

Supplementary Information for

**Investigation of the Molecular and Mechanistic Basis for the Regioselective  
Metabolism of Midazolam by Cytochrome P450 3A4**

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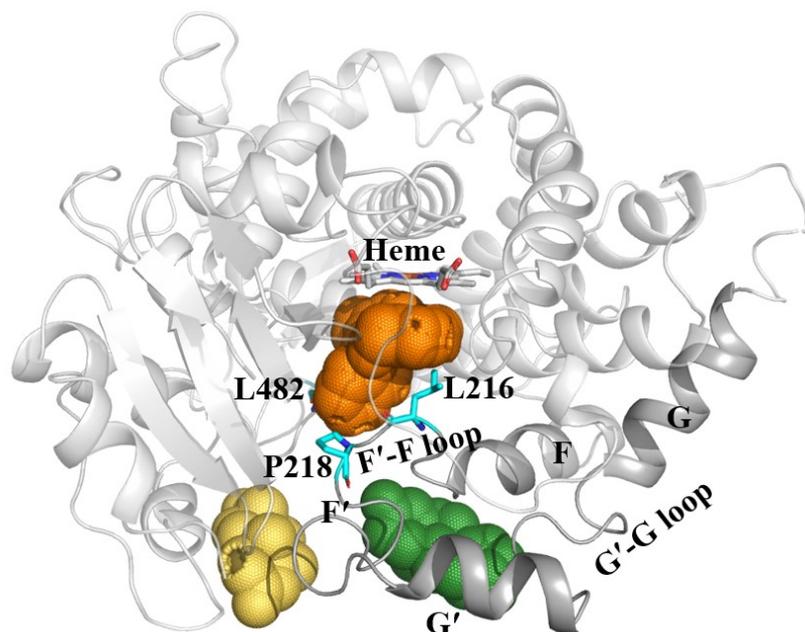
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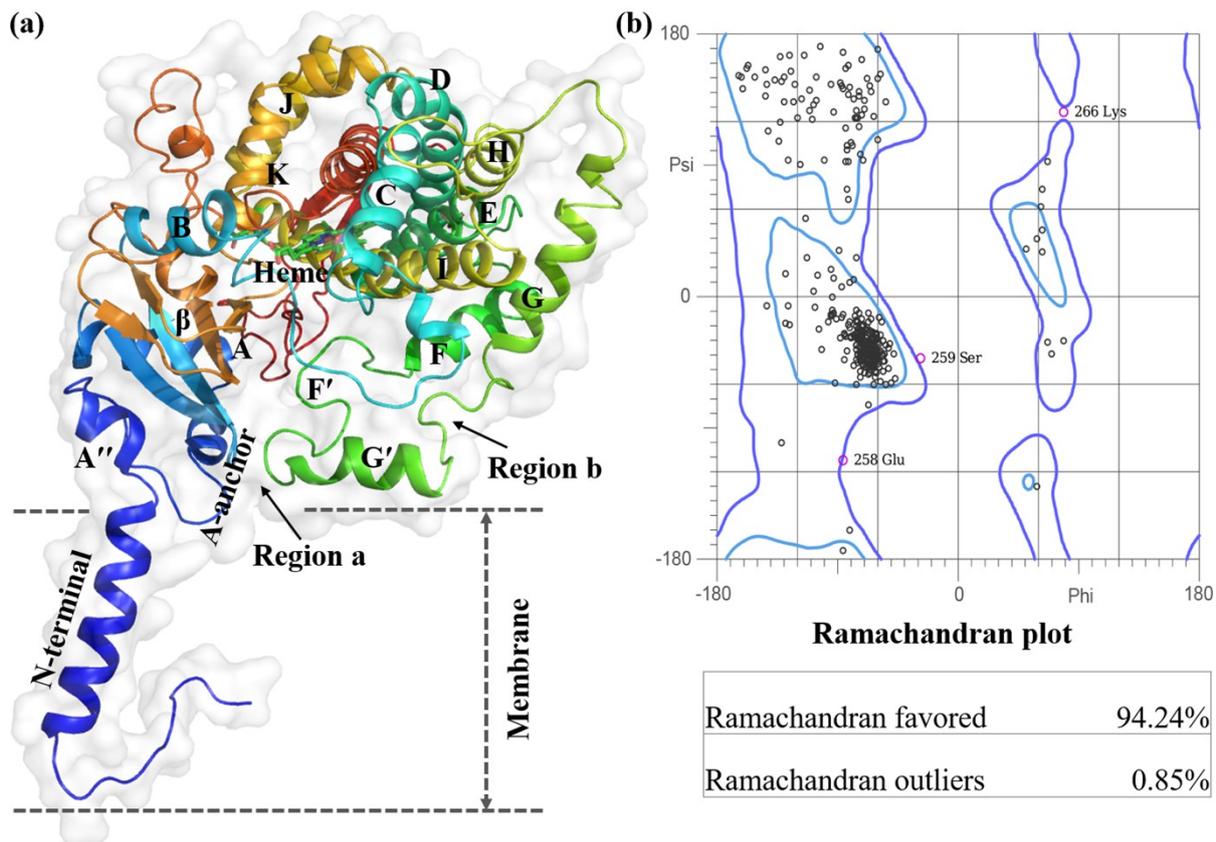
