

Supporting Information

The regioselectivity of the interaction between dextromethorphan and CYP2D6

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This supporting information contains nine supplementary figures (Figure S1-S10)

and one supplementary table (Table S1).

Supplementary figures

Model 3

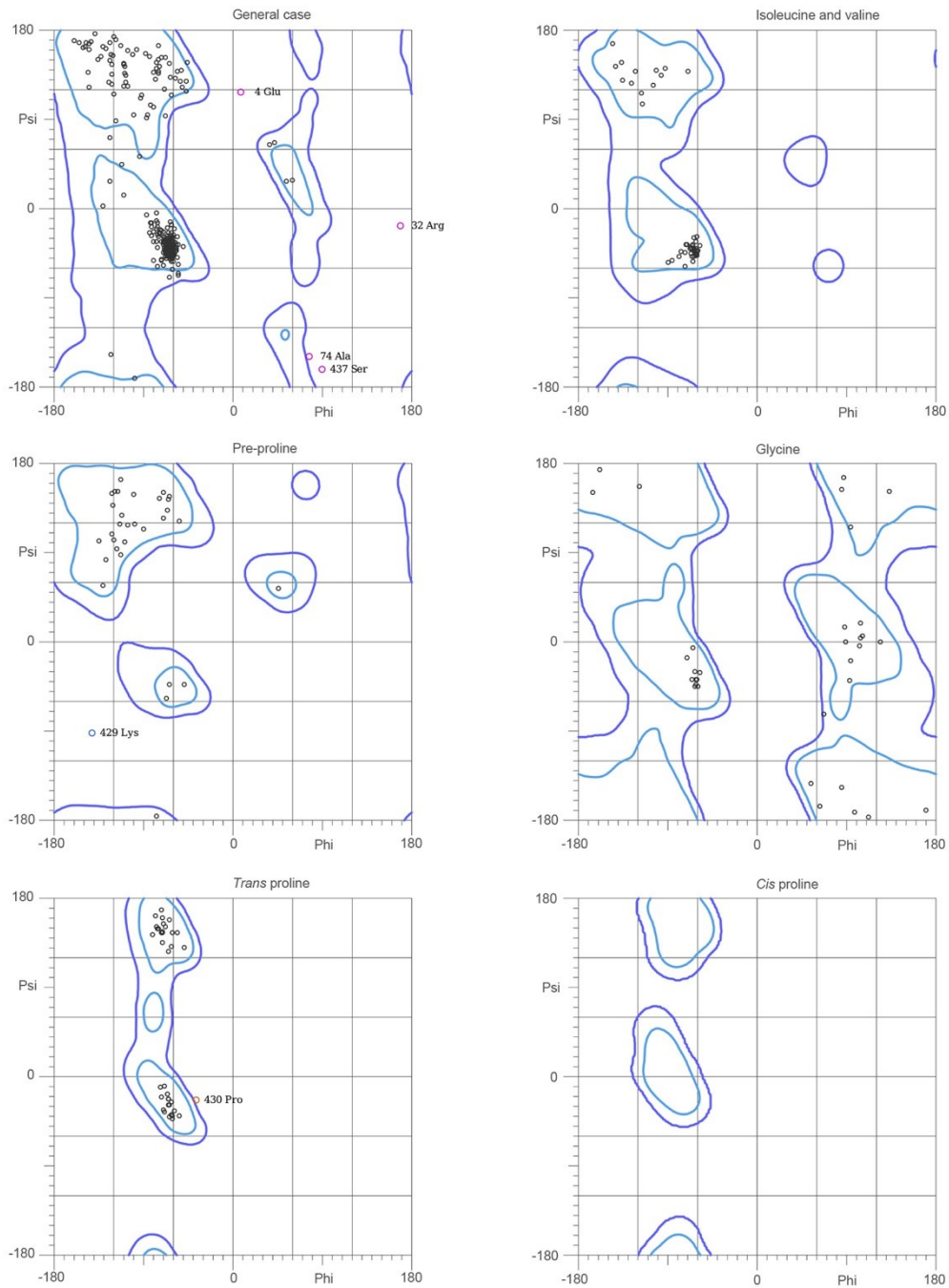


Figure S1. The ramachandran analysis results of model 3.

