Macrolides

Subjects: Chemistry, Medicinal
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Macrolides are a diverse class of hydrophobic compounds characterized by a macrocyclic lactone ring and distinguished by variable side chains/groups. Some of the most well characterized macrolides are toxins produced by marine bacteria, sea sponges, and other species. Many marine macrolide toxins act as biomimetic molecules to natural actin-binding proteins, affecting actin polymerization, while other toxins act on different cytoskeletal components. The disruption of natural cytoskeletal processes affects cell motility and cytokinesis, and can result in cellular death. While many macrolides are toxic in nature, others have been shown to display therapeutic properties. Indeed, some of the most well known antibiotic compounds, including erythromycin, are macrolides. In addition to antibiotic properties, macrolides have been shown to display antiviral, antiparasitic, antifungal, and immunosuppressive actions.

Keywords: macrolide ; toxin ; antibiotic ; antifungal ; antiviral ; antiparasitic ; immunosuppressant

1. Introduction

The study of macrolides over the past few decades has revealed a varied group of molecules with a range of structures and functions. Macrolides are hydrophobic compounds characterized by a macrocyclic lactone ring that typically contains at least 12 elements, while the remaining structure varies greatly between different classes of molecules [1][2].

Many macrolides have been discovered that display pharmaceutical properties, giving them potential as antibiotic, antiviral, antiparasitic, antimycotic, or immunosuppressant drugs [2][3]. While naturally produced macrolides may have limited use as drugs due to their instability in stomach acid, poor pharmacokinetics, and adverse side effects, synthetic macrolide derivatives have been developed to overcome these issues [1]. Many macrolides also exhibit toxic bioactivity, which may be a cause of the adverse side effects observed in response to the administration of macrolide drugs. Indeed, one of the largest classes of macrolides is toxins, many of which are produced from marine sources [4]. On the other hand, some macrolide mechanisms of toxicity have been manipulated for use in therapeutic applications.

2. Macrolide Classes

2.1. Toxins

Macrolide toxins originating from marine and microbial sources represent a vast library of chemical structures with varying mechanisms of toxicity. Marine macrolide toxins are of particular interest, as the number of known toxins has increased greatly over the past 50 years. Increasing knowledge of the biochemistry of these compounds has explained a wide range of toxic effects, from quick paralysis to more gradual changes in target cells. Marine macrolide toxins have also been of interest due to their potential therapeutic properties against cancer and fungal or parasitic infections, and their ability to act as immunosuppressants [3][4]. Toxins produced by bacterial species, such as the mycolactones from *Mycobacterium ulcerans*, also have a wide range of effects on host cells, many of which have yet to be discovered [5].

2.2. Antibiotics

Since the so-called “golden era” of antibiotic discovery between the 1930s and 1960s, macrolide antibiotics have been widely studied and prescribed for the treatment of infectious disease [6]. While antibiotics are used as first-line agents in treating infectious disease driven by bacteria, macrolide antibiotics often also exert immunomodulatory effects. In addition, recent studies have revealed potential clinical benefits of macrolides in the treatment of chronic inflammatory airway diseases [7]. Macrolide antibiotics display bacteriostatic and bactericide activity against various Gram-positive and Gram-negative species, as well as some Gram-indeterminate bacteria [6][8][9]. Because of their low toxicity, macrolide antibiotics are often selected as the safest option for antibacterial treatment [8]. This advantage is enhanced as allergic reactions to the macrolide antibiotics are noted to be rare; however, there have been some cases reported in the literature [10][11][12][13].

2.3. Antivirals and Antiparasitics

The discovery of macrolides that display antiviral and anthelmintic properties has greatly reduced the incidence of viral and parasitic diseases. Avermectins were discovered to be produced by *Streptomyces avermitilis* in 1973, and display highly specific anthelminthic, but generally not antibacterial or antifungal, activity [14][15]. Ivermectin is the most widely used avermectin derivative due to its safety and efficacy. After being used successfully in the agricultural and veterinary fields, ivermectin was introduced to treat onchocerciasis (also known as river blindness) in resource-poor tropical populations in 1987, where it was given to patients free of cost. This effort has been largely successful in the elimination of onchocerciasis in those regions, and ivermectin has been deemed a “wonder drug” [15][16]. Since then, ivermectin has been shown to have broad-spectrum antiparasitic properties, and has been used to treat lymphatic filariasis, strongyloidiasis, scabies, and head lice [15][17]. Balticolid, a plecomacrolide produced by a marine-derived ascomycetous fungus, was discovered more recently in driftwood off the Baltic Sea in Germany, and has been shown to display anti-HIV and anti-herpes simplex type I activity [18][19][20]. The bryostatins are a class of highly oxygenated macrocyclic lactones originating from marine bryozoan *Bugula neritina* [21][22]. There have been over 20 bryostatins isolated to date, some of which display antiviral activity [22].

2.4. Antifungals

Macrolide antibiotics that target fungi, including amphotericin B and nystatin, amongst others, are some of the most effective therapeutics against potentially life-threatening fungal infections in humans [23]. In 1950, nystatin was the first polyene macrolide antifungal compound to be discovered by Rachel Fuller Brown and Elizabeth Lee Haze. It was also the first widely available and effective antifungal treatment. Brown and Haze cultured *Streptomyces noursei* from soil found near a dairy farm in Fauquier County, Virginia, and determined its antifungal properties by screening it against *C. albicans* and *C. neoformans*. Nystatin was then purified and characterized from the *Streptomyces noursei* cultures [24][25]. This work led to the continuation of mycological studies and the subsequent discovery of amphotericin B (AmB) in 1955 at the E.R. Squibb Institute [25][26]. Amphotericin B, which is the current “gold standard” of treatment for fungal infections, was isolated from cultures of *Streptomyces nodosus* found in soil near the Orinoco River of Venezuela and has been shown to have broad antifungal activity, as well as antiparasitic activity [26]. Two additional antifungal compounds were discovered in 1955: natamycin (previously called pimaricin) and filipin [27][28]. Natamycin was isolated from a culture of *Streptomyces natalensis* found in soil from Natal, South Africa [27]. Filipin was named after its place of discovery, the Philippines, where it was isolated from *Streptomyces filipinesis* [28]. Cruentaren A and B were identified more recently and were isolated from *Byssovorax cruenta*. Cruentaren A is most commonly used as an antifungal treatment, as cruentaren B displays a lack of antifungal activity [29][30].

2.5. Immunosuppressants

The macrolide immunosuppressants represent a more recently discovered class of drugs that are used to prevent organ transplant rejection and treat inflammatory skin diseases [31]. Tacrolimus is an immunosuppressant that was discovered in 1984 in *Streptomyces tsukabaensis* cultures found from soil near Tsukuba, Japan [32][33]. It has been used to prevent kidney, liver, and bone marrow rejection in transplant patients [33][34][35]. A topical formulation of tacrolimus is the first non-glucocorticoid shown to be effective at treating atopic dermatitis [34]. Pimecrolimus is an ascomycin derivative that was developed specifically to treat inflammatory skin conditions, including psoriasis and atopic dermatitis [36][37]. Rapamycin, known by the common name sirolimus, was isolated from the actinomycete *Streptomyces hygroscopicus* from soil found on Easter Island, where it was first determined to display antifungal properties [38][39][40][41][42]. It was later found to display immunosuppressive properties, and has been developed for the prevention of renal, pancreatic islet cell, liver, and heart transplant rejection [38][43].

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