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APPLICATION OF D-AMINO ACIDS IN DRUG DESIGN (review)

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Dedication: To Professor Tamio Hayashi — a giant in the realm of asymmetric catalysis, a North Star of a man, whose guidance has gifted generations of chemists their most formative intellectual experiences.

D-Amino acids (D-AAs) have become indispensable building blocks in modern peptide drug design. Although relatively rare in higher organisms, D-AAs are widely utilized in nature, particularly in bacterial peptidoglycans and microbial antimicrobial peptides, where they confer proteolytic stability and unique biological activities. Inspired by these natural strategies, medicinal chemists have successfully incorporated D-Aas into synthetic peptides to overcome the inherent limitations of conventional peptide therapeutics, such as rapid enzymatic degradation and poor bioavailability. The incorporation of D-AAs offers several key advantages, including dramatically enhanced proteolytic resistance, prolonged plasma

half-life, reduced immunogenicity, and improved receptor selectivity. These properties have enabled the development of clinically successful drugs across multiple therapeutic areas. Prominent examples include the early antibiotic gramicidin D (1955), the immunosuppressive agent cyclosporine, D-penicillamine, daptomycin, etelcalcetide, difelikefalin, and voclosporin. These compounds illustrate the transformative impact of D-AAs on peptide pharmacology and their expanding role in treating infectious diseases, autoimmune disorders, nephrological conditions, and beyond.

This review highlights the strategic importance of D-AAs in pharmaceutical design, their natural occurrence, clinical applications, and major advances in synthetic methodologies, with particular emphasis on the versatile Ni(II) Schiff base complex approach for the preparation of tailor-made D-AAs. The evolution of D-AA-containing pharmaceuticals demonstrates how stereochemical engineering continues to drive innovation in peptide drug discovery and development.

Keywords: D-amino acids, chirality, chirobiotics, Ni(II) complexes, drug design, proteolytic stability, peptide therapeutics, marketed pharmaceuticals.

INTRODUCTION. The biochemistry of life exhibits a strong preference for homochiral peptides and proteins, composed almost exclusively of L-amino acids (L-AAs) [1-3]. This chiral homogeneity confers critical advantages in structural stability, folding efficiency, and functional precision that racemic or heterochiral mixtures cannot achieve. Consistent chirality enables the formation of stable, regular secondary structures, particularly α-helices and pleated β-sheets, which rely on uniform backbone dihedral angles (φ/ψ) and regular i to i+4 hydrogen bonding patterns [4-6]. Introducing D-amino acids (D-AAs) disrupts this geometry, preventing helix propagation and reducing the number of backbone hydrogen bonds (approximately 60% in homochiral proteins versus ~30% in demi-chiral models). This leads to a narrower and deeper folding funnel toward the native state, lowering the entropic cost of folding by restricting the unfolded ensemble and increasing the thermodynamic stability of compact conformations through enhanced enthalpy from helical collapse and backbone interactions. In contrast, racemic systems favor rippled β-sheets (as predicted by Pauling and Corey) [7], which exhibit distinct geometry and often stronger inter-strand associations but are incompatible with the compact, functional folds required for enzymatic active sites and molecular recognition. Homochirality further ensures precise stereospecific interactions with other chiral biomolecules (e.g., D-sugars in nucleic acids), supporting efficient catalysis, ligand binding, and biochemical cooperativity [4]. Evolutionarily, once a slight chiral bias emerged, via amplification through polymerization [8,9], self-disproportionation of enantiomers [10-12], and selection favored homochiral systems, as their superior folding reliability and functional competence provided a decisive competitive edge over mixed-chira-

lity alternatives in sustaining metabolism and replication. Thus, homochirality is not merely a historical contingency but a biochemical necessity enabling the sophisticated protein machinery central to terrestrial life [4].

Similar to the xenobiotic fluorine, which has revolutionized medicinal chemistry by conferring enhanced metabolic stability, bioavailability, and receptor affinity to pharmaceutical compounds [13-17], abiotic D-AAs, here termed chirobiotics, possess tremendous yet largely untapped potential in drug design, offering unique stereochemical advantages that can circumvent biological degradation pathways and modulate molecular interactions in ways unattainable with their L-configured counterparts. In this review article, we delve into the natural occurrence of D-AAs, ranging from their presence in bacterial peptidoglycans and antimicrobial peptides to their roles as neuromodulators in eukaryotic systems, while also examining state-of-the-art synthesis methodologies that enable scalable production for therapeutic applications. Moreover, we outline the major avenues for their pharmaceutical exploitation as chirobiotics, such as in the development of protease-resistant peptides for antimicrobial and anticancer therapies, enantioselective receptor agonists or antagonists for neurological disorders, and immunomodulatory agents that exploit chirality to enhance specificity and reduce immunogenicity. Furthermore, we trace the evolutionary trajectory of D-AA–containing drugs, from their serendipitous discovery in natural products like gramicidin [18] and cyclosporine [19], through preclinical optimizations addressing pharmacokinetic challenges, to pivotal milestones including the first regulatory approvals by agencies such as the U.S. Food and Drug Administration (FDA) for compounds like D-penicillamine in treating Wilson's disease and rheumatoid arthritis, thereby illustrating a paradigm shift toward incorporating abiotic chirality in modern pharmacopeia. This review article will be of interest to medicinal chemists, pharmacologists, biochemists, and drug discovery professionals seeking to harness D-amino acids as innovative chirobiotic tools in addressing unmet medical needs, fostering interdisciplinary collaborations to unlock their full therapeutic promise.

Natural occurrence. D-AAs occur naturally across a wide range of biological systems. They are particularly prominent in microorganisms, where D-alanine (D-Ala) and D-glutamic acid (D-Glu) serve as key components of the bacterial peptidoglycan in cell walls, contributing to structural integrity and resistance.

Beyond bacteria, D-AAs appear in numerous bioactive natural compounds, including peptides produced by algae, fungi, marine invertebrates, and even some vertebrates, with at least 132 documented peptide natural products incorporating D-AAs such as D-Ala, D-valine (D-Val), D-leucine (D-Leu), D-serine (D-Ser) (Fig. 1), and others. Across these organisms, D-AAs are not rare curiosities but purposeful molecular features that shape peptide stability, bioactivity, and ecological interactions. In marine organisms, this stability supports peptides that must persist in high-salinity or protease-rich surroundings [20]. In fungi and algae, D-AAs help maintain bioactive conformations that would otherwise be unstable [21].

Free D-AAs in higher organisms, including mammals and humans, arise through intrinsic biosynthesis, gut microbiota, diet, and age-related racemization. Among them, D-Ser is the key endogenous co-agonist at

the glycine site of *N*-methyl-D-aspartate receptors (NMDARs), enabling full receptor activation with glutamate. It is more potent than glycine and predominates in forebrain regions such as the cortex and hippocampus. Formed from L-serine by the serine racemase (mainly neuronal in adults), D-serine is released synaptically—often via glia—to drive calcium influx, synaptic plasticity (long-term potentiation and long-term depression, LTP/LTD), learning, memory, neuronal maturation, and cognitive processes including mood regulation and fear extinction [22].