96.2% (476/495) of all residues were in favored (98%) regions.

98.8% (489/495) of all residues were in allowed (>99.8%) regions.

4WNT

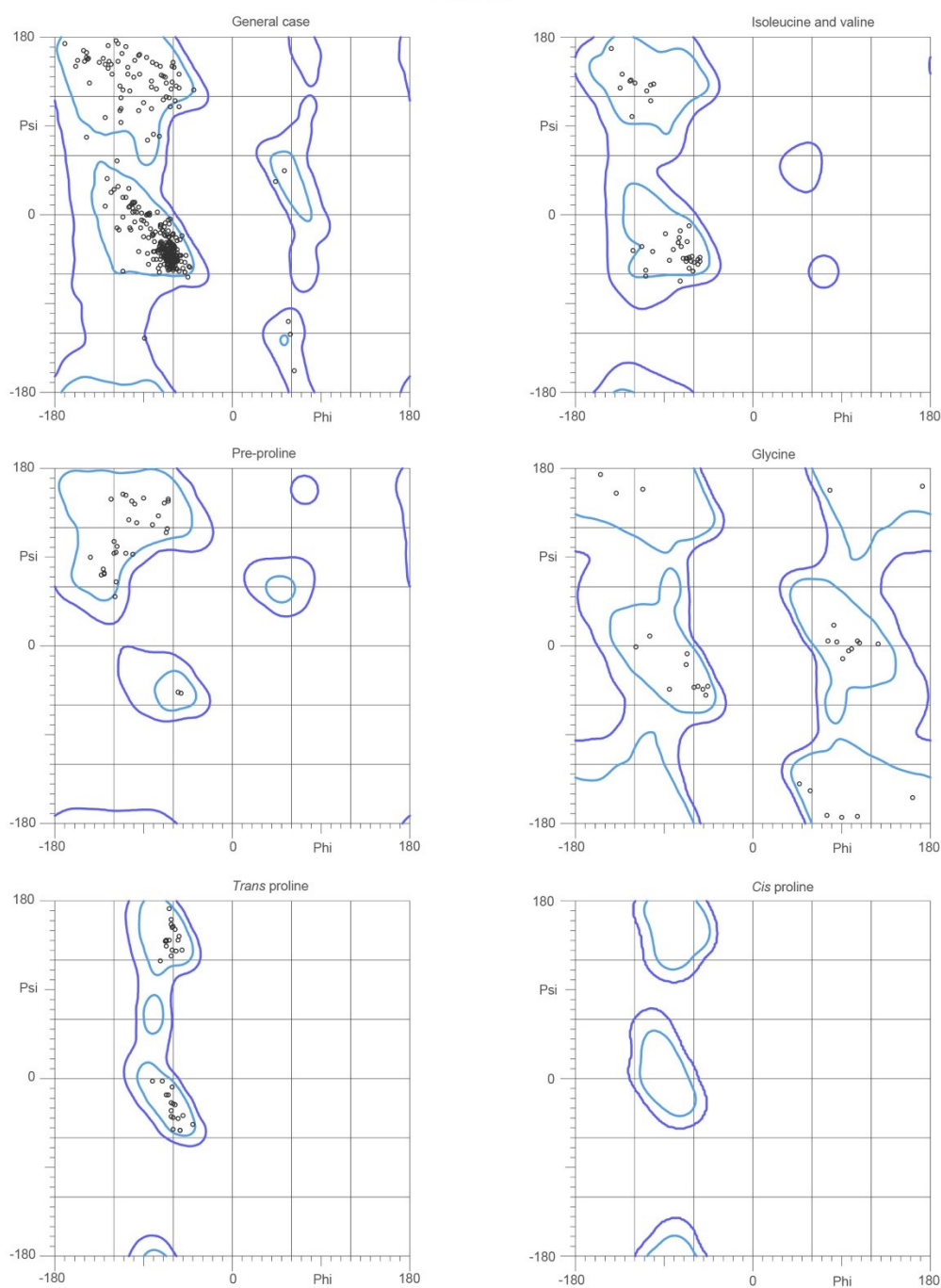


Figure S2. The ramachandran analysis results of crystal structure 4WNT.

