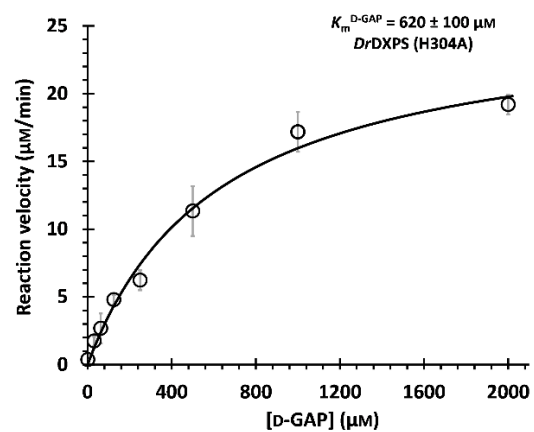
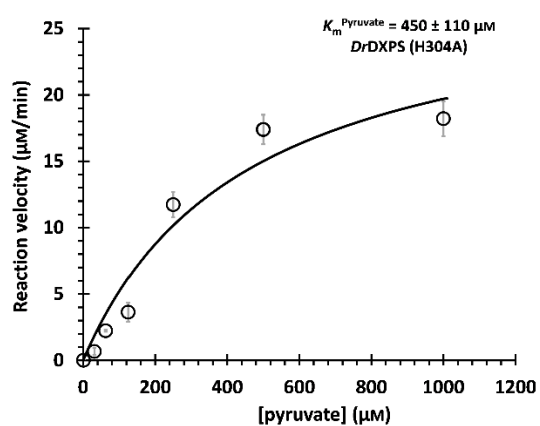
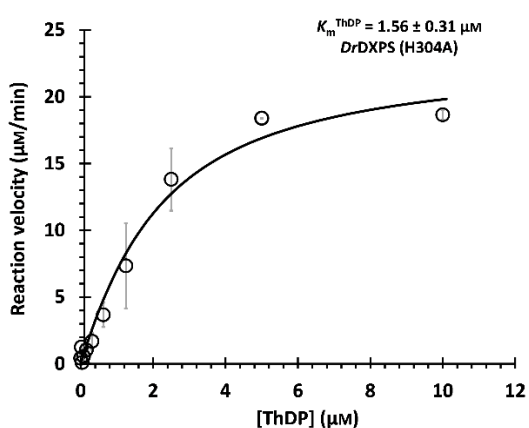
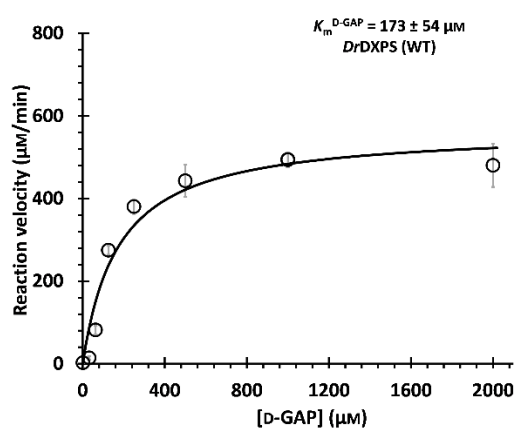
