RESEARCH PAPER

Amino Derived Drug Precursors for Drug Developments Using Biocatalyst

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Abstract:
Amino acid-derived drug precursors are essential intermediates in pharmaceutical synthesis because they provide structurally diverse and stereochemically defined building blocks for the development of modern therapeutics. Biocatalysis has emerged as a sustainable alternative to conventional chemical synthesis by enabling highly selective and environmentally friendly transformations. This review evaluates the role of biocatalysts in the synthesis of amino acid-derived drug precursors and highlights recent advances, pharmaceutical applications, industrial translation, emerging technologies, and future perspectives. A narrative review was conducted by critically analyzing recent literature on amino acid-derived drug precursors, enzyme classes, biocatalytic strategies, pharmaceutical applications, industrial process development, and emerging technologies. Relevant studies were synthesized to provide a comprehensive overview of current progress and future opportunities. Biocatalysts, including transaminases, dehydrogenases, imine reductases, hydrolases, cytochrome P450 enzymes, and multienzyme cascade systems, enable efficient synthesis of optically pure pharmaceutical intermediates with excellent chemo-, regio-, and stereoselectivity. Advances in protein engineering, artificial intelligence, synthetic biology, and metabolic engineering have further enhanced enzyme performance, process scalability, and industrial applicability while supporting sustainable pharmaceutical manufacturing. Biocatalysis has become a cornerstone technology for producing amino acid-derived drug precursors by integrating catalytic precision with green manufacturing principles. Continued innovation in enzyme engineering and computational technologies is expected to accelerate the development of efficient, scalable, and sustainable pharmaceutical production platforms.
Keywords: Amino acid-derived drug precursors; Biocatalysis; Enzyme engineering; Pharmaceutical synthesis; Green chemistry; Drug development.
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1. Introduction

Amino acid-derived compounds are one of the most significant classes of molecular building blocks in the modern pharmaceutical research due to their structural diversity, biological compatibility and capacity to produce highly selective therapeutic agents. With their special stereochemical features, it is possible to produce biologically active molecules with better receptor specificity, better pharmacokinetic characteristics and fewer adverse effects. A wide range of clinically significant drugs, such as antiviral, anticancer, cardiovascular, central nervous system, and peptide-based pharmaceutical, is produced directly or indirectly based on amino acid-derived intermediates. The growing need of structurally complex, optically pure structures has consequently placed the amino acid-based drug precursors as essential parts of contemporary medicinal chemistry and drug production (Slagman & Flessner, 2021).

The increasing complexity of pharmaceutical molecules has been increased, which has hastened the shift to conventional synthetic chemistry to enzyme-mediated synthesis. Originally used to perform comparatively simple biotransformations, biocatalysis has since become a highly complex platform which can catalyze highly selective reactions which are commonly challenging or impractical to achieve via conventional chemical methods. The ongoing improvement of enzyme discovery, molecular biology, protein engineering and computational design have greatly expanded the catalytic repertoire of enzymes, enabling them to be used in a variety of drug discovery and process development phases. As such, biocatalysis has become part and parcel of pharmaceutical research enabling the efficient synthesis of lead optimization and scalable production of active pharmaceutical substances and their important intermediates (Schwarz et al., 2020). The blistering growth of the field has been fuelled by the multitude of landmark discoveries which have shown the flexibility of enzymes in complex organic synthesis. Stereoselective carbon-carbon bonds, selective amination, hydroxylation, oxidation, reduction and multi-enzyme cascade reactions can now be accomplished using modern biocatalytic systems, greatly expanding the number of obtainable pharmaceutical molecules. The innovations have made biocatalysis a key technology in medicinal chemistry, allowing synthetically the production of structurally

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diverse molecules with high chemo-, regio-, and stereoselectivity (O'Connell et al., 2024).

The outstanding catalytic specificity is one of the main benefits of biocatalysis. Compared to traditional chemical catalysts, enzymes usually operate under mild reaction conditions, and show a high level of substrate selectivity and stereocontrol. These properties reduce unwanted side reactions, lessen the purification efforts, enhance the overall yield of products, and optimize the formation of optically pure products that are required in pharmaceutical usage. The introduction of designed enzymes has also increased the compatibility of substrates, enabling the efficient production of more complex small-molecule drug candidates and decreasing the complexity of the processes and manufacturing costs (Lalonde, 2016).

Sustainable pharmaceutical production also has a significant role played by biosynthesis. Enzyme reactions in water and under ambient temperatures and pressure consume less energy, reduce the use of dangerous organic solvents and toxic reagents, and anaerobic environment. These green characteristics are highly environmentally friendly and have been a close match to the concept of green chemistry and have pushed the pharmaceutical industry into adopting the use of enzyme processes in commercial production lines. Biocatalysis also enhances the reaction efficiency and allows the production of pharmaceutical compounds as an intermediate in large quantities with a uniform quality, in addition to lowering the environmental impact (Sun et al., 2018).

The use of biocatalysis during the pharmaceutical research and development has been further cemented by recent technological advances. The developments in enzyme engineering, high-throughput screening, directed evolution, computational protein design, and integrated synthetic platforms have allowed scientists to create highly efficient catalytic systems that are able to synthesize complex amino acid-based drug precursors with a high level of selectivity and usability in industry. Such advances are still closing the divide between discovery and commercial medicinal production of pharma-scale biocatalysis, and are making biocatalysis a foundation technology to next-generation drug development (France et al., 2023).

In addition to enhancement of selectivity and efficiency, biocatalysis is also a significant way of realizing sustainable pharmaceutical innovation. The implementation of renewable biocatalysts, reaction conditions which are environmentally benign, and manufacturing processes that are resource efficient aid global efforts to produce pharmaceuticals that are greener, but which still meet the high quality standards demanded of therapeutic compounds. With more pharmaceutical companies focusing on sustainability in addition to innovation, the enzyme-mediated synthesis will likely have an even more significant role in the future in the creation of amino acid-derived drug precursors and active pharmaceutical compounds (Alcantara, 2019).