96.9% (439/453) of all residues were in favored (98%) regions.

100% (453/453) of all residues were in allowed (>99.8%) regions.

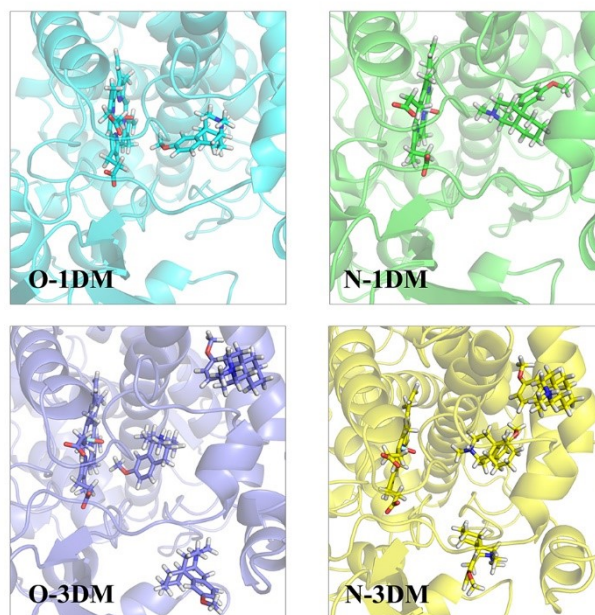


Figure S3. The four systems constructed in the present study. Cpd I and DM molecules are shown in stick.

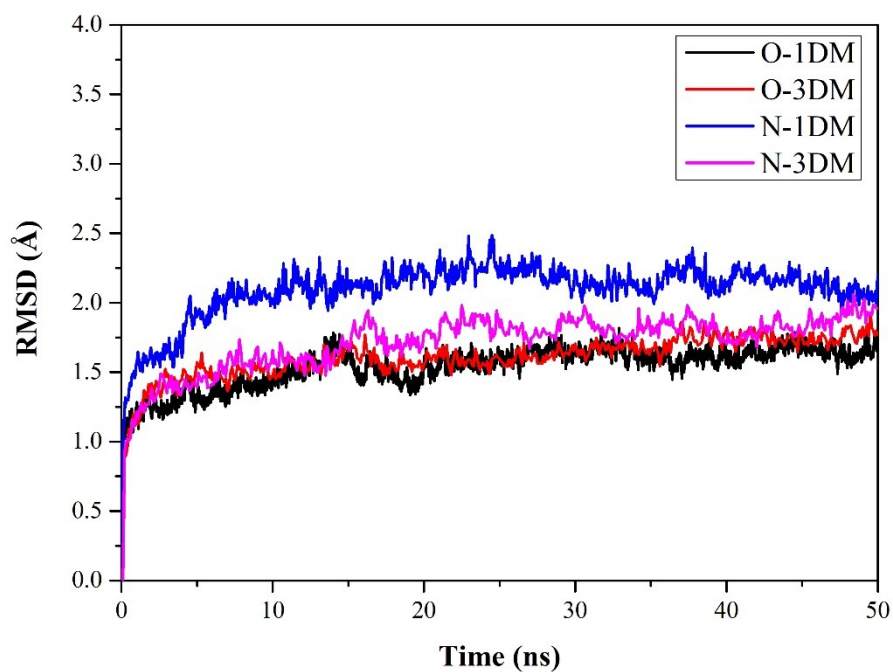


Figure S4. The RMSD results of 50ns simulations for the four systems in the present study.

