The Past, Present, and Future of Chemical Proteomics Using Covalent Chemistry Probes for Drug Discovery

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Covalent chemistry probes serve as valuable tools to investigate functions of proteins and to discover ligandability of proteins of interest. Despite efforts to expand toolbox of covalent chemistry probes for chemical proteomics (e.g., cysteine, lysine, and modified amino acid residues by post-translational modifications), the proteoforms remains inaccessible with limited number of covalent chemistry probes developed over the last two decades. Here, we introduce novel covalent probes (HHS-465, 475, and 482) named sulfur-triazole exchange (SuTEx) chemistry to target tyrosine and lysine residues with broad applications for chemical proteomics. Furthermore, covalent fragment-based ligand discovery (cFBLD) was performed in live cells to identify cell-active ligands. HHS-0701 was identified as a prostaglandin reductase 2 (PTGR2) ligand which inhibits capable of blocking biochemical activity of PTGR2. Ultimately, a set of pan-kinase probes was developed by application of SuTEx chemistry to investigate change of kinase activity in live cells. Collectively, we describe SuTEx as a novel covalent chemistry for chemical biology to study biological events.