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Insight into the effects of chiral isomers quinidine and quinine on CYP2D6 inhibition

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ABSTRACT

The distinct inhibitory effects against CYP2D6 enzyme of the stereoisomers quinidine and quinine were investigated in this work by employing various methods, including the comparative molecular field analysis (CoMFA), the comparative molecular similarity indices analysis (CoMSIA), the molecular electrostatic potential (MEP) analysis and the docking method. Several 3D-QSAR models with proper reliability were well established, with a CoMFA model with steric and electrostatic fields exhibiting 0.67, 0.99 and 0.88 of q^2, r^2 and r^2_{pred}, respectively, a CoMSIA model with steric, electrostatic and H-bond acceptor fields displaying 0.72, 0.97 and 0.84 of q^2, r^2 and r^2_{pred}, respectively. These models and related docking results reveal that quinidine binds to CYP2D6 in an inverse orientation as compared with quinine. Moreover, quinidine blocks the entrance of the active pocket of CYP2D6 more closely than quinine does, which explains well why the inhibitory activity of quinidine is of 2 magnitudes larger than quinine. This investigation provides a better understanding of the stereoisomeric effects on the bioactivities of the chiral isomers quinidine and quinine interacting with CYP2D6.

In human cytochrome P450 family, CYP2D6 plays a second major role after CYP3A4 as it mediates the metabolism and clearance of about 30% of the currently marketed drugs.[1,2] The common characteristics of CYP2D6 substrates have been recognized as that they possess at least one basic nitrogen atom with a distance of 5 Å or 7 Å to oxidation site, and a negative molecular electrostatic potential above the planar part of the molecule.[3,4] With some of these basic features quinidine and quinine, two stereoisomeric cinchona alkaloids,[5] are not only CYP2D6 substrates but also found to be CYP2D6 inhibitors with, however, different inhibition effects. As a matter of fact, quinidine shows a potent inhibitory activity of 2-order magnitude larger than quinine does.[6] Therefore, it is possible that the stereoisometric difference of the two molecules influence their bindings to CYP2D6 and, in this way, results in different inhibitory effects.

Once a structure–activity study of quinidine and quinine about their bindings to CYP2D6 was conducted by Hutzler et al.[6] McLaughlin also carried out a research on the critical residues of CYP2D6 interacting with quinidine molecule.[7] However, to our knowledge, there is still no investigation up to now showing the distinguished inhibitory effects of these chiral isomers on CYP2D6 from molecular structure.

In the present work, four computation methods including the Comparative Molecular Field Analysis (CoMFA), Comparative Molecular Similarity Indices Analysis (CoMSIA), Molecular Electrostatic Potential (MEP) surface analysis and Docking approach were applied to investigate the stereoisomeric effects of the two kinds of molecules interacting with CYP2D6. Using SYBYL programs, several CoMFA and CoMSIA models[8–11] of the two series of molecules were generated upon an atom-based alignment corresponding to their inhibitory effects. In order to compare the molecular shapes and the MEPs of the stereoisomers quinidine and quinine, the hybrid functional PBE1PBE[12] method was also employed to optimize their geometries at 6-31G* level, with the CUBEGEN program used to compute their MEP distributions using Gaussian 03 suite.[13] The optimized structures of quinidine and quinine were further docked into the active site of CYP2D6 enzyme (PDB Code: 2F9Q)[14] using Surflex-Dock package.[15,16]

In this work, a whole set of 27 molecules including quinidine, quinine and their analogues binding to P450 2D6 was used for the 3D-QSAR analysis[6] (Fig. 1). The dataset was randomly divided into two sets with a training set of 22 and a test set of 5 molecules. Their pIC_{50} values and molecular structures were shown in the supplemental information.

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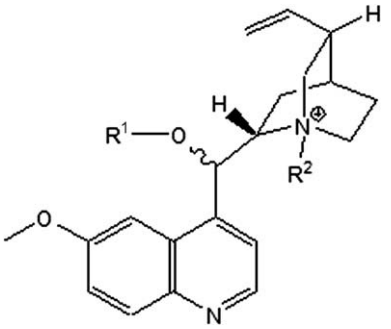

Figure 1. Structure of quinidine/quinine illustrating the substituted sites for analogues. R1 represents the ester/ether formation, and R2 represents the quaternary salt formation.

The CoMFA model was generated from steric and electrostatic fields at the grid lattice of 2 Å. A cross-validated q^2 of 0.67 was yielded based on the leave-one-out partial least squares (PLS) analysis using 6 PLS latent components, with a conventional correlation coefficient r^2 of 0.99. This model was also validated by an independent test set with an excellent r^2_{pred} of 0.88.

Several CoMSIA models were also generated using different descriptors with the optimal models employing the SEA and SEH fields, yet the SEAD model hardly presents any reliability as indicated by the poor predictive performance. The detailed statistic results of the obtained CoMFA and CoMSIA models were shown in the supplemental information.