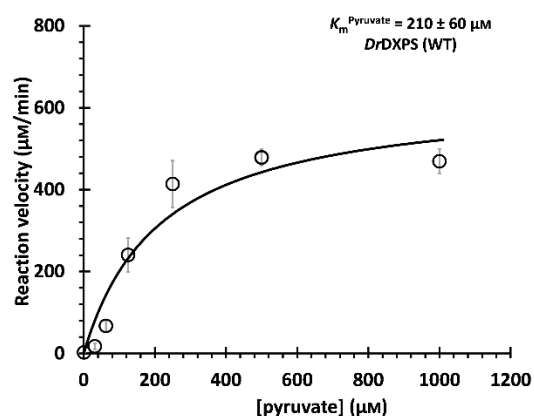
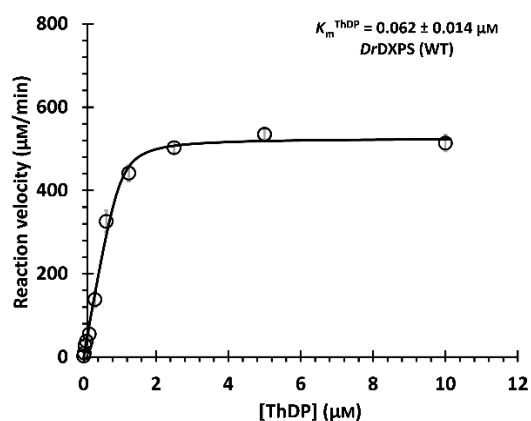
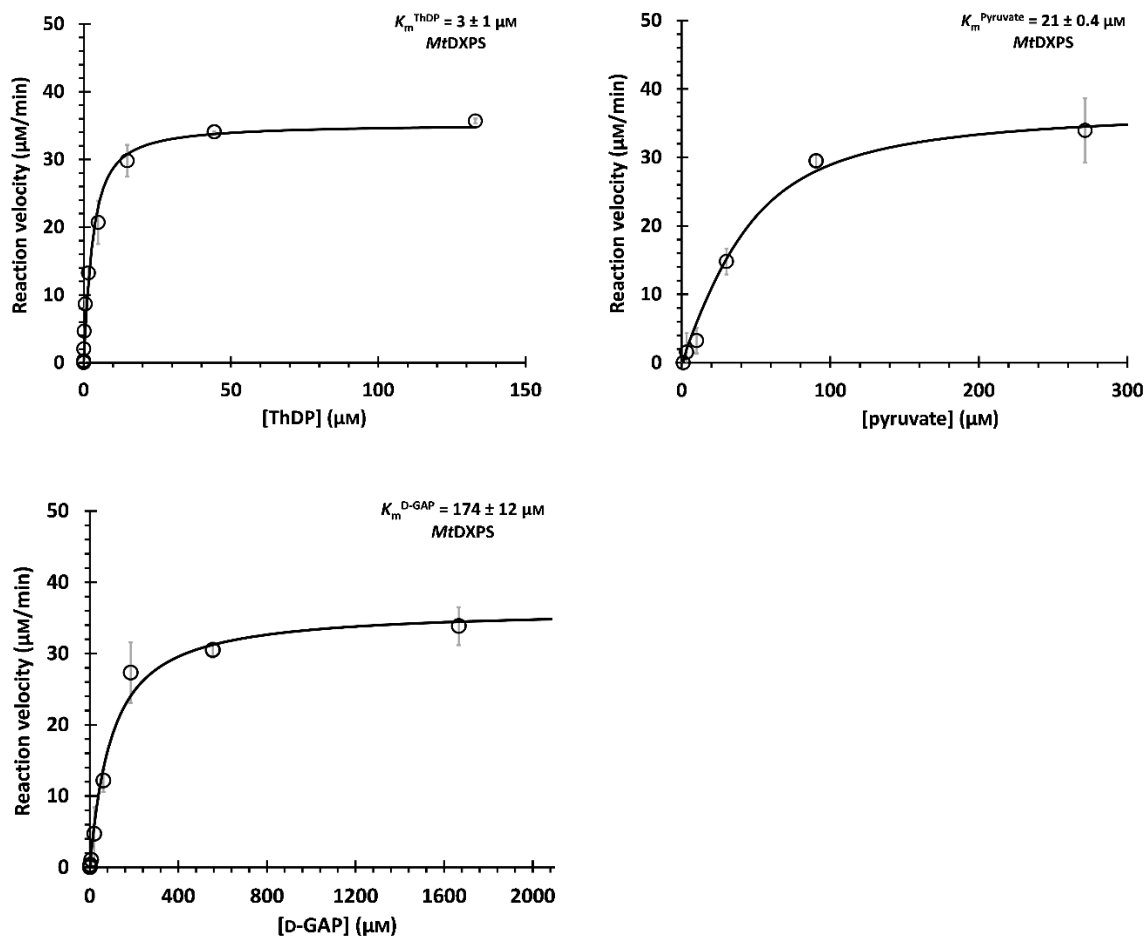
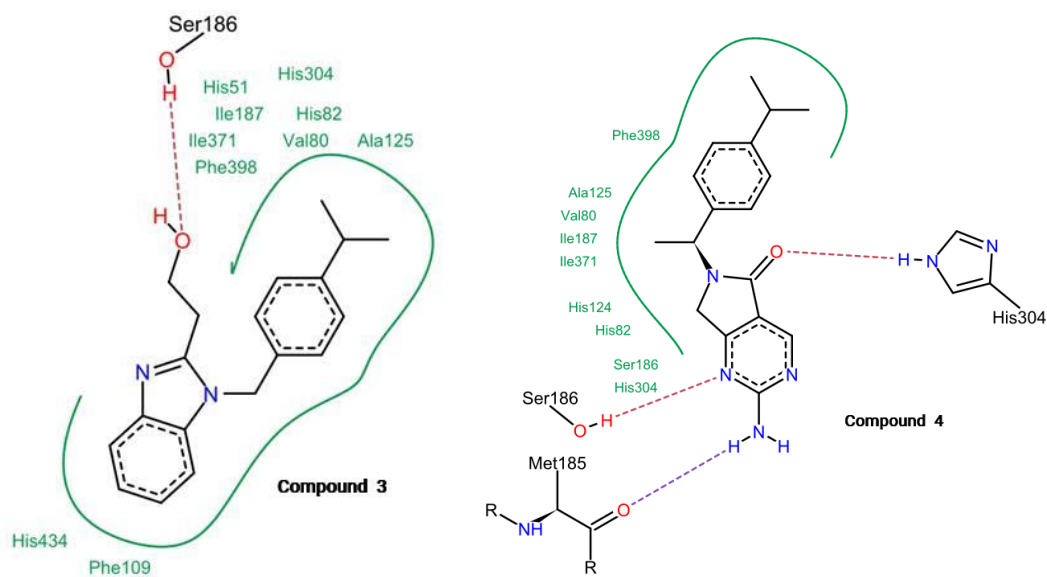


