Cyclic peptide therapeutics: past, present and future

Alessandro Zorzi,[1,2] Kaycie Deyle[1,2] and Christian Heinis[1,*]

[1]Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

[2]Authors contributed equally

*To whom correspondence should be addressed:

C.H.: Tel: +41 21 693 9350; Fax: +41 21 693 9895; Email: christian.heinis@epfl.ch

Abstract

Cyclic peptides combine several favorable properties such as good binding affinity, target selectivity and low toxicity that make them an attractive modality for the development of therapeutics. Over 40 cyclic peptide drugs are currently in clinical use and around one new cyclic peptide drug enters the market every year on average. The vast majority of clinically approved cyclic peptides are based on natural products, such as antimicrobials or human peptide hormones. New powerful techniques based on rational design and *in vitro* evolution have enabled the *de novo* development of cyclic peptide ligands to targets for which nature does not offer solutions. A look at the cyclic peptides currently under clinical evaluation shows that several have been developed using such techniques. This new source for cyclic peptide ligands introduces a freshness to the field, and it is likely that a *de novo* developed cyclic peptide will be in clinical use in the near future.

Introduction

Cyclic peptides show great success as therapeutics. Examples of widely applied cyclic peptide drugs are the hormones or hormone analogues oxytocin, octreotide and vasopressin, the antibiotics vancomycin, daptomycin and polymyxin B or the immunosuppressant cyclosporine [1,2]. The success of this restrained peptide format as a therapeutic can be attributed to several favorable properties. First, cyclic peptides display a large surface area that provides a high affinity and selectivity for protein targets, and the limited conformational flexibility of the macrocyclic

structure further improves their favorable binding properties by reducing the entropic penalty upon binding. Second, cyclic peptides often have little to no toxicity due to their benign amino acid make-up. Third, cyclic peptides are easily produced by automated chemical synthesis, and they are simple to modify, handle, and characterize, which are all important properties for therapeutics.

In this review, the first chapter provides a look into the past by discussing the cyclic peptide therapeutics that have reached the market in the last 10 years and details the techniques that were used to develop them. This chapter will highlight that nearly all of these drugs are based on natural products or derivatives thereof. In a second chapter, we look at the present by discussing cyclic peptides that are currently undergoing clinical studies. This overview will show that there are several original cyclic peptide drug candidates developed *de novo* by rational design or *in vitro* evolution instead of through the modification of natural products. In a third chapter, we will look to the future by discussing the most promising new cyclic peptide formats and predict the technologies that will comprise the next generation of cyclic peptide therapeutics.

Peptide macrocycle drugs approved in the last 10 years

In the last ten years, 2006-2015, the FDA and EMA have approved nine cyclic peptide drugs, which account for only 3% of the new drugs that entered the market in this time period [3]. Four of these cyclic peptides, telavancin, dalbavancin, oritavancin and anidulafungin, are employed in bacterial and fungal infections. Three peptides, lanreotide, romidepsin, and pasireotide are oncology drugs, and one, linaclotide, is specific for gastrointestinal disorders. The last drug, peginesatide, was developed for the treatment of anemia during dialysis but was withdrawn soon after approval due to safety concerns.

The three antibacterials on this list, telavancin, dalbavancin and oritavancin, are semi-synthetic cyclic lipoglycopeptides (Figure 1) [4]. They belong to the same drug class as the established antibiotics vancomycin and teicoplanin, which all contain a common heptapeptidic core with five fixed residues that serve as the main binding site for the D-Ala-D-Ala target. Binding of these drugs to their target blocks the transpeptidation of peptidoglycan precursors in the bacterial cell wall [5]. These three new antibiotics all contain a lipophilic side chain that is thought to increase the dwell time near the target by anchoring them to the cell membrane and/or serve to destabilize the bacterial membrane. Interactions of the hydrophobic tails with cell membranes and plasma

proteins also prolong the plasma half-life. These three drugs are used for the treatment of complicated skin and skin structure infections and nosocomial pneumonia. The small variations in their structures cause subtle differences in their pharmacologic effects by fine-tuning their activities towards different bacterial strains or differing pharmacokinetic properties.

