OPTIMIZATION OF PROTEIN KINASE A INHIBITOR ARC-1408 INTRACHAIN AMINO ACID

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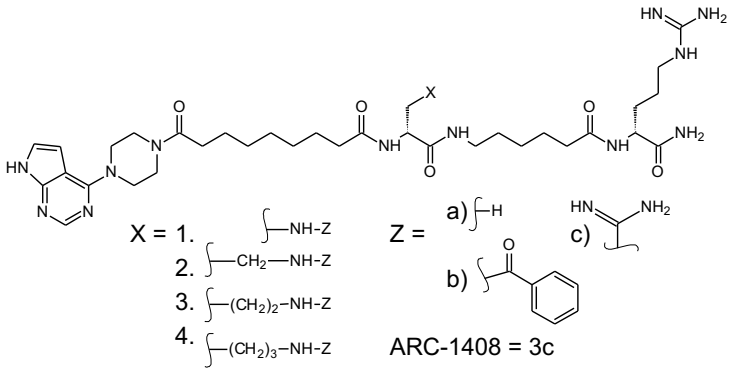
Protein kinases (PK) are enzymes which catalyse protein phosphorylation and consequently affect almost all cell functions via a myriad of mechanisms. An impaired activity of PKs has been linked to many diseases like cancer and Alzheimer`s disease among others [1]. Understanding the structures and interactions of PKs has led to the development of protein kinase inhibitors (PKI) providing us with 65 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 can 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 series of bisubstrate ARC-1408 [4] derivates were synthesised, in which the intrachain amino acid was modified. It was shown that a bulky benzoyl group can be used in the intrachain without a loss of affinity and the intrachain amino acid is well modifiable. The highest affinity compound in the series had D-α-amino-β-guanidinopropionic acid (1C) as the intrachain amino acid (K_D towards PKAcα = 0.07 ± 0.02 nM) and a 2.5-fold increased affinity compared to ARC-1408 (3C).



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