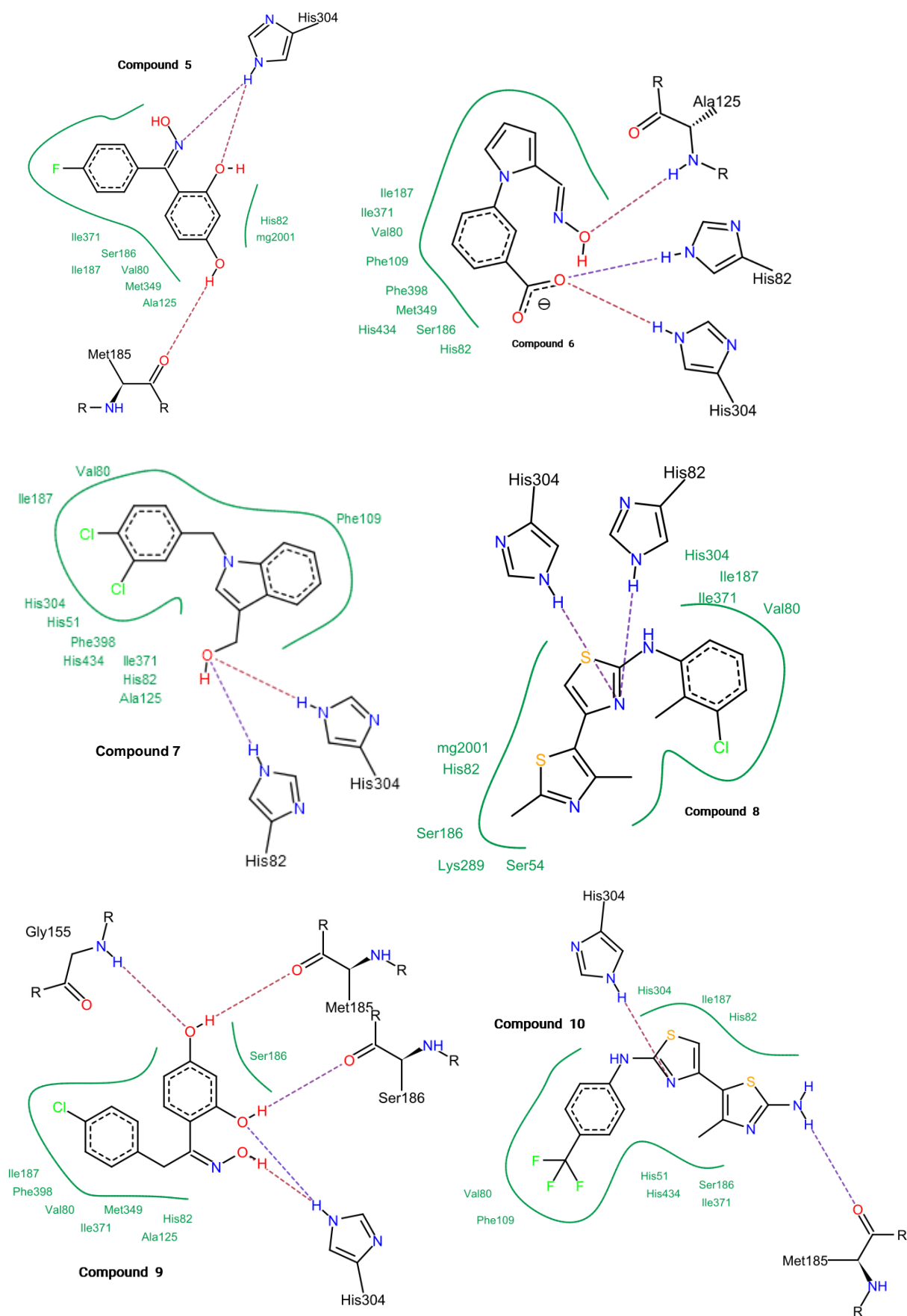
## Supplementary Figures





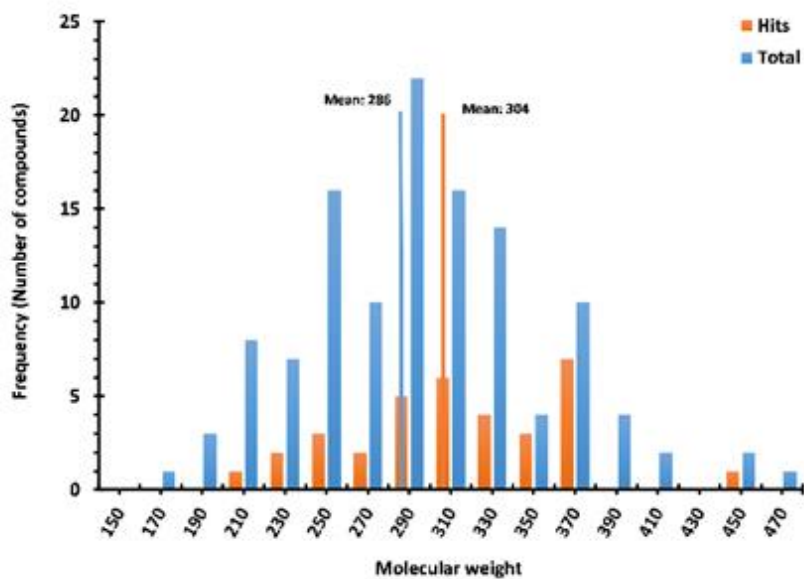
**Figure S1:** Kinetic characterization of *DrDXPS* (WT), *DrDXPS* (H304A) and *MtDXPS*.