The cyclic peptide anidulafungin is a member of the class of echinocandin antifungals to which caspofungin and micafungin, approved in 2001 and 2005, also belong [6]. All three drugs share a similar peptide core formed by six amino acids, two of which are proline derivatives and two are threonine or threonine derivatives. Anidulafungin, derived from echinocandin B, is a natural fermentation product of *Aspergillus nidulans* wherein the lineoyl side-chain tail is replaced by a lipophilic alkoxytriphenyl group. Like caspofungin and micafungin, anidulafungin inhibits the 1,3-β-D-glucan synthase responsible for fungal cell wall synthesis. Anidulafungin has a high affinity for human plasma proteins and a slow degradation time, giving it a half-life in the body of around 24 hours, doubling that of caspofungin and micafungin.

The oncology drugs lanreotide and pasireotide are analogues of the successful cyclic peptide drug octreotide, which itself is an analogue of the endogenous cyclic peptide hormone somatostatin [7]. Somatostatin blocks the release of hormones such as the growth hormone by inhibiting G-protein-coupled somatostatin receptors. These new mimetics that have a substantially longer plasma half-life than somatostatin are used to treat acromegaly and endocrine tumors. Lanreotide, like octreotide, is a disulfide cyclized octapeptide wherein four amino acids are identical and the other four are closely related. The two drugs also have rather similar pharmacologic properties. Pasireotide's structure was reduced to a hexapeptide cyclized through an amide bond and its sequence conserves only the D-tryptophan-lysine core of somatostatin [8]. Pasireotide differs from octreotide and lanreotide in its substantially higher affinity for certain receptor subtypes, making it more suitable for treating Cushing's disease and acromegaly in patients unresponsive to the other agents.

The third oncology drug, romidepsin is a natural product isolated from gram-negative *Chromabacterium violaceum,* approved for the treatment of T-cell lymphomas [9]. It is a depsipeptide composed of five backbone-cyclized residues and a disulfide bond that creates a bicyclic structure. The disulfide-cyclized romidepsin is a pro-drug that is significantly more stable

in plasma than the active drug. Once inside a cell, it is reduced to its active form wherein a free thiol group chelates the zinc ion in the active site of intracellular histone deacetylase (HDAC) enzymes. The drug inhibits the removal of acetyl groups from lysine residues of N-terminal histone tails, maintaining a more open and transcriptionally active chromatin state which alters gene expression. Romidepsin is the second HDAC inhibitor that entered the market after vorinostat, which is a small molecule drug.

Linaclotide is a 14-amino acid cyclic peptide derived from heat-stable enterotoxins, cyclic peptides produced by various *E.coli* strains which are a frequent cause of diarrhea [10]••. The drug provides well-tolerated relief in patients with chronic constipation and irritable bowel syndrome. Linaclotide contains three disulfide bonds that constrain the conformation of the peptide, providing high proteolytic stability. The drug acts by binding to guanylate cyclase C on the surface of intestinal epithelial cells [11]. Activation of the cyclase triggers a signaling pathway that leads to chloride and fluid secretions into the lumen, increasing colonic transit. The location of this target in the intestine allows for linaclotide to be orally administered while not orally available, as the drug does not have to pass through the gastrointestinal lining [12].

The final cyclic peptide approved in the last 10 years is peginesatide, an agonist of the erythropoietin receptor developed for severe anemia in which erythropoietin cannot be used [13]. This cyclic peptide was discovered through phage display panning against the erythropoietin receptor [14,15]•. It was then chemically dimerized with a polyethylene glycol (PEG), increasing the affinity, potency and circulation time in blood. It was voluntarily withdrawn from the market, however, one year after its approval due to safety concerns not experienced during the clinical trials. Unlike all other previously approved cyclic peptide drugs, peginesatide was the first to be developed *de novo*.

