

## Supplements

### **Prediction of the site of CYP3A4 metabolism of tolterodine by molecular dynamics simulation from multiple initial structures of the CYP3A4–tolterodine complex**

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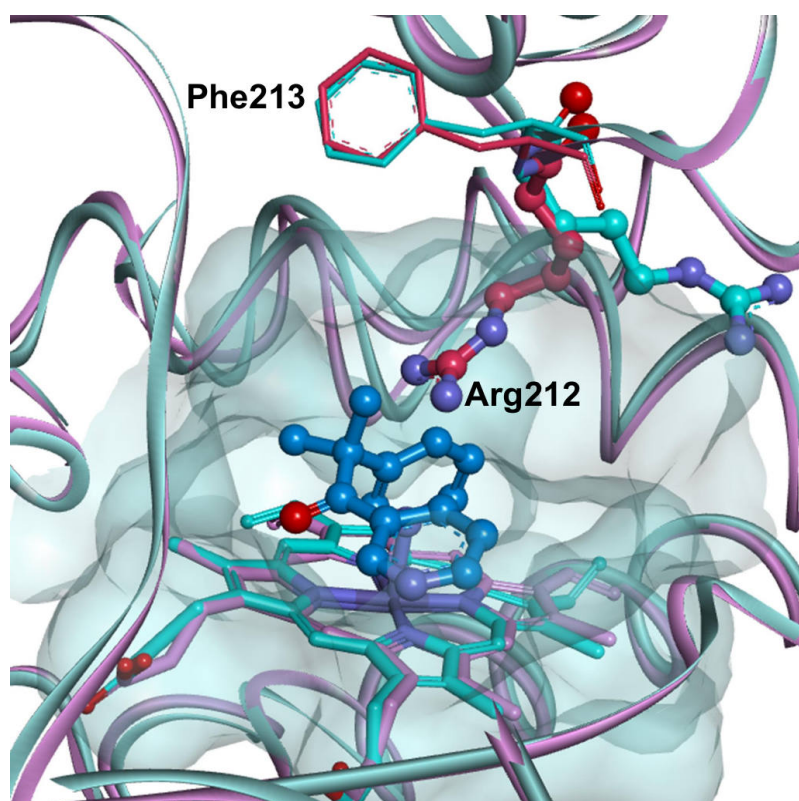
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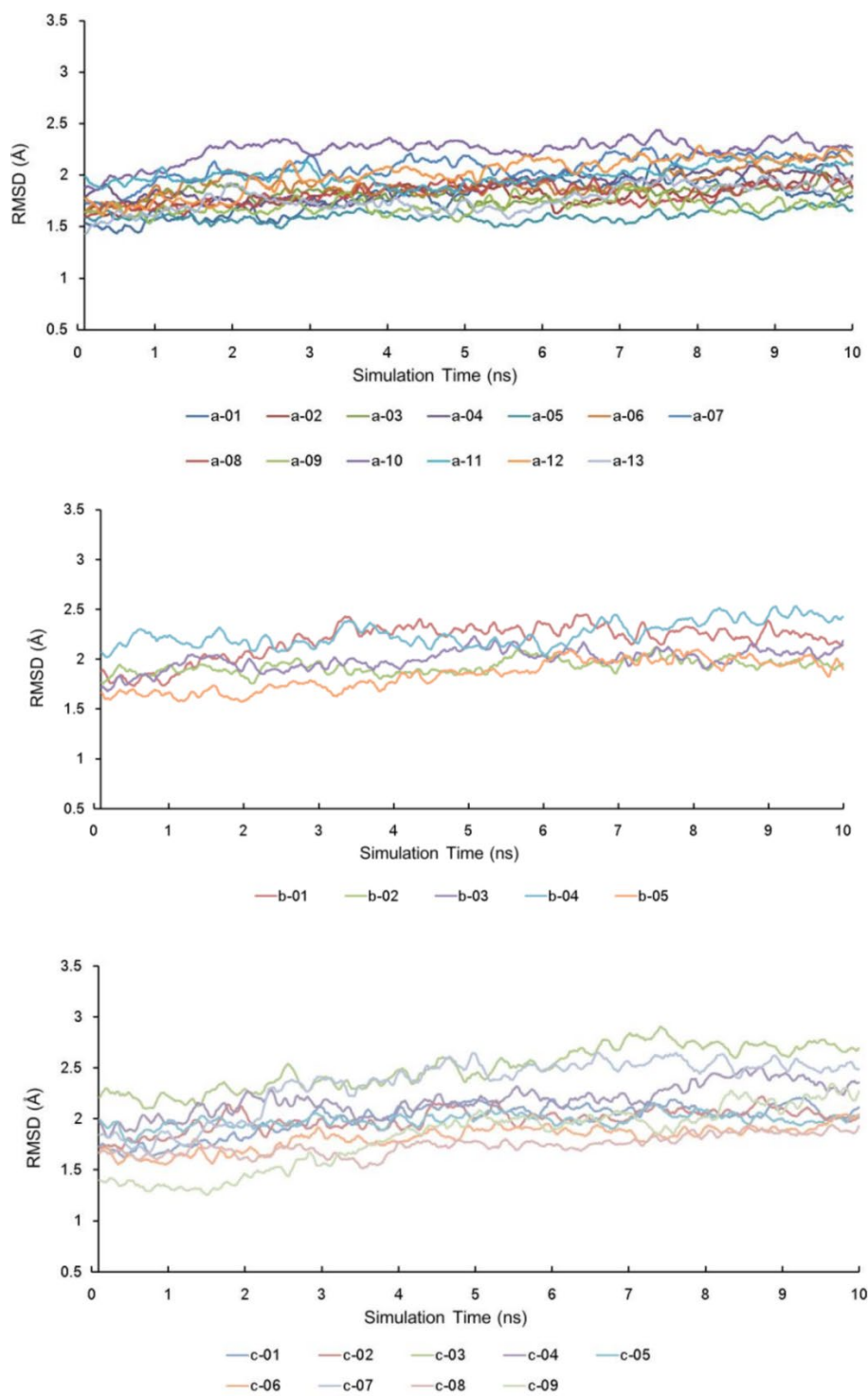