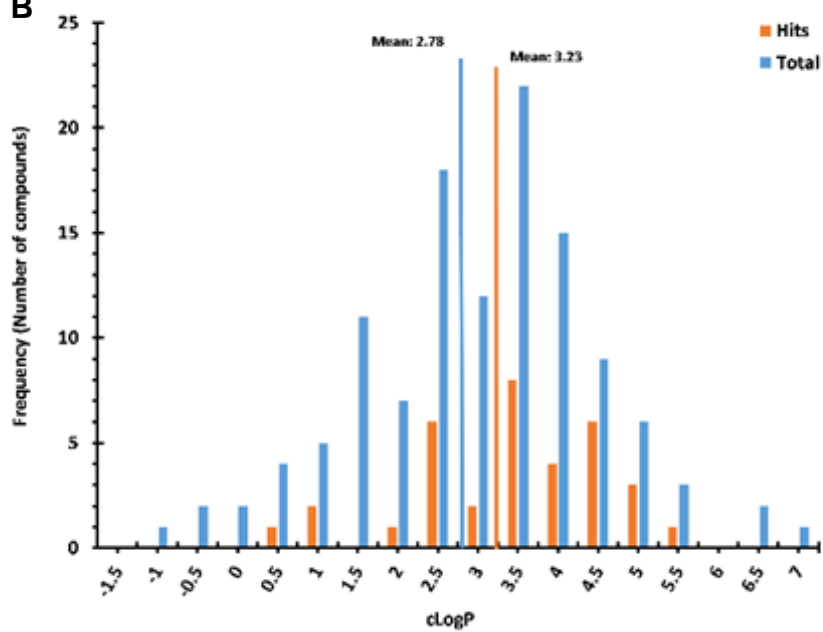


**Figure S2:** Top-ranked docking pose of compounds 3–10.

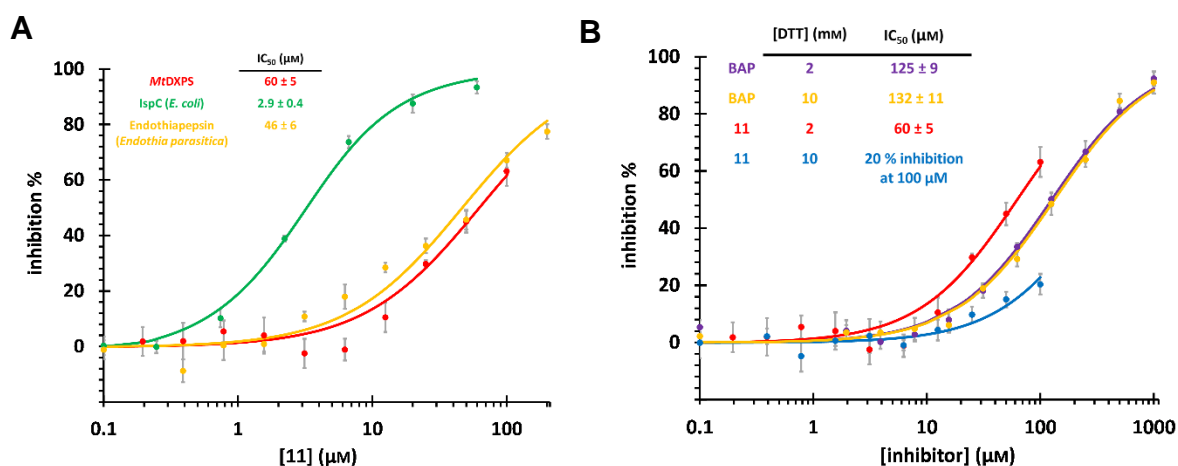
**A**



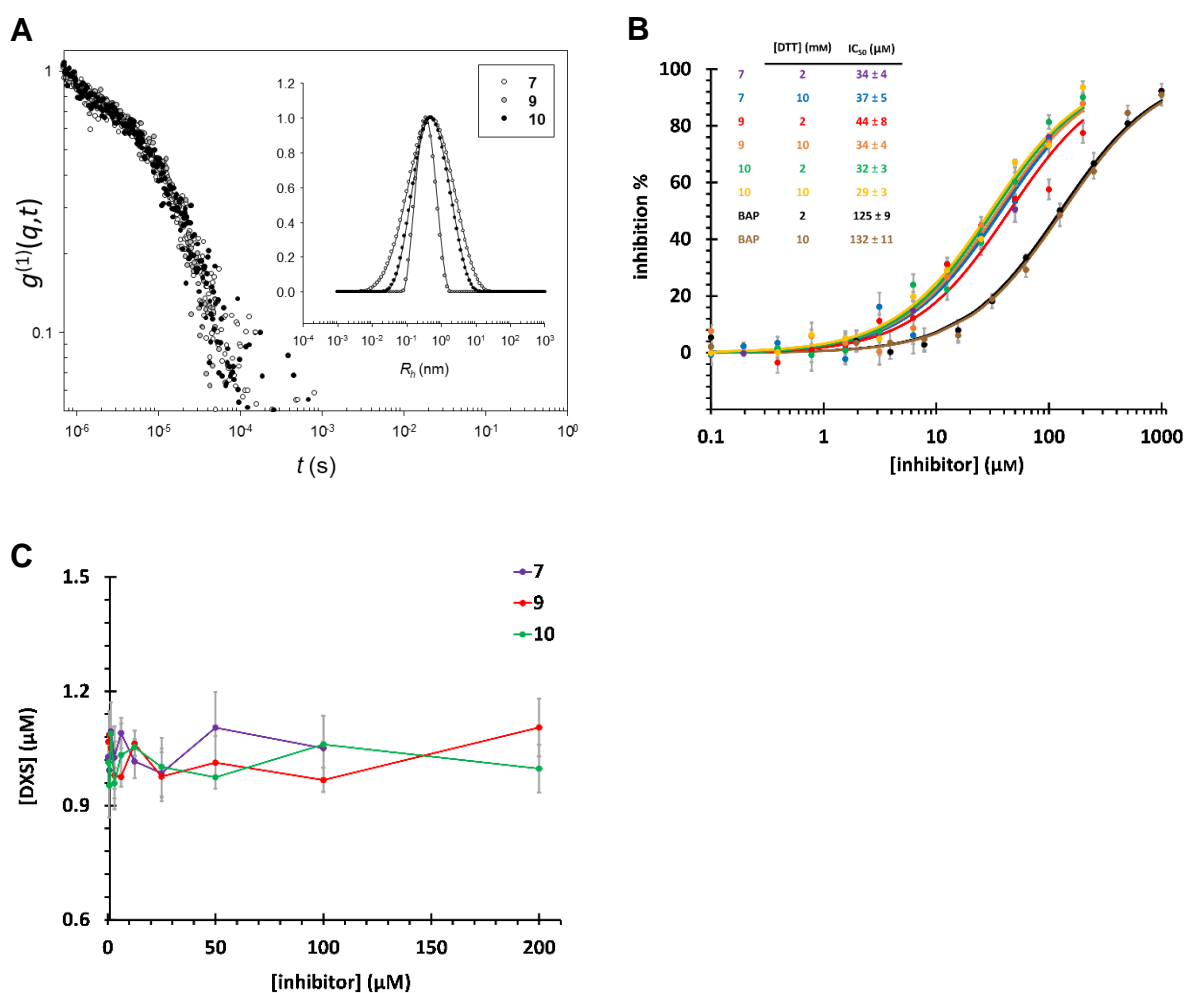