Taken together, eight of the newly approved nine drugs have a mechanism of action similar to established drugs and only one, linaclotide, is a first-in-class drug. Besides being a highly innovative drug and serving a large group of patients, linaclotide is also a highlight in terms of sales. It generated revenues of 460 million USD, improving upon the already impressive sales of 140 and 300 million USD in the two first years after approval, and it is likely to become a blockbuster drug within the next five years [16]. Lanreotide and romidepsin are the other two drugs

approved in the last ten years to have noteworthy sales, earning 440 and 70 million USD last year, respectively.

Peptide macrocycles in clinical development

Our database and literature search has identified over 20 cyclic peptides that are currently undergoing clinical evaluation. These molecules have been developed for a highly diverse set of medical conditions, including several types of cancer, various infectious diseases, endocrine/metabolic disorders, hematological diseases and cardiovascular disorders. A majority of the cyclic peptides, similar to those already approved, are derivatives of natural products from microorganisms or human hormones. Interestingly, several of the cyclic peptides in clinical trials were developed *de novo* using newer methods based on either rational design strategies or *in vitro* evolution (Table 2). We will focus in this sub-chapter on five of these peptides in order to shine a light on the new and innovative techniques for developing cyclic peptide therapeutics.

POL7080 is a *Pseudomonas aeruginosa*-specific antibacterial cyclic peptide with a new mode of action [17]• developed through multiple iterative rounds of peptide library synthesis and screening for enhanced antibacterial activity. The starting point of this evolution process was protegrin I, a β-hairpin peptide having broad antibiotic properties through membrane lytic activity. After stabilizing its secondary structure by a D-Pro-L-Pro β-turn motif, the basis of Polyphor's proprietary PEM technology, [18] and several rounds of optimization by amino acid substitution, the new 14-amino acid peptide showed reduced cell lysis but high activity and selectivity towards *Pseudomonas aeruginosa*. Analysis of the potent antibiotic revealed binding to the membrane protein LptD, involved in membrane biogenesis, and therefore demonstrated a new mode of action from the precursor. A phase 1 clinical trial established the clinical safety and tolerability of POL7080, and this antibiotic is currently under phase 2 evaluation for the treatment of *Pseudomonas aeruginosa* infections.

POL6326 is a bicyclic peptide inhibitor of the chemokine receptor CXCR4. Blockage of CXCR4 avoids the interaction with the ligand SDF-1 (stromal cell-derived factor 1), which induces hematopoietic stem cell (HSC) detachment from the bone marrow into the circulating blood [19]. The mobilization of hematopoietic stem cells is of interest for stem cell transplantation, tissue regeneration and chemotherapy. POL6326 was developed using a combination of rational design

and iterative optimization by peptide sequence variation and activity testing. In a first step, an analogue of the natural peptide polyphemusin II inhibiting CXCR4 was mounted onto the PEM technology D-Pro-L-Pro template to stabilize its β-strand conformation [18]. In a second step, the potency and various other properties of the receptor antagonist were optimized through several rounds of sequence modification, providing a final amino acid sequence for POL6326 that differs greatly from the starting polyphemusin II. A phase 1 study for HSC mobilization was completed, and phase 2 clinical studies have been initiated.

APL-2 is a PEGylated cyclic peptide inhibitor of C3, a central protein in the complement cascade. Excessive or uncontrolled activation of the complement system plays a role in a range of autoimmune and inflammatory diseases. APL-2 binds to a site on C3 that prevents binding of convertases and thus conversion to C3b. It is based on compstatin, a disulfide cyclized 13-amino acid peptide derived from a 27-mer peptide isolated by phage selection against C3b [20]. The addition of a PEG moiety to APL-2 prevents fast renal clearance and enables C3 inhibition for several days per injection. APL-2 is currently in phase 2 testing for age-related macular degeneration (AMD) and in phase 1 for paroxysmal nocturnal hemoglobinuria (PNH). For these two indications, the drug is applied by intravitreal and subcutaneous administration, respectively. A non-PEGylated form of the peptide, APL-1 is in development for inhalation treatment of chronic obstructive pulmonary disease (COPD).

