Review Article *http://www.alliedacademies.org/timely-topics-clinical-vaccine-research/*

Recent advances in process development of antiviral agents targeting the influenza virus: Amantadine-Remantadine-derived pharmaceutical agents.

Krishna SarmaPathy*

Department of Chemistry, IPL Research Center, Lucknow, India

Abstract

This review summarizes our work on the process development for synthesis of amantidine-remantadine. The presented publications have been sorted according to five basic criteria. Influenza is a serious infectious disease, which is life-threatening especially in children, seniors and immunocompromised patients. In addition to vaccination, the development of new anti-influenza agents represents a crucial defense strategy to combat seasonal and pandemic influenza strains. At present most attention is paid to the development of inhibitors of influenza neuraminidase, which has been established as a key drug target for the prophylaxis and treatment of influenza infections. However, the emergence of drug-resistant influenza variants highlights the need of continuously innovative strategies for the development of new drugs with improved antiviral effects, higher safety and increased tolerability.

The M2 proton channel of the Influenza A virus is the target of the anti-influenza drugs amantadine and rimantadine. The effectiveness of these drugs has been dramatically limited by the rapid spread of drug resistant mutations, mainly at sites S31N, V27A and L26F in the pore of the channel. Despite progress in designing inhibitors of V27A and L26F M2, there are currently no drugs targeting these mutated channels in clinical trials. The article traces the evolution of various synthesis approaches and provides a comparison for overall yield efficiency.

Amantadine hydrochloride is an antiviral drug used in prevention and treatment of influenza A infections. It has also been used for alleviating early symptoms of Parkinson's disease. Several methods for the preparation of Amantadine hydrochloride have been reported overall yields ranging from 50% to 52%. In this article, we describe procedure for the synthesis of Amantadine hydrochloride from N-(1-adamantyl)acetamide with an improved yield of 60%. The procedure was also optimized to reduce the use of toxic solvents and reagents, rendering it more environment-friendly. The procedure can be considered as suitable for large-scale production of amantadine hydrochloride.

Keywords: Antivirals, Influenza, Virus, Drugs, Production, Amantadine, Remantadine

Accepted April 25, 2018

Introduction

It is estimated that over 40 million people perished during the 1918 Spanish influenza pandemic, and nearly 35% of the global population was infected with the disease [1]. From Europe to America and even reaching as far as the wilderness of Alaska and remote Pacific islands, this virus was exceptionally widespread during a time when global travel was not very prominent. This pandemic has been regarded as one of the single most devastating infectious disease events in recorded history [1]. It is currently believed that the influenza strain responsible for the 1918 Spanish flu is genetically linked to the H1N1 influenza that emerged in 2009 and threatened another pandemic [1,2]. With the advent of modern vaccinations, the death toll from the flu virus has been substantially lowered, but there still remains the possibility for a recurrent epidemic. Should the virus mutate in such a way that a new variant circulates, there would be little defense against the spread of the disease and a global outbreak would be almost inevitable.

Since its identification in the 1930's, the influenza virus has been extensively studied and characterized, yet many aspects of its mechanism of infection still remain unclear. To date, only four antiviral drugs have been approved by the Food and Drug Administration (FDA) to treat influenza illness (Figure 1). Of those four drugs, two have developed resistance among the most common influenza A strains in circulation and are rarely used today. Although every year new developments in prophylactic vaccinations are made, few options for post-infection treatment are available. For this reason, there is a vast opportunity in this area for continued drug development.

The development of new antiviral drugs is hindered because of the relatively simple structure of the influenza virus (Figure 2) and the fact that few known areas in the viral life cycle can be targeted for inhibition. The two current drug inhibition targets in the influenza virus are the M2 proton channel, which aids in releasing virus particles from an infected host cell, and the neuraminidase (NA) enzyme, which is required for viral recognition and entry into a host cell (Figure 2).

The neuraminidase inhibitors (Figure 1) are currently the only useful FDA-approved treatments for the influenza virus, in that they have not yet acquired resistance within the virus. These