Table S5: **The residue type propensity at alignment positions that bind both ligands and proteins, bind ligands, or bind proteins in comparison to all solvent-exposed residues.**

| amino acid | Propensity at Ligand-only positions | (95% confidence interval) | Propensity at Protein-only positions | (95% confidence interval) | Propensity at Bi-functional positions | (95% confidence interval) |
|---|---|---|---|---|---|---|
| A | 1.027 | (0.993, 1.06) | 0.978 | * (0.967 , 0.989) | 0.943 | * (0.919, 0.964) |
| C | 1.425 | * ( 1.334 , 1.529) | 1.085 | * (1.06 , 1.119) | 1.002 | (0.942, 1.053) |
| D | 0.837 | * ( 0.802 , 0.869) | 0.996 | (0.984 , 1.008) | 0.932 | * (0.909, 0.956) |
| E | 0.685 | * ( 0.658 , 0.712) | 1.016 | * (1.004 , 1.029) | 0.831 | * (0.811, 0.852) |
| F | 1.367 | * ( 1.312 , 1.424) | 0.972 | * (0.953 , 0.987) | 1.178 | * (1.139, 1.211) |
| G | 1.277 | * ( 1.236 , 1.316) | 0.931 | * (0.92 , 0.941) | 1.095 | * (1.072, 1.117) |
| H | 1.332 | * ( 1.267 , 1.394) | 0.976 | * (0.954 , 0.997) | 1.179 | * (1.139, 1.225) |
| I | 1.172 | * ( 1.131 , 1.217) | 1.003 | (0.99 , 1.018) | 0.955 | * (0.928, 0.98) |
| K | 0.65 | * ( 0.622 , 0.677) | 1.002 | (0.99 , 1.014) | 0.904 | * (0.882, 0.927) |
| L | 1.103 | * ( 1.074 , 1.136) | 0.996 | (0.985 , 1.007) | 0.967 | * (0.946, 0.988) |
| M | 1.363 | * ( 1.283 , 1.442) | 1.012 | (0.987 , 1.036) | 1.114 | * (1.071, 1.16) |
| N | 0.912 | * ( 0.872 , 0.952) | 1.009 | (0.993 , 1.024) | 1.009 | (0.983, 1.041) |
| P | 0.748 | * ( 0.711 , 0.783) | 1.035 | * (1.019 , 1.049) | 0.893 | * (0.867, 0.92) |
| Q | 0.712 | * ( 0.67 , 0.748) | 1.024 | * (1.009 , 1.041) | 0.954 | * (0.922, 0.981) |
| R | 0.849 | * ( 0.815 , 0.884) | 1.04 | * (1.027 , 1.055) | 1.019 | (0.992, 1.044) |
| S | 0.925 | * ( 0.892 , 0.962) | 1.02 | * (1.007 , 1.032) | 1.059 | * (1.032, 1.084) |
| T | 0.971 | ( 0.934 , 1.006) | 1.007 | (0.993, 1.021) | 1.024 | ( 0.998, 1.051) |
| V | 1.152 | * (1.113 , 1.187) | 1.008 | (0.997, 1.022) | 0.978 | ( 0.954, 1.003) |
| W | 1.442 | * (1.348 , 1.529) | 0.946 | * (0.92, 0.972) | 1.33 | * ( 1.267, 1.383) |
| Y | 1.171 | * (1.122 , 1.221) | 0.991 | (0.975, 1.01) | 1.242 | * ( 1.205, 1.28) |

Bootstrap resampling was performed to compute 95% confidence intervals (CI) of the residue type propensities (Text Eqn 3). Propensities are considered significant (asterisk) at the $\alpha = 0.05$ level if their confidence intervals do not include the value 1.