ALRN-6924 is a dual inhibitor of MDM2 and MDMX based on a stapled peptide that interrupts p53 suppression and restores normal p53-mediated apoptosis activity in tumor cells [21]•. Stapled peptides stabilize α-helices through hydrocarbon linkers that bridge two amino acid side chains on the same face of a helix. In addition to forming a stable cyclic peptide, this process can facilitate peptide cell penetration. ALRN-6924 was developed by optimizing the stapled peptide ATSP-7041 which in turn was obtained by stapling the phage display peptide pDI with an 11 carbon linker through ring-closing metathesis. This final stapled peptide mimics an α-helix of p53 that binds to the same region of MDM2/MDMX. ALRN-6924 is currently undergoing testing in a phase 1/2 trial in patients with advance solid tumors or lymphomas expressing wild-type p53 protein, and in a phase 1 trial in patients with acute myeloid leukemia or advanced myelodysplastic syndrome.

RA101495 is a cyclic peptide that binds and allosterically inhibits the cleavage of the complement factor C5 into C5a and C5b [22]. The peptide was developed by screening mRNA display combinatorial libraries of cyclic peptides based on a combination of natural and unnatural amino acids [23]. Inhibition of C5 activation is of interest for the treatment of complement disorders such as PNH, refractory generalized myasthenia gravis and lupus nephritis. A C5 inhibitor based on a monoclonal antibody, eculizumab, is successfully used for the treatment of PNH and for atypical hemolytic uremic syndrome (aHUS), though it is administered intravenously. The peptide-based inhibitor RA101495 was developed for subcutaneous injection in order to enable more convenient self-administration. A phase 1 trial with RA101495 has been completed successfully.

A look the techniques used to develop these clinical candidates shows that all depended heavily on peptide library screening. In the case of the two peptides POL7080 and POL6326, natural peptides served as starting points but were extensively modified over several rounds of amino acid substitution and activity testing. As described above, POL7080 was so changed in its sequence that a new mechanism of action had evolved. The development of ALRN-6924 was encouraged by successes with stapled peptides that were rationally designed from the α-helices of p53 located at the p53-MDM2/MDMX binding interface. The template that was eventually used for the development of ALRN-6924 was derived from a phage display peptide library. Finally, the drug candidates APL-2 and RA101495 were developed by *in vitro* evolution through large random peptide library screening using either phage display or mRNA display. These and other powerful *in vitro* evolution techniques are now being broadly applied to develop a wide range of targets. It can be expected that many more *de novo* developed cyclic peptides with activities for interesting or previously unexplored targets will be fished out of random libraries by phage or mRNA display, and will soon be evaluated in clinical studies.

Future challenges and potential solutions

Several important challenges remain in the development of cyclic peptide therapeutics, the two most important ones being oral availability and cell permeability. Innovative approaches were developed in recent years to address one or both of these challenges, including the application of cell penetrating peptides [24], the stabilization of peptides in α-helical conformations with hydrocarbon linkers [25], or the *in vitro* evolution of N-methylated peptides [26]. In order to develop cyclic peptides that have a good oral availability and that efficiently enter cells by passive diffusion,

it might be required to develop molecules with smaller molecular weights and fewer peptide bonds. One could imagine that future macrocycles will contain only one or a few amino acids but additionally contain a polyketide type component in the backbone. A good role model is the orally available and cell permeable drug tacrolimus which contains a backbone based on one amino acid and a polyketide chain wherein the amino acid forms key interactions with the target. To develop such chimeric peptide/polyketide macrocycle ligands, it will be crucial to create efficient chemistries and strategies that allow the synthesis and screening of large combinatorial libraries.

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Potential Conflicts of Interest

C.H. is a scientific co-founder of Bicycle Therapeutics.

Highlights

- Nine new therapeutics based on cyclic peptides were approved in the last 10 years, including one first-in-class drug.
- More than 20 cyclic peptides are currently in clinical development including several peptides developed *de novo* with new techniques.
- New powerful strategies based on rational design and in vitro evolution have enabled the development of cyclic peptide drug candidates to new targets.
- Oral availability and cell permeability remain challenges to peptide therapeutics, but new technologies are emerging.

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[10]•• Linaclotide is a showcase for innovative peptide drug development. This paper describes the development story of this first-in-class drug.

