Content available at: https://www.ipinnovative.com/open-access-journals

Current Trends in Pharmacy and Pharmaceutical Chemistry

Journal homepage: https://www.ctppc.org/

Review Article

The role of bioisosterism in modern drug design: Current applications and challenges

Nancy Sharma[1], Anand Singh Chauhan[1]*, Vinay Jain[1]

[1]ShriRam College of Pharmacy Banmore, Gwalior, Madhya Pradesh, India

Abstract

Bioisosterism is a crucial strategy in modern drug design that involves the replacement of one functional group with another possessing similar physical and chemical properties to enhance drug efficacy, reduce toxicity, and improve pharmacokinetic properties. This approach has been instrumental in the development of novel drugs with better target selectivity and improved pharmacodynamics. The present review highlights the fundamental principles of bioisosterism, its applications in medicinal chemistry, and its role in addressing drug design challenges. Additionally, we discuss recent advancements, computational approaches, and future perspectives of bioisosterism in pharmaceutical research.

Keywords: Bioisosterism, Drug design, Pharmacokinetics, Pharmacodynamics, Medicinal chemistry, Computational chemistry.

Received: 11-03-2025; **Accepted:** 02-04-2025; **Available Online**: 05-05-2025

1. Introduction

Drug discovery and development involve a complex and iterative process that requires the optimization of lead compounds to enhance efficacy, reduce side effects, and improve overall therapeutic outcomes. One of the most effective strategies used in medicinal chemistry to achieve these goals is bioisosterism, which involves the systematic replacement of atoms, functional groups, or molecular fragments with structurally similar substitutes to modify biological activity.[1] Bioisosterism allows for the fine-tuning of pharmacokinetic and pharmacodynamic properties while maintaining or even enhancing the desired therapeutic effects of a drug candidate.[2] The concept of bioisosterism dates back to the early 20th century when medicinal chemists observed that certain functional groups could be interchanged without significantly altering biological activity. The term bioisostere was first introduced by Friedman in 1951 to describe functional groups or molecular entities that exhibit similar physicochemical properties and biological effects.[3] Since then, the field has evolved considerably, expanding from simple classical bioisosteric replacements to more sophisticated non-classical bioisosteres that mimic biological functions rather than structural features.[4] One of the primary motivations for using bioisosterism in drug design is to overcome limitations associated with existing drugs. Many lead compounds suffer from poor solubility, rapid metabolism, low bioavailability, or undesired toxicity. By replacing problematic functional groups with bioisosteric alternatives, medicinal chemists can address these challenges without compromising drug activity. For instance, the substitution of carboxyl (-COOH) groups with tetrazole (-C(NH)(NH)N) in angiotensin receptor blockers (ARBs) improves metabolic stability and enhances binding affinity to the target enzyme.[5]

Bioisosteric modifications play a crucial role in different aspects of drug design, including:

1. Enhancing Target Affinity and Selectivity: Bioisosteric replacements can be used to improve the binding interactions of a drug with its target protein, thereby increasing potency and reducing off-target effects. For example, replacing a phenyl ring with a bioisosteric

*Corresponding author: Anand Singh Chauhan
Email: chouhananand61@gmail.com

http://doi.org/ 10.18231/j.ctppc.2025.002

heterocycle like pyridine can modulate electronic properties and hydrogen bonding interactions.

2. Improving Pharmacokinetics: Many drug candidates fail in clinical trials due to poor pharmacokinetic properties. By introducing bioisosteric changes, the solubility, permeability, and metabolic stability of a drug can be optimized to ensure better absorption and prolonged half-life.
3. Reducing Toxicity: Certain functional groups are associated with toxicity risks. For example, replacing an aniline (-NH2) moiety with a pyridyl (-C5H4N) group can mitigate hepatotoxicity while retaining drug activity.[6]
4. Overcoming Drug Resistance: Microbial and cancer drug resistance is a significant challenge in modern medicine. Bioisosteric modifications have been employed to design new antibiotics and anticancer agents that evade resistance mechanisms.