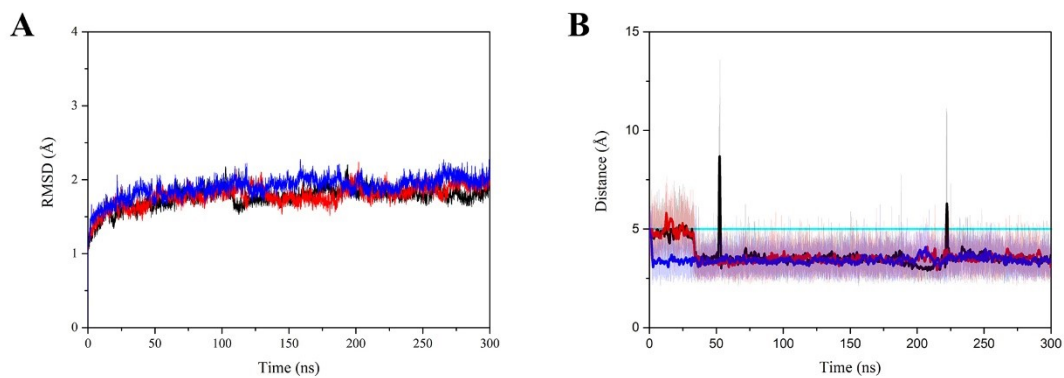


Figure S5. RMSD and distance measurement results of the **O-1DM** system. **A** shows the RMSD of the three parallel trajectories, which are colored in blue, red and black respectively. **B** shows the distance between the reactive site of DM (the $-\text{OCH}_3$ group) and the oxygen atom of Cpd I.