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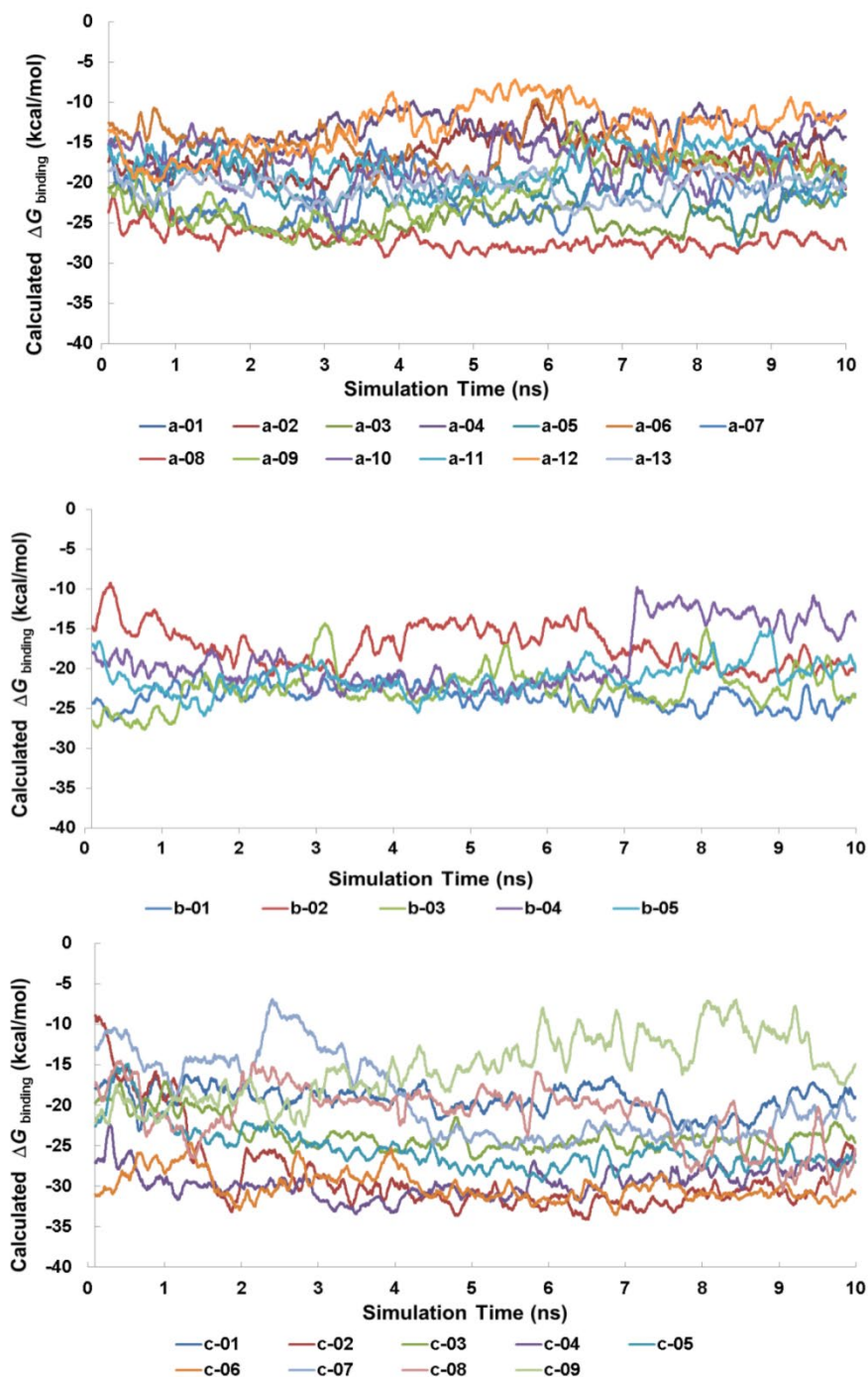
(Received March 15; accepted April 25; published online May 31, 2017)