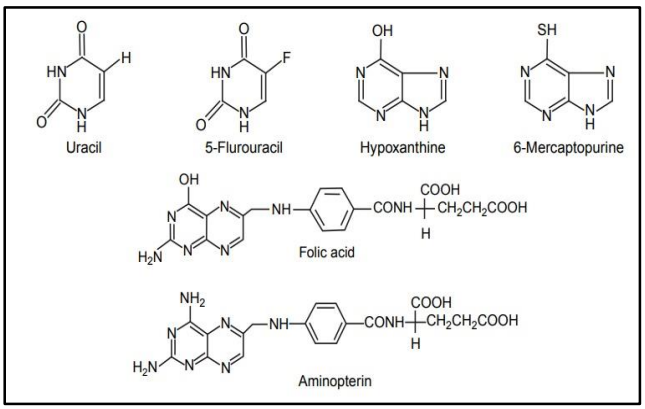

Figure 1: Drug design bioisosterism in dovelopment classification

The classification of bioisosteres has been refined over the years, and today they are broadly divided into classical and non-classical bioisosteres. Classical bioisosteres involve groups that have nearly identical steric and electronic properties, such as the replacement of hydrogen (H) with deuterium (D) to alter metabolic stability. In contrast, non-classical bioisosteres do not necessarily share structural similarity but retain functional equivalence in biological systems. Examples include replacing amide (-CONH-) groups with sulfonamide (-SO2NH-) moieties to alter metabolic properties while maintaining activity.[7] With the advent of computational drug design and artificial intelligence, bioisosterism has become even more precise. Modern computational tools, such as molecular docking, QSAR modeling, and machine learning algorithms, allow researchers to predict and evaluate the impact of bioisosteric replacements before synthesis.[8] This integration of computational methods has accelerated drug discovery and reduced the cost associated with traditional trial-and-error approaches.[9] In conclusion, bioisosterism is a fundamental strategy in medicinal chemistry that continues to play a pivotal role in modern drug design. By replacing problematic functional groups with optimized bioisosteres, researchers can enhance drug efficacy, minimize toxicity, and overcome pharmacokinetic challenges. The continuous advancement in computational and synthetic methodologies will further expand the application of bioisosteric principles in developing next-generation therapeutics.[10]

2. Concept and Types of Bioisosterism

Bioisosteres are classified into two main categories: classical and non-classical bioisosteres.

2.1. Classical bioisosteres

Classical bioisosteres involve the substitution of atoms or groups with similar electronic and steric properties.[11] Examples include:

1. Hydrogen (H) replacement with deuterium (D) to influence metabolic stability.
2. Hydroxyl (-OH) replaced by thiol (-SH) or amine (-NH2) for altered hydrogen bonding properties.
3. Carboxyl (-COOH) substituted with tetrazole (-C(NH)(NH)N) to enhance stability.[12]

2.2. Non-classical bioisosteres

Non-classical bioisosteres do not follow the strict steric and electronic similarities of classical bioisosteres but mimic the biological function of the original group. Examples include:

1. Phenyl ring replacements with bioisosteric heterocycles like thiophene or pyridine.[13]
2. Sulfonamide (-SO2NH2) substituting for carboxyl (-COOH) in some antihypertensive drugs.
3. Isosteric replacement of oxygen with sulfur or nitrogen to alter metabolic stability.[14]

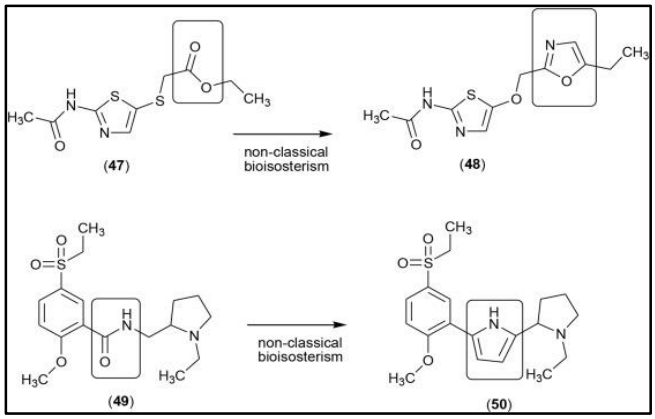

Figure 2: Classical and non-classical bioisosteres

2.3. Classical and non-classical bioisosterism

Bioisosterism is a fundamental strategy in drug design that involves replacing a functional group in a molecule with another that maintains similar biological properties while potentially improving efficacy, reducing toxicity, or enhancing pharmacokinetic characteristics. Bioisosteres are

classified into classical and non-classical categories, as illustrated **Figure 2**.