This paper gives an introduction to the use of biocatalysts in the production of amino acid-derived drug precursors and how they are increasingly becoming important in the development of modern pharmaceuticals. It also looks into the structural and stereochemical importance of amino acid-derived intermediates, the key classes of biocatalysts used to produce them and the enzymatic methods that are applied to produce pharmaceutically-relevant products. Moreover, the review addresses the potential therapeutic uses of the precursors, recent technological developments which have increased the efficacy of biocatalysts, industrial expression of enzyme-mediated reactions, the current challenges and future prospects of sustainable biocatalytic drug development. Overall, the review will seek to give a combined perspective on how biocatalysis is reshaping the synthesis of amino acid-based drug precursors and aids in the creation of safer, more efficient, and environmentally friendly pharmaceutical production techniques.

2. Amino Acid-Derived Drug Precursors

The drug precursors derived by condensing amino acids are a heterogeneous group of pharmaceutical building blocks with the key roles in the synthesis of structurally complex and biologically active molecules. They have rendered their structural diversity, stereochemical properties, and compatibility with biocatalytic transformations unique and essential to the contemporary drug discovery and development. These are classified, their structure, pharmaceutical importance, and key classes of intermediates as discussed in the following sections.

2.1 Classification of Amino Acid-Derived Drug Precursors

Amino acid-derived drug precursors refer to the natural amino acids or the structurally modified forms of amino acid-derived compounds that act as important intermediates in the process of producing APIs. The functional groups found within the compound allow them to be chemically or enzymatically converted into more complicated and highly active compounds. In contrast to the conventional synthetically produced intermediates, these compounds have defined structures that enhance their capacity to be recognized by biological systems and exert activity on them. These compounds can be categorized into canonical amino acids, non-canonical amino acids, β-amino acids, D-amino acids, amino alcohols, amino esters, and non-canonical amino acid analogues (Liang et al., 2016).

The significance of these precursors in the pharmaceutical industry goes beyond their chemical diversity. The ability of these precursors to undergo biocatalytic reactions makes it possible to synthesize very complex compounds without increasing the reaction complexity or the number of steps and with higher selectivity. The development of biocatalytic synthesis techniques has shown that they make it possible to achieve this within much shorter times compared to conventional synthetic methods (Simic et al., 2021).

2.2 Natural and Non-natural Amino Acids as Pharmaceutical Building Blocks

The naturally occurring amino acids have been used as the basic building blocks of molecules due to their great biocompatibility, metabolic compatibility, and structural heterogeneity. The increasing complexity of therapeutic targets has however led to the creation of non-natural amino acids that expand the chemical space accessible to natural amino acids beyond the twenty canonical amino acids. These synthetic molecules add novel functional groups and conformational restraints that enhance molecular recognition, target selectivity, and metabolic stability, and are useful functional groups in rational drug design.

Enzyme engineering has greatly enhanced the contribution of non-canonical amino acids that can be produced by sustainable biocatalytic methods, which are effective alternatives to the multistep chemical production (Alfonzo et al., 2022). Similarly, custom-made analogs of amino acids, such as aza-substituted amino acids, have become significant pharmaceutical synthons due to their desirable physicochemical and biological characteristics (Han et al., 2021). Non-canonical amino acid incorporation of peptide therapeutics has also revolutionized the process of peptide drug discovery through increased proteolytic stability, prolonged biological half-life, and receptor specificity improvement, overcoming some of the drawbacks of the traditional peptide-based drugs (Hickey et al., 2023) (Figure 1).

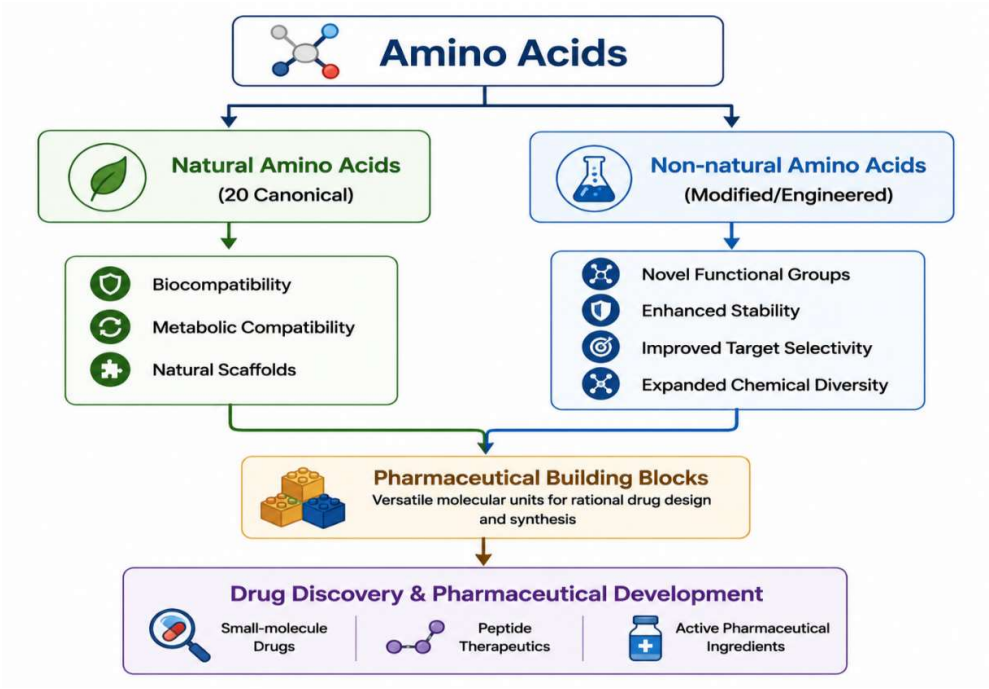

Figure 1. Classification of Amino Acid Building Blocks

As indicated in Figure 1 below, both natural and non-natural amino acids add unique value to pharmaceutical research. Natural amino acids, while offering biocompatibility for molecules, give way to structural diversity with non-natural amino acids, which introduce new functional groups and improved physicochemical properties. In this regard, all the afore mentioned compounds constitute the basis of drug discovery and design.

2.3 Structural Diversity and Stereochemical Significance

The remarkable structural diversity and stereochemical complexity of amino acid-derived precursors is believed to be the main contributor to their pharmaceutical utility. Minor changes in the structure of the side-chain, ring systems, functional group, or stereochemical structure can dramatically change molecular recognition, receptor binding, and biological activity. As a result, scaffolds derived from amino acids have gained not only as privileged structural motifs to build chemically diverse libraries in the process of identifying and optimizing leads, but also enable medicinal chemists to design compounds with better pharmacological properties.

