Teaching an old dog new tricks: chemical biology studies of pyrroloquinazolines

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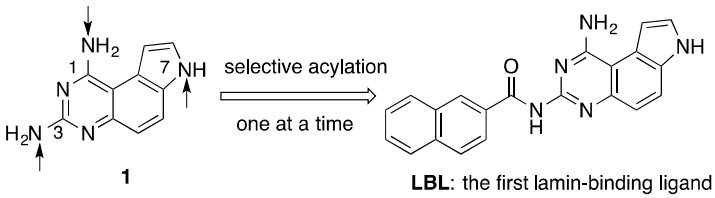
7*H*-Pyrrolo[3,2-*f*]quinazoline-1,3-diamine (**1**) is a privileged chemical scaffold with significant biological activities. These include inhibition of dihydrofolate reductase (DHFR), protease-activated receptors (PAR) and protein tyrosine phosphatase 1B (PTP1B). However, the currently accessible chemical space derived from **1** is rather limited. In this presentation, we expanded the chemical space related to **1** by developing efficient methods for regioselective monoacylation at N^1, N^3 and N^7, respectively. With this novel methodology, a focused library of mono-*N*-acylated pyrroloquinazoline-1,3-diamines were prepared and screened for anti-breast cancer activity. The structure-activity relationship (SAR) results showed that N^3-acylated compounds were in general more potent than N^1-acylated compounds while N^7-acylation significantly reduced their solubility. Among the compounds evaluated, **LBL1** possessed significantly more potent activity than **1** in MDA-MB-468 cells. More importantly, **LBL1** was not toxic to normal human cells. Further chemical biology and mechanistic studies showed that **LBL1** targets nuclear lamins to inhibit repair of double-strand DNA breaks (DSB) in breast cancer cells. The discovery of **LBL1** as the first lamin-binding ligand from a focused novel library of **1** supports that **1** is a privileged scaffold. The availability of **LBL1** should enable us to address the poorly understood molecular mechanisms of lamins in DSB repair processes.



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LBL: the first lamin-binding ligand