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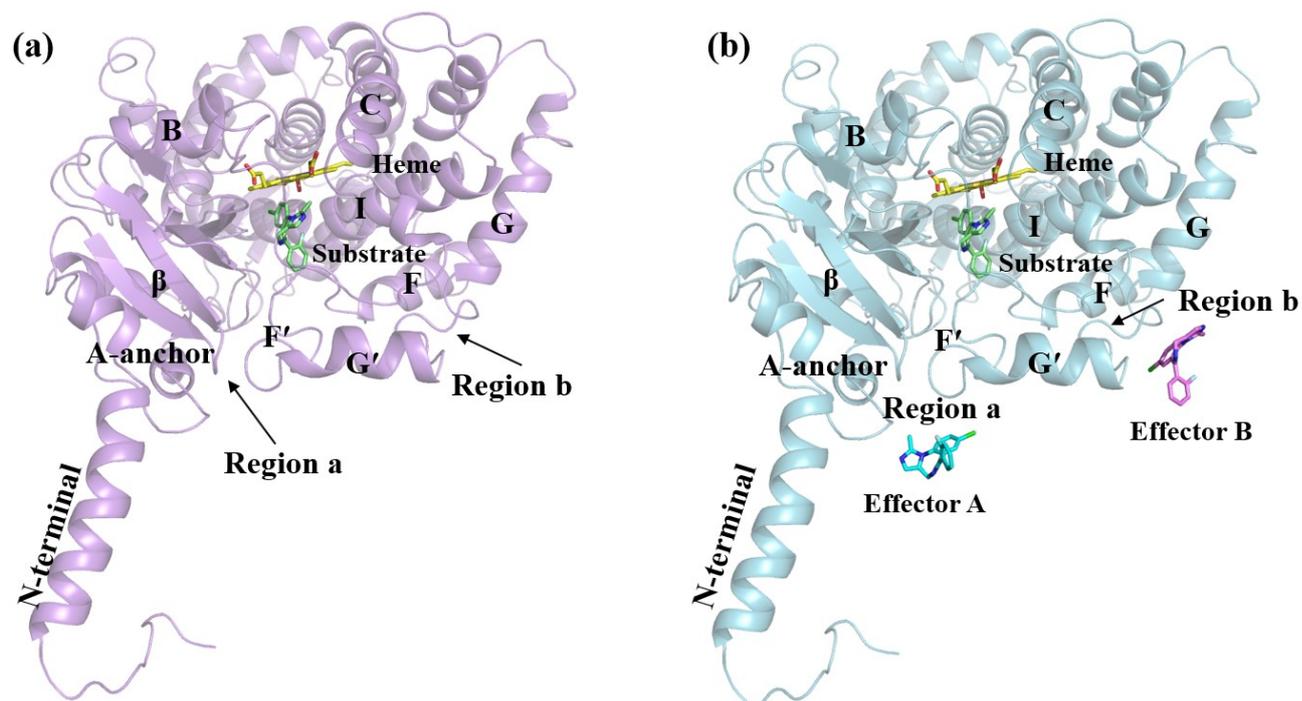
Acceptor	Donor	Fraction (%)	Average distance (Å)	Average angle (°)
<b>Pose A</b>				
MDZ@N2	S119@HG	34.6	2.83	156.97
MDZ@N2	R105@HE	1.77	2.89	147.46
<b>Pose B</b>				
MDZ@N2	S119@HG	11.8	2.85	158.40