Of these scaffolds, functionalized proline-derived amino acids are of particular interest due to their rigid bicyclic skeletons that allow better conformational regulation and tighter target binding, thus being useful intermediates in drug discovery (Serra et al., 2023). Simultaneously, the application of stereoselective biocatalytic technologies has allowed preparing structurally diverse pharmaceutical building blocks with high levels of chemo-, regio-, and stereoselectivity by undertaking highly selective transformations under environmentally friendly conditions, which uphold their relevance in the context of contemporary medicinal chemistry (Albarrán-Velo et al., 2018).

2.4 Importance of Chirality in Pharmaceutical Development

A characteristic of the molecular structure is chirality, which directly affects the efficacy, selectivity and safety of pharmaceutical compounds since the biological systems perceive individual stereoisomers with different rates. Stereochemical configuration differences may have profound impacts on receptor affinity, enzyme interactions, metabolic pathways, and toxicological profiles. This has led to the synthesis of optically pure compounds becoming an essential goal in the development of pharmaceuticals, especially of compounds with amino acid-derived pharmacophores.

Recent technological developments in asymmetric catalytic technologies have significantly enhanced access to enantiomerically pure drug intermediates and facilitated better lead optimization and production of active pharmaceutical ingredients (Burke, 2023). The biocatalysis, which complements these strategies, is highly stereoselective with the enzyme-catalyzed reactions, which occur under mild reaction conditions and with an outstanding substrate specificity. These strengths have made enzyme-mediated synthesis one of the most efficient and sustainable processes to produce chiral pharmaceutical at laboratory and industrial levels (Rossino et al., 2022).

2.5 Major Classes of Amino Acid-Derived Pharmaceutical Intermediates

Pharmaceutical derivatives of amino acids include a variety of structurally diverse classes that are key intermediates in the development of many drugs on the market and potential new therapeutic agents (Table 1). The different classes have their specific structural and physicochemical properties that determine the design of drugs, pharmacokinetic, and biological activities. Chiral amines are still one of the most common intermediates to use due to their role in synthesizing optically active pharmaceuticals, whereas the 2-amino acids and D-amino acids are more resistant to enzymes and enhance the stability of conformation, which is critical to peptide-based therapies. Similarly, the non-canonical amino acids widen the available chemical space by providing new structural properties that boost the target selectivity and metabolic functions. Amino alcohols and amino esters also enhance further the variety of pharmaceutical preparation by acting as flexible intermediates to 2-blockers, antimicrobial agents, prodrugs, and many bioactive molecules. Together, these intermediate classes offer a flexible platform to pharmaceutical innovation and serve to advance the creation of sustainable biocatalytic pathways to the synthesis of high-value therapeutic products (Alcántara & Alcántara, 2018).

Table 1. Major Classes of Amino Acid-Derived Pharmaceutical Intermediates

Intermediate Class	Key Characteristics	Representative Pharmaceutical Applications	Key References
Chiral amines	Enantiomerically pure nitrogen-containing intermediates	Antiviral, CNS, and cardiovascular drugs	Burke (2023); Simic et al. (2021)
β-Amino acids	Enhanced conformational and metabolic stability	Peptidomimetics and enzyme inhibitors	Serra et al. (2023)
D-Amino acids	Increased resistance to enzymatic degradation	Peptide therapeutics and bioactive peptides	Rossino et al. (2022)
Non-canonical amino acids	Expanded structural and functional diversity	Peptide drugs and targeted therapeutics	Alfonzo et al. (2022); Hickey et al. (2023)
Amino alcohols	Chiral synthetic building blocks	β-Blockers, antimicrobials, and heterocyclic drugs	Albarrán-Velo et al. (2018)
Amino esters	Versatile intermediates for further derivatization	Prodrugs and active pharmaceutical ingredients	Alcántara & Alcántara (2018); Han et al. (2021)

3. Biocatalysts Used for Amino Acid-Derived Drug Precursor Synthesis

Biocatalysts play an important role in the generation of amino acid-based drug precursors due to the ability of the process to achieve very selective and environmentally friendly chemical reactions. The development of new enzymes and biocatalysis has broadened the number of biocatalysts used, making it possible to manufacture drug intermediates with structural complexities and stereochemistry. The types of biocatalysts and their applications will be considered in the subsequent sections.

3.1 Fundamentals of Enzymatic Catalysis

Indeed, enzyme-catalyzed synthesis plays a key role in the biocatalysis as the technology provides highly selective chemical transformations that cannot be performed via common synthetic approaches. Chemo-, regio-, and stereo-specificity of enzymes makes it possible to produce optically pure precursors of the amino acid-based pharmaceutical drugs, reducing the number of protecting groups, by-products and their purification. The described features are especially important for the pharmaceutical industry as the stereospecificity is associated with the effectiveness and safety of drugs. Thus, besides increasing the effectiveness of chemical synthesis, biocatalysis contributes to more ecological manufacturing processes by lowering the energy consumption and using hazardous chemicals, providing one of the key tools for pharmaceutical intermediates production (Adams et al., 2019).

The use of biocatalysis in retrosynthesis illustrates the shift of paradigms in the medicinal chemistry when enzymes are used as a part of synthesis design, and not just to perform specific transformations. Such approach helps to build shorter and more effective synthetic paths, which additionally increases the sustainability and economics of manufacturing process. With the increase in complexity of the pharmaceutical targets, the enzyme-guided retrosynthesis of amino acid-based drugs and active pharmaceutical ingredients becomes even more widespread (de Souza et al., 2017).

3.2 Major Classes of Biocatalysts

The synthesis of amino acid-derived drug precursors involves a wide array of enzymes, each biocatalyst being able to solve diverse synthetic problems, and collectively increasing the pharmaceutical toolbox. Transaminases prevail in the synthesis of chiral amines in industry due to combining a wide substrate scope with high enantioselectivity, allowing the synthesis of optically pure intermediates with mild reaction conditions (Patil et al., 2018). Conversely, cofactor-dependent reductive amination is catalyzed by amino acid dehydrogenases to produce analogs of amino acids with high stereochemical fidelity, and expanded the synthetic repertoire by imine reductases that can directly reduce cyclic and acyclic imines, which are frequently hard to generate by traditional transamination reactions. In addition to amination chemistry, oxidative and hydrolytic enzymes have also been found to have significant roles in scaffold diversification. The reactive keto acid intermediates produced by amino acid oxidases are general substrates in their further transformation using other enzymes, whilst hydrolases can be used to cleave specific pharmaceutical intermediates enantiomerically enriched and with high selectivity and kinetic purity. Lyases are stereoselective in forming carbon to carbon and carbon to nitrogen bonds and raise the complexity of the molecules without having to undergo harsh conditions during the reaction. Alongside such changes, cytochrome P450 monooxygenases oxidize and hydroxylate a broad range of reactions in a highly regio- and stereoselective and efficient fashion, offering efficient access to late-stage functionalization of complex molecules based on amino acids, which are frequently inaccessible to conventional synthetic chemistry (Wei et al., 2018).