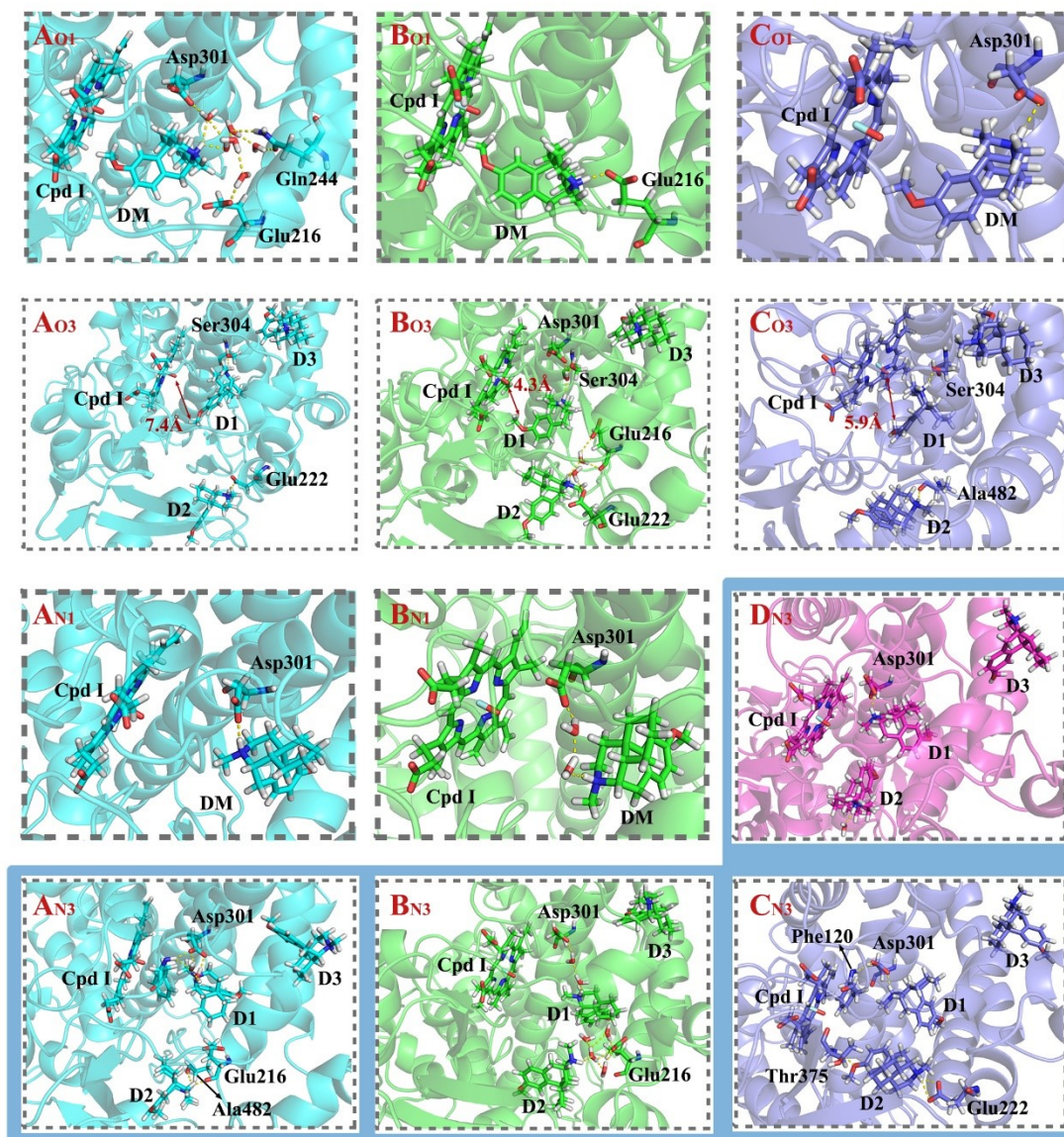


Figure S6. Details of the binding mode of the substrate and its interactions with the important residues. Different binding modes have been labeled in red at the top-left corner, and the four states of the **N-3DM** system are painted in blue background for the convenience of viewing.

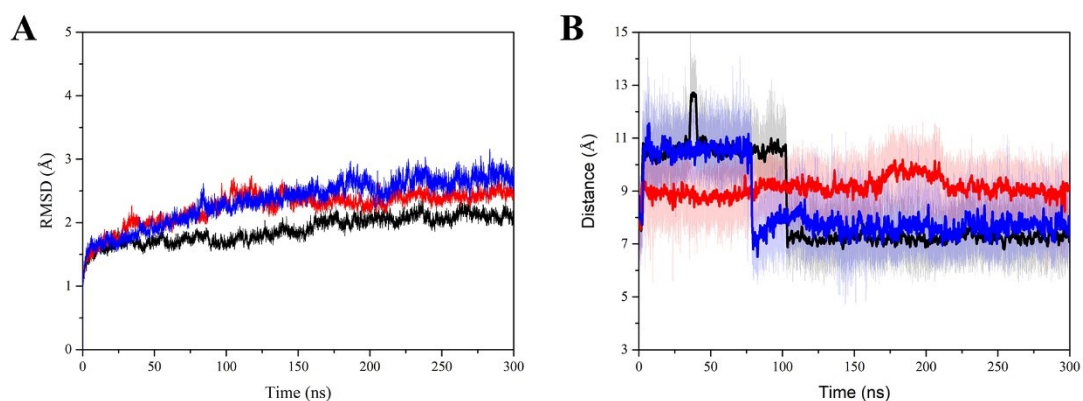


Figure S7. RMSD and distance measurement results of the **O-3DM** system. **A** shows the RMSD of the three parallel trajectories, which are colored in blue, red and black respectively. **B** shows the distance between the reactive site of D1 (the $-\text{OCH}_3$ group) and the oxygen atom of Cpd I.