**Figure S1.** Comparison of the positions of Arg212 in the 1TQN (magenta) and 1W0G (cyan) structures  
Arg212 occupies the center of the heme pocket in 1TQN.

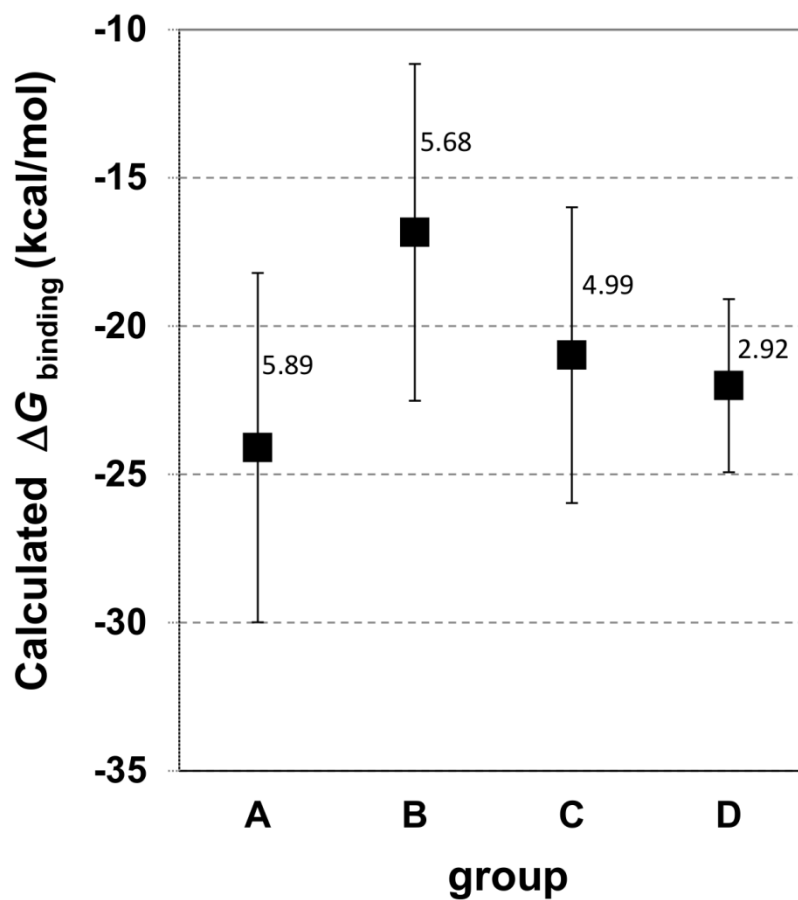


**Figure S2.** Time course of RMSDs for main chain atoms during 10-ns MD simulations  
The characters “a”, “b”, and “c” show categories of the MD initial structures and correspond to the characters in Figure 3. a-01 to a-13: 13 simulations which initial structures were selected with RMSD (top panel), b-01 to b-05: 5 simulations which initial structures were selected with PLIF + RMSD (center panel), c-01 to c-09: 9 simulations which initial structures were selected with PLIF (bottom panel).

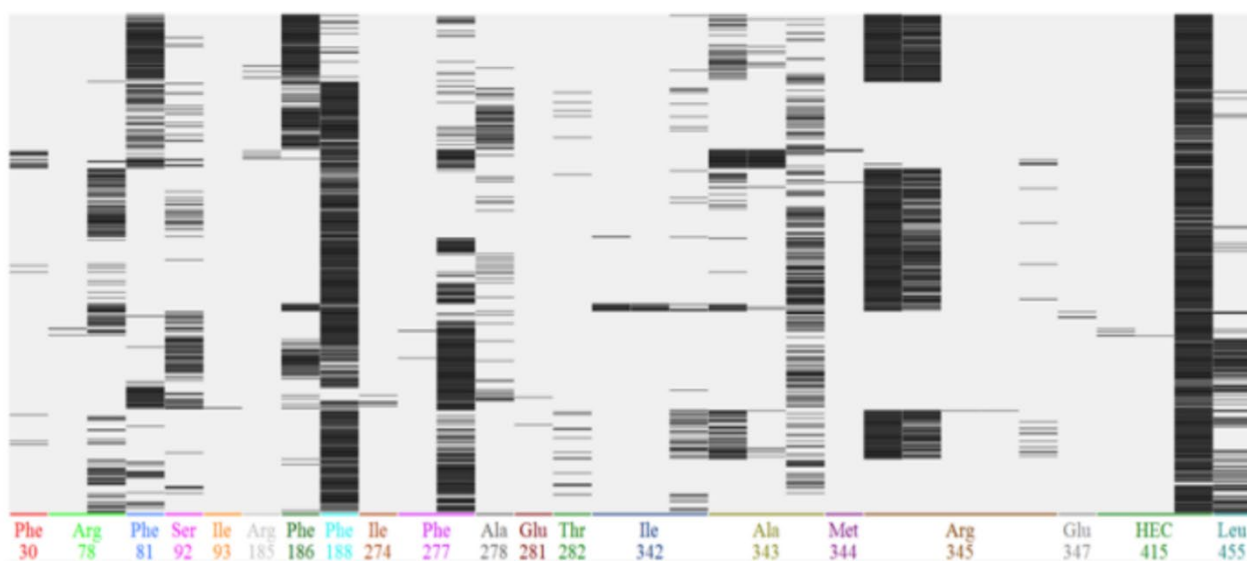


**Figure S3.** Time course of calculated  $\Delta G_{\text{binding}}$  values (calculated by means of the MM/PBSA method) during the 10-ns simulations

The characters “a”, “b”, and “c” show categories of the MD initial structures and correspond to the characters in Figure 3. a-01 to a-13: 13 simulations which initial structures were selected with RMSD (top panel), b-01 to b-05: 5 simulations which initial structures were selected with PLIF + RMSD (center panel), c-01 to c-09: 9 simulations which initial structures were selected with PLIF (bottom panel).



