013**, *18*, 14470–14495.
- (11) Dutour, R.; Poirier, D. Inhibitors of cytochrome P450 (CYP) 1B1. *Eur. J. Med. Chem.* **2017**, *135*, 296–306.
- (12) Dong, J.; Zhang, Q.; Cui, Q.; Huang, G.; Pan, X.; Li, S. Flavonoids and Naphthoflavonoids: Wider Roles in the Modulation of Cytochrome P450 Family 1 Enzymes. *ChemMedChem* **2016**, *11*, 2102–2118.
- (13) Zhou, S.-f.; Yang, L.-p.; Wei, M.; Duan, W.; Chan, E. Insights into the Structure, Function, and Regulation of Human Cytochrome P450 1A2. *Curr. Drug Metab.* **2009**, *10*, 713–729.
- (14) Itoh, T.; Yamamoto, K.; Takemura, H.; Shimoi, K. A 3D model of CYP1B1 explains the dominant 4-hydroxylation of estradiol. *J. Chem. Inf. Model.* **2010**, *50*, 1173–1178.
- (15) Wang, A.; Savas, U.; Stout, C. D.; Johnson, E. F. Structural Characterization of the Complex between α -Naphthoflavone and Human Cytochrome P450 1B1. *J. Biol. Chem.* **2011**, *286*, 5736–5743.
- (16) Shimada, T.; Guengerich, F. P. Inhibition of human cytochrome P450 1A1-, 1A2-, and 1B1-mediated activation of procarcinogens to genotoxic metabolites by polycyclic aromatic hydrocarbons. *Chem. Res. Toxicol.* **2006**, *19*, 288–294.
- (17) Shimada, T.; Yamazaki, H.; Foroozesh, M.; Hopkins, N. E.; Alworth, W. L.; Guengerich, F. P. Selectivity of polycyclic inhibitors for human cytochrome P450s 1A1, 1A2, and 1B1. *Chem. Res. Toxicol.* **1998**, *11*, 1048–1056.
- (18) Sansen, S.; Yano, J. K.; Reynald, R. L.; Schoch, G. A.; Griffin, K. J.; Stout, C. D.; Johnson, E. F. Adaptations for the oxidation of polycyclic aromatic hydrocarbons exhibited by the structure of human P450 1A2. *J. Biol. Chem.* **2007**, *282*, 14348–14355.
- (19) Walsh, A. A.; Szklarz, G. D.; Scott, E. E. Human cytochrome P450 1A1 structure and utility in understanding drug and xenobiotic metabolism. *J. Biol. Chem.* **2013**, *288*, 12932–12943.

- (20) Kim, S.; Ko, H.; Jae Eun Park, S.; Jung, Y. J.; Lee, S. K.; Chun, Y. J. Design, synthesis, and discovery of novel trans-stilbene analogues as potent and selective human cytochrome P450 1B1 inhibitors. *J. Med. Chem.* **2002**, *45*, 160–164.
- (21) Chun, Y.-j.; Lim, C.; Ohk, S. O.; Lee, J. M.; Lee, J. H.; Choi, S.; Kim, S. trans-Stilbenoids: potent and selective inhibitors for human cytochrome P450 1B1. *MedChemComm* **2011**, *2*, 402–405.
- (22) Chun, Y. J.; Kim, S.; Kim, D.; Lee, S. K.; Guengerich, F. P. A new selective and potent inhibitor of human cytochrome P450 1B1 and its application to antimutagenesis. *Cancer Res.* **2001**, *61*, 8164.
- (23) Shimada, T.; Tanaka, K.; Takenaka, S.; Murayama, N.; Martin, M. V.; Foroozesh, M. K.; Yamazaki, H.; Guengerich, F. P.; Komori, M. Structure-function relationships of inhibition of human cytochromes P450 1A1, 1A2, 1B1, 2C9, and 3A4 by 33 flavonoid derivatives. *Chem. Res. Toxicol.* **2010**, *23*, 1921–1935.
- (24) Schrödinger Suite 2017–4 Induced Fit Docking Protocol; Glide v7.7 and Prime v5.0, Schrödinger, LLC, New York, NY, 2017.
- (25) Desmond Molecular Dynamics System; D. E. Shaw Research: New York, NY, **2016**.
- (26) Bowers, K.; Chow, E.; Xu, H.; Dror, R.; Eastwood, M.; Gregersen, B.; Klepeis, J.; Kolossvary, I.; Moraes, M.; Sacerdoti, F.; Salmon, J.; Shan, Y.; Shaw, D. Scalable algorithms for molecular dynamics simulations on commodity clusters. Proceedings of the ACM/IEEE Conference on Supercomputing (SC06) Tampa, FL2006.
- (27) Sridhar, J.; Goyal, N.; Liu, J.; Foroozesh, M. Review of Ligand Specificity Factors for CYP1A Subfamily Enzymes from Molecular Modeling Studies Reported to-Date. *Molecules* **2017**, *22*, 1143–1161.
- (28) Mikstacka, R.; Rimando, A. M.; Dutkiewicz, Z.; Stefański, T.; Sobiak, S. Design, synthesis and evaluation of the inhibitory selectivity of novel trans-resveratrol analogues on human recombinant CYP1A1, CYP1A2 and CYP1B1. *Bioorg. Med. Chem.* **2012**, *20*, 5117–5126.
- (29) He, L.; He, F.; Bi, H.; Li, J.; Zeng, S.; Luo, H. B.; Huang, M. Isoform-selective inhibition of chrysin towards human cytochrome P450 1A2. Kinetics analysis, molecular docking, and molecular dynamics simulations. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6008–6012.
- (30) The measured distance between the imidazole group and the iron atom in the binding models was 4.275 Å in CYP1A1, 3.369 Å in CYP1A1, and 3.223 Å in CYP1B1.