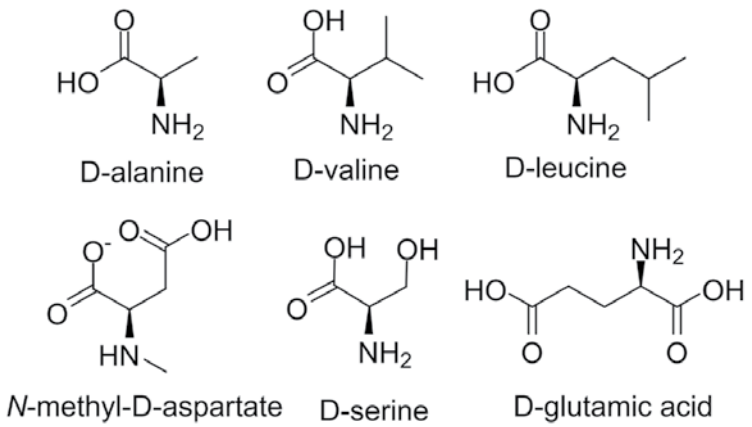


Fig. 1. Chemical structures of some D-AAs found in higher organisms.

Disrupted D-Ser signaling contributes to disease: reduced levels and NMDAR hypofunction are linked to schizophrenia, Alzheimer's disease, and age-related cognitive decline, whereas excess D-Ser can promote excitotoxicity in ischemia or epilepsy. In aging, forebrain D-Ser typically declines, correlating with impaired NMDAR activity, weaker plasticity, and deficits in learning and memory. Experimental D-Ser supplementation can restore NMDAR function, connectivity, and neuronal structure, improving cognitive performance in aging models [23].

In proteins, particularly long-lived ones like lens crystallins, tooth enamel, or certain brain proteins, L-AAs (mainly L-aspartate/L-asparagine) undergo time-dependent spontaneous racemization to D-forms (e.g., D-Asp) during aging. This alters protein higher-order structure, function, and stability, contributing to age-related diseases such as cataracts, Alzheimer's (via protein misfolding/aggregation), and other degenerative conditions. D-AAs accumulate progressively with age, serving as a molecular index of aging and protein "fatigue" damage [24].

D-AAs are also detected in plants, soils, aquatic environments, and processed foods, highlighting their broader ecological distribution and roles in physiological functions, microbial competition, and potentially disease-related processes [25].

Primary Advantages and Applications of D-AAs in drug design. L-AAs are fundamental to modern drug design [26-30]. They provide chiral, metabolically compatible building blocks that shape the three-dimensional archi-

tecture, stability, and biological activity of therapeutic molecules. Their natural stereochemistry allows medicinal chemists to construct peptides, peptidomimetics, and small-molecule scaffolds that engage protein targets with high affinity and selectivity, while minimizing immunogenicity and improving pharmacokinetic behavior. L-AAs contribute functional diversity through side-chain chemistry, enabling hydrogen bonding, hydrophobic packing, metal coordination, and covalent interactions, and their predictable metabolic pathways support rational optimization of absorption, distribution, and clearance [31-33].

Incorporating non-natural, tailor-made amino acids greatly expands the utility of L-AAs in drug design by introducing functions and physicochemical properties that natural residues cannot provide [32]. These engineered amino acids allow medicinal chemists to fine-tune molecular conformation, polarity, lipophilicity, metabolic stability, and target engagement with a level of precision that surpasses the natural amino acid repertoire. Side-chain modifications can introduce steric bulk, hydrogen-bonding motifs, redox activity, metal-binding groups, or conformational constraints that enhance potency and selectivity while reducing off-target effects or proteolytic degradation. Among these designer residues, fluorinated amino acids are the most extensively studied and widely applied. The unique electronic and steric characteristics of fluorine enable modulation of pK_a, dipole moments, hydrophobicity, and metabolic resistance, allowing strategic control over binding affinity, membrane permeability, and pharmacokinetic behavior. As a result, tailor-made—and especially fluorinated—amino acids serve as powerful tools for optimizing peptide therapeutics, stabilizing secondary structure, improving oral bioavailability, and designing next-generation peptidomimetics and small-molecule scaffolds [34–39].

The incorporation of D-AAs represents a cornerstone strategy in contemporary peptide and protein drug design, addressing key limitations of natural L-AAs-based therapeutics while enabling novel pharmacological profiles. Unlike their L-enantiomers, which predominate in eukaryotic biology, D-AAs confer distinct advantages rooted in stereochemical differences that disrupt recognition by endogenous proteases, alter conformational dynamics, and modulate biological interactions.

Enhanced Proteolytic Stability and Pharmacokinetic Profile. The most established rationale for D-AA incorporation is resistance to enzymatic degradation. Proteases exhibit high stereospecificity for L-configured peptide bonds, rendering D-AA-substituted sequences dramatically more stable in plasma, gastrointestinal environments, and intracellular compartments [40-42]. This often translates to extended half-lives (up to orders of magnitude in some cases), reduced dosing frequency, and improved bioavailability—critical for transitioning from injectable to potentially oral formulations. In practice, partial or full D-AA substitution (e.g., retro-inverso or mirror-image designs) [43] has been pivotal in developing long-acting analogs of natural peptides, such as somatostatin (octreotide with D-Trp) [44], and supports emerging oral peptide candidates like cyclic PCSK9 inhibitors [45].

Improved Conformational Rigidity and Target Binding. D-AAs introduce local stereochemical perturbations that favor specific secondary structures (e.g., β-turns via D-Pro or D-AA-induced turns), enhancing receptor affinity,

selectivity, and potency. In cyclic or constrained peptides, strategic D-AA placement stabilizes bioactive conformations, often yielding superior binding kinetics compared to all-L-configured counterparts. This is particularly valuable in targeting G-protein coupled receptors (GPCRs), ion channels, or enzymes where precise geometry dictates efficacy [46-48].

Reduced Immunogenicity and Toxicity. Full D-peptides (mirror-image proteins) evade immune surveillance due to non-recognition by major histocompatibility complex (MHC) presentation pathways and lack of proteolytic processing into immunogenic fragments. This property underpins mirror-image phage display technologies for discovering ultra-stable, non-immunogenic binders against challenging targets (e.g., human immunodeficiency virus (HIV) entry inhibitors like CPT31 in clinical trials). Heterochiral designs can also mitigate cytotoxicity in self-assembling biomaterials or amyloid-targeted therapies [49, 50].

Disruption of Biofilms and Antimicrobial Enhancement. D-AAs (especially free D-AAs or D-AA-rich peptides) interfere with bacterial peptidoglycan synthesis, quorum sensing, and biofilm integrity, offering synergistic effects with conventional antibiotics against resistant pathogens. This application extends to preventing microbial colonization in medical devices and combating chronic infections [51, 52].

Direct Therapeutic Effects and Emerging Roles. Certain D-AAs serve as bioactive entities themselves (e.g., D-Ser as an NMDA receptor co-agonist in neurological disorders; D-Trp/D-Phe modulators in neurology). D-AA-containing natural products inspire anticancer, antimicrobial, and neuroprotective agents, with some exerting antiproliferative effects via metabolic pathways (e.g., H_2S generation from D-Cys). In cancer, D-AAs show promise as prodrugs in oxidase-based therapies or as inhibitors of tumor proliferation [53, 54].

Facilitation of Advanced Delivery and Biomaterials. Heterochiral self-assembling peptides form nanostructured hydrogels with unexpected benefits, including altered gelation kinetics, reduced cytotoxicity, and enhanced drug release profiles for localized therapy (e.g., in wound healing or tissue engineering) [55, 56].

Illustrative Examples of FDA-Approved Therapeutics Incorporating D-Aas. Gramicidins. Gramicidins are a family of peptide antibiotics produced by the soil bacterium *Brevibacillus brevis* (formerly *Bacillus brevis*). They represent some of the earliest clinically used antibiotics, discovered in 1939 during intensive research into soil microbes. The sequence of gramicidin A was elucidated in 1964 with the ion-channel dimer structure confirmed by nuclear magnetic resonance (NMR) spectroscopy in the 1970s–1990s [57].

