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Structure–activity Relationship Studies of Natural Product Derivatives in Antiviral Drug Discovery

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Introduction

Viral infections remain one of the most significant threats to global health, ranging from acute illnesses such as influenza and COVID-19 to chronic diseases like hepatitis and HIV. The rapid mutation rates of viruses and their ability to develop resistance to existing therapies highlight the urgent need for new antiviral agents with improved efficacy and safety profiles. Natural products have long served as a rich reservoir for drug discovery, providing diverse chemical scaffolds with inherent biological activity. From the early discovery of nucleoside analogs inspired by marine sponges to more recent identification of flavonoids, alkaloids, and terpenoids with antiviral properties, natural compounds have continuously shaped antiviral pharmacology. However, translating natural products into clinically viable drugs requires systematic optimization. This is where Structure–Activity Relationship (SAR) studies play a critical role, enabling researchers to dissect the relationship between chemical modifications and biological outcomes, thereby guiding the rational design of potent natural product derivatives for antiviral therapy [1].

Description

SAR studies focus on understanding how specific functional groups, stereochemistry, or molecular frameworks influence the activity, selectivity, and pharmacokinetics of natural product derivatives. For antiviral drug discovery, this often involves iterative chemical modifications to improve viral target binding while reducing cytotoxicity to host cells. For example, flavonoids such as quercetin and luteolin exhibit broad-spectrum antiviral activity, but SAR studies have shown that hydroxyl group positioning on the flavone backbone critically influences their potency against viral proteases and polymerases. Similarly, alkaloids such as lycorine and berberine have been optimized through SAR to enhance selectivity against viral replication enzymes. By systematically substituting functional groups, modifying ring structures, or introducing halogen atoms, chemists can fine-tune natural product derivatives to maximize antiviral efficacy [2].

One notable case of SAR-guided antiviral development is the optimization of nucleoside analogs derived from natural products. These compounds mimic natural nucleosides and are incorporated into viral nucleic acids, thereby inhibiting replication. The marine sponge–derived arabinonucleosides led to the synthesis of cytarabine and vidarabine, which became pioneering antiviral and anticancer agents. SAR studies revealed that modifications to the sugar moiety and base substituents drastically influenced their stability, incorporation efficiency, and toxicity profiles. More recently, SAR-driven optimization of nucleoside analogs has yielded drugs like remdesivir, used against SARS-CoV-2, where alterations in the nucleobase and ribose structure were essential for broad-spectrum antiviral activity. These cases highlight how SAR transforms natural nucleoside leads into clinically relevant antivirals by guiding modifications that balance potency with metabolic stability [3].

Beyond nucleosides, terpenoids and polyphenols have also been extensively studied for antiviral activity, with SAR insights guiding their therapeutic potential. Triterpenoids such as glycyrrhizin, derived from licorice root, exhibit activity against hepatitis viruses and HIV. SAR investigations demonstrated that sulfation and glycosylation patterns significantly enhance binding affinity to viral proteins while reducing host toxicity. Similarly, derivatives of curcumin and resveratrol have been modified to improve solubility and metabolic stability, with SAR studies identifying key aromatic substitutions that increase antiviral potency. Terpenoid-based derivatives have also been developed into inhibitors of viral entry by altering hydrophobic side chains, thereby enhancing interactions with viral envelope proteins [4].

Additionally, advancements in structural virology, including cryo-electron microscopy and X-ray crystallography, allow visualization of viral protein–ligand interactions at atomic resolution, guiding the rational design of derivatives. When combined with traditional SAR experimentation, these computational methods reduce trial-and-error in natural product optimization, thereby accelerating the transition from lead identification to preclinical development [5].

Conclusion

Structure–activity relationship studies serve as an essential framework for transforming natural product derivatives into potent antiviral agents. By elucidating how chemical modifications influence viral inhibition and host interactions, SAR studies bridge the gap between natural chemical diversity and targeted drug design. From nucleoside analog optimization to flavonoid, alkaloid, and terpenoid derivatives, SAR-guided approaches have consistently yielded promising antiviral candidates. The integration of modern computational tools, high-throughput screening, and structural biology has further enhanced the predictive power of SAR, enabling more efficient discovery pipelines. Despite challenges such as drug resistance, metabolic instability, and the complexity of natural product synthesis, continued exploration of natural product derivatives guided by SAR principles holds immense promise. As the global community faces emerging viral threats, SAR-driven optimization of natural compounds may be instrumental in delivering the next generation of safe, effective and broad-spectrum antiviral therapies.

Acknowledgement

None.

Conflict of Interest

None.

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