2.4. Classical bioisosteres

Classical bioisosteres are structurally and electronically similar groups that adhere to the original bioisosteric principles established by Grimm and Erlenmeyer. These groups typically have similar valency, size, and electronic configurations, allowing them to replace each other without significantly altering the molecular function Examples include:

1. Hydrogen (H) vs. Fluorine (F) – The small size of fluorine makes it a suitable hydrogen bioisostere, often used to enhance metabolic stability.
2. Hydroxyl (-OH) vs. Amine (-NH2) – Both groups form hydrogen bonds, allowing interconversion in biologically active molecules.
3. Carboxyl (-COOH) vs. Tetrazole (-C(N3)N=NH) – Tetrazoles are more lipophilic and improve membrane permeability while retaining acidic properties, as seen in angiotensin receptor blockers (ARBs) like losartan.

2.5. Non-classical bioisosteres

Non-classical bioisosteres do not strictly follow classical valency rules but retain similar pharmacological activity through electronic and steric similarity. These substitutions often lead to significant improvements in drug properties, including receptor binding, selectivity, and metabolic stability Common examples include:

1. Phenyl (-C6H5) vs. Pyridine (-C5H4N) – Pyridine introduces nitrogen, modulating electron density and solubility while maintaining hydrophobicity.
2. Sulfonamide (-SO2NH2) vs. Urea (-NHCONH2) – Used to modify polarity and reduce enzymatic degradation in antibiotics and diuretics.
3. Ketone (-CO-) vs. Sulfone (-SO2-) – This replacement improves metabolic stability and alters binding interactions in enzyme inhibitors.

3. Current Applications of Bioisosterism in Drug Design

3.1. Improving drug efficacy and potency

Fluorine substitution is widely used to enhance metabolic stability and receptor binding affinity. A notable example is fluorinated steroids, which exhibit higher potency due to increased receptor selectivity.[14,15]

Statins, such as atorvastatin, utilize bioisosteric modifications to optimize HMG-CoA reductase inhibition and improve cholesterol-lowering effects.

3.2. Enhancing pharmacokinetics and metabolic stability

Bioisosteric replacement of hydrogen with deuterium has led to the development of deuterated drugs such as deutetrabenazine, which exhibits improved pharmacokinetics and a longer half-life.[16] The replacement of carboxylic acid with tetrazole rings in angiotensin receptor blockers (ARBs) like losartan improves bioavailability and stability.

3.3. Reducing toxicity and off-target effects

Bioisosteric modifications have been applied in NSAIDs (non-steroidal anti-inflammatory drugs) to reduce gastrointestinal side effects. For example, replacing a carboxyl group with a bioisosteric amide reduces irritation while maintaining anti-inflammatory activity.[17]

Aspirin derivatives with modified ester groups exhibit improved safety profiles by reducing hydrolysis in the gastrointestinal tract.

3.4. Drug resistance management in antimicrobial and anticancer agents

In antibiotic design, bioisosteric modifications are used to combat resistance by altering target binding without affecting efficacy. Fluoroquinolones, for instance, use fluorine substitution to enhance bacterial DNA gyrase inhibition.[14]

In oncology, modifications in kinase inhibitors, such as replacing purine rings with bioisosteric heterocycles, help evade resistance mechanisms while retaining efficacy.[15]

3.5. Challenges in bioisosteric drug design

Despite its advantages, bioisosterism faces several challenges:

1. Complexity in Predicting Biological Activity – While some bioisosteric replacements improve drug properties, others may lead to unexpected interactions or loss of function.
2. Metabolic and Toxicological Issues – Some modifications alter metabolic pathways, leading to undesirable metabolites or toxicity.[16]
3. Regulatory and Manufacturing Constraints – New bioisosteric drug candidates must undergo extensive testing to ensure safety and efficacy, increasing development costs and time.

4. Future Perspectives

Advancements in computational chemistry and AI-driven drug design are expected to enhance the predictive power of bioisosteric replacements. Additionally, structure-based drug design (SBDD) and quantum mechanics simulations are being integrated to refine molecular modifications for optimized pharmacological profiles.[17-20]

5. Conclusion

Bioisosterism remains a powerful strategy in modern drug design, contributing to improved efficacy, safety, and pharmacokinetic properties. However, challenges such as predicting biological outcomes and ensuring regulatory compliance require continuous research and technological

innovations. With the integration of computational models and advanced screening methods, bioisosteric modifications will continue to shape the future of drug discovery.