Gramicidins occur in multiple natural variants produced non-ribosomally. Gramicidin D (the primary commercial form) is a mixture of linear pentadecapeptides (Fig. 2) gramicidin A (80%), B (5%), and C (15%). The general sequence is formyl-L-X-Gly-L-Ala-D-Leu-L-Ala-D-Val-L-Val-D-Val-L-Trp-D-Leu-L-Y-D-Leu-L-Trp-D-Leu-L-Trp-ethanolamide, where X is Val or Ile, and Y is Trp (A), Phe (B), or Tyr (C). Alternating D- and L-AAs enables formation of a right-handed β-helix. In lipid bilayers, two monomers associate head-to-head into a transmembrane channel ~2.6 nm long that selectively conducts monovalent cations (K^+, Na^+) [58].

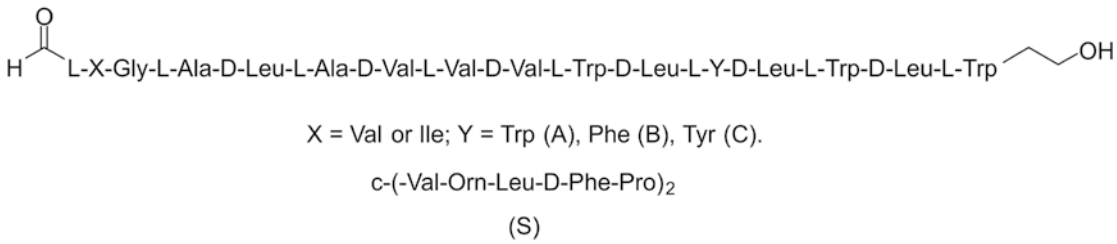


Fig. 2. Structures of gramicidins A, B, C, and S.

Gramicidin S is a distinct cyclic decapeptide: *cyclo*-(-Val-Orn-Leu-D-Phe-Pro)$_2$. It adopts an amphipathic antiparallel β-sheet conformation with a hydrophobic face (Val, Leu, D-Phe) and a positively charged ornithine face. This cyclic, symmetric structure differs markedly from the linear gramicidin D forms and confers broader membrane-disrupting activity [59].

As mentioned above, gramicidins are bactericidal ionophores or membrane disruptors. Linear gramicidin D forms cation-selective channels that collapse ion gradients, depolarize the membrane, and inhibit synthesis of adenosine triphosphate (ATP)—highly effective against Gram-positive bacteria (*Staphylococcus*, *Streptococcus*, *Bacillus*) but inactive against most Gram-negatives due to the outer membrane barrier. Gramicidin S inserts into bacterial membranes, increasing permeability and causing leakage of cellular contents. It shows activity against some Gram-negatives and fungi as well. Both are hemolytic and toxic to mammalian cells at higher concentrations, restricting use to topical applications. They exhibit rapid killing at low micromolar doses and low resistance potential because they target the lipid bilayer rather than a specific protein [60].

Owing to systemic toxicity (hemolysis, organ damage), gramicidins are used exclusively topically. Gramicidin D is formulated in ophthalmic solutions (often combined with neomycin and polymyxin B) for bacterial conjunctivitis, corneal ulcers, and external eye infections. It also appears in some skin/wound creams and throat lozenges. Gramicidin S has been applied for infected wounds, dental infections, and historically as a topical spermicide or treatment for genital ulcers. Veterinary use (e.g., in equine eye drops) is also common. They provide broad-spectrum coverage against Gram-positive pathogens in superficial infections where systemic antibiotics are unnecessary [61].

Gramicidins are produced by large-scale fermentation of *B. brevis* strains. Biosynthesis occurs via non-ribosomal peptide synthetases (NRPS): four large multimodular enzymes for linear forms and two (GrsA/GrsB) for the cyclic Gramicidin S, incorporating D-AAs and performing cyclization. The crude tyrothricin mixture is extracted, purified by chromatography or crystallization, and formulated into sterile ophthalmic drops, ointments, or creams. Production is well-established, cost-effective, and yields stable crystalline solids [62].

Gramicidin has long-standing FDA recognition as an active ingredient in approved combination products, e.g., neomycin/polymyxin B/gramicidin ophthalmic solution under Abbreviated New Drug Applications since the 1960s. It is listed in the FDA Orange Book for topical/ophthalmic use in superficial bacterial

infections. Gramicidins A-C and gramicidin S have not been granted new-drug approval for systemic administration or novel indications. Their use remains confined to traditional topical, multi-component preparations available by prescription or over the counter. The lack of recent FDA approvals highlights their mature, well-characterized profile as safe and effective topical antimicrobials [63].

Gramicidins exemplify early peptide antibiotics whose distinctive ion-channel-forming and membrane-disruptive activities remain clinically relevant for topical use, even though their intrinsic properties preclude systemic administration. Their discovery helped inaugurate the antibiotic era, and their unusual sequence architecture, most notably the incorporation of D-AAs that confer conformational rigidity, proteolytic stability, and defined channel geometry, continues to inspire contemporary research on membrane-active peptides. This combination of structural novelty and functional robustness underscores why gramicidins remain a foundational model for designing next-generation peptide therapeutics [57–63].

Cyclosporine. Cyclosporine (also known as ciclosporin or cyclosporine A, CsA) is a potent immunosuppressant and the prototype calcineurin inhibitor. It revolutionized organ transplantation and remains a cornerstone therapy for preventing graft rejection and treating certain autoimmune conditions [64].

Cyclosporine was first isolated in 1971 from the soil fungus *Tolypocladium inflatum* during routine screening for new antibiotics. A key breakthrough followed in 1972, when its potent immunosuppressive activity was identified in a functional screening assay, leading to further characterization of its selective T-cell–suppressive effects. The complete chemical structure was elucidated in 1976 (Fig. 3). Clinical efficacy in preventing organ rejection was subsequently demonstrated in kidney and liver transplantation, with the first patient receiving cyclosporine in 1980. The drug entered medical use after FDA approval in 1983 (as Sandimmune®) and is now included on the World Health Organization (WHO) List of Essential Medicines [65,66].

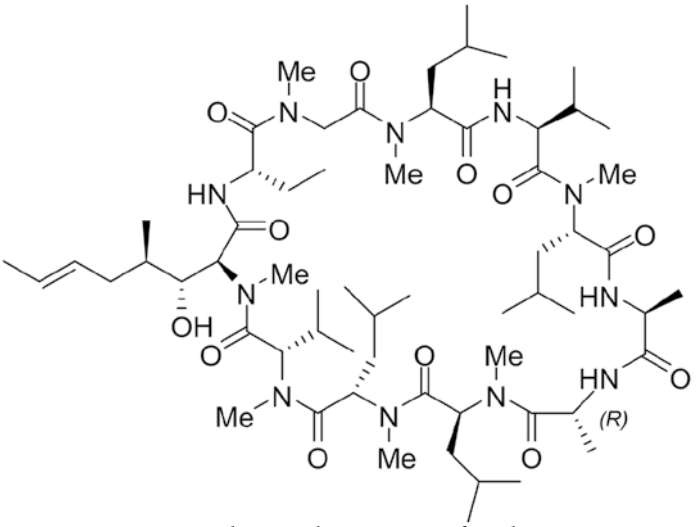


Fig. 3. Chemical structure of cyclosporine.