MDZ@N1	R105@HH12	2.64	2.91	151.89
<b>Pose C</b>				
MDZ@N2	S119@HG	1.11	2.87	157.96



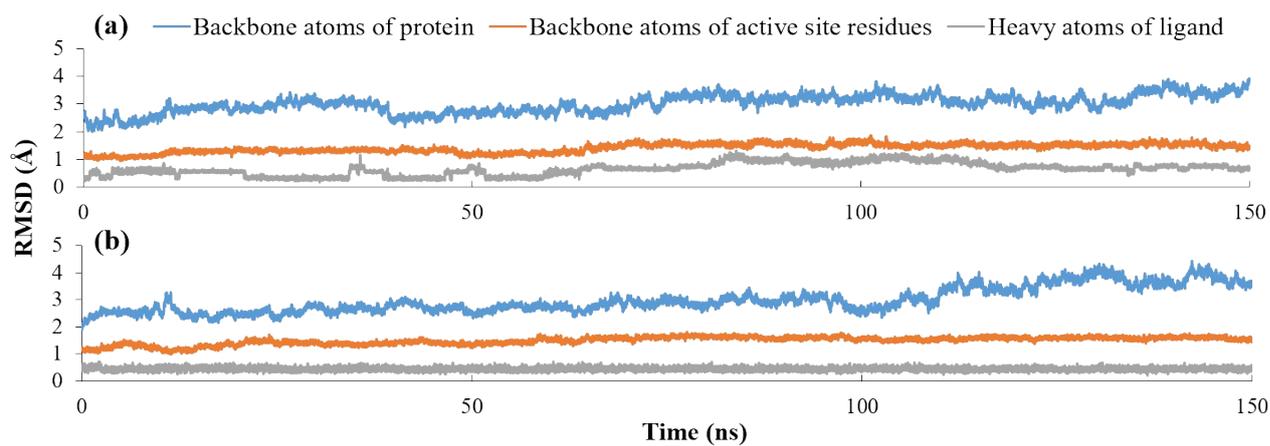
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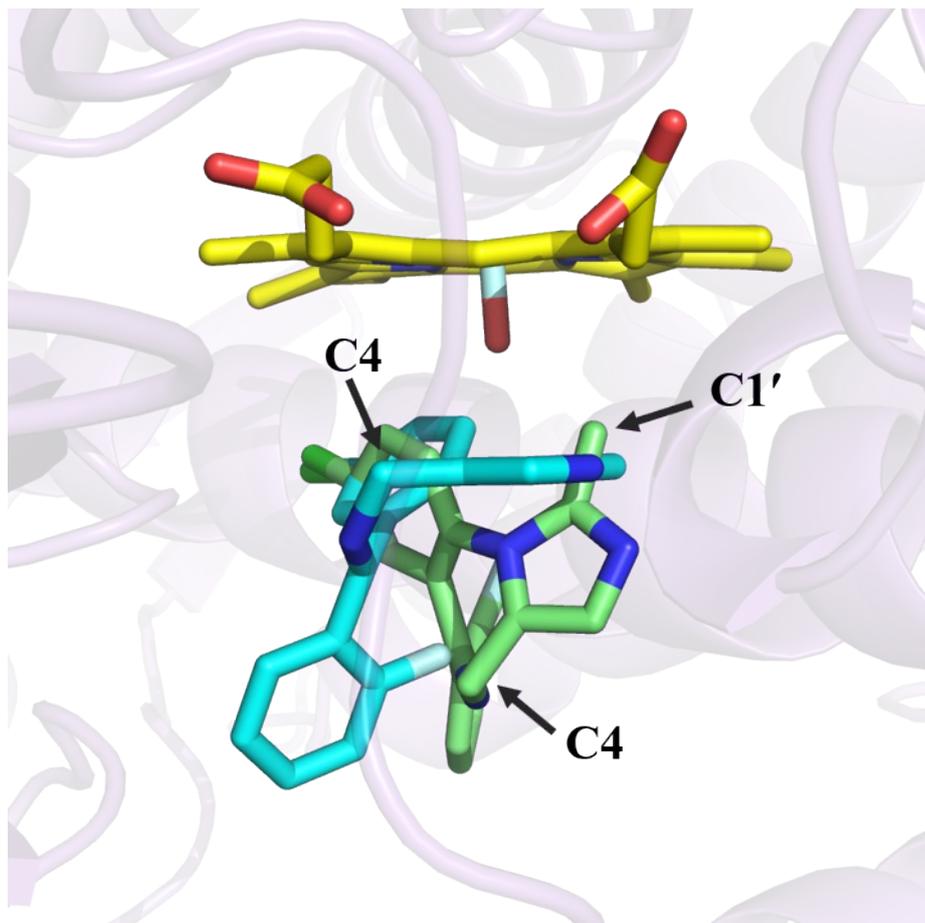
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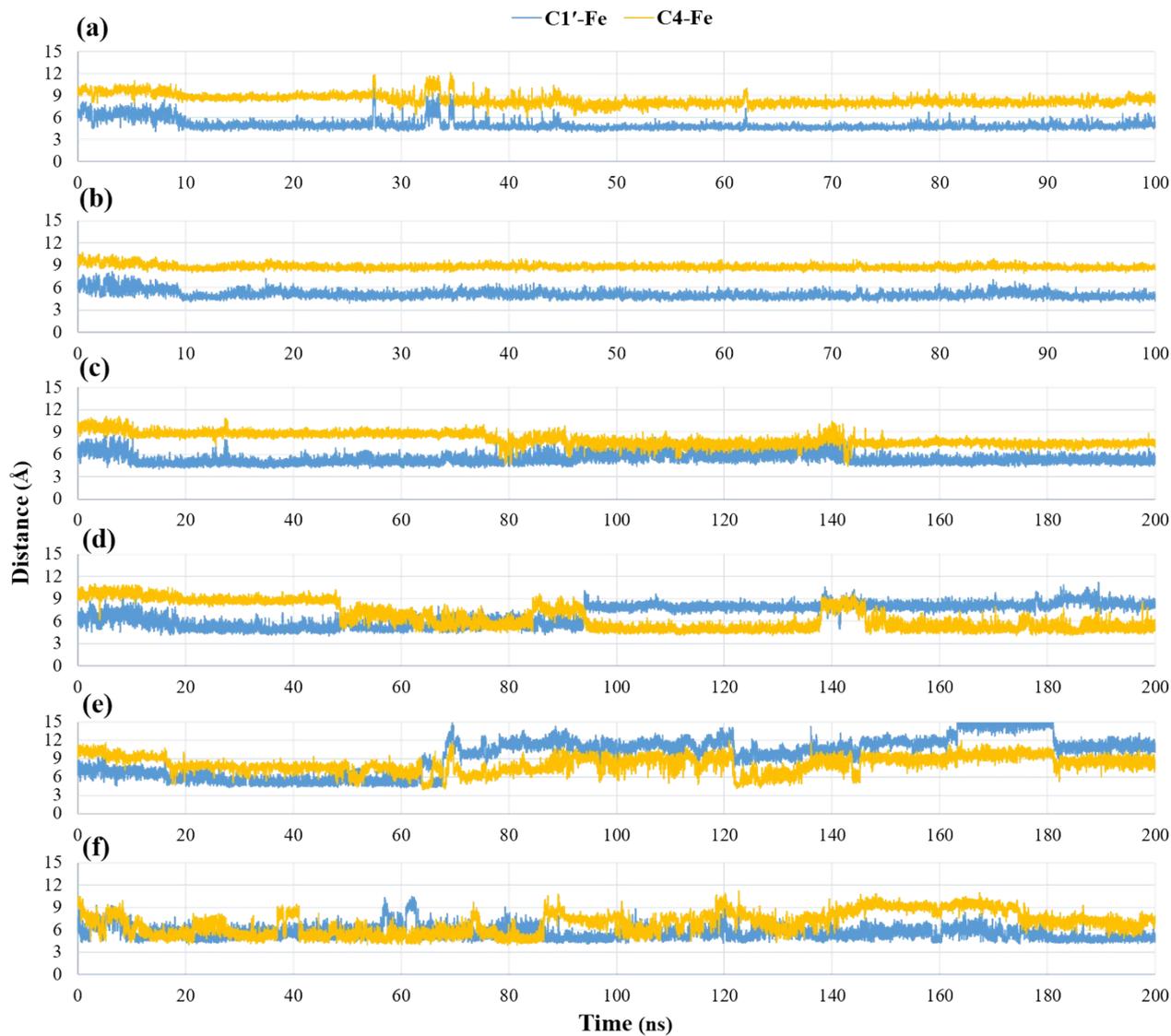