The ever-growing repertoire of enzymes with specific metabolism has greatly diversified the current catalytic repertoire that can be used in pharmaceutical synthesis, offering both novel reaction types and previously inaccessible molecular structures (Kries et al., 2024). In addition, the combination of the biocatalytic and chemoenzymatic approaches has made possible complementary catalytic sequences, which enhance the performance of reactions, reduce the synthesizing pathway, and allow the synthesis of structurally complex pharmaceutical intermediates, such as nucleoside analogues and other therapeutic building blocks of value, on a larger scale (Cosgrove & Miller, 2022). Figure 2 shows the key classes of biocatalysts used in the synthesis of amino acid-derived drug precursors, and the main catalytic functions.

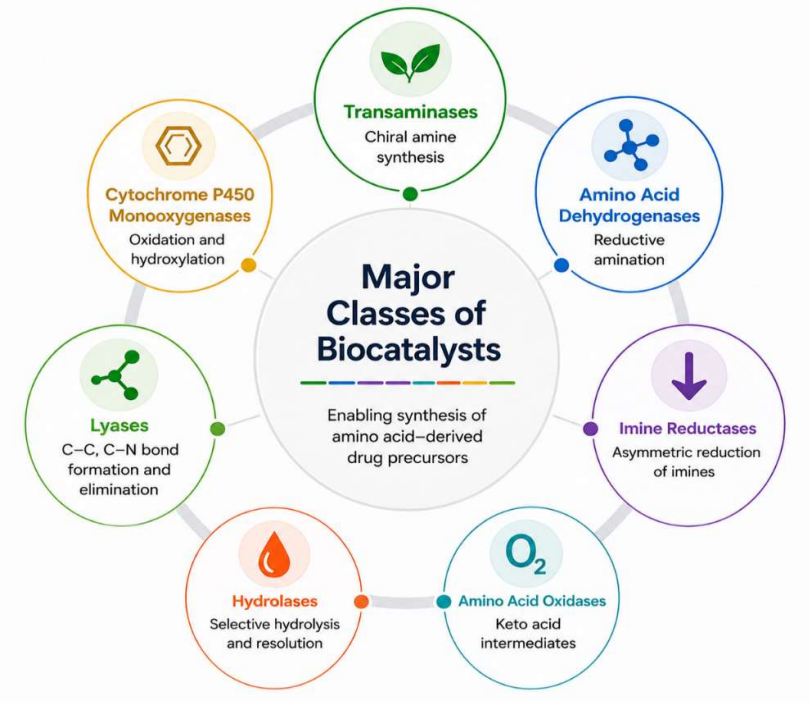

Figure 2. Major Classes of Biocatalysts

Figure 2 highlights the fact that various classes of biocatalysts have different catalytic roles that together contribute to the efficient production of the drug precursors obtained from amino acids. It is through the

reaction specificity of the various types of biocatalysts that bond formation, functional group transformation, and molecular diversification become possible.

3.3 Whole-Cell versus Isolated Enzyme Biocatalysis

The use of whole cell and isolated enzymes biocatalysis is common in pharmaceutical industry, and its choice is determined by the trade-off among catalytic performance, process complexity and economics of production. The whole cell biocatalysis has an advantage in terms of intrinsic cofactor regeneration, enzyme stability, and capability of carrying out intracellular multi-step reactions, thus being especially applicable to complicated biosynthesis processes. Meanwhile, the isolated enzymes ensure more controlled reaction conditions, better substrate availability and easy purification process, which makes them more useful in manufacturing valuable intermediates from amino acids in the same quality. In other words, today's process design takes into account the factors such as substrate affinity, mass transfer, catalyst reuse and production costs, not catalytic activity only (Hecht et al., 2020).

3.4 Protein Engineering and Directed Evolution

The development of pharmaceutical biocatalysis has been exceptional due to the innovations in protein engineering, directed evolution, that allows the systematic enhancement of enzyme activity, substrate specificity, thermostability, and solvent tolerance. Engineered enzymes have broken the barrier of naturally occurring biocatalysts through iterative mutation and selection to be able to catalyze reactions necessary to produce drug precursors based on amino acids more complex than those found in nature. More recently, the computational modelling and analysis of enzyme-substrate interactions has further enhanced the rate of finding useful mutations which reduce the amount of time spent on experimental screening and enhance catalytic performance (Satheeskumar et al., 2026).

In addition to improving the activity of existing enzymes, protein engineering has made it possible to develop catalysts with unprecedented selectivity in the synthesis of structurally diverse non-canonical amino acids. Along with metabolic engineering and optimization of pathways, these advancements are continuing to increase the chemical space available via biocatalysis and enhance the productivity of industries and facilitate the manufacturing of next-generation pharmaceutical intermediates sustainably (Hou et al., 2025).

3.5 Biocatalytic Cascade Reactions

Biocatalytic cascade reactions combine two or more enzyme-catalyzed reactions into a single reaction sequence, which avoids isolation of intermediates and greatly enhances the overall process efficiency. Cascade synthesis reduces synthetic pathways, improves atom economy, decreases solvent usage, and lowers downstream purification needs, by integrating complementary enzymatic reactions in a single reaction system. The latter benefits are especially significant in the synthesis of structurally complex amino acid-derived drug precursors, in which traditional multistep synthesis may be lengthy and resource intensive. Recent studies in enzymatic oxy-functionalization and amino-functionalization have additionally increased the repertoire of cascade biocatalysis, allowing the efficient synthesis of pharmaceutical intermediates with very high chemo-, regio-, and stereoselectivity. This led to the development of multienzyme cascade systems as one of the most promising approaches to process intensification and sustainable pharmaceutical production (Grandi et al., 2023).