6. Source of Funding

None.

7. Conflict of Interest

None.

References

1. Ballatore C, Huryn DM, Smith AB. Carboxylic acid (bio)isosteres in drug design. *Chem Med Chem*. 2013;8(3):385–95.
2. Shah P, Westwell AD. The role of fluorine in medicinal chemistry. *J Med Chem*. 2007;22(5):527-40.
3. Chakraborti AK, Garg SK, Kumar R, Motiwala HF, Jadhavar PS. Progress in COX-2 inhibitors: a journey so far. *Curr Med Chem*. 2010;17(15):1563–93.
4. Dasgupta N, Mathew DE, Chaudhury A. Bioisosteric modifications of tetrazole in drug discovery. *Future Med Chem.* 2017;9(4):357–69.
5. Hughes JD, Blagg J, Price DA, Bailey S, DeCrescenzo GA, Devraj RV, et al. Physiochemical drug properties associated with in vivo toxicological outcomes. *Bioorg Med Chem Lett*. 2008;18(17):4872–5.
6. Lovering F, Bikker J, Humblet C. Escape from flatland: increasing saturation as an approach to improving clinical success. *J Med Chem*. 2009;52(21):6752–6. doi: 10.1021/jm901241e.
7. Nayak S, Nalabothu P, Sandiford S, Bhogadi V, Adogwa A. Evaluation of wound healing activity of Allamanda cathartica L. and Laurus nobilis L. extracts on rats. *BMC Complement Altern Med*. 2006;6:12.
8. Okuda T, Yoshida T, Hatano T. Hydrolyzable tannins and related polyphenols. *Prog Chem Org Nat Prod*. 1995;66:1–117.
9. Zhang J, Yang PL, Gray NS. Targeting cancer with small molecule kinase inhibitors. *Nat Rev Cancer*. 2009;9(1):28–39.
10. García-Lafuente A, Guillamón E, Villares A, Rostagno MA, Martínez JA. Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease. *Inflamm Res*. 2009;58(9):537–52.
11. Kumazawa S, Taniguchi M, Suzuki Y, Shimura M, Kwon MS, Nakayama T. Antioxidant activity of polyphenols in carob pods. *J Agric Food Chem*. 2002;50(2):373–7.
12. Borrelli F, Izzo AA. The plant kingdom as a source of anti-ulcer remedies. *Phytother Res*. 2000;14(8):581–91.
13. Lobo F, Graul A. Bioisosterism and scaffold hopping in medicinal chemistry. *Drug Discov Today*. 2013;18
14. Singh M, Pandey R, Jain R. Recent advances in the development of bioisosteric analogues in drug design. *Eur J Med Chem*. 2021;223:113652. https://doi.org/10.1016/j.ejmech.2021.113652
15. Patani GA, LaVoie EJ. Bioisosterism: A rational approach in drug design. *Chem Rev*. 1996;96(8):3147–76.
16. Hernández-Rodríguez M, Trujillo-Ferrara JG, Medina-Franco JL. Bioisosterism as a strategy in drug design: Focus on epigenetic targets. *Drug Discov Today*. 2017;22(10):1472–81. https://doi.org/10.1016/j.drudis.2017.06.002
17. Hansch C, Leo A. Exploring QSAR: Fundamentals and applications in chemistry and biology. Washington, DC: American Chemical Society; 1995.
18. Graul A, Lobo, F. Bioisosteric replacements and scaffold hopping in modern drug design. *Nat Rev Drug Dis*. 2006;5(5):429–30. https://doi.org/10.1038/nrd2032
19. Lovering F, Bikker J, Humblet C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J Med Chem*. 2009;52(21):6752-6.
20. Brown DG, Boström J. Where do recent small molecule clinical development candidates come from? *J Med Chem*. 2018;61(21):9442–68.

Cite this article Sharma N, Chauhan AS, Jain V. **T**he role of bioisosterism in modern drug design: Current applications and challenges**.** *Curr Trends Pharm Pharm Chem*. 2025;7(1):6-9.