Many current small molecule drugs, like gefitinib for lung cancer, only bind to active sites and inhibit catalytic activities, thus limiting their effects to enzyme proteins. However, many disease-linked proteins are not enzymes and do not have accessible active sites. Enzyme inhibitors also lose therapeutic potential over time due to drug resistance. Proteolysis targeting chimaera (PROTAC) is a newly-emerging drug discovery platform aimed at addressing the limitations of small molecule drugs by inducing degradation of oncogenic proteins. These PROTAC degraders are bi-functional molecules that bind to both a target protein and an E3 ligase that tags the target protein with ubiquitin for degradation. For this project, we developed potent PROTACs against epidermal growth factor receptor (EGFR), an oncogenic protein mutated in over 60% of non-small cell lung cancers. The goal of this research was to determine the effectiveness of these new EGFR PROTACs, compare their efficacy to that of the current inhibitor and assess their specificity. Using two human EGFR mutant lung carcinoma cell lines, we carried out extensive biochemical and cellular assays, including western blot, cell viability assays and mass spectrometry, to characterize the EGFR PROTACs. We showed that our PROTACs can effectively decrease EGFR levels, downregulate downstream signaling targets and inhibit cell proliferation, while exhibiting high EGFR selectivity. From these findings, we show that our EGFR PROTACs exhibit greater efficacy than current inhibitors. Our study not only provides an alternative approach to targeting EGFR-driven cancers but also illustrates the potential utility to target other disease-linked proteins.