4. Biocatalytic Strategies for the Synthesis of Amino Acid-Derived Drug Precursors

The broad variety of different synthetic strategies available by biocatalysis facilitates the creation of drug precursors of amino acids with high chemo-, regio-, and stereoselectivity. The engineering of enzymes and reaction design has broadened the application of these methods allowing the synthesis of structurally complex pharmaceutical intermediates using sustainable and scalable processes. Table 2 gives a summary of the key biocatalytic methods used in the synthesis of drug precursors.

Table 2. Biocatalytic Strategies for Amino Acid-Derived Drug Precursor Synthesis

Biocatalytic Strategy	Key Transformation	Pharmaceutical Relevance	Key References
Asymmetric synthesis of chiral amines	Enantioselective amination	Produces optically pure chiral amine intermediates for APIs	Zawodny & Montgomery (2022); Vikhrankar et al. (2024); Arango et al. (2023)
Non-canonical amino acid synthesis	Enzyme-engineered amino acid formation	Expands chemical diversity and improves stability/selectivity	Almhjell et al. (2018); Adhikari et al. (2021)
Amino acid functionalization	Deuteration and hydroxylation	Enhances metabolic stability and structural diversity	Chun & Narayan (2020); Wang et al. (2023)
C–H amination and hydroxylation	Direct C–H bond functionalization	Enables late-stage modification of complex drug precursors	Charlton & Hayes (2022); Alfonzo et al. (2024); Majhi et al. (2024)
Multi-enzyme cascade synthesis	Sequential enzymatic transformations	Improves atom economy, reduces purification, and supports scalable synthesis	Parmeggiani et al. (2019); Cruz et al. (2022)

As is illustrated in Table 2, each type of biocatalysis has its unique strengths based on the desired reaction and end pharmaceutical use. Overall, these techniques have been instrumental in streamlining the process, increasing stereo selectivity, and making the process sustainable. These have made biocatalysis an ideal platform for the manufacture of valuable drugs from amino acid precursors.

4.1 Asymmetric Synthesis of Chiral Amines

One of the most successful uses of biocatalysis has been the asymmetric synthesis of chiral amines since these compounds are structural motifs in many active pharmaceutical compounds. Biocatalytic amination offers extraordinary and unprecedented chemo-, regios-, and enantioselectivity, allowing the synthesis of optically pure intermediates in environmentally friendly conditions with reduced by-products (Zawodny & Montgomery, 2022). Of the strategies available, transaminase-mediated reactions have been of interest due to their wide range of substrates, high stereocontrol and their ability to work with other industrial processes. New developments in protein engineering and reaction optimization have further enhanced the stability of enzymes, their catalytic activity, and substrate selectivity, rendering such systems more appropriate in commercial manufacturing (Vikhrankar et al., 2024). Moreover, continuous-flow transaminase systems have increased the productivity of reactions, and their scalability, which proved to have significant potential in the large-scale production of amino acid-based chiral building blocks (Arango et al., 2023).

4.2 Enzymatic Synthesis of Non-canonical Amino Acids

The non-canonical amino acids have gained importance as potential building blocks for pharmaceuticals due to their unique structure elements providing increased metabolic stability, receptor selectivity, and biological activity over canonical amino acids. The production of non-canonical amino acids has been greatly assisted by advances in enzyme engineering techniques that have provided more catalytic options to synthesize amino acid analogues having varied structures and precise stereochemistry (Almhjell et al., 2018). Moreover, in addition to small molecule synthesis, non-canonical amino acid-containing proteins have helped produce biomolecules with improved catalytic activities and biological properties. Hence, the biocatalytic synthesis of non-canonical amino acids has helped increase chemical space for designing novel pharmaceutical agents (Adhikari et al., 2021).

4.3 Biocatalytic Functionalization of Amino Acids

The selective functionalization of amino acids makes it possible to obtain different pharmaceutical precursors without changing the basic structure of the amino acid itself. Biocatalytic methods make it possible to modify specific parts with high selectivity; thus, medicinal chemists can increase the stability, biological activity, and physical and chemical characteristics of the molecule without additional manipulations. Stereoselective deuteration is one of the methods for improving the metabolic stability and pharmacokinetic characteristics of amino acid-based substances (Chun & Narayan, 2020). Hydroxylation using enzymes is another way to add oxygen-containing substituents which may act as intermediates for creating other pharmaceutical precursors (Wang et al., 2023).

4.4 Enzymatic C–H Amination and Hydroxylation

Enzymatic C-H functionalization has become a revolutionary approach to the synthesis of complex pharmaceutical molecules by direct functionalization of otherwise unreactive carbon hydrogen bonds. The highly regioselective hydroxylation reactions made possible by oxygenating enzymes allow post-synthetic diversification of drug candidates and enhance synthetic efficiency (Charlton & Hayes, 2022). More recently, artificial biocatalysts that enable C–H insertion with nitrene have offered efficient access to the production of α-amino esters with the power to broaden the scope of available intermediates derived from amino acids (Alfonzo et al., 2024). Equally, enzymatic C(sp^3)H amination has been improved, and the possibility to construct nitrogen-containing scaffolds with enzyme-catalyzed C-H activation has been demonstrated with increasing potential in the current pharmaceutical production (Majhi et al., 2024).

4.5 Multi-enzyme Cascade Synthesis

Multi-enzyme cascade production combines a series of enzymatic reactions into one reaction system, thus removing the need to isolate intermediates and enhancing the efficiency of the process. This approach eases artificial pathways, improves the economy of atoms and decreases the use of solvents, which is especially appealing in the production of sustainable pharmaceuticals. It's usefulness has been proven by biocatalytic retrosynthesis of the important sitagliptin precursor, with integrated reactions streamlining the synthesis of an important pharmaceutical amino acid-derived intermediate, and with excellent stereochemical control (Parmeggiani et al., 2019). Likewise, the example of the antiviral drug molnupir being synthesized by the enzyme exemplifies how cascade biocatalysis can be used to scale up drug production, which in turn can be utilized in next-generation drug production due to its high efficiency and scalability in multiple biomolecular steps (Cruz et al., 2022).

5. Pharmaceutical Applications of Amino Acid-Derived Drug Precursors

Amino acid-based drug precursors are now indispensable to modern pharmaceutical development since they can be used to produce structurally diverse therapeutics of high stereochemical purity and enhanced biological performance. Developments in biocatalysis have increased their use in a variety of therapeutic applications through efficient, sustainable, and scalable synthetic pathways to high-value pharmaceutical

intermediates. The key clinical uses of amino acid-derived drug precursors are presented in Figure 3.

