Flexible Nucleosides as Potential Ebola Inhibitors

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Abstract

The Ebola pandemic has brought the virus to the forefront of international concern. Ebola’s high capability of evading the body’s immune system is the reason Ebola is extremely virulent. Currently, there is no FDA approved treatment or vaccination for the Ebola virus and with fatality rates fluctuating above 90 percent, a reliable Ebola therapeutic is undeniably necessary. Nucleoside analogues have taken the spotlight as potential antivirals against Ebola; they can function as inhibitors by competing with DNA or RNA, preventing the binding of the natural substrate. Previous studies have shown that inhibiting the enzyme S-adenosylhomocysteine hydrolase (SAHase) has exhibited activity against Ebola. A compound known to inhibit Ebola through SAHase inhibition is the carbocyclic nucleoside 3-deazaNpcA (3-deazaNpcA, Fig. 1). My project’s specific aim is to synthesize a flexible version of 3-deazaNpcA, termed Flex-deazaNpcA, where the adenine base of NpcA is replaced by a 3-deazaadenine separated into its imidazole and pyridine moieties, connected by a carbon-carbon bond. We hypothesize that base flexibility modifications will allow for increased beneficial interactions that the stiff adenine base fails to form, all while maintaining the aromatic and hydrogen bonding characteristics of NpcA. This may lead to an enhanced SAHase binder, and therefore a more effective inhibitor.

Target Compounds

Figure 1: Adenosine, 3-deazaNeplanocin A and targets 1 & 2.

Background

The virus of interest in our project is the Ebola virus. Ebola threatened social panic when first detected in the United States, and although the Ebola threat has subsided, history has shown that a future outbreak is imminent. Thus it would be valuable to find an effective cure prior to thenext outbreak. One nucleoside inhibitor found to show considerable activity is 3-deazaNpcA (Fig. 1).

Neplanocin A, its 3-deaza analogue and other related carbocyclic nucleosides have been shown to exhibit significant broad-spectrum antiviral activity by irreversibly inactivating SAHase (Fig. 2) in various organisms. SAHase catalyzes the reversible hydrolysis of SAH into its two cellular components adenosine & homocysteine (Fig. 3), with the assistance of an enzyme-bound cofactor, NADH. Inhibition of SAHase by nucleoside inhibitors involves depletion of the NADH cofactor, which causes an intracellular accumulation of SAH, thereby elevating the SAH/S-adenosylmethionine (SAM) ratio. This imbalance in the SAH/SAM ratio results in cessation of SAM-dependent methylations, which leads to improper methylated DNA. Many modified nucleosides have proven to be exceptional inhibitors of SAHase, and as a consequence, methyltransferases are also inhibited via this biofeedback mechanism.

Results

To date, 1 has been successfully synthesized and 2 is almost complete. Once in hand, the compounds will be screened for activity.

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References