

**Table 3. *P* values corresponding to the average pairwise sequence identity levels computed between members of each family of designed sequences and the native sequence of the given protein, for which the fold name is given in the first column and the PDB ID code is given in the second**

Fold	PDB ID	Best-all	Min-all	Core	Surf
SH3	1cka	3.4e-16	4.1e-10	5.5e-15	3.4e-1
	1shg	1.6e-7	2.9e-5	2.2e-4	1.7e-2
	1pwt	2.4e-8	2.9e-5	5.7e-9	5.4e-1
	1sem	4.8e-11	2.4e-8	5.7e-9	9.9e-2
	1shf	4.1e-10	5.7e-6	1.1e-7	3.4e-1
	1qcf	2.4e-8	2.9e-5	5.7e-9	5.4e-1
	1ckb	4.2e-15	3.3e-9	2.4e-13	5.4e-1
	2src	2.4e-8	5.7e-6	1.1e-7	3.4e-1
	1bk2	1.6e-7	1.4e-4	1.7e-6	5.4e-1
	1abo	5.2e-13	4.1e-10	2.4e-10	3.4e-1
	1fmk	3.3e-9	5.7e-6	1.1e-7	5.4e-1
	average	2.0e-10	6.4e-7	4.7e-9	2.9e-1
	Homeobox	1enh	1.0e-6	2.9e-5	2.2e-4
Homeobox	1fjl	1.6e-7	2.1e-3	1.8e-3	3.4e-1
	9ant	5.2e-13	2.1e-3	1.7e-6	3.4e-1
	1mnm	2.9e-5	2.1e-3	2.1e-5	3.4e-1
	1au7	1.0e-6	6.9e-3	2.1e-5	5.4e-1
	1b72	2.4e-8	1.4e-4	1.1e-7	5.4e-1
	1b8i	3.3e-9	6.9e-3	2.1e-5	3.4e-1
	1du0	2.4e-8	4.9e-2	1.8e-1	5.4e-1
	2hdd	4.8e-11	5.7e-4	1.7e-6	5.4e-1
	average	1.8e-8	1.5e-3	3.9e-5	3.6e-1
	HTH	1r69	3.4e-16	4.1e-10	5.5e-15
	2cro	4.1e-10	2.9e-5	5.7e-9	5.4e-1
	1lmb	3.3e-9	2.9e-5	2.2e-4	9.9e-2
Protein G	1lli	2.4e-8	1.4e-4	2.1e-5	5.4e-1
	1b0n	1.6e-7	5.7e-4	2.2e-4	5.4e-1
	1per	1.8e-18	5.2e-13	5.5e-15	9.9e-2
	average	1.2e-11	4.9e-7	7.5e-9	2.3e-1
	Protein G	1pgb	1.6e-7	5.7e-4	1.1e-2
	2igd	4.1e-10	3.3e-9	2.4e-13	3.4e-1
	average	8.1e-9	1.4e-6	5.2e-8	3.4e-1
CI2	2ci2	2.4e-8	5.7e-6	5.7e-9	9.9e-2
	1cse	4.8e-11	1.6e-7	5.5e-15	1.7e-2
	1ypc	5.2e-13	3.3e-9	2.4e-10	9.9e-2
	2tec	3.3e-9	1.0e-6	2.4e-13	3.4e-1
	2sec	3.3e-9	2.9e-5	5.7e-9	3.4e-1
	1acb	4.8e-11	2.4e-8	2.2e-4	9.9e-2
	1coa	5.2e-13	1.6e-7	2.4e-13	9.9e-2
	average	1.1e-10	3.2e-7	1.3e-10	1.1e-1
Cold-shock	1csp	5.1e-12	2.4e-8	2.4e-13	3.4e-1
	1mjc	5.1e-12	4.1e-10	9.6e-17	9.9e-2

Fold	PDB ID	Best-all	Min-all	Core	Surf
	1c9o	5.1e-12	4.1e-10	2.4e-13	3.4e-1
	1csq	5.1e-12	2.4e-8	2.4e-10	9.9e-2
	average	5.1e-12	3.1e-9	1.9e-13	1.8e-1
Antifreeze	1ops	1.6e-7	1.6e-7	5.7e-9	5.4e-1
	1msi	2.4e-8	1.4e-4	2.2e-4	5.4e-1
	2jia	1.6e-7	2.9e-5	5.7e-9	5.4e-1
	1ame	1.6e-7	5.7e-4	2.2e-4	5.4e-1
	1b7i	3.3e-9	1.4e-4	1.7e-6	5.4e-1
	1ekl	4.1e-10	1.4e-4	2.2e-4	5.4e-1
	average	2.3e-8	4.3e-5	2.9e-6	5.4e-1

“average” in the second column denotes average values computed for the sequences designed for all the backbones of the fold. This average was computed as a geometric mean of the listed  $P$  values for the different backbones of each fold. To compute the  $P$  values, we used a uniform random sequence model and a binomial distribution of the sequence identity values. For further information and discussion of the results see main article.