Cyclosporine is a cyclic undecapeptide (Fig. 3) produced non-ribosomally. It contains seven *N*-methylated amide bonds, which confer exceptional metabolic stability, high lipophilicity, and a 'chameleonic' conformational flexibility that enables membrane permeation despite its large size. The peptide includes several unusual residues, most notably the unique amino acid at position 1, (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (MeBmt or Bmt), as well as sarcosine (*N*-methyl-glycine) and 2-aminobutyric acid (Abu). It also contains one single D-AA, i.e., D-Ala at position 8. The macrocycle is closed by a peptide bond, forming a highly stable 33-membered ring. This structural architecture enables cyclosporine to bind intracellular cyclophilin A. The resulting complex inhibits calcineurin, thereby blocking T-cell activation [66, 67].

As noted above, the FDA first approved cyclosporine (Sandimmune®) in 1983 for the prophylaxis of organ rejection in allogeneic kidney, liver, and heart transplantation. A microemulsion formulation with improved oral bioavailability (Neoral®) was subsequently approved. Ophthalmic emulsions (0.05%) for dry-eye disease (keratoconjunctivitis sicca) and additional topical formulations followed. Numerous generic versions are now available. In 2021, the structurally related analog voclosporin was also approved by the FDA [68].

Cyclosporine is a calcineurin inhibitor that selectively suppresses T-cell activation and proliferation by blocking interleukin-2 production. FDA-approved indications include: prevention of organ rejection in kidney, liver, and heart transplantation (typically in combination regimens); treatment of severe, recalcitrant plaque psoriasis in non-immunocompromised adults; rheumatoid arthritis inadequately controlled by methotrexate alone; and dry-eye disease, for which a 0.05% ophthalmic emulsion is approved for keratoconjunctivitis sicca associated with Sjögren's syndrome or meibomian gland dysfunction [69,70].

Additional or off-label uses include atopic dermatitis, ulcerative colitis, nephrotic syndrome, graft-versus-host disease, and certain veterinary applications (e.g., canine atopic dermatitis). Cyclosporine is administered primarily orally—with therapeutic drug monitoring due to its narrow therapeutic index—or topically; intravenous administration is reserved for specific situations. Major adverse effects include nephrotoxicity, hypertension, and an increased risk of infections and malignancies [70].

D-penicillamine. D-penicillamine is a chelating and disease-modifying therapeutic agent that has been used in medicine for several decades, particularly in the treatment of heavy metal poisoning, Wilson's disease, and certain autoimmune disorders. It is a degradation product of penicillin, although it does not possess antibiotic activity. Its discovery and therapeutic development represent an important example of how chemical derivatives of existing drugs can acquire entirely different medical applications [71].

D-penicillamine was first identified as a metabolite of penicillin during studies of penicillin degradation in the mid-20th century. Chemically, it is a dimethylated analog of the amino acid cysteine, containing a free sulfhydryl (-SH) group that gives it strong metal-binding properties (Fig. 4). This characteristic led to its recognition as an effective chelating agent capable of forming stable complexes with metals such as copper, lead, and mercury.

Its therapeutic importance became evident in the 1950s, when researchers discovered its ability to remove excess copper from the body, providing a breakthrough treatment for Wilson's disease [71-73].

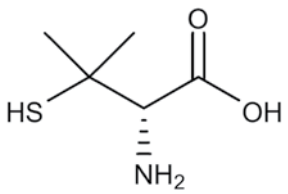


Fig. 4. Chemical structure of D-penicillamine.

The FDA approved D-penicillamine in the late 1950s and early 1960s for clinical use, and it was marketed under trade names such as Cuprimine® and Depen®. Its approval was particularly significant for Wilson's disease, as it became the first effective oral treatment for reducing copper accumulation and preventing severe liver and neurological damage [71–73].

Medically, D-penicillamine has three major therapeutic applications. The most important is in the treatment of Wilson's disease, a rare genetic disorder characterized by excessive copper accumulation in tissues, especially the liver and brain. By binding copper and promoting its urinary excretion, D-penicillamine helps reduce toxic copper levels and prevents disease progression [74-76].

A second important use is in the management of heavy metal poisoning, including lead and mercury intoxication. As a chelating agent, D-penicillamine binds toxic metals and facilitates their elimination from the body, although in many cases newer chelators are now preferred because of better safety profiles [72–76].

The third major use is in the treatment of severe rheumatoid arthritis, where D-penicillamine acts as a disease-modifying antirheumatic drug (DMARD). In rheumatoid arthritis, it helps reduce inflammation and slow joint damage, although its use has declined due to the availability of safer and more effective alternatives [71].

Additionally, D-penicillamine is used in the management of cystinuria, a hereditary disorder in which excessive cystine in the urine leads to recurrent kidney stone formation. The drug reacts with cystine to form a more soluble compound, thereby reducing stone formation.

Despite its effectiveness, D-penicillamine is associated with significant adverse effects, including skin reactions, bone marrow suppression, nephrotoxicity, and autoimmune complications such as drug-induced lupus. Because of these risks, its use requires careful medical supervision and regular monitoring [74].

D-Penicillamine is a remarkable example of a simple D-AA derivative produced by the chemical degradation of penicillin. This compound has emerged as a valuable therapeutic agent with key applications in heavy metal chelation and the treatment of autoimmune diseases. Its contribution to the management of Wilson's disease is especially noteworthy: introduced in the 1950s, it dramatically transformed a previously fatal inherited disorder into a treatable condition and remains an essential medicine in modern clinical practice.

Daptomycin. Daptomycin is a cyclic lipopeptide antibiotic and the first member of its class approved for clinical use. It represents a unique example of a complex molecule containing multiple D-AAs that exhibits potent bactericidal activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) [77].

Daptomycin was discovered in the late 1980s by researchers at Eli Lilly and Company from the soil actinomycete *Streptomyces roseosporus*. Early clinical development by Eli Lilly was halted due to concerns about skeletal muscle toxicity at high doses. In 1997, the rights were acquired by Cubist Pharmaceuticals, which optimized the dosing regimen (once-daily administration) to minimize toxicity while maintaining efficacy. Daptomycin was approved by the FDA in September 2003 under the brand name Cubicin® and has since become an important option for treating resistant Gram-positive infections [77-79].

Daptomycin is a 13-amino acid cyclic lipodepsipeptide (Fig. 5). It consists of a decanoyl fatty acid tail attached to the *N*-terminus of a linear tripeptide "handle", linked to a 10-amino acid macrocyclic core closed by an ester (lactone) bond: decanoyl-Trp^{1}-Asn^{2}-Asp^{3}-Thr^{4}-Gly^{5}-Orn^{6}-Asp^{7}-D-Ala^{8}-Asp^{9}-Gly^{10}-D-Ser^{11}-MeGlu^{12}-Kyn^{13} (10-residue lactone ring between Thr^{4} and Kyn^{13}). It contains three D-AAs (D-Asn at position 2, D-Ala at position 8, and D-Ser at position 11), as well as several non-proteinogenic amino acids including L-ornithine, (2*S*,3*R*)-3-methyl-L-glutamic acid, and kynurenine (Kyn) (2*S*)-2-amino-4-(2-aminophenyl)-4-oxobutanoic acid. The molecule is anionic and requires calcium ions (Ca^{2+}) for its membrane-inserting activity [78–80].

