Synthesis of -carbolines as novel cdk4 inhibitors - lab report example

Science, Chemistry

Synthesis of -carbolines as novel CDK4 inhibitors

The major objective of this investigation report is to understand the intrinsic steps followed in the synthesis of α-carbolines. The failure of the method involving formation of aromatic product followed by reduction of pyridine ring to α-carbolines triggered for the exploration of another method. Intuitively, this other method involves the formation of an amide then cyclizing it to yield α-carbolines even though it is always a poor yield. Despite limited success associated with the process, the reactions involve proved to be better as supported by existing literature.

Introduction

Background

Considering the importance of Cyclin-dependent kinases (CDKs), a set of protein kinases, it is essential to explore its mechanism that makes it relevant for the lab process. The kinases aid in regulating the cell cycles, transcription Mrna processing and differentiation of nerve cells. In the function of these kinases, cyclin is crucial considering that it acts as the regulatory protein which binds the CDKs. Consequently, this means that in the absence of cyclin, less kinase activity takes place because of the absence of cyclin-CDK complexes1.

CDK4, acting as a member of the cyclin-dependent kinase family, functions as an intrinsic catalyutic protein kinase complex for cell cycle G1 phase progression. D type cyclins and CDK inhibitor are important for the functioning of the kinase since they suppress the action of tumour in causing cell proliferation. The kinase works in phosphorylation of the retinoblastoma gene product thereby helping in preventing the occurring mutation of the

genes responsible for the tumuourigenesis of various types of cancer 2. Further, small compouds such as pentacyclic quaternary salt, act as promising factors in the direction for treatment of cancer. The action of the kinase in causing DNA-interchelation can be reduced by β-carboline which usually acts as a non-planner maintaining the activity of CDK4.

Fascaplysin acts as a pentacyclic quaternary salt used as an anti-cancer agent considering its action in suppressing certain leukemia cells in mice. Further, the salt also end up hindering CDK4 leading to arrest of cell cycle in both normal and tumours ncells in the G phase. The hindering process occurs because it binds to theATP pocket of the kinase, resulting to G arrest via a bidentate hydrogen bond donor/acceptor pair.

The chain involving phosphorylation of pRb enables the cell to pass through the G1 checkpoint leading to completion of division cycle because of the associated release of E2F proteins. Consequently, an inhibition on the early stages of the chain is essential for controlling the rate of cell proliferation.

Despite the action of Fascaplysin in preventing cancer, its high toxicity does not allow it to be effective. The high toxicity result from the susceptibility to interchelating with DNA. Consequently, this requires the development of less flexible fascaplysin derivative to reduce the toxicity of the structure3. The new structure, formed by removing some bonds from the rings, is non-linear and had greater flexibility around six bonds. Further, the addition of tetrahydro β-carboline promised as a factor of reducing the rotational freedom. The non-planar nature of this modified structure contributes to the reduced interchellation with DNA.

The research made use of a non-planar α-carbolines having an IC50 of below

30 um. The synthesis of α-carboline started by formation of aromatic product followed by selective reduction of the pyridine ring as described by Vera-Luque et al4. The scheme is as follows:

N

N

+ N

NH

The failure of the above scheme trigger for an alternative route which involved choosing alternative method for selective reduction of the pyridine rings. Consequently, this investigation will explore an alternative method through the help of reacting an indole and acrylonitrile in a high temperature bomb followed by column chromatography purification yielding cyanoindole as the product. In the presence of LiAlH4, the cyanoindole is reduced to amine followed by reacting it with an acid chloride to produce an amide. Cyclizing the amide leads to the production of the required α-carboline ring.

Bibliography

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