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Azabicyclo-Nonane Pyrimidine Hybrid Synthesis and Antiprotozoal Activity

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Abstract

Protozoan parasites are inhibited by 2,4-diaminopyrimidines and azabicyclo-nonanes. A series of fused hybrids were created and tested *in vitro* against malaria tropica and sleeping sickness pathogens. Compound activities and selectivities were heavily influenced by the substitution pattern of both ring systems as well as the position of the nitrogen atom in the bicycles. The most promising hybrids of 3-azabicyclo-nonane and 2-aminopyrimidine demonstrated submicromolar activity and high selectivity against *P. falciparum* NF54. A hybrid with pyrrolidino substitutions of the 2-azabicyclo-nonane and the pyrimidine moiety showed promising activity against the multiresistant *P. falciparum* K1 strain. A couple of hybrids of 2-azabicyclo-nonanes and 2-pyrimidines showed high activity and selectivity against Trypanosoma brucei rhodesiense.

Keywords: Azabicyclo-nonanes • Hybrids • Plasmodium falciparum • Pyrimidine

Introduction

Malaria and human African trypanosomiasis are both tropical diseases spread by infected insect bites. Plasmodium parasites cause malaria. There were approximately 241 million estimated cases of malaria in 2020, with approximately 627,000 reported deaths. There are five types of human malaria parasites, but Plasmodium falciparum, the deadliest malaria parasite, causes the vast majority of infections. Many Plasmodium falciparum strains have developed resistance to previous generations of drugs. Even resistance to recommended artemisinin-based therapies has become common in recent years across a growing area of Southeast Asia. There is mounting evidence that resistant strains have made their way to Africa. As a result, new compounds with distinct activity against Plasmodium falciparum are still needed. However, the need to ensure current and future pandemic preparedness presents a number of challenges, including equitable vaccine access and a rising trend of vaccine hesitancy at the individual and international levels, which are beyond the scope of this discussion. With this review article, we hope to shed light on current COVID-19 virus variants, in-hand vaccine types, mechanism of action, effectiveness, and safety profile Trypanosoma brucei parasites cause human African trypanosomiasis. The number of reported cases fell below 1000 in 2019 as a result of ongoing control efforts.

However, as history has shown, it may re-emerge, with an estimated 65 million people at risk. Infections caused by T. b. gambiense are chronic, lasting several years without any major signs or symptoms. Infections with T. b. rhodesiense, on the other hand, cause the acute form of the disease, which can last from a few weeks to several months and is fatal if left untreated. Because of the toxicity and complexity of the drugs currently in use, treating this East African sleeping sickness is difficult. Melarsoprol is the only effective treatment for T. b. rhodesiense infections of the central nervous system.

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Literature Review

These are modified versions of viruses from a different genus that are used as vectors. It interacts with immune cells, assisting them in recognising and outwitting the pathogenic virus. When a foreign antigen is injected into the body, the immune cells activate an immune response by producing antibody-producing B cells and T cells that seek out and destroy infected cells. T cells function by examining the storage of proteins expressed on cell surfaces. Because they can recognise the body's own proteins as'self,' when they come across a foreign protein, they initiate an immune response against the cell that is storing it. However, due to the increased risk of side effects, their use is restricted.

One of the most common and long-established vaccines is currently available in two forms: live attenuated and inactivated. The virus's genetic material is destroyed using chemicals, heat, and radiation to create inactivated vaccines. Because these vaccines are weak natural pathogens, the immune system activates a variety of defences, including killer T cells that recognise and destroy infected cells, helper T cells that support antibody production, and antibody-producing B cells that target pathogens. When they are introduced into the body, they elicit weak and short-lived antibody-mediated responses. As a result, they are always given with an adjuvant, and booster doses are frequently required.

Discussion

The COVID-19 pandemic was conceived as a massive threat not only to the general population, but also to a specific subset of the population, those with chronic diseases such as autoimmune conditions, those with ongoing immunosuppression, or those undergoing cancer treatment. Patients who are immunocompromised were not advised to use live attenuated vaccines because the risk of infection was higher in these patients. Similarly, while live vaccines were not recommended for cancer patients, vaccination against COVID-19 was recommended and deemed safe and effective for all cancer patients except those who are currently on anti-B cell therapies; in such patients, an interval of four to six months is advised for vaccination post medication cessation.

The immune response to the BNT162b2 vaccine has been reported to differ after the first dose. In comparison, the elderly had significantly lower

levels of antibodies than younger people who had their first vaccination. According to reports, the older age group had lower neutralising titers. Infants under the age of one are at a higher risk of developing severe COVID-19; therefore, all infants over the age of six months should receive the COVID-19 vaccine. The elderly are also more likely to have adjunct comorbidities, which are a significant risk factor for developing severe COVID-19. Several clinical studies have found that vaccination benefits people with underlying medical conditions just as much as people without underlying medical conditions.

An important note about the rapidly mutating Omicron variant: while the currently available vaccines have reduced neutralising capacity to this VOC, its detection in South Africa, where vaccine coverage is only 7.5%, may indicate that the vaccines are still protective against it. In an area with less vaccine coverage, the variant is more likely to mutate and spread. Multiple preprints published around the world are quickly demonstrating that a two-dose regimen is ineffective against the Omicron variant. A three-dose booster regimen has been shown to be more effective at protecting against and reducing morbid disease in people who have been exposed to this VOC. Several countries began testing various vaccines.

When it comes to autoimmune diseases, specifically multiple sclerosis, vaccination is advocated primarily without treatment discontinuation, owing to the possibility of disease worsening or relapse following therapy discontinuation. Vaccination is recommended for all patients with irritable bowel syndrome (IBS), but live attenuated vaccines are not recommended, and for patients with acute presentations, a gap before vaccination is recommended when the patient is taking a lower dose of corticosteroids [1-5].

Conclusion

The availability of so many vaccines in such a short period of time represents a huge victory for medical science. Within a year of the emergence of SARS-COV2, vaccines were prepared, phase III trials were initiated, and data was available to develop vaccine administration strategies. So far, the efficacy and safety of various COVID vaccines have been encouraging, and they may be a step forward in halting this pandemic. The need to ensure current and future pandemic preparedness presents numerous challenges, including equitable vaccine access and an increasing trend of vaccine hesitancy at the individual and international levels, which are beyond the scope of this discussion.

The next challenge is to increase global vaccine uptake in order to reduce transmission. In this age of globalisation, no country is safe until the entire world population develops mass immunity. Putting in place border control measures can help in the short term, but for long-term protection, it is critical that vaccine uptake is high everywhere in the world, not just in developed countries, as this will support variant emergence and thus reduce vaccine efficacy. Despite mass production of vaccines, current stocks may not be sufficient to meet the demand. Work should be done to help low-income countries become as self-sufficient in vaccine production as possible. Finally, the resources and investment used to produce COVID vaccines, as well as the new vaccine technologies developed, should not be limited to COVID and should be replicated to combat other infectious diseases.

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Conflict of Interest

There are no conflicts of interest by author.

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