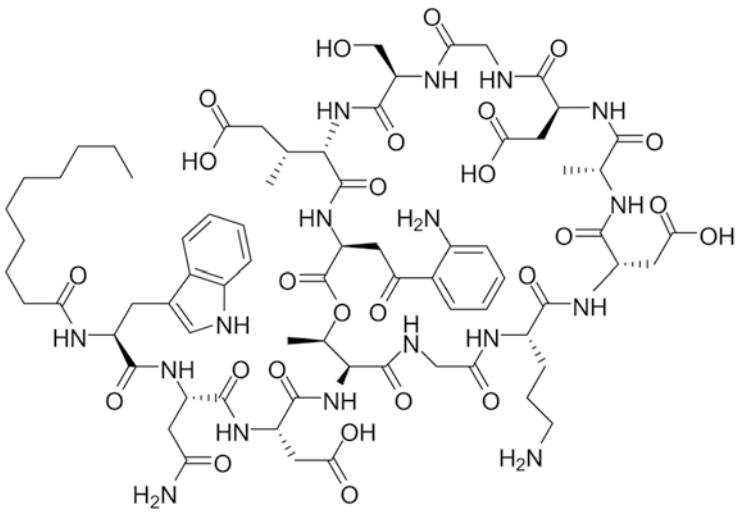


Fig. 5. Chemical structure of daptomycin.

As stated above, the FDA first approved daptomycin (Cubicin®) in 2003 for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive bacteria. In 2006, the indication was expanded to include *Staphylococcus aureus* bloodstream infections (bacteremia), including right-sided infective endocarditis caused by methicillin-susceptible and methicillin-resistant isolates. It is also approved for pediatric patients (1–17 years) for cSSSI and bacteremia. A new formulation (Cubicin® RF) was later approved for improved stability and shorter infusion time [77–81].

Daptomycin exerts rapid, concentration-dependent bactericidal activity by binding to the bacterial cell membrane in a calcium-dependent manner, inserting its lipid tail, and causing rapid depolarization of the membrane potential. This leads to disruption of multiple membrane functions, potassium efflux, and ultimately bacterial cell death without significant lysis. It is primarily used for serious Gram-positive infections [82].

Daptomycin is produced commercially by submerged fermentation of *Streptomyces roseosporus*. It belongs to the A21978C family of lipopeptides and is biosynthesized by a large NRPS system. The fatty acid side chain is added by supplying decanoic acid (or its precursors) during fermentation to direct production toward the decanoyl derivative. After fermentation, the compound is extracted and highly purified. Strain improvement, precursor feeding, and metabolic engineering have been used to significantly increase yields for industrial production [77, 79, 81].

Daptomycin itself remains the only clinically approved member of this specific lipopeptide class for systemic use. Semisynthetic derivatives and analogs have been explored in research to improve activity, reduce toxicity, or expand the spectrum, but none have yet reached broad clinical approval. Minor natural variants produced by the same organism differ mainly in the length of the lipid tail and show reduced potency [82].

Etelcalcetide. Etelcalcetide (brand name: Parsabiv®) is a synthetic peptide calcimimetic agent and the first intravenous calcimimetic approved for clinical use. It is a unique example of a chirobiotic peptide composed almost entirely of D-AAs, designed to act as an allosteric agonist of the calcium-sensing receptor (CaSR). It is used for the treatment of secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD) on hemodialysis [83, 84].

Etelcalcetide (originally known as AMG 416 or KAI-4169) was developed by Amgen (in collaboration with KAI Pharmaceuticals). It was designed as a novel, longer-acting chirobiotic alternative to the oral calcimimetic cinacalcet (Mimpara®). The compound entered clinical development in the early 2010s. Amgen submitted the New Drug Application to the FDA in 2015. It received approval from the European Medicines Agency (EMA) in November 2016 and from the FDA in February 2017 under the brand name Parsabiv® [83–85].

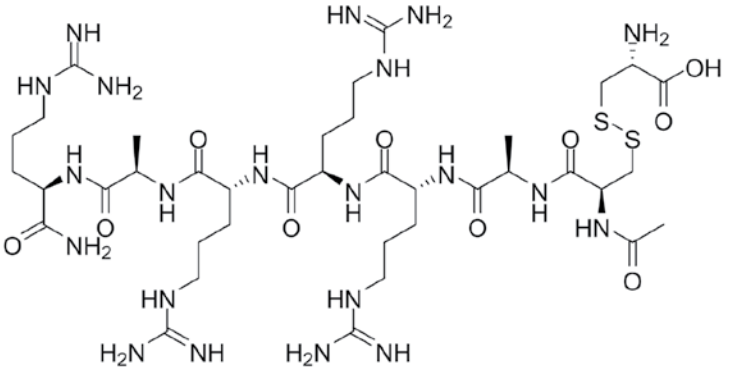


Fig. 6. Chemical structure of etelcalcetide.

Etelcalcetide is an 8-amino acid linear peptide with a disulfide linkage. It consists of a chain of seven D-AAs linked via a disulfide bond to an L-cysteine residue (Fig. 6).

The high content of D-AAs provides excellent proteolytic stability, allowing the chirobiotic peptide to remain active in circulation despite being a relatively small peptide [86].

Etelcalcetide (Parsabiv®) was approved in 2017 for the treatment of SHPT in adult patients with CKD on hemodialysis. It is administered as a bolus injection three times per week at the end of hemodialysis sessions. Etelcalcetide acts as a positive allosteric modulator (agonist) of the CaSR on the parathyroid glands. Activation of CaSR decreases the secretion of parathyroid hormone (PTH), lowers serum calcium and phosphorus levels, and helps control the mineral and bone disorder associated with CKD. It is indicated for secondary hyperparathyroidism in adult CKD patients on hemodialysis [86]. Unlike oral cinacalcet, etelcalcetide is given intravenously during dialysis, which improves adherence and ensures delivery in patients who have difficulty taking oral medications. Common side effects include hypocalcemia, nausea, vomiting, and muscle spasms. Serum calcium levels must be monitored closely [83–86].

Etelcalcetide is produced by chemical synthesis using solid-phase peptide synthesis (SPPS) technology. Because the molecule consists predominantly of D-AAs, it is assembled using protected D-AA building blocks. The disulfide bond is formed in a controlled oxidation step between the D-Cys and L-Cys residues. The final product is purified and converted to the hydrochloride salt for pharmaceutical use. As a synthetic peptide, it does not rely on fermentation or biological extraction [87, 88].

Difelikefalin. Difelikefalin (brand name: Korsuva™) is a synthetic tetrapeptide and a first-in-class, peripherally restricted kappa opioid receptor (KOR) agonist. It is a notable example of a peptide drug composed entirely of D-AAs, designed to selectively activate peripheral KORs while minimizing central nervous system penetration. It is approved for the treatment of moderate-to-severe pruritus (itch) associated with chronic kidney disease (CKD-aP) in adults undergoing hemodialysis [89, 90].

Difelikefalin (originally developed as CR845) was discovered and developed by Cara Therapeutics. The compound was engineered to create a potent and selective KOR agonist with minimal ability to cross the blood-brain barrier, thereby reducing the risk of centrally mediated side effects such as dysphoria or sedation commonly associated with traditional opioids. After successful Phase 3 clinical trials (KALM-1 and KALM-2), the FDA approved difelikefalin in August 2021 under the brand name Korsuva™, making it the first approved therapy specifically for chronic kidney disease-associated pruritus [89–90].

Difelikefalin is a tetrapeptide consisting of four D-AAs linked to a modified piperidine moiety (Fig. 7).

The exclusive use of D-AAs confers high resistance to proteolytic degradation, resulting in a favorable pharmacokinetic profile for intravenous administration. Difelikefalin was approved for the treatment of moderate-to-severe pruritus associated with chronic kidney disease (CKD-aP) in adults undergoing hemodialysis. It is administered as an intravenous bolus injection (0.5 mcg/kg) at the end of each hemodialysis session, typically three times per week. It has also received approval in several other countries, including the European Union and Australia [91].

