Opinion
Volume 15:03, 2025

Medicinal Chemistry

ISSN: 2161-0444 Open Access

Fragment-based Drug Discovery: Emerging Strategies and Applications

Nourhan Sami*

Department of Pharmaceutics, Minia University, Minia, Egypt

Introduction

Fragment-Based Drug Discovery (FBDD) has emerged as a transformative strategy in medicinal chemistry, offering a powerful and efficient alternative to traditional High-Throughput Screening (HTS) methods. Unlike conventional approaches that begin with large, complex molecules, FBDD starts with small, low-molecular-weight compounds known as fragments that exhibit weak binding to a biological target. These fragments serve as the foundational building blocks for designing potent and selective lead compounds through iterative optimization. Over the past two decades, FBDD has contributed to the development of multiple clinically approved drugs and has proven particularly valuable in addressing difficult-to-drug targets. Its precision, cost-effectiveness and adaptability to modern screening and computational platforms make it a compelling choice for early-phase drug discovery, particularly in oncology, neurodegeneration and infectious diseases [1].

Description

The fundamental principle of FBDD lies in the identification of fragment molecules, typically with molecular weights less than 300 Da, which bind to a protein's active or allosteric site with millimolar affinity. Despite their low binding strength, these fragments often display high ligand efficiency a measure of binding energy per atom which makes them excellent starting points for further development. After identifying promising fragments using biophysical techniques such as NMR spectroscopy, X-ray crystallography and Surface Plasmon Resonance (SPR), medicinal chemists utilize fragment-growing, merging, or linking strategies to enhance binding affinity and selectivity. One of the critical strengths of FBDD is its compatibility with structurally guided design. Structural information obtained through X-ray crystallography allows researchers to visualize fragment binding modes with atomic precision. This insight drives rational optimization, where fragments are chemically elaborated into larger molecules with improved pharmacological profiles. Notably, this approach has led to the development of successful drugs such as Vemurafenib (a BRAF inhibitor) and Venetoclax (a BCL-2 inhibitor), both of which originated from fragment-based efforts [2].

Recent innovations have expanded the capabilities of FBDD through integration with artificial intelligence and machine learning. These technologies enable the rapid screening and ranking of fragment libraries, predict binding affinities and guide synthetic decisions. Additionally, fragment libraries are increasingly being enriched with 3D-shaped, structurally diverse and rule-of-three-compliant fragments to explore broader chemical space and improve hit quality. Fragment-based strategies are particularly suited for targeting Protein-Protein Interactions (PPIs), which are often considered intractable by traditional drug discovery methods due to their large, flat binding surfaces. Fragments can identify shallow pockets or hotspots within these interfaces and be evolved into larger inhibitors capable of disrupting PPIs with high specificity. This opens avenues for developing new therapeutics in cancer, immunology and viral infections. Applications of FBDD are also expanding into covalent fragment screening, where electrophilic fragments form covalent bonds with nucleophilic residues (e.g., cysteine, serine) within the target protein. This irreversible mode of inhibition is gaining traction for designing targeted covalent inhibitors with long-lasting therapeutic effects, particularly against enzymes and mutant oncogenic kinases [3].

Despite its advantages, FBDD faces several challenges that must be carefully addressed. One key limitation is the requirement for highly sensitive biophysical detection methods, as fragment binding is often weak and transient. Additionally, the approach depends heavily on access to high-resolution structural data to accurately map fragment–target interactions. Fragment-derived leads typically need significant optimization to improve essential drug-like properties such as solubility, metabolic stability and membrane permeability. Synthetic elaboration of fragments can introduce complexity and ensuring that growing or linking strategies maintain target affinity while avoiding off-target effects requires considerable medicinal chemistry effort. Nevertheless, with advances in structural biology, machine learning and computational modeling, researchers are increasingly able to overcome these barriers, resulting in potent, selective and clinically viable compounds [4-5].

Conclusion

Fragment-Based Drug Discovery represents a paradigm shift in early-stage drug design, characterized by efficiency, rational design and adaptability. By leveraging small, high-efficiency molecular fragments and advancing them through structure-guided approaches, FBDD has led to the successful development of several breakthrough therapeutics. With ongoing advancements in screening technologies, computational modeling and fragment library design, the approach is poised to further accelerate the identification of novel drugs, especially against previously "undruggable" targets. As pharmaceutical research increasingly moves toward precision and personalization, FBDD offers a robust framework for innovation in medicinal chemistry, capable of addressing some of the most complex therapeutic challenges of the 21st century.

Acknowledgment

None.

Conflict of Interest

None.

***Address for Correspondence:** Nourhan Sami, Department of Pharmaceutics, Minia University, Minia, Egypt, E-mail: sami.nour@minia.eg*

Received: 02 June, 2025, Manuscript No. mccr-25-171785; **Editor assigned:** 04 June, 2025, PreQC No. P-171785; **Reviewed:** 16 June, 2025, QC No. Q-171785; **Revised:** 23 June, 2025, Manuscript No. R-171785; **Published:** 30 June, 2025, DOI: 10.37421/2161-0444.2025.15.778

References

1. Hecker, Scott J., K. Raja Reddy, Olga Lomovskaya and David C. Griffith, et al. "Discovery of cyclic boronic acid QPX7728, an ultrabroad-spectrum inhibitor of serine and metallo-β-lactamases." *J Med Chem* 63 (2020): 7491-7507.

2. Chen, Allie Y., Caitlyn A. Thomas, Pei W and Kundi Yang, et al. "Iminodiacetic Acid as a Novel Metal-Binding Pharmacophore for New Delhi Metallo-β-lactamase Inhibitor Development." *Chem Med Chem* 15 (2020): 1272-1282.

3. Lomovskaya, Olga, Ruslan Tsivkovski and Dongxu Sun. "QPX7728, an ultra-broad-spectrum B-lactamase inhibitor for intravenous and oral therapy: Overview of biochemical and microbiological characteristics." *Front Microbioly* 12 (2021): 697180.

4. Tsivkovski, Ruslan, Maxim Totrov, Olga Lomovskaya and Raja Reddy, et al. "Biochemical characterization of QPX7728, a new ultrabroad-spectrum beta-lactamase inhibitor of serine and metallo-beta-lactamases." *Antimicrob Agents Chemother* 64 (2020): 10-1128.

5. Sefton, Armine M. "Mechanisms of antimicrobial resistance: Their clinical relevance in the new millennium." *Drugs* 62 (2002): 557-566.

How to cite this article: Sami, Nourhan. "Fragment-based Drug Discovery: Emerging Strategies and Applications." *Med Chem* 15 (2025): 778.