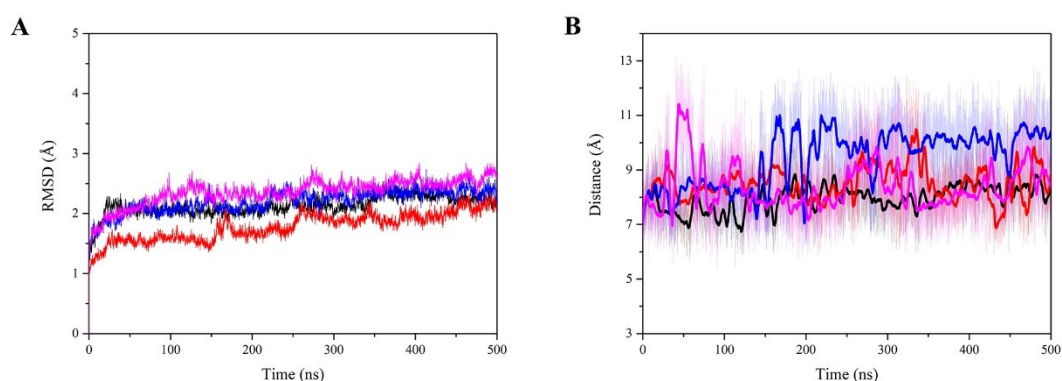


Figure S8. RMSD and distance measurement results of the **N-1DM** system. **A** shows the RMSD of the four parallel trajectories, which are colored in blue, red, purple and black respectively. **B** shows the distance between the reactive site of DM (the $-\text{NCH}_3$ group) and the oxygen atom of Cpd I.

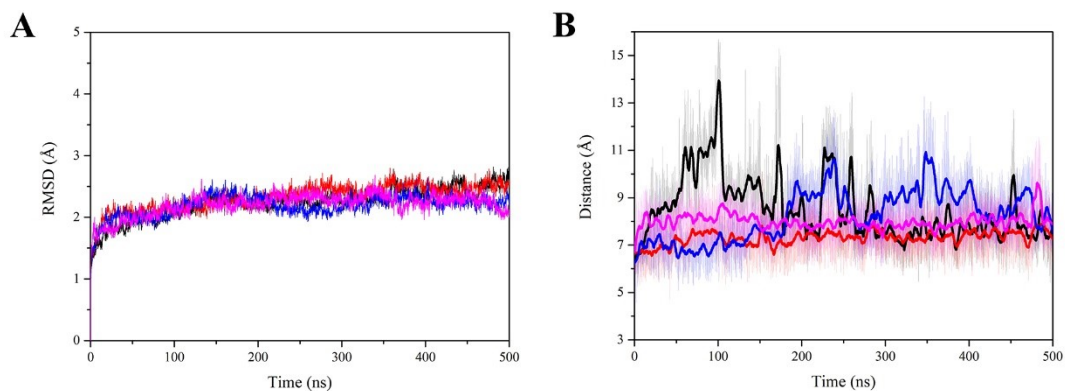


Figure S9. RMSD and distance measurement results of the **N-3DM** system. **A** shows the RMSD of the four parallel trajectories, which are colored in blue, red, purple and black respectively. **B** shows the distance between the reactive site of D1 (the -NCH_3 group) and the oxygen atom of Cpd I.

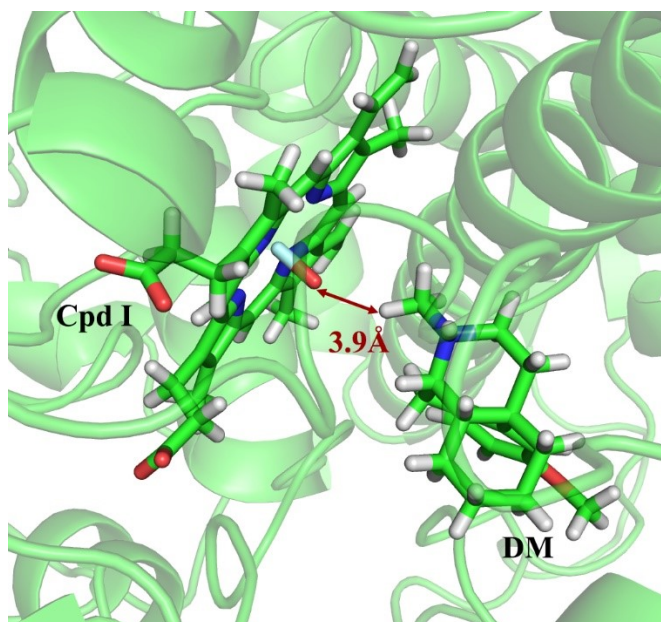


Figure S10. The structure of the **N-3DM** system with the reactive distance smaller than 5\AA

One supplementary table

Table S1 The timescale for each system in the present study

Systems	Timescale	Replications	Total timescale
O-1DM	300 ns	3	900 ns
O-3DM	300 ns	3	900 ns
N-1DM	500 ns	4	2000 ns
N-3DM	500 ns	4	2000 ns