Supplementary Materials

What features of ligands are relevant to the opening of cryptic pockets

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1. Interpretation of models

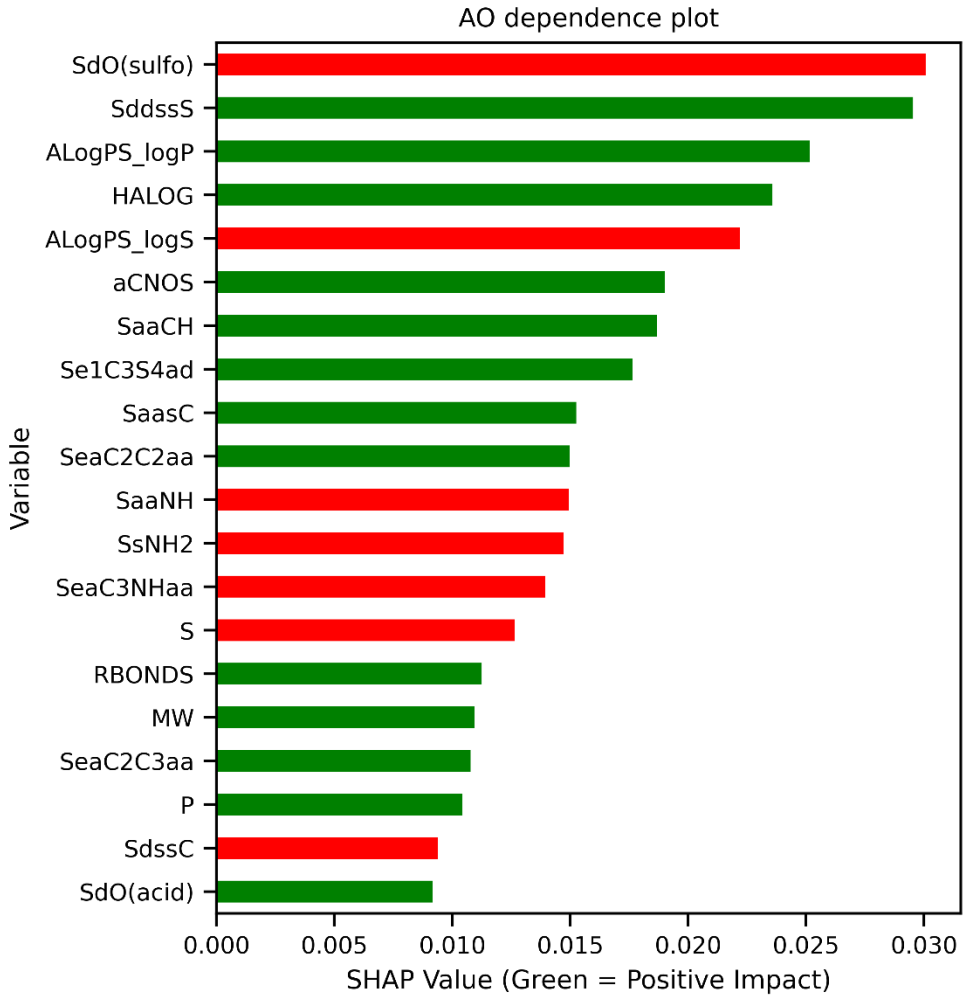

Figure S1. The SHAP values calculated for the filtered descriptors. Green: the bit has a positive impact (increasing the propensity to be inducers) on the target property; red: the bit has a negative impact on the target property.

2. Analysis on pocket residues

The distribution of pocket residues between inducer and non-inducer groups was investigated into four categories of amino acids (nonpolar aliphatic, polar charged, polar uncharged, and aromatic) as shown in Figure S2. For inducers, the number of hydrophobic amino acids in holo pockets was always larger than that in apo pockets, which was inconsistent with the result of Cimermancic et al[1]. This observation explains why inducers tended to have strong hydrophobicity and aromaticity.

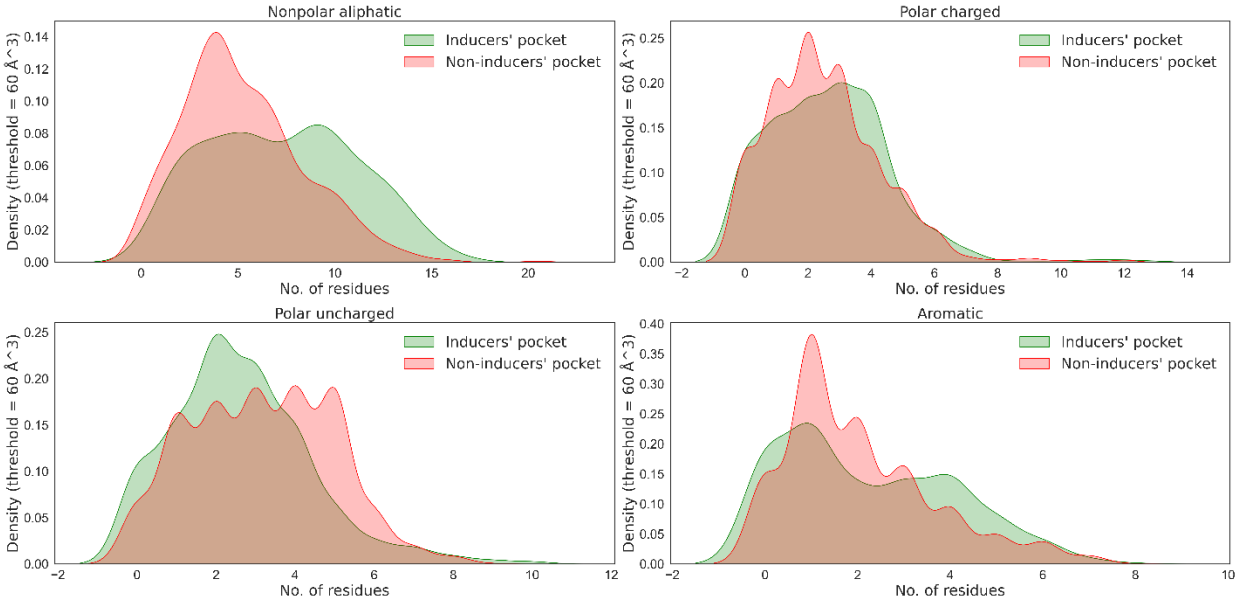

Figure S2. The distribution of pocket residues compared between holo and apo pockets for both groups of ligands (based on the optimal threshold = 60 Å^3).

Reference

1. Cimermancic, P.; Weinkam, P.; Rettenmaier, T.J.; Bichmann, L.; Keedy, D.A.; Woldeyes, R.A.; Schneidman-Duhovny, D.; Demerdash, O.N.; Mitchell, J.C.; Wells, J.A.; et al. CryptoSite: Expanding the Druggable Proteome by Characterization and Prediction of Cryptic Binding Sites. *Journal of Molecular Biology* **2016**, *428*, 709–719, doi:10.1016/J.JMB.2016.01.029.