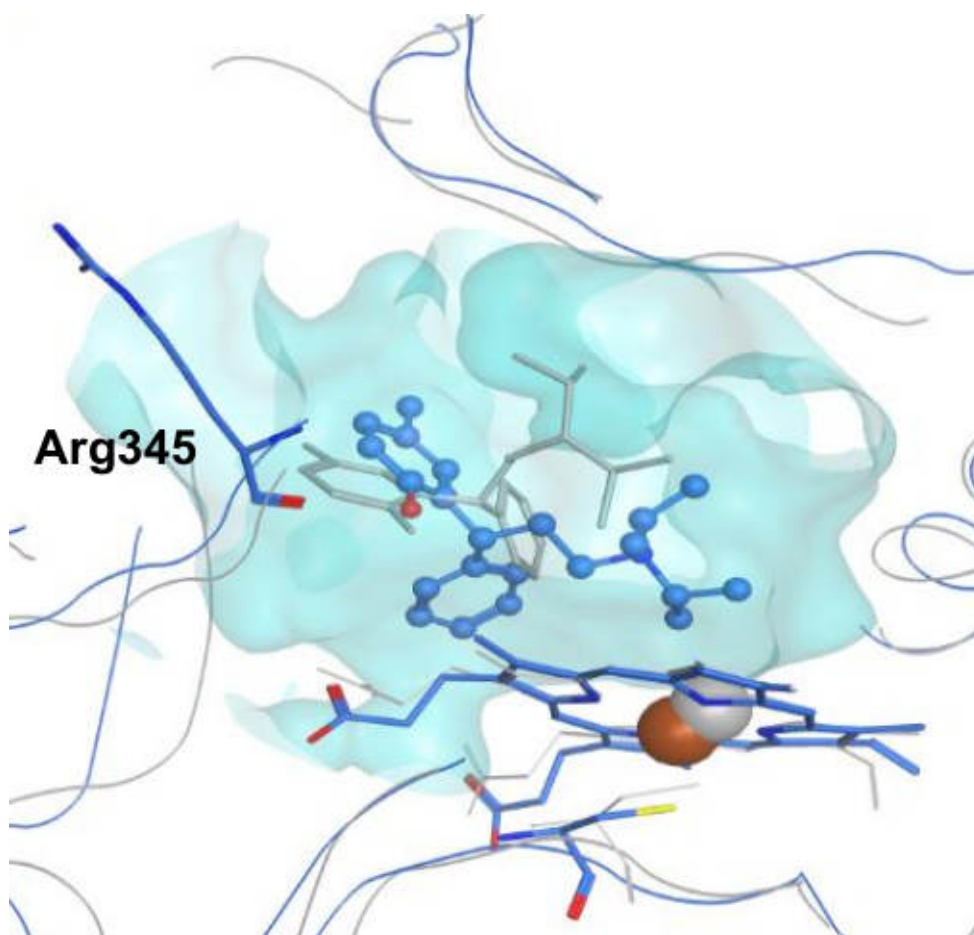
**Figure S4.** Average calculated  $\Delta G_{\text{binding}}$  values (black squares) for carbon atoms at groups A–D, calculated by means of the MM-PBSA method  
Error bars indicate standard deviations.



**Figure S5.** Heat map of PLIF for complexes in which group A was close to the heme ( $\leq 6 \text{ \AA}$ )  
The abscissa shows each amino acid, and the ordinate shows the MD snapshots.

**Table S1.** Results obtained with PLIF clustering for MD snapshots of group

Cluster	No. of snapshots	%	Average $\Delta G_{\text{binding}}$ (kcal/mol)	Average minimum Fe-C distance (Å)
<b>1</b>	<b>483</b>	<b>65.80</b>	<b>-25.57</b>	<b>4.18</b>
13	107	14.58	-21.61	4.40
11	61	8.31	-22.22	4.69
16	26	3.54	-25.26	5.36
9	14	1.91	-18.19	5.71
15	14	1.91	-13.11	5.10
<b>7</b>	<b>9</b>	<b>1.23</b>	<b>-29.46</b>	<b>5.82</b>
12	6	0.82	-13.40	4.08
14	4	0.54	-27.65	4.57
8	3	0.41	-12.16	3.75
6	2	0.27	-13.27	4.28
2	1	0.14	-16.58	3.82
3	1	0.14	-23.98	5.99
4	1	0.14	-22.00	3.76
5	1	0.14	-17.75	3.77
10	1	0.14	-14.97	3.46



**Figure S6.** The most stable complex in the cluster 1(blue), and the cluster 7 (gray) of group A  
The complex of cluster 1 has the lowest binding energy among all complexes.