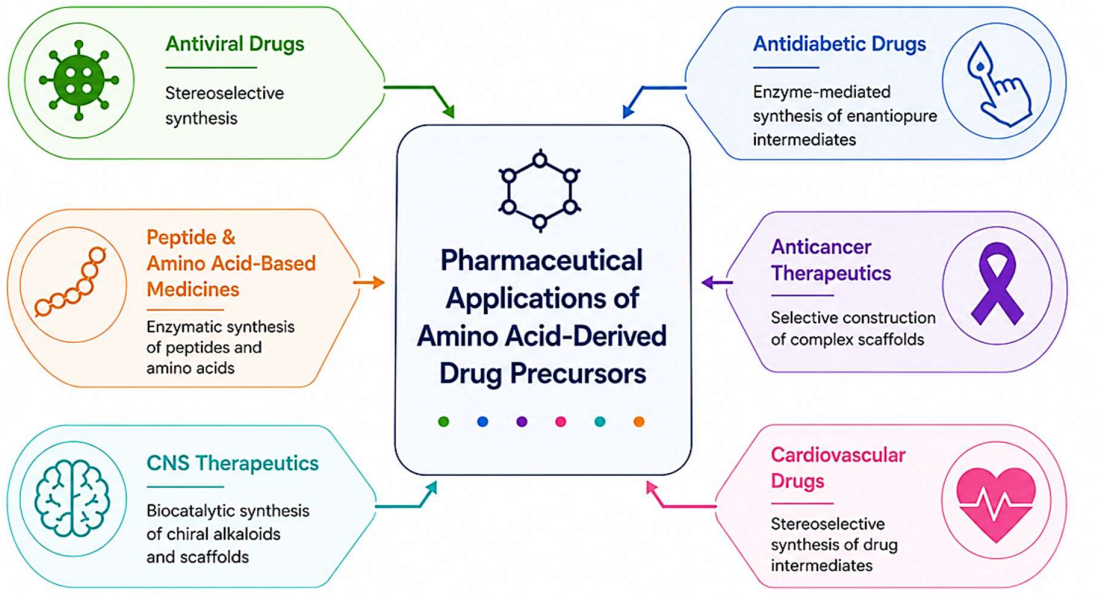

Figure 3. Pharmaceutical Applications of Amino Acid-Derived Drug Precursors

As shown in Figure 3, precursors from amino acids play an important role in the development of drugs used to target a wide variety of ailments such as viral infections, diabetes, cancers, heart diseases, and neurodegenerative diseases, as well as peptides and amino acids. The versatility of their structure and suitability for biocatalytic formation have made these intermediates important scaffolds in the development of future pharmaceuticals.

5.1 Antiviral Drug Synthesis

Due to the increasing structural complexity of the antiviral agents, the necessary synthetic strategies have become highly selective, requiring the ability to synthesize optically pure intermediates with a minimum of complexity to the process. Biocatalysis can overcome this limitation by facilitating stereoselective transformations that enhance synthetic performance and minimise the environmental impact of the production of pharmaceuticals. Recent developments have established that enzyme catalyzed reactions conducted in deep eutectic solvents increase stability of enzymes, solubility of the substrate and catalytic activity, offers sustainable reactions systems in the manufacture of antiviral active pharmaceutical compounds. Such advances make biocatalysis a more viable technology to scale-up antiviral drug production and consistent with the concepts of green pharmaceutical chemistry (Zhang et al., 2024).

5.2 Antidiabetic Drug Development

Enzyme-mediated synthesis of antidiabetic drug intermediates is increasingly becoming the method of choice due to the inherent limitation of asymmetric synthesis in terms of requiring many reaction steps and having poor stereochemical selectivity. To eliminate these limitations, biocatalysts are able to catalyze highly selective reductions and functional group transformations to produce enantiomerically pure precursors with enhanced process efficiency. The effective development of ketoreductases to synthesize the ipatasertib precursor is an example of how optimization of enzymes can greatly enhance catalytic efficiency, specificity to substrates, and usefulness in industry. These developments show that engineered biocatalysts are now becoming commercially feasible manufacturing platforms of complex antidiabetic pharmaceuticals, which are no more a laboratory instrument (Honda Malca et al., 2024).

5.3 Anticancer Therapeutics

The discovery and design of anticancer drugs often involves structurally complex molecules with specific stereochemical structures that would be hard to produce by standard synthetic chemistry. Biocatalysis provides the most selective catalytic pathways to building these molecular structures with the least by-products and increases the sustainability of reactions. In addition to easing synthetic routes, enzyme-mediated reactions allow the quick diversification of leads and analogue synthesis, allowing medicinal chemists to optimize biological activity with increased efficiency. As a result, biocatalysts have now become part of the contemporary anticancer drug discovery process, both in the early-stage molecular design and in the production of pharmaceutically-relevant intermediates in large quantities (Sengupta et al., 2023).

5.4 Cardiovascular Drugs

Most of the cardiovascular drugs have chiral structures, the pharmacological activity of which is influenced by its exact stereochemistry. It is possible to synthesize such optical active compounds through efficient bioconversion processes via selective biochemical transformations, resulting in high yields with decreased synthetic efforts. The development of artificial heme proteins, which can perform stereoselective carbene transfer reactions, made it possible to expand the scope of synthesis of cyclopropane containing cardiovascular precursors, highlighting increasing possibilities of bio-catalysts for creation of complex cardiovascular structures (Bajaj et al., 2016).

5.5 Central Nervous System Therapeutics

The synthesis of CNS drugs often relies on chiral alkaloids and nitrogen-containing heterocycles, where biological efficacy greatly depends on their stereopurity. The development of biocatalytic asymmetric synthesis has revolutionized this process by making it possible to selectively construct pharmacologically relevant structures with unparalleled catalytic efficiency. In addition to advancements in enzyme-catalyzed alkaloid synthesis, these developments have helped in opening new horizons in the synthesis of biochemically relevant CNS drugs that exhibit improved pharmaceutical profiles. This illustrates the increased significance of biocatalysis in CNS drug design and production (Cigan et al., 2021).

