

REVIEW

Adenine: an important drug scaffold for the design of antiviral agents



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Abstract Adenine derivatives, in particular the scaffold bearing the acyclic nucleoside phosphonates (ANPS), possess significant antiviral and cytostatic activity. Till now, several effective adenine derivatives have been marketed for the treatment of HIV, HBV, CMV and other virus-infected diseases. These compounds are represented by tenofovir (PMPA), a medicine for both HIV and HBV, and adefovir as an anti-HBV agent. More than this, other analogs, such as GS9148, GS9131, and GS7340, are also well-known anti-viral agents that have been progressed to the clinical studies for their excellent activity. In general, the structures of these compounds include an adenine nucleobase linked to a phosphonate side chain. Considerable structural modifications on the scaffold itself and the peripheral sections were made. The structure-activity relationships (SARs) of this skeleton will provide valuable clues to identify more effective adenine derivatives as antiviral drugs. Here, we systematically summarized the SARs of the adenine derivatives, and gave important information for further optimizing this template.

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1. Introduction

Human immunodeficiency virus (HIV), Rauscher murine sarcoma virus (R-MuLV), herpes simplex virus (HSV), cytomegalovirus (CMV), feline immunodeficiency virus (FIV), Epstein-Barr virus (EBV), hepatitis B virus (HBV) and hepatitis C virus (HCV) are highly contagious viruses endangering human health. Being the most important antiviral agents, acyclic nucleoside phosphonates (ANPS) play a significant role in the treatment of virus-infected diseases. In particular, adenine derivatives bearing the adenine nucleuses possess excellent antiviral activity against most of the double-stranded DNA viruses, such as the herpes group viruses and the orthopoxviruses^{1,2}. Previous SARs explorations proved that the concept of using the ANPs as chain terminators for antiviral was remarkably effective (**1**, Fig. 1)^{3,4}. A large number of adenine derivatives have been discovered as potential antiviral agents motivated by this hypothesis. For example, the novel agent 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA, adefovir, **2**, Fig. 1) was approved for the treatment of hepatitis B virus (HBV) infections by the US FDA in 2002⁵⁻⁷, while the (*R*)-9-[(phosphonomethoxy)propyl]adenine ((*R*)-PMPA, tenofovir, **3**, Fig. 1) was launched in the US market as a prodrug (tenofovir disoproxil fumarate, TDF) for the treatment of HIV infections in 2001 and for the treatment of HBV in 2008, respectively⁸. Besides, several adenine derivatives also have progressed to clinical exploration, such as GS9148⁹⁻¹¹ (**4**, Fig. 1), GS9131¹² (**5**, Fig. 1), and GS7340^{13,14} (**6**, Fig. 1). Undoubtedly, adenine derivatives are the most valuable inhibitors for the development of antiviral agents.

Through a key phosphate-carbon-oxygen bond, the adenine nucleobase of this template is attached to a phosphonate group, making these compounds more stable than those that contain the phosphate-oxygen-carbon bond of a phosphate group. Therefore, compounds containing the phosphate-carbon-oxygen linker achieve higher levels of the active metabolites in the cells. Moreover, they also possess a broad activity spectrum that also includes RNA viruses and retroviruses. However, owing to the

poor oral bioavailability caused by the negatively charged phosphonate moiety, the therapeutic use of these nucleoside phosphonates was limited¹⁵. In order to obtain the neutral and membrane-permeable prodrugs, great attention has been paid to the optimization of this template, and several highly potent virus inhibitors have been successfully produced. A thorough analysis of the SARs of this scaffold will provide useful clues for further structural optimization, which is achieved in this review.

2. Adenine nucleus

Adenine analogs **7** and **8** (Fig. 2) bearing a chlorine atom at the C-2 position of the adenine nucleus were synthesized by several groups¹⁶⁻¹⁹. Surprisingly, only by introducing this atom, the newly obtained compounds did not possess any anti-virus activity at all. Instead, they were effective as chemotherapeutic agents for the treatment of refractory chronic leukemia and hairy cell leukemia. The methylsulfanyl analogs (**9-11**, Fig. 2) produced similar results. These compounds exhibited a weaker agonistic activity toward the P2Y1 receptor²⁰.

The diamino-substituted (C-2 and C-6 positions) analogs **12** and **13** (Fig. 3) containing a trifluoromethyl group at the side chain were originally synthesized by Dvořáková in 1994²¹. Neither exhibited desired antiviral properties. Also, the addition of a fluorine atom to the C-2 position (analog **14**) (Fig. 3) reduced the antiviral activity against both the RNA viruses and the DNA viruses. The similar trend of decreasing antiviral activity was observed in the case of the tenofovir analogs, where the compound **15** (Fig. 3) completely lacked antiretroviral properties. Whereas the bis(amidate) prodrug **16** (Fig. 3) was moderately active against HIV-1 (EC₅₀ = 5.51 μmol/L), probably due to its improved bioavailability²². All these suggested that modifying the C-2 position of the adenine nucleus was utterly ineffective for improving the antiviral potency.

Analog **17a-e** (Fig. 4) and **18-21** (Fig. 4) bearing a fluorine atom at the C-6 position of the nucleus bases were synthesized as antiviral agents by several companies^{23,24}, but their activity was

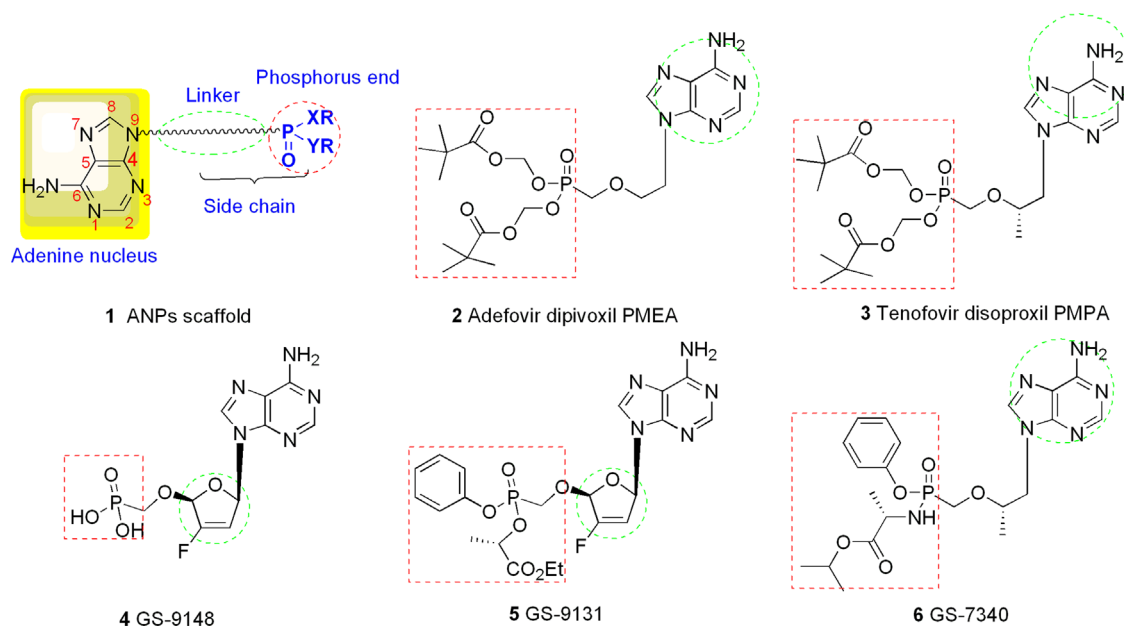


Figure 1 Structures of the novel adenine derivatives as antiviral agents.

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