The predicted and observed pIC_{50} values for the CoMFA (SE) and CoMSIA (SEA, SEH), models are well close to each other within one log unit both in training and test sets as shown in the supplemental information.

Figure 2 shows the generated CoMFA and CoMSIA contour maps. The graphical analysis was made based on the steric (a), electrostatic (b), hydrophobic (c) and hydrogen bond acceptor (d) fields. In Figure 2a, a bulky-disfavored yellow plot is located at the chiral center close to the hydroxyl group of quinidine, indicating that the inhibitory activity of quinidine will be decreased if the hydroxyl was esterified with bulky group. The esters of quinidine (compounds **2**–**8**) all exhibit smaller bioactivities than quinidine does. However, no linear correlation was observed between the size of the bulky substituents and their activities. No contours being observed around the hydroxyl of quinine reveals that the inhibition potency could be hardly influenced by bulky substituents. Accordingly, the esters of quinine (compounds **18**–**22**) all exhibit equivalent bioactivities with quinine except the acetyl ester (compound **17**) that might bind with CYP2D6 in a distinct conformation.

The addition of functional group to nitrogen for quinidine to become the quaternary salt is unfavorable (Fig. 2a), which was conformed by the experimental results that the activities of quaternary salt analogues (compounds **10**–**15**) are in the same magnitude as that of quinidine. A small green plot was found near the basic nitrogen of quinine, indicating that large bulky substitution at this site reduces its inhibitory activity. This explains why the activities of compounds **23**–**27** decreased as the additional bulk increases.

In Figure 2b, a red plot and a blue map were found around the hydroxyl group at the chiral position of quinidine and quinine, respectively. The red region indicates that an ionic interaction or hydrogen-bonding interaction between C(9) hydroxyl region and the amino residue might exists when the molecule binds to CYP2D6. This ionic interaction is usually a strong factor enhancing the molecular interactions, thus, it is reasonable that the activities of compounds **5**–**8**, four quinidine analogues with ester substituents instead of the –OH at C(9) position like quinidine, increase gradually with the richening electron density of these substituents. However, compared with quinidine itself, all ester analogues of quinidine exhibit lower inhibition potencies. All these hint us that when quinidine derivatives bind to CYP2D6, their interaction at

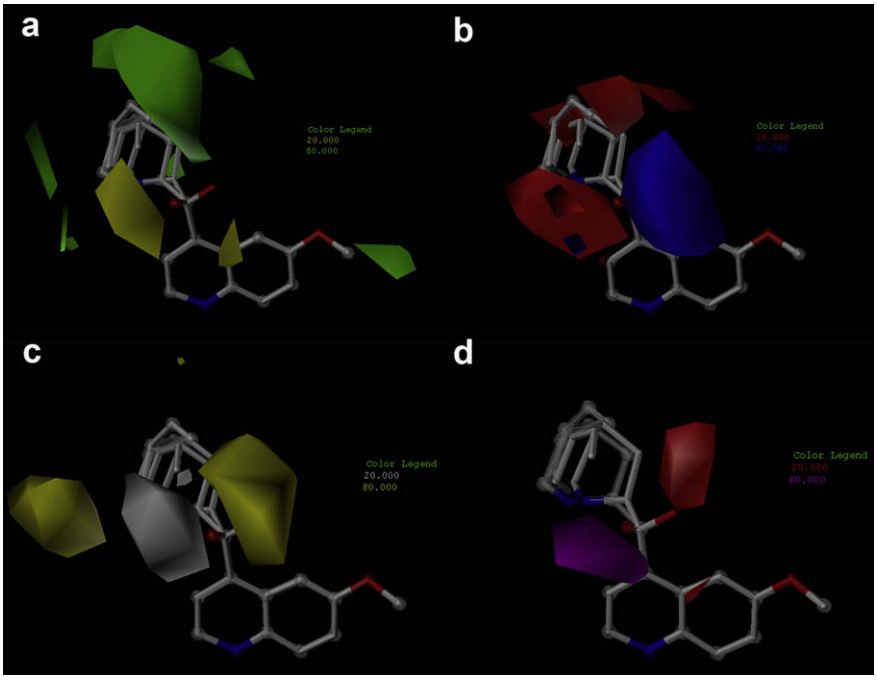

Figure 2. The view of the generated CoMFA and CoMSIA models. Quinidine and quinine were superimposed for visual clarity. Quinidine was shown in stick ball and quinine in capped stick. The color of contours are coded in the following manner: (a) green and yellow represent a region of favorable and unfavorable steric (bulk) interactions, respectively; (b) blue and red indicate electrostatic interactions with a positive charge and a negative charge respectively; (c) yellow and grey represent the hydrophobic and hydrophilic interactions respectively; (d) magenta and red denote the interactions with H-bond acceptor and donor, respectively.