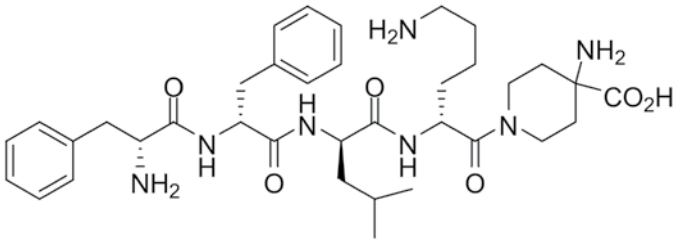


Fig. 7. Chemical structure of difelikefalin.

Difelikefalin selectively activates KORs located on peripheral sensory neurons and immune cells. This activation modulates itch signaling pathways without significant central opioid effects. It is the first and only FDA-approved treatment specifically indicated for CKD-associated pruritus, a condition that significantly impairs quality of life in hemodialysis patients. Clinical studies demonstrated significant reduction in itch intensity and improvement in itch-related quality of life compared to placebo. Common side effects include dizziness, somnolence, and paresthesia, which are generally mild to moderate. Because of its peripheral restriction, it has a lower risk of central side effects compared to non-selective opioids [92,93].

Difelikefalin is produced by chemical synthesis using SPPS. The peptide chain is assembled from protected D-AA building blocks, followed by coupling to the 4-aminopiperidine-4-carboxylic acid moiety. The final product is purified and formulated as a sterile solution for intravenous injection (often as the acetate salt). As a small synthetic peptide, it does not require biological fermentation or recombinant production [90-92].

Difelikefalin remains the only approved drug in its chirobiotic class. Oral formulations of Difelikefalin have been investigated for other indications such as postoperative pain and osteoarthritis pain but have not yet received broad regulatory approval. No major structural analogs are currently in late-stage clinical development.

Voclosporin. Voclosporin (brand name: Lupkynis®) is a semisynthetic cyclic undecapeptide and a next-generation calcineurin inhibitor. It is a structural analog of cyclosporine A with a modified side chain at the unique MeBmt residue. Voclosporin was specifically designed to offer improved potency, a more predictable pharmacokinetic profile, and potentially reduced nephrotoxicity compared to cyclosporine [94].

Voclosporin was developed by Isotechnika Pharma (later Aurinia Pharmaceuticals) in Edmonton, Canada. The molecule was created through a targeted chemical modification of cyclosporine A, replacing the MeBmt at position 1 with a modified amino acid containing a shorter unsaturated side chain. After successful Phase 2 and Phase 3 clinical trials (AURA-LV and AURORA), the FDA approved voclosporin in January 2021 under the brand name Lupkynis®, making it the first approved oral therapy for lupus nephritis in over a decade [94, 95].

Voclosporin is a cyclic undecapeptide (Fig. 8). It retains the core macrocyclic structure of cyclosporine A but features a modified side chain at position 1. The molecule contains seven *N*-methylated amide bonds and one D-AA (D-Ala at position 8), which contribute to its metabolic stability and membrane permeability [96].

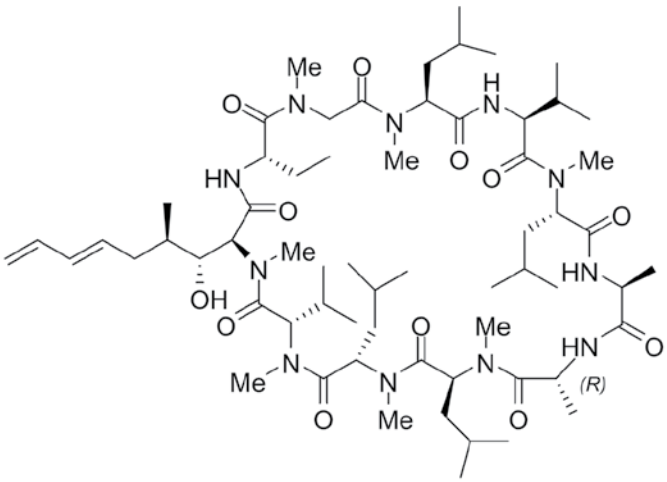


Fig. 8. Chemical structure of voclosporin.

The FDA approved voclosporin (Lupkynis®) for the treatment of adult patients with active lupus nephritis (LN), in combination with background immunosuppressive therapy (typically mycophenolate mofetil and low-dose corticosteroids). It is currently the only approved calcineurin inhibitor specifically indicated for LN [94,95].

Voclosporin acts as a calcineurin inhibitor by binding to cyclophilin A, forming a complex that inhibits the phosphatase activity of calcineurin. This prevents dephosphorylation of nuclear factor of activated T-cells (NFAT), thereby suppressing T-cell activation and interleukin-2 production. It is primarily used for active LN (Class III, IV, or V) in combination with standard-of-care therapy [97].

Voclosporin offers a more consistent pharmacokinetic profile and a narrower therapeutic index than cyclosporine, allowing for more predictable dosing with therapeutic drug monitoring. Common side effects include hypertension, nephrotoxicity, tremor, and increased infection risk. Regular monitoring of renal function and blood pressure is essential [98].

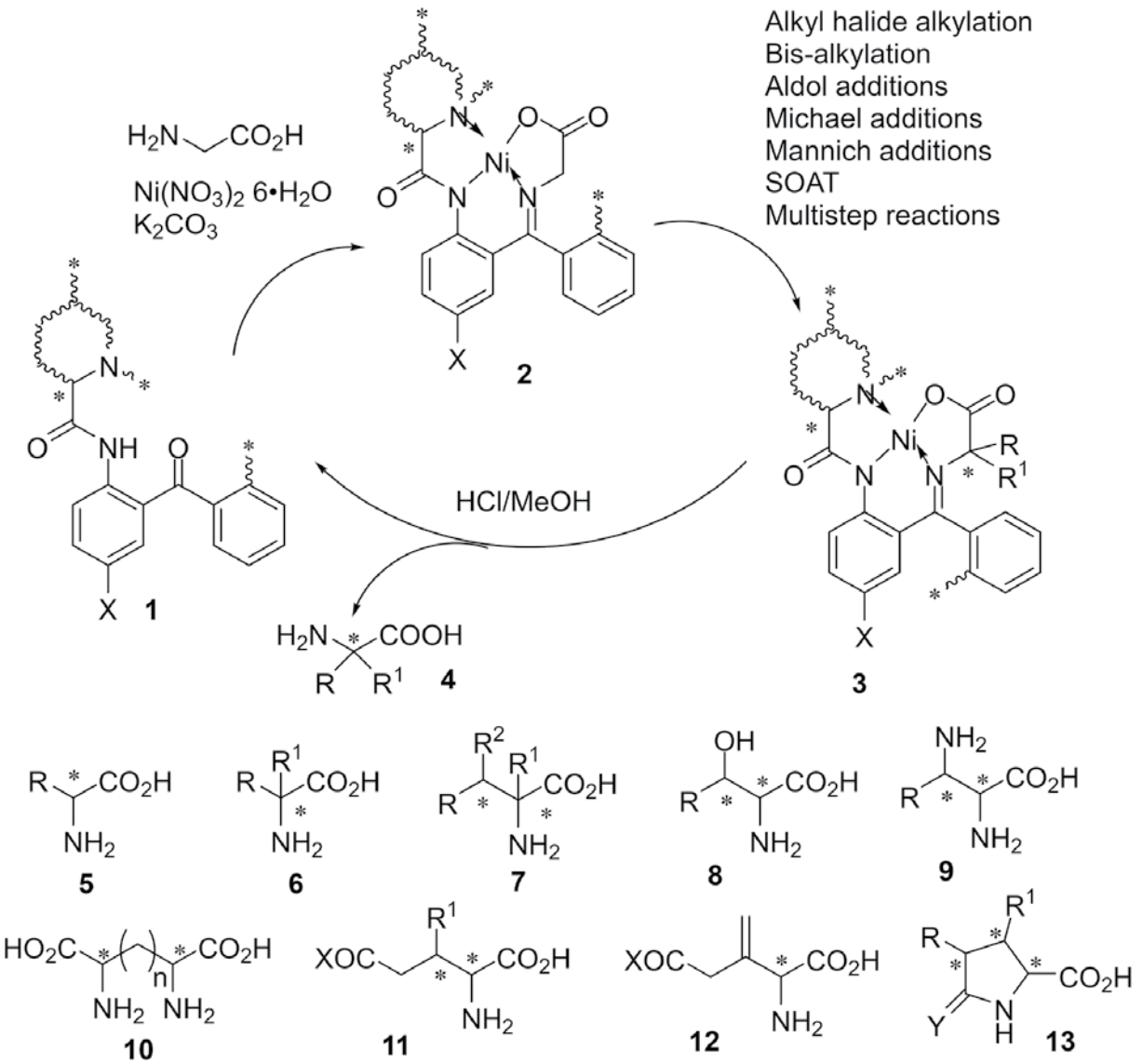
Voclosporin is produced by semisynthetic modification of cyclosporine A. The process begins with fermentation-derived cyclosporine A, followed by selective chemical transformation of the MeBmt side chain at position 1 to introduce the shorter unsaturated chain. The final product is purified by chromatography and formulated into soft-gelatin capsules for oral administration. This semisynthetic route is significantly more efficient than total chemical synthesis of the entire 11-residue macrocycle [96].

