Supporting information

Drug promiscuity of P-glycoprotein and its mechanism of interaction with paclitaxel and doxorubicin

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Figure S1. RMSD of P-gp (alpha-C).
Figure S2. Initial structure of the production run. Paclitaxel are colored yellow and Ala82 are colored red. P-gp is rendered as main chain new cartoons and the POPC membrane is rendered line. Doxorubicin in MD_2 was manually placed the same place with paclitaxel.
**Figure S3. Important inner residues in paclitaxel’s movement in MD_1.**
Paclitaxel is rendered as CPK spheres and P-gp is rendered as main chain new cartoons. Important inner residues are rendered as vdW models. Phe303 is very noticeable. (a) The first snapshot from the top view. (b) The last snapshot from the top view.

**Figure S4. Important inner residues in doxorubicin’s movement in MD_2.**
Doxorubicin is rendered as CPK spheres and P-gp are rendered as main chain new cartoons. Important inner residues are rendered as vdW models. (a) The first snapshot from the top view. (b) The last snapshot from the top view.
Figure S5. Distance between motif A and motif C. For human P-gp, Motif A is GNGSCGKS (residues 1070 to 1077), and its motif C is LSGGQ (residues 540 to 544). For another pair, Motif A is GSSGCGKS (residues 427 to 434), and its motif C is LSGGQ (residues 1176 to 1180). We use the distance between the fourth residue in motif A (G) and the third residue in motif C (G) to measure the NBD distance changes. (a) The distance curve of distance of motif A and motif C in MD_1. (b) The distance curve of distance of motif A and motif C in MD_2.
Figure S6. Some obviously flexible side chains of inner residues. (a) Ile297 residue. (b) The dihedral angle of Ile297 atoms 1, 2, 3, 4 in MD_1. (c) Phe938 residue. (d) The dihedral angle of Phe938 atoms 8, 7, 1, 2 in MD_2.

Figure S7. Chemical structures of paclitaxel (a) and doxorubicin (b).