Identifying Inhibitors of PDE4B2 Mutant Enzymes and Inhibitor Specificity Using Schizosaccharomyces pombe

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PDE inhibitors are frequently used as pharmaceuticals to treat conditions such as pulmonary diseases and erectile dysfunction via the cAMP dependent signaling pathway. However, PDE inhibitor development is hampered by a lack of substrate specificity. In the model organism S. pombe, PDE inhibition and subsequent PKA activity amplifies cell proliferation, prevents stationary phase entry, and leads to distinct morphological changes, allowing for the presence of cAMP to be easily determined. Prior studies have identified two mutant S. pombe strains with single amino acid alterations in the PDE4B2 protein, which result in reduced sensitivity to the PDE4 inhibitors rolipram and BC54. This study uses previously identified PDE4 inhibitors to screen for the inhibition of the mutant forms of PDE4B2. These inhibitors are identified and optimized, and the effectiveness of these compounds on other PDE subfamilies is determined. BC58 was shown to be the most specific PDE4 inhibitor, making it a potential drug target. This study allows for the analysis of the binding interaction between PDE4B2 and BC58. A deeper understanding of PDE inhibitor activity will aid pharmaceutical progress in the production of highly specific PDE inhibitors, thus permitting development of a broader range of PDE inhibitors with reduced mammalian pharmacological side effects. Such inhibitors would have the potential to treat certain cancers as well as HIV.

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