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Synthesis and Biological Study of Adenylyl Cyclase Inhibitors

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ABSTRACT

Adenylyl cyclase (AC) is a critical family of enzymes which modulates the dynamic cellular level of cAMP, cyclic adenosine monophosphate. The study of cAMP showed that it is indispensable for the signal transduction cascades during many physiological processes, such as immune responses and metabolism which highly relate to cancers. Previous studies of AC inhibitors have been limited due to a lack of isoform-selective small molecule modulators. Selectivity of the molecules is imperative to the activation of only the desired AC inhibitor. The design of the described project was to test the structure activity relationship (SAR) by synthesizing a class of AC I inhibitors and then use the results to develop a small molecule with maximum selectivity for therapeutic targeting. Multi-step synthesis featured an epoxide ring-opening reaction followed by the Friedel–Crafts reaction. Compounds were differentiated by changing substituents on the nitrogen atom. The synthetic molecules have been tested via SAR of AC I inhibitor and IC_{50} . Once synthesized, the compounds were tested for their inhibition rate and the results showed that the majority of scaffolds had great SAR rates at 40 μ M and two also had impressive rates as low as 4 μ M. Further investigation with IC_{50} studies is on-going. The results suggest that the current synthetic compounds are potentially great AC I inhibitors and further study will continue which will contribute to cancer research.

KEYWORDS

AC I inhibitor, synthesis, SAR, small molecule, cancer

REFERENCES

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