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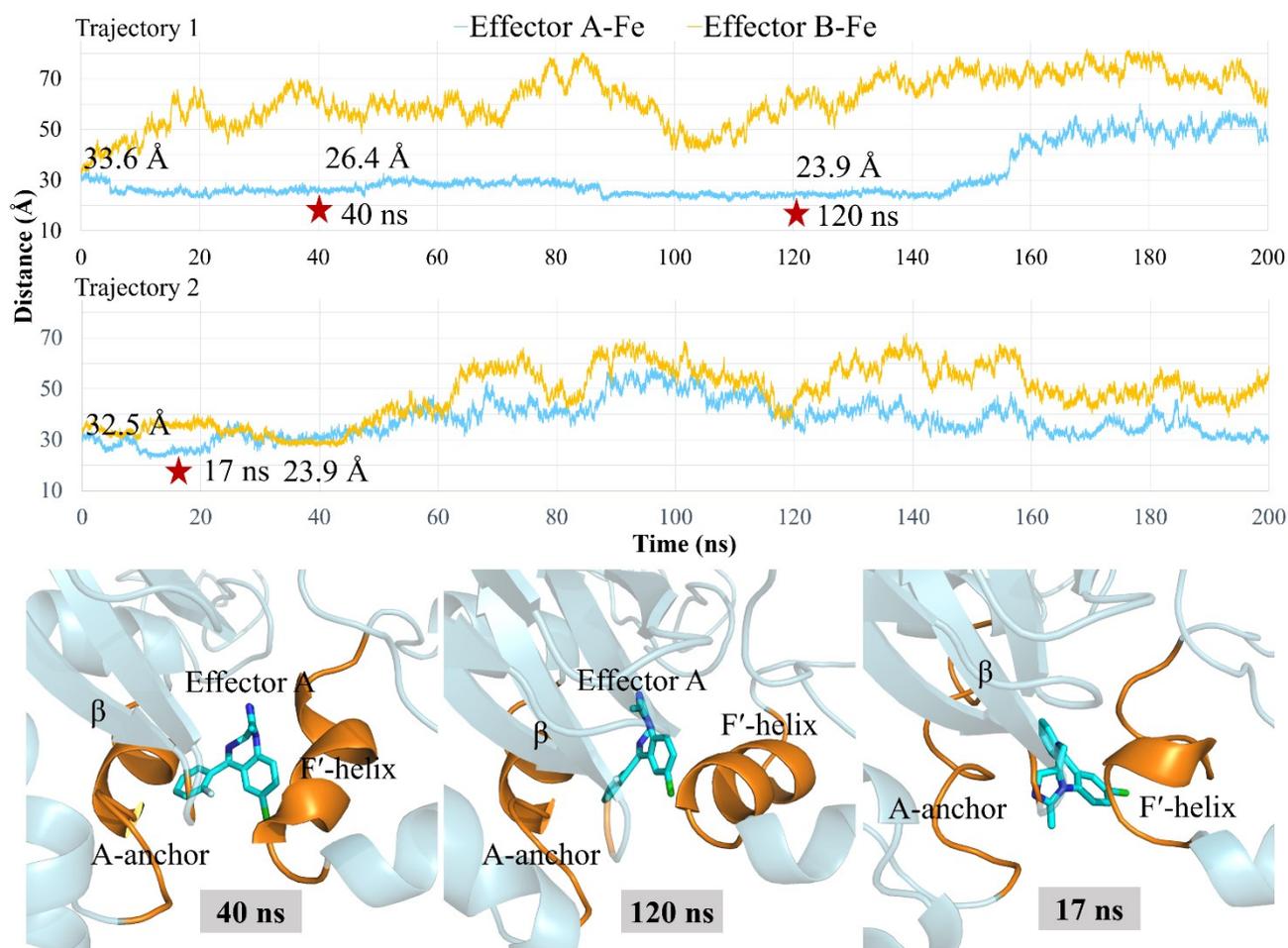
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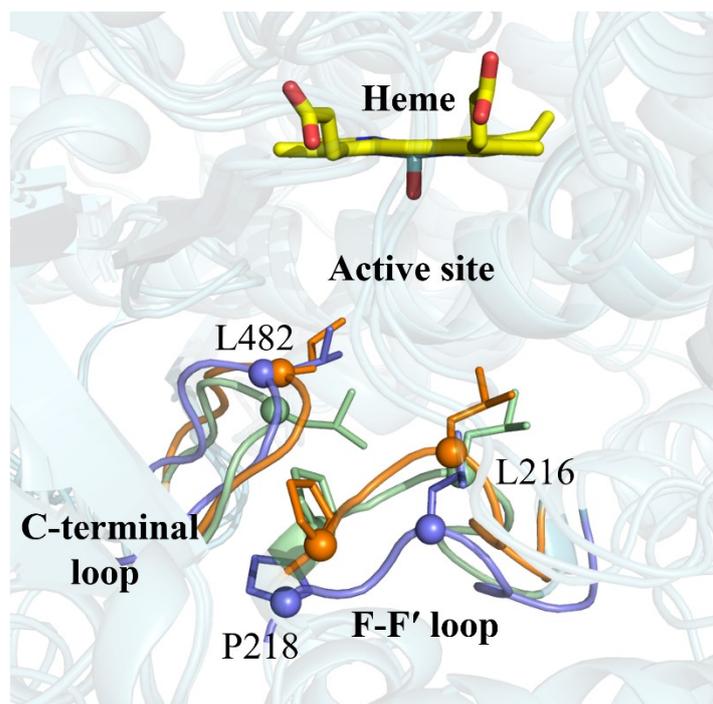
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**Fig. S7** The distance between effectors and heme iron in the aMD trajectories 1 and 2. The representative conformations of Effector A at 40, 120, 17 ns are shown as cartoons, respectively.



**Fig. S8** The superimposed conformation of three representative substrate-binding poses (pose **A**, **B** and **C**) in CYP3A4-MDZ-effectors complex. The F-F' and C-terminal loops are highlight in orange, pale green and blue in pose **A**, **B** and **C**, respectively.

## References

1. M. Redhair, J. C. Hackett, R. D. Pelletier and W. M. Atkins, *Biochemistry*, 2020, **59**, 766-779.
2. I. G. Denisov, Y. V. Grinkova, T. Camp, M. A. McLean and S. G. Sligar, *Biochemistry*, 2021, **60**, 1670-1681.