**B**



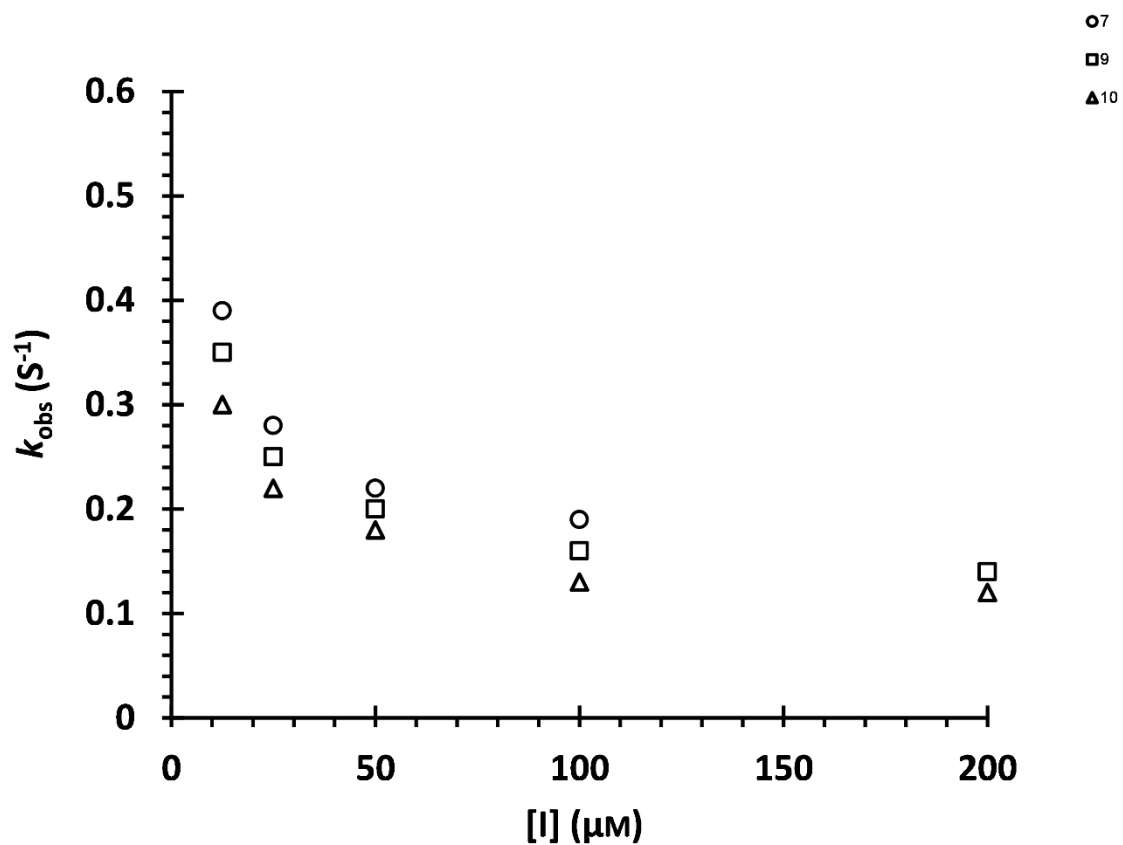
**Figure S3:** (A) Distribution of molecular weight of purchased candidates and hits. (B) Distribution of cLogP of purchased candidates and hits.