Voclosporin is currently the only approved derivative of cyclosporine specifically optimized for LN. Other experimental analogs of cyclosporine (such as alisporivir) have been investigated for antiviral indications but have not reached approval for autoimmune diseases.

Synthesis

The development of efficient, scalable, and environmentally sustainable synthetic methodologies for D-AAs is no longer a niche academic pursuit but a strategic necessity in pharmaceutical science. Continued innovation in asymmetric synthesis [99-108], biocatalysis

[109–115], and chemoenzymatic approaches [116–120] will be crucial to unlocking the full therapeutic potential of D-AA-containing peptides and to meeting the growing needs of the peptide drug pipeline. As the field of peptide therapeutics advances toward more stable, selective, and orally bioavailable candidates, robust access to diverse D-AAs will remain a cornerstone of future drug discovery and development.



Scheme 1. General application of chiral Ni(II) complexes for asymmetric synthesis of tailor-made amino acids.

The Ni(II) complexes of amino acid Schiff bases (Scheme 1) represent one of the most powerful and versatile general methodologies for the asymmetric synthesis of tailor-made α-amino acids [121–23]. In its most general form, as depicted in Scheme 1, this approach utilizes ligands **1** bearing a chiral auxiliary on the amino acid fragment, which are condensed with o-benzophenone or its derivatives. Ligand **1** is subsequently transformed into the corresponding Ni(II) complex **2** by reaction with glycine under basic conditions in the presence of Ni(II) ions. The Ni(II) ion serves a dual role: as a template that rigidly organizes the molecule and as a Lewis acid that dramatically increases the acidity of the α-hydrogen of the coordinated glycine. This enables highly stereoselective transformations at the α-position, including alkylation, dialkylation, aldol, Michael, and Mannich additions, as well as other C–C bond-forming reactions, under mild conditions. After the reaction, the products **3** can be readily disassembled under acidic conditions to release the enantiomerically enriched tailor-made amino acid **4**, while the chiral auxiliary is typically recovered and reused. Thanks to its high diastereoselectivity, operational simplicity, scalability, and broad substrate scope, the Ni(II)-complex methodology has become a widely adopted strategy for the preparation of structurally diverse, non-proteinogenic, and isotopically labeled α-amino acids required in modern medicinal chemistry and peptide drug development [121-123].

For example, amino acids of type **5** bearing virtually any substituents or functional groups on the side chain R can be readily prepared via alkylation of the Ni(II) glycine Schiff base complex with alkyl halides [124–127]. This methodology can be further extended to the synthesis of α,α-dialkyl-substituted amino acids **6** [128–131]. The approach also works efficiently with secondary alkyl halides, providing access to highly sterically hindered amino acids **7** containing both α- and β-stereogenic centers [132,133]. Additionally, the use of α,ω-dihaloalkanes enables the preparation of bis-amino acids of type **10** [134, 135]. β-Hydroxy amino acids **8** [136–138] and β-amino derivatives **9** [139, 140] are accessible through aldol and Mannich addition reactions, respectively. The Michael addition reaction of glycine Schiff base complex **2** [141–143] is particularly versatile, allowing the synthesis of a wide range of glutamic acid derivatives **11** [144–146], including β-methylene analogs **12** [147], as well as highly substituted pyroglutamates [148-150] and prolines **13** [151, 152]. Furthermore, multistep sequences employing these Schiff base complexes facilitate the preparation of more structurally complex targets, such as thalidomide derivatives [153-155], oxazolomycin and neooxazolomycin analogs [156], the AHOD (3-amino-2-hydroxy-octadecanoic acid) moiety of ralstonin A [157], and various derivatives of 1-amino-2-vinyl-cyclopropanecarboxylic acid [158–160].

Creative efforts in the structural design of ligands **1** [161–163] have led to the development of a new generation of chiral auxiliaries. These include derivatives featuring planar chirality **14** [164–166], (Fig. 9), axial chirality **15** [167, 168], and N–H-containing ligands **16** with a stereogenic nitrogen center [169–171]. Among the most practical and versatile structures is the Ni(II) complex **17** [172–174], which bears three strategically positioned chlorine atoms that enhance both reactivity and stereoselectivity. Notably, Ni(II) complexes **14** and **17** have proven particularly effective for the large-scale preparation of D-AAs.

