Despite notable successes in the development of ATP-competitive drugs, kinase inhibitors with alternative mechanisms-of-action may afford clinical candidates with distinct selectivity patterns and potentially improved therapeutic profiles. For this reason, our laboratory is pursuing the design and synthesis of allosteric, peptidomimetic, and covalent kinase inhibitors for the treatment of cancer. In one area, we are targeting the dual kinase/RNase IRE-1 (inositol-requiring enzyme 1) with covalent inhibitors that specifically engage a lysine residue in the RNase domain. We recently showed that the growth of chronic lymphocytic leukemia is highly dependent on IRE-1 hyperactivation, and that pharmacologic inhibition blocks the progression of CLL in a transgenic mouse model. The synthesis and SAR of tetrahydrometheno[3,4-c]pyridine lead structures, and their prodrug derivatives, resulted in the development of selective IRE-1 RNase inhibitors with efficacy against an array of B-cell cancers. In another area, we have focused on a versatile peptidomimetic approach to the non-ATP-competitive inhibition of kinases. Using conformationally extended peptide substrates as lead structures, new β-strand orthotics were developed for residue scanning applications. The design, synthesis, and conformational validation of azabicycloalkane, imidazopyridine, and tetrahydropyridazinedione β-strand mimics will be presented. Our structural motifs have been incorporated into peptidomimetic antagonists of Akt, an oncogenic kinase hyperactivated in over 50% of human tumors. This effort led to the rapid identification of potent kinase inhibitors based on a protein-protein disruption strategy, and holds promise as a universal approach for the mimicry other bioactive β-strands.