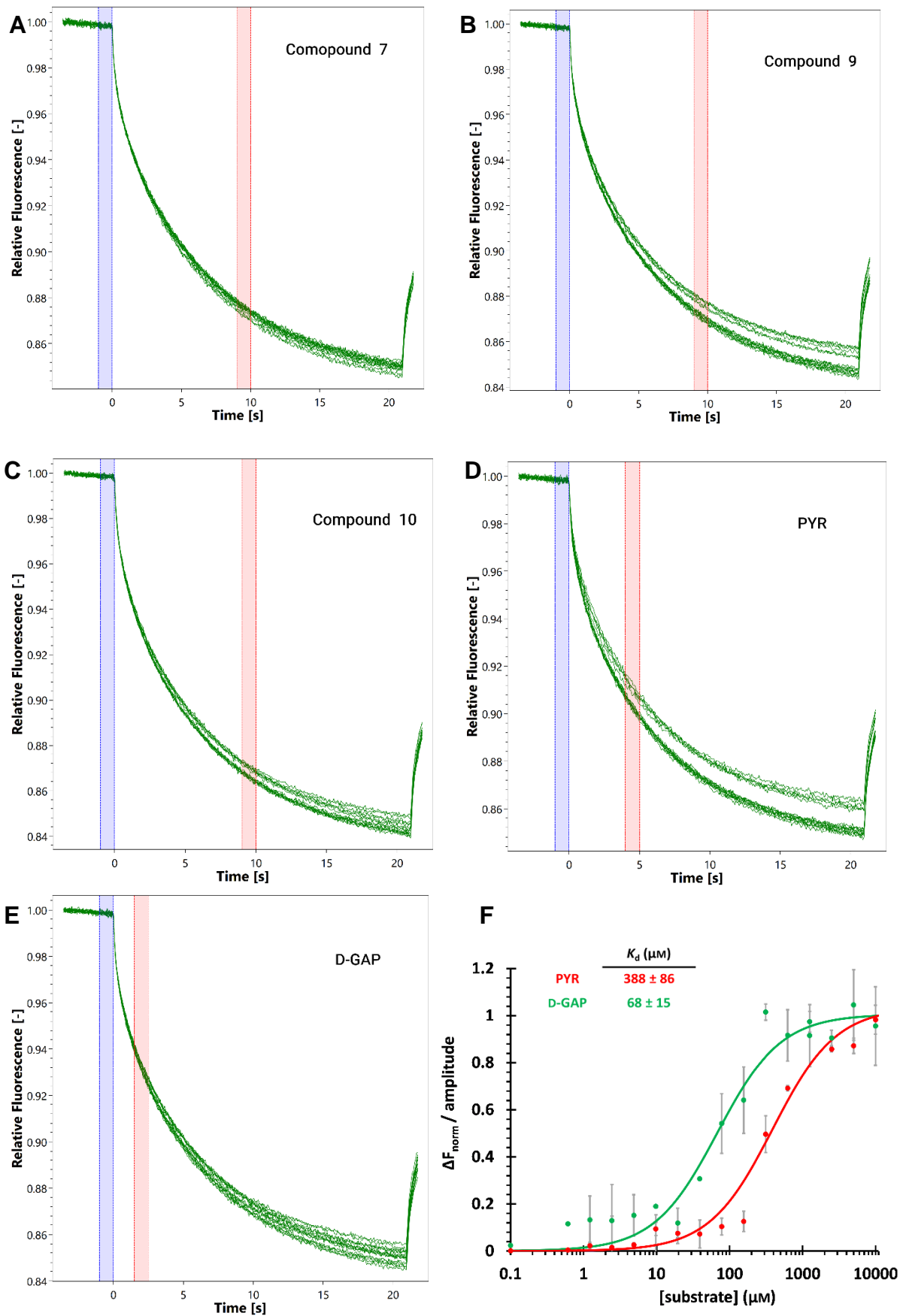
**Figure S4:** (A) Non-selective inhibition of **11** and (B) the effect of DTT concentration on the activity of **11**. Compound **11** was proved to be a reactive false positive against MtdXPS.



**Figure S5:** Hit validation of compounds **7**, **9** and **10** by (A) DLS, (B) DTT dependency and (C) DXPS co-precipitation. The hits were validated as true inhibitors against MtdXPS, not aggregators, reactive false positives or co-precipitators.



**Figure S6:** The hyperbolic curves for compounds **7**, **9** and **10** when comparing inhibitor concentration to  $k_{obs}$  confirms that the two-step Morrison model is appropriate to characterize the inhibitors' activity of the inhibitors against *MtDXPS*.



**Figure S7:** Raw data of MST analysis of the interaction between *MtDXPS* and ligands: Compounds (A) 7, (B) 9 and (C) 10, and substrates (D) pyruvate and (E) D-GAP. The blue and red squares represent the MST off and on time as used to extract the binding curves. (F) Binding curves of pyruvate and D-GAP with *MtDXPS*.