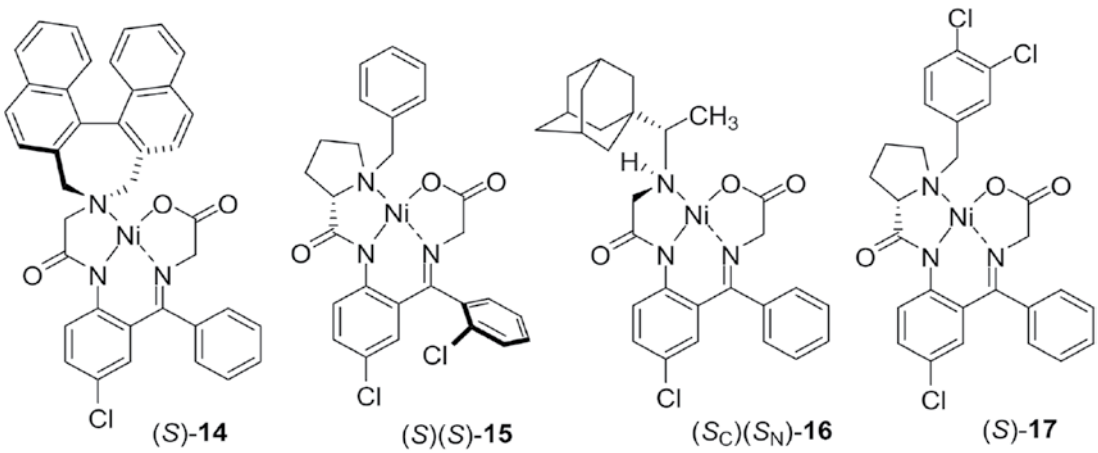
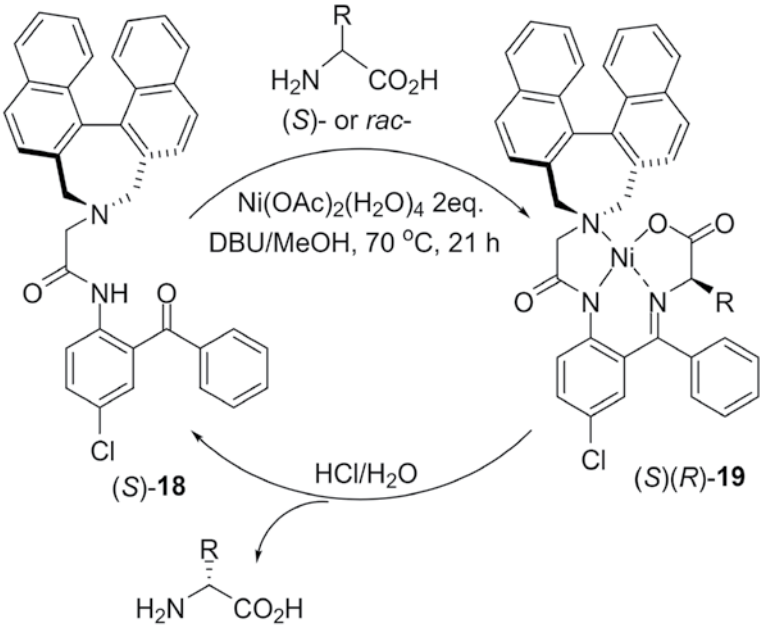


Fig. 9. New generation of chiral Ni(II) complexes.

D-AAs can be efficiently prepared via the Ni(II) Schiff base methodology using either L-to-D interconversion or deracemization strategies [175-177]. This allows the conversion of readily available L-AAs into their D-configured enantiomers or the direct transformation of inexpensive racemic (L/D) mixtures into the desired D-AAs with high selectivity [178-180]. As illustrated in Scheme 2, the planar chiral ligand **18** is reacted with an L-AA or its racemic counterpart to form the corresponding Ni(II) Schiff base complex **19**. The (*S*)-configuration of the chiral amine moiety in the ligand strongly favors (>95% diastereoselectivity) the formation of the D-configured amino acid. The resulting complex **19** is typically isolated by filtration and then disassembled under mild acidic conditions (aqueous HCl) to liberate the free D-AA while allowing recovery of the chiral ligand **18** [181–183]. Because the planar chirality of ligand **18** remains stable under the reaction conditions, it can be recovered and reused over multiple cycles without loss of performance. Owing to its high efficiency, excellent recyclability, and operational simplicity, this Ni(II) methodology is often more economically attractive than many catalytic approaches. It has been successfully scaled up to kilogram-scale production of various D-AAs.

Conclusions. In summary, the strategic incorporation of D-AAs has fundamentally transformed peptide therapeutics, converting inherently fragile and rapidly degraded biologics into stable, drug-like chirobiotic molecules with enhanced pharmacokinetic profiles, improved target specificity, and prolonged duration of action. This approach has significantly broadened the therapeutic utility of peptides across multiple therapeutic areas, including infectious diseases, metabolic disorders, oncology, autoimmune conditions, nephrology, and neurology. The evolution of D-AA–containing pharmaceuticals reflects more than seven decades of progress, from the early clinical use of gramicidin D in 1955 to modern approved drugs such as cyclosporine, daptomycin, etelcalcetide, difelikefalin, voclosporin, and others. This remarkable journey highlights the critical role of molecular chirality in drug dis-

covery and development. Advances in asymmetric synthesis, particularly Ni(II) Schiff base methodologies, computational design, mirror-image phage display, and peptidomimetic engineering have enabled the creation of increasingly sophisticated D-AA-rich peptides and macrocycles that were previously inaccessible. These innovations have delivered tangible clinical benefits, offering new treatment options for conditions with historically limited therapies, such as CKD-aP, LN, and rare complement-mediated disorders. By enhancing proteolytic stability and membrane permeability while reducing immunogenicity, D-AAs have helped bridge the gap between promising peptides and successful marketed drugs. Nevertheless, challenges remain. High manufacturing costs, potential off-target effects, and the need for specialized synthetic expertise continue to limit broader application. To fully unlock the potential of this class, future efforts should prioritize scalable and sustainable production methods, deeper structure–activity relationship studies, and the development of next-generation delivery systems. Overall, D-AA–containing chirobiotics exemplify how precise stereochemical design continues to drive innovation in pharmaceutical science. As synthetic methodologies mature and our understanding of peptide pharmacology deepens, D-AA strategies are poised to play an increasingly central role in the development of safer, more effective, and longer-lasting therapeutic agents for a wide range of human diseases.



Scheme 2. Procedure for the preparation of D-AAs.

AUTHORS' CONTRIBUTION. All authors have read the research results and approved the final version of the manuscript.

CONFLICT OF INTEREST. The authors declare no conflict of interest.

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ЗАСТОСУВАННЯ D-АМІНОКИСЛОТ У ДИЗАЙНІ ЛІКАРСЬКИХ ЗАСОБІВ (огляд)

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Присвята
Професору Таміо Хаяші – титану асиметричного каталізу, Полярній зірці в науці, чиє мудре керівництво стало для багатьох поколінь хіміків найформативнішим інтелектуальним досвідом.

D-амінокислоти стали незамінними будівельними блоками в сучасному дизайні пептидних лікарських засобів. Незважаючи на їхню відносну рідкісність у вищих організмах, D-амінокислоти є досить поширеними в природі, зокрема в бактеріальних пептидогліканах та мікробних антимікробних пептидах, де вони забезпечують протеолітичну стабільність і унікальну біологічну активність. Натхненні цими природними стратегіями, медичні хіміки успішно впровадили D-амінокислоти в синтетичні пептиди, щоб подолати притаманні обмеження традиційних пептидних препаратів, такі як швидка ферментативна деградація та низька біодоступність. Включення D-амінокислот пропонує низку ключових переваг, зокрема суттєво підвищену стійкість до протеолізу, подовжений період напіввиведення з плазми, знижену імуногенність та покращену селективність до рецепторів. Ці властивості дозволили розробити клінічно успішні препарати в багатьох терапевтичних галузях. Серед помітних прикладів – ранній антибіотик граміцидин D (1955), імуносупресивний агент циклоспорин, D-пеніциламін, даптоміцин, етелькальцетид, дифелікфалін та воклоспорин. Ці сполуки яскраво демонструють трансформаційний вплив D-амінокислот на пептидну фармакологію та їхню зростаючу роль у лікуванні інфекційних захворю-

вань, аутоімунних розладів, нефрологічних станів та багатьох інших патологій. Цей огляд висвітлює стратегічну важливість D-амінокислот у фармацевтичному дизайні, їхнє природне походження, клінічне застосування та значні досягнення в синтетичних методологіях з особливим акцентом на універсальний підхід на основі комплексів Шиффа Ni(II) для отримання tailor-made D-амінокислот. Еволюція лікарських засобів, що містять D-амінокислоти, демонструє, як стереохімічне конструювання продовжує стимулювати інновації у відкритті та розробленні пептидних препаратів.

Ключові слова: D-амінокислоти, хіральність, хіробіотики, комплекси Ni(II), дизайн лікарських засобів, протеолітична стабільність, пептидні терапевтичні засоби, лікарські препарати, що вийшли на ринок.

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