Dysregulated activation of non-canonical NF-κB (ncNF-κB) signaling contributes to the pathogenesis of various autoimmune and inflammatory diseases and human cancers. In the ncNF-κB pathway, NF-κB-inducing kinase (NIK) is a central regulatory component and its activity is essential for ncNF-κB activation. Consequently, selective small molecule inhibitors of NIK are highly desired as mechanistic chemical probes and potential therapeutics. Although active in mouse disease models, current ATP-competitive NIK inhibitors suffer from either off-target effects or poor drug-like properties. Allosteric kinase inhibitors are a validated approach towards achieving high selectivity for a desired kinase target, thereby overcoming limitations of ATP-competitive inhibitors. Therefore, in this project, we are developing allosteric NIK inhibitors. Through molecular dynamics (MD) simulations, we identified two putative allosteric sites on NIK that are amenable to small molecule binding. A virtual screen against these sites was performed that yielded 120 high-scoring small molecules that were subsequently screened for NIK enzymatic inhibition. Biochemical assays revealed 13 compounds that inhibit NIK enzymatic activity at or below 100 µM. Ongoing work is focused on further characterization and optimization of these hit compounds. Our novel NIK inhibitors, once fully optimized, will represent the first-in-class NIK allosteric modulators with anticipated high selectivity for NIK and the ability to regulate aberrant ncNF-κB signaling in disease models.