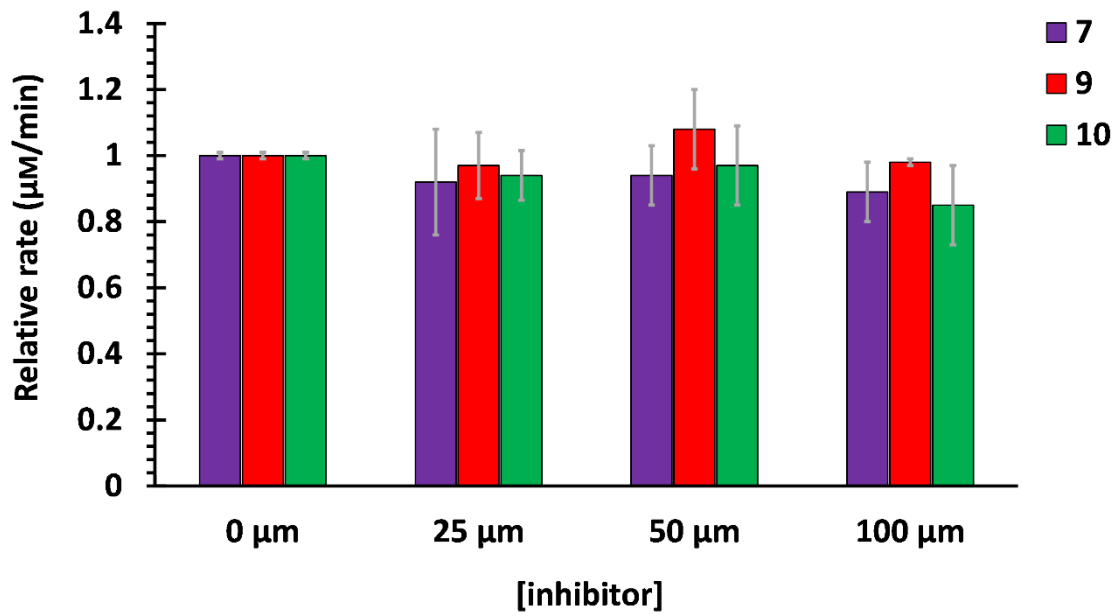


Figure S8: Dose-response bar-chart of the final hits against porcine PDH.