[15]• Impressive peptide engineering effort that led to a peptide-based erythropoietin mimetic.

[17]• Nice story describing the development of the antibiotic POL7080 that has a different mechanism of action than its precursor, the bacteriolytic peptide protegrin after it was heavily modified in several cycles of sequence modification and activity testing.

[21]• Paper describing the development of cell permeable peptides by α-helix stapling. A hydrocarbon stapled peptide presented in this work is the precursor of the clinical candidate ALRN-6924.

Tables

Approved[a]	Generic name	Indication	Mode of action	MW (Da)	Route of administration [b]	Company
2006	anidulafungin	fungal infections	fungal 1,3-ß-D-glucan synthase inhibitor	1140.2	IV infusion	Vicuron/ Pfizer
2007	lanreotide	acromegaly, neuroendocrine tumors	growth hormone release inhibitor	1156.4	SC, IM	Ipsen
2009	telavancin	complicated skin and skin structure infections (CSSSIs), nosocomial pneumonia*	bacterial cell-wall synthesis inhibitor	1755.6	IV infusion	Theravance
2009	romidepsin	cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphomas (PTCLs)	histone deacetylase inhibitor	540.7	IV infusion	Gloucester Pharmaceuticals/ Celgene
2012	peginesatide	anemia associated with chronic kidney disease	erythropoiesis stimulating agent	4800.8 + 40 kDa PEG	IV, SC	Affymax/ Takeda
2012	linaclotide	constipation-predominant irritable bowel syndrome (IBS-C) and chronic idiopathic constipation (CIC)	guanylate cyclase 2C receptor activator	1526.7	OR	Forest Labs/ Ironwood Pharmaceuticals
2012	pasireotide	Cushing's disease, acromegaly, neuroendocrine tumors	growth hormone release inhibitor	1047.2	SC, IM	Novartis
2014	dalbavancin	complicated skin and skin structure infections (CSSSIs)	bacterial cell-wall synthesis inhibitor	1816.7	IV infusion	Durata Therapeutics/ Teva
2014	oritavancin	acute bacterial skin and skin structure infections (ABSSSIs)	bacterial cell-wall synthesis inhibitor	1793.1	IV infusion	The Medicines Company

Table 1. Cyclic peptide drugs approved in the last 10 years by the FDA and/or EMA. a) Year of first approval by FDA or EMA for at least one of the indicated diseases, b) Administration route: IV, intravenous, SC, subcutaneous, IM, intramuscular, OR, oral.

Phase[a]	Name	Indication	Mode of action	Discovery platform	Company
2	POL7080	pseudomonas aeruginosa infections, gram-negative infections	LptD protein homolog inhibitor, inhibits outer-membrane biogenesis	iterative modification and screening of peptide libraries using cationic antimicrobial peptide protegrin I as starting point	Polyphor
2	POL6326	metastatic breast cancer, acute myocardial infarction, hematopoietic stem cell mobilization from donors	chemokine receptor CXCR4 antagonist prevents the binding of stromal derived factor-1 (SDF-1) to mobilize stem cells	designed protein epitope mimetic (PEM) based on natural CXCR4 inhibitor T22	Polyphor
2	APL-2	age related macular degeneration, paroxysmal nocturnal hemoglobinuria	complement factor C3 inhibitor, blocks complement activation, PEGylated	phage display screening of cyclic peptide library	Apellis
1/2	ALRN-6924	acute myeloid leukemia, hematological leukemia hematological malignancies, myelodysplastic syndromes, solid tumors	inhibitor of p53-MDM2/MDMX interaction, restores p53-mediated apoptotic activity in tumors	peptide isolated by phage display and modified into stapled peptide	Aileron
1	RA101495	paroxysmal nocturnal hemoglobinuria	complement factor C5 inhibitor, blocks complement induced hemolysis	mRNA display screening of cyclic peptide libraries containing unnatural amino acids	Ra Pharma

Table 2. Cyclic peptides developed by *de novo* design or *in vitro* evolution that are currently under clinical evaluation. a) For cyclic peptides tested for multiple indications, the most advanced clinical phase is indicated.