5.6 Peptide- and Amino Acid-Based Medicines

The incorporation of modified amino acids in therapeutic peptides is becoming more common in order to improve their metabolic stability, selectivity toward their target receptors, and pharmacokinetic properties. Therefore, amino acid precursors play a key role in modern peptide drug design. Biotransformation of lipases has added variety to the approaches for synthesizing pharmaceutical intermediates of peptides while providing good stereochemistry control (Verma et al., 2021). In parallel, biocatalytic synthesis of D-amino acids has provided the opportunity to obtain metabolically stable peptides that are more resistant to hydrolysis and demonstrate enhanced biological activity (Pollegioni et al., 2020). In addition, industrial use of transaminase biotechnology has allowed for the synthesis of optically active amino acid derivatives (Fuchs et al., 2015).

6. Industrial Translation and Process Development

The most important considerations in the successful industrial translation of biocatalytic synthesis are listed in Table 3. These include sustainable manufacturing, up-scaling of processes, optimisation of reactions, regulatory compliance as well as commercial implementation that altogether contribute to the efficient production of amino acid-derived pharmaceutical intermediates.

Table 3. Key Industrial Considerations for the Translation of Biocatalytic Drug Precursor Synthesis

Industrial Aspect	Key Focus	Relevance to Drug Precursor Synthesis	Key Reference
Green manufacturing	Sustainable synthesis, reduced waste, mild reaction conditions	Minimizes environmental impact while improving API production	Verma & Paliwal (2024)
Process scale-up	Enzyme immobilization, continuous processing, bioreactor engineering	Enhances catalyst stability and industrial productivity	Santi et al. (2021)
Process optimization	Cofactor regeneration, substrate loading, reaction engineering	Improves yield, efficiency, and manufacturing economics	Kinner et al. (2022)
Regulatory quality	GMP compliance, process consistency, patent protection	Ensures product quality and supports technology transfer	de María et al. (2019)
Commercial translation	Industrial implementation, scalable enzyme technologies	Facilitates commercial production of pharmaceutical intermediates	Poppe & Vértessy (2018)

The effectiveness of industrial implementation, as stressed in Table 3, is the combination of sustainable manufacturing plans and efficient process engineering and quality control. Each of these considerations is discussed further below, and their role in scalable and cost-effective biocatalytic pharmaceutical production highlighted.

6.1 Green Chemistry and Sustainable Manufacturing

Biotechnology is used in the industrial production of biocatalysis mainly because of the necessity to create pharmaceutical manufacturing methods that are environmentally friendly without affecting their synthetic efficiency. The enzyme-catalyzed reactions, in contrast to the classical chemical reactions, are run under mild conditions, have very high chemo-, regio-, and stereoselectivities, and consume many fewer harmful reagents, organic solvents, and energy-demanding operations. These features enhance atom economy, reduce the waste produced, and also reduce the total environmental impact of active pharmaceutical ingredient (API) manufacture. As a result, alternative synthetic approaches have been replaced by biocatalytic and chemoenzymatic strategies as a major part of the green pharmaceutical production process that contributes to economic feasibility and sustainability (Verma and Paliwal, 2024).

6.2 Scale-up of Enzymatic Processes

Although the catalytic performance exhibited by enzymes in the laboratory is excellent, in order to succeed in the industrial process enzymes must be able to be active, stable, and reproducible at large-scale manufacturing levels. The latest developments in bioreactor design, enzyme immobilization, continuous operation, and automation of processes have greatly enhanced the lifetime and robustness of catalysts, allowing the production of pharmaceutical intermediates on a commercial scale. The technological advances have lowered the cost of manufacturing and guaranteed the quality of products, which proves that biocatalysis on an industrial scale is a feasible solution now instead of a new concept (Santi et al., 2021).

6.3 Process Optimization

Bio-catalytic manufacturing cannot be a commercial success solely due to the performance of the enzymes but also due to the systematic optimization of the overall production process. Process efficiency and economic viability are dependent on parameters like substrate loading, cofactor regeneration, reaction kinetics, mass transfer, solvent choice and downstream purification. The trend in modern pharmaceutical production is to combine reaction engineering with enzyme engineering to achieve optimal levels of catalytic productivity at low production costs. This intensification in processes has significantly increased the synthesis of structurally complex amino acid-based drug precursors by industrial means and the competitiveness of biocatalytic manufacturing platforms (Kinner et al., 2022).

6.4 Regulatory and Quality Considerations

The pharmaceutical use of biocatalysis calls for the strict adherence to regulatory guidelines in order to assure the safety, quality, and consistency of manufacture of the products. Enzymatic reactions have to prove reliable catalytic activity, consistency, purity control, and suitability for GMP prior to their use in industry. On the other hand, the growing amount of patents on biocatalysis illustrates the trust placed in enzyme-based manufacture and emphasizes the role of intellectual property in the technology transfer from research to pharmaceutical manufacture (de María et al., 2019).

6.5 Commercial Success Stories

The success of biocatalysis as a business can be seen from the extensive use of biocatalysis in the production of pharmaceuticals, fine chemicals, and other valuable chiral intermediates. The development of enzymes and reaction engineering have made it possible for biocatalytic methods to replace the traditional synthetic approach in many industrial processes, making them more economical and environmentally friendly. This marks the arrival of the next era of biocatalysis in industry, where enzyme-based synthesis is considered an advanced manufacturing method for the increasing need of producing pharmaceuticals (Poppe & Vértessy, 2018).

7. Emerging Technologies Accelerating Biocatalytic Drug Development

Recent technological progress is changing the approach to biocatalytic drug discovery and development by combining computational technologies with enzyme engineering to speed up the discovery and optimization of catalysts. Artificial intelligence (AI) and machine learning have transformed enzyme engineering as an empirical investigation to a more data-driven forecasting of useful mutations, predicting enzyme-substrate interactions, and carrying out rapid screening of large sequences data sets to identify promising biocatalysts. They can significantly decrease the development time, increase catalytic efficacy, substrate selectivity, and enzyme stability, and create catalysts specific to the synthesis of amino acid-derived drug precursors (Yi et al., 2021). In addition to these computational methods, rational protein design has enabled the creation of enzymes with improved activity and a wider range of substrates to be targeted, increasing the number of biocatalytic transformations that can be used in the production of pharmaceuticals (Wu et al., 2021).