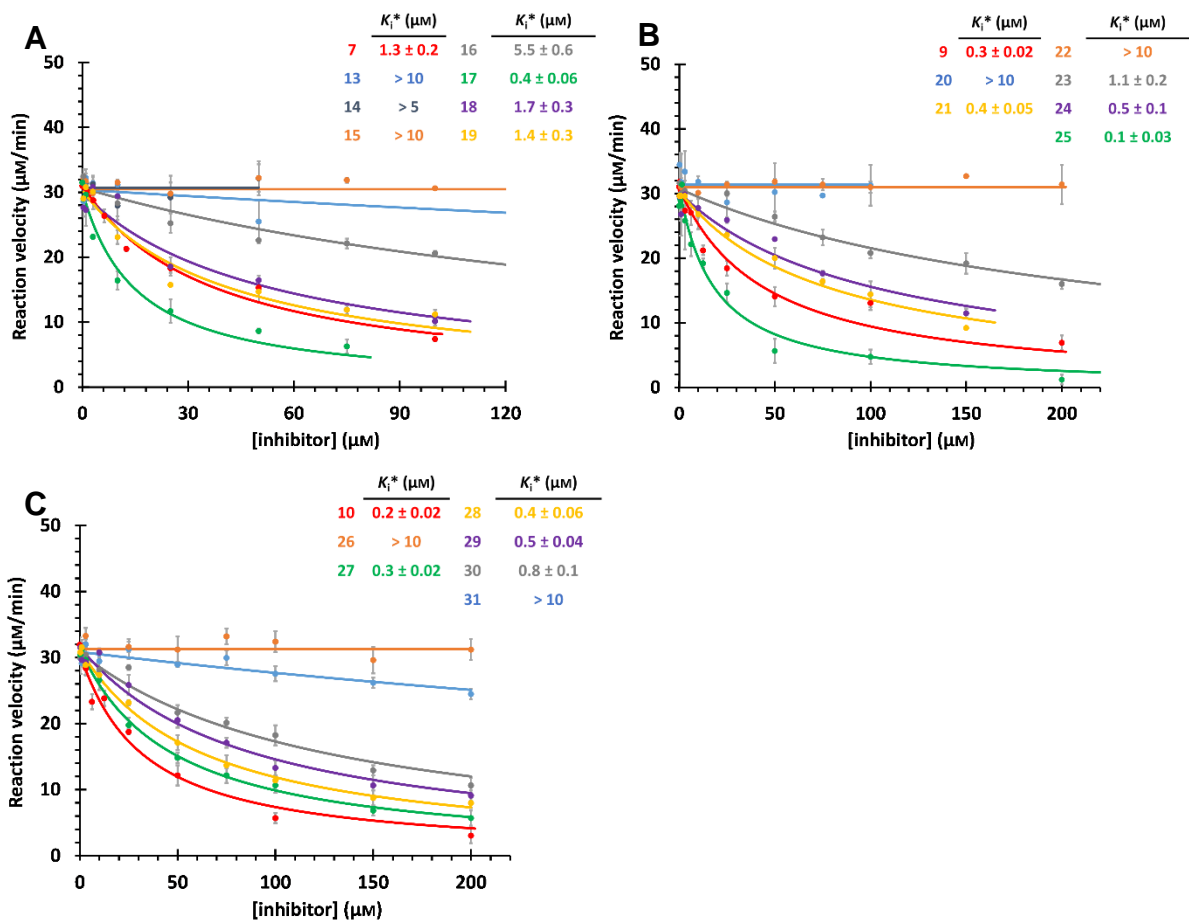
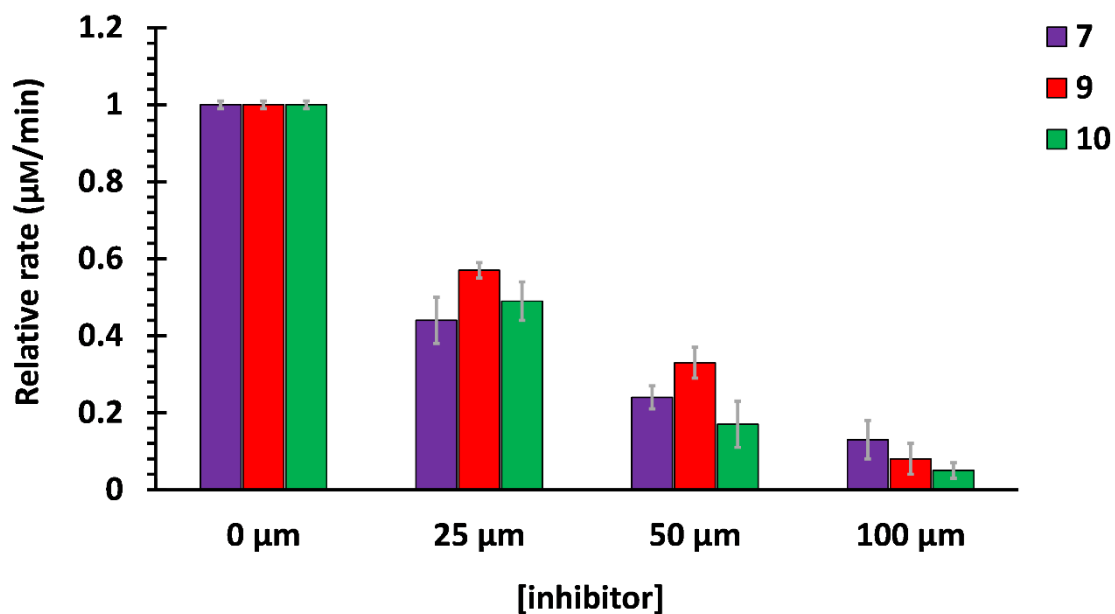
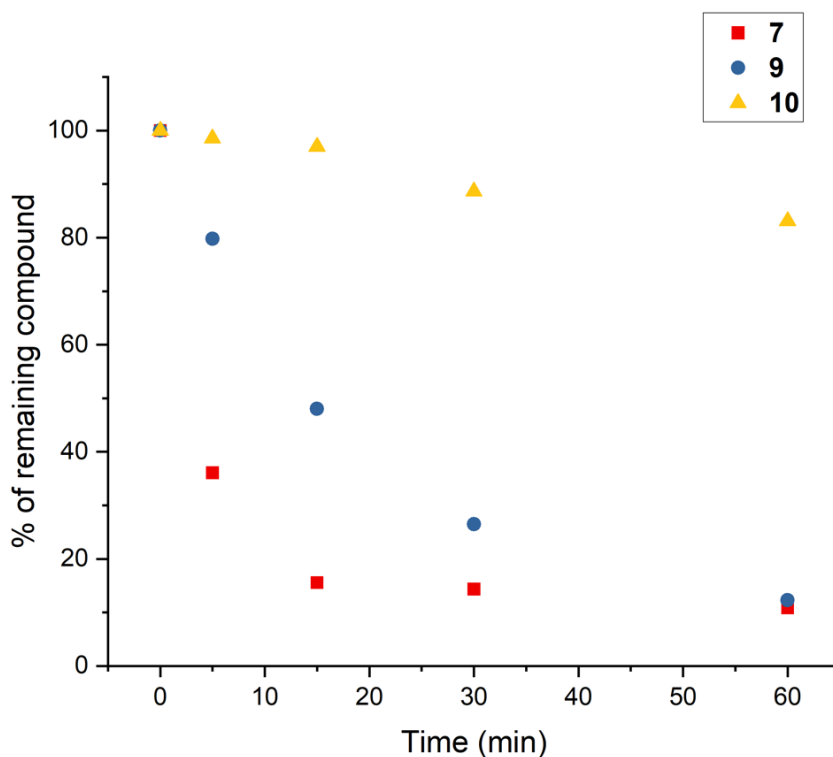


Figure S9: (A) (B) (C) Dose-response curves of the final hit derivatives used for  $K_i^*$  determination.





**Figure S10:** Dose-response bar-chart of compounds 7, 9 and 10 against *E. coli* DXPS.



**Figure S11:** Metabolic stability of 7, 9 and 10 in human liver S9 fraction. The residual percentage of the initial compound concentration is shown at different time points. Values are means of two independent determinations.