Figure

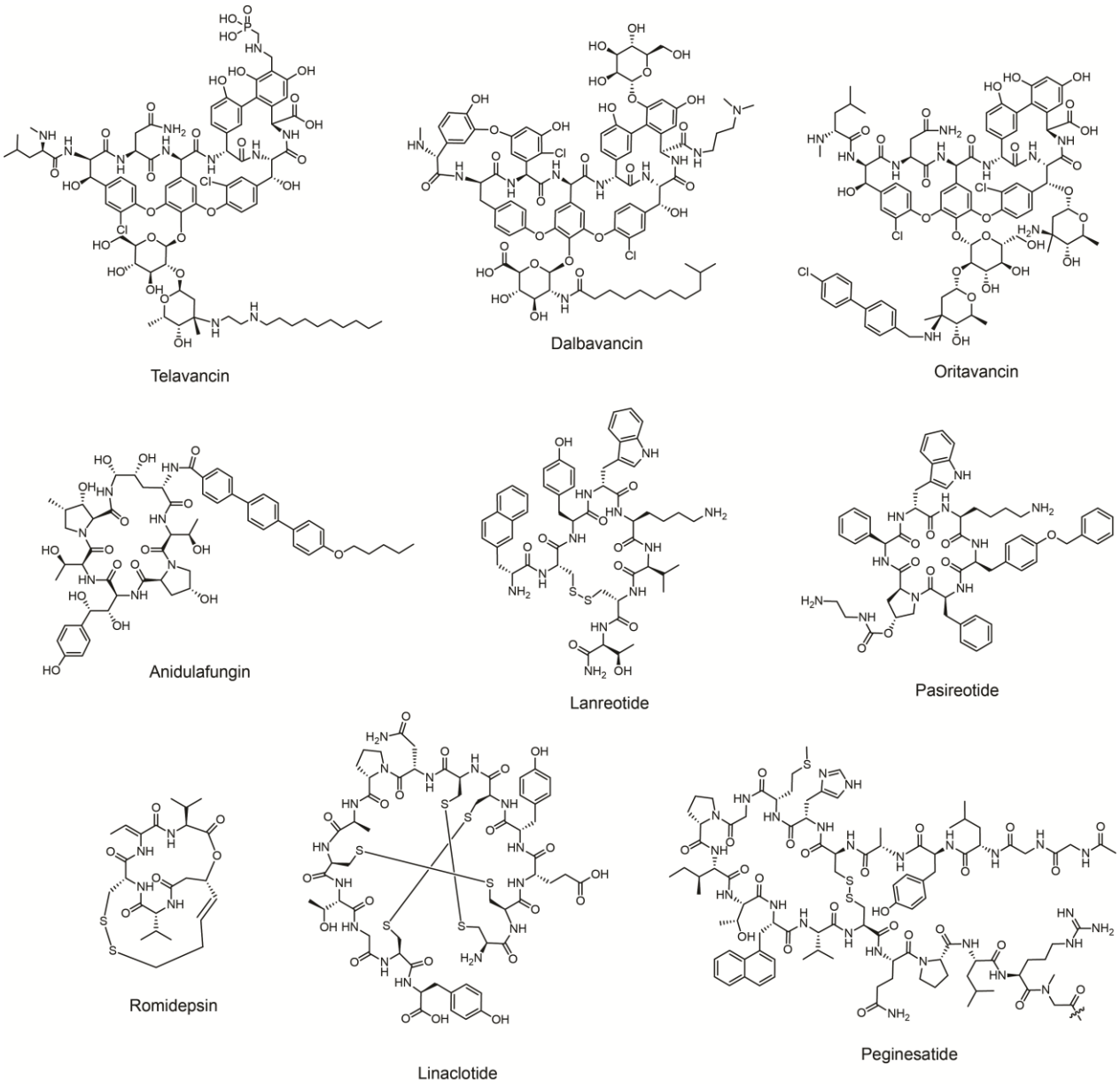

Figure 1. Cyclic peptide drugs approved in the last 10 years by the FDA and/or EMA. For peginesatide, the second identical peptide and the 40 kDa PEG are not shown.