Similar developments in synthetic biology and metabolic engineering have facilitated the synthesis of tailored biosynthetic pathways able to synthesize structurally complex amino acid-derived molecules in high yield and with high stereochemical fidelity. These artificial microbial systems optimize metabolic flux and enhance the availability of precursors and minimize the formation of by-products, thus increasing the commercial viability of producing pharmaceuticals using enzymes. Simultaneously, novel biocatalytic approaches, such as the formation of amide bonds through the use of enzymes, have offered effective and sustainable pathways to the synthesis of peptide-based therapeutics and other pharmaceutically relevant molecules, increasing the synthetic capacity of modern biocatalysis further (Lubberink et al., 2023). Moreover, nanoparticle-immobilized enzymes and nanobiocatalysts on advanced nanoparticles have enhanced better stability, reusability, and operational durability of catalysts, enabling continuous manufacturing processes and enhancing the industrial translation of sustainable biocatalytic technologies (Khafaga et al., 2023). Figure 4 summarizes the major emerging technologies that have propelled the next-generation biocatalytic drug development.

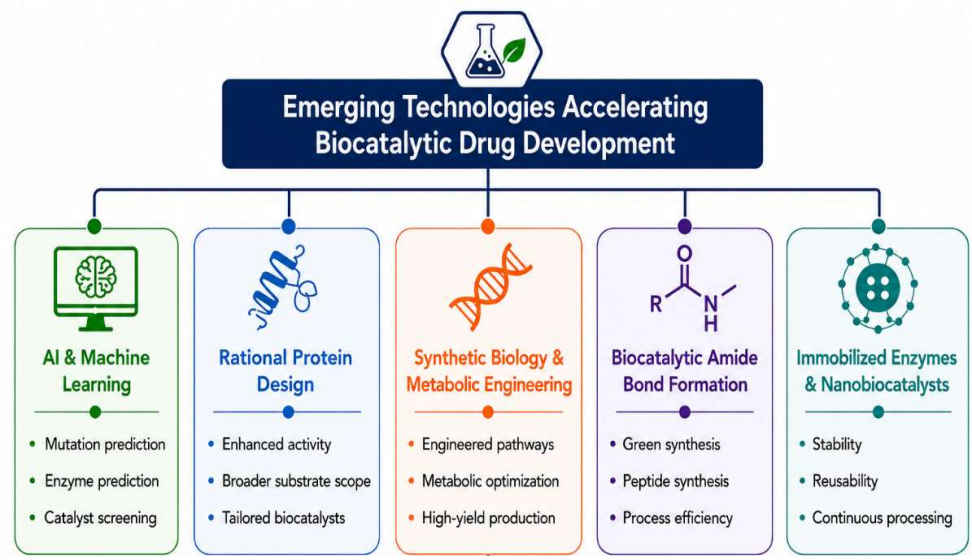

Figure 4. Emerging Technologies in Biocatalytic Drug Development

Figure 4 represents how these new technologies altogether improve the efficacy and flexibility of contemporary biocatalysis through the combination of computational prediction, enzyme engineering, synthetic biology, and cutting-edge catalyst technology. They are helping in the rapid development of biocatalysts, process sustainability, and mass production of drug precursors from amino acids.

8. Current Challenges and Future Perspectives

Biocatalysis has shown impressive advances in the production of pharmaceuticals, several challenges still hinder its extensive use in industries. The enzyme has a low operational stability in adverse manufacturing environments such as high temperatures, extreme pH and high substrate concentration, decreasing catalytic lifetime and process reliability. Also significant is the narrow range of substrates of a number of biocatalysts, which limits their use to structurally diverse amino acid-based drug precursors, and in many cases requires significant protein engineering. Moreover, enzymes that are dependent on cofactors need an effective system of regeneration to sustain catalytic activity, and large-scale manufacture is limited by the cost of enzyme production, subsequent processing and catalyst recovery. The solution to these limitations is to handle enzyme engineering through reaction engineering to enhance the catalytic robustness, expand substrate compatibility, and increase the economic viability of industrial biocatalytic processes.

It is anticipated that future advancements will enable biocatalysis, with enhancements in artificial intelligence, computational protein design, synthetic biology, and high-throughput enzyme discovery, to become an even more versatile platform to manufacture pharmaceuticals. The discovery of new enzymes in untapped microbial and metagenomic sources, along with enhanced approaches to metabolic engineering, will increase the range of available catalytic transformations and enable the production of more complex amino acid-based drug precursors. Simultaneously, continuous-flow processing, immobilized enzyme technologies, and integrated biocatalytic manufacturing will bring about enhanced scalability of processes, reusability of catalysts, and manufacturing efficiency. These developments, in combination, will make biocatalysis a key technology in the sustainable, economically feasible, and precision-driven production of next-generation pharmaceuticals, both facilitating drug discovery innovation and helping to shift pharmaceutical production towards a greener process.

Conclusion

Biocatalysis has emerged as a revolutionary method in the synthesis of amino acid-derived drug precursors, by offering highly selective, sustainable and economically viable alternatives to the traditional chemical synthesis. This overview indicates that amino acids-derived intermediates are structural diversified and stereochemically complex molecules that cannot be substituted in the development of antiviral, antidiabetic, anticancer, cardiovascular, central nervous system, and peptide-based drugs. The broadened repertoire of major classes of biocatalysts, such as transaminases, dehydrogenases, imine reductases, hydrolases, cytochrome P450 enzymes and multienzyme cascade systems, has greatly extended the ability to synthesize optically pure pharmaceutical intermediates with excellent chemo-, regio-, and stereoselectivity. Moreover, new breakthroughs in protein engineering, directed evolution, artificial intelligence, synthetic biology, and metabolic engineering have accelerated the process of enzyme discovery, increased catalytic efficiency, and industrial scalability. The review also points out that the key to successful industrial implementation is the ability to optimize the process, regulatory compliance and green manufacturing strategies that will enable sustainable pharmaceutical production. However, enzyme stability and substrate

spectrum, cofactor regeneration and economics of the process still hinder more widespread commercial use. The future will rely on the incorporation of computational technologies with the more advanced enzyme engineering to create robust and versatile catalytic platforms that can be used to synthesize an increasing number of complex drug molecules. Altogether, biocatalysis will have a much more prominent position in the next-generation pharmaceutical production as it will permit efficient, environmental-friendly, and precision-based production of amino acid-based therapeutics.

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