PHOTOCAGED BISUBSTRATE INHIBITOR OF cAMP-DEPENDENT PROTEIN KINASE

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Exerting an external spatial and temporal control over bioactive compounds is desired in medicine as well as in laboratory. For manipulating bioactive compounds covalently attached photocaging groups have been used, which render bioactive molecules inactive until irreversibly photolysed with UV-Vis irradiation. Protein kinases (PK) are enzymes catalysing protein phosphorylation and thus affecting almost all cell functions through a myriad of mechanisms. An impaired activity of PKs has been linked to many diseases like cancer and Alzheimer`s disease among others [1]. Understanding the structures and interactions of PKs has led to the development of protein kinase inhibitors (PKI) providing us with 48 approved PKI drugs thus far [2]. Although majority of approved PKI drugs are ATP-competitive, bisubstrate PKI-s which bind the ATP-pocket and peptide binding region simultaneously are able to achieve greater affinity and selectivity [3,4]. In addition to pharmacological perspective, PKIs are valuable chemical probes in PK related research.

In the current work a previously introduced extremely potent bisubstrate PKI was rendered inactive towards catalytic subunit of cAMP-dependent protein kinase (PKAc) when protected with a photocaging group. The bioactive inhibitor was released upon irradiation with UV-Vis and a significant more than five orders of magnitude increase in affinity was observed (Fig 1).

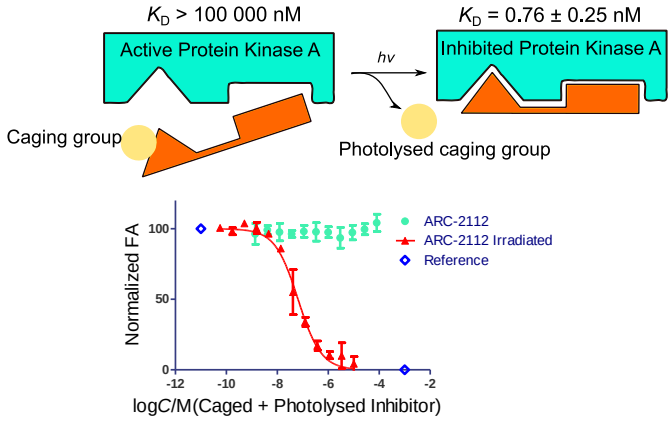

Figure 1. Association of compound ARC-2112 with PKAc prior and after irradiation as determined with binding assay based on fluorescence anisotropy (FA) measurements.

References

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