Nucleic acids fold into intricate three-dimensional structures, driven by the propensity of the bases to interact with each other through hydrogen bonding, stacking and van der Waals interactions. The power of SELEX (Systematic Evolution of Ligands by EXponential enrichment) comes from the ability to screen extremely large nucleic acid libraries (>10^14) for rare sequences able to recognize other molecules with high affinity and specificity through precise shape and functional group complementarity. However, the chemical diversity of nucleic acids is more limited than that of proteins and this has been a limiting factor for generating aptamers for certain molecular targets, including some proteins. We have focused on bridging this diversity gap by introducing functional groups that are absent in natural nucleic acids, but common in protein-protein contacts or interactions between small molecules and their protein targets. The 5-position of deoxyuridine is a convenient point of attachment through a conformationally-restricted amide linkage. The use of such modified DNA libraries, in which only one out of four bases is uniformly modified, has made a profound impact on the success rate of SELEX. Of the functional groups tested, hydrophobic aromatic side chains typically exhibit superior performance in SELEX and allow the identification of ligands with very low dissociation rates. The modified nucleotides also represent points at which additional diversity can be explored for affinity maturation or to optimize ligands for specific purposes. Based on co-crystal structures, these modifications create entirely new structural motifs and generate extensive hydrophobic binding surfaces, in contrast to mainly polar surfaces observed with conventional aptamers. These improvements have allowed us to build a collection of over 7,000 modified aptamer reagents to human proteins. This set of binding reagents, along with an assay that takes advantage of unique properties of aptamer-based ligands, enables unbiased and highly multiplexed monitoring of changes in protein expression that accompany a wide range of biological processes in health and disease.