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Bioisosteres and Scaffold Hopping: Strategic Tools in Drug Design

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Editorial

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INTRODUCTION

Drug discovery is a complex process that seeks to identify molecules with optimal efficacy, safety, and pharmacokinetic properties. Among the strategies used by medicinal chemists, bioisosterism and scaffold hopping play central roles in optimizing drug candidates. These approaches involve modifying molecular structures while preserving or enhancing biological activity. By carefully redesigning molecules through substitutions or core replacements, researchers can improve potency, reduce toxicity, overcome resistance, and generate intellectual property advantages. Together, bioisosteres and scaffold hopping have become essential in modern pharmaceutical research, enabling the design of novel therapeutics across diverse disease areas [1].

Discussion

Bioisosteres are atoms, groups, or molecules that can replace one another within a compound while maintaining similar biological or physicochemical properties. The concept, introduced in the early 20th century, has since become a cornerstone of medicinal chemistry. Bioisosteric replacements can be classified as classical (involving simple substitutions like –OH for $–NH_2$ or –H for –F) or non-classical (more complex structural replacements that mimic size, shape, or electronic properties) [2].

Bioisosterism serves multiple purposes in drug design. It can enhance potency and selectivity by improving interactions with the biological target. It can optimize pharmacokinetics, such as solubility or metabolic stability, ensuring that drugs are absorbed and distributed efficiently. Additionally, bioisosteric substitutions can reduce toxicity by eliminating reactive groups or preventing harmful metabolism. For example, replacing a carboxylic acid group with a tetrazole ring in antihypertensive drugs improves metabolic stability and binding affinity while maintaining activity [3].

Scaffold hopping, in contrast, involves replacing the core structure—or "scaffold"—of a molecule while retaining its biological activity. The scaffold defines the overall 3D shape of a drug, and modifying it allows chemists to explore new chemical space. Scaffold hopping is often used to overcome limitations such as poor solubility, off-target effects, or intellectual property restrictions [4].

There are several approaches to scaffold hopping. Topology-based hopping involves retaining key functional groups while altering the connectivity of atoms in the core. 3D pharmacophore-based hopping uses computational models to preserve essential molecular interactions while exploring alternative scaffolds. Scaffold hopping can also address drug resistance, particularly in infectious diseases and cancer, by generating new compounds that evade resistance mechanisms while maintaining efficacy [5].

The synergy between bioisosterism and scaffold hopping lies in their complementary goals. While bioisosteres often fine-tune specific functional groups, scaffold hopping allows broader structural changes. Together, they empower medicinal chemists to redesign molecules with improved pharmacological profiles. Notable successes include HIV protease inhibitors and kinase inhibitors, where scaffold modifications and bioisosteric substitutions have led to drugs with enhanced potency and reduced side effects.

Despite their utility, these strategies require careful application. Inappropriate substitutions may reduce activity or create unexpected toxicity. Computational modeling, structure-activity relationship (SAR) studies, and experimental validation are therefore critical to ensure success.

Conclusion

Bioisosteres and scaffold hopping are indispensable strategies in drug design, enabling chemists to refine and innovate therapeutic molecules. Bioisosteres provide subtle modifications that optimize functional groups, while scaffold hopping explores entirely new molecular backbones. Both approaches contribute to improved efficacy, safety, and resistance management, while also fostering innovation in intellectual property. As computational tools and structural biology continue to advance, the strategic use of bioisosterism and scaffold hopping will remain vital in the discovery of next-generation medicines, bridging creativity with scientific precision.

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